A comparison of costs and effectiveness of coronary revascularisation strategies in the Australian context

By

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Abstract

Coronary revascularisation is among the most widely studied procedures in the medical literature, attributable to the rising prevalence of coronary artery disease (CAD) and its burden on resource-scarce healthcare systems. CAD could be treated surgically through restoring blood flow from diseased coronary arteries to the coronary heart muscle (coronary revascularisation), by coronary artery bypass grafting (CABG) surgery or percutaneous coronary intervention (PCI). Other treatment options for CAD include pharmacotherapy, and lifestyle modification. The focus of this thesis was CABG and PCI for the treatment of CAD.

Traditionally, CABG is recommended to patients with complex multi-vessel CAD (MVCAD) and to those with diabetes mellitus (DM), and PCI, for patients with single-vessel CAD and acute coronary syndrome. Technological advancement in PCI, including the introduction of drug-eluting stents (DES), revived the debate on whether DES is an appropriate treatment for high-risk patients, those with MVCAD and additional comorbidities, and whether it is more effective and cost-effective than bare-metal stents (BMS). This doctoral thesis aims to address the gaps in evidence concerning the costs and effectiveness of CABG and PCI in these high-risk patient sub-groups, through conducting systematic reviews, and economic evaluations using data from routine, contemporary clinical practice in Australia.

To evaluate the *effectiveness* of CABG versus DES in patients with MVCAD and DM, a systematic review and meta-analysis was carried out pooling data from randomised controlled trials (RCTs) and non-randomised observational studies. At mean 3-year follow-up, CABG was unambiguously associated with significantly lower risk of major adverse cardiac and cerebrovascular events (MACCE) individually and collectively. Pooled analyses of data from non-randomised studies however, revealed differences between the groups for all end-points

except all-cause mortality, myocardial infarction, and cerebrovascular events at mean 3.5-years.

Another systematic review was performed to compare the *cost-effectiveness* of CABG versus PCI among patients with MVCAD from 12 months up to patient's life time. This analysis revealed that CABG compared with PCI is an economically attractive treatment option for people with MVCAD in the long term, from the healthcare payer's perspective. The true cost-effectiveness of CABG compared with PCI, however, was uncertain due to a paucity of studies that used a societal perspective, a life-time time horizon, and adopted health economic guidelines for reporting of results from economic evaluations.

To assess the cost-effectiveness of routine PCI versus CABG for MVCAD in the Australian context, an observational study was undertaken over the period from 2009 to 2013. The study used data from a single hospital administrative dataset, linked to datasets from the Melbourne Interventional Group (MIG), and the Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) registries. Propensity-score bin bootstrapping matching technique was used to balance CABG and PCI groups, in addition to a standard 1:1 matching technique. An incremental cost-effectiveness ratio (ICER) of AU$55,255/ MACCE avoided was observed for the overall cohort. The ICER varied across comparisons against bare-metal stents (ICER: $25,815/ MACCE avoided), all drug-eluting stents, DES ($56,861), 2nd generation DES ($42,925), and 3rd generation of DES ($88,535). Lower ICERs were apparent for high-risk sub-groups including those with diabetes ($42,819), acute coronary syndrome ($30,431), left-main CAD ($38,864), and heart failure ($36,966). The results from this evaluation revealed that at mean follow-up of 2.7 years, CABG compared with PCI was most economically attractive among high-risk patient subgroups, from the perspective of the Australian public hospital payer.

Furthermore, the cost-effectiveness of guideline-driven use of DES compared with BMS in Victorian public hospitals from 2004 to 2011 was examined, using multi-centre data from the MIG registry, published cost estimates, and a 1:1 propensity-score matching method. ICERs were evaluated for all patients, and sub-groups of patients with '0', 1, 2, or ≥3 indications for a DES. While the incremental cost per TVR avoided for these groups were AU$24,683, $44,635, $33,335, and $23,788, respectively, for those with ≥3 indications, DES compared with BMS was associated with cost savings. The cost-effectiveness of DES compared with BMS thus improved with increasing risk profile of patients, from those who had 1, 2, to ≥3 indications for a DES

In summary, this doctoral thesis provides important estimates of effectiveness, costs, and cost-effectiveness among high-risk patients treated with CABG or PCI. While the findings revealed that overall, CABG was more cost-effective as it prevented more subsequent hospitalisations than PCI, these results should be assessed with respect to limitations associated with finite follow-up, and generalisability only to the Australian context. A hallmark of this thesis were methodologies applied to evaluate medical technologies using data collected in routine care, as oppose to RCTs. This may render valuable evidence in the realm of health technology assessment in the future.

Declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes three original papers published in peer reviewed journals and two submitted publications. The core theme of the thesis was to investigate the cost-effectiveness of coronary revascularisation strategies through the use of observational data from clinical registries in Australia. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the Department of Epidemiology and Preventive Medicine, Monash University under the supervision of Professor Christopher M Reid, Dr Zanfina Ademi, Dr Baki Billah, and Professor Franklin Rosenfeldt.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research. In the case of Chapters 3, 4, 5, 6, and 7 my contribution to the work involved the following:

Thesis Chapter	Publication Title	Status *(published, in press, accepted or returned for revision, submitted)*	Nature and % of student contribution	Co-author name(s) Nature and % of Co-author's contribution*	Co-author(s), Monash student Y/N*
3	Prolonged effectiveness of coronary artery bypass surgery versus drug-eluting stents in diabetics with multi-vessel disease: An updated systematic review and meta-analysis.	Published	80%. Design of systematic literature search and review, statistical analysis, interpretation of results, development and writing the manuscript.	All authors provided input to manuscript through either abstract review (AR), and/or article selection (AS) and/or statistical analysis expertise (SAE), and/or editing (E), **totalling to 20% contribution**: 1. Zanfina Ademi, *AR, AS, E* 2. Cheng-Hon Yap, *AR, AS, E* 3. Baki Billah, *SAE, E* 4. Franklin Rosenfeldt, *E* 5. Bryan P. Yan, *E* 6. Christopher M. Reid *E*	No
4	A systematic review of cost-effectiveness of percutaneous coronary intervention vs. surgery for the treatment of multivessel coronary artery disease in the drug-eluting stent era.	Published	80% Design of systematic literature search and review, interpretation of results, development and writing the manuscript.	All authors provided input to manuscript through either abstract review (AR), and/or article selection (AS) and/or editing (E), **totalling to 20% contribution**: 1. Cheng-Hon Yap, *AR, AS, E* 2. Zanfina Ademi, *AR, AS, E* 3. Franklin Rosenfeldt, *E* 4. Stephen J. Duffy, *E* 5. Baki Billah, *E* 6. Christopher M. Reid *E*	No
5	The cost-effectiveness of guideline-driven use of drug-eluting stents: propensity-score matched analysis of a seven-year multicentre experience.	Submitted	80%. Study design, statistical analysis, interpretation of results, development and writing the manuscript.	All authors provided input to manuscript through either concept (*C*), and/or economic evaluation expertise (*EEE*), and/or statistical analysis expertise (*SAE*), and/or editing (*E*), **totalling to 20% contribution**: 1. Zanfina Ademi, *EEE, E* 2. Molla M. Huq, *SAE*, *E* 3. Stephen J. Duffy, *E* 4. Bryan P. Yan, *E* 5. Andrew E. Ajani, *E* 6. David J. Clark, *E* 7. Baki Billah, *E* 8. Angela L. Brennan, *E* 9. Gishel New, *E* 10. Nick Andrianopoulos, *E* 11. Christopher M. Reid, *C, E*	No
6	The real-world cost-effectiveness of coronary artery bypass grafting versus stenting in high-risk patients: propensity score analysis of a single centre experience	Submitted	80%.Study design, statistical analysis, interpretation of results, development and writing the manuscript.	All authors provided input to manuscript through either concept (*C*), and/or economic evaluation expertise (*EEE*), and/or statistical analysis expertise (*SAE*), and/or editing (*E*), **totalling to 20% contribution**: 1. Zanfina Ademi, *EEE, E* 2. Molla M. Huq, *SAE*, *E* 3. Franklin Rosenfeldt, *E* 4. Stephen J. Duffy, *E* 5. Bonny Parkinson, *EEE, E* 6. Cheng-Hon Yap, *E* 7. Julian Smith, *E* 8. Baki Billah, *E*	No

				9. Bryan P. Yan, *E* 10. Angela L. Brennan, *E* 11. Lavinia Tran, *E* 12. Christopher M. Reid, *C, E*	
7	Cardiovascular readmissions and excess costs following percutaneous coronary intervention in patients with chronic kidney disease: Data from a large multi-centre Australian registry.	Published	80%. Study design, statistical analysis, interpretation of results, development and writing the manuscript.	All authors provided input to manuscript through either concept (*C*), and/or statistical analysis expertise (*SAE*), and/or editing (*E*), **totalling to 20% contribution**: 1. Zanfina Ademi, *SAE*, *E* 2. Stephen J. Duffy, *E* 3. Nick Andrianopoulos, *E* 4. Baki Billah, *SAE*, *E* 5. Angela L. Brennan, *E* 6. Gishel New, *E* 7. Alexander Black, *E* 8. Andrew E. Ajani, *E* 9. David J. Clark, *E* 10. Bryan P. Yan, *E* 11. Cheng-hon Yap, *E* 13. Christopher M. Reid, *C, E*	No

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student signature: [redacted] Date: **17th April, 2017**

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

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Publications, presentations and awards

Published articles

- Ariyaratne, T. V., Yap, C. H., Ademi, Z. et al. A systematic review of cost-effectiveness of percutaneous coronary intervention vs. surgery for the treatment of multivessel coronary artery disease in the drug-eluting stent era. *European Heart Journal-Quality of Care and Clinical Outcomes*. 2016: qcw007.

- Ariyaratne, T. V., Ademi, Z., Yap, C. H. et al. Prolonged effectiveness of coronary artery bypass surgery versus drug-eluting stents in diabetics with multi-vessel disease: An updated systematic review and meta-analysis. *International journal of cardiology.* 2014; 176(2), 346-353.

- Ariyaratne, T. V., Ademi, Z., Duffy, S. J. et al. Cardiovascular readmissions and excess costs following percutaneous coronary intervention in patients with chronic kidney disease: Data from a large multi-centre Australian registry. *International journal of cardiology*. 2013; 168(3), 2783-2790.

Conference presentations

(Poster presentation unless otherwise stated)

- Ariyaratne T.V., Ademi Z, Huq M. et al. The Real-World Cost-Effectiveness of Coronary Artery Bypass Grafting Versus Stenting in High-Risk Patients: Propensity Score Analysis of a Single Centre Experience. *International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 21st Annual International Meeting*, **Washington DC, USA, May, 2016.**

- Ariyaratne, T. V., Yap, C. H., Ademi, Z. et al. A systematic review of cost-effectiveness of percutaneous coronary intervention vs. Surgery for the treatment of multivessel coronary artery disease in the drug-eluting stent era. *Australian Health Economics Society (AHES) Annual Meeting*, **Brisbane, Australia, October, 2015.**
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- Ariyaratne, T., Ademi, Z., Yan, B. P. et al. The cost-effectiveness of guideline-driven use of drug-eluting stents: propensity-score matched analysis of a seven-year

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- Ariyaratne, T., Ademi, Z., Yan, B. P. et al. PW241 The Cost-Effectiveness of Guideline-Driven Use of Drug-Eluting Stents in Victorian Public Hospitals*. World Congress of Cardiology*, **Melbourne, Australia, May 2014.**

- Ariyaratne, T., Ademi, Z., Yan, B. P. et al. The Cost-Effectiveness of Guideline-Driven Use of Drug-Eluting Stents in Victorian Public Hospitals*. National Heart Foundation Conference*, **Adelaide, Australia, May 2013.** [Oral presentation]

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- Ariyaratne, T. V., Ademi, Z., Duffy, S. J. et al. PSU10 Costs of Cardiovascular Readmissions Following Percutaneous Coronary Intervention in Patients With Chronic Kidney Disease: Data from a Large Multi-Centre Australian Registry*, Annual European Congress of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)*, **Berlin, Germany, November 2012.**

- Ariyaratne, T., Ademi, Z., Duffy, S. J. et al. Analysis of Readmission Rates and Costs Following Percutaneous Coronary Interventions in Patients with Chronic Kidney Disease: The MIG Experience. The Cardiac Society of *Australia and New Zealand (CSANZ) Annual Meeting*, **Brisbane, Australia, August 2012.**
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Media release

- Foulds J. of Hume Weekly. (2011, May 17). Getting to heart of the matter.
  One-page media release published in a local suburban newspaper that featured (entirely) my doctoral research proposal. This was written by the Heart Foundation of Australia for 'Heart Week' and their 'Go for Red for Women' campaign, uniting women in the battle against heart disease.

Awards

- Travel grant from the Centre for Cardiovascular Research and Education in Therapeutics (CCRET), Monash University, to attend the AHES conference in Brisbane, Australia, in October 2015.

- Travel grant from the National Heart Foundation (NHF) Australia to attend the NHF Conference in Adelaide, Australia, in May 2013.

- Postgraduate Travel Grant from Monash University to attend the Annual European Congress of ISPOR, in Berlin, Germany, in November 2012.

- Travel grant from the Centre for Cardiovascular Research and Education in Therapeutics (CCRET), Monash University, to attend the ISPOR Annual European Congress in Berlin, Germany, in November 2012.

- Travel grant from the International Society for Heart Research (ISHR) to attend the CSANZ Annual Meeting in Brisbane, Australia, in August 2012.

- Awarded the prestigious National Heart Foundation Postgraduate Research Scholarship in the Public Health Stream in January 2011.

- Awarded the Faculty of Medicine Postgraduate Research Scholarship in 2010.

Published articles during candidature not related to thesis

- Singh, S., Vashist, S., & Ariyaratne, T. V. One-year experience with the Cochlear™ Paediatric Implanted Recipient Observational Study (Cochlear P-IROS) in New Delhi, India. *Journal of Otology*, 10(2), 57-65.

- Sanderson, G., Ariyaratne, T. V., Wyss, J. et al. A global patient outcomes registry: Cochlear paediatric implanted recipient observational study (Cochlear™ P-IROS). *BMC Ear, Nose and Throat Disorders*. 2014; 14(1), 10.

- Ariyaratne, T. V., Billah, B., Yap, C. H, et al. An Australian risk prediction model for determining early mortality following aortic valve replacement. *European Journal of Cardio-Thoracic Surgery*. 2011; 39(6), 815-821

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Glossary

AMI	Acute Myocardial Infarction
ANZSCTS	Australian and New Zealand Society of Cardiac and Thoracic Surgeons
BMS	Bare Metal Stent
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CARDia	Coronary Artery Revascularisation In Diabetes (trial)
CEA	Cost-effectiveness Analysis
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CKD	Chronic Kidney Disease
CPI	Consumer Price Index
CUA	Cost-utility Analysis
CRF	Case Report Form
CVA	Cardiovascular Disease
CVE	Cerebrovascular Event
DES	Drug-eluting Stent
DSA	Deterministic Sensitivity Analysis
FREEDOM	Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease (trial)
GDP	Gross Domestic Product
HPI	Health Price Index
HTA	Health Technology Assessment
ICER	Incremental Cost-effectiveness Ratio
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LYG	Life Years Gained
MACCE	Major Adverse Cardiac and Cerebrovascular Events

MBS	Medicare Benefits Scheme
MI	Myocardial Infarction
MIG	Melbourne Interventional Group
MOOSE	Meta-analysis of Observational Studies in Epidemiology
MSAC	Medical Services Advisory Committee
MVCAD	Multivessel Coronary Artery Disease
NICE	National Institute for Health and Care Excellence
OECD	Organisation for Economic Cooperation and Development
OPCABG	Off-pump Coronary Artery Bypass Grafting
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PCI	Percutaneous Coronary Intervention
PPP	Purchasing Power of Parity
PSA	Probabilistic Sensitivity Analysis
PSBB	Propensity-score Bin Bootstrapping
PTCA	Percutaneous Transluminal Coronary Angioplasty
QALY	Quality Adjusted Life Years
RCT	Randomised Controlled Trial
STEMI	ST-Elevation Myocardial Infarction
SYNTAX	Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery (trial)
TAVI	Transcatheter Aortic Valve Implantation
UHC	Universal Health Care
VA CARDS	Veterans Affairs Coronary Artery Revascularization in Diabetes (trial)
WHO	World Health Organisation

1 Introduction

1.1 Chapter overview

This chapter provides background to the prevailing issues in the Australian healthcare system, in the context of cardiovascular disease burden and health technology assessment (HTA). Additionally, it will provide an overview of coronary artery revascularisation strategies, and identify current gaps in evidence, which will be further probed through analytical reviews provided in Chapter 3 and Chapter 4. The importance of patient registries will also be emphasised in the context of 'levels of evidence'. Given the foci of this thesis are cost-effectiveness analyses of coronary revascularisation procedures in high-risk patient populations, attention will be drawn to reimbursement of medical devices and related authorities in Australia and overseas, rather than assessments of safety (also a component of HTA) and the regulation of medical devices. Finally, this chapter will describe the overarching objectives of this thesis, and provide an overview of its structure.

1.2 Current issues and healthcare reforms in Australia

Australia has one of the best performing, efficient healthcare systems in the world (1). Over the past 50 years, Australia maintained relatively low levels of national expenditure on health, below 10% of GDP (8.8% of GDP, 2016), while offering high level of access to free or subsidised services through Medicare and achieving high performance in population health status metrics (2). Key metrics in population health status for Australia are illustrated in Figure 1 and Figure 2 (3). Australians enjoy high life expectancy, ranked sixth highest in the OECD (female, 84.5 years; male, 80.4 years in 2016) and achieved record rates of survival from breast, colorectal, and lung cancers (1). The level of tobacco consumption among Australians is one of the lowest in the world (1). However, like other high income nations, Australia is burdened with a growing ageing, and obese population, with Australia being ranked fifth obese in the OECD (28.3% aged ≥15 years) (1). The burden from chronic disease is rising in Australia. Among the nine key priority areas identified by the Australian National Strategic Framework for Chronic Conditions, include (4-6):

1. Cancer control,
2. Cardiovascular health,
3. Injury prevention and control,
4. Mental health,
5. Diabetes mellitus,
6. Asthma,
7. Arthritis and musculoskeletal conditions,
8. Obesity
9. Dementia.

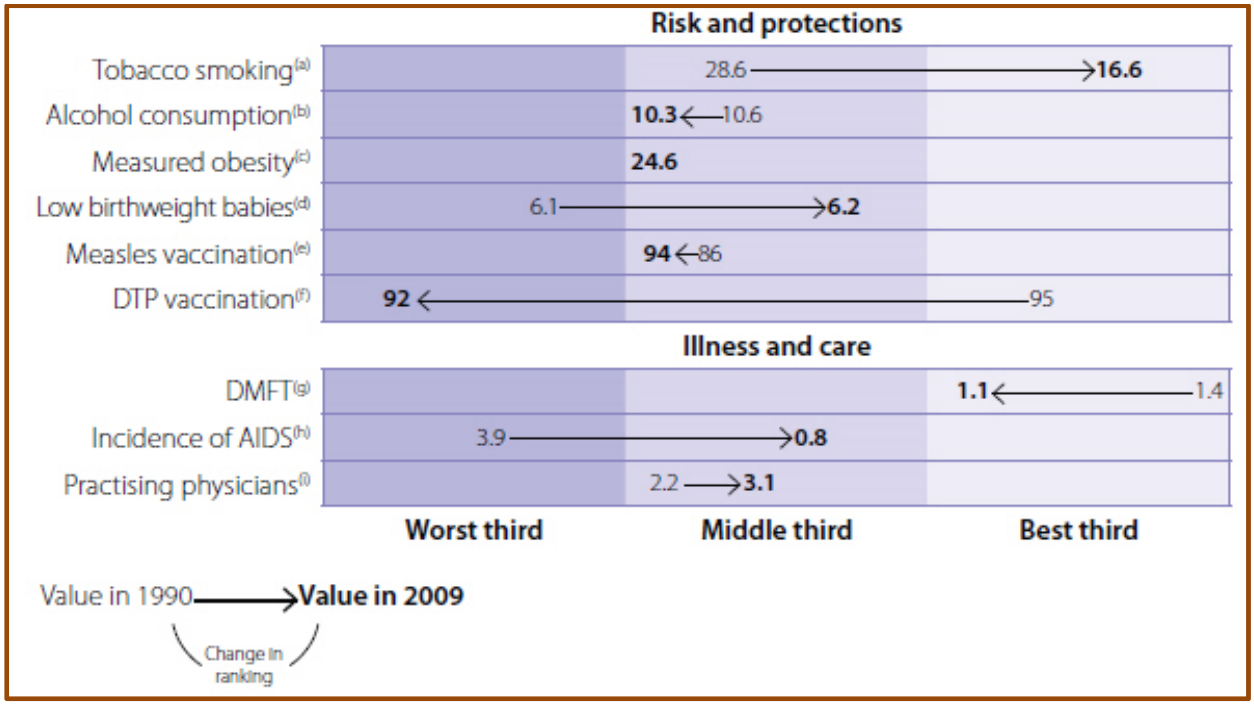


Figure 1 Australia's ranking among OECD countries, selected risk and illness indicators, 1990 and 2009 (or nearest preceding year) (3).

Abbreviations: AIDS, acquired immunodeficiency syndrome; DMFT, decayed, missing and filled teeth; DPT, diphtheria–pertussis–tetanus; OECD, Organisation for Economic Co-operation and Development.

Source: Adapted from Chapter 9 of Australia's Health 2014 Report, a series of reports published by the AIHW every two years. The figure shows an AIHW analysis of OECD StatExtracts (OECD 2013a).

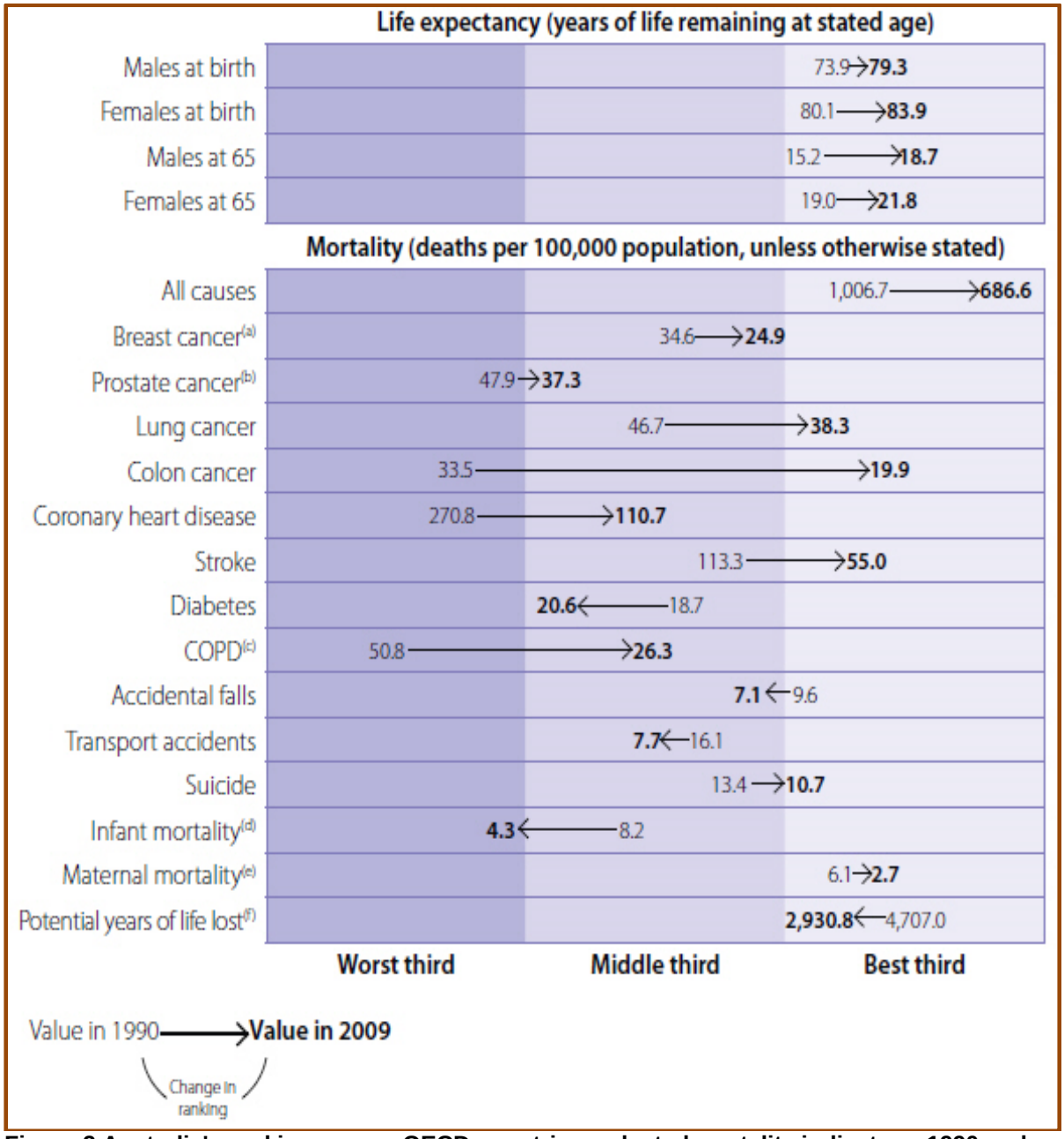


Figure 2 Australia's ranking among OECD countries, selected mortality indicators, 1990 and 2009 (or nearest preceding year) (3).
Abbreviations: COPD, chronic obstructive pulmonary disease.

Source: Adapted from Chapter 9 of Australia's Health 2014 Report, a series of reports published by the AIHW every two years. The figure shows an AIHW analysis of OECD StatExtracts (OECD 2013a).

Healthcare sustainability is an ongoing concern in Australia corresponding to a burgeoning consumption and expenditure on healthcare resources. The average cost per case-mix-adjusted hospitalisation, a measure of system efficiency and sustainability, increased from

2007–2011 by 23.5% with an average rise of 5.4% annually (not adjusted for inflation) (3). The average consumption of antidepressants, cholesterol-lowering drugs, and antibiotics in Australia is among the highest in the OECD (1). Australians spend more on out-of-pocket cost for healthcare than the OECD average (1). The per capita health expenditure in Australia is higher than OECD average, and is projected to grow significantly over the next 10 years, as illustrated in Figure 3 (2). The healthcare expenditure from 2004-2014 in Australia grew at a higher rate (5%) than the increase in GDP during the same period (2.4%) (4). Moreover, the long-term sustainability of existing healthcare resources is constrained through rising costs of caring for Australia's growing ageing population, unnecessary hospital admissions for chronic conditions, and expensive new medical treatments and technologies (4).

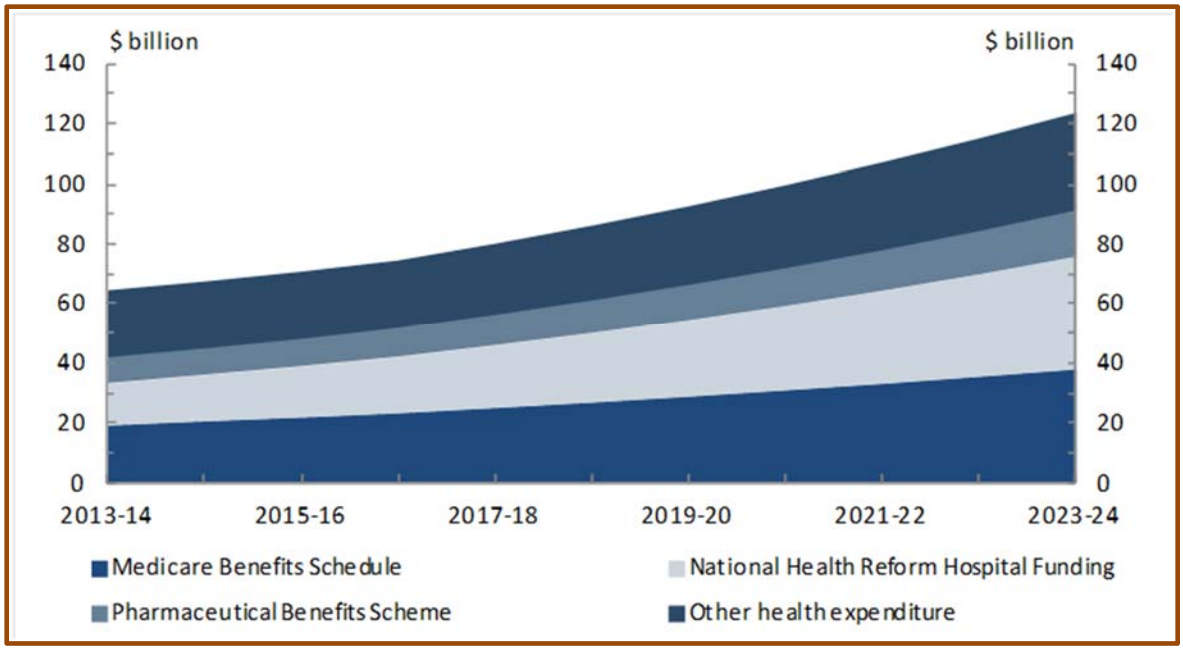


Figure 3 Projected growth in health spending in Australia (2).
Source: Adapted from the National Commission of Audit 2014.

To tackle emerging issues of healthcare sustainability, the Australian Government announced several major reviews for healthcare reform, beginning in 2015. The areas for new reform are summarised in Appendix A and include primary healthcare (4, 7, 8), Medicare rebates (9-11), private health insurance (PHI) and cost of prostheses (12-14), prescription medicine payments (15-18), mental health care (19-21), aged care (22), and electronic health records (15-18).

Summary:

Presently, the Australian healthcare system is subjected to significant reforms in Medicare, private health insurance, primary health care, and electronic medical records, among other areas of concern. The burden of Australia's growing ageing population, unnecessary hospital admissions for chronic conditions, rising costs of medical services and new technologies are threatening the long-term sustainability of existing healthcare resources. Consequently policy makers are forced to demand more evidence of healthcare efficiencies to support funding and reimbursement decisions.

1.3 Overview of coronary artery disease (CAD)

1.3.1 Definition

Coronary artery disease (CAD) is one of the subsets of cardiovascular disease (CVD). It is also referred to as coronary heart disease, ischemic heart disease, atherosclerotic heart disease, and coronary atherosclerosis. CAD is characterised by a narrowing of the coronary arteries which in turn prevents adequate blood supply to the heart muscle (23). CAD may progress to the point where the heart muscle is damaged due to lack of blood supply, which may lead to infarction (heart attack), arrhythmias, and heart failure (23). The underlying disease process in the blood vessels that results in CAD (and stroke), is known as atherosclerosis, the abnormal accumulation of lipid or fatty substances (plaque) in the lumen of coronary artery (23). While CAD can be asymoptomatic, its symptomatic form, 'acute coronary syndrome (ACS)' is characterised by unstable angina, non-ST segment elevation myocardial infarction (NSTEMI), or ST segment elevation myocardial infarction (STEMI), associated with a sudden rupture of plaque inside the coronary artery (23).

1.3.2 Risk factors

Three categories of risk factors are apparent for CAD, including behavioural, metabolic and other, which are listed in Box 1 (23). These factors essentially promote the process of atherosclerosis (23). There is robust evidence that suggest behavioural and metabolic risk factors are strongly associated with the aetiology of atherosclerosis (23).

Box 1 Risk factors associated with CAD (23).

Behavioural risk factors	Metabolic risk factors	Other risk factors
• Tobacco use • Physical inactivity • Unhealthy diet (rich in salt, fat, and calories) • Harmful use of alcohol.	• Hypertension • Diabetes • High cholesterol levels • Overweight and obesity	• Poverty and low educational status • Advancing age • Gender • Inherited (genetic) disposition

- Psychological factors (e.g., stress, depression)
- Other risk factors (e.g., excess homocysteine)

1.3.3 Global burden

Cardiovascular disease (CVD) and its risk factors are major contributors to global morbidity and mortality. CVD is a group of diseases that includes CAD, cerebrovascular disease (stroke), peripheral vascular disease, rheumatic heart disease, congenital heart disease, cardiac hypertension, arrhythmias and myopathy (23). Of all CVDs, CAD was the largest contributor to disability, as illustrated in Figure 4, contributing to 45% of CVD morbidity for males and 37% for females (24). Here, the disability was measured by disability-adjusted life year (DALY), expressed as the number of years lost due to ill-health, disability or early death (premature death).

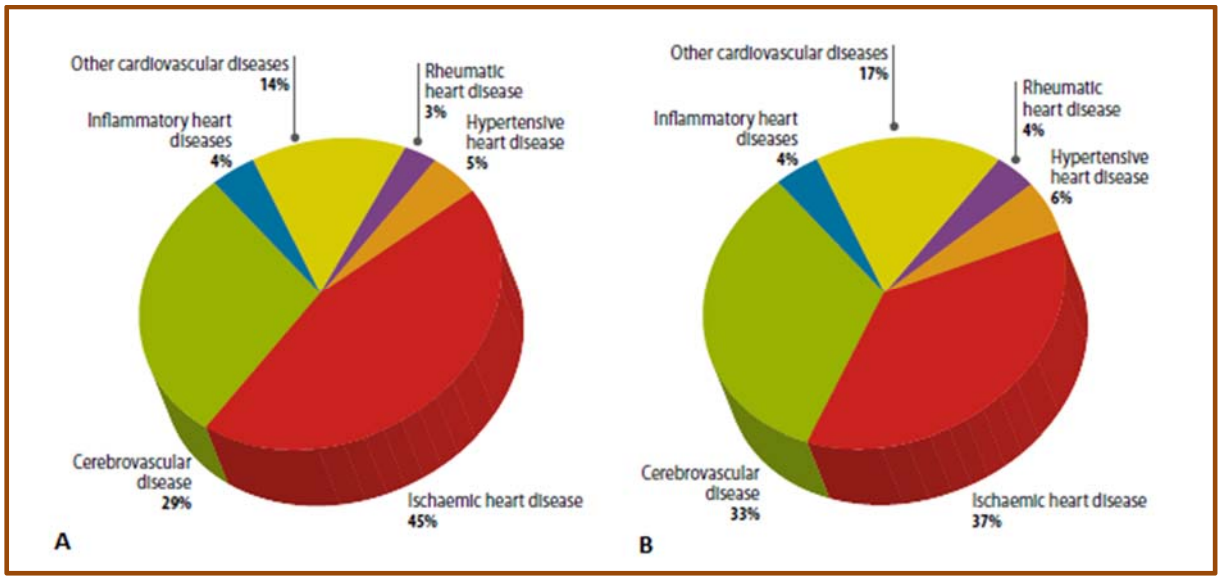


Figure 4 Distribution of global CVD burden (DALYs) due to heart attacks, strokes and other types of CVDs in (A) males and (B) females (23, 24).
Source: Adapted from WHO's Global Atlas on Cardiovascular Disease Prevention and Control Report 2011.

Despite high morbidity, the rate of mortality from CAD has declined dramatically in high income countries over the past two decades (23, 25, 26). The mortality rates for CAD across the world

are highlighted in Figure 5. Several reasons were attributed to this decline, including reduced incidence rates, and/or improved survival after cardiovascular events due to prevention and treatment interventions (23, 25, 26). For instance in the UK, 58% of the decline was attributed to population-wide risk factor reductions, while 42% of the decline was attributed to treatment: 11% to secondary prevention, 13% to heart failure treatment, 8% to initial treatment of acute myocardial infarction, and 3% to hypertension treatment (27).

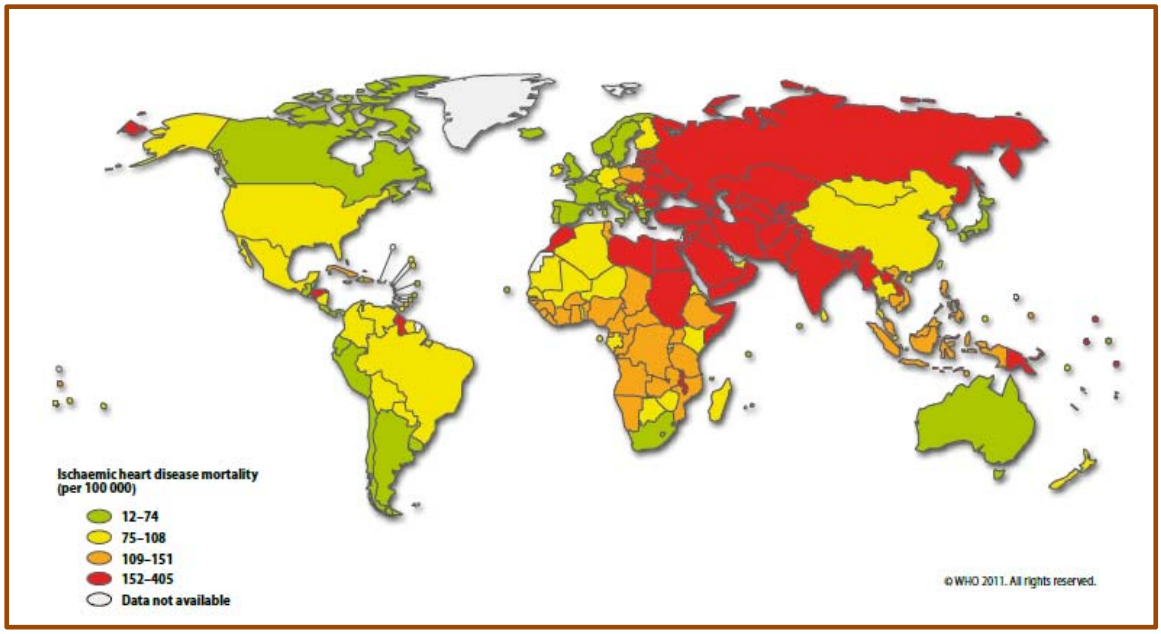


Figure 5 World map showing ischemic heart disease mortality rates (age standardized, per 100 000) (23, 28)
Source: Adapted from WHO's Global Atlas on Cardiovascular Disease Prevention and Control Report 2011.

1.3.4 Burden in Australia

Australia followed similar declining trends for CVD (and CAD) mortality and morbidity as other high income countries including UK and Canada (29). CAD claimed almost 20,000 Australian lives in 2015, representing 12% of all deaths in Australia, and 45% of all deaths from CVD(29, 30). Approximately one Australian dies every 27 minutes due to CAD, making it the single leading cause of death in Australia (29, 30). Majority of these deaths occurred in adults above age 35 years, and the rates of mortality due to CVD varied between different states and

territories of Australia (29). The overall trend in deaths due to CAD, however, is declining, with a fall of 15% reported for the period from 2004 to 2013 (29, 30).

The overall prevalence of CAD in Australia was 3% in 2011-2012, which included 591,800 Australians who lived with a long-term CAD condition (29, 30). However, the prevalence of CAD increased with age, at 5% for those aged from age 55-64 years, and 16% for those above age 75 years (29, 30). The measurement of actual incidence and prevalence of CAD and CVD conditions within communities remains challenging in Australia, as in most other countries, due to the lack of a population-based registry, and increasing reliance on statistics from hospital separations and self-reported data from individuals themselves (29).

In 2010, CAD contributed 7.8% of the total burden of DALYs in Australia, largest for any specific condition (29). However, the morbidity from CAD is declining (29, 30). A slow but substantial decline in the proportion of burden from CAD from 12.2% to 9.0%, was observed between 1990 and 2000 (29, 30). The proportion of hospitalisations attributable to CVD declined steadily between 2000 and 2013, from 7.3% to 5.5% (29, 30). The incidence of acute coronary events in adults over age 25 years has also fallen from 534 to 406 per 100,000 between 2007 and 2012 (29, 30).

While the above statistics are a cause for optimism, CVD remains the most expensive disease group in Australia with total annual spending of $7,605 million (2008-09), which was at 12% of total healthcare expenditure (31). CAD was the second most expensive CVD, contributing just over 25% of total annual CVD expenditure ($2,028 million, 2008-09), as per most recent evidence available to date (31). The total spending for CVD increased over the years, with costs of hospital services dominating the distribution of expenditure (Figure 6). The spending on hospital admitted patient services for CVD increased by 55%, between 2000-01 ($2,907

million) and 2008-09 ($4,518 million) (31). Australia's ageing population (discussed in Section 1.2) places further upward pressure on total healthcare expenditure for CVD and CAD. For men and women, the per person overall expenditure for CAD was highest among those aged 75-84 years, and aged 85+ years, respectively (31).

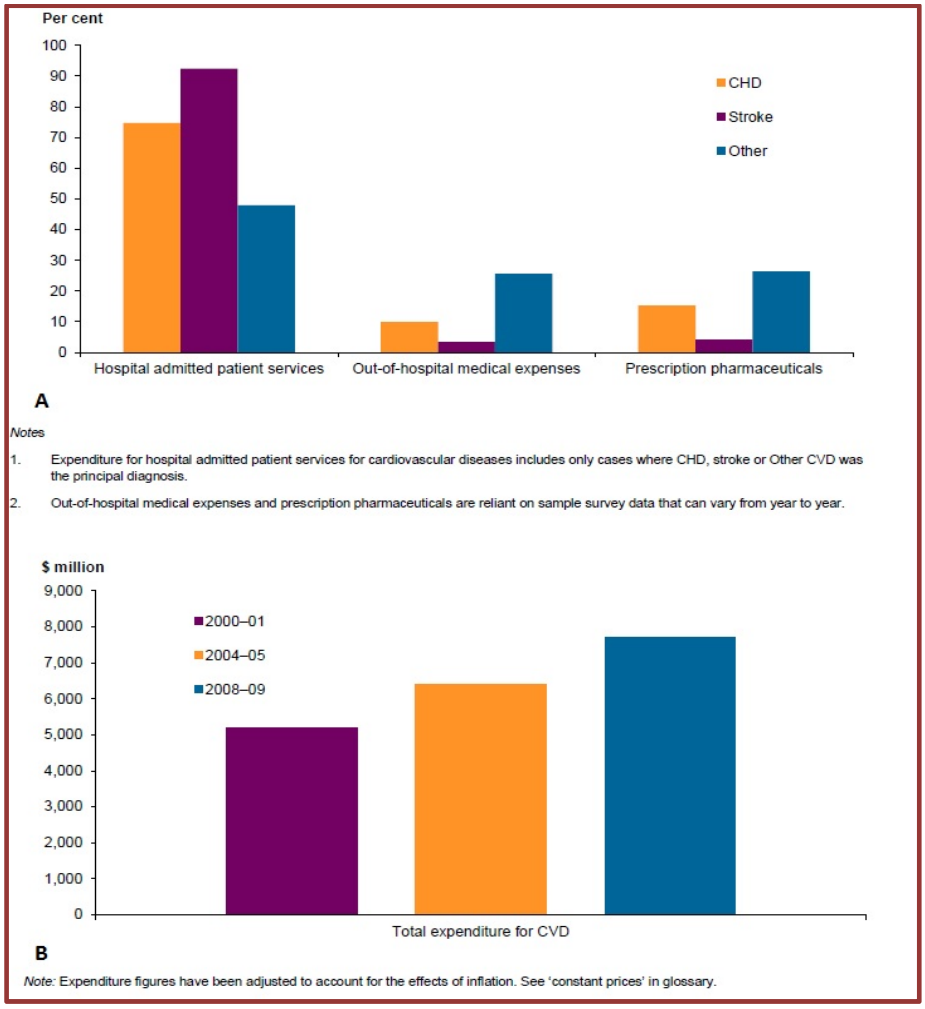


Figure 6 A. Cardiovascular disease expenditure, by health-care sector, constant prices, in Australia; B. Cardiovascular disease expenditure overtime: 2000–01, 2004–05, 2008–09, constant prices (31).
Source: Adapted from AIHW's Health-care expenditure on cardiovascular diseases report 2008–09, 2014.

Summary:

Global trends indicate that the mortality and burden from CAD is reducing due to several reasons, including declining incidence rates, and/or improved survival after cardiovascular events due to prevention and treatment interventions. Similar trends in mortality rates and morbidity due to CAD was also observed across Australia over the last decade. Despite decline in mortality and morbidity, the expenditure attributable to CAD is rising. In Australia, CVD accounts for 12% of total healthcare expenditure, and CAD, 25% of total annual CVD expenditure ($2,028 million, 2008-09). The total spending for CVD increased over the years, with costs of hospital services dominating the distribution of expenditure.

1.4 Treatments for CAD

1.4.1 Diagnostic procedures

There are number of diagnostic procedures for CAD, which will not be covered in detail in this thesis. A brief summary of existing diagnostic procedures for CAD is provided in Box 2.

Box 2 Diagnostic tests performed to identify CAD (32-34).

Diagnostic procedure	Definition
Blood tests	Check for markers of CAD in the blood stream e.g., levels of fats, cholesterol, sugar, and proteins in your blood. Abnormal levels might indicate the risk of CAD.
Stress tests	Test how heart reacts to physical exertion. The tests can be physiological i.e., exercise stress tests; or pharmacological, where medicines are given to increase heart rate.
Electrocardiogram	Also referred to as, ECG or EKG, records or displays an individual's heartbeat produced by electrocardiography.
Echocardiogram	An ultrasound test that can evaluate the structures of the heart, and the direction of blood flow within it. The tests produce images and videos, and often use a special probe or transducer that is placed in various places on the chest wall, to view the heart from different directions. The test may be performed before or after stress tests.
Nuclear cardiac imaging	Uses single photon emission computed tomography (SPECT) or cardiac positron emission tomography (PET) to detect movement of blood flow, damage, or death of heart muscle through images. The test may be taken before and after stress tests. Small amounts of radioactive materials called tracers are typically injected into the bloodstream, inhaled or swallowed prior to procedure.
Angiography	The most accurate procedure to examine coronary artery vessels. A surgical procedure known as 'coronary catheterisation' is performed whereby a long thin tube is placed into the body through femoral artery or radial artery and guided up to the heart. A special dye is then injected through the catheter into the coronary arteries, and X-ray is taken.
Fractional Flow Reserve (FFR)	FFR is measured during an angiogram using a thin pressure wire, and gauges the impact of plaque build-up by comparing the pressure in the artery beyond blocked area to the pressure in the aorta, where blood flows freely. It does not rely on how severely occluded an artery appears to be, but rather on how the constriction is actually impacting blood flow. By gauging the impact plaque build-up is having on blood flow, FFR has been shown to be more accurate than angiography alone.
Intravascular ultrasound (IVU)	IVU is not strictly a diagnostic procedure, and typically performed at the same time as a PCI. IVU is a combination of echocardiography and cardiac catheterization. IVU uses sound waves to produce an image of the coronary arteries to see their condition.

1.4.2 Medical therapy and lifestyle modification

Medical management and lifestyle modification are recommended as first line of treatments for stable CAD. Stable CAD is defined as established pattern of angina pectoris (chest pain), history of myocardial infarction, or the presence of plaque documented by catheterization (35). The goals of medical management include symptom alleviation, prevention of CVD events, and decrease in the risk of mortality from CAD (35). For the purpose of this thesis medical management and lifestyle modification interventions for CAD will not be covered. A brief summary of recommended interventions is provided in Box 3.

Box 3 Recommended treatments for stable CAD (35).

Medical therapy	Lifestyle modification
• Lipid-lowering drugs, e.g., statins, ezetimibe, fibrates, and nicotinic acid • Antihypertensive drugs, e.g., beta blockers, angiotensin-converting enzyme inhibitor, calcium channel blockers, angiotensin receptor blockers • Antiplatelet agents, e.g., aspirin, and clopidogrel • Nitrates for relaxation of blood vessels, and reduction of angina pectoris	• Tobacco cessation • Body mass index goal of 18.5-24.9 kg per m^2 • Moderate to intense activity for 30-60 minutes seven days a week • Alcohol consumption moderation • Low-sodium diet • 2-3 servings a day of fruit and vegetables • Saturated fat <10% of daily calories

For patients with stable or unstable CAD, 'coronary revascularisation' may be performed, depending on severity of disease.

1.4.3 Coronary artery bypass grafting (CABG)

Coronary artery bypass grafting (CABG) is a revascularisation strategy, used to restore blood flow to the heart from the site of occluded (blocked) arteries (36). The procedure involves creating an alternative route through a harvested artery or vein (a 'graft' or 'conduit'), so that normal blood flow is 'bypassed' from the site of blockage (stenosis) to an aortotomy in the proximal ascending aorta (36). This is performed through an incision made in the coronary artery distal to the stenosis, where the bypass graft is hand-sewn (anastomosed) end-to-side

to the incision, and again at the proximal anastomosis in the proximal ascending aorta, except for in situ arterial grafts in which the native arterial inflow is preserved (36). The most commonly used conduits for CABG include the left internal thoracic artery and the greater saphenous vein (36). Less routinely used grafts include the radial artery, the right internal thoracic artery, and the gastroepiploic artery, which have shown better patency than saphenous-vein grafts (36). There are two types of CABG:

- **Conventional (on-pump) CABG:** The first reported CABG in humans was performed by R Goetz in 1960 using internal thoracic artery graft (37). Introduced to clinical practice in the 1970s, conventional CABG utilises a cardiopulmonary bypass (CPB) machine to perform the function of the heart (36). The chest opened through sternotomy, and the heart is arrested by occluding the ascending aorta and perfusing the heart with cold, high-potassium cardioplegia solution (36). The CPB machine provides both perfusion pressure and oxygenation, to support the circulation during the 1-2 hour period of ischemic cardiac arrest (36).
- **Off-pump (beating heart) CABG (OPCABG):** Developed by Dr Amano Atsushi in the 1990s, OBCABG does not utilise a CPB machine, so that anastomoses of conduits is performed on a beating heart (38). The procedure may require full or partial sternotomy, and the use of procedure-specific special equipment (38). OPCABG was developed to address risks of using CPB machine, in particular, post-perfusion syndrome, which leads to post-operative cognitive decline, although literature have shown there is no difference between CABG and OPCABG in the long-term for low-risk patients.

CABG is considered a technically challenging surgery, even when performed on a non-beating heart. During the surgery, aided optical magnification is required by surgeons to perform anastomoses (36). An isolated CABG procedure may take between 3-4 hours to perform (36). Typically, patients undergoing CABG require to remain in hospital for 5-7 days following

procedure, including 1-2 days in an intensive care unit (ICU). Full recovery may not be achieved for further 6-12 weeks post-discharge (36).

1.4.4 Percutaneous coronary intervention

An alternative, less invasive revascularisation strategy for patients with AMI include percutaneous coronary intervention (PCI). PCI was first conceptualised in 1964 by Charles Theodore Dotter and introduced in humans in 1978 by Andreas Gruntzig (39). Over the past three decades, several ground-breaking technical innovations has revolutionised PCI. A summary of these innovations is briefly described.

1.4.4.1 Percutaneous transluminal coronary angioplasty (PTCA)

PTCA was the first minimally invasive revascularisation procedure introduced to clinical practice in the 1980s with the aim to restore blood flow to the heart by widening blocked coronary arteries due to atherosclerosis. PTCA may be performed as an extension to angiography particularly in emergent cases. The procedure is similar to an angiogram (see Box 2) (39). If a treatable blockage is identified through angiography, a guiding catheter, a guide wire, and a balloon catheter is advanced across to the site of the blockage site (39). The balloon is inflated for a few seconds to compress the blockage against the artery wall, and then deflated. This step may be repeated several times, after which the balloon catheter is removed (39). While PTCA was widely practised in the 1980s, it had several drawbacks related to acute vessel closure, restenosis, and higher repeat revascularisation rates compared with CABG (39, 40).

1.4.4.2 Bare metal stents

Bare metal stent (BMS) were introduced to clinical practice in the 1990s following the first trial by Paul and Sigwart in 1986 (39). Similar to balloon PTCA, BMS is applied to blocked coronary vessel through coronary catheterisation (39). The BMS comprises a mesh-like structure, composed of thin stainless steel wire. More recent ('second generation') BMS use cobalt

chromium alloy scaffold. Although BMS were successful in providing a scaffold that prevented acute vessel closure and late constrictive re-coil, it was noted that both PTCA and BMS exaggerated endothelial injury and inflammation, rendering both the stent and vessel highly thrombogenic. In fact, a patient implanted with a BMS was at risk of forming a sub-acute thrombotic coronary artery occlusion just two weeks post-implantation at a probability of 18%, thus requiring aggressive anticoagulant therapy (39, 41). Later, following two landmark trials, dual-antiplatelet therapy (DAPT) was introduced to clinical practice for patients who were implanted with BMS to mitigate risk of stent thrombosis (ST) (39, 42, 43). Although DAPT was effective, it was soon discovered that it did not ameliorate the risk of in-stent neointimal hyperplasia leading to in-stent restenosis, or the requirement for repeat target vessel revascularisation (TVR) (39).

1.4.4.3 Drug-eluting stents

Drug eluting stents (DES) were introduced to clinical practice in 2001 to address many of the problems experienced with PTCA and BMS, including in-stent restenosis (ISR) and requirement for repeat TVR (44). The first DES implantation was carried out by J Eduardo Sausa in Sao Paulo in 1999, using a Sirolimus-eluting DES (44). A DES is marked by a metallic (or non-metallic) scaffold, and a durable or biodegradable (bioabsorbable) polymer coating that embeds an anti-proliferative drug, which is released over time (44, 45). As summarised in Table 1, several generations of DES have been introduced to clinical practice since 2001, based on differing anti-proliferative drug coats and scaffold platforms including balloon expandable and self-expanding stents (45). First generation DES dramatically reduced ISR and TVR across all lesions and patient subsets compared with BMS (44). Their safety, however, was of concern because of suboptimal polymer biocompatibility leading to greater risk of late and very late ST and local immunological drug toxicity (44, 46). Moreover, the durable polymer used in first-generation DES was associated with mechanical complications and non-uniform coating, resulting in unpredictable drug distribution and release

(44, 47). To improve DES safety, second-generation DES were introduced, which comprised more durable, biocompatible polymers, which are eventually diluted to blood stream (44). Some trials suggested that bioabsorbable polymer-based DES are more effective than BMS, as it reduced the risk of very late ST. However, similar evidence of effectiveness of second generation non-bioabsorbable (fluorinated) against first-generation DES was also noted, disputing the belief that bioabsorbable polymers are necessary to minimise the risk of ST (44, 48-50). Third-generation DES introduced the platinum chromium platforms, which permitted similar radial strength, enabling a thinner strut design and subsequently significantly improved deliverability (44). Bioabsorbable vascular scaffold (BVS) is a relatively new technology introduced in fourth generation DES to address the limitations of the traditional metallic stents (44). These devices, however, are not widely used at present, and to-date have not demonstrated superiority in performance over metallic drug-eluting devices (44). Preliminary data showed that BVS are able to compete with the metallic stents in terms of safety and efficacy, however, it remains to be seen whether BVS can truly restore vascular integrity and function in ongoing and future clinical trials (44, 51-55). To-date there are four notable manufacturers of BVS, including Abbott (Absorb), Reva Medical (Fantom), Elixir Medical (DESolve 100), and Biotronik ('DREAMS') (56). The Absorb stent by Abbott, which is a BSV stent fully absorbed into bloodstream after three years, received FDA approval in July 2016.

Table 1 Characteristics of drug eluting stents by generation (44, 45).

Generation	Platform	Polymer	Drug	Examples
First	Bare metal (stainless steel) devices	Durable polymer not designed for biocompatibility	Sirolimus, Paciltaxel	Cypher, Taxus, Ion
Second	Cobalt chromium devices	Biocompatible polymers, non-bioabsorbable polymers (fluoride-based)	Zotarolimus Everolimus Biolimus A9	Endeavor, Xience V, Xience Prime, Resolute, Biomatrix, Nobori
Third	Platinum chromium alloy devices	Biodegradable polymers, biodegradable poly-L-lactide or magnesium based, polymer-free stents	Zotarolimus Everolimus	TAXUS Element, Promus Element, Promus Premier
Fourth	Bioabsorbable devices , also known as bioabsorbable vascular scaffolds (BVS)	Polymer-free	Sirolimus Biolimus A9	BioFreedom, Cre8

1.4.5 CABG vs. PCI: Indications, risk factors and complications

The traditional and non-traditional indications for PCI and CABG, benefit of each of these interventions, as well as corresponding pre-operative risk factors are listed in the Table 2 Table 3, and Box 4 respectively.

Table 2 'On label' and 'off-label' indications for PCI and CABG (36, 39).

	Indications for PCI with DES	Indications for CABG
'on-label'	For improving coronary luminal diameter in patients with symptomatic ischemic disease due to discrete de novo lesions in native coronary arteries: • <30 mm in length • 2.5-3.5 mm in diameter • 50%-99% stenosis	• Acute STEMI: o Coronary anatomy not amenable to PCI o Mechanical complications (e.g., ventricular septal defect, rupture of the free wall of the ventricle, or papillary-muscle rupture with severe mitral regurgitation) • Coronary artery disease other than acute STEMI: o Left main coronary artery disease (≥50% stenosis) and high complexity for PCI (SYNTAX score ≥33)

	o Three-vessel coronary artery disease (≥70% stenosis) and intermediate or high complexity for PCI (SYNTAX score ≥23) o Two-vessel coronary artery disease (≥70% stenosis) involving the LAD artery and intermediate or high complexity for PCI (SYNTAX score ≥23) • Other: o Clinically significant coronary artery disease (≥70% stenosis) in ≥1 vessel and refractory angina despite medical therapy and PCI o Clinically significant coronary artery disease (≥70% stenosis) in ≥1 vessel in survivors of sudden cardiac arrest presumed to be related to ischemic ventricular arrhythmia o Clinically significant coronary artery disease (≥50% stenosis) in ≥1 vessel in patients undergoing cardiac surgery for other indications (e.g., valve replacement or aortic surgery) o Diabetes o Renal dysfunction
'off-label' Lesion subsets o Multi-vessel disease (SYNTAX score ≤22) o Left main disease (SYNTAX score ≤32) o Bifurcation lesions o Chronic total occlusions (CTO) o In-stent restenosis (ISR) o Small vessels (<2.5 mm in diameter) or large vessels (>3.75 mm in diameter) o Long lesions requiring multiple or overlapping stents o Saphenous vein grafts (SVG) o Thrombus containing lesions (acute MI) High-risk comorbid conditions: • Diabetics • Renal dysfunction	

Abbreviations: CABG, coronary artery bypass grafting, DES, drug-eluting stent; PCI, percutaneous coronary intervention; STEMI, ST-Elevated myocardial infarction; SYNTAX, Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery (trial)

Table 3 Factors that increase benefit of CABG and PCI procedures (36, 39).

	CABG	PCI
Procedural	- Can address multiple atherosclerotic lesions	- Minimally invasive - Relatively short-stay in hospital (1-2 days) compared with 5-7 days following CABG
Survival	Improves survival in patients with: - Diabetes mellitus - Left ventricular dysfunction (ejection fraction ≤45%) - Chronic renal disease - Ischemic mitral regurgitation - Complex coronary lesions e.g., left anterior descending artery, left main CAD) - PCI failure with or without acute myocardial infarction	Improves survival in patients with: - Elevated risk of death with CABG - Elevated risk of stroke - Extreme frailty - Prior CABG - Emergent cases (acute STEMI at presentation)
Complications	Avoids risk of: - In-stent restenosis - Stent thrombosis - Need for additional repeat target vessel revascularisations in the long term	- Higher propensity for complications with CABG due to invasiveness of procedure, from minor events (e.g., pneumonia) to major adverse cardiac and cerebrovascular events (MACCE, e.g., death, myocardial infarction, stroke) - Post-perfusion syndrome

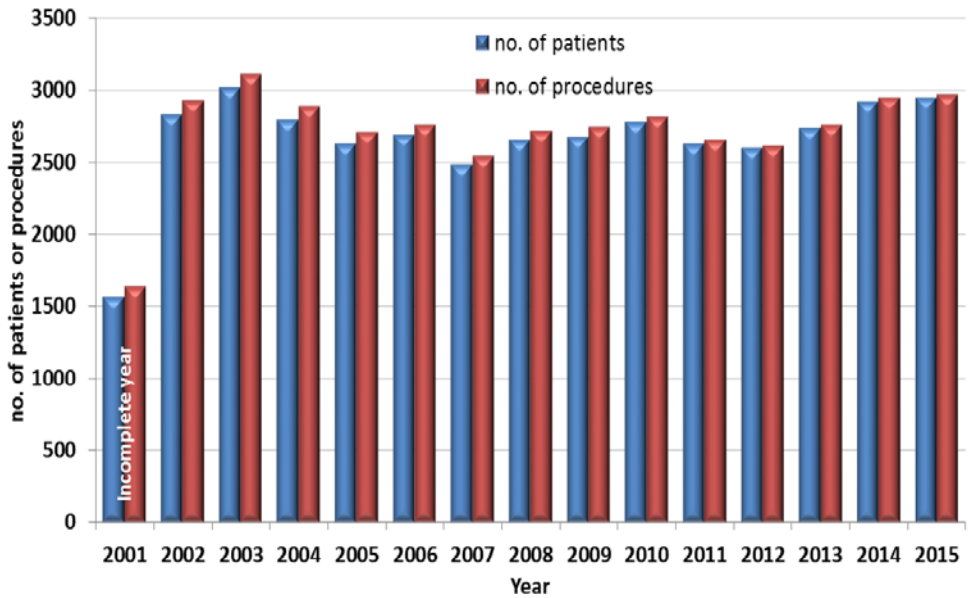
Box 4 Pre-operative risk factors associated with short-term mortality following CABG and PCI (57, 58).

CABG	PCI
• Age (>70 years) • Ejection Fraction <45% • Previous cardiac surgery • Chronic kidney disease (estimated glomerular filtration rate <90 ml/min/1.73 m^2) • Dialysis • Urgent/ Emergent/ Salvage cases • New York Heart Association class III or IV • Inotrope administration • Peripheral vascular disease • Previous myocardial infarction • Anticoagulant medication • Female • Cardiogenic shock • Intravenous nitrates administration	• Diabetes • Left anterior descending artery lesion • Female • Chronic kidney disease (plasma creatinine >0.2 mmol/L) • Myocardial infarction <24 hrs. • Left main coronary artery disease • Current heart failure

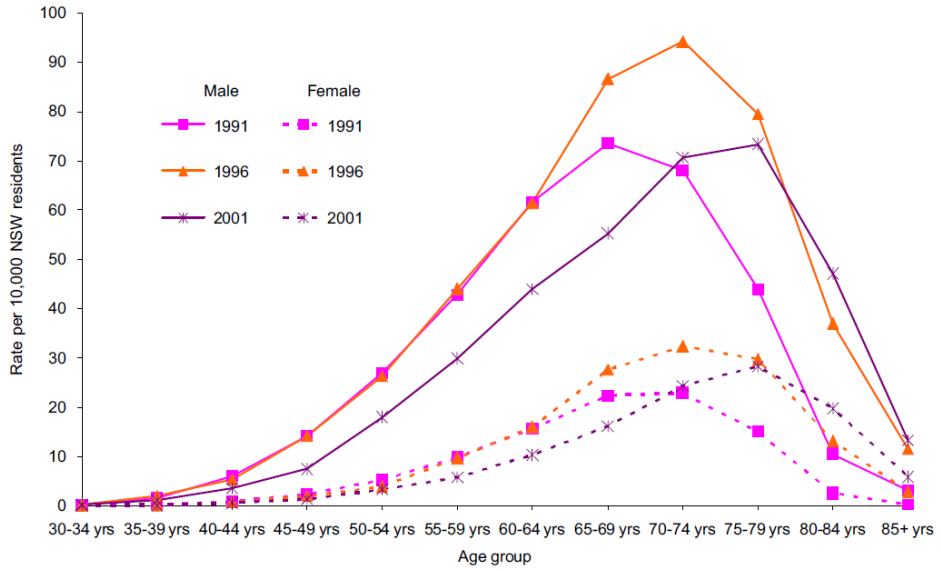
1.4.6 Utilisation of CABG and PCI in clinical practice

Since the advent of DES, the 'off-label' use of PCI has increased for patients presenting with complex coronary vascular lesions, and other conditions where traditionally CABG was thought to be the 'gold standard'. In fact, in 2005, 80-90% of coronary revascularisations performed the United States in the all-comer population were PCI with DES (59). In Australia, similar trends in the use of CABG and PCI were observed over the past three decades. In the absence of a national dataset reporting utilisation patterns for CABG and PCI, the various trends of CABG and PCI-use across Australian States (where data was available) were analysed, and are highlighted in Table 4.

Table 4 Utilisation patterns of CABG and PCI across various States of Australia.

State/ source	Trends in use of CABG or PCI
Victoria (60)	 Number of patients and procedures performed since 2001 from six large public hospitals in Victoria. Source: Adapted from the ANZSCTS Cardiac Surgery Database Program – Victorian Public Hospital Report 2015. Analysis* performed from a 2001-2015 data cut.

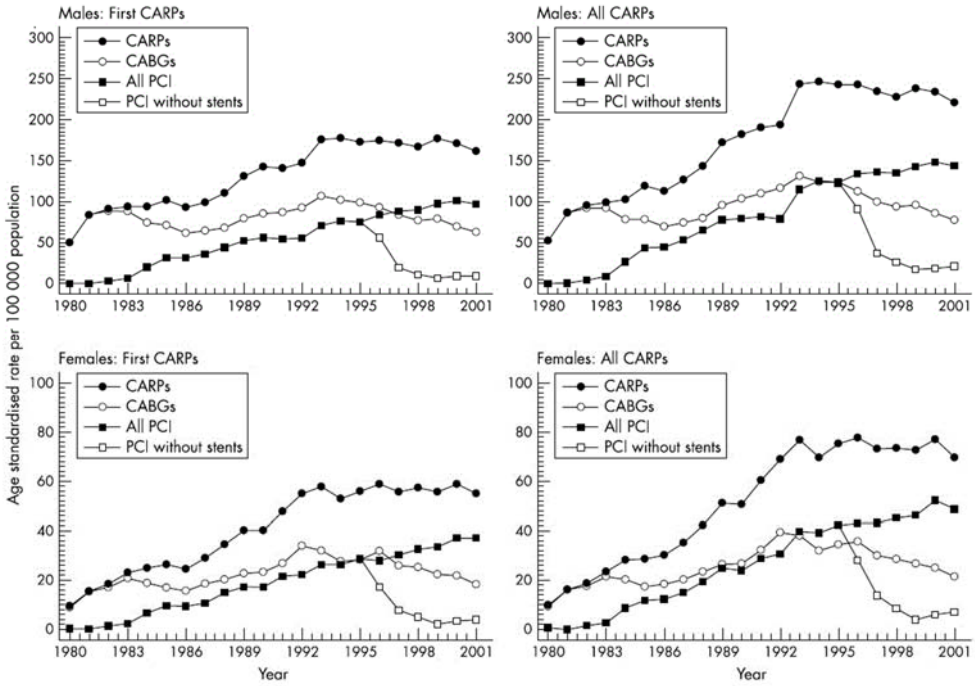
New South Wales (61)



CABG rates per 10 000 NSW residents aged 30 years and above by NSW, census years 1991, 1996 and 2001

Source: Adapted from Weerasinghe *et al* (2007). Analysis* of CABG surgeries performed among 72 668 patients extracted from the hospital inpatient statistics of the NSW Department of Health for the eperiod from 1991-2001.

Western Australia (62)



Age standardised rates of first and total coronary artery revascularisation procedures (CARPs) for men and women in Western Australia, 1980–2001.

Source: Adapted from Hobbs *et al*. (2003). The analysis* is based on on a subset of records extracted from the Western Australian Health Data Linkage System containing electronic records of all hospital admissions or deaths from any form of cardiovascular disease occurring in the period 1979–2001 inclusive.

Notes: * analysis did not delineate between isolated CABG or other related CABG surgeries.

During the period from 1990-2015, a declining pattern of CABG performed was observed across selected states of Australia (Table 4). A simulation exercise performed for the Western Australian dataset in 2008 suggested that, between 2001 and 2010, the total number of CABGs would decline by up to 19%, and the total number of PCIs would increase by up to 6% (63). Despite increasing utilisation patterns for PCI in the Australian setting, particularly in the DES-era, *there is no comparative local data available* concerning the effectiveness and cost-effectiveness of CABG compared with PCI in *routine clinical practice* for different high-risk patient subsets. In the absence of such data, inefficient practises for treatment of CAD in the Australian setting cannot be ruled out.

The advent of DES, however, brought about several randomised controlled trials (RCTs) investigating the efficacy, and cost-effectiveness of PCI with DES compared with CABG among patients with multi-vessel CAD, diabetes, and complex CAD including left main CAD (64-67). The landmark trials 'FREEDOM' and 'SYNTAX', concluded that over the lifetime, CABG was more cost-effective in the long-term than first-generation DES (68-70). However, these trials excluded high-risk patient subsets such as those with CKD, and did not include later-generation DES that are widely used in contemporary clinical practice. Thus, the results from these trials may have limited applicability to current clinical practice. To-date, a systematic review of the *cost-effectiveness* of CABG and PCI is not available, nor there is robust evidence on its effectiveness or cost-effectiveness in routine clinical practice, rendering the *real-world cost-effectiveness* of these interventions uncertain.

1.4.7 Utilisation of DES and BMS in clinical practice

Despite widespread use of DES in the current era, older PCI technologies including BMS, still have important roles in clinical practice for the management of patients presenting with varying degrees of severity of CAD (71). In fact, some suggest that the implantation of DES is far less than one would expect in routine clinical practise, when compared with BMS (44, 72), and

others dispute the long-term clinical effectiveness of BMS when compared with DES (73). Ultimately, the use of DES in the real-world is guided by criteria for appropriateness of use, based on clinical effectiveness and cost-effectiveness (44) (see Chapter 6). Nonetheless, recent reviews of cost-effectiveness of DES versus BMS suggest that comparisons of *cost-effectiveness* of DES and BMS in *routine clinical practice* are limited (72, 74, 75).

Summary:

CABG and PCI are coronary revascularisation procedures that aim to restore blood flow from blocked coronary arteries to the coronary muscle. The two procedures are significantly different. CABG is invasive, expensive, and require a long recovery period for the patient; whereas, PCI is minimally invasive, cheaper than CABG initially, and renders patient a short recovery period. While PCI offers relatively fast recovery for the patient, they may need repeat revascularisation procedures over time, thus increasing the costs of PCI to the healthcare payer, in the long term. The utilisation of PCI, however, has well surpassed CABG in Australia and world-wide. In 2005, 80-90% of coronary revascularisations performed were PCI with DES in the United States, with similar trends observed in Australia. The introduction of DES has also increased the costs of PCI. The latest generation DES are 2-4 times more expensive than a BMS. Despite the popular belief that DES use is also rising when compared with BMS, a number of sources suggest that clinicians may in fact prefer BMS over DES in routine clinical practice. Reaching a definitive conclusion about the optimal procedure however, is constrained by limited economic evaluations comparing the cost-effectiveness of CABG versus DES, or DES versus BMS, using data from the 'real-world'. Evidence available from RCTs are constrained by the exclusion of high-risk patient subsets, thus limiting the generalisability of findings.

1.5 RCTs versus patient registries, and cardiac registries

1.5.1 Levels of evidence

Hierarchical evidence ranking schemes, or simply, 'levels of evidence', were available from as far back as the early 1600s to scrutinise different sources of evidence. Scientific, and empirical evidence were established as the highest levels of evidence by René Descartes (1596-1650), a philosopher, scientist, and mathematician, who developed the 'Descartes pyramid of evidence' (76). In the 20th century, an evolution in the discernment of treatment effects in Medicine observed following the Thalidomide Tragedy, lead to the development of strict rules and regulations for research in humans (77). The earliest published evidence ranking schemes (in Medicine) authored by the Canadian Task Force on the Periodic Health Examination (78), and by Sackett and colleagues (79, 80), aimed at helping clinicians and researchers to appraise the quality of evidence for therapeutic effects (81, 82).

Several versions of levels of evidence are available online, commonly illustrated using hierarchical pyramids. These tools rank different sources of evidence according to the probability of bias they may produce (82). In its simplest form, the pyramid includes systematic reviews of randomised controlled trials (RCTs), and RCTs at the top, corresponding to highest strength of evidence (Figure 7). Observational evidence from cohort, case control, case series, and case reports are found directly below RCTs (Figure 7). At the bottom of the pyramid may constitute any one or more of evidence from ideas, editorials, opinions, animal studies, or in-vitro studies (Figure 7) (77). The advantages and drawbacks of RCTs, and observational evidence from registries, will be discussed in detail in Sections 1.5.1 and 1.5.3, respectively. Systematic reviews, a tool used in this thesis, will be discussed in Chapter 2, Section 2.5.

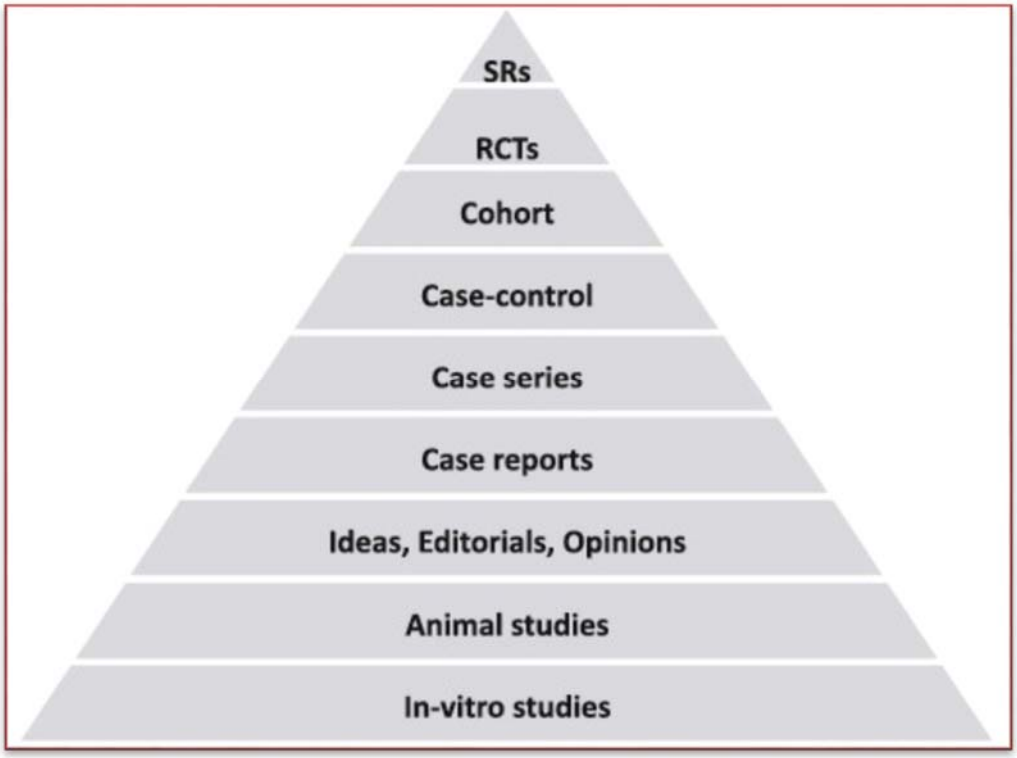


Figure 7 The pyramid of evidence (77).
Abbreviations: SRs, systematic reviews; RCTs, randomized controlled trials
Source: Adapted from cited Levi *et al.* (2009).

In modern times, new ranking schemes emerged with modified classification levels, and different motivations. New evidence ranking systems address the pitfalls of earlier schemes, which placed RCTs at the highest level, despite issues in quality and/ or appropriateness (81-83). New levels of evidence, including the Oxford Centre for Evidence-based Medicine Levels of Evidence (CEBM) and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework allow observational studies with large effect sizes to be upgraded, and low quality RCTs to be downgraded (81-83). New ranking systems also target developers of systematic reviews or guidelines, rather than clinicians (81, 82) .

1.5.2 Randomised controlled trials

1.5.2.1 RCTs: Definition and history

A clinical trial can be described as a pre-planned experiment that aims to assess the benefits or effects of one or more treatments in humans (77). The first systematic clinical experiment in the history of Medicine is credited to Dr James Lind in his investigation of the effect of citrus fruit for the treatment of scurvy in 1747 (84). More specifically, a RCT is a clinical trial that comprises several features for minimising experimental bias, that places it at the top of hierarchical evidence ranking schemes (Figure 7) (82). Among these features include, randomisation of participants to treatment and control (placebo) arms, longitudinal and prospective design, stratified block sampling ("stratification"), allocation concealment, and blinding investigators and subjects (85). RCTs were first introduced to clinical medicine for the evaluation of effectiveness of streptomycin for the treatment of tuberculosis in the 1940s (86, 87). The popularity of RCTs heightened following landmark review in 1982 (86, 88). The review concluded that clinical trials with historical controls (observational data) were subject to biases in patient selection that could favour results towards new interventions (86, 88).

1.5.2.2 Advantages of RCTs

In epidemiological studies, a RCT is regarded as 'gold standard' as it permits the ability to make causal inference, a concept pioneered by Sir Austin Bradford Hill, a British Epidemiologist (77, 89, 90). Other benefits of RCTs relate to their inherent features described above, including well-defined study populations, tightly controlled treatment conditions, and strict protocols that ensure patient compliance to treatment, thus leading to results with high internal validity, defined as the "correctness of results" (77, 85, 86, 90, 91).

1.5.2.3 Disadvantages of RCTs

Not all RCTs are created equal, or appropriate for all clinical questions. A key limitation of RCTs relates to their ability to only measure 'efficacy' of a treatment under controlled conditions, rather than 'effectiveness', which limits the generalisability of results to other patient subsets that may be excluded from RCTs (90). Another limitation of RCTs relates to prior knowledge that is required to calculate sample size, including the level of improvement that is clinically meaningful, and the expected variation of clinical benefit within the sample (90). As these factors are often unknown for new therapies, some RCTs may be marred by low power to detect meaningful differences, leading to negative results when in fact a true difference exists (82). In surgical RCTs in particular, the use of additional procedures, may lead to an over-estimation of true effect (92). RCTs also carry ethical dilemmas for clinicians and patients equally (93). Randomly subjecting one group of patients to treatment while another group to usual standard of care (or placebo), when all could potentially benefit from intervention, could present ethical challenges to professionals (77, 90, 93). For patients, participation in RCTs may be motivated by self-interest, than altruistic reasons (93). Moreover, RCTs are time-consuming, and expensive ventures (94). While RCTs are typically conducted over short-term, final outcomes from a published report may lag behind several years, withholding important information from the medical community (95). RCTs are also prone to high patient attrition rates due to undesirable side-effects of treatments and little incentive offered to patients to continue in the control arm (90). RCTs are carried out in controlled environments, and in selected groups of patients, which may also limit their external validity or generalisability to routine clinical practice (77). Despite its ability to generate causal inference, RCTs may not be the most appropriate study design when investigating prognosis of a disease, or effects of unhealthy practices, e.g., smoking on lung cancer where evidence from cohort studies would more appropriate (77, 82).

1.5.3 Patient registries

1.5.3.1 Observational studies: Definition and history

Observational studies including registries aim to observe outcomes of treatments (or exposures) initiated through standard medical management (or natural history of disease) (96). The earliest published record of an observational study was illustrated by the Graunt's Study of London's Bills of Mortality in the 1600s (95). The study reported that at the time, less than six percent of all-cause deaths were due to cardiovascular disease and cancer, while nearly 75% of all deaths were attributed to infectious diseases, malnutrition, and maternity complications (97). Observational studies when compared with RCTs, are characterised by the absence of a protocol to dictate or mandate care, where care is not provided as a result of randomisation or other forms of patient assignment (96). Observational studies, thus, are also known as 'non-interventional studies'. Despite earlier reports that observational studies bias results in favour of new therapies when compared with RCTs, more recent evidence suggest the reverse (86, 88). Results from well-designed cohort or case-control studies when compared with RCTs may complement rather than systematically overestimate the magnitude of the effects of new treatments (86).

1.5.3.2 Registries: definition

Registries can be viewed as platforms for observational studies, including cohort, case-control and case-cohort study designs (98). A registry by definition, is a prospective observational study that collects ongoing supporting data on well-defined outcomes of interest, for analysis and reporting of subjects with certain shared characteristics (96). In modern times, registries are typically electronic, and utilise electronic data capture (EDC) by way of mobile devices, desktop and laptop computers (web based or otherwise), or by telephone (96). The data is collected through questionnaires or electronic case report forms (eCRFs). Eight different classifications for registries were identified by the International Society for Pharmacoeconomic

and Outcomes Research (ISPOR), including: simple cohort, outcomes, safety surveillance, risk management, disease, therapeutic (drug or device class), management, and resource utilisation (96).

1.5.3.3 Advantages of registries

High-quality, well-designed patient registries, provide high degrees of research utility (95). Data on large patient samples are available from registries, comprising information on a diversity of patients and practices (91). Such data may enable researchers to study rare diseases, rare adverse outcomes, or infrequently performed procedures. Studies of outcomes with long latency periods, or persistence and compliance to treatment, are also possible from registries due to long observation periods of patients (91). Data from registries may also support the study of disease incidence, disease prognosis (mortality and morbidity), volume-outcome relationships, trends in the use of procedures, and disparities in health care. Patient registries also facilitate development of risk-assessment tools and drive quality improvement and clinical governance. The study of unhealthy practices, for example smoking, alcoholism, drug overdose etc., are also possible from registries. Registries are becoming a popular source for comparative effectiveness studies and health economic evaluations (91).

1.5.3.4 Disadvantages of registries

In hierarchical schemes for evidence, registry studies are ranked below RCTs for a number of reasons. Firstly, observational studies from registries, though prospective and longitudinal, cannot establish causal inference (95). Data from routine clinical practice are sensitive to a number of biases including selection bias (treatment bias), confounding bias, systematic bias and random bias (95, 98). In RCTs, protection from such biases are ensured through randomisation, stratification, allocation concealment, and blinding (85). Observational data from registries are prone to sampling error, missing data, and under-reporting, which could lead to systematic and confounding biases, if data elements are not missing at random (95).

For instance, minority groups of patients may be consistently underreported due to limited administrative resources at rural or small-scale centres (95) . Similar to RCTs, registries may also be subject to high patient attrition, due to loss to follow-up, resulting in further selection and systematic bias (91, 95, 99). Furthermore, registry studies require substantial financial and human capital for implementation, maintenance, and potential data linkages, thus making an on-going source of funding imperative (95). Especially, multi-centre registries require a full-time project manager and a multi-disciplinary team comprising of clinicians, data managers, and biostatisticians to ensure that the database remains relevant and contemporary (95). To remain applicable to contemporary routine clinical practice, registries may need to redefine data elements in eCRFs over time (95). To align previously collected data with new definitions, a substantial recollection of data may be required (95). While post-hoc adjustment through statistical analysis techniques may present one solution for dynamic variable definitions, the impact of such variables on outcomes is unclear (95).

1.5.4 Cardiac patient registries

In surgery, the notion of systematic data collection for the purpose of monitoring and improving patient outcomes was pioneered in the early 1900s by a US surgeon, Dr Ernest Amory Codman, who kept “end result cards” on his patients that included long-term outcomes data for at least 12 months (100, 101). Later, he used this data to publish several papers on the “end result idea” (101). Today, the monitoring of outcomes of cardiac patients through systematic data collection is routine across cardiothoracic and interventional units world-wide. Particularly noteworthy is the agreement of cardiothoracic surgeons and interventionists of otherwise competing hospitals, to contribute to collaborative efforts towards multi-centre patient registries, with the view to build valid assessments tools for quality of cardiac care (100).

Among the most notable collaborative national and international efforts leading outcomes data collection in cardiothoracic surgery include the Veterans Affairs (VA) Cardiac Surgery Database (102), Society of Thoracic Surgeons (STS) National Cardiac Database (103), European Association for Cardiothoracic Surgery Quality Improvement Programme (EACTS-QUIP) Cardiac Database (104), Society for Cardiothoracic Surgery in Great Britain and Ireland (SCTS) Cardiac Surgery Database (105), the Japan Cardiovascular Surgery Database Organisation (106), the Chinese CABG registry (107), and the Australian and New Zealand Society of Cardiac and Thoracic Surgeons Database (108). While the majority of these collaborative efforts focussed on adult cardiac patients, the STS now also include the Congenital Heart Surgery Database, with the option for anaesthesiology participation (100) .

In the realm of PCI, most notable collaborative efforts to collect patient outcomes data is demonstrated through the CathPCI Registry of the National Cardiovascular Data Registry (NCDR®), established by the American College of Cardiology Foundation (ACCF) (109). Other notable multi-centre registries include the Melbourne Interventional Group (MIG) registry (108), and population-based (e.g., the Victorian Cardiac Outcomes Registry) (110) and disease-specific (e.g. Acute Coronary Syndrome) registries relevant to PCI (111).

While majority of these collaborative efforts aimed to investigate trends in decision-making, care delivery, management practices, and outcomes (typically at 30 days), only few, namely the STS and NCDR registries embraced opportunities to collect long-term outcomes data (e.g., hospital readmission rates, reinterventions, and survival) and healthcare economics data (e.g., cost of patient care) through ongoing linkages to the Centers for Medicare and Medicaid Services (CMS) database (100, 111-113). Using data from these linked patient registries, a longitudinal study was recently established, namely the *ACCF-STS Collaboration on the Comparative Effectiveness of Revascularization Strategies (ASCERT)*', which aimed to

evaluate the comparative effectiveness of CABG and PCI (100, 114). To-date, two notable publications are available from the ASCERT study including a risk prediction tool for long-term survival following CABG (115), and a cost-effectiveness analysis of CABG versus PCI for MVCAD from the US healthcare payer perspective, using propensity-score matching approaches (116). One of the goals of this thesis is to investigate the same, but in the Australian context, through linkage of the ANZSCTS and the MIG registries to a hospital administrative clinical costing dataset (see Section 1.8 and Section 2.1).

Summary:

RCTs are the gold standard for causal inference, however, follow a strict protocol that typically exclude important high-risk populations, thus reducing the generalisability of findings. Methodological issues may harm the quality of RCTs, while ethical dilemmas can limit their widespread use. New evidence ranking schemes call for the ranking of high-quality observational studies above low-quality RCTs. Unlike RCTs, registries capture data from routine clinical practice, thus increasing the external validity of results. Registries require less financial capital than RCTs, allowing researchers to investigate hypotheses quickly and inexpensively. Research in relation to unhealthy practices can be easily performed through registries with no ethical implications. Large-scale multi-centre registries can dilute the negative impact of systematic bias due to missing values (not at random), errors, and under-reporting. Record linkage may allow registries to enhance its scope and value, providing opportunities to adjust for errors in patient recall, and gain access to mortality, morbidity, and resource utilisation data. Post-hoc matching methods can adjust for treatment bias apparent in observational data and produce quasi-randomised treatment groups appropriate for comparative effectiveness analyses.

1.6 Health technology assessment (HTA)

1.6.1 HTA: definition and history

Health technology assessment (HTA) has multiple definitions (117). One can simply define it as a dynamic, rapidly evolving process embracing different types of assessments that inform real-world decisions about the value of new and existing technologies (118, 119). HTA informs reimbursement and coverage decisions for medical interventions in some countries, and its use is rapidly expanding (117). HTA aims to answer the following questions concerning a medical intervention:

a) Is it safe?
b) Does it improve health outcomes?
c) Is it cost effective? (120).

HTA is closely linked to two other disciplines in Health including evidence based medicine (EBM), and comparative effectiveness research (CER) (118, 121). The links governing the relationships between these fields are illustrated in Figure 8 (118, 121, 122). The discipline of HTA is young, and was conceptualised by the Office of Technology Assessment (OTA) in the US in 1976 (121). Although not termed 'HTA', HTA techniques were also used as early as in 1954 by the Australian government to support decisions to reimburse drugs that are safe, effective, and cost-effective (see Section 1.7.3) (123). From its early beginnings, HTA was used within the healthcare system to make specific decisions within particular policy areas, with the goal of curbing rising healthcare costs while improving health outcomes (121). With similar goals, HTA was also simultaneously conceptualised in Sweden to evaluate selected healthcare technologies (121). The earliest assignments of the OTA included the assessments of the computed tomography (CT) scanner, CABG, radial mastectomy and other expensive surgical procedures (121). By the 1990s, HTA was formally established in Sweden and was rapidly being adopted by other countries in Western Europe (121). The focus of HTA in the

early years was to synthesise available information concerning efficacy and cost-effectiveness of medical interventions in a format helpful for policy makers (121). In modern times, the focus of HTA is devoted to effective dissemination and development, in order to influence administrators and clinicians (121). Currently, the majority of low and middle-income countries are developing and/or adopting HTA practices in order to rationalise scarce healthcare resources (121, 124).

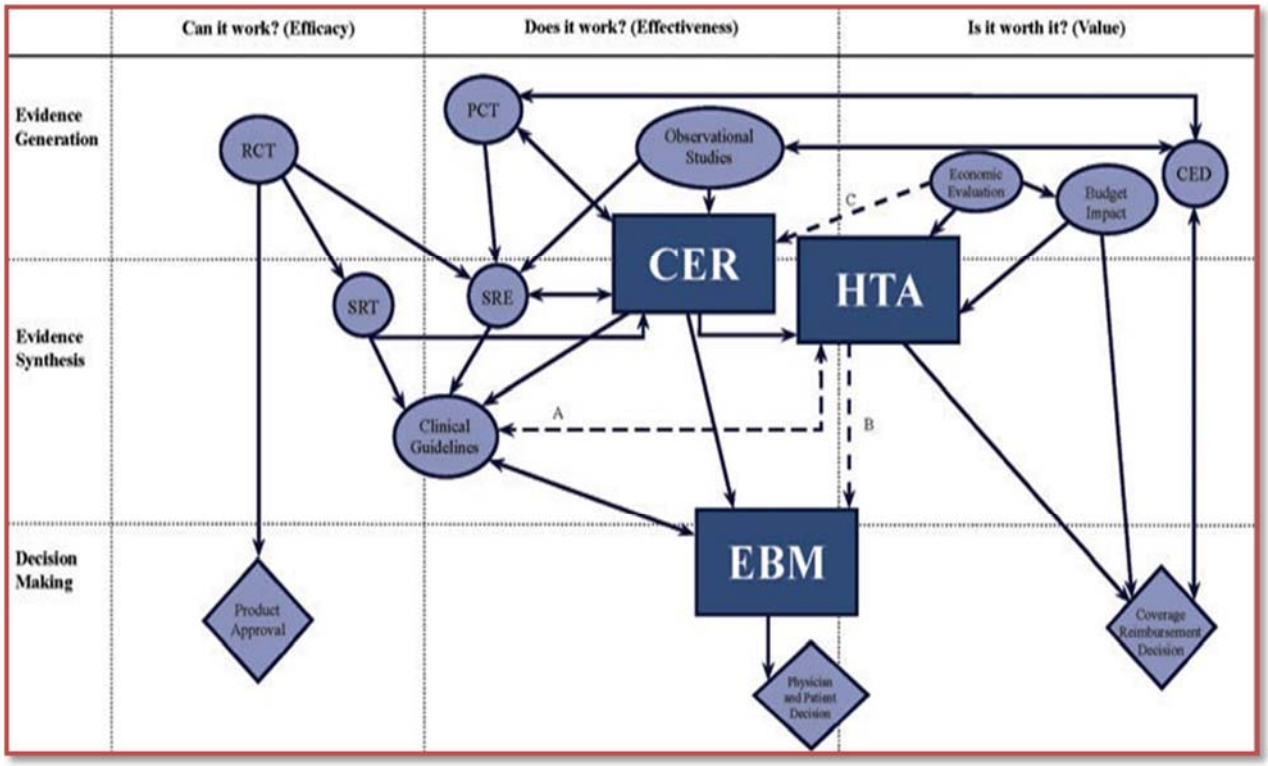


Figure 8 Relationship between evidence based medicine (EBM), comparative effectiveness research (CER), and health technology assessment (HTA) (122).
Abbreviations: CED, coverage with evidence development; CER, comparative effectiveness research; EBM, evidence-based medicine; HTA, health technology assessment; PCT, pragmatic clinical trial; RCT, randomized controlled trial; SRE, systematic review of evidence; SRT, systematic review of trials.

Notes: Solid lines indicate clear relationships, and dotted lines indicate disputed relationships. Diamonds represent decision processes, and circles and ovals represent all other evidence activities, except for the rectangles, which are reserved for EBM, HTA, and CER.

Source: Source: Adapted from Luce *et al.* (2010).

1.6.2 Global HTA landscape

HTA is currently only formally established in few high-income countries outside of Western Europe (117, 121, 125). HTA processes in HTA-established countries are marked by high level of institutionalisation, and memberships with HTA networks (117, 125). **Australia** has a centralised HTA process for assessments of pharmaceuticals and non-pharmaceuticals (see Section 1.7.3). Despite establishing the concept of HTA and coining the term, **the US** is still lacking a centralised HTA process, following the gradual phasing-out of the OTA (126). In the US, HTA is now conducted by several stakeholders, including governmental agencies, private insurance companies and healthcare plans, and for-profit and not-for-profit private organisations (126). The Agency for Healthcare Research and Quality (AHRQ), a government-funded agency informs coverage policies for US national and local Medicare programs assessed by the Centres for Medicare and Medicaid Services (CMS); however, it makes no recommendations (126). In **Canada**, HTA activities are largely undertaken by the Canadian Agency for Drugs and Technologies in Health (CADTH), funded by the federal, provincial, and territorial governments of Canada (127). The CADTH, established in 1989, focusses on the evaluation of pharmaceuticals and devices (127).

In Asia, **South Korea** achieved universal health coverage (UHC) in 1989, and subsequently implemented a semi-government funded institutionalised technology assessment processes (128). This was marked by the establishment of the Health Insurance Review and Assessment Service (HIRA) in 2000 (128). **Taiwan** too followed course, achieving UHC in 1995 through the National Health Insurance (NHI) scheme, and establishing formal HTA arrangements for evaluation of drugs (2007), medical devices (2011) and medical services (2014) (129). Despite achieving UHC as early as in 1961, and observing rapid expansion of HTA activities in the mid-1980s, **Japan** has been slow to implement national HTA regulations, marked by a failure in the application of HTA to health policy (130, 131). Nonetheless, several

committees related to HTA were established by Japan's Ministry of Health, Labour, and Welfare (MHLW) in the late 1990s, with the aim to reduce costs by culling excess or unnecessary healthcare services through the development of evidence-based clinical practice guidelines (130, 131). In line with new economic policy established in 2012, a comprehensive HTA system for Japan has recently been proposed (131).

The HTA agencies prominent across **Western Europe** is summarised in Appendix B. In the **UK** in particular, HTA is implemented by the National Institute for Health and Care Excellence (NICE) which was established in 1999 by the UK Department of Health as a non-departmental executive body (132, 133). Since establishment, NICE has gained international reputation for its methodological rigor in evaluations and guidelines which are used as models globally (132, 133). The NICE focuses on HTA policies and practice guidelines in clinical practice, health promotion, health technologies (pharmaceuticals, devices, and procedures), and guidance for social care services (132, 133).

With the establishment of the United Nations Sustainable Development Goal (3.8) to achieve UHC for all by 2030, HTA is gaining wide interest in the developing and middle-income nations as a mechanism to rationalise scarce healthcare resources (121, 124, 125, 134). The degree of HTA establishment across selected middle-income and developing countries, measured by a HTA mapping tool created by Oortwijn and colleagues (125) is summarised in Table 5. When scores (greater the better) were compared against countries with established HTA processes (Australia, Canada, and UK), Argentina, Brazil, Mexico and Malaysia achieved relatively high scores in the domain of having an institutionalised HTA processes in place, while Russia, India, and Indonesia achieved comparatively low scores indicating they were at various stages of development (Table 5) (125). A similar HTA status was reported for Central and Eastern European nations recently (135).

Table 5 Level of HTA Development per Domain (125).

	Country									
Domain	**Argentina**	**Brazil**	**India**	**Indonesia**	**Malaysia**	**Mexico**	**Russia**	**Australia**	**Canada**	**UK**
Level of institutionalisation	26	28	7	8	26	26	11	28	28	28
Identification of health technologies	3	4	1∗	1	2	1∗	1∗	11	13	13
Priority setting	3	11	6∗	6∗	10	8	6∗	11	12	18
Assessment	12	22	7∗	13	22	23	10	26	28	31
Appraisal	0	4	0∗	3	3	3∗	0∗	7	6	9
Reporting	7	9	2∗	5∗	4	7∗	6∗	11	11	11
Dissemination	4	6	1	4∗	5	5	1∗	8	8	11
Implementation	5	5	0∗	4∗	4	4	0∗	7	7	8

∗Scoring mainly based on a survey administered by Oortwijn and colleagues (31).

1.6.1 Health economic evaluations and HTA

Around the world, practise of HTA within its definition and objectives is heterogeneous. HTA, which generates evidence from research of technologies, is but one driver of influence on policy decisions (136). The relative placement of HTA with respect to political, economic, and institutional contexts is as illustrated in Figure 9 (136). Depending on context, the importance of HTA may also vary, as values, habits, tradition, policy contexts, and resources including budgets, among other factors, may play greater roles than HTA (136). In healthcare systems where HTA plays a significant role, the applications of HTA may span through the scope of regulatory (market entry) decisions, price negotiations, local formulary discussions, reimbursement, develop clinical practice guidelines, and communications to prescribers (137, 138). For the purpose of this thesis, hereafter, applications of HTA for reimbursement decisions will be a focus.

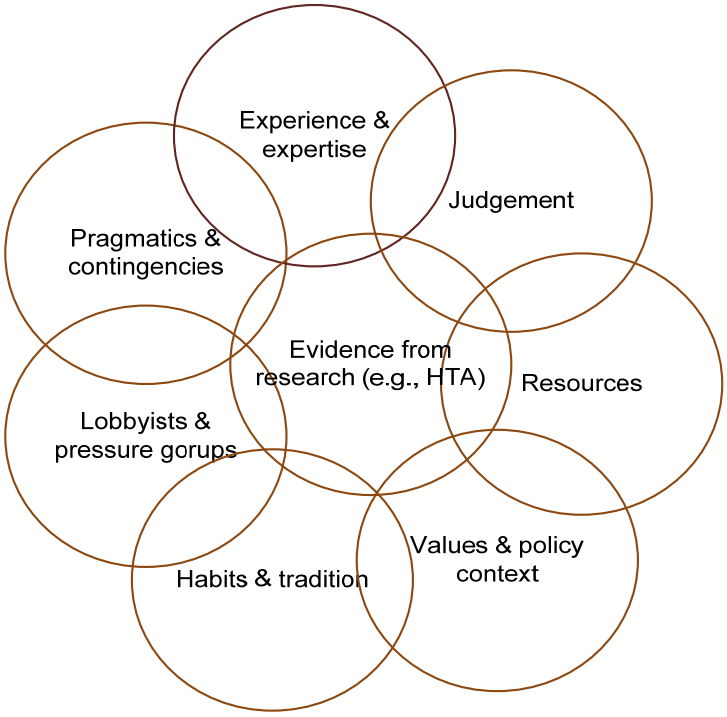


Figure 9 Factors that influence policy making (136).
Source: Adapted from Garrido (2008).

In healthcare systems with mature, centralised HTA processes, health economic evaluations (EE) and budget impact analyses (BIA) may be used to inform reimbursement decisions for medical treatments and technologies. The *methods* corresponding to execution of EEs are described in detail in Section 2.3. The different analytical approaches for EE considered by HTA agencies across different jurisdictions (excluding Australia) are summarised in Appendix C (139). The HTA processes for Australia are discussed in Section 1.7.3. A trend towards considering evidence from multiple types of EE is apparent across jurisdictions, including cost-effectiveness analyses (CEA), and cost-utility analyses (CUA), provided the chosen analytical approach is justified (139). The perspectives from which costs are analysed is also diverse, ranging from public healthcare payers to societal, with analyses from multiple perspectives also being accepted, as detailed in Appendix C (139). However, in some jurisdictions, the consideration of costs into HTAs has been controversial, as it raised explicit questions of rationing of care, which were not accepted widely by the public (139). For example, until recently, economic evaluations were not considered in France in the assessment of treatments and technologies for reimbursement due to this debate.

Conversely, in diverse, decentralized system with multiple payers, including insurers, healthcare organizations, and other providers, there may be a resistance to the consideration of EE to inform decision making. For instance, in the US, when compared with the UK, there appears to be a deep rooted disfavour for using EE to inform decision making. Obstacles for use of EE were driven by three factors: (1) institutional and political; (2) cultural; and (3) methodological factors associated with economic evaluation itself (140). Furthermore, inadequate resources and skills needed to conduct (and evaluate) good quality EE; and the limited value placed for “evidence-based” approaches such as EE in policy context, may limit the use of EE as a formal tool to inform decision-making in some jurisdictions (141).

Despite inconsistencies in the applications of HTA around the globe, there appears to be a sharp rise in the number of economic evaluations published in the literature (142). In the Asia Pacific region (excluding Australia) alone, the number of CUAs published has risen from 19 to 107 in the period from 2000-2004 to 2009-2012 (143). More than 50% of EE from the Asian region focussed on pharmaceutical interventions, while less than 10% evaluated surgical procedures, and only 3% considered medical devices, as illustrated in Figure 10 (143).

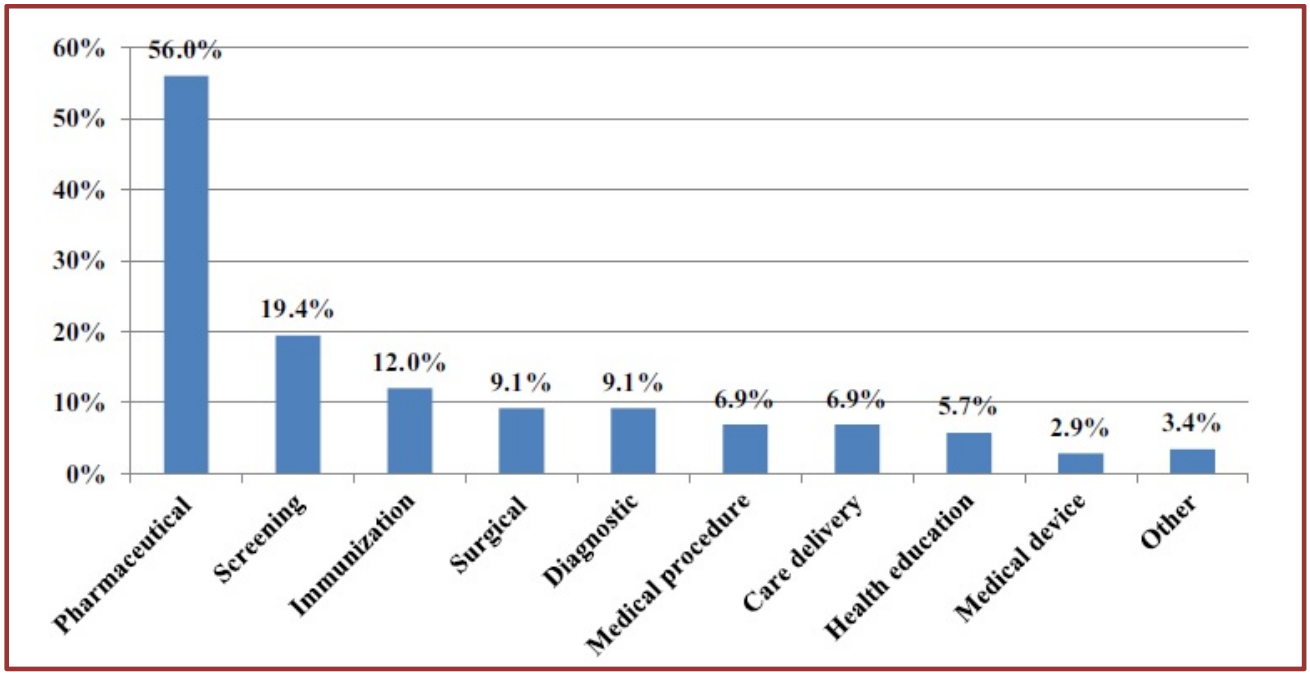


Figure 10 Asian cost-utility analyses by intervention type (2000–2012) (143).
Source: Adapted from Thorat *et al.* (2015).

1.6.2 HTA for medical devices vs. pharmaceuticals

There are number of important differences between medical and pharmaceutical technologies from the nature of the industry to the end-use of the product, that are not apparent in current guidelines established for HTA. Although current guidelines appear generic, they were developed from a 'pharmaceutical perspective', which may lead to inappropriate and even flawed assessments when evaluating medical devices for pricing and reimbursement decisions (144). The differences between medical and pharmaceutical technologies was

analysed in broad terms recently, and are summarised in Box 5 (145). The drivers of differences, including cost of production, size of market, ongoing manufacturer support, and alterations to product following market entry among other factors, may have important implications in the evaluation of medical technologies when compared with pharmaceutical (145).

Box 5 Broad generalisations of differences between medical and pharmaceutical technologies (145).

	Medical	Pharmaceutical
Cost of production	Ongoing manufacturing costs	Often low once on market
Direct doctor involvement in development	High	Low
Ongoing direct support by company once n market	High	Low
Size of market	Usually small	Often huge
Alterations to product once on the market	Continues evolving during trials and post-market	Does not continue evolving post-market
Typical size of company	Small	Large
Evidence required	Not established	Level I*
Effect on patient	Usually physical	Chemical action
Importance of therapy administration skills (e.g., surgeon)	High	Low
Usual development pathway	Invention of new medical device	Discovery of new chemical entities

* Evidence obtained from a systematic review of all relevant randomised controlled trials (146)

The use of methodologies applied to pharmaceuticals may be inappropriate when assessing clinical and cost-effectiveness of medical devices. The differences between medical devices and pharmaceuticals impose several challenges to economic evaluation of devices (144). Six reasons for these differences, and corresponding challenges are summarised in Table 6 (144).

Table 6 Six reasons why medical devices are different from pharmaceuticals, and corresponding challenges to economic evaluations (EE), summarised from (144).

Medical devices	Pharmaceutical	Challenges to EE
Most devices are often diagnostic	No diagnostic function	Value of improved diagnosis cannot be separated from improved patient outcomes due to treatment Diagnostic devices have multiple functions, e.g., scanners. Indivisible - overall value is weighed average of its use in multiple applications.
Difficult to undertake randomised controlled trials (RCTs)	No difficulties with RCTs – by Phase III RCT, dosage and route of administration already established.	Devices undergo product modifications frequently that may impact measurement of efficacy. No 'steady state' period – outcomes improve with time and experience following 'learning curve' Difficult to undertake blinding in RCTs – e.g. sham procedures are difficult and unethical. Limited patient participation of fear of being randomised to an invasive procedure rather than minimally invasive procedure.
'Learning Curve' associated with application/ insertion of device (for professionals), and use of device (for consumers).	No learning curve – drugs are 'embodied technology'	Significantly impact efficacy, as clinical outcomes depend on experience of surgeon. For devices with external components patient learning curve can impact efficacy.
Wider economic implications for implementation of new device.	No significant economic implications for new therapies.	Large investments to training of professionals, and local organisational context (e.g., ability to switch patients to day surgery) impacting cost-effectiveness of device.
Comparisons difficult as equivalent clinical evidence may not be available for all products.	Comparisons are not difficult as comparable clinical evidence on efficacy and safety is mandatory for all products.	Those undertaking economic evaluations are often quick to "genericize" recommendations based on device under evaluation (usually first to market). However, 'class effects' may not be appropriate and may be flawed for different devices of different manufacturers.

		Lack of evidence make indirect or mixed comparisons challenging.
Prices change over time.	Prices of drugs rarely change overtime, usually negotiated, and fixed until patent expires.	Device prices can change due to market entry of new products, or procurement procedures in healthcare systems.

Current approaches undertaken to evaluate medical technologies may have important downstream economic and patient-related implications (144):

- The analysis of clinical data arising from the use of medical devices is particularly challenging. If using observational data, a number of adjustments for user characteristics may be needed. The adjustment for treatment-centre effects is mandatory, given large interdependencies between surgeon experience (with the implantable devices) and clinical outcomes.
- The initial cost-effectiveness of medical technologies may be implicated as medical device manufacturers incur further expenses post-market, towards investment in training of professionals, patient support services etc.
- Trials to demonstrate performance of devices in clinical practice and longer term effectiveness are often over and above what is needed to achieve regulatory approvals (e.g., Conformité Européene, CE mark).
- There is tremendous disincentive for medical device manufacturers to invest in R&D and the costly market entry hurdle. Following achievement of market entry, other manufacturers are incentivised to be 'fast followers' claiming 'class effects' within same product category.
- Extrapolating evidence from one device to another may appear attractive in the short term, but this lower hurdle for later market entrants could also impact patient safety. Different devices, though having the same clinical indication or outcome, may have different physical properties, or modes or action, which should not be considered generic without adequate supporting evidence (144).

As a solution to challenges associated with assessments of medical devices, it was suggested that clinical and economic evaluations for medical devices should be an iterative process, with revisions made to the evidence as more evidence is gathered on effectiveness in routine clinical practice (144).

Summary:

The practise of HTA for reimbursement and funding of services and technologies is growing world-wide. The establishment of the UN Sustainable Development Goal (3.8), to achieve UHC for all by 2030 has provided impetus for many developing and middle-income countries to centralise HTA processes as a mechanism to rationalise scarce resources in their respective healthcare systems. Also noteworthy is the sharp rise in the number of economic evaluations published in the Asian setting over the period of a decade. Despite improvements to HTA over the past three decades, there are challenges prevailing in the evaluation of medical technologies, in particular procedures, and diagnostics. In particular, RCTs are not appropriate for evaluations of effectiveness of invasive or non-invasive procedures and devices, given 1) devices undergo product modifications frequently that may impact measurement of efficacy; 2) there is no 'steady state' period – outcomes improve with time and experience following 'learning curve; 3) difficulties associated with blinding in RCTs – e.g. sham procedures are difficult and unethical, and 4) limited patient participation of fear of being randomised to an invasive procedure rather than minimally invasive procedure.

1.7 Structure of the Australian healthcare system

Australian healthcare system is characterised by a two-tier, hybrid system of public and privatised care, financed through government funding, private health insurance providers, and individuals themselves, by way of taxation, payment of out-of-pocket expenses and premiums (147). In the Asia Pacific region, Australia was the second nation (20th in the world) to achieve UHC in 1974, and the first to establish a formal health technology assessment (HTA) process for pharmaceuticals and non-pharmaceuticals (discussed in detail in Section 1.7.3) (124, 148, 149). Under Medicare, all Australians have access to free care as a public patient in public hospitals, and subsidised medical services out of hospital (150). The services provided by the Australian healthcare system can be classified into three categories including primary care, hospitals, and 'other recurrent' services that includes administration and research. The public healthcare system of Australia is operated through three levels of government, including Federal ('Australian Government'), State, and Local, each with distinct regulatory and reimbursement responsibilities. From 1997-2000, the Australian Government introduced policy reforms to incentivise private health insurance (PHI) legislated and amended under the Private Health Insurance Act (2007), in order to reduce the increasing burden on the public healthcare system (151).

1.7.1 Public healthcare system

The Australian healthcare system is largely financed through government funding from taxation of individuals and revenue, which contributes to around 70% of total healthcare expenditure (149, 150). Two thirds of all government expenditure is borne by the Australian Federal Government (149, 150). All citizens and permanent residents of Australia are taxed a levy ('Medicare Levy') at 2% of their income if above a certain threshold (150). At the Federal level, the government plays a key role in 1) allocation of healthcare budget for States and Territories; 2) development of broad range of national policies related to health and research;

3) regulation of private health insurance, pharmaceuticals, and medical devices; and 4) subsidisation of medicines and medical services under the Pharmaceutical Benefits Scheme (PBS) and the Medicare Benefits Scheme (MBS – see Box **6**) (147, 150, 152, 153). State and Territory government are primarily responsible for the delivery and management of public hospitals and community healthcare programmes, and maintaining a direct relationship with healthcare providers, including registering and licensing providers (147, 150). Local governments also play a key role in community health and health promotion activities, and distinctly responsible for environmental-related services including provision of water, management of waste, and food hygiene (147, 150). The various services managed through different levels of Governments are highlighted in detail in Figure 11 (150).

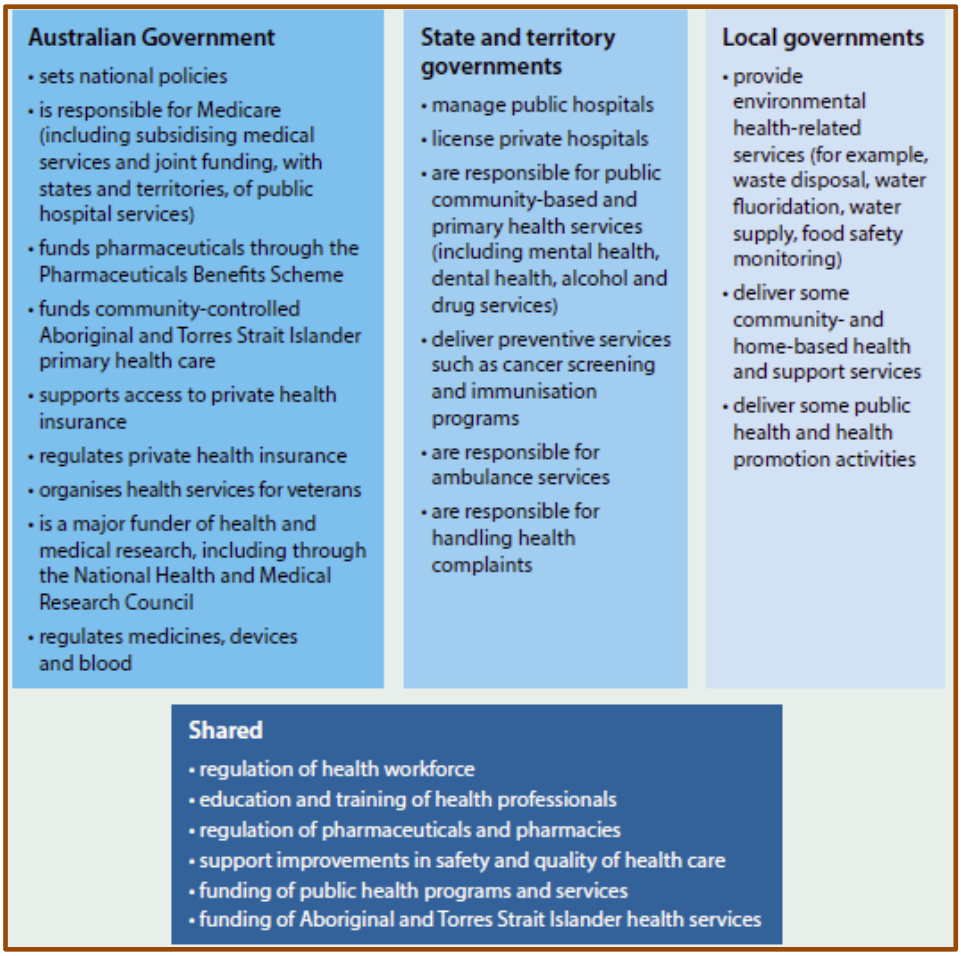


Figure 11 Main roles of government in Australia's health system (154).
Source: Adapted from cited website.

Box 6 Medicare benefits levels for professional service in Australia (152, 153).

The Medicare Benefits Schedule (MBS or 'Schedule') lists fees for professional (medical) services set by the Australian Government through the Medicare Benefit Scheme.

A Medicare benefit is the *percentage* paid to the service provider on behalf of the patient, based on Schedule fees determined for each medical service and whether it is an in-hospital or out-of-hospital service.

Legislated and amended under the Health Insurance Act 1973, the different levels of Medicare cover include:

1 Free treatment i.e., 100% coverage of MBS fees for patients treated at public hospitals (private patients can choose to be treated as a public patient)
2 In general, Medicare covers 85% of MBS fee for out-of-hospital services, with the exceptions of:
  a. Services provided by, or on behalf of a general practitioner, where, the coverage is 100% of MBS fee.
  b. Professional Services rendered to a private patient at a public hospital, private hospital, or a hospital-substitute setting where, the coverage is 75% of MBS fee.

Medical practitioners however, are not required to adhere to fees recommended by the MBS, and are able to set their own fees for their services, outside of a public hospital, unless they choose otherwise, i.e., 'bulk bill'. The difference between professional fees and Medicare rebate (% MBS fee reimbursed) represents a 'gap' or an out-of-pocket expense to the patient.

Note: Not all medical services are listed in the MBS (e.g., some allied health services), and additional relief is provided to patients who incur higher than usual out-of-pocket expenses for out-of-hospital medical treatments in a calendar year through policies known as Original Medicare Safety Net, and Extended Medicare Safety Net.

The latest Medicare Benefits Schedule information is available from MBS Online at http://www.health.gov.au/mbsonline

Example 1:
MBS listing for CABG:

Item no: 38500

Group: T8 - SURGICAL OPERATIONS

Subgroup: 6 - CARDIO-THORACIC

Subheading: 8 - SURGERY FOR ISCHAEMIC HEART DISEASE

CORONARY ARTERY BYPASS with cardiopulmonary bypass, using single arterial graft, with or without vein graft or grafts, including harvesting of internal mammary artery or vein graft material where performed, not being a service associated with a service to which items 38497, 38498, 38501, 38503 or 38504 apply

Fee: $2,200.00 **Benefit:** 75% = $1,650.00

Example 2:
MBS listing for PCI with stents:

Item no: 38306

Group: T8 - SURGICAL OPERATIONS

Subgroup: 6 - CARDIO-THORACIC

Subheading: 3 - ENDOVASCULAR INTERVENTIONAL PROCEDURES

TRANSLUMINAL INSERTION OF STENT OR STENTS into 1 occlusional site, including associated balloon dilatation for coronary artery, percutaneous or by open exposure, excluding associated radiological services and preparation, and excluding aftercare

1.7.2 Private healthcare system

By contrast, the private healthcare system of Australia is relatively smaller, unique, and extensively involved in the provision of services. The private sector only contributes to around 8% of total healthcare expenditure, financed by various PHI providers (150). Australia is the only country with a private healthcare system classified as both 'duplicate' and 'supplementary' (155). Services provided by the private sector include hospitals, and all medical professionals including general practitioners, specialists, consultant physicians, and other allied health personnel providing services outside of public hospitals, who are not required to adhere to fees recommended by the Medicare Benefits Schedule (147). The Australian Government also sets rules for PHI concerning prosthetics, including medical devices and human tissue that may be covered under PHI policies (156). Several age and income-dependent incentives and penalties have been introduced by the Australian Government to encourage the early uptake of PHI policies by individuals, as described in Box 7 (150, 157-159). Among the benefits of a PHI cover include the flexibility in the choice of healthcare providers, full or partial coverage of allied health services (some not covered under Medicare), and reduced long waiting periods. As at June 2015, 47% of the Australian population had some level of cover through PHI for hospital treatments ('duplicate' coverage), and 55% for general services ('supplementary' coverage) (150, 160) . Among OECD countries, Australia represents a unique case, where despite achievement of UHC, the proportion of population with a PHI cover is one of the highest (160, 161).

Box 7 Incentives and penalties introduced by the Australian Government to encourage individuals to uptake PHI (157-159).

Incentives:

- **Medicare rebate:** Medicare rebate is a partially subsidised amount (rebate) by the Australian Government on PHI premiums. It is designed to reduce the cost of PHI cover for hospital and general treatments, as well as ambulance polices. The rebate is age and income tested, such that levels of subsidisation differs according to person's age (<65 years, 65-59 years, 70+ years) and income tier*. The various levels of government subsidisation by income tier (and age brackets) from 1 April 2017 to 31 March 2017 were: *base tier* (26.8%, 31.2%, and 35.7%), *tier 1* (17.9%, 22.3%, and 26.8%), *tier 2* (8.9%, 13.5%, and 17.9%), and *tier 3* (0%, 0% and 0%)

Penalties:

- **Lifetime Health Cover (LHC):** LHC is a loading at 2% that an individual must pay in addition to premium of an appropriate# PHI cover for hospital treatment. LHC loading is applied when an individual takes up PHI cover after the first July following their 31st birthday. The LHC loading is applied to each year they were not covered under PHI, such that an adult age 40 years who takes up a PHI hospital cover for the first time pays a loading of 20% in addition to the base PHI premium. The LHC loading is designed to encourage individuals to take up PHI earlier in their life. New migrants to Australia, if above age 31 years are exempted from LHC loading if they take up a PHI cover within 12 months of registration for full Medicare benefits. Other individuals exempt from a LHC loading include those that take up a PHI cover before age 31 years, individuals who paid LHC loading continuously for 10 years or more, and individuals born before 1 July 1934.

- **Medicare Levy Surcharge (MLS):** MLS is a penalty rate as a percentage of income that must be paid by high income earners who do not have an appropriate# level of PHI hospital cover, in addition to their Medicare Levy (2% of annual total income). MLS is income and status-tested, such that penalty rates change according to whether an individual is single or have a family, and their total income level categorised under four tiers*. As at 1 July 2015, the penalty rates corresponding to these tiers were, 0%, 1%, 1.25%, and 1.5%.

* Income tiers: *base tier* (single, <$90k; family, <$180k), *tier1* (single, $90k-$105k; family, $180k-$210k), *tier 2*, (single, $105k-$140k; family, $210k-$280k), and *tire 3* (single, >$190k; family, >$280k)
# For singles, an appropriate level of cover is defined as that with excess of <$500, and for families the excess is <$1,000.

1.7.3 HTA in Australia

Most HTA activities in Australia are legislated under the policy and program framework of the Department of Health (162). The majority of HTA activities support decision making for national schemes, the Medicare Benefits Scheme (MBS), the Pharmaceutical Benefits Scheme (PBS), and the Repatriation PBS (coverage for veterans) and coordinated by the independent statutory bodies, the Medicare Services Advisory Committee (MSAC), and the Pharmaceutical Benefits Advisory Committee (PBAC), (123, 137, 163, 164). Additionally, through the collaborative efforts and funding by the Australian Government, and states/territories, the PBAC and the MSAC coordinate the HTA activities for the National Immunisation Program (NIP) and the National Blood Agreement (NBA) (123, 165). An independent non-statutory body, the Pharmaceutical Benefits Pricing Authority (PBPA),

review the prices of existing and new pharmaceuticals and vaccines supplied under the PBS and the NIP(123). In Australia, HTA activities are also undertaken when listing medical devices or human tissues in the Prostheses List (see Section 1.7.2) coordinated by the statutory body, the Prostheses List Advisory Committee (PLAC) (156, 166). More details concerning HTA advisory bodies and processes in Australia are provided in Figure 7, and Table 7.

The MBS, PBAC and the PLAC make recommendations and provide advice to the Australian Minister for Health about which therapeutics, medical services, and technologies should be reimbursed by either the Australian Government or PHI (for medical devices or human tissues only) (137, 163) (Table 7). Rather than a single formula for cost-effectiveness, the Australian Government relies on a number of factors in the decision to reimburse a medical intervention, including:

i. differing and sometimes conflicting community views on the technology or service of interest;
ii. the characteristics and size of the patient group impacted;
iii. the severity or impact of the disease being treated; and
iv. the availability of effective alternative treatments,

given the status of the budget and other priority areas for the Australian community (163). Not all healthcare funding schemes in Australia are subjected to HTA activities, including:

- National External Breast Prostheses Reimbursement Program;
- National Disability Insurance Scheme;
- National Diabetes Services Scheme;
- National Epidermolysis Bullosa Dressing Scheme;
- Stoma Appliance Scheme;
- Life Saving Drugs Program;

- Continence Aids Payment Scheme (CAPS);
- Type 1 Diabetes Insulin Pump Program;
- Australian Government Hearing Services Program; and
- Herceptin Program (167).

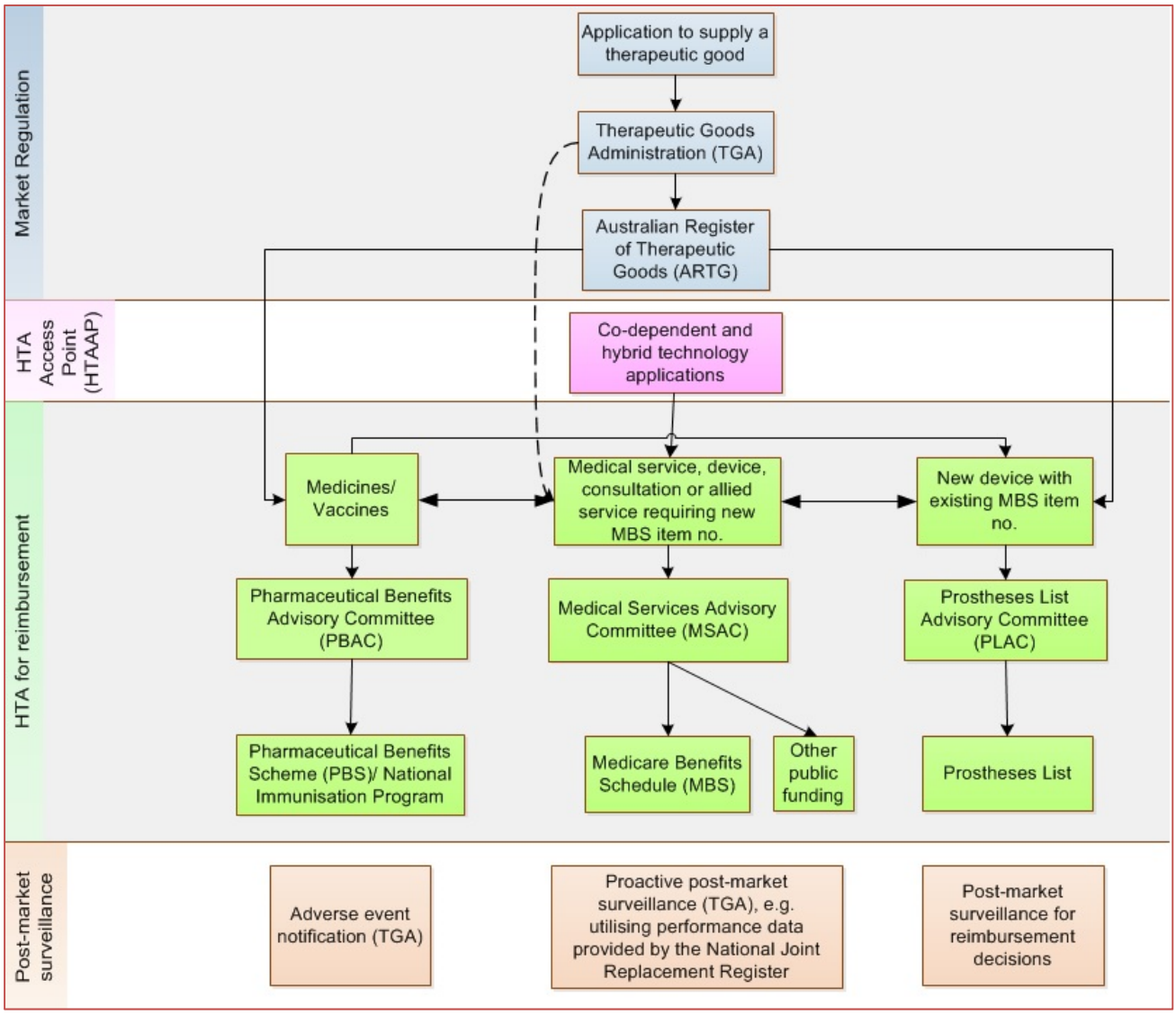
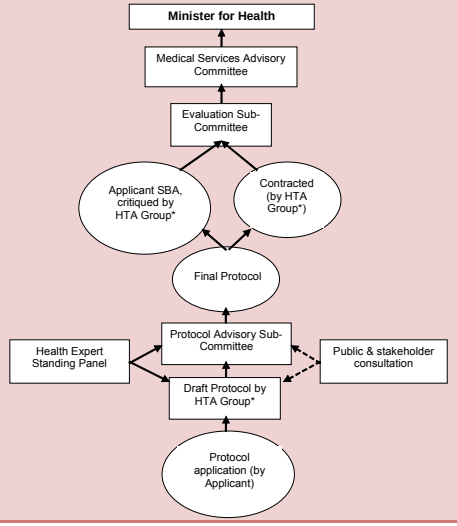
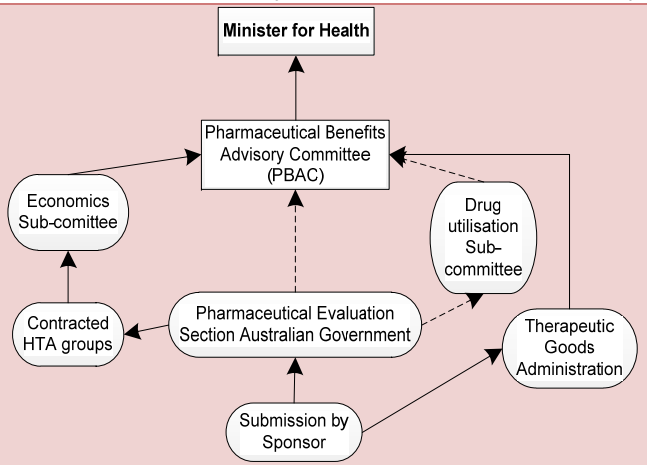
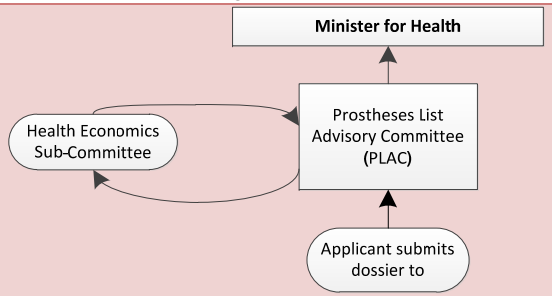


Figure 12 Map of current Australian Government HTA processes for market entry and for reimbursement processes (137).
Source: Adapted from cited website.

Table 7 HTA agencies in Australia, supporting schemes, legislation, economic considerations and processes (123, 147, 164-166, 168-173).

	MSAC	PBAC	PLAC
Year of formation	NHTAP (early 1980s) replaced by AHTAC (1986) replaced by MSAC in 1998.	1954	PDC (2004) replaced by PLAC in 2010.
National Schemes (Year commencing)	Medicare (1984) known as Medibank (1974) prior to 1984; & NBA (2002)* *MSAC assessment for new items in NBA began in 2010.	PBS (1948) & NIP (1953)# #PBAC assessment for new items in NIP began in 2006	-
Governing legislation	Health Insurance Act (1973); & National Blood Authority Act (2003)	National Health Act 1953; & National Health (Pharmaceutical Benefits) Regulations 1960	Private Health Insurance Act (2007)
Economic considerations	CUA, CEA, CMA. Also consider comparative costs including full spectrum of cost offsets. BIA mandatory.	CUA, CEA, CMA with preference for direct comparisons using RCT data. If indirect comparisons or non-randomised data are used, adaptation of the stepped approach is recommended. Preference for healthcare system perspective. BIA mandatory.	Economic data only required when applying for a premium over comparator, based on claim of superiority. EE not specified. Quantifiable clinical outcomes, cost savings, & utilisation data required.
HTA process			

Abbreviations: AHTAC, Australian Health Technology Advisory Committee; BIA, budget impact analysis; CEA, cost-effectiveness analysis; CMA, cost-minimisation analysis; CUA, cost-utility analysis; EE, economic evaluations; HTA, health technology assessment; MSAC, Medical Services Advisory Committee; NBA, National Blood Agreement; NHTAP, National Health Technology Advisory Panel; NIP, National Immunisation Program; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme ; PDC, Prostheses and Devices Committee; PLAC, Prostheses List Advisory Committee.

In March 2009, the Department of Health of Australia undertook an external review of existing HTA processes, with the aim to simplify and achieve better coordination between HTA processes, strengthen transparency, and procedural fairness in assessment, decision making and fee negotiation arrangements (145). The results from the HTA Review, comprising 16 recommendations was published in a final report in February 2010 (145) and are detailed in Appendix D (174). A phased approach to implementation of 13 recommendations of 16 (Recommendations '1'to'12', and '16') was undertaken by the Australian Government, beginning from allocation in the 2010-11 budget (175). Since the HTA Review (2009) in Australia, a summary of achievements to-date is provided in Appendix D (174). It is apparent there is still work to be done in the areas of:

- Australian Therapeutic Goods Authority's (TGA) involvement in post-market surveillance to patient safety, and steps to increase the rate of reporting of adverse events, including by health service providers and consumers (Recommendation '13'),
- Australian Government's involvement in the facilitation of the expansion and use of post-market surveillance data to inform safety, effectiveness and reimbursement decisions for devices and procedures (Recommendation '14'),
- Establishment of post-market surveillance of registries for medical devices and procedures (Recommendation '15') (174).

Summary:

The Australian healthcare system is complex and convoluted with multiple players in the funding and reimbursement of health services and technologies, including the Federal, State and Local governments, as well as PHI. Moreover, not all federal schemes utilise HTA for decision making. The majority of the 5,700 listed services in Medicare have limited evidence-base for clinical effectiveness, and cost-effectiveness. HTA in Australia is further constrained by limited involvement of the Federal government in the facilitation of the expansion and use of post-market surveillance data to inform safety, effectiveness and reimbursement decisions for devices and procedures through investment in patient registries.

1.8 Objectives

The primary objective of this doctoral thesis is to evaluate the cost-effectiveness of coronary revascularisation strategies in the Australian context. A major theme of this thesis is to utilise data collected in routine clinical practice from large multi-centre prospective registries, as well as emerging methods in propensity-score matching to compare the cost-effectiveness of CABG compared with PCI, and DES compared with BMS, among high-risk patients. A secondary objective is to contribute to the broader scientific literature concerning the effectiveness and cost-effectiveness of these strategies in the DES-era through conducting analytical reviews of the literature. Lastly, a tertiary objective of this thesis is to conduct cost analyses, and identify incremental costs and drivers of costs of revascularisation strategies in selected groups of high-risk patients.

1.9 Significance and implications

Today, the Australian health care system is the subject of several key reforms to Medicare, private health insurance rules, primary healthcare, and electronic health record system, among other areas of concern (Appendix A). In particular, special attention has been drawn by the Australian government to contain costs through funding focussed on value and outcomes rather than activity, better managing care of patients with complex comorbidities, improving efficiency through electronic medical records, and mitigating the rising cost of high-tech medical devices through funding cost-effective treatments. In light of these issues this thesis generates valuable evidence of cost-effectiveness of surgical treatments for CAD, in particular CABG and PCI, and costs and outcomes among patients with complex comorbidities. Thus, findings of this doctoral thesis may prove useful to policy makers, and clinicians alike, to understand the effectiveness and cost-effectiveness of revascularisation strategies among high-risk Australian patients in contemporary clinical practice.

1.10 Thesis outline

This thesis comprises eight chapters, followed by a bibliography of references and appendices. An outline of thesis structure is provided in Figure 13, followed by an overview of each chapter in brief.

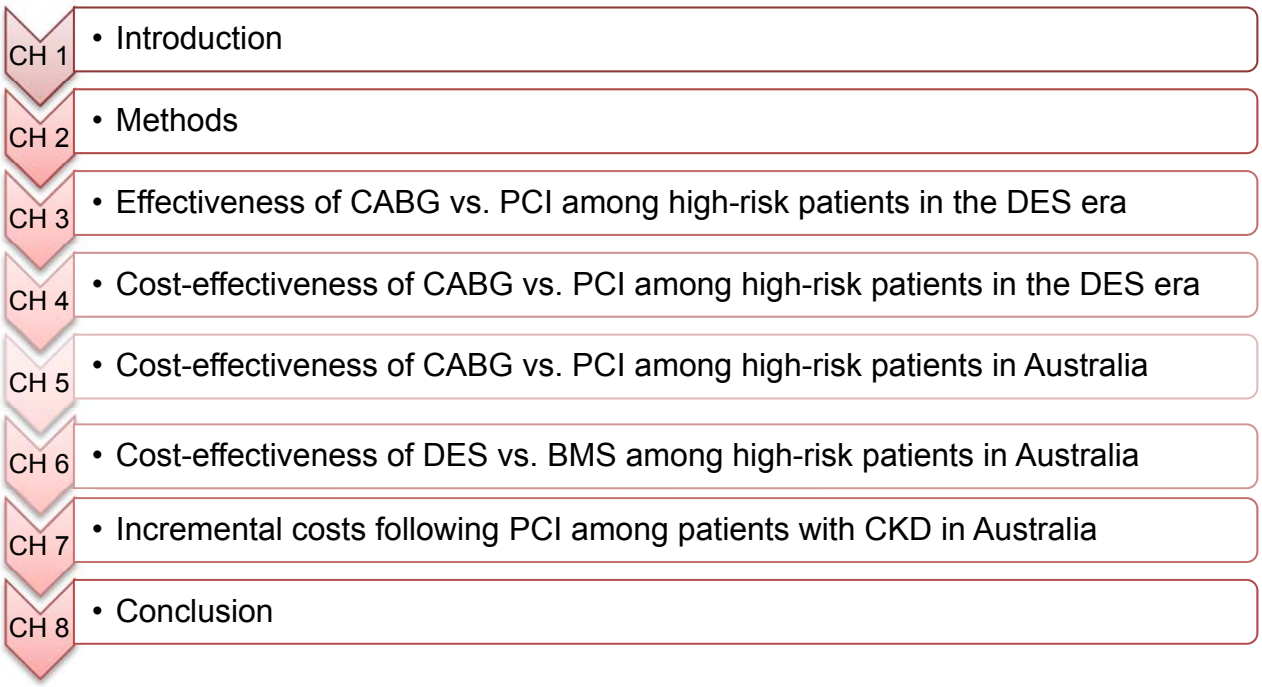


Figure 13 Outline of thesis structure
Abbreviations: BMS, bare-metal stents; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; DES, drug-eluting stents; PCI, percutaneous coronary intervention.

Chapter 1 provides the rationale for the aims and objectives of this doctoral thesis. It provides a background into current issues in the Australian healthcare setting and current reforms, global and Australian trends in the burden of CAD, an overview of coronary revascularisation strategies and their utilisation in Australia, a comparison of advantages and disadvantages of patient registries versus RCTs, a global overview of HTA and issues in evaluation of medical devices, and finally an overview of the structure of the Australian healthcare system and HTA in Australia.

Chapter 2 describes the study setting, datasets and methods utilised in the papers enclosed in Chapters 3-7. In particular, the Melbourne Interventional Group (MIG), and the Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) database projects are introduced. The types of costs, and measures of effectiveness used in this thesis are described and justified. A background to health economic evaluations, new and emerging propensity-score matching analyses, regression analyses, as well as analytical reviews, e.g., systematic reviews, is also provided.

Chapter 3 encloses a published manuscript of a systematic review and meta-analysis of effectiveness of CABG versus PCI using DES among patients with diabetes mellitus and MVCAD. It pools data from RCTs and non-randomised observational studies separately, and draws attention to the differences in findings. Effectiveness was measured with respect to all-cause mortality, myocardial infarction (MI), cerebrovascular events (CVE), repeat revascularisations, and major adverse cardiac and cerebrovascular events (MACCE) at mean 3 year follow-up.

Chapter 4 presents a published manuscript of a systematic review of cost-effectiveness of PCI versus surgery for the treatment of MVCAD in the DES-era. It reviews cost-effectiveness analyses of that compare CABG or OPCABG versus DES or BMS. The quality of health economic evaluations included were assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.

Chapter 5 includes an unpublished manuscript of a cost-effectiveness analysis of CABG versus stenting using data collected over a period of five years from the MIG and the ANZSCTS registries, from the perspective of the public hospital payer in Victoria, Australia. Record linkage was performed to obtain hospital administrative data including costs and

readmissions from a single-centre in Melbourne, Victoria. This analysis used two propensity score matching approaches including the 1:1 nearest neighbour matching method and the propensity-score bootstrap bin (PSBB) method.

Chapter 6 presents an unpublished manuscript of the cost-effectiveness of guideline-driven use of DES compared with BMS, from the perspective of the Australian public healthcare payer. Data from the MIG registry collected over a period of seven years, and published cost estimates were used to evaluate the cost-effectiveness of the revascularisation strategies at 12 months among patient with '0', 1, 2, or ≥3 indications for a DES. The DES and BMS groups were balanced using 1:1 nearest neighbour propensity-score matching method.

Chapter 7 includes a published evaluation of incremental costs incurred by patients with CKD compared with no CKD who underwent PCI, as well as drivers of costs among these patients at 12 months following PCI from the perspective of the public hospital payer in Victoria, Australia. The analysis used data from the MIG registry as well as published cost estimates.

Chapter 8 is the final chapter which brings together the findings of Chapter 3-7. This chapter discusses the key results and conclusion from this research, strengths and limitations, implication of the findings for policy and practice, and scope for future research.

2 Methods

This chapter provides an overview of the study design, data sources and statistical methods undertaken to address the research objectives of this thesis. It will provide background to the types of economic evaluations conducted (primary objective), propensity score matching techniques carried out, evidence based approaches used for synthesis of evidence (secondary objective), and regression modelling performed to assess costs in high-risk patient subsets (tertiary objective).

2.1 Data sources

2.1.1 MIG registry

The Melbourne Interventional Group (MIG) registry is a multi-centre, prospective, on-going procedural-centric PCI registry, founded in 2004 as a collaborative venture of collaborative effort between six Victorian public hospitals, including the Alfred Hospital, Austin Hospital, Box Hill Hospital, Geelong Hospital, Royal Melbourne Hospital, and Ballarat Hospital (108). The fragmented nature of data collection for PCI across Victoria, at the time gave rise to the concept of the MIG registry (108). The registry has grown over the years, and today it includes data from several additional public and private Cardiology Units across Victoria (108). The registry is supported by research funding from the National Health and Medical Research Council (NHMRC) and some unrestricted grants from industry sponsors (108).

The MIG registry provides a standardised collection of data for patients undergoing PCI across Melbourne and regional Victoria (108). It aims to monitor quality and safety of procedures as well as benchmark outcomes against national and international standards (108). The minimum dataset of the MIG registry was based on some existing PCI registries. These

included the American College of Cardiology – National Cardiovascular Registry (ACC-NCDR) and the Australia New Zealand Society of Cardiothoracic Surgeons (ANZSCTS) minimum dataset- version 5 (108). In this thesis, the data from MIG registry was used in two economic evaluations described in Chapter 5 and Chapter 6.

2.1.1.1 Data elements

The MIG minimum dataset comprises 172 core data elements with extra 52 elements per additional lesion treated, as per the MIG case report form available in Appendix E1. The classes of data collected by the MIG registry are shown in in Table 8.

Table 8 Classes of information collected by the MIG registry.

Patient non-clinical data	Clinical data	Follow-up data	Record linkage data
• **Patient demographics** • **Dates related to episode** • **Health insurance data**	• Patient risk factors • Previous interventions • Cardiac status at PCI procedure • Cath lab visit • PCI procedure/ lesion information • Outcomes/ discharge	• Mortality • Hospital readmissions • Medication use • Complications	• NDI data

Abbreviations: NDI, national death index; PCI, percutaneous coronary intervention
Source: Table created by author

2.1.1.2 Patient follow-up

Patient follow-up in the MIG registry occurs at 30 days and 12 months. Cardiac research nurses conduct follow-up through contacting patients or their families by telephone. Data is collected using follow-up case report forms (Appendix E2) and entered into a web-based electronic data capture registry platform (see section 2.2.2). Information collected includes medication use, and adverse events such as death, acute myocardial infarction (AMI), target lesion revascularisation (TLR) and target vessel revascularisation (TVR), and related hospital readmissions. All adverse events are confirmed by review of patients' medical records at the relevant hospitals. Additional data on fatal cases are obtained through linkage to the national

death index (NDI), collected by the Australian Institute of Health and Welfare (AIHW). The linkage to the NDI permits the follow-up of long-term survival of enrolled patients through the MIG registry (108).

2.1.2 ANZSCTS registry

The Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) registry prospectively collects demographic, clinical and procedural data from patients undergoing cardiac surgery at multiple sites in Victoria and other states (108). The programme receives funding from The Victorian Department of Health, Queensland Health, the Clinical Excellence Commission (NSW) and individual funding from participating units (176). The registry was established in 2001 to meet the need for a standardised data-definition-set for use in Australian cardiac surgical units (108). Initially, only the six major public hospitals in Victoria participated in data collection, including the Alfred Hospital, Austin Hospital, Box Hill Hospital, Geelong Hospital, Royal Melbourne Hospital and Western Hospital (108). In Australia, the ANZSCTS registry captures around 80% of the cardiac surgical procedures performed in public hospitals, and 60% across all Australian hospitals (177). The ANZSCTS database has since expanded nationally to involve 31 cardiac surgical units in total (176). In Chapter 6, data from the ANZSCTS were used for an economic evaluation.

2.1.2.1 Data elements

The ANZSCTS minimum dataset includes 287 variables under the broad classes of ‘pre-operative’, ‘intra-operative’, ‘post-operative’, and ‘follow-up’ information, as per ANZSCTS case report form available in Appendix F. The classes of information collected appear in Table 9.

Table 9 Classes of information collected by the ANZSCTS registry.

Patient non-clinical data	Clinical data	Follow-up data	Record linkage data
• **Patient demographics** • **Dates related to episode** • **Health insurance data**	• Patient risk factors • Pre-operative cardiac status • Medications at time of surgery • Previous interventions • Haemodynamic data • Operative Status/ Category • Minimally invasive surgery • Cardiopulmonary bypass and support • Coronary bypass surgery • Valve Surgery • Post-operative data • Complications	• Mortality • Hospital readmissions • Complications	• NDI data

Abbreviations: NDI, national death index
Source: Table created by author

2.1.2.2 Patient follow-up

Patients enrolled in the ANZSCTS registry are followed up at 30 days using the same approach as the MIG registry, described in Section 2.1.1.1 . Additional information may be requested from the patient's general practitioner. During follow-up, information relating to mortality, readmissions, and complications during the 30-day period post-surgery is collected. Further mortality information is collected through linkage to the NDI data collected by the AIHW (108).

2.1.3 Alfred Hospital clinical costing dataset

The Alfred Hospital clinical costing dataset is an administrative repository maintained by the Alfred Hospital's Clinical Performance Unit (CPU), a service that is part of the Hospital's Finance Department. These costs were derived from a bottom-up costing approach (178). For the purpose of this project, a request was made to the CPU to extract a dataset that included patient-level costs related to PCI and CABG procedures that were performed at the Alfred Hospital (sourced from MIG and ANZSCTS registries), as well as subsequent same-

hospital readmissions that occurred following each unique hospital episode. The CPU's Information Manager for Clinical Costing at the time (Mr Marco Luthe) performed all data linkages between clinical and administrative records, using unique identifies (patient 'UR number') and other common data elements (date of birth, hospital admission date, and discharge date). The clinical costing dataset was limited to hospital episodes that occurred from financial year 2010 onwards, with data censored on 31 December 2014. The linked dataset comprised costing information for 1440 CABG and 2068 PCI episodes collected from 1 July 2009 to 31 December 2013. Costing information related to 2135 and 3832 subsequent readmissions following CABG and PCI were available from 1 July 2009 to 31 December 2014. Clinical costing information from this dataset was used to investigate the cost-effectiveness of CABG compared with PCI for MVCAD at mean follow-up of 2.7 years in Chapter 5, and to estimate the initial average cost of a PCI procedure using DES compared with BMS in Chapter 6.

2.1.3.1 Data elements

The Alfred Hospital clinical costing dataset comprised patient-level micro costs from several departments at the Hospital, as highlighted in Box 1. The costs were split between direct and indirect costs for resource utilisation that occurred within each department ('cost bucket') per hospital episode. A table presenting these clinical costs buckets, in particular, the items that were considered under each 'bucket' appear in Appendix G.

Box 1 Departments contributing to the Alfred Hospital clinical costing dataset.

1. **Allied**
2. **Coronary care unit**
3. **Emergency**
4. **Intensive care unit**
5. **Imaging**
6. **Medical personnel (surgical)**
7. **Medical personnel (non-surgical)**
8. **Nursing personnel**
9. **Pathology**
10. **Pharmacy**
11. **Theatre/ Operating Room**
12. **Theatre/ non-Operating Room**

2.2 Data management and ethics considerations

2.2.1 Ethics and patient consent

The ethics approval was obtained from the Alfred Hospital's Ethics Committee, the primary Human Research Ethics Committee (HREC) for this project (Project number: Project no.: 142/15). The project was conducted according to ethical principles governed by the Declaration of Helsinki of 1964 (last revised in 2016, Fortaleza, Brazil) (179).

2.2.1.1 ANZSCTS and MIG registries

The use of data from the ANZSCTS and MIG registries for low-risk observational research was pre-approved by the HRECs of all participating hospitals in the MIG and ANZSCTS registry projects. The study protocols of MIG and ANZSCTS conforms to the ethical guidelines of the Declaration of Helsinki (179). All patients were provided with a patient information sheet (PIS) before discharge from the hospital. Patient consent was obtained using an 'opt-off' approach for both registries, and this approach was approved by the HREC committees of participating sites (180). Also known as an 'opt-out' or 'passive consent' approach, the 'opt-off' approach contacts patients without them volunteering to take part in the research. Patients are excluded only when they say they are unwilling to participate. Participating sites manage their delivery of PIS with opt-off information according to their own internal processes which are taken seriously are reviewed regularly (180). Sites ensure that every patient is afforded the right to withdraw/revoke their consent to data collection (180). Furthermore, if a patient is ever contacted for follow-up by hospital staff, consent is always reaffirmed at the time of contact and information about how to opt-off the Registry is available at this time (180). Patients who wished not to be enrolled in the registries are provided with a toll -free telephone number to call and request a withdrawal (180). Despite these factors, the opt-out rates remain very low at <0.2% (for the MIG registry, data not available for the ANZSCTS but expected to

be similar) which is unlikely to impact results from analyses conducted using the datasets (180).

2.2.2 Data Management

The MIG and ANZSCTS datasets are held and managed by the Centre of Cardiovascular Research and Education in Therapeutics (CCRET), a research body within the Department of Epidemiology and Preventive Medicine of Monash University (Melbourne, Australia). Data are captured on consecutive patients who underwent PCI or CABG at participating sites, through case report forms completed by fellows or research nurses. Before 2012, these forms were transmitted to the CCRET through fax, following which data were subsequently entered into the central electronic registry in de-identified format. Data queries concerning omissions and inconsistencies were subsequently raised. Post-2012, a web-based EDC system was introduced by both registries, where clinical and procedural data relating to PCI and CABG are directly entered into the central registry system, by an onsite data manager at each participating hospital. A proportion of the sites continue to submit their procedural data from a custom built internal databases into the central registry.

ANZSCTS does not capture all cardiac surgeries performed in Australia. In 2015 our data capture was estimated to be 60% compared to data from the AIHW (This was published in our annual report for 2015). This percentage is expected to increase in the next

De-identified data entered into the central registry undergoes salient audit programmes facilitated by the MIG and ANZSCTS registry teams on a regular basis to ensure data quality and integrity. An independent audit of randomly selected data at each participating institution is performed annually by an investigator not affiliated with that institution. Data accuracy of

97% has been achieved on baseline data, which is comparable to the accuracy of other large cardiac registries (108).

2.3 Health economic evaluations

2.3.1 Types of economic evaluations

Health economic analyses can be defined as comparisons of two different healthcare interventions in relation to their costs and benefits (181-183). The comparator in these evaluations are defined as the next best alternative treatment, and may include competing treatments, a current standard of care, or 'no treatment' (181-183). Health economic evaluations may fall into four categories, including cost-minimisation analyses, cost-effectiveness analyses, cost-utility analyses, and cost-benefit analyses. The attributes of each type of health economic evaluations are shown in Table 10. Cost-consequences analyses are a fifth type of economic evaluation, not widely used in the literature, but consider costs and effectiveness independently, forcing decision makers themselves to synthesise and formulate the value-for-money benefit of alternative treatments (181-183).

Table 10 Types of health economic evaluations and properties

Health economic evaluation	Effectiveness component	Cost component	Notes
Cost-minimisation analyses (CMA)	Equivalence of outcomes must be established between treatment and comparator groups	All costs as per perspective in monetary units	Assumptions: - Two interventions are equally effective - All costs are included - No uncertainty in clinical or economic outcomes
Cost –effectiveness analyses (CEA)	Benefits common to both alternatives, e.g., survival, complication rates, repeat procedures, blood pressure reduction etc.	Costs included as per perspective in monetary units	Effectiveness is measured in natural units Assumes benefits are achieved to different degrees by different treatments

Cost-utility analyses (CUA)	Effectiveness in terms healthy years, i.e., QALYs gained Health-related utilities gained or lost are used to measure QALYs Measures single or multiple effects not necessarily common to both alternatives	Costs included as per perspective in monetary units	Utilities can be derived from four methods; - Time-trade off - Standard gamble - Multi-attribute utility instruments - Visual analogue scales
Cost-benefit analyses (CBA)	Measured regarding monetary benefit Measures single or multiple effects not necessarily common to both alternatives	Costs included as per perspective in monetary units	Benefits gained reflect value to society Based on welfare theory Permits comparison of options between different areas of expenditure, e.g., education, transport, environment etc.

Sources: (181-183)

Cost-effectiveness analyses were used in this thesis, given cost-minimisation analyses were not applicable, cost-utility analyses were not feasible due to limited data (see Section 2.3.5) and measuring benefits of PCI or CABG in monetary terms were considered inappropriate, ruling out cost-benefit analyses. A cost-effectiveness analysis involves the comparison of costs and benefits of alternative treatments, where benefits are defined in natural units or health outcomes common to both alternatives (e.g., survival, complication rates, repeat procedures, blood pressure reduction etc.) (181-183). The cost component of a cost-effectiveness analysis is evaluated in monetary units (181-183). Cost-effectiveness analyses estimate the 'incremental cost-effectiveness ratio' (ICER) for the new intervention, as per the formula in Box 2 (181-183). In cost-utility analyses, an 'incremental cost-utility ratio' (ICUR) is calculated using the same formula, but replacing the measure of effectiveness with a measure of health-related quality of life (181-183).

Box 2 Formula for incremental cost-effectiveness and cost-utility ratio (ICER)

$$\text{ICER} = \frac{\text{Cost}_{\text{Treatment 2}} - \text{Cost}_{\text{Treatment 1}}}{\text{Benefit}_{\text{Treatment 2}} - \text{Benefit}_{\text{Treatment 1}}}$$

Sources: (181-183)

2.3.2 Decision analytical modelling

Decision analytical modelling uses data from multiple secondary sources to estimate the costs and effectiveness of alternative courses of healthcare interventions. The approach utilise analytical modelling techniques to make extrapolations concerning costs and benefits (183, 184). It takes into account of several limintations of clinical studies including (183):

1. consideration of only a few of all the relevant treatment alternatives,
2. not collecting data on all costs and outcomes that are relevant and appropriate for an economic evaluation,
3. finite follow-up, which is often too short in clinical studies to be considered appropriate time horizon in an economic evaluation,
4. inadequate information on final endpoints,
5. inadequate evidence specific to a particular setting or a group of patients.

Provided the timeframe in question be short, and recurring events are not important, a decision tree model may be appropriate to investigate the cost-effectiveness of an intervention (183, 184). A Markov model may be used when recurring events are important for an extended period, where individuals are transitioned from one health state to another across a series of short time intervals or 'cycles' (183, 184). When memory is important, an individual sampling model may need to be considered. Increasing the number of health states of a Markov model, to overcome the "Markovian assumption" may be too cumbersome for analysis(183, 184). Contrastingly, when the interaction between patients are important, i.e., when individuals cannot be assumed as independent entities, discrete event simulation (DES) or systems

dynamic models may be considered(183, 184). As examples, the interaction between patients are important in decision analysis for infectious diseases, and in organ transplantation, when there are shortages of dontations(183, 184).

Given this thesis focussed on patient-level data from clinical registries (see Section 2.1), analytical techniques including Markov models, decision tree models, or DES models, which largely rely on assumptions and probabilities of events were not used. Instead, purely a database approach for evaluation of cost-effectiveness was employed using patient-level clinical data, record linkage between clinical and administrative datasets to gather follow-up events (see Section 2.1.2), and propensity score matching to adjust for treatment bias observed in routine clinical practice (see Section 2.4).

2.3.3 Study setting and perspective

All evaluations undertaken as part of this research were performed from the Australian public healthcare payer perspective. In Chapter 5, the perspective was that of the Australian (Victorian) public hospital payer, the State Government of Victoria, Australia. By contrast, a perspective of the State Government of Victoria, and the Australian Federal Government, responsible for the PBS (see Section 1.7.3), were considered in the economic evaluation presented in Chapter 6, as it included medical costs related to hospital admissions, and pharmaceuticals. Clinical data for this thesis were obtained from the MIG and ANZSCTS registries, which collected data from routine clinical practice, and included 'all comer' populations.

2.3.4 Time horizon

Outcomes from observational cohorts were assessed over a period of 12 months (Chapter 6), and five years (mean 2.7) years through linking clinical records to administrative records (Chapter 5). The results from observational cohorts were not extrapolated beyond the

observed period, as outcomes were based on patient level data collected from routine clinical practice.

2.3.5 Measures of effectiveness

A number of measures of effectiveness were used in this thesis. These included:

- Rate of major adverse cardiac and cerebrovascular events (MACCE) at mean 2.7 years (Chapter 5)
- All-cause mortality at mean 2.7 years (Chapter 5)
- Life years lived at mean 2.7 years (Chapter 5)
- TVR at 12 months (Chapter 6)

As health-related utilities were not collected by the ANZSCTS and MIG registries, quality adjusted life years (QALYs) gained was not used as an outcome measure in the economic evaluations reported in Chapter 5 and Chapter 6. There were also no other sources of health-related quality of life data from Australian patients who underwent CABG or PCI from the two registries, available at the time of this thesis. Although published health-related utility weights from international sources were considered as an option, initially, a decision was made not to use these as inputs to the economic evaluations presented in Chapter 5 and Chapter 6, in order to prevent compromising the face validity of results.

2.3.6 Assessment of costs

Costs are by definition resources that deny the use of other resources (182). While there are two types of costs, *direct* and *indirect*, the costs primarily considered in this thesis were direct costs.

2.3.6.1 Direct costs

Direct costs include resources consumed which are directly attributable to the treatment or intervention (181, 182). Direct costs consider both medical and non-medical consumption of

resources and may include expenses related to the treatment, such as diagnostic, inpatient treatment, medication use, device use, medical care, therapy and rehabilitation (182). Direct non-medical costs may include all non-medical costs incurred as a consequence of treatment, including transport costs and community carer costs (182). In the economic evaluations presented in Chapter 5 and Chapter 6, only direct medical costs relevant to resource utilisation within public hospitals, and medication costs (only in Chapter 6) were considered.

2.3.6.2 Indirect costs

Indirect costs encompass all costs not directly related to the treatment or intervention including depreciation costs related to capital equipment in hospitals (182). Other types of indirect costs include losses of income and/or productivity due to treatment, for the patient and their members of family (carers, if applicable (181). Indirect costs were not included in the economic evaluations performed in Chapter 5 and Chapter 6, since there were no sources of evidence available among Australian patients who underwent CABG or PCI, at the time of this thesis. This prevented these economic evaluations from assuming a 'societal' perspective.

2.3.7 Adjustments of costs

2.3.7.1 Inflation

The concept that prices of all goods and services increase over time, such that relative prices do not change, is conferred by the term 'inflation' (182). In cost analyses, future inputs can be valued at current prices through deflation by a calculated rate (183). For older inputs, prices may be inflated by a calculated rate to reflect current prices (183). Adjustment for inflation is mandatory when dealing with costs collected at different time points in trials or observational studies that span over years (182). Inflation adjustment is made using a formula illustrated in Box 8 (183). The calculation of inflation involves placing all costs on a common base year, by using measures of domestic inflation such as the consumer price index (CPI) or a producer or industry-specific inflation measure, such as the health price index (HPI) (183).

In this thesis, adjustments for inflation of costs were addressed in Chapter 5. Chapter 6 only considered direct medical costs during a 12-month period.

Box 8 Formula for adjusting for inflation

$$\mathbf{Cost_n} = \mathbf{Cost_p} \times \frac{(\text{Index value})_p - (\text{Index value})_n}{(\text{Index value})_n}$$

Source: (183)
Notes: n = base year; p= calendar year of interest

2.3.7.2 Discounting

The principles governing discounting of costs are based on a human incentive to value current expenditure more highly than future expenditure (183). As an example, the price of airfares to a particular destination could be more expensive if booked to depart today, than for a trip planned six months ahead of time (182). As another example, an investment made today for $909.10, at an interest rate of 10% per annum, would yield $1,000.00 in 12 months. In other words, the present value of $1,000.00 in 12 months' time is $909.10 (182). This important concept is widely applied in health economic evaluations that model costs and outcomes beyond 12 months. Future costs beyond 12 months are weighted against (multiplied by) discount factors estimated using the formula illustrated in Box 3 (183). The discount rate, r, may vary, depending on the local context, and are subject to sensitivity analyses in many health economic evaluations (183). In this thesis, discounting was considered in Chapter 5, as the time horizon of the economic evaluation spanned more than 12 months. Net overall costs and benefits beyond first year were discounted by 5%, the standard rate as determined by the Australia's MSAC (see Section 1.7.3) (185)

Box 3 Formula for estimating discounting factor

$$\mathbf{D_n} = \frac{1}{(1+r)^n}$$

Source: (183)
Abbreviations: D_n, discount factor at year n; r, discount rate; n, number of years

2.3.7.3 Converting costs to a common currency

Conversion of costs to a single common currency may be relevant when dealing with studies that run across multiple countries, or reviewing international cost reference pricing for treatment. To-date, two methods have been widely used to convert currencies.

2.3.7.3.1 Exchange rates

Exchange rates are the rates at which currencies are bought and sold in the international market (183). Although theoretically the purpose of exchange rates is to equalize prices of internationally traded goods, they may be subjected to bias due to factors such as macroeconomic expectations and political uncertainty of a country (183). Exchange rates do not reflect prices of non-tradable goods and services such as healthcare (183). These issues limit the value of exchange rates as a tool for translating costs of a healthcare intervention in one country to a comparable healthcare intervention in another country.

2.3.7.3.2 Purchasing power of parity

The concept of purchasing power of parity (PPP) overcomes issues posed by exchange rates (183). The PPP calculates the costs of purchasing a standardised set of goods and services across different countries (183). To illustrate, if the rental expense of a serviced two-bedroom apartment in the city of New York is $850 per week compared with €500 per week in London, this suggests that $1.7 has the same power as €1, or €0.59 the same power as $1 (using the US dollar as the base). Using the PPP illustrated in this example, a health care intervention at the cost of €1500 in the UK may be translated to $2,542.40 in US dollars (= $1/ €0.59 *€1500) (183). To-date, several PPP measures have been introduced, including the Big Mac Index, and a European-specific PPP (183). This thesis uses the PPP produced by the World Bank, and OECD, which uses the US dollar as the reference base. In the systematic review included in Chapter 4, the PPP produced by OECD and World Bank was used to convert

published cost-effectiveness data from many countries into a common currency of US dollars (USD, 2014), appropriately inflated and deflated to account for time differences.

2.3.7.4 Adjustment of censored costs

Observations from patient registries and other observational studies are marked by finite follow-up. In particular, due to drop outs, loss to follow-up, or voluntary withdrawals, complete cost data may not be available for all study participants until the endpoint of interest. The outright exclusion of patients with incomplete follow-up may not be feasible as it compromises the effective sample size and may lead to erroneous inferences (186). To address the issue of censored cost data, two approaches are available including the Lin 1997 method (187) and the Bang and Tsiatis (B&T) method (188). Both these approaches comprise four steps (186):

1. Partition the study period into smaller time intervals;
2. Estimate the average costs over each interval for patients who are alive at the beginning of the interval;
3. Multiply the average total interval costs by the Kaplan-Meier survival probability of being alive at the beginning of the interval (*in the case of B&T method, probability of not being censored at the end of interval is estimated*); and
4. Calculate the mean total costs by summing up these weighted costs over the complete study period.

For the economic evaluation reported in Chapter 5 of this thesis, which contained censored cost data, the Lin 1997 (187) was applied. In this evaluation, the cohort was partition based on different periods for which patients were alive (1 year, 2 years, 3 years, 4 years, and 5 years) based on data from the NDI, and weighing total costs observed for that period by the survival probability of being alive at the beginning of that period.

2.3.8 Sensitivity analyses

Reporting standards for health economic evaluations call for the quantification of uncertainty around estimates of costs and benefits (189, 190). Sensitivity and uncertainty analyses have therefore become mandatory components of economic evaluations, and health technology assessments (HTA) (190). Currently, there are no strict definitions for delineating between a 'sensitivity analysis' and an 'uncertainty analysis'. The analysis of 'sensitivity' may refer to the quantification of the effect on outcome about the variability of a particular model parameter. By contrast, the quantification of the simultaneous and combined effect of uncertainty in all model parameters, on the outcome, may be thought of as an 'uncertainty analysis' (190). As an example, the estimation of a confidence interval (CI) around a parameter of interest is an analysis of the uncertainty of that parameter. Any given sensitivity or uncertainty analysis may only address part of all sources of uncertainty within a health economic evaluation (190). Four broad classes of uncertainties in decision models may implicate the robustness of health economic evaluations(190). These are described in Table 11 and the sensitivity analyses performed in this thesis are described further.

Table 11 Uncertainty for decision modelling: concepts and terminology, adapted from (191).

Preferred term	Concept	Other terms sometimes employed	Analogous concept in regression
Parameter uncertainty	The uncertainty in the estimation of parameter of interest	Second—order uncertainty	Standard error of the estimate
Heterogeneity	The variability among patients that can be attributed to characteristics of those patients	Variability Observed or explained heterogeneity	Beta coefficients (or the extent to which the dependent variable varies by patient characteristics)
Structural uncertainty	The assumptions inherent in the decision model	Model uncertainty	The form of the regression model (e.g., linear, log-linearetc.)
Stochastic uncertainty	Random variability in outcomes between identical patients	Variability Monte Carlo error First-order uncertainty	Error term

2.3.8.1 Parameter uncertainty

Parameter uncertainty arises from the decision maker's imperfect knowledge of the model inputs and is frequently addressed in health economic evaluations (190). In economic

evaluations reported in Chapter 5 and Chapter 6, parameter uncertainty was established using two methods, deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA).

2.3.8.1.1 Deterministic sensitivity analysis

Deterministic sensitivity analysis (DSA) evaluates outcomes precisely determined through known relationships between states and events, without room for random variation in outcomes (190). DSA includes one-way, two-way, or multi-way sensitivity analyses (190). For example, in one-way sensitivity analysis, each model input is varied by a known amount (e.g. ± 95% CI) to detect the effect of variation in the outcome. Two-way or multi-way analyses use a similar approach but with two or multiple parameters at a time, respectively. A 'what if' analysis is also a type of DSA (190).

2.3.8.1.2 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) uses a Bayesian or multi-parameter approach to assessing the joint uncertainty of all uncertain model parameters (190). PSA therefore, assumes that there is a degree of variability in outcomes as a consequence of chance or uncertainties inherent to model input parameters (190). PSA is performed using Monte Carlo simulations, a probability simulation method, through fitting an appropriate probability distribution around each uncertain parameter (190). The probability distributions commonly used for different types of input parameters are listed in Table 12 (181, 183, 184, 190).

Table 12 Probability distribution for different types of input parameters

Type of input parameter	Distribution
Prevalence or probability	Binomial or beta distribution
Rates	Gamma
Relative risk	Lognormal
Survival	Weibull or lognormal or gamma
Costs	Gamma distribution
DALY and QALY weights	Beta distribution

Sources: (181, 183, 184, 190)
Abbreviations: DALY, disability-adjusted life years; QALY, quality-adjusted life years;

Results from PSA simulations are commonly presented in scatter plots where the X-axis denotes the *difference in effectiveness* between treatment and comparator, and the Y-axis denotes the *difference in costs* between treatment and comparator (181, 183, 184, 190). These scatter plots are similar to a cost-effectiveness plane, but incorporates results from all iterations of a Monte Carlo simulation (181, 183, 184, 190). Alternatively results from PSA may be presented in cost-effectiveness acceptability curves, which plot probability that the intervention could reach a particular threshold for ICER, over a range of thresholds, based on ICERS calculated in all iterations of a Monte Carlo Simulation (181, 183, 184, 190).

2.3.8.2 Heterogeneity

Heterogeneity defined as the variability among patients due to different observed characteristics, and may be estimated through stratification or sub-group analyses (190). Technically, however, heterogeneity is not a type of uncertainty, as it can be observed and explained when evaluating the differences between patients, e.g., across different age groups, comorbidities etc. (190). Nonetheless, heterogeneity may lead to uncertainties in the outcome of interest (190). Heterogeneity was addressed through sub-group analyses in the economic evaluations presented in Chapter 5 and Chapter 6, respectively.

2.3.8.3 Structural uncertainty

Structural uncertainty may refer to uncertainty in modelling methods or assumptions inherent to the decision model (190). The structural uncertainty of decision models may have a much greater impact on results than parameter uncertainty (190). To-date, there are no set guidelines for ascertaining uncertainty in modelling methods, as such they are frequently ignored in published economic evaluations. Nonetheless, model assumptions may be tested through sensitivity analyses, deterministically (see Section 2.3.8.1.1) (190). For example, the impact of alternative discount rates, time horizons, and perspectives may be evaluated in health economic evaluations, through ‘what if’ analyses. In the economic analyses presented

in Chapter 5 and Chapter 6 uncertainties in the time horizon and discount rates were not tested, given these were fixed and limited by the duration of patient follow-up as determined by data sources used. Perspectives other than that of the Australian State and Federal governments could not be adopted, due to limitations of data sources available at the time of this project. Uncertainties in modelling methods were not addressed in these economic evaluations, given only patient-level analyses were carried out.

2.3.8.4 Sampling uncertainty

Sampling uncertainty may be addressed for selected parameters. In economic evaluations, several inputs can contribute to sampling uncertainty, including that obtained from clinical cohorts, for instance, treatment costs, health-related utility weights, etc. Where published inputs are concerned, a critical narrative assessment of these parameters may confirm the internal validity of results; whereas sensitivity analyses may confirm external validity of results (190). The sampling uncertainty registry data may be evaluated through the estimation of bootstrap 95% CI for cost estimates, as an example, as carried out in Chapter 5 and Chapter 6 of this thesis (191). Propensity score matching techniques aim to address issues around the selection of treatment received by patients in routine clinical practice, and assists in identifying balanced comparator groups for analyses. In Chapter 5 an alternative, emerging propensity-score matching approach was performed to validate base-case results obtained from using a standard matching technique (see Section 2.4.2)

2.4 Propensity score analysis

Since its introduction in 1983 by Rosenbaum and Rubin (192), propensity score analyses have gained wide popularity in health service research (193). Propensity score analyses are useful tools for minimising selection bias when using patient registries or observational data (193). Comparative analyses of effectiveness and cost-effectiveness using data from routine clinical practice may be characterised by imbalances between the treatment groups, leading to

selection bias (194). By contrast, in RCTs, randomisation minimises selection bias through the allocation of individuals to treatment and control groups, at random, before data collection (194). Propensity-score techniques, on the other hand, offer bias minimising approaches for posthoc data analysis of observational studies (194).

The propensity score is defined as the probability of exposure (e.g., to treatment) given observed data on other covariates (194). Two individuals with the same propensity score are considered to have the same probability or chance of being selected for treatment (194). There are several techniques for adjusting for imbalances in comparative treatment groups using propensity scores, including:

1. Propensity-score matching of pairs,
    a. Greedy matching
    b. Optimal matching
    c. Ratio matching
    d. Matching with replacement
2. Sub-classification,
    a. Stratified propensity scores analysis
    b. Propensity score bin bootstrapping
    c. Full-matching
3. Weighing by the inverse propensity score,
4. Adjusting for propensity score (194).

2.4.1 Propensity score matching

Propensity-score matching is a popular method for balancing comparative treatment groups. All matching techniques share four common steps (193):

1. **Define "closeness", a measure of similarity between two individuals. This step is governed by two aspects;**
    a. Covariate selection, where selected variables may include;
        i. All variables are known to be related to both treatment assignment and the outcome,
        ii. Variables associated with outcome in small samples, or
        iii. Same as ii, but including additional covariates for which the sample is not balanced, after checking of balance.
    b. Select a distance measure, D_{ij}, between individuals *I* and *j*, as per Table 13(193).

Table 13A summary of distance measures for propensity score matching adapted from (193)

Distance measure	Definition
Exact	$D_{ij}=\begin{cases} 0 & \text{if } X_i=X_j \\ \infty & \text{if } X_i \neq X_j, \end{cases}$
Mahalanobis	$D_{ij}=(X_i - X_j)' \sum^{-1} (X_i - X_j).$ If interest is in the average treatment effect on the treated (ATT), Σ is the variance-covariance matrix of X in the full control group; if interest is in the average treatment effect (ATE), then Σ is the variance-covariance matrix of X in the pooled treatment and full control groups. If X contains categorical variables they should be converted to a series of binary indicators, although the distance works best with continuous variables.
Propensity score	$D_{ij}=\lvert e_i - e_j \rvert.$ where e_k is the propensity score for individual k.
Linear propensity score	$D_{ij}=\lvert \text{logit}(e_i) - \text{logit}(e_j) \rvert.$ where e_k is the propensity score for individual k.

2. **Implement a matching method using regression. Several options are available, including;**
    a. Nearest neighbour matching ('greedy matching'): is the easiest to implement and most popular of all matching techniques. This method matches exposed ("treated") group individuals to those in the unexposed group, and discards unexposed individuals who are not selected as matches, i.e., those who are not part of 'common support' (193, 194). Individuals who lie within overlapping ranges of the

propensity score distributions for the two groups are referred to as *common support* (193, 194). The greedy method ensures individuals are matched as closely as possible, sequentially(193, 194). Thus, this method ignores the fact that a match (unexposed) selected at any given stage, may be a better match for an exposed individual considered at a later stage. Two possible algorithms may be used in Greedy matching (193, 194);

i. **Caliper method:** this algorithm requires the specification of the maximum distance, the 'caliper width', between the treated versus controls. A calliper width of 0.2 standard deviations of the logit of the propensity score is commonly used.

ii. **K->1 digit matching:** if k=5 for example, for each exposed person, selecting an unexposed individual who has a similar propensity score within the first five decimal places; if not available, then looking at a match within first four decimals places, and so on.

b. **Optimal matching:** is more appropriate than greedy matching, when the quality of matching of the individual pair is more important than the matching at the group level. Optimal matching takes into account the order in which individuals from treatment group are matched by considering the overall set of matches that minimises a global distance measure (195).

c. **Ratio matching:** is an appropriate method when there are more controls than treated individuals; where more than one control is assigned to each treated individual. Selecting the number of controls per individual involves a bias: variance tradeoff. Bias may increase due to 2nd, 3rd, 4th, or nth matches for each treated individual being further away than the 1st match; but variance may reduce as the power of the sample is increased due to a larger matched cohort (193, 194).

d. **With replacement:** is an appropriate method when there are fewer unexposed than exposed ('treated') individuals. By this method, more than one unexposed individuals may be assigned to each treated individual. This method can decrease bias given controls that look similar to many treated individuals can be selected multiple times, but increase variance due to resulting smaller matched cohort, and make drawing inferences more difficult given unexposed individuals are no longer independent (193, 194).

3. Assessing the quality of the match;

a. Numerical diagnosis;

   i. The standardised difference of means of the propensity score between the treated and untreated populations,

   ii. The difference in proportions of covariates (for categorical variables) or standardised difference in means for continuous variables,

   iii. Hypothesis testing or assessment of p-values for each covariate, although not greatly recommended by some authors (194).

   iv. The ratio of the variances of the propensity scores in the treated and control groups.

   v. For each covariate, the ratio of the variance of the residuals orthogonal to the propensity score in the treated and control groups (193, 194).

b. Graphical diagnosis;

   i. examine the distribution of the propensity scores in the original and matched groups;

   ii. quantile-quantile (QQ) plots for continuous covariates, to compare the empirical distributions of each variable in the treated and control groups. If

the two groups have identical empirical distributions, all points will lie on the 45-degree line.

iii. a plot of the standardised differences of means, to provide a quick overview of whether the balance has improved for individual covariates (193).

4. **Analysis of the outcome and estimation of the treatment effect, given the matching done in Step (3)(193).**

For the economic evaluations reported in Chapter 5 and Chapter 6, comparative treatment groups were identified using the Nearest Neighbour 1:1 matching approach through a caliper adjustment algorithm. The quality of propensity score matching was assessed using numerical and graphical approaches (only the numerical approach is reported).

2.4.2 Emerging propensity score techniques

Other propensity score methods including weighting by the inverse propensity score, propensity-score adjustment, sub-classification, full matching, and the recently introduced, *propensity score bin bootstrap (PSBB)* technique provide alternative approaches to paired matching of propensity scores (193, 194). These methods use the full observational cohort and avoid the loss of sample size that occurs in paired matching techniques, described above (193, 194). These alternative techniques are explained here in brief:

- **Inverse weighing adjustments:** transforms propensity scores into inverse probability weights estimating average treatment effect. Here, weighting serves to weight both the treated and control groups up to the full sample, in the same way, that survey sampling weights a sample up to a population (193, 194).

- **Propensity score adjustment:** is a method of adjustment by regression, where the effect of many confounders is considered by fitting the single propensity score variable alongside the exposure (treatment) variable.
- **Sub-classification:** also known as stratification, involves the formation of groups of individuals who are similar, for example as defined by quintiles of the propensity score distribution. Results are aggregated within quintiles and averaged across the groups to obtain a final estimate on average, for the cohort.
- **Propensity bin bootstrap technique:** is an extension of subclassification and involves the bootstrapping of results within 'bins' or propensity score quintiles generated through subclassification (193, 194).
- **Full matching:** is another extension of sub-classification, where the selected number of quintiles of propensity scores is automated, and can result in more than a handful of stratified groups. Thus, it creates a series of matched sets, which may range from several to several hundred, where each matched set contains, at least, one (or many) treated individual and, at least, one (or many) control individual (193, 194).

The PSBB approach (116) was used in Chapter 6, to validate the results derived from standard Nearest Neighbour 1:1 matching technique.

2.5 Evidence-based approaches for evidence synthesis

2.5.1 Systematic reviews

A systematic review is an approach for gathering and compiling evidence in relation to a specific topic, in a formal, planned, and objective manner, where each step is documented in protocol (194). Systematic reviews are characterised by a methodical search for literature, careful selection of articles, critical appraisal, structured presentation of results, and

reproducibility (194). This thesis includes two systematic reviews: a systematic review *and meta-analyses* to compare the *effectiveness* of CABG versus DES for patients with MVCAD and diabetes in Chapter 3, and a systematic review of *cost-effectiveness* of CABG versus PCI (BMS or DES) for MVCAD in Chapter 4.

2.5.2 Meta-analysis

A meta-analysis is a method of estimating the size of a clinical outcome through pooling data from multiple low-powered or high-powered studies (194). By combining data from different studies, a meta-analysis aims to increase the size of the sample and thereby increase the statistical power of the analysis(194). Systematic reviews may or may not include a meta-analysis, however, together they entail the basic elements of an evidence-based approach towards discernment of treatment effects – systematic reviews of RCTs being ranked the highest form of evidence in modern evidence ranking schemes (see Section 1.5.1). Guidelines for reporting of systematic reviews and meta-analyses are available from several institutions and/ or frameworks, including the Cochrane Collaboration, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) (194, 196, 197). Our meta-analysis in Chapter 3 included published data from RCTs as well as observational studies, pooled separately to yield different size of effects. For RCTs, guidelines as outlined by the Cochrane Collaboration (196) were followed, while for observational studies guidelines prescribed by the MOOSE group were adhered to (198).

Pooled estimates in meta-analyses can be marred by heterogeneity of data included. Heterogeneity in pooled estimates was evaluated using the Cochrane's Q (X^2 test) and I^2 statistics (199). An $I^2 \geq 50\%$ or a significant result from the X^2 test ($p<0.05$) indicated the presence of heterogeneity, which was undesirable in a meta-analysis (199). In meta-analyses with significant heterogeneity, pooled estimates were derived using a random-effects model

(REM), whereas if no significant heterogeneity was present, a fixed-effects model (FEM) was used (199). While it is recommended that meta-analyses investigate potential publication bias through meta-regression, this was not undertaken in Chapter 3 as there were less than 10 included studies for review, a threshold recommended by guidelines for meta-regression (196, 200, 201).

2.5.3 Systematic review of cost-effectiveness

Unlike systematic reviews for comparison of effectiveness, no clear guidelines or framework for the reporting of systematic reviews of *cost-effectiveness* are available to date. Several published systematic reviews comparing the cost-effectiveness of DES and BMS, however, were available at the time of this thesis (74, 75), as well as similar reviews of cost-effectiveness in other therapeutic areas (202, 203). Prior published systematic reviews of cost-effectiveness therefore guided the development of methodology for the systematic review presented in Chapter 4. While all steps relevant to a typical systematic review as outlined Section 2.5.1 were carried out in this Chapter, additional steps were undertaken, including:

1. Adjustment of costs using PPP, as discussed in Section 2.3.7.3.2, in order to convert published ICERs from many countries into a common denominator, US dollars (2014), appropriately inflated and deflated to account for time differences (202).
2. An assessment of quality of economic evaluations was necessary, due to the limited rigor of economic evaluations being published in medical journals (204). The very reason triggered several groups to develop frameworks for reporting of economic evaluations (205, 206), including the prominent 24-item checklist of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS), a statement endorsed by the ISPOR - Health Economic Evaluations Publication Guidelines Task Force (207). In Chapter 4, a scoring system was developed to assess all economic evaluations included in the systematic review against the 24 items recommended in the CHEERS guidelines.

3. Summarising incremental costs and benefits reported in different evaluations in cost-effectiveness planes in addition to tables, for the ease of interpretation of results.

2.6 Regression analysis

Regression models are an important tool in epidemiology. They permit the prediction of outcomes, significance of the effect of a single predictor, and impact of multiple predictors on an outcome (208). The application of regression models can vary from one therapeutic area to another; from the identification of significant biomarkers for metastatic cancer (209) to the analysis of important pre-operative risk factors associated with postoperative complications in cardiac surgery (210). There are several different types of regression models to choose from depending on the nature of the outcome variable in questions shown in Table 14 (208). Outcome variables may range from numerical (e.g., systolic blood pressure) or categorical (e.g., complication versus no complication); to numerical-discrete (i.e., count) or numerical-time variable; and categorical-binary, categorical-ordinal, or categorical-nominal. Also, further extensions to these models have been developed, as shown in Table 14 (211).

Table 14 Types of regression modelling based on nature of the outcome variable

Outcome classification	Outcome type	Regression model	Extensions
Numerical	Continuous	Linear	Generalised linear model
	Count	Poisson	
	Time-to-event	Cox proportional hazards	Stratified proportional hazards Additive hazard models
Categorical	Binary	Logistic	Conditional logistic regression Proportional odds Polytomous logistic
	Ordinal	Ordinal regression a.k.a. proportional odds	
	Nominal	Polytomous logistic	

Sources: (208, 211)

In the last decade, a myriad of research emerged about the development of risk prediction tools in the cardiac surgery setting (210). One such study is included in Appendix H (212). A regression analysis is reported in Chapter 7, investigating the predictors of readmission costs following PCI in a subset of patients with chronic kidney disease (CKD). Further considerations, must be taken into account when considering numerical cost variables in regression analyses.

Healthcare costs can add a layer of complexity for regression models, in the context of risk adjustment, resource allocation, technology assessment and policy evaluation. Typically, cost data is skewed, may have properties of heteroscedasticity (heterogeneous error variance leading to unreliable confidence intervals), may be censored (data may be incomplete or only partially known), and may include zero costs (e.g., if patients did not have any re-hospitalisations) (213). The appropriate regression models that address at least some of these issues are described in Table 15.

Table 15 Models used in cost analyses

	Skewness	Zero-cost	Censoring
Original scale models			
OLS	-	-	-
Tobit/ adjusted Tobit	-	X	-
GLM (gamma, log-gamma)	X	O	-
Transformed outcome variable			
OLS log(c_i +k)	-	O	-
Threshold logit models	X	X	-
Survival models			
Parametric (Weibull)	X	-	X
Semi-parametric (Cox proportional hazard)	X	-	O
Non-parametric additive regression	X	-	X
Mixed models	X	X	X
Weighted regression (187, 188)	X	-	X

Abbreviations: GLM, generalised linear model; OLS, ordinary least squares
Notes: "-", condition not satisfied; "O", conditional partially satisfied; "X", condition satisfied
Sources: Adapted from (213)

Cost analyses using regression models, may be employed to (i) predict mean costs of treating an illness in a clinical setting; (ii) test differences in costs between two or more groups of

patients in experimental settings; or (iii) cost profile in observational settings (213). Our analysis in Chapter 7 matches the first and last categories. There are several limitations to the use of different models described in Table 15. Estimation of the mean cannot be achieved through OLS log(ci+ k) or parametric (Weibull) models, or is only partially satisfied through threshold logit models, and semi-parametric (Cox proportional) models (213). While ordinary least squares (OLS) is a starting point when modelling with costs, it can lead to a violation of the assumptions of normality, independence, and no heteroscedasticity (214, 215). Nonetheless, models using OLS regression can achieve similar results as alternative models, and achieve improved performance with increased sample size (216). In Chapter 7, we used bootstrap OLS regression to investigate the differences in readmission costs between patients with and without CKD. The use of bootstrapping approach accounts for the violation of normality through use of standard OLS regression to estimate coefficients from skewed cost data (217).

2.7 Conclusion

A variety of methods, including economic evaluations, propensity score matching techniques, evidence-based approaches for data synthesis, and regression analyses were utilised in this thesis. An overview of these methods was provided in this chapter. Several statistical software programmes were used in this thesis, including STATA/IC version 11 (Windows, StataCorp LLC), Microsoft Excel (Microsoft Corp), and Ersatz software (EpiGear International), and R version 3.3.2 (Windows). The subsequent chapters' report individual investigations carried out to achieve research objectives of this thesis, and further details on the methods used to address each research objectives.

3 Effectiveness of CABG vs. PCI among high-risk patients in the DES era

3.1 Chapter overview

This chapter aims to synthesise evidence concerning the effectiveness of CABG versus DES in patients with diabetes and multi-vessel CAD (MVCAD) in the medium-term, using published results from RCTs and non-randomised studies. A systematic review and meta-analysis was carried out pooling data from RCTs, and non-randomised individually to understand outcomes from the different study designs. The findings from this review was published in the International Journal of Cardiology.

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Prolonged effectiveness of coronary artery bypass surgery versus drug-eluting stents in diabetics with multi-vessel disease: An updated systematic review and meta-analysis☆,☆☆

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Background: Currently, the appropriateness of percutaneous coronary intervention (PCI) using drug-eluting stents (DES) versus coronary artery bypass grafting (CABG) for patients with diabetes (DM) and multi-vessel disease (MVD) is uncertain due to limited evidence from few randomised controlled trials (RCTs). We aimed to compare the clinical effectiveness of CABG versus PCI-DES in DM-MVD patients using an evidence-based approach.

Methods: A systematic review and meta-analyses were conducted to compare the risk of all-cause mortality, myocardial infarction (MI), repeat revascularisation, cerebrovascular events (CVE), and major adverse cardiac or cerebrovascular events (MACCE).

Results: A total of 1,837 and 3,052 DM-MVD patients were pooled from four RCTs (FREEDOM, SYNTAX, VA CARDS, and CARDia) and five non-randomised studies. At mean follow-up of 3 years, CABG compared with PCI-DES was associated with a lower risk of all-cause mortality and MI in RCTs. By contrast, no significant differences were observed in the mean 3.5-year risk of all-cause mortality and MI in non-randomised trials. However, the risk of repeat revascularisations following PCI-DES compared with CABG was 2.3 (95% CI = 1.8–2.8) and 3.0 (2.3–4.2)-folds higher in RCTs and non-randomised trials, respectively. Accordingly, the risk of MACCE at 3 years following CABG compared with PCI-DES was lower in both RCTs and non-randomised trials [0.65 (: 0.55–0.77); and 0.77 (0.60–0.98), respectively].

Conclusions: Based on our pooled results, we recommend CABG compared with PCI-DES for patients with DM-MVD. Although non-randomised trials suggest no additional survival-, MI-, and CVE- benefit from CABG over PCI-DES, these results should be interpreted with care.

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1. Introduction

Type II diabetes mellitus (DM) is a leading predictor of development of atherosclerosis and a key contributor to the rising burden from cardiovascular disease [1]. Approximately 285 million of world's population are estimated to be living with this condition [Europe: 6.9%; North America: 10.2%; South Asia: 7.6%; Eastern Mediterranean and Middle-East: 9.3%], and this figure is expected to double by 2030 [2]. In particular, patients with co-existing DM and multi-vessel coronary artery disease (MVD) are at higher risk of mortality and morbidity following invasive treatment for coronary artery disease. Globally, the DM-subset alone makes up around 25 per cent of the all patients admitted for coronary revascularisation procedures [3].

Currently, coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) using drug-eluting stents (DES) offer two mechanisms of revascularisation for patients with coronary artery disease. Historically, CABG was known to offer better outcomes compared with PCI in patients with DM and MVD [3–5]. In fact, the BARI trial [6] has been the first study to report a significant survival benefit from

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CABG compared with PCI in diabetic patients in the bare-metal stent (BMS) era. However, a similar effect was not confirmed through large non-randomised registry studies [7]. Accordingly, some guidelines identify DM as an indication for surgery in patients with advanced MVD [8], while others acknowledges the gap in evidence concerning the effectiveness of surgery versus PCI in the drug-eluting stent (DES) era [9,10].

Although the early-generation stents such as BMS carried a high-risk of restenosis, this shortcoming was later ameliorated by the advent of DES, and the introduction of dual-antiplatelet therapy. However, until recently, the evidence base for the effectiveness of CABG versus PCI-DES was limited among DM-MVD patients. Between 2010 and 2013, four randomised controlled trials (RCTs) emerged with evidence on effectiveness of CABG versus PCI using DES in the DM-MVD subset [11–14]. However, two out of the four recent trials were too underpowered to demonstrate effectiveness [12,13]. This study therefore aims to synthesise evidence to compare the clinical effectiveness of CABG versus PCI-DES in the DM-MVD patient subset and the contrast results observed in randomised versus non-randomised trials.

2. Materials and methods

A meta-analysis was undertaken to compare the prolonged effectiveness of CABG versus PCI-DES in DM-MVD patients. Studies that complied with following pre-specified criteria were included: (i) comparative effectiveness studies of CABG versus PCI using DES; (ii) published data adult patients with pre-existing DM and MVD; (iii) all RCTs meeting the above criteria, or prospective observational studies with more than 12-months follow-up; (iv) reported outcomes in one or more of the following clinical end-points: all-cause mortality, myocardial infarction (MI), cerebrovascular events (CVE), repeat revascularisation, or major adverse cardiac or CVE (MACCE); and (v) were published in the English language. We adhered to methods outlined by the Cochrane Collaboration [15] and the guidelines set out by the 'Meta-analysis of Observational Studies in Epidemiology' group [16].

A search strategy was developed to identify all relevant literature meeting the pre-specified criteria. An electronic search for articles published to date (10th March 2013) was conducted in MEDLINE, Embase, PubMed, CINAHL, and the Cochrane databases. Keywords and medical subject headings (MeSH) were used for specific searches. In each database, the MeSH terms "stents" or "angioplasty, transluminal, percutaneous coronary," or "drug-eluting stents" were combined with the MeSH term "myocardial ischaemia". These terms were then combined with MeSH terms "coronary artery bypass" and "diabetes mellitus." The keyword terms corresponding to each of these MeSH terms were also mapped in a similar manner. The search was further refined by searching for the following terms on the title or abstract fields of the retrieved citations: "drug-eluting stents" or "sirolimus-eluting stents" or "paclitaxel-eluting stents"; "bypass" or "surgery" or "revascularisation" or "CABG" or "off-pump.

Following the retrieval of results to a citation manager from each database, duplicates were identified and removed. The abstracts of the remaining records were then systematically screened for relevance by three investigators (TVA, ZA, and CHY). Two investigators (TVA and ZA) participated in the extraction of data including numbers of observed outcomes, sample sizes, and study characteristics from the selected articles. Where there were disagreements in data extraction the investigators met to discuss and resolve issues.

2.1. Statistical analysis

We used both fixed- and random-effects models to analyse aggregate data from selected studies. Where significant study heterogeneity was detected, pooled estimates were derived from the random-effects model (REM). Pooled relative risks (RR) and 95% confidence intervals (CIs) were used to measure the association between clinical end points of interest and type of treatment, CABG or DES. We evaluated heterogeneity by calculating the Cochrane's Q (x^2 test) and I^2 statistics. An I^2 of greater than 50% or significant x^2 test (p b 0.05) was desired. A regression-based test for publication bias was not carried out due to inclusion of less than 10 trials in our study [15,17,18]. Sensitivity analysis was conducted by eliminating one study at a time from the pooled analyses, in order to measure whether any particular study disproportionately influenced the size of effect. Our meta-analysis was carried out using Stata/IC version 11 (Windows).

3. Results

3.1. Study selection

The manner in which we conducted our systematic literature search and study selection is highlighted in Fig. 1 and Appendix 1 (supplementary material). Overall, 222 citations were retrieved from five medical databases to a citation library, where 92 were identified as duplicate records. The remaining 130 citations were then observed for appropriateness for inclusion. By observation of abstracts alone, 30 records were shortlisted for retrieval. Upon retrieval however, 18 studies were excluded for the following reasons: one article was published in Chinese language; one article included patients receiving bare-metal stents (BMS); five articles did not have adequate data on the DM subset; one article included DM-MVD patients with left-main coronary artery disease (LMCAD) exclusively; three articles did not have adequate data specific to the MVD subset; one article investigated patients with single vessel disease only; one article included data from pre-DES era; one article included patients with diabetic retinopathy only; and four studies (non-randomised) conducted 12-month follow-up only. Furthermore, prior studies from the Asan Medical Center (Seoul, Korea) [two] [19] and the Arterial Revascularisation Therapies Study–Part II (ARTS-II) [20] [one] were removed. In the end, we identified nine studies, which included four RCTs [11–14], and five prospective observational reports [19–23] that matched our pre-specified inclusion criteria.

We considered pooled outcomes from 2,393 patients who underwent CABG [880 from RCTs; and 1513 from non-randomised studies] and 2,496 patients who underwent PCI-DES [957 from RCTs; and 1539 from non-randomised studies]. The clinical and demographical characteristics of each study as well as matching criteria are reported in Table 1. Of note, the average length of follow-up in our meta-analysis of observational studies corresponded to 3.5 years [between 24 and 60 months of maximum follow-up], whereas the mean follow-up in our meta-analysis RCTs was 3.0 years [between 12 and 60 months of maximum follow-up].

3.2. Clinical outcomes

We focussed on four clinical end-points (all-cause mortality, MI, repeat revascularisation, and cerebrovascular accident) and two combined events (composite outcome of all-cause mortality, MI, or CVE; and MACCE). The forest plots of these pooled analyses are illustrated in Figs. 2, 3, and 4. The definitions of each end point as described in each individual study are listed in Appendix II (supplementary material). Heterogeneity was not statistically significant for the majority of the above end points analysed (p N 0.05), except the pooled risk for MI and repeat-revascularisation from RCTs (p b 0.05).

3.2.1. Mortality

All included studies reported data on all-cause mortality. A significant survival benefit following CABG compared with PCI was observed in our meta-analysis of RCTs at mean 3.0-year follow-up (RR = 0.62; 95% CI = 0.42 to 0.94). However, we found no significant difference in mortality at mean 3.5 years post-revascularisation in the meta-analysis of non-randomised studies (RR = 1.14; 95% CI = 0.86 to 1.50) (Fig. 2.).

3.2.2. MI

All included RCTs and four non-randomised studies reported data on non-fatal MI. Again, no significant difference was observed among the two revascularisation strategies in the pooled analysis of non-randomised studies at mean follow-up (RR = 1.06; 95% CI = 0.49 to 2.29) (Fig. 2). However, the meta-analysis of RCTs found significantly lower risk of MI in patients who underwent CABG compared with PCI-DES (RR = 0.61; 95% CI = 0.47 to 0.80).

3.2.3. Repeat revascularisation

All included studies reported data on repeat revascularisation. Both non-randomised studies and RCTs demonstrated that CABG was associated with significantly lower risk of repeat revascularisation compared with PCI-DES (RR = 0.33; 95% CI = 0.24 to 0.44, and RR = 0.44; 95% CI = 0.35 and 0.56, respectively) (Fig. 3).

Table 1
Data abstraction from studies selected for pooled analyses of effectiveness of CABG versus PCI-DES in patients with DM-MVD.

Study	Dominguez-Franco et al (2009)	Tarantini et al (2009)	Yamagata et al (2010)	Kim et al (2012)	Onuma et al (2011)	Mack et al (2011)	Farkouh et al (2012)	Kamalesh et al (2013)	Kapur et al (2010)
Country (source of data)	Spain (local prospective hospital database)	Italy (local prospective hospital database)	Japan (local prospective hospital database)	Korea (local prospective hospital database)	USA, Europe, South America; (CABG arm: ARTS-I RCT; PCI arm: ARTS II prospective study)	USA, Europe (SYNTAX)	World-wide (FREEDOM)	USA (VA-CARDS)	USA (CarDia)
Period of recruitment of patients	2000–2004	2004–2005	2004–2006	2003–2005	2003–2009	2005–2007	2005–2010	2006–2010	2002–2007
Follow-up , in months [mean*, or median†]	24 months*	24 months*	42 months*	67 months†	60 months*	36 month*	46 month†	24 months*	12 months*
Proportion of patients with Diabetes (%)	100	100	100	38	21.4	25.1	100	100	100
Type of stent deployed (%)	Rapamycin-eluting or Paclitaxel-eluting DES (41/46)	Sirolimus-eluting or Paclitaxel-eluting DES or both (53/21/6)	Sirolimus-eluting DES (100)	Sirolimus-eluting or Paclitaxel-eluting DES (77/23)	Sirolimus-eluting DES (100)	Paclitaxel-eluting DES (100)	Sirolimus-eluting or Paclitaxel-eluting DES (51/43)	Sirolimus-eluting (100)	Sirolimus-eluting (100)
Type of conduit used, RA/IMA/SVG (%)**	NR/NR/0	13/50/36	46/51/3	NR	NR	NR	NR	NR	NR
Variable (CABG/PCI)									
No. of Diabetic patients	142/128	127/93	116/92	402/489	96/159	221/231	947/953	97/101	254/256
Mean age ± SD	65.3 ± 8/67.5 ± 7	66.5 ± 7.3/65 ± 9.0	70 ± 9/67 ± 7	62.8 ± 8.1/63.5 ± 9.3	63.0/65.0	65.4 ± 9.2§	63.1 ± 9.2/63.2 ± 8.9	62.1 ± 7.4/ 62.7 ± 7.1	63.6 ± 9.1/ 64.3 ± 8.5
Male (%)	65.5/62.5	81.1/81.7	73.0/72.0	68.4/62.2	69.0/67.0	71.0 §	69.5/73.2	99.0/99.0	77.9/70.9
Insulin-dependent Diabetes (%)	32.4/39.8	28.3/33.3	17.0/13.0	18.9/17.6	17.0/18.0	40.3 §	30.9/33.8	47.9/47.5	39.1/36.5
Mean HbA1c (%) ± SD	NR	NR	7.2 ± 1.2/ 6.6 ± 1.2	NR	NR	NR	NR	NR	7.9 ± 1.6/ 7.9 ± 1.4
Mean fasting glucose (mg/dl) ± SD	NR	NR	135 ± 48/ 132 ± 54	NR	NR	N110 in 82.2% §	NR	160.1 ± 58.1/ 157.3 ± 60.9	NR
Current smokers (%)	43.7/39.1	40.2/36.5	78.0/74.0	16.4/23.1	17.0/12.0	15.8 §	16.6/14.8	20.6/27.7	23.2/24.6
Hypertension (%)	59.2/71.1	86.6/90.1	92.0/91.0	64.4/64.0	56.0/80.0	69.9 §	NR	95.7/96.0	80.6/76.6
Hypercholesterolaemia (%)	49.3/43.0	63.8/47.3	84.0/82.0	50.2/21.5	49.0/74.0	81.5 §	NR	NR	87.3/92.9
Previous MI (%)	28.9/49.2	55.9/43.0	63.0/57.0	27.1/7.2	49.0/30.0	32.0 §	25.2/26.0	NR	NR
Previous cerebrovascular accident (%)	12.0/12.5	NR	NR	NR	NR	6.0 §	NR	8.5/6.9	5.6/3.5
Unstable angina (%)	-	19.7/33.3	19.0/22.0	NR	33.0/32.0	29.6 §	NR	NR	NR
Average EF (%)	54.2 ± 14/52.4 ± 13	62.2 ± 13.7/61.9 ± 14	48 ± 10/47 ± 10	54.7 ± 12.2/ 58.3 ± 9.2	60.0/60.0	NR	66.6 ± 10.5/ 65.7 ± 12.1	NR	60.0 ± 12.7/ 59.1 ± 14.4
3-Vessel disease (%)	81.0/57.8	83.5/45.2	97.0/13.0	83.6/47.2	35.0/50.0	71.0 §	84.5/82.3	NR	59.7/64.8
Left-main coronary artery disease (%)	37.3/7.8	0.0/0.0	0.0/0.0	25.6/9.4	NR	29.0 §	NR	NR	NR
Matching criteria ‡	2–5, 7, 9	1, 2, 5, 7, 8, 9	1, 2, 5–7, 9	2, 3, 5, 7, 9	2, 5, 7, 9, 10	2, 3, 4, 5, 7, 9, 10	1, 2, 4, 5, 6, 9, 10	1, 2, 4, 9, 10	1, 2, 4, 5, 6, 7, 9, 10

ARTS II, Arterial Revascularisation Therapies Study–Part II; CABG, coronary artery bypass graft; DES, drug-eluting Stent; EF, ejection fraction; IMA, internal mammary artery; MI, myocardial infarction; PCI, percutaneous coronary intervention; N.R, not reported; RA, radial artery; RCT, randomised controlled trial; SD, standard deviation; SVG, saphenous vein graft.

**% out of total vessels grafted.

§Overall results specific to the diabetic cohort.

‡(1) Included diabetic patients only; (2) multivessel disease; (3) left main coronary artery disease; (4) involvement of left anterior descending artery; (5) no prior revascularisation; (6) included off-pump coronary artery bypass surgery; (7) excluded patients undergoing revascularisation for acute myocardial infarction b1–7 days prior; (8) excluded patients with ejection fraction b30–45% (from information available); (9) investigated N1 outcome of interest; (10) multi-centre study; (11) exclusion criteria not stated.

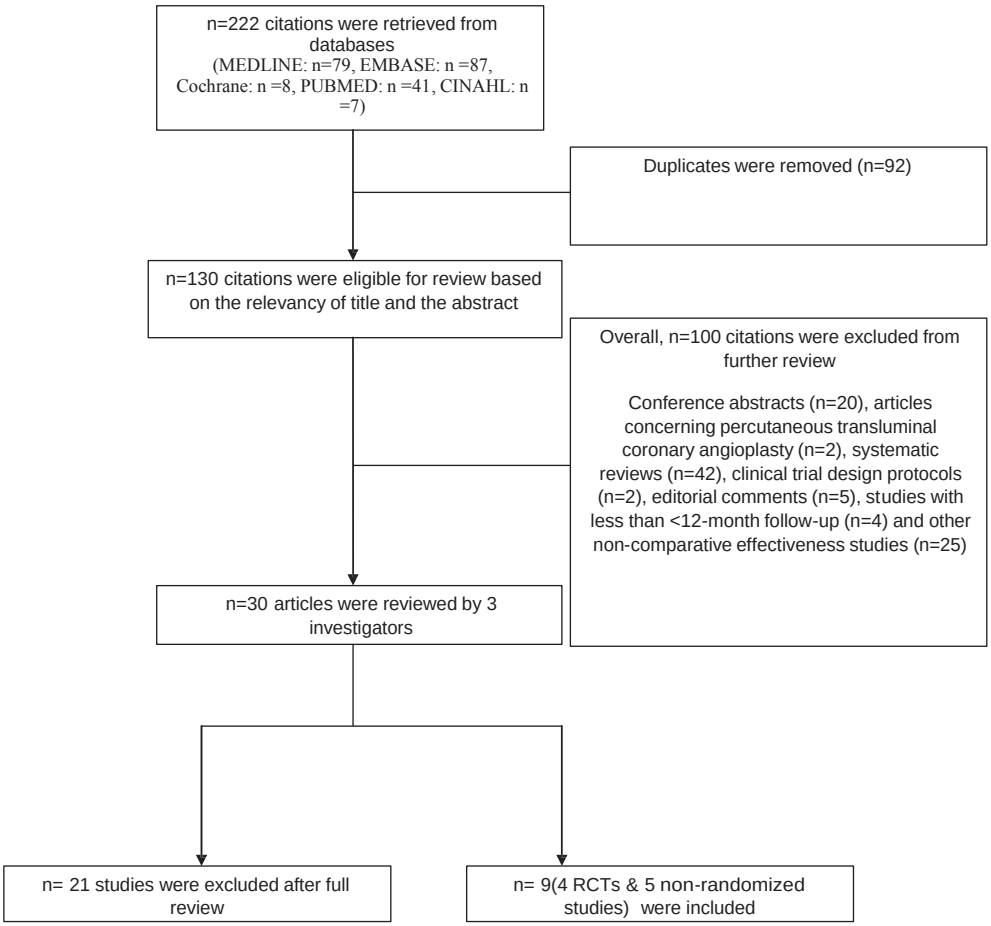

Fig. 1. A flow diagram demonstrating steps involved in our systematic review.

3.2.4. CVE

All but one non-randomised study reported data on CVE. The meta-analysis of non-randomised studies indicated an increased risk of CVE following CABG compared with PCI with marginal significance at mean follow-up (RR = 1.95; 95% CI = 0.96 to 3.98); while the increased risk reached statistical significance in the meta-analysis of RCTs (RR = 1.75; 95% CI = 1.11 to 2.75) (Fig. 3).

3.2.5. Composite outcome of all-cause mortality, MI or CVE

Data on composite outcome were available from two non-randomised studies and three RCTs. The pooled relative risk in non-randomised studies reached marginal significance indicating an increased risk of composite outcome following CABG compared with PCI-DES(RR = 1.27; 95% CI = 0.98 to 1.66) (Fig. 4). However, the meta-analysis of the RCTs found that the risk of the composite event was significantly lower in the CABG group compared with PCI-DES (RR = 0.74; 95% CI = 0.63 and 0.88).

3.2.6. MACCE

Data on MACCE were available from four non-randomised studies and three RCTs. At mean follow-up, pooled relative risks from RCTs and non-randomised studies demonstrated that CABG was associated with a significantly lower risk of MACCE compared with PCI-DES (RR = 0.6; 95% CI = 0.5 to 0.8; and RR = 0.77; 95% CI = 0.60 to 0.98, respectively) (Fig. 4.).

3.3. Sensitivity analysis

Our sensitivity analyses indicated robust results for all-cause mortality and repeat revascularisation. However, the exclusion of the ARTS-II study [20] from the pooled analysis of non-randomised studies for CVE lead to a significant association, considerably favouring PCI-DES rather than CABG at mean follow-up (RR = 3.48; 95% CI = 1.30 to 9.54). The exclusion of the ARTS-II study [20] further lead to an insignificant overall result for MACCE at mean follow-up (RR = 0.89; 95% CI = 0.66 to 1.2).

By contrast, the exclusion of the FREEDOM trial [11] from the meta-analysis of RCTs lead to an insignificant relative risk at mean-follow-up for CVE, as well as MI (RR = 1.94; 95% CI = 0.76 to 4.9; RR = 1.01; 95% CI = 0.43 to 2.39, respectively).

Furthermore, the exclusion of the VA-CARDS [12] trial from the pooled analyses of RCTs for MI and repeat-revascularisation markedly improved the study heterogeneity from point of significance ($p < 0.05$) to insignificance ($p > 0.05$), with no additional impact on the direction of the overall results.

4. Discussion

The present study is the largest meta-analysis to date comparing the long-term effectiveness of CABG versus PCI among individuals with DM and MVD in the DES era. In particular, using a judicious selection process, we cumulated data from randomised and non-randomised studies in an attempt (1) to compare the clinical effectiveness of CABG versus

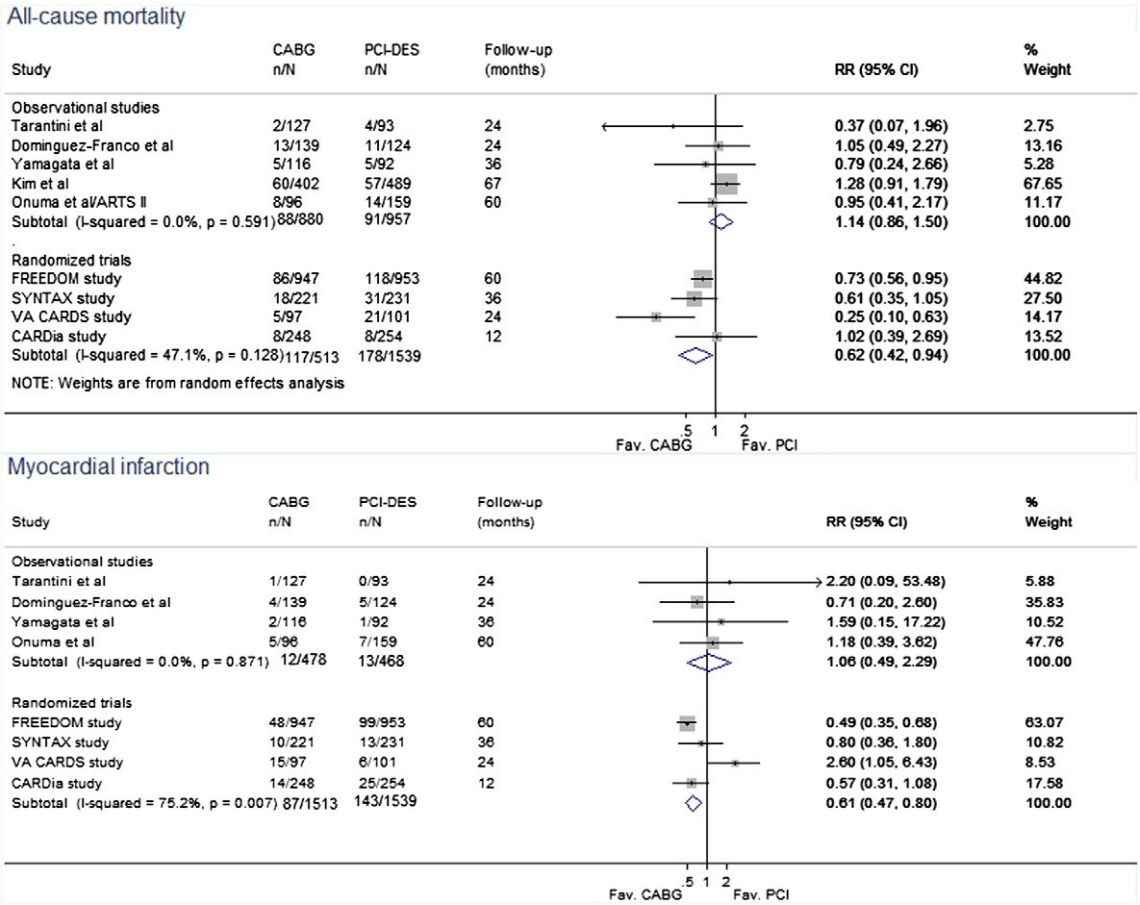

Fig. 2. Forest plots demonstrating pooled analyses of all-cause mortality and MI by non-randomised and randomised studies.

PCI-DES in DM patients with MVD and (2) to scrutinise the discrepancies in results observed from meta-analyses of RCTs and non-randomised trials

Few meta-analyses to-date have explored the performance of CABG versus PCI-DES in the DM-MVD subset. Using data of 24,218 patients from observational cohorts, Benedetto and colleagues [24] concluded that the rate of MACCE continues to be higher following PCI-DES when compared with CABG among patients with MVD. The authors convey that a comparable result was observed in a smaller subset of DM-MVD patients from two observational cohorts. The meta-analyses by Takagi et al. [25] and Bravata et al. [26] confirmed similar trends in the MVD cohort at longer-term follow-up, although the PCI group in the former study was limited to BMS. More recently, Lee and colleagues [27] evaluated the performance in the DM-MVD cohort and reported a favourable MACCE rate following CABG compared with PCI-DES at 1.5 year follow-up. However, the latter study was limited by the length of follow-up and the absence of data from RCTs.

Our meta-analysis of RCTs (1513 in CABG arm; and 1539 in PCI arm) demonstrated a significant 3.0-year survival advantage following CABG compared with PCI-DES in the DM-MVD subset. However, our meta-analysis of non-randomised studies (880 in CABG arm; 957 in PCI) demonstrated no significant difference between the strategies at mean follow-up of 3.5 years. The meta-analysis by Lee et al. [27] also found no significant difference in mortality between CABG and PCI-DES at mean follow-up of 1.5 years.

Surgical revascularisation in particular has the capacity to revascularise all ischemic territories and reduce progression of atherosclerosis beyond the flow-limiting epicardial coronary segments treated; as a result, CABG has often fared favourably in historical comparisons of effectiveness of surgery versus PCI [28]. However, the introduction of anti-stenotic DES in the early part of the last decade has sparked interest in the re-evaluation of the effectiveness of the two revascularization modalities in high-risk sub-groups [29,30].

Our meta-analysis of observational studies, again demonstrated no significant difference between the procedures for the risk of non-fatal MI at mean follow-up 3.5 years in patients with DM and MVD. Lee et al. [27] also made a similar observation with a meta-analysis of 1543 DM-MVD patients from five observational studiesat mean follow-up of 1.5 years. By contrast, our meta-analysis of RCTs demonstrated a higher risk of non-fatal MI in the PCI-DES group compared to CABG, further calling into question our findings from the observational registry studies.

The long-term prognosis of patients undergoing coronary revascularisation is further influenced by events such as stroke or other CVE. Our meta-analysis of RCTs demonstrated a significant benefit from PCI-DES compared with CABG at reducing long-term risk of CVE in DM-MVD patients. However, given CABG has been historically associated with a higher rate of stroke in the perioperative period, our result may be more representative of an outcome observed at shorter-term rather than longer-term follow-up. Due to the lack data reported on perioperative outcomes in the included studies, we were unable to meaningfully adjust for the latter effect. The pooled outcome for CVE from our meta-analysis of non-randomised studies by comparison reached marginal significance. Similarly, Lee et al. [27] reported a higher risk of CVE in the CABG group compared with PCI-DES at mean follow-up of 1.5 years.

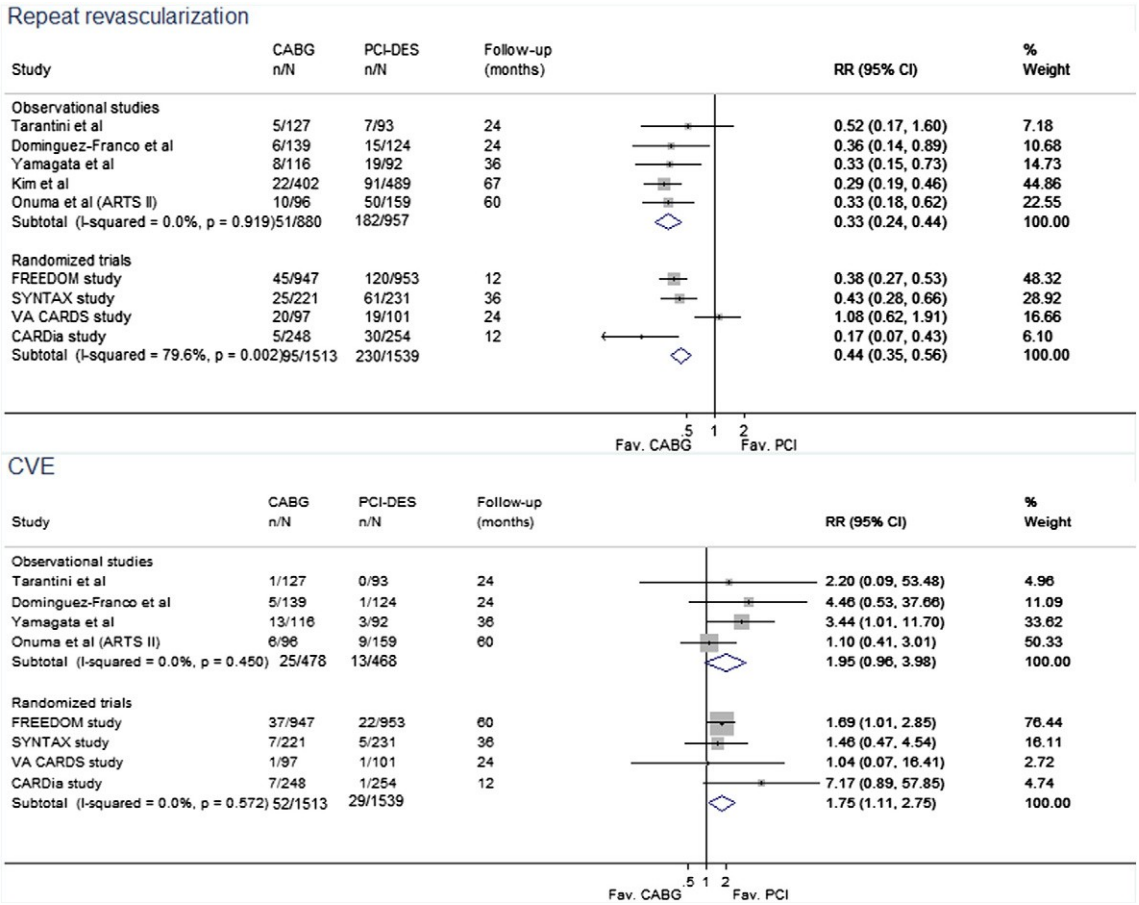

Fig. 3. Forest plots demonstrating pooled analyses of repeat revascularisation and CVE by non-randomised and randomised studies.

Despite the steady rise in use of PCI and its advancements over the past two decades, restenosis remains the Achilles' heel of coronary stenting. At the same time, outcomes in surgical revascularisation observed marked improvement due to advances in CABG, and the increasing use of multiple arterial grafts. In fact, our results demonstrate two and three fold rise in risk of repeat procedures following PCI-DES compared with CABG from our pooled analysis of RCTs and non-ranosmised studies. Of note, the combined risk of mortality, MI or CVE, which excludes the effect of repeat revascularistion showed no significant difference between the two procedures following 3 years. Lee eta al. [27] also observed a similar result in their meta-analysis of non-randomised studies at mean 1.5 years.

A number of reasons may be contributing to the discrepancies observed in our meta-analysis of RCTs and observational studies. Often, RCTs are undertaken in circumscribed populations that are not representative of the general population [31]. For instance, the VA-CARDS trial [12] comprised high-risk DM-MVD candidates who were predominantly male, elderly, and had worse heart and kidney function. Such patients are at higher risk of worse outcome through CABG compared with PCI-DES. Fifty percent or more diabetic patients undergoing revascularisation through CABG may have any number of complications such as repeat thoracotomy for bleeding, postoperative pneumonia, permanentpacemaker implantation, pleural effusions, renal failure requiring hemodialysis, atrial fibrillation, and ventricular tachycardia or ventricular fibrillation [32]. This estimate may be even higher among very high risk individuals who were enrolled in the VA-CARDS cohort. However, as the VA-CARDS cohort was small relative to our pooled randomised population (198/3052), the likely impact of this subgroup on our overall findings for RCTs may be minimal.

Several limitations in the present study must be carefully addressed. For instance, potential biases in the original non-randomised studies may render the calculation of a single summary estimate of effect of exposure (e.g. relative risk) potentially misleading [16]. Particularly, the choice of revascularisation strategy in physician-controlled studies is often determined by angiographic features, including the extent, location, nature of coronary disease, and the patient's predisposition towards one treatment over the other. Additionally, the decision for DES in certain cases may be influenced by the urgency of treatment (e.g., post-infarct patients), resource allocation decisions, and the focal nature of the disease. By contrast, revascularisation through surgery compared with PCI is traditionally favoured for patients with complex lesions such as LMCAD.

Importantly, access to patient-level data was limited; as such, the present study could not perform risk-adjustment of outcomes to account for difference in pre-procedural risk. Both RCTs and non-randomised registry studies may be prone to selection bias, as discussed above, which may lead to conflicting results. Moreover, the FREEDOM trial [11] may have unfairly influenced our pooled analyses due to robustness of the data included. Additionally, trials such as ARTS-II [20] were limited by the inclusion of non-concurrent data (i.e., patients who had undergone CABG from a previous era), while CarDia [13] included a small percentage of patients with single-vessel disease, respectively. However, our final results were robust against the exclusion of these trials from our pooled analysis of RCTs. Furthermore, the cumulative analysis of patient outcomes from several

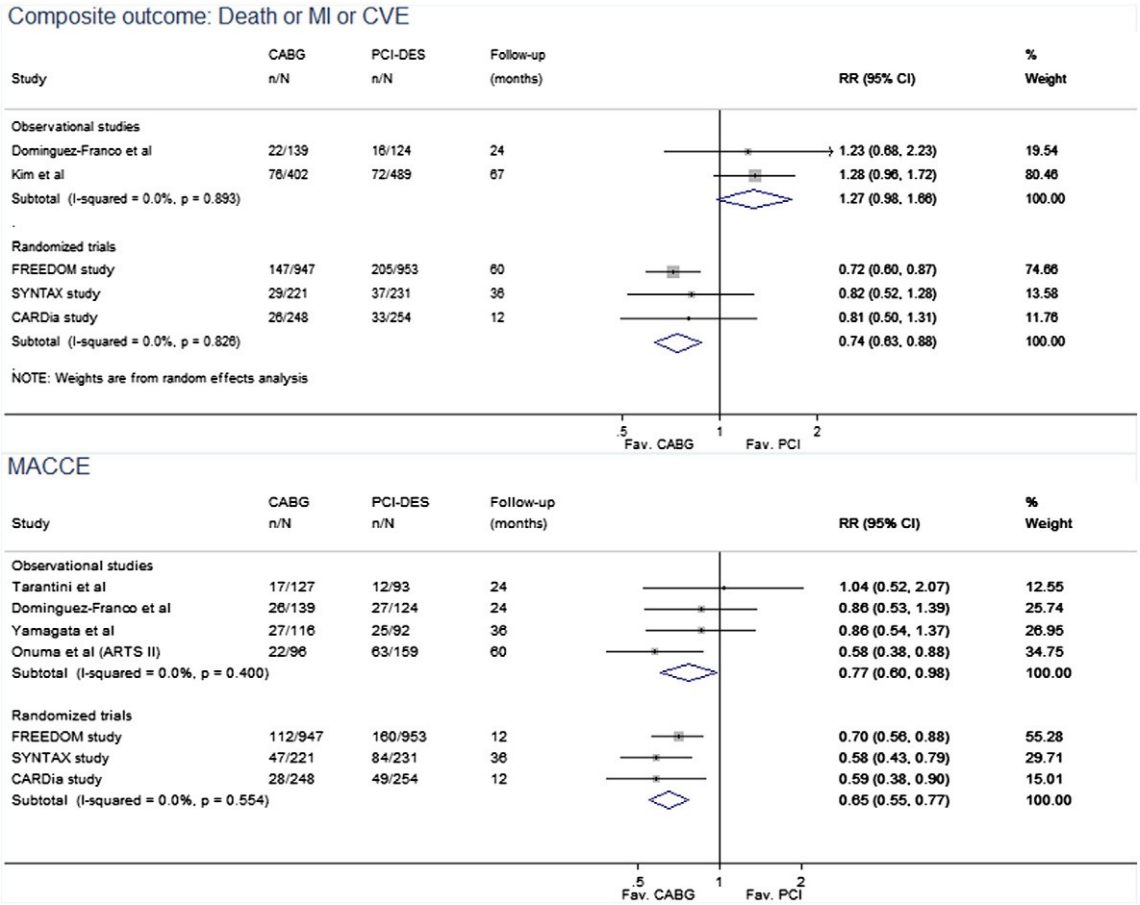

Fig. 4. Forest plots demonstrating the pooled analyses of composite outcome and MACCE by non-randomised and randomised studies.

studies may help enhance the statistical power. External validity of our meta-analysis is also improved through the availability of a larger pool of patients from a variety of observational clinical settings.

In conclusion, the present study provides concurrent evidence on the prolonged effectiveness of CABG versus PCI-DES in the DM- MVD subset. As expected, CABG was unambiguously associated with significantly lower risk of MACCE at mean 3-year follow-up. Although CABG appeared to have no survival, MI, and CVE benefit over PCI-DES at mean 3.5 years in our pooled analysis of non-randomised studies, these results should be interpreted with care.

Conflict of interest

The authors declare that there are no conflicts of interest.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2014.06.072.

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Supplementary Material

Appendix I: This table highlights our systematic literature search strategy in detail including the number of citations retrieved from five medical databases. The search was performed on 10th March 2013.

Database	Search	Queries	Hits
EMBASE	#1	'myocardial ischemia'/exp OR 'myocardial ischemia' OR (myocardial AND isch?m*) OR (myocardial AND infarct*) OR coronary NEAR/1 diseas* OR (disease NEAR/2 arter*):lnk,ab,ti	443,453
	#2	'stents'/exp OR 'stents' OR stent* OR 'angioplasty, transluminal, percutaneous' OR (percutaneous NEAR/2 coronary):lnk,ab,ti	109,545
	#3	#1 AND #2	41,451
	#4	'coronary artery bypass'/exp OR 'coronary artery bypass' OR coronary NEAR/4 bypass* OR (coronary:lnk,ab,ti AND bypass:lnk,ab,ti)	87,829
	#5	#3 AND #4	12,500
	#6	'diabetes mellitus'/exp OR diabet*	629,811
	#7	#5 AND #6	2,160
	#8	percut*:ti OR stent*:ti OR ('drug'/exp OR drug AND elu*:ti) OR pci*:ti OR des*:ti OR bms*:ti	736,410
	#9	by?pass*:ti OR cabg*:ti OR surg*:ti OR (off AND pum*:ti)	511,550
	#10	?eluting*:ti OR ('drug'/exp OR drug AND elu*:ti) OR ?eluting*:ab OR ('drug'/exp OR drug AND elu*:ab)	156,093
	#11	#7 AND #8 AND #9 AND #10	53
	#12	#11 AND [english]/lim	47

Medline	#1	exp Myocardial Ischemia/ or myocardial isch?em*.mp. or myocardial infarct*.mp. or (coronary adj1 diseas*).mp. or (disease adj2 arter*).mp.	376,932
	#2	exp Stents/ or stent*.mp. or exp Angioplasty, Transluminal, Percutaneous Coronary/ or (percutaneous adj2 coronary).mp.	80,438
	#3	#1 AND #2	38,990
	#4	exp Coronary Artery Bypass/ or (coronary adj4 bypass*).mp. or CABG*.ti. or CABG*.ab. or surgery*.ti. or surgery*.ab. or bypass*.ti. or bypass*.ab.	691,987
	#5	#3 AND #4	10,118
	#6	diabetes.mp. or exp Diabetes Mellitus/	356,214
	#7	#5 AND #6	1,107
	#8	(?eluting* or drug-elu*).ti. or ?eluting*.ab. or drug-elu*.ab.	9,749
	#9	(by?pass* or CABG* or surg* or off-pum* or revascu*).ti.	440,997
	#10	#7 AND #8 AND #9	81
	#11	Limit #10 to English language	71
Cochrane	#1	MeSH descriptor Myocardial Ischemia explode all trees	19,423
	#2	(myocardial isch?m*):ti,ab,kw	11,775
	#3	(myocardial infarct*):ti,ab,kw	11,790
	#4	(coronary NEAR/1 diseas*):ti,ab,kw	11,768

#5	(coronary NEAR/1 diseas*):ti,ab,kw	11,768
#6	(disease NEAR/2 arter*):ti,ab,kw	11,774
#7	(#1 OR #2 OR #3 OR #4 OR #5)	30,943
#8	MeSH descriptor Stents explode all trees	2,831
#9	(stent*):ti,ab,kw	11,759
#10	MeSH descriptor Angioplasty, Transluminal, Percutaneous Coronary explode all trees	3,031
#11	(percutaneous NEAR/2 coronary):ti,ab,kw	11,756
#12	(#7 OR #8 OR #9 OR #10)	16,513
#13	MeSH descriptor Coronary Artery Bypass explode all trees	4,504
#14	(coronary NEAR/4 bypass*):ti,ab,kw	11,767
#15	(coronary):ti,ab	9,565
#16	(bypass):ti,ab	9,551
#17	(#15 AND #16)	9,528
#18	(#13 OR #14 OR #17)	16,216
#19	(#12 AND #18)	12,242
#20	(stent* or percut* or drug-elu* or pci* or des* or bms*):ti	15,148
#21	(by?pass* or CABG* or surg* or off-pum*):ti	27,666
#22	(#19 AND #20 AND #21)	83
#23	(?eluting* or drug-elu*):ti or (?eluting* or drug-elu*):ab	514
#24	(#22 AND #23)	12
#25	MeSH descriptor Diabetes Mellitus explode all trees	13,412

	#26	(diabet*):ti,ab,kw	23,907
	#27	(#25 OR #26)	23,934
	#28	(#19 AND #27)	485
	#29	(by?pass* or CABG* or revascu* or surg* or off-pum*):ti	28,431
	#30	(#23 AND #28 AND #29)	7
CINAHL	#1	MM "Coronary Artery Bypass+"	54,752
	#2	MM "Diabetes Mellitus+"	4,736
	#3	"Angioplasty, Transluminal, Percutaneous Coronary"	6,485
	#4	(MM "Drug-Eluting Stents") OR (MM "Stents+")	6,364
	#5	S3 or S4	11,460
	#6	myocardial ischaemia	330
	#7	(MM "Myocardial Ischemia+")	39,345
	#8	S6 or S7	39,441
	#9	S1 and S2 and S5 and S8	32
PUBMED	#1	((((angioplasty[MeSH Terms]) OR (stents[MeSH Terms])) AND (myocardial ischemia[MeSH Terms]) AND (Coronary Artery Bypass[MeSH Terms])) AND ("Diabetes Mellitus"[Mesh]) AND (by?pass*[Title] OR CABG*[Title] OR surger*[Title] OR revascu*[Title] OR surgic*[Title] OR off-pum*[Title]) AND	32

(eluting*[Title/Abstract] OR drug-elu*[Title/Abstract] OR

DES[Title/Abstract])

Appendix II: This table highlights the definitions of end-points as per each study included in our meta-analysis.

Definitions of end-points	**Dominguez-Franco et al (2009)**	**Tarantini et al (2009)**	**Yamagata et al (2010)**	**Kim et al (2012)**	**Onuma et al (2011)**	**Mack et al (2011)**	**Farkouh et al (2012)**	**Kamalesh et al (2013)**	**Kapur et al (2010)**
Mortality	Death from any cause	-	Death from any cause	Death from any cause	Death from any cause	Death from any cause	Death from any cause	Death from any cause	Death from any cause
Myocardial infarction	Non-fatal MI, defined as at least two of : chest pain, development of Q waves in at least 2 contiguous leads of a surface electrocardiogram, and increased creatine to at least twice the normal laboratory range.	Non-fatal MI defined as elevation of serum creatine kinase MB isoenzyme five times the upper limit of the normal level in absence of pathological Q waves	Presence of 2 or more of the following: (1) typical chest pain >20 min not relieved by nitroglycerin, (2) serial ECG recordings showing changes from baseline in the ST-T and/or Q-waves in 2 or more contiguous leads, (3) total serum creatine phosphokinase greater than twice the upper limit of normal.	New pathologic Q waves after index treatment or follow-up MI requiring subsequent hospitalizations (i.e., emergency admission with a principal diagnosis of MI)	Within 7 days after the intervention, a diagnosis of MI was made if new abnormal Q waves and either a ratio of serum creatine kinase-myocardial band isoenzyme/total cardiac enzyme that was >0.1 or a creatine kinase-myocardial band value that was 5x the upper limit of normal were present. Beginning 8 days after the intervention,either abnormal Q waves or enzymatic changes were	The finding of a Q-wave either new, abnormal and 1 ratio of peak creatine kinase MB /peak total CK N of 10% (>10% if during 7-days post-intervention) or new, abnormal Q-waves and 1 plasma level of CK-MB 5x upper limit for normal.	Presence of new Q waves in 2 or more contiguous leads on electrocardiography, as compared with baseline. Following the first 30 days after any revascularization procedure, myocardial infarction was defined as either a typical increase in the troponin level or a more rapid rise and fall in the MB fraction of creatine kinase (CK-	A five-fold increase in creatine phosphokinase-MB plus diagnostic new Q waves on electrocardiography. During follow-up, new MIs were defined as either clinical (typical history with diagnostic electrocardiography changes and/or enzyme elevations) or silent (diagnostic changes on serial electrocardiograms or new fixed defect ≥20% of the myocardium on nuclear studies).	First 7 days post-revascularization, one or more of: CK or CKMB >3x ULN; Tn (T or I) >1 (units); ECG new Q waves. After first 7 days, at least 2 of: raised enzymes (CK/CKMB >x2 ULN or Troponin T or I >1); new

					sufficient for a diagnosis of MI.		MB) with the presence of one or more of the following factors: ischemic symptoms, development of pathologic Q waves on electrocardio graphy, changes indicative of ischemia on electrocardio graphy, he need for repeated coronary-artery intervention, or pathologic findings of an acute myocardial infarction.		Q waves on ECG; clinical evidence of ischemic symptom s
Repeat revasculariz ation	-	-	Repeat PCI or CABG performed because of restenosis or a new stenotic lesion in the target or non-target vessel.	Target vessel revascularizat ion regardless of whether the procedure was clinically or angiographica lly driven and nontarget-vessel	All repeat revascularizatio n procedures were recorded	Any PCI procedure or CABG surgery determined by the patient's physician to be clinically indicated and occurring after the index	Any PCI procedure or CABG surgery determined by the patient's physician to be clinically indicated and occurring after the index	-	-

				revascularization		revascularization procedure its indication	revascularization procedure. All stages of a staged index PCI procedure (as defined) will be considered part of the index revascularization procedure and not a repeated revascularization.		
Cerebrovascular event	-	Stroke, transient ischemic attacks, and reversible ischemic neurological signs	Stroke, transient ischemic attack or reversible ischemic neurological deficits as determined by a neurologist and confirmed by imaging modalities.	Neurologic deficits, as confirmed by a neurologist based on imaging studies	Stroke, transient ischemic attacks, and reversible ischemic neurologic deficits.	Any acute event related to the impairment of the cerebral circulation that lasts more than 24 hours and results in irreversible brain damage or permanent body impairment, as confirmed by a neurologist based on imaging studies.	Focal neurologic deficit of central origin lasting more than 72 hours or lasting more than 24 hours with imaging evidence of cerebral infarction or intracerebral hemorrhage, a nonfocal encephalopathy lasting more than 24 hours with imaging evidence of	-	Neurological signs/symptoms suspected to be of vascular origin that persist for >24 hours with a neurological imaging study that does not indicate a

							cerebral infarction or hemorrhage adequate to account for the clinical state, or retinal arterial ischemia or hemorrhage.		different etiology

4 Cost-effectiveness of CABG vs. PCI among high-risk patients in the DES era

4.1 Chapter overview

The objective of this chapter is to systematically compare and synthesise economic evidence of the cost-effectiveness of CABG compared with PCI for MVCAD. Given the limited number of published economic evaluations in the DES-era, this review was extended to include evaluations from the BMS era, and those that included off-pump CABG. The quality of each economic evaluation was scrutinised against a recent checklist (CHEERS) developed for reporting of health economic evaluations. The results from this review was published in the European Heart Journal – Quality of Care and Clinical Outcomes. As far as we are aware, this is the first published *systematic review* of its kind reporting the cost-effectiveness of CABG versus PCI for MVCAD.

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ORIGINAL ARTICLE

A systematic review of cost-effectiveness of percutaneous coronary intervention vs. surgery for the treatment of multivessel coronary artery disease in the drug-eluting stent era

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Aims The suitability of percutaneous coronary intervention (PCI), compared with coronary artery bypass grafting (CABG), for patients with complex multivessel coronary artery disease (MVCAD) remains a contentious topic. While the body of evidence regarding the clinical effectiveness of these revascularization strategies is growing, there is limited evidence concerning their long-term cost-effectiveness. We aim to critically appraise the body of literature investigating the cost-effectiveness of CABG compared with PCI using stents, and to assess the quality of the economic evidence available.

Methods and results A systematic review was performed across six electronic databases; Medline, Embase, the NHS Economic Evaluation Database, the Database of Abstracts of Reviews of Effects, the health technology assessment database, and the Cochrane Library. All studies comparing economic attractiveness of CABG vs. PCI using bare-metal stents (BMS) or drug-eluting stents (DES) in balanced groups of patients were considered. Sixteen studies were included. These comprised studies of conventional CABG vs. BMS (n ¼ 8), or DES (n ¼ 4); off-pump CABG vs. BMS (n ¼ 2), or DES (n ¼ 1); and minimally invasive direct CABG vs. BMS (n ¼ 2). The majority adopted a healthcare payer perspective (n ¼ 14). The incremental cost-effectiveness ratios (ICERs) reported across studies varied widely according to perspective and time horizon. Favourable lifetime ICERs were reported for CABG in three trials. For patients with left main coronary artery disease, however, DES was reported as the dominant (more effective and cost-saving) strategy in one study.

Conclusion Overall, CABG rather than PCI was the favoured cost-effective treatment for complex MVCAD in the long term. While the evidence base for the cost-effectiveness of DES compared with CABG is growing, there is a need for more evaluations adopting a societal perspective, and time horizons of a lifetime or 10 or more years.

Keywords Coronary artery bypass grafting (CABG) † Cost-effectiveness analysis † Drug-eluting stents (DES) † Systematic review † Health technology assessment † Percutaneous coronary intervention (PCI)

Introduction

Coronary artery disease (CAD) continues to impact the global burden of disease, with prevalence rates varying greatly from one region to another.[1] CAD leads to high complication rates, including mortality, resulting in poor quality of life, and high expenditure.[2] In the USA, the hospital utilization expenditures associated with managing and treating CAD was estimated at $100.00 billion or greater per year.[3] Currently, healthcare systems are becoming resource-scarce and, as a result, economic parameters such as cost-effectiveness and affordability are increasingly influencing clinical decisions.[4]

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In contemporary clinical practice, coronary artery bypass grafting (CABG) is recommended for treatment of complex patients, including those with multivessel coronary artery disease (MVCAD), while percutaneous coronary intervention (PCI) is preferred in patients with single-vessel disease or acute myocardial infarction (MI).[5–7] Technological advancement in PCI, such as the introduction drug-eluting stents (DES) in the past decade, however, revived the debate of whether PCI is appropriate for patients with complex multivessel disease, leading to several randomized clinical trials (RCTs) investigating the clinical and cost-effectiveness of CABG compared with PCI with DES.[5,8,9] Recent trials also showed that compared with bare-metal stents (BMS), DES were associated with significantly higher restenosis rates, higher initial procedural costs, small but significant risk of very late stent thrombosis, and similar mortality rates.[7,10–12]

From a health economic perspective, the selection of one strategy based on efficacy alone, may not be adequate, when two or more alternative treatments may be eligible for a group of patients. Decision makers may seek valid, contextual information related to costs and non-clinical consequences of treatment strategies. The use of a metric for assessment of value recommendations based on resource utilization, independent of a metric for assessment of clinical evidence, was recommended recently.[13] Nonetheless, when evaluating health economic analyses, there may be several challenges presented, given differing methodologies, quality of evidence, and temporal and regional dynamics of resource use.[13]

Published evidence of cost-effectiveness may be used by both governmental and non-governmental organizations, including the private sector, to increase funding for treatment of disease in hospitals, manufacture of devices, or to increase the pool of patients for whom treatment is covered by private or public insurance. Alternatively, published evidence may be used by healthcare professionals to make informed decisions in clinical practice, or to support their patients make informed decisions in the long term. The aim of this article is, therefore, to systematically review the published evidence of cost-effectiveness of CABG vs. PCI and to evaluate the quality of the current published evidence.[14]

Methods

A systematic review was conducted to gather all economic evidence comparing CABG vs. PCI using stents for the treatment of CAD and published in English. The PRISMA guidelines for systematic reviews were followed.[15] All types of economic evaluations were considered, including cost-effectiveness analyses (CEAs), cost-utility analyses (CUAs), cost-benefit analyses (CBAs), and cost-minimization analyses (CMAs) (see Box 1 for definitions).[16] Economic evaluations conducted alongside randomized controlled trials (RCTs) were considered. Additionally, non-randomized observational studies were included if treatment arms were matched for selection criteria. Studies that did not randomize patients into treatment arms, or matched treatment groups based on certain criteria, were excluded. All types of CABG were considered,

Box 1 Definitions of common terms used in health economic evaluations[16]

Base-case:
The results obtained from primary model inputs are referred to as 'base-case'. These results are typically contrasted to results obtained from sensitivity analyses.

Cost-benefit analysis (CBA):
A CBA is a type of economic evaluation that compares costs and consequences (effectiveness) of a treatment and its comparator, in monetary terms. Therefore, a monetary value may be assigned to the effectiveness measure, for example, a life year gained.

Cost-effectiveness analysis (CEA):
A CEA has two components: costs and consequences (effectiveness). In CEAs, effectiveness is typically measured in natural units [e.g. survival and repeat target vessel revascularisatons (TVR)].
A CEA calculates the ICER for a treatment that can be interpreted as 'incremental costs per life years gained' or 'incremental cost per TVR avoided'.

Cost-effectiveness plane (CEP):
A CEP plots incremental effectiveness of an intervention against incremental costs. The CEP is divided in to four quadrants. The North West and South West quadrants represent strategies that are 'less effective and more costly' and 'less effective and less costly', respectively. The North East and South East quadrants represent strategies that are 'more effective and more costly' and 'more effective and less costly', respectively. New strategies more commonly fall into the North East quadrant. Interventions that fall into the South East quadrant are regarded as 'dominant'.

Cost-minimization analysis (CMA):
A CMA only has one component, the cost component, as it assumes no difference in effectiveness between the new and the comparator treatments.

Cost-utility analysis (CUA):
Similar to CEAs, a CUA has two components: costs and consequences (effectiveness). In CUAs, the primary measure of effectiveness is the quality of life years (QALYs). The ICER is interpreted as the 'incremental cost per QALY gained'.

Deterministic or one-way sensitivity analysis:
An analysis sensitivity of findings to a model assumption or single-model input.

Dominant:
New treatments are considered 'dominant' if they corresponded to both gains in effectiveness and cost savings (lower costs), compared with the comparator treatment. If the new treatment is 'dominant', then the comparator treatment is dominated. Dominant treatments give rise to negative ICERs, which are not usually reported in health economic evaluations.

Incremental costs effectiveness ratios (ICERs):
ICERs are calculated in CEA and CUA. An ICER is defined as the differences in costs between a new treatment and a comparator treatment (numerator) divided by the differences in their effectiveness (denominator). An ICER is typically compared against a specific threshold, e.g. $50 000. An ICER lower than the prescribed threshold implies a favourable result for the intervention in question. The WHO defines this threshold as three times the GDP per capita of a country.

Probabilistic sensitivity analyses (PSAs):
A PSA investigates the joint uncertainty of multiple model parameters, using mathematical distributions for uncertainty around each model input, and Monte Carlo microsimulation. Results obtained from PSAs are typically presented in cost-effectiveness acceptability curves, also referred to as willingness-to-pay (WTP) curves or in cost-effectiveness planes.

including conventional CABG, off-pump CABG (OPCAB), and minimally invasive direct CABG (MIDCAB). For the alternative arm, only studies that considered PCI using either DES or BMS were included, to reflect current clinical practice.

Search strategy, data extraction, and management

The literature was identified from six electronic medical databases: Medline, Embase, the NHS Economic Evaluation Database, the Database of Abstracts of Reviews of Effects, the health technology assessment database, and the Cochrane Library. The search strategy and MeSH terms used for each database are described in Supplementary material online, AppendixS1. The first search was performed on 31 January 2015 and was updated on 22 June 2015. Two co-authors (T.V.A. and C.H.Y.) independently screened all citations and abstracts for relevance. The reviewers also solved any disagreement for study inclusion by arbitration and/or by a third reviewer (Z.A.). Full-text retrieval was performed for studies that met all pre-specified inclusion criteria.

To perform meaningful comparisons of economic evaluations, incremental cost-effectiveness ratios (ICERs) were expressed in US dollars (2014). Conversions were performed using purchasing power parity (PPP).[17] Exchange rates were derived from an OECD dataset for each included country and a series report on the consumer price index from the USA for the period of 1995–2014.[18,19]

The cost-effectiveness results from included studies were presented in bar plots and cost-effectiveness planes (CEPs). CEPs encompass four quadrants: North West, South West, South East, and North East, which represents strategies that are 'less effective and more costly', 'less effective and less costly', 'more effective and less costly', and 'more effective and more costly', respectively. The strategies that were 'more effective and less costly' were considered 'dominant' when compared with the comparator, while interventions that were 'less effective and more costly' were 'dominated' by the comparator.

Assessment of quality

The selected studies were assessed for quality by two authors (T.V.A. and C.H.Y.). Quality assessments were made against a 24-item checklist of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS), a statement endorsed by the ISPOR Health Economic Evaluations Publication Guidelines Task Force.[20] A scoring system was developed to grade each study against each item of the checklist.[18]

Results

Study selection

A total of 440 citations were identified from electronic medical databases. Figure 1 illustrates the article selection process. Eleven articles were excluded during the full-text review process as two were inaccessible,[21,22] two were commentary pieces rather than original work,[23,24] and six were excluded due to not balancing patient characteristics between CABG and PCI treatment groups.[25–30] One article was excluded as it was a budget impact analysis rather than a CEA.[31] The remaining 16 articles fulfilled the inclusion criteria and were included in this systematic review.[32–47] Reference tables of results are available in Appendix II (see the Supplementary material online), as an extension to information summarized here.

Overview of populations

An overview of the population characteristics and demographics of the included studies is provided in Supplementary material online, Table S2–I. Of 16 studies, 6 were from the USA,[32,33,37,38,44,46] 3 from the UK,[34,38,40] 3 from the Netherlands,[42,44,45] 1 from Canada,[35] and 1 each from Iran,[47] Brazil,[36] and Armenia.[41] As shown in Supplementary material online, Table S2–I, however, several trials included observations from multinational sites.[46,45,44,43,34]

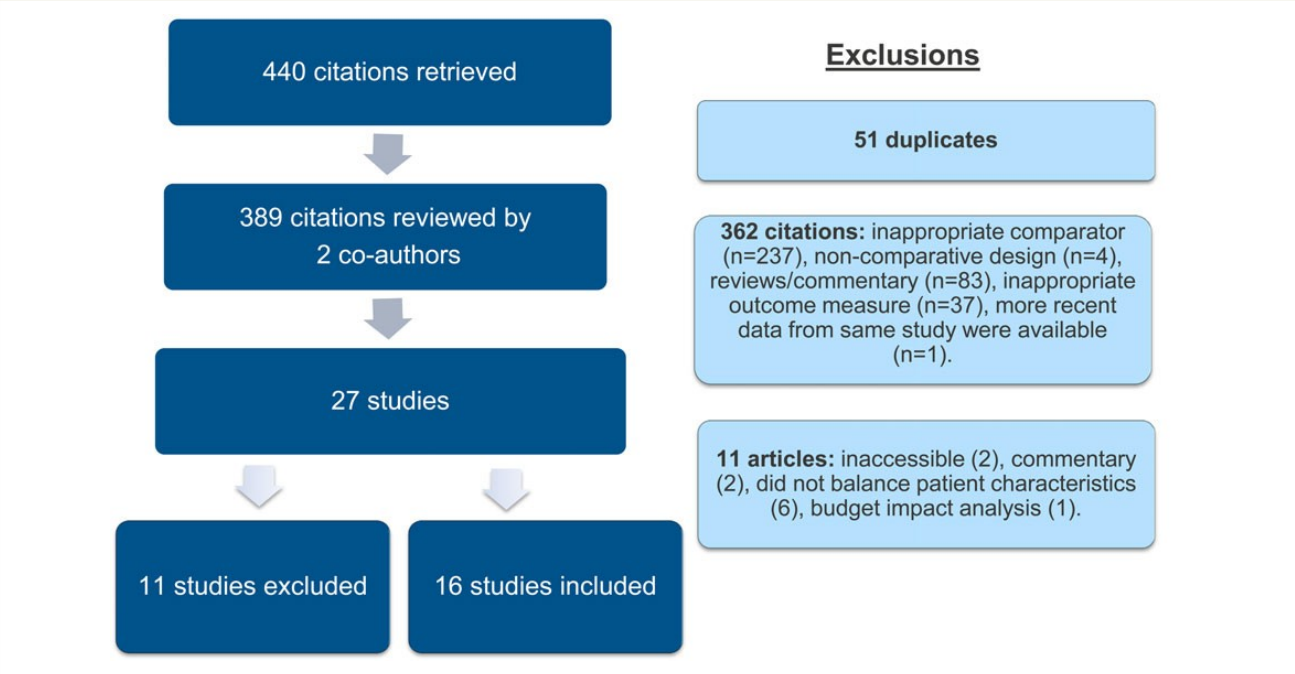

Figure 1 A flow chart describing the systematic process followed for article selection.

Of 16 studies, 4 compared CABG against DES,[28,37,39,42] 6, CABG vs. BMS,[29,30,33,34,40,41] 2, OPCAB vs. BMS,[31,38] 1, OPCAB vs. DES,[31] and 2, MIDCAB vs. BMS.[35,36] In two further comparisons, the type of stent used was not reported.[32,43] The procedural characteristics (where available) are described in Supplementary material online, Table S2–II.

Whereas 12 studies[33–37,39,40,42–46] used data from 11 different RCTs, 4 studies used non-randomized patient cohorts from single[38,41,47] or multiple centres.[32] Three out of four observational studies included treatment groups with balanced patient characteristics; two, achieved this through matching,[32,38] and one, balanced groups by way of patient selection.[47] One non-randomized study conducted post hoc analyses for the adjustment of differences between the treatment groups.[41] With exception to five studies,[37,39–42] all studies included patients with MVCAD.

Characteristics of economic evaluations

Types of economic evaluations

Of 16 studies, 6 were CEAs[35,37,38,41,44,45] and 4 were CUAs.[39,40,42,47] Six studies performed both CEA and CUA.[32–34,36,43,46] There were seven economic evaluations conducted alongside RCTs.[34,36,37,42,43,46,48] Projections beyond trial periods were made in two studies.[43,46] Decision analytical modelling using Markov models and life-table methods was employed in six studies.[32,33,40,43,46,47] Two studies conducted economic evaluations based on results from meta-analyses of RCTs.[35,40] The characteristics of economic evaluations are summarized in detail in Supplementary material online, Table S2–III.

Perspective and costs considered

The types of costs included in studies varied depending on the perspective of the economic evaluation, which ranged from healthcare perspective,[32,34,35,37–40,42,43,46] societal perspective,[33,47] to patient perspective.[41] All studies considered direct medical costs associated with index hospitalization for revascularization, and related follow-up events.[32–47] Only two studies[38,39] considered indirect costs, including patient/carer costs related to absence from work, and out-of-pocket expenses, e.g. travel costs, that must be included in evaluations undertaken from a societal perspective.[16]

Measures of effectiveness

The primary measure of effectiveness used in economic evaluations varied among studies, from life years gained (LYG),[32,34,37,46] major cerebrovascular and cardiac events (MACCE) avoided,[41,45,44] to quality-adjusted life years (QALY) gained, the most relevant metric for decision makers.[13,32–34,36,39,40,42,43,46,47] The incremental ICERs were reported in 13 studies as shown in Supplementary material online, Table S2–IV.[32–34,37,39–47] Cost-effectiveness thresholds of $50 000 and £20 000/QALY gained were used in 2 studies[43,46] and 1 study,[40] respectively, for the base-case (primary) analysis. A WHO-recommended threshold of three times of the national GDP per capita was adopted by one study.[47]

Sensitivity analyses

Sensitivity analyses were performed in 12 studies.[32,33,35,37,39–43,46,47] Deterministic or one-way sensitivity analyses were performed in seven studies, where influences of model inputs to ICER were tested individually by one-way varying selected parameters to upper or lower limits of 95% confidence intervals, or an arbitrary value.[32,33,35,39,41,47] Probabilistic sensitivity analysis (PSA) that assessed joint uncertainty of input parameters using distributions was performed in two studies.[32,40] The precision of estimated ICER was evaluated using a bootstrap method in four studies.[37,42,43,46] Five studies explored multiple thresholds via willing-to-pay (WTP) analysis.[32,40,41,43,46] Sensitivity to model assumptions, particularly regarding the survival benefit provided by CABG beyond a 5-year in-trial follow-up period was tested in three studies.[32,43,46] Whereas the base-case (primary) analysis of these studies assumed that the mortality hazard ratio for CABG vs. DES increased in a linear fashion from 5 to 10 years and there was no difference beyond 10 years, in sensitivity analyses two alternative assumptions were tested: (i) constant benefit from CABG from 5 to 10 years, and no difference beyond 10 years, and (ii) no additional benefit from CABG beyond in-trial follow-up of 5 years.[32,43,46]

Cost-effectiveness of CABG vs. PCI

The cost-effectiveness results are reported in detail in Supplementary material online, Table S2–IV and summarized in Figures 2–4 and Table 1.

CABG vs. DES

Of four studies that compared the cost-effectiveness of CABG vs. DES, all of them reported ICERs favouring CABG.[32,41,43,46] Three of these studies carried a healthcare payer perspective,[32,43,46] while one was conducted from the patient perspective.[41]

The highest lifetime ICER for CABG was reported by the ASCERT study [The Society of Thoracic Surgeons Collaboration on the Comparative Effectiveness of Revascularization Strategies][32] at $30 803/QALY gained for patients with MVCAD and age ≥ 65 years. The SYNTAX trial [Synergy between PCI with Taxus and Cardiac Surgery][46] reported a lifetime ICER of $16 537/QALY gained for patients with left main or MVCAD. The lowest lifetime ICER of $8132/QALY gained was reported by the FREEDOM trial [The Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease].[43] Sensitivity analyses of these studies[32,43,46] showed that the estimated ICERs were robust to a broad range of assumptions, including the protective survival effect conferred by CABG compared with PCI. In a non-randomized study performed from the Armenian patient perspective, CABG was found the dominant (more effective and cost-saving) strategy at 4-year follow-up.[41] Table 1 summarizes the results from subgroup analyses performed by the economic evaluations.

CABG vs. BMS

Of six studies that compared cost-effectiveness of CABG and BMS strategies, three were conducted from the perspective of the healthcare payer,[34,37,38] one from the societal perspective,[33] and three did not report the perspective.[36,44,45] BMS was treated as the 'comparator' in three studies[33,34,44] and as the 'intervention' in three studies.[37,38,45]

Yock et al.[33] established that over the lifetime, CABG was the dominant (more effective and cost-saving) strategy in patients with MVCAD using data from the BARI [Bypass Angioplasty Revascularization Investigation] trial. These results were robust to sensitivity analyses performed removing cost and consequences incurred through target lesion restenosis following PCI. Javanbhakt et al.,[47] using data from a retrospective study, also found that PCI with

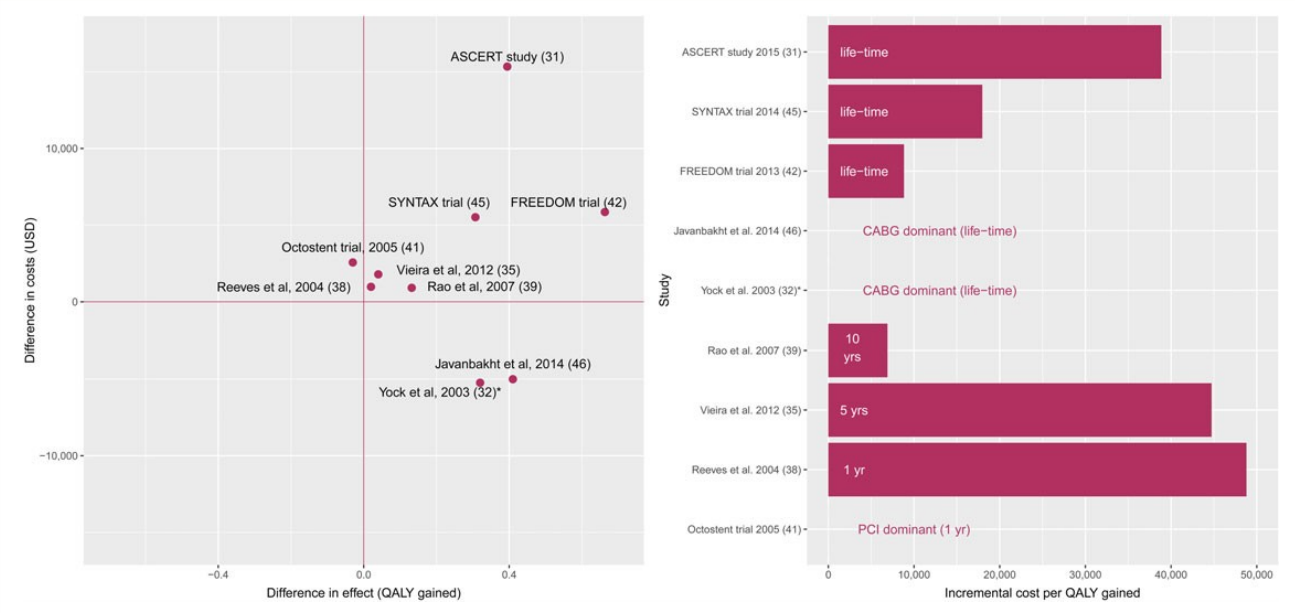

Figure 2 The incremental cost-effectiveness per QALY gained for CABG reported by nine economic evaluations (2014 USD). ASCERT, American College of Cardiology Foundation – The Society of Thoracic Surgeons Collaboration on the Comparative Effectiveness of Revascularization Strategies; CABG, coronary artery bypass surgery; FREEDOM, The Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease; PCI, percutaneous coronary intervention; QALY, quality-adjusted life years gained; SYNTAX, Synergy between PCI with Taxus and Cardiac Surgery; yrs, year/s.

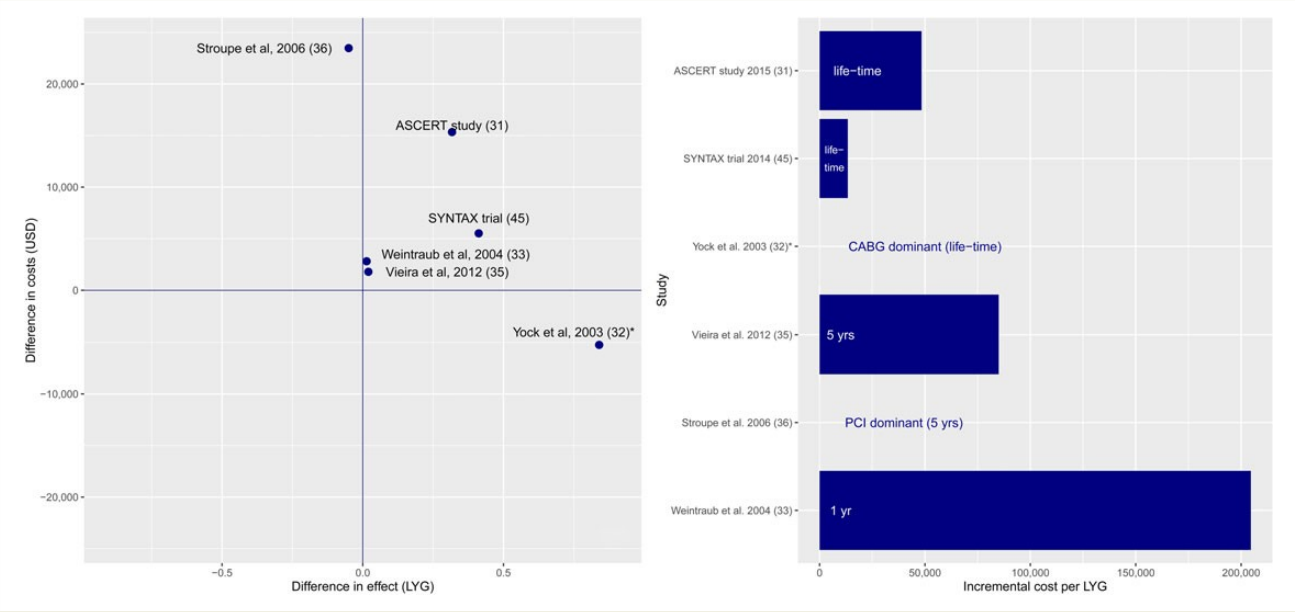

Figure 3 The incremental cost-effectiveness per LYG gained for CABG reported by included economic evaluations (2014 USD). ASCERT, American College of Cardiology Foundation – The Society of Thoracic Surgeons Collaboration on the Comparative Effectiveness of Revascularization Strategies; CABG, coronary artery bypass surgery; LYG, life years gained; PCI, percutaneous coronary intervention; SYNTAX, Synergy between PCI with Taxus and Cardiac Surgery; yrs, year/s.

stenting (type of stent not reported) was dominated by CABG over lifetime period from the societal perspective.

At 5-year follow-up, BMS was reported the dominant (more effective and cost-saving) strategy owing to better survival rates in an investigation that evaluated the cost-effectiveness of PCI vs. surgery in high-risk subjects with refractory angina in the AWSOME [Angina With Extremely Serious Operative Mortality Evaluation] trial.[37] Contrastingly, Vieira et al.[36] reported that CABG compared

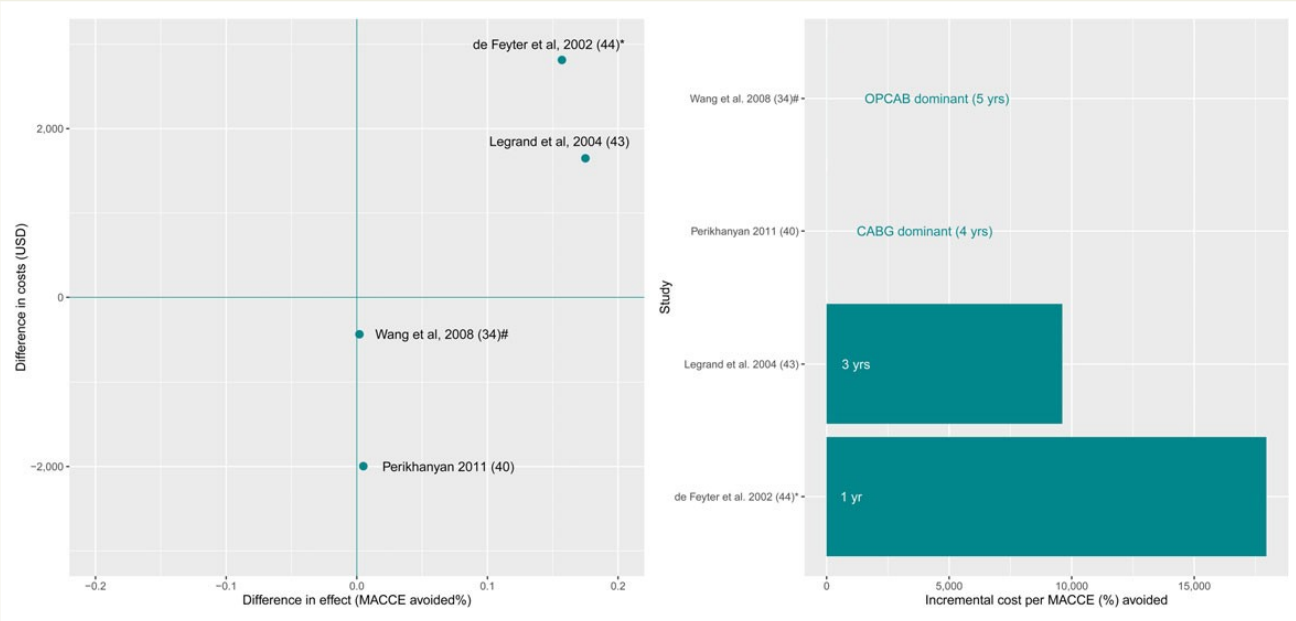

Figure 4 The incremental cost-effectiveness per MACCE avoided for CABG reported by included economic evaluations (2014 USD). CABG, coronary artery bypass surgery; MACCE, major adverse cardiac and cerebrovascular events; PCI, percutaneous coronary intervention; yrs, year/s.

Table 1 Summary of results from subgroup analyses performed in economic evaluation included in this review

Study	Intervention vs. comparator	Time horizon	ICER (USD, 2014)
Age ≥ 70 years			
ASCERT study, 2015[32]	CABG vs. DES	Lifetime	$40,520/QALY gained
SYNTAX trial, 2014[46]	CABG vs. DES	Lifetime	$36,942/QALY gained
FREEDOM trial, 2013[43]	CABG vs. DES	Lifetime	$21,440/QALY gained
Diabetes mellitus			
ASCERT study, 2015[32]	CABG vs. DES	Lifetime	$32,129/QALY gained
SYNTAX trial, 2014[46]	CABG vs. DES	Lifetime	$10,709/QALY gained
FREEDOM trial, 2013[43]	CABG vs. DES	Lifetime	$8,829/QALY gained
Heart failure			
ASCERT study, 2015[32]	CABG vs. DES	Lifetime	$31,038/QALY gained
Left main disease			
SYNTAX trial, 2014[46]	CABG vs. DES	Lifetime	PCI Dominant
Lesions in LAD			
FREEDOM trial, 2013[43]	CABG vs. DES	Lifetime	$8,513/QALY gained
Three-vessel disease			
ASCERT study, 2015[32]	CABG vs. DES	Lifetime	$34,164/QALY gained
SYNTAX trial, 2014[46]	CABG vs. DES	Lifetime	$5,325/QALY gained
FREEDOM trial, 2013[43]	CABG vs. DES	Lifetime	$6,867/QALY gained
Unstable Angina			
ASCERT study, 2015[32]	CABG vs. DES	Lifetime	$38,458/QALY gained
de Feyter et al., 2002[45]	BMS vs. CABG	1 year	$35,809/MACCE avoided

ASCERT, American College of Cardiology Foundation–The Society of Thoracic Surgeons Collaboration on the Comparative Effectiveness of Revascularization Strategies; BMS, bare-metal stent; CABG, coronary artery bypass surgery; DES, drug-eluting stent; FREEDOM, The Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease; PCI, percutaneous coronary intervention; MACCE, major adverse cardiac and cerebrovascular event; QALY, quality-adjusted life years; SYNTAX, Synergy between PCI with Taxus and Cardiac Surgery.

with BMS led to lower costs and greater benefits at 5-year follow-up, as measured by event-free life years gained, event-free-and-angina-free life years gained, and greater QALY gained, using data from MASS-II [Medicine, Angioplasty, or Surgery Study] trial. At 3-year follow-up, Legrand et al.[44] reported an ICER in favour of CABG of $9616 per MACCE free patient, using data from ARTS trial. At 2-year follow-up, Reynolds et al.,[38] who did not report an ICER, concluded that multivessel coronary stenting lead to cost savings, but higher rates of repeat revascularizations.

At 1-year follow-up, two studies[34,45] reported favourable results for BMS compared with CABG using data from SoS and ARTS trials, respectively. Weintraub et al.[34] established that initial high costs of CABG compared with BMS was not eliminated at 1 year, reporting an ICER of $204 603/life year gained for MVCAD patients, while de Feyter et al.[45] established ICERs of $16 530 and $32 983 per MACCE avoided for patients with stable and unstable angina, respectively, when comparing BMS against CABG.

OPCAB and MIDCAB vs. PCI

Two studies evaluated the economic attractiveness of OPCAB and BMS strategies from the Canadian and Dutch healthcare payer perspectives, respectively.[35,42] BMS was found the dominant (more effective and cost-saving) strategy at 1-year follow-up using data from the Octopus and OctoStent trials.[42] Sensitivity analyses confirmed the robustness of this finding (BMS dominant in 95% of bootstrap samples). At 5-year follow-up, OPCAB was slightly more expensive compared with BMS but was protective against MACCE.[35] OPCAB was the dominant strategy when compared with DES.[35]

The cost-effectiveness of MIDCAB vs. BMS at 12-month follow-up was explored from the perspective of the healthcare payer in the UK.[39,40] The AMIST trial[39] was underpowered to detect differences in effectiveness and reported a high ICER (- $50 000) for MIDCAB compared with BMS. Over a 20-year period, Rao et al. estimated that MIDCAB was more favourable compared with BMS (ICER of $3165/QALY gained), among patients with isolated lesions of the left anterior descending coronary artery.[40] The robustness of this estimate was confirmed through sensitivity analyses performed.

Assessment of quality

The results from the quality assessment are presented in Supplementary material online, Appendix SIII. Seven of 16 included studies achieved a score of '80%' or more, which was considered high quality.[32,33,37,39,43,46,47] Four of these studies reported a score of - 90%.[37,43,46,47] An improvement in the quality of economic evaluations was observed across time. No publication bias towards sponsored vs. un-sponsored studies was observed.

Discussion

Summary

As far as we are aware, this is the first systematic review examining the cost-effectiveness of CABG vs. PCI for patients with CAD. Since only a subset of patients with CAD may be eligible for either CABG or PCI, strict criteria were applied during the article selection process. We considered all economic evaluations performed alongside RCTs, used data from published RCTs, or from non-randomized trials that adjusted for differences in baseline features between CABG and PCI treatment groups. Sixteen evaluations were identified, of which four compared CABG against DES,[32,41,43,46] and six compared CABG vs. BMS.[33,34,37,38,44,45] Economic evaluations that compared OPCAB or MIDCAB with PCI were less common.[35,39,40,42] The majority of the studies were conducted from the healthcare payer perspective and included patients with MVCAD or at high risk of complications. The cost-effectiveness of CABG compared with PCI over a 'lifetime' time horizon, was only undertaken by five economic evaluations, by way of extrapolation of data from trials.[32,33,43,46,47]

Effect of follow-up time

The results of our review suggest that the economic advantage of surgery compared with PCI increased with the increasing length of follow-up or time horizons. Only a third of the studies that compared cost-effectiveness in the medium term (2–5 years) showed favourable results for PCI.[37,38] In contrast, the majority of economic evaluations that used a 12-month time horizon favoured PCI over CABG (conventional or otherwise).[34,39,42] The nature and invasiveness of the strategies may contribute to these results. Though CABG may confer a significant survival benefit over PCI,[34,49] these benefits could overshadow the disutility associated with longer recovery period and the need for intensive rehabilitation following surgery.[50] Given only one study evaluated the 12-month cost-effectiveness of conventional CABG vs. DES to date, the short-term economic advantage of DES use when compared with BMS use is uncertain.[51] Short-term results from the SYNTAX trial revealed that CABG compared with DES was favoured in patients with three-vessel MVCAD or left main coronary artery disease (LMD) and high angiographic complexity (SYNTAX scores - 32). Additionally, the initial costs of conventional CABG may be lower than the costs of PCI when considering the aggregate costs of repeat revascularisations driven by stent restenosis, in the longer term.[34,39,42] Much of the initial cost advantage of PCI using DES was eliminated during long-term follow-up due to additional MACCE following PCI.[8,9,52] Favourable costs and resource utilization outcomes were reported for CABG (conventional or otherwise) compared with PCI (DES or BMS), in all economic evaluations that compared cost-effectiveness over 10 years[40] or lifetime.[32,43,46,47] The 'lifetime' ICERs reported in these studies varied from dominance for CABG, i.e. negative costs,[47] to $3165,[40] $8132,[43] $16 537,[43] and $30 803 per QALY gained.[32] Thus, a time horizon of at least 5 years may yield a more realistic evaluation of value for money benefit of treatment of CABG compared with PCI in future analyses.

LMD

For patients with LMD only, CABG was dominated by DES, suggesting that PCI may be more favourable in patients with lesions in the left main coronary artery.[46] This finding, both unique and interesting, merits further investigation in future economic evaluations of CABG and PCI strategies.

Limitations

The economic evaluations included in this systematic review were diverse with variable quality. Less than half of the included studies were rated as 'high quality', when assessed against the CHEERS

Statement checklist.[20,32,33,37,39,43,46,47] A temporal improvement, nonetheless, was observed in the transparency and clarity of reporting from 2002 to 2015, the period across which included studies were published. This observation may in part reflect the increasing demand for high-quality economic evidence from a growing number of resource-scarce healthcare systems. Additionally, published guidelines for assessment of health economic evaluations in Cardiology were not available until recently,[13] while generic guidelines were not adopted widely.[20,53]

The direct comparison of ICERs from different economic evaluations is not recommended. While clinical practice across different healthcare systems may be similar, leading to similar clinical outcomes; a multitude of factors may contribute to varying ICERs across different studies. These factors may include differences in geographic context, perspective, healthcare system costs, policies governing stent use, the price differential between DES and BMS, and methodological aspects, such as the time horizon, health-related utility weights, and modelling methods considered in economic evaluations.

The recently published ACC/AHA Statement on Cost/Value Methodology echoes the need for more explicit and transparent assessment of the value of health care.[13] According to the 'Level of Value into Clinical Guideline Recommendations' criteria established in this Statement, CABG may be graded 'high value' in candidates eligible for both treatments—given the majority of high-quality studies reported ICERs below $50 000.[32,33,43,46,47] The ACC/AHA Cost/Value Methodology guidelines also recommend for the preferential use of the 'societal perspective' in systematic reviews of CEAs for defining cost-effectiveness.[13] Only two included studies in this review considered a societal perspective;[33,47] and both analyses did not consider the indirect costs related to treatment, the out-of-pocket expenses borne by the patient, or the costs associated with loss of income and/or productivity due to treatment.[33,47] Due to these limitations, this systematic review could not be conducted from a societal perspective alone. This review, however, summarizes evidence from all relevant economic evaluations published in the DES era that scrutinized costs and consequences of two alternate revascularization strategies, which may be useful for policymakers as well as clinicians in their decision-making.

Conclusions

Current evidence supports the notion that CABG compared with PCI is an economically viable treatment option, at least in the long term from the healthcare payer's perspective. While the inclusion/exclusion criteria in chosen populations were heterogeneous, the majority of studies included MVCAD patients. Anecdotal evidence suggests that DES compared with CABG may be favoured for patients with lesions in the left main coronary artery. The true economic attractiveness of CABG compared with PCI in eligible populations, however, remains uncertain due to a paucity of studies that used a societal perspective. From an entirely clinical perspective, a multidisciplinary approach to treatment of patients with complex MVCAD may enhance cost containment, as well as long-term clinical and non-clinical outcomes for the patient.[7] In the evaluation of cost-effectiveness of treatments, however, the adoption of guidelines established for health economic evaluations, the consideration of a 'lifetime' time horizon, and the inclusion of societal costs in the development of economic models may maximize the integration of economic evidence into clinical practice and policy guidelines in the future.

Supplementary material

Supplementary material is available at European Heart Journal – Quality of Care and Clinical Outcomes online.

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Online Supplementary Material

A Systematic Review of Cost-Effectiveness of Percutaneous Coronary Intervention versus Surgery for the Treatment of Coronary Artery Disease in the Drug-Eluting Stent Era

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APPENDIX I

Literature search strategy and MeSH terms used to identify literature

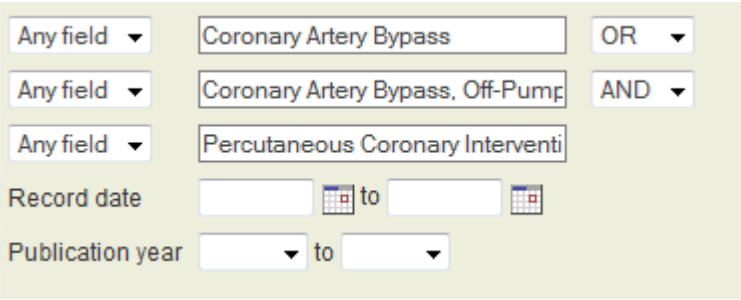
Medline

#1	exp Myocardial Ischemia/ or myocardial isch?em*.mp. or myocardial infarct*.mp. or (coronary adj1diseas*).mp. or (disease adj2arter*).mp.	420616
#2	exp Stents/ or stent*.mp. orexp Angioplasty, Transluminal, Percutaneous Coronary/ or (percutaneous adj2 coronary).mp.	99186
#3	1 and 2	47812
#4	exp Coronary Artery Bypass/ or (coronary adj4 bypass*).mp. or CABG*.ti. or CABG*.ab. or surgery*.ti. or surgery*.ab. or bypass*.ti. or bypass*.ab.	797514
#5	3 and 4	11778
#6	exp Cost-Benefit Analysis/ec, mt, ut [Economics, Methods, Utilization]	2469
#7	economics.m_titl.	4426
#8	cost-effectiveness.m_titl.	12226
#9	6 or 7 or 8	18263
#10	5 and 9	55

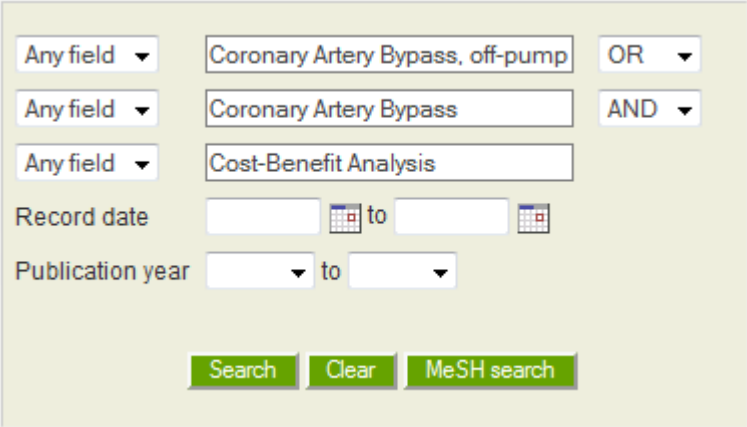
Embase

#1	'myocardial ischemia'/exp OR 'myocardial ischemia' OR (myocardial AND isch?m*) OR (myocardial AND infarct*) OR coronary NEAR/1 diseas* OR (disease NEAR/2 arter*):lnk,ab,ti	424,426
#2	'stents'/exp OR 'stents' OR stent* OR 'angioplasty, transluminal, percutaneous' OR (percutaneous NEAR/2 coronary):lnk,ab,ti	156,006
#3	#1 AND #2	46,552
#4	'coronary artery bypass'/exp OR 'coronary artery bypass' OR coronary NEAR/4 bypass* OR (coronary:lnk,ab,ti AND bypass:lnk,ab,ti)	83,891
#5	#3 AND #4	9,916
#6	'economics'/exp OR 'economics' OR economics* OR 'economics, cost-effectiveness, cost-utility':lnk,ab,ti	307,097
#7	'cost effectiveness'/exp OR 'cost effectiveness' OR cost AND effectiveness* OR 'cost effectiveness, cost utility, economics' OR (cost NEAR/2 effectiveness):lnk,ab,ti	137,116
#8	#6 OR #7	426,131
#9	#5 AND #8	342
#10	#5 AND #8 AND [english]/lim	329
#11	#5 AND #8 AND [english]/lim AND ([article]/lim OR [article in press]/lim OR [conference paper]/lim OR [review]/lim)	286
#12	#10 AND ([article]/lim OR [article in press]/lim)	172

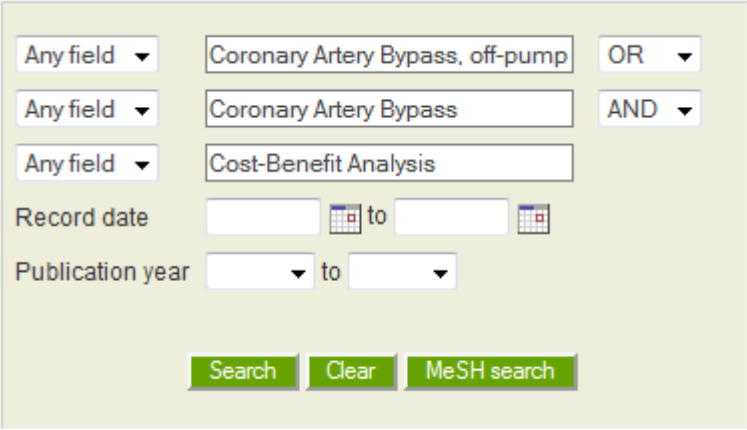
NHS-EED – (190 hits)



NHS-DARE – (13 hits)



NHS-HTA (10 hits)



APPENDIX II

Extended results – Reference tables for economic evaluations included in the review

Table S2-I The population demographics and characteristics of included economic evaluations

Study	Source of population/ Country	Target poulation/ sub-groups	Mean age	Period of recruitment/ follow-up	Type of surgery (N)	Type of PCI /stent (N)
Cohen et al, 2014 (44)	SYNTAX trial/ recruitment world-wide US perspective	Patients with with left main or MVD (3-vessel) coronary artery disease. Exclusion criteria as per SYNTAX trial.	64.9-65.3 yrs	2005-2007/ 5 yrs	CABG (N=870)	PCI/ DES (PES) (n=896)
de Feyter et al, 2002 (43)	ARTS trial sub-analysis/ recruitment world-wide Netherlands perspective	Patients with MVD and a left ventricular ejection of at least 30%, with or without unstable angina. Exclusion criteria as per ARTS trial.	61 yrs	1997-1998/1 yr	CABG (N=374 stable angina; N=226 unstable angina)	PCI with BMS (N=381 stable angina; N=224 unstable angina)
Javanbakht et al, 2014 (45)	A retrospective study Iran	Patients with MVD	53 yrs	2010/2 yrs	CABG (N=34)	PCI with stenting (N=75)
Legrand et al, 2004 (42)	ARTS trial/ recruitment world-wide Netherlands perspective	Patients with MVD. Exclusion criteria as per ARTS trial.	61 yrs	1997-1998/1-3 yrs	CABG (N=605)	PCI with stent (BMS) (N=600)

Magnuson et al, 2013 (41)	FREEDOM/ recruitment world-wide US perspective	Patients with MVD and diabetes. Exclusion criteria as per FREEDOm trial	62.9-63.1 yrs	2005-2010/ 5 yrs	CABG(N=947)	PCI with DES (N=953)
Nathoe et al. 2005 (40)	Octopus & OctoStent trials , multicentre Netherlands	MVD or SVD with no history of CABG and PCI (<6 mths), excl. emergent CABG, concominant valvular surgery, in-stent restenosis, MI<6 months.	58.9-60.3 yrs	1998-2000/ 1 yr	Off-pump CABG (N=142)	PCI with stenting/ BMS (N=138)
Perikhanyan 2011 (39)	Consecutive patients from single-centre (retrospective study) Armenia	Consecutively enrolled patients EXCEPT those age>70 yrs, prior revascularisation, cardiogenic shock, end-stage renal disease, severe left ventricular disfunction, cancer, and patients not covered by ministry of health.	NR - majority between 55-63 yrs	2004-2005/4 yrs	CABG (N=62)	PCI with DES (N=62)
Rao et al, 2007 (38)	Meta-analysis of RCTs comparing minimally invasive CABG with PCI (stenting) UK perspective	Patients with isolated lesions of the left anterior descending artery	61 yrs	NA	MIDCAB (NR)	PCI with stenting/BMS (NR)
Reeves et al, 2004 (37)	AMIST trial, multi-centre UK	Ischaemic heart disease with at least 50% stenosis of the LAD, with no signficant disease in another vessel (SVD).	54.5-58.8 yrs (median)	1999-2001/ 1 yr	MIDCAB† (N=50)	PTCA with stenting/BMS (N=50)

Reynolds et al, 2003 (36)	Single-centre, matched cohort USA	MVD with no history of previous CABG, previous or concurrent valvular surgery, emergency CABG, in-stent restenosis, MI<24 hrs.	62.0 yrs	1994-1998/2 yrs	CABG (N=200) 1.5% were off-pump CABG	PCI with stenting/BMS (N=100)
Stroupe et al. 2006 (35)	AWESOME trial, multicentre USA	High risk patients with medically refractory ischaemia- incl. prior open heart surgery, age>70 yrs, LVEF<35%, MI < 7 days, intra-aortic balloon pump indicated. Exclusions as per AWESOME trial.	67-68 yrs	1995-2000/ 5 yrs	CABG (N=227)	PCI with stenting/ BMS (N=218)
Vieira et al, 2012 (34)	MASS II trial Brazil	Patients with MVD and normal systolic ventricular function. Exclusion criteria as per MASS II trial.	60 yrs	NR/ 5 yrs	CABG (N=203)	PCI with stenting (N=205)
Wang et al, 2008 (33)	4 RCTS (ARTS, AWESOME, SoS, ERACI-II) comparing CABG vs PCI and literature reviews Canadian perspective	Patients with MVD	NR	NA	Off-pump CABG or On-pump CABG(NR)	PCI with DES or BMS (NR)
Weintraub et al, 2004 (32)	SoS trial/ recruitment in UK, Europe and Canada, multicentre (world-wide) UK perspective	MVD and no history of thoractomy or coronary revascularisation. Symptomatic. Exclusion criteria as per SoS trial.	NR	1996-1999/ 1 yr	CABG (N=500)	PCI with stenting/BMS (N=488)
Yock et al, 2003 (31)	BARI trial, multi-centre, recruitment in North America USA	MVD and no prior coronary revascularisation	61.5 yrs	1989-1991/ 4 yrs	CABG(N=NR)	Angioplasty with primary stenting/BMS (virtual arm)(N=NR)

Zhang et al, 2015 (30)	The ASCERT study, a collaborative observationalstudy of joint profressional society databases and Medicare and Medicaid Services/ matched-cohorts USA	Patients age>65 yrs with 2-3 vessel MVD.	74 yrs	2004-2008/ 4 yrs	CABG (N=86,244)	PCI with DES (N=103,549)

Abbreviations: **ACS, acute coronary syndrome; AMI, acute myocardial infarction; AMIST, The Angioplasty versus Minimally Invasive; Surgery Trial; ARTS, Arterial Revascularization Therapies Study; ASCERT, American College of Cardiology Foundation–The Society of Thoracic Surgeons Collaboration on the Comparative Effectiveness of Revascularization Strategies; AWESOME, Angina With Extremely Serious Operative Mortality Evaluation; BARI, Bypass Angioplasty Revascularisation Investigation; BMS, bare-metal stent; CABG, coronary artery bypass surgery; EE, economic evaluation; ERACI-II, Argentine Randomised Study: Coronary Angioplasty with Stenting versus Coronary Bypass Surgery in Patients with Multiple-Vessel Disease; FREEDOM, The Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease; hrs, hours; IMA, internal mammary artery; LAD, left anterior decending artery; LVEF, left ventricular ejection fraction; MASS II, The Second Medicine, Angioplasty, or Surgery Study; MI, myocardial infarction; MIDCAB, minimally invasive direct coronary artery bypass surgery; mths, months; MVD, multi-vessel desease; NA, not applicable; NR, not reported; OP-CABG = off-pump CABG;PCI, percutaneous coronary intervention;RCT, randomised controlled trial; SoS, stent or surgery trial; SYNTAX, Synergy between PCI with Taxus and Cardiac Surgery; SVD, single-vessel disease; yrs, year/s**

Table S2-II Procedural characteristics of CABG and PCI (where details were available) of included studies

Study	Type of conduit used RA/IMA/SVG in CABG (%)	Average no. of stents used/ vessel diameter in PCI	Notes
Yock et al, 2003 (31)	NR/82%/NR	NA*/>2.75mm	
Reynolds et al, 2003 (36)	NR/94%/NR	Stents: 2.8 (range: 2-6)/NR Balloons: 3.5 (range: 1-7)/NR	In some patient balloon angioplasty was applied (% NR)
Weintraub et al, 2004 (32)	NR/93%*/NR	2.6/ NR	
Reeves et al, 2004 (37)	0%/100%/0%	NR	In a minority group balloon angioplasty was used (% NR)
Nathoe et al. 2005 (40)	100% received ≥1 arterial graft: 98% IMA, 2% gastroepiploic artery. 3.8% also received vein graft.	1.4/NR	
Stroupe et al. 2006 (35)	2.9%/73.2%/NR	NR	Only 11% of patients received stents in 1st yr of recruitment; in final 2 years it was 88%
Zhang et al, 2015 (30)	NR	NR	
Cohen et al, 2014 (44)	NR	4.5±2.3	
Javanbakht et al, 2014 (45)	NR	NR	
Magnuson et al, 2013 (41)	NR	4.1 ± 1.9	
Perikhanyan 2011 (39)	NR	NR	

de Feyter et al, 2002 (43)	Arterial conduit in ~100% cases; IMA whenever feasible	NR
Vieira et al, 2012 (34)	NR	NR
Wang et al, 2008 (33)	NR	NR
Rao et al, 2007 (38)	IMA (100%)	NR
Legrand et al, 2004 (42)	NR	NR

Abbreviations: **CABG, coronary artery bypass grafting; IMA, internal mammary artery; NR, not reported; RA, radial artery; PCI, percutaneous coronary intervention; RA, radial artery; SVG, saphenous vessel graft.**

Table S2-III An overview of the characteristics of included economic evaluations

Study	Perspective	Type of EE/ model	Time horizon	Primary measure of benefit/s in EE	Types of costs incl.	Data sources for costs	Discounting	Sensitivity analysis
Cohen et al, 2014 (44)	Healthcare payer	RCT based CUA & CEA using life tables for projections	Life-time	QALY gained and LYG	Initial hospitalisation costs (revascularisation procedures, hospital stay plus ancillary services, physician fees), rehospitalisations, outpatient services, rehabilitation/skilled nursing days, medications, physician fees	Mean hospital acquisition cost at 3 surveyed US hospitals, Micromedex Red Book for medical therapies, micro-cost accounting systems of Saint Luke's Mid America Heart Institute, 2010 Medicare Provider and Review database, Medicare Part A data files, 2010 national Medicare fee schedule, 2010	3% (Costs , LYGs, QALY gained)	Sensitivity analyses were performed including nonfatal MI and stroke on long-term mortality, and alternative assumptions about the duration of the prognostic benefit of CABG relative to PCI. Bootstrap methodology was used to estimate

						Medicare Provider and Review		joint uncertainty in model inputs.
de Feyter et al, 2002 (43)	NR	RCT based CEA	1 yr	MACCE avoided	Direct medical costs associated with initial procedure and hospitalisation, re-hospitalisations, follow-up-event diagnostic test, medications.	Sources of costs NR.	NR	NR
Javanbakht et al, 2014 (45)	Societal perspective (Iran)	Markov model using estimates from a retrospective study/ CUA	5 yrs, 10 yrs, life-time	QALY	Costs of physician services; pharmaceutical and device, laboratory or diagnostic tests, inpatient and other related resource during initial revascularization. Outpatient costs and costs of re-hospitalisations.	Retrospective study, published sources, Iran Life tables 2011, Iran Central Bank Report	3% (Costs , QALY gained)	One-way sensitivity and probabilistic sensitivity analysis
Legrand et al, 2004 (42)	NR	Single-centre study based CEA	1 yr and 3 yrs	MACCE-free survival	Direct medical costs of initial and repeat revascularisation procedures, hospital days, medications, and rehabilitation services. Costs of all physician visits and hospitalizations occurring during follow-up.	Unit costs from a single-centre in Netherlands.	NR	NR
Magnuson et al, 2013 (41)	Healthcare payer (USA)	RCT based EE using microrosimulation and life tables/ CEA & CUA	Life-time	QALY gained	Costs relating to procedure and non-procedural costs for index procedure and any subsequent	Survey data (acquisition costs of revascularization procedures) from 3 US hospitals, Micromedex	3% (Costs , LYG, and QALY gained)	Sensitivity analyses were performed including alternative

					hospitalizations that involved a coronary revascularization procedure. Costs of follow-up hospitalizations that did not involve a revascularization procedure.	Red Book, micro-cost accounting systems of Saint Luke's Mid America Heart Institute, MEDPAR database, 2010 Medicare reimbursement rates for the DRG obtained from the Medicare Part A data files		assumptions about the duration of the prognostic benefit of CABG relative to PCI. Bootstrap methodology was used to estimate uncertainty in the joint distribution of model inputs.
Nathoe et al. 2005 (40)	Healthcare payer (Netherlands)	RCT based CUA	1 yr	QALY gained	Direct hospital costs associated with index hospitalisation and subsequent cardiac-related hospitalisations incl. outpatient rehabilitation and medication use.	Published sources, operated hospital, and Utrecht University Medical Centre.	NA	Bootstrap method for uncertainly
Perikhanyan 2011 (39)	Patient perspective	Single centre study based CEA with matching of groups. The ICER was further adjusted for other significant differences between groups.	4 yrs	MACE avoided	Aggregate costs of initial revascularisation and repeat CABG or PCI, MI, angiography and medication. Indirect costs were not considered.	Hospital price lists and ministry of health for costs.	NA	One-way sensitivity analysis to a variable or series of variable, INB analyses and CEACs.
Rao et al, 2007 (38)	Healthcare payer (UK)	Decision analysis using a markov simulation/ CUA	5 yr, 10 yr (base case), 15 yr, and 20 yr	QALY gained	Costs of initial procedure (preoperative costs, cost of operation, post-operative care), follow-up costs including costs of repeat revascularisation, myocardial infarction, and costs of medication.	Health technology assessment reports, and other published sources.	3.5% (Costs , QALY gained)	Probabilistic sensitivity analysis and alternative analyses for different demographics, time horizons, perspective

								(societal), and DES-use
Reeves et al, 2004 (37)	Healthcare payer (NHS, UK)	RCT based CUA	1 yr	QALY gained	Hospitalisation costs associated with initial procedures; costs of health and social services used during follow-up; patients' travel costs and out-of-pocket expenses; time patients and carers took off work. Cost on tests/drug-use during standard work-up on admission were excl.	Bristol Royal Infirmary, Personal Social Services Research Unit data on staff costs; British National Formulary; laboratory cost datasets; and New Earnings Survey.	NA	One-way sensitivity analysis on initial costs (±10% and ±50%)
Reynolds et al, 2003 (36)	Third party payer (USA)	Single-centre based CEA with matching	2 yrs	Composite of death or major MI and repeat revascularistions reorted.	Direct medical care costs for initial and subsequent procedures, physician fees (excl. ancillary services), outpatient costs incl. rehabilitation hospitalisation and diagnostic angiography, excl. physician visits, diagnostic test and medications).	Hospital accounting system, hospital costs from a subset of 2692 patients from 89 centres recruited in 4 multi-centre clinical trials, Massachusetts Medicare Fee Schedule, Massachusetts Medicaid Reimbursement Schedule.	NR	NR
Stroupe et al. 2006 (35)	Third party payer (USA)	RCT based CEA	3yrs, 5 yrs	LYG	Direct hospitalisation cost of initial procedure and follow-up costs incl. repeat procedures, unrelated hospitalisations incl. short-term hospital stays, rehabilitation for	Veteran Affairs and Medicare databases, other related data sources (e.g., Health Economic Resource Centre); Medicare claims data; Veteran	3% (Costs and LYGs)	Bootstrap method. Sensitivity to inclusion of pharmacy costs; and use of standard dollar amount for urban

					mental health care, and long-term care; outpatient visits; non-veteran hospital stays; pharmacy costs (only in sensitivity analysis).	Affairs Beneficiary Identification and Records Locator Subsystem Death Files.		areas than for "large urban" areas in the calculation of DRG prices.
Vieira et al, 2012 (34)	NR	RCT based CEA and CUA	5 yrs	Event-free LYG, Event-free and angina-free LYG, and QALY gained	Costs of initial hospitalisation follow-up costs incl. re-hospitalisations for repeat procedures; outpatients visits; medications; cardiovascular diagnostic tests; subsequent hospitalization for cardiovascular disease (MI, unstable angina, stroke, and death).	Hospital charges based on single-centre. Medication costs were based on ARTS trial.	NR	NR
Wang et al, 2008 (33)	Healthcare payer (Canada)	Decision model based on published literature , CEA	1 year	Combined rate of death, myocardial infarction (MI) and stroke.	Costs of initial CABG or PCI procedure including detailed costs of procedure, hospital length of stay (including intensive care unit, cardiac care unit and cardiac ward), and pharmacological agents. Cardiac-related events during the study period.	Hamilton Health Sciences Cardiac Case-Costing system, 2006 average Canadian manufactures' wholesale price , Ontario Drug Benefit Formulary and Ontario Physician Schedule of Benefits.	NR	One-way sensitivity analysis and scenario analysis.

Weintraub et al, 2004 (32)	Healthcare payer (NHS, UK)	RCT based CEA & CUA	1 yr	QALY gained and LYG	Costs of index procedure, and subsequent cardiac and non-cardiac hospitalisations, as a function of length of stay (incl. consumables, staff time for PCI, additional costs for stroke, bleeding, and not associated MI), rehabilitation and outpatient medication-use.	Published sources (British National Formulary, NHS reference costs), unpublished clinician survey, supplementary data from hospitals and manufacturers	NA	NR
Yock et al, 2003 (31)	Societal (USA)	Markov model with life tables, CEA & CUA	Life-time	QALY gained and LYG	Costs of initial, and repeat procedures (professional fees, devices, catherterisation laboratory time) & subsequent medical care (incl. subactute stent thrombosis)	Published reports , SEQOL, price survey	3% (Costs and QALYs)	One-way sensitivity analysis; analyses considering provisional stenting, restenosis, and post-surgical cognitive deficit
Zhang et al, 2015 (30)	Third party payer (USA)	Multicentre Registry based CEA & CUA using PS matching and life tables for projections	study period, Life-time	QALY gained and LYG	Direct hospital costs associated with index procedure, subsequent procedures.	Centres for Medicare and Medicaid Services dataset. Medicare Part A data file. Medicare fee schedule. Medicare participant per capita expenditure, stratified by age group.	3% (Costs , LYGs, QALY gained)	One-way sensitivity analysis and probabilistic sensitivity analysis.

Abbreviations: **ARTS, Arterial Revascularization Therapies Study; CABG, coronary artery bypass grafting; CEA, cost-effectiveness analysis; CEAC, cost-effectiveness acceptability curves; CEO, chief executive officer; CUA, cost-utility analysis; DES, drug eluting stent; DRG, diagnostic related group; EE, economic evaluation; excl, excluding; ICER, incremental cost-effectiveness ratio; incl., included; INB, incremental net benefit; LYG, life years gained; MACCE, major adverse cardiac and cerebrovascular event; MEDPAR, Medicare Provider and Analysis Review; MI, myocardial infarction MOH, ministry of health; NHS, national health care**

system; no, Number; NA, not applicable, NHS, national health system; NR, not reported; PCI, percutaneous coronary intervention; PSM, propensity-score matching; QALY, quality adjusted life year; RCT, randomised controlled trial; SEQOL, Study of Economics and Quality of Life; yrs, year/s

Table S2-IV A summary of the incremental cost-effectiveness ratios as reported by included economic evaluations

Study/ country of origin	Intervention vs. comparator	Time horizon (max reported)	ICER threshold	Currency and base year used	ICER/ other (reported)	ICER (USD, 2014)
Cohen et al, 2014 (45) USA	CABG vs DES	Life-time	$50,000	USD, 2010	$16,537/ QALY gained $12,329/LYG Diabetes mellitus: $9,864/QALY gained Age >70 yrs: $34,027/QALY gained LM disease only: PCI dominant 3-vessel disease: $4,905/ QALY gained	$16,537/ QALY gained $12,329/LYG Diabetes mellitus: $9,864/QALY gained Age >70 yrs: $34,027/QALY gained LM disease only: PCI dominant 3-vessel disease: $4,905/ QALY gained

de Feyter et al, 2002 (44) Netherlands	BMS vs CABG	1 yr	NR	NR*	Stable angina: $16,530/ MACCE avoided Unstable angina: $32,983/ MACCE avoided	Stable angina: $16,530/ MACCE avoided Unstable angina: $32,983/ MACCE avoided
Javanbakht et al, 2014 (46) Iran	CABG vs PCI (type of stent NR)	Life-time	NR	USD, 2011	CABG dominant	CABG dominant
Legrand et al, 2004 (43) Netherlands	CABG vs BMS	3 yr	NR	NR*	€10,492 per event free patient; €142,391 per CVA or MI free patient	$9,616 per event free patient; $130,510 per CVA or MI free patient
Magnuson et al, 2013 (42) USA	CABG vs DES	Life-time	$50,000	USD, 2010	$8,132/ QALY gained $6,791/ LYG Age≥70 yrs: $19,748/QALY gained LAD: $7,841/ QALY gained 3-vessel disease: $5,826/ QALY gained	$8,132/ QALY gained $6,791/ LYG Age≥70 yrs: $19,748/QALY gained LAD: $7,841/ QALY gained 3-vessel disease: $5,826/ QALY gained
Nathoe et al. 2005 (41) Netherlands	BMS vs Off-pump CABG	1 yr	NR	Euros, 1999	PCI dominant	PCI dominant

Perikhanyan 2011 (40) Armenia	CABG vs DES	4 yr	NR	USD, NR*	CABG dominant	CABG dominant
Rao et al, 2007 (39) UK	MIDCAB vs BMS	20 yr	£20 000	GBP, NR*	£2,878.98/ QALY gained	$3,165/ QALY gained
Reeves et al, 2004 (38) UK	MIDCAB vs BMS	1 yr	NR	GBP, 1999	£44,600/QALY gained £58,724 /QALY gained if patient costs incl.	$48,800/QALY gained $64,254/QALY gained (patient costs included)
Reynolds et al, 2003 (37) USA	BMS vs. CABG	2 yrs	NR	USD, 2000	ICER NR. Multivessel coronary stenting lead to cost-savings but higher rates of repeat revascularisations.	-
Stroupe et al. 2006 (36) USA	BMS vs CABG	5 yr	NR	USD, 2004	PCI dominant	PCI dominant

Vieira et al, 2012 (35) Brazil	CABG vs DES	5 yr	NR	USD, NR*	ICER NR. CABG had lower costs and greater event-free LYG, event-free angina-free LYG, and greater QALYs compared with PCI, i.e., CABG dominant.	-
Wang et al, 2008 (34) Canada	Off-pump CABG vs DES, On pump-CABG vs DES, Off-pump CABG vs BMS, On pump CABG vs BMS	5 yr	NR	CAD, 2006	ICER NR. Off-pump CABG (vs DES) was dominant. Off-pump CABG (vs BMS) was slightly more expensive but reduced rates of events. On-pump CABG (vs DES) was less costly but resulted in more events. On-pump CABG dominated by BMS.	-
Weintraub et al, 2004 (33) UK	CABG vs BMS	1 yr	NR	GBP, 2000	£189,982/LYG	$204,603/LYG
Yock et al, 2003 (32) USA	CABG vs. BMS (primary stenting)	Life-time	NR	USD, 2000	CABG dominant	CABG dominant

Zhang et al, 2015 (31) USA	CABG vs DES	Life-time	Multiple explored; $30,000, $50,000, & $100,000	USD, 2004	$30,803/QALY gained $38,330/ LYG Diabetes mellitus: $25,467/QALY gained Age >75 yrs: $32,118/QALY gained Unstable agina: $30,484/QALY gained ≥3 -vessel disease: $27,080/QALY gained HF: $24,602/QALY gained	$38,861/QALY gained $48,457/ LYG Diabetes mellitus: $32,129/QALY gained Age >75 yrs: $40,520/QALY gained Unstable agina: $38,458/QALY gained ≥3 -vessel disease: $34,164/QALY gained HF: $31,038/QALY gained

Abbreviations: **BMS, bare-metal stent; CABG, coronary artery bypass surgery; DES, drug-eluting stent; ; ICER, incremental cost-effectiveness ratio; LYG, life years gained PCI, percutaneous coronary intervention; MACCE, major adverse cardiac and cerebrovascular event; QALY, quality adjusted life years**

Notes: ***, base year for costs was assumed as published year, given this information was not available in the paper or through author correspondence.**

APPENDIX III

Assessment of quality of economic evaluations using Consolidated Health Economic Evaluation Reporting Standards (CHEERS)

A score of either "0", "0.5", "1" or "NA" were applied depending on the level of transparency of reporting (16). All evaluations were marked for quality out of a total score of 24 (for studies that did not include decision analytical modelling a total score of 22 was applied) and multiplied by 100. All studies that achieved a score of ≥80% were considered "high quality".

Appendix III -Quality Assessment_CHEERS.xlsx

Quality Assessment using the CHEERS checklist

Item No	Section	Recommendation	Yock et al.,2003	Reynolds et al, 2003	Weintraub et al., 2004	Reeves et al., 2004	Nathoe et al., 2005	Stroupe et al., 2006	Poulin et al., 2007	Zhang et al, 2015	Cohen et al, 2014	Javanbakht et al, 2014	Magnuson et al, 2013	Perikhanyan 2011	de Feyter et al, 2002	Vieira et al, 2012	Wang et al, 2008	Rao et al, 2007	Legrand et al, 2004
1	Title and abstract	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	1	0.5	0	0	1	1	1	1	1	1	1	1	0	1	0	1	0
2		Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0.5	1	1
3	Introduction	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0.5	1	1
4	Methods	Describe characteristics of the base case population and subgroups analysed, Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	0.5	0.5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
5		State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	0	0	0.5	0.5	0.5	1	1	1	1	1	1	1	0	0	1	1	0
6		Describe the perspective of the study and relate this to the costs being evaluated.	0.5	0	0	0.5	0	1	1	0.5	1	1	1	1	0	0	1	1	0
7		Describe the interventions or strategies being compared and state why they were chosen.	1	1	0.5	1	1	1	1	1	1	1	1	1	1	1	1	1	1
8		State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
9		Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	1	0	0	0	0	1	1	0.5	1	1	1	1	0	0	1	1	0
10		Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1	1
11		**11a** Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data. **11b** Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	1	0.5	0.5	0.5	0.5	1	1	1	1	1	1	1	0	0	0	1	1
12		If applicable, describe the population and methods used to elicit preferences for outcomes.	1	NA	1	1	0	NA	NA	0	0	0	0	NA	NA	0	NA	1	NA
13		**13a** Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs. **13b** Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	1	1	1	1	1	1	1	1	1	1	1	1	0.5	1	0	1	1
14		Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	1	1	1	0.5	1	1	1	0	1	1	1	0	1	0	1	0	0
15		Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	0
16		Describe all structural or other assumptions underpinning the decision-analytical model.	1	NA	1	1	0	NA	1	1	1	1	1	NA	NA	0	NA	1	NA
17		Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	1	1	1	1	1	1	1	1	1	1	1	0.5	0	1	1	1	0
18	Results	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	1	1	0	1	1	1	1	1	0.5	1	0.5	1	1	0.5	1	1	0
19		For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0
20		**20a** Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective). **20b** Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	1	0	0	1	1	0	1	1	1	1	1	0.5	0	0	1	1	0
21		If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	0	1	1	1	1	1	0	1	1	0	1	0	1	0	0	1	0
22		Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	1	1	0.5	1	1	1	1	1	1	1	1	1	1	1	1	1	0
23	Other	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other nonmonetary sources of support.	1	0	1	1	1	1	0	1	1	1	1	0	0	1	0	1	0
24		Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	0	0	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1
		Total points allocated (denominators vary)	20	14.5	16	20	19	21	21	21	22.5	22	22.5	17	9.5	13.5	15	23	9
		Overall quality score	83%	66%	67%	83%	79%	95%	91%	88%	94%	92%	94%	77%	43%	56%	68%	96%	41%

Referen Husereau, Don, et al. "Consolidated health economic evaluation reporting standards (CHEERS) statement." BMC medicine 11.1 (2013): 80.
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http://www.biomedcentral.com/1741-7015/11/80

Points

Scoring system:
1 transparent/ included
0.5 transparent but less detailed or not clear
0 not transparent/ not included

5 Cost-effectiveness of CABG vs. PCI among high-risk patients in Australia

5.1 Chapter overview

The objective of this chapter is to assess the cost-effectiveness of routine CABG versus PCI for MVCAD in contemporary clinical practice in Australia, using data collected from the MIG and the ANZSCTS registries. To balance the characteristics of patients included in the CABG and PCI groups, two propensity-score matching approaches, the 1:1 Nearest Neighbour, and the PSBB techniques (see Section 2.4) will be utilised. Through carrying out record linkage to a hospital administrative dataset, resource utilisation data with respect to hospital readmissions and associated direct medical costs will be gathered. The results from this chapter will be compared to that drawn from Chapter 4. A manuscript presenting the findings of this chapter was submitted to the Applied Health Economics and Health Policy international journal in May 2017.

The real-world cost-effectiveness of coronary artery bypass surgery versus stenting in high-risk patients: propensity score matched analysis of a single centre experience

Running head: The cost-effectiveness of CABG versus PCI in the Australian context

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Abstract

Background: There are limited economic evaluations comparing coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) for multi-vessel coronary artery disease (MV-CAD), in contemporary, routine clinical practice.

Objective: To perform a cost-effectiveness analysis comparing CABG and PCI from the perspective of the Australian public hospital payer, using observational data sources.

Methods: Clinical data from the Melbourne Interventional Group (MIG) and the Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) registries were analysed for 1,022 CABG (treatment) and 978 PCI (comparator) procedures performed between June 2009 and December 2013. Clinical records were linked to same-hospital admissions, and national death index (NDI) data. The incremental cost-effectiveness ratios (ICERs) per major adverse cardiac and cerebrovascular and event (MACCE) avoided were evaluated. Propensity score bin bootstrapping (PSBB) approach was used to validate base-case results.

Results: At mean follow-up of 2.7 years, CABG compared with PCI was associated with increased costs, greater all-cause mortality, but significantly lower rate of MACCE. An ICER of AU$55,255/ MACCE avoided was observed for the overall cohort. The ICER varied across comparisons against bare-metal stents (ICER: $25,815/ MACCE avoided), all drug-eluting stents, DES ($56,861), 2nd generation DES ($42,925), and 3rd generation of DES ($88,535). Lower ICERs were apparent for high-risk sub-groups including those with diabetes ($42,819), acute coronary syndrome ($30,431), left-main CAD ($38,864), and heart failure ($36,966).

Conclusions: In contemporary clinical practice, at early follow-up CABG was most economically attractive among high-risk subgroups. A personalised, multidisciplinary approach to treatment of patients may enhance cost containment, as well as improving clinical outcomes following revascularisation strategies.

Key points

- There are limited economic evaluations comparing the cost-effectiveness of CABG and PCI using data from routine clinical practice.
- Economic evaluations that used data from RCTs are constrained by reduced generalisability to real-world practice, as they excluded high-risk patient subsets.
- This evaluation, using observational data, and sophisticated propensity-score matching methods appropriate for small sample size cohorts (propensity score bin bootstrapping) revealed that CABG is most economically attractive among high-risk subgroups, including those with diabetes, acute coronary syndrome, left main CAD, and heart failure, at mean follow-up of 2.7 years.
- A personalised, multidisciplinary approach to treatment of patients may enhance cost containment, as well as improving clinical outcomes following revascularisation strategies.

1. Introduction

Over the last three decades, treatment of coronary artery disease (CAD) through coronary revascularisation has undergone rapid advancements [1]. Improvements to coronary artery bypass grafting (CABG) was associated with a three-fold reduction of in-hospital mortality [2]. The introduction of drug-eluting stents (DES) for percutaneous coronary intervention (PCI) reduced the risk of target revascularisation by 30%-55% [3, 4]. CABG is traditionally recommended for patients with complex multi-vessel CAD (MVCAD) and those with diabetes mellitus, and PCI is recommended for those with single-vessel CAD and acute coronary syndrome (ACS) [5, 6]. Significant improvements in clinical safety and efficacy of PCI with DES triggered several randomised controlled trials (RCTs) comparing the clinical and cost-effectiveness of CABG versus PCI among non-traditional patients for PCI, including those with MVCAD [6-12].

RCTs are the gold-standard for comparative efficacy studies, however, several issues are apparent in their execution and application in the real-world [13]. Firstly, RCTs are expensive and time consuming. Secondly, the timeliness of evidence from RCTs is poor and results may lag several years behind. Thirdly, due to their controlled nature, the generalisability of results from RCTs to routine clinical practice may be limited. For instance, in routine clinical practice patients may have more co-morbidities and receive less intensive treatment and monitoring than in RCTs. These drawbacks with RCTs flow through to economic evaluations conducted within RCTs.

The use of observational data from clinical registries and administrative databases may overcome the apparent drawbacks of RCTs; although these datasets carry their own limitations [14]. For instance, administrative datasets may be limited by the aggregation of service use, censored cost data, perspective mismatch, limited timely updates, missing resource utilisation data, and the limited ability to pool data from different centres due to inconsistencies in coding and costing approaches [15, 16]. Observational datasets from clinical registries and administrative databases however, provide quick, inexpensive, and relevant data for comparisons of treatment strategies in contemporary clinical practice [14]. The drawbacks of clinical registries, including treatment bias, and finite patient follow-up and missing data, may be accounted for through use of propensity-score matching, and record linkage approaches [14].

To date, several comparative *effectiveness* evaluations for CABG and PCI have been carried out using data from different clinical registries across various jurisdictions [5, 17-21]. However, only a limited number of studies utilised real-world data to evaluate the *costs*, and *cost-effectiveness* [22, 23]. These evaluations were primarily carried out by collaborating researchers of large clinical and quality registries in the USA, including the Society for Thoracic Surgery (STS), and the 'CathPCI' registry, which were linked recently to Medicare claims data [24-26]. Although contemporary clinical practice is largely similar across developed Western economies, results from the US may not be generalisable to other jurisdictions due to differences in healthcare systems [27]. The current evaluation investigates the real-world cost-effectiveness of CABG versus PCI for MVCAD, using data from two prominent clinical registries in Australia, and a local administrative dataset.

2. Methods

2.1. Study population

2.1.1. Data sources

Data from two large Australian prospective multi-centre cardiac databases were used, including the Australia New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) registry for CABG, and the Melbourne Interventional Group (MIG) registry for PCI. The ANZSCTS and MIG registries have been described in detail previously [28]. The study population comprised all patients who underwent either CABG or PCI at a single centre, The Alfred Hospital, a major metropolitan quaternary teaching hospital in Melbourne, Australia, from 1 July 2009 to 31 December 2013. The data from ANZSCTS and MIG registries were linked to the Australian National Death Index (NDI). The records were further linked to an administrative clinical costing dataset maintained by the Alfred Hospital Clinical Performance Unit. The data were censored at 31 December 2014. The study was approved by the Alfred Hospital's Human Research Ethics Committee (Project number: 142/15).

2.1.2. Inclusion and exclusion criteria

All patients who had multi-vessel coronary artery disease or left main coronary artery disease and underwent isolated CABG, or PCI using DES and/or bare metal stents (BMS) were included in this evaluation. Patients who underwent other procedures concomitant with CABG surgery (such as valve surgery), PCI without stents, or had incomplete administrative clinical costing records were excluded from the study population.

2.1.3. Sub-group analyses

Sub-group analyses were performed for patients with diabetes, chronic kidney disease (CKD), age>75 years, ACS, left main coronary artery disease (LMCAD), heart failure (CHF), who underwent PCI with BMS, and PCI using second and third generation DES. Different generations of DES were defined based on design similarities (Online Resource 1)

2.2. Clinical endpoints

Two primary clinical endpoints were used including major adverse cardiac and cerebrovascular events (MACCE), and all-cause mortality. Only same-hospital readmissions were considered, obtained through the linkage of ANZSCTS and MIG records to administrative clinical costing data. Clinical endpoints were defined using the Australian-refined diagnostic related group (AR-DRG) code included in each linked subsequent hospital episode record (Online Resource 1). Two additional clinical endpoints were considered including, other cardiovascular events (OCVE); and non-cardiovascular events (NCVE).

MACCE was defined as a combination of hospital readmissions for repeat CABG, repeat PCI, stroke, cerebrovascular events, acute myocardial infarction, heart failure, angina, chest pain, and arrhythmia. Subsequent hospitalisations that were not MACCE, but were cardiovascular related, were defined as OCVE (Online Resource 1). All subsequent hospitalisations that were not MACCE or OCVE were defined as NCVE (Online Resource 1).

2.3. Costs and resource utilization

Medical costs of hospitalisations were obtained from the administrative clinical costing dataset maintained by the Alfred Hospital Clinical Performance Unit (Online Resource 1).

2.4. Statistical analysis

Propensity score (PS) matching analysis was performed to select the CABG and PCI groups for the economic evaluation using the 1:1 Nearest Neighbour approach [29, 30] and the propensity score bin bootstrap (PSBB) technique [29, 31] (Online Resource 1). The PSBB approach was used for sub-group analyses, as sample sizes were too small to undertake matching through 1:1 Nearest Neighbour matching technique. Statistical analyses were conducted using R Version 3.3.2 (Windows) and Microsoft Excel 2013 (Windows). A program for the PSBB technique in R was developed for the purpose of this cost-effectiveness analysis.

2.5. Economic evaluation

2.5.1. Type of analysis

The real-world cost-effectiveness of CABG compared with PCI was estimated using a purely database approach and cohorts defined by 1:1 propensity-score matching. Costs and benefits were not projected beyond the observation period – similar to a within-trial analysis.

2.5.2. Treatment

To be consistent with prior economic evaluations, CABG was defined as the 'treatment' under consideration, despite being standard of care for patients with MVCAD and/or left-main CAD.

2.5.3. Comparator

The comparator was defined as PCI with BMS or DES. All generations of DES deployed in routine clinical care were included. Different generations of DES were defined based on design similarities (Online Resource 1).

2.5.4. Perspective

The evaluation took the perspective of the Australian public hospital payer.

2.5.5. Costs

Only medical costs related to hospital episodes were considered. Out-of-pocket costs and other costs related to loss of productivity of patients or carers, travel time, and lost income were not included. Medical costs associated with pharmaceuticals, and rehabilitation beyond hospital episode were not included due to absence of data. The base year for costs was 2013. All costs were measured in Australian dollars (AU$, AU$ 1 = USD 1.37, January 06, 2017). Costs were weighted using the Lin 1997 method [32], a time interval-based approach for adjusting mean costs according to the survival probability of patients at various time periods for which they were completely observed.

2.5.6. Economic measure

The economic measure under consideration was the incremental cost-effectiveness ratio (ICER). Three primary ICERs were calculated, including the incremental costs per deaths avoided, per life-years gained (LYG), and per MACCE avoided. For the matched cohort, the incremental cost per OCVE avoided and per NCVE avoided were also evaluated. Due to the absence of quality-of-life data from this population an incremental cost per quality-adjusted life years (QALY) could not be generated. To compare ICERs, willingness to pay thresholds of $45,000, $60,000, and $75,000 were used, based on current considerations by the Australian Medical Services Advisory Committee [33].

2.5.7. Time horizon

A maximum period of observation ranging from 6 months (0.5 years) to 60 months (five years) was estimated for the study population. Outcomes were censored at 1 July 2014.

2.5.8. Inflation adjustment

All costs were adjusted for inflation using the Australian Total Health Price Index [34]

2.5.9. Discounting

Net overall costs and benefits beyond first year were discounted by 5%, the standard rate as determined by the Australian Medicare Services Advisory Committee [35].

2.5.10. Sensitivity analyses

The structural uncertainty of base-case results (primary ICERs) was evaluated using the PSBB technique. As only same-hospital readmissions were considered in this analysis, the sensitivity of ICERs to different MACCE rates were evaluated (assumed +5%, 10% to 95% greater than observed rate). Probabilistic sensitivity analysis was inappropriate for this evaluation as it did not consider any published inputs and used only observational data.

3. Results

3.1. Study population

3.1.1. Baseline characteristics

At baseline, there were 2000 patients who underwent either isolated CABG (n=1022) or PCI (n=978) and met the inclusion criteria. Prior to matching, the two cohorts were similar ($p>0.05$) in several characteristics, but were significantly different ($p<0.05$) in relation to multi-vessel disease status, urgency of procedure, and history of prior MI (Online Resource 1). The size of CABG and PCI cohorts were reduced to 1094 patients in total (547 in each group) following PS-matching. Post-matching, the majority of baseline characteristics were similar between the CABG and PCI cohorts (Online Resource 1).

3.1.2. Clinical and procedural features

Among patients who underwent isolated CABG, 98.4% (n=1,006) received an arterial graft, while the remainder received vein grafts only. In the PCI group, DES, BMS, or both were deployed in 59% (n=579), 39% (n=379), and 2% (n=20) of procedures, respectively. On average, 1.1±0.37 stents were used per PCI procedure. Sixty percent of PCI procedures (n=351) used a third-generation DES, while 37% (n=213) used a second-generation DES. A first-generation DES was used only in 3% of PCI procedures. Following propensity-score matching, similar distributions of clinical and procedural characteristics were apparent in the matched PCI and CABG cohorts.

3.1.3. Follow-up

All patients were followed-up for a maximum of five years, and a minimum of six months. The average follow-up period was 2.7 years, which was not significantly different ($p>0.05$) between the CABG and PCI groups (2.69 years vs. 2.72 years).

3.2. Costs and effectiveness

3.2.1. Effectiveness

The clinical outcomes of the PS-matched cohorts and the discounted benefits are presented in Table 1. The probability of survival to each event were illustrated in Kaplan-Meier (KM) curves (Online Resource 2).

MACCE

At the end of observation period, those treated with PCI had a significantly higher number of MACCE, than CABG (287 vs. 54). The mean number of MACCE avoided from treatment with CABG compared with PCI was 0.42 (95% CI: 0.33 to 0.52) per patient treated at mean follow-up. With the 5% discount rate applied, the benefit was reduced to 0.38 (0.29 to 0.46).

The clinical outcomes related to individual components of MACCE are presented in Online Resource 2.

OCVE

There were fewer OCVE following CABG than PCI at the end of the observation period (122 vs. 173). However, at mean follow-up, the mean number of OCVE prevented by CABG, was not significant.

NCVE

Greater NCVEs were observed following CABG compared with PCI at the end of the observation period (784 vs. 632). However, the mean difference of NCVE between CABG and PCI groups did not reach significance.

All-cause mortality

The total number of deaths (any) at the end of the observation period was greater in the CABG group than PCI group (33 vs. 7). The adjusted mean number of deaths avoided by CABG was -0.04 (95% CI: -0.06 to -0.02).

Life years

The total life years lived by both CABG and PCI groups were similar at the end of the period (1473 vs. 1487), as such the mean difference (i.e. LYG) did not reach significance.

3.2.2. Costs

The costs within PS-matched groups related to the initial procedure, readmissions, and total costs, before and after adjustments for censoring and discounting, are reported in Table 2.

Initial costs

The total initial procedural costs of CABG was around 3-4 times greater than PCI. The mean incremental initial cost of CABG was $26,728 (95%CI: $25,029 to $30,466).

Readmissions costs

The total unadjusted cost of MACCE-related readmissions was approximately 13 fold greater for the PCI group than the CABG group at the end of the observation period. After adjusting for censoring through the Lin 1997 method (Table 2 and Online Resource 2), and discounting, the mean difference was -$3,164 (-$3,967 to -$2,360). The costs related to individual components of MACCE are available in Online Resource 2.

Similar to MACCE, the total unadjusted costs for OCVE- and NCVE-related readmissions were greater for the PCI than the CABG group, by 1-2 fold. The mean difference in costs for OCVE and NCVE readmissions did not reach significance.

The total unadjusted costs related to all readmissions were 2-3 fold greater for the PCI group than the CABG group. The adjusted incremental (CABG-PCI) costs of all readmissions was -$6,140 (-$8,945 to -$3,335).

Total costs

Compared with PCI, the total unadjusted cost, inclusive of initial and all readmissions costs, was 1-2 times greater for the CABG group. The adjusted incremental total cost of CABG compared with PCI at mean follow-up was $20,997 (95% CI: 16,897 to $25,098).

3.2.3. Cost-effectiveness

The ICERs corresponding to primary and secondary outcomes at mean follow-up are presented in Table 3. Given CABG was associated with greater total costs, but also greater total benefits in terms of MACCE and OCVE (not significant) when compared with PCI, ICERs of $55,255 per MACCE avoided, and $262,462 per OCVE avoided was apparent for the cohort. As for NCVE, all-cause mortality and LYG, CABG was deemed less effective (not significant for NCVE and LYG), and more costly.

3.3. Sensitivity Analyses

The outputs from the evaluation of structural uncertainty of base-case results using the PSBB approach are reported in Table 4. The probabilities of cost-effectiveness for those outcomes that yielded value-for-money benefits in the base-case analysis (only MACCE) are reported in Table 5. For the overall PS-matched cohort, an ICER of $56,153 per MACCE avoided was reported, similar to the corresponding base-case ICER (Table 4). For the overall PS-matched cohort, probabilities of cost-effectiveness in terms of MACCE avoided of 30.6%, 43.3%, and 56.5% were reported at thresholds $45,000, $60,000, and $75,000, respectively (Table 5). Similar to base-case results, CABG was less effective, and more costly in terms of deaths avoided at mean follow-up for the entire PS-matched cohort (Table 4). Although the ICER reported for LYG was high for the overall PS-matched cohort ($1,120,243 per LYG), the mean difference in LYG between the CABG and PCI groups was not significant, similar to base-case results (Table 4). One-way deterministic analyses for the evaluation of sensitivity of MACCE rates demonstrated an improvement in ICER for CABG with uniform increase of observed MACCE rates for both groups (Online Resource 2).

3.4. Sub-group analyses

The cost-effectiveness results for small groups of high-risk MVCAD patients including diabetics, elderly (age>75 years), those with AMI, CKD, LMCAD, and CHF, as well as device-specific sub-groups are reported in Table 4 and Table 5. There were not enough patients treated with 1st generation DES (3% of original PCI cohort) to generate cost-effectiveness results.

3.4.1. High-risk patients

In terms of ICER per MACCE avoided, CABG was most cost-effective among patients with diabetes, ACS, LMCAD and CHF (Table 4), for whom resulting in ICERs were <$50,000, and probabilities of cost-effectiveness of CABG were high (>50%) (Table 5). CABG resulted in significant incremental costs and all-cause mortality when compared with PCI for all high-risk patient sub-groups, deeming CABG less effective and more costly, in terms of ICER per death avoided. Elderly patients and those with CKD were among those that incurred highest incremental costs (Table 4). The difference in life years lived (i.e., LYG) at mean follow-up did not reach significance within any sub-group (Table 4).

3.4.2. Device-specific sub-groups

At mean-follow-up, CABG was unanimously associated with greater incremental costs, and lower mean MACCE (i.e., greater mean MACCE avoided) when compared against BMS, DES, 2nd and 3rd generations of DES (Figure 1 and Table 4). However, with each comparative technological advancement of PCI, an increase in ICER (in terms of MACCE avoided) and a reduction in probabilities of cost-effectiveness were apparent (Table 4 and Table 5). In terms of mean all-cause mortality, CABG resulted in significantly higher deaths (any) at mean follow-up, when compared with all PCI groups except 2nd generation DES, where the difference did not reach significance (Table 4). In terms of mean LYG, there were no significant differences between the CABG group and the DES and BMS groups in general, however, CABG resulted in significantly lower LYG when compared against 2nd generation DES, and the reverse, significantly higher LYG when compared against 3rd generation DES (Figure 2 and Table 4).

4. Discussion

4.1. Summary of findings

In contemporary clinical practice, CABG compared with PCI was associated with significantly lower MACCE, but also significant incremental total costs for patients with MVCAD, at mean follow-up of 2.7 years. An ICER of $55,255 per MACCE avoided was reported for the overall cohort, from the perspective of the Australian public hospital payer. Despite being associated with lower overall MACCE, CABG was associated with a significant incremental all-cause mortality at mean follow-up, however, the mean LYG between CABG PCI groups did not reach significance.

Sub-group analyses revealed that CABG was more economically attractive than PCI among MVCAD patients with diabetes (ICER: 42,819 per MACCE avoided), ACS ($30,431), LMCAD ($38,864) and CHF ($36,966). The incremental costs of CABG compared with PCI were the highest among elderly patients (age >75 years) and those with CKD.

Device-specific sub-group analyses revealed that the ICER for CABG (in terms of MACCE avoided) increased with each comparative technological advancement of PCI, including BMS (ICER: $25,815), DES ($56,861), 2nd generation DES ($42,925), and 3rd generation of DES ($88,535). Variable results were observed for all-cause mortality and LYG, which may be hypothesis-generating for future economic evaluations. When compared with 2nd generation DES, CABG was associated with significantly lower LYG, although no significant difference observed for all-cause mortality at mean follow-up. When compared against 3rd generation DES, CABG resulted in significantly higher LYG, but also significantly higher deaths (any) at mean follow-up.

4.2. How current findings compare to prior evidence

The current paper presents the first economic evaluation of CABG and PCI for MVCAD patients in Australia, in the setting of a large, quaternary hospital that typically treats complex cases. The evaluation, however, only assessed costs and benefits over a short-to-medium-term time horizon (mean 2.7 years). Our recent systematic review of cost-effectiveness of CABG and PCI in an international cohort, revealed that in the long-term, CABG was more cost-effective than PCI, whereas PCI may be more favourable in the short-term [27].

The current evaluation revealed that CABG was associated with significant incremental total costs, when compared with PCI. The total incremental cost of CABG ($20,997) was largely driven by its mean procedural cost, which was more expensive than PCI by $26,728 initially.

By comparison, CABG incurred significantly lower total readmissions costs than PCI (-$6,140) at mean follow-up, suggesting that the clinical benefit of CABG is still overshadowed by its high initial cost in the short-to-medium term. This is a notion that is consistent across published economic literature for CABG [27].

Only four prior economic evaluations comparing CABG and PCI reported ICERS in terms of MACCE ('events') avoided by CABG compared with PCI [27, 36-39]. In an economic model that was developed from the perspective of the Canadian healthcare payer, traditional CABG was found *less effective and more costly* in terms of MACCE avoided, when compared with BMS, and DES at 1-year follow-up [36]. In a 3-year analysis of costs and benefits yielded from the Arterial Revascularization Therapy Study, CABG was found *more costly*, but also *more effective*, when compared with BMS in terms of event free survival, driven significantly by a lower repeat revascularisation rate [38]. This evaluation was carried out from the Netherlands healthcare payer perspective [38]. The same group also reported an ICER of $35,809 per MACCE avoided for patients with unstable angina at 1-year follow-up [39]. The latter findings are consistent with our results for the ACS sub-group (includes patients with unstable angina), but with limits. In an economic evaluation conducted from the patient perspective in Armenia, CABG compared with DES was found *more effective and less costly* in terms of MACCE avoided at 5-year follow-up [37].

More recent economic evaluations from large RCTS, comparing CABG versus 1st generation DES suggest that CABG is more cost-effective for high-risk MVCAD patients, within the trial periods, and over a life-time time-horizon [10, 11]. Direct comparisons of our results with these findings was not possible as these studies reported effectiveness in terms of QALYs gained, using the EuroQOL (EQ-5D) health status instrument [10, 11].

An economic evaluation from the ASCERT study, which used observational data from the STS, CathPCI, and Medicare Claims registries, also employed QALY gained as the primary measure, sourcing health-related utility estimates from a local longitudinal study [22, 26, 40]. Nevertheless, ICERs reported by the ASCERT study were higher than that reported using data from RCTs [27]. Perhaps, this may be as a result of inclusion of more complex cases treated in routine care, who may have had greater resource utilisation needs, and therefore greater costs, particularly following CABG than PCI.

Our evaluation showed that PCI conferred a significant mortality benefit at mean of 2.7 years for MVCAD patients when compared with CABG, yet, there was no difference in life years lived between those treated with CABG and PCI. These finding are *inconsistent* with

cotemporary comparisons of effectiveness CABG and PCI [12, 41]. Perhaps centre-specific factors, such as the severity of cases treated may have attributed to these findings. Our results also suggest that relative to CABG, a significant benefit in terms of LYG may be conferred through implanting 2nd generation DES, than 3rd generation DES. These results may be consistent with emerging evidence of non-inferiority of 2nd generation DES when compared with CABG [42]. Yet, the benefit of 2nd generation DES, which are characterised by biocompatible polymers, over 3rd generation DES, that feature biodegradable polymers warrants further substantiation through large-scale longitudinal observational studies.

4.3. Strengths and limitations

This evaluation is strengthened by the use of standard and emerging PS-matching techniques for adjusting baseline differences between CABG and PCI groups. Only two prior economic evaluations of CABG and PCI utilised such approaches [22, 43]. Reynolds and colleagues [43] used a simple 2:1 matching approach based on several patient risk factors. The ASCERT study [22] used the PSBB approach, which was introduced by Faries and colleagues [31]. The current evaluation also used the PSBB approach in addition to the nearest neighbour 1:1 PS-matching technique, which was used to derive base-case results [30]. Several advantages were apparent with the use of the PSBB approach, including the retention of all observations found in the original CABG and PCI cohorts, and overcoming issues of truncated cohorts resulting from standard PS-matching techniques, thus enabling valid sub-group analyses [30]. The PSBB approach was also used to estimate willingness-to-pay probabilities using bootstrap results. The PSBB approach may therefore be an appropriate tool to assess structural sensitivity of results yielded from standard PS-matching methods [30].

Our economic evaluation also yielded cost-effectiveness estimates for high-risk MVCAD patients, including those with CKD, HF, and ACS, who have been typically excluded from RCTs comparing CABG and PCI [27]. In particular, the CKD group remains an under-examined group in relation to costs and benefits of different revascularisation strategies, despite evidence of an incremental risk and resource burden from renal failure [44-46]. Further evidence is therefore warranted for this patient subset from similar economic evaluations but over a longer time horizon.

The current analysis was impacted by limitations inherent to data sources used. We could not estimate the QALY gained from CABG compared with PCI, due to absence of local

evidence of health-related quality of life following revascularisation. Patient follow-up beyond 30 days and 12 months (MIG only) were not available through ANZSCTS and MIG registries, thus enforcing the use of record linkage to collect readmissions data, albeit only up to five years and from a single-centre. Multiple administrative datasets from different centres could not be used for this evaluation, as technical difficulties were anticipated merging such datasets in addition to obtaining permission from different sites. Difficulties with inter-hospital merging of admissions records in Australia are further amplified by issues related to data linkage capacity, its dependencies, timeliness of data supply, and different linkage maturities across States, Territories, and public-private institutions, and privacy legislation [47]. Issues related to the use of censored medical costs for this evaluation was accounted for by the Lin 1997 method [32]. To overcome issues pertaining to analyses of only same-hospital readmissions, a sensitivity analysis was carried out, which suggested an improvement of ICER (for CABG) with uniform increase of MACCE rates. The perspective of the analysis was limited to that of the Australian public hospital payer, as data related to outpatient physician visits were not available. Future economic analyses may consider broader perspectives such as that of the society, including patient perspectives. Finally, although the use of propensity-score matching analysis led to some removal of selection bias, we cannot eliminate unobservable bias, including the impact of unknown confounders that were not part of the ANZSCTS or MIG data collection. For instance, circumstances beyond clinician control e.g., resource constraints at hospitals, urgency of procedures, anticipated adherence to medication by the patient etc., may force clinical decisions outside of guideline-driven revascularisation with CABG or PCI with BMS or DES

4.4. Conclusions

CABG was cost-effective when compared with PCI in terms of MACCE avoided. It was most economically attractive among high-risk subgroups, including those with diabetes, acute coronary syndrome, left main CAD, and heart failure. Thus, a personalised, multidisciplinary approach to treatment of patients may enhance cost containment, as well as clinical outcomes following revascularisation strategies. Policy makers, clinicians and health technology evaluators may benefit from findings of the current economic evaluation, although, due to single-centre nature of this evaluation, results should be interpreted with care.

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6. Compliance with Ethical standards

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6.2. Ethics committee

This record linkage study undertaken as part of this evaluation at the Alfred Hospital, was approved on 24 March 2015 by the Alfred Hospital's Ethics Committee in the category of a 'low risk review' (Project number.: 142/15).

6.3. Conflict of interest

All authors declare no competing interests and takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. The authors report no relationships that could be construed as a conflict of interest.

6.4. Data availability statement

The datasets generated and analysed during the current study are not publicly available as they contain sensitive patient and hospital-specific information. They may be available in the de-identified form, from the corresponding author on reasonable request.

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8. Tables

Table 1 Clinical outcomes in propensity-matched cohorts, at mean 32 months (2.7 years) post-intervention.

		Total events or life years		Mean events or life years			
		CABG	PCI	CABG	PCI	Increment[a]	95% CI
MACCE	Overall, unadjusted	54	287	0.10	0.52	0.43	0.33 to 0.52
	Overall+ 5% discount			**0.09**	**0.46**	**0.38**	**0.29 to 0.46**
OCVE	Overall, unadjusted	122	173	0.22	0.32	0.09	-0.07 to 0.25
	Overall + 5% discount			**0.19**	**0.28**	**0.08**	**-0.06 to 0.22**
NCVE	Overall, unadjusted	784	632	1.43	1.55	-0.28	-2.07 to 1.51
	Overall + 5% discount			**1.26**	**1.36**	**-0.24**	**-1.81 to 1.32**
All-cause mortality	Overall, unadjusted	33	7	0.06	0.01	-0.05	-0.07 to -0.02
	Overall + 5% discount			**0.05**	**0.01**	**-0.04**	**-0.06 to -0.02**
Life years	Overall, unadjusted	1473	1487	2.69	2.72	-0.025	-0.17 to 0.12
	Overall+ 5% discount			**2.36**	**2.38**	**-0.022**	**-0.15 to 0.11**

Abbreviations: CABG, coronary artery bypass grafting; ICER, incremental cost-effectiveness ratio; LYL, life years lived; MACCE, major adverse cardiac and cerebrovascular event; OCVE, other cardiovascular event; NCVE, non-cardiovascular event; PCI, percutaneous coronary intervention
Notes: a. Increment= number of events avoided through treatment by CABG

Table 2 Medical costs related to the index procedure and readmissions in propensity-matched cohorts, at mean 32 (2.7 years) months post-intervention.

		Unadjusted total costs (AU$)		Mean estimates (AU$)			
		CABG	PCI	CABG	PCI	Increment	95% CI
Index procedure	Overall, unadjusted	21,600,607	6,422,858	39,489	11,742	26,728	25,029 to 30,466
	Overall, unadjusted	163,729	2,126,102	299	3,887	-3,588	-4,490 to -2,685

MACCE re-admissions	Overall, Lin 1997 method[a]			327	3,938	-3,611	-4,528 to -2,694
	Overall, Lin 1997 method + 5% discount			**287**	**3,451**	**-3,164**	**-3,967 to -2,360**
OCVE re-admissions	Overall, unadjusted	817,099	1,301,476	1,494	2,379	-885	-1,932 to 161
	Overall, Lin 1997 method[a]			1,685	2,411	-725	-1,838 to 388
	Overall, Lin 1997 method + 5% discount			**1,477**	**2,112**	**-635**	**-1,611 to 340**
NCVE re-admissions	Overall, unadjusted	1,992,382	3,255,132	3,642	5,951	-2,308	-4,623 to 6.0
	Overall, Lin 1997 method[a]			4,070	6,029	-1,960	-4,399 to 480
	Overall, Lin 1997 method + 5% discount			**3,566**	**5,283**	**-1,717**	**-3,855 to 421**
All readmissions	Overall, unadjusted	2,896,854	6,980,475	5,296	12,761	-7,465	-10,511 to -4,420[b]
	Overall, Lin 1997 method[a]			5,922	12,929	-7,007	-10,209 to -3,806 [b]
	Overall, Lin 1997 method + 5% discount			**5,189**	**11,329**	**-6,140**	**-8,945 to -3,335**
Total medical costs	Overall, unadjusted	23,936,938	13,222,340	43,760	24,172	19,588	15,245 to 23,931
	Overall, Lin 1997 method[a]			48,454	24,491	23,963	19,284 to 28,643
	Overall, Lin 1997 method + 5% discount			**42,457**	**21,460**	**20,997**	**16,897 to 25,098**

Abbreviations: CABG, coronary artery bypass grafting; ICER, incremental cost-effectiveness ratio; LYL, life years lived; LYG, life years gained; MACCE, major adverse cardiac and cerebrovascular event; OCVE, other cardiovascular event; NCVE, non-cardiovascular event; PCI, percutaneous coronary intervention

Notes:

[a], observed medical costs were weighed by a factor 1/(Pr(survival from censoring)) for multiple periods (see Appendix D of Supplemental for more information);

Exchange rate: 1 AU$ = 0.9244 USD as at June 30, 2013.

Table 3 The ICERs corresponding to primary and secondary outcomes, at mean 32 (2.7 years) months post-intervention.

Clinical event	Incremental effectiveness (95% CI)[a]	Incremental total costs (95% CI)[b]	ICER at 2.7 years
MACCE	0.38 (0.29, 0.46)	20,997 (16,897, 25,098)	55,255
OCVE	0.08 (-0.06, 0.22)	20,997 (16,897, 25,098)	262,462
NCVE	-0.24 (-1.81, 1.32)	20,997 (16,897, 25,098)	CABG LE, MC
All-cause mortality	-0.04 (-0.06, -0.02)	20,997 (16,897, 25,098)	CABG LE, MC
Life years	-0.02 (-0.15, 0.11)	20,997 (16,897, 25,098)	CABG LE, MC

Abbreviations: CABG, coronary artery bypass grafting; ICER, incremental cost-effectiveness ratio; 'LE, MC', less effective, more costly; LYL, life years lived; MACCE, major adverse cardiac and cerebrovascular event; OCVE, other cardiovascular event; NCVE, non-cardiovascular event; PCI, percutaneous coronary intervention

[a], outcomes discounted by 5%;

[b], total medical costs were adjusted by Lin 1997 method and discounted at 5%.

[c], ICER = incremental cost per event avoided, or life years gained

Exchange rate: 1 AU$ = 1.37 USD, January 06, 2017.

Table 4 Results from matching using the PSBB approach: Incremental costs and effectiveness and ICERs at mean 32 months (2.7 years) as observed for patient sub-groups from the original cohort.

			Incremental effectiveness[a]			Incremental costs[b] (AU$)	ICER at mean 2.7 years (AU$)		
Sub-group	N		All-cause mortality	Life years	MACCE		per Death avoided	per LYG	per MACCE avoided
	CABG	PCI							
All	1022	978	-0.04 (-0.06, -0.02)*	0.018 (-0.16, 0.20)	0.37 (0.26, 0.41)*	20,816 (16,541, 24,672*	CABG LE, MC	1,120,243	56,153
Diabetes	362	286	-0.05 (-0.08, -0.02)*	-0.04 (-0.35, 0.21)	0.50 (0.33, 0.61)*	21,386 (14,280, 28,715)*	CABG LE, MC	CABG LE, MC	42,819

Unstable angina (3)	573	642	-0.05 (-0.07, -0.02)*	0.09 (-0.04, 0.21)	0.56 (0.30, 0.80)*	17,203 (9,785, 24,510)*	CABG LE, MC	188,461	30,431
Age >75 years (4)	267	268	-0.07 (-0.09, -0.03)*	0.14 (-0.01, 0.31)	0.33 (0.18, 0.44) *	24,520 (18,286, 30,217)*	CABG LE, MC	169,792	73,970
Chronic Kidney Disease	265	235	-0.10 (-0.14, -0.06)*	0.05 (-0.14, 0.25)	0.38 (0.16, 0.56)*	23,873 (12,227, 34,199)*	CABG LE, MC	456,895	62,299
Left Main Coronary Artery Disease (2)	301	73	-0.05 (-0.07, -0.04)*	-0.21 (-0.48, 0.05)	0.47 (0.21, 0.67)*	18,096 (9,925, 26,266)*	CABG LE, MC	CABG LE, MC	38,864
Heart Failure (2)	106	64	-0.11, (-0.17, -0.05)*	-0.03 (-0.19, 0.12)	0.45 (0.20, 0.70)*	16,796 (7,540 , 28,050)*	CABG LE, MC	CABG LE, MC	36,966
PCI – BMS (4)	1022	379	-0.05 (-0.07, -0.02)*	-0.11 (-0.27, 0.09)	0.54 (0.24, 0.56)*	13,645 (9,159, 18,816)*	CABG LE, MC	CABG LE, MC	25,815
PCI – DES	1022	579	-0.04 (-0.06, -0.02)*	0.06 (-0.08, 0.25)	0.37 (0.27, 0.43)*	21,305 (18,493, 25,884)*	CABG LE, MC	323,558	56,861
PCI – 2nd generation DES	1022	213	-0.02 (-0.06, 0.018)	-0.78 (-0.91, -0.63)*	0.47 (0.23, 0.64)*	20,345 (14,082, 26,577)*	CABG LE, MC	CABG LE, MC	42,925

PCI – 3rd generation DES	1022	351	-0.06 (-0.08, -0.03)*	0.7 (0.47, 0.95)*	0.25 (0.16, 0.31)*	22,424 (19,477, 27,459)*	CABG LE, MC	31,997	88,535

Abbreviations: BMS, bare-metal stents; CABG, coronary artery bypass grafting; DES, drug-eluting stents; ICER, incremental cost-effectiveness ratio; 'LE, MC', less effective, more costly; LYG, life years gained; MACCE, major adverse cardiac and cerebrovascular event; PCI, percutaneous coronary intervention; PSBB, propensity-score bin bootstrap.
Notes: [a], outcomes discounted at 5%; [b], total medical costs were adjusted by Lin 1997 method and discounted at 5%; c, included direct medical costs of all hospitalizations and index hospital costs. Exchange rate: 1 AUD = 1.37 USD, January 06, 2017.

Table 5 Results from matching using the PSBB approach: Probabilities of cost-effectiveness for CABG compared with PCI when considering incremental costs per MACCE avoided at mean 32 months (2.7 years).

	Probabilities of cost-effectiveness of CABG vs. PCI				Probabilities of cost-effectiveness relative to threshold		
Sub-group	% CABG LE, MC	% CABG LE, LC	% CABG ME, LC	% CABG ME, MC	AU$ 45,000	AU$ 60,000	AU$ 75,000
All	0.04%	0.0%	0.5%	99.4%	30.6%	43.3%	56.5%
Diabetes	0.6%	0%	3.3%	96.1%	55.8%	69.9%	79.2%
Unstable Angina (4)	0.0%	0.0%	3.0%	97.0%	57.9%	67.3%	72.6%
Age >75 years	4.2%	0.0%	0.05%	95.7%	21.3%	36.9%	51.3%
Chronic Kidney Disease	7.4%	2.1%	7.2%	83.4%	52.6%	60.7%	64.9%
Left Main Coronary	2.6%	0.0%	1.1%	96.3%	54.8%	60.5%	66.2%

Artery Disease (2)							
Heart Failure (2)	7.7%	2.9%	11.7%	77.5%	67.3%	73.6%	77.4%
PCI – BMS (4)	0.2%	0.0%	4.2%	95.6%	56.9%	69.6%	81.8%
PCI – DES	0.2%	0.0%	2.9%	96.9%	21.5%	40.5%	61.3%
PCI – 2nd generation DES	7.1%	0.02%	0.64%	92.1%	68.0%	76.2%	79.1%
PCI – 3rd generation DES	3.5%	0.02%	2.9%	93.6%	18.2%	25.5%	33.8%

Abbreviations: BMS, bare-metal stents; CABG, coronary artery bypass grafting; DES, drug-eluting stents; ICER, incremental cost-effectiveness ratio; LYG, life years gained; MACCE, major adverse cardiac and cerebrovascular event; PCI, percutaneous coronary intervention; PSBB, propensity-score bin bootstrap method.

9. Figure Legends

Figure 1: Scatter plots generated from evaluations of cost-effectiveness in terms of incremental cost per major adverse cardiac and cerebrovascular events (MACCE) avoided using the propensity-score bin bootstrap (PSBB) approach.

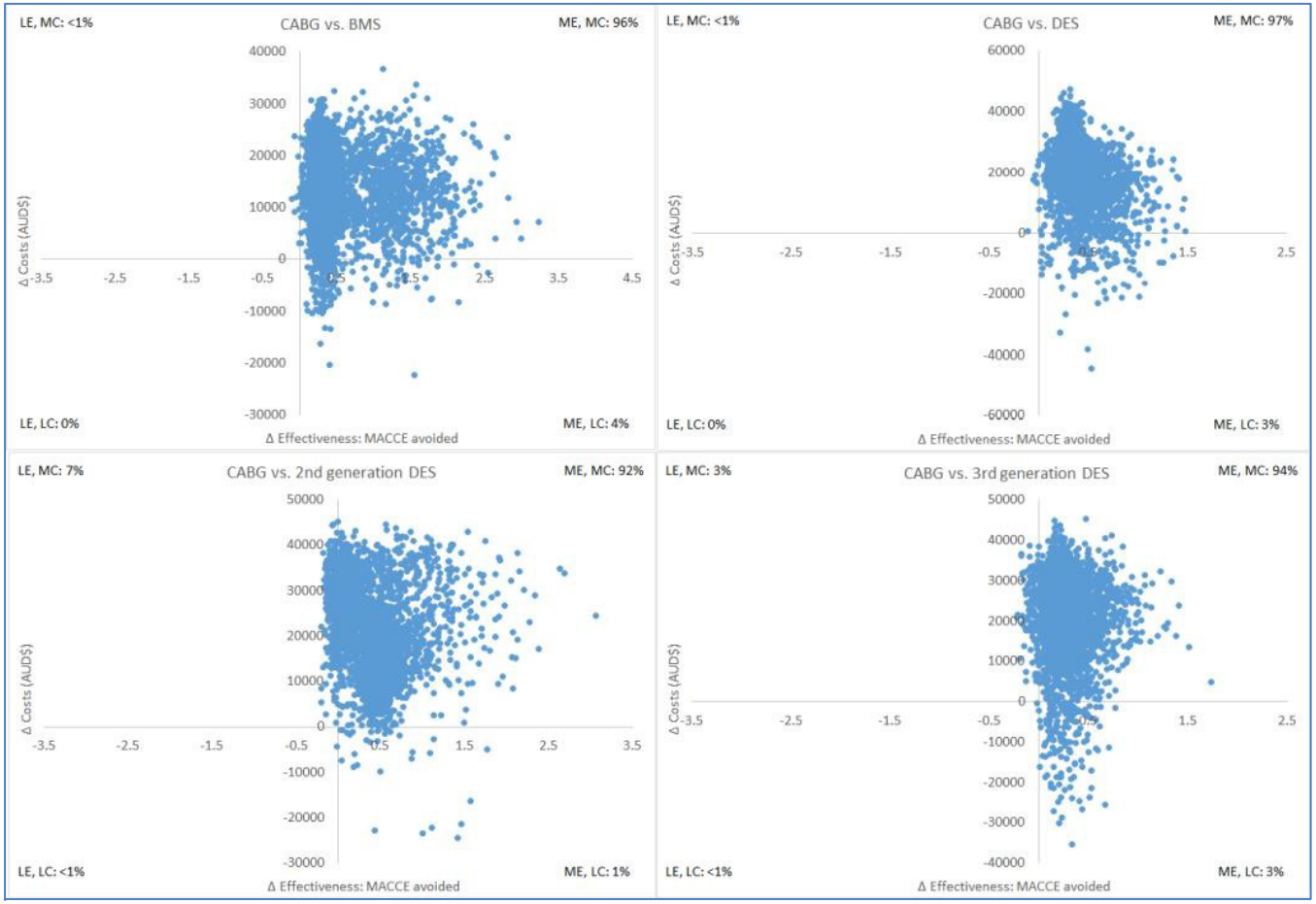

Figure 2: Scatter plots generated from evaluations of cost-effectiveness in terms of incremental cost per life years gained (LYG) using the propensity-score bin bootstrap (PSBB) approach.

Online Resource 1 - Methods

The real-world cost-effectiveness of coronary artery bypass surgery versus stenting in high-risk patients: propensity score analysis of a single centre experience

Running head: The cost-effectiveness of CABG versus PCI in the Australian context

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Australian-refined diagnostic related group (AR-DRG) corresponding to clinical end-points

Event type	DRG recorded	Event sub-type
Major adverse cardiac and cerebrovascular events (MACCE)	F05A Coronary Bypass W Invasive Cardiac Investigation, Major Complexity F05B Coronary Bypass W Invasive Cardiac Investigation, Minor Complexity F06A Coronary Bypass W/O Invasive Cardiac Investigation, Major Complexity F06B Coronary Bypass W/O Invasive Cardiac Investigation, Minor Complexity	Repeat revascularisation (CABG)
	F10A Interventional Coronary Procedures, Admitted for AMI, Major Complexity F10B Interventional Coronary Procedures, Admitted for AMI, Minor Complexity	Repeat revascularisation (PCI) + AMI
	F15A Interventional Coronary Procs, Not Adm for AMI, W Stent Implant, Major Comp F15B Interventional Coronary Procs, Not Adm for AMI, W Stent Implant, Minor Com F16A Interventional Coronary Procs, Not Adm for AMI, W/O Stent Implant, Major Comp F16B Interventional Coronary Procs, Not Adm for AMI, W/O Stent Implant, Minor Comp	Repeat revascularisation (CABG)
	B69A TIA and Precerebral Occlusion, Major Complexity B69B TIA and Precerebral Occlusion, Minor Complexity B70A Stroke and Other Cerebrovascular Disorders, Major Complexity B70B Stroke and Other Cerebrovascular Disorders, Intermediate Complexity B70C Stroke and Other Cerebrovascular Disorders, Minor Complexity B70D Stroke and Other Cerebrovascular Disorders, Transferred <5 Days	Cerebrovascular events
	B70A Stroke and Other Cerebrovascular Disorders, Major Complexity B70B Stroke and Other Cerebrovascular Disorders, Intermediate Complexity B70C Stroke and Other Cerebrovascular Disorders, Minor Complexity B70D Stroke and Other Cerebrovascular Disorders, Transferred <5 Days	Stroke only
	F41A Circulatory Disorders, Adm for AMI W Invasive Cardiac Inves Proc, Major Comp F41B Circulatory Disorders, Adm for AMI W Invasive Cardiac Inves Proc, Minor Comp	Acute Myocardial Infarction (AMI)
	F62A Heart Failure and Shock, Major Complexity F62B Heart Failure and Shock, Minor Complexity F62C Heart Failure and Shock, Transferred <5 Days	Heart Failure (HF)
	F76A Arrhythmia, Cardiac Arrest and Conduction Disorders, Major Complexity F76B Arrhythmia, Cardiac Arrest and Conduction Disorders, Minor Complexity	Arrhythmia
	F74A Chest Pain, Major Complexity F74B Chest Pain, Minor Complexity	Chest pain
	As per national death index (NDI) data	Death
Other cardiovascular related events (OCVE)	F01A Implantation and Replacement of AICD, Total System, Major Complexity F01B Implantation and Replacement of AICD, Total System, Minor Complexity F02Z Other AICD Procedures F03A Cardiac Valve Procedures W CPB Pump W Invasive Cardiac Investigation, Major Comp F03B Cardiac Valve Procedures W CPB Pump W Invasive Cardiac Investigation, Minor Comp F04A Cardiac Valve Procedures W CPB Pump W/O Invasive Cardiac Invest, Major Comp	

	F04B	Cardiac Valve Procedures W CPB Pump W/O Invasive Cardiac Invest, Interm Comp	
	F04C	Cardiac Valve Procedures W CPB Pump W/O Invasive Cardiac Invest, Minor Comp	
	F07A	Other Cardiothoracic/Vascular Procedures W CPB Pump, Major Complexity	
	F07B	Other Cardiothoracic/Vascular Procedures W CPB Pump, Intermediate Complexity	
	F07C	Other Cardiothoracic/Vascular Procedures W CPB Pump, Minor Complexity	
	F08A	Major Reconstructive Vascular Procedures W/O CPB Pump, Major Complexity	
	F08B	Major Reconstructive Vascular Procedures W/O CPB Pump, Intermediate Complexity	
	F08C	Major Reconstructive Vascular Procedures W/O CPB Pump, Minor Complexity	
	F09A	Other Cardiothoracic Procedures W/O CPB Pump, Major Complexity	
	F09B	Other Cardiothoracic Procedures W/O CPB Pump, Intermediate Complexity	
	F09C	Other Cardiothoracic Procedures W/O CPB Pump, Minor Complexity	
	F11A	Amputation, Except Upper Limb and Toe, for Circulatory Disorders, Major Comp	
	F11B	Amputation, Except Upper Limb and Toe, for Circulatory Disorders, Minor Comp	
	F12A	Implantation and Replacement of Pacemaker, Total System, Major Complexity	
	F12B	Implantation and Replacement of Pacemaker, Total System, Minor Complexity	
	F13A	Amputation, Upper Limb and Toe, for Circulatory Disorders, Major Complexity	
	F13B	Amputation, Upper Limb and Toe, for Circulatory Disorders, Minor Complexity	
	F14A	Vascular Procedures, Except Major Reconstruction, W/O CPB Pump, Major Complexity	
	F14B	Vascular Procedures, Except Major Reconstruction, W/O CPB Pump, Interm Comp	
	F14C	Vascular Procedures, Except Major Reconstruction, W/O CPB Pump, Minor Complexity	
	F17A	Insertion and Replacement of Pacemaker Generator, Major Complexity	
	F17B	Insertion and Replacement of Pacemaker Generator, Minor Complexity	
	F18A	Other Pacemaker Procedures, Major Complexity	
	F18B	Other Pacemaker Procedures, Minor Complexity	
	F19A	Trans-Vascular Percutaneous Cardiac Intervention, Major Complexity	
	F19B	Trans-Vascular Percutaneous Cardiac Intervention, Minor Complexity	
	F20Z	Vein Ligation and Stripping	
	F21A	Other Circulatory System OR Procedures, Major Complexity	
	F21B	Other Circulatory System OR Procedures, Intermediate Complexity	
	F21C	Other Circulatory System OR Procedures, Minor Complexity	
	F40A	Circulatory Disorders W Ventilator Support, Major Complexity	
	F40B	Circulatory Disorders W Ventilator Support, Minor Complexity	
	F42A	Circulatory Dsrds, Not Adm for AMI W Invasive Cardiac Inves Proc, Major Comp	
	F42B	Circulatory Dsrds, Not Adm for AMI W Invasive Cardiac Inves Proc, Minor Comp	
	F43A	Circulatory Disorders W Non-Invasive Ventilation, Major Complexity	
	F43B	Circulatory Disorders W Non-Invasive Ventilation, Minor Complexity	
	F61A	Infective Endocarditis, Major Complexity	
	F61B	Infective Endocarditis, Minor Complexity	
	F63A	Venous Thrombosis, Major Complexity	
	F63B	Venous Thrombosis, Minor Complexity	
	F64A	Skin Ulcers in Circulatory Disorders, Major Complexity	

	F64B Skin Ulcers in Circulatory Disorders, Intermediate Complexity F64C Skin Ulcers in Circulatory Disorders, Minor Complexity F65A Peripheral Vascular Disorders, Major Complexity F65B Peripheral Vascular Disorders, Minor Complexity F66A Coronary Atherosclerosis, Major Complexity F66B Coronary Atherosclerosis, Minor Complexity F67A Hypertension, Major Complexity F67B Hypertension, Minor Complexity F68A Congenital Heart Disease, Major Complexity F68B Congenital Heart Disease, Minor Complexity F69A Valvular Disorders, Major Complexity F69B Valvular Disorders, Minor Complexity F73A Syncope and Collapse, Major Complexity F73B Syncope and Collapse, Minor Complexity F75A Other Circulatory Disorders, Major Complexity F75B Other Circulatory Disorders, Intermediate Complexity F75C Other Circulatory Disorders, Minor Complexity	
Non-cardiovascular related events (NCVE)	All DRGs that do no match above	

Clinical Cost Buckets in the Alfred Hospital Clinical Performance Unit Dataset

The dataset captured real costs across time for multiple clinical cost buckets, including “allied health”, “coronary care unit”, “emergency”, “incentive care unit”, “imaging”, “medical-surgical staff”, “non-medical staff”, “nursing staff”, “pathology”, “pharmacy”, “theatre (operating room)”, “theatre (non-operating room)”, and “other”. See table more for resource utilisation variables considered.

Allied Health	Coronary Care Unit (CCU)	Emergency	ICU	Imaging	Medical - Surgical	Medical - Non-Surgical	Nursing	Pathology:	Pharmacy:	Theatre (OR)	Theatre (non-OR)	Other Costs
Audiology	Includes:	Includes:	High Dependency Unit (HDU)	Cardiotocograph (CTG)	Anaesthetists	Consultants/Sessionals	Breast-Feeding Assessment	Anatomical Pathology	Imprest	Anaesthetics (including consumables, gases)	Angiography	
Child Abuse	medical and nursing costs	medical and nursing costs	Intensive Care Unit (ICU)	Computerised Tomography (CT Scan)	Consultants/Sessionals	Hospital Medical Officers (HMO)	Chemotherapy	Andrology	Scripted - Including Pharmaceutical Benefits Scheme (PBS)	Anaesthetic Drugs	Cardiac Catheterisation Laboratory	
Child Development Centre			Neonatal Intensive Care Unit (NICU)	Magnetic Resonance Imaging (MRI)	Hospital Medical Officers (HMO)	Registrars	Clinical Sterile Supply (CSSD)	Biochemistry	Section 100 (S100)	Clinical Sterile Supply (CSSD)	Electrocardiography	
Dietetics			Special Care Nursery (SCN)	Mammography	Registrars	Residents	Delivery Suites	Blood Bank		Day Surgery	Endoscopy Suite	
Interpreters			Ventilation Weaning Unit	Nuclear Medicine	Residents	Visiting Medical Officer (VMO)	Domiciliary Suites	Clinical Pharmacology		Endoscopy Suite	Gait Laboratory	
Medical Illustration			Includes:	Positron Emission Tomography (PET)	Visiting Medical Officer (VMO)	excludes:	Hospital in the Home (HITH)	Cytogenetics		Perfusionists	Hyperbaric	
Neuropsychology			medical and nursing costs	Prosthesis for Imaging	excludes:	Radiologists,	Lactation Consultant	Cytology		Pre-operative Lounge	Lithotripsy	
Occupational Therapy				Radiology	Radiologists,	Pathologists,	Outpatient Nursing and Consumables	Haematology		Pre-operative Nursing	Prostheses for Cath Lab	
Optometry			Includes:	Ultrasound	Pathologists,	Emergency Physicians,	Renal Dialysis	Histology		Prosthetics	Radiotherapy	
Orthoptics			SCN if co-located with an ICU		Emergency Physicians,	Intensivists and	Special Care Nursery	Immunology		Recovery Nursing	Sleep & Respiratory Laboratory	
Orthotics				Includes:	Intensivists and	Neonatologists	Stomal Therapy	Microbiology		Theatre Consumables		
Pastoral Care (Chaplaincy)				Medical Radiologists and Nursing Radiolo costs	Neonatologists		Transit Lounge	Serology		Theatre Nursing		
Physiotherapy							Transport - Patient	Virology		Theatre Technicians		
Play Centre - Play Therapy (RCH)							Ward Catering	Includes:				
Podiatry							Ward Nursing and Ward Consumables	Pathologists				
Psychology							excludes:					
Sexual Assault Clinic							CCU, Emergency and ICU					
Social Work							may include SCN if not co-located					
Speech Therapy							with NICU					

Drug eluting stents (DES) recorded in the MIG registry, and generations classified based on design similarities

Commercial name of DES	Generation
Cordis Cypher	1st
Taxus	1st
Taxus - Liberte	2nd
Destiny	2nd
Endeavour	2nd
Xience	2nd
Promus	2nd
Endeavour Resolute	2nd
Endeavour Sprint	2nd
Promus Element	3rd
Xience Prime	3rd
Resolute Integrity	3rd
Absorb BVS	3rd
Orsiro Hybrid	3rd
Xience Xpedition	3rd
BioMatrix Flex	3rd
Promus Premier	3rd
Resolute Onyx	4th

Table 1 Characteristics of drug eluting stents by generation [1, 2].

Generation	Platform	Polymer	Drug	Examples
First	Bare metal (stainless steel) devices	Durable polymer not designed for biocompatibility	Sirolimus, Paciltaxel	Cypher, Taxus, Ion
Second	Cobalt chromium devices	Biocompatible polymers, non-bioabsorbable polymers (fluoride-based)	Zotarolimus Everolimus Biolimus A9	Endeavor, Xience V, Xience Prime, Resolute, Biomatrix, Nobori
Third	Platinum chromium alloy devices	Biodegradable polymers, biodegradable poly-L-lactide or magnesium based, polymer-free stents	Zotarolimus Everolimus	TAXUS Element, Promus Element, Promus Premier
Fourth	Bioabsorbable devices , also known as bioabsorbable vascular scaffolds (BVS)	Polymer-free	Sirolimus Biolimus A9	BioFreedom, Cre8

A description of the propensity score matching methods and statistical analysis techniques used

Nearest neighbour 1:1 matching

Propensity score (PS) matching analysis was used to select the CABG and PCI groups for the economic evaluation. A PS was generated for each patient, using the Nearest-Neighbour 1:1 matching algorithm (with no replacement) with a caliper width of 0.25 times the standard deviation (SD) of the PS distribution [3, 4]. Multiple logistic regression was utilised for both the generation of the PS using the type of treatment (CABG or PCI) as the dependent variable and the identification of matching variables based on significant predictors of long-term all-cause mortality. Baseline variables selected for matching included age, diabetes, diabetes treated with insulin, dialysis user, heart failure, cerebrovascular disease, cardiogenic shock, intra-operative balloon pump, admission status, number of diseased vessels, left main coronary artery disease and the AUSSCORE-II [5].

Propensity score bin bootstrap method (PSBB)

An additional emerging technique, the PSBB technique was also used in this evaluation. The PSBB technique relates to sub-classification (stratification), which involves the formation of groups of individuals who are similar defined by quintiles of the PS distribution [6]. Results are aggregated within quintiles and averaged across the groups to obtain a final estimate on average, for the cohort. PSBB is an extension of sub-classification, and involves the bootstrapping of results within 'bins' or PS quintiles generated through stratification [3].

Additional statistical analyses performed

Differences in baseline characteristics between CABG and PCI were compared through the Chi-square test for categorical variables, and the Student's t-test for continuous variables, using a significant level (alpha) at 0.05. Kaplan-Meier (KM) curves were generated for all clinical end-points, including all components of major adverse cardiac and cerebrovascular events (MACCE).

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Online Resource 2 - Results

The real-world cost-effectiveness of coronary artery bypass surgery versus stenting in high-risk patients: propensity score analysis of a single centre experience

Running head: The cost-effectiveness of CABG versus PCI in the Australian context

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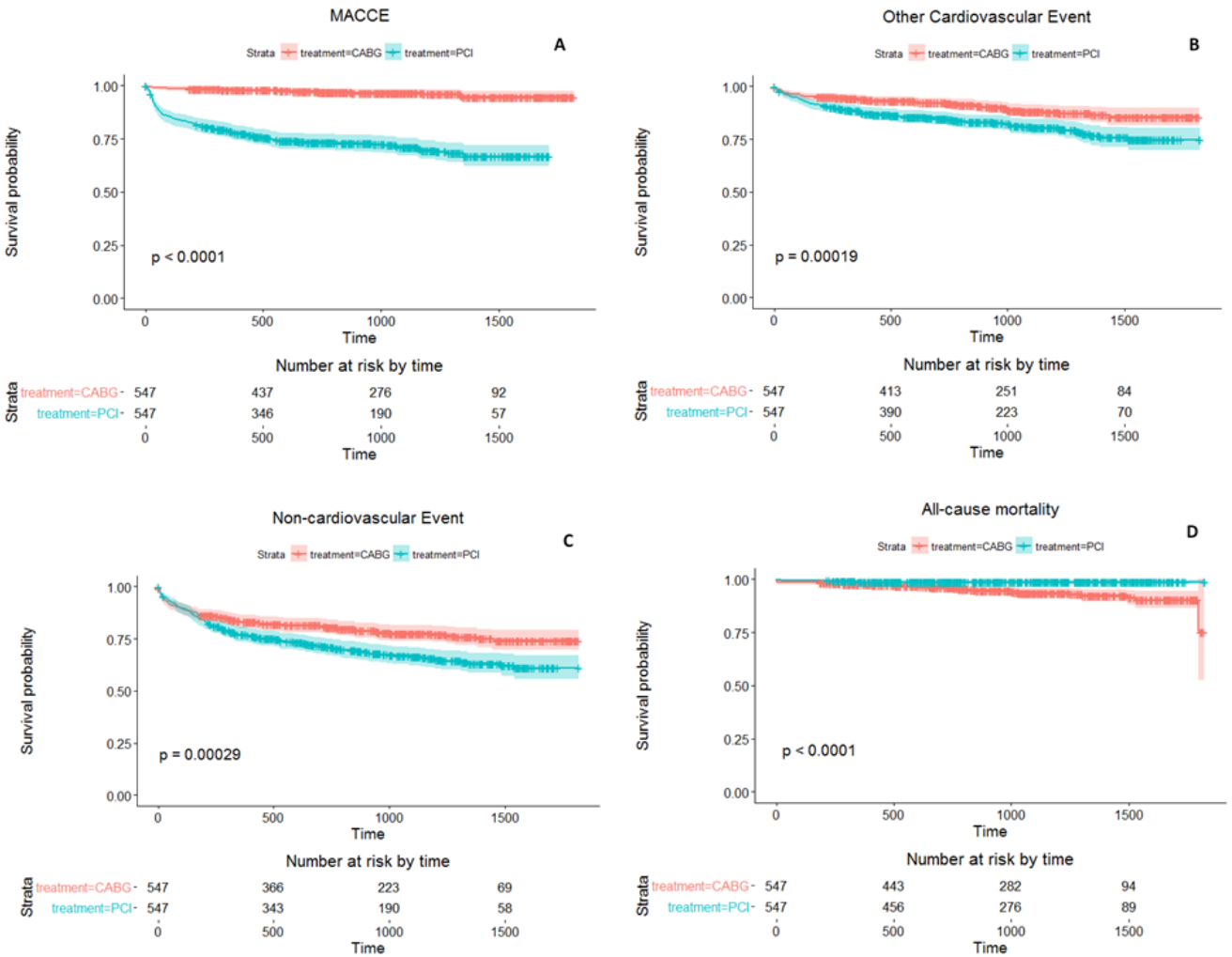
Baseline characteristics of CABG and PCI cohorts pre- and post-propensity-score matching.

	Unmatched cohort			Propensity-score matched cohort		
Variable	CABG **N=1022**	PCI **N=978**	**P-value**	CABG **N=547**	PCI **N=547**	**P-value**
Mean age (SD)	67.0 (10.7)	67.4 (11.6)	**0.434**	67.3 (11.0)	67.4 (11.5)	**0.920**
Male (%)	824 (80.6)	759 (77.6)	**0.108**	434 (79.3)	434 (79.3)	**1.000**
Mean BMI (SD)	29.3 (14.1)	28.2 (5.31)	**0.020**	28.5 (6.92)	28.2 (5.50)	**0.950**
Current smoker (%)	176 (25.6)	210 (21.6)	**0.066**	91 (25.5)	91 (16.7)	**0.002**
Diabetes (%)	362 (35.4)	286 (29.3)	**0.004**	184 (33.6)	181 (33.1)	**0.898**
Insulin (%)	100 (9.78)	76 (7.77)	**0.131**	51 (9.3)	54 (9.9)	**0.837**
Dialysis (%)	17 (1.66)	14 (1.43)	**0.811**	9 (1.6)	9 (1.6)	**1.000**
Hypertension (%)	878 (85.9)	761 (77.8)	**<0.001**	467 (85.4)	450 (82.3)	**0.189**
Hypercholesterolemia (%)	892 (87.3)	776 (79.4)	**<0.001**	472 (86.3)	457 (83.7)	**0.265**
Prior MI (%) <24 hrs	25 (2.45)	299 (35.2)	**<0.001**	11 (2.0)	131 (29.1)	**<0.001**
1-7 days	204 (20.0)	343 (40.4)		124 (22.7)	150 (33.3)	
>7 days	344 (33.7)	0 (0.00)		181 (33.1)	0 (0.00)	
Prior HF (%)	106 (10.4)	64 (6.55)	**0.003**	46 (8.4)	52 (9.5)	**0.597**
Peripheral vascular disease (%)	122 (11.9)	104 (10.6)	**0.400**	60 (11.0)	60 (11.0)	**1.000**
Cerebrovascular events (%)	109 (10.7)	84 (8.60)	**0.137**	54 (9.9)	58 (10.6)	**0.765**
Prior cardiac surgery (%)	19 (15.0)	141 (14.4)	**0.976**	8 (10.3)	106 (19.4)	**0.073**
Shock (%)	19 (1.86)	38 (3.89)	**0.010**	8 (1.5)	11 (2.0)	**0.643**
IABP (%)	42 (4.11)	15 (1.53)	**0.001**	8 (1.5)	6 (1.1)	**0.788**
Status (%) Elective	552 (54.0)	322 (32.9)	**<0.001**	251 (45.9)	262 (47.9)	**0.193**
Rescue	0 (0.00)	10 (1.02)		0 (0.00)	3 (0.55)	
Urgent	439 (43.0)	646 (66.1)		295 (53.9)	282 (51.6)	
Mean EF percentage (SD)	51.7 (14.4)	52.5 (10.4)	**0.442**	51.6 (13.6)	52.7 (10.2)	**0.426**
MVD (%) Three vessels	735 (71.9)	385 (39.4)	**<0.001**	318 (58.1)	335 (61.2)	**0.324**
Two vessels	287 (28.1)	593 (60.6)		229 (41.9)	212 (38.8)	
Left main disease (%)	301 (29.5)	73 (7.49)	**<0.001**	85 (15.5)	68 (12.5)	**0.178**
Mean AusSCORE-II (SD)	0.02 (0.04)	0.02 (0.04)	**0.03**	0.02 (0.4)	0.02 (0.3)	**0.199**

Abbreviations: BMI, body mass index; EF, ejection fraction; HF, heart failure; IABP, intra-operative balloon pump; MI, myocardial infarction; MVD, multi-vessel disease; SD, standard deviation.

Kaplan-Meier (KM) survival curves for A. major adverse cardiac and cerebrovascular event; B. other cardiovascular event; C. non-cardiovascular event; and D. all-cause mortality, for 1:1 matched treatment and comparator groups.



Components of MACCE, iincremental costs and benefits at 32 months (2.7 years) as observed in propensity-score matched cohorts.

Clinical endpoint	Total no. events (n/N)		Unadjusted total costs of all events (AUD$)		Mean cost-effectiveness		
					Incremental effectiveness (95% CI)[a]	Incremental total costs (95% CI)[b]	ICER at 2.7 years[c]
	CABG	PCI	CABG	PCI			
Repeat revascularizations	5/547	128/547	60,336	1,420,172	0.19 (0.16, 0.23)	20,997 (16,897, 25,098)	110,510
CABG	1/547	12/547	37,657	449,397	0.02 (0.01, 0.03)	20,997 (16,897, 25,098)	1,049,850
PCI	4/547	116/547	22,678	970,776	0.18 (0.02, 0.22)	20,997 (16,897, 25,098)	116,650
Cerebrovascular events	1/547	6/547	25,315	38,922	0.01 (-0.00, 0.02)	20,997 (16,897, 25,098)	2,099,700
Stroke	1/547	5/547	25,315	35,388	0.01 (-0.00, 0.02)	20,997 (16,897, 25,098)	2,099,700
Acute myocardial infarction	0/547	43/547	0	429,042	0.07 (0.05, 0.09)	20,997 (16,897, 25,098)	299,996
Heart failure	7/547	55/547	35,345	380,382	0.08 (0.03, 0.11)	20,997 (16,897, 25,098)	262,462
Angina	1/547	22/547	31,851	106,758	0.03 (0.01, 0.05)	20,997 (16,897, 25,098)	699,900
Arrhythmia	7/547	26/547	10,882	73,209	0.03 (0.00, 0.06)	20,997 (16,897, 25,098)	699,900

Abbreviations: CABG, coronary artery bypass grafting; ICER, incremental cost-effectiveness ratio; MACCE, major adverse cardiac and cerebrovascular event

Notes:

[a], outcomes discounted by 5%;

[b], total medical costs were adjusted by Lin 1997 method and discounted at 5%.

[c], ICER = incremental cost per event avoided

Exchange rate: 1 AUD = 1.37 USD, January 06, 2017.

Lin 1997 Method: Observed direct costs weighed by a factor 1/Pr(survival from censoring) for multiple periods. These periods and probability weights are presented in the table.

Event	Complete observation period	Total event/N or mean life years		Pr survival (weight)	
		CABG	PCI	CABG	PCI
MACCE	12 months	16/67	27/46	0.976 (1.02)	0.987 (1.01)
	24 months	9/107	41/130	0.960 (1.04)	0.987 (1.01)
	36 months	14/138	44/127	0.936 (1.06)	0.987 (1.01)
	48 months	8/129	88/143	0.924 (1.08)	0.987 (1.01)
	60 months	7/106	87/101	0.753 (1.33)	0.987 (1.01)
OCVE	12 months	1/67	5/46	0.976 (1.02)	0.987 (1.01)
	24 months	16/107	22/130	0.960 (1.04)	0.987 (1.01)
	36 months	21/138	40/127	0.936 (1.06)	0.987 (1.01)
	48 months	57/129	65/143	0.924 (1.08)	0.987 (1.01)
	60 months	27/106	41/101	0.753 (1.33)	0.987 (1.01)
NCVE	12 months	18/67	39/46	0.976 (1.02)	0.987 (1.01)
	24 months	36/107	79/130	0.960 (1.04)	0.987 (1.01)
	36 months	78/138	206/127	0.936 (1.06)	0.987 (1.01)
	48 months	578/129	204/143	0.924 (1.08)	0.987 (1.01)
	60 months	74/106	104/101	0.753 (1.33)	0.987 (1.01)
Life years	12 months	0.66	0.77	0.976 (1.02)	0.987 (1.01)
	24 months	1.49	1.53	0.960 (1.04)	0.987 (1.01)
	36 months	2.52	2.48	0.936 (1.06)	0.987 (1.01)
	48 months	3.44	3.46	0.924 (1.08)	0.987 (1.01)
	60 months	4.51	4.40	0.753 (1.33)	0.987 (1.01)

Abbreviations: Major adverse cardiac and cerebrovascular events (MACCE); non-cardiovascular related events (NCVE); other cardiovascular related events (OCVE);

Sensitivity analysis to varying MACCE rates

Base-case MACCE event rate for PCI and CABG *plus* additional event rate of:	Δ Incremental mean cost	Δ Incremental mean effectiveness	ICER/ MACCE avoided
+5%	$ 21,955	0.45	$ 49,088
+10%	$ 21,679	0.47	$ 46,269
+20%	$ 21,128	0.51	$ 41,334
+30%	$ 20,576	0.55	$ 37,158
+40%	$ 20,025	0.60	$ 33,579
+50%	$ 19,473	0.64	$ 30,477
+60%	$ 18,921	0.68	$ 27,763
+70%	$ 18,370	0.72	$ 25,368
+80%	$ 17,818	0.77	$ 23,239
+90%	$ 17,267	0.81	$ 21,335
+95%	$ 16,991	0.83	$ 20,456

Abbreviations: ICER, incremental cost-effectiveness ratio; MACCE, major adverse cardiac and cerebrovascular events

6 Cost-effectiveness of DES vs. BMS in the Australian context

6.1 Chapter overview

In light of evidence of limited adherence to guidelines established for the use of DES in public hospitals in Victoria that may impact patient outcomes (218), this chapter aims to evaluate the cost-effectiveness of guideline-driven use of DES compared with BMS from the perspective of the Australian healthcare payer. Multi-centre data from the MIG registry, published cost estimates, and a 1:1 Nearest Neighboured propensity-score matching approach will be employed to assess the value-for-money benefit of DES compared with BMS among patients who met ‘0’, ‘1’, ‘2’ or ‘≥3’ criteria for a DES. A manuscript presenting the findings of this chapter was submitted to the Cost Effectiveness and Resource Allocation journal in September 2017.

THE COST-EFFECTIVENESS OF GUIDELINE-DRIVEN USE OF DRUG-ELUTING STENTS: PROPENSITY-SCORE MATCHED ANALYSIS OF A SEVEN-YEAR MULTICENTRE EXPERIENCE

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ABSTRACT

Background: In routine clinical practice, the implantation of a drug-eluting stent (DES) versus a bare metal stent (BMS) for percutaneous coronary intervention (PCI) has been guided by criteria for appropriate use. The cost-effectiveness (CE) of adopting these guidelines, however, is not clear, and was investigated from the perspective of the Australian healthcare payer.

Methods and Results: Baseline and 12-month follow-up data of 12,710 PCI patients enrolled in the Melbourne Interventional Group (MIG) registry between 2004 and 2011 were analysed. Costs inputs were derived from a clinical costing database, and published sources. Propensity-score-matching was performed for DES and BMS groups within sub-groups. Incremental cost-effectiveness ratios (ICERs) were evaluated for all patients, and sub-groups of patients with '0', 1, 2, or ≥3 indications for a DES. While the incremental cost per target vessel revascularization (TVR) avoided for these groups were $24,683, $44,635, $33,335, and $23,788, respectively, for those with ≥3 indications, DES compared with BMS was associated with cost savings. At willingness to pay thresholds of $45,000-$75,000, probability of cost-effectiveness of DES for the overall cohort was 71-91%, '0' indications, 49-67%, 1 indication, 56-82%, 2 indications, 70-90%, and ≥3 indications, 97-99%.

Conclusions: The CE of DES compared with BMS increased with increasing risk profile of patients, from those who had 1, 2, to ≥3 indications for a DES. When compared with BMS, DES was least CE among patients with '0' indications for a DES. Based on these results, selective use of DES implantation is supported. These findings may be useful for evidence-based clinical decision-making.

1. INTRODUCTION

Drug-eluting stents (DES) signifies a breakthrough in interventional cardiology. Compared with bare-metal stents (BMS), DES offer limited incidence of restenosis [1]. Not long after its widespread use, however, DES was found associated with a small but significant risk of late and very-late stent thrombosis, leading to the establishment of guidelines to limit its use [2]. In the United Kingdom, the use of DES in PCI was limited to patients who were at high risk of restenosis. In the United States, it was limited to 'on-label' use [3, 4]. Off-label use of DES, however, has become more prevalent in modern times [3].

In Victoria (a state of Australia), guidelines were established by the Victorian Department of Health that recommended DES for patients who were at high risk of restenosis, including those with diabetes mellitus, small vessels, long lesions, bifurcation lesions, ostial lesions, in-stent restenosis, and/or chronic total occlusions [5]. The decision to use a DES was nonetheless a clinical judgment based on individual patient assessment and the complexity of each case, as per these guidelines. These recommendations were displayed on the wall of cardiac catheter laboratories across all Victorian public hospitals [5]. Non-compliance to guidelines, however, was apparent from an analysis that included routine clinical data collected from seven Victorian public hospitals from the Melbourne Interventional Group (MIG) registry [5]. Forty percent of the PCI procedures was reported to have used a BMS when DES was more appropriate, and 16% in the reverse situation [5]. Adherence to guidelines was recommended, especially for high-risk patient subsets to improve clinical outcomes [5].

Presently, several economic evaluations of DES and BMS are available in various settings, including in unrestricted populations [6, 7], and in selected subgroups [8, 9]. None, however, investigated the cost-effectiveness of guideline-driven use of DES. The current economic evaluation compares the cost-effectiveness of guideline-driven use of DES compared with BMS in Victorian public hospitals.

2. METHODS

2.1. Study population

For the purpose of this evaluation, clinical, procedural, and resource utilization data collected by the MIG registry during a 12-month period were considered. The details of the MIG registry has been published previously [10, 11]. The MIG registry is an 'all-comer', multi-centre clinical registry, which used an 'opt-out' patient consent approach. The protocol of the MIG registry was approved by the human research ethics committees of all participating hospitals [10, 11]. Between April 2004 and December 2011, 17,769 consecutive patients who underwent PCI across 14 cardiology units in Victoria were enrolled in the MIG registry study.

2.2. Inclusion and exclusion criteria

Index PCI procedures from eight tertiary public hospitals were considered for analysis. Patients were included if they were treated with one or more of DES or BMS exclusively. Procedures that used both DES and BMS (n=386), or no stents (n=1,048) were excluded. All patients admitted to private hospitals (n=393), holding private health insurance (n=1,668), or Department of Veteran Affairs insurance (n=145) were also excluded as DES use in these patients is unrestricted. Patients with incomplete 12-month follow-up data were also excluded (n=1,419). In the end, 12,710 PCI procedures were included in the analysis.

2.3. Patient subgroups

The study population was stratified based on whether a patient met '0', 1, 2, or ≥3 indications for a DES, irrespective of whether a DES or BMS was actually implanted. A separate analysis was also carried out in 'all patients', to determine the cost-effectiveness of observed routine use of DES compared with BMS. The indications for DES use in Victorian Public Hospitals have been described previously [5]. The definitions of the indications as per MIG registry are supplied in Online Resource 1. A patient who met '0' indications for a DES was regarded as, "low-risk", 1 indication, "moderate risk", 2 indications, "moderate-to-high-risk", and ≥3 indications, "high-risk".

2.4. Statistical analysis

2.4.1. Propensity score matching

Propensity-score (PS) matching was performed between DES (treatment) and BMS (control) groups within each subgroup and within the 'all patient' cohort, in order to adjust for treatment bias [12, 13]. A 1:1: Nearest-Neighbour matching algorithm (with no replacement) with caliper adjustment was used, based on 25 variables (see Online Resource 1). Univariable logistic regression was used to identify variables for matching at the 0.05 significance level for 12-month major adverse cerebrovascular and cardiovascular events (MACCE). Multiple logistic regression with stent type (DES or BMS) as the dependent variable was used to generate a PS for each patient. A caliper width of <0.2 times the standard deviation (SD) of the PS estimated [14]. Stata/IC version 11(Windows), and Microsoft Excel 2010 (Windows) were used for all statistical analyses (Online Resource 1).

2.1. Economic evaluation

2.1.1. Type of analysis

An economic model was developed using observed and published inputs, based on clinical outcomes and resource utilisation observed within PS-matched cohorts, similar to a within-trial analysis.

2.1.2. Treatment

The treatment under consideration was DES, whereas the comparator was BMS. Individual analyses for different generations of DES was not performed due limited sample size of these cohorts to carry out PS-matching and sub-group analyses based on recommended indications for DES use.

2.1.3. Effectiveness and resource utilisation

The primary clinical outcome measure was the number of target vessel revascularizations (TVR) avoided (defined in Online Resource 1). The 12-month mortality rate between the DES and BMS-treated groups from the MIG cohort was considered but confirmed as not significant [15]. Resource utilisation related to cardiovascular readmissions and medication use over a 12-month period was considered [16] (see Online Resource 1).

2.1.4. Costs

All costs were expressed in Australian dollars (AUD, base year 2015) adjusting for inflation using the Australian Health Price Index [17].

The initial procedural costs of PCI using DES and BMS were based on clinical costing data collected from a single centre (Alfred Hospital, Melbourne, Victoria) cohort of 396 patients who underwent PCI between 30 June 2009 and 1 July 2011. Multiple administrative datasets from different centres could not be used for this evaluation, as technical difficulties were anticipated merging such datasets in addition to obtaining permission from different sites. The medical costs were estimated using a bottom-up micro-costing approach, considering direct medical costs across various departments (Online Resource 1). These costs were aggregated for each patient and averaged across the BMS and DES groups, and then applied to the economic model.

For costs of hospital readmissions, estimates from Australia's National Hospital Cost Data Collection 2008-09 report as per section 'Public Hospitals in Victoria' were used [18]. Costs associated with hospital readmissions were estimated using Australian-refined (AR) 'diagnostic related group' (DRG) price corresponding to each readmission event [18]. Seven AR-DRG admission diagnoses were considered including, F06A, F06B, F15Z, F05A, F05B, F41A, and F41B.

For medication costs, data from the Australian Pharmaceutical Benefit Scheme (PBS) was used [19]. Using methods described previously, a weighted mean cost was estimated for costs of readmissions and medication use [20]. All cost inputs are summarised in Online Resource 1.

2.1.5. Perspective

The economic evaluation was carried out from the perspective of the Australian Public Hospital Payer (the State government of Victoria, Australia) and the PBS (Australian federal government).

2.1.6. Economic measure

The incremental cost-effectiveness ratio (ICER) was evaluated for all subgroups. The ICER was defined as the incremental cost per TVR avoided. To compare ICERs, willingness to pay thresholds of $45,000, $60,000, and $75,000 were used, based on current considerations by the Australian Medical Services Advisory Committee [21].

2.1.7. Time horizon

A time horizon of 12 months was considered.

2.1.8. Discounting

Discounting of cost and benefits was not performed as the time horizon was limited to 12 months.

2.1.9. Sensitivity analysis

Sensitivity analyses were carried out for all uncertain parameters, which included initial hospital costs, readmissions costs, medication costs, and TVR events (Online Resource 1). One-way sensitivity analysis was performed by varying each cost input to the upper and lower limit of its 95% CI (if known), and/or by applying ± 25-75% uncertainty around the estimate. Probabilistic sensitivity analysis (PSA) was carried out to quantify the level of confidence around model outputs through independently simulating each uncertain cost parameter. Monte Carlo simulation with 5,000 iterations was used for this purpose. A gamma distribution was assumed for uncertainty in hospital-related costs, and a beta distribution was assumed for uncertainty in TVR events. Cost-effectiveness acceptability curves were used to illustrate the probability of cost-effectiveness of DES compared with BMS, as a function of the willingness to pay (WTP).

3. RESULTS

3.1. Patient population

3.1.1. Baseline characteristics

Of the 12,710 patients included in this study who underwent PCI at eight Victorian public hospitals from 2004 to 2011, 41.8% received DES, and 58.2% received BMS. Baseline characteristics the two groups were significantly different ($p<0.05$; see Online Resource 2). The proportion of patients who had '0', 1, 2 or ≥3 indications for a DES, was 30%, 41%, 21% and 7%, respectively. Overall, 44.3% (4,010/8,848) of patients who had one or more indications for a DES were treated with a BMS. However, the use of DES was greatest (81.7%) among patients who had ≥3 indications for a DES, and least (12.4%) among patients who had '0' indications for a DES (Online Resource 2). An analysis of rates of DES and BMS by year showed that the use of BMS peaked in 2007 to 60%, but from 2007 onwards the 'off-label' use of DES trended upwards.

3.1.2. PS-matched analysis

The baseline characteristics of the PS-matched overall cohort, and subgroups of patients with '0' indications, 1 indication, 2 indications, ≥3 indications for a DES, are summarised in Table 1. Overall, PS-matching resulted in retention of approximately 51% of the overall cohort ("all patients"), and 23%, 70%, 55%, and 32% of the individual subgroups, respectively. There were 3265, 445, 1,852, 741, and 141 matched BMS and DES pairs within these cohorts, respectively. The matched DES and BMS groups were similar across the majority of the key variables of interest ($p>0.05$; Table 1).

3.1.3. Clinical outcomes and resource utilization

The differences in the 12-month TVR and TLR rates were more pronounced following PS-matching. Significantly higher TVR rates were observed following BMS implantation compared with DES implantation across all groups ($p<0.05$; Online Resource 2). The frequencies of hospitalizations for 12-month repeat revascularizations followed a similar pattern in the PS-matched cohorts (Online Resource 2). The frequencies of medication use have been reported previously[13] .

3.2. Base-case results

The mean 12-month incremental costs, effectiveness, and ICERS from the base-case analysis using pre-determined model inputs (Online Resource 1) are summarised in Table 2.

3.2.1. Costs

At 12 months, the mean costs associated with DES was greater when compared with BMS for all groups except those who had ≥3 indications. The differences however, reached significance only for those who had 1 indication for a DES. The highest mean incremental cost was observed among patients with '0' indications for a DES.

3.2.2. Effectiveness

Treatment with DES compared with BMS was significantly associated with higher mean incremental effectiveness (TVR avoided) at 12 months, for all groups except for those who had '0' indication for a DES, where the difference did not reach significance. The incremental effectiveness was greatest among patients who had ≥3 indications for a DES.

3.2.3. Cost-effectiveness

For routine DES implantation ('all patients'), the ICER was $24,683 per TVR avoided. By comparison, DES compared with BMS for low-risk ('0' indications for DES), moderate-risk (1 indication), and moderate-to-high-risk (2 indications) patients resulted in ICERs of $44,635, $33,335, and $23,788 per TVR avoided, respectively. For high-risk patients (≥3 indications), DES compared with BMS was associated with lower costs and greater benefits in terms of TVR avoided ('dominant').

3.3. Sensitivity analyses

The results from PSA for the individual subgroups are summarised in Table 2, and Figures 1. If the-the willingness to pay (WTP) threshold was $45,000, a routine DES strategy was cost-effective 71% of the time. For low-risk ('0' indications DES), moderate-risk (1 indication), moderate-to-high-risk (2 indications), and high-risk patients (≥3 indications) patient groups, the comparable probabilities were 49%, 56%, 70%, and 97%, respectively (Table 2; Figure 1). By contrast, at a WTP threshold of

$75,000, the probabilities of cost-effectiveness for the groups were 91% (all patients), 67% ('0' indication for DES), 82% (1 indication), 90% (2 indications), and 99% (≥3 indications) (Table 2; Figure 1). Scatter plot diagrams of PSA results suggested that treatment with DES compared with BMS was associated with lower costs and greater TVR avoided ('dominant') for 'all patients', those with '0' indications and ≥3 indications for DES, at probabilities of 23.1%, 17.0%, and 57.0%, respectively (Online Resource 2).

One-way sensitivity analyses showed that the base-case results were most sensitive to initial procedural costs of PCI using DES or BMS (Online Resource 2). The base-case results were least sensitive to readmissions costs, and medication costs (Online Resource 2). DES was associated with lower costs and higher effectiveness ('dominant') in two instances; i) when the mean procedural cost of PCI using DES was lowered to the lower limit of its 95% confidence interval (CI); and ii) when the mean procedural cost of PCI using BMS was increased to the upper limit of its 95% CI (Online Resource 2).

4. DISCUSSION

As far as we are aware, this is the first evaluation of its kind reporting the cost-effectiveness of guideline-driven use of DES from the perspective of the Australian government. Economic evaluations were undertaken within PS-matched subgroups of patients with 0, 1, 2, or ≥3 indications for a DES based on guidelines established by the Victorian Department of Health [5]. Although these guidelines are not linked to any physician or hospital reimbursement strategies, this evaluation aimed at informing the economic impact of the application of these guidelines to a routine population. Our results suggested that the cost-effectiveness of DES compared with BMS, increased with increasing risk profile of patients from those with 1, 2, to ≥3 indications for a DES (ICERs: $33,335, $23,788, and 'dominant', respectively). When compared with BMS, DES was least cost-effective among patients with '0' indications for a DES ($44,635). Routine treatment with DES compared with BMS (in 'all patients') corresponded an ICER of $24,683.

4.1. Adherence to guidelines

The use of DES in low-risk patients may lead to high expenditure in hospitals. A year-by-year analysis of data from the MIG registry in this evaluation showed a growing preference for use of DES among low-risk patients, where a BMS may have been appropriate. In the United States, 70% PCI procedures used a first-generation DES "off-label", which was shown to lead to worse outcomes after two years, when compared with a BMS strategy [3]. A 2012 survey of 31 centres across Europe and Asia, however, revealed that there were still clinical justifications for use of BMS, primarily driven by a concern for either bleeding or compliance to dual antiplatelet therapy (41% cases) among other reasons, including large vessel diameter (32%), acute MI (18%), stent costs (9%) and planned non-cardiac surgery (6%) [22, 23]. In Australia, concerns of non-compliance to guidelines for DES were first raised in 2006 [5]. A DES is around 3-4 times more expensive than a BMS in Australia (Luthe M., Alfred Clinical Performance Unit; personal communication). As such, non-adherence to guidelines may increase the opportunity cost of DES, imposing greater cost burden on scarce healthcare resources. The results from this evaluation supports this notion.

4.2. Comparision to similar studies from literature

The cost-effectiveness of DES compared with BMS has been explored widely, in unrestricted populations [6, 7] and selected patient subgroups [8, 9]. The comparison of our findings to results of each of these studies is not feasible or appropriate. While clinical practice across different countries and healthcare systems may be alike, leading to similar clinical outcomes, several factors may lead to differences in cost-effectiveness ratios reported by different economic evaluations. These factors may range from differences in contexts (i.e., healthcare systems), policies governing DES use, the price difference between DES and BMS, to methodological aspects, including time-horizon, costs and health-related utility weights modelling methods considered.

Bagust et al. [24], was one of the first studies that examined the cost-effectiveness of DES according to the number of risk factors observed in patients. The study used data from an audit of 2884 consecutive patients from a single-centre in the UK during 2000-2002. Indications for the evaluation were identified through a regression analysis, rather than clinical guidelines. Using a decision analysis model, the 12-month cost-utility of a DES strategy was investigated in 'elective' patients who had 0, 1, 2, or 3-4, of four indications (calcification, angulation>45, restenotic lesion, and triple vessel disease) [24]. A separate analysis was also carried out in the non-elective sub-group. Although 12-month follow-up was conducted, the analysis assumed that each patient had one repeat procedure each, as the audit occurred in a period DES use was not common [24]. The bias in this assumption was not tested through sensitivity analyses. The direct comparison of results of Bagust et al. [24] to our findings may not be appropriate, due to the differences in the UK and Australian healthcare systems, modelling methods, measures of effectiveness (quality adjusted life years, QALYs versus TVR avoided in the current evaluation) and model assumptions. Their evaluation showed that a DES compared with BMS was associated with lower costs and higher effectiveness ('dominant') for high-risk patients who had ≥3 indications, and the cost-utility of DES increased with increasing risk profile of patients. Bagust et al. [24] also found that cost-utility of a DES compared with BMS strategy declined with increasing number of stents deployed during PCI [24]. While our analysis could not

confirm this, similar results would be expected, given the high cost of DES (3-4 times) than a BMS, at least initially.

4.3. Comparison to previous Australian data

A prior economic analysis conducted from the Australian healthcare payer perspective concluded that use of DES compared with BMS was cost-effective at 12 months, although the results may be sensitive to changes in clinical practice, market price, and the number of stents per patient [25]. This analysis was based on a hypothetical cohort generated through systematic review of RCTs that considered patients with a single denovo coronary lesion of 51%–99% vessel diameter stenosis, with or without restenotic lesions [25]. Sensitivity analysis performed in this economic evaluation suggested that if costs and TVR rates were *reduced by 50%,* the resulting ICERs ranged from cost-saving to $25,150 per target lesion revascularisation avoided, or an additional $314,385 per QALY gained [25]. Despite these findings corresponding to first generation DES, they were consistent with our results for the 'all patient' cohort (ICER: $24,683), suggesting that resource-use in RCTs may be significantly higher when compared with routine clinical practice (by ~50%), perhaps as a result of protocol-mandated angiography [25-28].

4.4. Propensity–score matching in CEA

Our study was strengthened by the use of PS-matching that produced quasi-randomised groups. Two other studies to date used a similar approach to evaluate the cost-effectiveness of DES compared with BMS, in real-world cohorts, though their findings may not be directly comparable with the present study, due to differences in context, populations considered, and outcomes measured [12, 13]. A Canadian evaluation [13], showed that after two years, results were more favourable for patients with ≥2 of three risk factors (diabetes, small vessel, and long lesion) investigated. As with Bagust study [24], these risk factors, however, were not reported as being linked to guidelines issued by a local health or reimbursement authority. Baulmer and colleagues [12] , by comparison, found that DES use was not cost-effective for patients who had AMI prior to PCI, using data from a large administrative German medical fund.

4.5. Limitations

There were several limitations to this study that must be acknowledged. Due to several reasons mentioned already, the findings of this economic evaluation may not be generalisable to healthcare systems outside of Australia. Ultimately, this economic evaluation was limited by the constraints of data sources used. As patient follow-up by the MIG registry was limited to one year, the time horizon of this economic evaluation was 12 months, although this is the time frame when restenosis is most likely. Initial PCI procedural costs were based on clinical costing data collected from a single centre rather than from all the centres involved. This was appropriate given in the state of Victoria, the device costs are equivalent across public hospitals owing to the implementation of a uniform competitive pricing policy through a tendering process. Individual analyses for different generations of DES was not performed due limited sample size of these cohort. Furthermore, though PS-matching analysis was associated with removal of treatment bias as indicated by high degree of matching between DES and BMS groups, the impact of unobserved factors that was not part of MIG data collection remains uncertain. For instance, circumstances beyond clinician control e.g., resource constraints at hospitals, urgency of procedures, anticipated adherence to medication by the patient etc., may force clinical decisions outside of guideline-driven use of BMS or DES

Despite limitations, this evaluation was strengthened by the use of observational data from routine clinical practice, and PS-matching analysis, which may provide more plausible estimates than reported previously [24, 25]. Future economic evaluations in the Australian context, may address above limitation including a long-term time-horizon (life-time or >10 years) to measure the impact of very late stent thrombosis and the cumulative cost of dual antiplatelet therapy, which may differ substantially between BMS and DES groups independent of clinical practice guidelines.

4.6. Conclusion

Although DES was significantly associated with reduced rates of TVR, its use was only cost-effective among patients who had at least one indication for a DES. The economic attractiveness of DES compared with BMS was highest for patients who had ≥3 indications, as it was associated with cost-savings to the healthcare payer, and improved clinical outcomes (reduced TVR) for the patient. When compared with BMS, DES was least favourable among patients who had '0' indications for a DES.

Based on these results, selective use of DES implantation is supported. These findings may be useful for evidence-based clinical decision-making.

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5. TABLES

Table 1 Results from propensity-score matched analysis: the distribution of patient, lesion, and stent characteristics in matched DES and BMS treated groups.

	All patients			'0' indications			1 indication			2 indications			≥3 or more indications		
	DES	BMS	P-value	DES	BMS	P-value	DES	BMS	P-value	DES	BMS	P-value	DES	BMS	P-value
Number of PCIs (N)	3265	3265	-	445	445	-	1852	1852	-	741	741	-	141	141	-
Male (%)	75.1	75.2	0.932	81.8	83.4	0.536	74.6	74.8	0.880	73.5	72.7	0.725	73.0	69.5	0.511
Age >80 years (%)	10.2	10.4	0.745	9.4	7.9	0.404	10.0	9.9	0.869	13.2	12.3	0.586	13.5	17.0	0.408
Diabetes (%)	26.8	28.1	0.244	0.0	0.0	-	22.0	21.2	0.529	64.5	60.3	0.068	80.8	75.9	0.311
Insulin requiring (%)	5.9	6.2	0.534	0.0	0.0	-	4.6	4.3	0.634	14.6	15.2	0.715	19.1	18.4	0.879
Dialysis (%)	1.5	1.4	0.827	1.8	0.23	0.019	1.3	0.9	0.201	2.0	2.7	0.395	2.8	5.0	0.344
Previous MI (%)	28.6	30.3	0.143	30.3	31.9	0.612	26.8	27.0	0.853	32.2	34.5	0.349	31.9	33.3	0.799
Previous PCI (%)	24.3	24.8	0.625	25.6	29.0	0.259	20.7	23.4	0.047	22.1	26.3	0.060	18.4	27.7	0.066
Previous CABG (%)	9.9	10.4	0.486	16.0	15.3	0.782	9.5	9.34	0.866	12.8	11.1	0.298	12.8	9.9	0.453
Total acute coronary syndromes (%)	62.0	62.0	1.000	58.0	57.3	0.839	62.6	62.3	0.865	67.9	66.0	0.440	70.2	66.0	0.443
Unstable angina (%)	11.5	11.1		12.6	13.3		10.7	10.5		11.6	11.7		4.3	7.1	
Non-ST-elevated MI (%)	28.3	27.7	0.772	26.1	25.6	0.975	29.5	28.9	0.943	29.4	27.9	0.866	34.7	31.2	0.579
ST-elevated MI (%)	22.1	23.1		19.3	18.4		22.3	23.0		26.9	26.3		31.2	27.7	

Cardiogenic shock (%)	1.8	1.8	1.000	2.2	2.5	0.825	1.4	1.6	0.684	3.0	4.7	0.079	2.8	2.1	0.702
In stent restenosis (%)	2.6	3.0	0.327	0.0	0.0	-	1.0	2.0	0.015	3.6	5.8	0.050	8.5	12.1	0.327
Ostial lesion (%)	4.9	4.8	0.908	0.0	0.0	-	4.0	3.7	0.608	9.2	9.0	0.928	26.2	24.1	0.681
Bifurcation lesion (%)	9.7	10.7	0.153	0.0	0.0	-	5.9	6.1	0.836	23.6	21.5	0.320	46.8	48.9	0.721
Chronic total occlusion (%)	1.8	2.2	0.332	0.0	0.0	-	0.5	0.8	0.296	4.7	5.0	0.809	12.8	12.8	1.000
Small vessels ≤2.5mm (%)	29.3	29.2	0.957	0.0	0.0	-	27.8	28.3	0.715	39.0	43.4	0.082	61.0	63.8	0.623
Long lesions ≥20 mm (%)	36.4	39.5	0.009	0.0	0.0	-	38.7	38.0	0.636	54.9	54.9	1.000	73.8	73.0	0.893

Notes:

Our propensity-score matching analysis lead to a drop out of 48.6% observations from the original overall cohort (i.e., all patients) and 30.0-77.0% observations from original sub-groups. The analysis used a caliper width of 0.01613.

Abbreviations:

BMS, bare-metal stent; CABG, coronary artery bypass graft; DES, drug-eluting stent; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 2 Results from base-case economic evaluation for matched DES and BMS groups, and corresponding probabilities of cost-effectiveness at specific WTP thresholds based on results from PSA.

		Average total cost (AUD):	Average number of TVR	Incremental cost (95% CI)[a]	Incremental effectiveness (95% CI)	ICER per TVR avoided	Probabilities of cost-effectiveness at WTP thresholds		
							$45,000	$60,000	$75,000
All patients	DES	$16,428	0.05	$1,315 (-$568 to $3,323)	0.05 (0.04 to 0.07)	$24,683	71%	83%	91%
	BMS	$15,113	0.10						
0 indications	DES	$20,352	0.05	$1,705 (-$11,489 to $15,201)	0.04 (-0.002 to 0.08)	$44,635	49%	59%	67%
	BMS	$18,647	0.09						
1 indications	DES	15,637	0.04	$1,494 ($693 to $2,293)	0.04 (0.03 to 0.06)	$33,335	56%	70%	82%
	BMS	14,143	0.09						
2 indications	DES	$19,369	0.08	$1,445 (-$6,389 to $9,391)	0.06 (0.02 to 0.10)	$23,788	70%	82%	90%
	BMS	$17,925	0.14						
≥3 indications	DES	$30,421	0.08	-$953 (-$43,526 to $41,835)	0.13 (0.02 to 0.23)	DES ME, LC	97%	99%	99%
	BMS	$31,374	0.21						

Abbreviations: BMS, bare metal stent; CI, confidence interval; DES, drug-eluting stent; ICER, incremental cost-effectiveness ratio; ME,LC, more effective, less costly; PSA, probabilistic sensitivity analysis, TVR, target vessel revascularization; WTP, willingness to pay. *Notes:* [a] Bootstrap 95% confidence interval

6. FIGURE LEGENDS

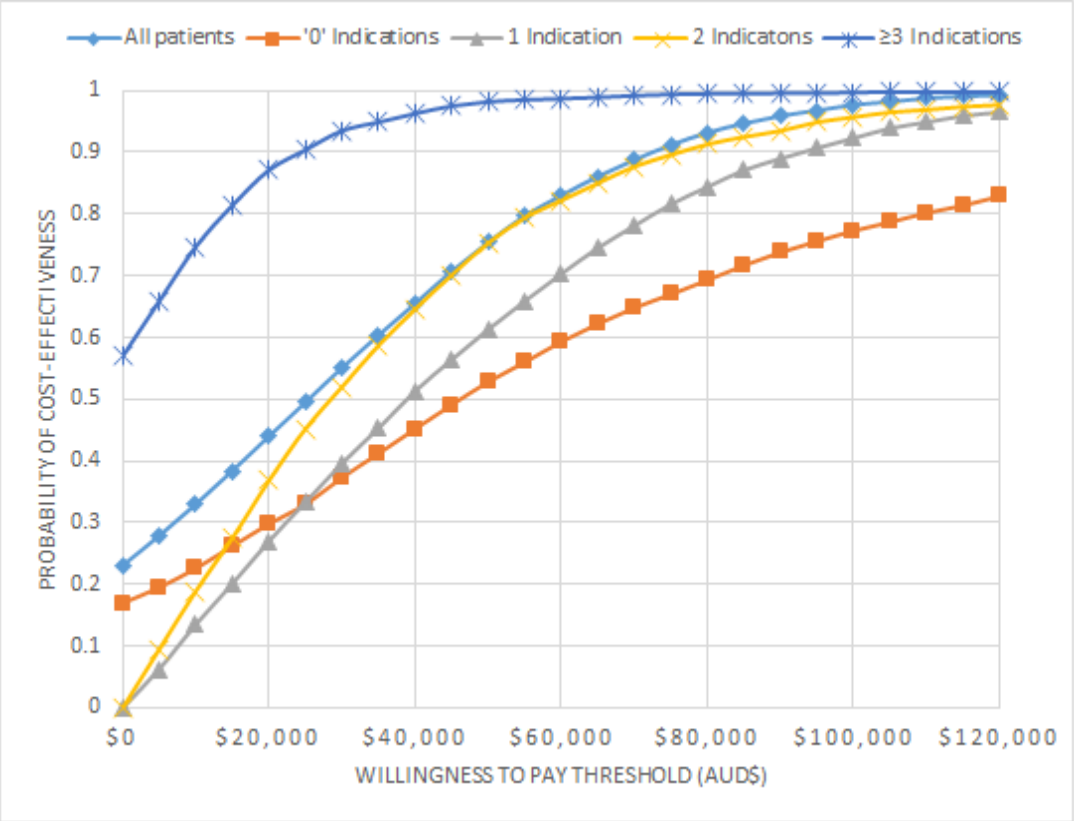

Figure 1 Cost-effectiveness acceptability curves derived from PSA for the matched overall, and indication subgroups.

Abbreviations: BMS, bare-metal stent; DES, drug-eluting stent; PSA, probabilistic sensitivity analysis

Online Resource 1: Methods

THE COST-EFFECTIVENESS OF GUIDELINE-DRIVEN USE OF DRUG-ELUTING STENTS: PROPENSITY-SCORE MATCHED ANALYSIS OF A SEVEN-YEAR MULTICENTRE EXPERIENCE

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Seven indications for a DES, definition as per Melbourne Interventional Group (MIG) registry

- Diabetes mellitus: indicated if the patient has a history of diabetes regardless of duration of disease or need for anti-diabetic agents.

- Small vessels: target vessel diameter ≤2.5mm, total diameter of stents implanted was ≤2.5mm.

- Long lesion: target lesion length ≥20mm, where total length of stents implanted was ≥20mm.

- Bifurcation lesions: indicated if the lesion is at a bifurcation / trifurcation. A bifurcation / trifurcation is a division of a vessel into at least two branches, each of which is >2 mm or greater in diameter. In a bifurcation / trifurcation the plaque extends on both sides of the bifurcation point. It need not progress down both branches.

- Ostial lesions: indicated if the lesion is within 3mm of the origin of the vessel.

- In-stent restenosis: lesion that has had a prior stent to that site (or within 5mm of the proximal and distal prior stent edges).

- Chronic total occlusions: a lesion>3 months old and/or bridging collaterals. These lesions have 100% pre-procedure stenosis and should not relate to a clinical event leading to this procedure.

Box A1 Variables used in the propensity-score matching method

1. Age, 2. Sex, 3. previous PCI, 4. history of smoking, 5. chronic obstructive pulmonary disease, 6. diabetes, 7. hypertension, 8. history of coronary artery disease, 9. cerebrovascular disease, 10. congestive heart failure (≥2 weeks prior to the PCI), 11. previous MI (≥7 days prior to the PCI), previous CABG, previous valve surgery, cardiogenic shock, 12. angina,	13. glycoprotein IIb / IIIa inhibitors, 14. fibrinolytics, 15. lesion type (as per ACC/AHA classification), 16. ostial lesion, 17. bifurcation lesion, 18. in-stent restenosis, 19. disease extent (single vessel or multi-vessel disease), 20. out-of-hospital cardiac arrest, 21. proximal coronary lesion, 22. target vessel diameter ≤2·5mm, 23. target lesion length ≥20mm, 24. chronic total occlusion. 25. use of intra-aortic balloon pump

Statistical analyses (continued)

Within the propensity-score matched cohorts, differences in baseline, lesion, and procedural characteristics between the DES- and BMS-treated groups were compared the using the chi-square tests for categorical variables, and the independent group student's t-test for continuous variables. Categorical variables were summarised using percentages while continuous data were summarised using mean and standard deviation (SDs).

Initial hospital costs were summarised using median and interquartile range (IQR) as the costs followed a non-normal distribution. Total costs at 12 months were estimated for each patient, using inputs summarised in Table A1, and averaged across treatment sub-groups of interest. The 95% confidence intervals (CIs) around mean total cost for each subgroup were generated from bootstrapping estimates imputed for each patient, through repeated sampling, with replacement for 1000 iterations.

Chi-square test was also used to identify significant differences in target vessel (or lesion) revascularizations at 12 months between the DES- versus BMS-treated groups.

Clinical outcomes and resource utilisation from the MIG registry

- **Target vessel revascularisation (TVR) :**
  A TVR was defined as the revascularization of a previously treated coronary artery, which included target lesion revascularizations (TLR). A TLR was defined as a repeat revascularization within 5 mm of either side of the stent in a previously treated lesion. Resource utilization through hospital readmissions for subsequent PCI or CABG with or without associated myocardial infarction (MI) was considered.

- **Medication use:**
  As information related to pharmacotherapy use over 12 months was available, cardiovascular medication usewas considered, with assumptions around average dosage, and compliance (assumed 100%). The rates of medication use were published previously [13]. The medications considered included;
  - aspirin,
  - clopidogrel,
  - prasugrel,
  - warfarin,
  - angiotensin-converting enzyme inhibitor (ACE-I),
  - angiotensin II receptor blockers (ARB),
  - beta-blockers,
  - calcium-channel blockers,
  - statins, spironolactone,
  - fibrate,
  - ezetimibe, and
  - eplerenone.

- **Hospitalisations:**
  - Initial PCI procedure using either DES or BMS
  - Hospitalisations for cardiovascular events during 12 month follow-up;
    - Repeat CABG with no AMI

- Repeat CABG with AMI
- Repeat PCI with no AMI
- Repeat PCI with AMI
- Repeat PCI and CABG with or without AMI

Cost assignment method for the initial PCI procedure

The direct medical costs associated with various departments and/or personnel were considered for the estimation of the mean initial cost of a PCI episode, using a bottom-up micro-costing approach. The direct costs from the following hospital units were included;

- Allied (e.g. physiotherapy, psychology, social work, interpreters etc.)
- Coronary care unit
- Emergency
- Intensive care unit
- Imaging (e.g. CTG, CT Scan, MRI, PET, radiology, nuclear medicine etc.)
- Medical personnel (surgical)
- Medical personnel (non-surgical)
- Nursing personnel
- Pathology
- Pharmacy
- Theatre/ Operating Room
- Theatre/ non-Operating Room

The costs across these departments were aggregated for each patient and averaged across 198 matched patient pairs (total N = 396) who underwent PCI using DES or BMS between 30 June 2009 and 1 July 2011.

Table A1 Model input parameters for base case analysis, one-way sensitivity and probabilistic sensitivity analysis

Inputs[a]	Base case value for input (inflated to 2015 prices)	Probabilistic model distribution	Source
In-hospital costs (AUD)[b]:			
PCI with BMS[c]	Mean cost (95% CI): $11,097 ($8,365 to $13,829) Median cost (IQR): $8,636 ($5,452 to $12,043)	Gamma	Alfred Hospital Clinical Performance Unit
PCI with DES[d]	Mean cost (95% CI): $13,189 (10,997 to $15,383) Median cost (IQR): $10,847 ($8,008 to $15,084)		
Readmissions costs (AUD)[b]:	Average costs:		
Repeat CABG	$39,068	Gamma	
Repeat PCI (with stent)	$9,715		
Repeat PCI and CABG	$52,579		Victorian DRG prices 2008-09
Associated AMI (with repeat PCI or CABG)	$8,268		
Medication costs (AUD)[b]:	Cost per month		
Aspirin	$2·39		
Clopidogrel	$63.87		
Prasugrel	$117.48		
Warfarin	$16.03		
ACE inhibitor	$19.10		
Angiotensin II inhibitor	$25.06		
Beta-blocker	$23.59	N/A[e]	PBS schedule
Ca^{2+} Channel blocker	$19.12		
Statins	$62.96		
Spironolactone	$4.37		
Fibrate	$42.55		
Ezetimibe	$73.54		
Eplerenone	$116.86		

Abbreviations:
AMI, acute myocardial infarction; ARTS, arterial revascularization therapies study; BMS, bare metal stent; CABG, coronary artery bypass surgery; CI, confidence interval; DES, drug-eluting stent; DRG, diagnosed related group; IQR, interquartile range; PBS, pharmaceutical benefit scheme; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty.
Notes:
a The rate of TVRs observed during 12 months, is not shown here. They are reported on Table 3. An uncertainty distribution was not applied around this parameter, as we did not rely on published estimates; we used data collected by the MIG registry. The 12-month clinical outcomes recorded in MIG were considered representative of real-world clinical outcomes expected of patients in the Australian public healthcare system.
b Costs are expressed in Australian dollars (AUD), based on the costing for financial year (FY) of 2013 in Australia.
c For a BMS, the relative value per unit was 490 AUD based on costing for FY 2012.
d For a DES, the relative value per unit was 1,780 AUD based on costing for FY 2012.
e An uncertainty distribution was not applied for medication costs, as these prices were fixed, across Australia. Per month costs were converted to per annum costs, assuming average dose cited on the PBS schedule.

Online Resource 2: Results

THE COST-EFFECTIVENESS OF GUIDELINE-DRIVEN USE OF DRUG-ELUTING STENTS: PROPENSITY-SCORE MATCHED ANALYSIS OF A SEVEN-YEAR MULTICENTRE EXPERIENCE

Thathya V. Ariyaratne[1], *PhD candidate*; Zanfina Ademi[1,2], *Ph.D*; Molla M Huq[1,3], MSc*;* Stephen J. Duffy[4], *FRACP, PhD*; Bryan P. Yan[1,5], *FRACP, MD*; Andrew E. Ajani[1,6], *FRACP, MD*; David J. Clark[7], *FRACP*; Baki Billah[1], *PhD*; Angela Brennan[1], *CCRN*; Gishel New[8], *FRACP, PhD*; Nick Andrianopoulos[1], *MBBS*; Christopher M Reid[1,9¥], *PhD*

Table A2 Baseline patient, lesion, and stent characteristics DES and BMS groups from the MIG registry.

	Drug-eluting stent	Bare-metal stent	P-value
Number of PCIs, n (%)	**5318 (41·8)**	**7392 (58·2)**	**-**
Male, n (%)	3961 (74·5)	5585 (75·5)	0·168
Age (mean ± SD)	64·1 ± 11·5	64·4 ± 12·1	0·129
Age >80 years, n (%)	481 (9·0)	815 (11·0)	<0·001
Current smoker, n (%)	1118 (21·1)	2062 (28·0)	<0·001
Diabetes, n (%)*	1783 (33·5)	1381 (18·7)	<0·001
Insulin requiring, n (%)	443 (8·3)	282 (3·8)	<0·001
Hypertension, n (%)	3724 (70·0)	4745 (64·2)	<0·001
Systolic blood pressure (mean ± SD)	131·2 ± 24·1	129·6 ± 25·4	0·076
Estimated glomerular filtration rate<30 %	477 (9·2)	642 (8·9)	0·678
Dialysis, n (%)	83 (1·6)	72 (1·0)	0·003
Family history of CAD, n (%)	2333 (42·2)	2827 (38·6)	<0·001
Body mass index (mean ± SD)	28·5 ± 5·2	28·3 ± 5·1	0·073
Dyslipidemia, n (%)	4035 (76·1)	5031 (68·4)	<0·001
Ejection fraction (mean ± SD)	54·5 ± 11·6	53·1 ± 11·5	<0·001
Cerebrovascular disease, n (%)	347 (6·1)	524 (7·5)	0·214
Peripheral vascular disease, n (%)	389 (7·3)	481 (6·5)	0·071
Congestive heart failure , n (%)	209 (3·9)	273 (3·7)	0·490
Previous MI, n (%)	1833 (34·5)	1812 (24·5)	<0·001
Previous PCI, n (%)	1761 (33·1)	1328 (18·0)	<0·001
Previous CABG, n (%)	608 (11·4)	528 (7·1)	<0·001
Total acute coronary syndromes, n (%)	2956 (55·6)	5073 (68·8)	<0·001
Unstable angina, n (%)	690 (13·0)	746 (10·1)	<0·001
Non-ST-elevated MI, n (%)	1392 (26·2)	1955 (26·5)	<0·001
ST-elevated MI, n (%)	874 (16·4)	2372 (32·1)	
Cardiogenic shock, n (%)	68 (1·7)	276 (3·7)	
Lesion characteristics			
Number of lesions treated, n (%)	**6105 (42·5)**	**8265 (57·5)**	**-**
De novo , n (%)	5490 (90·0)	8133 (98·4)	
Restenosis, n (%)	41 (0·7)	20 (0·2)	<0·001
In stent restenosis , n (%)*	572 (9·4)	110 (1·3)	
ACC/AHA Type B2/C lesions, n (%)	3284 (0·5)	3704 (0·4)	<0·001
Ostial lesion, n (%)*	371 (6·1)	288 (3·5)	<0·001
Bifurcation lesion, n (%)*	716 (11·7)	628 (7·6)	<0·001
Chronic total occlusion, n (%)*	260 (4·3)	101 (1·2)	<0·001
Glycoprotein IIb/IIIa inhibitor use, n (%)	1518 (0·2)	2585 (0·3)	<0·001
Small vessels ≤2·5mm, n (%)*†	2678 (43·9)	1346 (16·3)	<0·001
Long lesions ≥20 mm, n (%)*‡	2667 (43·7)	1919 (23·2)	<0·001

Notes:
*An indication for the implantation of a DES
† Stent diameter was used as a proxy
‡Stent length was used as a proxy
Abbreviations:
ACC/AHA, American College of Cardiology/American Heart Association; CABG, coronary artery bypass graft; CAD, coronary artery disease; MI, myocardial infarction; MIG, Melbourne Interventional Group; PCI, percutaneous coronary intervention.

Figure A1 The rates of DES and BMS use by the munber of indications for a DES that was present

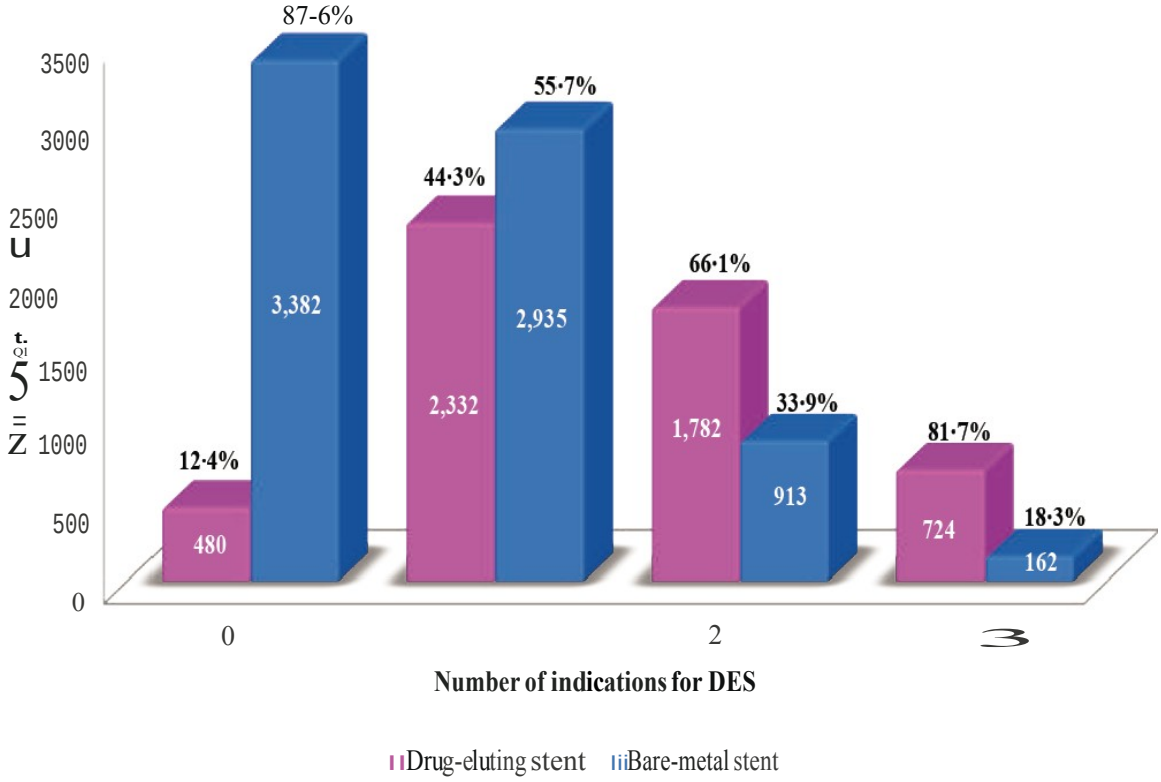
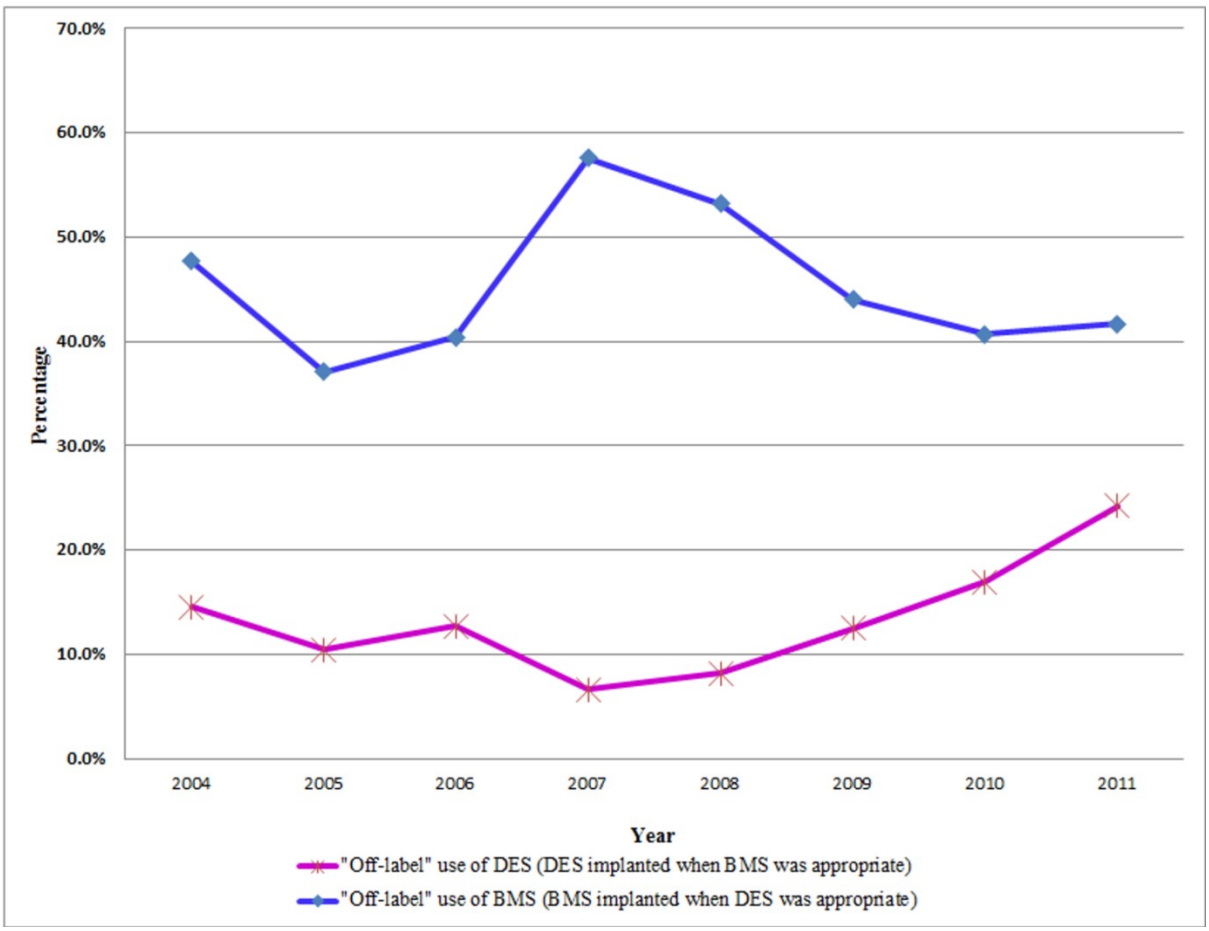


Figure A2 A year-by-yearanalysisof'off-label'use of DES and BMS in Victorian Public Hospitals from April 2004 to December 2011



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Abbreviations:

BMS, bare-metal stent; DES, drug-eluting stent.

Notes:

The graph shows a year-by-year analysis of use of DES and BMS. Non-adherence to guidelines was defined as "off-label" use". The "off-label" use of BMS peaked to 60% in 2007. The significance in trends was examined using the Cuzick's test – DESand BMS-use followed a non-normal distribution, and the year groups could be ordered. The results showed a significant increasing trend in the 'off-label' use of DES ($p<0{\cdot}001$). For BMS, this trend was not significant ($p=0{\cdot}327$).

Table A3 Frequencies of 12-month hospital readmissions for repeat revascularisations.

	All patients		**0 criteria**		**1 criteria**		**2 criteria**		**≥3 criteria**	
	DES	BMS	DES	BMS	DES	BMS	DES	BMS	DES	BMS
Repeat CABG(%)	1.3	2.4	1.3	1.8	0.9	1.8	2.8	2.8	0.7	7.1
Repeat PCI (%)	3.5	7.7	3.8	7.2	3.2	6.7	5.0	10.7	7.8	14.2
Repeat CABG and PCI (%)	0.0	0.1	0.0	0.0	0.0	0.1	0.0	0.4	0.0	0.0
AMI associated repeat CABG (%)	0.2	0.3	0.2	0.4	0.1	0.3	0.7	0.3	0.0	0.7
AMI associated repeat PCI (%)	1.7	3.3	1.1	2.0	1.6	2.9	3.2	4.9	6.4	5.7
AMI associated repeat CABG and PCI (%)	0.0	0.1	0.0	0.0	0.0	0.1	0.0	0.3	0.0	0.0

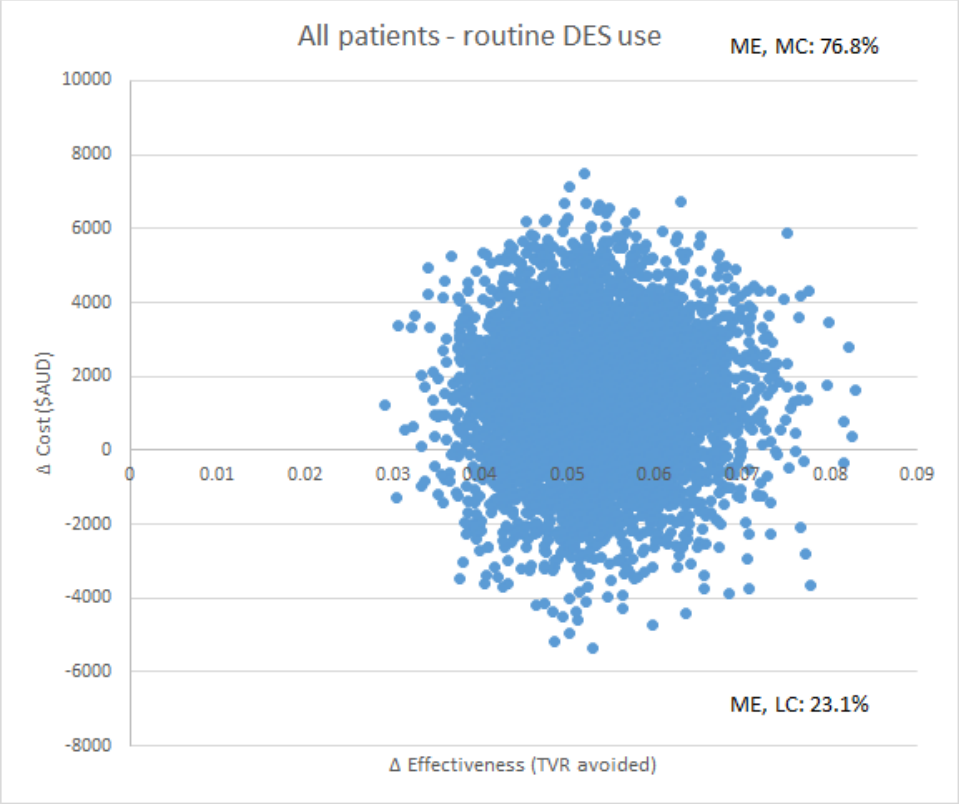
Abbreviations:
AMI, acute myocardial infarction; BMS, bare metal stent; CABG, coronary artery bypass surgery; DES, drug-eluting stent; PCI, percutaneous coronary intervention.
Notes:
This table summarises the rates of hospital readmissions for TVR or TLR during the 12-month follow-up period, by sub-group, and stent-group.

Table A4 Twelve-month repeat revascularization rates (%), pre- and post-propensity score matching.

	Before propensity-score matching			**After propensity-score matching**		
	DES	**BMS**	**P-value**	**DES**	**BMS**	**P-value**
All patients						
TVR*	278 (5.2)	524 (7.1)	<0.001	134 (4.1)	282 (8.6)	<0.001
TLR	149 (2.8)	384 (5.2)	<0.001	65 (2.0)	205 (6.3)	<0.001
'0' indications						
TVR*	22 (4.6)	180 (5.3)	0.496	19 (4.3)	37 (8.1)	0.013
TLR	9 (1.9)	138 (4.1)	0.018	8 (1.8)	27 (6.1)	0.001
1 indication						
TVR*	86 (3.7)	226 (7.7)	<0.001	64 (3.5)	144 (7.8)	<0.001
TLR	48 (2.1)	158 (5.4)	<0.001	38 (2.0)	102 (5.5)	<0.001
2 indications						
TVR*	113 (6.3)	94 (10.3)	<0.001	45 (6.1)	79 (10.7)	0.001
TLR	54 (3.0)	71 (7.8)	<0.001	18 (2.4)	61 (8.2)	<0.001
≥3 indications						
TVR*	57 (7.9)	24 (14.8)	0.006	11 (7.8)	22 (15.6)	0.042
TLR	38 (5.2)	17 (10.5)	0.012	10 (7.1)	16 (11.3)	0.217

Abbreviations: BMS, bare metal stent; DES, drug-eluting stent; TLR, target lesion revascularization; TVR, target vessel revascularization.
Notes:
**includes TLR*
This table summarises the numbers of patients who experienced at least one TVR or a TLR during 12 months follow-up. As a patient may experience more than one event, the number of TVRs reported here are different to the total numbers of TVR considered in the base-case economic evaluation.

Figure A3 Scatterplot of PSA results from 5000 bootstrap iterations for the matched overall cohort.



Abbreviations: BMS, bare-metal stent; DES, drug-eluting stent; ME,MC, more effective, more costly; ME,LC, more effective, less costly; PSA, probabilistic sensitivity analysis; TVR, target vessel revascularisation.

Figure A4 Scatterplot of PSA results from 5000 bootstrap iterations for the matched indication subgroups.

Abbreviations: BMS, bare-metal stent; DES, drug-eluting stent; ME,MC, more effective, more costly; ME,LC, more effective, less costly; PSA, probabilistic sensitivity analysis

Table A4 Results from one-way price sensitivity analysis of initial procedural on the ICER (cost per TVR avoided) for DES compared with BMS.

			-75%	-50%	-25%	+75%	+50%	+25%
		Basecase ($11,097.37)	**$ 8,323.03**	**$ 5,548.68**	**$ 2,774.34**	**$ 19,420.39**	**$ 16,646.05**	**$ 13,871.71**
PCI with BMS	All patients	$ 24,683.35	$ 76,742.12	$ 154,830.28	$ 213,396.40	$ 198,754.87	$ 181,673.09	$ 168,861.75
	'0' indications	$ 44,634.62	$ 117,257.10	$ 226,190.82	$ 307,891.12	$ 287,466.04	$ 263,636.79	$ 245,764.85
	1 indication	$ 33,334.75	$ 95,239.35	$ 188,096.24	$ 257,738.91	$ 240,328.24	$ 220,015.79	$ 204,781.46
	2 indications	$ 23,788.25	$ 69,472.41	$ 137,998.66	$ 189,393.35	$ 176,544.67	$ 161,554.56	$ 150,311.97
	≥3 indications	-$ 7,462.20	$ 14,270.15	$ 46,868.66	$ 71,317.55	$ 65,205.33	$ 58,074.40	$ 52,726.21
		Basecase ($13,189.82)	**$ 9,892.37**	**$ 6,594.91**	**$ 3,297.46**	**$ 23,082.19**	**$ 19,784.74**	**$ 16,487.28**
PCI with DES	All patients	$ 24,683.35	-$ 37,191.33	-$ 99,066.00	-$ 160,940.68	$ 210,307.38	$ 148,432.70	$ 86,558.03
	'0' indications	$ 44,634.62	-$ 41,681.14	-$ 127,996.90	-$ 214,312.65	$ 303,581.90	$ 217,266.14	$ 130,950.38
	1 indication	$ 33,334.75	$ 40,242.22	$ 113,819.19	$ 187,396.16	$ 254,065.66	$ 180,488.69	$ 106,911.72
	2 indications	$ 23,788.25	$ 30,509.86	$ 84,807.97	$ 139,106.07	$ 186,682.57	$ 132,384.47	$ 78,086.36
	≥3 indications	-$ 7,462.20	-$ 33,292.27	-$ 59,122.34	-$ 84,952.41	$ 70,028.02	$ 44,197.94	$ 18,367.87
			Lower Limit 95%CI	Upper Limit 95%CI	Lower Limit IQR	Upper Limit IQR		
		Basecase ($11,097.37)	**$ 8,365.55**	**$ 13,829.17**	**$ 5,451.90**	**$ 12,043.08**		
PCI with BMS	All patients	$ 24,683.35	$ 75,944.10	-$ 26,577.21	$ 130,617.05	$ 6,937.70		
	'0' indications	$ 44,634.62	$ 116,143.86	-$ 26,874.34	$ 192,413.14	$ 19,879.28		
	1 indication	$ 33,334.75	$ 94,290.40	$ 27,620.66	$ 159,303.58	$ 12,232.89		
	2 indications	$ 23,788.25	$ 68,772.11	$ 21,195.44	$ 116,750.35	$ 8,215.56		
	≥3 indications	-$ 7,462.20	$ 13,937.01	-$ 28,861.32	$ 36,760.66	-$ 14,870.26		
	PCI with DES	**Basecase ($13,189.82)**	**$ 10,996.63**	**$ 15,383.01**	**$ 8,008.33**	**$ 15,084.53**		
PCI with DES	All patients	$ 24,683.35	-$ 16,470.51	$ 65,837.01	-$ 72,544.08	$ 60,236.28		
	'0' indications	$ 44,634.62	-$ 12,775.40	$ 102,044.37	-$ 90,998.56	$ 94,231.30		
	1 indication	$ 33,334.75	$ 15,602.49	$ 82,271.76	$ 82,281.20	$ 75,611.78		
	2 indications	$ 23,788.25	$ 12,326.31	$ 59,902.64	$ 61,533.66	$ 54,987.72		
	≥3 indications	-$ 7,462.20	-$ 24,642.20	$ 9,717.72	-$ 48,050.56	$ 7,379.65		

Abbreviations: BMS, bare metal stents; CI, confidence interval; DES, drug-eluting stents; ICER, incremental cost-effectiveness ratio; IQR, interquartile range; PCI, percutaneous coronary intervention; TVR, vessel target revascularisations; *Notes:* negative (-) values in the table indicate that DES is more effective, and less costly when compared with BMS (i.e., 'dominant').

Table A5 Results from one-way price sensitivity analysis of readmissions costs on the ICER (cost per TVR avoided) for DES compared with BMS.

			-75%	-50%	-25%	+75%	+50%	+25%
		Basecase ($39067.60)	**$ 29,300.70**	**$ 19,533.80**	**$ 9,766.90**	**$ 68,368.30**	**$ 58,601.40**	**$ 48,834.50**
Repeat CABG	All patients	$ 24,683.35	$ 26,591.82	$ 29,454.54	$ 31,601.57	$ 31,064.81	$ 30,438.59	$ 29,968.93
	'0' indications	$ 44,634.62	$ 45,783.67	$ 47,507.24	$ 48,799.92	$ 48,476.75	$ 48,099.72	$ 47,816.94
	1 indication	$ 33,334.75	$ 35,217.53	$ 38,041.69	$ 40,159.81	$ 39,630.28	$ 39,012.50	$ 38,549.16
	2 indications	$ 23,788.25	$ 23,788.25	$ 23,788.25	$ 23,788.25	$ 23,788.25	$ 23,788.25	$ 23,788.25
	≥3 indications	-$ 7,462.20	-$ 2,578.75	$ 4,746.43	$ 10,240.31	$ 8,866.84	$ 7,264.45	$ 6,062.67
		Basecase ($9,714.99)	**$ 7,286.24**	**$ 4,857.50**	**$ 2,428.75**	**$ 17,001.24**	**$ 14,572.49**	**$ 12,143.74**
Repeat PCI (with stent)	All patients	$ 24,683.35	$ 26,581.68	$ 29,429.18	$ 31,564.80	$ 31,030.90	$ 30,408.01	$ 29,940.84
	'0' indications	$ 44,634.62	$ 46,777.63	$ 49,992.15	$ 52,403.04	$ 51,800.32	$ 51,097.15	$ 50,569.76
	1 indication	$ 33,334.75	$ 35,236.78	$ 38,089.83	$ 40,229.62	$ 39,694.67	$ 39,070.56	$ 38,602.49
	2 indications	$ 23,788.25	$ 26,001.11	$ 29,320.40	$ 31,809.86	$ 31,187.50	$ 30,461.40	$ 29,916.83
	≥3 indications	-$ 7,462.20	-$ 6,247.83	-$ 4,426.26	-$ 3,060.09	-$ 3,401.64	-$ 3,800.10	-$ 4,098.95
		Basecase ($52,578.82)	**$ 39,434.12**	**$ 26,289.41**	**$ 13,144.71**	**$ 92,012.94**	**$ 78,868.23**	**$ 65,723.53**
Repeat PCI and CABG	All patients	$ 24,683.35	$ 24,985.53	$ 25,438.79	$ 25,778.74	$ 25,693.75	$ 25,594.60	$ 25,520.24
	'0' indications	$ 44,634.62	$ 44,634.62	$ 44,634.62	$ 44,634.62	$ 44,634.62	$ 44,634.62	$ 44,634.62
	1 indication	$ 33,334.75	$ 33,651.49	$ 34,126.60	$ 34,482.93	$ 34,393.85	$ 34,289.92	$ 34,211.97
	2 indications	$ 23,788.25	$ 24,664.56	$ 25,979.03	$ 26,964.89	$ 26,718.42	$ 26,430.88	$ 26,215.23
	≥3 indications	-$ 7,462.20	-$ 7,462.20	-$ 7,462.20	-$ 7,462.20	-$ 7,462.20	-$ 7,462.20	-$ 7,462.20
		Basecase ($8,268.04)	**$ 6,201.03**	**$ 4,134.02**	**$ 2,067.01**	**$ 14,469.07**	**$ 12,402.06**	**$ 10,335.05**
Associated AMI with repeat PCI or CABG	All patients	$ 24,683.35	$ 25,360.47	$ 26,376.16	$ 27,137.92	$ 26,947.48	$ 26,725.30	$ 26,558.67
	'0' indications	$ 44,634.62	$ 45,242.57	$ 46,154.48	$ 46,838.42	$ 46,667.44	$ 46,467.95	$ 46,318.34
	1 indication	$ 33,334.75	$ 34,007.15	$ 35,015.75	$ 35,772.20	$ 35,583.09	$ 35,362.46	$ 35,196.99
	2 indications	$ 23,788.25	$ 24,293.52	$ 25,051.42	$ 25,619.85	$ 25,477.74	$ 25,311.95	$ 25,187.61
	≥3 indications	-$ 7,462.20	-$ 7,347.37	-$ 7,175.11	-$ 7,045.93	-$ 7,078.22	-$ 7,115.90	-$ 7,144.16

Abbreviations: AMI, acute myocardial infarction; BMS, bare metal stents; CABG, coronary artery bypass grafting; DES, drug-eluting stents; ICER, incremental cost-effectiveness ratio; PCI, percutaneous coronary intervention; TVR, vessel target revascularisations. *Notes:* negative (-) values in the table indicate that DES is more effective, and less costly when compared with BMS (i.e., 'dominant').

Table A6 Results from one-way price sensitivity analysis of medication costs (per month) on the ICER (cost per TVR avoided) for DES compared with BMS.

			-75%	-50%	-25%	+75%	+50%	+25%
		Basecase ($2.39)	**$ 1.79**	**$ 1.19**	**$ 0.60**	**$ 4.18**	**$ 3.58**	**$ 2.99**
Asprin	All patients	$ 24,683.35	$ 24,678.15	$ 24,670.34	$ 24,664.49	$ 24,698.96	$ 24,717.17	$ 24,730.82
	'0' indications	$ 44,634.62	$ 44,632.79	$ 44,630.05	$ 44,628.00	$ 44,640.10	$ 44,646.50	$ 44,651.29
	1 indication	$ 33,334.75	$ 33,327.93	$ 33,317.69	$ 33,310.02	$ 33,355.22	$ 33,379.10	$ 33,397.01
	2 indications	$ 23,788.25	$ 23,784.50	$ 23,778.87	$ 23,774.66	$ 23,799.50	$ 23,812.62	$ 23,822.47
	≥3 indications	-$ 7,462.20	-$ 7,461.80	-$ 7,461.20	-$ 7,460.76	-$ 7,463.39	-$ 7,464.79	-$ 7,465.83
		Basecase ($63.87)	**$ 47.91**	**$ 31.94**	**$ 15.97**	**$ 111.78**	**$ 95.81**	**$ 79.84**
Clopidogrel	All patients	$ 24,683.35	$ 23,754.46	$ 22,361.12	$ 21,316.11	$ 27,470.03	$ 30,721.16	$ 33,159.50
	'0' indications	$ 44,634.62	$ 43,614.03	$ 42,083.15	$ 40,934.98	$ 47,696.39	$ 51,268.45	$ 53,947.50
	1 indication	$ 33,334.75	$ 32,232.52	$ 30,579.18	$ 29,339.18	$ 36,641.43	$ 40,499.23	$ 43,392.57
	2 indications	$ 23,788.25	$ 22,996.02	$ 21,807.68	$ 20,916.43	$ 26,164.93	$ 28,937.72	$ 31,017.31
	≥3 indications	-$ 7,462.20	-$ 7,780.24	-$ 8,257.31	-$ 8,615.11	-$ 6,508.07	-$ 5,394.91	-$ 4,560.05
		Basecase ($117.48)	**$ 88.11**	**$ 58.74**	**$ 29.37**	**$ 205.58**	**$ 176.22**	**$ 146.85**
Prasugrel	All patients	$ 24,683.35	$ 24,684.19	$ 24,685.46	$ 24,686.41	$ 24,680.82	$ 24,677.86	$ 24,675.65
	'0' indications	$ 44,634.62	$ 44,581.93	$ 44,502.89	$ 44,443.61	$ 44,792.70	$ 44,977.12	$ 45,115.44
	1 indication	$ 33,334.75	$ 33,335.99	$ 33,337.85	$ 33,339.24	$ 33,331.04	$ 33,326.70	$ 33,323.45
	2 indications	$ 23,788.25	$ 23,816.64	$ 23,859.23	$ 23,891.16	$ 23,703.08	$ 23,603.71	$ 23,529.19
	≥3 indications	-$ 7,462.20	-$ 7,480.15	-$ 7,507.07	-$ 7,527.26	-$ 7,408.36	-$ 7,345.54	-$ 7,298.43
		Basecase ($16.03)	**$ 12.02**	**$ 8.02**	**$ 4.01**	**$ 28.06**	**$ 24.05**	**$ 20.04**
Warfarin	All patients	$ 24,683.35	$ 24,690.08	$ 24,700.17	$ 24,707.73	$ 24,705.84	$ 24,703.63	$ 24,701.98
	'0' indications	$ 44,634.62	$ 44,626.84	$ 44,615.17	$ 44,606.42	$ 44,608.60	$ 44,611.16	$ 44,613.07
	1 indication	$ 33,334.75	$ 33,347.14	$ 33,365.72	$ 33,379.65	$ 33,376.17	$ 33,372.11	$ 33,369.06
	2 indications	$ 23,788.25	$ 23,790.57	$ 23,794.04	$ 23,796.65	$ 23,795.99	$ 23,795.23	$ 23,794.66
	≥3 indications	-$ 7,462.20	-$ 7,456.52	-$ 7,448.00	-$ 7,441.61	-$ 7,443.21	-$ 7,445.08	-$ 7,446.47

		Basecase ($19.10)	**$ 14.32**	**$ 9.55**	**$ 4.77**	**$ 33.42**	**$ 28.64**	**$ 23.87**
ACE inhibitor	All patients	$ 24,683.35	$ 24,649.07	$ 24,597.64	$ 24,559.07	$ 24,568.71	$ 24,579.96	$ 24,588.40
	'0' indications	$ 44,634.62	$ 44,714.94	$ 44,835.42	$ 44,925.77	$ 44,903.18	$ 44,876.83	$ 44,857.06
	1 indication	$ 33,334.75	$ 33,274.70	$ 33,184.63	$ 33,117.07	$ 33,133.96	$ 33,153.66	$ 33,168.44
	2 indications	$ 23,788.25	$ 23,754.67	$ 23,704.31	$ 23,666.53	$ 23,675.97	$ 23,686.99	$ 23,695.25
	≥3 indications	-$ 7,462.20	-$ 7,497.47	-$ 7,550.39	-$ 7,590.07	-$ 7,580.15	-$ 7,568.58	-$ 7,559.90
		Basecase ($25.06)	**$ 18.80**	**$ 12.53**	**$ 6.27**	**$ 43.86**	**$ 37.59**	**$ 31.33**
Angiotensin II inhibitor	All patients	$ 24,683.35	$ 24,683.28	$ 24,683.17	$ 24,683.09	$ 24,683.11	$ 24,683.13	$ 24,683.15
	'0' indications	$ 44,634.62	$ 44,555.20	$ 44,436.06	$ 44,346.70	$ 44,369.04	$ 44,395.10	$ 44,414.65
	1 indication	$ 33,334.75	$ 33,315.20	$ 33,285.87	$ 33,263.88	$ 33,269.37	$ 33,275.79	$ 33,280.60
	2 indications	$ 23,788.25	$ 23,791.73	$ 23,796.95	$ 23,800.87	$ 23,799.89	$ 23,798.75	$ 23,797.89
	≥3 indications	-$ 7,462.20	-$ 7,448.97	-$ 7,429.13	-$ 7,414.25	-$ 7,417.97	-$ 7,422.31	-$ 7,425.57
		Basecase ($23.59)	**$ 17.69**	**$ 11.79**	**$ 5.90**	**$ 41.28**	**$ 35.38**	**$ 29.48**
Beta-blocker	All patients	$ 24,683.35	$ 24,629.82	$ 24,549.52	$ 24,489.30	$ 24,504.36	$ 24,521.92	$ 24,535.10
	'0' indications	$ 44,634.62	$ 44,579.82	$ 44,497.61	$ 44,435.95	$ 44,451.36	$ 44,469.35	$ 44,482.83
	1 indication	$ 33,334.75	$ 33,242.28	$ 33,103.58	$ 32,999.55	$ 33,025.56	$ 33,055.90	$ 33,078.66
	2 indications	$ 23,788.25	$ 23,774.42	$ 23,753.69	$ 23,738.13	$ 23,742.02	$ 23,746.56	$ 23,749.96
	≥3 indications	-$ 7,462.20	-$ 7,477.60	-$ 7,500.69	-$ 7,518.02	-$ 7,513.68	-$ 7,508.63	-$ 7,504.84
		Basecase ($19.12)	**$ 14.34**	**$ 9.56**	**$ 4.78**	**$ 33.46**	**$ 28.68**	**$ 23.90**
Ca Channel Blocker	All patients	$ 24,683.35	$ 24,685.11	$ 24,687.74	$ 24,689.72	$ 24,689.23	$ 24,688.65	$ 24,688.22
	'0' indications	$ 44,634.62	$ 44,568.83	$ 44,470.14	$ 44,396.12	$ 44,414.62	$ 44,436.21	$ 44,452.40
	1 indication	$ 33,334.75	$ 33,337.20	$ 33,340.87	$ 33,343.62	$ 33,342.93	$ 33,342.13	$ 33,341.53
	2 indications	$ 23,788.25	$ 23,807.85	$ 23,837.24	$ 23,859.29	$ 23,853.78	$ 23,847.35	$ 23,842.53
	≥3 indications	-$ 7,462.20	-$ 7,458.75	-$ 7,453.57	-$ 7,449.69	-$ 7,450.66	-$ 7,451.79	-$ 7,452.64
		Basecase ($62.96)	**$ 47.22**	**$ 31.48**	**$ 15.74**	**$ 110.18**	**$ 94.44**	**$ 78.70**
Statins	All patients	$ 24,683.35	$ 24,557.02	$ 24,367.53	$ 24,225.41	$ 24,260.94	$ 24,302.39	$ 24,333.48
	'0' indications	$ 44,634.62	$ 44,580.46	$ 44,499.21	$ 44,438.28	$ 44,453.51	$ 44,471.28	$ 44,484.61
	1 indication	$ 33,334.75	$ 33,131.93	$ 32,827.71	$ 32,599.53	$ 32,656.58	$ 32,723.13	$ 32,773.04
	2 indications	$ 23,788.25	$ 23,643.27	$ 23,425.79	$ 23,262.69	$ 23,303.46	$ 23,351.04	$ 23,386.72

	≥3 indications	-$ 7,462.20	-$ 7,425.91	-$ 7,371.48	-$ 7,330.65	-$ 7,340.86	-$ 7,352.76	-$ 7,361.69
		Basecase ($4.37)	**$ 3.28**	**$ 2.19**	**$ 1.09**	**$ 7.65**	**$ 6.56**	**$ 5.46**
Spironolactone	All patients	$ 24,683.35	$ 24,683.56	$ 24,683.88	$ 24,684.12	$ 24,684.06	$ 24,683.99	$ 24,683.94
	'0' indications	$ 44,634.62	$ 44,636.36	$ 44,638.96	$ 44,640.91	$ 44,640.42	$ 44,639.86	$ 44,639.43
	1 indication	$ 33,334.75	$ 33,334.69	$ 33,334.60	$ 33,334.54	$ 33,334.55	$ 33,334.57	$ 33,334.59
	2 indications	$ 23,788.25	$ 23,788.57	$ 23,789.04	$ 23,789.39	$ 23,789.31	$ 23,789.20	$ 23,789.12
	≥3 indications	-$ 7,462.20	-$ 7,462.53	-$ 7,463.03	-$ 7,463.41	-$ 7,463.32	-$ 7,463.21	-$ 7,463.12
		Basecase ($42.55)	**$ 31.91**	**$ 21.28**	**$ 10.64**	**$ 74.46**	**$ 63.83**	**$ 53.19**
Fibrate	All patients	$ 24,683.35	$ 24,699.67	$ 24,724.16	$ 24,742.52	$ 24,737.93	$ 24,732.57	$ 24,728.56
	'0' indications	$ 44,634.62	$ 44,623.67	$ 44,607.25	$ 44,594.93	$ 44,598.01	$ 44,601.60	$ 44,604.29
	1 indication	$ 33,334.75	$ 33,352.63	$ 33,379.45	$ 33,399.56	$ 33,394.53	$ 33,388.67	$ 33,384.27
	2 indications	$ 23,788.25	$ 23,806.45	$ 23,833.76	$ 23,854.23	$ 23,849.11	$ 23,843.14	$ 23,838.66
	≥3 indications	-$ 7,462.20	-$ 7,480.22	-$ 7,507.26	-$ 7,527.54	-$ 7,522.47	-$ 7,516.56	-$ 7,512.12
		Basecase ($73.54)	**$ 55.16**	**$ 36.77**	**$ 18.39**	**$ 128.70**	**$ 110.32**	**$ 91.93**
Ezetimibe	All patients	$ 24,683.35	$ 24,655.35	$ 24,613.34	$ 24,581.84	$ 24,589.72	$ 24,598.91	$ 24,605.80
	'0' indications	$ 44,634.62	$ 44,533.50	$ 44,381.81	$ 44,268.05	$ 44,296.49	$ 44,329.67	$ 44,354.56
	1 indication	$ 33,334.75	$ 33,334.75	$ 33,334.75	$ 33,334.75	$ 33,334.75	$ 33,334.75	$ 33,334.75
	2 indications	$ 23,788.25	$ 23,779.67	$ 23,766.80	$ 23,757.15	$ 23,759.56	$ 23,762.38	$ 23,764.49
	≥3 indications	-$ 7,462.20	-$ 7,385.08	-$ 7,269.40	-$ 7,182.64	-$ 7,204.33	-$ 7,229.64	-$ 7,248.62
	Eplerenone	**Basecase ($116.86)**	**$ 87.65**	**$ 58.43**	**$ 29.22**	**$ 204.51**	**$ 175.29**	**$ 146.08**
Eplerenone	All patients	$ 24,683.35	$ 24,692.75	$ 24,706.86	$ 24,717.43	$ 24,714.79	$ 24,711.70	$ 24,709.39
	'0' indications	$ 44,634.62	$ 44,636.34	$ 44,638.92	$ 44,640.85	$ 44,640.37	$ 44,639.80	$ 44,639.38
	1 indication	$ 33,334.75	$ 33,349.53	$ 33,371.71	$ 33,388.34	$ 33,384.18	$ 33,379.33	$ 33,375.69
	2 indications	$ 23,788.25	$ 23,785.33	$ 23,780.95	$ 23,777.66	$ 23,778.48	$ 23,779.44	$ 23,780.16
	≥3 indications	-$ 7,462.20	-$ 7,442.72	-$ 7,413.51	-$ 7,391.60	-$ 7,397.07	-$ 7,403.46	-$ 7,408.26

Abbreviations: BMS, bare metal stents; DES, drug-eluting stents; ICER, incremental cost-effectiveness ratio; TVR, vessel target revascularisations. *Notes:* negative (-) values in the table indicate that DES is more effective, and less costly when compared with BMS (i.e., 'dominant').

7 Incremental costs following PCI among patients with CKD in Australia

7.1 Chapter overview

The burden of CKD in the context CAD and acute coronary syndrome (ACS) is imminent (219). The impact of CKD on coronary revascularisation outcomes have been largely under studied due to the exclusion of high-risk CKD patients from RCTs (219). In Chapter 5, the cost-effectiveness of CABG compared with PCI among patients with CKD was evaluated in a sub-group analysis, which revealed second highest incremental costs for this subgroup following CABG when compared with PCI. This chapter aims to evaluate the impact (cost of illness) of CKD among patients who underwent PCI using multi-centre data from the MIG registry, and published cost estimates. The findings from this analysis were published in the International Journal of Cardiology.

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Cardiovascular readmissions and excess costs following percutaneous coronary intervention in patients with chronic kidney disease: Data from a large multi-centre Australian registry ☆,☆☆

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abstract

Background: Chronic kidney disease (CKD) is a well-established risk factor for adverse events in patients undergoing percutaneous coronary intervention (PCI). However, few data exists on the subsequent healthcare resource use and related incremental costs in this patient subgroup. The present study compares the rates of cardiac-related hospitalisations and the associated direct costs, post-PCI in patients with and without CKD.
Methods: Healthcare costs were estimated for 12,998 PCI patient-procedures from the Melbourne Interventional Group (MIG) registry, collected between February 2004 and October 2010. Information collected included the use of cardiovascular drugs and cardiac-related hospitalisations from those that completed 12-month follow-up. Individual patients were assigned unit costs based on published data from the National Hospital Cost Data Collection for Admissions in Victoria (2008–2009) and the Pharmaceutical Benefit Scheme (PBS) schedule (2011–2012). Bootstrap multiple linear regression was used to estimate the direct excess healthcare costs, adjusting for age and gender and relevant comorbidities.
Results: Excess cardiac-related readmissions occurred among patients with "severe CKD or dialysis" (estimated glomerular filtration rate (eGFR): b30 ml/min/1.73 m^2; n = 330; 35%), compared to "moderate CKD" (eGFR: 30–60 ml/min/1.73 m^2; n = 2648; 28%), or the "referent CKD status" (eGFR: ≥ 60 ml/min/1.73 m^2; n = 10,020; 24%). On average, excess (95%CI) overall direct costs were significantly higher in patients with severe CKD or dialysis compared to those with referent CKD status [$AUD 2206 ($AUD 1148 to 3688)].
Conclusions: From the healthcare payer's perspective, PCI patients with severe CKD compared to no-CKD imposed significantly higher burden on subsequent healthcare resources. Hospitalisations accounted for the majority of these expenditures.

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1. Introduction

Chronic kidney disease (CKD) is estimated to affect one in nine Australian and American adults [1,2]. The global burden from renal insufficiency is characterised by growing rates of CKD, end-stage renal failure (ESRF), and rising global prevalence of CKD-related comorbidities such as obesity, diabetes, and hypertension [3–6]. CKD is a well-established risk factor for early mortality and morbidity in coronary artery disease (CAD) [7–9]. Hospitalisations due to adverse events are common in the CKD-CAD population [10–12]. In particular, patients with CKD undergoing percutaneous coronary intervention (PCI) are at increased risk of mortality and reduced MACCE-free (major adverse cardiovascular or cerebrovascular event-free) survival [13–16]. This association is more pronounced in patients with ESRF.

Despite marked evidence of complications and excess resource use in patients with CKD and CAD, few studies in health services literature had quantified the monetary impact of CKD in the context of percutaneous coronary intervention (PCI). In fact, two prior studies demonstrated renal insufficiency as a significant independent cost-driver of PCI [17,18]. In an analysis of predictors of adverse outcomes and in-hospital costs of PCI, Pohlen and colleagues [18] identified a baseline creatinine level of >2 mg/dl as a major driver of in-hospital PCI costs. Meyer and colleagues [17] further established the impact of different CKD stages on the direct in-hospital costs of PCI. Yet, no cost of illness study exists on the healthcare resource utilisation from discharge to 12-month follow-up post-PCI. Such data could provide valuable evidence for the identification of preventable hospitalisations following coronary interventions and the implementation of cost saving strategies by healthcare decision-makers.

As such, we aimed to compare the rates and excess costs of cardiac-related readmissions following discharge from PCI in patients with and without CKD, from the perspective of the Australian government. Data from the Melbourne Interventional Group (MIG) registry, a large interventional registry comprising details of more than 17,000 'all-comer' patients to PCI, was used in this study.

2. Methods

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

2.1. The MIG registry

The MIG registry is an on-going collaborative venture of interventional cardiologists practising in eight public referral hospitals, in Victoria, Australia [19]. Australia has a universal healthcare system, where the majority of inpatient and outpatient services are provided by the public system, which is government funded.

The MIG registry has previously been described in detail [19–21]. Data collected include baseline, demographic, clinical features of patients, and their in-hospital outcomes. In addition, follow-up at 30-day- and 12-month-endpoints is also conducted. Case report forms (CRFs) at baseline and follow-up are used to aid data collection [21]. Cardiac research nurses collect follow-up data by means of phone calls where information documented includes medication use, as well as adverse events such as death; acute myocardial infarction (MI); target lesion and vessel revascularisation (TLR and TVR); and hospital readmissions. All adverse events were confirmed by review of patients' medical records at the relevant hospitals. The MIG study protocol has been approved by the ethics committee in each participating hospital [19]. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. Consent was obtained from patients using the "opt-out" approach [19–21]. An independent audit of randomly selected procedures at each institution is performed annually at all enrolling sites by an investigator not affiliated with that institution [22]. Data accuracy of 97% has been achieved on baseline data, which is comparable to the accuracy of other large registries [23].

2.2. Data collection

2.2.1. Definition of population

Data from the MIG registry were available for 17,029 patients who underwent PCI procedures between 1st April 2004 and 10th February 2011. Given a baseline serum creatinine record was required to calculate a patient's creatinine clearance in this study, we excluded all patients with a missing baseline serum creatinine level (n = 474). As the study focussed on 12-month follow-up readmissions post-PCI discharge, we excluded patients who did not have 12-month follow-up (n = 3291), following the censoring of our dataset to 31st October 2010, a date which maximised our follow-up numbers to more than 90%. Additionally, patients who died during the 12 month post-PCI were also excluded from the study (n = 266). Overall, 12,998 patients were eligible for our final analysis. Data on in-hospital outcomes for the full cohort of patients (excluding those missing a serum creatinine level record at baseline) are available in Appendix I.

Patients undergoing PCI were classified into three groups according to their baseline estimated glomerular filtration rate (eGFR) using the most recent serum creatinine level as documented prior to PCI. The Kidney Health Australia (KHA) guidelines [1] were used to group individuals as follows: 'severe CKD/dialysis' (eGFR: b30 ml/min/1.73 m^2: CKD stages 4 and 5), 'moderate CKD' (eGFR: 30–59 ml/min/1.73 m^2: CKD stage 3), and 'referent group' (eGFR: ≥60 ml/min/1.73 m^2: CKD stages 1 and 2). The eGFR estimation was based on the four-component MDRD (Modification Diet in Renal Study) equation [24].

2.2.2. Hospitalisations

We defined readmissions as per definitions of cardiovascular (CV)-related events as described on MIG follow-up CRF [21] and the Australian-refined diagnostic related groupings (AR-DRGs) [25]. The DRG design in Australia currently comprises 661 classifications of hospital episodes based on homogeneous resource consumption [25]. We extracted the information of 44 AR-DRGs that were cardiac-related and matched our admission definitions. These comprised hospitalisations for: (1) elective angiogram alone; (2) heart failure (HF); (3) arrhythmia; (4) unstable angina pectoris alone (UAP alone); (5) UAP plus angiogram; (6) stroke alone; (7) MI alone; (8) MI plus angiogram; (9) MI plus PCI; (10) MI plus coronary artery bypass grafting (CABG); (11) MI plus PCI and CABG; (12) non-MI plus PCI; (13) non-MI plus CABG; and (14) non-MI plus PCI and CABG.

2.2.3. Medication use

MIG data collection on medication use at follow-up included drugs prescribed to patients for the management of cardiovascular disease. Information from the following therapeutic classes was included: anti-platelet agents (aspirin, clopidogrel, and prasugrel), oral anticoagulants (warfarin), HMG CoA reductase inhibitors (statins) and other lipid-lowering agents (fibrates and ezetimibe), diuretics (spironolactone and eplerenone), beta-blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin-II receptor antagonists. Although the collection of data regarding use of anti-diabetic agents was not part of MIG follow-up, this information (insulin, or oral medication such as biguanides, sulfonamides and thiasolidinediones) was collected from patients at baseline, and was assumed for compliance during the 12 months following PCI. The medicine used in the MIG registry was consistent with the Australian Institute of Health and Welfare report on the use of cardiovascular medicines [26].

2.3. Costs

All estimations of health-care-related costs were calculated from the perspective of the Australian government, this being at federal government level for pharmaceuticals and state government level for hospitalisations [27]. As this study sought to estimate the direct costs to the government, co-payments and costs related to private health-care admissions were not considered. We used a 'bottom-up' costing approach by assigning unit costs to each health-care item based on published estimates [28]. The estimated direct health-care costs were based on patient reported data on cardiac-related hospitalisations at public hospitals and the use of medications prescribed for the management of cardiovascular disease during the 12-month follow-up. As we had no access to hospital billing data, costs relating to the index procedure and in-hospital complications were not included in our analysis.

2.3.1. Hospitalisation costs

We sought cost data inputs from Australia's National Hospital Cost Data Collection (2008–09) for the state of Victoria [29]. Costs of readmissions were estimated by matching each patient-reported hospitalisation to its relevant AR-DRG grouping and related DRG price available in the cost report [29]. These unit costs are in fact related to Casemix funding, which hallmarks State funding of public hospitals in Australia. Casemix distributes a fixed State budget based on the type and number of patients treated and the average cost of treating patients as reported by hospitals [25]. DRG prices represent an agreed price (on average) that is paid by the State Government per hospital separation as defined by the AR-DRG. For clinical events or cardiovascular interventions that could be classified using more than one AR-DRG, we applied the mean weighed price of all relevant AR-DRGs applicable for that readmission relative to the percentage of total (sum of) individual separations used in the 2008–09 period [30,31]. Using the total health price index of the 2008–09 financial period as a reference [29], all costs were updated to 2011–12 values, which resulted in 10.7% rise in costs over the three year period. The unit costs per hospital episode used are reported in Appendix II.

2.3.2. Pharmaceutical costs

We sought cost data inputs from Australia's Pharmaceutical Benefit Scheme (PBS) in order to estimate the direct medication costs associated with CV-medication use over 12 months [32]. The MIG registry collects all drugs relevant to a particular therapeutic class; therefore, market share data were used for the period of January 2011 to January 2012 [33]. For each therapeutic class, a weighted mean daily cost was estimated by

calculating the sum-product of the cost of each drug-dose and its proportional market share [30,31,34]. The daily doses used reflected current treatment guidelines [35,36]. Annual costs were estimated by multiplying the daily costs by 365.25, on the assumption that patients were compliant with their prescribed medication/s over the course of follow-up. A number of examples of such calculations have been highlighted previously [30,31,34]. The classes of medications collected by the MIG registry and the estimated daily and yearly costs of drugs are described in Appendix III.

2.4. Statistical analysis

Differences in baseline, lesion, and procedural characteristics between CKD groups were compared using chi-square tests for categorical variables, and the test for analysis of variance for continuous variables. Overall direct healthcare costs (hospitalisations and cardiovascular medications) were stratified according to CKD status, and summarised by means (standard deviations [SDs]). As the distribution of direct costs followed a non-normal distribution, we also reported median costs and the interquartile range (IQR: 25th and 75th percentiles). Resource use was summarised by percentages. A multiple linear regression model was used to estimate the excess direct annualised healthcare costs in patients with moderate or severe CKD/dialysis (compared to the referent group), adjusting for age, gender and CKD-related comorbidities (diabetes, hypertension and dyslipidemia), despite their individual significance [31]. The 95% confidence intervals (CIs) for these estimates were obtained using 1000 bootstrap sample iterations.

Additionally to explore the impact of other baseline factors on the relationship between CKD status and total direct follow-up costs, a univariate regression analysis was performed. All variables that were significant at $p = 0.02$ threshold in the univariate analysis were included in the multiple linear regression analysis, and were observed for significance at $p = 0.05$ threshold. Statistical analysis was performed using Stata/IC version 11 (Windows).

2.5. Sensitivity analysis

Sensitivity analyses were carried out to detect disproportionate influence of inclusion and exclusion criteria on study results. We examined the effect of inclusion of patients who died during the 12-month follow-up post-PCI, who were excluded in the study, through including them in the study population. Furthermore, in order to detect the influence of elective/scheduled angiograms and (non-MI) PCI procedures on study estimates, multiple regression analysis was carried out excluding these procedures from the definition of readmissions.

3. Results

3.1. Baseline and procedural characteristics

The distribution of patients according to CKD status (referent, moderate, or severe CKD/dialysis) is shown in Fig. 1. Patients with dialysis represented 40% ($n = 131$) of our severe CKD/dialysis subgroup. The baseline and procedural characteristics of the three CKD groups are presented in Table 1. The ratio of females to males was below 50% across all three groups (20.9%, 38.1% and 37.4%, respectively; $p < 0.001$), reflecting the low rates of female admissions to PCI. Patients with moderate CKD were older (71.9, SD: 9.9), compared to those who had severe CKD/dialysis (69.3, SD: 11.5) or referent CKD status (62.2, SD: 11.5, $p < 0.001$). As expected, severe CKD/dialysis status was associated with significantly higher prevalence of diabetes, hypertension, and dyslipidemia, compared to moderate CKD or the referent CKD statuses ($p < 0.001$). The prevalence of complex coronary disease (e.g. left main CAD) also appeared to increase with worsening CKD ($p < 0.001$).

3.2. Hospitalisations

Twelve-month hospitalisation rates are presented in Table 2, classified by DRG assignment into different cardiovascular events. The readmission rates signify the number of patients experiencing at least one (≥ 1) cardiovascular event per 1000 patients undergoing PCI. Among patients with severe CKD/dialysis, the three major causes of a CV-related hospitalisation were: HF (rate: 88 per 1000 patients), non-MI PCI (rate: 88 per 1000 patients), and UAP alone (rate: 73 per 1000 patients). Similarly among patients with moderate CKD, the three most common reasons for readmission were: non-MI PCI, UAP alone, and HF. In contrast, rates of non-MI PCI, UAP alone, and UAP + angiogram were greatest for the referent group. The percentages of patients having CV-related hospitalisations increased with worsening CKD as shown in Table 3 (24%, 28%, and 35%, respectively).

3.3. Hospitalisation costs

Table 3 also displays the direct costs associated with hospitalisations; and the average adjusted or 'excess' costs according to CKD group. The mean direct costs (SD) related to CV-related hospitalisations per patient increased with rising CKD severity as follows: $AUD 2861 ($7299); $AUD 3257 ($7555); and $AUD 5311 ($10,713), respectively. On average, a PCI patient with severe CKD/dialysis compared to a patient with the referent CKD status incurred excess directs costs of $AUD 2238 ($1270 to 3554) at 12-month follow-up. Whereas, the mean adjusted cost of a patient with moderate CKD compared to the referent CKD status was $AUD 323 ($27 to 680).

3.4. Medication use

The percentage of use of cardiovascular medication according to CKD status is reported in Table 4. The use of aspirin, beta-blockers, ACE-inhibitors, statins, clopidogrel and prasugrel decreased with increasing CKD severity. However, the differences in use of these drugs across the three groups were marginal, with exception to ACE-inhibitors, for which there was a 20% absolute reduction in use between the referent CKD status and the severe CKD/dialysis. The

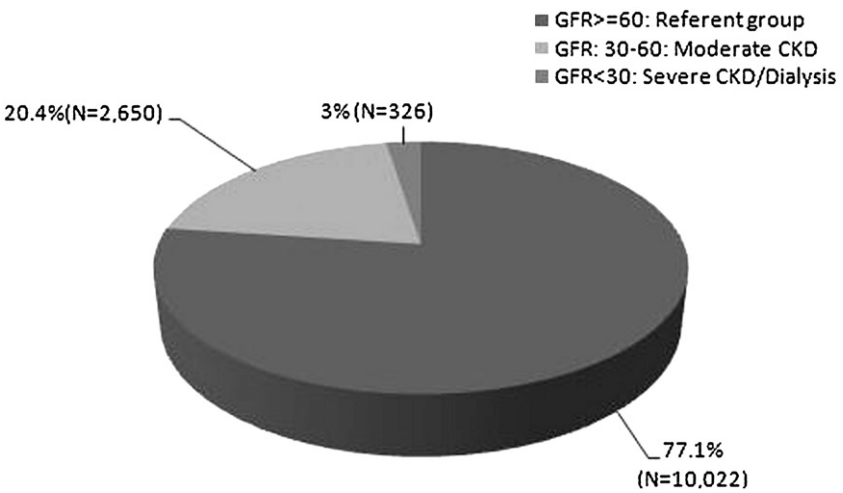

Fig. 1. Profile of patients undergoing percutaneous coronary intervention (PCI) from the Melbourne Interventional Group (MIG) registry according to their estimated glomerular filtration rate (eGFR) (ml/min/1.73 m^2) at baseline.

Table 1
Baseline characteristics of PCI patients by CKD sub-group, and the univariate analysis of predictors of direct follow-up costs, post-PCI.

Variable	CKD sub-groups				Univariate analysis of direct follow-up costs post-PCI (p-value, direction of relationship)
	Referent (n = 10,020)	Moderate CKD (n = 2648)	Severe CKD/dialysis (n = 330)	p-Value	
Baseline characteristics					
Female %	20.9	38.1	37.0	b0.001	N.S.
Mean age(SD), years	62.2 (11.5)	71.9 (9.9)	69.3 (11.5)	b0.001	N.S.
Smoking					
Never smoked %	30.2	40.3	37.7	b0.001	N.S.
Previously smoked %	43.1	47.5	55.2		
Current smoker %	26.6	12.3	7.1		
Diabetes mellitus, overall %	21.1	30.9	52.9	b0.001	b0.001, negative
Diabetes mellitus, diet regulated %	4.6	6.1	7.0	0.002	N.S
Diabetes mellitus, oral medication controlled%	14.1	18.6	18.5	b0.001	b0.001, positive
Diabetes mellitus, insulin regulated %	3.7	8.7	29.1	b0.001	b0.001, positive
Hypertension %	61.3	78.0	92.4	b0.001	b0.001, negative
Mean SBP (SD), mmHg	130.4 (23.4)	135.4 (24.1)	141.3 (32.5)	b0.001	N.S.
Dyslipidemia %	72.3	74.0	81.1	0.001	b0.001, negative
Acute coronary syndrome %	63.3	60.3	65.1	0.010	N.S.
Recent onset of HF %	2.8	8.6	14.3	b0.001	b0.001, negative
Previous MI %	26.8	35.5	41.5	b0.001	b0.001, negative
Mean BMI (SD), kg/m^2	28.3 (5.0)	28.3 (5.3)	28.3 (6.0)	0.964	0.008, positive
LVEF					
Reference: >60%	16.9	15.7	8.3	b0.001	b0.001, positive
Mild: 46–60%	59.5	54.6	53.8		
Moderate: 30–45%	21.8	26.5	33.8		
Severe: b30%	1.8	3.2	4.1		
Mean LVEF % (SD)	54.2 (11.2)	52.5 (12.2)	49.8 (11.3)	b0.001	b0.001, negative
Cardiogenic shock %	1.2	3.1	2.7	b0.001	b0.001, negative
Multi-vessel disease %	55.9	65.4	74.0	b0.001	b0.001, positive
Estimated GFR	85.4 (30.2)	49.1 (7.7)	18.6 (13.3)	–	b0.001, positive
Prior PCI	24.3	27.7	31.5	b0.001	0.002, negative
Prior CABG	7.3	15.1	18.8	b0.001	0.013, negative
Cerebrovascular disease %	5.3	9.8	16.7	b0.001	0.003, negative
Lesion characteristics					
Mean number of lesions treated (SD)	1.18 (0.4)	1.20 (0.4)	1.20 (0.4)	0.011	–
De-novo lesions %	93.7	93.4	91.2	0.299	b0.001, negative
ACC/AHA type B2/C lesions %	50.7	52.1	55.8	0.094	b0.001, positive
Ostial lesion	4.3	5.7	6.1	0.004	0.003, positive
Chronic total occlusion	0.2	0.3	0.3	0.580	N.S.
Vessel treated					
Left main coronary artery %	0.7	1.3	2.4	b0.001	N.S.
Left anterior descending artery %	35.9	34.8	28.5	0.015	N.S.
Proximal left anterior descending artery %	17.4	16.1	13.3	0.061	N.S.
Left circumflex artery %	14.1	14.2	17.9	0.154	NS
Right coronary artery %	32.9	32.7	30.6	0.686	NS
Bypass grafts %	2.3	5.0	7.9	b0.001	b0.001, positive
Stents					
Drug-eluting stents %	41.6	43.3	48.8	0.012	N.S.
Bare-metal stents %	53.4	51.4	44.5	0.002	b0.001, negative
Balloon angioplasty %	14.6	18.3	19.1	b0.001	N.S.

ACC/AHA = American College of Cardiology/American Heart Association; BMI: body mass index; HF: congestive heart failure; CKD: chronic kidney disease; LVEF: left ventricular ejection fraction; MI: myocardial infarction; N.S.: not significant ($p > 0.05$) SBP: systolic blood pressure; SD: standard deviation.

overall use of cardiovascular medication is highlighted in Table 3. In general, patients with a referent CKD status observed the highest rate of use of CV-medication (91%) compared to those with moderate CKD (90%) or severe CKD/dialysis (84%).

3.5. Pharmaceutical costs

Direct costs associated with CV-medication, and the mean excess costs according to CKD group, are presented in Table 3. On average, the mean direct costs (SD) associated with CV-medication use per patient decreased with increasing CKD severity as follows: $AUD 1527 ($724); $AUD 1500 ($1745); and $AUD 1431 ($820), respectively. The mean adjusted costs (95% CI) associated with CV-medication use were lower by $AUD 106 ($17 to 193) for every patient with severe CKD/dialysis compared to the referent CKD status. No significant difference in mean adjusted costs was observed between the moderate CKD and the referent groups (−$AUD 2 [$−34 to 31]).

3.6. Total costs and predictors

Overall, the mean (SD) total post-discharge healthcare expenditure on cardiovascular disease for PCI at 12-month follow-up was substantially higher for patients with severe CKD/dialysis: $AUD 6958 ($10,836); compared to those with moderate CKD: $AUD 4851 ($7636); or the referent CKD status: $AUD 4442 ($7377) (Table 3). The mean excess costs adjusted for patients' age, gender, diabetes, hypertension and dyslipidemia are available in Table 3 and Appendix IV. The additional cost (95%CI) per severe CKD/dialysis patient, compared to a patient with the referent CKD status was $AUD 2206 ($1148 to 3688). In contrast, the differences in mean adjusted costs

Table 2
Number of patients experiencing at least one (≥1) cardiovascular event by readmission reason and CKD status (rate per 1000 patients undergoing PCI).

Readmission reasons	CKD subgroup			
	Referent (n = 10,020)[a]	Moderate CKD (n = 2648)[a]	Severe CKD/dialysis (n = 330)[a]	Total (n = 12,998)
HF	103 (10)	113 (43)	29 (88)	245 (19)
Arrhythmia	132 (13)	54 (20)	6 (18)	192 (15)
UAP alone	478 (48)	154 (58)	24 (73)	656 (50)
UAP + angiogram	393 (39)	100 (38)	6 (18)	499 (38)
Stroke alone	33 (3)	23 (9)	8 (24)	64 (5)
Angiogram (alone)	305 (30)	59 (22)	7 (21)	371 (28)
MI (alone)	48 (5)	41 (15)	18 (54)	107 (8)
MI + angiogram	67 (7)	20 (8)	11 (33)	98 (7)
MI + PCI	150 (15)	64 (24)	16 (48)	230 (18)
MI + CABG	19 (2)	8 (3)	9 (3)	30 (2)
MI + PCI + CABG	5 (0)	0 (0)	0 (0)	5 (0)
Non-MI PCI	1064 (106)	260 (98)	29 (88)	1353 (104)
Non-MI CABG	208 (21)	50 (19)	9 (27)	267 (20)
Non-MI + PCI + CABG	2 (0)	0 (0)	1 (3)	3 (0)

CABG: coronary artery bypass grafting; CKD: chronic kidney disease; HF: heart failure; MI: myocardial infarction; PCI: percutaneous coronary intervention; UAP: unstable angina pectoris.
[a] Total readmissions observed (absolute values): referent group = 3302; moderate CKD = 1055; severe CKD/dialysis = 205.

between those with moderate CKD and referent CKD did not reach statistical significance ($AUD 335 [$−4 to 704]).

Furthermore, in a separate comprehensive analysis, a number of factors individually associated with healthcare expenditure from discharge to 12-month follow-up for PCI were identified (insulin-regulated diabetes mellitus, body mass index [BMI], left ventricular ejection fraction [LVEF], estimated GFR, ostial lesions, multi-vessel disease, and PCI of bypass graft, Table 1). Following adjustment for these factors, we noted a significant positive association between the CKD status and direct follow-up costs post-PCI.

3.7. Sensitivity analysis

We observed no significant differences in direct costs in our sensitivity analysis when we included patients whose exclusion could have resulted in an underestimation of the final estimates, such as those who had died during the 12-month follow-up period (n = 271). Additionally no significant differences were observed when we excluded patients whose inclusion could have resulted in an over-estimation of the excess direct costs, such as those being readmitted for scheduled/elective angiograms (n = 1740), or non-MI PCIs (n = 2706), that may not be related to the initial PCI procedure.

4. Discussion

To the best of our knowledge this is the first study comparing the direct costs of CV-related hospital readmissions and -medication use at 12 months following PCI in patients with and without CKD. We conducted our analysis from the Australian government perspective, using Australian dollars (roughly equivalent to US dollars). According to our results, patients with severe CKD/dialysis incurred significantly higher direct healthcare costs during 12 months post-PCI compared to those with the referent CKD status. Among patients with moderate or severe CKD and CAD (who will be termed the 'CKD-CAD subset' from this point onward), 67% to 76% of the cardiovascular-related healthcare burden was borne by CV-related hospital readmissions. Up to 20% to 31% of this burden was due to pharmaceutical costs related to CV-medication use, which were significantly lower among patients with severe CKD/dialysis compared to the referent CKD status.

In fact, in the current literature, studies quantifying the burden of CKD following PCI are limited, despite reports of an increased risk of MACCE among patients with CKD [13–16]. In fact, only one other study by Meyer and colleagues [17] had suggested an increasing trend of in-hospital costs (of PCI) with increasing severity of CKD. However, this study was limited by lack of follow-up data on PCI outcomes. By comparison, our study reported a trend of increasing direct follow-up healthcare costs, with worsening CKD, during the immediate 12 months following PCI.

Other evidence indicates a significant impact of renal disease on initial hospital costs of PCI. Pohlen and colleagues [18] showed that several renal and cardiovascular factors were associated with in-hospital costs of PCI and adverse events. Among these factors, patients with creatinine level > 2 mg/dl were found to cost 93% more (95% CI: 71–116%), compared to patients with creatinine level b 2 mg/dl. Other factors identified (LVEF, prior stroke, PCI of a arterial/venous bypass surgery, intracoronary thrombus present, 3-vessel disease, Canadian Cardiovascular Society [CCS] class IV, and BMI b 25 kg/m^2) were shown to have lesser impact on excess costs. Similarly our study also demonstrated a significant association between a number of factors (e.g. BMI, multi-vessel disease, LVEF, and PCI of bypass grafts) and increasing direct costs post-PCI at the individual level. Other cardiovascular-related factors, such as prior stroke, CCS class, etc. may also be associated with 12-month post-PCI direct healthcare costs, and as such merits evaluation.

As expected, we demonstrated higher rates of cardiovascular re-hospitalisations among patients who underwent PCI and had severe CKD/dialysis, compared to those with moderate CKD status or the referent 'normal' CKD status. Our findings are consistent with two prior studies, one which demonstrated a graded association between rising CKD severity and increasing CV-related events [9]; and the other which illustrated an elevated risk of hospitalisation when CKD interacts with CV-related conditions such as myocardial infarction [10]. However, given both these studies were based on the general population, they may be less comparable to the present study, which only included patients who underwent PCI due to restricting coronary artery disease [11,13–16].

Our findings also revealed that, HF, non-MI PCI, and UAP alone were the three most common causes of a CV-related hospital readmission in the CKD-CAD subset post-PCI. These data are consistent with prevailing clinical knowledge, which supports a substantial link between CKD and HF in the cardiovascular–renal axis [37]. Furthermore, prior studies had also demonstrated an increased risk of repeat revascularisation following PCI in patients with CKD [38,39]. However, as our definition for non-MI PCI readmissions included hospitalisations for elective (non-MI) PCIs, as well as index procedure-related complications (e.g. TLR or TVR), another explanation for these results could be the greater extent of CAD progression in patients. Nonetheless, as our overall findings proved robust to sensitivity analysis that excluded scheduled or elective readmissions for (non-MI) PCIs, it is unlikely that we had overestimated excess direct costs in the CKD-CAD subset.

Table 3
Resource use (%) post-percutaneous coronary intervention (PCI) and direct costs ($AUD)[a] at 12-month follow-up by CKD group[b].

Sub-groups	n/N (%)	Mean total cost per patient $AUD (SD)	Median total cost per patient $AUD (IQR)	Excess mean total cost $AUD (95% CI)†	p-Value
Hospitalisation costs					
Referent	2447/10,020 (24%)	2861 (7299)	0 (0, 0)	Ref.	–
Moderate CKD	754/2648 (28%)	3257 (7555)	0 (0, 3153)	323 (27, 680)	0.040
Severe CKD/dialysis	115/330 (35%)	5311 (10,713)	0 (0, 7828)	2238 (1270, 3554)	b0.001
Cardiovascular medication costs					
Referent	9104/10,020 (91%)	1527 (724)	1743 (1056, 2020)	Ref.	–
Moderate CKD	2375/2648 (90%)	1500 (1745)	1743 (1056, 2020)	−2 (−34, 31)	0.914
Severe CKD/dialysis	279/330 (84%)	1431 (820)	1567 (1017, 2020)	−106 (−193, −17)	0.021
Total costs					
Referent	–	4442 (7377)	2020 (1269, 3138)	Ref.	–
Moderate CKD	–	4851 (7636)	2020 (1286, 5173)	335(−4, 704)	0.052
Severe CKD/dialysis	–	6958 (10,836)	2105 (1350, 9409)	2206 (1148, 3688)	b0.001

CI: confidence interval; CKD: chronic kidney disease.
[a] Exchange rate: $AUD 1 = $US 1.02724 (24th July 2012).
[b] Adjusted for age, gender and comorbidities (diabetes, hypertension and dyslipidemia) using linear regression with 1000 bootstrap iterations for the estimation of 95% CIs.

In addition to results discussed above, we also demonstrated lower observed use of CV-related medication, and lower excess CV-related pharmaceutical costs among patients with severe CKD/dialysis compared to the referent CKD status. This result in particular appeared to be driven primarily by a reduction in use of ACE inhibitors with worsening CKD status. This is also appropriate, as ACE inhibitors are known to often worsen the renal function in patients with existing renal impairment [40].

Overall, our study was advantaged by a large complete follow-up of patients who had undergone PCI, and a robust costing methodology, which involved costing all patient-reported cardiac related readmissions within 12 months following PCI. We believe our study would assist policy decision makers about the allocation of resources for the efficient management of those severely diseased patients. Furthermore, our study provides valuable information on the extent to which post-PCI cost increases with increasing severity of CKD, independent of comorbidities. We believe that this is very important for informed decision making as this information was previously unknown in Australia.

4.1. Study limitations

The present study has general limitations that need to be carefully addressed. Most importantly, the number of patients in the CKD groups was uneven; in particular, the severe CKD/dialysis group comprised only 3% of the study cohort. However, this observation was concordant with other PCI registries, which reported prevalence of severe CKD between 3.0% (excluding dialysis patients) and 4.8% (including dialysis patients) [17,41]. The estimated healthcare costs in this study were limited to those that were directly relevant to cardiovascular conditions owing to the nature of the MIG registry. As such, any costs relating to the management of CKD or dialysis, ambulatory care or any primary care physician visits were not included in this analysis. Care should be taken when comparing costs in different healthcare settings. Given the large variability in health funding models, our costing data might not reflect equivalent excess costs in other countries. However, clinical management of CKD patients post PCI in Australia might be similar to other developed countries, and therefore overall information derived from this cost study is likely to be applicable.

Other limitations may relate to our use of MDRD equation, DRG prices, and registry-based data collection. In contemporary time, the CKD-EPI equation has gained much authority as a more accurate, and less biased estimation of the GFR, compared to the MDRD, especially at higher levels (GFR over 60 ml/min/1.73 m^2) [42]. Nonetheless, our 'referent CKD' group was comprised of patients with an 'estimated GFR' greater than 60 ml/min/1.73 m^2, which is adequate for most patients. As such, our study is unlikely to be impacted by bias associated with use of MDRD.

In addition, DRG prices especially correspond to resource use within a single hospital episode and hence disregard costs that may be related to transfers of cases between hospitals [43]. Therefore the actual healthcare resource use related to CV-events post-PCI may be higher than described in this study. However, given our reliance on patient reported hospitalisation in this study, the use of DRG prices was appropriate, as they represent most reliable estimate of average direct expenditure to the Government on a particular hospital separation in a Victorian public hospital in Australia. Moreover, assumptions were also made about the pharmaceutical costs, which were necessary, as costs of each class were based on current patterns of use in Australia [30,31,44].

Furthermore, pre-operative risk-assessment tools such as EuroSCORE, SYNTAX-score and AusSCORE may prove useful in the identification of specific CKD groups contributing to more healthcare costs following PCI [45–47]. However, the MIG registry currently does not collect all variables required to calculate such scores, which may have helped further in the estimation of healthcare costs post-PCI.

In the context of patient-reported outcomes, recall errors may also underestimate hospitalisation rates and use of CV-related medication, especially in the elderly, and the severely comorbid patients sub-groups [48]. Nonetheless, all MIG follow-up data on re-hospitalisations undergo validation as described in our Methods section.

Overall, this study provides useful data for future optimisation studies aiming to examine the cost-effectiveness of invasive treatment of CAD in patients with CKD and CAD [38]. Such data may also provide important evidence regarding healthcare resource utilisation for healthcare providers with a focus on reducing rates of preventable hospitalisations.

Table 4
Medication use at 12-month follow-up by CKD group.

Medication	CKD sub-groups		
	Referent (n = 10,020)	Moderate CKD (n = 2648)	Severe CKD/dialysis (n = 330)
Beta-blocker %	60	57	58
Aspirin %	85	81	76
ACE-inhibitors %	55	48	35
Angiotensin II inhibitor %	17	25	22
Ca^{2+} channel blocker %	15	22	27
Statin %	84	79	71
Clopidogrel %	58	56	57
Warfarin %	4	8	6
Spironolactone %	2	4	2
Fibrate %	2	2	3
Ezetimibe %	6	8	8
Prasugrel %	1	0	1
Eplerenone %	1	1	1

ACE: angiotensin-converting enzyme; CKD: chronic kidney disease; Ca: calcium.

5. Conclusion

In summary, CKD is not only a clinically devastating disease; it creates a major economic burden that increases with severity of the renal dysfunction. This study demonstrated that PCI patients with severe CKD/dialysis compared to those with better renal function contributed significantly to higher excess direct costs from discharge to 12 month follow-up. The results of this study could form valuable inputs for future modelling studies aiming to predict the economic impact of CKD in PCI.

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Appendix A. Supplementary data

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SUPPLEMENTARY MATERIAL

Appendix I. This table highlights the frequency (%) of in-hospital adverse events following PCI, by CKD subgroup in the original study cohort. The p-value indicates the significance of the association ($p<0.05$) between in-hospital complications and future direct healthcare costs.

	CKD sub-groups*			
Variable	Referent (n=12,606)	Moderate CKD (n=3,449)	Severe CKD/ Dialysis (n=500)	P-value
In-hospital mortality %	0.75	4.6	9.4	<0.001
Complications				
Myocardial infarction %	1.2	1.2	1.8	0.523
Bleeding %	2.0	3.0	3.6	<0.001
Congestive heart failure %	1.8	6.5	10.8	<0.001
Renal impairment[€]%	0.4	3.2	3.6	<0.001
Rise in serum creatinine (>200umol/L, and 2x the baseline level) %	0.4	3.3	10.0	<0.001
CVA/stroke %	0.2	0.4	1.2	<0.001
Emergency PCI %	0.6	0.8	0.2	0.299
Emergency CABG%	0.6	0.8	1.0	0.163
MACE %	2.7	6.5	11.8	<0.001

CABG: coronary artery bypass graft; CVA: cerebrovascular accident; MACE: major adverse cardiovascular events; PCI:percutaneous coronary intervention.

*N=474 patients were excluded from analysis due to missing baseline creatinine level record

[€] New requirement for dialysis

Appendix II. This table highlights the unit cost per hospital episode which was calculated as the mean weighed price of all relevant AR-DRGs applicable for that readmission relative to the percentage of total (sum of) individual separations used in the 2008-09 period. All costs are updated to 2011-12 values.

Clinical outcomes	Australian- DRGs	Unit Costs(AUD)
Heart failure	F62A, F62B	7,828.07
Arrhythmia	F70A, F70B,, F71A, F71B	3,153.01
Angiogram alone	F42A, F42B	5,556.86
UAP	F72A, F72B	2,866.97
UAP+ angiogram	F72A, F42A, F72B, F42B	4,395.20
Stroke	B69A, B69B, B70A, B70B, B70C	7,955.61
non-MI PCI	F15Z	8,803.00
non-MI CABG	F05A, F05B, F06A, F06B	38,464.76
non-MI PCI + CABG	F15Z, F05A, F05B, F06A, F06B	21,115.13
MI alone	F60A, F60B, F60C	5,518.89
MI + angiogram	F41A, F41B	7,491.88
MI + CABG	F60A, F60B, F60C, F05A, F05B, F06A, F06B	11,936.81
MI + PCI	F10Z	13,243.79
MI + PCI + CABG	F10Z, F05A, F05B, F06A, F06B	22,858.18

MI: acute myocardial infarction; CABG: coronary artery bypass grafting; DRG: diagnostic related group; PCI: percutaneous coronary intervention; UAP: unstable angina pectoris.

Appendix III. This table highlights the average weighed unit costs associated with use of cardiovascular medications per day and per year according to therapeutic subclass. All costs represent 2011-12 values.

CV medications	Average weighted costs per day ($)	Average weighted costs per year ($)
Cardiovascular agents		
Beta-blocker	0.76	277.13
Angiotensin-converting enzyme (ACE) -inhibitor	0.61	224.36
Angiotensin II antagonist	0.81	294.45
Calcium Channel blocker	0.62	224.63
Eplerenone	3.76	1,372.97
Spironolactone	0.14	51.35
Anti-platelet agents		
Aspirin	0.08	28.07
Clopidogrel	2.05	750.46
Prasugrel	3.78	1,380.22
Oral Anticoagulants		
Warfarin	0.52	188.37
Lipid-lowering agents		
Statin	2.03	739.71
Fibrate	1.37	499.92
Ezetimibe	2.37	864.06

Anti-diabetic agents		
Insulin	1.64	598.98
Oral medication (Biguanides, Sulfonamides, urea derivates, Thiazolidinediones)	0.66	241.83

Appendix IV. This table highlights the excess post-PCI direct healthcare costs (beta-coefficient) associated with having moderate, or severe CKD, adjusted for various confounding factors such as age, female gender, dyslipidaemia, hypertension, and diabetes. The p-value ($p<0.05$) and 95% CIs indicate the significance of the association.

Predictor	β –coefficient ($)	95% CI	P-value
Referent CKD	-	-	-
Moderate CKD	335	-4 – 704	0.052
Severe CKD/Dialysis	2,206	1,148 – 3,688	<0.001
Age	-7	-19 – 5	0.271
Female	-150	-428 – 177	0.327
Dyslipidemia	-141	-443 – 144	0.360
Hypertension	-104	-408 – 204	0.496
Diabetes	-1,196	-1,544 – -841	<0.001

8 Conclusion

8.1 Chapter overview

This chapter provides a summary of key results drawn from Chapters 3-7, the strengths and limitations of this work, implications of findings, and recommendations for future directions based on key learnings and insights gained from this project. Final remarks will be highlighted in the conclusion section.

8.2 Summary of key findings

The key findings for the primary, secondary, tertiary objectives of this thesis are described here:

Primary objective: ***To evaluate the cost-effectiveness of coronary revascularisation strategies in the Australian context.***

A cost-effectiveness analysis of CABG versus PCI for patients with MVCAD was undertaken from the perspective of the Australian public hospital payer (Chapter 5). At mean follow-up of 2.7 years, CABG compared with PCI was most cost-effective among high-risk sub-groups of patients, including those with diabetes (ICER: $42,819), acute coronary syndrome ($30,431), left-main CAD ($38,864), and heart failure ($36,966). Three key factors were apparent from this economic evaluation: firstly, relative to CABG, recipients of second generation compared with third generation DES carried a significant mortality benefit; secondly, despite constraints, administrative data and record linkage studies provide rich sources of evidence for economic evaluations; and thirdly, the propensity-score bin bootstrap (PSBB) approach is an effective method for matching treatment and comparator groups without compromising original sample size of cohorts. Future clinical effectiveness and economic evaluations in the contemporary

clinical practice for CABG or PCI may benefit from these findings, although, due to single-centre nature of this evaluation, results should be interpreted cautiously.

An economic evaluation was undertaken to compare the cost-effectiveness of guideline-driven use of DES compared with BMS at 12 months, from the perspective of the Australian healthcare payer (Chapter 6). The incremental cost per TVR avoided reduced with increasing risk profile of patients. For patients with '0', '1', and '2' indications for a DES, ICERs of $44,635, $33,335, and $23,788 were yielded, respectively. The ICER for routine DES implantation, when compared with BMS, was $24,683. For high-risk patients with '≥3' indications for a DES, the adoption of DES compared with BMS was associated with cost-savings, and greater clinical improvement in terms of significantly reduced rates of TVR. Cost-effectiveness was least favourable among patients with '0' indications for a DES. While this analysis was strengthened by the use of multi-centre data from eight tertiary public hospitals in Victoria, and propensity score matching using the nearest neighbour 1:1 matching approach, there were several limitations. The procedural cost inputs were based on data obtained from a single centre, while readmissions costs were based on published estimates. The bias in these estimates, however, was accounted for through sensitivity analyses, which yielded robust results.

Secondary objective: To contribute to the broader scientific literature concerning the effectiveness and cost-effectiveness of these strategies in the DES-era through conducting analytical reviews of the literature.

A systematic review and meta-analyses were conducted to compare the risk of all-cause mortality, myocardial infarction (MI), repeat revascularisation, cerebrovascular events (CVE), and MACCE among patients with diabetes mellitus (DM) and MVCAD who underwent either CABG or PCI with DES (Chapter 3). A total of 1,837 and 3,052 patients were pooled from

four RCTs (FREEDOM, SYNTAX, VA CARDS, and CARDia) and five non-randomised studies. At mean three years, pooled analyses of RCTs favoured CABG compared with DES for all end-points but CVE: CABG compared with DES was associated with a lower risk of all-cause mortality (Relative Risk: 0.62; 95% Confidence Interval: 0.42-0.94), MI (0.61; 95% CI: 0.47-0.80), repeat revascularisation (0.44; 95% CI: 0.35-0.56) and MACCE (0.6; 95% CI: 0.5 to 0.8); but higher risk of CVE (1.75; 95% CI: 1.11-2.75). Pooled analyses of non-randomised studies showed no difference between CABG and DES for all-cause mortality, MI and CVE at mean 3-year follow-up. These results however should be interpreted with care, given inherent biases associated with unmatched non-randomised comparisons.

Another systematic review was performed to evaluate the cost-effectiveness of CABG compared with PCI among patients with complex MVCAD (Chapter 4). All studies comparing cost-effectiveness of CABG (or OPCABG) versus PCI in the BMS and DES-eras were included if balanced groups of patients were considered irrespective of randomisation. Sixteen studies were included. The ICERs reported across studies varied widely according to perspective and time horizon. Favourable lifetime ICERs were reported for CABG by the FREEDOM, SYNTAX trials, and a large US-based registry study that utilised propensity score matching methods. For patients with left main coronary artery disease, however, DES was reported as the dominant (more effective and cost-saving) strategy in one study. An analysis of quality of included studies revealed that few met all standards set by guidelines for reporting of health economic evaluations, and that there was a substantial need for more economic evaluations adopting a societal perspective, and time horizons of a lifetime or ≥10 years.

Tertiary objective: ***To conduct cost analysis, and identify incremental costs and drivers of costs of revascularisation strategies in selected groups of high-risk patients.***

A cost analysis was undertaken to compare cardiac-related complications and associated direct costs among patients with and without CKD (including dialysis) at 12 months post-PCI (Chapter 7). Bootstrap regression analysis was undertaken to estimate the direct excess healthcare costs, adjusting for age and gender and relevant comorbidities. As expected, the incremental direct costs associated with CKD compared with no CKD was significantly high, averaging at $2,206 (95% Confidence Interval: $1,148-$3,688). A number of factors were individually associated with costs, including insulin-regulated diabetes mellitus, body mass index, left ventricular ejection fraction, estimated GFR, ostial lesions, multi-vessel disease, and PCI of bypass graft. Overall, this study revealed that PCI patients with severe CKD/dialysis compared with those with better renal function imposed a significant burden on healthcare resources. The estimates from this study could be used to inform future modelling studies aiming to evaluate the burden of disease associated with CKD.

8.3 Key strengths and limitations

This doctoral thesis addressed a number of evidence gaps in the literature, highlighted in Chapter 1:

1. There were no published systematic reviews comparing the effectiveness of CABG versus PCI, in the DES era at the beginning of this project. In light of this, a systematic review of effectiveness of these strategies among high-risk patients (MVCAD and diabetic) was published using data from literature available at the time (Chapter 3). This systematic review was unique to other published reviews, in that it also compared outcomes yielded from RCTs versus observational studies, by pooling data from these

study designs separately using appropriate guidelines including Cochrane Collaboration (196) and a proposal for Meta-analysis of observational studies in epidemiology (MOOSE) (198).

2. The absence of a published systematic review comparing the cost-effectiveness of CABG versus PCI for patients with complex CAD was apparent at the beginning of this project. In response, the first ever systematic review of cost-effectiveness analysis comparing CABG versus PCI was published (Chapter 4). This analysis included evaluations of cost-effectiveness performed in the DES and BMS-era, as well as comparison of OPCABG versus PCI. In the absence of published guidelines for systematic reviews of cost-effectiveness, unique ways of presenting ICER data from different studies were conceptualised. Furthermore, the quality of economic evaluations published to-date in the topic of interest were analysed using the CHEERS checklist (189).
3. Given the current economic and political environment of the Australian healthcare system, as highlighted in Appendix A, an economic analysis was carried out to investigate the value-for-money benefit of 'traditional' versus modern coronary revascularisation techniques (e.g., PCI using DES) for patients with complex CAD (Chapter 5). Given the debate concerning the over-utilisation of high-cost medical devices in Australia, and evidence of non-compliance to guideline-driven use of DES (218), this thesis also examined the cost-effectiveness of guideline-driven use of DES versus BMS (Chapter 6). Large gaps in published Australian-specific literature on these topics were apparent especially from the perspective of the public hospital payer, thus all costs were evaluated form this perspective.
4. To-date, few economic evaluations utilised data from clinical registries and advanced matching methods to measure the cost-effectiveness of coronary revascularisation strategies (116, 220). Given biases associated with use of non-randomised studies

(Section 1.5.3.4), propensity score matching methods were employed to match treatment and comparator groups derived from interventional and surgical clinical registries in Australia (Chapter 5 and Chapter 6). In particular, PSBB, an emerging propensity-score matching technique (116), was applied using a program developed in R by an independent third party specifically for this project. In the absence of resource utilisation data, effort was made to carry out data linkage of clinical records from registries to hospital administrative datasets where possible via third parties (Chapter 5), or if otherwise use published cost estimates (Chapter 6).

5. While CKD imposes significant burden among patients with CAD and acute coronary syndrome, the impact of CKD on coronary revascularisation outcomes have been largely under studied due to the exclusion of high-risk CKD patients from RCTs (219). Currently, there are no published evidence of cost-effectiveness of revascularisation strategies for this group of patients in the international literature. This thesis examined the cost-effectiveness of CABG versus PCI for patients with CKD and MVCAD from the perspective of the Australian public hospital payer (Chapter 5). Using the same perspective, incremental costs, and related predictors of post-operative readmissions were also investigated for CKD patients who underwent PCI (Chapter 7).

While this thesis was strengthened by addressing several important evidence gaps in the scientific literature detailed above, there were several notable limitations:

- Though short-term outcomes data do not prevent researchers from conducting 'modelled' economic analyses, the purpose of this thesis was to utilise real-world data to inform cost-effectiveness analyses. As such, all economic evaluations in this thesis investigated cost-effectiveness of revascularisation strategies using data from routine clinical practice, rather than 'modelling' published estimates. In doing so, however, these evaluations were unequivocally constrained by the properties of observational

data sources utilised. In the context of patients with stable CAD, where revascularisation is predominantly undertaken for symptoms, patient-reported outcomes or effectiveness measures (PROM or PREM) are increasingly becoming important in health economic evaluations (221). The ANZSCTS and MIG registries, while prominent multi-centre registries in Australia, do not collect health-related quality of life or patient preferences information. Consequently, in this thesis we were limited to using objective end-points (e.g., repeat revascularisation) and therefore conducting cost-effectiveness analyses, rather than cost-utility analyses that could have yielded ICERs measuring the cost per QALY gained. With the availability of sufficient funding and recognition of the importance of PROMs and PREMs, the ANZSCTS and MIG registries may collect such outcomes from patients in the future. Given the short-term time horizons of the evaluations undertaken in these thesis, no difference in life years gained (LYG) were observed for all comparisons of effectiveness (Chapter 5 and Chapter 6).

- Despite great effort made at the beginning of this project to obtain a longitudinal multi-centre hospital administrative dataset capturing all patient hospital admissions to all hospitals across Victoria, and related costs through a record linkage study, we were not successful in obtaining this dataset due to a conflict of interest with the Department of Human Services, Victoria.
- With respect to methodologies utilised in this thesis, one cannot avoid the argument against propensity score matching methods for biasing evaluations by not accounting for variables unobserved or not collected by the data sources (222). Although the use of propensity-score matching analysis led to some removal of selection bias, we cannot eliminate unobservable bias, including the impact of unknown confounders that were not part of the ANZSCTS or MIG data collection. For instance, circumstances beyond clinician control e.g., resource constraints at hospitals, urgency of procedures,

anticipated adherence to medication by the patient etc., may force clinical decisions outside of guideline-driven revascularisation with CABG or PCI with BMS or DES. However, in the absence of RCTs, high-quality comparisons of effectiveness or cost-effectiveness using advanced matching methods may yield more generalisable estimates of the value-for-money benefit of medical devices in routine clinical practice.

- Other issues relating transferability of results yielded from economic evaluations were discussed in each chapter individually. In general, results from cost-effectiveness are not typically generalisable to jurisdictions outside the boundaries of healthcare system in which the evaluations were conducted, unless otherwise justified (Chapter 4).

Despite limitations, methods applied in this thesis may be useful for HTA practitioners across Australia. This thesis provided an application of existing and emerging propensity-score matching methods for cost-effectiveness analyses using data from clinical registries rather than RCTs (Chapter 5 and Chapter 6). In particular, it highlighted that PSBB may be an appropriate matching technique, especially where sample sizes are small (e.g., rare high-risk patients), as it achieves matching without truncating size of treatment and comparator groups (Chapter 5). Moreover, this thesis included an evaluation of quality of reporting of cost-effectiveness analyses in the scope of coronary revascularisation strategies, against prescribed guidelines (e.g., CHEERS; Chapter 4). A recent analysis of the quality of reports prepared by MSAC's external HTA contractor groups revealed a number of interesting findings as illustrated in Figure 14 (223). Overall, there were no significant differences between quality of reports prepared for surgical, diagnostic, and therapeutic technologies across all domains (223). The quality ranking of HTA reports for the domain of 'economic evaluations' was relatively high (~70%), however did not exceed ranking of 'assessment of safety' (>90%) (223). Moreover, quality of HTA reports ranked poorly with respect to domains 'general methodological aspects' (50-60%), 'context' (~40%), 'technical descriptions' (50-70%), and

‘ethical, social, psychological and equity aspects’ (10-30%), suggesting there is still room for improvement in HTA reports produced by contractor groups (223). We believe the current thesis will contribute to the enhancement of general methodological and technical aspects for conducting health economic evaluations using data collected from routine clinical practice.

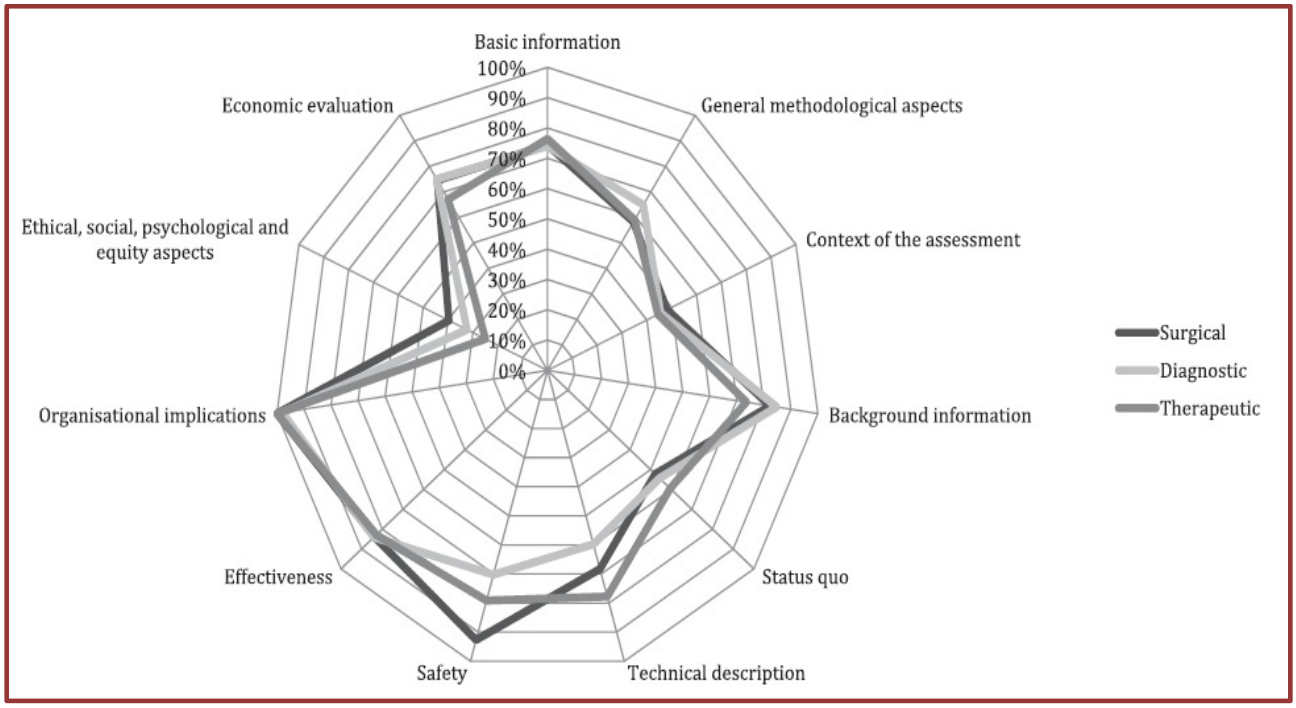

Figure 14 The quality of HTA reports prepared for MSAC, by quality domain, stratified by surgical, diagnostic, and non-surgical therapeutic technologies (223).
Source: Adapted from Hua *et al.* (2016)

8.4 Potential implications and future directions

8.4.1 Multidisciplinary approach to management of CAD patients

The findings from this thesis suggest that while majority of high-risk patients may benefit from CABG in the long-term, some patients (e.g., isolated lesions in the left anterior descending artery) (Chapter 4) including those treated with second-generation DES (Chapter 5) may experience non-inferior outcomes with PCI with DES. The selection of the optimal

revascularisation strategy may require personalised and evidence-based approach for each patient facilitated by a team of multidisciplinary experts in coronary care, also known as a 'Heart Team' (224). A number of factors may influence decision making, ranging from patient's preference, to the potential completeness of revascularisation achieved by the strategy, as illustrated in Figure 15 (225). A potential pathway for treatment of those patients with stable but complex CAD is illustrated in Figure 16 (225).

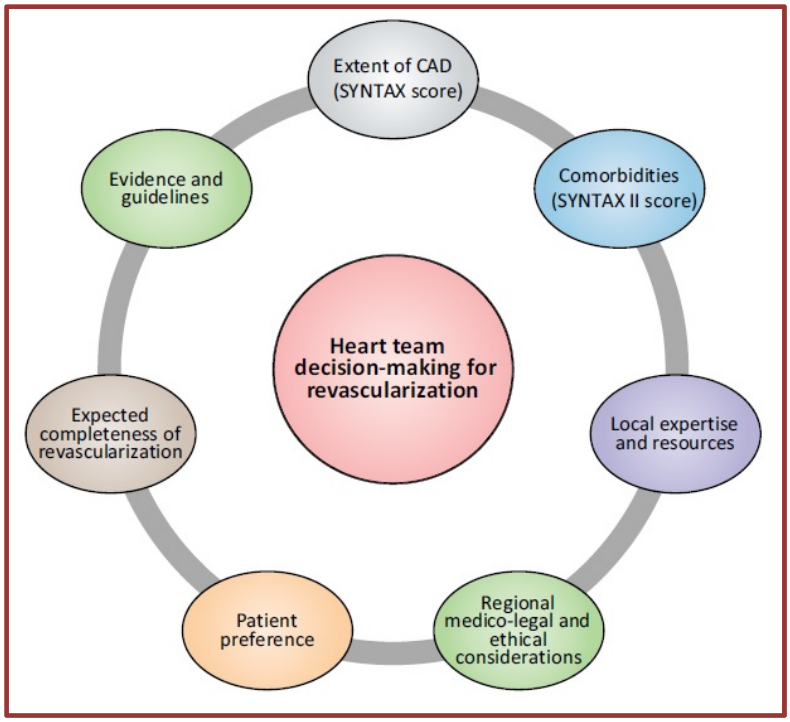

Figure 15 Factors influencing decision making for revascularisation of patients with CAD (225).
Abbreviations: CAD, coronary artery disease; SYNTAX, Synergy between PCI with Taxus and Cardiac Surgery
Source: Adapted from Iqbal *et al.* (2014)

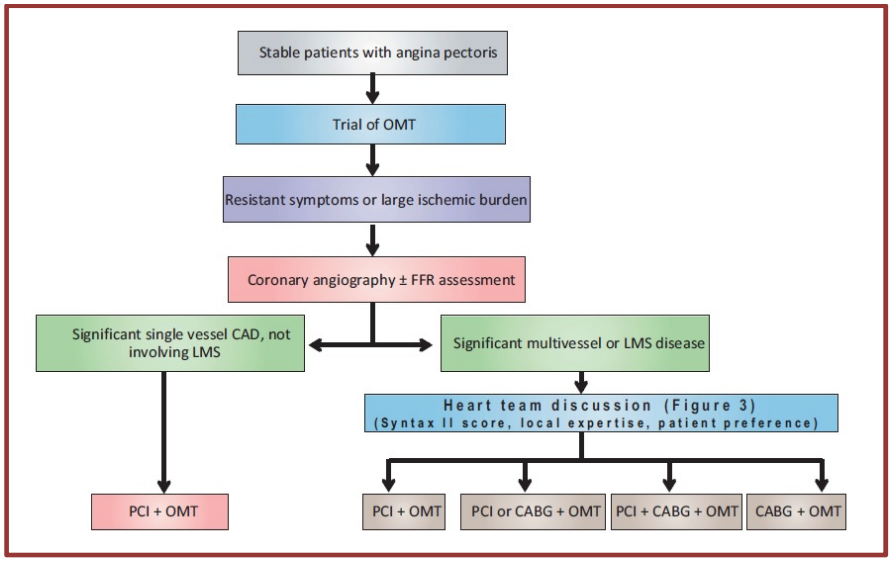

Figure 16 A potential revascularization pathway for patients with stable angina pectoris (225).
Abbreviations: CAD, coronary artery disease; CABG, coronary artery bypass graft; FFR, fractional flow reserve; LMS, left main stem; OMT, optimal medical therapy; PCI, percutaneous coronary intervention.
Source: Adapted from Iqbal *et al.* (2014)

The concept of a multidisciplinary team to manage patients with complex CAD with or without additional comorbidities (diabetes mellitus, CKD) is not new to Australia. In fact, the majority of large, tertiary hospitals would have a Heart Team, while smaller private hospitals may not. While Heart Teams function well in theory, the true spirit of collaboration may be hampered by clinician and funding factors in many cardiac service units across Australia.

In Australia, the service of a Heart Team is not funded through Medicare. While the MBS comprises over 5700 item numbers corresponding to services for reimbursement, the service of a Heart Team is not listed as a separate item for funding. Nor, is the use of a Heart Team mandated as a rule in the MBS item descriptors for CABG or PCI (Box 6). For other therapeutic areas such as Oncology, however, funding is available for case conferencing (MBS item number: 871). Current work being carried out for reimbursement of Transcatheter Aortic Valve Implantation (TAVI) in Australia, suggest that future MBS item descriptors for new cardiac procedures may mandate the decision making facilitated by a Heart Team, as highlighted by the proposed MBS item descriptor for TAVI in Appendix I (226).

While the development of a separate MBS code to ensure reimbursement of service(s) provided by a Heart Team is still in its infancy, it is nevertheless underway (227). Recent evidence suggested that the use of a multidisciplinary Heart Team improves outcomes for TAVI (228, 229). To fully utilise the capacity of a Heart Team to generate efficient outcomes, we recommend the billing services provided by a Heart Team service(s) for patients with complex CAD too, under this proposed MBS item number. To this end, a modification to existing MBS item codes for CABG and PCI (see Box 6) may be necessary to stipulate decision-making facilitated by a Heart Team, and thereby to enforce behavioural change among clinicians who are not current advocators of a multidisciplinary approach to the management of high-risk CAD patients. The Australian-specific evidence gathered from this doctoral thesis may provide a good rationale for the establishment of high performing Heart Teams across cardiac service units in Australia, who are then appropriately reimbursed for their services.

8.4.2 Advocating outcome ascertainment through mandated registry study and cost-effectiveness analysis

A hallmark of this thesis was to utilise routinely collected data from patient registries to assess cost-effectiveness of revascularisation strategies. To-date, however, very little has been accomplished by the Australian government to advocate patient registries for emerging technologies, despite mounting evidence their utility, as elaborated in Section 1.4.7 (95, 174, 175). In 2009, the Australian government did not consider recommendation no. 15 of the HTA Review (see Section 1.7.3, and Appendix D as a priority area for funding (174, 175). The recommendation no. 15 stipulated the establishment of registers and/or related procedures for high-risk implantable medical devices, with the consideration of (174, 175):

- how key stakeholders such as clinicians, health consumers and industry can participate in governance of and contribution to registries;
- establishment of mechanisms to apply data from the register to future HTA;
- the feasibility, benefits and methodologies for data linkage to be explored in a pilot project in regard to a particular device identified by the high-risk implantable devices register;
- consideration of how developments in e-health and data linkage could improve the efficiency of the post-market surveillance of medical technology more generally; and
- the development of criteria, the identification of opportunities and the consideration of strategies for improvements in public investment in medical devices.

A significant underutilisation of data from patient registries is now apparent in Australia, perhaps as a consequence of limited resources, and ad hoc procedures in place for collaborative data collection. A recent analysis of 11 resubmissions to the MSAC showed that only two Sponsors utilised data from patient registries to support the evidence gaps (230). The 11 technologies were among 17 that attracted interim funding between 1998 and 2015 by the MBS, based on the judgement that the technology is 'promising but lacking in sufficient evidence of effectiveness and/ or cost-effectiveness, however, eligible for temporary funding, while further data is being collected' (230). The two technologies for which Australian-specific registries were subsequently created included capsule endoscopy (imaging technique) and endoluminal grafting (surgical procedure) (230). The Sponsors of these medical devices focussed on collecting data on mid-to-long term safety and effectiveness, with post-operative follow-up of >5 years (in the case of endoluminal grafting) as well as diagnostic performance, patient management, and economics (in the case of capsule endoscopy) (230). These medical devices represent just a handful of cases where utilisation of evidence from patient registries lead to successful achievement of reimbursement, perhaps more cost-effectively

than a RCT. The issue of underutilisation of clinical registries was most prominent in the recent MSAC evaluation of TAVI in Australia, where the lack of adequate evidence delayed reimbursement of TAVI by three years since initial submission to the MSAC in May 2013 (226, 231). Moreover, whereas several countries including the USA, UK, and Germany had successfully set up TAVI-dedicated patient registries for the assessment of long-term safety, effectiveness, and cost-effectiveness of surgery versus minimally invasive intervention for severe aortic stenosis, Australia has still not produced such a registry due to a failure in collaborative effort between the various stakeholders involved (232-235).

There may be several barriers to the setup of patient registries for implantable medical devices in Australia, and mitigation of these factors may be necessary to enhance their utilisation, in particular to support HTA decisions. Apart from the clear limitation of Federal or State funding, other barriers may include design and methodological gaps in the assessment of quality of evidence, lack of buy-in from professional bodies or researchers to run the registries, and failure of decision makers to stipulate clinical registries as a source of desired evidence (230). Furthermore issues related to data linkage capacity in Australia, its dependencies, permissions, timeliness of supply, and different linkage maturities across different States, territories, cross-borders and between public-private institutions could further hamper utility of clinical registries (236). To this end, we recommend a reappraisal of the recommendation no. 15 of the Australian HTA Review (2009) by the Australian government, and the development of regulations and/or a funding schemes to ensure ascertainment of mandatory multi-centre registries for emerging implantable medical devices, as soon as first trial in human is successfully completed. Furthermore, development of foresight into feasibility of potential data linkages for the collection of important utilisation data e.g., medication use, hospital readmissions, and medical costs, during the design phase of registries is also recommended

to avoid downstream complications related to conflict of interest, and legal, privacy or technical issues.

8.4.3 Cost-effectiveness analyses using data from routine clinical practice

The results from this thesis suggest that ICERs yielded from routine clinical practice may be substantially different, and sometimes higher than ICERs obtained from RCTs. However, our analyses of cost-effectiveness of coronary revascularisation strategies (Chapter 5 and Chapter 6) were limited to the short-term, with no modelling performed for a life-time time horizon, whereas recent published comparisons of cost-effectiveness of CABG versus DES were based on RCTs and utilised modelling to make projections to a life-time horizon (Chapter 4). Results from our comparison of cost-effectiveness of guideline-driven use of DES versus BMS in the Australian context (Chapter 6) suggest that due to absence of protocol-mandated angiographic follow-up, resource-use estimates in observational studies might be lower than when compared with RCTs. Given the uncertainty of long-term cost-effectiveness of coronary revascularisation using observational data, further research towards modelling of data from observational studies is warranted.

More importantly, utilisation patterns of medical devices in the real-world may vary widely, sometimes debunking popular beliefs yielded from RCTs, rendering cost-effectiveness analyses using observational data important. Recent evidence from the MIG dataset suggest that the use of BMS peaked in 2007 to 60%, however, from 2007 onwards a pattern of increasing use of DES among patients who had no indications for DES was apparent, suggesting a growing preference for DES compared with BMS in modern times (Chapter 6). A 2012 survey of 31 centres across Europe and Asia, however, revealed that there were still clinical justifications for use of BMS, primarily driven by a concern for either bleeding or

compliance to dual antiplatelet therapy (41% cases) among other reasons, including large vessel diameter (32%), acute MI (18%), stent costs (9%) and planned non-cardiac surgery (6%) (71, 72). Nevertheless, the findings of this doctoral thesis suggest that the use of DES among patients who had no indications for a DES was cost-*ineffective* at 12 months, at least from the Australian public hospital payer perspective (Chapter 6). Given data from RCTs are usually applicable only to a highly selected group of patients, decision makers including the MSAC ought to stipulate evidence of cost-effectiveness estimates yielded from routine clinical practice (e.g., registries), to garner a fair understanding of real-world cost-effectiveness of new technologies that warrant public funding.

8.5 Final remarks

In the current political and economic environment of the Australian healthcare system, special attention has been brought towards funding based on value and outcomes rather than activity, better managing care of patients with complex comorbidities, improving efficiency through electronic medical records, and mitigating the rising cost of high-tech medical devices through funding cost-effective treatments. This doctoral thesis addressed several important gaps in literature within the scope of cost-effectiveness of coronary revascularisation strategies for patients with complex comorbidities, drawing a focus on DES, a high-cost medical device that has attracted contentious debate in relation to its value when compared with traditional revascularisation techniques. Additionally, this thesis utilised data from clinical and administrative databases, record linkage, and emerging propensity-score matching approaches, to answer important health economic questions. The methods and insights drawn from this thesis may prove useful to policy makers, health technology assessors, and clinicians alike to understand the value of observational data to support optimal clinical and reimbursement decisions that can achieve sustainable use of healthcare resources within resource-scarce healthcare systems.

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Appendix A: Australian healthcare system: Current issues and reforms

Table A.1 An analysis of on-going issues in the Australian healthcare system, reforms from 2015-2017, and outcomes achieved to-date.

Reform area	Issues	Outcomes achieved to date (February 2017)	References
Medicare rebates	• Funding focused on activity rather than on value or outcomes is wasting valuable health dollars. • MBS funds 5,700 listed services, some carry little clinical relevance today, and have limited evidence-base for clinical effectiveness, and cost-effectiveness.	• A MBS Review Taskforce established in July 2015, followed by a comprehensive stakeholder and public consultation. Interim report submitted to Minister of Health in January 2016. Final recommendations expected in 2017. • 23 MBS items were identified by Clinical Committees as obsolete. o Diagnostic Imaging: 58706, 58924, 59503, 59715, 59736, 59760, 61465 o Ear, Nose and Throat Surgery: 11321, 18246, 41680, 41695, 41758, 41761, 41846, 41849, 41852 o Gastroenterology:13500, 13503, 30493, 32078, 32081 o Obstetrics: 16504 o Thoracic Medicine: 11500	(9-11)
PHI and Prostheses List	• PHI is becoming expensive for individuals with rising price of premiums. • Apparent discrepancies in the cost of medical devices in private vs. public healthcare systems: o E.g., cardiac stents costs 2-3 times more for PHI than public payers. • Need to improve efficiency of PHI and incentives for individuals to uptake PHI policies, without inadvertently reducing competition and innovation in the medical device industry.	• PHI consultations opened in October 2015, with the formation of Industry Working Group comprising representatives of Medical Device Supply Chain, and four roundtable meeting held from February-March 2016. • In October 2016, the following reforms to PHI and Prostheses List were issued effective 20 February 2017: o Reducing listed benefit (price) of 2440 medical devices across 4 categories by: ▪ 10% for cardiac devices, ▪ 10% for intraocular lenses, ▪ 7.5% for knee replacements, and ▪ 7.5% for hip replacements. o Expected savings for PHI: $86 million in the 1st year, and $500 million in the next 6 years. • In October 2015, further announcements were made regarding plans to: o Reconstitute the PLAC.	(12-14)

		o Investigate the development of a more robust and transparent price disclosure model of ongoing, and sustainable reductions to the cost of medical devices. o Improve efficiencies in listing of innovative technology. o Find a transparent way to reimburse hospitals for the costs of maintaining inventory of medical devices so that they are on hand when needed.	
Electronic health records	• Currently, Australians do not have a unique digital health record of their medical history. • A functioning national medical record system is beneficial for both patients and clinicians equally: o Patients can visit different providers (e.g., GPs, nurses, pharmacists) or change providers without having the burden to inform new providers their entire medical history. o HC providers will not have to take a gamble on medical unknowns when making decisions due to limited knowledge of a patient's medical history. • The lack of a unique digital medical record can impact quality, safety and efficiency of HC delivery.	• An Australian Digital Health Agency formed in April 2015 with appointment of Chair and Members. An independent eHealth Implementation Taskforce Steering Committee appointed in October 2015 responsible for establishment Australian Commission for eHealth. • In the 2015-16 budget, $485 million was allocated for the redevelopment of the My Health Record system, which attracted a budget of $1.15 billion for the development of electronic platform and enrolment through opt-in method, from 2009-2016. • A trial to use another approach, opt-out method, was undertaken from March-October, 2016 in Far North Queensland, and the Blue Mountains, NSW. o Record contains a health summary written by a GP, records of medicines and allergies and results of scans and blood tests. • An opt-out rate of 1.9% was achieved in the trial of 971,000 individuals, which is similar to international experience. • The national roll-out of My Health Record is expected in 2017 with 9326 HC organisations are currently registered to use the system.	(15-18)
Prescription Medicines (PBS)	• The current cost of PBS is unsustainable for investment into new medicines and patient support services in the long-term. • Low competition in the pharmaceutical sector.	• Announcement of Government's Pharmaceutical Benefit Scheme (PBS) Access Sustainability Package of reforms in May 2015, issued in consultation with PBAC. Among the 13 reforms implemented include: o doubling of investment in new and existing support programmes for patients to $1.2 billion over the next five years;	(11, 237, 238)

		o all pharmacy programmes, new and existing to be scrutinised by MSAC; o option for pharmacists to discount the patient-co-payment by up to $1; o Removing some over the counter medicines from PBS; o Price disclosure amendments; o Streamlining PBAC, and increasing human resources. • In May 2015, the Government also reached in-principle agreement with pharmacists for a new pharmacy agreement valued at $18.9 billion over the next five years	
Primary healthcare	• Patients with chronic and complex conditions are high users for health services, but receive care from many health providers, working in different locations, and different part of HC system. • Concerns for quality and safety of patient care due to challenges in effective communication between HC 'team'. • Payments for HC is largely based on 'fee for service' model. • $5.7 billion spending by MBS to provide access to GPs, but limited opportunity for allied health & alternatives. • Very high GP attenders saw 3x as many different GPs compared low attenders. • Despite high spending, care provided is not achieving outcomes community expects. • < 1/3 of GP patients with high blood pressure achieve satisfactory control. • <1/2 of diabetic patients achieve recommended levels of blood sugar, cholesterol and blood pressure control.	• A Primary Health Care Advisory Group established in July 2015, and comprehensive national consultation process undertaken. Final report with 15 recommendations published in December 2015. • 7 million Australians *with chronic and complex illnesses* asked to enrol with single GP practice/ Aboriginal Medical Service, termed 'Health Care Home'. • $21 million committed to roll out of Healthier Medicare, a primary care package co-ordinated through Health Care Homes, responsible of on-going co-ordination, management, and support of patients with chronic or complex illnesses: o Bundled upfront and quarterly payments to Health Care Homes (i.e., GPs). o Salaried care-coordinators. o Flexible funding arrangements to HC providers to adopt new health care innovations, e.g., remote monitoring devices. o Improved data collection on primary health care through the creation of a quality improvement framework and the foundation of a National Minimum Data Set (*My Health Record*). o Trial to run from 1/07/2017 to 30/06/2019 for 65,000 Australians across 200 practices. • Expansion of rural HC workforce through the introduction of the Integrated Rural Training Pipeline (IRTP).	(4, 7, 8)

Mental healthcare	• Australia's mental health system suffers from fundamental structural shortcomings: o Complex, and fragmented HC service delivery system; and o Resource-poor. • Response to mental illness too late or lack follow-up. • Does not see the 'whole' person in diagnosis and treatment.	• In December 2015, the Australian Government issued the Response to the Review of Mental Health Programmes and Services Report published by the National Mental Health Commission (formed 2012) in December 2014, outlining principle reforms to take place in 2015-2019: o A new tiered system categorising people into at risk, mild, moderate and severe mental illness. o People with severe and complex mental illnesses to have access to "integrated care package", similar to packages offered by the NDIS, tailored to individual's needs; Medicare subsidies offered to those with 'moderate' mental illness; and online counselling services for those with 'mild' disease . o Re-directing funding from emergency intervention in hospitals to PHN's and community-based programs. o A single helpline for people living with mental illness consolidating 30 existing government-funded phone and online services. o Addressing mental healthcare needs of children, with a new school-based initiative covering early childhood to the end of secondary school rolled out from 1/07/2016.	(19-21)
Aged care	• Rising ageing population in Australia • Corresponding burden on public HC system.	• The Australian Government is undertaking a three-phased approach to implementing Aged Care reforms issued 10 years earlier. • There are many achievements to date. • On 1/07/2015 Commonwealth Home Support Programme (CHSP) began as a one consolidated programme providing entry-level home support for older people needing assistance to keep living independently.	(22)

Abbreviations: GP, general practitioner; HC, healthcare; MBS, Medicare Benefits Schedule; MSAC, Medical Services Advisory Committee; NDIS, National Disability Insurance Scheme; PBS, Pharmaceutical Benefit Scheme; PBAC, Pharmaceutical Benefits Advisory Committee; PHI, private health insurance ;PHN, primary healthcare networks; PLAC, Prostheses List Advisory Committee.
Source: Table created by author. See citations within the table for references of sources
.

Appendix B: Institutions responsible for HTA across European nations

Table B.1 Organisations responsible for HTA process, reimbursement decisions and price negotiation in European countries (139).

	Organisation responsible for HTA process	Organisation responsible for decision on reimbursement	Organisation responsible for price negotiation / decision
Belgium	National Institute for Sickness and Invalidity Insurance (INAMI)/Commission for Reimbursement of Medicines [Institut National d'Assurance Maladie-Invalidité/Commission de Remboursement des Médicaments]	Ministry of social affairs	Ministry of economic affairs, with advice of the committee for price setting (inter-ministry body)
Denmark	Reimbursement Committee/Danish Centre for Evaluation and Health Technology Assessment (CEMTV)	Outpatient drugs: Danish health and medicines authority. Hospital drugs: KRIS	For hospital drugs, purchasing agency carries out tenders
France	Economic Committee on Health Products (CEPS)/Transparency Commission [Commission de la Transparence]	Ministry of Health decides on listing and Union of social health insurance funds decides on reimbursement rate	Committee on health products(inter-ministry body)
Germany	Federal Joint Committee/Institute for Quality and Efficiency in Health Care (IQWiG)/German Agency for Health Technology Assessment (DAHTA).	Federal Joint Committee (G-BA)	Prices negotiated after G-BA assessment
Italy	Committee on Pharmaceuticals/Italian Medicines Agency (AIFA) [CIP Farmaci/Agenzia Italiana del Farmaco]	AIFA technical scientific committee	AIFA pricing and reimbursement committee (inter-ministry body)
Netherlands	Pharmaceutical Care Committee (CFH) /Health Care Insurance Board (CVZ)	Ministry of health, welfare and sport	Ministry of health, welfare and sport
Norway	Pharmaceuticals Pricing Board (PPB)/Norwegian Medicines Agency (NoMA)	NoMA, MOH when budget impact is high	NoMA
Spain	Spanish Agency for Health Technology Assessment (AETS)	MOH	Inter-ministerial pricing committee

Sweden	Pharmaceutical Benefits Board (LFN / TLV)/Swedish Council on Technology Assessment in Health Care (SBU)	TLV	TLV
UK (England and Wales)	National Institute for Health and Care Excellence (NICE) /National Coordinating Centre for Health Technology Assessment (NCCHTA)	There is no systematic assessment of new medicines, NICE assesses on request. All medicines with marketing licenses are automatically reimbursed unless NICE says no.	In general, manufacturers are free to set list prices. The government controls profit levels of the industry. The MOH may negotiate Patient Access Schemes with manufacturers if NICE rejects a drug.

Appendix C: Economic evaluations and analytical approaches recommended by HTA institutions world-wide

Table C.1 Analytical approaches for economic evaluation, as per submission guidelines or recommendations issued by HTA bodies (139)

Country and Authors of guidelines	Perspective adopted and preferred analytical technique
Belgium Health Care Knowledge Centre (KCE, 2012)	**Perspective:** health care payer (social insurance and patients) **Analytical methods:** If improving life expectancy is the main objective of the treatment and the most important outcome for the patient: CEA; if the treatment has an impact on health-related quality of life that is significant to the patient or if there are multiple patient-relevant clinical outcome parameters expressed in different units that cannot be translated into one common unit in a valid way: CUA (CBA not accepted)
Canada Canadian Agency for Drugs and Technologies in Health (CADTH, 2011)	**Perspective:** several perspectives accepted but should be presented separately **Analytical methods:** Where clinical outcomes are final (an event that is relevant and noticeable to patients): CEA/CUA Where clinical outcomes are intermediate (subjective clinical measures where extrapolation of health benefits to life-years or QALY is more difficult, non-clinical endpoints, or surrogate endpoints): CEA/CUA If data are not available to support the relationship between surrogate and final clinical outcomes a CCA is required
Italy	No guidelines
Korea Health Insurance Review and Assessment service (HIRA)	**Perspective:** public payer or societal **Analytical methods:** CEA/CUA
Norway The Norwegian Medicines Control Authority (NoMA, 2005)	**Perspective:** Limited Societal perspective **Analytical methods:** CMA, CEA, CUA, CBA are accepted but the choice of technique must be justified.
Sweden	**Perspective:** Societal

Pharmaceutical Benefits Board (TLV, 2003)	**Analytical methods:** CEA/CUA is recommended, CBA where QALY are difficult to use. If the effects of the new products are comparable to those of the best comparable treatment, then a cost comparison is sufficient.
Netherlands Foundation for Health Care and University (2006)	**Perspective:** societal **Analytical methods:** CEA, CUA, no CMA
UK: Scotland Scottish Medicine Consortium (SMC, 2007)	**Perspective:** National health system and patients **Analytical methods:** CMA, CEA, CCA, CUA, CBA accepted, choice needs to be justified.
UK: England & Wales National Institute for Health and Care Excellence (NICE, 2008)	**Perspective:** National Health System and Personal Social Services (PSS) **Analytical methods:** CEA or CUA for the reference case are the preferred forms of economic evaluation.
France Haute Autorité en Santé (HAS, 2011)	Pharmaco-economic assessment used in R&P process from October 2013. **Perspective:** all financing agents **Analytical methods:** CEA/CUA
Germany Institute for quality and efficiency in health care (IQWiG, 2009)	Pharmaco-assessment is not used in the R&P process. **Perspective:** statutory health insurance and patients **Analytical methods**: Efficiency frontier method based on a CEA, but CUA also possible.

Abbreviations: CBA, cost-benefit analysis; CCA, cost-consequence analysis; CEA, cost-effectiveness analysis; CMA, cost-minimisation analysis; CUA, cos-utility analysis; R&P, reimbursement and pricing; QALY, quality-adjusted life years.

Appendix D: Australian HTA Review (2009): Recommendations and achievements

Table D.1 Achievements to date following Australian HTA Review (2009) (174).

Recommendation	Achievements to date (February 2017)
1. That the impact of the proposed changes to the Australian Government Health Technology Assessment (HTA) system approved by the Australian Government be evaluated within three years of the Government's response to this review.	MSAC and PBAC were both reformed in 2016 after extensive review. New PLAC terms of reference were issued by the Minister in October 2016.
2. That the rigorous consideration of evidence be consistently applied across all Australian Government HTA processes to ensure sustainability of the Australian Government's health financing arrangements.	Both MSAC and PBAC are considered as two of the most rigorous HTA agencies globally.
3. That the Australian Government HTA system be guided by the vision, goal, objectives and principles articulated in the *Review of Health Technology Assessment in Australia* (HTA Review) Report.	All three bodies; MSAC, PBAC, and PLAC, strive to always be guided by these.
4. That DoHA establish a website for Australian Government HTA processes by July 2010 which: a) describes the roles, responsibilities and relationships between the different HTA processes; b) facilitates access to all related Australian Government HTA websites to ensure that policy and guidance for all Australian Government HTA processes are easily accessible; and c) regularly publishes reports on agreed performance and activity data to clearly demonstrate the performance of the system and focus attention on areas requiring performance improvement.	While 4a) and 4b) are done reasonably well, there are still pockets that lack transparency in the process, e.g., targeted consultation with stakeholders on the MSAC submissions is not always available to the Sponsor. Item 4c) is not done well, but that is because there are currently 13 reviews in the healthcare space that have overridden item c)
5. That the procedural fairness and consistency of Australian Government HTA processes be improved by 2011, by: a) establishing independent review mechanisms and opportunities for re-submissions in a consistent manner for Australian Government HTA processes (where they are currently not available); b) updating operating procedures for administering Australian Government HTA processes, including publishing specific milestones and timeframe targets for each individual HTA process;	The new reforms in MSAC and PBAC take account of these (see Table A1). The new terms of reference for PLAC should account for these.

c) improving public disclosure of Australian Government HTA processes, including advisory committee membership, performance and activity data, and assessment and appraisal outcomes (including the rationale for those outcomes); d) establishing and publicising specified communication points with applicants throughout each process, including providing opportunities for pre-lodgement meetings; and e) adopting and implementing transparent and consistent policies and procedures for the management of conflict of interest for all external parties involved in Australian Government HTA processes.	
6. That in order to improve the efficiency of HTA, DoHA establish a single entry point (SEP) by July 2010 to receive applications for subsidy under the Medicare Benefits Schedule (MBS), Pharmaceutical Benefits Schedule (PBS) and Prostheses List. The role of the SEP will be to: a) provide a single point of contact to help applicants throughout the HTA process; b) determine the most appropriate advisory committee(s) to appraise the technology; c) identify the most appropriate assessment pathway for an application, including maintaining and reinforcing current processes where these are the most efficient for the technologies submitted to a particular process; d) conduct an initial risk and impact assessment and determine the most appropriate methodology to be used in assessing the technology; e) ensure the timely assessment and appraisal of co-dependent and hybrid technologies, or technologies being assessed concurrently for both public and private reimbursement and coordinate the provision of comprehensive advice to the Minister for Health and Ageing (the Minister); f) achieve synergies through sharing and sustaining HTA expertise across the advisory committee secretariats; and g) develop and report on the achievement of performance targets for HTA reimbursement.	The single entry point HTA Access Pint (HTAAP) is working well. The on-line PLMS is better than the old paper based PL Applications.
7. That applicants have the option of applying to different HTA processes concurrently. Finalisation of each HTA process may be subject to the completion of a critical antecedent process (such as inclusion on the Australian Register of Therapeutic Goods (ARTG) prior to MBS or Prostheses List listing). This will require procedures to be put in place by July 2010 to allow the efficient flow of information between HTA processes (including from the TGA to other HTA agencies, subject to confidentiality constraints).	This system is working well, but there is still work to be done by each of the HTA agencies to better coordinate their activities with the TGA. For example, a TGA approval can occur anytime, so a TGA listing is often not aligned with the PLAC, MSAC, or PBAC approvals.
8. That the Therapeutic Goods Administration (TGA), in the context of international harmonisation:	More reforms happening in this area (see Table A1).

a) continue its role as the independent national regulator solely responsible for assessing the safety, quality and efficacy of therapeutic goods for entry on The Australian Register of Therapeutic Goods (ARTG) and marketing in Australia; b) respond to the issues raised in consultations regarding third party conformity assessment by July 2010, with a view to implementing changes agreed by government by 2011; c) increase the rigour of regulatory assessment of higher risk medical devices by 2011, to ensure an appropriate level of evidential review is undertaken to ensure safety, quality and efficacy of these devices prior to entry on the ARTG and to provide a sound evidence basis for Australian Government HTA processes; and d) develop protocols by July 2010 for sharing information with other HTA agencies through the SEP (subject to commercial-in-confidence constraints) on the outcomes of its safety assessments.	
9. That by July 2010, MSAC strengthen and streamline its operations and improve the flexibility of its regulatory processes by: a) providing advice to the Minister based on a critique of an applicant's comparative clinical and economic evaluations, as an alternative to the current process and in the context of agreeing specific timeframes for assessment with the applicant; b) ensuring that data collection requirements supporting a recommendation for interim funding for a professional service for listing on the MBS are sufficiently rigorous and reliable to provide a sound basis for a final decision on funding; c) ensuring that its advice to the Minister addresses all aspects of the proposed change to the MBS, especially in regard to the proposed MBS item descriptor and fee; and d) streamlining current processes for accessing expert advice to improve timeliness of assessment processes and set a target of all advisory panels being established within six weeks of accepting an application.	The new MSAC system is better than the old one, but there are still some minor issues to resolve around transparency of stakeholder feedback.
10. That in order to reduce regulatory costs: a) the terms of reference for the Prostheses and Devices Committee (PDC) and its subcommittees be revised by July 2010 so that it is clear that its assessments of prostheses only consider clinical effectiveness (including comparative cost and comparative safety); and b) channels of communication between the TGA and PDC should be formalised to ensure that any concerns the PDC encounters regarding the intrinsic safety of prostheses are immediately referred to the TGA and dealt with appropriately.	The new PLAC terms of reference address better alignment between MSAC and PLAC (see Table A1).

11. That the PDC be restructured by July 2010 to ensure that its membership is balanced and: a) includes individuals with expertise in current clinical practice, health policy and health economics; b) includes representation from health consumers, health service providers, and the health insurance and health technology industries; and c) has an independent chair.	New PLAC terms of reference cover this (see Table A1).
12. That the arrangements for the Prostheses List be changed by 2011, with appropriate consultation, to: a) accept applications on a continuous basis, but still make the Prostheses List every six months; b) establish and maintain groups of products with similar clinical effectiveness; c) abolish the negotiation of benefits for individual listed products, and instead establish and maintain a single (benchmark) benefit for the products included in each group, with sponsors being required to accept this benefit in order to be listed; d) abolish the negotiation, setting or publication of maximum benefits, to eliminate the potential for gap payments for patients who have Private Health Insurance (PHI); and e) permit the establishment of new product groups (or sub-groups) where a sponsor establishes clear superiority of their product compared to those in an existing group.	This was achieved, but new reforms to pricing mechanisms should see more improvements in the future (see Table A1).
13. That, in order to improve the contribution of post-market surveillance to patient safety, the TGA take steps to increase the rate of reporting of adverse events, including by health service providers and consumers.	This recommendation was subject to further consideration by government, with no further progress in to-date.
14. That, in order to improve the contribution of post-market surveillance to the sustainability of the health system and the longer-term regulatory efficiency of HTA processes, DoHA explore options for consideration by government in 2011 to facilitate the expansion and use of post-market surveillance data to inform safety, effectiveness and reimbursement decisions for devices and procedures.	This recommendation was subject to further consideration by government in 2011, with no further progress in to-date. Currently, there is reluctance amongst clinicians to be engaged in such activities and the industry doesn't want to pay for it due to limited co-operation from clinicians.
15. That registers for high-risk implantable medical devices and/or procedures be established, with: a) key stakeholders such as clinicians, health consumers and industry to participate in governance of and contribution to registries; b) establishment of mechanisms to apply data from the register to future HTA;	This recommendation was subject to further consideration by government in 2011, with no further progress in to-date.

c) the feasibility, benefits and methodologies for data linkage to be explored in a pilot project in regard to a particular device identified by the high-risk implantable devices register; d) consideration of how developments in e-health and data linkage could improve the efficiency of the post-market surveillance of medical technology more generally; and e) the development of criteria, the identification of opportunities and the consideration of strategies for improvements in public investment in medical devices.	
16. That the Australian Health Ministers' Conference be asked to consider the need for a national approach to HTA processes, including processes required to evaluate blood and blood products.	MSAC assessment for new items in NBA began in 2010

Abbreviations: DoHA, Department of Health and Ageing; HTA, health technology assessment; MBS, Medicare benefits schedule; MSAC, Medical Services Advisory Committee; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme; PDA, Prostheses and Devices Committee; TGA, Therapeutics Goods Authority.

35782

Return completed forms to CCRET on fax: 1800 022 730

Procedure ID ☐☐☐☐☐☐

MIG_BL_V6

MIG Registry

Please refer to the MIG data definitions manual for a detailed explanation of all fields

Baseline Procedure Form

Hospital code ☐☐

Hospital codes can be updated as new hospitals join the study

1 Melbourne Private
2 Geelong Private
3 Peninsula Private
4 Warringal Private
5 Royal Melbourne
6 Alfred
8 Austin
9 Box Hill
10 Geelong
11 Frankston
12 Knox
13 Western
15 Northern
16 Ballarat Base

Section 1. DEMOGRAPHICS

1.1 **Hospital UR number** ☐☐☐☐☐☐☐

1.2 **Patient first name** ☐☐☐☐☐☐☐☐☐☐☐☐☐☐

1.3 **Patient middle name** ☐☐☐☐☐☐☐☐☐☐☐☐☐☐

1.4 **Patient last name** ☐☐☐☐☐☐☐☐☐☐☐☐☐☐

1.5 **Date of birth** ☐☐ / ☐☐ / ☐☐☐☐ (DD / MM / YYYY)

1.6 **Sex** ○ Male ○ Female

1.7 **Postcode** ☐☐☐☐

1.8 **Race**
- ○ Caucasian
- ○ Asian
- ○ Aboriginal/Torres Strait Islander
- ○ Indian/Sri Lankan/Pakistan/Bangladesh
- ○ Other (specify) _____

1.9 **Insurance status** ○ Medicare ○ Overseas Visitor ○ DVA ○ Self Insured ○ Private

1.10 **Medicare number** ☐☐☐☐ ☐☐☐☐ ☐☐☐

1.11 **DVA number** ☐☐☐☐☐☐☐☐

Section 2. ADMISSION

2.1 **Admission status**
- ○ Referral
- ○ Elective
- ○ Emergency Department
- ○ Transfer from other facility
- ○ Other (specify) _____

2.2 **Date of admission** ☐☐ / ☐☐ / ☐☐☐☐ (DD / MM / YYYY)

2.3 **Number of cath lab visits this admission** ☐☐

Section 3. HISTORY AND RISK FACTORS

3.1 **Height** ☐☐☐ cm

3.2 **Weight** ☐☐☐ kg

3.3 **Smoking status**
- ○ Currently Smoking
- ○ Previously Smoked
- ○ Never Smoked

3.4a **Chronic Lung Disease** ○ Yes → If YES, 3.4b **Type** ○ COPD ○ Asthma ○ No

3.5a **Diabetes** ○ Yes → If YES, 3.5b **Treatment** ○ Diet ○ Oral ○ Insulin ○ No

3.6 **Baseline serum creatinine** ☐☐☐☐ µmol/L

3.7 **Dialysis requiring** ○ Yes ○ No

3.8 **Functioning renal transplant** ○ Yes ○ No

3.9 **Hypertension** ○ Yes ○ No

3.10 **Dyslipidaemia** ○ Yes ○ No

3.11 **Previous MI** (Existing >7days prior) ○ Yes ○ No

3.12 **Family history of CAD** ○ Yes ○ No

3.13 **Congestive Heart Failure** (Existing >2 weeks prior) ○ Yes ○ No

3.14 **PVD** ○ Yes ○ No

3.15 **Cerebrovascular disease** ○ Yes ○ No

3.16 **Obstructive Sleep Apnoea** ○ Yes ○ No

3.17 **Rheumatoid Arthritis** ○ Yes ○ No

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Section 4. PREVIOUS INTERVENTIONS

4.1a **Previous PCI** ○ Yes ○ No — 4.1b **Date of most recent PCI** DD / MM / YYYY

4.2a **Previous CABG** ○ Yes ○ No — 4.2b **Date of most recent CABG** DD / MM / YYYY

4.3a **Previous valvular surgery** ○ Yes ○ No — 4.3b **Date of most recent valvular surgery** DD / MM / YYYY

Section 5. CARDIAC STATUS AT PCI PROCEDURE

5.1 **Congestive Heart Failure** (Existing <2 weeks prior) ○ Yes ○ No

5.2 **Rhythm** (At commencement of PCI) ○ AF ○ SR ○ Other

5.3 **NYHA** (See MIG instruction sheet) ○ I ○ II ○ III ○ IV

5.4 **Killip class** (For AMI patients only) ○ 1 ○ 2 ○ 3 ○ 4

5.5 **Functional ischaemia** ○ Not applicable ○ Positive ○ Negative ○ Equivocal

5.6 **Cardiogenic shock** ○ Yes ○ No

5.7 **IABP** ○ Yes ○ No

5.8 **Out of hospital cardiac arrest** ○ Yes ○ No

5.9 **Acute Coronary Syndrome** ○ Yes ○ No

5.10a **Angina type**
○ NONE ○ UAP
○ Atypical ○ NSTEMI
○ Chronic Stable ○ STEMI

} Please complete 5.10b ACS Time Period

5.10b **ACS time period**
○ <6 Hrs
○ 6 - 24 Hrs
○ >24 Hrs - 7 Days

STEMI EVENT TIMING

Please complete date and time if <24 hours since onset of STEMI symptoms

	Time (HH : MM)	Date (DD / MM / YYYY)
5.11a **Time of STEMI onset**		
5.11b **Time of arrival at first hospital** (For patients transferred only)		
5.11c **Time of arrival at PCI hospital**		
5.11d **Time of first balloon inflation**		

5.11e **MICA-activated MI** ○ Yes ○ No

Section 6. CATH LAB VISIT

6.1 **Date of procedure** DD / MM / YYYY

6.2a **PCI status** ○ Elective ○ Urgent ○ Rescue

→ 6.2b **Staged PCI** ○ Yes ○ No

6.3 **Cath/PCI same lab visit** ○ Yes ○ No

6.4 **Blood pressure** (At start of procedure) SBP / DBP mmHg

6.5 **On IV inotropes** ○ Yes ○ No

6.6 **Heart rate** (At start of procedure) bpm

MEDICATIONS

6.7 **Thrombolytics** ○ No ○ <3 hrs ○ 3 - 6 hrs ○ >6-12hrs ○ <7 days

6.8 **IIb / IIIa Blockade** ○ No ○ Prior ○ During ○ After

6.9 **Heparin** ○ No ○ Prior ○ During ○ After

6.10 **LMWH** ○ No ○ Prior ○ During ○ After

6.11 **Bivalirudin** ○ No ○ Yes

6.12 **Aspirin** ○ No ○ Yes

6.13a **Clopidogrel** ○ No ○ Prior ○ During/After

6.13b **Prasugrel** ○ No ○ Prior ○ During/After

6.13c **Ticagrelor** ○ No ○ Prior ○ During/After

6.13d **Planned duration** (Clopidogrel, Prasugrel or Ticagrelor) ○ 1 Month ○ 3 Month ○ 6 Months ○ 12 Months ○ >12 Months

PERCUTANEOUS ENTRY

6.14 **Percutaneous entry location** ○ Brachial ○ Radial ○ Femoral

6.15 **French size** (Guiding catheter) ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ Other (Specify)

6.16 **Closure device** ○ No ○ Seal ○ Suture ○ Other (Specify) _____

EF STATUS

6.17 **EF test modality** ○ Cath ○ Nuclear ○ Echo ○ MRI

6.18a **EF %** — 6.18b **EF value** ○ Estimated ○ Derived

(Don't use a 'greater than' or 'less than' symbol)

EXTENT OF CORONARY DISEASE

6.19a **Disease extent** ○ Single vessel disease ○ Multi vessel disease

→ 6. 19b ○ 2 vessel ○ 3 vessel

→ 6. 19c **Left main** ○ Yes ○ No

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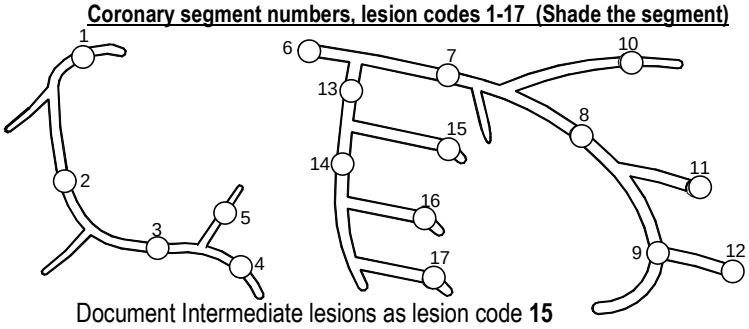
Section 7. PCI PROCEDURE / LESION INFORMATION

NATIVE

Coronary segment numbers, lesion codes 1-17 (Shade the segment)



Document Intermediate lesions as lesion code **15**

GRAFT

Graft PCI lesion codes 18-25. Also record grafted native coronary vessel

	Target Vessel		Target Vessel
○ LIMA		○ SVG 3	
○ RIMA		○ RAD 1	
○ SVG 1		○ RAD 2	
○ SVG 2		○ RAD 3	

Lesion Code

1	RCA prox	**14**	LCX distal
2	RCA mid	**15**	OM1
3	RCA distal	**16**	OM2
4	PDA	**17**	OM3
5	PLV	**18**	LIMA
6	Left MAIN	**19**	RIMA
7	LAD prox	**20**	SVG1
8	LAD Mid	**21**	SVG2
9	LAD Distal	**22**	SVG3
10	D1	**23**	RAD1
11	D2	**24**	RAD 2
12	D3	**25**	RAD3
13	LCX prox		

Complete for all lesions. Complete and attach additional lesion form if necessary.

Lesion 1

7.1a **Coronary lesion**
- ○ De novo
- ○ Restenosis (No prior stent) → 7.1b **Date of POBA** ___ / ___ / ____ (DD - MM - YYYY)
- ○ In stent restenosis → 7.1c **Prior stent type** ○ DES ○ BMS ○ Mixed DES & BMS

7.1d **Date implanted** ___ / ___ / ____ (DD - MM - YYYY)

7.1e **Stent thrombosis** ○ Yes ○ No

7.1f **Lesion code (1-25)** ___

7.1g **Location in graft** (complete for graft PCI only. Lesion codes 18-25 only) ○ Ostial ○ Distal ○ Mid ○ Proximal ○ Anastomosis ○ Native

7.1h **Lesion type** ○ A ○ B1 ○ B2 ○ C

7.1i **Chronic total occlusion** ○ Yes ○ No

7.1j **Ostial lesion** ○ Yes ○ No

7.1k **Bifurcation lesion** ○ Yes ○ No (If side branch, enter as lesion 2)

7.1l **Pre-stenosis %** ___ 7.1m **TIMI Flow (pre)** ___ (0-3)

7.1n **Post-stenosis %** ___ 7.1o **TIMI Flow (post)** ___ (0-3)

7.1p **Estimated lesion length** ___ mm

7.1q **Acute closure** ○ Yes ○ No

7.1r **Dissection** ○ Yes ○ No

7.1s **Perforation** ○ Yes ○ No

7.1t **No Reflow** ○ No ○ Transient ○ Persistent

7.1u **Lesion result** ○ Successful ○ Unsuccessful

STENT DETAILS FOR LESION 1

	7.1v Stent code	7.1w Length	7.1x Diameter
#1			.
#2			.
#3			.
#4			.

For **stent codes** please refer to the MIG instruction sheet.

Stent codes will be added as new devices come into use.

If a device is not present please call CCRET on 1800 285 382 to add.

7.1y **Maximum balloon size used** ___ . ___ mm

7.1z **Intracoronary devices used**
- ○ No devices deployed
- ○ Balloon only
- ○ Bare Metal Stent
- ○ DES
- ○ Rotablator
- ○ Other _____
- ○ Cutting Balloon
- ○ IVUS
- ○ Pressure Wire
- ○ Flowire
- ○ Brachytherapy
- ○ Distal Embolic Protection → ○ Filter ○ Balloon
- ○ Proximal Embolic Protection → ○ Proxis™ ○ Other
- ○ Thrombectomy Device → ○ Export™ ○ Other

Lesion 2

7.2a **Coronary lesion**
- ○ De novo
- ○ Restenosis (No prior stent) → 7.2b **Date of POBA** ___ / ___ / ____ (DD - MM - YYYY)
- ○ In stent restenosis → 7.2c **Prior stent type** ○ DES ○ BMS ○ Mixed DES & BMS

7.2d **Date implanted** ___ / ___ / ____ (DD - MM - YYYY)

7.2e **Stent thrombosis** ○ Yes ○ No

7.2f **Lesion code (1-25)** ___

7.2g **Location in graft** (complete for graft PCI only. Lesion codes 18-25 only) ○ Ostial ○ Distal ○ Mid ○ Proximal ○ Anastomosis ○ Native

7.2h **Lesion type** ○ A ○ B1 ○ B2 ○ C

7.2i **Chronic total occlusion** ○ Yes ○ No

7.2j **Ostial lesion** ○ Yes ○ No

7.2k **Bifurcation lesion** ○ Yes ○ No (If side branch, enter as lesion 2)

7.2l **Pre-stenosis %** ___ 7.2m **TIMI Flow (pre)** ___ (0-3)

7.2n **Post-stenosis %** ___ 7.2o **TIMI Flow (post)** ___ (0-3)

7.2p **Estimated lesion length** ___ mm

7.2q **Acute closure** ○ Yes ○ No

7.2r **Dissection** ○ Yes ○ No

7.2s **Perforation** ○ Yes ○ No

7.2t **No Reflow** ○ No ○ Transient ○ Persistent

7.2u **Lesion result** ○ Successful ○ Unsuccessful

STENT DETAILS FOR LESION 2

	7.2v Stent code	7.2w Length	7.2x Diameter
#1			.
#2			.
#3			.
#4			.

For **stent codes** please refer to the MIG instruction sheet.

Stent codes will be added as new devices come into use.

If a device is not present please call CCRET on 1800 285 382 to add.

7.2y **Maximum balloon size used** ___ . ___ mm

7.2z **Intracoronary devices used**
- ○ No devices deployed
- ○ Balloon only
- ○ Bare Metal Stent
- ○ DES
- ○ Rotablator
- ○ Other _____
- ○ Cutting Balloon
- ○ IVUS
- ○ Pressure Wire
- ○ Flowire
- ○ Brachytherapy
- ○ Distal Embolic Protection → ○ Filter ○ Balloon
- ○ Proximal Embolic Protection → ○ Proxis™ ○ Other
- ○ Thrombectomy Device → ○ Export™ ○ Other

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Lesion 3

7.3a **Coronary lesion**
- ○ De novo
- ○ Restenosis (No prior stent) → 7.3b **Date of POBA** __ / __ / ____ (DD - MM - YYYY)
- ○ In stent restenosis → 7.3c **Prior stent type** ○ DES ○ BMS ○ Mixed DES & BMS

7.3d **Date implanted** __ / __ / ____ (DD - MM - YYYY)

7.3e **Stent thrombosis** ○ Yes ○ No

7.3f **Lesion code (1-25)** __

7.3g **Location in graft** (complete for graft PCI only. Lesion codes 18-25 only) ○ Ostial ○ Distal ○ Mid ○ Proximal ○ Anastomosis ○ Native

7.3h **Lesion type** ○ A ○ B1 ○ B2 ○ C

7.3i **Chronic total occlusion** ○ Yes ○ No

7.3j **Ostial lesion** ○ Yes ○ No

7.3k **Bifurcation lesion** ○ Yes ○ No (If side branch, enter as lesion 2)

7.3l **Pre-stenosis %** ___ 7.3m **TIMI Flow (pre)** __ (0-3)

7.3n **Post-stenosis %** ___ 7.3o **TIMI Flow (post)** __ (0-3)

7.3p **Estimated lesion length** __ mm

7.3q **Acute closure** ○ Yes ○ No

7.3r **Dissection** ○ Yes ○ No

7.3s **Perforation** ○ Yes ○ No

7.3t **No Reflow** ○ No ○ Transient ○ Persistent

7.3u **Lesion result** ○ Successful ○ Unsuccessful

STENT DETAILS FOR LESION 3

	7.3v Stent code	7.3w Length	7.3x Diameter
#1	__	__	__.__
#2	__	__	__.__
#3	__	__	__.__
#4	__	__	__.__

For **stent codes** please refer to the MIG instruction sheet.

Stent codes will be added as new devices come into use.

If a device is not present please call CCRET on 1800 285 382 to add.

7.3y **Maximum balloon size used** __.__ mm

7.3z **Intracoronary devices used**
- ○ No devices deployed
- ○ Balloon only
- ○ Bare Metal Stent
- ○ DES
- ○ Rotablator
- ○ Other _____
- ○ Cutting Balloon
- ○ IVUS
- ○ Pressure Wire
- ○ Flowire
- ○ Brachytherapy
- ○ Distal Embolic Protection → ○ Filter ○ Balloon
- ○ Proximal Embolic Protection → ○ Proxis™ ○ Other
- ○ Thrombectomy Device → ○ Export™ ○ Other

Additional Lesion Pages Attached ○ Yes ○ No

Section 8. OUTCOMES / DISCHARGE

8.1 **Periprocedural MI** ○ Yes ○ No

8.2 **Emergency PCI** ○ Yes ○ No

8.3 **Stent thrombosis** ○ Yes ○ No

8.4 **Unplanned CABG** ○ Yes ○ No

8.5 **Cardiogenic shock** ○ Yes ○ No

8.6 **Arrhythmia** ○ Yes ○ No

8.7a **CVA / stroke** (CT confirmation) ○ Yes ○ No
- If Yes → 8.7b ○ Haemorraghic ○ Ischaemic

8.8 **Tamponade** ○ Yes ○ No

8.9 **Contrast reaction** ○ Yes ○ No

8.10 **Congestive Heart Failure** ○ Yes ○ No

8.11 **New renal impairment** ○ Yes ○ No

8.12a **Post procedural rise in creatinine** ○ Yes ○ No
- If Yes → 8.12b ____ µmol/L

VASCULAR COMPLICATIONS

8.13a **Bleeding** ○ Yes ○ No

If YES, 8.13b **Transfusion of blood products required after lab visit** ○ Yes ○ No

8.13c **Bleeding site**
- ○ Retroperitoneal
- ○ Percutaneous entry site
- ○ Other _____

8.14 **Access site occlusion** ○ Yes ○ No

8.15 **Loss of distal pulse** ○ Yes ○ No

8.16 **Dissection** ○ Yes ○ No

8.17 **AV fistula** ○ Yes ○ No

8.18a **Pseudoaneurysm** ○ Yes ○ No

If YES, 8.18b **Treatment**
- ○ Ultrasound compression
- ○ Surgery
- ○ Other _____

8.19a **CK ULN** ____ IU/L

8.19b **CK peak** ____ IU/L ○ Unavailable

8.19c **CK test date** __ / __ / ____ __ : __ (DD MM YYYY HH MM)

8.20a **CK MB ULN** ____ IU/L

8.20b **CK MB peak** ____ IU/L ○ Unavailable

8.20c **CK MB test date** __ / __ / ____ __ : __ (DD MM YYYY HH MM)

8.21a **Troponin type** ○ T (ng/ml) ○ I (mcg/L)

8.21b **Troponin ULN** ___.__

8.21c **Troponin levels** ___.__ ○ Unavailable

8.21d **Troponin test date** __ / __ / ____ __ : __ (DD MM YYYY HH MM)

DISCHARGE

8.22 **Date of discharge** __ / __ / ____ (DD MM YYYY)

8.23 **Discharge status** ○ Alive ○ Deceased

8.24 **Date of death** __ / __ / ____ (DD MM YYYY)

8.25 **Primary cause of death**
- ○ Cardiac
- ○ Renal
- ○ Infection
- ○ Neurological
- ○ Vascular
- ○ Pulmonary
- ○ Other (specify) _____

8.26 **Location of death** ○ In Lab ○ Out of Lab

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MELBOURNE INTERVENTIONAL GROUP FOLLOW-UP FORM

MIG_FU_V6

Section 1 PATIENT DETAILS

1.1 **Procedure No.**

1.2 **UR No.**

1.3 **Patient DOB** DD / MM / YYYY

1.4 **Hospital code**

Hospital codes

1 Melbourne Private
2 Geelong Private
3 Peninsula Private
4 Warringal Private
5 Royal Melbourne
6 Alfred
8 Austin
9 Box Hill
10 Geelong
11 Frankston
12 Knox
13 Western
15 Northern
16 Ballarat Base

Section 2 FOLLOW-UP DETAILS

2.1 **Type of Follow-up** ○ 30 day ○ 12 month

2.2 **Date of Follow-up** DD / MM / YYYY

2.3a **Vital Status** ○ Alive ○ Deceased →

2.3b **Primary Cause** ○ Cardiac ○ Non cardiac ○ Unknown

2.3c **Date of Death** DD / MM / YYYY

2.4 **Smoking Status** ○ current ○ prior ○ never ○ unknown

2.5 **Height** cm

2.6 **Has patient been readmitted to hospital?** ○ Yes ○ No If **YES**, record all events below.

Section 3 CURRENT MEDICATIONS

	Yes	No	Unk	
3.1 Aspirin	○	○	○	
3.2 Clopidogrel	○	○	○	
3.3 Prasugrel	○	○	○	
3.4 Ticagrelor	○	○	○	
3.5 Warfarin	○	○	○	
3.6a Dabigatran	○	○	○	3.6b Dose _____ mg ○ Unk Freq
3.7 Nitrate	○	○	○	
3.8 Spironolactone	○	○	○	
3.9 Eplerenone	○	○	○	
3.10 Fibrate	○	○	○	
3.11 Ezetimibe	○	○	○	
3.12 Ivabradine	○	○	○	
3.13a Beta Blocker	○	○	○	
3.13b Agent _____				3.13c Dose _____ mg ○ Unk Freq
3.14a ACE Inhibitor	○	○	○	
3.14b Agent _____				3.14c Dose _____ mg ○ Unk Freq
3.15a AII Blocker	○	○	○	
3.15b Agent _____				3.15c Dose _____ mg ○ Unk Freq
3.16a Ca Channel	○	○	○	
3.16b Agent _____				3.16c Dose _____ mg ○ Unk Freq
3.17a Statin	○	○	○	
3.17b Agent _____				3.17c Dose _____ mg ○ Unk

Section 4 READMISSION DETAILS

	4.1 Readmission Date	4.2 Readmission Location	4.3 Readmission Reason	4.4 Angio	4.5 AMI	4.6 PCI	4.7 CABG
1	DD - MM - YYYY	Code / If Other, specify	Code / If Other, specify	○ No ○ Yes	○ No ○ STEMI ○ NSTEMI	○ No ○ TLR → ○ TVR ○ Non TVR Lesion No.	○ No ○ Yes → TVR ○ Yes ○ No
2	DD - MM - YYYY	Code / If Other, specify	Code / If Other, specify	○ No ○ Yes	○ No ○ STEMI ○ NSTEMI	○ No ○ TLR → ○ TVR ○ Non TVR Lesion No.	○ No ○ Yes → TVR ○ Yes ○ No
3	DD - MM - YYYY	Code / If Other, specify	Code / If Other, specify	○ No ○ Yes	○ No ○ STEMI ○ NSTEMI	○ No ○ TLR → ○ TVR ○ Non TVR Lesion No.	○ No ○ Yes → TVR ○ Yes ○ No
4	DD - MM - YYYY	Code / If Other, specify	Code / If Other, specify	○ No ○ Yes	○ No ○ STEMI ○ NSTEMI	○ No ○ TLR → ○ TVR ○ Non TVR Lesion No.	○ No ○ Yes → TVR ○ Yes ○ No
5	DD - MM - YYYY	Code / If Other, specify	Code / If Other, specify	○ No ○ Yes	○ No ○ STEMI ○ NSTEMI	○ No ○ TLR → ○ TVR ○ Non TVR Lesion No.	○ No ○ Yes → TVR ○ Yes ○ No
6	DD - MM - YYYY	Code / If Other, specify	Code / If Other, specify	○ No ○ Yes	○ No ○ STEMI ○ NSTEMI	○ No ○ TLR → ○ TVR ○ Non TVR Lesion No.	○ No ○ Yes → TVR ○ Yes ○ No
7	DD - MM - YYYY	Code / If Other, specify	Code / If Other, specify	○ No ○ Yes	○ No ○ STEMI ○ NSTEMI	○ No ○ TLR → ○ TVR ○ Non TVR Lesion No.	○ No ○ Yes → TVR ○ Yes ○ No
8	DD - MM - YYYY	Code / If Other, specify	Code / If Other, specify	○ No ○ Yes	○ No ○ STEMI ○ NSTEMI	○ No ○ TLR → ○ TVR ○ Non TVR Lesion No.	○ No ○ Yes → TVR ○ Yes ○ No

CODES

Dose Frequency: 1 = Once daily, 2 = Twice daily, 3 = Three times daily, 4 = Other

Readmission Reason:

1 = CHF
2 = AMI
3 = Recurrent Angina
4 = Arrhythmia
5 = PCI - Planned
7 = CABG
8 = Other, please specify
9 = CVA / Stroke

Fax forms to CCRET on fax: 1800 022 730

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Medical Record No. [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]

The National Cardiac Surgery Database Program Data Collection

Section 1. Patient Demographics

Surname [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]

First name [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]

Middle name [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]

Date of Birth [ ][ ] / [ ][ ] / [ ][ ][ ][ ]
d d m m y y y y

Address _____

_____ Postcode [ ][ ][ ][ ]

Phone No 1 ____ – _____

Phone No 2 ____ – _____

Gender ○ Male ○ Female

Medicare No. [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ] **OR** ○ Patient does not have a Medicare No. registered

Race Is patient Aboriginal or Torres Strait Is. ○ YES ○ NO

Which racial groups (select all that apply) ○ Aboriginal ○ Torres Strait Is.

Insurance ○ Private ○ DVA ○ Medicare ○ Self Insured ○ Overseas ○ Other

Elective Day of Surgery Admit (DOSA) patient: ○ YES ○ NO

Admission Date [ ][ ] / [ ][ ] / [ ][ ][ ][ ]
d d m m y y y y

Surgery Date [ ][ ] / [ ][ ] / [ ][ ][ ][ ]
d d m m y y y y

Operation Number of the day for this patient: (1-6) [ ]

Discharge Date [ ][ ] / [ ][ ] / [ ][ ][ ][ ]
d d m m y y y y

Section 2. Patient Risk Factors

Smoking History	○ YES	○ NO	***if YES***	**Current Smoker**	○ YES ○ NO
Family History of CAD	○ YES	○ NO	○ Undiscovered		
Diabetes	○ YES	○ NO	***if YES***	**Control**	○ None ○ Diet ○ Oral ○ Insulin
Hypercholesterolaemia	○ YES	○ NO			
Renal	**Last Pre-Op Creatinine:** [ ][ ][ ][ ] µmol/l (For conversion from mmol see overleaf)				
	Dialysis	○ YES	○ NO	**Transplant**	○ YES ○ NO
Hypertension	○ YES	○ NO			
Cerebrovascular Disease	○ YES	○ NO	***if YES***	**Type:**	○ Coma ○ CVA ○ RIND/TIA ○ Carotid>75%
				When:	○ CVA <=2wks ○ CVA >2wks
Peripheral Vascular Disease	○ YES	○ NO			
Respiratory Disease	○ Yes	○ No	***if YES***	**Type:**	○ Mild ○ Moderate ○ Severe
Infective Endocarditis	○ YES	○ NO	***if YES***	**Type**	○ Active ○ Treated
Immunosuppressive Rx	○ YES	○ NO			

DEFINITIONS OVERLEAF ⇒

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Section 1. Patient Demographics	
Medicare Number	The full Medicare number of the patient (i.e. family number plus person number) if the patient is registered with Medicare.
DOSA Patient	Patient admitted for **scheduled elective procedure on same day as procedure**.
Admission Date	Date patient admitted/transferred to hospital where surgery performed.
Surgery Date	Date on which the first surgical incision was made for the current cardiac surgical procedure.
Discharge Date	Date Patient discharged from being an inpatient at the hospital where the procedure was performed. Discharge to Hospital in the Home, rehabilitation hospital or unit or to a local referring hospital is considered as discharge from hospital.
Operation Number	Number of operation(s) done on the day for this patient.

Section 2. Patient Risk Factors	
Smoking History	A history confirming any form of tobacco use in the past.
Current Smoker	Smoked within one month of surgery.
Family History of CAD	Direct blood relatives having following at **age <55.** a.) angina; b.) myocardial infarct; c.) sudden cardiac death without obvious cause (presume Ischaemic Heart Disease); d.) Previous coronary intervention.
Diabetes	A history of diabetes, regardless of duration of disease or need for anti-diabetic agents.
Hypercholesterolaemia	History of fasting cholesterol > 5.0 mmol/L, HDL <1.0 mmol/L or triglycerides >2.0 mmol/L or on treatment.
Creatinine	Enter creatinine in µmol/L. To convert from mmol/L multiply by 1000 (ie move decimal point 3 spaces to the right).
Hypertension	Blood pressure exceeding 140/90 mmHg or a history of high blood pressure, or the need for anti-hypertensive medications.
Cerebrovascular Disease	Documentation by any of the following; Unresponsive coma >24hrs or CVA or RIND (recovery within 72hrs) or TIA or non-invasive carotid test with 50% diameter stenosis (equivalent to 75% cross-sectional area stenosis).
Peripheral Vascular Disease	Any of the following; claudication or amputation for arterial insufficiency or vascular reconstruction or documented aortic aneurysm or renal artery stenosis or positive non-invasive testing.
Respiratory Disease	Specify if any, and severity of chronic lung disease. **Mild** = on chronic inhaled or oral bronchodilator therapy. **Moderate** = chronic oral steroid therapy aimed at lung disease **Severe** = room air pO2<60 or Room air pCO2>50 or mechanical ventilation for chronic lung disease
Infective Endocarditis	A patient presenting with valvular disease of infectious aetiology with past or present positive blood culture or postop pathology confirmation. Active = currently being treated for endocarditis
Immunosuppressive Rx	Use of any form of immunosuppressive therapy within 30 days or less preceding the operative procedure (eqv. to Prednisolone dosage ≥ 5mg).

Medical Record No. | | | | | | | | | | |

Section 3. Preoperative Cardiac Status

Myocardial infarction ○ YES ○ NO *if YES* **When** ○ <=6 Hrs ○ 8 - 21 Days ○ >6 - <24 Hrs ○ >21 Days ○ 1 - 7 Days

Type ○ NSTEMI ○ STEMI

Angina CCS Class (see definition overleaf) [ ] (0 - 4)

Treatment of Angina (during current admission & continuing to surgery)

i-v GTN ○ YES ○ NO

i-v Heparin ○ YES ○ NO

Full dose Low MW heparinoids (eg s.c. Clexane, s.c.Fragmin) ○ YES ○ NO

History of Congestive Heart Failure (CHF) ○ YES ○ NO *if YES* **CHF at current admission** ○ YES ○ NO

Dyspnoea NYHA Class (see definition overleaf) [ ] (I - IV)

Cardiogenic Shock ○ YES ○ NO

Resuscitation (within 1 hour pre-op) ○ YES ○ NO

Arrhythmia ○ YES ○ NO *if YES* **Type** ○ Atrial ○ Heart Block ○ Ventricular ○ Other

if ATRIAL **type** ○ Paroxysmal ○ Persistent ○ Permanent

Permanent Pacemaker In Situ ○ YES ○ NO

Medications at time of Surgery

Inotropes ○ YES ○ NO

IV nitrates ○ YES ○ NO

Anticoagulation therapy ○ YES ○ NO

Steroids ○ YES ○ NO

Aspirin or other antiplatelet therapy within 7 days of surgery

Aspirin	○ YES	○ NO	*if YES* **When**	○ =<2 days	○ 3 - 7 days
Clopidogrel	○ YES	○ NO		○ =<2 days	○ 3 - 7 days
IIb/IIIa (Abciximab)	○ YES	○ NO		○ =<2 days	○ 3 - 7 days
Aggrostat (Tyrofiban)	○ YES	○ NO		○ =<2 days	○ 3 - 7 days
Other	○ YES	○ NO		○ =<2 days	○ 3 - 7 days

DEFINITIONS OVERLEAF ⇒

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Section 3. Preoperative Cardiac Status

Myocardial Infarction	History hospitalisation for a MI in the medical record. Specify if MI is either NSTEMI or STEMI:	
	1. Non ST Elevation MI (NSTEMI) **A**. BIOCHEMICAL indicators of myocardial necrosis. 1. Troponin T or I > the institutional decision limit on at least one occasion during the first 24 hrs after the index event. 2. CKMB >**2x** the upper limit of normal on one occasion during the first 24 hrs. 3. CKMB > upper limit of normal on 2 successive samples. **AND one of the following:** **B**. ECG CHANGES - either ST segment depression OR T-wave abnormalities **OR** **C**. CLINCAL ISCHAEMIC SYMPTOMS such as: 1. Unexplained nausea or vomiting, &/or 2. Persistent SOB secondary to LVF, &/or 3. Unexplained weakness, dizziness or syncope	**2. ST elevation MI (STEMI)** **A**. BIOCHEMICAL indicators as for NSTEMI **AND** **B**. ECG CHANGES 1. ST segment elevation: New or presumed new ST elevation at the J-point in two or more contiguous leads with cut-off points => 0.2 mV in leads V1, V2 or V3 OR => 0.1mV in other leads. OR 2. Development of any new Q wave in leads V1 through V3 OR a new Q wave with duration =>0.03 sec and => 1mm deep in any other two contiguous leads.
History of Congestive Heart Failure	A history of CHF diagnosed by one of the following; paroxysmal nocturnal dyspnoea (PND), Dyspnoea on exertion due to HF, or X-ray showing pulmonary congestion, OR medication prescribed to treat CHF.	
Cardiogenic Shock	A clinical state of hypoperfusion characterised by hypotension (systolic pressure < 90 mmHg &/or OR CI <0.2 for at least 30 mins or the need for supportive measures to maintain a systolic pressure > or = 90 mmHg or a CI >2.0.	
Resuscitation	CPR or initiation of treatment for cardiogenic shock within 1 hr of procedure.	
Arrhythmia	The presence of AF/flutter requiring therapy, heart block, VT or VF, or other arrhythmia.	
Aspirin or other antiplatelet therapy within 7 days of surgery	Patient has taken aspirin or other antiplatelet agent within the last seven days.	

Classification Key

CCS Class	CCS (Canadian Cardiovascular Class)
0	No Angina.
1	Ordinary physical activity, such as walking or climbing the stairs does not cause angina. Angina may occur with strenuous, rapid or prolonged exertion at work or recreation.
2	There is slight limitation of ordinary activity. Angina may occur with moderate activity such as walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals or in the cold, in the wind, or under emotional stress, or walking more than two blocks on the level, and climbing more than one flight of stairs at normal pace under normal conditions.
3	There is marked limitation of ordinary physical activity. Angina may occur after walking one or two blocks on the level or climbing one flight of stairs under normal conditions at a normal pace.
4	There is inability to carry on any physical activity without discomfort; angina may be present at rest.

NYHA Class	NYHA (New York Heart Association functional class)
I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnoea.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, or dyspnoea.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity results in fatigue, palpitations, or dyspnoea.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Medical Record No. | | | | | | | | | | |

Section 4. Previous Intervention

Previous Cardiothoracic Intervention (surgical or percutaneous) ○ YES ○ NO *if YES*

No. Prior cardiac operations with cardiopulmonary bypass [ ]

No. Prior cardiac operations without cardiopulmonary bypass [ ]

Types of Previous surgery (select all that apply) ○ CABG ○ OFF PUMP CABG ○ Valve ○ OTHER Cardiac
(Any other previous cardiac surgery, including operation on the ascending aorta and /or aortic arch, including pericardiectomy)

Previous Percutaneous Intervention

PTCA/Stent ○ YES ○ NO **in which admission?** ○ Prior Admission ○ This Admission

if YES on this Admission, then **Interval** [ ] hrs

Thrombolysis (if same admission) ○ YES ○ NO *if YES* **Interval** (if same admission) [ ] hrs

Non Surgical Balloon Valvuloplasty ○ YES ○ NO

ASD Device Closure ○ YES ○ NO

VSD Device Closure ○ YES ○ NO

Percutaneous SVT/VT Ablation ○ YES ○ NO

Section 5. Haemodynamic Data

Patient Height [ ] cm
Patient Weight [ ] kg
} *Perfusionist to complete*

Catheter: ○ YES ○ NO *if YES* **Date** d d / m m / y y y y

LVEF Method ○ No ○ LVgram ○ Radionuclide ○ ECHO ○ MRI

EF: [ ] %

If Estimate: ○ Normal(>60%) ○ Mild Impairment(46-60%) ○ Mod(30-45) ○ Severe(<30%)

Left Main Stenosis >50%: ○ YES ○ NO

No. Diseased Systems: (0,1,2,3) [ ] (left main=2, or=3 if left dominant)

DEFINITIONS OVERLEAF ⇒

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Section 4. Previous Intervention

Previous Cardiothoracic Intervention	Has the patient undergone any previous cardiovascular intervention, either surgical or non-surgical, which may include those done during the current admission. This includes all forms of percutaneous angioplasty and thrombolytic therapy for cardiac indications.
ASD Device Closure	Closure by percutaneous technique of Atrial Septal Defect
VSD Device Closure	Closure by percutaneous technique of Ventricular Septal Defect

Section 5. Haemodynamic Data

LVEF Method	Was the Left Ventricular Ejection Fraction measured, and how was this information obtained? 1 = None of the following were done 2 = Left Ventriculogram 3 = Radionuclide 4 = Echocardiogram 5 = Magnetic Resonance Imaging
Left Main Stenosis > 50%	Any stenosis that involves any parts of the Left Main. Left Main Coronary stenosis is present when there is > 50% compromise of vessel diameter in any angiographic view.
Number of Diseased Coronary System	The number of major coronary systems (LAD system, Circumflex system, and/or Right System) with > 50% narrowing in any angiographic view. The number of diseased systems should be the number of systems requiring surgical approach at that operation. NOTE: Left main disease (>50%) is counted as TWO systems (LAD and Circumflex). For example, left main and RCA would count as THREE in total. Dominant circumflex counts as TWO systems.

Medical Record No. first character here ↓ [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]

Section 6. Operation Status/Category

Consultant Surgeon [ ][ ][ ] (code)

Operating Surgeon ○ Consultant ○ Senior Registrar ○ Trainee Registrar ○ Overseas Fellow ○ Oversight

Status: ○ Elective ○ Urgent ○ Emergency ○ Salvage

Direct transfer from cathlab to theatre ○ YES ○ NO
(see definition overleaf)

Category:

Coronary Artery Bypass	○ YES	○ NO	
Valve	○ YES	○ NO	
Other Cardiac	○ YES	○ NO	***if YES*** ○ LV Aneur. ○ acq.VSD ○ ASD ○ Trauma ○ Other ○ LVOT Myectomy for HOCM ○ LV Rupture Repair ○ Pericardiectomy ○ Pulm. Thrombo-Endarterectomy ○ LV Reconstruction ○ Pulmonary Embolectomy ○ Cardiac Tumour ○ Cardiac Transplant ○ Other Congenital ○ Permanent LV epicardial lead ○ Atrial Arrhythmia Surgery *(complete section below)*
Atrial Arrhythmia Surgery *If YES to Other Cardiac-Atrial Arrhytmia Surgery,* Indicate the PREDOMINANT Lesion Set and Technique	**Lesion Set** [ ] (1 - 8)	**Energy Source** [ ] (1 - 8)	
Aortic Procedure	○ YES	○ NO	
Aortic aneurysm	○ YES	○ NO	***if YES*** Type: ○ Asc ○ Arch ○ Desc ○ Thor/Abd
Aortic dissection	○ YES	○ NO	***if YES*** Type: ○ Asc ○ Desc (only) When: ○ Acute(<=2 weeks) ○ >2 weeks
Acute Traumatic Aortic Transection: (within 2 weeks of trauma)	○ YES	○ NO	
Other Non Cardiac Procedure	○ YES	○ NO	
Carotid Endarterectomy	○ YES	○ NO	
Lung Resection	○ YES	○ NO	
Other Vascular	○ YES	○ NO	
Other Thoracic	○ YES	○ NO	
Other	○ YES	○ NO	

Draft

Section 6. Operation Status/Category

Status

Elective	The procedure could be deferred without increased risk of compromised cardiac outcome.
Urgent	Not routine - **medical reasons for operating this admission** - a) Within **72 hours from angiography** if on the same admission that angiography was performed (in this case,"same admission"includes the situation when angiogprahy is performed at another hospital and the patient is transferred directly to the hospital where surgery is to be performed) or 2) Within **72 hours after an unplanned admission** (in a patient who had a previous angiogram and was scheduled for surgery but was admitted acutely).
Emergency	**Unscheduled surgery required in next available theatre on same day** due to refractory angina or cardiac compromise.
Salvage	**The patient is undergoing CPR en route** to the operating room prior to surgical incision.

Direct Transfer from Cathlab to Theatre

	As a result of a cardiac catheter lab complication, in the opinion of the operator or the responsible physician, the patient needed to be moved directly to surgery from the cath lab or hospital ward. Typically due to indications such as ongoing ischaemia, rest angina despite maximal treatment, pulmonary oedema requiring intubation, or shock.

Other Cardiac

LVOT Myectomy for HOCM	This procedure is performed for either hypertrophic obstructive cardiomyopathy or left ventricular muscular dynamic LVOT obstruction, or in cases of tunnel stenosis in the left ventricular outflow tract. This procedure involves excision of left ventricular endocardial muscle out of the left ventricular outflow tract.
LV Rupture Repair	This is ischaemic rupture of the free wall of the left ventricle. Therefore does not include traumatic rupture.
Pulm. Thrombo-Endarterectomy	Operation performed for chronic pulmonary thrombo-embolic disease. It involves cardiopulmonary bypass, and mostly hypothermic circulatory arrest, and incisions are made in the right and left (or both) pulmonary arteries, and an endartectomy performed out into the distal branches.
LV reconstruction	Reshaping of the left ventricle by lateral excision (Batista) or antero-septal reconstruction (Dor). Does **not** include resection and repair of left ventricular aneurysm, by whatever technique.
Permanent LV epicardial lead	Insertion of a permanent LV Epicardial Lead **in association with a cardiac procedure.**
Atrial Arrhythmia surgery	Current surgical procedure is for paroxysmal, persistent or permanent atrial tachy arrhythmia.

Atrial Arrhythmia surgery

Lesion Set:	**Technique or Energy Source:**
1=Cox-Maze III	1=Cut & Sew
2=Radial	2=Unipolar RF
3=Mini-Maze	3=Bipolar RF
4=Left Atrial Reduction	4=Cryoblation
5=Pulmonary Vein Isolation	5=Microwave
6=Left Arial Only	6=Laser
7=Right Atrial Only	7=Ultrasound
8=Other	8=Other

Medical Record No. | | | | | | | | | | |

Section 7. Minimally Invasive

Minimally Invasive Technique Attempted (non-standard incision) ○ YES ○ NO *if YES* Indication ○ Surgeon/Patient choice ○ Contraind Std Approach ○ Comb Cath Intervention

Operation performed Off Pump ○ YES ○ NO

Robotically Assisted ○ YES ○ NO

Section 8. Cardiopulmonary Bypass and Support Data

Cardiopulmonary Bypass used ○ YES ○ NO

Cardioplegia ○ YES ○ NO

Cumulative cross-clamp time | | | | min

Cumulative cardiopulmonary bypass time | | | | min

IABP ○ YES ○ NO

When ○ Preop ○ Intraop ○ Postop

Indication ○ Haemodynamic instability ○ CBP Wean ○ PTCA support ○ Prophylactic ○ Unstable Angina

Rota-pump ○ YES ○ NO

When ○ Preop ○ Intraop ○ Postop

Indication ○ Haemodynamic instability ○ CBP Wean ○ PTCA support ○ Prophylactic ○ Unstable Angina

Other mechanical support (VAD/ECMO etc) ○ YES ○ NO

When ○ Preop ○ Intraop ○ Postop

Indication ○ Haemodynamic instability ○ CBP Wean ○ PTCA support ○ Prophylactic ○ Unstable Angina

Intra-Operative TOE ○ YES ○ NO *if YES* Type: ○ Elective Insertion ○ Non-Elective Insertion

Intra-Operative antifibrinolytic use ○ YES ○ NO *if YES* Type: ○ Trasylol ○ Tranexamic ○ Other

Section 9. Coronary Bypass Data

Intraoperative decision to graft coronary artery ○ YES ○ NO

IMA used ○ YES ○ NO *if YES* **LIMA** ○ YES ○ NO **RIMA** ○ YES ○ NO

No. of Distal Arterial grafts ☐

No. of IMA Distal Anastomoses ☐

No. of RA Conduits harvested ☐

No. of Radial Distal Anastomoses ☐

No. of Vein Distal Anastomoses ☐

No. of GEPA Distal Anastomoses ☐

Were Arterial T or Y grafts used ○ YES ○ NO

Total No. Distal Anastomoses ☐

DEFINITIONS OVERLEAF ⇒

Section 7. Minimally Invasive

Minimally Invasive Technique Attempted	Was a non-standard incision used to minimise trauma, either as a beating heart off-pump coronary artery procedure or as an on-pump cardiac procedure, utilising any form of cardiopulmonary bypass.
Robotically Assisted	Any procedure performed with the assistance of a robot (e.g. DaVinci, AESOP)

Section 8. Cardiopulmonary Bypass and Support Data

Cross Clamp Time	Total number of minutes the aorta is completely cross-clamped and the heart was ischaemic during bypass. Enter zero if no cross clamp was used.
Cumulative Cardiopulmonary Bypass Time	Total number of minutes on cardiopulmonary bypass. Enter zero if no cardiopulmonary bypass was used.
Intra-Operative TOE	**Elective Insertion** = Routine Insertion of TOE, planned before commencement of operation. **Non-Elective Insertion** = Unplanned insertion of TOE, for whatever reason.

Section 9. Coronary Bypass Data

IMA used	Was an Internal Mammary Artery Used for Coronary Bypass?

Medical Record No.

Section 10. Valve Surgery Data

	Procedure	Prosthesis					
Aortic		Implant	Model No		Serial		Size
		Explant	Model No		Serial		Size
Mitral		Implant	Model No		Serial		Size
		Explant	Model No		Serial		Size
Tricuspid		Implant	Model No		Serial		Size
		Explant	Model No		Serial		Size
Pulmonary		Implant	Model No		Serial		Size
		Explant	Model No		Serial		Size

Procedure codes:

1 No
2 Annuloplasty Only
3 Replacement
4 Repair/Reconstruction with Annuloplasty
5 Repair/reconstruction without Annuloplasty
6 Root Reconstruction with Valve Conduit
7 Root Reconstruction with Valve Sparing
8 Resuspension Aortic Valve
9 Resection Sub-Aortic Stenosis
10 Commissurotomy with annuloplasty ring
11 Commissurotomy without annuloplasty ring
12 Repair Paravalvular leak
13 Valvectomy (no replacement)
14 Valvotomy
15 Ross procedure
16 Inspection only
17 Decalcification of valve only

Valve Pathophysiology

Valve Data	Aortic	Mitral	Tricuspid	Pulmonary
Stenosis	○ YES ○ NO	○ YES ○ NO	○ YES ○ NO	○ YES ○ NO
Insufficiency (0-4) (see definition overleaf)				
Aetiology (see definition overleaf)				

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Section 10. Valve Data

Code	Insufficiency
0	None
1	Trivial
2	Mild
3	Moderate
4	Severe

Code	Aetiology
1	Rheumatic
2	Congenital
3	Ischaemic
4	Idiopathic Calcific
5	Myxomatous degen.
6	Failed prior repair
7	Prosthetic valve failure
8	Peri-prosthetic leak
9	Prosthetic valve thrombosis
10	Active Infection
11	Previous Infection
12	Marfans
13	Annuloaortic ectasia
14	Other degen. disease
15	Dissection
16	Tumour
17	Trauma
18	Iatrogenic
19	Functional (mitral valve)
20	Functional (tricuspid valve)
99	Other

first character here ↓

Medical Record No. | | | | | | | | | | |

Section 11. Postoperative Data

Blood Bank Products:

RBC ○ YES ○ NO

Non RBC ○ YES ○ NO

PERIOPERATIVE TRANSFUSION (not autologous)

Bank RBC (units) | |

Platelets (units) | |

Novo 7 (units) | |

FFP (units) | |

Cryo (units) | |

ICU Admission - Date/Time d d / m m / y y y y hrs

Extubation - Date/Time d d / m m / y y y y hrs

ICU Discharge - Date/Time d d / m m / y y y y hrs

Readmitted to ICU ○ YES ○ NO

Reintubation ○ YES ○ NO

Reintubation - Date/Time d d / m m / y y y y hrs

Reextubation - Date/Time d d / m m / y y y y hrs

ICC LOSS (First 4 hours post surgery): | | | | mls

Complications

Return to theatre ○ YES ○ NO ***if YES***

- Reop Valve Dysfunction ○ YES ○ NO
- Reop Bleeding or Tamponade ○ YES ○ NO
- Reop Graft Occlusion ○ YES ○ NO
- Reop Deep Sternal Infection ○ YES ○ NO
- Reop Other Cardiac ○ YES ○ NO
- Reop Other Non Cardiac ○ YES ○ NO

New Renal Failure ○ YES ○ NO ***if YES***

- Haemofiltration ○ YES ○ NO
- **Highest post-op Creatinine level** | | | | **µmol/l**

Peri-Operative AMI ○ YES ○ NO

Peri-op Cardiogenic Shock ○ YES ○ NO

Cardiac (Mark all that apply) *Inotrope use*

- for longer than 4 hours post-operatively ○ YES ○ NO
- for Low Cardiac Output Syndrome ○ YES ○ NO
- for Low SVR Syndrome ○ YES ○ NO

New Cardiac Arrhythmia ○ YES ○ NO ***if YES***

- Heart Block (requiring PPM) ○ YES ○ NO
- Other Brady-arrhythmia (requiring PPM) ○ YES ○ NO
- Cardiac Arrest ○ YES ○ NO
- Atrial Arrhythmia (requiring Rx) ○ YES ○ NO
- Ventricular Tachycardia ○ YES ○ NO

New Neurologic →

- Stroke Permanent (>72hrs) ○ YES ○ NO
- Stroke Transient ○ YES ○ NO
- Continuous Coma > 24 hrs ○ YES ○ NO

New Pulmonary →

- Ventilation Prolonged >24 hrs ○ YES ○ NO
- Pulmonary Embolism ○ YES ○ NO
- Pneumonia ○ YES ○ NO
- Reintubation & Ventilation ○ YES ○ NO

New Infection →

- Sternal Deep ○ YES ○ NO
- Thoracotomy ○ YES ○ NO
- Septicaemia ○ YES ○ NO

New Vascular →

- Aortic Dissection ○ YES ○ NO
- Acute Limb Ischaemia ○ None ○ Upper Limb ○ Lower Limb

New Other →

- Anticoagulant Complications ○ YES ○ NO
- GIT Complications ○ YES ○ NO
- Multi-system Failure ○ YES ○ NO

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Section 11. Postoperative Data

Blood Products: RBC	Were red blood cell products transfused intra and/or postoperatively? Do **not** include pre-donated blood, pump residual blood, cellsaver blood or chest tube recirculated blood.
Blood Products: Non RBC	Was a transfusion of blood products other than RBC (eg. FFP, Platelets) given intra and/or post-operatively? (Exclude Albumin)
Perioperative Transfusion Units	Indicate the number of units of Bank RBC, Platelets, Novo 7, FFP and Cryo units used.
ICU Admission - Date/Time	Indicate the date and time of admission to ICU from OR.
Extubation - Date/Time	Indicate the date post-operation when the patient was extubated.
ICU Discharge - Date/Time	Indicate the date and time of discharge from ICU to HDU or General Ward or death.
Readmitted to ICU	Was patient readmitted to ICU following transfer to the HDU or General Ward?
Reintubation	Indicate whether the patient was reintubated during hospital stay after the initial extubation.
Reintubation - Date/Time	Indicate the date and time when the patient was reintubated.
Reextubation - Date/Time	Indicate the date and time when the patient was extubated following the reintubation.
ICC loss	Indicate the fluid loss in mls from the Pericardial/mediastinal drains in the first 4hrs postoperation.
New Renal Failure	**At least two** of the following: a.) creatinine increased to > 0.2mmol/l; b.) a doubling or greater increase in creatinine over pre-op value; c.) a new requirement for dialysis/haemofiltration
Haemofiltration	Acute institution of haemofiltration for renal failure. Excludes haemofiltration for removal of fluid with normal serum urea and creatinine
Perioperative Cardiogenic Shock	A clinical state of hypoperfusion characterised by hypotension (systolic pressure < 90 mmHg &/or OR CI <0.2 for at least 30 mins or the need for supportive measures to maintain a systolic pressure > or = 90 mmHg or a CI >2.0.
Return to Theatre	Did patient return to the operating theatre for management of complications. Includes operative procedures done in the ICU that normally would be performed in the operating theatre.
Perioperative MI	Diagnosed by finding **at least two** of the following criteria: a.) **Enzyme level elevation**: either 1)CK-MB>30; or 2) troponin >20.0 micrograms /L , or established level at own institution; b.) **New wall motion abnormalities**; c.) Serial ECG (at least two) showing **New Q waves**.
Cardiac- Inotrope Use for Low Cardiac Output Syndrome	When an inotrope is administered with the intent to improve cardiac output, irrespective of the reasons for that decision.
Cardiac- Inotrope Use for Low SVR Syndrome	When a primarily alpha adrenergic agonist is given with the intent to increase SVR. This is usually in presence of high cardiac output. Does not include Noradrenalin given with Milrinone.
Heart Block	**New** heart block requiring implantation of permanent pacemaker.
Other Brady-Arrhythmia	**New** other Brady-arrhythmia requiring implantation of PPM.
Cardiac Arrest	Either a.) VF; b.) VT with haemodynamic instability; c.) asystole.
New Atrial Arrhythmia	**New** onset atrial fibrillation/flutter requiring treatment.
New Ventricular Tachycardia	**New** onset of ventricular tachycardia (> 6 beat run) requiring treatment.
Stroke Permanent	A central neurological deficit persisting for > 72 hours.
Stroke Transient	A transient neurological deficit (TIA, RIND).
Continuous Coma > 24hrs	**New** postoperative coma that persists for at least 24 hours.
Intubation Prolonged > 24hrs	Pulmonary insufficiency requiring ventilatory support > 24hrs (cumulative).
Pulmonary Embolism	Diagnosed by study such as V/Q scan or angiogram.
Pneumonia	Diagnosed by **positive cultures** and c/w clinical findings.
Infection - Sternal Deep	Involves muscle and bone, with or without mediastinal involvement, as demonstrated by surgical exploration. Must have wound debridement and **one of** following: a.) positive culture; b.) treatment with antibiotics.
Infection - Thoracotomy	Involving thoracotomy or parasternal site (Conditions as above).
Infection - Septicaemia	Septicaemia requires positive blood cultures supported by at least two of the following indeces of clinical infection: a.) Fever; b.) Elevated granulocyte cell counts; c.) Elevated and increasing CRP, d.) Elevated and increasing ESR, post-operatively.
Aortic Dissection	Dissection occuring in any part of the aorta.
Acute Limb Ischaemia	Any complication producing limb ischaemia.
Anticoagulation comps.	Bleeding, hemorrhage, and /or embolic events related to anticoagulant therapy.
GI complications	Postop occurrence of any GI complication including: a.) GI bleeding requiring transfusion; b.) pancreatitis requiring nasogastric suction; c.) cholecystitis requiring cholecystectomy or drainage; d.) mesenteric ischaemia requiring exploration; e.) other GI comps.
Multi-system failure	**Two or more** of the following major organ systems fail concurrently for at least 48 hours: a.) Renal - New renal failure (defined previously); b.) Respiratory - Requires endotracheal intubation for respiratory dysfunction; c.) Cardiac - the use of inotropes and/or IABP to treat low cardiac output.

Medical Record No. | | | | | | | | | | |

Section 12. Mortality / Discharge/ Readmission

Discharge: ○ Home ○ Hospital in the Home ○ Rehabilitation Unit/Hospital ○ Local or Referring Hospital ○ Hospital Mortality

Mortality:

Post Discharge within 30 days of surgery: ○ YES ○ NO

Mortality Date: d d / m m / y y y y

Provide date of death in hospital during the index admission at any time after the procedure, or death after discharge from hospital within thirty days of the procedure

Mortality Location: ○ Operating Room ○ Hospital ○ Home (incl.hospital in the home) ○ Other Care facility

Mortality Primary Cause:
(choose **one** of the following)

- ○ Cardiac — **If yes** → ○ Ischaemic ○ Other
- ○ Neurologic
- ○ Renal
- ○ Vascular
- ○ Multisystem failure
- ○ Infection — **If yes** → ○ Septicaemia ○ Endocarditis ○ Other
- ○ Respiratory Failure
- ○ Valvular
- ○ Other
- ○ Unknown
- ○ Pulmonary Embolism
- ○ Aortic Dissection

Cognisant patient elected to withdraw from treatment (see definition) ○ YES

Readmission:

Readmitted <=30 Days from procedure: ○ YES ○ NO
(Does not include planned transfer to Rehabilitation facility)

Readmitted reason:
(choose **one** of the following)

- ○ Anticoagulant Complication
- ○ Arrhythmia
- ○ Congestive Heart Failure (CHF)
- ○ Valve Dysfunction
- ○ Pericardial Effusion
- ○ Cardiac Tamponade
- ○ Other Complication related to Cardiac Surgery (e.g. renal, hepatic, GI etc)
- ○ Deep sternal Infection
- ○ Other Incisional Complication
- ○ Pneumonia or other Respiratory Complication
- ○ Myocardial Infarction (MI)
- ○ Recurrent Angina
- ○ Other readmission unrelated to Cardiac Surgery

Definitions

Discharge	**1 = Home:** Discharged to home, with no planned contact before routine review. **2 = Hospital in the home:** Discharged to home, with planned visits to home by medical or paramedical staff. **3 = Rehabilitation Hospital:** Discharged for inpatient rehabilitation. **4 = Local or referring hospital:** Discharged for continuing acute care. **5 = Hospital Mortality**
Mortality Post-discharge	Specify whether the patient died after discharge from hospital.
Mortality - Cardiac complication	Specify whether the patient died from cardiac ischaemia or from another cardiac complication.
Mortality - Infection complication	Specify whether the patient died from septicaemia, endocarditis or other infection.
Cognisant patient withdraws from treatment	Patient who was aware of the consequences to his/her actions, elected to withdraw treatment in circumstances where they would survive if treatment was continued. NOTE: Completing "yes" to this field implies automatic review of patient's hospital file and permission for ASCTS personnel to review their case.
Congestive heart failure	Readmitted within 30 days from the date of surgery for CHF, diagnosed by one of following; paroxysmal nocturnal dyspnoea (PND), dyspnoea on exertion due to HF, X-ray showing pulmonary congestion, **OR** medication prescribed to treat CHF - ACE inhibition, diuretics, Carvedilol or digoxin.
Recurrent angina	Objective confirmation that chest pain is due to ischaemia by exercise test (nuclear, echo, treadmill or angiography).
Pneumonia or other respiratory complication	Diagnosed by one of the following; **positive cultures** of sputum or trans-tracheal aspirate and consistent with clinical findings of pneumonia.

Appendix G: Alfred Hospital clinical costing dataset: Cost buckets

CCSAA Cost Buckets and their contents (each direct/indirect/total) plus additional columns

Allied Health	Coronary Care Unit (CCU)	Emergency	ICU	Imaging	Medical - Surgical	Medical - Non-Surgical
Audiology			High Dependency Unit (HDU)	Cardiotocograph (CTG)	Anaesthetists	Consultants/Sessionals
Child Abuse			Intensive Care Unit (ICU)	Computerised Tomography (CT Scan)	Consultants/Sessionals	Hospital Medical Officers (HMO)
Child Development Centre			Neonatal Intensive Care Unit (NICU)	Magnetic Resonance Imaging (MRI)	Hospital Medical Officers (HMO)	Registrars
Dietetics			Special Care Nursery (SCN)	Mammography	Registrars	Residents
Interpreters			Ventilation Weaning Unit	Nuclear Medicine	Residents	Visiting Medical Officer (VMO)
Medical Illustration				Positron Emission Tomography (PET)	Visiting Medical Officer (VMO)	
Neuropsychology				Prosthesis for Imaging		
Occupational Therapy				Radiology		
Optometry				Ultrasound		
Orthoptics						
Orthotics						
Pastoral Care (Chaplaincy)						
Physiotherapy						
Play Centre - Play Therapy (RCH)						
Podiatry						
Psychology						
Sexual Assault Clinic						
Social Work						
Speech Therapy						
	includes: medical and nursing costs	includes: medical and nursing costs	includes: medical and nursing costs includes: SCN if co-located with an ICU	includes: Medical Radiologists and Nursing Radiolo costs	excludes: Radiologists, Pathologists, Emergency Physicians, Intensivists and Neonatalogists	excludes: Radiologists, Pathologists, Emergency Physicians, Intensivists and Neonatalogists

Nursing	Pathology:	Pharmacy:	Theatre (OR)	Theatre (non-OR)	Other Costs
Breast-Feeding Assessment	Anatomical Pathology	Imprest	Anaesthetics (including consumables,	Angiography	
Chemotherapy	Andrology	Scripted - including Pharmaceutical Be	Anaesthetic Drugs	Cardiac Catheterisation Laboratory	
Clinical Sterile Supply (CSSD)	Biochemistry	Section 100 (S100)	Clinical Sterile Supply (CSSD)	Electrocardiography	
Delivery Suites	Blood Bank		Day Surgery	Endoscopy Suite	
Domiciliary Suites	Clinical Pharmacology		Endoscopy Suite	Gait Laboratory	
Hospital in the Home (HITH)	Cytogenetics		Perfusionists	Hyperbaric	
Lactation Consultant	Cytology		Pre-operative Lounge	Lithotripsy	
Outpatient Nursing and Consumables	Haematology		Pre-operative Nursing	Prostheses for CathLab	
Renal Dialysis	Histology		Prosthetics	Radiotherapy	
Special Care Nursery	Immunology		Recovery Nursing	Sleep & Respiratory Laboratory	
Stomal Therapy	Microbiology		Theatre Consumables		
Transit Lounge	Serology		Theatre Nursing		
Transport - Patient	Virology		Theatre Technicians		
Ward Catering					
Ward Nursing and Ward Consumables					
excludes: CCU, Emergency and ICU may include SCN if not co-located with NICU	includes: Pathologists				

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An Australian risk prediction model for determining early mortality following aortic valve replacement☆,☆☆

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Abstract

Objective: To develop a multivariable logistic risk model for predicting early mortality following aortic valve replacement (AVR) in adults, and to compare its performance against existing AVR-dedicated models. **Methods:** Prospectively collected data from the Australasian Society of Cardiac and Thoracic Surgeons (ASCTS) database project were used. Thirty-five preoperative variables from AVR literature were considered for analysis by chi-square method and multiple logistic regression. Using the bootstrap re-sampling technique for variable selection, five plausible models were identified. Based on models' calibration, discrimination and predictive capacity during *n*-fold validation, a final model, the AVR-Score, was chosen. An additive score, derived from the final model, was also validated externally in a consecutive cohort. The performance of AVR-dedicated risk models from the North West Quality Improvement Program (NWQIP) and the Northern New England Cardiovascular Study (NNE) groups were also assessed using the receiver operating characteristic (ROC) curve and the Hosmer–Lemeshow (H–L) chi-square test. **Results:** Between July 2001 and June 2008, a total of 3544 AVR procedures were performed. Early mortality was 4.15%. The AVR-Score contained the following predictors: age, New York Heart Association class, left main disease, infective endocarditis, cerebrovascular disease, renal dysfunction, previous cardiac surgery and estimated ejection fraction. Our final model (AVR-Score) obtained an average area under ROC curve of 0.78 (95% confidence interval (CI): 0.76, 0.80) and an H–L *p*-value of 0.41 ($p > 0.05$) during internal validation, indicating good discrimination and calibration capacity. External validation of the additive score on a consecutive cohort of 1268 procedures produced an ROC of 0.73 (0.62, 0.84) and an H–L *p*-value of 0.48 ($p > 0.05$). The NWQIP and NNE risk models achieved acceptable discrimination of ROC of 0.77 (0.73, 0.81). However, both models obtained H–L *p*-values of 0.002 ($p < 0.05$), indicating a poor fit in our cohort. **Conclusion:** Existing AVR-dedicated risk models were deemed inappropriate for risk prediction in the Australian population. A preoperative risk model was developed using prospective data from a contemporary AVR cohort.
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Keywords: 30-Day mortality; Risk factors; Aortic valve replacement; Trans-catheter aortic valve implantation; Bootstrap method; Prediction model

1. Introduction

Aortic valve replacement (AVR) has seen considerable growth in the past 50 years and still remains the gold standard treatment for degenerative aortic valve diseases [1]. It is estimated that more than 200 000 AVR procedures are performed annually worldwide [2]. On average, the expected in-hospital mortality rate for patients undergoing isolated AVR procedures is 2.8%, and for those undergoing simultaneous coronary artery bypass grafting (CABG), it is 5.3% [3].

Although post-AVR mortality rates have reduced over the years, the age and overall risk profile of patients has increased [2]. It is estimated that severe aortic lesions are prevalent in approximately 4.5% of individuals above the age of 75 years [4]. According to recent reports, nearly 32% patients with severe aortic stenosis (AS) are not referred to surgery [5]. Morton and Nga [6] have confirmed similar trends in Australian patients. Most common reasons for non-operative management included old age, severe co-morbidities and patient refusal [7]. Whilst conventional surgical AVR can be achieved with an early mortality of 1–2% in low-risk patients, the risks of complications increase in elderly patients with severe co-morbidities. Trans-catheter aortic valve implantation (TAVI) techniques currently under trial

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may present an alternative lower-risk, less invasive approach for treatment of AS in high-risk surgical patients. Early reports have shown acceptable morbidity and mortality (30-day) outcomes following TAVI [8].

Accurate AVR risk models enable the comparison of results between institutions and surgeons by adjusting for differing case-mix. They are also useful in the areas of clinical decision making, preoperative patient education and consent and in the selection of patients for TAVI [9]. Currently, high-risk patients, defined as having a European System for Cardiac Operative Risk Evaluation (logistic EuroSCORE) [10] between 9.2% and 19.9% (median = 11%), are being considered for TAVI in Europe [9]. However, Parolari and colleagues [11] have recently provided evidence of poor performance of both additive and logistic EuroSCORE in valve cohorts, strongly recommending the use of alternative risk algorithms in valve surgery. Whilst several valve- and AVR-specific risk prediction models have been developed internationally [12—14], few used robust methods for both variable selection and model validation. We aim to validate two recent risk models developed by the North West Quality Improvement Program (NWQIP) [12] and the Northern New England Cardiovascular Study (NNE) Group [13]. We hypothesise that an AVR risk prediction model derived locally would outperform existing AVR-specific risk scores.

2. Methods

2.1. The database

The Australasian Society of Cardiac and Thoracic Surgeons (ASCTS) database is a large, multicentre registry that was formed in 2001. The main goal of the project was to develop a standardised data-definition set that could be used throughout Australian cardiac surgical units for purposes of generating performance indicators and establishing national standards for benchmarking surgical performance [15,16]. Currently, the registry has over 22 centres participating, with a capture of 80% of public hospitals performing cardiac surgery in Australia. The institutional review board of each participating hospital had approved the use of these databases for research; hence, the need for individual patient consent was waived for this study. The minimum ASCTS data set comprises 287 variables. ASCTS data collection and audit methods have been previously published in detail [17,18]. A 30-day follow-up is performed for all patients to obtain re-admission and mortality data. Mortality information is further validated through linkage to national death index (NDI) data.

2.2. Patient population

From a total of 23 016 cardiac surgical procedures collected between July 2001 and June 2008, an AVR subset comprising 4153 procedures was considered for analysis. To maintain homogeneity of the sample, pulmonary and tricuspid valve, cardiac or non-cardiac procedures performed concomitantly with AVR were excluded. The final cohort comprised 3544 patients, who underwent AVR with or without CABG or a mitral valve procedure (MVP) (i.e., AVR $\pm$ CABG $\pm$ MVP). The clinical outcome of interest was early postoperative death, defined as in-hospital mortality or mortality within 30 days of surgery.

3. Statistical methods

3.1. Model development

All data were collected in a customised database, de-identified and exported for data analysis. Stata version 10.1 was used for data cleaning and statistical analysis. Thirty-five preoperative risk factors were considered for analysis. The decisions for inclusion of candidate variables were based on existing literature and recommendations by a clinician.

The individual association between each candidate variable and mortality was tested using chi-square analysis. All variables with a p-value less than 0.10 from chi-square analysis were considered for entry into multivariable analysis. Bootstrap multiple logistic regression was used for model development [13,16,19]. The proportion of times a variable was identified as a significant predictor in 1000 repeated bootstrap samples was recorded [16]. Five plausible multiple logistic regression models were developed from variables that were significant in at least 80%, 70%, 60% and 50% of the bootstrap samples. One model comprising all variables was developed for comparison of results. The first-degree interaction effect between clinically relevant risk factors and multicollinearity for all possible pairs of risk factors was also investigated. Based on models' Akaike Information Criterion (AIC) estimate [20], prediction mean square error (MSE) (indicators of distance between prediction and truth) and performance during validation, a final optimal multiple logistic model (AVR-Score) was chosen [16].

A simplified additive score system was also developed by transforming the β-coefficients corresponding to each predictor in the AVR-Score. Additive scores were obtained by dividing β-coefficients by the absolute value of the smallest existing β-coefficient and rounding off to the nearest whole number. To calculate an individual's total risk, additive scores relevant to his/her preoperative profile were summed up to obtain a 'total additive score'. In a conversion table, the average expected mortality rate corresponding to the range of total additive scores obtained from the cohort (n = 3544) were tabulated.

3.2. Model validation

All five candidate models were subjected to n-fold internal validation using the bootstrap re-sampling technique [12,16]. Based on 100 random samples created with replacement of 70% of data, the average area under the receiver operating characteristic (ROC) curve and the average Hosmer—Lemeshow (H—L) goodness-of-fit p-value [21] were estimated: the former, to assess the (average) percentage of times the models will predict a higher probability of mortality for observed cases (non-survivors) than observed non-cases (survivors) (i.e., discrimination capacity) and the latter, to assess the models' overall fit in the cohort (i.e., calibration capacity). Furthermore, the AVR-Score was validated internally in the single sample (n = 3544) to compare performance with other existing international

models that only underwent single-sample validation. To further ascertain the generalisability of our final model, the AVR-Score was externally validated on 1258 consecutive AVR procedures performed between 1 July 2008 and 30 June 2009.

To benchmark AVR-Score's performance against existing AVR-dedicated risk scores, two concurrent risk models developed by NWQIP and NNE groups were chosen and validated using ROC and H—L goodness-of-fit test. To obtain a fair evaluation of model performance, our data set inclusion criteria and the outcome variable of interest were adjusted in concordance with models' original inclusion criteria and end point.

3.3. Missing values

The highest number of missing values incurred in the following variables: unstable angina (1.2%); New York Heart Association (NYHA) class (2.8%) and ejection fraction estimate (3.0%). Any patient with one or more missing observations was excluded from the analysis. In the final model chosen (AVR-Score), 226 patients were excluded due to missing values.

4. Results

Our cohort comprised of 3544 AVR procedures collected by the ASCTS database between June 2001 and June 2008, where 3.6% (126) of procedures were redo valve operations. The majority of the patients were male (62.2%). One in five patients was over 80 years of age, and as a group, octogenarians observed the highest mortality rate (7.0%). Majority of procedures in the study cohort comprised of isolated AVR (47.6%) and AVR and CABG (45.7%), observing mortality rates of 3.3% and 4.8%, respectively.

Out of 35 preoperative variables, 27 were identified as potential predictors of mortality from chi-square analysis, and were therefore considered for entry into bootstrap variable selection method. Patient's sex ($p = 0.671$) was forced into multivariable analysis, despite its lack of significance. Table 1 summarises the results obtained from the 1000 random, repeated samples generated during bootstrap variable selection. No preoperative variable (of 27 variables) was found significant in all (100%) bootstrap samples. Three variables (age, renal dysfunction and left main disease) were selected as significant predictors of early mortality, in at least 80% of the samples. A further three variables (NYHA class, infective endocarditis and previous cardiothoracic surgery) were significant in at least 70% of the samples. Two additional variables (ejection fraction and cerebrovascular disease) were selected as determinants of early mortality in at least 60% of the samples. A further two variables (arrhythmia and peripheral vascular disease) were found to be significant in at least 50% of the samples. The remaining 17 variables appeared in less than 50% of the bootstrap samples, and were therefore labelled as 'noise' variables.

Using multiple logistic regression, we developed four models with variables selected at least 80% of the time (Model 1), 70% of the time (Model 2), 60% of the time (Model 3) and 50% of the time (Model 4) by bootstrap method. Furthermore, a 'control' model comprising all potential variables was also developed for comparison of results (Model 5). The AIC estimates and prediction MSE, obtained by each of the plausible models, during model creation, are shown in Table 2, whilst their average ROC, average H—L *p*-value (from *n*-fold validation) and ROC and H—L *p*-value (from single-sample validation) are summarised in Table 3.

Results from *n*-fold validation demonstrate that all models had acceptable calibration capacity, achieving H—L *p*-value greater than 0.05 (Table 3). When comparing overall model performance (AIC, MSE, average H—L *p*-value and average ROC), it was apparent that Model 4 achieved the best average predictive and discrimination capacity (AIC: 1027; MSE: 0.036; average H—L *p*-value: 0.12; and average ROC: 0.78)

Table 1. Number (and %) of times each candidate variable was selected in 1000 bootstrap samples drawn from the dataset.

Variable	Frequency	%
Age	966	96.6
Renal dysfunction	907	90.7
Left main disease	833	83.3
Prior cardiothoracic surgery	776	77.6
Active endocarditis	770	77.0
NYHA class	743	74.3
Cerebrovascular disease	619	61.9
EF	613	61.3
Peripheral vascular disease	553	55.3
Arrhythmia	527	52.7
Pre-op inotropes	473	47.3
Chronic lung disease	461	46.1
Hypercholesterolaemia	285	28.5
Previous MI	272	27.2
Diabetes	268	26.8
Unstable angina	267	26.7
BSA	251	25.1
Procedure type	233	23.3
Angina CCS class	208	20.8
Operation status	208	20.8
Sex	198	19.8
Cardiogenic shock	194	19.4
Hypertension	192	19.2
Resuscitation	188	18.8
Rheumatic aortic valve	187	18.7
Bicuspid defect	180	18.0

BSA: body surface area; CCS: Canadian Cardiovascular Society Class; EF: ejection fraction; MI: myocardial infarction; and NYHA: New York Heart Association.

Table 2. AIC an MSE obtained during model development and % missing values incurred for all five plausible models generated.

Model #	% of time variables are significant in the bootstrap models	Model creation		
		AIC	MSE	% Missing values
1	At least 80%	1129	0.038	0.48
2	At least 70%	1066	0.037	3.39
3	At least 60%	1032	0.037	6.38
4	At least 50%	1027	0.036	6.91
5	All variables	1033	0.035	8.80

AIC: Akaike Information Criterion; and MSE: mean square error.

Table 3. Average ROC, H–L *p*-value and prediction MSE obtained during *n*-fold ($n = 100$) validation of the five plausible models in 70% of data ($n = 2480$) with replacement.

Model #	% of time variables are significant in the bootstrap models	*n*-Fold validation ($n = 100$)		Single-sample validation	
		Average ROC (95% CI)	Average H–L *p*-value	ROC (95% CI)	H–L *p*-value
1	At least 80%	0.71 (0.69, 0.73)	0.50	0.71 (0.70, 0.73)	0.59
2	At least 70%	0.77 (0.75, 0.78)	0.51	0.77 (0.75, 0.78)	0.67
3	At least 60%	0.78 (0.76, 0.80)	0.41	0.78 (0.77, 0.79)	0.46
4	At least 50%	0.78 (0.76, 0.80)	0.12	0.78 (0.77, 0.80)	0.024
5	All variables	0.79 (0.77, 0.81)	0.53	0.79 (0.78, 0.81)	0.77

CI: confidence interval; H–L: Hosmer–Lemeshow; and ROC: receiver operating characteristic.

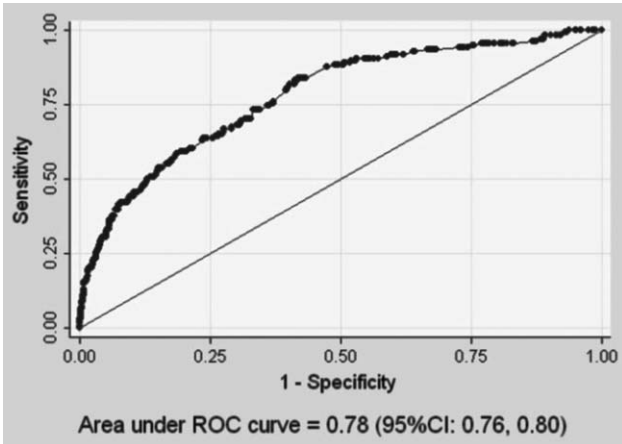

Fig. 1. ROC obtained during 100-fold validation of AVR-Score in the study population ($n = 3544$) (2001–2008).

(Table 3). Nevertheless, Model 4 achieved a significant H–L *p*-value ($p < 0.05$) during single-sample validation, indicating a poor fit in our population. Subsequently, Model 3, the model with the next best AIC, MSE, average H–L *p*-value and ROC combination (1032.16, 0.037, 0.41 and 0.78, respectively) was chosen as our final model for risk prediction, the 'AVR-Score' (Fig. 1). The model comprised eight predictors (age, NYHA class, left main disease, infective endocarditis, cerebrovascular disease, renal dysfunction, previous cardiac surgery and estimated ejection fraction), which were found significant in at least 60% of bootstrap samples (Table 1). The AVR-Score correctly classified 59.4% of observed cases (non-survivors) and 79.4% of observed non-cases (survivors) within our cohort. Overall, the model correctly classified early mortality outcome of 79.6% of patients.

Using the estimated β-coefficients of the final model, displayed in Table 4, the risk of early mortality was predicted for all patients as shown in example 1. The AVR-Score predicted an overall mortality rate of 4.16% (95% confidence interval (CI): 3.48%, 4.84%) in the study population, a very accurate approximation of the actual mortality observed (4.15%). The model was also used to predict risk of early mortality in several key subgroups of patients with good results.[1] Furthermore, Table 4 highlights a simple additive risk score system derived from the β-coefficients. According to the additive score conversion table (Table 5), a male patient presenting with the following risk profile: 75 years old (additive score = 5), severe renal dysfunction (additive score = 8), NYHA class III (additive score = 1), moderately impaired left-ventricular function (additive score = 2) and left main disease (additive score = 3), has a corresponding total additive score of 19, indicating an estimated early mortality risk of 25%. During its external validation in a consecutive cohort, the additive score achieved an ROC of 0.73 (Fig. 2) and an H–L *p*-value of 0.478 ($p > 0.05$), indicating fair performance in the local cohort.

The performance of the AVR-Score score was further benchmarked against existing AVR-dedicated risk models in Table 6. The models from the NWQIP and NNE groups, which examined patients' in-hospital mortality risk (only) were validated in a cohort restricted to 3306 (AVR $\pm$ CABG) procedures collected by the ASCTS database (2001–2008). Both models, upon validation, achieved acceptable discrimination (ROC: 0.77); but obtained *p*-values less than 0.05 in the H–L goodness-of-fit test ($p = 0.002$), suggesting poor calibration. When the observed overall in-hospital mortality (3.63%) was compared with that predicted by each model, the NNE model showed greater accuracy in its prediction (3.92%) than the NWQIP model (6.92%).

5. Discussion

This is the first study to investigate the preoperative risk factors associated with early mortality in a cohort of patients undergoing AVR in Australia. Due to salient data collection and audit mechanisms employed by the ASCTS database [17,18], we experienced minimal erroneous data and very few variables with missing values. Using the bootstrap method of variable selection, eight preoperative risk factors were found to be truly independent predictors of early mortality in Australian patients. Results from internal and external validation suggest that the AVR-Score had acceptable discrimination (ROC = 0.78 and 0.73, respectively) and calibration capacity (H–L *p*-value <0.05) amongst Australian patients undergoing AVR.

Most predictors identified by bootstrap variable selection were consistent with the existing AVR literature. Nevertheless, preoperative factors relating to operation status (e.g., emergency or urgent status) and complexity of operation (e.g., concomitant CABG or MVP) appeared less significant in our cohort. In particular, these variables appeared significant in less than 50% of the random bootstrap samples generated during variable selection (Table 1). It is

[1] Additional material is available from the author upon request.

Table 4. β-Coefficients, additive scores, p-values, and odds ratios of the predictors in the final model, the AVR-Score.

Predictor	β-Coefficients	Additive score	p-value	Odds ratio (95% CI)
Cerebrovascular disease				
Coma	0.805	3	0.002	2.24 (1.34, 3.75)
CVA	0.422	2	0.23	1.52 (0.77, 3.03)
RIND/TIA	0.417	2	0.34	1.52 (0.65, 3.56)
EF grade				
Mild EF: 46—60%	0.233	1	0.31	1.26 (0.80, 1.98)
Moderate EF: 30—45%	0.377	1	0.15	1.46 (0.87, 2.44)
Severe EF: <30%	0.742	3	0.011	2.10 (1.18, 3.73)
NYHA class				
III	0.557	2	0.009	1.75 (1.15, 2.65)
IV	1.129	4	0.001	3.09 (1.84, 5.21)
Prior operation				
Previous CABG	0.959	4	0.001	2.61 (1.50, 4.53)
Previous valve surgery	0.256	1	0.60	1.29 (0.49, 3.38)
Previous other cardiac surgery	1.425	6	0.003	4.16 (1.64, 10.56)
Active infective endocarditis	1.351	5	0.001	3.86 (1.81, 8.26)
Left main disease	0.775	3	0.003	2.17 (1.30, 3.64)
Renal dysfunction (estimated GFR)				
Mild (60—89)	0.789	3	0.10	2.20 (0.86, 5.65)
Moderate (30—59)	0.990	4	0.042	2.69 (1.04, 6.98)
Severe (15—29)	1.873	7	0.002	6.51 (2.02, 20.97)
End-stage kidney disease (<15)	1.909	7	0.001	6.74 (2.25, 20.23)
Age group				
60—69 years	0.576	2	0.23	1.78 (0.69, 4.56)
70—79 years	1.122	4	0.013	3.07 (1.26, 7.46)
80+ years	1.564	6	0.001	4.78 (1.90, 11.98)
Constant	−6.084			

CI: confidence interval; CABG: coronary artery bypass graft; CVA: cerebrovascular accident; EF: ejection fraction; GFR: glomerular filtration rate, in millilitres per minute; NYHA: New York Heart Association; RIND: reversible ischaemic neurological deficit; and TIA: transient ischaemic attacks.

Example 1: Calculating predicted risk using patient data and logistic regression coefficients.

Probability of mortality = $e^A/(1 + e^A)$, where, $A = \sum X\beta$, β = beta coefficient X = risk factor. For a male AVR patient who is 75 years old and has the following four preoperative risk factors: NYHA = NYHA class III, GFR = 25, EF = 40%, left main disease, and no prior history of cardiothoracic surgery, the risk of early mortality is: $e^{-1.378}/(1 + e^{-1.378}) = 0.2031$ (20.31%) where, $A = 1.125$ (75 years old) + 0.310 (NYHA III) + 1.877 (severe renal dysfunction) + 0.381 (moderate EF) + 0.779 (left main disease) + −5.850 (constant) = −1.378.

Table 5. Conversion table of the simple additive score system for evaluating early mortality following AVR.

Total additive score	Pooled estimated mean mortality (95% CI) (%)
0	0.2 (0.0, 0.5)
1	0.3 (0.0, 0.6)
2	0.4 (0.1, 0.8)
3	0.5 (0.1, 0.9)
4	0.7 (0.2, 1.1)
5	0.9 (0.4, 1.4)
6	1.1 (0.6, 1.7)
7	1.5 (0.8, 2.2)
8	1.9 (1.2, 2.7)
9	2.5 (1.6, 2.4)
10	3.1 (2.2, 4.1)
11	4.1 (3.0, 5.2)
12	5.2 (3.9, 6.4)
13	6.5 (5.2, 7.9)
14	8.5 (6.9, 10.0)
15	10.9 (9.2, 12.6)
16	13.4 (11.7, 15.5)
17	16.5 (14.4, 18.5)
18	20.8 (18.6, 23.1)
19	25.0 (22.6, 27.4)
20	31.1 (28.5, 33.6)
21	37.9 (35.3, 40.6)
22	42.4 (39.7, 45.2)
23	50.3 (47.5, 53.0)
24	51.3 (48.5, 54.0)
25	60.4 (57.7, 63.1)

likely that such variables dropped out during bootstrap variable selection as a consequence of low numbers of patients undergoing emergency (1.7%) or highly complex procedures (6.7%). Further, it is possible that a slight increase in procedural complexity is no longer a determinant of poor early outcomes. Tjang and colleagues [22] also found little grounds for 'concomitant CABG' as a predictor of post-AVR

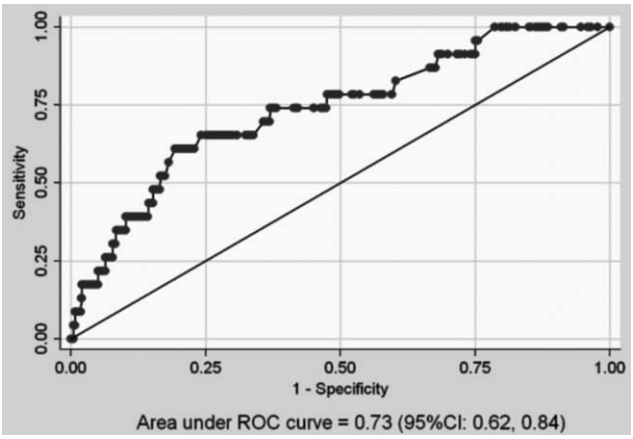

Fig. 2. ROC obtained from external validation of the additive score in consecutive cohort (n = 1258) (2008—2009).

Table 6. Comparison of performance by NWQIP and NNE models to the AVR-Score.

Model	*N*	Procedures included	Single-sample validation		Mortality rate (%)	
			ROC (95% CI)	H—L *p*-value	Observed	Expected (95% CI)
NWQIP	3306	AVR ± CABG	0.77 (0.73, 0.82)	0.002	3.63[a]	6.92 (6.63, 7.22)
NNE	3306	AVR ± CABG	0.77 (0.73, 0.81)	0.002	3.63[a]	3.58 (3.44, 3.71)
AVR-Score	3544	AVR ± CABG ± MVR	0.78 (0.77, 0.79)	0.46	4.15[b]	4.16 (3.48, 4.84)

AVR: aortic valve replacement; CABG: coronary artery bypass graft; CI: confidence interval; H—L: Hosmer—Lemeshow; MVR: mitral valve replacement; ROC: receiver operating characteristic; NWQIP: North West Quality Improvement Program; and NNE: Northern New England Cardiovascular Study.

[a] In-hospital mortality only.

[b] Composite of in-hospital and 30-day mortality.

mortality, further implying that such procedures may no longer pose extra risk in patients undergoing AVR in contemporary populations.

The benefit of using bootstrap aggregating 'bagging' technique in cardiac risk models has been highlighted in several recent studies [16,23]. The methodological approaches for 'bagging' ensured the selection of highly robust variables into our final model, whilst ascertaining reliable results in model validation. Our AVR-Score comprised predictors that were concordant with those found in recent AVR-dedicated risk models developed by the NWQIP [12] and the NNE [13] cohorts. Both models employed bootstrap methods at either variable selection or model validation stages of model development. The AVR-Score, on the other hand, was strengthened by use of bootstrap-repeated sampling at both variable selection and model validation stages.

According to our results, the AVR-dedicated models by the NWQIP and NNE groups fitted poorly in our cohort (H—L *p*-value <0.05). The NNE model, in particular, was based on an 'earlier' (1991—2003) multicentre cohort of 5793 AVR ± CABG patients, which may have affected its capacity to calibrate well in our contemporary population. In addition, upon further comparison of the two cohorts, it was apparent that the NNE group had higher proportions of urgent surgeries (41.4% vs 21.9%), history of chronic heart failure (51.7% vs 26.1%) and patients with a high NYHA classification (NYHA III: 51.3% vs 39.9% and NYHA IV: 17.7% vs 9.4%) compared with the ASCTS cohort. The original NWQIP cohort by contrast was fairly recent (2001—2008) and comprised 4550 AVR ± CABG patients, who also displayed baseline characteristics similar to the ASCTS cohort. Nevertheless, the NNE model yielded a more accurate estimate of overall risk of in-hospital mortality than the NWQIP model (Table 6).

In contrast to examining patients' in-hospital-mortality status only, we analysed a composite of in-hospital and 30-day mortality outcomes following AVR. This, in essence, may be more practical and conform to the guidelines [24] that advocate the inclusion of a time-related end point (30, 60, 90 days, etc.). Edwards and colleagues [25] also highlighted that the 30-day mortality outcome in patients undergoing heart valve replacement contributes to approximately 56—57% of deaths observed at 1-year post procedure, based on a series of factors (e.g., sex, age, position of valve lesion, primary or redo surgery and prosthesis type). Thus, 30-day risk prediction models could prove useful in the estimation of survival at 12 months following surgery. Nevertheless, morbidity may now present an increasingly appealing end point in modern cardiac risk models due to increasing survival rates following cardiac surgery across the board. However, such studies may be prone to bias, unless based on cohorts comprising large numbers of homogenous morbidity end points, relative to the size of the study population.

Limitations of the current study may be the relatively limited number of AVR cases in the ASCTS database. However, with over 22 institutions currently contributing to the data set, and the analysis being undertaken after 7 years of collection, one may argue that further delay may result in the lack of a contemporary data set for development. Other limitation of the AVR-Score could extend to its reliability in comparing provider performance across centres. The need for a national benchmark for AVR could perhaps be addressed in future studies, using hierarchical or multilevel models that control for non-random variation in observations within institutions. Nevertheless, the AVR-Score at present could prove a valuable tool for identifying 'high risk' candidates for TAVI and for improving the overall management of severe AS in the elderly and highly morbid patients.

6. Conclusion

This study confirmed that a locally derived AVR risk prediction model has better calibration in a local AVR cohort. We also found that most predictors identified were consistent with existing literature. The strength of our final model, AVR-Score, compared with existing models is the application of the bootstrap method in both variable selection and model validation stages of model development. We anticipate many potential benefits from the use of the AVR-Score as a bedside tool for risk evaluation, including greater awareness amongst clinicians of the preoperative risk factors truly associated with early mortality following AVR in adults and the validation of clinical decisions for surgery versus trans-catheter intervention in high-risk patients.

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French B, Hewitt N; *Mater Health Services*: Diqer AM, Archer J; *Monash Medical Centre*: Smith J, Baxter H; *Prince of Wales Hospital*: Wolfenden H, Weerasinge D; *Royal Melbourne Hospital*: Skillington P, Law S; *Royal Prince Alfred Hospital*: Wilson M, Turner L; *St George Hospital*: Fermanis G, Redmond C; *St Vincent's Hospital, VIC*: Yii M, Newcomb A, Mack J, Duve K; *St Vincent's Hospital, NSW*: Spratt P, Hunter T; *The Canberra Hospital*: Bissaker P, Butler K; *Townsville Hospital*: Tam R, Farley A; and *Westmead Hospital*: Costa R, Halaka M.

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Appendix I: Proposed MBS descriptor for TAVI

Box I.1 Proposed MBS item descriptor for Transcatheter Aortic Valve Implantation (226)

Category 3 – Therapeutic Procedures

MBS XX
Transcatheter aortic valve replacement for the treatment of symptomatic severe aortic stenosis in a suitable patient formally assessed by a heart MDT to have an unacceptably high risk for surgical aortic valve replacement.
(Anaes.) (Assist.)
(i) Percutaneous approach

Explanatory notes
A multidisciplinary 'heart team' is required to formally document approval regarding the patient's suitability for treatment. The core personnel of the heart team should include an interventional cardiologist, a cardiothoracic surgeon and a TAVI nurse / case manager. The multi-disciplinary extended team could additionally include: a general cardiologist, a cardiac anaesthetist, an imaging cardiologist / radiologist, an intensive care physician, a geriatrician or general physician and a vascular surgeon.

In most cases, this item is claimable once per lifetime. In a small subset of patients where a repeat procedure is indicated; formal documentation of reassessment and consensus approval by the heart team is required.

Fee: $1,909.60

Category 3 – Therapeutic Procedures

MBS XX
Transcatheter aortic valve replacement for the treatment of symptomatic severe aortic stenosis in a suitable patient formally assessed by a heart MDT to have an unacceptably high risk for surgical aortic valve replacement.
(Anaes.) (Assist.)
(i) Minimally invasive surgical approach

Explanatory notes
A multidisciplinary 'heart team' is required to formally document approval regarding the patient's suitability for treatment. The core personnel of the heart team should include an interventional cardiologist, a cardiothoracic surgeon and a TAVI nurse / case manager. The multi-disciplinary extended team could additionally include: a general cardiologist, a cardiac anaesthetist, an imaging cardiologist / radiologist, an intensive care physician, a geriatrician or general physician and a vascular surgeon.

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