MONASH University

Drug-eluting stent utilization and impact in contemporary Australian interventional cardiology practice: insights from the Melbourne Interventional Group Registry

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Summary

Percutaneous coronary intervention (PCI) has undergone tremendous progress over the last decade. The introduction of drug-eluting stents (DES) in 2003 represented one of the most important technical advances in interventional cardiology since the first PCI was performed in 1977. Drug-eluting stent was developed to address the limitation of restenosis encountered with earlier generation bare-metal stents. Although proven to be effective in clinical trials, the safety and efficacy of DES use in 'real-world' clinical practice remains uncertain in circumstances not tested in randomized trials in the current era of expanding use of PCI.

This thesis consists of a selection of published work based on data from the Melbourne Interventional Group (MIG) PCI registry pertaining to (i) evaluate the pattern of DES use in "real-world" PCI practice in Australia; (ii) address the concern of late stent thrombosis associated with DES; (iii) assess the efficacy and safety of DES in clinical circumstances and populations where evidence is lacking such as the elderly, high and low risk coronary lesion subsets; (iv) compare risk profile and outcomes of PCI with coronary artery bypass grafting; and (v) comparison with other Asia-Pacific countries to investigate regional differences in clinical characteristics and PCI outcomes.

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Declaration

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.

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Abstract Presentations

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Thesis including published works 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 10 original papers and 2 review papers published in peer reviewed journals. The core theme of the thesis is drug-eluting stent use in Australian practice. The ideas, development and writing up of all the papers (except the first paper) in the thesis were the principal responsibility of myself, the student, working within the Department of Epidemiology and Preventive Medicine under the supervision of Prof. Chris Reid, A/Prof. Andrew Ajani and the late Prof. Henry Krum

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 2-8, my contribution to the work involved the following:

Thesis Chapter	Publication Title	Status	Nature and % of student contribution	Co-author name(s) Nature and % of Co-author's contribution	Co-author(s) Monash student
2	The Foundation and Launch of the Melbourne Interventional Group: A Collaborative Interventional Cardiology Project	Published	10%. Concept and collecting data and revision of draft	Ajani AE (20%), Szto G (2%), Duffy SJ (10%), Eccleston D (2%), Clark DJ (10%), Lefkovits J (2%), Chew DP (2%), Warren R (2%), Black A (2%), New G (4%), Walton A (2%), Lew R (2%), Shaw J (2%), Horrigan M (2%), Sebastian M (2%), Brennan A (4%), Meehan A (2%), Reid C (10%), Krum H (10%).	*No*
3	Use of Drug-Eluting Stents in Victorian Public Hospitals	Published	60%. Concept and collecting data and writing first draft	Ajani AE (5%), Duffy SJ (2%), New G (2%), Horrigan M (2%), Szto G (2%), Walton A (2%), Eccleston D (2%), Lefkovits J (2%), Black A (2%), Sebastian M (2%), Brennan AL (2%), Reid CM (5%), Clark DJ (10%).	*No*
3	Recent trends in Australian percutaneous coronary	Published	60%. Concept and collecting data and writing first draft	Ajani AE (20%), Clark DJ (2%), Duffy SJ (2%), Andrianopoulos N (2%), Brennan AL	*No*

	intervention practice: Insight from the Melbourne Interventional Group Registry.			(2%), Loane P (2%), Reid CM (10%).	
3	The Asia Pacific Evaluation of Cardiovascular Therapies (ASPECT) Collaboration - Improving the Quality of Cardiovascular Care in the Asia Pacific Region	Published	50%. Concept, collecting data and revision of draft	Reid CM (30%), Wan Ahmad WA (2%), Bang LH (2%), Hian SK (2%), Chua T (2%), Chan M (2%), Beltrame J (2%), Duffy SJ (2%), Brennan A (2%), Ajani A (2%)	No
4	Clinical characteristics and early mortality of patients undergoing coronary artery bypass grafting compared to percutaneous coronary intervention: Insights from the Australasian Society of Cardiac and Thoracic Surgeons (ASCTS) and the Melbourne Interventional Group (MIG) registries.	Published	60%. Concept and collecting data and writing first draft	Clark DJ (10%), Buxton B (2%), Ajani AE (2%), Smith JA (2%), Duffy SJ (2%), Shardey GC (2%), Skillington PD (2%), Farouque O (2%), Yii M (2%), Yap CH (2%), Andrianopoulos N (5%), Brennan A (2%), Dinh D (2%), Reid CM (5%)	*No*
4	Does prior percutaneous coronary intervention adversely affect early and mid-term survival after coronary artery surgery?	Published	50%. Concept and collecting data and writing first draft	Yap CH (20%), Akowuah E (2%), Dinh DT (2%), Smith JA (2%), Shardey GC (2%), Tatoulis J (2%), Skillington PD (2%), Newcomb A (2%), Mohajeri M (2%), Pick A (2%), Seevanayagam S 2%), Reid CM (10%)	*No*
5	An Evaluation of Octogenarians Undergoing Percutaneous Coronary Intervention from	Published	65%. Concept and collecting data and writing first draft	Gurvitch R (2%), Duffy SJ (2%), Clark DJ (2%), Sebastian M (2%), New G (2%), Warren R (2%), Lefkovits J (2%), Lew	*No*

	the Melbourne Interventional Group (MIG) Registry			R (2%), Brennan AL (2%), Reid C (5%), Andrianopoulos N (2%), Ajani AE (10%)	
6	Contemporary treatment of in-stent restenosis and the incidence of recurrent in-stent restenosis in the era of drug-eluting stents.	Published	70%. Concept and collecting data and writing first draft	Ajani AE (10%), Clark DJ (2%), Eccleston D (2%), Walton A (2%), Lew R (2%), Meehan A (5%), Brennan A (2%), Reid C (3%), Duffy SJ (2%)	*No*
6	Drug-eluting stents for the treatment of in-stent restenosis: A clinical review	Published	80%. Concept and collecting data and writing first draft	Ajani AE (10%), Waksman R (10%)	*No*
7	Are drug-eluting stents indicated in large coronary arteries? Insights from a multi-centre percutaneous coronary intervention registry.	Published	60%. Concept and collecting data and writing first draft	Ajani AE (5%), New G (2%), Duffy SJ (2%), Farouque O (2%), Shaw J (2%), Sebastian M (2%), Lew R (2%), Brennan A (2%), Andrianopoulos N (5%), Reid C (5%), Clark DJ (10%)	*No*
8	Rates of Stent Thrombosis in Bare-Metal versus Drug-eluting Stents (From a Large Australian Multi-Center Registry).	Published	60%. Concept and collecting data and writing first draft	Duffy SJ (5%), Clark DJ, Lefkovits J (2%), Warren R (2%), Gurvitch R (2%), Lew R (2%), Sebastian M (2%), Brennan A (5%), Andrianopoulos N (5%), Reid CM (5%), Ajani AE (10%)	*No*
8	Double Jeopardy: Balance between bleeding and stent thrombosis with prolonged dual-antiplatelet therapy after drug-eluting stent implantation	Published	90%. Concept and collecting data and revision of draft	Gurvitch R (5%), Ajani AE (5%)	*No*

**If no co-authors, leave fields blank*

I have not renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

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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.

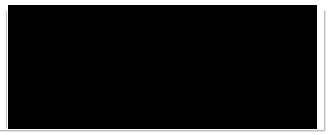
Main Supervisor signature:  **Date:** 18 Jul 2017

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TABLE OF CONTENTS

ABBREVIATIONS

ASPECT = Asia Pacific Evaluation of Cardiovascular Therapies Collaboration

BMS = Bare-metal stent

CABG = Coronary artery bypass graft

CAD = Coronary artery disease

CCRE = Monash Centre of Cardiovascular Research & Education

DAPT = Dual antiplatelet therapy

DES = Drug-eluting stent

ISR = In-stent restenosis

LST = Late stent thrombosis

MACE = Major adverse cardiovascular events

MIG = Melbourne Interventional Group

PCI = Percutaneous coronary intervention

RCT = Randomized controlled trial

TVR = Target vessel revascularization

CHAPTER 1: OVERVIEW

Since the first percutaneous transluminal coronary angioplasty by Andreas Gruentzig (1) in 1977, this rapidly evolving procedure has become the most common method of revascularization for patients with symptomatic coronary artery disease (CAD). (2, 3) Two key technological advances after the introduction of balloon angioplasty that have improved outcomes following PCI are bare-metal stents (BMS) in the 1980s and drug-eluting stents (DES) since 2002. A DES is a BMS that slowly release a drug such as paclitaxel, sirolimus and everolimus to block cell growth. This prevents smooth muscle cell proliferation and fibrosis that could block the stented artery, a process called neointimal hyperplasia leading to in-stent restenosis (ISR). In-stent restenosis has been a major limitation of PCI with BMS where up to 30-50% required repeat revascularization as a consequence of ISR (4). In clinical trials, rates of target vessel revascularization (TVR) with DES are approximately 10%; however, “real world” TVR rates in routine clinical practice may differ (4).

A critical appraisal of early DES randomized controlled trials (5) suggested the impressive clinical benefits of DES were subject to overestimation owing to (i) inferior BMS comparators in these trials which used older stent designs associated with higher restenosis risk than currently available stents; (ii) protocol-mandated coronary angiography within the first 12 months biased TVR rates against the BMS group because of visualization of asymptomatic lesions that would not otherwise have warranted repeat intervention; (iii) studies underpowered to assess myocardial infarction and mortality and (iv) underestimated the risk of very late stent thrombosis (LST) as most early pivotal trials were short in duration (9 to 12 months). In a recent randomized controlled trial of current era DES and BMS, the relative and absolute reduction in TVR rates associated with DES were 24% and 3.3%, respectively; but there were no significant differences in rates of death or myocardial infarction at 6 years follow-up (6).

About 34,000 PCIs are performed in Australia each year and this number is growing because of increasing prevalence of coronary artery disease in our rapidly ageing population (7). Unresolved issues potentially offsetting the benefits of DES include (i) concern about LST due to delayed endothelialization (i.e. healing) by anti-proliferative drugs; (ii) rising use of DES in clinical situations where evidence is lacking (e.g. elderly); (iii) preferential use of PCI in low-risk populations (e.g. large vessels) and (iv) limited cost-effectiveness of DES and data comparing PCI with other treatments. In an era of expanding use of PCI in clinical circumstances not tested in randomised trials, data collected in a “real-world” registry which uses contemporary techniques, clinically driven revascularization and designed to capture late adverse events could address some of the above issues to ensure safe and appropriate evidence-based use of DES that is relevant to local clinical practice. The data collected will also enable monitoring of institutional and professional performance, identifying needs gaps in PCI services, guiding quality improvement initiatives and informing resource allocation.

CHAPTER 2: MELBOURNE INTERVENTIONAL GROUP REGISTRY

"Observational studies (including registries) and randomised trials provide complementary evidence about the effects of treatment on mortality and major morbidity." (8)

- McMahon, Lancet, 2001

Although randomized controlled trials (RCT) remain the gold standard for determining efficacy of PCI, extrapolating trial results to routine clinical practice is limited by (i) selection bias that often exclude high-risk patients with complex disease encountered in routine clinical practice; (ii) rapid improvement in PCI technology that outpace trial protocols; (iii) insufficient study power to determine PCI effects among different patient subgroups or clinical settings; (iv) limited generalizability of results achieved in PCI centers of excellence participating in trials; (v) misperception between prognostic endpoints (i.e. avoidance of death or re-infarction) with quality-of-life endpoints (i.e. avoidance of target vessel revascularization as a marker of angina-free status) within composite outcomes; (vi) inadequate sample size to detect rare but important long-term adverse outcomes such as LST.

Most developed countries have registries that enroll and evaluate large numbers of patients undergoing coronary interventions. The Melbourne Interventional Group (MIG) Registry was established in 2004 as a collaborative venture of interventional cardiologists practicing at 7 public hospitals in Melbourne, designed to prospectively record data pertaining to PCI and to perform long-term follow-up. The MIG registry longitudinally tracks patient outcomes in relation to baseline patient characteristics, indications for intervention, coronary anatomy and procedural techniques. Such a registry could detect trends in PCI practice and adverse events, monitoring of procedural safety and efficacy; and benchmarking of PCI performance against similar registries around the world. Such registries can contribute to quality of care by providing data feedback on a wide range of

performance metrics to participating canters and facilitate local and regional quality improvement efforts. The MIG registry is coordinated by the Monash Centre of Cardiovascular Research & Education (CCRE), Department of Epidemiology and Preventive Medicine at the Monash University, Melbourne.

The paper in this chapter describes the foundation and design of the MIG registry (**Appendix 1**). Demographic, clinical, procedural characteristics and inpatient outcomes on consecutive patients undergoing PCI are documented in a standardised case report form with clear definitions provided. The MIG v4.1 Data Collection Form (**Appendix 2**) has been developed base on the American College of Cardiology (ACC): National Cardiovascular Data Registry® (NCDR) Cath Lab Module v3.04 Data Collection Form and v3.02 Data Definitions (9). The MIG registry employs an 'opt-off consent' which requires the patient to sign a declaration only if they refuse to contribute their relevant information, or do not want to be followed up beyond the coronary intervention. This method also assists in minimizing the "Hawthorne effect" (i.e. a phenomenon in observational research where outcome variables are affected by the fact that the participants of the study know they are participating in the study). An independent audit of 10 randomly selected verifiable fields from 3% of all patients enrolled from each site by an investigator not affiliated with that institution demonstrated 96.6% overall data accuracy (10).

I was involved in planning and revision as a co-author of this paper (**Appendix 1**) and I contributed to the design and revision of the Data Collection Form (**Appendix 2**).

CHAPTER 3: PCI TRENDS & PATTERN OF DRUG-ELUTING STENT USE

Uptake of DES in Australia was rapid after their introduction in 2003 with use as high as 90% in some hospitals (11). Due to significant incremental costs associated with DES compared to BMS at the time, the Victorian Department of Human Services (DHS) recommended restricting the use of DES for 30% to 40% of PCI performed in public hospitals. Clinical guideline for the use of DES was developed by the DHS together with a working group of cardiologists from hospitals across Victoria to reserve DES for patients at the highest risk of restenosis who would theoretically derive the greatest benefit. These criteria included (i) diabetes mellitus; (ii) target vessel diameter ≤2.5mm; (iii) lesion length ≥20mm; (iv) bifurcation lesion; (v) chronic total occlusion; (vi) ostial lesion; (vii) in-stent restenosis.

In the first 2 papers, we evaluated the pattern of DES use between 2004 and 2007 in Victorian public hospitals (**Appendix 3 & 4**). The second paper further examined overall PCI practice and outcome trends in the era of DES (**Appendix 4**). The third paper compared DES use between different Asian-Pacific countries to investigate regional differences in clinical characteristics. (**Appendix 5**).

In Victorian public hospitals participating in the MIG registry, 66.2% of PCI were eligible for DES according to DHS guidelines (as above) but only 45.3% of PCI received a DES between 2004 and 2005. In accordance to the DHS guidelines, DES was predominantly used in patients at high risk of restenosis (87.7%). However, DES was also used in 16.5% of cases without criteria and a BMS was used in 39.9% of cases with criteria for DES. This was the first paper to document the pattern of DES use in Australian practice (**Appendix 3**).

In a follow-up study, we evaluated the temporal trend in PCI practice and 12-month clinical outcomes between 2004 and 2008 (**Appendix 4**). During this period, the use of DES declined steadily from 53.9% in 2004-2005 to 32.0% in 2007-2008, despite increases in lesion complexity and patient risk profile. Despite the reduction in DES use, there were no significant differences in 12-month clinical outcomes across the years. This may have reflected better selection of DES for patients at high risk of restenosis (as per Victorian Department of Human Services criteria) and were expected to derive the most benefit from DES. At the time of publication, this was the largest study of Australian PCI practice trends in the era of DES and the first to show that selective use of DES was an independent predictor of better 12-month clinical outcomes.

In the final paper, the Asia Pacific Evaluation of Cardiovascular Therapies (ASPECT) Collaboration collected PCI data from existing registries from Australia, Hong Kong, Malaysia and Singapore involving >56,000 patients in 30 hospitals with aims to (i) understand differences in patient and procedural characteristics; (ii) develop ethnic specific risk adjustment model and (iii) compare outcomes of patients undergoing PCI across the Asia Pacific Region (**Appendix 5**). In Australia, both the MIG (n=20,556) and the Coronary Angiography Registry Database of South Australia (CADOSA) registries (n=1001) contributed. Differences in patients and procedural characteristics were noted across the region. In Australia, DES was used in <50% of procedures compared to the highest rates of DES use reported in Hong Kong. As there was no standard indication for the choice of DES versus BMS across the region, these differences may be related to local guidelines or policy, funding requirements, or operator selection.

I was the principal author for the first and second paper (**Appendix 3 & 4)** and equal first author for the third paper (**Appendix 5)**. I was responsible for the design, analysis and writing of these papers. Prof. Andrew Ajani and Chris Reid were involved in the revision process.

CHAPTER 4: PCI vs. CABG IN THE ERA OF DRUG-ELUTING STENTS

Coronary artery bypass grafting (CABG) and PCI are alternative strategies for the treatment of CAD. Generally, CABG is the preferred strategy in patients with left main or triple-vessel coronary disease with reduced left ventricular function (12). PCI is generally preferred in patients with single- or double-vessel disease (13). The major limitation of PCI with BMS compared to CABG has been a greater need for repeat revascularization due to ISR (14). The introduction of DES has significantly reduced ISR and the need for repeat revascularization. In a recent meta-analysis of 6 randomized trials and 4,686 patients with unprotected left main CAD, PCI was associated with greater rates of unplanned revascularization but similar rates of mortality compared with CABG at a median follow-up of 39 months (15). In patients with low SYNTAX score, PCI was associated with lower mortality and conversely, CABG was associated with lower mortality in patients with high SYNTAX score. As a result, PCI with DES is increasingly performed in more complex lesions and patients who have traditionally been referred for CABG.

The first paper compared clinical characteristics, in-hospital and 30-day outcomes between patients who underwent isolated CABG and patients who underwent PCI (**Appendix 6**). Despite the introduction of DES, CABG remained the preferred strategy for patients with multi-vessel disease, especially triple vessel-disease with reduced left ventricular function. However, approximately 60% of PCI were performed on patients with multi-vessel disease and it was not known whether multi-vessel PCI or complete revascularization was performed on these patients. We found the risk profile of patients undergoing CABG were different to that of patients having PCI in the era of DES. Patients who underwent PCI had a higher incidence of recent myocardial infarction within 7 days as the indication for revascularisation. On the other hand, patients who underwent CABG had a higher incidence of diabetes mellitus, heart failure, multi-vessel coronary artery disease

and stroke. In-hospital and 30-dat mortality rates were low (<2%) and similar between PCI and CABG. Independent predictors of short-term mortality also differed between treatment strategies. In the CABG group, prior CABG was the strongest predictor of 30-day mortality (OR 6.56, 95%CI 2.43-17.31).

As increasing numbers of patients undergoing CABG have previously undergone PCI, the second paper evaluated the impact of previous PCI on CABG outcomes (**Appendix 7**). We analyzed consecutive first-time isolated CABG procedures within the Australasian Society of Cardiac and Thoracic Surgeons Database from June 2001 to May 2008. Of 13,184 patients who underwent CABG, 11.1% had prior PCI and we found no significant differences in major adverse cardiovascular outcomes between treatment modalities with a mean follow-up of 3.3 years. We concluded that prior PCI was not associated with increased short- or mid-term mortality after CABG.

I was the principal author for the first paper (**Appendix 6)** and equal first author for the second paper (**Appendix 7)**. I was responsible for the design, analysis and writing both papers. Prof. Andrew Ajani and Chris Reid were involved in the revision process.

CHAPTER 5: DRUG-ELUTING STENT USE IN HIGH-RISK PATIENT SUBSETS

The world's population is rapidly ageing and as the number of elderly increases, the burden of CAD is set to grow. Percutaneous coronary intervention is a well-established treatment for symptomatic CAD but elderly patients are less likely to undergo revascularization than younger patients despite more extensive CAD (16, 17). Age alone is often the main reason why PCI is avoided. Moreover, elderly patients are often frail and have multiple comorbidities which increase their risks associated with PCI (18, 19). Over the last decade, advancements in PCI outcomes have led to increasing number of elderly patients undergo revascularization (20). Evidence-based data to guide coronary revascularization has been limited in clinical trials which generally under-represent elderly patients. Recently, 2 randomized studies evaluated the use of DES compared to BMS in elderly patients >75 years of age (21, 22). Both studies showed DES with a short duration of dual antiplatelet therapy was associated with better safety and efficacy benefits compared to BMS. However, there remains limited data pertaining to octogenarians undergoing PCI in 'real world' clinical practice.

In this paper, we examined clinical outcomes of elderly patients undergoing PCI in the MIG registry (**Appendix 8**). In this paper, octogenarians comprised a significant cohort (11.3%) of all patients undergoing PCI. Octogenarians had more complex coronary artery lesions and multi-vessel disease. Procedural success rates were lower and complication rates were higher compared to patients <80 years. Overall, mortality was four times higher in octogenarians at 30 days and 12 months. Higher risk clinical presentation such as ST-elevation myocardial infarction and cardiogenic shock and the presence of comorbidities such as chronic renal failure were more predictive of 12-month mortality than age per se. By contrast, there were no significance differences in MACE rates in octogenarians who

presented with stable angina. In the era of DES, incidence of TVR at 12 months remained low and similar between the 2 age groups. This paper demonstrated that age per se should not deter against PCI and thorough clinical evaluation is mandatory in selecting elderly patients who would gain the most clinical benefit from an invasive approach (compared with conservative management) because of their higher baseline risk.

In this paper, I was the principal author responsible for designing the study, performing the statistical analyses and subsequently writing the paper (**Appendix 8**). I was aided by Prof. Chris Reid and Andrew Ajani in the revision process.

CHAPTER 6: DRUG-ELUTING STENT USE IN HIGH-RISK LESION SUBSETS

In-stent restenosis remains a major limitation of PCI with BMS with reported rates of ISR in 10% to 50% of patients (23, 24). The optimal treatment of ISR remains uncertain with high rates of recurrence from 30% to 80% (25). Drug-eluting stents have significantly reduced the incidence of ISR and are more effective than angioplasty alone or repeat BMS for the treatment of ISR (26, 27).

In the 2 papers in this chapter, the challenging subgroup of ISR lesions is examined (**Appendix 9 & 10**). In the first paper, we assessed the treatment of ISR and rates of recurrent ISR in the era of DES from the MIG Registry (**Appendix 9**). The majority of ISR occurred after BMS (87%) and was treated with additional DES in almost all cases (98%). The incidence of recurrent DES restenosis was low (5%) at 12 months. Our study suggested that DES was effective, safe and the preferred treatment for ISR.

In the second paper, the treatment of ISR with DES was reviewed (**Appendix 10**). The efficacy of DES in complex ISR (i.e. diabetic patients, diffuse pattern, recurrent ISR) was less effective than in focal ISR or de novo lesions. Drug-eluting stents was likely to become the predominant treatment strategy for BMS ISR because of their ease of use and availability. Although the incidence of ISR in DES was low, the management of DES restenosis will be an ongoing challenge as DES use becomes more widespread.

I was the principal author for the second paper (**Appendix 10**) and equal first author for the first paper (**Appendix 9**). I was responsible for the design, analysis and writing both papers. Prof. Andrew Ajani was involved in the revision process.

CHAPTER 7: DRUG-ELUTING STENT USE IN LOW-RISK PATIENT SUBSETS

Drug-eluting stents have been shown to be superior to BMS in reducing restenosis in most types of coronary lesions (28). However, in patients at low risk of restenosis such as large coronary arteries ≥3.5mm where restenosis rates are low (<10%), the absolute benefit from DES in these low risk patients may be attenuated (29, 30). Subgroup analyses of randomized trials have shown modest differences in clinical outcomes between BMS and first generation DES in large vessels (27, 30-33). A recent randomized controlled trial of 2,314 patients requiring 3mm or larger stents demonstrated significant benefits of newer second generation DES in TVR reduction but no significant differences in death or myocardial infarction compared to BMS (34). On the other hand, there are risks of bleeding associated with the need for prolonged dual-antiplatelet therapy (DAPT) after DES implantation. (35-37)

In this paper, 12-month clinical outcomes were compared between BMS and DES implantation in large native coronary vessels ≥3.5mm from the MIG registry (**Appendix 11**). Our findings were consistent with results from randomized studies and other large registries which found little or no significant benefit of DES in large coronary arteries (27, 30, 31, 38-41). Based on our results, in patients with large coronary vessels, one must weigh the risk of restenosis against the potential risk of stent thrombosis, the need for prolonged anti-platelet therapy and incremental cost with DES compared to BMS. Further studies are warranted to establish whether there is a subgroup of patients with large vessels who may benefit more from DES.

I was the principal author of the paper (**Appendix 11**). I was responsible for the design, analysis and writing both papers. Prof. Andrew Ajani and Dr. David Clark were involved in the revision process.

CHAPTER 8: LONG-TERM OUTCOMES OF DRUG-ELUTING vs. BARE-METAL STENTS IN REAL WORLD CLINICAL PRACTICE

The main benefits of DES compared with BMS included reduction in occurrence of ISR and the need for subsequent repeat revascularization. An early comprehensive analysis of 38 randomized controlled trials in 18,023 patients confirmed a 58%–70% reduction in restenosis-related repeat revascularization with DES compared to BMS (28). In a recent randomized controlled trial of current era DES and BMS, the relative and absolute reduction in TVR rates associated with DES were 24% and 3.3%, respectively; but there were no significant differences in rates of death or myocardial infarction at 6 years follow-up (6). Although proven to be effective in clinical trials, it remains uncertain as to whether current DES and PCI use reflects evidence-based medicine in maximizing population health in 'real world' clinical practice. Little is known about long-term outcome trends in the era of DES in Australia.

In the first paper, we evaluated PCI practice trends and 12-month clinical outcomes in consecutive patients undergoing 9,204 PCI between 2004 and 2008 (**Appendix 4**). Over the study period, we observed steadily high procedural success rates and low rates of adverse clinical outcomes at 12 months despite increasing risk profile of patients undergoing PCI and lesion complexity. Interestingly, this was achieved with declining use of DES from 53.9% in 2004 to 32.0% in 2007 (in line with the Victorian Department of Human Services recommendation for 30%-40% DES at the time). Drug-eluting stent was an independent predictor of 12-month major adverse cardiac events (odds ratio 0.68, 95% confidence interval 0.56-0.81, $p<0.01$) which was expectedly driven by reduction in TVR. There were no significant differences in terms of mortality and myocardial infarction rates between DES and BMS at 12 months.

Concerns over the safety of DES linked to the risk of late (>30 days) and very late (>12 months) stent thrombosis were first raised in 2004 as a consequence of drug induced

delayed healing and impaired endothelialization of stent struts (42). Delayed endothelialization prolongs the period of thrombogenic risk and raises the susceptibility of DES to late stent thrombosis (LST). Compared with restenosis, LST is uncommon but carries a much higher risk of myocardial infarction (70% vs. 10%), with mortality rates between 31% and 45% (43, 44). This was a particular pertinent question to address because DES use was restricted by the Victorian Department of Human Services to those at high of restenosis (such as those with diabetes mellitus, long and complex lesions and small vessels) who may also be at higher risk of LST which may offset the benefits in reducing restenosis. A substantial body of research has focused on determining the magnitude of these competing events, often reaching contradictory results even with analyses of the same data. Although larger, adequately powered, randomized trials are needed to fully assess the net clinical effects of DES compared with BMS, the evidence seems to suggest that the net clinical benefit of DES may outweigh their risks. Meta-analyses to date have demonstrated a risk of LST (excess of 0.5%) at 12 months in DES patients compared with BMS patients (4). However, findings of randomised clinical trials so far have not shown that DES result in excess mortality after 4-5 years of follow-up (45).

In the second paper, we evaluated the incidence of LST after DES and BMS (**Appendix 12**). The overall incidence of LST (1.0%) was low and most were classified as possible stent thrombosis according to the definitions by the Academic Research Consortium where (i) definite stent thrombosis requires the presence of an acute coronary syndrome with angiographic or autopsy evidence of thrombus or occlusion; (ii) probable stent thrombosis included unexplained deaths within 30 days after PCI or acute myocardial infarction involving the target-vessel territory without angiographic confirmation and (iii) possible LST included all unexplained deaths occurring >30 days after PCI (44). Using these definitions may have overestimated our rates of LST. It was reassuring that use of DES in patients at high risk of restenosis in our study was not associated with increased

risk of LST, mortality or myocardial infarction compared to BMS. Although longer term follow-up beyond 12 months is imperative to evaluate the continuing risk of very LST, extremely large-scale randomized trials comparing DES and BMS would be needed to address this issue which is unlikely to be performed. Therefore, large 'real-world' registries such as the MIG registry remain invaluable in the assessment of late and very late stent thrombosis.

Prolonged dual anti-platelet therapy (DAPT) up to 12 months with aspirin and clopidogrel has become the standard of care after first generation DES to prevent stent thrombosis (46). Compared with first-generation DES, newer-generation DES have improved safety profile and lower risk of LST. Therefore, current guideline recommend shorter-duration DAPT can be considered for patients at lower ischemic risk (e.g. stable angina) with high bleeding risk, whereas longer-duration DAPT may be reasonable for patients at higher ischemic risk (e.g. ACS) with lower bleeding risk (46). A recent meta-analysis of 11 randomized controlled trials demonstrated no significant differences in incidence of death, myocardial infarction stent thrombosis between 12-months and 3 to 6 months DAPT (47).

In the second paper, we reaffirmed the absence of clopidogrel was a strong predictor of all (OR 3.94, 95% CI 1.61-10.31) and early (OR 16.39, 95% CI 3.89-71.43) thrombosis in first-generation DES (**Appendix 12**). In the third paper, we highlighted the concern of increased risk of bleeding with prolonged DAPT after DES and the potential risk of stent thrombosis if dual antiplatelet therapy is prematurely discontinued or interrupted (**Appendix 13**). The increased risk of bleeding is an important issue for patients who need to undergo cardiac or non-cardiac surgery. In patients undergoing CABG, exposure to clopidogrel markedly increase post-operative bleeding, transfusion requirement and re-exploration rates nearly 10-fold (48-50). Cessation of clopidogrel may be required up to 10 days before surgery because recovery of platelet function can occur 7-10 days after

discontinuation of clopidgrel (51). In the absence of data on how best to manage anti-platelet therapy after DES implantation in the peri-operative period, we advocated the need to balance the perceived risk of stent thrombosis by interrupting and the risk of severe bleeding by continuing DAPT on a case-by-case basis.

I was the principal author of all 3 papers (**Appendix 4, 12 & 13)**. I was responsible for the design, analysis and writing all 3 papers. Prof. Chris Reid was involved in the revision process of the first 2 papers and Prof. Andrew Ajani in all 3 papers.

CHAPTER 9: CONCLUSIONS AND FUTURE DIRECTIONS

Over the last decade, PCI has become the most common revascularization treatment for coronary artery disease in Australia. Drug-eluting stents represent one of the most important advances in PCI technology which has significantly reduce the occurrence of in-stent restenosis and need for repeat intervention compared to BMS. This thesis aimed to analyze data from a prospective PCI registry to address some unresolved issues regarding the use of DES in “real world” clinical practice where evidence is lacking.

The MIG registry is the first large-scale prospective multi-center Australian PCI registry with long-term follow-up that reflect “real-world” clinical practice (**Appendix 1 & 4**). From 2004 to 2008, the use of DES steadily declined from 50% to 30% despite increasing patient risk profile and lesion complexity (**Appendix 4**). Drug-eluting stents were predominantly used for patients at high risk of restenosis but up to a third of patients with indication for DES received a BMS (**Appendix 3**). In the era of DES, CABG remained the preferred strategy for patients with 3-vessel disease and should be considered complementary to PCI for patient with different risk profile (**Appendix 6 & 7).**

Our data demonstrated that selected use of DES in patients at high risk of restenosis and BMS in lower risk population is associated with comparable clinical outcomes (**Appendix 4, 6, 7-9, 11)** and low risk of late stent thrombosis up to 12 months (**Appendix 12)**. Marginal improvement in outcomes from DES use in low risk patients is unlikely to be cost-effective.

The ASPECT Collaboration is an initiative to better understand the delivery of cardiac care and outcome for patients undergoing PCI across the Asia Pacific region. Our initial report (**Appendix 5**) raised a number of issues for further studies. Firstly, definitions differ between registries and there is a need for prospective standardization of a minimum

data set across the region. Secondly, collation of individual patient data for pooed central registry analysis was hampered by varied ethical requirements for cross-border transfer of patient information between countries. In this study, clinical information from each registry was de-identified and aggregated at the local level and then uploaded centrally to the Monash University Centre for Cardiovascular Research and Education in Therapeutics (CCRET) for data analysis. A major limitation of this approach was that individual-patient data was not available for analysis. Thirdly, patient outcomes including complications, death and repeat procedure were not available in all participating sites. Individual patient data will enable the development of ethnic or country specific risk adjustment models and benchmark quality of PCI procedures across the Asia Pacific region. Lastly, sustainable funding for registry management and analyses will be one of the major challenges facing each individual registry.

In the future, the MIG registry can become the template for a national PCI registry. Information gathered and analyzed would be of interest to cardiologists, cardiac surgeons, hospital cardiac units, hospital quality assurance and finance departments, government, health insurance funds and, most importantly, patients. Present data collection in Australia is fragmented and contains little long-term outcome information. Many PCI centres routinely collect data on PCI performed, but definitions may vary and usually only catheterization laboratory (“procedural success”) or inpatient outcomes are recorded. There is ample evidence that long-term (>12 months) patient status serves as a more comprehensive measure of procedural outcome than inpatient results. Information available from such a registry would enable clinicians and health planners to compare PCI outcomes with international standards and the opportunity to assess the clinical efficacy and cost-effectiveness of new technologies (such as DES) relevant to local clinical practice and potentially highlight any areas that need to be improved. This would ensure safer and appropriate evidence-based use of limited resources in an era of expanding use of PCI in

clinical circumstances not tested in randomized trials. These data would potentially benefit patients by providing more information that might guide their choices among treatment options to maximize return on health expenditure.

In 2012, a state-wide Victorian Cardiac Outcomes Registry (VCOR) was established to monitor the performance of health services in both the public and private sectors (52), VCOR is coordinated by Monash University in conjunction with the Victorian Cardiac Clinical Network and participating hospitals; and funded by the Department of Health, Victoria. VCOR collects procedural details and follows up on medical outcomes and complications up to 30 days. The primary focus is to provide relevant feedback to hospitals for benchmarking and to improve quality-of-care. Agreed-on analytical outputs can be used (by professional groups, consumers, health policymakers and researchers) for monitoring institutional and professional performance, identifying needs gaps in PCI services, guiding quality improvement initiatives and informing resource allocation. Additionally, patients might in the future be able to review outcomes from the MIG and VCOR PCI database and compare these with overseas PCI registries as well as the Australasian Society of Cardiac and Thoracic Surgeons (ASCTS) registry which captures complete details of treatment and follow-up care for every patient undergoing coronary bypass surgery in Victoria. Linking these databases may improve information flow to all stakeholders. Empowerment of patients with respect to knowledge of treatment options may reduce medico-legal issues. Monitoring outcomes can improve patient management by encouraging appropriate application of clinical guidelines. Finally, information available in such a database may lead to better planning of health services and infrastructure, leading to economic benefits. Ultimately, it is anticipated that this will facilitate improvement in short- and long-term outcomes for patients with coronary artery disease undergoing PCI.

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Appendix 1

ORIGINAL ARTICLE

Original Article

The Foundation and Launch of the Melbourne Interventional Group: A Collaborative Interventional Cardiology Project

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The Melbourne Interventional Group (MIG) is a voluntary collaborative venture of interventional cardiologists practicing at 12 major public and private hospitals in Victoria, designed to record data pertaining to percutaneous coronary interventions (PCI) and perform long-term follow-up. The potential advantages of collaboration involve large-scale analysis of current interventional strategies (e.g. drug-eluting stents, evaluation of new technologies and cost-effective analysis), provide a basis for multi-centred clinical trials and allow comparison of clinical outcomes with cardiac surgery. The established registry documents demographic, clinical and procedural characteristics of consecutive patients undergoing PCI and permits analysis of those characteristics at 30 days and 12 months. The registry is co-ordinated by the Centre of Clinical Research Excellence (CCRE), a research body within the Department of Epidemiology and Preventive Medicine (Monash University, Melbourne). The eventual goal of MIG is to provide a contemporary appraisal of Australian interventional cardiology practice, with opportunities to improve in-hospital and long-term outcomes of patients with coronary artery disease.

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Introduction

The ability to record clinical data pertaining to interventional coronary angioplasty procedures is the foundation for evaluating future outcomes. In Australia, the majority of institutions collect information for local use only, with varied data elements collected and variable definitions used. At present, no uniform data collection or clinical follow-up exists, indicating a need for a large-scale collaborative group. Multicentre data collection has proven to be a useful tool in examining short and long-term success, with an ability to identify variables associated with higher

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risks. These variables can ultimately be used to develop predictive risk-adjusted multivariate models.[1–4] Cardiology registries also address the gap between the highly selected type of patient enrolled in randomised clinical trials and real-world practice.[5] Retrospective analyses also bring in to play problems of missed data and recall bias; hence, prospective data collection via a central standardised registry is essential.

The Melbourne Interventional Group is a collaborative venture to record current interventional coronary procedures and perform longer term follow-up. This model is similar to the established Cardiac Surgical database (Australasian Society of Cardiac and Thoracic Surgeons).[6,7] The potential advantages of collaboration involve large-scale analysis of current interventional strategies (e.g. drug-eluting stents, evaluation of new technologies and cost-effective analysis), provide a basis for multi-centred clinical trials and allow comparison of clinical outcomes with our surgical colleagues.

Aims of Melbourne Interventional Group

The goals of MIG are twofold: (1) To establish a collaborative coronary angioplasty registry with 30-day and 12-month clinical follow-up and (2) facilitation of multi-centred randomised clinical trials targeted at interventional cardiology. The development and implementation of the registry appears critical as it provides a basis for performing clinical trials. The eventual goal of MIG is to provide a contemporary appraisal of Australian interventional cardiology practice, with opportunities to improve in-hospital and long-term outcomes of patients with coronary artery disease. Ultimately, it is hoped that if this model is successful, it may become the platform to launch a national interventional cardiovascular registry.

The collaborative group of interventionists is envisaged to act as a 'sounding board' for individual research ideas and projects. All participants have access to and utilisation of the MIG database. It is anticipated that opportunities will arise for education and training (e.g. by attracting interventional cardiology trainees) with plans for a regular annual meeting around the Cardiac Society of Australia and New Zealand annual meeting, or ultimately stand-alone meetings. Interaction with other collaborative groups and educational bodies, e.g. the Cardiac Society of Australia and New Zealand appears paramount. Future involvement in internationally based clinical trials will be a central goal of MIG.

Methodologic Approaches

Establishing a Dataset

MIG case report forms are designed to document detailed demographic, clinical and procedural characteristics and current interventional practice patterns for patients undergoing PCI in Victoria (Supplementary data, Appendix B). Additionally, we aim to document medical therapy in the peri-procedural period. These factors are analysed with reference to in-hospital and 12-month clinical outcomes.

The four-page standardised data abstraction form was developed by a database working group within MIG. The members of this group have had considerable experience in the implementation and analysis of cardiology databases. Consensus was achieved for the final fields for the MIG registry after a number of interventional workshops.

Reference was made to a number of current interventional databases including the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR), and established interventional databases at Cleveland Clinic and Washington Hospital Centre (USA).[1] A spreadsheet of the potential data fields from all referenced databases was developed and these were then compared and refined. We anticipated somewhere between 100 and 120 data fields would be sufficient to provide a comprehensive yet manageable dataset. It was important to ensure this dataset was not too large, yet detailed enough to address important clinical questions. It was not designed to cover all research needs as this would potentially lead to a cumbersome dataset that would likely remain incomplete. Each patient-related variable and clinical diagnosis required a standardised definition for uniform application across different hospitals. The dataset (current MIG database) was finalised for field use after field testing at two interventional centres (Royal Melbourne and Austin Hospitals).

The specific data, which we felt were important to record, included indication for the interventional procedure, peri-procedural anticoagulation strategies and planned duration of clopidogrel use post-procedure (Supplementary data, Appendix B). Lesion characteristics are captured in significant detail, as is the interventional treatment including stent type, size and length. At 30-day and 12-month follow-up, standard events are documented (e.g. death, myocardial infarction, target lesion and vessel revascularisation). Additionally, we targeted medication therapy and the development of heart failure.

Data Collection

Consecutive patients undergoing PCI by participating interventionalists are enrolled in the registry. The data abstraction form is completed at each site by interventional cardiology fellows or research nurses. Case-report forms are then transmitted via fax to the central registry for entry of de-identified data into a computerised database (Department of Epidemiology and Preventive Medicine, Monash University) where they are checked for possible errors or omissions. The registry is co-ordinated by the Centre of Clinical Research Excellence (CCRE), a research body within the Department of Epidemiology and Preventive Medicine (Monash University, Commercial Road, Melbourne). Data queries are referred to the originating centre before being processed into the databank. A contact phone number is provided for the central site to optimise communication with participating centres, and allows data queries to be addressed. Individual hospital or composite MIG updates can be readily obtained. The data are queried and a regular audit program is planned to ensure data are of high quality.

Thirty-day and 12-month follow-up is performed by a research co-ordinator at the respective hospital. Follow-up annually to 5 years has been targeted, and this goal depends on future resource allocation. This duration of follow-up would allow comparison with the National Cardiac Surgery Database, providing critical appraisal of coronary revascularisation strategies within Australia.[6]

It is anticipated that a centralised follow-up system will ensue (from the Department of Epidemiology and Preventive Medicine, Monash University); however, steps towards this transition are in their infancy. Since June 2004, 1100 PCI patients have been enrolled in the registry and 30-day follow-up has been completed in 800 PCI patients. Analyses are prospectively planned by a central publication committee to ensure data quality, the absence of publication bias and feedback to and acknowledgement of all investigators. The initial patient registry will provide data for analysis of clinical efficacy and cost effectiveness of drug-eluting stents.

Informed Consent

Collection of patient data and follow-up for the MIG database was approved by the ethics committee of each participating institution. A written 'plain-language' statement is provided to patients preceding their interventional procedure, which explains the purpose of obtaining patient and procedural information (Appendix A). We employed an 'opt-off consent' which requires the patient to sign a declaration only if they refuse to contribute their relevant information, or do not want to be followed up beyond the coronary intervention. This model has been used for the National Cardiac Surgery Database, and has been a highly effective consent tool with high rates of participation.[6] This method also assists in minimising the "Hawthorne effect" (i.e. a phenomenon in observational research where outcome variables are effected by the fact that the participants of the study know they are participating in the study).

Participating Centres

The Melbourne Interventional Group (MIG) is a collaborative venture of interventional cardiologists practicing at 12 major public and private hospitals in Victoria. The participation of individual interventional cardiologists is purely voluntary. The MIG collaboration felt that targeting individual cardiologists rather than institutions, and having a democratic management structure would be more beneficial for harmonious working of the group.

The following hospitals have selected interventional cardiologists contributing to this venture: Royal Melbourne and Melbourne Private Hospitals; Austin and Warringal Hospitals; Alfred Hospital; Western Hospital Footscray; Geelong and Geelong Private Hospitals; Box Hill Hospital; Frankston and Peninsula Hospitals; Knox Private Hospital.

Conclusions

The MIG collaborative group comprising a broad range of Victorian hospitals will provide an insight into contemporary Australian interventional Cardiology practice. The established registry documents demographic, clinical and procedural characteristics of consecutive patients undergoing PCI and permits analysis of those characteristics at 30 days and 12 months. The collaborative venture will facilitate multi-centred randomised clinical trials targeted at interventional cardiology. Ultimately, it is anticipated that this will facilitate improvements in short and long-term outcomes for patients with coronary artery disease.

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Appendix A. Patient Information Sheet

Melbourne Interventional Group Database

ROYAL MELBOURNE HOSPITAL. **Background**

You are about to have (or have recently had) a coronary artery procedure ("intervention") that aims to improve the blood supply to your heart and improve your symptoms. Most procedures involve the use of a balloon ("angioplasty") and a metal scaffold ("stent") to open up any blockages in your coronary arteries. Generally, these procedures are successful and improve the quality of the patient's life, with a small risk of death or major complications. Your doctor will have explained these risks to you. Some people, however, can have a recurrence of their original symptoms, usually due to re-narrowing of the vessel ("restenosis"). There are continuous improvements in techniques and equipment that reduce the risk of complications and restenosis in clinical trials, but whether these improve outcomes in "real life" is often unknown.

In order to improve the immediate success and long-term outcomes of these coronary procedures, we need to know what factors increase a patient's risk of complications and restenosis. By knowing this we hope to improve procedural success and long-term outcomes of patients undergoing these procedures. As you would reasonably expect, many hospitals already have databases on the in-hospital outcome of coronary interventions, but there is no statewide or national data available about long-term outcomes in Australia. To obtain this important information a group of cardiologists (heart specialists) have formed a group called the Melbourne Interventional Group. There are representatives from most Melbourne hospitals in this group. **Our aim is to set up a statewide database that will record information on *every* adult coronary artery interventional procedure**. The success of the database depends on the amount of information we get, and to be truly representative we want to include all patients.

We are asking you to participate in the Melbourne Interventional Group Database by allowing us to document information about your cardiac condition and procedure. Importantly, we also want to see how you progress over time by collecting follow-up information about your cardiac health.

What Information Do We Need?

The information we require includes your name, date of birth, Medicare number, hospital identification number, the name of your hospital, the reason you are having a coronary intervention, technical details of the procedure, any complications that you have in hospital, and your follow-up cardiac health information. All of your information will be freely available to you from your treating hospital.

We Will Keep Your Information Confidential

Your personal information is confidential and cannot be used outside the database. Procedures are in place to protect your information and keep it confidential. You will be assigned a unique number which will be used to identify you. The data is accessible by authorised staff of the Melbourne Interventional Group Database project. Only group data will be made available publicly to groups such as participating hospitals, the Department of Health and the National Heart Foundation. You cannot be identified in any reports produced by the database project.

How Will We Collect the Information?

The hospital staff will complete the forms that contain the relevant details during your hospital stay. You will be called 30 days, 1 and 2 years after your procedure to briefly obtain information about your cardiac health. We will ask you about any new heart symptoms, any further procedures that you have had, and what medications you are taking. The information will be entered into a secure database computer.

Risks and Benefits to You

Your information is protected and we are not allowed to identify you by law. The database will produce general reports on the short- and long-term success of coronary procedures, which we anticipate will improve the quality of procedures in the future.

You Can Choose Not to be in the Database

We understand that not everyone is comfortable about having details related to their heart procedures entered into a database. If you feel this way, and do not want your information added to the database or to be contacted for follow-up, please contact the Project Coordinator (Angela Brennan) on 1800 285 382 at any time.

A decision on whether or not you wish to be involved in the database does not affect your treatment in any way.

Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.hlc.2005.08.001.

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Appendix 2

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Return completed forms to CCRET on fax: 1800 022 730

Procedure ID

MIG_BL_V4

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	9 Box Hill
2 Geelong Private	10 Geelong
3 Peninsula Private	11 Frankston
4 Warringal Private	12 Knox
5 Royal Melbourne	13 Western
6 Alfred	14 Cabrini
8 Austin	15 Northern

Section 1. DEMOGRAPHICS

1.1 Hospital UR number

1.2 Patient last name (1st three letters)

1.3 Patient first name (1st three letters)

1.4 Date of birth DD / MM / YYYY

1.5 Sex ○ Male ○ Female

1.6 Postcode

1.7 Race
- ○ Caucasian
- ○ Asian
- ○ Aboriginal/Torres Strait Islander
- ○ Indian/Sri Lankan/Pakistan/Bangladesh
- ○ Other (specify) _____

1.8 Insurance status ○ Medicare ○ DVA ○ Private ○ Overseas Visitor ○ Self Insured

1.9 Medicare number

1.10 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

3.6a Renal failure (Cr >= 0.20 mmol/L) ○ Yes → If YES, 3.6b Treatment ○ Med Mx ○ Dialysis ○ Transplant ○ No

3.7 Baseline serum creatinine . mmol/L

3.8 Hypertension ○ Yes ○ No

3.9 Dyslipidaemia ○ Yes ○ No

3.10 Total cholesterol . mmol/L

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

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** ○ Yes ○ No
(Existing <2 weeks prior)

5.2 **Rhythm** ○ AF ○ SR ○ Other
(At commencement of PCI)

5.3 **NYHA** ○ I ○ II ○ III ○ IV
(See MIG instruction sheet)

5.4 **Killip class** ○ 1 ○ 2 ○ 3 ○ 4
(For AMI patients only)

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 5.8b ACS Time Period

5.10b **ACS time period**
○ <6 Hrs
○ 6 - 24 Hrs
○ >24 Hrs - 7 Days

5.11 **Canadian Cardiovascular Score (CCS)** ○ CCS 0 ○ CCS 1 ○ CCS 2 ○ CCS 3 ○ CCS 4
(See MIG instruction sheet)

STEMI EVENT TIMING (Please complete if <24 hours since onset of STEMI symptoms)

5.12a **STEMI time of onset** hour : minutes

5.12b **Time of arrival at first hospital** hour : minutes
(For patients transferred only)

5.12c **Time of arrival at PCI hospital** hour : minutes

5.12d **Time of first balloon inflation** hour : minutes

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

MEDICATIONS

6.4 **Thrombolytics** ○ No ○ <3 hrs ○ 3 - 6 hrs ○ >6-12hrs ○ <7 days

6.5 **IIb / IIIa Blockade** ○ No ○ Prior ○ During ○ After

6.6 **Heparin** ○ No ○ Prior ○ During ○ After

6.7 **LMWH** ○ No ○ Prior ○ During ○ After

6.8 **Bivalirudin** ○ Yes ○ No

6.9 **Aspirin** ○ Yes ○ No

6.10 **Clopidogrel** ○ No ○ >72 hrs before PCI ○ <72 hrs before PCI ○ During/After PCI

6.11 **Planned duration of clopidogrel** ○ 1 Month ○ 3 Month ○ 6 Months ○ 12 Months ○ >12 Months

PERCUTANEOUS ENTRY

6.12 **Percutaneous entry location** ○ Brachial ○ Radial ○ Femoral

6.13 **French size** (Guiding catheter) ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ Other (Specify)

6.14 **Closure device** ○ No ○ Seal ○ Suture ○ Other (Specify) _____

EF STATUS

6.15 **EF test modality** ○ Cath ○ Nuclear ○ Echo ○ MRI

6.16a **EF %** 6.16b **EF value** ○ Estimated ○ Derived
(Don't use a 'greater than' or 'less than' symbol)

EXTENT OF CORONARY DISEASE

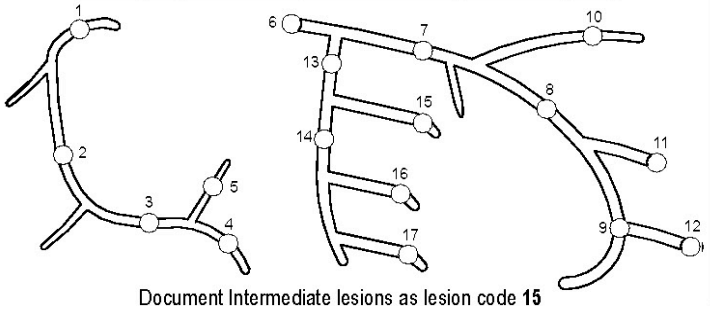
6.17 **Disease extent** ○ Single vessel disease ○ Multi vessel disease

Section 7. PCI PROCEDURE / LESION INFORMATION

Lesion Code
1 RCA prox
2 RCA mid
3 RCA distal
4 PDA
5 PLV
6 Left MAIN
7 LAD prox
8 LAD Mid
9 LAD Distal
10 D1
11 D2
12 D3
13 LCX prox
14 LCX distal
15 OM1
16 OM2
17 OM3
18 LIMA
19 RIMA
20 SVG1
21 SVG2
22 SVG3
23 RAD1
24 RAD 2
25 RAD3

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	

Complete for all lesions. Complete and attach additional lesion form if necessary.

Lesion 1

7.1a **Coronary lesion**
○ De novo
○ Restenosis (No prior stent)
○ In stent restenosis → 7.1b **Prior stent type** ○ DES ○ BMS

7.1c **Lesion code (1-25)** ☐☐

7.1d **Lesion type** ○ A ○ B1 ○ B2 ○ C

7.1e **Chronic total occlusion** ○ Yes ○ No

7.1f **Ostial lesion** ○ Yes ○ No

7.1g **Bifurcation lesion** ○ Yes ○ No (If side branch, enter as lesion 2)

7.1h **Pre-stenosis %** ☐☐☐ **TIMI Flow (pre)** ☐ **(0-3)**

7.1i **Post-stenosis %** ☐☐☐ **TIMI Flow (post)** ☐ **(0-3)**

7.1j **Estimated lesion length** ☐☐ mm

7.1k **Acute closure** ○ Yes ○ No

7.1l **Dissection** ○ Yes ○ No

7.1m **Perforation** ○ Yes ○ No

7.1n **No Reflow** ○ No ○ Transient ○ Persistent

7.1p **Lesion result** ○ Successful ○ Unsuccessful

STENT DETAILS FOR LESION 1

	7.1q Stent code	7.1r Length	7.1s 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.

7.1t **Maximum balloon size used** ☐.☐ mm

7.1u **Intracoronary devices used**
○ No devices deployed ○ Cutting Balloon ○ Distal Embolic Protection → ○ Filter ○ Balloon
○ Balloon only ○ IVUS
○ Bare Metal Stent ○ Pressure Wire ○ Proximal Embolic Protection → ○ Proxis™ ○ Other
○ DES ○ Flowire
○ Rotablator ○ Brachytherapy ○ Thrombectomy Device → ○ Export™ ○ Other
○ Other _____

7.1v **Location in graft** (complete for graft PCI only)
○ Ostial ○ Distal ○ Mid ○ Proximal ○ Anastomosis ○ Native

Lesion 2

7.2a **Coronary lesion**
○ De novo
○ Restenosis (No prior stent)
○ In stent restenosis → 7.2b **Prior stent type** ○ DES ○ BMS

7.2c **Lesion code (1-25)** ☐☐

7.2d **Lesion type** ○ A ○ B1 ○ B2 ○ C

7.2e **Chronic total occlusion** ○ Yes ○ No

7.2f **Ostial lesion** ○ Yes ○ No

7.2g **Bifurcation lesion** ○ Yes ○ No (If side branch, enter as lesion 2)

7.2h **Pre-stenosis %** ☐☐☐ **TIMI Flow (pre)** ☐ **(0-3)**

7.2i **Post-stenosis %** ☐☐☐ **TIMI Flow (post)** ☐ **(0-3)**

7.2j **Estimated lesion length** ☐☐ mm

7.2k **Acute closure** ○ Yes ○ No

7.2l **Dissection** ○ Yes ○ No

7.2m **Perforation** ○ Yes ○ No

7.2n **No Reflow** ○ No ○ Transient ○ Persistent

7.2p **Lesion result** ○ Successful ○ Unsuccessful

STENT DETAILS FOR LESION 2

	7.2q Stent code	7.2r Length	7.2s 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.

7.2t **Maximum balloon size used** ☐.☐ mm

7.2u **Intracoronary devices used**
○ No devices deployed ○ Cutting Balloon ○ Distal Embolic Protection → ○ Filter ○ Balloon
○ Balloon only ○ IVUS
○ Bare Metal Stent ○ Pressure Wire ○ Proximal Embolic Protection → ○ Proxis™ ○ Other
○ DES ○ Flowire
○ Rotablator ○ Brachytherapy ○ Thrombectomy Device → ○ Export™ ○ Other
○ Other _____

7.2v **Location in graft** (complete for graft PCI only)
○ Ostial ○ Distal ○ Mid ○ Proximal ○ Anastomosis ○ Native

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Return completed forms to CCRET on fax: 1800 022 730

Procedure ID

MIG_BL_V4

Lesion 3

7.3a **Coronary lesion**
- ○ De novo
- ○ Restenosis (No prior stent)
- ○ In stent restenosis → 7.3b **Prior stent type** ○ DES ○ BMS

7.3c **Lesion code (1-25)**

7.3d **Lesion type** ○ A ○ B1 ○ B2 ○ C

7.3e **Chronic total occlusion** ○ Yes ○ No

7.3f **Ostial lesion** ○ Yes ○ No

7.3g **Bifurcation lesion** ○ Yes ○ No (If side branch, enter as lesion 2)

7.3h **Pre-stenosis %** **TIMI Flow (pre)** (0-3)

7.3i **Post-stenosis %** **TIMI Flow (post)** (0-3)

7.3j **Estimated lesion length** mm

7.3k **Acute closure** ○ Yes ○ No

7.3l **Dissection** ○ Yes ○ No

7.3m **Perforation** ○ Yes ○ No

7.3n **No Reflow** ○ No ○ Transient ○ Persistent

7.3p **Lesion result** ○ Successful ○ Unsuccessful

STENT DETAILS FOR LESION 3

	7.3q Stent code	7.3r Length	7.3s 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.

7.3t **Maximum balloon size used** . mm

7.3u **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

7.3v **Location in graft** (complete for graft PCI only)
○ Ostial ○ Distal ○ Mid ○ Proximal ○ Anastomosis ○ Native

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

8.7 **CVA / stroke** (CT confirmation) ○ Yes ○ No
If Yes → ○ 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

8.12 **Post procedural rise in creatinine** ○ Yes ○ No
If Yes → . mmol/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** mmol/L

8.20b **CK MB peak** mmol/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

Appendix 3

Use of drug-eluting stents in Victorian public hospitals
Yan, Bryan P;Ajani, Andrew E;Duffy, Stephen J;New, Gishel;et al
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Use of drug-eluting stents in Victorian public hospitals

Bryan P Yan, Andrew E Ajani, Stephen J Duffy, Gishel New, Mark Horrigan, Gregory Szto, Antony Walton, David Eccleston, Jeffery Lefkovits, Alexander Black, Martin Sebastian, Angela L Brennan, Christopher M Reid and David J Clark
on behalf of the Melbourne Interventional Group (MIG) investigators

ABSTRACT

Objective: We aimed to assess the pattern of use of drug-eluting stents (DESs) in patients undergoing percutaneous coronary interventions (PCIs) in Victorian public hospitals.

Design, setting and patients: Prospective study comparing the use of one or more DESs versus bare-metal stents (BMSs) only, in consecutive patients undergoing 2428 PCIs with stent implantation from 1 April 2004 to 31 December 2005 at seven Victorian public hospitals.

Main outcome measures: Adherence to current Victorian Department of Human Services guidelines which recommend DES use in patients with high-risk features for restenosis (diabetes, small vessels, long lesions, in-stent restenotic lesions, chronic total occlusions and bifurcation lesions).

Results: Of the 2428 PCIs performed, at least one DES was implanted in 1101 (45.3%) and BMSs only were implanted in 1327 (54.7%). In 87.7% (966/1101) of PCI with DESs, there was at least one criterion for high risk of restenosis. DESs were more likely to be used in patients with diabetes (risk ratio [RR], 2.45; 95% CI, 2.02–2.97), small vessels (RR, 3.35; 95%CI, 2.35–4.76), long lesions (RR, 3.87; 95% CI, 3.23–4.65), in-stent restenotic lesions (RR, 3.98; 95%CI, 2.67–6.06), chronic total occlusions (RR, 1.30; 95% CI, 0.51–2.88) and bifurcation lesions (RR, 2.23; 95%CI, 1.57–3.17). However, 66.2% (1608/2428) of all PCIs were in patients eligible for DESs according to Victorian guidelines, and in 39.9% (642/1608) of these PCIs, a BMS was used.

Conclusion: In Victorian public hospitals, DESs have been largely reserved for patients at high risk of restenosis in accordance with Department of Human Services guidelines. However, many patients with high-risk criteria for restenosis did not receive DESs. Greater use of DESs in these patients may improve outcomes by reducing the need for repeat revascularisation.

MJA 2006; 185: 363–367

Stent implantation has significantly improved the short-term and long-term outcomes of patients undergoing percutaneous coronary interventions (PCIs) for obstructive coronary artery disease compared with balloon angioplasty alone.[1] However, in-stent restenosis may lead to recurrent ischaemia and repeat intervention at rates approaching 30% in high-risk patient subgroups, including those with diabetes, long lesions and small vessels.[2-4] Recently, drug-eluting stents (DESs) that are impregnated with anti-proliferative agents have emerged as an effective strategy in preventing restenosis.[5,6] In two large randomised controlled trials evaluating stents eluting paclitaxel and sirolimus, there was about a 50% reduction in the rate of target vessel failure (defined by death, myocardial infarction, or patients having undergone target vessel revascularisation) in patients receiving DESs compared with conventional bare-metal stents (BMSs).[7,8]

In Australia, the cost of DESs is about three to four times that of conventional BMSs. As a result, DES use in the public health system is not ubiquitous, but is reserved for selected cases. This restriction does not apply to private patients because DESs can be claimed as a prosthesis from their insurance fund.

In Victorian public hospitals, the Department of Human Services has provided funding for DESs in 30%–40% of PCI cases. DESs are therefore reserved for patients at high risk of restenosis, who will theoretically derive the greatest benefit. Current Department of Human Services indications for DESs in Victorian public hospitals are listed below in the Methods.

We aimed to evaluate the use of DESs in patients undergoing PCI in Victorian public hospitals, and whether DESs were implanted in patients at high risk of restenosis in accordance with Department of Human Services guidelines.

METHODS

We examined PCI with stent implantation procedures in consecutive patients between 1 April 2004 and 31 December 2005 at seven Victorian public hospitals.

Our data were part of those collected for the Melbourne Interventional Group registry. This registry is a voluntary, collaborative venture by interventional cardiologists practising at these seven hospitals, designed to record data pertaining to PCI and to perform long-term follow-up. Demographic, clinical and procedural characteristics of consecutive patients undergoing PCI are prospectively recorded on a standard case report form with standardised definitions for all fields.[9] The registry is coordinated by the Centre of Clinical Research Excellence in Therapeutics, a research body within the Department of Epidemiology and Preventive Medicine at Monash University, Melbourne. Case record forms for the collection of registry data have been developed using Teleform, version 9 (Cardiff, Vista, Calif, USA). Completed forms are faxed to the data centre, verified on receipt, and electronically uploaded into the central database. A query system has been developed to identify missing data, data inconsistencies and out-of-range values. The database is built on a Microsoft SQL Server platform (Microsoft Corporation, Redmond, Wash, USA) with a Microsoft Access (Microsoft Corporation, Redmond, Wash, USA) user interface.

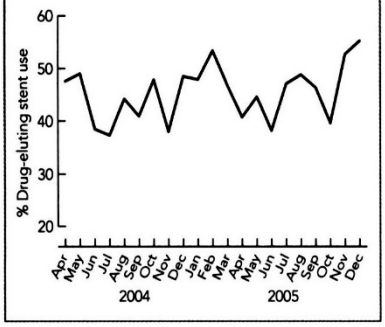
The study population was classified into two groups based on stent type used — patients in the DES group had at least one DES used, while those in the BMS group had only BMSs implanted. Patients were excluded if no stent was used, or if they had private health insurance (to avoid stent selection bias as DESs are fully reimbursed in these patients).

The study protocol was approved by the ethics committee in each participating hospital. "Opt-out" informed consent was obtained in all patients, as previously described.[9]

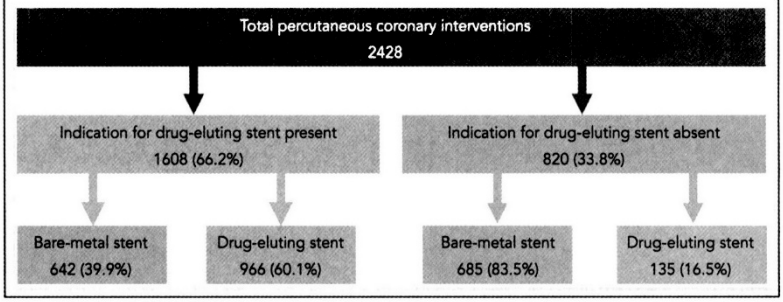
Procedures and post-intervention medications

The interventional strategy and stent selection was left to the discretion of the operator in all procedures. Total stent length was used as a surrogate measure for target lesion length, and stent diameter for target vessel

1 Drug-eluting stent use per month, 1 April 2004 to 31 December 2005



2 Stent use according to whether percutaneous coronary interventions met Victorian Department of Human Services criteria for implanting drug-eluting stents



diameter. Periprocedural glycoprotein IIb/IIIa inhibitors were used according to the operator's decision. Oral antiplatelet therapy followed current internationally accepted guidelines, which recommend combination of aspirin and clopidogrel for a minimum of 4 weeks for BMSs and for 6–12 months for DESs.[10]

Criteria for use of drug-eluting stents

In 2003, the Victorian Department of Human Services, with the aid of a working group of cardiologists from all hospitals performing PCI, developed clinical guidelines for use of DESs in public hospitals. The resulting criteria for use of DESs included one or more of the following: (i) diabetes mellitus; (ii) target vessel diameter ≤ 2.5 mm; (iii) target lesion length ≥ 20 mm; (iv) bifurcation lesion; (v) ostial lesion; (vi) in-stent restenosis; and (vii) chronic total occlusions. These guidelines were displayed in all cardiac catheter laboratories of Victorian public hospitals, and the reason for DES use was documented in all PCIs.

Statistical analysis

Continuous variables were expressed as mean ± SD, and categorical data expressed as percentages. Continuous variables were compared by means of Student *t* tests, and categorical variables were compared by means of Fisher exact or χ^2 tests and presented as risk ratios (RR) with 95% CIs. All *P* values < 0.05 were considered statistically significant.

RESULTS

There were 2428 PCI procedures, with stent implantation in 2976 coronary artery lesions during the study period. Of the 2428 PCIs, 1101 (45.3%) involved insertion of at least one DES, and BMSs were inserted in the remaining 1327 (54.7%). The proportion of DES use was stable over the study period (Box 1). The rates of PCI involving BMSs and DESs according to whether Department of Human Services criteria for DESs were present are shown (Box 2). In 87.7% of PCIs in which DESs were implanted (966/1101), there was at least one Department of Human Services criterion for DES use. However, of the total 2428 PCIs, 1608 (66.2%) were eligible for a DES according to Department of Human Services criteria, and in 642 (39.9%) of these procedures in patients at high-risk of restenosis, only BMSs were used.

Characteristics of patient and procedures associated with DES use

Patients treated with DESs had more diabetes (32.5% v 16.5%; $P < 0.01$), previous myocardial infarction (30.8% v 27.4%; $P = 0.04$)

3 Baseline characteristics of patients undergoing percutaneous coronary intervention (PCI)

	Drug-eluting stents	Bare-metal stents	*P*
Number of PCIs performed	1101 (45.3%)	1327 (54.7)	—
Patient characteristics			
Age (±SD)	64.1 ± 12 years	64.3 ± 12 years	0.77
Mean LVEF (±SD)	57.2% ± 14.5%	56.5% ± 13.6%	0.47
Sex (proportion male)	73.8%	73.1%	0.38
Diabetes	32.5%	16.5%	< 0.01
Insulin requiring	7.2%	3.0%	< 0.01
Hypertension	60.3%	62.3%	0.17
Hypercholesterolaemia	70.0%	71.0%	0.31
Smoking	72.4%	77.3%	0.01
Previous myocardial infarction	30.8%	27.4%	0.04
Previous PCI	26.8%	18.8%	< 0.01
Previous CABG	10.3%	6.3%	< 0.01
Moderate to severe renal dysfunction (creatinine > 0.20 mmol/L)	3.3%	2.4%	0.13
Clinical presentation			
Total acute coronary syndromes	59.8%	63.2%	0.06
Unstable angina	19.0%	19.6%	0.20
Non-STEMI	23.3%	21.2%	0.71
STEMI	17.5%	23.3%	0.01
Cardiogenic shock	0.9%	1.4%	0.22

LVEF = left ventricular ejection fraction; CABG = coronary artery bypass grafting; STEMI = ST-elevation myocardial infarction. ◆

4 Characteristics of percutaneous coronary intervention procedures

	Drug-eluting stents	Bare-metal stents	*P*
Number of lesions	1309 (44%)	1667 (56%)	—
Target vessel			
Left main coronary artery	1.1%	0.5%	< 0.01
Left anterior descending artery	37.7%	27.7%	< 0.01
Proximal left anterior descending artery	17.6%	12.5%	< 0.01
Bypass graft	3.3%	1.5%	< 0.01
Mean stent diameter (mm ± SD)	2.78 ± 0.37	3.07 ± 0.5	< 0.01
Stent diameter ≤ 2.5 mm	45.2%	17%	< 0.01
Mean stent length (mm ± SD)	20.1 ± 8.2	17.2 ± 7.6	< 0.01
Total stent length ≥ 20 mm	46.9%	17.3%	< 0.01
ACC/AHA lesion type B2/C	55.0%	41.3%	< 0.01
Chronic total occlusion	1.4%	0.8%	< 0.01
Ostial lesions	2.2%	2.2%	0.89
Bifurcation lesions	8.6%	5.6%	0.02
In-stent restenosis	7.9%	2.0%	< 0.01
Glycoprotein IIb/IIIa inhibitor use	27.6%	29.3%	0.16

ACC/AHA = American College of Cardiology/American Heart Association. ◆

5 Rate of drug-eluting stent use in high-risk subgroups and associated risk ratios

Characteristic	Drug-eluting stent use/total PCIs	Risk ratio (95% CI)
In-stent restenosis	93/123 (75.6%)	3.98 (2.67–6.06)
Total stent length ≥ 20 mm	520/769 (67.6%)	3.87 (3.23–4.65)
Stent diameter ≤ 2.5 mm	474/693 (68.4%)	3.35 (2.35–4.76)
Diabetes	358/576 (62.2%)	2.45 (2.02–2.97)
Bifurcation lesion	92/144 (63.9%)	2.23 (1.57–3.17)
Ostial lesion	19/34 (55.9%)	1.53 (0.78–3.03)
Chronic total occlusion	13/25 (52.0%)	1.30 (0.51–2.88)

PCI = percutaneous coronary intervention. ◆

6 Likelihood of receiving drug-eluting stents according to number of criteria satisfied

Number of criteria	Risk ratio (95% CI)
1	1.34 (1.14–1.58)
2	4.52 (3.61–5.68)
3 or more	10.41 (6.13–17.5)

and previous coronary artery bypass graft (10.3% v 6.3%; $P < 0.01$) than those in whom only BMSs were used (Box 3). A greater proportion of left-anterior-descending artery and left-main-stem lesions were treated with DESs compared with BMSs (37.7% v 27.7%; $P < 0.01$ and 1.1% v 0.5%; $P < 0.01$, respectively). More lesions treated with DESs were complex (American College of Cardiology/American Heart Association, type B2/C lesions) than those treated with BMSs (55% v 41.3%; $P < 0.01$). More DESs than BMSs were implanted in small vessels (≤ 2.5 mm stents; 45.2% v 17%; $P < 0.01$), long lesions requiring 20 mm or more in length of stent (46.9% v 17.3%; $P < 0.01$), chronic total occlusions (1.4% v 0.8%; $P < 0.01$), bifurcation lesions (8.6% v 5.6%; $P = 0.02$) and in-stent restenotic lesions (7.9% v 2%; $P < 0.01$) (Box 4). Conversely, in patients who presented with ST-elevation myocardial infarction (STEMI) and cardiogenic shock, more were treated with BMSs than DESs (23.3% v 17.5%; $P = 0.01$ and 1.4% v 0.9%; $P = 0.22$, respectively). There was no significant difference in stent preference in patients presenting with non-ST-elevation acute coronary syndromes.

The percentages of PCIs in which DESs were used in accordance with Department of Human Services criteria is shown in Box 5. DES use ranged from a high of 75.6% for in-stent restenosis down to 52.0% for chronic total occlusions. The likelihood of receiving a DES increased with the number of criteria satisfied (Box 6), from an RR of 1.34 (95% CI, 1.14–1.58) with one criterion present to a RR of 10.41 (95% CI, 6.13–17.5) when three or more criteria were present.

DISCUSSION

In 66.2% of PCIs in this large, contemporary cohort study in the Australian public health care system, patients were eligible for DES use according to Department of Human Services guidelines, and in 45.3% of PCIs, they actually received DESs. In both instances, the requirement for DESs exceeded the 30%–40% for which the Department of Human Services provides funding. In accordance with Department of Human Services guidelines, DESs were predominantly implanted in PCIs involving patients at high risk of restenosis (87.7%), and were more frequently used in patients with diabetes, small vessels (≤ 2.5 mm), and complex lesions (long segments of disease, bifurcation and ostial lesions, chronic total occlusions and in-stent restenosis). However, in 39.9% of PCIs involving patients who met criteria for DES implantation, a BMS was used.

The uptake of DESs by the interventional cardiology community is not uniform. In the United States, 17 266 PCIs were performed in Veteran Health Administration medical centres from 2002 to 2004, with DES use reported in 52% of cases.[11] On the other hand, a German registry of 3579 interventions at 102 centres reported less than 10% DES use between April 2002 and December 2003.[12] In Australia, DES use in public hospitals varies considerably between states. There are very high rates of DES use (about 90%) in Western Australia, compared with about 60% in South Australia and 50% in New South Wales, where rates in some hospitals were less than 10% (J Rankin, Interventional Cardiologist, Royal Perth Hospital, Perth, WA; D P Chew, Interventional Cardiologist, Flinders Medical Centre, Bedford Park, SA; and D M Muller, Interventional Cardiologist, Director of Cardiac Catheterisation Laboratory,

St Vincent's Hospital, Darlinghurst, NSW; personal communications, March 2006). A recent preliminary report found DES use in Victorian private hospitals exceeded 94% — about twice that of Victorian public hospitals.[13]

The rationale for selective use of DESs is twofold. Firstly, the greatest clinical benefit of DESs is expected for patients at the highest risk of restenosis. A number of clinical and angiographic features are known to increase the risk of restenosis after bare-metal stenting.[14-21] Lesion-related factors are described above. The major patient-related factor is diabetes mellitus, which doubles the risk of in-stent restenosis.[20,21] DESs have been shown to be safe and effective in each of these subgroups.[14,16-18,22-25] A recent study showed the strategy of selective DES use in patients with high-risk features (including diabetes, left ventricular ejection fraction < 35%, lesions in the left anterior descending artery and left main stem artery, saphenous vein grafts, chronic total occlusions, ostial or bifurcation lesions) was associated with a significant decrease in major adverse cardiac events, defined as a composite of death, myocardial infarction and target vessel revascularisation (hazard ratio [HR], 0.45; 95% CI, 0.29–0.72), whereas no difference was observed in patients without high-risk features (HR, 0.95; 95% CI, 0.40–2.28).[26]

Secondly, unrestricted DES use is not economically viable under the public health system. A recent cost-effectiveness analysis in the US suggested the sirolimus-eluting stent would be a cost effective treatment strategy when the rate of restenosis exceeds 18.5%.[27] However, not all patients undergoing PCI are at high risk of restenosis. A recent study of 5239 patients undergoing PCI identified factors (eg, native vessels, de novo lesions, reference diameter > 3.5 mm, lesion length < 5 mm, absence of diabetes and non-ostial lesions) which predicted a low (4%–10%) risk of repeat revascularisation at 9 months.[28] Marginal improvement in outcomes from DES use in these low-risk patients is unlikely to be cost-effective, thus providing the economic basis for current Victorian guidelines. A recent Australian study showed that limiting DES use to patients at the highest risk of restenosis might improve the cost-effectiveness of DESs in an Australian model based on randomised trial results.[29]

A significant number of high-risk patients in our study did not receive DESs. There are a number of possible explanations for why patients who had an indication for a DES received a BMS. First, implanting DESs in tortuous and calcified vessels is more difficult than implanting newer generation low-profile BMSs. The operator may choose to use a more deliverable BMS instead of a DES in the event of failure to deliver a DES. Second, prolonged dual antiplatelet therapy including clopidogrel, which is mandatory after DES implantation, may be undesirable in patients awaiting non-cardiac surgery, at high risk of bleeding or unable to comply with prolonged dual antiplatelet therapy. Third, patients with significant comorbidities or poor prognosis may be excluded. Fourth, acute STEMI was initially considered a relative contraindication for DES use by some operators, resulting in more patients with STEMI receiving BMSs despite having high-risk features, such as diabetes. This stemmed from the lack of randomised trial data and the potential risk of stent thrombosis in the local thrombotic environment of the infarction-related lesion. Recent studies have found DESs to be safe in patients with STEMI.[30] Finally, DESs were only funded for 30%–40% of PCIs, and 66.2% of PCIs in this study involved patients with at least one criterion for receiving DESs. Therefore, operators could not use DESs in many appropriate patients without markedly exceeding the allocated budget.

DESs were implanted during some PCIs (16.5%) without an indication (Box 2). In-stent restenosis in the left main and left anterior descending arteries are associated with worse clinical outcome,[31-34] and may explain why DESs were more often implanted in these vessels even though target vessel type was not one of the criteria for DES use in Victorian Department of Human Services guidelines.

Establishing a nationwide registry with long-term outcomes is essential for assessing whether current DES use is appropriate in Australian interventional practice. Follow-up data to 12 months in our cohort will provide efficacy data for cost-effectiveness analysis and for a selective DES implantation policy relevant to the Australian health system.

Our study has several limitations. Firstly, not all Victorian public hospitals were represented, so our findings may not reflect DES use in non-participating hospitals. However, we would anticipate similar results given that these hospitals are also regulated by the 30%–40% reimbursement limit in Victoria. Secondly, the final choice of stent was at the discretion of the interventionalist, and some of the procedural and patient factors precluding the use of DESs may not have been captured. Finally, because quantitative coronary angiography is not performed routinely in Victorian public hospitals, we used stent length and diameter as surrogates for the lesion length and vessel diameter. However, these measures correlate closely in clinical practice.

In summary, we have shown that in Victorian public hospitals, DESs have been used predominantly in patients with risk factors for restenosis, in accordance with current guidelines. However, many patients at high risk of restenosis did not receive DESs, and greater use of DESs in these patients may substantially improve clinical outcomes by reducing restenosis.

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COMPETING INTERESTS

None identified.

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Appendix 4

RESEARCH

Recent trends in Australian percutaneous coronary intervention practice: insights from the Melbourne Interventional Group registry

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ABSTRACT

Objective: To evaluate percutaneous coronary intervention (PCI) practice trends and 12-month outcomes in Australia in the era of drug-eluting stents (DES).

Design, setting and patients: Prospective study of consecutive patients undergoing 9204 PCIs between 1 April 2004 and 31 March 2008 at seven Victorian public hospitals.

Main outcome measures: Temporal trends in baseline characteristics and in-hospital and 12-month clinical outcomes including death, myocardial infarction (MI), target vessel revascularisation (TVR) and composite major adverse cardiac events (MACE), from year to year.

Results: Between 2004–2005 and 2007–2008, the mean age of patients undergoing PCI was stable (65 ± 12 years), and comorbidities such as hypertension, hyperlipidaemia, peripheral arterial disease and stroke increased ($P < 0.05$). There were fewer elective and more urgent PCIs, especially for MI < 24 hours (17.6% in 2004–2005 to 27.2% in 2007–2008, $P < 0.01$). Overall stent use remained high (mean, 94.6%), but use of DES declined steadily (53.9% in 2004–2005 to 32.0% in 2007–2008, $P < 0.01$), despite increases in complex lesions. Planned clopidogrel therapy of ≥ 12 months after insertion of DES increased from 54.7% in 2004–2005 to 98.0% in 2007–2008 ($P < 0.01$). The overall procedural success rate was high (mean, 95.9%), and 12-month rates of mortality (3.8%), MI (4.8%), TVR (6.8%) and stent thrombosis (1.8%) remained low. Selective use of DES was an independent predictor of freedom from MACE at 12 months (odds ratio, 0.68; 95% CI, 0.56–0.81).

Conclusions: Use of DES declined steadily from 2004–2005 to 2007–2008, despite increasing patient risk profile and lesion complexity. Procedural success remained high and 12-month adverse outcomes remained low, with increasing use of prolonged dual antiplatelet therapy.

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Over the past decade, percutaneous coronary intervention (PCI) has replaced coronary artery bypass graft surgery as the most common coronary revascularisation strategy for treating coronary artery disease in Australia.[1] Current procedural success rates are high, with improved clinical outcomes as a result of increasing operator experience and technological and pharmacological advances, including potent antiplatelet therapy, aggressive secondary prevention and drug-eluting stents (DES).[2]

Uptake of DES was rapid after their introduction in 2003, with use as high as 90% in 2004.[3,4] Initial enthusiasm was tempered by concerns over the long-term safety of DES, associated with the potential increased risk of late (> 30 days) and very late (> 12 months) stent thrombosis, myocardial infarction (MI) and mortality.[5-7] This led to a significant fall in the use of DES worldwide from 2006.[3] However, the safety of DES up to 5-year follow-up has been confirmed in recent studies.[8,9] The impact of this controversy relating to DES highlights the need for accurate PCI outcome data in an era of rapid evolution of device technology.

Little is known about PCI practice and outcome trends in the era of DES in Australia. Previous studies that analysed temporal trends of PCI in Australia predate the introduction of DES and lack detailed clinical and patient information to determine trends in patient risk profile.[10,11] We aimed to evaluate PCI practice trends and 12-month outcomes in consecutive patients undergoing PCI using data from a large Australian PCI registry.

METHODS

Patient population and registry design

The study population consisted of consecutive patients undergoing 9204 PCI procedures between 1 April 2004 and 31 March 2008 that were recorded in the Melbourne Interventional Group (MIG) registry. We divided the data into four yearly periods (starting 1 April and ending 31 March the following year) for analysis.

The MIG registry (http://www.ccretherapeutics.org.au/research/mig) has been previously described.[4,12] Demographic, clinical and procedural characteristics for consecutive patients undergoing PCI at seven Australian public tertiary referral hospitals are prospectively recorded on case-report forms using standardised definitions for all fields.

An "opt-out" consent process is used, in which patients are provided with an information sheet that describes the registry and its purpose and explains that routine follow-up will be performed. Patients can call a 1800 free-call number if they do not wish to be included in the registry. This model has been recommended in clinical-quality registries and is currently used in other Australian registries.[13-15] The study protocol was approved by the ethics committee in each participating hospital.

An independent audit was conducted at all enrolling sites by an investigator not affiliated with the institution. Fifteen verifiable fields from 5% of patients enrolled from each site were randomly audited and demonstrated an overall accuracy of 96.6%.

Procedures and post-intervention medications

The interventional strategy and stent selection were left to the discretion of the operator. In 2003, the Victorian Department of Human Services, with the aid of cardiologists, developed clinical guidelines for use of DES in public hospitals, restricting their use to patients at high risk of restenosis who will theoretically derive the greatest benefit.[16] The criteria for using DES included one or more of: diabetes mellitus, small target vessels (≤ 2.5 mm diameter), long lesions (≥ 20 mm), and complex lesions such as chronic total occlusion, in-stent restenosis, and bifurcation and ostial lesions.

The PCI procedure was defined as urgent if it was required during an emergency admission to minimise the chance of further clinical deterioration, including unstable angina, heart failure, acute MI and cardiogenic shock.[17] Total stent length was used as a surrogate for target lesion length, and stent

1 Trends in baseline characteristics for patients undergoing percutaneous coronary intervention (PCI), by year*

	Overall	2004	2005	2006	2007	*P*
Procedures	9204	1195	2665	2926	2418	
Mean patient age (years)	64.6	64.7	64.9	64.3	64.7	0.45
Age group (years)						
< 65	48.0%	46.9%	46.5%	49.3%	48.7%	
65–80	41.1%	42.1%	42.2%	40.3%	40.4%	
> 80	10.9%	11.0%	11.3%	10.4%	10.9%	
Male	74.7%	72.9%	73.3%	75.1%	76.5%	< 0.01
Comorbidities						
Diabetes mellitus	24.0%	23.6%	22.5%	24.5%	25.3%	0.05
Hypertension	64.3%	60.7%	62.7%	65.0%	67.0%	< 0.01
Hyperlipidaemia	71.3%	64.9%	73.1%	72.1%	71.4%	0.02
Current smoker	22.5%	22.0%	21.8%	23.0%	22.9%	0.32
Peripheral arterial disease	7.0%	5.7%	6.5%	6.8%	8.2%	< 0.01
Stroke	5.9%	4.6%	5.4%	6.2%	6.6%	< 0.01
Moderate/severe renal disease	4.1%	5.3%	4.0%	0.3%	4.8%	0.73
Cardiac history						
History of myocardial infarction	30.4%	31.8%	27.3%	32.1%	31.1%	0.14
History of heart failure	3.8%	3.7%	3.5%	4.0%	4.2%	0.24
Prior PCI	24.4%	24.1%	24.1%	24.1%	25.3%	0.37
Prior coronary artery bypass graft	9.4%	7.5%	9.7%	9.8%	9.6%	0.13

* Each year is from 1 April to 31 March the following year.

diameter for target vessel diameter. Procedural success was defined by a residual stenosis of < 20% in stent procedures with TIMI (Thrombolysis in Myocardial Infarction) 3 flow.

Oral antiplatelet therapy followed the recommendations at the time, based on the original randomised trials of bare-metal stents (BMS) and DES, which used a combination of aspirin and clopidogrel for a minimum of 4 weeks for BMS and 3, 6 or 12 months for DES.[18]

Clinical outcomes

In-hospital complications were recorded at time of discharge. Major bleeding complication was defined as bleeding that occurred during or after the procedure until discharge, that required transfusion and/or prolonged hospital stay and/or caused a drop in haemoglobin level > 3.0 g/dL.[17] Thirty-day and 12-month follow-up was conducted by telephone, and cardiac events including death, MI, target vessel revascularisation (TVR; revascularisation of a previously treated coronary artery) and composite major adverse cardiac events (MACE; consisting of death, MI and TVR) were recorded. Cause of death outside hospital was confirmed with the patient's primary care physician. Stent thrombosis was classified as early (0–30 days after PCI) or late (31–365 days). Patients' medical records were reviewed to substantiate recorded events including MI, TVR and major bleeding. Any queries or inconsistencies were adjudicated by the site principal investigator (a cardiologist).

Statistical analysis

Temporal trends in baseline variables were examined with the linear-by-linear association test for categorical variables and by linear regression for continuous variables. The Kaplan–Meier method was used to estimate event-free survival rates, with log-rank tests used for curve comparisons.

Logistic regression models were used to adjust outcomes for differences across years and to estimate odds ratios (ORs) for adverse outcomes. Variables considered in the univariate analysis were: year of procedure; age; sex; use of DES; diabetes mellitus; hypertension; hyperlipidaemia; smoking history; renal impairment; prior heart failure; recent heart failure; family history of coronary artery disease; peripheral arterial disease; previous PCI; previous coronary artery bypass graft; acute coronary syndrome; cardiogenic shock; stroke; previous MI; use of glycoprotein IIb/IIIa inhibitor; multivessel disease; left main, left anterior descending or right coronary artery treated; bypass graft treated; American College of Cardiology/American Heart Association (ACC/AHA) type B2 and C lesions;[19] ostial, bifurcation and restenotic lesions; chronic total occlusion; stent length ≥ 20 mm; stent diameter ≤ 2.5 mm; and intended duration of clopidogrel therapy. Univariate variables with $P < 0.1$ were included in the multivariate model.

All calculated P values were two-sided, and $P < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS version 17.0 for Windows (SPSS Inc, Chicago, Ill, USA).

RESULTS

Baseline clinical characteristics

Baseline characteristics are shown in Box 1. During the study period, the mean age of patients was stable (65 ± 12 years). Prevalences of comorbidities such as hypertension, hyperlipidaemia, peripheral arterial disease and stroke increased from 2004–2005 to 2007–2008 (all $P < 0.05$).

Procedural characteristics

During the study period, there were increasing proportions of urgent procedures, and procedures for ST-elevation MI (STEMI) and MI < 24 hours (all $P < 0.01$) (Box 2). Other than an increase for the left anterior descending artery ($P = 0.03$), there were no significant changes in the types of vessels treated. The mean number of lesions treated per procedure declined ($P < 0.01$). Overall stent use remained high (mean, 94.6%), but use of DES declined from 53.9% in 2004–2005 to 32.0% in 2007–2008 ($P < 0.01$), despite an increase in complex lesions being treated, such as in-stent restenosis ($P = 0.02$), chronic total occlusion, bifurcation and ostial lesions (all $P < 0.01$). The likelihood of receiving DES decreased in successive years and was lowest in patients with cardiogenic shock and STEMI (Box 3). The use of glycoprotein IIb/IIIa inhibitors increased ($P < 0.01$), consistent with the increased proportion of patients with STEMI and non-STEMI being treated (Box 2). Procedural success remained high across the years (mean, 95.9%).

Despite the fall in use of DES, overall planned clopidogrel therapy of ≥ 12 months increased from 43.4% in 2004–

2 Trends in percutaneous coronary intervention procedural characteristics, by year*

	Overall	2004	2005	2006	2007	*P*
Procedures	9204	1195	2665	2926	2418	
Procedure type						
Elective procedure	44.8%	56.9%	52.0%	44.2%	35.5%	< 0.01
Urgent procedure	53.3%	40.7%	45.8%	56.9%	63.3%	< 0.01
Rescue procedure	1.9%	2.4%	2.2%	1.9%	1.2%	< 0.01
Myocardial infarction (MI), < 24 hours	23.0%	17.6%	20.4%	24.2%	27.2%	< 0.01
MI, 1–7 days	23.2%	16.4%	20.0%	25.3%	27.7%	< 0.01
Acute coronary syndrome	61.5%	63.4%	60.3%	59.4%	64.4%	0.22
ST-elevation MI	24.4%	19.6%	20.5%	26.5%	28.4%	< 0.01
Non-ST-elevation MI	23.7%	11.0%	28.1%	31.5%	26.6%	< 0.01
Shock	2.3%	2.3%	2.0%	2.3%	2.8%	0.13
Heart failure at presentation	5.0%	6.0%	6.0%	4.9%	5.6%	0.35
Cardiac anatomy and function						
Ejection fraction < 40%	10.9%	10.3%	11.3%	10.1%	11.5%	0.06
Multivessel disease	59.0%	56.3%	59.1%	57.8%	61.1%	0.05
Mean number of lesions treated	1.21	1.28	1.22	1.21	1.18	< 0.01
Glycoprotein IIb/IIIa inhibitor	28.1%	27.7%	25.2%	28.6%	30.8%	< 0.01
Vessel treated						
Left main coronary artery	0.9%	0.7%	0.8%	0.7%	1.2%	0.07
Left anterior descending artery	33.1%	32.4%	31.3%	34.1%	34.2%	0.03
Left circumflex artery	13.9%	15.4%	13.6%	13.4%	14.0%	0.33
Right coronary artery	31.5%	31.1%	32.3%	31.8%	30.5%	0.40
Bypass graft	3.0%	1.8%	3.3%	3.1%	3.1%	0.10
Lesion characteristics						
ACC/AHA type B2 or C	48.4%	45.0%	48.8%	51.3%	46.1%	0.68
In-stent restenosis	5.8%	5.1%	5.6%	5.7%	6.8%	0.02
Bifurcation	9.1%	6.6%	7.3%	8.4%	13.6%	< 0.01
Chronic total occlusion	3.2%	0.9%	3.2%	4.2%	3.3%	< 0.01
Ostial	5.3%	4.4%	4.2%	5.1%	7.4%	< 0.01
Mean maximum stent/balloon size (mm)	3.03	2.93	2.98	3.04	3.12	< 0.01
Mean stent length (mm)	18.54	18.26	18.60	18.56	18.62	0.62
Devices used						
Stents, any	94.6%	94.9%	94.8%	94.8%	93.8%	< 0.01
Bare-metal stent (BMS)	53.3%	46.5%	47.9%	52.3%	63.8%	< 0.01
Drug-eluting stent (DES)	44.7%	53.9%	50.5%	46.1%	32.0%	< 0.01
Mixed BMS and DES	3.4%	5.4%	3.6%	3.6%	2.1%	< 0.01
Balloon angioplasty alone	5.4%	5.1%	5.2%	5.2%	6.2%	
Procedural success	95.9%	95.7%	95.9%	95.6%	96.3%	0.37

ACC/AHA = American College of Cardiology/American Heart Association. * Each year is from 1 April to 31 March the following year.

2005 to 58.5% in 2007–2008 ($P < 0.01$) (Box 4). Planned duration of clopidogrel therapy was significantly longer after DES than BMS, with planned therapy of ⩾ 12 months after DES increasing from 54.7% in 2004–2005 to 98.0% in 2007–2008 ($P < 0.01$), and remaining at about a third for BMS.

In-hospital outcomes

Overall in-hospital mortality, MI and emergency coronary artery bypass graft rates remained low and steady (mean, 1.5%, 1.5% and 0.7%, respectively) (Box 5). However, the incidence of major bleeding increased from 1.0% in 2004–2005 to 2.3% in 2007–2008 ($P = 0.001$). In contrast, rates of stroke decreased ($P = 0.03$).

Twelve-month outcomes

Twelve-month follow-up was completed for 96.5% of procedures. Overall rates of MI (mean, 4.8%), death from any cause (3.8%) and TVR (6.8%) remained stable, but stent thrombosis (1.8%) increased significantly ($P = 0.03$) (Box 5). Kaplan–Meier estimates of 12-month MACE-free survival were similar for each year studied ($P = 0.06$) (Box 6). Unadjusted MACE rates at 12 months were lower in patients who received DES compared with BMS, driven mainly by lower TVR rates (Box 7).

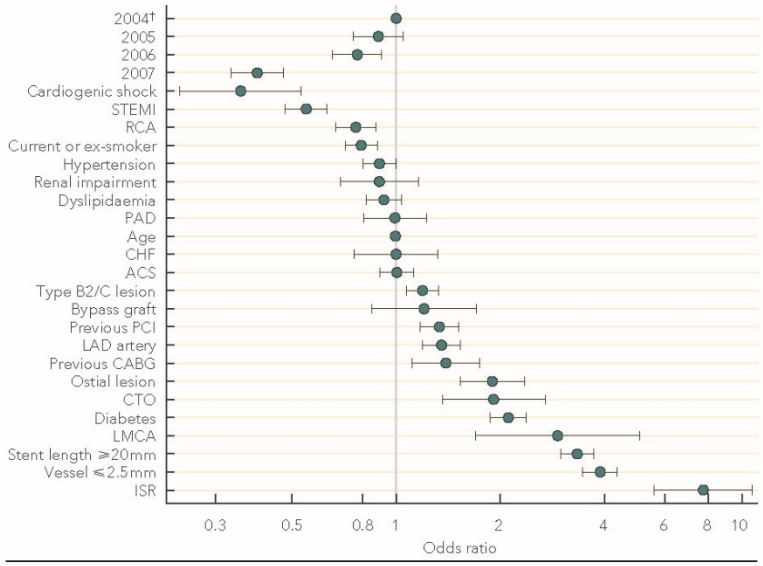
After adjustment, multivariate analysis demonstrated that use of DES was the only independent predictor of freedom from MACE at 12 months ($P < 0.01$), whereas increasing age, diabetes mellitus, renal failure, cardiogenic shock, peripheral arterial disease and multivessel disease were some of the independent predictors of 12-month MACE (all $P < 0.01$) (Box 8).

DISCUSSION

Our study represents the largest contemporary Australian multicentre analysis of PCI practice in the DES era. We observed several trends from 2004–2005 to 2007–2008, including increasing patient risk profile and lesion complexity; declining use of DES; an increase in planned clopidogrel therapy of ⩾ 12 months after DES; high stable rates of procedural success and low rates of 12-month adverse outcomes; and selective use of DES independently predicting improved outcome at 12 months.

National data show that although overall use of PCI in Australia has increased considerably since its introduction in the 1980s, its growth has slowed in recent years.[1] The reasons for this are unknown, but may include reduced need for re-intervention with the advent of DES, and aggressive secondary prevention contributing to reduced cardiovascular event rates. Findings from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, which showed that PCI had no mortality benefit over optimal medical therapy in patients with stable coronary artery disease,[20] have been shown to have an impact on the management of stable angina, with catheterisation referral volume decreasing, medication use increasing, and the use of medical therapy rather than revascularisation increasing among patients with coro-

3 Odds ratios* for likelihood of receiving a drug-eluting stent



ACS = acute coronary syndrome. CABG = coronary artery bypass graft. CHF = congestive heart failure. CTO = chronic total occlusion. ISR = in-stent restenosis. LAD = left anterior descending. LMCA = left main coronary artery. PAD = peripheral arterial disease. PCI = percutaneous coronary intervention. RCA = right coronary artery. STEMI = ST-elevation myocardial infarction. * Bars indicate 95% CIs. † 2004–2005 is reference group. Each year is from 1 April to 31 March the following year. ◆

nary disease.[21] Our findings of decreasing elective and increasing urgent PCI, especially for MI < 24 hours, support these observations.

There is considerable evidence that PCI in the setting of acute coronary syndromes reduces death and recurrent MI.[22] PCI is increasingly used to treat patients with acute MI. In particular, primary PCI is becoming the strategy of choice in most hospitals with cardiac catheterisation laboratory capabilities, and use of primary PCI has grown considerably in recent years due to 24-hour primary PCI services in most centres. According to the National Coronary Angioplasty Register, in Australia in 1999, the main uses of PCI were for stable angina (42%), unstable angina (42%) and acute MI (9%).[23] In our registry, acute coronary syndromes accounted for more than 60% of cases (> 20% STEMI). The increase in in-hospital incidence of major bleeding that we found may be related to increased proportions of patients with acute MI and use of glycoprotein IIb/IIIa inhibitors, which are known predictors of increased bleeding risk.[24]

The high rate of stent use has enabled more complex procedures to be undertaken in more acute situations. In 1995, coronary

4 Planned duration of clopidogrel therapy, by stent type and year*

Months	Overall	2004	2005	2006	2007
1†	24.7%	18.3%	22.4%	21.6%	33.9%
BMS	46.1%	41.5%	46.8%	41.2%	51.6%
DES	0.7%	0.6%	0.7%	0.5%	0.9%
3†	6.3%	9.5%	8.0%	5.2%	4.4%
BMS	7.9%	6.3%	9.6%	8.7%	6.5%
DES	4.4%	11.6%	6.6%	1.3%	0.3%
6†	15.6%	28.8%	25.0%	12.0%	3.2%
BMS	12.3%	24.4%	19.8%	10.3%	4.4%
DES	19.7%	33.0%	29.7%	14.3%	0.8%
≥ 12†	53.4%	43.4%	44.6%	61.1%	58.5%
BMS	29.8%	27.8%	23.8%	39.8%	37.6%
DES	57.2%	54.7%	63.0%	73.8%	98.0%

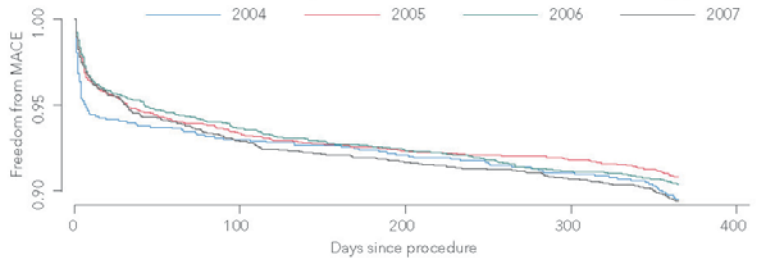
BMS = bare-metal stents. DES = drug-eluting stents. * Each year is from 1 April to 31 March the following year. † *P* for trend < 0.01. ◆

5 Clinical outcomes, by year*

	Overall	2004	2005	2006	2007	*P* (trend)
Mean length of stay, days	3.6	3.2	3.2	3.8	3.8	< 0.001
In-hospital outcomes (*n*)	9204	1195	2665	2926	2418	
Death	1.5%	1.3%	1.5%	1.5%	1.5%	0.64
Myocardial infarction	1.5%	1.8%	1.1%	1.2%	1.6%	0.15
Major bleeding	1.9%	1.0%	1.5%	2.4%	2.3%	0.001
Stroke	0.2%	0.6%	0.2%	0.1%	0.2%	0.03
Unplanned CABG	0.7%	0.6%	0.9%	0.6%	0.6%	0.51
30-day outcomes (*n*)	9204	1195	2665	2926	2418	
Death	1.8%	1.4%	2.0%	1.7%	2.0%	0.5
Myocardial infarction	2.2%	3.1%	1.8%	2.2%	2.5%	0.81
Target vessel revascularisation	2.1%	2.5%	2.0%	2.2%	2.0%	0.49
MACE	5.3%	6.5%	5.1%	1.9%	5.3%	0.31
Stent thrombosis	0.6%	0.3%	0.4%	0.8%	0.8%	0.01
12-month outcomes (*n*)	8885	1166	2631	2775	2313	
Death	3.8%	2.7%	4.0%	4.0%	4.0%	0.41
Myocardial infarction	4.8%	5.1%	3.9%	4.9%	5.4%	0.17
Target vessel revascularisation	6.8%	7.5%	6.5%	6.8%	8.2%	0.18
MACE	12.6%	13.3%	12.3%	12.7%	14.7%	0.09
Stent thrombosis, > 30 days	1.0%	0.8%	0.9%	1.1%	1.1%	0.32
Stent thrombosis, total	1.8%	1.5%	1.3%	2.3%	2.2%	0.03

CABG = coronary artery bypass graft. MACE = major adverse cardiac events (composite of death, myocardial infarction and target vessel revascularisation). * Each year is from 1 April to 31 March the following year. ◆

6 Estimates of freedom from major adverse cardiac events (MACE),* by year†



*Composite of death, myocardial infarction and target vessel revascularisation. † Each year is from 1 April to 31 March the following year. $P = 0.06$.

7 Clinical outcomes at 12 months, by stent type and year*

	Drug-eluting stents					Bare-metal stents				
	2004	2005	2006	2007	P†	2004	2005	2006	2007	P†
Death	1.4%	3.7%	3.0%	3.0%	0.05	3.8%	4.0%	4.6%	4.3%	0.88
MI	5.6%	3.9%	4.5%	6.6%	0.50	4.4%	4.2%	4.6%	4.3%	0.76
TVR	7.0%	4.7%	4.9%	5.2%	0.10	6.9%	6.7%	6.7%	8.0%	0.85
MACE	12.4%	10.3%	10.1%	12.3%	0.16	12.8%	12.4%	12.6%	14.2%	0.93

MI = myocardial infarction. TVR = target vessel revascularisation. MACE = major adverse cardiac events (composite of death, MI and TVR). * Each year is from 1 April to 31 March the following year. † For trend.

8 Independent predictors of 12-month major adverse cardiac events

Variable	Odds ratio (95% CI)
Drug-eluting stent	0.68 (0.56–0.81)*
Age (per year increase)	1.01 (1.00–1.02)*
Glycoprotein IIb/IIIa use	1.32 (1.11–1.58)*
Diabetes mellitus	1.30 (1.10–1.54)*
Left anterior descending artery	1.34 (1.11–1.61)*
Cerebrovascular disease	1.40 (1.08–1.82)†
Peripheral arterial disease	1.48 (1.15–1.91)*
Multivessel disease	1.53 (1.29–1.81)*
Renal failure	2.26 (1.70–3.01)*
Cardiogenic shock	4.36 (3.01–6.33)*

* $P < 0.01$. † $P = 0.01$.

stents were used in 30% of PCI procedures as bail-out for complications, but, by 2000, they were used in 89% of cases.[1] We have shown that overall stent insertion rates were close to 95%, although use of DES declined to 32% in 2007–2008 (in line with the Victorian Department of Human Services recommendation for 30%–40% use).[16]

Concerns over the safety of DES linked to the risk of late stent thrombosis were first raised in 2004.[25] Although subsequent meta-analyses and large observational studies have shown efficacy of DES without major safety concerns, this controversy has influenced clinical decisions, with many registries demonstrating lower use of DES during 2007.[3,26] Our data suggest that use of DES was already decreasing before 2006, when the first large study demonstrating safety concerns was presented.[6] Patient selection for DES in the MIG registry hospitals remains focused on those at highest risk of restenosis, who should be tolerant of dual antiplatelet therapy. The rate of use of DES in the long term remains uncertain, and will be strongly influenced by the efficacy and safety balance of newer-generation DES.

We have previously reported that in Victorian public hospitals, DES have been used predominantly in patients with risk factors for restenosis (87.7% of PCIs with DES had at least one criterion for high risk of restenosis),[4] in accordance with current guidelines. However, many patients deemed at high risk of restenosis did not receive DES, and we hypothesised at the time that greater use of DES in these patients may improve clinical outcomes by reducing restenosis. We have also previously reported that patients who received DES had similar mortality rates to those who received BMS (propensity score-adjusted OR, 0.82 [95% CI, 0.56–1.20]; $P = 0.31$) and significantly lower TVR rates (propensity score-adjusted OR, 0.66 [95% CI, 0.48–0.90]; $P < 0.01$) at 12 months.[27] In the current study, despite increasing patient risk profile and lesion complexity, highly selective use of DES in 32% of PCI procedures in 2007–2008 achieved comparable low rates of adverse outcomes at 12 months to those seen with higher use of DES (54% of PCI) in 2004–2005. Furthermore, selective use of DES is likely to be a more cost-effective strategy.[28]

Dual antiplatelet therapy (aspirin and clopidogrel) was almost universally prescribed for at least 12 months after DES in 2007–2008, as per the recommendation of the ACC/AHA guidelines (released in late 2007) for patients at low risk of bleeding.[19] We recently reported results showing the clear benefits of longer dual antiplatelet therapy.[29] Given that the optimal duration of clopidogrel therapy after DES is not established, the dramatic increase in the proportion of patients prescribed ⩾12 months of clopidogrel after DES in this study may suggest a trend towards indefinite use of dual antiplatelet therapy in clinical practice.

Our study has some limitations. As not all Victorian public hospitals were represented, our findings may not reflect PCI practice in non-participating hospitals. A registry has inherent limitations and biases that may not be completely adjusted for by modelling. For example, the choice of stent was at the discretion of the operator, and some of the procedural and patient factors precluding the use of DES may not have been captured. Appraisal of low-frequency clinical events such as late thrombosis is limited. The MIG registry has now been linked to the National Death Index to acquire longer-term (>12 months) mortality rates. Finally, the MIG registry is procedure-based rather than patient-based, so any patients who underwent multiple PCIs during the study period were not accounted for. We are currently performing patient-specific analysis to assess specific cohorts, such as patients returning on multiple occasions with in-stent restenosis.

Interventional cardiology continues to evolve in respect to selection of patients, devices used, and adjunctive drug treatment. Despite increasing risk profiles of patients undergoing PCI, procedural success has remained high and adverse outcomes

remain low. These results were achieved with more selective use of DES and longer duration of dual antiplatelet therapy.

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COMPETING INTERESTS

None relevant to this article declared (ICMJE disclosure forms completed).

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Appendix 5

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The Asia-Pacific Evaluation of Cardiovascular Therapies (ASPECT) Collaboration —Improving the quality of cardiovascular care in the Asia Pacific Region ☆

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ABSTRACT

Background: Clinicians and other stakeholders recognize the need for clinical registries to monitor data in order to improve the outcome and quality of care in the delivery of medical interventions. The establishment of a collaboration across the Asia Pacific Region to inform on variations in patient and procedural characteristics and associated clinical outcomes would enable regional benchmarking of quality.
Aims & methods: The aims of the collaboration are a) to identify the characteristics of patients undergoing PCI across the Asia Pacific region, b) to report on outcomes of patients undergoing PCI, c) to develop an appropriate ethnic and region specific risk adjustment model for patients undergoing PCI and d) to establish a registry framework for research, education and training in the area of cardiovascular interventions across the Asia Pacific Region. Descriptive characteristics of patient undergoing PCI over a 12 month period were collated and reported.
Results: Representatives from 27 hospitals attended the inaugural meeting with interested parties from Australia, Singapore, Malaysia and Hong Kong. In every country, males predominated PCI activity. Subjects were older and had higher rates of family history of cardiovascular disease in Australia, while Asian subjects had higher rates of diabetes, dyslipidemia and renal failure. STEMI presentation was higher in Australia than in Asia and drug eluting stent use was higher in Asia. Procedural success rates were similar across the region (>95%).
Conclusions: Procedural success was similar across the region despite differing patient characteristics across countries in terms of pre-procedural risk factors and clinical presentation.

1. Introduction

Cardiovascular disease is emerging as one of the major health issues facing the Asia Pacific region in the 21st century [1]. Rapid epidemiological transition is occurring in the space of decades where previously this evolution would have taken centuries. Fuelled by rapid economic development, many of the countries in the Asia Pacific region have evolved from states where high rates of infectious diseases dominated the cause for mortality to where non-communicable disease now takes precedence [2,3]. Cardiovascular disease across the region is fuelled by increasing rates of obesity, diabetes and hypertension resulting from rapid urbanization, dietary changes, high smoking rates and decreasing physical activity [4]. Add to the mix the fact that Asia, like most other countries across the globe, is also facing population aging; it is not surprising that cardiovascular disease prevention and management is a major focus [5].

Pharmacotherapy for blood pressure control, lipid lowering, antiplatelet and anti-thrombotic agents are now well accepted and widely used across the region. Importantly, strategies are being developed to implement cost-effective approaches including the development of

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the poly-pill [6]. The rapid economic development in Asia has also enabled major advances and investment in medical therapy and technology to be made available to combat the epidemic of cardiovascular disease across the region. Modern interventional procedures such as cardiac surgery and percutaneous coronary intervention have also become embedded into cardiovascular disease treatment strategies across the region. For example, there are cardiac surgical and interventional centers in Asia with expertise and facilities equal to anywhere in the world. In addition, these centers may be doing between up to a thousand of cases a year [7]. These new, and expensive, technologies are introduced with the expectation of providing improved clinical outcomes and quality of life. However, the evaluations of these new technologies are undertaken in predominantly European and North American populations and health care systems and not in the clinical situations or populations in which they are applied in the Asia Pacific region.

Furthermore, there is wide variation across the region in training and supervision. There are also issues of lack of certification and review of trainees with no outcome assessment and an insufficient platform for continuing professional development [7].

It has been well recognized for many years that establishing a cardiac registry for the monitoring of interventional activity and outcomes is a cornerstone of ensuring and maintaining quality in the delivery of cardiac interventions [8,9]. This has also been recognized in Asia and a number of countries have implemented data collection programs [10–12]. Regional differences across Asia in terms of service level, availability, facilities, training and ethnicity may greatly affect the characteristics of patients undergoing cardiac interventions, the procedural activity and the clinical outcomes across the region. Establishing a harmonized data repository that would allow for the assessment of these characteristics and early and longer outcomes would make a valuable contribution to optimizing patient care [12].

The Asia Pacific Evaluation of Cardiovascular Therapies (ASPECT) Collaboration was established in 2011 with the aims of a) understanding the characteristics of patients undergoing cardiac procedures across the Asia Pacific region, b) developing an appropriate ethnic specific risk adjustment model for patients undergoing cardiac procedures across the Asia Pacific Region, and c) reporting on the outcomes of patients undergoing cardiac procedures across the Asia Pacific Region. In addition, the ASPECT Collaboration would enable a registry framework for research, education and training in the area of improving outcomes from cardiovascular procedures across the Asia Pacific Region.

2. Methods

The inaugural meeting of the ASPECT Collaboration was held in Singapore at the ASEAN Congress of Cardiology in 2011. A review of literature and personal correspondence had identified existing registry initiatives in Singapore, Hong Kong, Malaysia and Australia. Local registry leads were identified and invited to participate in the meeting.

An international registry governance framework was discussed where de-identified information from each of the registries would be contributed centrally to a registry custodian to undertake statistical analyses and risk model development. Key issues identified in the establishment of an international databank were, a) ethical requirements, b) data security and c) risk adjustment for outcome comparison across the region.

2.1. Ethics

As not one ethics approval process covers an international registry initiative, it was identified that ethical requirements for cross border transfer of de-identified clinical information would vary markedly from country to country across the Asia Pacific Region. Asia Pacific countries have participated in multi-national randomized trials, however the patient consent process is the vehicle through which data usage and transfer are facilitated. However, in Australia for example, opt-off consent is the recommended mechanism and individual patient consent is not obtained. Opt-off consent has been shown to be critical in ensuring that participant bias is minimized in registry data analysis [13]. The ASPECT Collaboration agreed that approval for data aggregation across the region would be obtained from each participating registry at the local level prior to data merging at the individual patient level.

2.2. Data security

Despite data being de-identified, security issues were raised as a major concern for international pooling of registry data. Secure data file transfer protocols (SFTP) to an ISO27000 compliant data facility was considered as a standard to which the ASPECT registry should be conducted. The Monash University Centre for Cardiovascular Research and Education in Therapeutics (CCRET) was identified as a suitable custodian for the international registry satisfying the data security requirements.

2.3. Risk adjustment

The very nature of comparing outcomes across countries is an area of concern when the underlying characteristics of the patient populations are not well understood. There is ample literature to identify that clinical characteristics vary amongst different ethnic groups and health service providers. The ASPECT Collaboration identified the development of an Asia Pacific risk adjustment model as the critical step prior to the assessment of clinical outcomes across the region.

In summary, the ASPECT collaborators agreed to pursue the attainment of ethical approval at the country level to aggregate individual patient data and in the interim to provide tabulated data on the patient characteristics and procedural details in each of the existing registries.

2.4. Alignment of existing registry data

Data dictionaries from Singapore, Australia, Hong Kong and Malaysia were collated at CCRET. Data collected systematically for all patients and having a consistent definition across all centers was identified and is shown in web Appendix 1.

3. Results

3.1. Participating sites

Existing registries from Australia, Hong Kong, Malaysia, and Singapore agreed to contribute to the ASPECT Collaboration. In Australia, both the Melbourne Interventional Group Registry and the Coronary Angiography Registry Database of South Australia (CARDOSA) registries participated. Table 1 illustrates the number of individual hospital sites, the year the registry commenced data collection and the number of cases contributing towards the pooled analysis for the current report.

3.2. Patient Demographics

Across all countries, the majority of procedures were conducted on males ranging from 75–81% of all procedures (Table 2). The youngest groups undergoing PCI were from Singapore and Malaysia with the oldest cohorts from Australia. Of note, there were 2 to 3 times as many patients with a family history of coronary artery disease in the Australian cohorts in comparison to others. Surprisingly cigarette smoking rates were highest in Australia. Patients in Hong Kong and Malaysia had the highest rates of prior myocardial infarction and the Australian cohorts had a greater proportion of patients who had undergone a previous PCI or cardiac surgery. Rates for diabetes, hyperlipidemia and hypertension were highest in the Asian countries.

3.3. Procedural details

Fig. 1 illustrates the primary reason for PCI in the contributing cohorts. Acute coronary syndromes (ACS) were the major indication for PCI in Australia, particularly in South Australia. Nearly half of all ACS was associated with nonST elevated myocardial infarction (NSTEMI).

Table 1
Participating sites in the Asia-Pacific Evaluation of Cardiovascular Therapies Collaboration.

Country	Sites	Established	Cases
Melbourne	8	2004	19,555
Hong Kong	1	2009	2500
Malaysia	14	2007	25,472
Singapore	3	2000	4080
South Australia	4	2011	1001

Table 2
Demographic characteristics of patients undergoing PCI in the ASPECT registry.

Characteristic	Victoria	Hong Kong	Malaysia	Singapore	South Aust
% male	76	78	81	82	75
Age (x ± s.d)	65±	64±	57±	59 ± 11	63±
Dyslipidemia (%)	66	56	73	72	63
Family CAD (%)	36	16	19	12	43
Diabetes (%)	25	37	46	40	28
Hypertension (%)	70	64	74	66	63
Smoker (%)	24	24	18	29	32
Hx CAD (%)	7	6	2	14	5
Hx PVD (%)	6	1	1	2	4
Renal failure (%)	2	2	7	7	
Hx MI (%)	25	52	41	26	22
Hx PCI (%)	26	14	23	31	19
Hx CABG (%)	7	3	4	8	7

Procedural details varied considerably across the countries. In Malaysia and Singapore, 40% of all procedures were conducted using radial access. In South Australia, the figure was 54%, while it was less than 15% in Victoria and Hong Kong (Fig. 2). In-stent restenosis accounted for less than 10% of procedures in all countries and single vessel disease was the most prominent presentation. Peri-procedural thrombolytics were used in less than 5% of cases in all cohorts and 2B/3A use ranged from 30% in Victoria to 5% in Malaysia. Unfractionated heparin was used in more than 90% of cases in all cohorts. 95% of all procedures in all cohorts involved the deployment of stents. Drug eluting stent use varied being lowest in Victoria (43%) and highest in Hong Kong, Malaysia, and Singapore (Fig. 2).

3.4. Procedural outcomes and management

A high level of procedural success (>90%) was obtained across all contributing cohorts (Table 3). 98% of all patients undergoing PCI in Australia, Singapore, Malaysia and Hong Kong were commenced on aspirin. A similar proportion commenced on clopidogrel across the region with the exception of South Australia (88%).

4. Discussion

The ASPECT Collaboration provides the first opportunity to examine the variation in characteristics in patients undergoing PCI across the Asia Pacific Region and there are major differences in cohorts which may well impact on explaining variation in outcomes. These differences are also important factors to include in the development of risk adjustment models to enable meaningful outcome comparisons and the establishment of benchmarks for the region which will aid in the quality of care provided to patients. National registries for PCI have been well developed in the United States with the NCDR CathPCI Registry®

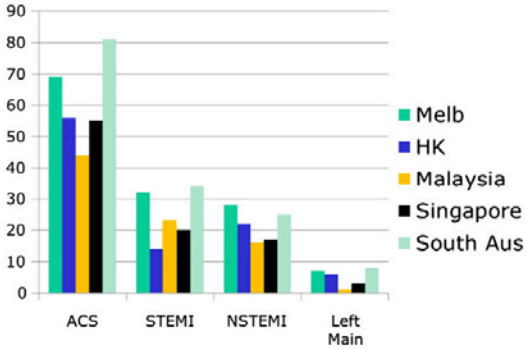

Fig. 1. Primary indication of PCI in the ASPECT registry.

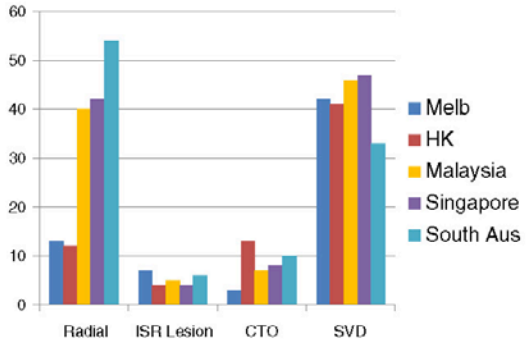

Fig. 2. Procedural details in ASPECT (add stents, DES).

collecting detailed clinical, process-of-care and outcome data for patients undergoing coronary angiography and percutaneous coronary intervention (PCI) in the USA [14]. The registry contributes to quality of care by providing data feedback on a wide range of performance metrics to participating centers and by facilitating local and national quality improvement efforts. From inception in 1998, more than 12 million records have been submitted from 1577 participating US centers [14]. The concept of a PCI registry for the ever increasing number of procedures undertaken in the region is not new and Japan and Korea have established registries with a focus on the use of drug-eluting stents [12,15].

Patients from the Australian centers were generally older on presentation for PCI in comparison to the Asian cohorts. This is similar to that reported in the Reduction of Atherothrombosis for Continued Health (REACH) Registry where the average age of patients with or at high risk of atherothrombosis was 65 years in Asia compared with 72 years in Australia [16]. A number of factors may underlay this observation including the prevalence of underlying risk factors, extent of drug treatment for risk factor management, and life expectancy. For example, rates of dyslipidemia and diabetes were highest in Singapore and Malaysia with the diabetes rates almost 50% higher than in the Australian cohorts. Australian cohorts had higher rates of family history of coronary artery disease and this may reflect a different stage of the cardiovascular disease epidemic across the region. Australia reached the peak of cardiovascular disease deaths in the mid 1970's and has declined ever since while these rates are still increasing across Asian countries [17]. A quarter to a third of all patients across the regions presented as current smokers highlighting the importance of smoking as a risk factor for coronary heart disease across all countries.

Acute coronary syndromes were the primary indication for PCI in all cohorts with the majority of presentation being NSTEMI.

Procedural details differed with the highest rates of radial access being reported in South Australia, Singapore and Malaysia with the lowest rates being reported in Hong Kong and Melbourne. This may well highlight operator preferences and training but also may be an important determinant of complications and outcomes.

In Australia, drug eluting stents were used in less than 50% of procedures with the highest rates of DES use reported in Hong Kong. As there is no standard indication for the choice of DES versus BMS across the region, these differences may be related to local guidelines or policy,

Table 3
Procedural outcomes and management in the ASPECT registry.

Characteristic	Victoria	Hong Kong	Malaysia	Singapore	South Aust
Procedural success (%)	96	95	97	97	97
Aspirin use (%)	98	98	97	96	98
Clopidogrel use (%)	98	97	98	95	88

funding requirements, or operator selection. In Hong Kong for example, the choice of stent is mainly determined by the patient's willingness to pay although some patients who cannot afford DES and fall below a certain income bracket, government subsidies may apply.

Procedural success rates were similar across the region and ranged from 95% in Hong Kong to 97% in Malaysia, South Australia & Singapore. Virtually all patients (>95%) were prescribed aspirin pre-procedure in all cohorts and similar high rates of clopidogrel use were seen in all cohorts with the exception on South Australia (88%). These rates are similar to that reported in registries across Europe and the United States.

4.1. Study limitations

There are a number of limitations that need to be considered in the interpretation of these results. Firstly, definitions do differ between registries and we have focused only on data elements which have the same definition across all registries. The registries vary in the number of contributing hospitals and hence cannot be considered as a complete representation of the country (with the exception of Singapore where all PCI centers contribute to the database). Individual-patient data are not included in the current report which represents tabulated data from each country. Patient outcomes including complication rates, death, myocardial infarction stroke, and bleeding are not available in all participating registries.

4.2. Future directions

The ASPECT Collaboration is an initiative driven by clinicians and investigators wanting to get a better understanding of the delivery of cardiac care and outcomes for patients across the Asia Pacific region. This initial report has highlighted a) the need for prospective standardization of a minimum data set across the region, b) collation of individual patient data for pooled central registry analysis, and c) inclusion of key patient outcome information including complication rates, death, myocardial infarction stroke, and bleeding events.

Sustainable funding for registry management and analysis is one of the major challenges facing each individual registry. Various models exist ranging from National and State Government support through to consortium funding from industry and other key stakeholders. Current funding for the ASPECT Collaboration is from NHMRC Program Grant support to CMR however long term and stable support is required for the initiative to maximize its potential.

Each registry faces its own challenges in ensuring that high quality data is collected and all cases are collected in the registry. Data audit is seen as a critical success activity to be undertaken and reported by each registry [18].

5. Conclusions

The ASPECT Collaboration reports on the characteristics, clinical management and outcomes of patients undergoing PCI in centers across the Asia Pacific region. In comparison to Australia, Asian cohorts were younger and exhibited higher underlying risk factor profiles. This is likely to reflect underlying cardiovascular disease development of emerging economies as they go through the epidemiological transition. Individual patient data and expansion of the ASPECT registry to include more countries will enable the development of ethnic specific risk adjustment models and benchmark quality of PCI care across the region.

Acknowledgments

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Appendix 6

ORIGINAL ARTICLE

Original Article

Clinical characteristics and early mortality of patients undergoing coronary artery bypass grafting compared to percutaneous coronary intervention: Insights from the Australasian Society of Cardiac and Thoracic Surgeons (ASCTS) and the Melbourne Interventional Group (MIG) Registries

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Objectives: **Controversy continues over the optimal revascularisation strategy for patients with multi-vessel coronary artery disease. Clinical characteristics, risk profile, and mortality of patients undergoing coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) are thought to differ but there are limited contemporary comparative data.**

Methods: **We compared clinical characteristics, in-hospital and 30-day mortality of 3841 consecutive patients undergoing isolated CABG and 4417 undergoing PCI. Independent predictors of 30-day mortality were determined by multiple logistic regression analysis.**

Results: **CABG patients were older ($p < 0.01$). The CABG group had a higher incidence of diabetes, heart failure, left ventricular ejection fraction <45%, multi-vessel coronary artery, peripheral vascular and cerebro-vascular disease (all $p < 0.01$). Patients undergoing PCI had a higher incidence of recent myocardial infarction (MI) as the indication for revascularisation ($p < 0.01$). In-hospital and 30-day mortality was 1.8% and 1.7% in the CABG**

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group, and 1.4% and 1.8% in the PCI group, respectively. Independent predictors of 30-day mortality after CABG were age (odds ratio 1.1 per year, 95% confidence interval 1.0–1.1), cardiogenic shock (4.10, 1.7–10.5) and previous CABG (6.6, 2.4–17.7). Predictors after PCI were diabetes (2.7, 1.4–5.1), female gender (3.0, 1.6–5.5), renal failure (3.2, 1.2–8.0), MI < 24 h (4.0, 2.2–7.6), left main intervention (5.4, 1.0–27.7), heart failure (6.0, 2.6–14.0) and cardiogenic shock (11.7, 5.4–25.2).

Conclusions: **In contemporary clinical practice, CABG is preferred in patients with multi-vessel coronary and associated non-coronary vascular disease, while PCI is the dominant strategy for acute MI. Despite this, in-hospital and 30-day mortality rates were similar. Predictors of early mortality after CABG differ to those of PCI.**

(Heart, Lung and Circulation 2009;18:184–190)

Keywords. Coronary artery bypass surgery; Percutaneous coronary intervention

Introduction

Coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) with or without stent implantation are alternative strategies for the treatment of ischaemic obstructive coronary artery disease. Generally, CABG is the preferred strategy in patients with left main or triple-vessel coronary disease with reduced left ventricular function [1]. PCI is generally preferred in patients with single or two-vessel disease unless adverse lesion characteristics are present [2]. The major limitation of PCI with bare-metal stents (BMS) compared to CABG has been a greater need for repeat revascularisation [3,4]. Recently, the introduction of drug-eluting stents (DES) has been shown to significantly reduce the incidence of restenosis and hence the need for repeat revascularisation in certain lesion and patient subsets [5,6]. This has led to widespread uptake of DES in more complex lesions compared with those used in randomised trials [7]. As a result, PCI is increasingly performed for indications in patients who have traditionally been referred for CABG.

Despite this, there are presently limited registry and randomised data regarding the clinical characteristics, risk profile, and mortality of patients undergoing CABG compared to PCI in the era of DES. We aimed to compare the clinical characteristics of patients undergoing CABG vs. PCI and determine the risk factors for early mortality utilising two large multi-centre Australian registries.

Methods

The study population comprised 8258 operations and procedures performed from 1 April 2004 to 30 June 2006. This consisted of 3841 consecutive patients undergoing isolated CABG in the Australasian Society of Cardiac and Thoracic Surgeons (ASCTS) registry (CABG group) and 4417 consecutive patients undergoing PCI in the Melbourne Interventional Group (MIG) registry (PCI group).

The ASCTS registry collects data on patients undergoing CABG at all public cardiac surgical centres in Victoria, Australia [8]. The MIG registry is a collaborative venture of interventional cardiologists practicing at seven Victorian public tertiary referral hospitals [9]. Both registries are independently coordinated through an academic outcomes research centre at Monash University, Melbourne, Australia. Demographic, clinical and procedural characteristics were prospectively recorded using standardised definitions for all fields [8,9]. Ethical approval and "Opt-out" informed consent was obtained in all patients, as previously described [8,9].

The ASCTS database is subject to regular random audits where 5% of cases are audited for 38 out of >200 fields. The quality of data collection has been consistently excellent. An independent random MIG audit examined 10 verifiable fields from 3% of all patients enrolled from each site. Overall data accuracy in the MIG registry was 97%.

Multi-vessel disease is defined as >50% stenosis in two coronary systems. Coronary systems are defined as (i) left anterior descending and diagonal arteries, (ii) left circumflex and obtuse marginal arteries and (iii) right coronary artery. Left main coronary artery is considered multi-vessel disease as it gives rise to the left anterior descending and left circumflex artery systems.

Current heart failure was defined in the MIG registry as clinical heart failure within 14 days of index procedure whereas in the ASCTS registry, it is defined as clinical heart failure during the same admission. The most recent assessment of left ventricular ejection fraction (LVEF) by SPECT imaging, echocardiography or left ventricular angiography, prior to intervention or surgery was used. In the ASCTS registry, LVEF was expressed as normal (>60%), mildly (45–60%), moderately (30–44%) or severely (<30%) reduced. In the MIG registry, LVEF was estimate and expressed as a percentage. Otherwise, all other field definitions between the two groups were identical.

In-hospital complications were recorded at time of hospital discharge. Thirty-day mortality was obtained by telephone contact with patient, family member or treating medical practitioner. Cause of death outside hospital was confirmed with the patient's primary care physician.

CABG Procedures

Bypass grafting strategy, peri-operative management of antiplatelet therapy and the choice of using cardiopulmonary bypass was at the discretion of the individual surgeon.

PCI Procedures

The interventional strategy and stent selection was at the discretion of the operator. In 2003, PCI guidelines were developed for use of DES in public hospitals restricting their use for patients at high-risk of restenosis who will theoretically derive the greatest benefit, though this would be considered as largely "off-label" use [7]. The resulting criteria for use of DES included one or more of the

Table 1. *Baseline Characteristics.*

	CABG	PCI	*p*-Values
Number	3841	4417	–
Age (years) mean ± S.D.	66.0 ± 10.2	64.9 ± 12.0	<0.01
Male (%)	77.3	73.0	<0.01
Height (m) mean ± S.D.	1.69 ± 9.4	1.70 ± 9.7	0.02
Weight (kg) mean ± S.D.	81.1 ± 15.8	80.9 ± 15.8	0.56
BMI (kg/m^2) mean ± S.D.	28.4 ± 4.7	28.1 ± 4.9	0.03
Current smoking (%)	15.7	22.1	<0.01
Diabetes mellitus (%)	32.8	23.0	<0.01
Insulin requiring (%)	8.1	4.6	<0.01
Renal failure			
Creatinine (mmol/L) mean ± S.D.	0.10 ± 0.1	0.10 ± 0.1	<0.01
Creatinine ≥0.2 mmol/l (%)	2.6	3.7	<0.01
Dialysis (%)	1.6	0.9	<0.01
Hypertension (%)	76.6	62.2	<0.01
Hypercholesterolaemia (%)	82.5	72.1	<0.01
History of myocardial infarction			
<24 h (%)	2.6	21.0	<0.01
1–7 days (%)	12.8	20.8	<0.01
>7 days (%)	40.0	28.9	<0.01
History of heart failure			
Current (%)	6.6	3.7	<0.01
Previous (%)	13.5	3.5	<0.01
Peripheral vascular disease (%)	13.5	6.9	<0.01
Cerebral vascular disease (%)	12.0	5.5	<0.01
Previous CABG (%)	2.8	9.9	<0.01
Previous valve surgery (%)	0.1	0.6	<0.01
Cardiogenic shock (%)	2.2	2.1	0.65
Intra-aortic balloon pump (%)	5.0	1.8	<0.01
Indication			
Urgent (%)	46.3	50.0	<0.01
Elective (%)	53.7	50.0	<0.01
Left ventricular ejection fraction			
Mean% ± S.D.	55.4 ± 13.6	56.2 ± 13	<0.01
Extent of disease			
Single vessel (%)	4.0	41.2	<0.01
Mutli-vessel (%)	96.0	58.8	<0.01

BMI = body mass index; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

following: diabetes mellitus, renal failure, small target vessels (≤2.5 mm), long lesions (≥20 mm) and complex lesions such as chronic total occlusions, in-stent restenosis, bifurcation and ostial lesions.

Total stent length was used as a surrogate for target lesion length, and stent diameter for target vessel diameter. Peri-procedural glycoprotein IIb/IIIa inhibitors were used at the operator's discretion. Oral anti-platelet therapy followed guidelines which recommend combination of aspirin and clopidogrel for a minimum of 4 weeks for BMS and between 3 and 12 months for DES [2].

Statistics

Datasets were merged after common definitions of all fields were identified. Unadjusted comparison of clinical characteristics, in-hospital and 30-day mortality between registries were performed. Continuous variables were expressed as mean ± S.D., and categorical data expressed as percentages. Continuous variables were compared using Student's *t*-tests. Categorical variables were compared using Fisher exact tests. Univariate and multivariate predictors of in-hospital and 30-day mortality for PCI and CABG were identified by logistic regression. All significant univariate variables at $p < 0.10$ were then included in multivariate models to identify independent predictors ($p < 0.05$). All statistical analysis was performed using SPSS Version 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Baseline Characteristics

Patients who underwent CABG compared to PCI were older (66.0 ± 10.2 vs. 64.9 ± 12.0, $p < 0.01$) (Table 1). However, octogenarians were more likely to undergo PCI than CABG (11.2 vs. 5.7%, $p < 0.01$) (Fig. 1).

Patients undergoing CABG had a higher incidence of diabetes (32.8 vs. 23.0%, $p < 0.01$), history of heart failure (current, 6.6 vs. 3.7%, $p < 0.01$ and previous 13.5 vs. 3.5%, $p < 0.01$), MI >7 days (40.0 vs. 28.9%, $p < 0.01$), more diffuse vascular disease including multi-vessel coronary artery disease (96.0 vs. 58.8%, $p < 0.01$), peripheral vascular disease (13.5 vs. 6.9%, $p < 0.01$) and cerebrovascular disease

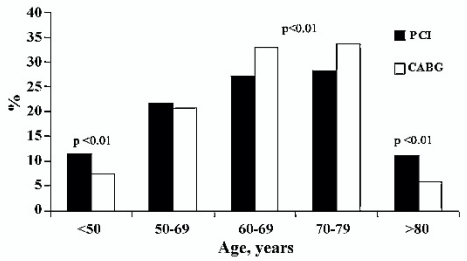

Figure 1. *Proportion of patient by age group (BMS = bare-metal stents; DES = drug-eluting stents).*

(12.0 vs. 5.5%, $p < 0.01$). Conversely, patients undergoing PCI had a higher incidence of recent MI (<24 h, 21.0 vs. 2.6%, $p < 0.01$ and 1–7 days, 20.8 vs. 12.8%, $p < 0.01$, respectively). Somewhat surprisingly, there was no difference in the incidence of cardiogenic shock between the two groups (2.1 vs. 2.2%, $p = 0.65$).

Procedural Characteristics

CABG. Coronary artery bypass grafting is still utilised primarily for three vessels disease (74%) with a mean total of 3.3 ± 1.0 bypass grafts per procedure (Table 2). Arterial bypass grafts were predominantly used; mean of 2.4 ± 1.1 arterial grafts compared to a mean of 0.9 ± 1.0 saphenous venous grafts. Single and bilateral internal thoracic arterial grafts were used in 96.1% and 12.6% of cases, respectively. Most CABG procedures were performed with cardiopulmonary bypass; only 4.6% were conducted off-pump. Reoperation was performed in 2.8% of cases. More patients received intra-aortic balloon pump compared to patients who underwent PCI (5.0 vs. 1.8%, $p < 0.01$).

PCI. Left main coronary, left anterior descending artery and bypass graft interventions were performed in 0.7%, 32.0% and 3.1% of patients, respectively (Table 3). A mean of 1.22 ± 0.5 lesions were treated per procedure. Stents were implanted in 94.6% of case, of which drug-eluting stents were used in 51.7% of patients.

Clinical Outcomes

In-hospital and 30-days follow up was complete in 100% and 95%, respectively. Unadjusted in-hospital (1.8 vs. 1.4%, $p = 0.14$) and 30-day mortality rates (1.7% vs. 1.8%, $p = 0.87$) in patients who underwent CABG were similar to patients who underwent PCI (Fig. 2). There was no difference in 30-days survival on Kaplan–Meier analysis (Fig. 3). In the PCI group, the rate of stent thrombosis was 0.7% ($n = 32$).

Table 2. *Coronary Bypass Procedural Characteristics.*

	CABG
Number of diseased vessels (%)	
Single	4.0
Two	21.7
Three	74.0
Mean number of bypass grafts ± S.D.	3.3 ± 1.0
Mean number of arterial grafts ± S.D.	2.4 ± 1.1
Mean number of saphenous venous grafts ± S.D.	0.9 ± 1.0
Single internal mammary arterial graft used (%)	96.1
Bilateral internal mammary arterial graft used (%)	12.6
Off-pump procedure (%)	4.6

CABG = coronary artery bypass grafting.

Table 3. *Percutaneous Coronary Intervention Procedural Characteristics.*

	PCI
Mean number of lesions treated ± S.D.	1.22 ± 0.5
Vessel treated (%)	
Left main coronary artery	0.7
Left anterior descending artery	32.0
Proximal left anterior descending artery	14.5
Left circumflex artery	13.9
Right coronary artery	32.2
Bypass grafts	3.1
ACC/AHA Type B2/C lesions (%)	50.2
Stents (%)	94.6
Drug-eluting stent	51.7
Bare-metal stent	42.9
Balloon angioplasty alone (%)	5.4

ACC/AHA = American College of Cardiology/American Heart Association; PCI = percutaneous coronary intervention.

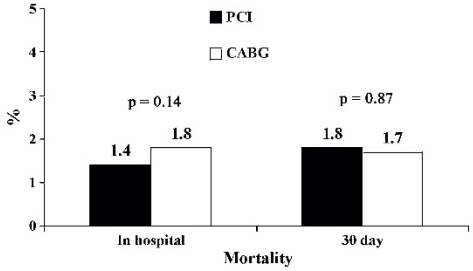

Figure 2. *In-hospital and 30-day mortality (BMS = bare-metal stents; DES = drug-eluting stents).*

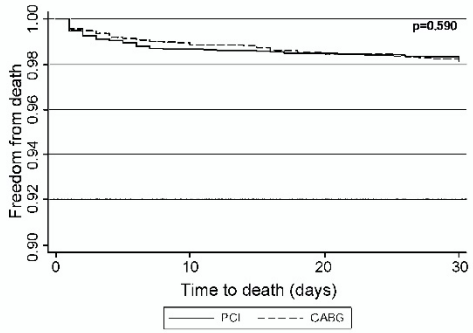

Figure 3. *Kaplan–Meier survival curve (BMS = bare-metal stents; DES = drug-eluting stents).*

Table 4. *Independent Predictors of 30-day Mortality.*

	CABG Odds Ratio (95% Confidence Interval)	PCI
Age/year	1.08 (1.04–1.13)	–
Diabetes	–	2.72 (1.44–5.13)
Left anterior descending artery	–	2.40 (1.34–4.31)
Female	–	2.99 (1.63–5.48)
Creatinine >0.2 mmol/l	–	3.16 (1.24–8.06)
Myocardial infarction <24 h	–	4.06 (2.17–7.60)
Left main coronary artery	–	5.37 (1.04–27.65)
Current heart failure	–	5.98 (2.55–14.04)
Cardiogenic shock	4.10 (1.67–10.05)	11.70 (5.43–25.22)
Prior CABG	6.56 (2.43–17.71)	–

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

Predictors of 30-day Mortality

Using the predetermined variables listed above, independent predictors of 30-day mortality in patients who underwent CABG were age (odds ratio (OR) 1.1 per year, 95% confidence interval (CI) 1.04–1.13), cardiogenic shock (OR 4.10, 95%CI 1.67–10.48) and previous CABG (OR 6.56, 95%CI 2.43–17.71) (Table 4). Independent predictors of 30-day mortality in patients who underwent PCI were different to those who underwent CABG with the exception of cardiogenic shock. They included diabetes mellitus (OR 2.72, 95%CI 1.24–8.06), female gender (OR 2.99, 95%CI 1.63–5.48), MI < 24 h (OR 4.06, 95%CI 2.17–7.60), current heart failure (OR 5.98, 95%CI 2.55–14.04), left main coronary artery disease (OR 5.37, 95%CI 1.04–27.64) and cardiogenic shock (OR 11.70, 95%CI 5.42–25.22).

Discussion

There are several important findings from this observational study of two databases (CABG and PCI) that demonstrate current utilisation of these revascularisation strategies. There were significant differences in clinical characteristics and risk profile between the two groups. Octogenarians were more likely to undergo PCI. Diabetics and patients with multi-vessel coronary, peripheral vascular and cerebral vascular disease were more likely to undergo CABG. PCI was overwhelmingly used in patients who presented with recent MI < 7 days. There were no differences in early (30-day) mortality rates between the two revascularisation strategies. Independent predictors for early mortality were different between treatment strategies. Females, diabetics and patients who presented with MI < 24 h who underwent PCI were at increased risk of short-term mortality whereas these variables were not associated with early mortality in the surgical group. For patients who underwent CABG, advancing age and previous CABG were independent predictors of mortality. Cardiogenic shock was the only clinical variable associated with increased mortality for both CABG and PCI.

Percutaneous coronary intervention and CABG are complementary methods of coronary revascularisation. The decision to offer patients CABG continues to be largely determined by the extent of coronary artery disease and LVEF. In patients with multi-vessel disease, CABG is still associated with higher rates of complete revascularisation and a greater durability than PCI with BMS, resulting in lower rates of repeat revascularisation. However, in patients who present with recent MI (STEMI or NSTEMI), the speed of reperfusion and the relatively low morbidity of PCI are distinct advantages over CABG. In our study, 21% of PCI compared to 2.6% of CABG were performed in patients who presented with MI < 24 h (mostly acute STEMI). The ACC/AHA STEMI guidelines recommend PCI as the initial reperfusion strategy for acute STEMI contingent upon rapid initiation [10]. This is based on multiple randomised trials demonstrating the superiority of rapid primary PCI over fibrinolysis in STEMI [11]. Moreover, CABG in the setting of acute MI is associated with increased mortality risk [12].

Clinical decision-making in coronary artery disease relies heavily on evidence-based medicine. Although randomised controlled trials (RCT) constitute the highest order of evidence and remain the standard for comparisons between therapies, RCT study populations are often highly selected and extrapolation of trial results to a more heterogeneous general population may be problematic. While comprehensive observational databases can be subject to numerous biases, they have significant value in validating real-world use of technologies and represent a more accurate accounting of everyday clinical care. We found that despite the introduction of DES in 2003, CABG remained primarily used for patients with multi-vessel, especially triple-vessel coronary artery disease and reduced left ventricular function. Nevertheless, 58.5% of PCI were performed in patients with multi-vessel disease. It is not known whether multi-vessel PCI or complete revascularisation was performed in these patients. This may affect long-term clinical outcome as failure of stenting to achieve complete revascularisation in patients with multi-vessel coronary artery disease has been associated with reduced survival [13].

Although DES reduce the risk of restenosis and the need for repeat revascularisation, there is no convincing evidence of DES reducing the risk of mortality or subsequent MI compared to BMS [14,15]. Furthermore, late (>30 days) and very-late (>12 months) stent thrombosis appears to be a potentially important limitation of DES. Stent thrombosis is associated with a high-risk of MI of 65–70% and mortality of 25–45% [16]. The annual risk of DES thrombosis is estimated at between 1% and 3% depending on the

complexity of the lesion, patient comorbidities and use in off-label situations [7].

It is unclear how contemporary PCI with DES compare with CABG in patients with a risk profile that is more advanced than in published RCTs. There are three large ongoing randomised trials (FREEDOM, SYNTAX and CARDIA) comparing DES against CABG in patients with diabetes, multi-vessel and left main coronary disease. Given the recent concern regarding late stent thrombosis with DES, the long-term outcomes of these three studies will be critical in determining the safety and effectiveness of stenting compared to CABG in these high-risk patients population.

Limitations

Our study has the inherent limitation of being a retrospective observational study. There were minor differences in definitions between the two registries. Discrepancy in the assessment of LVEF and incomplete data in this field may account for the wide variation in LVEF estimates.

Conclusions

The risk profile of patients undergoing CABG differs to those of patients having PCI. While there was no difference in short-term mortality, the predictors of poor outcome differed according to the revascularisation strategy. Not surprisingly, PCI was the dominant strategy for acute MI while CABG is preferred in patients with multi-vessel coronary and associated vascular disease. Long-term follow-up will aid randomised studies in determining the best revascularisation strategy for specific patient cohorts. Ultimately, instead of being competitive, CABG and PCI will be seen to be complementary.

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Appendix A.

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Appendix 7

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Does Prior Percutaneous Coronary Intervention Adversely Affect Early and Mid-Term Survival After Coronary Artery Surgery?

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Objectives To determine the association between previous percutaneous coronary intervention (PCI) and results after coronary artery bypass graft surgery (CABG).

Background Increasing numbers of patients undergoing CABG have previously undergone PCI.

Methods We analyzed consecutive first-time isolated CABG procedures within the Australasian Society of Cardiac and Thoracic Surgeons Database from June 2001 to May 2008. Logistic regression and propensity score analyses were used to assess the risk-adjusted impact of prior PCI on in-hospital mortality and major adverse cardiac events. Cox regression model was used to assess the effect of prior PCI on mid-term survival.

Results Of 13,184 patients who underwent CABG, 11,727 had no prior PCI and 1,457 had prior PCI. Mean follow-up was 3.3 ± 2.1 years. Patients without prior PCI had a higher EuroSCORE value (4.4 ± 3.3 vs. 3.6 ± 3.0, $p < 0.001$), were older, and more likely to have left main stem stenosis and recent myocardial infarction. There was no difference in unadjusted in-hospital mortality (1.65% vs. 1.55%, $p = 0.78$) or major adverse cardiac events (3.0% vs. 3.0%, $p = 0.99$) between patients with or without prior PCI. After adjustment, prior PCI was not a predictor of in-hospital (odds ratio: 1.22, 95% confidence interval [CI]: 0.76 to 2.0, $p = 0.41$) or mid-term mortality at 6-year follow-up (hazard ratio: 0.94, 95% CI: 0.75 to 1.18, $p = 0.62$).

Conclusions In this large registry study, prior PCI was not associated with increased short- or mid-term mortality after CABG. Good outcomes can be obtained in the group of patients undergoing CABG who have had previous PCI. (J Am Coll Cardiol Intv 2009;2:758–64) © 2009 by the American College of Cardiology Foundation

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Percutaneous coronary intervention (PCI) is emerging as the main treatment option for coronary artery disease and the number of PCI procedures are rapidly increasing worldwide (1–4). The widespread use of PCI has resulted in an increasing number of patients being referred for coronary artery bypass graft surgery (CABG) who have undergone prior PCI. Patients with a history of prior PCI undergo subsequent CABG either because of failure of the original PCI (10% to 30% of patients develop in-stent restenosis after PCI with stent implantation) or more commonly because of progression of native disease (5). The timing of

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subsequent CABG after prior PCI is usually around 12 months (6). One of the reasons accounting for the rapid increase in PCI use is the perception that if PCI fails, patients can safely be referred to surgery without adverse consequences. However, there are very little data on early and long-term outcomes in patients undergoing CABG with a history of prior PCI in the stenting era. Historical data in patients undergoing CABG having had previous percutaneous transluminal balloon angioplasty suggested worse early mortality in this group (7). Moreover, several reports have demonstrated worse outcomes in patients who have had prior PCI undergoing noncardiac surgery (8). In this large multicenter registry report, we aim to assess the association between prior PCI and short- and mid-term mortality after subsequent revascularization by CABG.

Methods

Study population. The study population comprised of 13,184 consecutive patients who underwent first-time, isolated CABG surgery in the ASCTS (Australasian Society of Cardiac and Thoracic Surgeons) Cardiac Surgery Database between June 2001 and May 2008. Patients with prior PCI (PCI group) were compared with patients without prior PCI (non-PCI group). Patients who underwent PCI during the same admission as their CABG were excluded from the analysis. This was to exclude those patients who may have had an unsuccessful PCI necessitating CABG on an urgent or emergent basis. Isolated CABG refers to the performance of CABG only; those patients requiring concomitant valve or other cardiac, such as atrial fibrillation surgery, or aortic procedures were thus excluded from this study.

All 6 Victorian public hospitals that perform adult cardiac surgery—The Royal Melbourne Hospital, The Alfred Hospital, Monash Medical Centre, The Geelong Hospital, Austin Hospital, and St Vincent's Hospital Melbourne—were involved in the prospective data collection for the ASCTS database during the entire study period. Additionally, 8 cardiac surgical units from South Australia, New South Wales, and Queensland joined the database in the last 12 months of the study period and contributed a total of 13.4% of the total patient numbers. The ASCTS database contained detailed information on patient demographics, pre-operative risk factors, operative details, post-operative hospital course, and morbidity and mortality outcomes. These data were collected prospectively using an agreed dataset and definitions as part of clinical care by surgeons, perfusionists, hospital medical officers, and database managers. Data collection and audit methods have been previously described (9–11). In the state of Victoria, the collection and reporting of cardiac surgery data is compulsory and mandated by the Victorian state government; hence it is all-inclusive. The data are subject to external audit measures with an overall data accuracy of 97.4% recently reported (11). 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 study end points were in-hospital death and major adverse cardiac events (MACE) and mid-term survival after CABG. We defined MACE as a composite end point of in-hospital death, myocardial infarction (MI), or stroke. Cause of in-hospital death was defined as cardiac or noncardiac. Mid-term survival status of patients was obtained from the Australian National Death Index. The closing date was June 30, 2008.

Abbreviations and Acronyms

CABG = coronary artery bypass graft surgery
MACE = major adverse cardiac events
MI = myocardial infarction
PCI = percutaneous coronary intervention

Pre-operative data analyzed were age; sex; the presence of diabetes mellitus, hypercholesterolemia, hypertension, cerebrovascular disease, peripheral vascular disease, renal failure, and respiratory disease; recent MI, congestive heart failure, or unstable angina; New York Heart Association functional class; presence of left main coronary artery stenosis >50%; degree of left ventricular impairment; and operation urgency and EuroSCORE value (additive). Hypercholesterolemia was defined as a history of fasting cholesterol >5.0 mmol/l or treatment of high cholesterol. Hypertension was blood pressure exceeding 140/90 mm Hg or a history of high blood pressure, or the need for antihypertensive medications. Cerebrovascular disease was any prior unresponsive coma >24 h, stroke or transient ischemic attack, or carotid stenosis >75%. Peripheral vascular disease was defined as any of the following: claudication, amputation for arterial insufficiency, aorto-iliac occlusive disease reconstruction or peripheral vascular surgery, or documented abdominal aortic aneurysm. Renal failure was defined as last pre-operative serum creatinine level >200 μmol/l or pre-operative dialysis-dependence. The most recent assessment of left ventricular function by nuclear imaging, echocardiography, or left ventricular angiography before surgery was used. Left

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ventricular ejection fraction was expressed as normal (>60%) or reduced: mildly (45% to 60%), moderately (30% to 44%), or severely (<30%). Recent MI is defined as the occurrence of an MI within 21 days of CABG. Urgency status is defined as elective, urgent (needing inpatient surgery), and emergent (needing surgery within 24 h).

Bypass grafting strategy, perioperative management of antiplatelet therapy, and the choice of using cardiopulmonary bypass were at the discretion of the individual surgeon.

Statistical methods. Continuous variables are presented as mean ± 1 SD. Fisher exact test and Mann–Whitney *U* test were used to compare categorical and discrete variables, respectively. Differences in in-hospital mortality and MACE between the PCI and non-PCI groups were assessed using multiple variable logistic regression and propensity score methods to account for differences in patient characteristics. In the former, the 17 variables listed in Table 1 were forced into a multiple logistic regression model with in-hospital mortality and MACE as the outcomes to obtain the adjusted odds ratio (OR) for the prior PCI variable. In the propensity score method, the 17 variables were entered into a stepwise logistic regression model to obtain the propensity score with prior PCI as the outcome variable. The propensity score model was assessed by checking for balance of each variable between the PCI and non-PCI groups across quartiles of risk. The propensity score and the prior PCI variable were then forced into a logistic regression model with in-hospital mortality and MACE as the outcome to obtain the adjusted odds ratio for the prior PCI variable.

Kaplan-Meier analysis was used to estimate mid-term survival. Differences in mid-term survival were assessed by the log-rank test. A Cox proportional hazards model using the 17 variables in Table 1 was constructed to assess the

Table 1. Pre-Operative Characteristics of Patients Undergoing Isolated CABG

Variable	Prior PCI (n = 1,457)	No Prior PCI (n = 11,727)	p Value
Age, yrs, mean ± SD	63.3 ± 10.5	66.0 ± 10.2	<0.001
<60, %	37.3	27.5	
60–69, %	33.5	33.0	
70–79, %	24.8	33.5	
≥80, %	4.5	6.0	
Female sex, %	20.3	22.8	0.03
Diabetes, %	32.5	32.2	0.79
Hypercholesterolemia, %	87.2	80.2	<0.001
Hypertension, %	78.6	75.2	0.005
Cerebrovascular disease, %	9.5	11.3	0.044
Peripheral vascular disease, %	11.8	12.8	0.28
Renal failure, %*	2.8	2.7	0.74
Respiratory disease, %	12.3	12.5	0.86
Myocardial infarction within 21 days, %	15.6	24.0	<0.001
History of congestive heart failure, %	16.6	17.7	0.27
Unstable angina, %†	8.3	9.9	0.06
NYHA functional class, %			0.38
I	35.1	36.4	
II	37.3	36.8	
III	21.1	19.5	
IV	6.6	7.3	
Left main stenosis >50%, %	18.5	25.8	<0.001
LV function, %			0.41
Normal or mild LV impairment (EF >45%)	70.1	68.6	
Moderate impairment (EF 30%–45%)	25.8	26.8	
Severe impairment (EF <30%)	4.1	4.7	
Urgency status, %			0.002
Elective	61.8	57.0	
Urgent	34.9	38.8	
Emergent	3.3	4.1	

*Defined as serum creatinine >0.20 mmol/l. †Defined as need for intravenous nitrates until arrival in the operating theater.
CABG = coronary artery bypass graft surgery; EF = ejection fraction; LV = left ventricular; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.

effect of prior PCI on mid-term survival. Tests were 2-sided, and $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS version 16.0 for Windows (SPSS Inc., Chicago, Illinois).

Results

BASELINE CHARACTERISTICS. Of 13,184 consecutive patients undergoing first-time isolated CABG, 1,457 (11.1%) had previously undergone PCI and 11,727 (88.9%) had no previous PCI (Table 1). Patients with previous PCI were younger (63.3 ± 10.5 years vs. 66.0 ± 10.2 years, $p < 0.001$); less likely to be female (20.3% vs. 22.8%, $p = 0.03$), have cerebrovascular disease (9.5% vs. 11.3%, $p < 0.05$), left main coronary artery stenosis (18.5% vs. 25.8%, $p < 0.001$), or recent MI (15.6% vs. 24.0%, $p < 0.001$); or undergo urgent CABG (34.9% vs. 38.8%, $p = 0.004$). The lower surgical risk profile of the patients who have had prior PCI is reflected in a lower EuroSCORE value (3.6 ± 3.0 vs. 4.4 ± 3.3, $p < 0.001$).

Operative characteristics. Intraoperatively, patients with a prior PCI had, on average, fewer distal coronary anastomoses performed (3.0 ± 1.1 vs. 3.3 ± 1.0, $p < 0.001$), shorter cross-clamp times (61.5 ± 34.8 min vs. 68.0 ± 35.7 min, $p < 0.001$), and shorter bypass times (83.6 ± 43.4 vs. 91.7 ± 42.6 min, $p < 0.001$). Use of the internal mammary artery graft was slightly lower in the PCI group (95.3% vs. 97.3%, $p < 0.001$), as was the use of off-pump CABG (8.2% vs. 11.3%, $p < 0.001$).

CLINICAL OUTCOMES. There was no difference in unadjusted in-hospital mortality between patients with or without previous PCI (1.65% vs. 1.55%, $p = 0.78$). There was no preponderance of cardiac death in either group (49% vs. 56%, $p = 0.67$). In-hospital MACE rates were 3.0% in both

Table 2. Multiple Variable Logistic Regression Analysis of Variables Associated With In-Hospital Mortality and MACE

Variable	In-Hospital Mortality Odds Ratio (95% CI)	p Value	In-Hospital MACE Odds Ratio (95% CI)	p Value
Age, yrs				
<60	1.00	—	1.00	—
60–69	1.11 (0.66–1.89)	0.69	1.14 (0.82–1.60)	0.43
70–79	2.35 (1.46–3.77)	<0.001	1.81 (1.33–2.48)	<0.001
≥80	5.19 (2.99–9.02)	<0.001	2.87 (1.90–4.29)	<0.001
Female sex	1.40 (1.01–1.93)	0.04	1.09 (0.85–1.39)	0.50
Diabetes	1.23 (0.89–1.68)	0.20	1.13 (0.90–1.42)	0.29
Hypercholesterolemia	0.83 (0.58–1.19)	0.32	0.83 (0.64–1.08)	0.17
Hypertension	1.15 (0.76–1.71)	0.51	1.04 (0.79–1.36)	0.79
Cerebrovascular disease	1.33 (0.91–1.94)	0.14	1.64 (1.25–2.16)	<0.001
Peripheral vascular disease	1.70 (1.19–2.42)	0.003	1.44 (1.10–1.89)	0.008
Renal failure*	2.32 (1.33–4.04)	0.003	1.83 (1.16–2.91)	0.01
Respiratory disease	1.09 (0.74–1.62)	0.66	0.96 (0.71–1.30)	0.80
Myocardial infarction within 21 days	1.41 (0.98–2.02)	0.06	1.36 (1.04–1.79)	0.02
History of congestive heart failure	2.26 (1.59–3.20)	<0.001	1.55 (1.19–2.00)	0.001
Unstable angina†	1.62 (1.11–2.37)	0.01	1.49 (1.10–2.01)	0.009
NYHA functional class				
I	1.00	—	1.00	—
II	0.91 (0.58–1.42)	0.69	1.19 (0.88–1.59)	0.25
III	1.24 (0.77–1.97)	0.37	1.35 (0.98–1.88)	0.07
IV	1.54 (0.93–2.55)	0.09	1.49 (1.02–2.18)	0.04
Left main stenosis >50%	1.32 (0.96–1.82)	0.08	1.16 (0.92–1.47)	0.22
Left ventricular function				
Normal or mild LV impairment (EF >45%)	1.00	—	1.00	—
Moderate impairment (EF 30%–45%)	1.20 (0.84–1.71)	0.32	1.24 (0.84–2.8)	0.61
Severe impairment (EF <30%)	2.89 (1.87–4.47)	<0.001	2.89 (1.19–6.99)	0.02
Urgency status				
Elective	1.00	—	1.00	—
Urgent	1.82 (1.22–2.71)	0.003	1.33 (1.02–1.75)	0.04
Emergency	4.07 (2.28–7.24)	<0.001	2.86 (1.85–4.42)	<0.001
Prior PCI	1.26 (0.77–2.08)	0.35	1.19 (0.83–1.68)	0.34

*Defined as serum creatinine >0.20 mmol/l. †Defined as need for intravenous nitrates until arrival in the operating theater.
CI = confidence interval; MACE = major adverse cardiac events; other abbreviations as in Table 1.

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groups (p = 0.99). After adjusting for patient characteristics by logistic regression, prior PCI was not an independent predictor of in-hospital mortality (OR: 1.26, 95% confidence interval [CI]: 0.77 to 2.08, p = 0.35) or MACE (OR: 1.19, 95% CI: 0.83 to 1.68, p = 0.34) (Table 2). The propensity score model was well-balanced (63 of 64 variables assessed were balanced between PCI groups). Similar results were obtained after adjustment with propensity score; prior PCI was not associated with in-hospital mortality (OR: 1.22, 95% CI: 0.76 to 1.99, p = 0.41) or MACE (OR: 1.15, 95% CI: 0.72 to 1.84, p = 0.56).

Mean patient follow-up was 3.3 ± 2.1 years (median: 3.2 years, range 0 to 7 years). Survival at 1, 3, and 5 years was higher in the PCI group compared with the non-PCI group (97.3% vs. 96.5%, 94.4% vs. 93.2%, and 91.1% vs. 87.7%; log-rank test: p = 0.013) (Fig. 1). After adjusting for patient characteristics, prior PCI was not an independent predictor of mid-term mortality (hazard ratio: 0.94, 95% CI: 0.75 to 1.18, p = 0.62) (Fig. 2).

Discussion

There are several possible mechanisms by which prior PCI may affect the outcome of subsequent CABG. The recent increase in the number of patients undergoing PCI has stimulated interest in the effect of prior PCI in these patients.

First, prior PCI may limit the number of distal anastomoses, which are performed during subsequent CABG. In patients with an occluded stent, it may be technically difficult to graft the coronary artery distal to a stent if the stent has been positioned in the distal portion of the vessel. Moreover, vessels with patent stents are usually not grafted because graft patency rates, especially of arterial grafts, are significantly reduced in the absence of significant coronary stenosis. However, leaving vessels with patent stents ungrafted may lead to post-operative MI should the stent occlude given the post-operative prothrombotic state of patients and the perioperative cessation of antiplatelet agents. A possible solution here would be to place vein grafts on all coronary vessels with patent stents. We do not have data on whether patent stented vessels were grafted in this study.

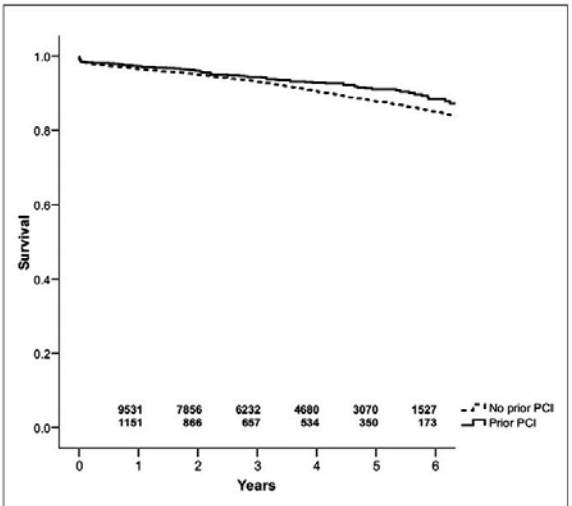

Figure 1. Unadjusted Survival Post-CABG With and Without Prior PCI

At a mean patient follow-up of 3.3 ± 2.1 years, survival was higher in the PCI group than in the non-PCI group (1 year: 97.3% vs. 96.5%, 3 years: 94.4% vs. 93.2%, and 5 years: 91.1% vs. 87.7%; log-rank test: p = 0.013). CABG = coronary artery bypass graft surgery; PCI = percutaneous coronary intervention.

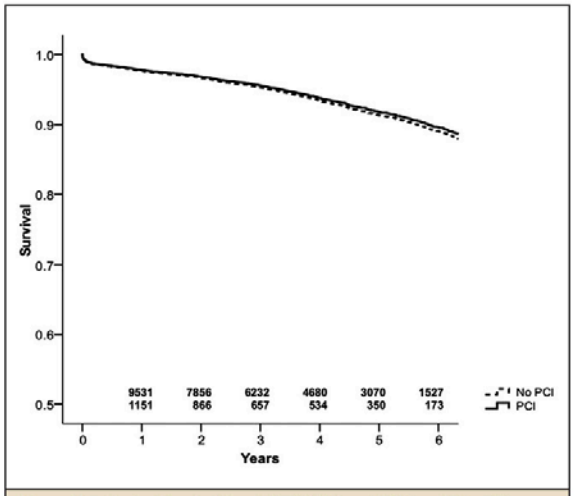

Figure 2. Adjusted Survival Post-CABG With and Without Prior PCI

After adjusting for patient characteristics, prior PCI was not an independent predictor of mid-term mortality (hazard ratio: 0.94, 95% CI: 0.75 to 1.18, p = 0.62). Abbreviations as in Figure 1.

Second, prior PCI may reduce the patency of coronary artery bypass grafts. This is because the distal run-off from the graft may be compromised by multiple overlapping stents compromising collateral blood flow or because the surgeon is forced to graft more distal parts of the coronary artery due to a proximally placed stent.

Third, it has become increasingly clear that stents in general and drug-eluting stents in particular may affect coronary artery endothelial function (12,13).

Fourth, patients undergoing initial PCI may represent a cohort of patients who may have been assessed as likely to have suboptimal outcomes from CABG, due to being poor targets or debility out of proportion to age for instance. Such factors are not adjusted for as they are not measured, thus confounding subsequent analysis of CABG outcomes.

Finally, patients who have PCI and subsequently present for CABG may represent a cohort of patients with more aggressive atherosclerosis (14).

For these reasons, there have been concerns in the cardiac surgical community about the effect of prior PCI after subsequent CABG. These concerns have been supported by a number of reports suggesting worse outcomes after CABG in patients with prior PCI. The earliest and largest report was in 6,032 patients, 15% of whom had undergone PCI prior to subsequent CABG between 1996 and 2000 from 2 Canadian centers (15). In that study, patients with prior PCI had greater in-hospital mortality (OR: 1.93, p = 0.003) despite less comorbidity. The main limitation of that report was the historical nature of the data. For example, there were no patients with drug-eluting stents. Thielmann et al. have published 2 articles on the subject. The first compared 2,626 patients with no prior PCI with 679 patients with prior PCI undergoing subsequent CABG (16). The second article, a subset analysis of the first, compared the impact of prior PCI on 621 diabetic patients with triple vessel disease (17). In both these articles, Thielmann et al. reported significantly worse early mortality and adverse clinical events in patients with prior PCI. In the most recent report from the IMAGINE (Ischemia Management with Accupril Post-Bypass Graft via Inhibition of the Converting Enzyme) study, 430 patients with prior PCI were compared to 2,059 patients referred to CABG without prior PCI (18). Interestingly, that was the first article to report no difference in early mortality although they did report an increase in unstable angina requiring hospitalization and increased coronary revascularization in the prior PCI group. The main limitation of that study, however, remains that it is a reanalysis of data from a study not specifically designed to answer this question (19).

The principal finding of this analysis of a large Australian registry is that prior PCI was not a predictor of operative mortality or MACE, defined as a composite end point of in-hospital death, MI, or stroke after CABG. Similarly, prior PCI does not negatively affect survival at a mean follow-up of 3.3 years after subsequent CABG. Our study has several strengths. It is a large study with over 13,000 patients; it reports mid-term data; and because it is mandatory, all-inclusive, registry data from multiple cardiac surgery units it is likely to reflect real-world practice. In our opinion, these are the principal reasons why our results differ from those published previously.

Study limitations. Notwithstanding these advantages, our study has certain limitations. The lack of cardiac catheterization data precluded the identification of target vessels for prior PCI and the target vessels for subsequent CABG, thus preventing the determination of the mode of failure of PCI (i.e., restenosis vs. de novo development of occlusive lesions at remote sites). In addition, the lack of available cardiac catheterization data at the time of initial PCI did not allow us to determine whether PCI was performed in the setting of single-vessel or multivessel disease or whether balloon angioplasty alone was performed or in combination with stent placement. Data are lacking concerning the interval between PCI and subsequent CABG or on the volume of stents in place at time of CABG. Both of these variables may be important determinants of outcome after CABG. Finally, this study does not assess the potential for cardiac death or MI in the interval between initial PCI and subsequent surgery. Large registry studies have shown that in the setting of multivessel disease managed with an initial strategy of PCI, 4% to 9% of patients die within 12 months (20–22). Hence, our study does not allow us to draw conclusions on the safety or effectiveness of a strategy of PCI first and CABG later.

Conclusions

There was no association between prior PCI and short- and mid-term mortality after CABG. Good outcomes can be obtained in the group of patients undergoing CABG who have had previous PCI.

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Key Words: coronary disease ■ surgery ■ revascularization ■ angioplasty ■ stents.

APPENDIX

For full acknowledgments, please see the online version of this article.

Appendix 8

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An Evaluation of Octogenarians Undergoing Percutaneous Coronary Intervention From the Melbourne Interventional Group Registry

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Objectives: The objective of this study was to evaluate the clinical characteristics and outcomes of octogenarians (≥80 years of age) in a contemporary, multi-centre percutaneous coronary intervention (PCI) registry. **Background:** Octogenarians are increasingly referred for PCI. This patient population frequently has significant comorbidities, which result in major therapeutic challenges. **Methods:** The study population consisted of consecutive patients undergoing PCI in seven major Australian hospitals, who were treated over a 2-year period (2004–2005). **Results:** Of 4,360 PCI's, 11.3% (n = 491) were performed in octogenarians and 88.7% (n = 3,869) in patients <80 years. Octogenarians (compared with patients <80 years of age) were more likely female and have greater comorbidities such as cerebrovascular disease, renal impairment, congestive heart failure, and chronic airway disease. Octogenarians more frequently presented with acute coronary syndromes and cardiogenic shock. Octogenarians had significantly increased 30-day (6.0 vs. 1.4%, $P < 0.01$) and 12-month mortality (8.4% vs. 2.5%, $P < 0.01$), and major adverse cardiac event rates [(MACE), 30 days 11.3% vs. 5.4%, $P < 0.01$ and 12-months 18.7% vs. 12.9%, $P = 0.04$]. Cardiogenic shock, ST-segment elevation myocardial infarction, chronic renal failure, and age ≥80 years were independent predictors of 12-month mortality. **Conclusions:** Octogenarians comprise a significant cohort of patients undergoing PCI. Octogenarians have more comorbidities, and higher rates of mortality and MACE, mandating thorough clinical evaluation before acceptance for PCI.

Key words: percutaneous coronary intervention; acute coronary syndrome; angiography; coronary

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INTRODUCTION

Octogenarians are the most rapidly growing sector of the Western population. In Australia, the proportion of people aged 85 years and over is projected to increase from 1.2% in 1997 to 4.8% in 2051 [1]. This age group is characterized by a high prevalence of coronary artery disease (CAD) [2]. As such, the prevalence of CAD requiring revascularization is likely to increase with an ageing population.

The management of octogenarians with CAD remains a major therapeutic challenge. This population is often referred late for revascularization and is at the highest risk of procedural complications owing to the high prevalence of associated comorbidities. However, the elderly have the potential to gain the most clinical benefit from an early invasive approach (compared with conservative management) because of their higher baseline risk [3–5]. Evidence-based data to guide coronary revascularization has been limited to clinical trials that generally under-represent elderly patients, and observational studies that represent single-institutional experience with small patient cohorts. Studies in the prestenting era have shown reduced success and increased adverse outcomes after percutaneous coronary interventions (PCI) in the elderly [6–10]. Routine stenting has improved procedural outcomes and reduced complications [11–13]. Drug-eluting stents (DES) have shown further reduction in repeat revascularization in selected populations and lesion subgroups. However, there is currently a paucity of data pertaining to octogenarians undergoing PCI in the contemporary era of DES.

Our study aimed to investigate clinical characteristics and outcomes in octogenarians undergoing PCI from a large multi-centered registry and to determine predictors for adverse clinical outcomes.

MATERIALS AND METHODS

The study population consisted of 4,360 consecutive patients undergoing PCI from April 2004 to December 2005 enrolled in the Melbourne Interventional Group (MIG) registry. Octogenarians (aged $\geq$ 80 years; n = 491) were compared with patients <80 years of age (n = 3,869).

The registry is a voluntary, collaborative venture of interventional cardiologists practicing at seven Australian tertiary referral hospitals, designed to record data pertaining to PCI and to perform long-term follow-up. The MIG registry has been previously described [14,15]. Demographic, clinical, and procedural characteristics of consecutive patients undergoing PCI are prospectively recorded on case report forms using standardized definitions for all fields [14]. The registry is coordinated by the Centre of Clinical Research Excellence, a research body within the Department of Epidemiology and Preventive Medicine (Monash University, Melbourne, Australia). The study protocol was approved by the ethics committee in each participating hospital. "Opt-out" informed consent was obtained in all patients, as previously described [14].

Procedures and Post-Intervention Medications

The status of PCI was divided into elective, urgent, and rescue procedures. Elective PCI were performed in stable patients where procedures could be deferred without increased risk of compromised clinical outcomes. Urgent PCI were nonelective procedures required during the same admission in order to minimize risk of further clinical deterioration [e.g. cardiac failure, acute myocardial infarction, unstable angina with intravenous nitrate therapy or rest angina (but stabilised patient] may be included). Rescue PCI was defined as PCI after failed fibrinolysis for patients with continuing or recurrent myocardial ischemia. The interventional strategy and stent selection was left to the discretion of the operator in all procedures. Total stent length was used as a surrogate for target lesion length, and stent diameter for target vessel diameter. Angiographic success is defined by a residual stenosis of <50% with thrombolysis in myocardial infarction (TIMI) three flow. Periprocedural glycoprotein IIb/IIIa inhibitors were used according to the operator's discretion. Oral antiplatelet therapy followed current guidelines which recommend combination of aspirin and clopidogrel for a minimum of 4 weeks for bare-metal stents and between 6 and 12 months for DES [16]. Postprocedural medical therapy including aspirin, clopidogrel, statin, beta-blocker, angiotensin-converting enzyme-inhibitors (ACE), and angiotensin-receptor blockers (ARB) were recorded at 30-day and 12-month follow-up.

Clinical Outcomes

In-hospital complications were recorded at time of discharge. Thirty-day and 12-month follow-up was conducted by telephone and all cardiac events were documented including death, myocardial infarction (MI), target vessel revascularisation (TVR), and composite major adverse cardiac events (MACE, consisting of death, MI and TVR). Patients are deemed eligible for 12-month follow-up at least 12 months after index PCI. Patient medical records were reviewed to substantiate recorded events.

Death included all cause mortality. MI was defined as either a rise in creatine kinase or creatine kinase MB of more than three times the upper limit of normal or evolutionary ST-segment elevations, development of

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TABLE I. Baseline Characteristics

	Age ≥ 80	Age < 80	*P* value
Patients, *n* (%)	491 (11.3)	3869 (88.7)	–
Age, years ± SD	83.1 ± 2.7	62.4 ± 10.7	<0.01
Female (%)	48.3	24.1	<0.01
Diabetes mellitus (%)	25.6	22.6	0.15
Hypertension (%)	73.5	60.1	<0.01
Hypercholesterolaemia (%)	66.9	70.7	0.09
Current smoking (%)	3.2	24.1	<0.01
Previous myocardial infarction (%)	36.8	28.0	<0.01
Left ventricular ejection fraction (%), mean ± SD	54 ± 14	56 ± 12	0.12
History of congestive cardiac failure (%)	7.8	2.9	<0.01
History of cerebral vascular disease (%)	9.3	4.6	<0.01
History of chronic airway disease (%)	9.5	4.0	<0.01
History of peripheral vascular disease (%)	12.1	5.7	<0.01
Moderate to severe renal impairment (Creatinine >200 μmol/L or 2.27 mg/dL) (%)	10.6	3.4	<0.01
Clinical presentation			
Acute coronary syndrome (%)	65.3	60.2	0.08
STEMI (%)	18.7	21.2	0.24
NSTEMI (%)	25.3	21.9	0.10
Unstable angina (%)	21.6	17.7	0.04
Non acute coronary syndrome (%)	35.0	40.0	0.02
Cardiogenic shock (%)	2.9	2.0	0.24
Cardiac failure (<2 weeks) (%)	9.0	3.4	<0.01

STEMI, ST elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction.

TABLE II. Lesion and Procedural Characteristics

	Age ≥ 80	Age < 80	*P* value
Lesions, *n* (%)	600 (11.2)	4767 (88.2)	–
Target vessel			
Left main (%)	2.2	0.7	<0.01
Left anterior descending (%)	32.5	31.4	0.61
Right coronary (%)	28.0	32.3	0.04
Circumflex (%)	13.5	14.3	0.62
Bypass grafts (%)	6.0	2.5	<0.01
Multivessel disease (%)	71.6	56.0	<0.01
Restenotic lesion (%)	5.7	5.2	0.66
Type B2 and C lesion (%)	54.0	48.9	0.02
Mean total stent length, mm ± SD	16.0 ± 5.0	16.8 ± 5.3	<0.01
Mean stent diameter, mm ± SD	2.9 ± 0.5	2.9 ± 0.5	0.56
Glycoprotein IIb/IIIa use, (%)	22.2	27.0	0.02
Drug-eluting stent use, (%)	57.0	54.6	0.28
Intra-aortic balloon pump use, (%)	2.0	1.9	0.73
Angiographic success (%)	94.0	97.0	0.01

new Q-waves in two or more contiguous ECG leads, or new LBBB pattern on the ECG. Target vessel revascularization (TVR) was a repeat revascularization in the follow-up period due to restenosis either within the target lesion or within the same epicardial coronary artery. Late (>30 days after index procedure) stent thrombosis was defined as (i) an ACS with angiographic documentation of either vessel occlusion or thrombus within or adjacent to a previously successfully stented vessel or, (ii) in the absence of angiographic confirmation, acute MI in the distribution of the treated vessel. Major bleeding was defined by a drop in haemoglobin >3.0 gm/dL and/or requiring transfusion. Acute renal failure was defined by an increase of serum creatinine to >200 μmol/L (2.27 mg/dL) (or two times the baseline creatinine level), or need for dialysis. Stroke was defined by onset of persistent loss of neurological function caused by an ischemic or hemorrhagic event during or after PCI. Cardiogenic shock was defined by hypotension (systolic BP < 90 mm Hg for at least 30 min or needing supportive measures), evidence of end-organ hypoperfusion or cardiac index <2.2 L/(min m^2) and pulmonary capillary wedge pressure of ≥18 mm Hg.

Statistical Analysis

Continuous variables were expressed as mean ± SD, and categorical data expressed as percentages. Continuous variables were compared using Student's *t* tests or ANOVA. Categorical variables were compared using Fisher exact or χ^2 tests as appropriate. All calculated *P*-values were two-sided and *P*-values <0.05 were considered statistically significant. Multivariate logistic regression analysis was used to determine independent predictors of 30-day and 12-month mortality. Cumulative survival from MACE was estimated according to the Kaplan–Meier method and the log-rank test was used to evaluate differences between octogenarians and patients <80 years. All statistical analysis was performed using SPSS Ver. 12.0 for Windows (SPSS, Chicago, IL).

RESULTS

Of the 4,360 PCI's, 11.3% (n = 491) were performed in octogenarians (mean age 83.1 ± 2.7 years) and 88.7% (n = 3,869) were in patients <80 years [mean age 62.4 ± 10.7 years (Table I)]. Octogenarians were more likely female (48.7% vs. 24.1%, $P < 0.01$) and had more comorbidities, including history of prior MI (36.8% vs. 28.0%, $P < 0.01$), hypertension (73.5% vs. 60.1%, $P < 0.01$), peripheral vascular disease (12.1% vs. 5.7%, $P < 0.01$), cerebral vascular disease (9.3% vs. 4.6%, $P < 0.01$), renal failure (10.6% vs. 3.4%, $P < 0.01$), congestive cardiac failure (7.8% vs. 2.9%, $P < 0.01$), and chronic obstructive airway disease (9.5% vs. 4.0%, $P < 0.01$). Octogenarians were less likely to present for elective PCI without ACS (35.0% vs. 40.0%, $P = 0.02$). More octogenarians pre-

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sented with clinical heart failure within 2 weeks of PCI (9.0 vs. 3.4, $P < 0.01$). There was no difference in the incidence of cardiogenic shock at presentation.

The elderly cohort had a greater number of left main stem (2.2% vs. 0.7%, $P < 0.01$) and bypass grafts (6.0% vs. 2.5%, $P < 0.01$) treated and were more likely to have multi-vessel disease (71.6% vs. 56.0%, $P < 0.01$, [Table II]). Lesions treated were more complex (American College of Cardiology/American Heart Association, type B2/C lesions) in octogenarians than in patients <80 years (54.0% vs. 48.9%, $P = 0.02$). This is reflected by the lower angiographic success rate in octogenarians (94.0% vs. 97.0%, $P = 0.01$). The use of DES was similar in both cohorts (57.0% vs. 54.6%, $P = 0.28$), while glycoprotein IIb/IIIa inhibitors were used less frequently in octogenarians (22.2% vs. 27.0%, $P = 0.02$).

TABLE III. Clinical Outcomes at Hospital Discharge, 30 Days and 12 Months

	Age ≥80	Age <80	*P* value
In-hospital outcomes, *n* (%)	*n* = 492	*n* = 3,868	
Death	20 (4.1)	43 (1.1)	<0.01
MI	9 (1.9)	59 (1.6)	0.61
Unplanned TVR	5 (1.1)	30 (0.8)	0.57
Acute renal failure	12 (2.4)	39 (1.0)	0.01
Stroke	6 (1.2)	8 (0.2)	<0.01
Major bleeding	7 (1.4)	55 (1.4)	0.99
30-day Outcomes, *n* (%)	*n* = 469	*n* = 3,656	
Death	28 (6.0)	52 (1.4)	<0.01
MI	20 (4.3)	82 (2.2)	<0.01
TVR	13 (2.8)	88 (2.4)	0.63
MACE	53 (11.3)	197 (5.4)	<0.01
12-month Outcome, *n* (%)	*n* = 155	*n* = 1,182	
Death	11 (8.4)	30 (2.5)	<0.01
MI	11 (7.9)	56 (5.4)	0.16
TVR	9 (5.8)	87 (7.4)	0.74
MACE	29 (18.7)	152 (12.9)	0.06
Late stent thrombosis	2 (1.3)	7 (0.6)	0.28

MI, myocardial infarction; TVR, target vessel revascularization; MACE, major adverse cardiac events (Death, MI, and TVR).

In-Hospital Events

In-hospital follow-up was complete in all patients (Table III). Overall mortality was four-times higher in octogenarians (4.1% vs. 1.1%, odds ratio (OR) 3.8, 95% confidence interval (CI) 2.2–6.5, $P < 0.01$). Acute renal failure and stroke occurred more frequently in octogenarians. However, there were no significant differences in rates of MI, unplanned TVR, or major bleeding.

Clinical Outcomes at 30 Days

Ninety-five percent ($n = 4{,}125/4{,}360$) of patients completed 30-day follow-up. Unadjusted mortality in octogenarians at 30 days (6.0% vs. 1.4%, OR 4.40, 95% CI 2.75–7.04, $P < 0.01$) was again four-times higher than patients <80 years (Table III). The frequency of MI was significantly higher (4.3% vs. 2.2%, $P < 0.01$), but rates of TVR (2.8% vs. 2.4%, $P = 0.63$) were comparable at 30 days. Overall MACE at 30 days (11.3% vs. 5.4%, $P < 0.01$) was significantly higher in octogenarians.

We further analyzed 30-day outcomes into patients who presented with stable angina and those with ACS at the index procedure. A subgroup of ACS patients presented with STEMI was also compared (Table IV). There was an incremental increase in 30-day mortality (1.6% vs. 8.4% vs. 21.2%, $P < 0.01$) and MACE (4.8% vs. 14.8% vs. 29.4%, $P < 0.01$) in octogenarians who presented with stable angina, ACS, and STEMI, respectively. In patients presenting with stable angina, there was no difference in rates of MACE between age groups (4.8% vs. 3.7%, $P = 0.5$). However, in patients presenting with ACS and STEMI, the rates of MACE were 2- to 3-fold higher in octogenarians (Table IV).

We also compared 30-day outcomes between procedures performed electively, urgently or as rescue PCI after failed thrombolysis (Table V). Similarly, there was an incremental increase in 30-day mortality (2.0% vs. 10.0% vs. 28.6%, $P < 0.01$) and MACE (5.6% vs. 17.5% vs.

TABLE IV. 30-Day Outcomes According to Clinical Presentation

	Presentation mode								
	Stable angina (*n* = 1,266)			Acute coronary syndrome (*n* = 2,375)			STEMI (*n* = 858)		
	≥80 yr	<80 yr		≥80 yr	<80 yr		≥80 yr	<80 yr	
30-Day follow-up	*n* = 124	*n* = 1,142	*P*	*n* = 297	*n* = 2,078	*P*	*n* = 85	*n* = 773	*P*
Death, *n* (%)	2 (1.6)	3 (0.3)	0.08	25 (8.4)	46 (2.2)	<0.01	18 (21.2)	34 (4.4)	<0.01
MI, *n* (%)	2 (1.6)	24 (2.1)	0.73	16 (5.4)	42 (2.0)	<0.01	6 (7.1)	14 (1.8)	0.01
TVR, *n* (%)	3 (2.4)	24 (2.1)	0.74	10 (3.4)	59 (2.8)	0.58	5 (5.9)	34 (4.4)	0.58
MACE, *n* (%)	6 (4.8)	42 (3.7)	0.46	44 (14.8)	133 (6.4)	<0.01	25 (29.4)	75 (9.7)	<0.01

MI, myocardial infarction; TVR, target vessel revascularization; MACE, major adverse cardiac events (Death, MI, and TVR); STEMI, ST elevation myocardial infarction.

TABLE V. 30-Day Outcomes According to Status of Procedure

	Status of procedure								
	Elective ($n = 2,209$)			Urgent ($n = 1,830$)			Rescue ($n = 80$)		
	≥80 yr	<80 yr		≥80 yr	<80 yr		≥80 yr	<80 yr	
30 Day follow up	$n = 251$	$n = 1,958$	P	$n = 211$	$n = 1,619$	P	$n = 7$	$n = 78$	P
Death, n (%)	5 (2.0)	6 (0.3)	<0.01	21 (10.0)	40 (2.5)	<0.01	2 (28.6)	6 (7.7)	<0.01
MI, n (%)	8 (3.2)	45 (2.3)	0.38	12 (5.7)	34 (2.1)	<0.01	0 (0)	3 (3.8)	
TVR, n (%)	4 (1.0)	34 (1.7)	0.87	9 (4.3)	50 (3.1)	0.40	0 (0)	4 (5.1)	
MACE, n (%)	14 (5.6)	72 (3.7)	0.16	37 (17.5)	112 (6.9)	<0.01	2 (28.6)	13 (16.7)	0.60

MI, myocardial infarction; TVR, target vessel revascularization; MACE, major adverse cardiac events (Death, MI, and TVR); STEMI, ST elevation myocardial infarction.

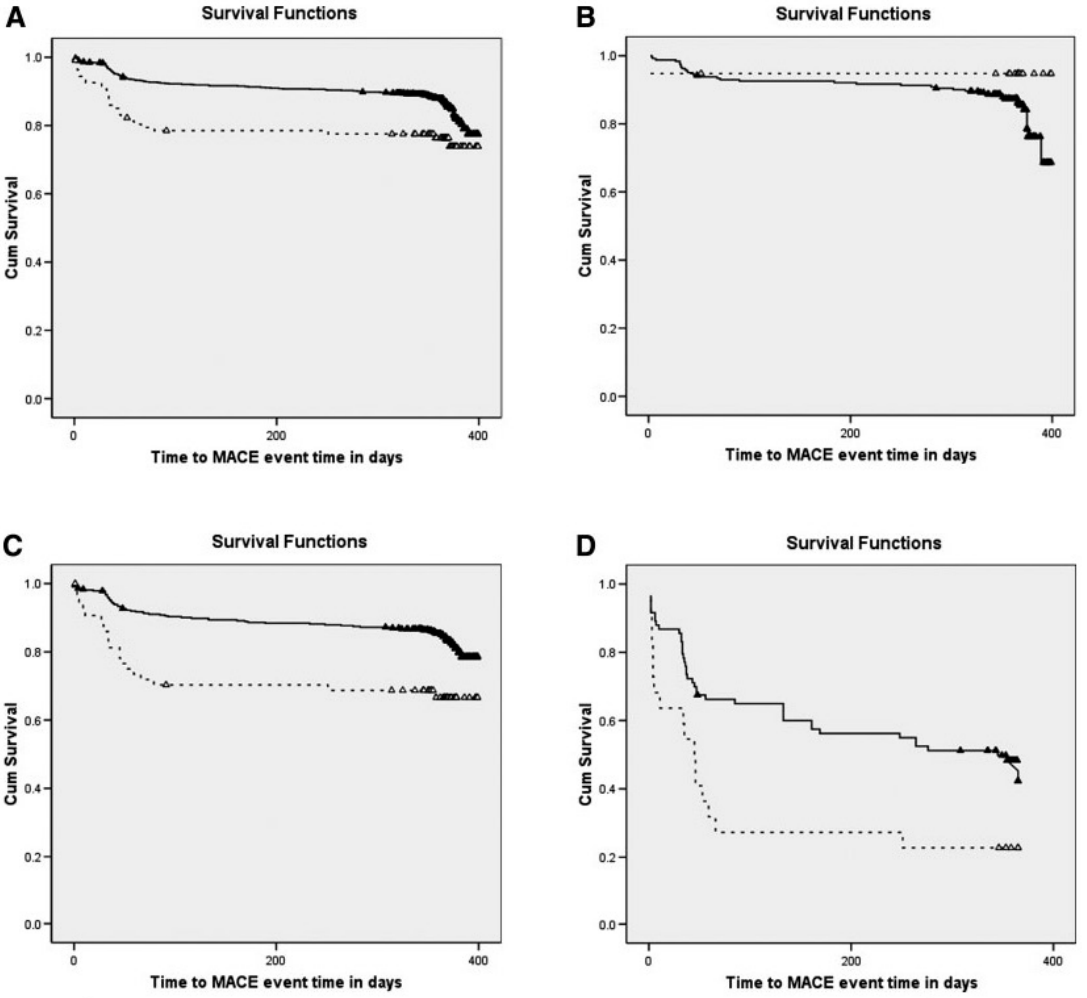

Fig. 1. Kaplan–Meier estimates of cumulative survival from major adverse cardiac events. Panel A shows Kaplan–Meier curve for survival of major adverse cardiac events (MACE, including death, MI and TVR) at 12-months follow-up in octogenarians (dotted line) and patients <80 years old (solid line). Panels B, C, and D show Kaplan–Meier curves for survival of MACE in patients presenting with stable angina, acute coronary syndrome and ST-elevation MI, respectively.

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TABLE VI. Medical Therapy at 30 Day and 12 Month

	Age ≥ 80	Age < 80	*P* value
30 days (*n*)	*n* = 469	*n* = 3,656	
Aspirin (%)	87.4	93.5	<0.01
Clopidogrel (%)	85.0	88.4	0.04
Statin (%)	79.5	89.3	<0.01
Beta-blocker (%)	55.1	64.7	<0.01
ACE/ARB (%)	73.2	73.5	0.91
12 month (*n*)	*n* = 155	*n* = 1,182	
Aspirin (%)	81.1	85.0	0.22
Clopidogrel (%)	59.2	52.2	0.13
Statin (%)	77.5	86.2	<0.01
Beta-blocker (%)	60.3	54.5	0.21
ACE/ARB (%)	70.9	70.2	0.92

ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

28.6%, $P < 0.01$) in octogenarians who underwent elective, urgent, and rescue PCI, respectively.

Clinical Outcomes at 12 Months

Twelve-month follow-up was completed in 95.8% (n = 1,337/1,395) of patients eligible for 12-month follow-up. Unadjusted mortality in octogenarians at 12 months (8.4% vs. 2.5%, OR 3.52, 95% CI 1.79–6.90, $P < 0.01$) remains significantly higher than patients <80 years (Table III). The frequency of MI was not statistically different at 12 months (7.9% vs. 5.4%, $P = 0.26$). The rates of TVR were low and similar in both groups at 12 months (5.8% vs. 7.4%, $P = 0.74$). The incidence of late stent thrombosis was not statistically different between age groups (1.3% vs. 0.6%, $P = 0.28$). Overall MACE at 12 months (18.7% vs. 12.9%, $P = 0.04$) was significantly higher in octogenarians. The difference in rates of MACE between age groups peaked at 30-days and remained stable up to 12-months in the overall cohort and in patients who presented with ACS and STEMI (Fig. 1A, C, and D, respectively). In contrast, there was no difference in MACE rates up to 12 months in patients who presented with stable angina (Fig. 1B).

Medical Therapy at 30-Days and 12-Months

At 30-day follow-up, the use of aspirin, clopidogrel, statin, and beta-blockers were significantly lower in octogenarians than in patients <80 years (Table VI). These differences were no longer observed at 12-months except in statin therapy which remained significantly lower in octogenarians. There was no difference in the use of ACE/ARB between age groups. Among octogenarians, compliance with medical therapy was maintained up to 12-month follow-up. The decline in clopidogrel therapy between 30-day and 12-month follow-up is likely due to recommendation for 6- to 12-months dual-antiplatelet therapy after DES implantation.

Predictors of Mortality at 30-Days and 12-Months

Independent predictors of mortality at 30 days in all patients include cardiogenic shock (OR 27.0, 95% CI 14.3–51.1, $P < 0.01$), STEMI (OR 4.3, 95% CI 2.2–8.7, $P < 0.01$), age ≥ 80 years (OR 4.2, 95% CI 2.3–7.6, $P < 0.01$), chronic renal failure (OR 3.5, 95% CI 1.6–7.5, $P = 0.01$), and diabetes mellitus (OR 2.6, 95% CI 1.5–4.7, $P = 0.01$). In the cohort at 12 months, cardiogenic shock (OR 14.9, 95% CI 5.2–42.2, $P < 0.01$), STEMI (OR 5.2, 95% CI 1.2–22.7, $P = 0.03$), chronic renal failure (OR 5.1, 95% CI 2.0–13.1, $P = 0.01$), and age ≥ 80 years (OR 2.8, 95% CI 1.3–8.7, $P = 0.01$) remained predictive of mortality. Diabetes mellitus was no longer predictive of 12-month mortality.

DISCUSSION

The principal findings of this analysis of a contemporary PCI registry are as follows: (i) octogenarians form a significant percentage of all patients undergoing PCI (11%); (ii) octogenarians have more complex lesions and multivessel disease, lower rates of angiographic success, and increased complication rates compared with patients <80 years; (iii) overall, mortality was four times higher in octogenarians at 30 days and 12 months; (iv) high-risk clinical presentations (i.e. STEMI and cardiogenic shock) and the presence of significant comorbidities (i.e. chronic renal failure) were more predictive of 12-month mortality than age per se in octogenarians undergoing PCI; (v) the higher mortality rates of octogenarians (compared with patients <80 years), drove the increased MACE at 12 months, with no difference in rates of MI or TVR.

A recent study comparing outcomes of PCI in patients of different age groups according to modes of presentation also showed that adverse events including mortality increase with age and with the severity of emergency of the presentation [17]. In patients undergoing emergency PCI, cardiogenic shock (OR 17.3, 95%CI 11.9–22.3, $P < 0.01$) was a stronger independent predictor of in-hospital mortality than age ≥80 years (OR 9.4, 95%CI 6.3–14.1, $P < 0.01$, [17]). In our study, cardiogenic shock at presentation was the strongest predictor of mortality both at 30 days and 12 months.

Our findings were consistent with other PCI trials and registries regarding octogenarians [17–21]. Octogenarians have a higher prevalence of comorbidities and were more likely to present with cardiogenic shock. The elderly have more extensive CAD and more complex coronary lesions. All these factors contribute to adverse outcomes after PCI. Our overall in-hospital mortality of 4.1% among octogenarians is comparable with 3.8% mortality in 7,472 octogenarians form the

National Cardiovascular Network data (1994–1997) and 3.8% in 8,828 octogenarians from the American College of Cardiology/National Cardiovascular Data Registry (1998–2000, [18,20]) despite the advent of newer devices and adjunctive treatments in the present cohort.

Elderly patients are often treated conservatively and therefore referred late for revascularization; probably due to the perception of an unfavorable risk-benefit ratio with intervention. Despite higher risk profiles, elderly patients have paradoxically greater absolute risk reduction with revascularization compared with younger patients. The Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) Registry demonstrated improved long-term survival in octogenarians with CAD treated with either surgical or percutaneous revascularization compared with medical therapy [5]. The randomized Trial of Invasive versus Medical therapy in Elderly patients (TIME) demonstrated that although an invasive approach carried an increased early periprocedural risk, medical management was associated with an almost 50% chance of later hospitalization and revascularization at 4 years [3]. Failure of medical therapy in octogenarians may be due to under utilization of medical therapy compared with younger patients as found in our study. Possible reasons for this include higher incidence of side-effects (e.g. statin induced myopathy and bleeding secondary to antiplatelet therapy) and contraindications of medical therapy.

In the era of DES, Hassani et al. demonstrated a low mortality rate in octogenarians with stable angina (4.1%) at 6-months, however, mortality rates in ACS (15%) and STEMI (31%) remained significantly higher [22]. This study is consistent with our findings of significant lower rates of death and MACE in octogenarians who presented with stable angina versus ACS and when PCI was performed electively versus emergently. This further supports the advantage of early treatment of CAD in octogenarians as complications increase exponentially when the elderly present with unstable syndromes in need of urgent revascularization.

Patient selection for PCI is important. On the basis of our logistic regression analysis, clinical characteristics were more predictive of adverse outcomes than procedural factors. Octogenarians who were female, with diabetes, renal failure, or presenting with STEMI and cardiogenic shock were at the highest risk. The absolute benefit of PCI in these patients may be marginal. However, without a control octogenarian group, we are unable to assess whether conservative management or surgery is a better strategy than PCI in this extremely high risk subgroup.

Percutaneous intervention in octogenarians is often performed for symptoms rather than aiming for complete revascularization or prognostic benefit, despite more extensive coronary disease than younger patients [23]. Our study showed that although PCI in octogenarians has a high angiographic success, short- and long-term adverse events remain significant. These adverse events are critical to contemplate when considering PCI in elderly patients.

This study provides important insights into contemporary PCI practice where data are limited. Our study shows that DESs were used in just over 50% of PCI procedures, and that the use is similar in octogenarians and younger patients. We found no significant difference in mortality in octogenarians between DES and bare-metal stent implantation. This is consistent with current data for DES, which principally demonstrated a reduction in repeat revascularization. Although we did not find an increased incidence of stent thrombosis, concern remains regarding late-stent thrombosis beyond 12 months and the need for long term (potentially lifelong) clopidogrel therapy after DES deployment [23–27]. One obvious concern in the elderly is higher bleeding rates with long term dual antiplatelet therapy [28]. Managing interruptions in antiplatelet therapy at times of surgery will become a frequent issue in the elderly population.

Limitations

This database was not specifically designed to test the effect of age on outcomes of patients enrolled in our PCI registry. However, the data were collected prospectively with a view to examine multiple clinical and procedural predictors of outcome, and we have independent adjudication of clinical events. There is incomplete 12-month follow-up for the entire cohort as many patients were not yet eligible for 12-month follow-up.

CONCLUSIONS

The prevalence of octogenarians undergoing PCIs is increasing with an ageing population. Octogenarians have a higher risk profile compared with younger patients. Rates of repeat revascularisation remain low. Octogenarians, especially those who present with acute coronary syndromes, have substantially higher mortality and rates of MACE, mandating thorough clinical evaluation before acceptance for percutaneous coronary intervention.

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APPENDIX

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Original Article

Contemporary Treatment of In-Stent Restenosis and the Incidence of Recurrent In-Stent Restenosis in the Era of Drug-Eluting Stents

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On behalf of the Melbourne Interventional Group (MIG) Investigators

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Background: Optimal treatment of in-stent restenosis (ISR) remains uncertain in the era of drug-eluting stents (DES). This study aims to determine contemporary treatment of ISR and to assess recurrent ISR rates in the era of DES.

Methods: We examined 60 patients presenting for treatment of ISR (one lesion per patient) who were enrolled in the Melbourne Interventional Group Registry (4% of total population of 1423 patients) between April 2004 and January 2005. Twelve-month follow-up is complete for all patients.

Results: The majority of ISR treated occurred in bare metal stents [BMS ($n = 52$, 87%)] and had a focal (<10 mm) pattern of ISR (53%). In-stent restenosis of DES occurred in eight (13%) patients. The majority of ISR were treated with additional stenting with a preference for DES over BMS in almost all cases. At 12 months, one patient died of non-cardiac cause and four patients (7%) presented with recurrent ISR. The incidence of recurrent ISR in DES was 5% ($n = 3$). No late thrombosis was reported despite only 50% of patients having ≥12 months of clopidogrel therapy.

Conclusions: Our study suggests drug-eluting stents are safe, effective and the preferred therapy for in-stent restenosis. The incidence of recurrent drug-eluting stent restenosis at 12 months is low.

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Keywords. Drug-eluting stents; In-stent restenosis; Recurrent in-stent restenosis

Introduction

In-stent restenosis (ISR) remains the major limitation of percutaneous coronary intervention (PCI) with bare-metal stent (BMS) implantation (10–50%).[1,2] Drug-eluting stents (DES) have significantly reduced the incidence of ISR from that seen with BMS.[3,4] Until recently, intracoronary radiation therapy (IRT) has been the only proven therapy for ISR.[5,6] Recent studies have shown DES implantation to be a superior therapy for the treatment of ISR compared to balloon angioplasty and IRT.[7–9] Despite limited evidence for their long-term clinical efficacy, DES has become the primary therapy for ISR.[10] The aim of this study was to determine contemporary treatment of ISR in Australian PCI practice and to assess recurrent ISR rates in the era of DES.

Material and Methods

We analysed patients treated for ISR from the Melbourne Interventional Group (MIG) PCI registry. The MIG is a voluntary collaborative venture of interventional cardiologists practising at seven major cardiology hospitals in Melbourne, Australia.[11] Consecutive patients undergo-

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ing elective and urgent PCI at participating hospitals are prospectively enrolled in this registry. The MIG registry is co-ordinated and managed by the Centre of Clinical Research Excellence (CCRE), a research body within the Department of Epidemiology and Preventive Medicine, Monash University. Ethics approval was granted from participating centres and informed consent was received from all patients for follow-up.

Specific recorded data pertaining to the PCI includes the indication for the interventional procedure, from which the subset of patients with ISR was identified. Patients with ISR were classified according to ISR type, based on the length and pattern of restenotic lesion in relation to the stented portion of the vessel.[12] We analysed the treatment strategy for ISR lesions, specifically whether this was balloon angioplasty (PTCA) alone, or repeat stenting with DES or BMS. The Sirolimus eluting Bx Velocity (*Cypher*, Cordis, Miami Lakes, Florida) and the Paclitaxel eluting Express II stent (*Taxus*, Boston Scientific, Boston, Massachusetts) were available for implantation throughout the study period. Intracoronary radiation therapy was not performed at any of the participating institutions.

Thirty-day and 12-month follow-up is conducted by phone call and cardiac events were documented including death, myocardial infarction, target lesion (TLR) and vessel revascularisation (TVR), late thrombosis and composite major adverse cardiac events (MACE). Additionally, we recorded medication therapy, and specifically the duration of clopidogrel therapy. Patient medical records were reviewed to substantiate recorded events.

Descriptive statistical analysis was conducted with continuous data presented as means ± standard deviation and categorical data as percentages. Continuous data was analysed using the one-way ANOVA test. All p values <0.05 were considered statistically significant.

Results

Between April 2004 and January 2005, 1357 patients received stent implantation [BMS = 575 (42%); DES = 782 (58%)] out of 1423 patients enrolled in the MIG registry. Of these, 60 patients (4%) presented for treatment of ISR (one ISR per patient). The mean age of the ISR cohort was 63.6 ± 13.1 years with 48 (80%) males and 13 (22%) diabetics (Table 1). The majority of patients [n = 36 (60%)] presented with an acute coronary syndrome. Two (3%) of these patients presented with ST-segment elevation myocardial infarction (MI) secondary to late stent thrombosis confirmed by angiography. Both patients have ceased dual antiplatelet therapy.

The ISR lesions involved predominantly native coronary arteries [n = 59, 98% (Table 2)]. The mean duration of ISR presentation from initial stent implantation was 184 ± 32 days. The majority of ISR involved BMS (n = 52, 87%), and ISR occurred in DES in 13% of the cohort (8 of 60 patients).

The mean reference vessel diameter was 2.9 ± 0.3 mm. The pattern of ISR was focal (Type I) in 53% of patients and diffuse (Type II–IV) in 47% of patients. The mean lesion length for the total cohort was 12.7 ± 11.4 mm, being predominantly diffuse in the BMS ISR (13.6 ± 11.8 mm) and focal in the DES ISR group (5.1 ± 2.5 mm, p < 0.001).

Table 1. *Baseline Characteristics*

	N (%)
Total ISR patients, *n*	60
Age (years) ± S.D.	63.6 ± 13.1
Male, *n* (%)	48 (80)
Diabetes mellitus, *n* (%)	13 (22)
Hypertension, *n* (%)	37 (62)
Smoking history, *n* (%)	33 (55)
Hypercholesterolaemia, *n* (%)	40 (67)
Prior myocardial infarction, *n* (%)	41 (68)
Prior coronary artery bypass grafts, *n* (%)	1 (2)
Clinical presentation	
Acute coronary syndromes, total *n* (%)	36 (60)
Unstable angina, *n* (%)	22 (37)
NSTEMI	12 (20)
STEMI	2 (3)

ISR: in-stent restenosis; NSTEMI: non ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction.

Procedural success was achieved in all patients with varying treatments shown (Fig. 1). Treatment of BMS ISR involved PTCA alone in 7 (13%) patients, and additional stenting in 45 patients (87%) [Cypher n = 19 (42%), Taxus n = 25 (56%), and BMS n = 1 (2%)]. Additional stent length was 21.3 ± 9.5 mm. Treatment of DES ISR involved PTCA alone in two (25%) patients and additional stenting in six (75%) patients [Cypher n = 3 (50%), Taxus n = 3 (50%)]. Additional stent length was 19.3 ± 14.5 mm. The planned duration of clopidogrel therapy after treating ISR was ≥12 months in 30 patients (50%), and in all patients with DES ISR. All procedures were free of major adverse events and no in-hospital complications were reported.

No clinical events were reported at 30-day follow-up (Table 3). Twelve-month follow-up was complete (100%) for all patients. At 12 months, one patient died of non-

Table 2. *Lesion Characteristics*

	N = 60 (%)
ISR of BMS	52 (87)
ISR of DES	8 (13)
Target vessel ISR	
LAD	20 (33)
LCX	19 (32)
RCA	20 (33)
Bypass graft	1 (2)
Reference vessel diameter (mm)	2.9 ± 0.3
Mean lesion length of total cohort (mm) ± S.D.	12.7 ± 11.4
BMS ISR lesion length	13.6 ± 11.8[a]
DES ISR lesion length	5.1 ± 2.5[a]
Pattern of ISR, *n* (%)	
Focal (Type I)	32 (53)
Diffuse in-stent (Type II)	15 (25)
Diffuse proliferative (Type III)	7 (12)
Total occlusion (Type IV)	6 (10)

BMS: bare metal stent; DES: drug eluting stent; ISR: in-stent restenosis; LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery.
[a] p < 0.001.

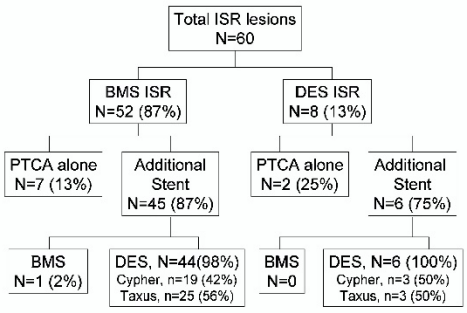

Figure 1. *Treatment of in-stent restenosis (ISR) according to type of stent implanted at index procedure. BMS: bare metal stents; Cypher: sirolimus-eluting BX velocity stent (Cordis, Miami Lakes, Florida); DES: drug-eluting stents; PTCA: percutaneous coronary angioplasty; Taxus: paclitaxel-eluting Express II stent (Boston Scientific, Boston, Massachusetts).*

Table 3. *Clinical Outcomes*

	30 Days, $N = 60$	12 Months, $N = 60$ (%)
Death	0	1 (2)
Myocardial infarction	0	1 (2)
TLR	0	4 (7)
TVR	0	4 (7)
CABG	0	1 (2)
Late thrombosis	0	0
MACE (death, MI, TVR)	0	6 (10)

CABG: coronary artery bypass graft; MACE: major adverse cardiac events; TLR: target lesion revascularisation; TVR: target vessel revascularisation.

cardiac cause. Four patients (7%) presented with recurrent ISR. Two of these patients had initial BMS ISR treated with DES. Subsequent treatment for recurrent ISR was additional DES in one patient and coronary artery bypass grafting in the second. Two patients with initial DES ISR, treated initially with PTCA alone in one and DES the other, were treated with additional DES for recurrent ISR. The incidence of recurrent ISR in DES is therefore 5% ($n = 3$). No late thrombosis was reported at 12-month follow-up.

Discussion

Since the inception of our interventional cardiology registry, ISR remains a relatively uncommon indication for PCI (4%). Our practice suggests that with either BMS or DES ISR, balloon angioplasty alone or additional stenting with DES are preferred treatment strategies with low subsequent clinical event rates. Debulking techniques such as rotational atherectomy or intracoronary radiation therapy were not utilised. The majority of ISR occurred in BMS (87%) and was treated with additional stenting with a DES. Our current rate of DES use for *de novo* lesions has exponentially increased (at present approximately 60% of all PCI), mirroring practice in the United States and Europe, and so the incidence of DES ISR will inevitably increase. Projections in the United States alone estimate ≥100,000 patients will need treatment for ISR of DES annually. Thus, treatment of ISR will continue to demand attention from the interventional community.

Although IRT is currently the only approved treatment of ISR, DES has superseded IRT as the treatment of choice for ISR of BMS in clinical practice. Two recent randomised studies have shown that DES are superior to IRT in the treatment of ISR of BMS.[7,8] In the Sirolimus-Eluting Stent versus Intravascular Brachytherapy in the Treatment of Patients with In-stent Restenotic Coronary Lesions (SISR) trial there was significantly lower incidence of target vessel failure with DES compared to IRT (12.4% vs. 21.6%, respectively, $p = 0.023$) at nine months.[7] There was a similar reduction in target vessel failure in the TAXUS V ISR trial (19.5% vs. 11.5%, $p = 0.003$) at nine months.[8]

If DES is to become first line therapy for ISR, which DES should be used? The Intracoronary Stenting and Angiographic Results-Drug-Eluting Stents for In-Stent Restenosis (ISAR-DESIRE) study was the first randomised study to demonstrate that a strategy of DES was superior to conventional PTCA in BMS ISR.[13] Although the study was not designed to compare the efficacy of Cypher and Taxus, the secondary analysis of the study was the first to demonstrate that use of Cypher stents was superior to Taxus with a reduced rate of TVR (8% vs. 19%, respectively, $p = 0.02$).

The aetiology of DES restenosis appears to be multi-factorial, and our understanding of this remains incomplete. Potential mechanisms include: (i) stent under-expansion (intravascular ultrasound guided stent placement was not used routinely in our registry); (ii) asymmetric stent strut distribution; (iii) stent fracture; (iv) polymer disruption; (v) peri-stent vessel wall injury; (vi) drug failure or drug resistance; (vii) polymer (or drug) hypersensitivity These factors are speculative and challenging to identify in individual patients.[14–18]

The pattern of restenosis associated with DES implantation is predominantly focal and treatment with either BMS or DES has good success rates, with 75% enjoying no MACE and 25% requiring repeat PCI.[14,19] This focal pattern was identified in our DES ISR population, in contrast to the diffuse pattern seen in BMS ISR.

Currently, there are no data on optimal treatment of ISR in DES. Therapeutic options include repeat DES implantation with the same or a different DES, intracoronary radiation therapy or coronary bypass grafting. If DES failure occurs in a sirolimus-eluting stent, is this a marker for a specific drug resistance, therefore favouring treatment with a non-sirolimus-eluting stent? The incidence of recurrent DES ISR at 12 months in our study (5%) was low. This may reflect low risk of recurrent ISR associated with focal pattern of restenosis in about half the patients. By contrast, a study of 24 patients with DES restenosis undergoing repeat percutaneous intervention showed rates of recurrent restenosis as high as 43% at median follow-up of 279 days.[20] Further studies are needed to determine optimal therapy for DES ISR.

Despite only 50% of patients having planned clopidogrel ≥12 months, no late thrombosis was reported in our study at 12 months. However, the patient who initially presented with late stent thrombosis 341 days post DES implan-

tation highlights the need for vigilance in maintenance antiplatelet therapy. On the basis of recent reports of late thrombosis in DES, and the associated broader benefits of dual antiplatelet therapy in patients with recurrent coronary events, we believe at least 12 months dual-antiplatelet therapy is indicated.[21–24]

The limitations of this study include the relatively small patient numbers for subgroup analysis of ISR. Our study only enrolled patients undergoing PCI for ISR and may underestimate the incidence of ISR. Some of these patients may have been treated medically or have undergone bypass surgery. However, the incidence of recurrent ISR after PCI is captured with complete follow-up. There may be a selection bias for relatively low risk patients with predominantly focal pattern of restenosis as reflected by the low incidence of 12 months MACE. The choice of stent used was at the discretion of the interventionalists. Despite the inherent drawbacks of registry studies, consecutive patients were enrolled, with the data collected prospectively and adjudicated independently to ensure the data integrity.

Conclusions

The majority of in-stent restenotic lesions treated in contemporary Australian interventional practice were in bare-metal stents and had a focal pattern of in-stent restenosis. Most of these lesions were treated with additional stenting, with a preference for DES over BMS. The incidence of recurrent drug-eluting stent restenosis is low. However, widespread use of drug-eluting stents in increasingly complex lesions will result in increasing in-stent restenosis related to drug-eluting stent failure. Despite a lack of data to support the use of drug-eluting stents for recurrent in-stent restenosis, our registry suggests that drug-eluting stents is the preferred therapy for this indication.

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Appendix

Melbourne Interventional Group Investigators: The following investigators and institutions participated in the Melbourne Interventional Group registry. *Alfred Hospital*: S.J. Duffy, J. Shaw, A. Walton, C. Farrington, R. Gunaratne, A. Broughton, J. Federman, C. Keighley, A. Dart. *Austin Hospital*: D.J. Clark, J. Johns, M. Horrigan, O. Farouque, L. Oliver, J. Brennan, R. Chan, G. Proimos, T. Dortimer, B. Chan, A. Tonkin, L. Brown, N. Campbell, A. Sahar, K. Charter. *Box Hill Hospital*: G. New, L. Roberts, H. Liew, M. Rowe, G. Proimos, N. Cheong, C. Goods. *Frankston Hospital*: R. Lew, G. Szto, R. Templin. *Geelong Hospital*: A. Black, M. Sebastian, T. Yip, L. Ponnuthrai, M. Rahmen, J. Dyson, T. Duplessis. *Monash University*: H. Krum, C. Reid, A. Brennan, A. Meehan, P. Loane, L. Curran, F. Groen. *Peninsula Private Hospital*: G. Szto, V. O'Shea. *Royal Melbourne Hospital*: A.E. Ajani, R. Warren, D. Eccleston, J. Lefkovits, B.P. Yan, P. Roy, S. Shetty, R. Gurvitch. *Western Hospital*: Y.-L. Lim, D. Eccleston, A. Walton.

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Appendix 10

ELSEVIER

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CARDIOVASCULAR REVASCULARIZATION MEDICINE

Drug-eluting stents for the treatment of in-stent restenosis
A clinical review

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Abstract Treatment of in-stent restenosis (ISR) remains problematic despite the widespread application of drug-eluting stents (DES). Challenging lesion cohorts such as diffuse ISR and restenosis after failed intracoronary radiation therapy (IRT) maybe best treated with DES. The overall benefit of DES appears inferior to their utility in treating de novo coronary lesions. Randomised trials comparing DES and IRT will soon be available to determine the optimal therapy for ISR. The challenge to treat ISR in the DES era is the next frontier of interventional cardiology.

Keywords: In-stent restenosis; Drug-eluting stents; Sirolimus; Paclitaxel; Intracoronary radiation therapy

1. Introduction

In-stent restenosis (ISR) remains a major limitation of percutaneous coronary intervention (PCI) with bare-metal stent implantation. Rates of restenosis have been reported to occur in 10% to 50% in clinical practice [1,2]. The treatment of ISR is associated with a high recurrence of restenosis, from 30% to 80% in complex lesions [3]. Intracoronary radiation therapy (IRT) has been the only proven therapy for ISR [4,5]. However, drug-eluting stents (DES) hold promise as comparable therapy. Sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) have been shown to reduce ISR and the need for repeat revascularisation to <10% in patients with de novo lesions [6,7]. Promising results obtained in the primary prevention of ISR in de novo lesions has led to interest in extending DES application to more complex lesions, such as the treatment of ISR. The safety and efficacy of DES for the treatment of ISR are less defined. This paper reviews current evidence for DES implantation for the treatment of ISR.

2. In-stent restenosis

The principal cause of ISR is neointimal hyperplasia resulting from the excessive proliferation of smooth muscle cells in response to injury during stent implantation [8]. Factors known to increase the risk of ISR include smaller vessel diameter, prior restenosis, length of stented vessel, and diabetes mellitus [3]. Effective treatment of ISR requires suppression of this intimal proliferation.

Sirolimus and paclitaxel suppress both smooth muscle proliferation and intimal hyperplasia [9,10]. The efficacy of SES (Cypher, Cordis J&J) and PES (TAXUS, Boston Scientific) in reducing intimal hyperplasia in de novo lesions has been observed with intravascular ultrasound (IVUS) in several trials [6,7]. The use of DES to treat ISR is an attractive option. Compared with IRT, stent implantation is simple and requires no additional personnel (e.g., radiation oncologist) or equipment. To date, a number of studies have shown the novel use of DES to treat ISR with

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Table 1
Summary of published studies on SES for treatment of ISR

Study	Degretekin et al. [11]	Sousa et al. [12]	Saia et al. [13,18]	Werner et al. [14]	Kastrati et al. [15]	Iofina et al. [16]	Airoldi et al. [17]
Number of patients	16	25	44	22	100	28	60
Diabetes mellitus (%)	25	24	25	50	31	25	23
Diffuse ISR (%)	81	68	58	100	76	71	86
Recurrent ISR (%)	N/A	20	25	77	N/A	N/A	24
Mean lesion length (mm)	18.4	13.6	17.5	23.4	12.4	10.6	15.5
Follow-up (months)	9	12	9	12	6	9	6
Binary restenosis rate (%)	20	4	14.6	14	14.3	13	13
Late loss (mm)	0.21±0.62	0.36±0.46	0.17	0.39±0.54	0.1	0.29±0.52	0.35±0.73
TLR (%)	8.3	0	16.3	14	8	11	10.9
MACE (%)	18.7	0	18.5	14	8	14	10.9

SES and PES to be safe and effective (Tables 1 and 2; [11–19,21,22]).

3. Sirolimus-eluting stents

Initial clinical data on SES for ISR arose from two small studies involving 16 patients from Rotterdam, the Netherlands, and 25 patients from São Paulo, Brazil, with ISR in native vessels [11,12]. The lesion characteristics in the Rotterdam series were more complex than in the São Paulo series. Diffuse ISR was present in 68% of the São Paulo patients and 81% of Rotterdam patients. Mean lesion length was 18.4 mm in the former and 13.6 mm in the latter study. Four Rotterdam patients presented with ISR following failed IRT. These differences in risk profile were reflected in 1-year outcomes. One patient from São Paulo developed binary restenosis (≥50% diameter stenosis) on routine angiography, but there were no target lesion revascularisation (TLR) or major adverse cardiac events (MACE). By comparison, event rates were higher in the Rotterdam group, with three patients developing restenosis (TLR=8.3%, MACE=18.7%, with one myocardial infarction and two deaths).

Since April 2002, the Rotterdam University Hospital Thoraxcenter had adopted SES implantation as the default strategy for all coronary interventions as part of the Rapamycin-Eluting Stent Evaluation at Rotterdam Cardiology Hospital (RESEARCH) Registry. From this registry, 44 consecutive patients without previous IRT were treated with SES for ISR [13]. At baseline, 42% of the lesions were focal, 21% diffuse, 26% proliferative, and 11% occluded, with small vessel size (reference diameter ≤2.5 mm) in 49% and a mean lesion length of 17.5 mm. Binary restenosis occurred in 14.6% of the lesion at 6-month angiographic follow-up. At 9-month clinical follow-up, there were no deaths, 4.7% myocardial infarction, and 16.3% TLR. Of note, no restenosis was observed at follow-up in focal lesions. There were no differences in the rates of repeat restenosis between the diffuse (22.2%), proliferative (25%), or chronic total occlusions (20%), in which rates of repeat restenosis have been reported to be 35%, 50%, and 85%, respectively, with conventional treatment [3]. SES may be less effective in nonfocal lesions but appeared to be equally effective in diffuse, proliferative, and occlusive ISR.

The e-CYPHER Registry: Real World use of Sirolimus-Eluting Stents for the Treatment of In-Stent Restenosis has been presented (AHA 2004, New Orleans). This international, Internet-based e-CYPHER Registry was established in April 2002 to assess the performance of the SES in a real-world setting. At the time of presentation, there were 1827 patients (12% of registry) with ISR-treated with SES. Patient characteristics were comparable with the registries described above, with 30% diabetes mellitus, 77% AHA/ACC Type B2 or C lesions, and mean lesion

Table 2
Summary of published studies on PES for the treatment of ISR

Study	Iofina et al. [16]	Radke et al. [19]	Tanabe et al. [22]	Kastrati et al. [15]
Drug	Nonpolymer (ACHIEVE, Cook)	Nonpolymer (ACHIEVE, Cook)	Polymer (TAXUS, Boston Scientific)	Polymer (TAXUS, Boston Scientific)
Number of patients	24	22	28	100
Diabetes mellitus (%)	21	23	14	31
Diffuse ISR (%)	78	76	64	40
Recurrent ISR (%)	N/A	N/A	N/A	N/A
Mean lesion length (mm)	13.7	13.3	13.6	12.4
Follow-up (months)	9	12	12	6
Binary restenosis rate (%)	20	20	16	14.3
Late loss (mm)	0.43±0.47	0.44±0.53	0.54±0.51	0.1
TLR (%)	8	9	21.4	8
MACE (%)	8	9	29	11

length of 18.2 mm. Six-month outcomes were encouraging, with 2.1% TLR and 3.8% MACE.

4. SES in complex ISR

Patients with diabetes mellitus and diffuse and recurrent ISR are associated with the highest risk of recurrent stenosis [3]. A study of 22 patients with a high prevalence of these risk factors was performed by Werner et al. [14]. In this cohort of patients, 50% had diabetes mellitus, 77% had more than one previous ISR, and all had diffuse or occlusive ISR. The mean lesion length of 23 mm was longer than the lesions studied in the Rotterdam (18.4 mm), São Paulo (13.6 mm), and RESEARCH (17.5 mm) registries [11–13]. Despite these high-risk characteristics, angiographic restenosis, TLR, and MACE (all 14%) were comparable to the registry results shown above.

The SECURE (Compassionate use of Sirolimus-Eluting Stents) trial enrolled 252 patients who had complex lesions with no acceptable alternative treatment, including IRT and coronary arterial bypass grafting (CABG). In this study, the majority of patients had ISR (87% had >1 episode of restenosis, 72% had previous IRT, 39% had diabetes mellitus, and 21% had bypass grafts). At 6 months, a higher incidence of MACE was observed in patients who had a previous IRT failure (23.5%) than in patients without previous IRT (8.5%). MACE and TLR in the group treated for bypass grafts (20% and 16.7%) were identical to outcomes in patients who received SES (21.5% and 20%) for native vessel ISR. These favourable results were the first experience of DES in bypass graft ISR.

5. DES versus other treatments of ISR

A number of studies compared the efficacy of DES in the treatment of ISR with other percutaneous treatment modalities, such as balloon angioplasty (PTCA), cutting balloon (CB) angioplasty, and IRT.

5.1. DES versus balloon angioplasty

The Intracoronary Stenting and Angiographic Results-Drug-Eluting Stents for In-Stent Restenosis (ISAR-DESIRE) study was the first randomised controlled data on the efficacy of DES versus PTCA for ISR [15]. This trial randomised 300 consecutive patients with ISR to PTCA or one of either SES or PES. The primary endpoint of the study was angiographic restenosis at 6 months, which showed a marked reduction of recurrent restenosis with both DES. When compared with PTCA, SES was associated with a 68% reduction in the risk of angiographic restenosis ($P<.001$) and a 76% reduction of the need for target vessel revascularisation ($P<.001$). The relative reductions in restenosis and TLR with PES were 51% and 42%, respectively, compared with PTCA ($P=.001$ and $P=.02$, respectively). This study demonstrated that a strategy using DES was superior to conventional balloon angioplasty for the treatment of ISR. The mechanism yielding lower restenosis rate could be explained by a larger acute gain and a smaller late loss achieved with DES than with PTCA alone.

Another study also showed the superiority of DES over PTCA for the treatment of ISR [16]. In this study, 70 patients with native coronary artery ISR were treated with either PTCA alone ($n=25$), PES ($n=24$), or SES ($n=28$). Nine-month angiographic restenosis rates were 61%, 20%, and 13% and TLR rates were 32%, 8%, and 11% in the PTCA, PES, and SES groups, respectively.

5.2. DES versus CB angioplasty

SES were compared with CB angioplasty for ISR in a study of 55 patients treated with SES and a group of 214 patients with matched lesions characteristics from the CB arm of the Restenosis Cutting Balloon Evaluation Trail (RESCUT; [17]). The results of the study showed a 57% relative reduction in the incidence of recurrent restenosis with SES implantation compared with that observed in the CB group ($P=.038$).

5.3. DES versus intracoronary radiation therapy

Three studies attempted to compare the efficacy of DES with that of IRT for the treatment of ISR. In a study by Saia et al. [18], 44 patients with ISR treated with SES were compared with a historical cohort of 43 patients treated with IRT. The outcomes of both groups were similar at 9 months. Rates of TLR and freedom from MACE were 16.3% and 81.5% in the SES group and 11% and 79.1% in the IRT group, respectively. Radke et al. [19] compared 22 patients receiving nonpolymer PES (ACHIEVE, Cook) with 141 patients from a registry of patients who had IRT for ISR. In this study, lesion length and vessel diameter were pair matched in both groups. At 12 months, 9% of the patients in the paclitaxel group and 24% of patients in the IRT group experienced MACE due to recurrent restenosis (all TLR).

The Treatment of Patients with an In-stent Restenotic Native Coronary Artery Lesion (TROPICAL) study was a multicenter, nonrandomised study of SES in ISR of native coronary lesions compared with the combined historical control patients with ISR treated with IRT from the GAMMA I and II Trials (EuroPCR 2004, Paris). A total of 162 consecutive patients was treated with SES. Mean lesion length was 15.8 mm. Clinical outcomes at 180 days in the SES group showed 2.5% TLR and 3.7% MACE. These results compared favourably with the historical control group (TLR: 2.5% vs. 14%, $P<.001$; MACE: 3.7% vs. 18.8%, $P<.001$; [20]). The major limitations of these three studies were that all were nonrandomised and

comparison groups had different treatment periods, inclusion criteria, and lesion characteristics. More patients treated with SES in the study by Saia et al. [18] had focal lesions (43%) than in the IRT group (23%). The suggestion by these studies that DES and IRT are equally effective in the treatment of ISR needs to be interpreted with caution.

Randomised controlled trials are imperative to compare the relative efficacy of DES and IRT in ISR. At present, the Sirolimus-Eluting BX Velocity Balloon Expandable Stent vs. Intracoronary Brachytherapy in the Treatment of Patients with In-Stent Restenotic Coronary Artery Lesion (SISR) Trial is an ongoing multicenter, randomised trial (26 sites, 400 patients) of SES versus beta or gamma IRT for ISR. The primary endpoint is target vessel failure (target vessel revascularisation, cardiac death, or myocardial infarction) at 9 months, and results are expected by mid-2005. Slow release formulation PES (TAXUS, Boston Scientific) for the treatment of ISR will be randomised against beta IRT in the TAXUS V-ISR Trial. This multicenter trial, involving 37 centers, has completed the enrolment of 421 patients with ISR with lesion length <46 mm and vessel diameter between 2.5 and 3.75 mm. The primary endpoint is target vessel failure at 9 months. These trials will help define the roles of DES and IRT in the treatment of ISR.

6. Paclitaxel-eluting stents

The first experience with PES in ISR came from a negative study, which used a paclitaxel derivative eluting stent (QuaDS-QP2, Quanum Medical) on 15 patients with ISR from two centers [21]. Although 6-month angiographic follow-up demonstrated a restenosis rate of 13.3%, by 12 months, this had deteriorated to 61.5%. TLR at 12 months was an excessive 60%.

Two studies evaluated the use of nonpolymer paclitaxel stents (ACHIEVE, Cook) in the treatment of ISR. The study by Iofina et al. [16] described above showed that angiographic restenosis at 9 months in patients treated with PTCA, PES, and SES were 61%, 20%, and 13%, respectively (P=.042). A second study had 22 patients treated with PES and 141 patients treated with IRT pair matched in lesion length and vessel diameter [19]. Angiographic binary restenosis at 6 months was 20% in the paclitaxel group and 14% in the IRT group (P=NS). At 12 months, 9% of patients in the PES group and 24% of patients in the IRT group underwent TLR (P=NS).

The TAXUS III feasibility trial examined PES (TAXUS, Boston Scientific) for ISR in 28 patients [22]. The vessels treated were between 3 and 3.5 mm, with a mean lesion length of 13.6 mm (64% diffuse ISR). At 1 year, MACE occurred in 29% and TLR in 21.4% of patients. This study demonstrated that TAXUS stent was safe and efficacious in the treatment of ISR.

The efficacy of the TAXUS stent in ISR was confirmed in the randomised controlled ISAR-DESIRE trial [22] described above. Compared with PTCA, receiving a TAXUS stent was associated with a relative risk of target vessel revascularisation of 0.58 (95% CI=0.35–0.94). Although ISAR-DESIRE was not designed to compare the efficacy between SES and PES, the secondary analysis of the study was the first to show that SES had a significantly lower TLR (8% vs. 19%, P=.02) and late lumen loss in-stent (2.45 vs. 2.21, P<.05) than did PES. Compared with PES, receiving an SES was associated with a reduced risk of target vessel revascularisation of 0.42 (95% CI=0.19–0.92). This suggested that SES may be superior to PES for the treatment of ISR.

7. Other DES

Other DES, such as everolimus-eluting stent (Guidant), ABT-578-eluting stents (Abbott Vascular and Medtronic), A9 Biolimus-eluting stents (Terumo, Biosensors), and Tacrolimus-eluting stents, are currently in various phases of development. Their efficacy in de novo lesions will need to be proven first before attempts to extend their applications to more complex lesions, such as ISR.

8. DES for failed brachytherapy

Recurrent ISR after IRT occurs in 17–32% of patients at 1 year [23]. The option of a second IRT procedure to treat ISR after IRT failure has been evaluated in 51 patients [24]. A TLR rate of 23.5% and a MACE rate of 29.4% were reported at 9-month follow-up. The most common pattern of restenosis after IRT failure was focal (<10 mm; [23]).

Three small studies evaluated the use of SES for ISR after IRT failure ([25–27]; Table 3). In a study of 12 patients from the RESEARCH registry, at 9-month follow-up, TLR rate was 25% and MACE was 42% [25].

Table 3
Summary of published studies on DES for failed intracoronary radiation

Study	Saia et al. [25]	Iakovou et al. [26]	Shiele et al. [27]
Drug	Sirolimus (CYPHER, Cordis)	Sirolimus (CYPHER, Cordis)	Sirolimus (CYPHER, Cordis)
Number of patients	12	15	25
Diabetes mellitus (%)	25	27	20
Diffuse ISR (%)	75	N/A	N/A
Recurrent ISR (%)	100	93	100
Previous IBT (%)	100	100	100
Mean lesion length (mm)	N/A	25.8	15.4
Follow-up (months)	9	12	6.9
Binary restenosis rate (%)	40	17	8
Late loss (mm)	0.68±1.2	N/A	0.5±0.5
TLR (%)	25	13	4
MACE (%)	41.6	20	N/A

A second study of 15 patients showed 13% TLR and 20% MACE at 12-month follow-up [26]. A third study of 25 patients used IVUS analysis to assess SES implantation in patients with either first episode of ISR or recurrent ISR after failed IRT [27]. The results showed that SES was equally effective in both groups. Late lumen loss and intimal hyperplasia cross-sectional areas in the group with first episode of ISR were 0.2 ± 0.7 mm and 0.2 mm^2 and in the recurrent ISR after IRT group were 0.5 ± 0.5 mm and 0.3 mm^2, respectively (P=NS). These results were comparable with the results observed in studies on SES in de novo ISR [11–13]. Results from these three studies suggest SES implantation to be effective in the treatment of ISR after IRT failure.

9. In-stent restenosis in drug-eluting stents

DES has significantly reduced the incidence of ISR; however, it has not been eliminated. As the indications for DES continue to expand and more DES are implanted, the prevalence of ISR may, in fact, increase. Studies have shown that the pattern of restenosis associated with DES implantation has changed to a predominantly (84% to 100%) focal pattern and the lesions are mostly in-stent rather than edge restenosis [28,29]. Areas of stent discontinuity are particularly at risk; thus, overlapping DES is recommended.

Currently, there are no data on optimal treatment of ISR in DES. Therapeutic options include repeat DES implantation with the same or a different DES, IRT, or CABG. A study of 24 patients with post-SES restenosis undergoing repeat PTCA (11%), repeat bare-metal stent (4%), or repeat DES (85%) showed high rates of recurrent restenosis of 42.9% overall [30]. Debulking techniques such as rotablation, DCA, or CB angioplasty have no proven additional advantage.

10. Conclusion

SES and PES show promise for the treatment of ISR. SES may be superior to PES for the treatment of ISR. There is more evidence for the use of SES in high-risk patients with diffuse and recurrent ISR, with or without prior IRT. However, the efficacy of DES in complex ISR is, as expected, less effective than in focal ISR and in de novo lesions. The durability of DES treatment benefit beyond 12 months remains uncertain. There may be late "catch-up" (delayed restenosis), mandating the need for long-term follow-up. Evidence of the preserved efficacy of DES in de novo lesions at 3 years is encouraging [31]. Despite limitations of IRT, there is currently no head-to-head comparison between DES and IRT to support the superiority of either treatment strategy. Ongoing randomised controlled trials will help decide the role of DES and IRT in the treatment of ISR. However, given the ease of use and availability of DES, they are likely to become the predominant strategy for ISR. As DES implantation becomes more widespread, ISR in DES will continue to challenge interventional cardiologists.

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Appendix 11

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Are drug-eluting stents indicated in large coronary arteries? Insights from a multi-centre percutaneous coronary intervention registry

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Abstract

Background: Restenosis rates are low in large coronary vessels ≥3.5 mm after bare-metal stent (BMS) implantation. The benefit of drug-eluting stents (DES) in large vessels is not established.
Objective: We aim to assess clinical outcomes after deployment of BMS compared to DES in patients with large coronary vessels ≥3.5 mm.
Methods: We analysed 672 consecutive patients undergoing percutaneous coronary interventions with ≥3.5 mm stent implantation in native coronary artery de-novo lesions from the Melbourne Interventional Group (MIG) registry. Baseline characteristics, 30-day and 12-month outcomes of patients receiving BMS were compared to DES. Multivariate analysis was performed to identify predictors of major adverse cardiac events [MACE, consisting of death, myocardial infarction (MI) and target vessel revascularisation (TVR)].
Results: Of the 672 PCIs performed in 844 lesions, DES was implanted in 39.5% (n=333) and BMS in 60.5% (n=511) of lesions. Patients who received DES compared to BMS were older, more likely to be diabetic, had left ventricular dysfunction <45% or complex lesions. Significantly fewer patients who presented with ST-elevation MI received DES compared to BMS. There were no significant differences in 12-month mortality (0.5 vs. 2.9%, p=0.07), TVR (3.6 vs. 4.8%, p=0.54), MI (6.3 vs. 3.4%, p=0.15), stent thrombosis (0.9 vs. 1.0%, p=0.88), or MACE (9.4 vs. 9.4%, p=0.90) in patients who received DES vs. BMS. Stent length ≥20 mm was the only independent predictor of 12-month MACE (Odds Ratio 2.07, 95% CI 1.14 3.76, p=0.02).
Conclusion: In this registry, BMS implantation in large native coronary vessels ≥3.5 mm was associated with a low risk of MACE and repeat revascularization at 12 months that was comparable to DES.

Keywords: Percutaneous coronary intervention; Drug-eluting stents; Bare-metal stents

1. Introduction

Vessel size is an important determinant of restenosis in patients undergoing percutaneous coronary intervention

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(PCI) with stent implantation. Restenosis rates are low (<10%) in large coronary arteries after bare-metal stent (BMS) implantation [1–5]. Drug-eluting stents (DES) have been shown to be superior to BMS in reducing restenosis across a wide range of coronary lesions [6]. However, the absolute benefit from DES in patients at low risk of restenosis is reduced [7,8]. Subgroup analyses of randomised trials have shown only modest differences in clinical outcomes between BMS and DES in large vessels [8–12]. Further, there is the small risk of late adverse events such as stent thrombosis (ST) and bleeding risk associated with the need for prolonged dual-antiplatelet therapy after DES implantation [13–15]. In the recent randomised BASKET trial comparing DES and BMS in an unselected population, there was an increased rate of late death or MI in patients who received DES in large coronary arteries ≥3 mm [8]. The aim of this study was to assess the clinical outcomes 1 year after deployment of BMS compared to DES in patients with large coronary vessels ≥3.5 mm.

2. Methods

2.1. Patient population and registry design

The study population consisted of 672 patients undergoing consecutive PCI with either a ≥3.5 mm stent or a ≥3.5 mm balloon for post-stent dilatation in 844 native coronary artery de-novo lesions from April 2004 to December 2005 from the Melbourne Interventional Group (MIG) registry. The study population was classified into 2 groups based on stent type deployed: (i) the DES group had utilisation of one or more DES (ii) the BMS group had utilisation of one or more BMS only.

The registry is a collaborative venture of interventional cardiologists practicing at 7 Australian tertiary referral hospitals, designed to record data pertaining to all PCI and to perform follow-up at 30 days and 1 year. The MIG registry has been previously described [16,17]. Briefly, demographic, clinical and procedural characteristics of consecutive patients undergoing PCI are prospectively recorded on case report forms using standardized definitions for all fields [16]. The registry is co-ordinated by the Centre of Clinical Research Excellence, a research body within the Department of Epidemiology and Preventive Medicine (Monash University, Melbourne, Australia). An external audit of 10 fields from 3% of procedures at each institution was performed in May 2007; accuracy was 97%. The study protocol was approved by the ethics committee in each participating hospital. "Opt-out" informed consent was obtained in all patients, as previously described [16].

2.2. Procedures and post-intervention medications

The interventional strategy and stent selection was left to the discretion of the operator in all procedures. However, DES use in the Australian public health system is restricted for patients at high risk of restenosis who may theoretically derive the greatest benefit. Current guidelines for DES use include diabetes mellitus, small vessels (≤2.5 mm), long lesions (≥20 mm) and complex lesions including chronic total occlusions, in-stent restenosis, bifurcation and ostial lesions [17]. These guidelines were followed in all participating cardiac catheter laboratories, and the reason for DES use was documented in all PCIs.

Total stent length was used as a surrogate for target lesion length, and either stent or maximal balloon diameter for target vessel diameter because quantitative coronary angiography was not routinely used at all the participating centres. Angiographic success was defined by a residual stenosis of <50%. Peri-procedural glycoprotein IIb/IIIa inhibitors were used according to the operator's decision. Oral antiplatelet therapy during the study period followed guidelines recommending combination of aspirin and clopidogrel for a minimum of 4 weeks for BMS and between 6 to 12 months for DES [18].

2.3. Clinical outcomes

In-hospital complications were recorded at time of discharge. Cardiac research nurses conducted 30-day and 12-month follow-up by telephone. All cardiac events were documented including death, myocardial infarction (MI), stent thrombosis, target lesion revascularisation (TLR), target vessel revascularisation (TVR), and composite major adverse cardiac events (MACE, consisting of death, MI and TVR). Patient medical records were reviewed to substantiate recorded events. Death included all cause mortality. Peri-procedural MI was defined as either a rise in creatinine kinase or creatinine kinase MB of ≥ three times the upper limit of normal or evolutionary ST-segment elevations, development of new Q-waves in ≥2 contiguous ECG leads, or new LBBB pattern on the ECG. Target vessel revascularization is a repeat revascularization in the follow-up period due to restenosis either within the target lesion or within the same epicardial coronary artery. Stent thrombosis was defined as early (<30 days) or late (>30 days) after the index procedure, and was defined as (i) *Definite*: an acute coronary syndrome (ACS) with angiographic documentation of either vessel occlusion or thrombus within or adjacent to a previously successfully stented vessel or autopsy evidence of stent thrombosis, (ii) *Probable*: acute myocardial infarction in the distribution of the treated vessel or unexplained death <30 days and (iii) P*ossible*: unexplained death >30days [19].

2.4. Statistical analysis

Continuous variables were expressed as mean±SD, and categorical data expressed as percentages. Continuous variables were compared using Student's *t*-tests or ANOVA. Categorical variables were compared using Fisher exact or chi-square tests as appropriate. All calculated *p*-

Table 1
Baseline characteristics of the 672 patients undergoing PCI with DES compared to BMS

	DES	BMS	*p*-value
N (%)	239 (35.6)	433 (64.4)	–
Age, years mean±SD	65.5±12.3	62.6±12.3	<0.01
LVEF<45%, *n* (%)	26 (10.9)	26 (6.0)	0.02
Male, *n* (%)	175 (73.2)	331 (76.4)	0.35
Diabetes, *n* (%)	63 (26.5)	61 (14.1)	<0.01
Hypertension, *n* (%)	151 (63.4)	267 (61.7)	0.68
Hypercholesterolaemia, *n* (%)	156 (65.8)	299 (69.9)	0.30
Current Smoking, *n* (%)	46 (20.2)	127 (29.4)	<0.01
Previous myocardial infarction, *n* (%)	58 (24.3)	94 (21.8)	0.50
Previous PCI, *n* (%)	42 (17.6)	56 (12.9)	0.11
Previous CABG, *n* (%)	13 (5.4)	18 (4.2)	0.45
Renal dysfunction (Baseline Cr.>0.20 mmol/L), *n* (%)	9 (3.8)	14 (3.2)	0.83
Clinical presentation, n (%)			
Acute coronary syndromes (total)	148 (61.9)	287 (66.3)	0.27
Unstable angina	56 (23.4)	82 (18.9)	0.20
Non-STEMI	53 (22.2)	81 (18.7)	0.31
STEMI	39 (16.3)	124 (28.6)	<0.01
CHF	6 (2.5)	9 (2.1)	0.79
Cardiogenic shock	5 (2.1)	10 (2.3)	0.76

BMS = bare-metal stents; CABG = coronary artery bypass grafting; CHF = congestive cardiac failure; DES = drug-eluting stents; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction.

values were two-sided and *p*-values <0.05 were considered statistically significant. Cumulative incidence of TVR and MACE was estimated according to the Kaplan–Meier method and the log-rank test was used to evaluate differences between groups. Univariate and multivariate logistic regression analysis was used to determine independent predictors of TVR and MACE at 12 months. Variables used in univariate analysis included age, sex, diabetes mellitus, renal failure, ACS, ST-elevation MI (STEMI), cardiogenic shock, presentation with congestive cardiac failure (CHF), chronic total occlusion, stent length ≥20 mm, bifurcation and ostial lesions. Univariate predictors with $p<0.20$ were then added to a multivariate model. All statistical analysis was performed using SPSS Ver. 12.0 for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

Of the 672 PCIs performed in 844 native coronary artery de-novo lesions, DES was implanted in 39.5% ($n=333$) and BMS in 60.5% ($n=511$) of lesions. Four patients received a combination of DES and BMS. Patients who received DES compared to BMS were older (65.5±12.3 vs. 62.6±12.3 years, $p<0.01$), were more likely to be diabetic (26.5 vs. 14.1%, $p<0.01$) or have left ventricular dysfunction, LVEF<45% (10.9 vs. 6.0%, $p=0.02$) (Table 1). Significantly less patients who presented with STEMI received DES compared to BMS (16.3 vs. 28.6%, $p<0.01$).

The DES group had a greater number of left main stem (3.0 vs. 1.0%, $p<0.04$) and left anterior descending artery (34.2 vs. 22.9%, $p<0.01$) treated compared to the BMS group (Table 2). Lesions treated were more likely to be American College of Cardiology/American Heart Association, type B2/C lesions (47.1 vs. 39.5%, $p=0.03$), involve bifurcations (6.3 vs. 1.8%) or be ostially located (6.9 vs. 2.0%) in the DES than in the BMS group.

3.1. Clinical outcomes

In-hospital, 30-day and 12-month follow-up was complete in 100% ($n=672/672$), 95% ($n=638/672$) and 90% ($n=602/672$) of patients, respectively (Table 3). Unadjusted mortality in patients who received DES at 12 months (0.5 vs. 2.9%, $p=0.07$) was lower but not statistically significant than in patients who received BMS (Table 3). The frequency of MI was not statistically different at 12 months (6.3 vs. 3.4%, $p=0.15$). The cumulative incidence of stent thrombosis (definite, probable and possible) was 0.9 vs. 1.0% ($p=0.88$) in DES and BMS groups, respectively. The rates of TVR were low in both groups at 12 months (3.6 vs. 4.8%, $p=0.54$). Overall MACE at 12 months (9.4 vs. 9.4%, $p=0.90$) was the same in both groups (Fig. 1).

A subgroup analysis of patients at high risk for restenosis ($n=333/672$) who met criteria for DES in the Australian public health system (i.e. diabetes mellitus, long lesions (≥20 mm) and complex lesions including chronic total occlusions, bifurcation and ostial lesions) showed no difference in 12-month TVR (3.6 vs. 3.4%, $p=0.91$) and

Table 2
Procedural characteristics pertaining to the 844 lesions treated with DES compared to BMS

	DES	BMS	*p*-value
Lesions, *n* (%)	333 (39.5)	511 (60.5)	–
Target Vessel, ***n* (%)**			
Left main	10 (3.0)	5 (1.0)	0.04
Left anterior descending	114 (34.2)	117 (22.9)	<0.01
Left circumflex	30 (9.0)	77 (15.1)	0.01
Right coronary	144 (43.2)	229 (56.8)	<0.01
Mean number of stents, *n*±SD	1.06±0.4	1.12±0.5	0.07
Mean stent diameter, mm±SD	3.3±0.4	3.5±0.4	<0.01
Mean stent length, mm±SD	18.2±8.2	18.6±8.9	0.60
Total stent length ≥20 mm, %	29.7	26.0	0.27
Type of drug-eluting stent, %			
Cypher[a]	38.7	–	–
Taxus[b]	61.3		
ACC/AHA lesion type B2/C, %	47.1	39.5	0.03
Chronic total occlusion, *n* (%)	3 (5.4)	4 (3.7)	0.69
Ostial lesions, *n* (%)	23 (6.9)	10 (2.0)	<0.01
Bifurcation lesions, *n* (%)	21 (6.3)	9 (1.8)	<0.01
Angiographic success, *n* (%)	99.5	99.4	0.50
Glycoprotein IIb/IIIa inhibitor *n*, (%)	27.4	30.4	0.48

ACC/AHA = American College of Cardiology/American Heart Association; BMS = bare-metal stents; DES = drug-eluting stents.
[a] Cordis J & J, Miami, FL.
[b] Boston Scientific Corporations, Natick, MA.

Table 3
Clinical outcomes at 30 days and 12 months

	DES	BMS	*p*-value
30 days, *n* (%)			
Death	0	4 (1.0)	
Cardiac	0	3 (0.7)	0.30
Non-cardiac	0	1 (0.2)	
Myocardial infarction	9 (3.9)	8 (2.0)	0.20
TLR	3 (1.3)	8 (2.0)	0.75
TVR	4 (2.0)	8 (1.7)	1.00
MACE	12 (5.2)	18 (4.4)	0.70
Stent thrombosis	1 (0.5)	0 (0)	0.33
12 months, *n* (%)			
Death	1 (0.5)	11 (2.9)	
Cardiac	0	4 (1.1)	0.07
Non-cardiac	1 (0.5)	7 (1.8)	
Myocardial infarction	14 (6.3)	13 (3.4)	0.15
TLR	5 (2.3)	15 (4.0)	0.35
TVR	8 (3.6)	18 (4.8)	0.54
MACE	21 (9.4)	36 (9.4)	0.90
Stent thrombosis (all)	2 (0.9)	4 (1.0)	0.88
Definite	1 (0.5)	2 (0.5)	0.24
Probable	1 (0.5)	0 (0)	–
Possible	0 (0)	2 (0.5)	–

CABG = coronary artery bypass graft; MACE = major adverse cardiac events; PCI = percutaneous coronary interventions; TLR = target lesion revascularisation; TVR = target vessel revascularisation.

MACE (10.6 vs. 10.5%, $p=0.96$) between patients receiving DES compared to BMS.

3.2. Predictors of clinical outcomes

Using the predefined variables for univariate analysis, there were no significant predictors of TVR. Univariate predictors of 12 month MACE (Table 4) were stent length ≥20 mm (Odds Ratio (OR) 1.87, 95% CI 1.08–3.25, $p=0.03$), presentation with heart failure (OR 3.22, 95% CI 1.01–10.25, $p=0.05$) and cardiogenic shock (OR 4.14, 95% CI 1.25–13.66). The only multivariate independent predictor

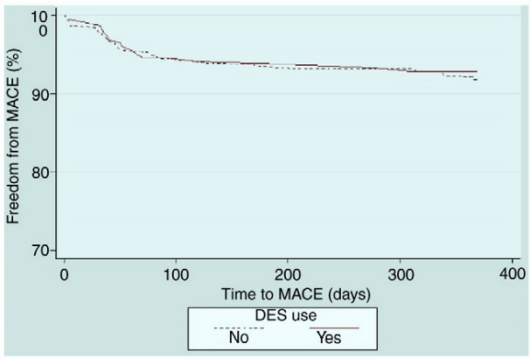

Fig. 1. Kaplan–Meier estimates of cumulative freedom from major adverse cardiac events (MACE, including death, MI and TVR) at 12-month follow-up in patients who received drug-eluting stent (solid line) and bare-metal stent (dotted line) implantation.

Table 4
Univariate Predictors of Major Adverse Cardiac Events

Univariate variables				Multivariate variables		
	Odds ratio	95%CI	*p*-value	Odds ratio	95% CI	*p*-value
Age	0.99	0.97–1.00	0.20	0.99	0.97–1.01	0.35
Male	1.28	0.66–2.50	0.46	–	–	–
Diabetes	0.71	0.33–1.55	0.40	–	–	–
Cardiogenic shock	4.14	1.25–13.66	0.02	3.64	0.98–13.49	0.05
STEMI	1.49	0.82–2.72	0.20	1.33	0.68–2.58	0.41
ACS	1.17	0.66–2.09	0.58	–	–	–
Stent≥20 mm	1.87	1.08–3.25	0.03	2.07	1.14–3.76	0.02
LAD	1.60	0.91–2.81	0.10	1.50	0.82–2.72	0.19
Renal Failure	2.22	0.72–6.80	0.16	1.56	0.42–5.71	0.51
Current CHF	3.22	1.01–10.25	0.05	2.52	0.62–10.16	0.20
Bifurcation lesion	1.90	0.63–5.73	0.26	–	–	–
Ostial lesion	1.07	0.32–3.66	0.91	–	–	–
CTO	1.62	0.19–13.66	0.66	–	–	–
Drug-eluting stent	0.99	0.57–1.75	0.98	–	–	–

ACS = acute coronary syndrome; CTO = chronic total occlusion; LAD = left descending coronary artery; STEMI = ST-elevation myocardial infarction.

of 12 month MACE was stent length ≥20 mm (OR 2.07, 95% CI 1.14–3.76, $p=0.02$).

4. Discussion

In this study, PCI in large native coronary arteries (≥3.5 mm) was associated with a low incidence of adverse events irrespective of stent type used. There were no significant differences in 12-month mortality, TVR, MI, stent thrombosis, or MACE in patients who received ≥3.5 mm diameter DES vs. BMS. Most importantly TVR was less than 5% in large coronaries after deployment of either BMS or DES.

Our findings are consistent with results from randomised studies and other large registries which found little or no benefit of DES in large coronary vessels [5,8–10,20–22]. In the TAXUS-IV and V trials, benefit of DES was limited to vessels ≤3 mm [9,10]. In the randomised BASKET trial comparing DES and BMS in an unselected population, DES conferred no benefit in large native vessels ≥3 mm in reducing TVR rates (HR 0.75, $p=0.38$) [23]. In the recent National Heart, Lung, and Blood Institute Dynamic Registry comparing BMS and DES use for off-label indications in 6551 patients, DES use in vessels ≥3.75 mm in diameter was associated with a trend towards less need for repeat revascularization (HR 0.63, 95% CI 0.37–1.08) [21]. Similarly, another study by Quizhpe et al. showed excellent 1-year clinical outcomes after large vessels (>3 mm) PCI irrespective of type of stent used [22].

Why do BMS stents have such low rate of repeat revascularization in large coronary arteries? Although a mean late luminal loss (a surrogate of neointimal hyperplasia) of 0.17–0.29 mm reported with DES is a theoretical advantage over late loss of 0.6–1.2 mm reported with BMS [9,24–26], the extent of restenosis is critically dependent on reference vessel diameter. In vessels ≥3.5 mm in diameter, late loss reported with BMS is unlikely to cause significant angiographic or clinical restenosis.

There are two reasons why DES should not be routinely used for patients who are at low risk for restenosis such as those with large vessels. First and foremost, recently published meta-analyses of the randomised sirolimus and paclitaxel trials found a small risk of late DES thrombosis out to 4 years [27–29]. Unlike restenosis, stent thrombosis is associated with myocardial infarction and significant mortality as high as 50% [30]. Further, it has been shown that premature cessation of clopidogrel therapy is a very strong predictor of DES thrombosis (HR 89.8; 95% CI 29.9–269.6, $p<0.001$) [30]. As a result, prolonged dual-antiplatelet therapy up to 12 months (or perhaps indefinitely) is mandatory after DES implantation [31]. Concerns with prolonged dual-antiplatelet therapy include higher bleeding risk and issue with managing interruptions in antiplatelet therapy at times of surgery [32].

Secondly, the 3 to 4 fold incremental cost associated with DES makes unrestricted DES use not economically viable in most public health systems. A cost-effectiveness analysis suggested the sirolimus-eluting stent would only become a cost-effective treatment strategy when the rate of restenosis exceeds 18.5% [33]. This is much higher than the 4.8% BMS 12-month target vessel revascularisation rate in our study. Marginal improvement in outcomes from DES use in these low-risk patients with large coronary arteries is unlikely to be cost-effective.

Are there subgroups of patients with large vessels that have characteristics (e.g. diabetes or complex lesions) that may benefit from DES? In our study, long stent length was associated with higher MACE. Although DES can reduce restenosis in long lesions, there is a reported increased risk of stent thrombosis with long stent length [30,34]. Similarly diabetes and bifurcation lesions have both found to be risk factors for drug-eluting stent thrombosis [30,35,36]. Thus, even in selected patients with large vessels, potential benefit may be outweighed by risk.

4.1. Limitations of study

First, there are inherent limitations in analysis of non-randomised patient groups. In our study, there were differences in the characteristics of patients receiving DES compared to BMS that may have influenced outcomes. Secondly, the final choice of stent was at the discretion of the treating physician. Third, quantitative coronary angiography was not routinely performed and we used stent length and diameter as surrogates for the lesion length and vessel diameter. Finally, long-term follow-up is now desirable for all studies reporting outcomes of DES.

5. Conclusions

In this study, DES implantation in large native coronary vessels ≥3.5 mm was associated with a low risk of MACE and repeat revascularization that was comparable to BMS. Before using DES in these patients one must weigh the risk of restenosis against the increased risk of stent thrombosis and the need for prolonged antiplatelet therapy. Further studies are warranted to establish if there is a subgroup of patients with large vessels that may gain long-term benefit from DES. Until such time, BMS use may be the preferred strategy.

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Appendix A

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Rates of Stent Thrombosis in Bare-Metal Versus Drug-Eluting Stents (from a Large Australian Multicenter Registry)

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Recent reports suggest that drug-eluting stents (DESs) may increase the risk of stent thrombosis (ST) relative to bare-metal stents (BMSs). Therefore, the aim of this study was to compare DES and BMS outcomes with a specific focus on ST. We analyzed 30-day and 1-year outcomes of 2,919 patients who underwent percutaneous coronary intervention with stent implantation from the Melbourne Interventional Group registry. Academic Research Consortium definitions of ST were used: (1) definite ST (confirmed using angiography in patients with an acute coronary syndrome), (2) probable ST (unexplained death <30 days or target-vessel myocardial infarction without angiographic confirmation), and (3) possible ST (unexplained death >30 days). Multivariate analysis was performed to identify predictors of ST. The incidence of ST (early or late) was similar between BMSs and DESs (1.6% vs 1.4%; p = 0.66), and DES use was not predictive of ST. Independent predictors of ST included the absence of clopidogrel therapy at 30 days (odds ratio [OR] 2.58, 95% confidence interval [CI] 1.29 to 5.29, p <0.01), renal failure (OR 3.30, 95% CI 1.43 to 7.59, p <0.01), index procedure presentation with an acute coronary syndrome (OR 2.59, 95% CI 1.14 to 5.87, p = 0.02), diabetes mellitus (OR 2.25, 95% CI 1.19 to 4.23, p = 0.01), and total stent length ≥20 mm (OR 1.85, 95% CI 1.00 to 3.42, p = 0.04). In conclusion, DESs were not associated with increased risk of ST compared with BMSs at 12 months in this large Australian registry that selectively used DESs for patients at high risk of restenosis. (Am J Cardiol 2008;101:1716–1722)

Given the concern about the long-term safety of drug-eluting stents (DESs) and the potential duration of incremental risk, indiscriminate use of DESs in all patients undergoing percutaneous coronary intervention may no longer be advisable.[1–4] In patients at low risk of restenosis, the clinical benefit of a decrease in restenosis derived from DESs may be offset by an increased risk of stent thrombosis (ST), which carries significant mortality and morbidity. A strategy that restricts use of DESs in patients at high risk of restenosis (such as those with diabetes mellitus, long lesions, and small vessels) may shift the benefit-risk ratio in favor of DESs and avoid exposing patients at low risk of restenosis to the unnecessary risk of ST.[5] Nevertheless, it may be this group of patients who are at highest risk of late ST. The aim of this study was to examine the incidence and predictors of ST in a large real-world multicenter registry in which DES use was restricted to patients at high risk of restenosis.

Methods

The study population consisted of patients with 2,919 percutaneous coronary interventions with stent implantation in 3,583 lesions from the Melbourne Interventional Group registry (April 1, 2004, to October 10, 2006). The DES group had ≥1 DES used, and the bare-metal stent (BMS) group had only BMSs implanted.

The registry is a voluntary collaborative venture of interventional cardiologists practicing at 7 Australian public (government-funded) hospitals designed to record data pertaining to percutaneous coronary intervention and perform long-term follow-up. The Melbourne Interventional Group registry was previously described (Monash University, Melbourne, Australia[6,7]). Demographic, clinical, and procedural

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Table 1
Baseline characteristics of the study population

Variable	Overall (n = 2,919)	DES (n = 1,630)	BMS (n = 1,289)	p Value*
Age (yrs)	65.0 ± 11.9	65.4 ± 11.9	64.4 ± 12.0	0.02
Men (%)	73.1%	73.0%	73.2%	0.90
Hypertension (%)	61.2%	61.0%	61.5%	0.81
Hypercholesterolemia (%)	69.4%	68.9%	70.0%	0.52
Current smoking (%)	21.5%	18.2%	25.6%	<0.01
Diabetes mellitus (%)	22.7%	29.6%	14.0%	<0.01
Insulin requiring (%)	4.8%	6.7%	2.3%	<0.01
Renal failure (%)	4.7%	4.9%	4.6%	0.73
Previous myocardial infarction (%)	29.1%	31.3%	26.2%	<0.01
Left ventricular ejection fraction (%)	56.3 ± 13.2	56.2 ± 12.9	56.5 ± 13.6	0.69
Acute coronary intervention at presentation (%)	61.4%	59.9%	63.2%	0.07
Unstable angina pectoris (%)	19.3%	20.9%	17.2%	0.01
Non–ST-elevation myocardial infarction (%)	22.5%	22.8%	22.0%	0.61
ST-elevation myocardial infarction (%)	19.6%	16.2%	24.0%	<0.01
Cardiogenic shock (%)	2.5%	1.8%	3.3%	<0.01
Lesions	3,583	2,127 (59.4%)	1,456 (40.6%)	—
Coronary vessel treated				
Left main stem (%)	0.9%	1.1%	0.7%	0.23
Left anterior descending artery (%)	32.5%	33.9%	30.3%	0.02
Left circumflex artery (%)	14.5%	13.8%	15.5%	0.15
Right coronary artery (%)	31.7%	25.8%	40.3%	<0.01
Bypass graft (%)	2.8%	3.3%	2.1%	0.03
Type B2/C lesion (%)	46.1%	51.2%	38.5%	<0.01
Bifurcation lesion (%)	6.7%	9.0%	3.4%	<0.01
Chronic total occlusion (%)	1.5%	1.9%	0.8%	<0.01
Ostial lesion (%)	3.6%	5.0%	1.6%	<0.01
Stent length (mm)				
Total	18.5 ± 8.5	19.4 ± 8.8	17.4 ± 7.9	<0.01
≥20 (%)	31.1%	38.0%	20.9%	<0.01
Stent diameter (mm)	2.9 ± 0.5	2.8 ± 0.4	3.1 ± 0.5	<0.01
≤2.5 (%)	31.1%	39.4%	19.0%	<0.01
Stents per lesion	1.1 ± 0.4	1.1 ± 0.4	1.1 ± 0.4	0.09
Glycoprotein 2B/3A inhibitor (%)	26.4%	25.3%	27.9%	0.12
Planned clopidogrel duration (mo)				
1 (%)	19.4%	0.5%	43.2%	<0.01
3–6 (%)	35.2%	38.5%	31.3%	<0.01
≥12 (%)	45.4%	61.0%	25.5%	<0.01
Absence of clopidogrel at				
30 d (%)	13.8%	8.0%	21.2%	<0.01
12 mo (%)	52.7%	38.7%	58.3%	<0.01

Values expressed as mean ± SD or number (percent) unless noted otherwise.
* DES versus BMS.

characteristics of consecutive patients undergoing percutaneous coronary intervention were prospectively recorded on case-report forms using standardized definitions for all fields.[6] The study protocol was approved by the ethics committee in each participating hospital. An independent audit was conducted at all sites by an investigator not affiliated with that institution. Ten verifiable fields from 3% of all patients enrolled from each site were randomly selected and audited. Overall data accuracy was determined to be 96.6%.

Interventional strategy and stent selection were left to the discretion of the operator in all procedures. In 2003, the governmental body funding the participating hospitals developed clinical guidelines for the use of DESs in publicly funded hospitals, restricting their use for patients at high risk of restenosis. The resulting criteria for DES use included ≥1 of diabetes mellitus, small target vessels (≤2.5 mm), long lesions (≥20 mm), and such complex lesions as chronic total occlusions, in-stent restenosis, bifurcation, and ostial lesions. These guidelines were followed in all participating cardiac catheter laboratories, and the reason for DES use was documented.

Total stent length was used as a surrogate for target-lesion length, and stent diameter, for target-vessel diameter. Procedural success was defined as residual stenosis <20% with Thrombolysis In Myocardial Infarction 3 flow in the absence of in-hospital complications. Oral antiplatelet therapy use followed the recommendations at the time, which were to use a combination of aspirin and clopidogrel for a minimum of 4 weeks for patients with BMSs and either 3, 6, or 12 months for patients with DESs.[8]

In-hospital complications were recorded at the time of

Table 2
30-Day and 12-month clinical outcomes

	Overall	DES	BMS	p Value*	OR (95% CI)
30 Days					
Death	2.6%	2.0%	3.3%	0.03	0.60 (0.38–0.95)
Myocardial infarction	2.3%	2.5%	2.0%	0.43	1.22 (0.74–2.01)
Target-lesion revascularization	1.7%	1.7%	1.7%	0.98	1.00 (0.57–1.77)
Target-vessel revascularization	1.9%	2.0%	1.9%	0.84	1.06 (0.62–1.80)
MACEs	6.0%	5.8%	6.4%	0.50	0.90 (0.66–1.22)
12 Months					
Death	4.5%	3.9%	5.3%	0.08	0.73 (0.52–1.04)
Myocardial infarction	4.5%	4.7%	4.2%	0.49	1.13 (0.79–1.62)
Target lesion revascularization	4.5%	3.7%	5.6%	0.01	0.65 (0.46–0.92)
Target vessel revascularization	6.1%	5.8%	6.6%	0.36	0.87 (0.64–1.17)
MACEs	12.9%	12.3%	13.6%	0.32	0.90 (0.71–1.11)

* DES versus BMS.

discharge. Thirty-day and 12-month follow-up were conducted by telephone, and patient medical records were reviewed. All cardiac events were documented, including death, myocardial infarction, target-lesion revascularization, target-vessel revascularization, and composite major adverse cardiac events (MACEs; consisting of death, myocardial infarction, or target-vessel revascularization). Death included all-cause mortality. Myocardial infarction was defined as either (1) increase in creatinine kinase or creatinine kinase-MB ≥3 times the upper limit of normal and/or (2) significant ST-segment change, development of new Q waves in ≥2 contiguous electrocardiogram leads, or new left branch bundle block pattern. Target-lesion revascularization referred to revascularization within 5 mm (proximal and distal edges) of a previously treated lesion, and target-vessel revascularization referred to revascularization of a previously treated coronary artery.

ST was classified by the Academic Research Consortium (ARC) definitions of definite, probable, or possible and early (0 to 30 days) and late (31 to 365 days).[9] The definition of definite ST required the presence of an acute coronary syndrome with angiographic or autopsy evidence of thrombus or occlusion. Probable ST included unexplained deaths ≤30 days after the procedure or acute myocardial infarction involving the target-vessel territory without angiographic confirmation. Possible ST included all unexplained deaths occurring >30 days after the procedure.[9] Patient medical records, angiographic films, and autopsy reports were reviewed by 2 independent observers (who classified ST according to ARC definitions). In patients who received both DESs and BMSs, the angiogram was reviewed to identify the thrombosed stent. If this was not possible, ST was assumed to be related to the DES.

Continuous variables were expressed as mean ± SD, and categorical data were expressed as percentages. Continuous variables were compared using Student's *t* test. Categorical variables were compared using Fisher's exact or chi-square test. Event-free survival for the DES and BMS groups was analyzed (Kaplan-Meier method).

Independent predictors of stent thrombosis (i.e., early and late) were determined using multiple logistic regression models for predictors at $p < 0.10$ in simple logistic regression models (25 clinical and procedural variables were analyzed). All calculated p values were 2 sided, and $p < 0.05$ was considered significant. Statistical analysis was performed using SPSS, version 12.0 (SPSS Inc., Chicago, Illinois), for Windows (Microsoft Corp., Redmond, Washington).

Results

Of patients with 2,919 percutaneous coronary interventions with stent implantation, 1,630 patients (55.8%) received ≥1 DES, and 1,289 patients (44.2%) received only BMSs (Table 1). In the DES cohort, both DESs and BMSs were implanted in 8.7% of patients (n = 142) and 1.2% (n = 42) of lesions. Patients who received a DES compared with a BMS were older (65.4 ± 11.9 vs 64.4 ± 12.0 years; $p < 0.02$), less likely to be current smokers (18.2% vs 25.6%; $p < 0.01$), more likely to have diabetes (29.6% vs 14.0%; $p < 0.01$), and experienced a previous myocardial infarction (31.3% vs 26.2%; p = 0.03). Patients presenting with ST-elevation myocardial infarction (16.2% vs 24.0%; $p < 0.01$) and cardiogenic shock (1.8% vs 3.3%; $p < 0.01$) were less likely to receive a DES than a BMS. Right coronary arteries (often larger caliber than left coronary arteries) were more likely to receive a BMS (25.8% vs 40.3%; $p < 0.01$). As expected, given the criteria for stent use, more DESs than BMSs were implanted in complex lesions (American College of Cardiology/American Heart Association type B2/C lesions), chronic total occlusions, long lesions ≥20 mm in length, small vessels ≤2.5 mm, bifurcation, and ostial lesions (all $p < 0.01$).

The planned duration of clopidogrel therapy was significantly longer after DES than BMS implantation ($p < 0.01$; Table 1). Clopidogrel therapy was stopped in a significant proportion of both the DES and BMS groups at 30 days (8.0% vs 21.2%; $p < 0.01$) and 12 months (38.7% vs 58.3%; $p < 0.01$) of follow-up.

Unadjusted mortality rates in patients who received a DES at 30 days (2.0% vs 3.3%; odds ratio [OR] 0.6, 95% confidence interval [CI] 0.38 to 0.95, $p < 0.03$) were significantly lower than in patients who received a BMS (Table 2). The 30-day rates of recurrent myocardial infarction (2.5% vs 2.0%; p = 0.43), target-vessel revascularization (2.0% vs 1.9%; p = 0.84), and overall MACEs (5.8% vs 6.4%; p = 0.50) were similar.

At 12 months, there was a trend toward lower mortality in patients who received a DES (3.9% vs 5.3%; p = 0.08). Rates of recurrent myocardial infarction were not statistically different at 12 months (4.7% vs 4.2%; p = 0.49). The rate of target-lesion revascularization (3.7% vs 5.6%; p = 0.01) was lower in the DES group, although rates of target-vessel revascularization (5.8% vs 6.6%; p = 0.36) were not different. Overall MACEs at 12 months (12.3% vs 13.6%; p = 0.32) were similar (Figure 1).

At 12-month follow up, the overall incidence of ST (definite, probable, and possible) was 1.5% (n = 44), of which 0.5% (n = 15) were early and 1.0% (n = 29) were late ST (Table 3). Rates of ST were not different between

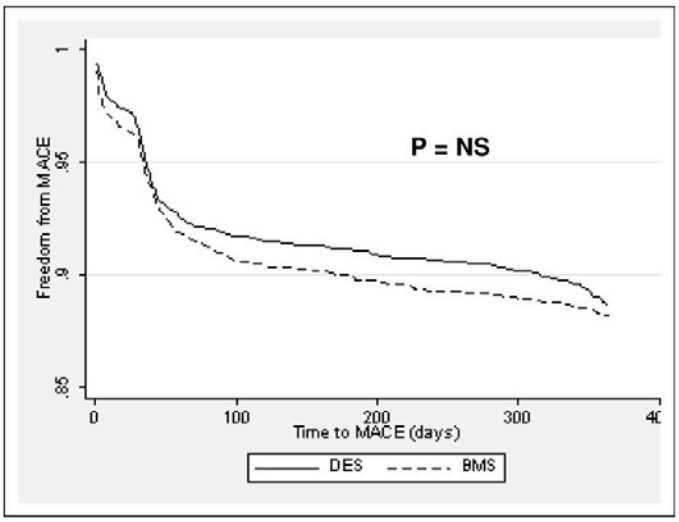

Figure 1. Event-free survival comparing the DES with the BMS cohort at 12-month follow-up.

Table 3
Incidence of stent thrombosis (ST) according to Academic Research Consortium definitions

ST	Overall	DES	BMS	p Value*	OR (95% CI)
Early	15 (0.5%)	11 (0.7%)	4 (0.3%)	0.17	2.18 (0.69–6.87)
Definite	8	6	2	0.27	—
Probable	7	5	2	0.47	—
Late	29 (1.0%)	15 (0.9%)	14 (1.1%)	0.65	0.85 (0.41–1.76)
Definite	10	5	5	0.51	—
Probable	3	2	1	0.78	—
Possible	16	8	8	0.35	—
Total	44 (1.5%)	26 (1.6%)	18 (1.4%)	0.66	1.15 (0.63–2.10)

* DES versus BMS.

patients who received DESs and BMSs (1.6% vs 1.4%; p = 0.66). There were no significant differences between rates of early (0.7% vs 0.3%; p = 0.17) and late ST (0.9% vs 1.1%; p = 0.65) in the DES and BMS groups, respectively. Most patients with late ST were classified as possible ST (55%).

Patients who had ST (n = 44; 1.5%) compared with patients without ST (n = 2,875; 98.5%) at 12-month follow-up were more likely to have diabetes mellitus (40.9% vs 22.4%; p <0.01), renal failure (18.6% vs 4.5%; p <0.01), and decreased left ventricular systolic function (47.3 ± 15.0% vs 56.4 ± 13.0%; p <0.01) and present with acute coronary syndromes (81.8% vs 61.0%; p <0.01; Table 4). ST occurred more in the left anterior descending artery (54.5% vs 32.2%; p <0.01), ostial lesions (9.1% vs 3.6%; p = 0.05), and patients treated with stent lengths ≥20 mm (47.7% vs 30.9%; p = 0.02). Median time to ST was 142 days (interquartile range 11 to 290). Clopidogrel therapy was absent significantly more in patients who had ST than those without ST at both 30-day (36.4% vs 13.5%; p <0.01) and 12-month follow-up (65.9% vs 47.1%; p = 0.01).

Patients who had late ST (n = 29; 1.0%) compared with those who had early ST (n = 15; 1.5%) were more likely to be men (82.8% vs 53.3%; p = 0.04) and present initially with an acute coronary syndrome (89.7% vs 66.7%; p = 0.06). Clopidogrel therapy was absent at 30-day follow-up in 60% of patients with early ST and 24.1% of patients with late ST (p <0.01). Median time to early ST was 5 days (interquartile range 3 to 15), and to late ST, 195 days (interquartile range 94 to 329).

Independent predictors for ST included renal failure (OR 3.30, 95% CI 1.43 to 7.59, p <0.01), absence of clopidogrel therapy at 30 days (OR 2.58, 95% CI 1.19 to 4.23, p = 0.01), diabetes mellitus (OR 2.25, 95% CI 1.9 to 4.23, p = 0.01), acute coronary syndrome at the index procedure (OR 2.59, 95% CI 1.14 to 5.87, p = 0.02), and stent length ≥20 mm (OR 1.85, 95% CI 1.00 to 3.42, p = 0.05; Table 5). The only independent predictor for early ST was absence of clopidogrel therapy at 30 days (OR 5.88, 95% CI 2.99 to 24.39, p <0.01). For late ST, independent predictors were acute coronary syndrome at the index procedure (OR 5.25, 95% CI 1.57 to 17.56, p <0.01) and renal failure (OR 4.49, 95% CI 1.71 to 11.83, p <0.01).

Independent predictors for DES thrombosis included absence of clopidogrel therapy at 30 days, renal failure, diabetes mellitus, and ostial lesions (Table 6). Independent predictors of early and late DES thrombosis are also listed (Table 6).

Discussion

The principal findings of this large Australian registry that selectively used DESs for patients at high risk of restenosis included (1) low (1.5%) overall ST rates after DES implantation; (2) DESs were not associated with increased risk of ST, mortality, or myocardial infarction compared with BMSs; (3) target-vessel revascularization and MACE rates were low and similar between the DES and BMS groups; (4) planned duration of clopidogrel therapy was longer in patients who received a DES compared with a BMS and may have offset the potential higher risk of ST associated

Table 4
Comparison of patients with or without stent thrombosis (ST)

Variable	ST		p Value
	Yes (n = 44; 1.5%)	No (n = 2,875; 98.5%)	
Age (yrs)	66.8 ± 14.0	65.0 ± 11.9	0.30
Men (%)	72.7%	73.1%	0.95
Hypertension (%)	72.7%	61.1%	0.12
Hypercholesterolemia (%)	68.2%	69.4%	0.86
Current smoking (%)	18.2%	21.5%	0.59
Diabetes mellitus (%)	40.9%	22.4%	<0.01
Insulin requiring (%)	9.1%	4.7%	0.18
Renal failure (%)	18.6%	4.5%	<0.01
Previous myocardial infarction (%)	31.8%	29.0%	0.69
Left ventricular ejection fraction (%)	47.3 ± 15.0	56.4 ± 13.0	<0.01
Acute coronary intervention at presentation (%)	81.8%	61.0%	<0.01
Unstable angina pectoris (%)	11.4%	19.4%	0.18
Non–ST-elevation myocardial infarction (%)	40.9%	22.2%	<0.01
ST-elevation myocardial infarction (%)	29.5%	19.5%	0.10
Cardiogenic shock (%)	0	2.5%	0.63
Coronary vessel treated			
Left main stem (%)	0%	0.9%	1.00
Left anterior descending artery (%)	54.5%	32.2%	<0.01
Left circumflex artery (%)	9.1%	14.6%	0.31
Right coronary artery (%)	20.5%	31.8%	0.11
Bypass graft (%)	0%	2.9%	0.64
B2/C lesion (%)	56.8%	45.9%	0.15
Bifurcation lesion (%)	0%	6.8%	0.07
Chronic total occlusion (%)	2.3%	1.5%	0.66
Ostial lesion (%)	9.1%	3.6%	0.05
Stent length (mm)			
Total	20.4 ± 8.6	18.5 ± 8.5	0.13
≥20 (%)	47.7%	30.9%	0.02
Stent diameter (mm)	2.9 ± 0.3	2.9 ± 0.5	0.51
≤2.5 (%)	27.3%	31.1%	0.59
Stents per lesion	1.2 ± 0.4	1.1 ± 0.4	0.22
DES use (%)	59.1%	55.8%	0.66
Glycoprotein 2B/3A inhibitor (%)	34.1%	26.3%	0.24
Planned clopidogrel duration (mo)			
1 (%)	15.9%	19.4%	0.48
3–6 months (%)	40.9%	35.1%	
≥12 (%)	43.2%	45.4%	
Absence of clopidogrel at			
30 d (%)	36.4%	13.5%	<0.01
12 mo (%)	65.9%	47.1%	0.01
Time to stent thrombosis (d)			—
Mean ± SD	142 ± 142	N/A	
Median (interquartile range)	93 (11–290)		

Values expressed as mean ± SD or percent unless noted otherwise.

with these higher risk lesions (although 39% of patients with a DES were not on clopidogrel therapy at 12 months); and (5) independent predictors of ST included the absence of clopidogrel use at follow-up, diabetes mellitus, renal failure, and stent length ≥20 mm. Despite selective use of DESs for patients with complex lesions, we did not show an increased incidence of DES ST.

ST rates in our registry were similar to and consistent with other large registries reporting ST.[10–13] The Western Denmark Heart Registry included 3,548 patients with DES and 8,847 patients with BMS implantation and found ST occurred in 1.80% and 2.15% (at 15 months) using ARC definitions, respectively.[10] In the e-Cypher postmarket surveillance registry of 15,000 patients, ST rates at 1 year were 0.87%.[11] In a DEScover registry of 6,906 patients who received either a DES or BMS, no difference in 12-month clinical outcomes or ST was found.[12] In a large meta-analysis of DES randomized trials (up to 4-year follow-up), ST rates were similar between DESs and BMSs (1.5% vs 1.2%, hazard ratio 1.0, 95% CI 0.68 to 1.63, p = 1.0).[13]

About one third of total and DES thromboses in our study were classified as possible ST (unexplained death >30 days) according to the ARC definition. Inclusion of all possible cases of ST in our analysis may have overstated the true incidence of ST. Excluding possible ST, the incidence of overall and late DES thrombosis would decrease to

Table 5
Independent predictors of any stent thrombosis

Variable	OR	95% CI	p Value
All (n = 44)			
Renal failure	3.30	1.43–7.59	<0.01
Acute coronary syndrome at index procedure	2.59	1.14–5.87	0.02
Absence of clopidogrel at 30 d	2.58	1.29–5.29	<0.01
Diabetes mellitus	2.25	1.19–4.23	0.01
Total stent length ≥20 mm	1.85	1.00–3.42	0.05
Early (n = 15)			
Absence of clopidogrel at 30 d	5.88	2.99–24.39	<0.01
Late (n = 29)			
Acute coronary syndrome at index procedure	5.25	1.57–17.56	<0.01
Renal failure	4.49	1.71–11.83	<0.01

Table 6
Independent predictors of drug-eluting stent thrombosis

Variable	OR	95% CI	p Value
All (n = 22)			
Absence of clopidogrel at 30 d	3.94	1.61–10.31	<0.01
Renal failure	3.91	1.42–10.78	<0.01
Diabetes mellitus	2.90	1.26–6.67	0.01
Early (n = 11)			
Absence of clopidogrel at 30 d	16.39	3.89–71.43	<0.01
Late (n = 11)			
Acute coronary syndrome at index procedure	10.01	1.27–78.66	0.03
Renal failure	9.56	2.85–32.06	<0.01
Ostial lesion	5.58	1.37–22.70	0.02
Diabetes mellitus	4.89	1.52–15.78	<0.01

0.98% and 0.43%, respectively. The ARC definitions have inherent limitations and may overestimate true ST rates.

The primary benefit of DESs is the decrease in restenosis and need for repeated revascularization. The absolute benefit of DESs appears to be greatest in patients at highest risk of restenosis, such as diabetic patients. However, these patients are also at higher risk of late ST.[1,5,14,15] The risk in patients with diabetes and renal failure may relate to a higher atherosclerotic burden of disease and increased endothelial dysfunction and coagulation disorders. Although ST was associated with high risk of death and myocardial infarction, BMS restenosis was not completely benign. At least 10% of all patients with BMS restenosis presented with myocardial infarction, which carried some mortality risk.[16,17] In addition, in our study, late ST occurred just as frequently with BMSs as DESs. Clinical judgment is imperative to balance the individual risk of restenosis versus the risk of ST.

In our study, 66% of ST cases occurred in the absence of clopidogrel therapy. Although the optimal duration was not established, a minimum of 12 months of uninterrupted therapy was recommended by the updated American College of Cardiology/American Heart Association guidelines in patients at low risk of bleeding.[18] Indications for clopidogrel beyond 12 months are controversial. First, 20% to 50% of late ST occurred in patients who were still on dual-antiplatelet therapy, suggesting other mechanisms were important, as outlined previously.[4] Second, in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial, combined clopidogrel and aspirin therapy was not superior to aspirin alone and was associated with significantly more bleeding.[19] However, increased 2-year survival was shown in patients receiving DESs who were maintained on dual-antiplatelet therapy compared with those who stopped clopidogrel therapy.[20] Third, premature discontinuation of antiplatelet therapy was common. A study showed that 13.6% of 500 patients who received DESs after myocardial infarction stopped clopidogrel therapy within 30 days.[21] These patients had increased rates of 12-month mortality (7.5% vs 0.7%; p <0.01). The difficulty arose when antiplatelet therapy was interrupted for noncardiac surgery and in patients with significant bleeding risk. In these clinical scenarios, DESs are best avoided.

Long-term follow-up >12 months is imperative regarding the continuing risk of very late ST associated with DESs. A study of 8,146 unselected patients treated with DESs showed that ST accrued at a steady rate of 0.6%/year from 30 days and 3 years of follow-up.[4] In addition, it was uncertain whether these rates exceeded those of patients treated with BMSs (no BMS control group). The Swedish Coronary Angiography and Angioplasty Registry found that patients receiving DESs experienced death and/or myocardial infarction at a rate of 0.5% to 1.0% higher/year than patients receiving BMSs.[3] Extremely large-scale randomized trials comparing DESs and BMSs would be needed to address this issue and are unlikely to be performed. Therefore, large-scale registries such as ours remain invaluable in the assessment of stent thrombosis in real-world clinical practice.

The present definitions may overestimate rates of late ST. Planned duration of clopidogrel use was a crude surrogate marker of duration of treatment and did not account for noncompliance or interruption of therapy. Follow-up >12 months is mandatory in analyzing very late ST.

Appendix

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Appendix 13

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CARDIOVASCULAR REVASCULARIZATION MEDICINE

Double jeopardy: balance between bleeding and stent thrombosis with prolonged dual antiplatelet therapy after drug-eluting stent implantation

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Abstract Prolonged dual antiplatelet therapy with aspirin and clopidogrel is mandatory after drug-eluting stent (DES) implantation because of potential increase risk of stent thrombosis compared to bare-metal stents. As more DES are being implanted, many of these patients will undergo non-cardiac surgery whilst on antiplatelet therapy. The optimal management of perioperative antiplatelet therapy is not well established. The risk of excessive bleeding associated with antiplatelet therapy needs to be balanced against the risk of stent thrombosis with interruption of antiplatelet therapy on a case-to-case basis.

Keywords: Drug-eluting stent; Antiplatelet therapy; Clopidogrel; Bleeding; Stent thrombosis; Noncardiac surgery

1. Introduction

The use of dual antiplatelet therapy (aspirin and clopidogrel) in the setting of percutaneous coronary intervention with stent implantation has become the standard of care to prevent stent thrombosis (ST). Although rare, ST is associated with high mortality and morbidity [1–3]. In the era of drug-eluting stents (DES), prolonged antiplatelet therapy is mandatory because of potential increase risk of ST secondary to delayed endothelialisation associated with DES compared to bare-metal stents (BMS) [4,5]. There have been reported cases of ST many months after DES implantation with cessation of antiplatelet therapy [6,7]. The concern with prolonged dual antiplatelet therapy is an increase in bleeding risk [8]. The management of perioperative antiplatelet therapy after DES implantation is an important issue. The risk of excessive bleeding whilst on antiplatelet therapy needs to be balanced against the risk of stent thrombosis with interruption of antiplatelet therapy. This article aims to review the risk of DES thrombosis and the risk of bleeding associated with prolonged dual antiplatelet therapy.

1.1. Bare-metal stent thrombosis

Stent thrombosis occurs in <1–2% of patients after BMS implantation, provided adequate antiplatelet therapy is taken [1]. Current practice recommends at least one month of clopidogrel following BMS to cover the period of highest thrombotic risk [9]. Late ST involving BMS rarely occurs unless associated with intracoronary radiation therapy [2,3]. The clinical consequence of ST is severe with mortality in excess of 20% and death or myocardial infarction in >70% of patients [1]. Impaired intimal healing and endothelialisation associated with radiation therapy extends the period during which stents are prone to thrombosis [10,11]. Prolonged dual antiplatelet therapy up to 12 months is recommended following intracoronary radiation therapy [12].

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Table 1
Incidence of stent thrombosis in major clinical trials and registries comparing drug-eluting stents and bare-metal stents

	Iakovou et al. [5]		Moreno et al. [17]			Morice et al. [18]		Jeremias et al. [19]	Ong et al. [20]			Urban et al. [21]
Study	Registry		Meta-analysis of 10 RCT			RCT		Registry	Registry			Registry
Duration of clopidogrel (months)	≥3[a] (≥6[b])		2–3[a] (6[b])			≥2[a] (≥6[b])		≥ 3	≥3[a] (≥6[b])			≥2
Follow-up (months)	9		6–12			12		1	6			12
Stent	SES	PES	SES	PES	BMS	SES	PES	SES	SES	PES	BMS	SES
Patients (*n*)	1062	1167	878	959	2428	701	685	652	1017	989	506	15157
Total stent thrombosis (%)	0.8	1.7	0.57	0.73	0.54	0.7	1.9	1.1	1.0	1.0	1.2	0.87
Acute (%)	–	–	–	–	–	0.3	0.6	–	0.1	0.1	0.4	0.13
Subacute (%)	0.4	0.8	0.46	0.31	0.29	0.4	1.0	1.1	0.9	0.9	0.7	0.56
Late (%)	0.5	0.8	0.11	0.42	0.25	0	0.3	–	0	0	0	0.19

BMS=bare-metal stent; PES=paclitaxel-eluting stent; RCT=randomised controlled trials; SES=sirolimus-eluting stent.
[a] After SES.
[b] After PES.

1.2. Drug-eluting stent thrombosis

Drug-eluting stents are impregnated with antiproliferative agents that reduce neointimal proliferation and the incidence of in-stent restenosis [13–15]. Similar to intracoronary radiation therapy, there is delayed healing and incomplete endothelialisation of stent struts up to 4 years after DES implantation [16]. Delayed endothelialisation prolongs the period of thrombogenic risk and raises the susceptibility of DES to late thrombosis. Reports have shown that in patients presented with late ST in whom both DES and BMS were implanted, only the DES developed thrombosis, whereas the BMS remained patent [6,7].

The incidence of DES thrombosis appears comparable to BMS in clinical trials and "real-world" registries (Table 1) [5,17–21]. A meta-analysis of 10 randomised controlled trials showed that the overall rate of ST after DES implantation was ~0.6% and did not differ from BMS or between sirolimus- and paclitaxel-eluting stents [17]. However, these trials were not powered to detect or exclude an effect of DES on rare events such as ST. The incidence of late ST from 4 large real-world registries was low, ranging from 0.2% to 0.8% at 12 months [18–21].

The risk of late ST persists long after cessation of antiplatelet therapy. McFadden et al. [6] reported 4 cases of late ST as late as 442 days after DES implantation. In a large study of 2006 patients, ST occurred in eight cases between 2 to 26 months after DES implantation whilst on aspirin monotherapy or when antiplatelet agents were discontinued [7]. No events occurred while patients were on dual therapy. The strongest predictor of DES thrombosis was premature discontinuation of antiplatelet therapy (HR 89.8, 95% CI 29.9–269.6, $P<.001$) [5]. Undergoing noncardiac surgery was the main reason in most cases of premature discontinuation of antiplatelet therapy. However, the incidence of ST in patients undergoing surgery is not well established. Clinical predictors of late ST include insulin-dependent diabetes, acute coronary syndrome at presentation, advanced age, decreased left ventricular function, and renal failure, whereas procedural predictors include stenting in bifurcation and totally occluded, in-stent restenotic, or calcified lesions [5,22]. Hypersensitivity to stent polymer has been implicated as possible mechanism for thrombotic occlusion after DES implantation [23].

1.3. Duration of clopidogrel therapy after drug-eluting stent implantation

The optimal duration of dual antiplatelet therapy after DES implantation is not known. Based on clinical trials, dual antiplatelet therapy should be given for at least 3 months after implantation of a sirolimus-eluting stent (Cypher, Cordis Johnson Johnson) and for 6 months following a paclitaxel-eluting stent (Taxus Express, Boston Scientific) [14,15]. Despite the lack of randomised evidence, given the risk of late thrombosis, prolonged dual antiplatelet therapy up to 12 months is recommended [24].

1.4. Bleeding risk associated with dual antiplatelet therapy

Increased risk of excessive bleeding is an important issue with prolonged antiplatelet therapy, especially for patients undergoing surgery after DES implantation. Recovery of platelet function can occur 7–10 days after discontinuation of clopidogrel [25]. Exposure to clopidogrel markedly increases postoperative bleeding, transfusion requirement, and reexploration rates (nearly 10-fold) after coronary artery bypass graft (CABG) surgery [26–28]. Of the 2072 patients who underwent CABG in the Clopidogrel for Unstable Angina to Prevent Recurrent Events (CURE) study, there was an overall 1% excess of major bleeding [29]. No excess in any bleeding was observed for patients who stopped clopidogrel for >5 days before surgery, and there was a nonsignificant excess in major bleeding for those who continued clopidogrel within 5 days of surgery [29]. Major bleeding post noncardiac surgery is less compared to CABG and mainly occurs with cessation of antiplatelet therapy <10 days of surgery [30–32].

The risk of gastrointestinal (GI) bleeding is significant (1.3%) within 30 days of combined antiplatelet therapy and as high as 12% in high-risk population with prior peptic ulcer bleeding [33,34]. The risk of adverse GI events depends on the dose and duration of antiplatelet therapy. In the CURE study, the risk of GI bleeding up to 1 year with combining clopidogrel (75 mg) with high-dose aspirin (>200 mg) is significantly greater than with low-dose aspirin (≤100 mg) (3% vs. 4.9%, $P=.0009$) [8]. Prophylactic acid-suppression therapy with proton pump inhibitors may be reasonable for patients requiring prolonged dual antiplatelet therapy after DES implantation; however, clinical trials are needed to support this strategy.

1.5. Management of antiplatelet therapy for surgery

There are currently no data on how antiplatelet therapy after DES implantation should be managed in the perioperative period. One must balance the risk of excessive bleeding against the risk of ST when antiplatelet therapy is discontinued for surgery. Physiological stress and catacholamine release associated with operative procedure creates a prothrombotic state that may further increase the risk of perioperative ST [30,31].

Postponing elective noncardiac surgery for 2–6 weeks after bare-metal stent implantation appears safe and allows completion of antiplatelet therapy and endothelialisation [30–32]. Patients with DES are at an increased risk for ST for a longer period, compared with patients who receive a BMS. For this reason, balloon angioplasty or BMS may be preferable in patients who are known to need noncardiac surgery. Following DES implantation, elective noncardiac surgery should be delayed, if possible, for several months to allow completion of combined antiplatelet therapy and time for endothelialisation.

Antiplatelet therapy may be safely continued in surgery with low bleeding risk [30]. Consideration should be given to performing noncardiac surgery without stopping aspirin or continuing low-dose aspirin (≤100 mg) for lower-risk patients. For patients at the highest risk (eg, more recent DES, history of in-stent thrombosis, unprotected left main or bifurcation stenting), the use of a short-acting intravenous glycoprotein IIb/IIIa inhibitor could be considered "bridge" therapy, beginning before surgery and stopping as needed for as short a time as possible during and after surgery until oral agents can be reinitiated [35]. There is currently no data to support any of the above strategies, and further research is urgently needed.

2. Conclusions

The benefits of drug-eluting stents are coupled with the risk of bleeding associated with, and the risk of late stent thrombosis without, prolonged dual antiplatelet therapy. Prolonged dual antiplatelet therapy up to 12 months maybe justified given the risk of late stent thrombosis. As more drug-eluting stents are being implanted, many of these patients will inevitably undergo noncardiac surgery. In the absence of outcome data, cardiologists, surgeons, and anaesthetists will need to weigh the perceived risks and benefits of continuing or stopping antiplatelet agents through the perioperative period on a case-by-case basis to optimally reduce the risk of stent thrombosis without unduly increasing the risk of severe bleeding.

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