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Complex Percutaneous Coronary Intervention: The Treatment of Chronic Total Occlusions, Ectatic Infarct Related Arteries, Bleeding Outcomes after Percutaneous Coronary Interventions in Octogenarians and Bifurcation Lesions in ST Elevation Myocardial Infarction.

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ABSTRACT

Cardiovascular disease is the leading cause of death in Australia. Coronary artery disease (CAD) affected around 1.4 million Australians and claimed the lives of over 21,500 (14% of all deaths) in 2011[1]. Percutaneous coronary intervention (PCI) has made significant progress in the management of obstructive CAD over the past three decades. Since the introduction of percutaneous balloon angioplasty by Gruntzig in 1977 [2], PCI techniques have evolved dramatically to be one of the most commonly performed medical techniques in the western world[2]. Although the enigma of treating severely stenotic arteries seems to be resolved to a large extent, several lesion subsets still continue to present unique technical challenges. The complexity of these lesions remain challenging and such lesions could be stratified in a number of ways; by morphological criteria, including extensive calcification, thrombus and chronic occlusions or by virtue of their location, such as at bifurcations, in saphenous vein grafts and left main. Apart from characteristics of the lesion, certain clinical characteristics of the patient such as elderly age remain an important predictor of mortality with PCI.

Balloon angioplasty had an indispensable risk of coronary flow-limiting dissections and restenosis. Two main studies comparing balloon angioplasty and coronary stenting (STRESS and BENESTENT)[3-4] showed a substantial reduction in restenosis rate with use of stents. Thus, the advent of bare metal stents (BMS) caused a substantial increase in the type of patients undergoing PCI[5]. Stents remain the most widely used devices in coronary intervention, despite the occurrence of subacute stent thrombosis, which was prevented using Dual Antiplatelet Therapy and in-stent restenosis, which was significantly reduced with the

development of Drug Eluting Stents (DES). Several large randomized controlled studies have evaluated the outcomes of DES in selected patient populations, and demonstrated the efficacy of these stents to treat relatively simple lesions[6]. Current clinical practice involves treatment of complex lesions, and complex subsets of patients, the majority of whom were excluded from these large studies[7-10].

The unifying hypothesis of this body of research is that, complex coronary intervention can be performed safely and effectively. It emphasizes that this can be achieved by a subset specific approach: (1) Stenting ectatic culprit infarct arteries when these cases present with ST elevation myocardial infarction (STEMI) results in better clinical outcomes (2) Pre-procedural judicious use of bleeding score systems, to rationalize the usage of blood-thinning medication after non-emergency percutaneous coronary intervention helps to keep bleeding rates at an acceptable level in the very elderly (3) With systematic adaption of newer procedural techniques by establishment of a dedicated Chronic Total Occlusion (CTO) program, Chronic Total Occlusion – Percutaneous Coronary Intervention (CTO-PCI) can be performed safely and with high success rates. (4) Bifurcational primary percutaneous coronary intervention has comparable acute procedural outcomes, but increased 1 year Major Adverse Cardiovascular Events (MACE) rates, which could be improved by increased usage of radial approach, glycoprotein IIb/IIIa inhibitors, newer antiplatelets like ticagrelor or prasugrel.

The thesis is centered on four major themes related to complex coronary intervention, each of which is addressed in separate chapters that follow. The specific aims of the thesis are:

- to determine the performance of a high-volume, single Australian PCI center in treating patients with CTO, with a view to guiding the development of a dedicated CTO program: (Chapter 2).
- to assess the prevalence and characteristics of ectatic infarct related arteries in patients presenting for PCI after STEMI, and to compare their characteristics and outcomes with those having non-ectatic infarct related arteries: (Chapter 3).
- to determine the in-hospital bleeding and procedural outcomes after non-emergency PCI in octogenarians, in a real-world setting: (Chapter 4).
- to examine the procedural and clinical outcomes of patients with STEMI who undergo bifurcational percutaneous coronary intervention (chapter 6).

This thesis also:

- provides a review of novel technology and newer strategies, which have helped to overcome the historically stagnant success rates of PCI for CTO (chapter 1).
- presents an overview of percutaneous coronary revascularization in a complex patient subset - the very elderly (Chapter 5).

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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.

Signature: 

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Date: 06/12/2017

Publications in peer-reviewed journals

1. BoganaShanmugam, V., et al. Chronic Total Occlusion - Percutaneous Coronary Intervention (CTO-PCI) Experience in a Single, Multi-operator Australian Centre: Need for dedicated CTO-PCI programs.Heart Lung Circ.2016;25(7): 676-682.
2. Bogana Shanmugam, V., et al. Outcomes After Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction Caused by Ectatic Infarct Related Arteries.Heart Lung Circ. 2017;26(10): 1059-1068.
3. Bogana Shanmugam V., et al. An Overview of PCI in the Very Elderly. J Geriatr Cardiol. 2015; 12 (2): 174 – 184.
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Abstract presentations at national and international scientific meetings

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2. Bleeding outcomes after non-emergency percutaneous coronary intervention (PCI) in the very elderly Canadian Cardiovascular Congress, Vancouver, BC, Canada, October 2014.

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 4 original papers, 2 papers published in peer reviewed journals (Chapter 2 and 3), 1 accepted for publication (Chapter 4), 1 submitted for publication (Chapter 6) and 2 review articles 1 published (Chapter 5), 1 unpublished (Chapter 1). The core theme of the thesis is Complex Percutaneous Coronary Intervention with focus on Chronic Total Occlusion, Ectatic infarct related arteries, Bleeding outcomes after PCI in Octogenarians and Bifurcational lesions in ST Elevation Myocardial Infarction. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the Monash Cardiovascular Research Centre, Monash HEART, Department of Medicine (Monash Medical Centre), Monash University.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input in to team-based research.

In the case of chapters 2 – 6 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 Y/N*
2	Chronic Total Occlusion-Percutaneous Coronary Intervention (CTO-PCI) experience in a single, multi-operator Australian centre: Need for dedicated CTO-PCI programs	Published	80%. Formulation of concept, collecting data, writing first draft and final completion	1) Peter. Psaltis, input to manuscript 10% 2) Dennis Wong, Data analysis, input to manuscript 2% 3) Sujith Seneviratne, provision of coronary angiographic data, input to manuscript, 2% 4) James Cameron, input to the manuscript, 2% 5) Ian Meredith, input to the manuscript, 2% 6) Yuvaraj Malaiappan, input in to the manuscript, 2%	No
3	Outcomes after primary percutaneous coronary intervention (P-PCI) for ST elevation myocardial infarction (STEMI) caused by ectatic infarct related arteries (EIRA)	Published	45%. Formulation of concept, collecting data, writing first draft and final completion	1. Peter. Psaltis, Formulation of concept, input into all stages of manuscript 45% 2. Dennis Wong, Data analysis, input into manuscript 4% 3. Ian Meredith, data input to the manuscript, 1% 4. Yuvaraj Malaiappan, input to the manuscript, 2% 5. Wally Ahmer, input to the manuscript, 3%	No

4	Bleeding outcomes after non-emergency percutaneous coronary intervention (PCI) in the very elderly	Published.	80%. Formulation of concept, collecting data, writing first draft and final completion	1. Peter. Psaltis, input to manuscript 10% 2. Dennis Wong, Data analysis, input to manuscript 3% 3. James Cameron, Input to the manuscript, 2% 4. Hashrul Rashid, input to the manuscript, 2% 5. Yuvaraj Malaiappan, input to the manuscript, 3%	No
5	An overview of PCI in the very elderly	Published	80%. Formulation of concept, collecting data, writing first draft and final completion	1. Peter. Psaltis, input to manuscript 15% 2. Ian Meredith, input to the manuscript, 1% 3. Yuvaraj Malaiappan, input to the manuscript, 2% 4. Richard Harper, input to the manuscript, 2%	No
6	Procedural and Clinical outcomes in Management of Bifurcational Lesions in ST Elevation Myocardial Infarction.	Submitted for Publication	80%. Formulation of concept, collecting data, writing first draft and final completion	1. Peter. Psaltis, input to manuscript 10% 2. Lesley Tay, Data analysis, input to the manuscript,4% 3. James Cameron, Input to the manuscript, 2% 4. Yuvaraj Malaiappan, input in to the manuscript, 2% 5. Wally Ahmer, input to the manuscript, 2%	No

I have 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.

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CHAPTER 1

AN OVERVIEW OF CHRONIC TOTAL OCCLUSION – PERCUTANEOUS CORONARY INTERVENTION (CTO – PCI)

1.1 INTRODUCTION

Percutaneous coronary intervention (PCI) for Chronic Total Occlusion (CTO) poses the challenges of longer procedure times, increased radiation and contrast exposure and relatively lower success rates. Not infrequently, the treatment strategy for a patient is changed on the basis of presence or absence of a CTO[1]. The definition of a CTO remains variable, though it is commonly defined as "the presence of TIMI 0 flow within an occluded arterial segment of greater than three months standing"[2]. CTOs are a commonly encountered complex lesion subset previously reported in 15% to 30% of all patients presenting for coronary angiography[3]. In contemporary clinical practice intervention for CTO accounts for only 3.2% of PCIs[4] in Australia and 6% to 10% of PCIs [5] in the US. In the SYNTAX study, it was shown that only 35% of CTOs are revascularized[6].

The probable benefits of opening a chronically occluded artery include

(a) Symptom control and increased quality of life[7](b) reduced need for CABG [8](c) improved left ventricular (LV) function[9] (d) improved survival[10]. However, DECISION CTO which is the largest randomized controlled trial, comparing percutaneous revascularization vs. optimal medical therapy (OMT), in treating CTO's, failed to show any significant difference in the primary composite endpoint which included non-fatal myocardial infarction (MI), mortality of any cause, and any revascularization at 3 years follow-up[11]. This trial was stopped prematurely due to difficulty in enrolling patients, and had 18.1% of patients in optimal medical therapy (OMT) cross-over to PCI.

The EXPLORE trial evaluated whether patients with STEMI and concurrent CTO in a non-infarct related artery would benefit from CTO-PCI shortly after Primary PCI. There was no difference in the primary outcomes of left ventricular ejection fraction (LVEF) and left ventricular end diastolic volume on cardiac magnetic resonance imaging after 4 months, between those who underwent CTO-PCI and those who were managed medically. However, subgroup analysis revealed that patients with CTO located in the left anterior descending artery territory who were randomised to CTO-PCI had a significantly higher LVEF compared to those who were medically treated[12].

Thus, the perceptions about safety, technical difficulty and procedural complexity may be in the way of translating these benefits to the patient subset with this type of complex lesions. This review article focuses on three measures to improve success rates of CTO-PCI: (1) Adoption of newer technology (2) Implementation of newer techniques and (3) Establishment of a dedicated CTO-Program.

1.2 SUCCESS IN PATIENTS UNDERGOING CTO-PCI

An increasing trend in the angiographic success rates after CTO-PCI has been observed since the beginning of this decade[13.] This has been facilitated by the development of new crossing and re-entry devices, micro-catheters, and guidewires[14]. In addition, the introduction of newer techniques and strategies to negotiate the occluded artery, such as the use of Dual injections,

dissection & re-entry techniques, and the retrograde approach along with interventionalists specialized in dedicated to CTO-PCI likely account for the higher success rates[15,16].

1.3 INNOVATIONS IN TECHNOLOGY TO FACILITATE CTO-PCI

Advances in technology have led to a significantly improved ability to cross CTO's. In general, registry data have demonstrated that these novel devices achieve success in more than 50% of lesions in which standard devices fail[17]. Thus, the newer interventional devices hold promise for improving the success rates of CTO-PCI. Novel interventional devices, used during CTO-PCI include:

1.3.1 Corsair Catheter

The Corsair microcatheter (Asahi Intecc Co. Ltd, Aichi, Japan) is an over- the-wire hybrid catheter that has features of a microcatheter and a support catheter. Although it was initially used during the retrograde approach, as a collateral channel dilator, the characteristics of the catheter also make it useful for antegrade wire support and exchange. The shaft of the catheter is 150 centimeters (cm) long and consists of eight thin wires spirally wound with 2 larger wires, which helps in torque transmission. The spiral structure allows bidirectional rotation to be transmitted to the distal shaft, which helps in crossing the collaterals which may be small and tortuous. The distal 60-cm is coated with hydrophilic polymer to provide lubricity and crossability. The maximum outside diameter is 0.93mm and the inner diameter is 0.45 mm. The inner lumen of the catheter is lined with a fluoropolymer layer to enable injections through it and facilitate movement of the guide wire. It provides better crossability and backup guidewire support compared to the conventional microcatheter and therefore, could be the first

choice for the CTO-PCI with severe or complex lesion morphology. A Japanese multi-centric registry had shown that with the availability of the Corsair catheter, collateral channel crossing with guide wires and catheters had increased without increasing channel dilators[18].

1.3.2 Guidewires

Selection of a guidewire is influenced greatly by personal preference and experience. Guide wires to cross a CTO are continually developed and improved. Different operators may prefer different wires, to achieve the same final success. Guidewires specific to CTOs may be constructed with certain specific characteristics. (1) Greater tip stiffness for increased penetrating force (2) Hydrophilic coating to traverse through the occluded segment (3) Tapered tip for micro channel engagement.

The following guide wires can be used to approach a CTO [19]:

1.3.2.1 Polymer Jacketed, Tapered Tip, (0.009-Inch) HydrophilicWires

These wires are useful to traverse micro-channels, and for soft tissue probing. They are easy to get sub-intimal, and can be used for knuckle techniques. Examples include Fielder XT wire (Asahi Intecc, Nagoya, Japan), Runthrough taper wire (Terumo Corporation, Tokyo, Japan).

1.3.2.2 Polymer Jacketed, Non-Tapered Tip HydrophilicWires

They help collateral channel crossing in retrograde approach. Examples include Fielder FC wire (Asahi Intecc) and Pilot 50 wire (Abbott Vascular, Santa Clara, California).

1.3.2.3 Polymer Jacketed, Non-Tapered Tip, Moderately High Gram Force (4g to 6g) Guidewire

They are used for crossing long lesions, complex lesions. They also help in knuckle technique and dissection/re-entry strategy. It is specifically useful in tortuous segments. Example: Pilot 200 wire (Abbott Vascular).

1.3.2.4 Non-Jacketed, Tapered Tip, High Gram Force (12g) Guidewire

It helps penetration techniques, cap puncture, complex lesion crossing, and lumen re-entry techniques. Example: Confianza Pro 12 wire (Asahi Intecc).

1.3.2.5 Wires for Externalization

A wire used for externalization needs to be 300 cm or more, with moderate stiffness in the shaft to make the push out possible. Examples include: RG3 wire (Asahi Intecc), Viper 335 (CSI), R350 (Vascular solutions, Minneapolis, MN)- 350cm nitinol wire with softer body and tip [20].

1.3.3 The CTO Crossing System

A Crossing catheter and re-entry system (BridgePoint Medical System, BridgePoint Medical, Plymouth, Minnesota) has shown to help in achieving high success rates without increasing complications[17].

This system has 3 parts (1) An over-the-wire Crossing catheter (2) Re-entry balloon catheter and (3) Guidewire.

1.3.3.1 Crossing Catheter:

The CrossBoss (Boston Scientific, Natick, MA, USA) is an over-the-wire device (6F guide catheter and 0.014 guidewire compatible). It has a 1-millimeter blunt tip which is rotated rapidly ahead of the guidewire into the lesion using the "fast spin technique". This dissipates the friction and facilitates crossing the occluded segment either by creating a controlled subintimal track or through the true lumen, whilst remaining within the vessel architecture. When it enters the subintimal space distally, it is advanced next to the angiographically visible true lumen distal to the CTO re-entry site, an exchange wire is left in place and the second component, the re-entry balloon catheter is taken to the re-entry site[21].

1.3.3.2 Re-Entry Balloon Catheter:

The Stingray over-the-wire, orienting balloon catheter is 2.5 mm in diameter and 10 mm in length and has a flat shape with 2 side exit ports which are located on diametrically opposite balloon surfaces immediately proximal to two radiopaque markers. Upon low pressure (2-4 atmospheres) inflation it orients one exit port automatically toward the true lumen[22].

1.3.3.3 Guidewire:

The third part of the crossing system is the Stingray guidewire. It is a stiff guidewire (12-gram) with a 20-cm distal radiopaque segment and a 0.0009-inch tapered tip with a 0.0035-inch distal taper. The Stingray guide wire can be directed toward 1 of the 2 side ports of the Stingray balloon under fluoroscopic guidance allowing it to re-enter the true vessel lumen through the

exit port of the Stingray balloon that is facing the distal true lumen. If intraluminal position is not achieved, the balloon is deflated and moved to attempt re-entry from another arterial segment. Once this guidewire enters the distal true lumen, an over-the-wire balloon is inserted and the re-entry wire can be exchanged for a workhorse wire[22].

1.3.4 Role of Imaging In CTO-PCI: Intra-Vascular Ultrasound (IVUS), Multi slice Computed Tomography (MSCT) And Optical Coherence Tomography (OCT)

IVUS can be used to locate the entry point of an occlusion, when the proximal cap is ambiguous[23]. It can also facilitate repositioning of a guidewire in case of an inadvertent sub-intimal passage. IVUS has been shown to guide appropriate selection of balloon size during reverse Controlled Antegrade and Retrograde Tracking (CART)[24]. Forward looking IVUS, might help to select the proper entry point for penetration of the proximal occlusion cap[25].

Multi Slice CT can facilitate detailed analysis of the extent of calcification, length of the occluded segment and its tortuosity, which help in pre-procedural planning and estimation of probability of success of the CTO-PCI. It has been shown that three-dimensional volume-rendered images of the occluded coronary artery, obtained from CT, can be displayed in the catheterization lab during CTO-PCI to guide the advancement of the wire, thereby improving chances of successful lesion crossing[26].

OCT can provide useful additional information which may help to guide the procedure safely. Forward looking OCT systems use multiple longitudinal OCT slices to generate cross-sectional images of occluded arteries. Preliminary ex vivo experience with this system appears

promising. OCT was able to differentiate between occluded lumen and different layers of the arterial wall, and showed potential to identify microchannels [27]. This information might help to direct the guidewire to cross the proximal cap of the occlusion. Once the proximal cap has been crossed, OCT can provide information about the composition of the plaque which is causing the occlusion. Also, when dissection occurs, OCT can help to differentiate between true and false lumen. OCT based Doppler techniques could, potentially help assess the presence of microchannels. Thus, employing imaging techniques to guide interventional therapies may provide an opportunity to improve results in CTO intervention. However, its routine usage for CTO-PCI remains controversial because of the following reasons. 1. The need to clear the lumen of blood for usage of OCT remains a potential disadvantage during antegrade dissection and re-entry, as antegrade dye injection might lead to hydraulic dissection of the sub intimal space. 2. There are currently no clinical trials confirming the usage of OCT in CTO-PCI.

1.4 TECHNIQUES FOR CTO-PCI

Typically, a bilateral femoral approach and large bore catheters have been advocated by experts [28,29], though experienced trans-radial operators have shown that CTO-PCI can be successfully performed using smaller 6French (F) catheters[30]. Dual arterial access is commonly used (bifemoral, biradial, femoral-radial). Several techniques which provide additional support when required include, subselective intra coronary insertion of wire (Anchoring wire technique)[31], anchoring balloon [32] techniques and dedicated "mother and child catheter", such as Guideliner catheter[33](Vascular Solutions, Minneapolis, Minnesota). Dual injection is of critical importance during CTO-PCI and has shown to be effective in increasing its success rates, hence should preferably be performed in all cases where contralateral collaterals exist[34].

1.4.1 Strategic Innovations For CTO-PCI

1.4.1.1 The Hybrid Approach

A hybrid approach is defined as the approach that focuses on recanalizing the CTO, using all feasible techniques in the most safe, effective and efficient way. It was developed through the combined experiences of high volume North American CTO-PCI operators[35]. It has been shown that the hybrid approach is a teachable method, which not only facilitates reproducible procedural success, but also helps to minimize contrast use, radiation exposure and procedural time[36,28]. The hybrid approach can be best adapted by following an algorithmic approach[19].

Success and time efficiency are the guiding principles of this approach. It involves changing strategies between antegrade and retrograde to attain success with minimal procedural times. The main guiding principles of this approach are (1) Anatomy dictates the strategy adapted (2) Sequential adaptable strategic plans are mapped out pre-procedure. (3) An early change is made from a failing strategy, with a view to make continuous progress (4) Radiation and contrast limits are set and when these limits are crossed the procedure is concluded and rescheduled.
(5) A failure does not prevent a repeat attempt (6) Limited requirement in inventory.

It advocates a four-wire strategy inclusive of a Polymer jacketed low gram force wire (Example: Fielder XT: Asahi Intecc, Nagoya, Japan); Collateral channel crossing wire (Example: Fielder FC wire: Asahi Intecc); Polymer jacket moderate-gram-force wire
(Example: Pilot 200 wire: Abbott Vascular); Non-polymer jacket high-gram-force wire (Confianza Pro 12 wire (Asahi Intecc).

1.4.1.1.1 Techniques

The hybrid approach to CTO-PCI includes the following strategies; when the lesion is approached antegrade: Wire escalation, Dissection/re-entry, limited antegrade subadventitial tracking (LAST) and when the lesion is approached retrograde: controlled antegrade and retrograde subintimal tracking (CART) or reverse CART is chosen.

1.4.1.1.1.1 Wire Escalation

It refers to the use of guidewires with increasing stiffness to cross a CTO. Escalation is favored from a low gram force, tapered-tip, polymer jacketed guidewire (Fielder XT, Asahi Intecc). If this wire does not progress, goes off-line or buckles, it is deemed in-effective and is exchanged to either a stiff, non-tapered, polymer-jacketed wire (Pilot 200, Abbott Vascular) when the course of the occluded segment is uncertain, long, tortuous (or) a stiff-tapered tip wire (Confianza Pro 12, Asahi Intecc) when the course of the occluded segment is clear and short. When escalation of wires fail or the wire repeatedly enters the sub-intimal space this strategy is abandoned and dissection re-entry is performed.

1.4.1.1.1.2 Dissection Re-Entry Technique

In this technique, antegrade dissection is performed using a Cross Boss catheter (Bridgepoint Medical Inc. Plymouth, MN, USA) or with knuckled wire. In the Knuckle wire approach, a loop is formed with a polymer jacketed wire (Example includes: Fielder XT wire: Asahi Intecc, Pilot 200 wire: Abbott Vascular) which is advanced into the occluded segment, in the direction of the distal CTO segment. The stiff-to-floppy transition point of the wire forms the leading edge of the knuckle. The purpose of using either with the Cross Boss or the knuckle wire is to

create a smaller subadventitial space, which is less likely to accumulate blood. This will facilitate use of a wire or devices to re-enter into the distal true lumen. Re-entry is performed either with a wire (LAST technique) or with the Stingray balloon and guide wire, BridgePoint, Medical).

1.4.1.1.1.3 LAST Technique

It is used as a bail out strategy when all other options like wire escalation, Stingray-facilitated re-entry have failed. A micro-catheter is positioned near the site preferred for re-entry, after which the knuckle wire with which a subintimal space is created is withdrawn and a stiff polymer jacket and/or stiff tapered guide wire is directed to enter the true lumen beyond the occlusion[37].

1.4.1.1.1.4 Reverse CART technique[38]

This is the most common method used during the retrograde approach, to connect the proximal and the distal true lumen. In this technique, the retrograde wire is positioned in the distal false lumen within the CTO segment created either by the wire escalation or the knuckle wire technique. The antegrade wire is advanced into the CTO segment, after which a balloon is taken over it and positioned adjacent to the retrograde microcatheter and inflated. This creates a connection between the antegrade and the retrograde sub-intimal spaces. The retrograde wire is then passed into the proximal vessel after which wire externalization or retrograde balloon angioplasty can be performed. In certain situations, the CART technique can be performed.

1.4.1.1.1.5 CART Technique[39]

It is considered when a CTO is approached from both antegrade and retrograde directions and both the wires often land up in the sub-intimal space. In this technique, a balloon is advanced over the retrograde wire and inflated within the sub-intimal space to create a connection between the proximal and distal sub-intimal space. This facilitates entry of the antegrade wire into the distal true lumen.

The initial strategy adapted during the hybrid approach: antegrade or retrograde, is decided by the anatomy of the CTO visualized by dual angiography and is based on the nature of the proximal cap, the length of the occluded segment, characteristics of the distal cap and suitability of the collateral channels connecting the occluded segment and the donor artery. When the occluded segment is short (<20mm) with clearly identified proximal cap and good distal vessel, the lesion is initially approached by antegrade wire escalation strategy. If the occlusion is longer and complex with clearly identified proximal cap and good distal target, a primary dissection re-entry approach is favoured. Other lesions with ambiguous proximal cap and poor distal targets favour an initial retrograde approach.

1.4.1.2 Other Techniques for Recanalization of CTOs

1.4.1.2.1 Sub – Intimal Tracking Techniques

The technique of Subintimal tracking and re-entry (STAR) was introduced by Colombo et al [40]. It involves creating a dissection in the sub-intimal plane by advancing a 0.014-inch hydrophilic wire with a J-loop configuration to allow blunt dissection between the anatomical planes of the vessel[40].When the wire is further manipulated it reaches a point where the

dissection cannot be further propagated, thereby achieving re-entry into the true lumen of the vessel[40]. It is not preferred because of the higher restenosis rates associated this technique [31,14].

Carlino later developed the modified STAR technique with the use of contrast guidance. In this technique, contrast is injected via a micro-catheter or over-the-wire (OTW) balloon instead of the J –configured guide wire was used to create sub-intimal dissection. This technique was also limited by high rates of restenosis[42].

In the Mini-STAR variant, a soft polymeric guidewire is forced with support from a microcatheter, creating a J tip automatically within the occlusion, which allows for "mini subintimal tracking "and creation of small sub-intimal spaces. The re-entry point generally occurs immediately after occlusion where less resistance is offered by the tissue[43].

1.4.1.2.2 The Retrograde Approach

The concept of accessing an occluded artery from its distal segment stems from the initial experience of Geoff Hartzler who opened a native coronary artery from the reverse side via a saphenous vein graft. The ability to use coronary septal collaterals as an access for the retrograde approach was explored by Osamu Katoh [44].

The Retrograde approach to revascularize a CTO involves five key steps[37]: (1) Wire crossing of collaterals from the donor artery into the distal bed of the recipient artery, usually with a soft polymer-coated wire (2) Device (microcatheter or over-the –wire balloon) crossing of the

collateral to facilitate an exchange for a CTO-specific guidewire (3) Crossing the occlusion with the CTO guide wire and balloon dilatation of the CTO with a retrograde balloon (4) Passing a guidewire antegrade through the recanalized segment into the distal true lumen (5) Stent placement.

1.4.1.2.2.1 Importance of Assessment of Collaterals

Collateral circulation is generally seen when the degree of arterial narrowing exceeds 90%. Angiographic visualization of collaterals, is of paramount importance whilst considering the retrograde approach. Twenty-one different collateral pathways have been described [45], but for the purpose of intervention, the basic divisions into septal and epicardial connections is sufficient. Collaterals develop to their full functional capacity between 4 to 12 weeks after an artery gets occluded[46]. The collateral supply at the occluded territory is at a low pressure and hence this results in a functional reduction of the distal vessel size and underestimation of the distal vessel dimension during a recanalization procedure[47]. The widely used Rentrop grading of collaterals shows a weak correlation with invasive parameters of collateral function, and does not actually rate the collaterals themselves but their effect in filling the occluded segment[48]. The important feature of a collateral that needs to be assessed is its diameter. This was initially graded in 3 categories of collateral connection (CC) size; CC0: No angiographic continuous connection; CC1: thread like connection (<0.4mm); CC2: side branch like connection (>0.4 mm), CC3: Large connections especially via the apex of >1mm diameter[49]. It has been shown that even well-developed collaterals do not prevent ischemia during exercise. Collaterals lose part of their functional capacity and regress once the native occluded artery gets revascularized[50].

When septal and epicardial collaterals co-exist, the septal collaterals are preferred as they are dilatable and often shorter[16]. The epicardial collaterals may appear large and promising, but the additional length of this way around the apex, limited pushability around the apex, inevitably more problematic to control than damage to a septal collateral, should be kept in mind[16].

1.4.1.2.2.2 Wire Crossing of Collaterals

Large (7French(F) or 8F) and shortened guide catheter of 90cm length is generally preferred. Pre-existing lesions in the donor artery may require treatment before attempting retrograde access. Frequent checking (every 20 to 30 minutes) of activated clotting time (ACT) is mandatory (target ACT: 300 to 350)[14]. Active balloon dilatation of the collateral channel with 1.0 mm or 1.25 mm may be occasionally required. The gradual advancement of the Corsair catheter facilitates dilatation of the septal channel without the need for balloon pre-dilatation.

1.4.1.2.2.3 Externalization

Once a retrograde wire is successfully manipulated across the CTO, the micro-catheter is advanced across the lesion into the antegrade guide catheter[51]. The wire used to cross the lesion is then exchanged for a 300-cm wire (Fielder FC; ASAHI Intecc), 300 cm Pilot 200 guide wire or a 330-cm guide wire (RG3; ASAHI Intecc) with a view to externalize it[52].

10 to 15 cm of the wire is externalized, just sufficient to facilitate rapid exchange over it. The externalized wire creates tension within the coronaries and hence extreme care to avoid deep seating and unintentional advancement of guide catheters cannot be over-emphasized. Externalization provides the best support for a balloon and stent to be advanced reversely over this wire.

1.4.1.2.3 Kissing Wire Technique

In this technique, after successful wire crossing of the collateral, the guide wire is attempted to cross the distal cap via the retrograde approach and is advanced as far as possible, after which a distal channel is created by small balloon dilatation. Using this retrograde wire as a landmark, antegrade recanalization is initiated. Attempts are made to track the antegrade wire through the proximal cap, occluded segment and the distal–created channel to the distal true lumen. Eventually, the antegrade and retrograde guide wires meet or "kiss"[53]. Thus, CTO penetration is achieved from the antegrade route, and once the lesion is crossed with the antegrade wire, pre-dilatation is performed. This technique is rarely performed, as reverse controlled antegrade and retrograde tracking and dissection (CART) technique provides more consistent results.

1.5 STENT PLACEMENT

Stent implantation is mandatory in all CTOs (with rare exceptions: very small vessels). Balloon angioplasty and Bare Metal Stent (BMS) implantation have shown to be associated with high re-occlusion rates[54].

A randomized controlled study comparing BMS and Sirolimus eluting stent (SES) has shown that patients treated with SES had superior short-term angiographic and clinical results which was maintained during long term 5 year follow-up[55]. A meta-analysis of studies reporting outcomes after DES in CTO, has shown that DES (SES and /or paclitaxel eluting stents - PES) were associated with a significant reduction in angiographic restenosis and repeat revascularization with a similar long term incidence of death, MI and stent thrombosis[56].

Prospective, randomized trial comparing SES with zotarolimus –eluting stent (ZES) had shown that the clinical outcomes did not vary significantly between the two groups[57]. Studies comparing everolimus –eluting stents (EES) with PES have shown lower angiographic and clinical restenosis with EES[58]. In a meta-analysis comparing first-generation DES with second generation DES, it was found that second generation DES was associated with a lower incidence of death, target vessel revascularization, binary angiographic restenosis, and reocclusion, but similar incidence of MI and stent thrombosis[59]. Thus, usage of DES has been shown to reduce mortality compared with bare-metal stents when used for CTO PCI [60].

1.6 COMPLICATIONS OF CTO-PCI

A German registry comparing patients undergoing PCI for a CTO with PCI for non-occlusive lesions noted that after CTO-PCI, fluoroscopy time was double and contrast usage was significantly higher. Severe intra-procedural and in-hospital complications (including death, non-fatal myocardial infarction, stroke, tamponade, and emergency CABGS)-were similar for CTO and non-CTO lesions[61] . Similarly, in the EuroCTO online registry (2008-2010) of 4,820 patients, in-hospital complications after CTO-PCI were similar to PCI of non-occlusive vessels[62]. A meta-analysis of 65 studies published between 2000 to 2011reported that compared to successful CTO-PCI, unsuccessful procedures had higher rates of death (0.42% vs. 1.54%, $p < 0.0001$), perforation (3.65% vs. 10.70%, $p < 0.0001$), and tamponade (0% vs. 1.65%, $p < 0.0001$)[13]. Although coronary perforations are common, most perforations are related to localized wire exit sites from the vessel architecture and limited to angiographic evidence of contrast staining. The above meta-analysis [13] had shown that though the rate of

perforation was 2.9%, the rate of tamponade was 0.3%. Over the long term, especially after the usage of DES among 560 patients undergoing CTO-PCI in Japan, aneurysms were observed in 7.3% of those whose occlusion was treated retrograde and 2.6% of those who were treated antegradely[14]. Major adverse cardiac events however are more after retrograde approach (2 -3 times) than after antegrade approach[63]. MI was 3.1% following antegrade and 7.1% after retrograde approach through septal collaterals and 20% after retrograde approach through epicardial collaterals[13]. Complications specific to retrograde approach include collateral perforation, septal hematoma, aortic dissection, collateral vessel dissection or thrombosis, and severe wire entrapment. A single center study in which Cross Boss and Stingray devices were used showed that patients treated with these devices had similar long term outcomes compared to those in whom other crossing strategies were used[14].

1.7 DEVELOPMENT OF A CHRONIC TOTAL OCCLUSION-PROGRAM

A dedicated CTO-Program can be established specifically through several measures like (1) Didactic lectures by experts (2) On site Proctoring (3) Adaption of advanced techniques which are facilitated by novel technology in selected cases (4) 2 operators / case policy (5) Specific days of a week dedicated for CTO-PCI (6) Establishing in-hospital guidelines for anti-thrombotic therapy, contrast exposure, ionizing radiation exposure (7) Education of participating catheterization laboratory staff. It has been demonstrated that systematic adaption of CTO-PCI through a dedicated CTO-Program can facilitate high success rates and low complication rates[64].

1.8 CONCLUSION

A significant proportion of patients with CTO do not get revascularized, though treating chronically occluded arteries has been established to be beneficial. Complications after CTO-PCI remain comparable to those after PCI to non-occluded arteries. With systematic adoption of newer procedural techniques by establishment of a dedicated CTO program, CTO-PCI can be performed safely and effectively.

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CHAPTER 2

CHRONIC TOTAL OCCLUSION – PERCUTANEOUS CORONARY INTERVENTION (CTO-PCI) EXPERIENCE IN A SINGLE, MULTI-OPERATOR AUSTRALIAN CENTRE: NEED FOR DEDICATED CTO-PCI PROGRAMS.

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2.1 ABSTRACT

Background

Chronic total occlusions (CTOs) represent a unique set of lesions for percutaneous coronary intervention (PCI) because of the complexity of techniques required to treat them.

Methods

We retrospectively reviewed the CTO-PCI experience between January 2010 and December 2012, in a multi-operator single centre, which is one of the largest volume PCI centres in Australia.

Results

Eighty-two patients (62.6±11.3 years, 85% males) who had CTO-PCIs were included. The most common site of CTO was the right coronary artery (44%), followed by the left circumflex (30%) and left anterior descending (26%) arteries. Using the Japanese CTO scoring system, 34% of lesions were classified as easy, 37% intermediate, 23% difficult and 6% very difficult. All PCIs were performed by antegrade approach. Selected procedural characteristics included: re-attempt procedure 10%; multiple access sites 21%; more than one guidewire 77%; additional support modality 60%; drug-eluting stents 97%; stent number 1.6±0.8; total stent length 40.1±24.5 mm; fluoroscopy time 33±17 min; contrast volume 257.2±110.8 mL. Overall CTO success rate was 60%. In-hospital adverse outcomes included 1.2% mortality, 9.8% peri-procedural myocardial infarction, 4.9% emergency bypass surgery, 3% cardiac tamponade and 4.9% contrast induced nephropathy.

Conclusion

We report modest success rates in a single Australian centre experience in a relatively conservative cohort of CTO-PCI prior to the initiation of a dedicated CTO revascularisation program.

2.2 INTRODUCTION

Chronic total occlusion (CTO) is defined as a completely occluded coronary artery with an angiographically documented or clinically suspected duration of occlusion of at least three months with absolutely no flow through the lesion [1]. Percutaneous coronary intervention (PCI) for CTO remains a complex procedure with limited, but improving success rates. Although technically challenging, performing successful CTO-PCI may confer benefits to the patient's symptoms, their left ventricular (LV) function and long-term survival [2]. Meta-analysis data have shown that successful CTO recanalisation is associated with improvement in mortality and reduction in the need for coronary artery bypass grafting (CABG) compared to CTOs managed medically as a result of attempted but failed recanalisation [3]. However, although up to 35% of patients undergoing coronary angiography have at least one CTO lesion [4], CTO-PCI accounts for only around 5% of all elective PCI procedures [5]. Moreover, one study has reported that CTO lesions were present in 36% of PCI patients whose lesions were incompletely revascularised [6]. Not surprisingly CTO-PCI has been referred to as the "Final frontier of PCI" [7]. There have been limited published data on CTO-PCI outcomes from Australian centres with previously reported success rates ranging from 56% [6] to 72% [8], which is considerably lower than those currently achieved in the US and Japan which range from 80% to 90% [9].

In recent years, international experts have advocated a considered and strategic approach to performing CTO-PCI, supported by advancement in technology [10]. Dedicated guidewires are available, which are chosen based on the strategy adapted to treat a given lesion [11]. Although the learning curve for interventional cardiologists to develop the necessary acumen and skill-set to treat these lesions remains steep, the adoption of these newer techniques

coupled with focussed, highly specialised training have impacted positively on procedural success rates for CTO procedures in individual centres [12].

This study was undertaken to determine the performance of a high-volume single Australian PCI centre in treating patients with CTO, with a view to guiding the development of a dedicated CTO program involving a limited number of specially trained operators and implementation of state-of-the-art procedural and performance guidelines. In addition to reporting our past experience and outcomes with CTO-PCI, we will also discuss the strategies taken to establish such a program.

2.3 METHODS

This is a single centre, retrospective analysis of consecutive CTO patients who presented for revascularisation over a three-year period from January 2010 to December 2012. We reviewed our departmental database, hospital medical records and each angiogram to evaluate baseline patient, lesion and procedural characteristics, procedural and in-hospital outcomes. A total of 10 interventional cardiologists performed CTO-PCI procedures. Inclusion criteria were patients requiring non-emergency PCI to treat a 100% occlusion of a coronary artery, defined as a CTO as described below. We excluded those with TIMI≥1 coronary flow or with occlusions known to be of less than three-months duration.

2.3.1 Definitions and Study Endpoints

Chronic total occlusions (as defined earlier) where the duration of occlusion was not clear, angiographic images were reviewed by two experienced operators to reach a consensus as to whether the lesion appearance was consistent with a CTO.

Lesion success: Successful passage of guidewire followed by balloon angioplasty and stenting of the occlusion with <50% residual stenosis of CTO segment with final TIMI III flow.

Procedural success: Lesion success and absence of in-hospital death, myocardial infarction or emergency PCI or CABG.

Peri-procedural myocardial infarction (MI): Elevation of serum troponin level (measured routinely in all patients as per hospital protocol), by more than five times the 99th percentile of the upper limit of normal in patients with normal baseline values, or rise in troponin level of >20%, if the baseline values were elevated but stable or falling [13].

In-hospital outcomes included all-cause death, MI and emergency CABG.

Additional secondary endpoints included: (1) coronary perforation requiring pericardiocentesis, prolonged balloon inflation or other intervention; (2) stent thrombosis as per Academic Research Consortium (ARC) criteria[14]; (3) bleeding requiring blood product transfusion; (4) stroke; (5) access site vascular complications like haematoma >5 cm, pseudoaneurysm, retroperitoneal bleed; and (6) contrast-induced nephropathy which was defined as post-procedural increase in serum creatinine to >0.5 mg/dl or >25% from baseline[15].

Data on left ventricular (LV) function were obtained from LV angiography, transthoracic echocardiography (TTE) or radionuclide studies. Adjunctive modalities used to assist PCI recanalisation such as intravascular ultrasound (IVUS) and coronary CT angiography (CTCA) were also recorded. The angiographic characteristics were obtained from detailed qualitative assessments of the lesions and Japanese – Chronic Total Occlusion (J-CTO) score was

estimated. Based on the J-CTO scoring system[16] angiographic morphology of the entry point was classified as tapered (1 point) if the occluded segment ended in a funnel-shaped form or blunt (0 point) if it did not.

Calcification within the CTO segment was assigned to be present (1 point) or absent (0 point). Angulation (1 point if present and 0 if absent) was defined as at least 1 angle of >45° within the occluded segment. The occlusion length was measured from the proximal occlusion to the distal retrograde filling from contralateral collaterals. Occlusion length was categorised as either >20 mm (1 point) or <20 mm (0 point). Finally, a previous failed attempt was allocated 1 point and 0 if there were no previous attempts. A sum of the scores obtained from the above evaluation was calculated. Chronic total occlusion lesions were then classified as easy if the score was 0, intermediate if 1, difficult if 2 and very difficult if the score was 3 or more.

2.3.2 Statistical Analysis

The baseline clinical, lesion and procedural characteristics, angiographic and clinical outcomes were evaluated by descriptive statistics. For continuous variables, mean and standard deviation values were calculated. For categorical variables, count and percentages were determined. Normally distributed continuous variables were compared by two-tailed unpaired t-test and categorical variables were compared by chi-square test. A p-value of <0.05 was established as the level of statistical significance for all the tests. All statistical calculations were performed using the SPSS statistics version 22.0.0.

2.4 RESULTS

During the three-year study period, a total of 9,703 patients underwent coronary angiography and 3,443 underwent PCI at our institution. 1.9% (182/9703) of all patients who had undergone coronary angiography were found to have a CTO. 2.4% (n=82/3443) of PCIs were for a CTO. Of the CTOs diagnosed at our institute, 45.0% (82/182) were treated by attempted or successful PCI, 24.2% (44/182) were treated by CABG and 30.8% (56/182) were managed medically, as they were either asymptomatic or their symptoms were controlled with optimal medical therapy.

2.4.1 Clinical and Angiographic Characteristics

The baseline clinical characteristics of the study population and lesion characteristics are shown in detail in Table 2.1. According to the J-CTO score, 34.1% of lesions (n=28) were scored as 0, 37.8% (n=31) as 1, 22.0% (n=18) as 2, and 6.1% (n=5) as 3 or higher. Coronary collateral circulation was graded according to conventional Rentrop classification [17], with grade 3 collaterals present in 30.5% (n=25), grade 2 in 53.7% (n=44) and grade 1 in 15.9% (n=13).

Table 2.1 Baseline clinical characteristics and indications for CTO-PCI (N=82)

Age (years)	62.6±11.3
Male	85.4%
Prior PCI	22.0%
Prior CABG	6.1%
Prior MI	11.0%
History of smoking	20.7%
Hyperlipidaemia	67.1%
Diabetes mellitus	23.2%
Hypertension	69.5%

Multivessel coronary disease	78.0%
Target vessel	
Left anterior descending artery	25.6%
Left circumflex artery	30.5%
Right coronary artery	43.9%
Left ventricular (LV) systolic function	
Normal (EF = 55 – 70%)	65.9%
Mild LV dysfunction (EF: 40 – 54%)	18.3%
Moderate LV dysfunction (EF: 35 – 39%)	8.5%
Severe LV dysfunction (EF: ≤ 35%)	4.9%
Unknown	2.4%
Indication for CTO revascularisation	
Angina/dyspnoea	95.1%
Asymptomatic	4.9%

Data represented as per cent or mean±standard deviation.

EF = Ejection Fraction.

2.4.2 Procedural and Clinical Outcomes

The number of cases done by each operator varied from 3 to 16, with five operators performing at least eight or more cases. Procedural details are summarised in Table 2.2. Multi-detector CTCA was used to plan treatment in 22% cases (n=18). More than one arterial access site was obtained in 20.7% (n=17), however engagement and angiography of the contralateral coronary artery was used in only 13.4% cases (n=11), and only antegrade approach was used for all lesions. Successful wire crossing of the lesion was achieved in 68.3% (n=56), with the successful wire used being a Pilot 50 in 39% of all cases attempted (n=32), Fielder XT in 11% (n=9), Miracle 3 in 4.9% (n=4), Miracle 4.5 in 4.9% (n=4), Pilot 150 in 3.7% (n=3), Gaia in 3.7% (n=3), Fielder XTR in 1.2% (n=1) and Conquest Pro in 1.2% (n=1). The median number of guidewires per case was two (range: 1 - 7). The average total stent length per target vessel was 40.1±24.5 mm and the mean number of stents per lesion was 1.6±0.8. Drug-eluting stents were deployed in 97.4% of all cases. An additional support modality was used in 59.8% (n=49), with seven cases requiring more than one additional support modality. Support modalities comprised balloon support in 28 cases, microcatheter in 17, buddy wire in eight, while IVUS guidance was only used for two procedures.

Table 2.2 Procedural characteristics (N=82)

>1 access site	20.7%
Contralateral injection	13.4%
Catheter/sheath size	
6F	84.1%
7F	14.6%
8F	1.2%
>1 guidewire to cross CTO	76.8%
Median number of guidewires per case	2 (1-7)

Stent length (mm)	40.1±24.5
Stent number per patient	1.6±0.8
Drug-eluting stent usage	97.4%
Intravascular ultrasound	2.4%
Procedural outcomes	
Lesion success	59.8%
Procedural success	50.0%
Contrast volume (mL)	257.2±110.8
Fluoroscopic time (min)	33±17
Procedure time (min)	88.1±39.1

Data represented as per cent or mean±standard deviation or median (range).

Procedural outcomes are also displayed in Table 2.2. Lesion success was achieved in 59.8% (49 cases), with an overall procedural success rate of 50% (n=41). Overall procedural success rates according to J-CTO score were: 57.1% (J-CTO Score of 0); 45.2% (score of 1); 50% (score of 2); 40% (score of 3 or above). The most common reason for failure of a CTO-PCI was inability to cross the CTO with a coronary guidewire (81.8%). Ninety per cent of patients with failed CTO-PCI had multivessel disease. Mean contrast volume used was 257.2±110.8 ml, with mean fluoroscopy time 33±17 min and mean procedure time 88.1±39.1 min.

Success rates of individual operators and the average number of PCI procedures performed per operator per year at our centre varied considerably and were as follows: operator 1 (20%; 77cases/year), operator 2 (50%; 78 cases/year), operator 3 (33.3%; 79 cases/year), operator 4 (62.5%; 107 cases/year), operator 5 (44.4%; 110 cases/year), operator 6: (66.7%; 113 cases/year), operator 7 (62.5%; 136 cases/year), operator 8 (63.6%; 140 cases/year), operator 9 (33.3%; 146 cases/year) and operator 10 (43.8%; 159 cases/year). Most operators performed PCIs at more than one institute, with their case-load and success rates at other centres not included in this analysis.

We did not observe significant differences in success rates for CTO-PCI among: (1) Those who had pre CTCA planning versus those who had no planning (61% vs 59% p=0.89); (2) those who had an additional support modality versus those who had none (61% vs 58% p=0.92); (3) those who did (82%) versus those who did not have contralateral injections to guide PCI (82% vs 56% p=0.20) and (4) between operators who performed <8 and ≥8 CTO-PCI cases (63% vs 54% p=0.56).

In-hospital adverse outcomes are shown in Table 2.3. In-hospital mortality was 1.2% (n= 1). The overall frequencies of other adverse outcomes were: Cardiac tamponade 1.2% (n=1); stroke 1.2% (n=1); need for emergency CABG 4.9% (n=4); coronary perforation 7.3% (n= 6); and peri-procedural MI 9.8% (n=8). Overall the adverse outcomes were significantly more frequent in patients in whom the lesion could not be treated successfully (39.4%, 13 of 33) compared to those with successful PCI (16.3%, 8 of 49) (p=0.02). Notably, there were no cases of early stent thrombosis, bleeding requiring transfusion, pseudoaneurysm or AV fistula

involving the arterial access site, or retroperitoneal bleed, although groin haematoma >5 cm was seen in 6.1% (n= 5) and contrast nephropathy in 4.9% (n=4). Overall complication rates according to J-CTO score were 7.3% for score=0, 8.5% for score=1, 8.5% for score=2 and 1.2% for score ≥3.

Table 2.3 In-hospital procedural outcomes (N=82)

Death	1.2%
Peri-procedural MI	9.8%
Emergency PCI or CABG	4.9%
Cardiac tamponade	1.2%
Coronary perforation	7.3%
Stroke	1.2%
Stent thrombosis (ARC definite/probable)	0.0%
Bleeding requiring transfusion	0.0%
Contrast-induced nephropathy	4.9%
Vascular complications	
Retroperitoneal bleed	0.0%
Haematoma >5cm	6.1%
Pseudoaneurysm/AV fistula	0.0%

Data represented as per cent.

2.5 DISCUSSION

This retrospective study of CTO-PCI in a single, large Australian centre was aimed to evaluate our previous CTO-PCI practice, as a part of the initiation phase of a new, dedicated CTO Program that was heralded in 2013. Its main findings are: (1) a low frequency of attempted CTO-PCI cases compared to the overall PCI cohort; (2) a relatively conservative overall approach to tackling CTO-PCI, including the low rate of dual injection for optimal delineation of the CTO segment, universal use of the antegrade approach only, and limited usage of moderate or high gram force guidewires, microcatheters or novel lumen re-entry technologies;

(3) modest success rates (60% lesion success, 50% procedural success) compared to contemporary standards in high volume international centres of excellence; and (4) higher rates of adverse outcomes.

International procedural success rates for CTO-PCI have been steadily improving. In the pre-stent era, success rates were in the order of 50% [11]. From 1990 onwards with the introduction of stents, these increased sharply, with studies by Olivari et al., [12] and Hoye et al., [18] respectively reporting success in 65.1% and 73.3% patients who were predominantly treated with stents. There was then a plateau period in procedural outcomes until the late 2000s when the introduction of dedicated, systematic approaches to CTO-PCI and advances in guidewire and microcatheter technology led to another spike in technical success rates to ≥80%. [6,8,9]By comparison, the paucity of data reporting Australian CTO-PCI experiences has indicated lower success rates[6,7], as was also the case in our current study. Together, the small body of published CTO-PCI literature from Australian groups emphasises that

considerable efforts are still required for Australian coronary interventional practice to rise to contemporary international standards.

In our cohort, the commonest reason for technical failure was the inability to cross the CTO (81.8%). This is very similar to reports from other centres treating this complex lesion subset [19]. On evaluation of the techniques adopted, we noted that all our cases were done antegradely and wire escalation strategy was predominantly utilised. There were 10 operators treating these patients, with variable levels of experience, skill-sets and philosophies with regard to CTO-PCI strategy and risk tolerance, which is likely to have been an important determinant when operators decided to end unsuccessful procedures. Only one operator was involved per case, whereas international centres which have achieved considerable success rates in CTO-PCI have advocated a two-operator per case policy [15]. In our study the mean length of CTO lesion was only 10.1±7.7 mm, with the majority of cases having a J-CTO score of 0 or 1. This reflects much shorter CTO lesion lengths than in other series. In this context, our modest success rates emphasise the ineffectiveness of our existing approaches to CTO-PCI. The use of stiffer guidewires specifically designed for CTOs [20], advanced techniques (e.g. antegrade dissection and reentry approach, retrograde true lumen puncture or retrograde dissection and reentry) and an algorithmic approach have been proposed to optimise the efficiency, safety, and effectiveness of CTO-PCI[10]. Adopting newer technologies and improved commitment appears feasible through establishment of a dedicated CTO program which has been proven to be associated with higher success rates even in cohorts of more complex and resistant CTO lesions [21].

The J-CTO score has an excellent discriminative capacity for predicting successful guidewire crossing and overall CTO-PCI success rates [16]. It also has been shown to be a useful guide while preparing the case-list for the day when CTO-PCI is being performed, to optimise case-load and reduce the risk of subsequent case cancellation [22]. Our study is the first to report the pattern of distribution of J-CTO scores of Australian patients presenting for CTO-PCI. However, in the vast majority of procedures these scores were not determined prospectively to help guide the CTO-PCI strategy. In the future, our practice will routinely adopt a prospective approach to CTO complexity scoring to assist in management strategy.

Features influencing the successful recanalisation of CTOs, like occlusion length, location and extent of calcification and course of the occluded segment can be better visualised by CTCA than conventional angiography. Such accurate lesion assessment helps to design the strategy of revascularisation before PCI. However, the role of routine CTCA for CTO-PCI remains to be established. In our study, we did not observe an increase in success rates in patients who had CTCA, and 70% of procedural failure in these cases was due to inability to cross the lesion. Once again, it is difficult to know how much this reflects the utility of CTCA, given our centre's lack of adoption of contemporary strategies to improve crossing chronically occluded segments.

2.5.1 Complications and Outcomes

Traditionally because of lower success rates and high incidence of adverse events documented in the early reports of CTO-PCI, large populations of patients with CTOs have been managed medically, and such lesions have been the most common reason for referral to bypass surgery rather than PCI [9]. The incidence of outcomes reported in our series should be viewed with caution because of our small sample size. We found that our procedural time, fluoroscopy time and contrast usage were less compared to studies from higher volume CTO-PCI centres [9,15], although this could reflect the more conservative strategy our operators adopted, especially a lower threshold for procedural bail-out.

Our in-hospital mortality and adverse outcome rates were higher than those of previous studies [9,15]. Adverse events were three-times as frequent in those patients who had an unsuccessful attempt at revascularisation, with all cases of death, pericardial tamponade or need for emergency CABG occurring in this group. As reported in previous studies, technical failure was more frequent among patients with multivessel disease [18, 23-26], and this was also the case in our experience. Peri-procedural MI, which occurred in 9.8% of our patients, may be caused by a variety of factors, including side branch closure, coronary artery dissection, atheroembolism to ipsilateral collaterals and prolonged balloon inflation. Other centres have reported widely divergent rates, ranging from 0% to 19.4% [22,27]. The incidence of peri-procedural MI may be reduced by taking greater care to preserve side branches and collateral vessels, with the latter also helping to keep retrograde strategies available for repeat procedures to improve patient success rates. A philosophy of alternating wiring strategy relatively quickly during unsuccessful attempts to cross the lesion would

also help to reduce overall procedural times and by extension procedural complications, with better long-term outcomes.

2.5.2 Development of a Dedicated CTO Program

We adopted a dedicated program for CTO revascularisation in 2013, consisting of three interventional cardiologists who had declared their interest and commitment for dedicated and ongoing training in CTO-PCI. Each of these operators had performed at least 200 PCIs annually (inclusive of PCIs they had performed in all the centres at which they were practising) for more than four years prior. Volunteering catheterisation laboratory staff members were educated through didactic lectures, while on-site proctorship of physicians and staff was performed by an internationally recognised CTO expert. A two operator per case policy has been implemented, with one day per week reserved for scheduling CTO cases, and the number of CTO-PCI cases to be listed on this day guided by the J-CTO Score. Guidelines were established with respect to contrast and radiation exposure, in keeping with international recommendations as shown in Table 2.4[28].

Table 2.4 Program guidelines for radiation exposure, contrast exposure, procedural planning and monitoring

Radiation exposure
• Procedures done in 7.5 or 10 frames/sec rather than 15 to 30 frames/sec
• Collimating the screen throughout the procedure
• Frequent altering of the image intensifier angle
• Image intensifier close to the patient
• Abort procedure if lesion not crossed by 8 Gy, or when fluoro dose reaches 12 Gy at any time point
• Delay repeat procedure for at least 60 days unless emergency indication
• Patients receiving higher radiation are recommended dermatologist or radiation oncologist consultation
Contrast exposure
• Saline hydration for all

• Dilution of contrast whenever possible
• Using anatomical landmarks, and using wires for markers
• Higher threshold for CTO-PCI in patients with compromised renal function
• Intraprocedural contrast volume monitoring and frequent reporting of contrast dose used
Procedural planning and monitoring
• Plan prior to the procedure the initial approach and alternative approaches
• Two consultant interventional cardiologists per case
• Specific CTO-PCI cath lab days
• CTO-PCI specialist nurses
• Half hourly ACT (300-500 for retrograde cases and 250 to 300 for antegrade cases)
• Indications for planning CTCA:
- J-CTO score of 2 or more
- Calcified lesions
- Long lesions
- Second attempt

In order to minimise the risk of contrast-induced nephropathy, we have adopted the following hydration protocol: (A) Intravenous hydration with 0.9% sodium chloride is commenced at a rate of 1.5 millilitres/kilogram/hour (ml/kg/h) six hours pre-procedure and is continued for four hours after PCI. (B) Maximum Accepted Contrast Dose (MACD) is calculated for all patients, and the operator and catheter laboratory team are informed of it pre-procedure. (C) Left ventricular end diastolic pressure (LVEDP) is measured at the start of the case and the rate of IV hydration is adjusted accordingly, such that when LVEDP is <13 mmHg it is increased to 5 ml/kg/h, when LVEDP is 13-18 mmHg the rate is increased to 3 ml/kg/h and when LVEDP is >18 mmHg the rate is continued at 1.5 ml/kg/h. (E) Serum creatinine is measured before discharge or at least 48 hours post-procedure. We have a higher threshold to perform CTO-PCI in patients with compromised renal function. Along with the above-mentioned steps, a nurse assistant keeps a running count of contrast being used with every injection and the operators set out to conserve contrast by using angiographic anatomical landmarks as much as possible during the case. For patients in whom baseline renal function presents a concern, we are also more likely to use contrast partially diluted with normal saline. Finally, there is a very low threshold to stop the procedure once the MACD is reached.

All consecutive patients undergoing CTO-PCI are now being entered into a prospective database, with a view to comparing outcomes after initiation of the dedicated CTO-PCI program with those presented in this study. Given that only 1.9% of patients presenting for angiography at our centre were noted to have a CTO, the following measures have been adopted to bolster the case-load of our CTO-program: (1) Our existing network of general practitioners have been informed about initiation and existence of a dedicated CTO-PCI program. (2) All internal departmental cardiologists have been informed about the program

with a view to increasing internal referral. (3) A CTO-PCI expert who has trained extensively overseas has been recently appointed to our department. (4) Our department has begun proctoring to other centres in Australia. (5) We also intend to run CTO-PCI workshops on a regular basis to bring in cases from centres which proctors cannot easily visit.

The overall objective of this CTO-PCI program is to improve the historically stagnant outcomes and achieve a clinically significant and meaningful advancement in CTO-PCI, thereby improving the standards for Australian CTO-PCI practice to contemporary international levels. Specifically, our goals are to (1) increase the willingness and frequency with which we tackle CTO-PCI given the demonstrated benefits of intervening in CTO lesions [3,27],2) increase our scope for tackling more difficult cases with a broader repertoire of strategies, and (3) improve our outcomes, to the point where successful CTO-PCI can be accomplished more routinely.

2.5.3 Study Limitations

This study is subject to the inherent limitations of a retrospective single centre study. The precise duration of coronary occlusion was not definitively documented in all cases, a limitation applicable to all observational studies of CTO lesions. Independent core lab analysis of QCA data was not performed. We also have limited our analysis to only patients who attended for PCI revascularisation, and do not have outcomes of patients whose CTO lesions were treated with medical therapy or surgical revascularisation, nor have we presented long-term data.

2.6 CONCLUSION

Soberingly modest PCI success rates were achieved in a relatively conservative CTO cohort, in this single centre experience, prior to the initiation of a dedicated CTO revascularisation program. These results emphasise the need for Australian centres to adopt a systematic and specialised approach to CTO-PCI to meet with current international guidelines.

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CHAPTER 3

OUTCOMES AFTER PRIMARY PERCUTANEOUS CORONARY INTERVENTION (P-PCI) FOR ST ELEVATION MYOCARDIAL INFARCTION (STEMI) CAUSED BY ECTATIC INFARCT RELATED ARTERIES (EIRA)

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3.1 ABSTRACT

Background

There is minimal published data on outcomes of patients presenting with ST elevation myocardial infarction (STEMI) due to an ectatic infarct-related artery (EIRA). The aim of this study was to analyse the clinical characteristics and outcomes of these patients presenting for primary percutaneous coronary intervention (P-PCI) in comparison with non-EIRA.

Methods

Of the 1834 patients who presented at our institution for P-PCI between February 2008 and November 2013, 25 (1.4%) were identified as having an EIRA. These patients were compared with those with non-EIRA (80 patients) who were age, gender and lesion matched. Further sub-group analysis on in-hospital and long-term outcomes was done comparing EIRA stented and non-stented patients. Clinical events evaluated include death, recurrent infarction, unstable angina, or target lesion revascularisation (TLR).

Results

Baseline characteristics were similar between patients with EIRA and non-EIRA although none of those with EIRA had diabetes mellitus. By comparison to the non-EIRA group, the major procedural differences for patients with EIRA were (1) a greater incidence of large thrombus burden (96.0% vs 22.5%, $p = 0.0001$), (2) increased usage of peri-procedural glycoprotein IIb/IIIa inhibitors (72.0% vs 37.5%, $p = 0.01$) and post-procedural anticoagulation(28.0% vs 5.0%, $p = 0.004$), (3) larger mean stent dimension (3.9 ± 0.8 mm vs 3.4 ± 0.6 mm, $p = 0.04$) and (4) a higher percentage of P-PCI cases that did not have stent deployment (44.0% vs 7.5%, $p = 0.0001$). Patients

with STEMI from EIRA had similar in-hospital outcomes but a higher long-term incidence of composite cardiovascular events at mean follow-up of 36.6 ± 14.1 months (44.0% vs 16.3% for non-EIRA, p = 0.01). Although patients with EIRA who received stenting had better in-hospital outcomes than the non-stented cohort (composite cardiovascular event rate: 0.0% vs 36.4%, p = 0.03), long-term outcomes were comparable (35.7% vs 54.6%, p = 0.59) due to a relatively high frequency of non-fatal MI and unstable angina in both groups.

Conclusion

Patients with STEMI due to EIRA carry worse long-term outcomes than those with non-EIRA. While successful stent deployment in the setting of EIRA improves procedural and inpatient success rates, it does not necessarily convey benefit to long-term event rates due to recurrent acute coronary syndromes.

3.2 INTRODUCTION

Coronary artery ectasia is defined as a segment of coronary artery that is dilated by more than 1.5 times the diameter of the nearby segments. [1] Ectasia can be found in 0.3% to 4.9% of patients undergoing coronary angiography. [2] Atherosclerosis is considered as an aetiologic factor in more than 50% of cases. [3] Patients with coronary ectasia are known to have a higher incidence of myocardial infarction (MI) compared to those with coronary artery disease without ectasia. [2]

Primary percutaneous coronary intervention (P-PCI) has become the predominant reperfusion strategy for ST-elevation myocardial infarction (STEMI). However, 2.6% to 4.8% of patients presenting with STEMI have an ectatic infarct related artery (EIRA),[4,5] which is frequently accompanied by technical and decision making challenges. There is a paucity of published literature examining the characteristics and outcomes of this complex niche subset of STEMI. Therefore, we set out to compare the clinical, angiographic, procedural characteristics and cardiovascular outcomes of patients with STEMI due to EIRA and a non-ectatic culprit vessel.

3.3 METHODS

Between February 2008 and November 2013, 1834 patients presented to our institution with STEMI. All angiographic images were examined by two independent operators, who identified those cases caused by a culprit lesion in an EIRA. The clinical, angiographic data, procedural and in-hospital outcomes of this cohort of patients were collected prospectively in a

standardised fashion and entered into a registry of consecutive patients with EIRA. The luminal diameter of the ectatic vessel and length of the lesion were measured by quantitative coronary angiography (QCA) analysis. Thrombus burden was classified according to Sianos classification. [6] A second group of patients without EIRA who underwent P-PCI for STEMI during the same time period was selected based on matching for age, gender and lesion site with the EIRA cohort (80 consecutive patients). Potential confounding factors were identified and considered for matching between the cases and controls, after which the study population was analysed by univariate and multivariate logistic regression analysis. Both cohorts were followed for a mean duration of 36 months (range 6.7 to 57.3 months) by a combination of clinic visits, telephone calls and review of case records.

3.3.1 Definitions

We classified cases with EIRA based on the classification system proposed by Markis et al. [7] In decreasing order of severity, diffuse ectasia of two or three vessels was classified as Type I, diffuse ectasia in one vessel and localised disease in another vessel as Type II, diffuse ectasia of one vessel only as Type III and localised or segmental ectasia as Type IV. Multi-vessel disease was defined by the presence of a >50% lesion in two or more major coronary arteries. Left ventricular (LV) systolic function was classified as normal or abnormal based on assessment by left ventriculography or transthoracic echocardiography. Prior vascular disease included carotid, aorto-femoral or lower extremity vascular disease documented by previous radiological study or vascular intervention. Coronary artery lesion type (A/B1/B2/C) was defined according to ACC/AHA classification. [8] Those with grade 4 thrombus burden were defined as having large thrombus burden. [9] Patients with an eGFR <60ml/min/1.73m2 on

presentation were considered to have renal impairment. No-reflow was defined angiographically, as an acute reduction in coronary flow (TIMI grade 0-1) in the absence of dissection, thrombus, spasm, or high-grade residual stenosis at the target lesion. Lesser degrees of flow impairment (TIMI grade 2) were referred to as "slow-flow"[10]. TIMI Flow was defined as follows: Grade 0: No perfusion, Grade 1: Penetration without perfusion, Grade 2: Partial perfusion with impaired rate of entry or rate of clearance and Grade 3: Complete perfusion[11].

The myocardial perfusion was angiographically assessed via myocardial blush grade (TMPG) as follows. TMP grade 0: No apparent tissue-level perfusion (no ground-glass appearance of blush or opacification of the myocardium) in the distribution of the culprit artery; TMP grade 1: Presence of myocardial blush but no clearance from the microvasculature (blush or a stain present on the next injection); TMP grade 2: Blush clears slowly (blush is strongly persistent and diminishes minimally or not at all during 3 cardiac cycles of the washout phase); and TMP grade 3 : Blush begins to clear during washout (blush is minimally persistent after 3 cardiac cycles of washout)[12].

Angiographic success was defined as <20% residual stenosis in the target lesion. Procedural success was defined as angiographic success without in-hospital major complications such as death, MI, cerebrovascular accident, or emergency coronary artery bypass graft surgery (CABG). Clinical cardiovascular events were defined as death after PCI, emergency revascularisation (either with CABG or repeat PCI), nonfatal MI or unstable angina. Myocardial infarction was defined as the presence of at least two of the three following criteria: ischaemic symptoms; elevation of troponin (>5 × 99th percentile upper reference limit in patients with normal baseline value, or a rise in troponin level of >20% if the baseline level

was elevated and stable or falling); or new electrocardiographic changes compatible with MI. Death was defined as all-cause mortality.

3.3.2 Statistical Analysis

Baseline risk factors, clinical and angiographic characteristics, procedural and in-hospital outcomes and long-term outcomes were compared between those with and without EIRA. Categorical variables are expressed as number and percentages and continuous variables as mean ± standard deviation. Categorical variables were compared by chi-square test and continuous variables by parametric unpaired t-test or non-parametric Mann-Whitney test after assessment of their normality of distribution. Clinical events were also analysed among the subgroups of patients with EIRA who were stented and those who were not. A p-value of <0.05 was considered statistically significant. All statistical analysis was performed using SPSS software (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp).

3.4 RESULTS

3.4.1 Baseline Demographic Characteristics of Patients with EIRA vs Non-EIRA

During the study period 1834 patients presented with STEMI, of whom 25 (1.4%) had an EIRA (Figure 3.1). Baseline clinical characteristics for both the EIRA and non-EIRA groups are presented in Table 3.1. Risk factor profiles of the two groups were comparable with the notable exception being that no patient with EIRA had diabetes mellitus as compared to 26.3% in the non-EIRA group ($p = 0.01$).

Figure 3.1. Angiographic appearances of EIRA in STEMI.

Coronary angiogram of the A) left anterior descending artery (Antero-posterior caudal projection) occluded proximally adjacent to a coronary ectatic segment (white arrow) and B) right coronary artery (left anterior oblique projection) showing occlusion in the ectatic mid segment (white arrow).

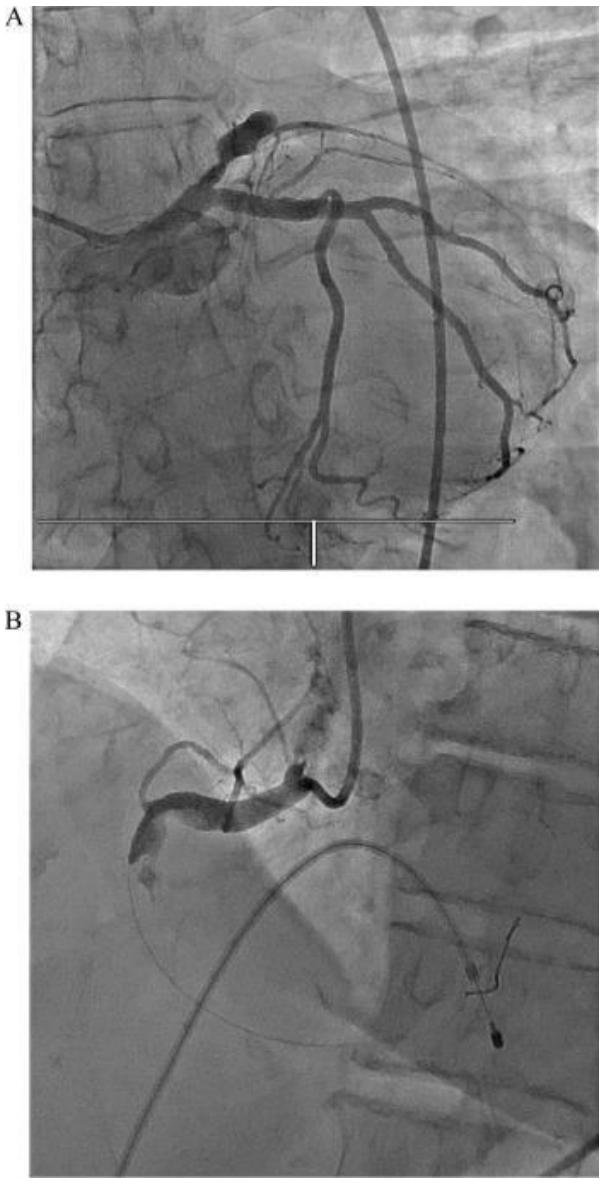

Table 3.1 Baseline characteristics of patients with and without EIRA.

	EIRA	Non-EIRA	p-value
	(N = 25)	(N = 80)	
Age (years)	52.8 ± 14.6	56.5 ± 9.8	0.35
Male	22 (88.0%)	78 (97.5%)	0.16
Hypertension	10 (40.0%)	33 (41.3%)	0.91
Diabetes mellitus	0 (0.0%)	21 (26.3%)	0.01
Dyslipidaemia	8 (32.0%)	32 (40.0%)	0.63
Smoking	16 (64.0%)	58 (72.5%)	0.57
Family history	9 (36.0%)	18 (22.5%)	0.28
Chronic renal failure	2 (8.0%)	13 (16.3%)	0.48
Prior myocardial infarction	2 (8.0%)	4 (5.0%)	0.94
Prior stroke	0 (0.0%)	1 (1.3%)	0.57
VF on presentation	3 (12.0%)	6 (7.5%)	0.77
LV systolic function			
Normal	7 (28.0%)	30 (37.5%)	0.48
Mild LV dysfunction	8 (32.0%)	28 (35.0%)	1.00
Moderate LV dysfunction	8 (32.0%)	18 (22.5%)	0.43
Severe LV dysfunction	0 (0.0%)	3 (3.8%)	1.00
Unknown	2 (8.0%)	1 (1.2%)	0.14

EIRA − Ectatic infarct related artery, LV − Left ventricular, VF − Ventricular fibrillation.

Data presented as n-value (percentage) or mean ± standard deviation.

3.4.2 Angiographic Characteristics

At the time of P-PCI, 88.0% of patients with EIRA and 78.7% with non-EIRA (p = 0.39) presented with complete occlusion of the culprit artery and pre-procedural TIMI 0 and TMPG 0. A higher percentage of EIRAs contained large thrombus burden (96.0% vs 22.5%, p = 0.0001) and single vessel disease (72.0% vs 52.5%, p = 0.14) than was the case for non-EIRAs. The most common culprit vessel was the right coronary artery (RCA) in both groups (48.0% vs 53.8%, p = 0.79), and the culprit lesion site predominantly involved the proximal (32.0% vs 33.8%, p = 1.00) or mid segments (40.0% vs 56.2%, p = 0.18) of the affected artery. The mean luminal diameter of the culprit lesion site was 6.2 ± 1.0 mm vs 2.9 ± 0.7 mm (p = 0.0001) and the overall mean culprit lesion length was 22.7 ± 17.8 mm vs 20.3 ± 10.6 mm (p = 0.11). With regard to ectasia classification, 36.0% of EIRA patients had Type I, 12.0% Type II, 16.0% Type III and 36.0% Type IV coronary artery ectasia. The angiographic characteristics of patients with and without ectatic culprit arteries are summarised in Table 3.2.

Table 3.2 Angiographic characteristics of patients with and without EIRA.

	EIRA	Non-EIRA	p-value
	(N = 25)	(N = 80)	
Single vessel disease	18 (72.0%)	42 (52.5%)	0.14
Culprit artery			
LAD	8 (32.0%)	33 (41.3%)	0.55
LCx	5 (20.0%)	4 (5.0%)	0.05
RCA	12 (48.0%)	43 (53.8%)	0.79
Overall culprit lesion site			
Proximal vessel	8 (32.0%)	27 (33.8%)	1.00
Mid vessel	10 (40.0%)	45 (56.2%)	0.18

Distal vessel	7 (28.0%)	8 (10.0%)	0.55
Large thrombus burden (Sianos Classification) [9]	24 (96.0%)	18 (22.5%)	0.0001
TIMI flow grade on presentation			
Grade 0	22 (88.0%)	63 (78.7%)	0.39
Grade 1	1 (4.0%)	0 (0.0%)	0.24
Grade 2	1 (4.0%)	3 (3.9%)	1.00
Grade 3	1 (4.0%)	14 (17.5%)	0.11
Overall mean luminal diameter at the culprit lesion site (mm)	6.2 ± 1.0	2.9 ± 0.7	0.0001
Mean luminal diameter (mm)			
LAD	5.9 ± 0.5	2.8 ± 0.5	0.0001
LCx	6.8 ± 1.2	2.6 ± 0.7	0.02
RCA	6.2 ± 1.1	3.0 ± 0.7	0.0001
Overall mean length of the culprit lesion (mm)	22.7 ± 17.8	20.3 ± 10.6	0.11

EIRA − Ectatic infarct related artery, LAD − Left anterior descending, LCx − Left circumflex, RCA − Right coronary artery, TIMI − Thrombolysis in myocardial infarction. Data represented as n-value (percentage) or mean ± standard deviation.

3.4.3 Procedural Characteristics

The procedural characteristics of both groups are shown in Table 3.3. Mean total procedural time was higher in those with an ectatic culprit artery (56.6 ± 33.9 min vs 47.8 ± 25.6 min, p = 0.04). The EIRA cohort did show a non-significant trend towards higher usage of manual thrombus aspiration with export catheter (76.0% vs 56.3%, p = 0.13), with a higher percentage of patients receiving thrombus aspiration as the sole reperfusion strategy (16.0% vs 1.3%, p = 0.01). EIRA patients also received higher rates of peri-procedural GPI (72.0% vs 37.5%, p = 0.01), prolonged (>24 hours) post-procedural GPI (33.3% vs 1.3%, p = 0.0001) and post-procedural anticoagulation (28.0% vs 5.0%, p = 0.004) than did those without EIRA.

Table 3.3 Procedural characteristics of patients with and without EIRA.

	EIRA	Non-EIRA	p-value
	(N = 25)	(N = 80)	
Median time from onset of chest pain to ER (min)	116.0 (60 – 1440)	134.5 (1 – 4320)	0.72
Median door-to-balloon time (min)	55.0	64.0	0.30
Total procedure time (min)	56.6 ± 33.9	47.8 ± 25.6	0.04
Successful wiring of culprit lesion	23 (92.0%)	77 (96.3%)	0.74
Balloon pre-dilatation	18 (72.0%)	62 (77.5%)	0.60
Direct stenting	2 (8.0%)	15 (18.8%)	0.35
IVUS	1 (4.0%)	0 (0.0%)	0.24
Sole thrombus aspiration	4 (16.0%)	1 (1.3%)	0.01
Overall thrombus aspiration	19 (76.0%)	45 (56.3%)	0.13
Peri-procedural GPI	18 (72.0%)	30 (37.5%)	0.01
Post-procedural GPI (>24 hrs)	9 (33.3%)	1 (1.3%)	0.0001
Post-procedural anti-coagulation	7 (28.0%)	4 (5.0%)	0.004
Not stented	11 (44.0%)	6 (7.5%)	0.0001
Average stent diameter	3.9 ± 0.8	3.4 ± 0.6	0.04
1st generation DES	1 (7.2%)	1 (1.3%)	0.29

2nd generation DES	3 (21.4%)	40 (52.6%)	0.04
BMS	10 (71.4%)	35 (46.1%)	0.14

BMS − Bare-metal stent, DES − Drug-eluting stent, EIRA − Ectatic infarct related artery, ER − Emergency room, GPI − Glycoprotein IIb/IIIa inhibitor, IVUS − Intravascular ultrasound.

Data represented as median (range), mean ± standard deviation, or n-value (percentage).

Ectatic coronary segments precluded stenting in nearly half of EIRA cases (44.0% vs 7.5%, p = 0.0001), while in those that did receive stents, the average stent diameter was predictably larger than in the non-EIRA group (3.9 ± 0.8 mm vs 3.4 ± 0.6 mm, p = 0.04). On evaluation of the stent type used, bare-metal stents (BMS) in the EIRA group (71.4% vs 46.1%, p = 0.14) and second generation drug-eluting (DES) stents in non-EIRA group (21.4% vs 52.6%, p = 0.04) were predominantly used. Post-dilation was performed in all stented cases in the EIRA group using non-compliant balloons. 5 mm balloons were used in 42.9%, 4.5 mm balloons in 14.3%, 4 mm balloons in 21.4% and 3.5 mm balloons in 21.4%. The final mean stent diameter after post-dilatation in EIRA patients was 5.3 mm.

In patients who were stented, a higher percentage of those with ectatic culprit arteries had slow flow phenomenon after stent deployment and post-dilation (21.4% vs 2.7%, p = 0.02), and fewer had TIMI III flow (71.5% vs 95.9% p = 0.01), although no-reflow (7.1% vs 1.4%, p = 0.29) did not differ statistically.

3.4.4 Stented Versus Non-Stented EIRA Cases

Comparing the features of the stented (n = 14) and non-stented (n = 11) subgroups of patients with EIRA (shown in Tables 3.4 and 3.5), ectasia classification and lesion location did not differ statistically, although this was possibly due to small sample sizes. Mean luminal diameter at the site of lesion was identical, while TIMI coronary flow grade at the time of presentation was also comparable. Of the 11 patients with EIRA who were not stented, 8 had persistent large thrombus burden with poor visualisation of the distal vessel even after manual thrombus aspiration, 1 had multi-vessel disease treated after manual thrombectomy with referral for CABG, 1 had TIMI III flow with <20% residual angiographic stenosis after manual thrombus aspiration, and 1 had a non-stenotic culprit lesion confirmed by IVUS after initial management with thrombus aspiration and GPI.

Table 3.4 Angiographic characteristics of patients with stented versus not stented EIRA.

	Stented	Not stented	p-value
	(N = 14)	(N = 11)	
Culprit vessel type (Markis classification) [7]			
Type 1	4 (28.6%)	5 (45.4%)	0.43
Type 2	1 (7.1%)	2 (18.2%)	0.57
Type 3	2 (14.3%)	2 (18.2%)	1.00
Type 4	7 (50.0%)	2 (18.2%)	0.21
Culprit lesion site			
Proximal LAD	3 (21.5%)	1 (9.1%)	0.60
Mid LAD	2 (14.4%)	1 (9.1%)	1.00
Distal LAD	1 (7.1%)	0 (0.0%)	1.00
Proximal LCx	1 (7.1%)	0 (0.0%)	1.00
Distal LCx	1 (7.1%)	3 (27.3%)	0.29
Proximal RCA	1 (7.1%)	2 (18.1%)	0.57
Mid RCA	4 (28.6%)	3 (27.3%)	1.00

Distal RCA	1 (7.1%)	1 (9.1%)	1.00
TIMI flow grade on presentation			
Grade 0	13 (92.9%)	9 (81.8%)	0.56
Grade 1	0 (0.0%)	1 (9.1%)	0.44
Grade 2	0 (0.0%)	1 (9.1%)	0.44
Grade 3	1 (7.1%)	0 (0.0%)	1.00
TIMI flow grade post thrombus aspiration			
Grade 0	5 (35.7%)	3 (27.3%)	1.00
Grade 1	5 (35.7%)	2 (18.2%)	0.41
Grade 2	2 (14.3%)	4 (36.3%)	0.35
Grade 3	2 (14.3%)	2 (18.2%)	1.00
Persistent large thrombus Burden after thrombus aspiration	11 (78.6%)	6 (54.5%)	0.39
Mean luminal diameter at the culprit lesion site (mm)	6.2 ± 1.0	6.2 ± 1.0	0.57
Mean luminal length of the culprit lesion (mm)	20.6 ± 15.1	25.6 ± 21.6	0.61

EIRA − Ectatic infarct related artery, LAD − Left anterior descending, LCx − Left circumflex, RCA − Right coronary artery, TIMI − Thrombolysis In myocardial infarction. Data presented as

n-value (percentage) or mean ± standard deviation, Type 1 − Diffuse ectasia of 2 or more Vessels, Type 2 − Diffuse ectasia of 1 vessel and localised ectasia in one vessel, Type 3 −Diffuse ectasia of 1 vessel only, Type 4 − Localised ectasia only.

Table 3.5 Outcomes of patients with stented versus non-stented EIRA.

	Stented	Not stented	p-value
	(N = 14)	(N = 11)	
Angiographic success	6 (42.9%)	0 (0.0%)	0.04
Procedural success	6 (42.9%)	0 (0.0%)	0.04
In-hospital cardiovascular events	0 (0.0%)	4 (36.4%)	0.03
In-hospital mortality	0 (0.0%)	1 (9.1%)	0.90
Major bleeding (BARC definition)	0 (0.0%)	1 (9.1%)	0.90
All-cause mortality (at the end of follow-up)	1 (7.1%)	1 (9.1%)	0.86
Composite cardiovascular events (at the end of follow-up)	5 (35.7%)	6 (54.6%)	0.59

BARC − Bleeding Academic Research Consortium, EIRA − Ectatic infarct related artery. Data represented as n-value (percentage).

3.4.5 In-Hospital Procedural Outcomes

Outcomes of patients with and without EIRA are summarised in Table 3.6. Overall, post-procedural TIMI III flow (48.0% vs 91.3%, p = 0.0001), TMP grade 3 (24.0% vs 52.5%, p = 0.02), angiographic success (24.0% vs 92.5%, p = 0.0001) and procedural success (24.0% vs 77.5%, p = 0.0001) were all considerably lower in EIRA patients. However, composite clinical event rates in the short-term, comprising pooled data for mortality, recurrent MI, unstable angina and need for

CABG, did not differ significantly between groups (16.0% vs 11.3%, p = 0.78) and neither did the incidence of major bleeding complications (4.0% vs 2.5%, p = 0.69), or in-hospital stent thrombosis (0.0% vs 0.0%, p = 1.00). There were also no significant differences in peak creatine kinase (CK) (2214.1 ± 1421.5 IU/L vs 2507.9 ± 2391.6 IU/L, p = 0.10) or troponin-I levels (65.3 ± 52.5 ng/ml vs 74.9 ± 105.3 ng/ml, p = 0.16). On sub-analysis of the EIRA patients, TIMI 3 flow (71.4% vs 18.2%, p = 0.03), angiographic success (42.9% vs 0.0%, p = 0.04) and procedural success rates (42.9% vs 0.0%, p = 0.04) were all considerably higher in the stented group, which in turn had no in-hospital clinical events (0.0% vs 36.4%, p = 0.03).

Table 3.6 Outcomes of those with and without EIRA.

	EIRA	Non-EIRA	p-value
	(N = 25)	(N = 80)	
Final TIMI flow grade			
Grade 3	12 (48.0%)	73 (91.3%)	0.0001
Grade 1 or 2	10 (40.0%)	2 (2.5%)	0.0001
Grade 0	3 (12.0%)	5 (6.2%)	0.61
Final TMPG			
Grade 0	6 (24.0%)	6(7.5%)	0.03
Grade 1	7 (28.0%)	9 (11.3%)	0.06
Grade 2	6 (24.0%)	23 (28.7%)	0.80
Grade 3	6 (24.0%)	42 (52.5%)	0.02
Peak creatine kinase (IU/L)	2214.1 ± 1421.5	2507.9 ± 2391.6	0.10
Peak troponin-I (ng/ml)	65.3 ± 52.5	74.9 ± 105.3	0.16
Angiographic success	6 (24.0%)	74 (92.5%)	0.0001
Procedural success	6 (24.0%)	62 (77.5%)	0.0001

In-hospital cardiovascular events	4 (16.0%)	9(11.3%)	0.78
In-hospital mortality	1 (4.0%)	6 (7.5%)	0.88
Major bleeding (BARC definition)	1 (4.0%)	2 (2.5%)	0.69
Length of hospital admission (days)	6.4 ± 3.0	5.6 ± 7.3	0.47
Stent thrombosis	0 (0.0%)	0 (0.0%)	1.00
All-cause mortality (at the end of follow-up)	2 (8.0%)	6 (7.5%)	0.93
Composite cardiovascular events (at the end of follow-up)	11 (44.0%)	13 (16.3%)	0.01

BARC − Bleeding Academic Research Consortium, EIRA − Ectatic infarct related artery, TIMI − Thrombolysis in myocardial infarction, TMPG − TIMI myocardial perfusion grading.

Data represented as n-value (percentage) or mean ± standard deviation.

3.4.6 Long-Term Outcomes

Over a mean follow-up duration of 36.6 ± 14.1 months, all-cause mortality did not differ between the EIRA and non-EIRA patients (8.0% vs 7.5%, p = 0.93), however those with EIRA had a higher composite clinical event rate (44.0% vs 16.3%, p = 0.01), driven by death in two patients, recurrent MI in three, unstable angina in three and emergency CABG in three patients. Among those with EIRA the clinical event rates for the stented and non-stented groups did not differ significantly, despite a trend for fewer long-term events in the former (35.7% vs 54.6%, p = 0.59).

3.4.7 Influence of Medication Use

At the time of hospital discharge following index presentation, medication use was as follows for the EIRA and non-EIRA groups respectively: 100% vs 97.1% (p = 0.99) were on more than one antiplatelet agent, 83.3% vs 94.3% (p = 0.22) were on a beta blocker, 87.5% vs 90% (p = 0.73) were on an ACE inhibitor and 95.8% vs 98.6% (p = 0.42) were on a statin. At the end of follow-up, 95.8% EIRA patients vs 100% non-EIRA patients (p = 0.77) were on at least one anti-platelet, 79.2% vs 86.1% were on a beta blocker (p = 0.70), 83.3% vs 90.7% (p = 0.62) remained on an ACE inhibitor, and 83.3% vs 97.7% (p = 0.10) were on a statin. Therefore, the short and long-term use of guideline recommended pharmacotherapies was similarly high between the two groups.

On specific review of the use of antiplatelets and oral anticoagulants medications in EIRA patients, we observed that the majority were discharged on dual antiplatelet therapy, with 76.0% on aspirin and an adenosine diphosphate (ADP) antagonist, 8.3% on an ADP antagonist and warfarin, and 16.7% on triple therapy consisting of aspirin, ADP antagonist and warfarin (Table 3.7). Further sub-analysis of the procedural characteristics of the EIRA group based on warfarin use, showed non-significant trends for lower incidence of TIMI 3 flow (16.7% vs 57.9%, p = 0.20) and stenting (33.3% vs 63.2%, p = 0.34) in patients who were prescribed warfarin than those who were not. Interestingly, despite these seemingly adverse characteristics, the long-term clinical event rate in EIRA patients discharged on warfarin was only 16.7% compared to 52.6% in those who were not, although the low patient numbers may have prevented this difference from reaching statistical significance. In regards to the duration of therapy, a little more than half of those with EIRA were maintained on long-term additional

blood-thinning medication for the duration of follow-up, with 45.8% maintained only on aspirin beyond 12 months. We did not observe a significant difference for long-term composite event rates between patients on long-term dual blood-thinning therapy and those on aspirin alone after the first year (23.1% vs 36.4%, p = 0.66).

Table 3.7. Outcomes of EIRA patients with and without warfarin.

	On warfarin	Not on warfarin	p-value
Number	6 (24.0%)	19 (76.0%)	
TIMI 3 flow	1 (16.7%)	11 (57.9%)	0.16
Stenting	2 (33.3%)	12 (63.2%)	0.19
Composite cardiovascular events (at the end of follow-up)	1 (16.7%)	10 (52.6%)	0.18

TIMI − Thrombolysis in myocardial infarction. Data are presented as n-value (percentage).

3.5 DISCUSSION

The main findings from this single centre evaluation of STEMI due to EIRA are as follows: (1) patients with EIRA had similar baseline characteristics as those without, with the exception of a lower frequency of diabetes; (2) procedurally, EIRA was associated more frequently with large thrombus burden on presentation and persistent large thrombus burden after attempted PCI, lower TIMI flow grade and TMPG after PCI, higher usage of GPI and less frequent deployment of stents due to large vessel diameter; (3) composite overall clinical event rates were not significantly worse in the short-term after P-PCI for EIRA; however, (4) EIRA patients did have a higher frequency of long-term

cardiovascular events particularly driven by recurrent MI, unstable angina and need for CABG; (5) patients with EIRA who underwent successful stenting had fewer in-hospital events than those who were not stented, although their long-term event rates remained relatively high.

3.5.1 Prevalence and Characteristics of EIRA

The prevalence of EIRA in our series was 1.4%, which is lower than that reported in the existing literature. [4,5] There were no cases of diabetes mellitus in those with EIRA. This is consistent with previous data, [10] and may in part be due to two important mechanisms believed to result in compensatory vessel enlargement in CAE that are mitigated in the presence of diabetes. Firstly, patients with CAE have been found to have over-expression of Matrix Metalloproteinase (MMP), which contributes to excessive vessel dilatation and aneurysm formation. Diabetic subjects have downregulation of Matrix Metallo Proteinase (MMP) in the smooth muscle cells of the vessel wall thereby preventing vessel dilatation.resulting in negative remodelling. [11] Secondly, chronic overstimulation of the endothelium with excessive nitric oxide (NO) is also known to result in abnormal coronary dilatation and enhanced NO production in CAE has been documented. Diabetic patients are known to have an alteration in synthesis and inhibition of NO resulting in reduction of endothelium-dependent vasodilatation, thereby possibly preventing positive remodelling in response to atherosclerosis. [12]

In our experience, most patients with EIRA had single vessel disease and the RCA was commonly involved. Prior studies have shown a similar pattern of coronary artery distribution, [13,14] the exact reason for which remains unclear. [15] Although the TIMI flow on

presentation was not different, large thrombus burden was observed more commonly when the infarct artery was ectatic. A Taiwanese study evaluating infarct-related arteries with aneurysmal dilatation reported similar findings [4]. Such high thrombus burden may be secondary to increased platelet activation, decreased coronary flow velocity and changes in flow pattern in ectatic vessels. [16]

3.5.2 Management of EIRA in STEMI

On analysis of the treatment strategies adopted for STEMI at our centre, the most striking finding was that the use of thrombus aspiration as the sole management strategy was significantly higher in those with EIRA. Thrombus aspiration in STEMI has been shown to reduce distal embolisation and improve coronary perfusion, myocardial blush grade and prevent no-reflow. [17]

There have been previous case reports of successful use of lone manual thrombus aspiration without stenting for management of patients presenting with EIRA. [18] Aspiration thrombectomy along with GPI can occasionally help to achieve a satisfactory outcome when the culprit artery is ectatic, and stenting is not desirable. [19] Although recent randomised trials have indicated a lack of benefit for its routine use, several earlier trials had shown its benefits compared to conventional PPCI especially when the thrombus burden was moderate or large and when surrogate endpoints, such as angiographic flow assessment, Left Ventricular Ejection Fraction (LVEF) assessment, infarct size reduction by perfusion imaging, enzymatic analysis and ST segment resolution were used. This may explain our group's practice of frequent aspiration use. [21–23] We did not observe strokes complicating the use of aspiration thrombectomy in our patient population, which could be

either due to the small sample size, absence of computed tomography or magnetic resonance imaging for evaluation of stroke or because of increased usage of GPI.

While measures decreasing thrombus burden are intuitively helpful in the management of these patients, evidence for this has really only been provided by anecdotal reports. [20] In our study, a significantly higher proportion of patients with EIRA received GPI infusion during the procedure and for longer than 24 hours post-procedure, without any significant increase in major bleeding. Adjuvant treatment with GPI has been demonstrated to reduce thrombus grade, size and burden [27], and improve outcomes compared with placebo or control therapy in high-risk STEMI patients. [24] A case series evaluating STEMI patients with EIRA has reported beneficial effects after usage of GPI to treat these patients. [25]

Stenting of EIRA poses the inherent challenges of optimal stent sizing, stent misplacement, stent embolisation and acute or sub-acute stent thrombosis. [26] Almost half of those who had ectatic culprit arteries in our analysis were not treated with stents. Understandably, large vessel size and persistence of large thrombus burden even after thrombus aspiration and initiation of GPI were the predominant reasons that precluded stenting, although, interestingly, the mean luminal diameter and lesion length of the culprit segment did not differ significantly between the EIRA-stented and non-stented subgroups. A multi-centre evaluation has previously shown a similar pattern, whereby a significant proportion of those with an ectatic culprit artery could not be treated with stents. [27] Though successful management of these patients with large sized peripheral stents, parallel stenting with two DES and implantation of covered stents have all been reported, [28] none of these strategies have been adequately evaluated to warrant implementation in daily clinical practice and were not used in our study. We observed a non-significant increase in the use of BMS in those with

EIRA, and a significantly higher usage of second-generation stents in those without EIRA. Although there is a lack of published evidence regarding the merits of different types of stents in the management of patients with ectatic culprit arteries, a randomised controlled trial has compared the use of first generation DES, second generation DES and BMS in patients requiring stents of 3.0 mm or more in diameter[29]. This revealed a clinically significant reduction in the rate of target vessel revascularisation with both first and second generation DES, even though patients with stents in large vessels are at reduced risk for clinically relevant restenosis. However, in this study the incidence of death and non-fatal MI was similar between those receiving BMS or DES with no significant difference in event rates between the first-generation and second-generation DES at two years of follow-up. [29]

Intravascular ultrasound has been used effectively to estimate the nature of the underlying lesion, and size of the vessel and thereby provide guidance regarding the necessity and possibility of stenting to treat the culprit lesion in EIRA cases. In our series, one patient with STEMI from EIRA returned for IVUS evaluation after initial management with thrombus aspiration, which was then followed by 48 hours of GPI infusion. In this instance, the culprit lesion was found to not contain a severe stenosis and a decision was made to defer stenting. [19]

Another important finding from our study is that a considerably higher percentage of patients with EIRA were left with post P-PCI TMP grade 0 and fewer with TMP grade 3. This could be the impact of large thrombus burden seen in these individuals. Slow-flow phenomenon was also significantly higher in the ectatic cohort, although the incidence of no-reflow did not differ.

However, the mean levels of peak CK and troponin-I did not vary significantly between the two groups.

Our cohort of EIRA cases was associated with a high incidence of long-term cardiovascular events, mainly due to non-fatal recurrent acute coronary syndromes. This emphasises the need for better and more definitive secondary prevention strategies, particularly given the heterogeneity we observed for the practice of prescribing and continuing oral anti-platelet and anti-coagulant agents in the long-term. At the time of hospital discharge, 24.0% of patients with EIRA were managed with warfarin and these showed a non-significant trend towards fewer clinical events. Several studies have proposed long-term anticoagulation with warfarin to reduce the thrombosis resulting from flow alterations within ectatic coronary segments, [30] although as yet there are no randomised data to demonstrate the impact of this strategy on clinical outcomes. Furthermore, there also remains a lack of evidence relating to the optimal duration of dual antiplatelet therapy in the complex subset of EIRA patients, with no real distinction made between those managed with or without stent deployment. Future studies that evaluate the roles for warfarin, dual anti-platelet and triple blood-thinning therapy and their optimal duration will help to guide secondary prevention management of patients with EIRA and hopefully improve outcomes.

3.5.3 Prognosis

A study comparing patients with aneurysmal and non-aneurysmal coronary disease noted that the presence of ectasia did not affect the adjusted five-year survival (75.0% vs 81.0%, $p = 0.41$).[2] Similarly, in our study, the mortality rates between those with and without EIRA were comparable. Another two-year follow-up analysis of patients treated with primary angioplasty

for lesions located in an ectatic coronary segment reported a high rate of clinical events at follow-up. [24] In keeping with this, our analysis revealed that long-term adverse cardiovascular outcomes were higher in EIRA patients over a mean period of three years. Although stenting was associated with better in-hospital prognosis for EIRA patients, long-term event rates were still relatively high, albeit not quite to the level as for those patients who were not stented.

3.5.4 Study Limitations

Our study has several limitations. Firstly, this was a single centre, retrospective experience and because EIRA is an uncommon entity, we were only able to identify a limited number of cases. Secondly, as we relied on telephone calls, inpatient hospitalisation and consultation records for follow-up, we may not have captured all long-term cardiovascular event rates. Finally, we also have limited our analysis to only patients who presented for P-PCI, and therefore do not have outcomes for STEMI patients with EIRA who presented after initial medical stabilisation.

3.6 CONCLUSION

This study demonstrates that large thrombus burden accompanies almost all ectatic culprit arteries in the setting of STEMI, leading to higher rates of usage of post-procedural anticoagulation and glycoprotein IIb/IIIa inhibitors. Almost half of EIRA cases cannot be treated by stent deployment. The high long-term cardiovascular event rates associated with culprit vessel ectasia in STEMI are driven primarily by recurrent non-fatal acute coronary syndromes, and are not significantly improved by index procedure stenting.

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CHAPTER 4

BLEEDING OUTCOMES AFTER NON – EMERGENCY PERCUTANEOUS CORONARY INTERVENTION (PCI) IN THE VERY ELDERLY

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4.1 ABSTRACT

Background Octogenarians constitute an increasing proportion of patients presenting for non-emergency percutaneous coronary intervention (PCI). **Methods** This study evaluated the in-hospital procedural characteristics and outcomes, including the bleeding events of 293 octogenarians presenting between January 2010 and December 2012 for non-emergency PCI to a single large volume tertiary care Australian center. Comparisons were made with 293 consecutive patients aged less than or equal to 60 years or lesser, whose lesions were matched with the octogenarians. **Results** Non-ST-elevated myocardial infarction was the most frequent indication for non-emergency PCI in octogenarians. Compared to the younger cohort, they had a higher prevalence of co-morbidities and more complex coronary disease, comprising more type C and calcified lesions. Peri-procedural use of low molecular weight heparin (LMWH; 1.0% *vs*. 5.8%; $P< 0.001$) and glycoprotein IIb/IIIa inhibitors (2.1% vs. 9.6%; $P< 0.001$) was lower, while femoral arterial access was used more commonly than in younger patients (80.9% vs. 67.6%; $P< 0.001$). Overall, there was a non-significant trend towards higher incidence of all bleeding events in the elderly (9.2% vs. 5.8%; $P = 0.12$). There was no significant difference in access site or non-access site bleeding and major or minor bleeding between the two cohorts. Sub-analysis did not reveal any significant influence on bleeding rates by the use of LMWH, glycoprotein IIb/IIIa inhibitors or femoral arterial access. In addition, there were no significant differences in the rates of in-hospital mortality, stroke or acute stent thrombosis between the two groups. **Conclusion** In this single center study, we did not observe significant increases in adverse in-hospital outcomes including the incidence of bleeding, in octogenarians undergoing non-emergency PCI.

4.2 INTRODUCTION

The very elderly, defined as ≥ 80 years, represent an increasing population presenting for left heart catheterization and percutaneous coronary intervention (PCI), yet they remain an under-represented group in prospective clinical trials of PCI.[1] One of the most frequent and important complications from PCI procedures remains bleeding.[2] The risk of this has become accentuated with the use of anti-platelet and anti-thrombotic agents designed to improve ischemic outcomes after angioplasty and stenting. Post-PCI bleeding is most commonly access site related, although the risk of other types of major bleeding (e.g., gastrointestinal and central nervous system) is also increased after emergency and non-emergency PCI.[3] Importantly, the occurrence of bleeding remains an important predictor of short and long-term mortality in PCI patients.[4]Such concerns regarding post-PCI bleeding and its implications have led to the development of bleeding risk scores such as the Integer-based bleeding risk score,[4] the CRUSADE bleeding risk score,[5] and the National Cardiovascular Data Registry (NCDR) bleeding risk score,[6] designed to identify patients at increased bleeding risk and guide PCI strategy (including the use of blood-thinning agents) accordingly. All these scoring systems take into account increased age as an independent predictor of bleeding outcomes.

There is a paucity of data on bleeding outcomes after non-emergency PCI in the very elderly, as many trial protocols exclude this age group. In light of this, we set out to interrogate the patient, lesion and procedural characteristics as well as short-term outcomes, inclusive of bleeding, in octogenarian patients receiving non-emergency PCI, in a large volume centre in a real-world setting.

4.3 METHODS

4.3.1 Patient population

All consecutive non-emergency PCI procedures (defined by those who did not require PCI within 24 hours of presentation) in patients aged ≥ 80 years, at Monash Medical Centre, Clayton, Victoria, Australia from January 2010 to December 2012, were eligible to be included for analysis. Two hundred and ninety-three very elderly patients were identified and further sub-classified by their mode of clinical presentation as either non-ST-elevated myocardial infarction (NSTEMI), unstable angina, stable angina or silent ischemia. We compared these patients with a lesion matched control group composed of two hundred and ninety-three consecutive patients, aged ≤ 60 years or below undergoing non-emergency PCI during the same time period. Patients requiring emergency PCI, including those presenting with cardiogenic shock, STEMI, or ventricular arrhythmia (ventricular fibrillation or ventricular tachycardia) were excluded from analysis.

4.3.2 Procedure and data collection

All data were collected by consulting our institutional PCI database into which details were entered prospectively along with the patient case records. The data collected included baseline and procedural characteristics and in-hospital outcomes comprising angiographic and procedural success, bleeding events, stent thrombosis, peri-procedural myocardial infarction (MI), cerebrovascular accidents (CVA) and death. In addition, we retrospectively determined the predicted bleeding risk for all patients based on the updated NCDR bleeding risk score.[6]

Though it was our departmental policy to evaluate the bleeding risk pre-procedure, the tool used was at the discretion of the individual operators.

All interventions were performed according to the practice guidelines for PCI at the time of enrolment. All patients received at least 100 mg of aspirin and a loading dose of either clopidogrel 300 to 600 mg, or ticagrelor 180 mg or prasugrel 60 mg before or during the procedure. Heparin (70 to 100 units/kg) was administered at the beginning of the procedure. Administration of glycoprotein (GP) IIb/IIIa inhibitors was at the discretion of the operator. After the intervention, all patients were prescribed aspirin 100 to 150 mg/day and either clopidogrel 75 mg/day, or ticagrelor 90 mg twice daily or prasugrel 5 mg once daily for at least 12 months.

4.3.3 Definitions

The very elderly cohort comprised patients aged $\geq$ 80 years and the young cohort patients aged $\leq$ 60 years. Patients included for evaluation were further identified based on their mode of presentation either with NSTEMI, unstable angina or chronic stable angina. Unstable angina was diagnosed if no biomarker was detected in the blood stream at least 6 h after the initial onset of ischemic chest pain with one or more of 3 principal presentations: (1) rest angina (usually lasting > 20 min); (2) new-onset (< 2 months previously) severe angina, and (3) a crescendo pattern of angina (increasing in intensity, duration, frequency, or any combination of these factors). Patients were diagnosed as having NSTEMI based on elevations in cardiac biomarkers [cardiac-specific Troponin I or muscle and brain fraction of creatinine kinase (CK-MB)] with one or more of the three principal presentations mentioned above with or without electrocardiographic changes of ST

depression and/or prominent T-wave inversions. Patients with angina on effort of duration more than three months not responding to optimal medical therapy and presenting for PCI were classified as those with chronic stable angina.

Multi-vessel disease was defined by the presence of a > 50% lesion in $\geq$ 2 major coronary arteries. Renal failure was defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min per 1.73m^2 according to the Modification of Diet in Renal Disease (MDRD) formula: eGFR= 175 × (Serum Creatinine)$^{-1.154}$ × (Age)$^{-0.203}$ × 0.742 (if female). Left ventricular systolic function was classified as normal [ejection fraction (EF) ≥ 55%] or abnormal (EF <55%), based on assessment by transthoracic echocardiography. Prior vascular disease included carotid, aorto-femoral or lower extremity vascular disease documented by previous radiological study or vascular intervention. Coronary artery lesion type (A/B1/B2/C) was defined according to ACC/AHA classification.[7]

The bleeding risk of each patient was evaluated retrospectively using the updated bleeding model to predict the risk of post-procedure bleeding among patients undergoing PCI from the NCDR CathPCI registry.[6] According to this, for each patient the presence or absence of several variables inclusive of age, body mass index, previous PCI, chronic kidney disease, gender, haemoglobin, indication of the procedure and hemodynamic status of the patient on presentation were scored. Patients with a score of < 25 were considered to be in the low risk category, those with scores between 25 and 65 were considered to be of intermediate risk and those with a score > 65 were considered to be at high risk for bleeding. The updated NCDR bleeding risk score was chosen as, unlike the other bleeding risk scores, it was developed from

patients undergoing elective PCI rather than including those who had an urgent, emergency or salvage PCI.[6]

Several studies have shown that the rate of bleeding is dependent on the definition used.[8] We utilized the standardized Bleeding Academic Research Consortium (BARC) definition to classify the severity of bleeding events observed.[9] Minor bleeding was defined by BARC type 1 and 2 and major bleeding was defined by BARC type 3, 4 and 5.

Angiographic success was defined as < 20% residual stenosis in the target lesion. Procedural success was defined as angiographic success without in-hospital major complications such as death, MI, CVA, and emergency coronary artery bypass surgery (CABG). Major adverse cardiac events (MACE) were defined as death after PCI, emergency revascularization (either with CABG or repeat PCI), and nonfatal MI. MI was defined as the presence of at least two of the three following criteria: ischemic symptoms; elevation of troponin (> 5 × 99th percentile upper reference limit) in patients with normal baseline values or a rise in troponin values > 20%, if the baseline values were elevated and stable or falling; or new electrocardiographic changes compatible with MI. Death was defined as all-cause mortality. CVA was defined by onset of persistent loss of neurological function caused by an ischemic or haemorrhagic event either during or after PCI.

4.3.4 Statistical analysis

Baseline risk factors, clinical characteristics, clinical presentation, angiographic and lesion characteristics, procedural characteristics and in-hospital procedural outcomes and bleeding

outcomes were compared between the very elderly and the young cohort. Categorical variables are ex-pressed as number and percentages and continuous variables as mean ± SD. Categorical variables were compared with a chi-square test and continuous variables were compared with Student's *t* test. Bleeding outcomes were also analysed among several sub-groups based on use of Low Molecular Weight Heparin (LMWH), GP IIb/IIIa inhibitors, and type of peripheral arterial access and were compared between the two groups being studied. A *P* value of < 0.05

was considered statistically significant. All statistical analysis was per-formed using SPSS software (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp).

4.4 RESULTS

The two groups comprised 293 patients each. Their base-line clinical characteristics are presented in Table 4.1. The mean ages of the two groups were 83.8 ± 3.4 and 51.5 ± 6.0years respectively. The octogenarian group contained a higher proportion of females (45% vs. 15%; $P< 0.001$), and had a higher baseline prevalence of renal impairment, reduced LV function and prior CABG. Notably there were no significant differences between the groups in terms of mode of clinical presentation, with NSTEMI being the commonest form of presentation, followed by chronic stable angina and unstable angina.

Table 4.1 Baseline patient characteristics of the study population.

Baseline characteristics	≥80 years (N = 293)	≤ 60 years (N = 293)	P - value
Age	83.8 ± 3.4	51.5 ± 6.0	
Male	162(55.3%)	250(85.3%)	0.0001
Smoking			
Current	6(2.0%)	98(33.4%)	0.0001
Ex-smoker	63 (21.5%)	87 (29.7%)	0.030
Non - smoker	224 (76.5%)	108 (36.9%)	0.0001
Diabetes Mellitus	28.0% (82)	25.6% (75)	0.576
Hypertension	234 (79.9%)	160 (54.6%)	0.0001
Dyslipidemia	201 (68.6%)	195 (66.6%)	0.659

Family History	19 (6.5%)	98 (33.5%)	0.0001
Obesity	29 (9.9%)	46 (15.7%)	0.048
Prior PCI	91 (31.1%)	89 (30.4%)	0.929
Prior CABG	34 (11.6%)	16 (5.5%)	0.012
Prior Vascular Disease	76 (25.9%)	129 (44.0%)	0.0001
Renal Failure	161 (54.9%)	21 (7.2%)	0.0001
LV Function			
Normal	175 (59.7%)	231 (78.8%)	0.0001
Reduced	118 (40.3%)	62 (21.2%)	0.0001
Indications			
NSTEMI	124 (42.3%)	128 (43.7%)	0.803
Unstable Angina	64 (21.8%)	68 (23.2%)	0.767
Stable Angina	99 (33.8%)	91 (31.1%)	0.537
Asymptomatic	6 (2.1%)	6 (2.0%)	1.000

Data are presented as mean $\pm$ SD or *n* (%). CABG: coronary artery bypass graft; Ex-smoker: someone who has smoked greater than 100 cigarettes in their lifetime but has not smoked in the last 28 days; LV: left ventricular; NSTEMI: non-ST elevation myocardial infarction; PCI: percutaneous coronary intervention.

Baseline procedural characteristics were as summarized in Table 4.2. As described above, the two groups were matched for lesion coronary artery site, with the left anterior descending artery (LAD) being the most commonly treated vessel. The very elderly group had higher prevalence of single

vessel disease, calcified lesions and type C lesions and a higher rate of rotational atherectomy use. Conversely, the younger cohort more often had multi-vessel disease, and underwent PCI to treat bifurcation lesions or chronic total occlusions (CTO). Other notable differences between the two groups were that more patients in the younger group received peri-procedural LMWH, glycoprotein (GP) IIb/IIIa inhibitors and had radial artery peripheral access. Notably, the overall use of GP IIb/IIIa inhibitors in this non-emergency PCI setting was low (2.1% vs. 9.6%; $P< 0.001$). With regard to the use of oral antiplatelet agents, our institution had only just begun to utilize the newer agents ticagrelor and prasugrel by the end of the study inclusion period and therefore the use of both medications was low, although ticagrelor was used more commonly in the elderly patients than their younger counterparts. Use of drug eluting stents (DES) versus bare-metal stents (BMS) did not differ significantly between the two cohorts, with overall use of DES being in the order of 70%80%. The stent length (24.7 $\pm$ 12.8 mm vs. 26.7 $\pm$ 15.9 mm) was greater in the younger population.

Table 4.2 Procedural characteristics of the study Population

Lesion Characteristics	≥80 years	≤ 60 years	P - value
Vessel disease			
Single Vessel	144 (49.2%)	85 (29.0%)	0.0001
Multivessel	149 (50.8%)	208 (71.0%)	0.0001
Vessel Treated			
LMS	8 (2.7%)	8 (2.7%)	1.0000
RAMUS	6 (2.0%)	6 (2.0%)	1.0000
GRAFT	4 (1.4%)	4 (1.4%)	1.0000
LAD	133 (45.5%)	133 (45.4%)	1.0000
LCX	60 (20.5%)	60 (20.5%)	1.0000
RCA	82 (28.0%)	82 (28.0%)	1.0000
Lesion Type	N = 294	N = 301	

A	24 (8.2%)	45 (15.0%)	0.014
B1	109 (37.1%)	129 (42.9%)	0.175 (NS)
B2	76 (25.8%)	70 (23.2%)	0.522 (NS)
C	81 (27.5%)	53 (17.6%)	0.005
ISR	4 (1.4%)	4 (1.3%)	0.973 (NS)
Bifurcation	16 (5.5%)	50 (17.1%)	0.0001
Calcification	280 (95.6%)	20 (6.8%)	0.0001
CTO	9 (3.1%)	26 (8.9%)	0.005
IVUS	3 (1.0%)	24 (8.2%)	0.0001
Rotational atherectomy	22 (7.5%)	6 (2.1%)	0.004
Aspirin	292 (99.7%)	293 (100%)	0.317 (NS)
Clopidogrel	273 (93.2%)	292 (99.7%)	0.0001
Ticagrelor	14 (4.8%)	0	0.0004
Prasugrel	4 (1.4%)	0	0.132 (NS)
Post procedural LMWH	3 (1.0%)	17 (5.8%)	0.003
Post procedural Unfractionated Heparin	2 (0.7%)	1 (0.3%)	0.563(NS)
GP IIB / IIIA Inhibitor	6 (2.1%)	28 (9.6%)	0.0002
Access Site			
Radial	56 (19.1%)	95 (32.4%)	0.0003

Femoral	237 (80.9%)	198 (67.6%)	
Type of Stent	N = 276	N = 293	
BMS	71 (25.7%)	58 (19.8%)	
DES	194 (70.3%)	229 (78.2%)	0.085 (NS)
POBA	11 (4.0%)	6 (2.1%)	

Data are presented as *n* (%). BMS: bare metal stent; CTO: chronic total occlusion; DES: drug eluting stent; GP IIB/IIA: glycoprotein IIb/IIIa in-hibitor; IVUS: intra vascular ultrasound; LAD: left anterior descending artery; LCX: left circumflex artery; LMWH: low molecular weight heparin; LMS: left main stem; POBA: plain old balloon angioplasty; RCA: right coronary artery; RIM: ramus intermedius.

The procedural and in-hospital adverse outcomes of the very elderly in comparison with those of the younger population are presented in Table 4.3. There were no statistically significant differences between the very elderly and young cohorts in terms of overall procedural success (elderly 75.0% vs. young 81.0%) which was mainly influenced by peri-procedural enzyme elevation (19.5% vs. 16.4%), in-hospital death (1.0% vs. 0.3%), CVA (0 vs. 0), and stent thrombosis (0 vs. 0). However, contrast-induced nephropathy was more common in the very elderly (12.0% vs 7.0%; $P < 0.05$).

The bleeding outcomes between the two cohorts and their NCDR bleeding risk scores are shown in table 4.4. A significantly higher proportion of the very elderly were classified as having a high risk of bleeding as per the up-dated bleeding NCDR score (NCDR score > 65:

61.0% vs. 4.1%; *P*< 0.001). Although the mean NCDR score in octogenarians was 69.3 ± 18.4 compared to 32.3 ± 16.6 in the younger cohort, the incidence of all observed bleeding events was not statistically different between the two groups (9.2% vs. 5.8%), nor were there significant differences for major bleeding rates (2.0% vs. 1.3%) and minor bleeding rates (7.2 % vs. 4.5%). Despite trends toward higher bleeding rates in the very elderly in specific subgroups, statistical comparisons between the elderly and young were not significant for bleeding in patients who received LMWH (25.0% vs. 5.9%), GP IIb/IIIa inhibitors (16.7% vs. 12.0%), or among those whose access site was femoral (10.1% vs. 7.6%) or radial (5.4% vs. 2.1%). The mean duration of hospital stay was 4.4 days in the very elderly compared to 3.3 days in the younger cohort (*P*< 0.01). Neither univariate nor multivariate analysis identified any predictors of bleeding in elderly patients (Table 4.5)

Table 4.3 Procedural outcomes of the study population

Procedural Outcomes	≥80 years (n = 293)	≤ 60 years (n = 293)	P - value
Peri procedural enzyme elevation	57 (19.5%)	48 (16.4%)	0.332
Procedural Success	219 (75.0%)	237 (81.0%)	0.091
Death	3 (1.0%)	1 (0.3%)	0.616
CVA	0	0	1.0000
Stent thrombosis	0	0	1.0000

Values are *n* (%). CVA: cerebrovascular accident.

Table 4.4 Bleeding outcomes of the study population

Bleeding Outcomes	≥ 80 years(n = 293)	≤ 60 years(n = 293)	P - value
NCDR Score			
< 25	0	88 (30.0%)	0.0001
25 – 65	114 (39.0%)	193 (65.9%)	0.0001
>65	12 (61.0%)	179 (4.1%)	0.0001
BARC Bleeding			
0	266 (90.8%)	276 (94.2%)	0.158
1	21 (7.2%)	10 (3.5%)	0.065
2	0	3 (1.0%)	0.247
3a	4 (1.3%)	1 (0.3%)	0.369
3b	2 (0.7%)	3 (1.0%)	0.653
4	0	0	1.000
5	0	0	1.000
All Bleeding	27 (9.2%)	17 (5.8%)	0.158
Access Site Bleeding	20 (74.7%)	11 (64.7%)	0.746
Non Access Site Bleeding	7 (25.3%)	6 (35.3%)	
Mortality among those with bleeding	0	0	1.000

Bleeding among patients receiving LMWH	25.0%	5.9%	0.822
Bleeding among patients receiving GPIIbIIIa inhibitors	16.7%	12.0%	0.681
Bleeding among those with femoral access site	10.1%	7.6%	0.448
Bleeding among those with Radial access site	5.4%	2.1%	0.543

Values are presented as *n* (%) or %. BARC: bleeding academic research consortium; GP IIb/IIIa inhibitors: glycoprotein IIb/IIIa inhibitor; LMWH: low molecular weight heparin; NCDR: National Cardio Vascular Data Registry.

4.5 DISCUSSION

This study represents a single-center, real-world experience of in-hospital and bleeding outcomes in octogenarians undergoing non-emergency PCI. Our study shows that although the bleeding risk as defined by validated scoring systems is higher in this complex subset of patients, bleeding outcomes in comparison with those less than sixty years were not

significantly different. Our results indicate that non-emergency PCI in octogenarians can be performed effectively and safely.

Octogenarians constitute an increasing proportion of patients presenting for PCI for stable angina and acute coronary syndromes.[10] By comparison to optimal medical therapy, revascularization of coronary artery stenoses in the very elderly has been shown to translate to
better absolute reduction in all-cause mortality compared to the younger cohort (11.0% vs. 1.8%).[11] Despite this, elderly patients, particularly those with multiple co-morbidities, are poorly represented in clinical trials and several studies have re-ported that the use of invasive cardiac procedures declinesas patients get older.[12–14] There may often be reluctance from clinicians to use an invasive strategy to treat coronary artery disease in the very elderly due to a perceived higher risk of complications.[15] Recently, a randomized controlled multi-center trial (After Eighty Study) found a significant reduction in a composite clinical endpoint when octogenarians with acute coronary syndrome were managed with an early invasive strategy rather than by conservative medical management.[16]

Elderly patients in our study had more co-morbidities compared to the younger cohort, which is consistent with several previous studies.[17–20] We found that more octogenarians treated with PCI were women, had prior CABG, renal disease, and abnormal left ventricular function, whereas more patients in the younger cohort were smokers, had a positive family history and were obese.

Table 4.5 Univariate and multivariate analysis for predictors of bleeding

Variable	**P - value**	**Beta co-efficient**
Univariate analysis		
Age group	0.155	1.676
Gender	0.974	1.013
Diabetes Mellitus	0.680	0.842
Hypertension	0.120	1.950
Total Cholesterol	0.072	2.282
Obesity	0.490	0.653
Prior Vascular Disease	0.443	1.318
Access Site (Femoral Vs Radial)	0.129	2.118
Body Mass Index	0.155	1.026
GP IIb IIIa Inhibitor	0.428	1.652
Bifurcation	0.232	1.754
Calcification	0.350	1.394
Chronic Total Occlusion	0.996	0.996
Impaired renal function	0.230	1.737
Multivariate analysis		
Impaired Renal Function	0.464	1.467
Age group	0.367	1.796

Hypertension	0.503	1.394
Total cholesterol	0.205	1.879
Access Site	0.163	2.014
Bifurcation	0.100	2.273
Calcification	0.601	0.735

4.5.1 Procedural and bleeding outcomes in the very elderly

Age is an important predictor of procedural outcome after PCI. Batchelor *et al*. evaluated the outcome trends in the elderly after PCI and showed that there was a declining trend in major adverse events during their four-year study period among octogenarians, though their procedural success rates (84.0% vs. 89.0%; $P< 0.001$) were relatively lower and major adverse cardiac events (4.9% vs. 1.9%; $P< 0.001$) relatively higher compared to younger patients.[17]

Bleeding events are common and have been reported to occur in 2.2% to 14% of patients undergoing PCI.[17,21,22] These events have been associated with increases in short-and long-term mortality, nonfatal MI, stroke and length of hospital stay[17,21-27]. Factors which predict bleeding complications include age, mode of presentation, and comorbidities such as renal disease and congestive heart failure.[28,29]In our study, there was no significant difference in overall bleeding rates, major and minor bleeding between the two groups being studied. This could be for several reasons. Firstly, our study was done on patients presenting for non-emergency PCI. Several risk algorithms evaluating post-PCI bleeding clearly indicate that the risk

of bleeding is higher after an emergency PCI (e.g., for STEMI) compared to non-emergency PCI. Secondly, as per hospital protocol the use of bleeding risk score was encouraged for all PCI procedures though the tool used was left to the operator's discretion. It has been shown previously, that pre-procedural estimation of bleeding risk may reduce bleeding complications after PCI, especially for patients considered intermediate or high risk.[30] Thirdly, LMWH and GP IIb/IIIa inhibitors were used less frequently in our study in octogenarians. Finally, as with most previous studies evaluating octogenarians, the possibility that our small sample size resulted in the observed statistical non-significance cannot be excluded. Thus, we believe that with appropriate case selection as described above, non-emergency PCI can be performed in the very elderly with bleeding rates comparable to the younger population. Also, there was no significant difference in bleeding rates between old and young cohorts even among subgroups receiving LMWH or GP IIb/IIIa inhibitors. Although this statistical non-significance may have been due to small study numbers, lower than

expected bleeding rates have also been reported by other investigators in the setting of vigilant anticoagulant use.[23]

Although the overall usage of radial access was relatively low in our study, especially in the very elderly (19.1% vs. 32.4%), there was no significant difference between the overall bleeding and access-site bleeding rates between old and young. Moreover, in subgroup analysis, bleeding was not significantly different between the young and old for either radial or femoral approach, although once again this may have been influenced by relatively small sample sizes. Although radial artery access has been found to be associated with a significant reduction in access site bleeding, it is still being less frequently implemented in patients who are at higher risk of such complications.[31] Trans-radial catheterization in the elderly may be

difficult because of a higher incidence of radial and brachiocephalic trunk tortuosity or stenosis of the upper limb artery in these patients.[32] Also heavier calcification burden, more advanced atherosclerosis and tortuosity of the aorta and subclavian arteries may make trans-radial procedures in the elderly challenging.[33] These technical challenges encountered during the radial approach may discourage interventionists from adopting it.[34] It remains to be seen if the greater implementation of trans-radial access for PCI, along with use of newer anti-thrombotics (e.g., bivalirudin) which may have different safety profiles, further affects bleeding outcomes in this group of patients.

It has been previously reported that access site injury, stroke and mortality are higher in octogenarians than those < 60 years after emergency PCI.[20] However, in our study stroke, bleeding rates, and mortality after non-emergency PCI were not significantly different between the two groups. Our data support the findings of the After Eighty Study in which no significant differences in stroke and mortality rates were observed between those elderly patients who had an early invasive strategy or conservative non-invasive approach to their management.[16] These data indicate that anxieties about referral of elderly patients for PCI due to concerns about complications may be overstated, and suggests that timely intervention in these patients would offerbenefits which would potentially outweigh the risks secondary to the procedure. It reassures that invasive management can be done in octogenarians without compromising safety.[35] This is especially so, as although octogenarians present with a higher risk profile, they paradoxically have been shown to have a greater absolute risk reduction with revascularization compared to younger patients.[36]

In summary, there may be ongoing perception that PCI in the very elderly should be deferred because of co-morbidities and predicted high rates of adverse outcomes. The published data indicate that elderly patients have a greater risk reduction from revascularization than do younger patients. Many of the treatment modalities have been evaluated in younger patients in clinical scenarios that are not altogether representative of real-world scenarios, where the very elderly represents a significant and growing proportion of our interventional cases. Our data show that despite co-morbidities and high predicted bleeding scores, low bleeding rates and overall satisfactory short-term outcomes can be achieved in the very elderly in real-world PCI practice. We suspect that judicious use of bleeding score systems to rationalize the use of certain blood-thinning medication helps to keep bleeding rates at an acceptable level. Our cohort represents a distribution of non-emergency PCI cases, with a good representation of early PCI procedures for NSTEMI and unstable angina (acute coronary syndrome) and also for elective stable angina. Acknowledging the important limitations of small sample size and retrospective analysis, our data indicate that elective and ACS-PCI can be performed with similar bleeding outcomes and adverse events in the very elderly as with the young, despite the very elderly having complex lesion characteristics.

4.5.2 Study limitations

Firstly, this is a single center, retrospective study, investigating a relatively small sample size. Secondly, the bleeding episodes were site-reported which might result in under-estimation of actual bleeding rates. Thirdly, it is possible that patients with elective PCI may have been discharged early before recognition of bleeding complications. Fourthly, as with any retrospective analysis, there is a potential for unmeasured confounders. Randomized controlled trials ad-dressing bleeding outcomes in the very elderly population are needed in the future.

Also, we could not account for the sheath size, time when the sheaths were removed, duration of manual compression, or use of vascular closure device, each of which has the potential to influence post-procedural bleeding. Finally, the current study has not reported long-term follow-up data.

4.6 CONCLUSION

In this single center study we did not observe significant increases in adverse in-hospital outcomes including the incidence of bleeding in octogenarians undergoing non-emergency PCI. This confirms that PCI in this at-risk cohort has an acceptable safety profile.

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CHAPTER 5

AN OVERVIEW OF PCI IN THE VERY ELDERLY

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5.1 ABSTRACT

Cardiovascular disease, and in particular ischemic heart disease (IHD), is a major cause of morbidity and mortality in the very elderly (> 80 years) worldwide. These patients represent a rapidly growing cohort presenting for percutaneous coronary intervention (PCI), now constituting more than one in five patients treated with PCI in real-world practice. Furthermore, they often have greater ischemic burden than their younger counterparts, suggesting that they have greater scope of benefit from coronary revascularization therapy. Despite this, the very elderly are frequently under-represented in clinical revascularization trials and historically there has been a degree of physician reluctance in referring them for PCI procedures, with perceptions of disappointing outcomes, low success and high complication rates. Several issues have contributed to this, including the tendency for older patients with IHD to present late, with atypical symptoms or non-diagnostic ECGs, and reservations regarding their procedural risk-to-benefit ratio, due to shorter life expectancy, presence of comorbidities and increased bleeding risk from antiplatelet and anticoagulation medications. However, advances in PCI technology and techniques over the past decade have led to better outcomes and lower risk of complications and the existing body of evidence now indicates that the very elderly actually derive more relative benefit from PCI than younger populations. Importantly, this applies to all PCI settings: elective, urgent and emergency. This review discusses the role of PCI in the very elderly presenting with chronic stable IHD, non ST-elevation acute coronary syndrome, and ST-elevation myocardial infarction. It also addresses the clinical challenges met when considering PCI in this cohort and the ongoing need for research and development to further improve outcomes in these challenging patients.

5.2 INTRODUCTION

The definition of elderly varies in different studies, and currently there is no consensus as to who should be considered elderly, though the 2002 ACC/AHA guidelines for the management of acute coronary syndromes considered patients > 75 years as an “at-risk” group.[1] In this review, individuals ≥ 80 years (octogenarians) will be referred to as very elderly, and those between 60 to 79 years as elderly. An analysis from British centers looking at patients undergoing percutaneous coronary cntervention (PCI) from 2000 until 2008 had noted a shift in terms of aging of the patient population being treated with PCI, to more patients in both the 60 to 79-year-old age bracket and especially in the 80 year and above age group. [2] Here, we address the unique set of challenges and considerations that this rapidly growing group of patients present.

5.3 PREVALENCE OF CORONARY ARTERY DISEASE IN THE VERY ELDERLY

Age is a major cardiovascular risk factor and coronary artery disease (CAD) is the most common cause of death in the elderly. [3] There has been an annual rise of more than 160,000 octogenarians in the United States, and it is predicted that this population will increase nearly fivefold by 2040. [4] Understandably, ageing of a country's population as a result of sustained low fertility, combined with increasing life expectancy is likely to continue. The main risk factor for CAD is age and its prevalence increases markedly as age increases. CAD has its greatest impact on the elderly where hospitalization and death rates are usually much higher than for younger patients. 83.0% of men and 87.1% of women aged 80 or more in the US have cardiovascular disease (CVD) and about 66% of all CVD deaths occur in people aged 75 or older. [5]

5.4 CORONARY LESIONS IN THE VERY ELDERLY

The same British analysis mentioned above also observed a significant increase in the complexity of lesions being treated in the latter part of the 2000s. [2] In their study, octogenarians represented the fastest growing group of patients undergoing PCI, and 46% of them had calcified lesions. Comparing lesion characteristics of patients aged < 80 years to those

> 80 years undergoing PCI, the octogenarians had a higher prevalence of calcified lesions, tortuous lesions, ostial lesions, multi-vessel disease and left main stenosis. Interestingly, when analyzing the trends from the early part to the latter part of the decade, they also identified a significant increase in the number of octogenarians undergoing left main coronary artery PCI. Thus, to summarize, their landmark report showed that: (1) there has been a significant increase in the number of octogenarians undergoing PCI; (2) octogenarians have more complex lesions compared to the younger populations; and (3) are now undergoing more complex PCI procedures than was previously the case.

5.5 OUTCOMES AFTER PCI IN THE VERY ELDERLY

A recent seminal report from the Mayo Clinic has shown a marked temporal switch in the causes of death after PCI from predominantly cardiac to non-cardiac causes over the past two decades. [6] This trend was seen across all age groups, in single and multivessel disease and whether PCI was done for stable angina or acute coronary syndrome (ACS). A decrease in cardiac mortality was noted independent of baseline clinical characteristics and an increase in non-cardiac mortality was observed which was associated with increased non-cardiac comorbidities. [6]

The clinical outcome of octogenarians with unprotected left main disease after PCI with drug eluting stents (DES) has also been evaluated in a large multinational registry. At a median follow-up of 1088 days, there were no difference in death, cerebrovascular accident (CVA) or myocardial infarction (MI) among octogenarians revascularized with PCI versus coronary artery bypass graft (CABG) surgery. [7] Therefore, long term outcomes after PCI in the very elderly appear to be acceptable. A systematic review of clinical studies performed to identify the health-related quality of life (HRQOL) after PCI in the elderly, which is an important measure of procedural success, showed that the elderly has significant improvements in cardiovascular well-being after PCI. The HRQOL was encouragingly found to improve for at least one year across a broad range of health domains. [8] Also the elderly with symptomatic CAD not only had improved Quality Of Life (QOL) with PCI but also had similar if not greater improvement in angina burden than younger patients despite having a higher risk profile. [9],[10]

5.6 PERI-PROCEDURAL BLEEDING IN THE VERY ELDERLY

The most common non-cardiac complication in patients undergoing PCI is bleeding.[11] It has been shown that peri-procedural bleeding in the elderly is associated with an increased risk of death, MI, CVA, prolonged length of hospital stay and added cost.[12]–[14] The detrimental effects of bleeding in the elderly are in large part because blood loss can cause harmful effects through hypovolemia, hypotension, reduced oxygen carrying capacity, drug discontinuation and blood transfusion.[15] These are generally poorly tolerated in the elderly who often have reduced left ventricular (LV) function and generalized vascular disease, including increased vascular stiffness and endothelial dysfunction.[16] As stated above, age has been identified as

an independent risk factor for bleeding in patients undergoing PCI.[13] The higher incidence of bleeding and other procedural outcomes after PCI in the elderly may be due to the higher incidence of comorbidities, including more extensive atherosclerosis, hypertension and renal insufficiency, as well as their more frequent presentation with hemodynamic instability or shock and the more frequent usage of femoral arterial access.[17]

Given its clinical significance, bleeding risk stratification is a vital part of management of patients presenting for PCI. Several risk scores have been developed and validated to assess bleeding risk: the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines (CRUSADE) bleeding score,[18] the Acute Catheterization and Urgent Intervention Triage Strategy and The Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (ACUITY-HORIZONS) risk score,[19] the Acute Coronary Treatment and Intervention Outcomes Network Registry−Get With the Guidelines (ACTION Registry-GWTG) risk score,[20] and the Updated NCDR bleeding risk score.[21] Among these, only the updated NCDR bleeding risk score has incorporated patients presenting for elective PCI, the other risk scores have been developed to assess bleeding risk of ACS patients.

Nearly all studies have shown an increased risk of access site related complications and associated bleeding events in the elderly. [22] Octogenarians seem to have a higher rate of bleeding even after elective PCI. [23] It remains to be seen if increasing the adoption of radial artery access and the application of pre-procedural bleeding risk score estimation to guide anti-thrombotic strategy helps in lowering the risk of bleeding complications in the very elderly.

The transradial approach for PCI was first described to be safe and effective by Campeau,[24] with transradial coronary stenting performed shortly after by Kiemeneij.[25] Transradial catheterization in the elderly may be more difficult because of a higher incidence of radial, subclavian, brachiocephalic and aortic tortuosity, calcification and stenosis.[26],[27] These technical challenges encountered during the radial approach may discourage interventionists from adopting the technique.[28] On the flip-side, advanced age itself is a significant risk factor

for bleeding and other vascular access complications after PCI, and the transradial approach has been clearly shown to be associated with a low incidence of these complications compared to femoral artery access.[29] Therefore, the use of transradial access may be potentially beneficial in the elderly. It has been demonstrated that even in the emergency setting of primary PCI for ST-elevation myocardial infarction (STEMI), PCI in the very elderly can be performed transradially without significant difference in terms of reperfusion time and with reduction in bleeding complications compared to trans-femoral access despite higher incidence of peri-procedural GP IIb/IIIa inhibitor use. [30]– [34]

5.7 ANTITHROMBOTIC THERAPY IN THE VERY ELDERLY

The use of blood thinning agents is well known to reduce cardiovascular mortality and ischemic complications in patients undergoing PCI.[35] Although the hemostatic balance in the very elderly seems to shift towards increased clotting and decreased fibrinolysis, there are other factors in these patients, such as distinct pharmacokinetic and pharmacodynamic responses, polypharmacy resulting in drug–drug interactions and increased comorbidities, which all contribute to an increased risk of bleeding after peri-procedural antithrombotic therapy.[36]

Dual antiplatelet therapy (DAPT) is currently recommended prior to and after PCI, in all patients irrespective of age, [37] although the duration of treatment may vary according to the type of presentation (elective versus acute) and the type of stent being deployed (bare-metal versus first generation DES versus second generation DES). DAPT in the elderly compared to the younger population has the following concerns which not only influence the choice of stent during PCI, but also the mode of management of CAD: (1) higher bleeding risk; (2) concurrent warfarin therapy for atrial fibrillation, which is more common with increasing age; [38] (3) higher likelihood of requiring non-cardiac surgery in the near future after PCI; and (4) increased risk of falls.

The ACC/AHA guidelines, also applicable to the elderly, recommend the use of aspirin in patients undergoing PCI. [39] A dosage of 75 mg to 150 mg of aspirin is as effective as higher doses with lower risk of adverse effects. In patients presenting with ACS and undergoing PCI, guidelines also recommend the use of clopidogrel in addition to aspirin. [40] Prasugrel a more potent P2Y12 inhibitor in the thienopyridine drug-class was associated with a 19% relative risk reduction in ischemic events compared to clopidogrel in high risk ACS patients undergoing PCI in the TRITON TIMI 38 trial. [41] However, it was associated with a 32% increased risk of bleeding especially in the elderly (> 75 years). Hence, prasugrel is generally not recommended in patients ≥ 75 years. Ticagrelor, which belongs to another class of P2Y12 receptor antagonists, showed a greater absolute (2.8% vs. 1.3%) and relative reduction (17.0% vs. 15.0%) of ischemic end-points in elderly (> 65 years) compared to younger patients in the PLATO trial, with lower incidence the primary composite end-point of cardiovascular death, MI or CVA compared to clopidogrel (9.0% vs. 10.7%). There was no difference between clopidogrel and ticagrelor groups in the rates of total major bleeding or severe bleeding. This trial therefore concluded that ticagrelor may be a better

option than clopidogrel for patients with ACS for whom an early invasive strategy with PCI is planned. [42]

Bivalirudin and unfractionated heparin (UFH) are the two anticoagulant options most widely used during PCI. Bivalirudin has been touted as being as effective as UFH, but with nearly half the rate of bleeding shown in several land mark studies: HORIZONS AMI [43] trial, EUROMAX [44] trial in STEMI; BAT trial [45] and ISAR-REACT 3[46] in NSTEACS. Several reports however have indicated that patients on bivalirudin may have increased risk of early stent thrombosis. With regard to the elderly, an observational study of elective PCI in 2766 octogenarians, found that bivalirudin as compared with UFH was associated with a decreased risk of in-hospital bleeding (HR: 0.41; 95%CI: 0.23–0.7) and lower rate of major adverse cardiovascular events (MACE) at 6 months (adjusted HR: 0.5; 95%CI: 0.4–0.7).[47] In addition, the ACUITY trial[48] demonstrated an absolute reduction in bleeding events with the use of bivalirudin instead of heparin which was more pronounced in the elderly. A meta-analysis of randomized controlled trials however has questioned the reduction in bleeding with bivalirudin relative to UFH. [49] Thus, further investigation is still required to confirm the purported superior safety profile of bivalirudin in the elderly, especially given its higher cost than UFH. This is particularly in the elective PCI setting and in the context of contemporary dual antiplatelet agents and increased use of radial arterial access. As it currently stands, UFH remains the standard peri-procedural antithrombotic therapy in most centers.[50]

Guidelines for the peri-procedural usage of GP IIb/IIIa inhibitors during PCI have no modification for the elderly, although higher bleeding risk in these patients is a cause of concern.[40] Data surrounding their merits and risks in older patients are somewhat conflicting between different

agents. In one study, the routine use of abciximab in elderly individuals undergoing primary PCI, while safe, was not found to be as efficacious as in the young.[51] Similarly, even after NSTEMI, abciximab when used as an adjunctive therapy in the context of PCI, was shown to be of lesser benefit in elderly patients.[52] In the case of eptifibatide, an age sub-group analysis in patients with unstable angina reported that bleeding was highest in octogenarians.[53] Another trial excluding patients with renal failure, demonstrated a greater absolute (7.2% vs. 1.3%) and relative (52.6 vs. 16.0%) benefit of eptifibatide in elderly (defined as patients older than 65 years), compared to younger patients, for reducing the combined end-point of death, MI or revascularization.[54] In contrast, another study of tirofiban use in patients with unstable symptoms, showed similar treatment effect between older and younger patients.[55] Overall, a meta-analysis review of trial data involving GP IIb/IIIa inhibitors has concluded declining benefit in ACS patients of advanced age, with their usage associated with only a 4% non-significant beneficial effect in the elderly (> 70 years) and a concerning 62% increased risk of major bleeding.[56]

In summary with respect to the general use of antithrombotic therapy, the elderly seem to experience lower efficacy and disproportionately higher rates of bleeding compared to younger patients. This reinforces the importance of judicious patient selection when implementing and choosing between adjunctive blood-thinning agents during PCI, with careful consideration required to balance the risk of bleeding complications versus benefit of reducing thrombotic events. Particular emphasis should be given to taking into account the individual patient's comorbid state, and ensuring that where applicable creatinine clearance and weight adjustment are used for determining appropriate dosing.

5.8 ELECTIVE PCI IN THE VERY ELDERLY

Historically octogenarians undergoing elective PCI have consistently shown lower rates of procedural success and higher rates of complications including in-hospital mortality, stroke, vascular complications, recurrent MI, and renal failure compared to younger cohorts.[57]–[59] The past decade has seen the development of newer generation coronary stents, increased adoption of transradial access and several adjuvant drug therapies, which are effective at improving outcomes and reducing complications.[59]–[64] Several studies on elderly patients suggest that the absolute benefit of these developments may be even higher in the elderly due to their high baseline risk.[57],[63] A study from the USA showed that octogenarians undergoing elective PCI have good outcomes with higher procedural success rates and minimal morbidity suggesting that PCI is a safe and effective treatment modality of stable CHD even among the very elderly patients.[64]

5.9 PCI FOR STEMI IN THE VERY ELDERLY

Timely primary revascularization for STEMI has been proven to result in decreased mortality and morbidity compared with thrombolytic therapy or medical management alone. [65] The very elderly with STEMI are more likely to have contraindications to thrombolytic reperfusion. Eligibility for thrombolytic reperfusion appears to decline with age, and moreover the very elderly is less likely to receive reperfusion even if they are eligible. Many elderly patients present with atypical symptoms, and have a higher likelihood of death after STEMI, much of which appears secondary to arrhythmic and mechanical complications. More than half of octogenarians with STEMI experience heart failure from either diastolic or systolic dysfunction.[66] A randomized multicenter, open-label clinical trial that compared primary PCI with thrombolysis in patients with a mean age of 80 years presenting with STEMI within the first six hours of symptom onset has

shown that primary PCI improved outcomes in this setting.[67] There was a substantial reduction in recurrent ischemia in the PCI arm compared to thrombolytic therapy which remained significant throughout the one year of follow-up. In addition, there were no significant differences in major bleeding or transfusion requirements between the two treatment groups, presumably because of careful dosing and monitoring of anticoagulant and antithrombotic medications. [67] The risk-to-benefit ratio therefore favors primary PCI over thrombolytic therapy in the elderly, with major benefit from the former being a reduction in re-infarction and need for target-vessel revascularization, though mortality reduction appears less robust. Thus, primary PCI appears to be the reperfusion strategy of choice in octogenarians with STEMI, with thrombolytic therapy (particularly when given early) a viable alternative when primary PCI is not available. [67]

Key studies dedicated to investigating primary PCI for STEMI in the elderly and very elderly are summarized in Table 5.1. The Western Denmark registry compared outcomes after primary PCI in octogenarians and nonagenarians with STEMI, and found that TIMI III flow was achieved in 86.3% and 83.3% of these patients, respectively. The overall 30-day cumulative mortality was 17.9%, whilst the 1-year cumulative mortality was 27.2% and 5-year cumulative mortality was 41.1%. [68] Generally, the 30-day and 1-year mortality rates in octogenarians after STEMI are higher than their younger counterparts, probably because of associated

comorbidities and a higher incidence of previous IHD with subsequent left ventricular dysfunction which may contribute to unfavorable prognosis. The relative risk decrease provided by primary PCI has been found to be the same in elderly and younger patients, and therefore the absolute benefit may be greater in the elderly. [69]

Table 5.1 Key studies of primary PCI in the elderly and very elderly with STEMI.

Study name	Nature of study	Number of patients	Main results	Study limitations
TRIANA [67] (RCT)	PPCI *vs*. Fibrinolysis in patients ≥ 75 years	266	Primary endpoint (30-day death, re-infarction, or disabling stroke) was achieved in 18.9% of patients treated with PPCI when compared with 25.4% of the patients thrombolysed ($P = 0.43$), with no significant difference in complication like major hemorrhage, blood transfusion or renal failure. Benefits were persistent at the	Halted prematurely due to slow recruitment. Primary endpoint underpowered. Healthier population enrolled with considerable exclusion of

Study name	Nature of study	Number of patients	Main results	Study limitations
			end of one year with a significant reduction in recurrent ischemia (0.8% *vs*. 11.9%; $P <$ 0.001) in the PCI arm.	patients with comorbidities, limiting extrapolation to broader populations.
Western Denmark Heart Registry [68]	Analysis of octo- & Nonagenarians undergoing PPCI from health care database	1322	Annual proportion of octogenarians undergoing PPCI doubled during the study period (2002–2009). Overall 30-day mortality was 17.9%,whilethe1-year cumulative mortality was 27.2% and 5-year cumulative mortality was 41.1%. Acceptable outcome with a 5-year survival of more than 50% in octogenarians and nonagenarians.	Non-randomized trial. Study focused on mortality rates, however no breakdown of cause of death provided. Other endpoints like MI, bleeding complications and renal failure after PPCI not assessed.
SENIOR PAMI [80](RCT)	PPCI *vs*. Fibrinolysis in patients ≥ 70 years	481	PPCI was superior to thrombolytic therapy (11.6% *vs*. 18.0%, $P = 0.005$) at reducing the combined secondary endpoint of death/CVA/re-infarction at 30	Study was stopped prematurely due to recruitment issues.

			days. PPCI did not reduce the primary endpoint of 30-day death or disabiling stroke (1.3% vs. 13%, p = 0.57).	Primary endpoint Not statist ically due to signif insufficient icant sample size
PCAT-2 [81](Meta-analysis of 22 RCTs)	PPCI *vs*. Fibrinolysis	410 octogenarians of the 6763 patients studied	Octogenarians undergoing PPCI had a lower incidence of all-cause mortality (18.3% *vs*. 26.4%, *P* = 0.04) at 30-day follow-up compared to those who were thrombolysed.	Elderly patients included in these trialsform a selected group, hence the observed favorable effects might not be fully extrapolated to the general population.

CVA: cerebrovascular accident; HF: heart failure; PAMI: primary angioplasty in myocardial infarction; PCI: percutaneous coronary intervention; PPCI: primary percutaneous coronary intervention; RCT: randomized controlled trial.

5.10 DRUG ELUTING STENT (DES) VERSUS BARE METAL STENT (BMS) IN THE ELDERLY

Drug-eluting stensts (DES) have rapidly replaced bare-metal stents (BMS) for PCI treatment of CAD because of their superior capability to reduce restenosis and the need for target lesion and vessel repeat revascularization. With the establishment of DES, it was evident that DAPT had to

be given for a longer time after stent implantation to avoid stent thrombosis. The greater burden of comorbid conditions in octogenarians makes them more susceptible to complications

due to DAPT, while these patients also have more frequent need for interruptions of this treatment (e.g., during the peri-operative period for non-cardiac surgery). These safety concerns may be the reason why DES are used relatively less frequently in the very elderly.[70] An analysis of a historical cohort of octogenarians comparing first generation DES and BMS revealed that there was no significant relationship between the type of stent used and either mortality or occurrence of adverse clinical events at one year of follow-up.[71] A multicenter randomized trial undergoing stent placement for symptomatic patients has shown that use of second generation DES when compared with BMS reduces the incidence of MI and target vessel revascularization in the subsequent year. However, there was no impact on all-cause death, CVA, and major haemorrhage between the two groups.[72] Thus, in octogenarians with an indication of revascularization, current generation DES can be safely used, with some benefits in ischemic outcomes compared to BMS. There are emerging data indicating that for elective PCI, DAPT may be limited to as little as one or three months of continuation after second generation DES deployment, so concerns about having to use prolonged DAPT in elderly patients who are at risk of bleeding may not be as great as was traditionally the case. There are also ongoing studies to determine if shorter duration of DAPT can be used after PCI on ACS cohorts with new generation DES. All of this will impact on decision making as to whether to use DES instead of BMS.

A study comparing short and long term outcomes of elderly patients undergoing stenting with those of younger patients reported a higher rate of angiographic restenosis in the elderly (47% vs. 28%, P = 0.0007). This may be due to a higher incidence of ostial lesions, triple vessel disease, calcified

lesions and complex lesions in the them compared to younger patients. [73] These factors make the usage of DES often desirable in the elderly. Repeat procedures and repeat revascularization may also not be desired in the elderly, because of technical challenges due to access issues, vascular tortuosity and because of the desire to avoid resubjecting elderly patients to contrast load or risk of access bleeding.

5.11 PCI IN NON-ST ELEVATION ACUTE CORONARY SYNDROME

Advanced age is considered as an independent risk factor for early morbidity and mortality following non-ST elevation acute coronary syndrome (NSTEACS).[74] The very elderly have more complex coronary artery disease, more comorbidities and are more likely than younger patients to suffer complications after revascularization for NSTEACS.[75] Relatively little data is directly available for outcomes of PCI in the setting of NSTEACS in aged populations (Table 5.2). An analysis of 18,466 patients in the GRACE registry, of whom 16% were octogenarians showed that in-hospital outcomes inclusive of heart failure, recurrent ischemia, major bleeding and death were lower among the very elderly who had revascularization compared to those who had medical management. Furthermore, at the end of six-months death, MI and MACE were significantly lower among those who underwent revascularization compared to medical therapy. Multiple logistic regression analysis confirmed the benefit of revascularization on the primary study endpoint (6-month stroke, death, MI) in the very elderly. [76] Thus it appears clear that for the very elderly with NSTEACS revascularization combined with optimal medical therapy is preferred to optimal medical therapy alone. In the absence of robust randomized clinical data on PCI treatment strategies for the very elderly, observational study results remain valuable in providing insights into the outcomes after PCI. In the Treat angina with Aggrastat and determine Cost of Therapy with an invasive or Conservative Strategy-Thrombolysis in Myocardial infarction 18 (TACTICS-TIMI 18) study, [77] elderly patients (> 75 years) treated with an early invasive approach had a significantly

lower risk of death or MI at 6 months (OR: 0.44, P = 0.02) compared to those who were treated with a consistent message that emerges is that revascularization is better than medical therapy in octogenarians presenting with NSTEACS. A few trials on outcomes of patients with NSTEACS are summarized in Table 5.2.

Table 5.2 Key studies of PCI in the elderly and very elderly with NSTEACS.

Study name	Nature of study	Number of patients	Main results	Study limitations
GRACE Registry [76]	PCI *vs*. medical therapy	Of the 35,512 patients enrolled 15,625 (44%) were older than 70 years.	Favorable in-hospital mortality difference for those between 70-80 years (4.3% *vs*. 6.2%, $P < 0.001$) and > 80 years (7.0% *vs*. 11%, $P = 0.001$) who underwent revascularization. Six-month combined endpoint of death, MI and stroke was reduced in those between 70–80 years (7% *vs*. 13%, $P < 0.0001$) and in those > 80 years (17% *vs*. 25%, $P < 0.0001$) who underwent revascularization.	Non-randomized observational study.

TACTICS TIMI – 18 [77](RCT)	Early invasive *vs*. conservative strategy	Of the 2220 patients analyzed, 962 were 65 years of age or older	Early invasive rather than conservative strategy in the elderly resulted in reduction in the composite incidence of death or non-fatal MI at 30 days (5.7% *vs*. 9.8%; *P* = 0.019) and at 6 months (8.8% *vs*. 13.6%; *P* = 0.018).	Lack of standardization and poor precision of available troponin assays, must be considered before putting these study results into practice.
NEW YORK Registry [82]	Early invasive *vs*. initial conservative strategy	968,542 octogenarians	Primary outcome (in-hospital mortality) was significantly lower in octogenarians who had early invasive treatment (4.7% *vs*. 8.6%, unadjusted OR 0.52; 95%CI: 0.51–0.53).	Retrospective, observational study.

MI: myocardial infarction; NSTEACS: Non-ST elevation acute coronary syndrome; PCI: Percutaneous coronary intervention; RCT: Randomized controlled trial.

5.12 FUTURE DIRECTIONS

In order to guide decision making and ultimately improve PCI outcomes in older patients with CAD, there is a clear need for clinical trials to be conducted that are specifically dedicated to the very elderly population, or as minimum randomized trials need to make a point of enrolling adequate numbers of very elderly patients with less rigid exclusion criteria, to better translate their results to current real-world practice. Possible barriers in achieving this include the perceptions that older patients have an increased risk of harm than benefit from invasive procedures, not to mention

their shorter life expectancy. Secondly, incorporation of functional and symptom outcomes as a measurement of treatment effect (e.g., QOL, independent living scores, angina burden) in addition to hard endpoints such as mortality or re-infarction, should be evaluated. Therapies that provide no significant reduction in mortality can be considered in the very elderly if substantial functional benefit is conferred, and their use can be justified on the basis of patient satisfaction and benefit to wider society, including reduction of costs that result from repeat hospitalizations and long term institutional care. Although, invasive management of chronic stable IHD is associated with increased initial costs of revascularization, this has been shown to be later balanced by reduced medical practitioner charges and less symptom driven late revascularization than in elderly patients whose IHD is managed medically.[78] Similar cost-effectiveness has been demonstrated for invasive PCI management of octogenarians presenting with ACS.[79] Finally, with advancements in PCI techniques and increased adoption of hybrid surgical procedures, it must be remembered that elderly patients are the ideal targets for these minimally invasive strategies, as has become the case for the burgeoning field of percutaneous intervention in structural heart disease, most notably with transcutaneous aortic valve implantation.

5.13 CONCLUSIONS

Key observations regarding the use of PCI in very elderly patients, along with some practical guidelines are provided in Table 5.3. To summarize, we also make the following five take-home messages: (1) the frequency of octogenarians presenting for PCI continues to increase; (2) the transradial approach to PCI, although potentially more challenging in the very elderly, reduces bleeding complications and improves outcomes as compared to the femoral approach;

(3) it is important to tailor antithrombotic therapy in the elderly based on individual risk assessment; (4) new generation DES in octogenarians reduces recurrent ischemic events compared to BMS; and (5) Narrowing the current gaps in our knowledge, along with advancement in technology and pharmacotherapy, will hopefully continue to enable PCI-related outcomes to be improved and the function and independence of elderly patients with symptomatic CHD to be preserved.

Table 5.3 Key points and practical consideration in performing PCI in the very elderly.

General	• PCI in the very elderly is associated with a decrease in cardiac mortality, significant improvement in cardiovascular well-being, HRQOL and angina burden.
	• Elective PCI is a safe and effective treatment modality of stable CAD, when clinically indicated.
	• The predominant causes of death after all types of PCI in the very elderly may now be non-cardiac in nature.
	• Second generation DES compared to BMS reduce the incidence of MI, TVR with no impact on all-cause mortality.
Complications	• Antithrombotic therapy is associated with lower efficacy and higher bleeding rates compared to younger patients.
	• Reductions in peri-procedural bleeding complications may be achieved by greater use of transradial artery access and pre-procedural bleeding risk assessment with validated scoring systems. Attention to weight and creatinine clearance is required where applicable to ensure correct dose adjustment of certain antithrombotics.

	• Withholding of nephrotoxic medications, attention to pre and post-procedural intravenous hydration guided by assessment of LV end-diastolic pressure recording, and judicious use of contrast may help to reduce risk of contrast-induced nephrotoxicity.
Acute coronary syndrome	• Ticagrelor may be a better option than clopidogrel for those with ACS for whom an early invasive strategy is planned, while prasugrel is contraindicated in the very elderly due to higher bleeding risk than clopidogrel.
	• In those presenting with NSTEACS, revascularization combined with optimal medical therapy is preferred to optimal medical therapy alone.
	• In NSTEACS, an early invasive approach is associated with significantly lower risk of death or MI at 6 months compared to those treated with delayed conservative strategy.
	• PPCI compared to thrombolysis, improves outcomes in the very elderly presenting with STEMI, and hence is the reperfusion strategy of choice.
	• Thrombolytic therapy (particularly when given early) remains a viable alternative when PPCI is not available.

ACS: acute coronary syndrome; BMS: bare metal stent; CAD: coronary artery disease; DES: drug eluting stent; LV: left ventricular; MI: myocardial infarction; NSTEACS: non-ST

elevation acute coronary syndrome; PCI: percutaneous coronary intervention; PPCI: primary percutaneous coronary intervention; STEMI: ST elevation myocardial infarction; TVR: target vessel revascularization.

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CHAPTER 6

PROCEDURAL AND CLINICAL OUTCOMES IN MANAGEMENT OF BIFURCATIONAL LESIONS IN ST ELEVATION MYOCARDIAL INFARCTION.

6.1 ABSTRACT

Background: Bifurcation percutaneous coronary intervention (PCI) remains a challenging frontier in interventional cardiology, especially in the setting of ST-elevation myocardial infarction (STEMI). We examined the procedural and clinical outcomes of this patient subset.

Methods: We conducted a retrospective case–control study. Between February 2006 and March 2011, 129 patients with STEMI underwent bifurcation PCI at our institution. 129 control STEMI patients with non-bifurcation PCI were selected from the institutional database, matched for age, gender, culprit vessel, and lesion location. Patients with cardiac arrest, cardiogenic shock, or who required mechanical ventilation were excluded. Twelve-month follow up data were collected by telephone calls and examination of the medical records.

Results: The average age of patients presenting with STEMI was 61.6 ± 13.1in the bifurcation group and 61.5+ 31.1 in the non-bifurcation group. There was no difference in lesion type, use of thrombus aspiration catheters, or glycoprotein inhibitors (GPI) among them. Also, the use of drug eluting stent (DES), total cumulative length of stent used, and diameter of the post-dilation balloon were similar. Final kissing balloon post-dilation was performed in 40.3% of bifurcation PCI cases. The incidence of procedural failure (TIMI 0 flow) was 1.5% vs. 0%; $p = 0.478$. At 12-months follow up, the bifurcation PCI group had higher incidence of target lesion revascularisation (TLR) (10.9% vs. 3.9%, $p = 0.050$), mortality (10.1% vs. 2.3%, $p = 0.020$), and stent thrombosis (9.3% vs. 1.6%; $p = 0.013$); comprising one acute, nine subacute, and two late vs. two subacute stent thrombosis).

Conclusions: During acute STEMI, bifurcation PCI has excellent acute procedural outcomes, but significantly increased incidence of TLR, stent thrombosis and mortality at 12 months.

6.2 INTRODUCTION

Bifurcational coronary artery lesions are not uncommonly encountered in the setting of primary percutaneous coronary artery intervention (PPCI)[1]. Bifurcation lesions alone are associated with a higher risk of complications including in-stent restenosis and stent thrombosis as compared to non-bifurcation lesions[2-5].In the setting of STEMI there are additionally a number of factors including thrombus burden, platelet hyperactivity, potential for undersizing stents and a hypercoagualable milieu which can further lead to an increased risk of complications and adverse events in treating bifurcation lesions. As there are limited published data on the safety and efficacy of management of bifurcation coronary artery lesions in the setting of STEMI, we aimed to assess these issues in this single center retrospective study.

6.3 METHODS

6.3.1 Patient population:

Between the period of February 2006 and March 2011, 1070 patients presented for treatment of STEMI and PPCI at our institute, 129 of whom were identified as having a culprit bifurcation lesion following angiographic assessment by two independent operators. Bifurcation lesions were classified by these two operators as per the Medina classification system, with total agreement achieved for all lesions[6]. STEMI was defined as a clinical syndrome with characteristic symptoms of myocardial ischemia in association with persistent electrocardiographic (ECG) ST elevation and subsequent release of biomarkers of myocardial necrosis[7].The bifurcation group of patients was matched with STEMI patients without bifurcation lesions, for age, gender and lesion location from our institutional database, into which all data concerning patient demographics, lesional characteristics and procedural details

had been prospectively entered. Patients with cardiogenic shock and/or those who required mechanical ventilation on presentation with STEMI were excluded.

6.3.2 Procedures and medications:

All patients were pre-treated with aspirin 300mg and loaded with clopidogrel 300mg or 600mg prior to their interventional procedure. Heparin was administered at a minimum of 70units per kilogram. Post procedure all patients were placed on a maintenance of aspirin 100mg and clopidogrel 75mg for a minimum of 12 months. The type and number of stents deployed, use of complex or simple stenting strategies, use of aspiration catheters, GPI and post dilatation kissing balloon inflation post stent deployment was left to the discretion of individual operators.

6.3.3 Clinical Definitions:

Thrombolysis in Myocardial Infarction (TIMI) flow was assessed as documented previously[8]. Major adverse cardiac events were defined as death, target vessel acute myocardial infarction and target lesion revascularisation (TLR). Stent thrombosis was defined as per the ARC definition[9].

6.3.4 Clinical Follow-up:

Information regarding baseline clinical characteristics, procedural details and in-hospital events was obtained from our electronic Institutional database. Post discharge data, including twelve month clinical outcomes like death, acute myocardial infarction (AMI) and target lesion revascularisation (TLR), were obtained via telephone calls to patients, referring medical

practitioners and analysis of our database. The cause of death was ascertained to be cardiac or non-cardiac, the term AMI was used when there was an evidence of myocardial injury (defined as an elevation of cardiac troponin values with at least one value above the 99th percentile. upper reference limit) with necrosis in a clinical setting consistent with myocardial ischaemia.TLR was defined as either repeat percutaneous or surgical revascularization for a lesion anywhere within the stent or the 5-mm borders proximal or distal to the stent

6.3.5 Statistical Analysis:

Data were analyzed retrospectively. Continuous variables are presented as mean ± SD and categorical variables as n-value with percentage frequency. Analysis of categorical variables was performed using the Chi-square test, while comparisons of continuous variables involved parametric or non-parametric T-tests depending on normality of data distribution.

6.4 RESULTS

6.4.1 Baseline Characteristics

Between February 2006 and March 2011, 1070 patients presenting with STEMI underwent PPCI, of whom 129 patients (12%) were classified as having culprit bifurcation lesions. These were retrospectively matched with 129 non-bifurcation STEMI patients for age, gender and lesion location from our Institutional database. Table 6.1 summarizes the baseline demographic data for both groups, showing that the majority of patients were male (79%), of mean age 61 years, with the most prevalent documented cardiovascular risk factors being hypertension, hyperlipidaemia, current or ex-cigarette smoking and diabetes mellitus.

6.4.2 Lesion and Procedural Characteristics

The commonest location for culprit lesions in both groups was the left anterior descending (LAD) and diagonal artery system, with the vast majority of lesions fulfilling Type B2 or Type C criteria (93.0% in the bifurcation group and 86.8% in the non-bifurcation cohort, p=0.148) (Table 6.2). In bifurcation cases, the most common Medina classification was 1,1,1 (65.9%) followed by Medina 0,1,1 (12.4%) (Table 6.2).

Table 6.1 Patient Characteristics of Bifurcation and non-Bifurcation STEMI patients.

Values are presented as *n* (%) or mean ± standard deviation.

	BIFURCATION N = 129	**NON-BIFURCATION N = 129**	**P-value**
Male	102 (79%)	102 (79%)	1.000
Female	27 (21%)	27 (21%)	1.000
Age	61.6 ± 13.1	61.5 ± 13.1	0.941
Diabetes	22 (17.1%)	17 (13.2%)	0.486
Hypertension	58 (45.0%)	53 (41.1%)	0.582
Hyperlipidemia	40 (31.0%)	46 (35.7%)	0.509
Smoking– Current	42 (32.6%)	51 (39.5%)	0.300
Smoking–Ex	23 (17.8%)	16 (12.4%)	0.297
Non-Smoker	64 (49.6%)	62 (48.1%)	0.901
Family History IHD	31 (24.0%)	28 (21.7%)	0.767

Table 6.2 Lesion Location and Characteristics in Bifurcation and non-Bifurcation

CHARACTERISTICS	BIFURCATION	NON-BIFURCATION	p-value
Lesion Location			
LMS	2 (1.5%)	2 (1.5%)	1.000
LAD/D	81 (62.8%)	82(63.6%)	0.897
LCx/OM	28 (21.7%)	27 (20.9%)	0.879
RCA/PLV/PDA	16 (12.4%)	16 (12.4%)	1.000
Ramus IM	1 (0-8%)	1 (0-8%)	1.000
SVG	1 (0-8%)	1 (0-8%)	1.000
Lesion Type			
Type A	0 (0%)	1 (0.8%)	0.316
Type B1	8 (6.2%)	15 (11.6%)	0.189
Type B2	61 (47.3%)	51 (39.5%)	0.254
Type C	59 (45.7%)	61 (47.3%)	0.901
Type B2 or C	120 (93.0%)	112 (86.8%)	0.148
Diffuse	1 (0-8%)	1 (0-8%)	1.000
Medina Classification			
Medina 1,0,0	9 (7.0%)	N/A	-
Medina 0,1,0	7 (5.4%)	N/A	-
Medina 0,0,1	1 (0.8%)	N/A	-
Medina 1,1,1	85 (65.9%)	N/A	-

Medina 0,1,1	16 (12.4%)	N/A	-
Medina 1,0,1	7 (5.4%)	N/A	-
Medina 1,1,0	4 (3.1%)	N/A	-

Values are presented as *n* (%) or %.

Two wires (wiring both the main vessel and side branch) were used in 79.1% of bifurcation PPCI cases (Table 6.3). Drug eluting stents (DES) were deployed in 47.3% of cases in the bifurcation group, compared to 38.8% in non-bifurcation cases (P=0.209), with first generation DES in 24.8% vs 14.8% (p=0.113) and second generation DES in 22.5% vs 24.0% (p=0.883). In bifurcation lesions, an average of 1.3 $\pm$ 0.7 stents was deployed, with average stent diameter of 3.0 $\pm$ 0.5 and stent length of 20.1 $\pm$ 6.3, with none of these parameters showing statistical difference compared to the matched non-bifurcation group. Overall use of aspiration thrombectomy and/or intravenous GPI was relatively modest and comparable in both groups (Table 6.3). A two-stent (main vessel and side branch) PCI strategy was undertaken in only 11.0% of the bifurcational cases, with most cases involving a single-stent, provisional approach (Table 6.3). Kissing balloon dilatations after stent deployment were performed in 40.3% of bifurcation PPCI. One important difference between the two cohorts related to fluoroscopic dose, which was significantly prolonged for bifurcation lesions (1343.7$\pm$ 547.7mGy vs 1218.1$\pm$450.1mGy, p= 0.045). TIMI 3 flow post PPCI procedure was similar in both groups at 91.5% with 1.5% of cases in the bifurcation group having TIMI 0 flow (Table 6.3). The access site was radial in 16.3% of bifurcation cases vs 15.5% of non-bifurcation cases (p=0.865), and the LV systolic function assessed post PPCI was impaired in 38.8% vs 48.1% (p=0.167) of cases.

Table 6.3 Procedural Characteristics in Bifurcation and non-Bifurcation STEMI patients

Procedure Details	**Bifurcation**	**Non- Bifurcation**	**p-value**
Type of Stent DES (First Gen)	32 (24.8%)	19 (14.8%)	0.113
DES (Second Gen)	29 (22.5%)	31 (24.0%)	0.883
DES (All)	61 (47.3%)	50 (38.8%)	0.209
BMS	68 (52.7%)	79 (61.2%)	0.209
Average number of stents	1.3 ± 0.7	1.2 ± 0.4	0.160
Average diameter of stent	3.0 ± 0.5	3.0 ± 0.5	1.000
Average length of stent	20.1 ± 6.3	19.5 ± 5.7	0.423
Average diameter of post dialatation balloon	3.2 + 0.5	3.3 + 0.5	0.110
Two wires (MV and SB)	102 (79.1%)		
Single Wire	27 (20.9%)		
2 stent strategy	14 (11.0%)		
1 stent strategy	115 (89.0%)		
Kissing Balloon	52 (40.3%)	-	-
Aspiration Catheter	28 (21.7%)	35 (37.2%)	0.385
GP2B3A use	43 (33.3%)	35 (37.2%)	0.343
Radiation dose (mGy)	1343.7 ± 547.7	1218.1 ± 450.1	0.045
TIMI 0 (Post PPCI)	2 (1.5%)	0 (0%)	0.479
TIMI 3 (Post PPCI)	118 (91.5%)	118 (91.5%)	1.000
Radial access	21 (16.3%)	20 (15.5%)	0.865

Femoral access	108 (83.7%)	109 (84.5%)	0.865

Values are presented as *n* (%) or mean ± standard deviation.

6.4.3 Clinical Outcomes

The outcomes of patients with and without bifurcation lesions were similar during the hospital stay, with target lesion revascularisation in 4.7% vs 0.8% (p=0.125) and death in 5.4% vs 0.8% (p=0.073). However, at 12 month follow up there was a greater MACE rate in the bifurcation group 19% vs 7% (p=0.003), primarily due to TLR (10.9% vs 3.9%; p=0.050) and death (10.1% vs 2.3%; p=0.020) (Table 6.4). In the bifurcation group, 85.7% of the TLR was to the main vessel and 14.3% was to the side branch. There was no difference in the rate of recurrent AMI.

Table 6.4 MACE (Target lesion revascularisation, AMI and Mortality)

MACE OUTCOME	Bifurcation	Non- Bifurcation	p-value
12 month MACE	27 (20.9%)	8 (6.2%)	0.001
12 month TLR	14 (10.9%)	5 (3.9%)	0.050
12 month Mortality	13 (10.1%)	3 (2.3%)	0.020
12 month AMI	7 (5.4%)	4 (3.1%)	0.538

Values are presented as *n* (%) or %.

The frequency of stent thrombosis was substantially higher in the bifurcation group 9.3% vs 0.1.6%; (p=0.013), with most cases being subacute (between 24 hours to 30 days) (Table 6.5). Among patients with stent thrombosis in the bifurcation group 33.3% had received a DES (Of

these four patients, two had received a first generation and two a second-generation DES) and 66.7% (eight patients) had a BMS.

Table 6.5 Stent Thrombosis in Bifurcation and non-Bifurcation STEMI patients

	BIFURCATION	**NON-BIFURCATION**	**P-Value**
Total Stent Thrombosis	12 (9.3%)	**2 (1.6%)**	**0.013**
Acute Stent Thrombosis	1 (0.8%)	0	0.316
Sub-Acute Stent Thrombosis	9 (7.0%)	2 (1.6%)	0.065
Late Stent Thrombosis	2 (1.6%)	0	0.478

Values are presented as *n* (%) or %.

Mortality was significantly higher in bifurcation group 10.1% vs 2.3% (p=0.020). Of the 13 deaths in the bifurcation group, seven were cardiac in origin (two patients had sub-acute stent thrombosis, and the rest had heart failure), two patients had a respiratory cause and in the remaining four the referring GP could not ascertain the cause of death. Of the three deaths in non-bifurcation group, two were cardiac and in one the cause could not be ascertained by the referring GP. Bifurcation stenting was the only univariate and multivariate predictor of MACE (p=0.001) (Table 6.6).

Table 6.6 Multivariate Analysis Including Variables <0.2 In Univariate Analysis

Variables in the Equation

	B	S.E.	Wald	df	Sig.	Exp(B)
Bifurcation(1)	1.520	.437	12.112	1	.001	4.571
Approach(1)	1.320	.766	2.968	1	.085	3.743

Post dilation (1)	.836	.448	3.476	1	.062	2.307
Length of Stay	-.032	.032	1.016	1	.314	.968
Constant	-3.539	1.078	10.773	1	.001	.029

Variable(s): Bifurcation, Approach, POSTDILATION, LENGTHOFSTENT.

MACE – Univariate Analysis (supplemental Data)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	Bifurcation(1)	1.387	.424	10.685	1	.001	4.004
	Constant	-2.716	.365	55.368	1	.000	.066

a. Variable(s) entered on step 1: Bifurcation.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	Aspiration Catheter (1)	.294	.450	.426	1	.514	1.341
	Constant	-2.079	.401	26.905	1	.000	.125

a. Variable(s) entered on step 1: ASPIRATIONCATHETER.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	Hypercholesterolaemia(1)	.063	.367	.029	1	.865	1.065
	Constant	-1.887	.277	46.387	1	.000	.152

a. Variable(s) entered on step 1: Hypercholesterolaemia.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	DM(1)	-.712	.373	3.632	1	.057	.491
	Constant	-1.386	.289	23.062	1	.000	.250

a. Variable(s) entered on step 1: DM.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	FamilyHistory(1)	.483	.474	1.036	1	.309	1.621
	Constant	-2.234	.430	27.037	1	.000	.107

a. Variable(s) entered on step 1: FamilyHistory.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	Aspirin (1)	-.431	.442	.953	1	.329	.650
	Constant	-1.504	.391	14.807	1	.000	.222

a. Variable(s) entered on step 1: ASPIRIN.

Variables in the Equation

	B	S.E.	Wald	df	Sig.	Exp(B)

Step 1[a]	ACEI(1)	.468	1.065	.193	1	.661	1.596
	Constant	-2.303	1.049	4.820	1	.028	.100

a. Variable(s) entered on step 1: ACEI.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	BetaBlocker(1)	.358	1.070	.112	1	.738	1.430
	Constant	-2.197	1.054	4.345	1	.037	.111

a. Variable(s) entered on step 1: BetaBlocker.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	Statin (1)	-.582	.539	1.164	1	.281	.559
	Constant	-1.335	.503	7.055	1	.008	.263

a. Variable(s) entered on step 1: STATIN.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	GP2b3ai1hibitor(1)	.092	.401	.053	1	.818	1.097
	Constant	-1.917	.339	32.035	1	.000	.147

a. Variable(s) entered on step 1: GP2b3ai1hibitor.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	ATII(1)	19.360	28420.696	.000	1	.999	2.558E8
	Constant	-21.203	28420.696	.000	1	.999	.000

a. Variable(s) entered on step 1: ATII.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	Lesion type			.255	4	.993	
	Lesion type (1)	.000	40193.849	.000	1	1.000	1.000
	Lesion type (2)	19.593	28421.965	.000	1	.999	3.231E8
	Lesion type (3)	19.365	28421.965	.000	1	.999	2.570E8
	Lesion type (4)	19.312	28421.965	.000	1	.999	2.439E8
	Constant	-21.203	28421.965	.000	1	.999	.000

a. Variable(s) entered on step 1: LESIONTYPE.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	Thrombus(1)	.106	.392	.073	1	.787	1.112
	Constant	-1.939	.239	65.718	1	.000	.144

a. Variable(s) entered on step 1: Thrombus.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	Approach(1)	1.252	.749	2.792	1	.095	3.497
	Constant	-2.970	.725	16.786	1	.000	.051

a. Variable(s) entered on step 1: Approach.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	Post dilation (1)	.604	.413	2.142	1	.143	1.830
	Constant	-1.991	.213	87.157	1	.000	.137

a. Variable(s) entered on step 1: POSTDILATION.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	Post dilation (1)	.604	.413	2.142	1	.143	1.830
	Constant	-1.991	.213	87.157	1	.000	.137
		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	TIMIFlowPrePCI			1.878	3	.598	
	TIMIFlowPrePCI(1)	-.262	.479	.300	1	.584	.769
	TIMIFlowPrePCI(2)	-.056	.584	.009	1	.924	.946
	TIMIFlowPrePCI(3)	-1.435	1.104	1.689	1	.194	.238
	Constant	-1.609	.414	15.110	1	.000	.200

a. Variable(s) entered on step 1: TIMIFlowPrePCI.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	Number of stent			1.684	4	.794	
	Number of stent (1)	19.359	40192.357	.000	1	1.000	2.556E8
	Number of stent (2)	19.331	40192.357	.000	1	1.000	2.485E8
	Number of stent (3)	.000	44028.633	.000	1	1.000	1.000
	Number of stent (4)	21.203	40192.357	.000	1	1.000	1.615E9
	Constant	-21.203	40192.357	.000	1	1.000	.000

a. Variable(s) entered on step 1: NMBEROFSTENT.

6.5. DISCUSSION

This retrospective study has shown that bifurcational PPCI is associated with excellent acute procedural success as evidenced by similar TIMI 3 flow post PCI, rate of in-hospital stent thrombosis, TLR and mortality compared to non bifurcational group. However, at the end of 12 months follow up bifurcational PPCI was an independent predictor of stent thrombosis, TLR and mortality. Dariusz Dudek et al[10], in their analysis of the impact of bifurcational PPCI on clinical outcomes noted that there was no difference between the groups in the rate of death, stent thrombosis and target vessel revasculatisation during three-year follow-up, which may in part be related to the protocol-required exclusion of patients who, required a two-stent strategy for treatment of bifurcation lesions. Abdel-Hakim et al[1] reported the outcomes of 646 patients undergoing PPCI. Bifurcation lesion was found in 23% and provisional T-stenting was used in

89% of cases. In their analysis, in-hospital and 1-year total MACE rates was comparable in bifurcation and non-bifurcation groups. Unlike in other studies, in our analysis, mortality was greater in the bifurcation group, with higher number of cardiac than non-cardiac deaths. Though the exact reason for this remain unclear, it could in part be due to the varied bifurcational strategies deployed to treat these lesions.

The complexity of management of true bifurcations in STEMI is highlighted by our findings that all cases of stent thrombosis occurred in this cohort of patients, who also had a greater need for TLR within the first twelve months after PPCI. The need to improve the rates of such adverse outcomes following bifurcation PPCI prompts consideration that there should be greater use of intravascular ultrasound scanning (IVUS) to guide stenting of these lesions. In our study, none of the patients in either group had undergone IVUS. In non-bifurcation PPCI the use of IVUS has not been found to lead to improved clinical outcome nor improve stent thrombosis[11,12]. In elective bifurcation cases, there has been conflicting evidence published on the utility of IVUS in improving MACE with a number of published registries showing a benefit in decreasing TLR[13, 14]. There are no studies however which have assessed the utility of the use of IVUS or other intravascular imaging in the management of bifurcation lesions in STEMI. It may prove beneficial in the management of the true bifurcation subset of patients where a significant territory of myocardium is at risk.

DES has shown to reduce TLR and stent thrombosis compared with BMS with conflicting data on improved mortality[15]. Although collection of our study cohorts coincided with the post-DES era, we surprisingly found that use of DES was less common than BMS in both the bifurcation and non-bifurcation PCI groups. We suspect that this may be because our institution's use of DES was previously tempered by the early studies that suggested an increased risk of stent

thrombosis and in particular late stent thrombosis when first-generation DES were used in STEMI cases post 2006[16]. Additionally, our use of DES in STEMI situations may have been compromised by an uncertainty of possible impending surgical procedures or the possibility of increased bleeding risk accompanying prolonged dual antiplatelet therapy usage in this subset of patients. 52.3% of patients in our study were treated with BMS. Similarly, in the study byAbdel Hakim et al[1], BMS was used in all patients with bifurcation lesions who required stenting and also, in the assessment of impact of bifurcation lesions inPPCI by Frangos et al[17]from Montreal, BMS was implanted in 94.3% of patients.

The presence of thrombus potentially leading to pseudolesions may prompt the greater use of gpII/IIIa inhibitors (GPI) and aspiration thrombectomy, which have both been shown in some but not all studies to improve MACE after STEMI[18-21]. In our study, treatment with intravenous GPI and/or aspiration thrombectomy occurred in approximately one third of cases, which is significantly less than in other studies of PPCI for STEMI[1,17]. We cannot rule out that a higher frequency of usage of GPI and thrombus aspiration will not have led to improved MACE outcomes in our cohort of bifurcation PPCI.

Furthermore, none of our patients received bivalirudin, whose usage in the PPCI setting has come under recent controversy. In the HORIZONS-AMI trial[10], bivalirudin compared with heparin plus GPI showed a bleeding reduction, mortality reduction and an increase in acute stent thrombosis. When bivalirudin was started in the ambulance and followed with a prolonged infusion, in the EUROMAX trial[22], it showed a bleeding reduction and excess acute stent thrombosis compared to heparin alone with or without GPI. In the HEAT-PPCI trial[23] from Liverpool, where 2000 patients were studied, a reduction in MACE was found in favour

of heparin alone compared with bivalirudin alone with no reduction in bleeding with bivalirudin. However, in the Italian MATRIX trial,[24] with 7000 patients comparing bivalirudin vs heparin with or without GPI, there was a reduction in bleeding and a 30% reduction in mortality for bivalirudin.

In the subgroup of STEMI patients in the RIVAL trial[25] as well as in the MORTAL trial[26] and the RIFLE-STEAC trial[27], there was a significant reduction in mortality with the radial approach as opposed to the femoral approach. It may have been related to a decrease in access site and bleeding complications, more liberal use of antithrombotic agents associated with the radial approach. In the subset of STEMI patients treated with PPCI, in PLATO study[28], treatment with ticagrelor versus clopidogrel reduced the occurrence of definite stent thrombosis. Similarly in patients undergoing PPCI, prasugrel was more effective than clopidogrel for prevention of ischaemic events, without an apparent excess in bleeding[29]. Thus, the increased usage of radial artery access and newer antiplatelet agents such as Ticagelor and Prasugrel may also result in improved mortality and stent thrombosis outcomes after bifurcation PPCI.

There has been considerable debate as two whether both the main vessel and side branch should be stented in bifurcation lesions. The current consensus is that the provisional stenting strategy should be favoured in bifurcation lesions. A majority of side branch lesions although appearing angiographically significant are not physiologically significant[30,31]. In STEMI, the presence of thrombus and its potential to “snow plough” into adjacent branchespost predilatation may potentially amplify the severity of lesions (in the main vessel or side branch) which may in fact be pseudolesions further favouring that only the culprit vessel be stented. Studies have favoured

the provisional stenting strategy in the treatment of bifurcation lesions and in the STEMI situation with the potential for thrombus induced as well as platelet hyperactivity state, this should be the default strategy [32-34]. In our study this was the case, with only 11% of cases having complex stenting, despite 71% of cases having both vessels wired. The use of kissing balloon dilatation post stenting is additionally debatable. In a randomised comparison of final kissing balloon dilatation (FKBD) versus no final kissing balloon dilatation (NFKD) in coronary bifurcation lesions, it was noted that FKBD was associated with reduced angiographic side branch restenosis, compared to NFKBD group[35]. Approximately 39% of bifurcation stenting in our study was completed by kissing balloon post dilatation which appeared to reflect a concern that the side branch was potentially compromised and jeopardising a not insignificant territory of myocardium.

6.6 LIMITATIONS

Our study has limitations inherent to a retrospective single center study, with a relatively small sample size. In particular, in order to achieve the patient numbers analyzed here, we used a relatively broad time period of patient collection from 2006 to 2011. Coronary interventional practice has undergone substantial changes over the past decade, many of which occurred during this interval, notably the increased use of radial artery access, second generation DES, reconsiderations in the use of gp2b/3a inhibitors, aspiration thrombectomy and greater usage of ticagrelor and prasugrel. Paradigms concerning broad bifurcational PCI practice and mechanisms and prevention of in-stent restenosis and thrombosis have also undergone change. Thus our own institutional policies for PPCI would also have undergone considerable transition during the time period of this study, probably resulting in some heterogeneity of procedural

practice. Nevertheless, this does reflect real world practice and our results concerning the inferior clinical outcomes following bifurcational PPCI highlight the challenges in managing this more complex cohort of patients and call for greater attention to be given to strategies to improve their prognosis, such as the use of IVUS-guidance.

6.7 CONCLUSION

In conclusion, the management of bifurcational cases in PPCI was found to have excellent procedural outcomes however there was a greater incidence of TLR, stent thrombosis and mortality at 12 months. These findings highlight the difficulties in the management of this challenging anatomic subset.

6.8 REFERENCES:

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CHAPTER 7

CONCLUSIONS AND FUTURE DIRECTIONS

While complex lesions, and complex patients may be encountered not infrequently in clinical practice, limited data was previously available regarding the safety and efficacy of percutaneous coronary intervention in this subset. The results of this thesis have advanced the understanding of the complex percutaneous coronary intervention on four main fronts.

Firstly, the results presented demonstrate that there was a low frequency of percutaneous coronary intervention for chronic total occlusion, despite the evidence from existing literature that a significant proportion of patients with these complex lesions are left unrevascularized. By conducting an analysis that included all patients undergoing recanalization of chronically occluded arteries, the results reflect a 'modest real world' success rates. Moreover, the results suggest that there was limited adoption of novel technology and techniques that have helped to improve the historically stagnant success rates in the western world. It emphasizes the need for Australian centers to adopt a systematic and specialized approach to chronic total occlusion-percutaneous intervention to meet with international guidelines.

Secondly, the results presented show that almost all patients with ectatic infarct related arteries have a large thrombus burden and nearly half of them could not be treated with stents. Though there was a greater usage of post-procedural anticoagulation, glycoprotein IIb/IIIa inhibitors to treat them, there was no difference in major bleeding in comparison with those whose culprit arteries were non-ectatic. Patients with ectatic infarct related arteries had similar in-hospital but poor long-term outcomes on comparison with those without ectatic infarct related arteries. Patients with ectatic infarct related arteries who could be stented had better in-hospital but similar long term outcomes than those who could not be treated with stents.

Thirdly, a “real world” analysis of octogenarians presenting for non-emergency percutaneous coronary intervention highlighted that the bleeding outcomes and in-hospital outcomes were comparable with those aged less than sixty years. The results indicate that this cohort of patients could be treated effectively with acceptable procedural success and adverse outcomes.

Fourthly, the results presented illustrate that during acute ST elevation myocardial infarction, bifurcation percutaneous coronary intervention has good acute procedural outcomes, but an increased incidence of target lesion revascularisation, stent thrombosis and mortality at 1 year. This could be mitigated by increased adaption of radial approach, usage of intra vascular ultrasound to optimise outcomes, and newer antiplatelets like ticagrelor or prasugrel.

Fifth, a review outlining the advances in percutaneous coronary intervention for chronic total occlusion discusses the newer devices available and the newer strategies which have evolved to treat chronic total occlusions. Adoption of this, wherever appropriate would help to improve the success rates of recanalization of these complex lesions.

Finally, an overview of percutaneous coronary intervention in the very elderly emphasizes the role of interventional management of octogenarians presenting with chronic stable angina and acute coronary syndromes. In addition, it evaluates the anti-thrombotic therapy to assist these procedures.

Overall, the results of this thesis have demonstrated that complex coronary intervention can be performed with acceptable procedural and adverse outcomes. Amongst the evolving technical advances in improving the outcomes of these procedures, we will undoubtedly continue to see,

this body of research has helped to define the clinical efficacy and appropriate clinical role of complex coronary intervention in contemporary clinical practice.

APPENDIX

INTRAVASCULAR ULTRASOUND – GUIDED MANAGEMENT OF LARGE THROMBUS BURDEN IN AN ANEURYSMAL CORONARY ARTERY IN A YOUNG MALE.

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ABSTRACT

Management of acute thrombotic occlusion of coronary artery aneurysms is challenging with a lack of randomized trial evidence. We report an unusual case of a 30-year-old Indian Australian male who presented with an extensive anterior STEMI because of very large thrombus burden in a dilated proximal left anterior descending artery. A relatively conservative treatment approach comprising emergency aspiration thrombectomy and ongoing infusion of glycoprotein IIb/IIIa inhibitor, guided by surveillant inpatient angiography and intravascular ultrasound, helped achieve a satisfactory outcome in a complex setting in which percutaneous coronary angioplasty and stenting were not desirable.

INTRODUCTION

Cardiovascular disease is the leading cause of death in India, resulting in premature death, disability, and significant economic burden [1]. Coronary heart disease is likely to account for at least one third of total deaths by the year 2015 and is expected to replace infectious disease as the number one cause of mortality in Indians [2]. About 37% of Indians presenting with acute coronary syndrome present with ST Elevation Myocardial Infarction (STEMI) [3]. Early reperfusion has been proven to save lives of patients presenting with STEMI [4]. Nearly 30% of patients presenting with STEMI have large thrombus burden [5].

Coronary artery aneurysms are defined as localized dilatations that exceed 1.5 times the diameter of the adjacent "normal" segment of artery. While the majority of aneurysms are atherosclerotic in origin, other causes include connective tissue disorders, vasculitis, mycotic infection, trauma, congenital, and idiopathic. Although coronary aneurysms often remain

silent, they can lead to angina because of impaired coronary flow, STEMI resulting from thrombus formation or embolization, sudden rupture or congestive cardiac failure, because of formation of coronary fistulas [6]. Despite the fact that 30–50% of cases of coronary aneurysm that present to medical attention do so with STEMI [6], there remains a paucity of evidence from randomized controlled trials regarding best practice management in these patients. We present the case of a young migrant Indian male presenting at a tertiary Australian hospital with an acute anterior STEMI caused by very large thrombus burden in an aneurysmal left anterior descending artery (LAD), in whom we adopted a management strategy guided by intravascular ultrasound (IVUS).

CASE REPORT

30-year-old Indian male presented to the Emergency Department within 50 minutes of the onset of his first ever episode of ischemic chest pain, brought on during jogging. His only known cardiovascular risk factor was that of a positive family history. His electrocardiogram (ECG) showed 2–3 mm ST segment elevation in all anterior leads leading to a diagnosis of acute anterior STEMI. He was loaded with aspirin 325 mg and prasugrel 60 mg and was immediately taken to the cardiac catheterization laboratory. Coronary angiography was performed from 7F right femoral arterial access, revealing complete occlusion in the very large calibre proximal segment of his LAD artery, with the impression of substantial thrombus burden (Fig.A-1A). The patient was heparinized (100 U/kg) and a 7F EBU 3.5 guiding catheter (Medtronic), was used to engage the left main coronary artery. The LAD occlusion site was easily crossed with a 0.014″ Balance Middle Weight universal wire (Abbott Vascular), resulting in TIMI 1 flow. On the basis of the large thrombus burden, a 7F Export catheter (Medtronic) was used to initiate manual aspiration thrombectomy and tirofiban was administered as an intravenous bolus, followed by

commencement of an infusion. Initially nine passes with the Export catheter were performed across the occlusion site and large amounts of red clot were retrieved. However, there was only slight improvement in angiographic thrombus appearance and coronary flow grade from TIMI 1 to 2 (Fig. A-1B) without change to the patient's pain score or ST segment elevation.

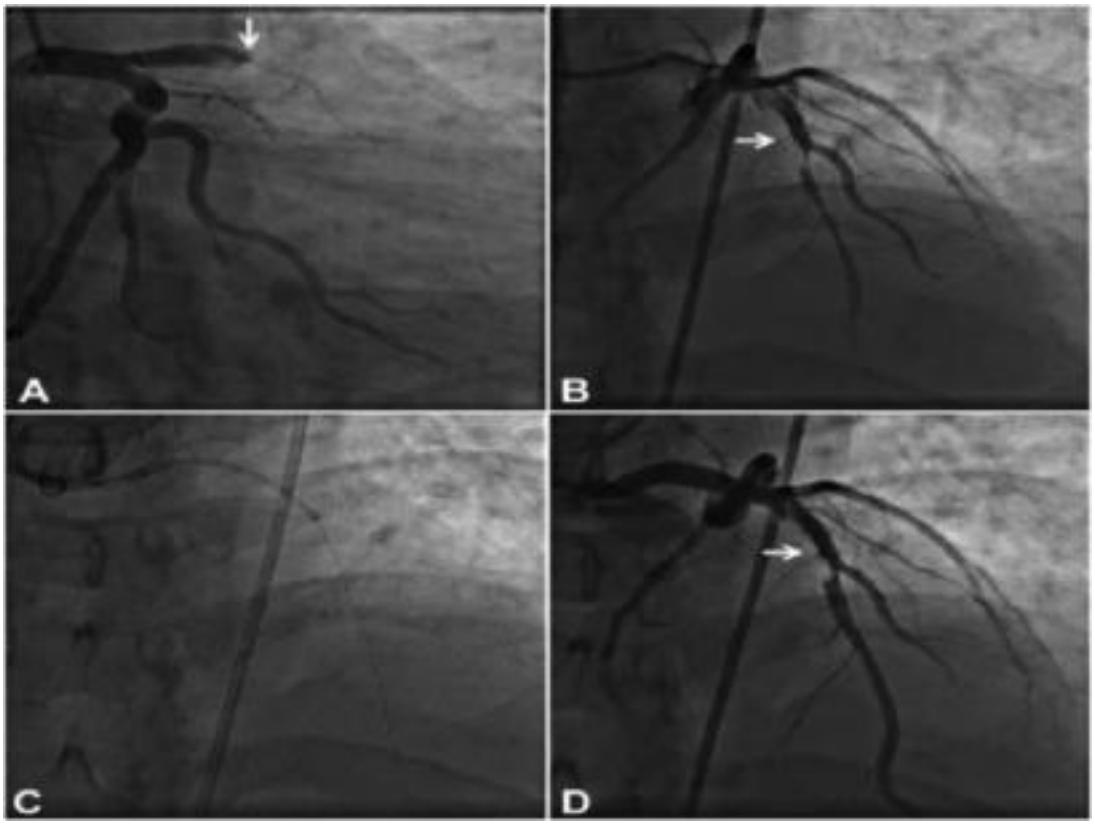

Figure A- 1. (A) Initial RAO caudal projection showing occlusion of proximal LAD (arrow). (B) AP cranial projection showing thrombus burden (arrow) in proximal LAD immediately after aspiration thrombectomy with Export catheter. (C) Introduction of STO1 daughter catheter to perform further aspiration of occlusion site. (D) Subsequent angiographic

appearance of LAD, showing residual thrombus (arrow) and stenosis but TIMI 3 flow after extensive aspiration.

In order to try to facilitate greater thrombus extraction, a 5F 120 cm STO 1 (child) catheter (Terumo, Tokyo, Japan) was advanced through the 7F guiding catheter (Figure A-1C) to the site of maximal thrombus and further blood and thrombus were aspirated. This resulted in restoration of TIMI 3 flow throughout the LAD without significant distal embolization and TIMI perfusion grade 2–3. Door to TIMI 3 time was 1 hour 54 minutes. By this stage, there was an improvement in the patient's pain score but only <30% resolution of the ST segments. There remained considerable residual thrombus, leaving 40–50% residual stenosis in the proximal LAD and 80–90% stenosis at the bifurcation of the LAD and first diagonal branch (Fig.A-1D). On account of this thrombus burden, as well as the very large dimension of the proximal LAD (estimated angiographic luminal dimension of 6.2 mm by QCA), a decision was made to continue IV tirofiban for the next 48 hours and defer angioplasty and stenting. Left ventriculography revealed marked anterior and apical severe hypokinesis. The groin was closed with an 8F Angioseal.

Over the next 48 hours, the patient remained pain-free, the ECG showed further partial resolution (30–50%) of the ST segments, with peak creatine kinase level of 4,826 U/L. Echocardiogram on day 2 revealed severe hypokinesis of the entire apex, mid septal, inferior and anterior segments with an estimated left ventricular ejection fraction (EF) of 40%. The patient returned for repeat coronary angiography after 48 hours, which showed that the LAD had maintained TIMI 3 flow, with marginal regression of thrombus size and residual stenosis of 75% at the origin of the diagonal branch (Fig.A-2A). At this point, an IVUS study was performed using a 40 MHz Atlantis SR Pro catheter probe (Boston Scientific, Santa Clara, CA) to assess the mechanism of acute thrombus

formation and document luminal dimensions to guide management further. IVUS demonstrated eccentric mild atheroma plaque (Fig.A-3A and B) beginning proximal to the adherent thrombus (Fig. 3C) in the proximal LAD. The large calibre of the proximal LAD corresponded to a region of positive remodeling with the presence of eccentric plaque, while the ostium of the LAD, which angiographically appeared narrower, was in fact normal vessel without plaque. There was good lumen preservation in the thrombotic region of the proximal LAD measuring approximately 16 mm^2, whilst the LAD adjacent to the diagonal ostium had a lumen area of just over 12 mm^2. Minimal vessel diameter in the proximal LAD at the site of the lesion was 6.80 mm, compared to 4.04 mm proximal to the lesion and 3.67 mm distal to the lesion. Thrombus could be appreciated for a length of 15 mm. Plaque burden was only 24% and total lesion length 32 mm. IVUS therefore clarified that the underlying pathology was that of a true aneurysm, associated with a long segment of mild atheroma and large thrombus burden with adequate preservation of luminal area to allow coronary flow. We therefore decided against angioplasty and stenting, given the issues of correct stent sizing and risk of causing distal embolization.

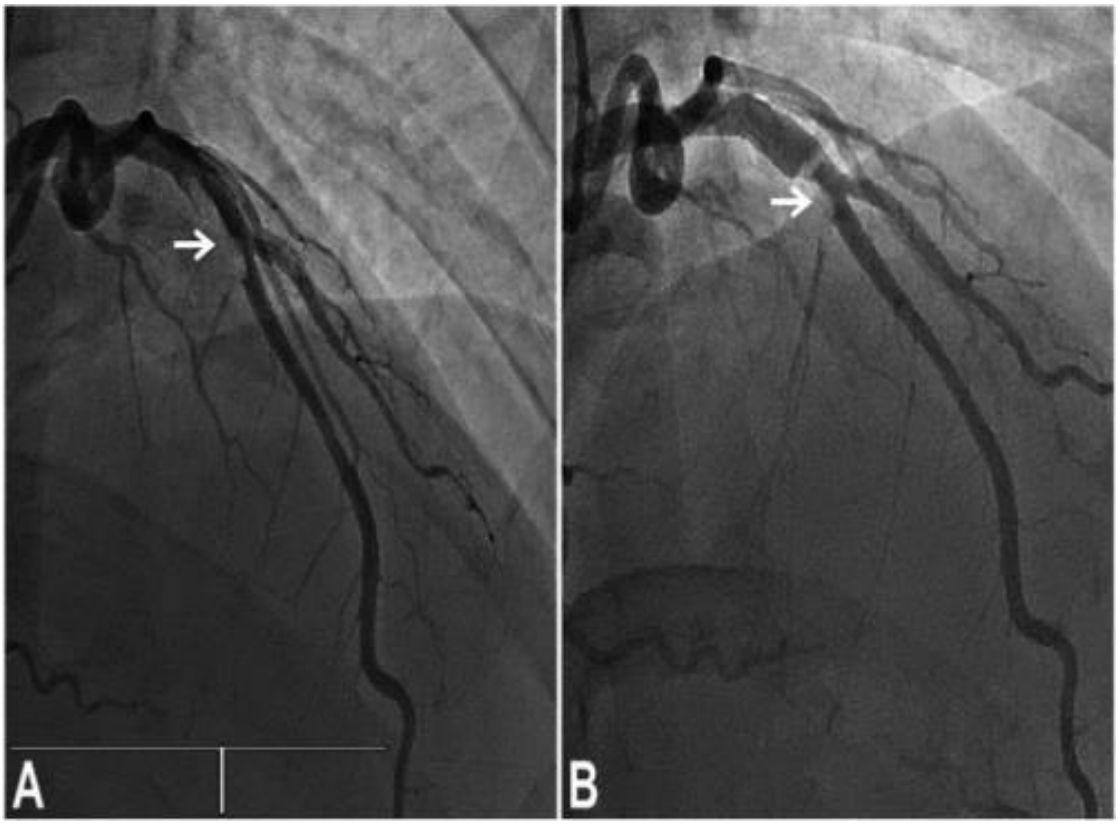

Figure A-2. Angiographic appearances in RAO cranial projections at (A) day 2 and (B) day 4 of admission, after continuation of intravenous tirofiban. Arrows denote diminishing residual thrombus burden.

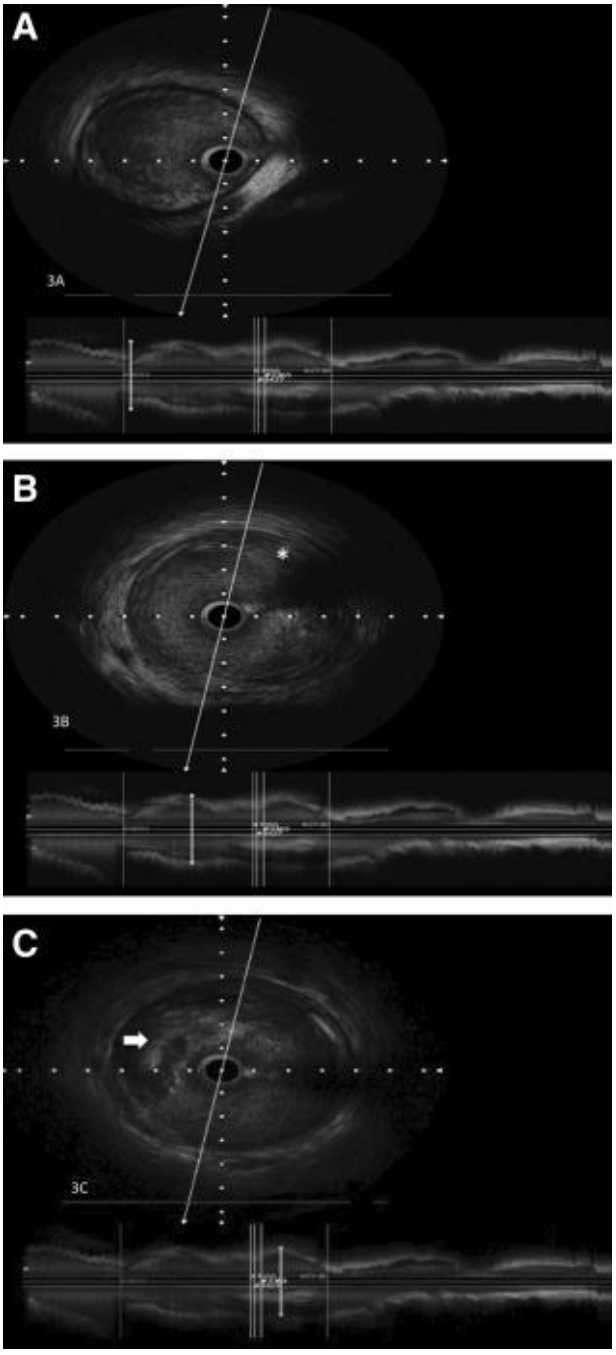

Figure A-3. (A) Intravascular ultrasound (IVUS) image of the proximal LAD. (B) IVUS image showing the eccentric plaque with 25% plaque burden seen proximal to the thrombus burden, which is suspected to be the culprit lesion. Asterix * in the image indicates the eccentric plaque.

(C) IVUS image showing the aneurysmal vessel with thrombus in the proximal LAD (Arrow ⟶ in the image indicates the thrombus).

The patient remained well over the next 48 hours and underwent a third coronary angiogram on day 4 of his admission, which showed considerable dissolution of thrombus in the proximal LAD, with a much-reduced filling defect just proximal to the origin of the diagonal branch, leaving a residual angiographic stenosis of 50% (Fig. A-2B). By this time, he had developed abdominal pain which was evaluated by CT abdomen with the finding of a small retroperitoneal hematoma that resolved with conservative management including cessation of tirofiban. The patient was discharged on day 7 on aspirin, newly commenced coumadin, a beta-blocker, ACE inhibitor and statin. Repeat echocardiography just prior to discharge demonstrated severe apical hypokinesis extending to the mid septum and mid anterior wall with improvement in EF to 45%. He remains well six months later.

DISCUSSION

Thrombus burden predicts increased distal embolization and peri-procedural complications following primary percutaneous coronary intervention (PPCI). Large thrombus burden at the time of STEMI is associated with higher rates of acute failure (8.2%) and higher cardiac major adverse events (MACE) at two years [7]. The management of large thrombi causing STEMI in patients with coronary artery aneurysm has not yet been the subject of randomized controlled trials. Several strategies have been adapted in different clinical scenarios to manage large thrombus burden during PPCI which include guide catheter aspiration and the use of distal protection devices and filter wires [8]. The data on pharmacotherapy in this setting are also limited. Several cases have been reported whereby intracoronary glycoprotein IIb/IIIa inhibitors were used [8]. Various

intracoronary vasodilators, such as verapamil, nicardipine, glyceryl trinitrate, nitroprusside, along with adenosine, have been tried in this setting to treat concomitant spasm and microvascular dysfunction that also contribute to reduced flow. Retroperitoneal haemorrhage occurs rarely after percutaneous coronary intervention and is independently associated with an increased risk of mortality and adverse events, however its incidence has decreased over time contributed significantly by a transition to transradial access.

In the case presented here, stenting was initially deferred and ultimately decided against, in view of the (1) large diameter of the culprit segment, (2) restoration of TIMI 3 flow after mechanical aspiration and pharmacotherapy, and (3) persistence of substantial thrombus. Stenting especially with Jostent or self-expanding Polytetrafluoroethylene (PTFE) stents in coronary artery aneurysms has been shown to carry a considerable risk of restenosis (31%) and subacute thrombosis (5.7%) [9]. Hence, we initially opted for a conservative, surveillant approach by treating with intravenous tirofiban before repeating angiography with IVUS assessment after 48 hours.

The role of IVUS in coronary artery aneurysms has been studied previously by Maehara et al. who found that 27% of aneurysms were true aneurysms, 4% pseudo-aneurysms, 16% complex plaques and the remaining 53% normal arterial segments adjacent to >1stenosis [10]. In our case, IVUS helped to clarify the underlying cause of coronary thrombosis, which was a nonocclusive, eccentric plaque in an aneurysmal segment of the LAD artery, excluding other causes like false aneurysm and complex atheroma, and directing us to continue tirofiban for a

further 48 hours and decide against treating with PCI. It also guided our decision to treat the patient with longterm anticoagulation.

Optical coherence tomography (OCT) although not used in our case because of operator preference, would also have been a suitable alternative to IVUS to interrogate the characteristics of the underlying culprit lesion. In particular, it would have provided excellent spatial resolution and the ability to differentiate between white and red thrombus, evaluate the underlying plaque, as well as enabling estimation of maximal luminal diameter and longitudinal dimension of the aneurysmal segment. In a study by Adlam et al, OCT was used to follow patients with coronary artery aneurysms after stenting, wherein it identified peri-stent leaks and guided further management. In this setting it would also provide insight into the process of re-endothelialization and neo-intimal proliferation for larger caliber coronary abnormalities during follow-up [11].

CONCLUSION

Management of large thrombus burden in an aneurysmal coronary artery remains challenging even in the current era. In our present report a combined mechanical and pharmacological approach, guided by IVUS was helpful to produce a desirable outcome. A careful consideration of strategy weighing the ischemic benefits with bleeding risks is recommended on a case by case basis in the absence of randomized controlled trials and guidelines to help in the management of this complex subset of patients.

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LIST OF ABBREVATIONS:

CAD: Coronary artery disease

PCI: Percutaneous coronary intervention

BMS: Bare metal stents

DES: Drug eluting Stents

STEMI: ST elevation myocardial infarction

CTO: Chronic total occlusion

CTO-PCI: Chronic total occlusion – percutaneous coronary intervention

MACE: Major adverse cardiovascular events

GPI: Glycoprotein IIb/IIIa inhibitors

EIRA : Ectatic infarct related artery

TIMI: Thrombolysis in myocardial infarction

CABG: Coronary artery bypass surgery

LV: Left ventricular

OMT: Optimal medical therapy

LVEF: Left ventricular ejection fraction

EF: Ejection fraction

Cm: Centimeter

IVUS: Intra-vascular ultrasound

MSCT: Multi slice computed tomography

OCT: Optical coherence tomography

CART: Controlled antegrade and retrograde tracking

CT: Computed tomography

F: French

LAST: Limited antegrade subadventitial tracking

STAR: Subintimal tracking and re-entry

OTW: Over-the-wire

CC: Collateral connection

SES: Sirolimus eluting stent

MI: Myocardial Infarction

ZES: Zotarolimus –eluting stent

EES: Everolimus –eluting stents

ARC: Academic research consortium

TTE: Transthoracic echocardiography

CTCA: Coronary CT angiography

J-CTO: Japanese – Chronic total occlusion

mm: millimetre

ml: millilitre

min: minutes

AV: Atrioventricular

Gy: Gray

ACT: Activated clotting time

kg: Kilogram

h: Hour

LVEDP: Left ventricular end diastolic pressure

MACD: Maximum accepted contrast dosage

P-PCI: Primary percutaneous coronary intervention

TLR: Target lesion revascularisation

QCA: Quantitative coronary angiography

ACC/AHA: American college of cardiology/ American heart association

eGFR: Estimated glomerular filtration rate

TMPG: TIMI myocardial blush grade

VF: Ventricular fibrillation

LAD: Left anterior descending artery

LCx: Left circumflex artery

RCA: Right coronary artery

ER: Emergency room

BARC: Bleeding academic research consortium

CK: Creatine kinase

ACE: Angiotensin convertase enzyme

ADP: Adenosine diphosphate

MMP: Matrix metalloproteinase

NO: Nitric oxide

CAE: Coronary artery ectasia

NCDR: National cardiovascular data registry

NSTEMI: Non-ST-elevated myocardial infarction

CVA: Cerebrovascular accident

CK-MB: Brain fraction of creatinine kinase

MDRD: Modification of diet in renal disease

SD: Standard deviation

LMWH: Low molecular weight heparin

LMS: Left main stem

POBA: Plain old balloon angioplasty

RIM: Ramus intermedius

CVD: Cardio vascular disease

ACS: Acute coronary syndrome

HRQOL: Health-related quality of life

QOL: Quality of life

FKBD: Final kissing balloon dilatation

NFKD: No final kissing balloon dilatation

DAPT: Dual antiplatelet therapy

UFH: Unfractionated heparin

CHD: Coronary heart disease

IHD: Ischemic heart disease

RCT: Randomized controlled trial

NSTEACS: Non-ST elevation acute coronary syndrome

TVR: Target vessel revascularization

TLR: Target lesion revascularisation

ECG: Electrocardiogram

AMI: Acute myocardial infarction

PDA: Posterior descending artery

PLV: Posterior Left ventricular branch

RAMUS IM: Ramus intermedius

MV: Main vessel

SB: Side branch

GP2B3A: Glycoprotein IIb/IIIa Inhibitors

DM: Diabetes mellitus

CT: Computed tomography

PTFE: Polytetrafluoroethylene