THESIS TITLE

Screening for asymptomatic coronary heart disease in the siblings of young myocardial infarction patients (SACHSMI).

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ABSTRACT

The concept of screening entails detecting subclinical disease in the hope of altering the natural progression and thereby reducing long term mortality and morbidity. For a screening program to be effective it must be targeted at a disorder that is prevalent with accepted treatments and diagnostic tools. Coronary heart disease (CHD) is ideally positioned in this respect. There are multiple strategies available to diagnose asymptomatic CHD but the emerging field of coronary computer tomography angiography (CCTA) appears to have many of the required qualities. It is non-invasive, safe and has high sensitivity to diagnose CHD. The radiation dose has markedly decreased with evolving technology and the cost is comparable to current non-invasive cardiac investigation. An effective screening strategy for CHD maybe beneficial at all ages but applying it to the young may have a greater impact on society. The aim of this thesis was to highlight the burden of CHD in the young and to asses potential screening strategies to detect asymptomatic disease. In particular the potential role of CCTA as a screening tool has been investigated.

Chapters 3 and 5 discusses the results of reviews looking at the literature focusing on myocardial infarction (MI) in the young and screening for asymptomatic CHD in the young respectively.

Chapter 4 discusses the findings of a study that demonstrated the prevalence of MI in the young (defined as ≤55 years) in a low socioeconomic Australian urban setting was approximately 32%. The younger patients were more likely
to be male, have a family history of premature CHD and be current smokers compared to the older cohort. In general this prevalence is higher than what is reported in the literature.

Chapter 6 highlights the findings of a study that used CCTA to demonstrate the prevalence of asymptomatic CHD in the siblings of young MI patients. The participants of the study were aged 30-55 and 30-60 years if males and females respectively. Obstructive CHD (defined as ≥50% stenosis of at least one epicardial coronary artery) was demonstrated in 18% of participants. All of those with obstructive CHD were either current or ex-smokers. No statistically significant association was found between traditional cardiovascular risk scores and obstructive CHD by CCTA. A similar study conducted for this research project at another healthcare centre found the prevalence of asymptomatic CHD via screening CCTA in an all comer population was 18%. Males and those over the age of 55 years were more likely to have obstructive CHD. These results are discussed in chapter 7. Compared to the published literature the prevalence of obstructive CHD by CCTA demonstrated in these two studies is higher.

Screening strategies have been demonstrated to alter modifiable risks in those who participate. Chapter 8 discusses the findings of a study that demonstrated 60% of the participants of a screening program for CHD using CCTA either stopped or reduced smoking one month after undergoing CCTA. This change was largely sustained at 12 months with 55% either stopping or
reducing smoking. This rate appears to be high compared to more traditional methods such as nicotine replacement therapy.

For CCTA to be accepted as an effective screening modality for CHD the risks of radiation exposure need to be as low as possible. Chapter 9 discusses the results of a study comparing the radiation doses associated with three new generation CT scanners when used to perform CCTA; the Siemens Somatom Definition Flash CT scanner, the GE Revolution CT scanner and the Toshiba Aquilion ONE ViSION CT scanner. The study found all three scanners exposed subjects to below a median dose of 5 mSv, fulfilling the Australian National Health and Medical Research Council guidelines of <5 mSv for research purpose. In addition it found the Siemens Somatom Definition Flash CT scanner exposed subjects to the lowest median radiation of 1.76 mSv. This appears to suggest the new generation CT scanners expose subjects to low enough radiation for CCTA to be a viable screening modality.

In summary this thesis demonstrates a high prevalence of both symptomatic CHD (in the form of MI) and asymptomatic CHD in the young. It highlights the importance of family history of premature CHD and smoking as important risk factors for the presence of asymptomatic CHD in the young as detected by CCTA. In addition asymptomatic CHD as detected by CCTA has been shown to be more prevalent in males and those over the age of 55 years. Participation in a screening program for CHD is also shown to be an effective and sustained means of modifying smoking habits. Finally the very low radiation exposure that can be achieved with the use of the latest generation...
of CT scanners is illustrated. In combination these findings support further research investigating the use of CCTA in a screening strategy for CHD.
DECLARATION

This is to certify that:

i. the thesis comprises only my original work towards the completion of the degree of Doctor of Medical science,

ii. due acknowledgement has been made in the text to all other material used,

iii. the thesis is less than 100,000 words as approved by the Research Higher Degrees Committee and

iv. the studies reported in this thesis have not been submitted for a degree at this or any other university.

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Australi
PREFACE

This thesis presents the results of two literature reviews focusing on myocardial infarction in the young and the role of screening for coronary heart disease in the young. I conducted these reviews independently and the results have been published in two articles in peer-reviewed journals. My coauthors were invaluable in providing me guidance and support in preparing the manuscripts but I conducted the majority of the work in preparation for publication.

This thesis reports the results of a retrospective analysis highlighting the differences between myocardial infarction in young compared to older adults. I designed this study with the aid of Assoc. Prof. Kean Soon. Dr. Christopher Wang and Miss. Vanessa Lee shared the task of data collection for this study. I independently, however, analysed the data and prepared the manuscript for publication. Again my coauthors supported me with guidance and support in preparing the manuscript for publication.

I independently conducted participant recruitment, data collection and analysis for the Screening for Asymptomatic Coronary Heart disease in the Siblings of young Myocardial Infarction patients (SACHSMI) study. Assoc. Prof. Kean Soon and I designed the study. The coronary computed tomography angiograms were analysed by Assoc. Prof. Kean Soon and I. My coauthors were invaluable in providing me guidance and support in preparing the manuscript for this study but I conducted the majority of the work in
preparation for submission to a peer-reviewed journal. This paper has been accepted for publication by a peer-reviewed journal.

A retrospective analysis of screening coronary computed tomography angiograms was conducted to detect the prevalence of occult asymptomatic coronary heart disease. Assoc. Prof. Kean Soon and I designed this study. Drs. Carl Blecher and Daniel Schneider aided in data collection. I independently, however, analysed the data and prepared a manuscript that has been accepted by a peer-reviewed journal for publication. Again my coauthors supported me with guidance and support in preparing the manuscript.

Data interpretation of the Screening for Asymptomatic Coronary Heart disease in the Siblings of young Myocardial Infarction patients (SACHSMI) study was conducted to analyse whether knowledge of screening coronary computed tomography angiogram results affect smoking habits. I independently designed this study and have prepared a manuscript in preparation for submission to a peer-reviewed journal. Again my coauthors supported me with guidance and support in preparing the manuscript.

A retrospective analysis comparing the radiation exposure of coronary computed tomography angiograms conducted using three separate computed tomography equipment was conducted. Assoc. Prof. Kean Soon and I designed this study. I shared the task of data collection and analysis with Drs. Odgerel Tumur and Daniel Schneider. Drs. Odgerel and I shared the task of

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preparing a manuscript for submission to a peer-reviewed journal but I conducted more than 50% of the total work towards this study.

Funding for the Screening for Asymptomatic Coronary Heart disease in the Siblings of young Myocardial Infarction patients (SACHSMI) study was provided from the Western Health Research Grant 2013.

An Australian Government Research Training Program Scholarship provided financial support for the degree of Doctor of Medical Science.
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I. Assoc. Prof. Kean Soon for providing the initial spark that ignited my research and then for his continuing guidance and encouragement over the last three years. I could not have hoped for a better primary supervisor who has always strived to exceed what is expected of him. He has provided me with a vast amount of his valuable free time to assist me in the completion of this work whenever I have requested it. Due to him I have grown in the last three years not only as a researcher but also in many other aspects of my professional and private life.

II. Prof. Anne-Maree Kelly for her valuable assistance in the initial planning stage of my research and then for her ongoing assistance with the preparation of multiple published manuscripts. She has vast research experience that has allowed her to edit and improve all of the manuscripts she has coauthored with me.

III. Assoc. Prof. Chiew Wong for his internal optimism and numerous professional opportunities he has provided me. Without this it would not have been possible for me to complete my research.
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V. Miss. Vanessa Lee, Dr. Daniel Schneider, Dr. Odgerel Tumur and Dr. Christopher Wang for their assistance with data collection.

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IX. My two wonderful children, Maher and Zabeer, who have spent many hours without their father due to commitments to this work.

X. My father, Mohammed Shahabuddin, for always believing in me and encouraging me to achieve and not to take the “easy road”.

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PUBLICATIONS AND PRESENTATIONS RELATED TO THIS WORK

Publications in peer reviewed journals


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ABBREVIATIONS

ACC = American College of Cardiology
ACE = angiotensin converting enzyme
AHA = American Heart Association
ALARA = as low as reasonably achievable
ApoA1 = apolipoprotein A1
ApoB = apolipoprotein B
ARB = angiotensin II receptor blocker
BMI = body mass index
CABG = coronary artery bypass grafting
CAC = coronary artery calcification
CCTA = coronary computer tomography angiography
CHD = coronary heart disease
CI = confidence interval
CT = computer tomography
CVA = cerebrovascular accident
DECT = dual energy computer tomography
DLP = dose length product
ECG = electrocardiograph
ESC = European Society of Cardiology
EST = exercise stress test
FOB = faecal occult blood
GE = General Electric
HDL = high-density lipoprotein

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HR = heart rate
HU = Hounsfield unit
IQ = interquartile
LDL = low-density lipoprotein
LMCA = left main coronary artery
MACE = major adverse cardiovascular event
MDCT = multidetector row computer tomography
MI = myocardial infarction
MPI = myocardial perfusion imaging
mSv = millisievert
NSTEMI = non ST-elevation myocardial infarction
OR = odds ratio
PACS = picture archiving and communication system
PAF = population attributable fraction
PAR = population attributable risk
PCI = percutaneous coronary intervention
PVD = peripheral vascular disease
ROC = receiver-operating characteristic
SACHSMI = The Screening for Asymptomatic Coronary Heart disease in the Siblings of young Myocardial Infarction patients study
SCD = sudden cardiac death
SCORE = Systemic Coronary Risk Evaluation
SD = standard deviation
SE = stress echocardiography
STEMI = ST-elevation myocardial infarction

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TAVI = transcatheter aortic valve implantation

TVR = target vessel revascularisation
CHAPTER 1: INTRODUCTION

“I saw many people who had advanced heart disease and I was so frustrated because I knew if they just knew how to do the right thing, simple lifestyle and diet steps, that the entire trajectory of their life and health would have been different”. Mehmet Oz.

“The importance of heart health became very real for me when my father died of heart disease seven years ago. Having experienced the loss first hand, I am inspired to do everything I can to break the cycle and prevent families from losing loved ones to this preventable disease”. Monica Potter

Coronary heart disease (CHD) is defined as accumulation of plaque within coronary arteries (1). CHD plagues the world and continues to not only be the leading cause of death in the world (2) but also in Australia (3). Myocardial infarction (MI), commonly known as a heart attack, results from CHD and is caused by a sudden interruption of blood flow to heart muscle (1). People of all ages can be affected by CHD and MI but the risk increases with age (4). Publication bias with more studies focusing on older adults may result in lack of data on CHD in the young. This can therefore lead to under appreciation of the extent to which CHD affects younger adults.

Chronic diseases, such as CHD, have the potential to have a greater negative impact on younger adults. This can be appreciated if one considers the

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greater life expectancy of younger adults with the associated psychosocial and socioeconomic ramifications that this entails. In addition younger adults are more likely to have dependents that have a high likelihood of being affected by the detrimental effects of CHD. Hence although detecting and altering the natural history of CHD may be beneficial for all, there is potential for greater benefit in younger adults if we can detect CHD at an earlier stage and alter the natural history.

Screening is the concept of detecting subclinical disease in asymptomatic individuals (5). It potentially allows early detection of disease and, depending on available effective therapies, improve outcome. Currently screening for CHD lacks robust evidence and hence does not have strong recommendation from most international cardiovascular guidelines. Nevertheless there is varying degree of adherence to the guidelines and many subjects are screened for CHD with differing modalities usually governed by the experience of the clinician.

Many modalities are available that may help in risk assessment and screening for CHD. Traditional cardiovascular risk scores are used widely for risk assessment and most are readily available to clinicians. They are not ideal for screening purposes however as they provide a population attributable risk rather than providing an individual risk. Cardiac stress tests such as exercise electrocardiography, stress myocardial perfusion imaging and stress echocardiography are commonly used to diagnose CHD in symptomatic
patients. In terms of their role in screening for CHD in asymptomatic patients, however, their sensitivity and specificity are limited.

Coronary computer tomography angiography (CCTA) is an emerging non-invasive imaging modality that allows indirect visualisation of the coronary arteries. It is highly sensitive for the detection of CHD and has therefore the potential to be used for screening. It involves the use of ionizing radiation that can be a concern for screening purpose. With advancement of technology this concern has become a lesser issue.

Screening has the potential to benefit those with risk factors for the development of CHD. Smoking appears to be one of the most important risk factors with respect to young adults (6). Offering screening to those who smoke therefore may not only detect subclinical asymptomatic CHD, it may also alter or motivate the participants of the screening program to change their smoking habits.

The subsequent chapters in this thesis include chapters 3 and 4 that explore the prevalence and characteristics of young MI and highlight the differences comparing to an older cohort; chapter 5 explores the current thinking about screening tools; chapter 6 looks at the prevalence of asymptomatic CHD via CCTA in a young at risk population; chapter 7 investigates the prevalence of asymptomatic CHD via CCTA in an all comer population; chapter 8 looks at the effects of screening with CCTA and change in smoking habit and finally
chapter 9 investigates radiation exposure with the latest generation of CCTA scanners.
CHAPTER 2: OBJECTIVES

The objectives of this thesis were as below:

- To review the literature focusing on myocardial infarction in the young and potential screening strategies,
- To assess the potential use of coronary computer tomography angiography (CCTA) as a screening tool for the detection of coronary heart disease (CHD) in the young,
- To investigate the prevalence of asymptomatic CHD as detected by CCTA and
- To investigate the role of screening in modifying risk factors for CHD.

Two reviews and five clinical studies were conducted to address these objectives. The specific outcomes of the studies were as follows:

- To investigate the prevalence of myocardial infarction (MI) in the young in a low socioeconomic Australian urban setting and to highlight any potential difference as compared to older adults (Chapter 4).
- To investigate the prevalence of asymptomatic CHD via screening CCTA in a young at risk population (Chapter 6).
- To investigate the prevalence of asymptomatic CHD via screening CCTA in an all comer population (Chapter 7).
- To assess if a screening program for CHD using CCTA alters smoking habits (Chapter 8).
To compare radiation dose of three new generation CCTA scanners (Chapter 9).
CHAPTER 3: MYOCARDIAL INFARCTION IN THE “YOUNG”: RISK FACTORS, PRESENTATION, MANAGEMENT AND PROGNOSIS

3.1 Introduction

The leading cause of death in the world is coronary heart disease (CHD) (2) and while there is a large body of data available for CHD, literature focusing on premature CHD and myocardial infarction (MI) in the “young” is lacking. Consequences of MI can be devastating particularly at a “young” age due to its greater potential impact on the patient’s psychology, ability to work and the socioeconomic burden. As “young” MI patients maybe the main income producer of the family, the aftermath of MI can also affect multiple dependents. Clinicians may not appreciate the differences that exist between “young” and older MI patients.

In this paper we report the differences in rate, risk factor profile, presentation, management and prognosis between “young” and older MI patients.

3.2 Methods

A literature search was conducted via MEDLINE and GOOGLE for the years between 1980 and 2015 using the keywords “young” and “myocardial infarction”. The search was restricted to papers published in the English language and in peer reviewed journals.
3.3 Definition and epidemiology

There is disparity in the literature on the definition of “young” with respect to premature CHD and MI. The term “young” varies from ≤40 (7-9) to ≤55 years of age (10). Others have suggested 45 years as a cut off when defining “young” with respect to MI (11-13). As there is no universally accepted age cut-off this review will not use a single definition but rather will accept the cut-off or range used by the authors of the data being reviewed.

There is a paucity of data on MI in the “young” relative to literature on CHD as a whole. Perhaps the most well known of all epidemiological studies in cardiovascular medicine is The Framingham Heart Study which reported a ten year incidence of “young” MI (defined as <55 years of age) as high as 51.1/1000 in men and 7.4/1000 in women (4). In contrast, McManus et al reported an incidence of 66/100,000 of MI among patients aged between 25 and 54 years (14). While this may appear relatively low, McGill et al demonstrated an unexpectedly high prevalence of CHD in men under the age of 35 years with 20% shown to have advanced coronary artery lesions at autopsy (15). Fournier et al have reported higher rates of “young” MI with an incidence of approximately 4% in those aged ≤40 years (16). Meanwhile Doughty et al demonstrated >10% of all MI patients admitted at their institution were “young”, where they defined “young” as ≤45 years of age (17). One of the highest rates of MI in the “young” was reported by Loughnan et al who examined admissions to hospitals in Melbourne, Australia over a 6 year
period and reported that 20% were younger than 55 years of age (18). This represented approximately 0.1% of the Melbourne population aged less than 55 years during the study period (19). In contrast approximately 1% of the Melbourne population older than this age experienced MI over the same period (18,19).

3.4 Risk factors

The extent of relative risk for future events of traditional cardiovascular risk factors are comparable in “young” and older adults (20). The majority of patients suffering MI at a “young” age are reported to have at least one identifiable cardiovascular risk factor (11,21-23). Hoit et al reported higher prevalence of smoking, family history of premature CHD and male gender among “young” MI patients compared with their older counterparts (11). Others have supported this finding and, in addition, have demonstrated higher rates of hyperlipidaemia and lower rates of prior history of CHD, diabetes mellitus and hypertension in “young” MI patients compared to older MI patients (6,21,22,24,25).

There is data that suggests smoking maybe the most important modifiable risk factor among “young” MI patients (6). Yusuf et al identified it as one of the most important risk factors associated with “young” MI (26). They suggested the association of smoking and MI in the “young” has an odds ratio (OR) of 3.33 (99% confidence interval (CI), 2.86-3.87) compared to controls (26). This was significantly higher than older individuals (OR 2.44: 99% CI, 2.86-3.87)
(26). Smoking rates among “young” MI patients are quoted between 51% and 89% (6,7,9,11,14,21,24,27-30). The high prevalence of smoking among patients presenting to hospital with premature MI was also highlighted by Aggarwal et al (7). Smoking was found to be five times more prevalent among “young” MI patients than age and gender matched patients presenting to hospital with non cardiac complaints (7). In comparison to older patients, “young” MI patients smoked a greater number of cigarettes per day but had a lower pack year history as expected due to their younger age (6). Of “young” MI patients presenting with ST-elevation myocardial infarction (STEMI), the rate of smoking was found to be highest among the youngest (31). Oliveira et al studied the association between smoking and MI among “young” men aged ≤45 years that smoked more than fifteen cigarettes a day (13). They demonstrated an OR for MI of 4.56 (95% CI, 2.32-9.00), in comparison with ex smokers (13). This data appears to confirm the enduring detrimental effect of continuing smoking. The population attributable fraction (PAF) or risk (PAR) is a theoretical measure of the proportion of the disease burden attributable to a risk factor in the population at large. The PAF of smoking for MI among “young” men aged ≤45 years, according to Oliveira et al, is 63.5% (95% CI, 42.0-80.6) (13).

A family history of CHD or a family history of premature CHD (which is usually defined in the literature as documented CHD in a first-degree relative before the age of 55-60 years) is reported in 41% - 71% of “young” MI patients (6,9,11,24,27,28,30). Compared to older individuals, “young” MI patients appear to have double the prevalence of family history of CHD (11,30)
although some data suggests the increase in prevalence maybe as high as four fold (21). This was illustrated by Chan et al who reported an OR of 2.98 (95% CI, 2.26-3.94) for family history of premature MI among MI patients aged ≤45 years compared to older MI patients (21). Zimmerman et al reported that the prevalence of family history of CHD in “young” MI patients is only greater in men compared to their older counterparts (24). Oliveira et al demonstrated the adjusted OR of MI among “young” men aged ≤45 years that had a family history of MI in a first-degree relative of 1.84 (95% CI, 1.07-3.17), compared with those who did not (13). The PAF of family history of MI for MI among “young” men aged ≤45 years, according to Oliveira et al, is 14.4% (95% CI, 5.3-33.9) (13). Yusuf et al confirmed a similar PAF (14.8% (99% CI, 11.7-18.5)) and highlighted the importance of family history as a risk factor in younger individuals (26).

There is a large gender bias with the vast majority of “young” MI occurring in men. The gender distribution of “young” MI in men is reported to be between 79 - 95% (6,7,14,21,27,28). Chan et al reported that 90% of patients presenting with MI who are aged 45 years or less were male compared to 68.4% (OR 3.59: 95% CI, 2.37-5.44) of older patients (21). This is one potential reason that women, and “young” women in particular, may experience delays in prompt care and may appear to be neglected when they truly present with MI (32). Contributing factors in women receiving prompt management of potential MI include cultural factors that may not be universal (32).
Hyperlipidaemia is a traditional risk for CHD in all age groups and appears to be associated with “young” MI (21,25). The link however does not appear to be as robust as the risk factors already discussed. The presence of hyperlipidaemia is reported in more than half of “young” patients presenting with MI (7,28) but there is discordance in the literature. Some studies suggest a similar or lower prevalence of hyperlipidaemia among “young” MI compared to older patients (24,27,30) while others report a higher prevalence (21). The definition of hyperlipidaemia also varied between the studies and included having a reported history of elevated fasting concentration of total cholesterol or triglycerides; undergoing treatment for elevated fasting concentration of total cholesterol or triglycerides; fasting serum low density lipoprotein (LDL) > 130 mg/dL, total cholesterol:high density lipoprotein (HDL) ratio > 4.5 or non-HDL cholesterol > 160 mg/dL (7,21,28). Familial-combined hyperlipidaemia is reported to have relatively high prevalence in “young” MI patients with Wiesbauer et al reporting a prevalence of 38% (9). “Young” MI patients also appear to exhibit higher endogenous cholesterol synthesis (33) and have higher levels of non-HDL cholesterol (29). In a recent study the association of non-HDL cholesterol with MI in patients aged ≤40 years was found to have an adjusted OR of 5.02 (95% CI, 2.75-9.15) compared to controls adjusted for age, gender and other traditional cardiovascular risk factors (29).

Apolipoprotein B (ApoB) and apolipoprotein A1 (ApoA1) are the main surface proteins of LDL and HDL particles respectively. ApoB/ApoA1 ratio has been demonstrated to have a strong association with MI (34). Yusuf et al evaluated this in a large case-control study that demonstrated the ApoB/ApoA1 ratio to
be the strongest risk factor for MI among the multiple risk factors investigated (OR 3.25: 99% CI, 2.81-3.76 for top vs. lowest quintile; PAR 49.2%: 99% CI, 43.8-54.5 for top four quintiles vs. lowest quintile) (26). This association was even stronger in the “young” (OR 4.35: 99% CI, 3.49-5.42 for top vs. lowest quintile; PAR 58.9%: 99% CI, 50.9-66.5 for top four quintiles vs. lowest quintile) where “young” was defined as ≤55 and ≤65 years for men and women respectively. (26). Assays for ApoB and ApoA1 are not universally performed in clinical practice as they are expensive. Hence they are not included in most traditional cardiovascular risk scores.

Diabetes and hypertension were reported to be present in 14.7% and 38.1% respectively of “young” MI patients (14,28). This is significantly lower than the rates reported in patients suffering MI at an older age (6,21,24,27). There appears to be higher rates of untreated hypertension in the “young” (OR 2.99: 95% CI, 2.00-4.46) suggesting the prevalence of hypertension among “young” MI patients is under appreciated (21). The prevalence of diabetes in “young” MI patients may be relatively low but it is still associated with high risk (13). Compared to those who do not have diabetes, the adjusted odds ratio (OR) of MI among “young” men aged ≤45 years with diabetes has been shown to be 8.34 (95% CI, 1.67-41.6) (13). Yusuf et al suggests the PAR of diabetes for MI is higher in younger patients of both sexes (PAR 12.4% (99% CI, 10.3-14.9) and 8.6% (99% CI, 6.9-10.7) in “young” and older patients respectively) (26). Hypertension however appears to have a higher PAR in younger women only and has been reported by Yusuf et al with a PAR of 31.9% (99% CI, 25.7-38.6) compared to 25.4% (99% CI, 17.1-35.8) in older female patients (26).
Patients suffering MI at a younger age are reported to have higher body mass index (BMI) and more central obesity compared to age and gender matched controls (7,29). In addition the prevalence of obesity among “young” MI patients is increasing (14), which suggests the potential for a future increase in the incidence of “young” MI. The current epidemic of obesity has been identified as having the potential for a future explosion in CHD burden (35,36).

As with many disease processes there appears to be an association with low socioeconomic status and increased rate of MI, which may be exhibited even more profoundly in the “young” (13,37). A number of other potential but uncommon causes have been described as precipitants of MI in the “young” including cocaine use (38), spontaneous coronary artery dissection (39), Kawasaki disease (40), factor V Leiden (41), low levels of oestrogen (42) and oral contraceptives in “young” women (43). The role of homocysteine in development of CHD is controversial but data suggests there may be a correlation between hyperhomocysteinaemia and “young” MI (8).

3.5 Clinical presentation and angiographic findings

Up to two thirds of “young” MI patients will present with non-ST elevation myocardial infarction (NSTEMI) with approximately a third presenting with STEMI (14). It appears that overall the incidence of STEMI is reducing among the “young” but the proportion of “young” patients diagnosed with STEMI is increasing (14). Most “young” MI patients do not report a history of previous screening for asymptomatic coronary heart disease in the siblings of young myocardial infarction patients (SACHSMI).

Dr. Nadim Mohammed Shah, 22 May 2017.
angina, MI or congestive heart failure and they report this less frequently in their histories than their older counterparts (11,17). Egiziano et al reported only about 25% of “young” MI patients complained of chest pain in the month prior to their acute presentation for MI (44). The rate was even lower among “young” women (44). By way of comparison, in a study of all comers with MI, chest pain was reported among two thirds of patients and those presenting with chest pain had a median age of 67 years (45).

Coronary angiography usually reveals less extensive disease in “young” MI patients than older patients (11,30). Zimmerman et al reported normal coronary arteries in 16% of men and 21% of women (24). By comparison only 2% of older men and 11% of older women had normal coronary arteries (24). Three vessel disease is infrequent with Fournier et al reporting it in less than 10% of “young” MI patients (16). In that study there was no report of left main coronary artery stenosis in “young” MI patients which is supported by other authors (16,44). Single vessel disease is more frequent among “young” MI patients compared to their older counterparts (27) and the left anterior descending artery is most commonly affected (24). Spontaneous coronary artery dissection is not an infrequent finding at angiography in “young” MI patients. Tweet et al described the occurrence of spontaneous coronary artery dissection in a group of “young” patients with a mean age of 43 years, who were mostly female (46). Approximately 50% of these patients presented with STEMI and conservative management was associated with an uncomplicated in-hospital course (46).
3.6 Management

The management of MI generally is not dependent on age and guideline suggested therapies are just as applicable to younger patients as they are to their older counterparts (47,48). With respect to STEMI management, the benefits of primary angioplasty over thrombolysis are as applicable in “young” patients as they are in older individuals and no particular age cohort has a greater relative benefit (49). “Young” age is an independent predictor for favourable prognosis following thrombolysis (50) and hence thrombolysis should still be utilized where timely primary angioplasty cannot be offered. Given the longer expected survival of younger patients, the rate of repeat revascularisation would be expected to be high. One study suggests a rate of about 50% at a median of 4.7 years (51).

Data to guide management of “young” NSTEMI is lacking as younger patients are under represented in the clinical trials and hence it is difficult to suggest routine early coronary angiography in addition to other evidence based therapies. An invasive strategy post NSTEMI has been associated with improved survival regardless of age but this observation is based upon data from a study where the mean age of the invasive strategy cohort was 67 years (52). In a controversial study published in 1994 Negus et al suggest routine coronary angiography post MI in those who are asymptomatic, aged 40 years or less and do not exhibit spontaneous or provokable post-infarction ischaemia is not warranted (53). This conclusion was based upon their finding that no patient with these characteristics who underwent coronary
angiography required revascularisation (53). This study, however, was conducted over 20 years ago and only included 129 “young” MI patients. Current equipment, therapies and techniques afford for better outcomes. In a real world setting invasive management in “young” NSTEMI patients is a norm rather than an exception. Nonetheless, further studies are therefore necessary to fully address the utility of this approach.

In addition to medical treatment of acute events, risk factor modification is of utmost importance in any patient post MI. As highlighted above smoking is one of the most important modifiable risk factors among “young” MI patients; addressing this may yield the highest reward. Critchley et al studied the benefit of smoking cessation in patients with CHD in a systematic review. They report a 36% reduction in crude relative risk of mortality for patients with CHD who quit smoking compared to those who continued to smoke (relative risk 0.64: 95% CI, 0.58-0.71) (54). This benefit did not appear to be affected by age (54). Recurrent coronary events also appear to be reduced by smoking cessation. Rea et al demonstrated a relative risk of 1.51 (95% CI, 1.10-2.07) for recurrent coronary events among continued smokers compared to non-smokers (55). Smoking cessation is a difficult task for patients and health care professionals. It often requires multiple strategies including counseling, personalised prescription and management of co-occurring mental health conditions (56).

3.7 Prognosis
In-hospital and short-term outcomes are generally favourable in “young” MI patients. In-hospital and 6-month mortality has been shown to be 0.7% and 3.1%, respectively (6). This compares favourably to their older counterparts whose in-hospital and 6-month mortality were 8.3% and 12%, respectively (6). Beyond 5 years post MI however there is an alarming drop in survival among “young” MI patients with mortality exceeding 15% at 7 years (24) and being between 25-29% at 15 years (10,57). Heart failure, malignant ventricular arrhythmias, angina pectoris and re-infarction were found to be associated with higher mortality (57). The strongest independent risk factor reported is left ventricular ejection fraction of ≤45% (OR 4.4: 95% CI, 1.6-12.4) (57). In particular the rate of sudden cardiac death appears to be dramatically increased in “young” MI patients compared to the general population of a similar age. Risgaard et al demonstrated a more than 74 fold increase in mortality (58). Nonetheless, over last 3 decades, in-hospital and 30-day mortality have markedly decreased probably due to improved acute management of MI (14).

Heart failure is a potentially debilitating complication of MI in “young” patients. They are often at the peak of their productive lives and may have multiple dependents. As illustrated above heart failure is also an important predictor for long term prognosis. Fortunately the rate of heart failure has markedly reduced from 20% in 1970s to below 6% in 2005 among “young” MI patients (14). This is likely due to a combination of factors and not least the use of prophylactic implantable cardiac defibrillators. The MADIT II trial demonstrated their utility in reducing mortality in patients with previous MI and
severe reduction in left ventricular ejection fraction (59). The mean age of patients in the study was approximately 65 years but sub group analysis demonstrated benefit among patients aged <60 years (59). Even so it is vital to diagnose heart failure early and instigate evidence-based management to limit progression and improve outcomes.

There is significant reduction of health-related quality of life post MI in “young” MI patients. Depression is common after MI (60) with Denollet et al reporting post-MI depressive symptoms in approximately 47% of patients with a mean age of 54 years (61). Hence identifying and managing depression following MI in “young” patients is important. Angina is also a significant contributor to lower health-related quality of life post MI but it appears improving control of angina leads to greater improvement in health-related quality of life in older patients only (62).

3.8 Summary

The incidence of MI in “young” patients is substantial. Smoking remains one of the most important risk factors and should be the target of any program aimed to reduce the rate of MI in the “young”. “Young” MI patients often lack warning symptoms of escalating chest pain. Coronary angiography in the “young” tends to reveal less extensive disease in comparison with their older counterparts and hence they are more often managed with percutaneous revascularisation. Short-term outcomes post MI at a “young” age are good but
longer prognosis is relatively poor, particularly when there is reduced left ventricular ejection fraction.
CHAPTER 4: MYOCARDIAL INFARCTION IN YOUNG VERSUS OLDER ADULTS: AN ANALYSIS OF DIFFERENCES IN PROPORTION, RISK FACTORS, CLINICAL DEMOGRAPHICS, ANGIOGRAPHIC FINDINGS AND IN-HOSPITAL OUTCOMES

4.1 Introduction

Coronary heart disease (CHD) is the largest cause of death worldwide and accounted for the deaths of more than 7 million people in 2012 (63). Traditionally CHD is viewed as a disease of older adults. There is increasing evidence, however, to suggest a significant proportion of those presenting with CHD and myocardial infarction (MI) are young (17,18). The potential consequences of MI at a young age may have a significant impact on future health and wellbeing due to possible higher psychological and socioeconomic implications. These challenges are often faced not only by the patient but also their family members and dependents. Previous studies have highlighted important differences in clinical risk factors and demographics of young patients presenting with MI compared to older adults where young was defined as age of less than or equal to 45 years (11,21). Others have demonstrated differences in angiographic findings with less extensive disease found in younger patients (16,24). In-hospital outcomes in patients presenting with MI at a young age also appear to be better (6). There is, however, a relative scarcity of data examining MI in the young from an Australian demographic. This is particularly the case in the western suburbs of
Melbourne which has relatively low socioeconomic status (64). Hence, we retrospectively examined data for patients presenting to our tertiary cardiac unit with acute MI to ascertain what proportion was young. Our aim was to also identify any differences in risk factors, demographics, angiographic findings and in-hospital outcomes between young and older patients.

4.2 Methods

4.2.1 Patient selection

We undertook a retrospective analysis of all patients presenting to Western Health, Melbourne, Victoria, Australia, between August 2013 and July 2014 with acute MI and at least 50% stenosis demonstrated in at least one epicardial coronary artery via diagnostic coronary angiography. Patients less than 18 years of age and those presenting with spontaneous coronary artery dissection or stent thrombosis were excluded. This was to ensure capture of patients presenting with primary coronary atherosclerosis. The patients were divided into two sub-groups by age; those who were aged 55 years or younger and those who were older. There is disparity in the literature on the definition of young with respect to premature CHD and MI. The term young varies from ≤40 (7-9) to ≤55 years of age (10). Others have suggested 45 years as a cut off when defining young with respect to MI (11-13). As there is no universally accepted age cut-off we have elected to investigate the higher age cut-off.
The patients were identified from the local cardiac catheterisation database. All procedures were performed at Western Health, which is a tertiary cardiac referral centre for a large area in Melbourne, Australia and surrounding rural areas. Coronary angiography was performed by our experienced interventional cardiologists in a General Electric Inova cathlab. The degree of coronary stenosis was visually determined. Ad-hoc percutaneous coronary intervention (PCI) was performed to the culprit lesion based on the discretion of the performing cardiologist. Written consent was obtained from every patient and the local human research ethics committee approved the study.

4.2.2 Definitions

Acute MI was defined by evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia (65). Evidence of myocardial necrosis was confirmed by detection of a rise and/or fall of cardiac troponin (Siemens TnT-Ultra, on a Centaur XP analyser) with at least one value above the 99th percentile upper reference limit and with at least one of the following: symptoms of ischemia, new or presumed new significant ST-segment–T wave changes or new left bundle branch block, development of pathological Q waves in the electrocardiogram (ECG), presence of severe coronary stenosis or identification of an intracoronary thrombus by coronary angiography (65). ST-elevation myocardial infarction (STEMI) was defined if there was at least 0.2mV new ST elevation at the J point in contiguous precordial leads or 0.1mV elevation in other contiguous leads on ECG (65). Non ST-elevation
myocardial infarction (NSTEMI) was diagnosed when the criteria of acute MI were fulfilled without the presence of at least one of the features of STEMI (65).

Previous MI was defined if there was prior medical record entry clearly stating history of MI. Previous PCI was defined if there was a history of previous coronary angioplasty with or without stent insertion. Family history of premature CHD was defined as history of MI, PCI or coronary artery bypass grafting (CABG) in a first-degree relative if they were ≤55 years of age and male or ≤65 years of age and female. Ex-smoking was defined as having quit at least 30 days prior to inclusion. History of peripheral vascular disease and previous cerebrovascular accident (CVA) was recorded if it was clearly documented in the medical records.

In terms of outcomes data, in-hospital MI was determined if further ischaemic symptoms lasting more than 30 minutes occurred in association with new ECG changes, biomarker (troponin) rise or both. CVA was defined as a new focal neurologic deficit of presumed vascular cause persisting for more than 24 hours and without evidence of a nonvascular cause according to a neurologic imaging study. Death was defined as all-cause mortality and subdivided into two categories, ‘cardiovascular’ and ‘non-cardiovascular’. Major adverse cardiovascular event (MACE) was defined as the combination of death, new MI, target vessel revascularisation (TVR) for in-hospital stent thrombosis and CVA.
4.2.3 Outcomes of interest

Particular outcomes of interest include the proportion of young patients presenting with acute MI and potential differences that exist in risk factors, demographics, angiographic findings and in-hospital outcomes between young and older patients.

4.2.4 Statistical analysis

Categorical variables were expressed as numbers and percentages, while continuous variables were expressed as mean and standard deviation. Comparison of categorical variables between young and older patient groups was performed using Chi-squared or Fisher’s exact test. Continuous variables were compared using an unpaired t-test. Odds ratios (OR) were calculated using binary logistic regression. Statistical tests were performed using Minitab 17 Statistical Software (2010) and a 2 sided p value ≤ 0.05 was considered statistically significant. Data capture was complete with no identifiable missing information.

4.3 Results

Over the study period, 368 patients were admitted to our unit with acute MI who met the study criteria. Of these, 119/368 (32.3%) were ≤55 years of age and 249/368 (67.7%) were older. Demographic and risk factor profiles for the
cohorts are shown in Table 5.1. The majority of patients in both groups were male; noticeably there was a larger proportion of males in the younger cohort. The proportion of patients with family history of premature CHD was greater in those aged ≤55 years by a factor of almost five. The proportion of younger patients who were current smokers was more than twice that of the older cohort.
<table>
<thead>
<tr>
<th>Total cohort (n=368)</th>
<th>Patients ≤55 years of age (n=119)</th>
<th>Patients &gt;55 years of age (n=249)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years ± SD)</td>
<td>61.1 ± 12.8</td>
<td>46.7 ± 5.7</td>
<td>68.1 ± 8.9</td>
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<tr>
<td>Mean BMI (kg/m² ± SD)</td>
<td>28.6 ± 5.2</td>
<td>29.0 ± 5.0</td>
<td>28.4 ± 5.2</td>
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<tr>
<td>Male, n (%)</td>
<td>298 (81.0%)</td>
<td>105 (88.2%)</td>
<td>193 (77.5%)</td>
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<tr>
<td>Previous MI, n (%)</td>
<td>93 (25.3%)</td>
<td>12 (10.1%)</td>
<td>81 (32.5%)</td>
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<tr>
<td>Previous PCI, n (%)</td>
<td>61 (16.6%)</td>
<td>13 (10.9%)</td>
<td>48 (19.3%)</td>
</tr>
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<td>Previous CABG, n (%)</td>
<td>29 (7.9%)</td>
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<td>Family history of premature CHD, n (%)</td>
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<td>50 (42.0%)</td>
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<td>Type 1 diabetes mellitus, n (%)</td>
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<td>3 (2.5%)</td>
<td>3 (1.2%)</td>
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<tr>
<td>Type 2 diabetes mellitus, n (%)</td>
<td>114 (31.0%)</td>
<td>25 (21.0%)</td>
<td>89 (35.7%)</td>
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<tr>
<td>Hypertension, n (%)</td>
<td>223 (60.6%)</td>
<td>59 (49.6%)</td>
<td>164 (65.9%)</td>
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<tr>
<td>Dyslipidaemia, n (%)</td>
<td>202 (54.9%)</td>
<td>73 (61.3%)</td>
<td>129 (51.8%)</td>
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<td>Smoking current, n (%)</td>
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<td>75 (63.0%)</td>
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<tr>
<td>Smoking ex, n (%)</td>
<td>75 (20.4%)</td>
<td>9 (7.6%)</td>
<td>66 (26.5%)</td>
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<td>PVD, n (%)</td>
<td>13 (3.5%)</td>
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<td>CVA, n (%)</td>
<td>16 (4.4%)</td>
<td>4 (3.4%)</td>
<td>12 (4.8%)</td>
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</table>

BMI = body mass index, MI = myocardial infarction, PCI = percutaneous coronary intervention, CABG = coronary artery bypass grafting, CHD = coronary heart disease, PVD = peripheral vascular disease, CVA = cerebrovascular accident. *p is for comparison between patients ≤55 years of age and patients >55 years of age.
Clinical characteristics are shown in Table 2. The mean peak serum troponin I and mean peak creatine kinase was higher in patients ≤55 years of age. Patients aged >55 years were more likely to have severe reduction of their left ventricular systolic function and were more likely to present in Killip class 4.

Angiographic characteristics are shown in Table 3. Multivessel disease was identified in over two-thirds of patients >55 years of age. On multivariate analysis being male and having dyslipidaemia were found to be independent predictors for multivessel disease in the younger cohort (Table 4). In the older cohort, type 2 diabetes mellitus was the only independent predictor for multivessel disease (Table 5).

Three hundred and thirteen patients proceeded to PCI. Of these, 103/119 (86.6%) were from the young cohort and 210/249 (84.3%) were older (p=0.641). In the patients who proceeded to PCI, the proportion of patients with culprit vessel occlusion was higher in the younger group (48/103 (46.6%) vs. 73/210 (34.8%), p=0.043).

In-hospital clinical outcomes are shown in Table 6. There were significantly more in-hospital deaths and MACE among patients >55 years of age. All deaths were deemed to be secondary to a cardiac cause.
Table 4.2: Patient clinical data

<table>
<thead>
<tr>
<th></th>
<th>Total cohort (n=368)</th>
<th>Patients ≤55 years of age (n=119)</th>
<th>Patients &gt;55 years of age (n=249)</th>
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<tbody>
<tr>
<td>STEMI, n (%)</td>
<td>190 (51.6%)</td>
<td>61 (51.3%)</td>
<td>129 (51.8%)</td>
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<td>NSTEMI, n (%)</td>
<td>178 (48.4%)</td>
<td>58 (48.7%)</td>
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<td>Mean admission serum creatinine (micromol/L ±SD)</td>
<td>88.1 ± 74.7</td>
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<td>Mean peak TNI (micrograms/L ± SD)</td>
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<td>Mean peak CK (units/L ± SD)</td>
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<td>ECG changes</td>
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<td>ECG ST elevation, n (%)</td>
<td>190 (51.6%)</td>
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<td>121 (48.6%)</td>
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<td>ECG ST depression, n (%)</td>
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<td>4 (3.4%)</td>
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<td>ECG T wave inversion, n (%)</td>
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<td>Arrhythmias</td>
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<td>Heart block, n (%)</td>
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<td>105 (88.2%)</td>
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<td>Killip class</td>
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<td>Killip I, n (%)</td>
<td>321 (87.2%)</td>
<td>114 (95.8%)</td>
<td>207 (83.1%)</td>
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<td>Killip II, n (%)</td>
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<td>Killip III n (%)</td>
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<td>Killip IV, n (%)</td>
<td>13 (3.5%)</td>
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LV systolic function

<table>
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<tr>
<th>LV Preserved, n (%)</th>
<th>LV Mild, n (%)</th>
<th>LV Moderate, n (%)</th>
<th>LV Severe, n (%)</th>
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<tr>
<td>168 (46.7%)</td>
<td>99 (27.5%)</td>
<td>73 (20.3%)</td>
<td>20 (5.6%)</td>
</tr>
<tr>
<td>64 (54.2%)</td>
<td>32 (27.1%)</td>
<td>20 (17.0%)</td>
<td>2 (1.7%)</td>
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<td>104 (43.0%)</td>
<td>67 (27.7%)</td>
<td>53 (21.9%)</td>
<td>18 (7.4%)</td>
</tr>
</tbody>
</table>

Thrombolysis, n (%)

<table>
<thead>
<tr>
<th>Thrombolysis, n (%)</th>
<th>Proceed to CABG, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 (5.2%)</td>
<td>20 (5.4%)</td>
</tr>
<tr>
<td>8 (6.7%)</td>
<td>8 (6.7%)</td>
</tr>
<tr>
<td>11 (4.4%)</td>
<td>12 (4.8%)</td>
</tr>
</tbody>
</table>

STEMI = ST-elevation myocardial infarction, NSTEMI = non ST-elevation myocardial infarction, L = litre, TNI = troponin I, CK = creatine kinase, ECG = electrocardiogram, AF = atrial fibrillation, VT/VF = ventricular tachycardia or ventricular fibrillation, Heart block = Mobitz II or complete heart block, LV Preserved = left ventricular systolic function preserved (left ventricular ejection fraction > 50%), LV Mild = mild reduction of left ventricular systolic function (left ventricular ejection fraction > 40% - 50%), LV Moderate = moderate reduction of left ventricular systolic function (left ventricular ejection fraction 35 - 40%), LV Severe = severe reduction of left ventricular systolic function (left ventricular ejection fraction < 35%), CABG = coronary artery bypass grafting.
### Table 4.3: Angiographic characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total cohort (n=368)</th>
<th>Patients ≤55 years of age (n=119)</th>
<th>Patients &gt;55 years of age (n=249)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial access, n (%)</td>
<td>118 (32.1%)</td>
<td>53 (44.5%)</td>
<td>65 (26.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Crossover, n (%)</td>
<td>2 (0.5%)</td>
<td>1 (0.8%)</td>
<td>1 (0.4%)</td>
<td>0.543</td>
</tr>
<tr>
<td>Number of diseased</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vessels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 vessel, n (%)</td>
<td>136 (37.0%)</td>
<td>61 (51.3%)</td>
<td>75 (30.1%)</td>
<td></td>
</tr>
<tr>
<td>2 vessels, n (%)</td>
<td>123 (33.4%)</td>
<td>36 (30.3%)</td>
<td>87 (34.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3 vessels, n (%)</td>
<td>109 (29.6%)</td>
<td>22 (18.5%)</td>
<td>87 (34.9%)</td>
<td></td>
</tr>
<tr>
<td>Multivessel disease, n (%)</td>
<td>232 (63.0%)</td>
<td>58 (48.7%)</td>
<td>174 (69.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCI, n (%)</td>
<td>313 (85.1%)</td>
<td>103 (86.6%)</td>
<td>210 (84.3%)</td>
<td>0.577</td>
</tr>
<tr>
<td>GPIIbIIIa inhibitor, n (%)</td>
<td>100 (27.2%)</td>
<td>43 (36.1%)</td>
<td>57 (22.9%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Bivalirudin, n (%)</td>
<td>5 (1.4%)</td>
<td>2 (1.7%)</td>
<td>3 (1.2%)</td>
<td>0.712</td>
</tr>
<tr>
<td>IABP, n (%)</td>
<td>2 (0.5%)</td>
<td>0 (0%)</td>
<td>2 (0.8%)</td>
<td>1</td>
</tr>
</tbody>
</table>

Crossover = arterial access crossover from radial to femoral or vice versa, PCI = percutaneous coronary intervention, GPIIbIIIa = glycoprotein IIb/IIIa, IABP = intra-aortic balloon pump. Multivessel disease = angiographic stenosis of at least 50% stenosis in at least two epicardial coronary arteries. *p is for comparison between patients ≤55 years of age and patients >55 years of age.
### Table 4.4: Predictors of angiographic multivessel disease in patients ≤55 years of age

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Patients with outcome</th>
<th>Univariable</th>
<th></th>
<th></th>
<th>Multivariable</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Odd ratio (95% CI)</td>
<td>p</td>
<td></td>
<td>Odd ratio (95% CI)</td>
<td>p</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>57</td>
<td>15.44 (1.95, 122.32)</td>
<td>0.010</td>
<td></td>
<td>14.57 (1.66, 128.04)</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>Ref -</td>
<td>-</td>
<td></td>
<td>Ref -</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Previous MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
<td>0.73 (0.22, 2.44)</td>
<td>0.606</td>
<td></td>
<td>1.04 (0.18, 6.13)</td>
<td>0.961</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>53</td>
<td>Ref -</td>
<td>-</td>
<td></td>
<td>Ref -</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Family history of premature CHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>29</td>
<td>1.90 (0.91, 3.98)</td>
<td>0.087</td>
<td></td>
<td>1.37 (0.58, 3.21)</td>
<td>0.473</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>29</td>
<td>Ref -</td>
<td>-</td>
<td></td>
<td>Ref -</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>2.14 (0.19, 24.29)</td>
<td>0.538</td>
<td></td>
<td>2.68 (0.17, 43.18)</td>
<td>0.488</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>56</td>
<td>Ref -</td>
<td>-</td>
<td></td>
<td>Ref -</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>14</td>
<td>1.45 (0.60, 3.51)</td>
<td>0.415</td>
<td></td>
<td>1.34 (0.46, 3.94)</td>
<td>0.592</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>44</td>
<td>Ref -</td>
<td>-</td>
<td></td>
<td>Ref -</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>30</td>
<td>1.18 (0.58, 2.43)</td>
<td>0.648</td>
<td></td>
<td>0.71 (0.28, 1.80)</td>
<td>0.468</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>28</td>
<td>Ref -</td>
<td>-</td>
<td></td>
<td>Ref -</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
CI = confidence interval, Ref = reference class, MI = myocardial infarction, CHD = coronary heart disease. * Multivariable analysis is adjusted for age, body mass index, sex, previous MI, previous percutaneous coronary intervention, family history of premature CHD, type 1 diabetes mellitus, type 2 diabetes mellitus, hypertension, dyslipidaemia, smoking current and ex.
Table 4.5: Predictors of angiographic multivessel disease in patients >55 years of age

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Patients with outcome</th>
<th>Univariable</th>
<th>Multivariable*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odd ratio</td>
<td>p</td>
<td>Odd ratio</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td></td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>36</td>
<td>Ref</td>
<td>-</td>
</tr>
<tr>
<td>Yes</td>
<td>138</td>
<td>1.39 (0.74, 2.62)</td>
<td>0.301</td>
</tr>
<tr>
<td>Previous MI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>116</td>
<td>Ref</td>
<td>-</td>
</tr>
<tr>
<td>Yes</td>
<td>58</td>
<td>1.13 (0.63, 2.03)</td>
<td>0.680</td>
</tr>
<tr>
<td>Family history of premature CHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>159</td>
<td>Ref</td>
<td>-</td>
</tr>
<tr>
<td>Yes</td>
<td>15</td>
<td>0.92 (0.36, 2.35)</td>
<td>0.856</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>102</td>
<td>Ref</td>
<td>-</td>
</tr>
<tr>
<td>Yes</td>
<td>72</td>
<td>2.41 (1.30, 4.47)</td>
<td>0.005</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>56</td>
<td>Ref</td>
<td>-</td>
</tr>
<tr>
<td>Yes</td>
<td>118</td>
<td>1.33 (0.76, 2.33)</td>
<td>0.323</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>81</td>
<td>Ref</td>
<td>-</td>
</tr>
<tr>
<td>Yes</td>
<td>93</td>
<td>1.24 (0.72, 2.14)</td>
<td>0.430</td>
</tr>
<tr>
<td>Smoking current</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>126</td>
<td>Ref</td>
<td>-</td>
</tr>
<tr>
<td>Yes</td>
<td>48</td>
<td>1.21 (0.65, 2.26)</td>
<td>0.557</td>
</tr>
<tr>
<td>Smoking ex</td>
<td>No</td>
<td>Ref</td>
<td>-</td>
</tr>
<tr>
<td>------------</td>
<td>-----</td>
<td>-----</td>
<td>----</td>
</tr>
<tr>
<td></td>
<td>124</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>50</td>
<td>1.49 (0.78, 2.83)</td>
<td>0.226</td>
</tr>
</tbody>
</table>

CI = confidence interval, Ref = reference class, MI = myocardial infarction, CHD = coronary heart disease. Multivariable analysis is adjusted for age, body mass index, sex, previous MI, previous percutaneous coronary intervention, family history of premature CHD, type 2 diabetes mellitus, hypertension, dyslipidaemia, smoking current and ex.
## Table 4.6: In-hospital clinical outcomes

<table>
<thead>
<tr>
<th></th>
<th>Total cohort (n=368)</th>
<th>Patients ≤55 years of age (n=119)</th>
<th>Patients &gt;55 years of age (n=249)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, n (%)</td>
<td>13 (3.5%)</td>
<td>0 (0%)</td>
<td>13 (5.2%)</td>
<td>0.011</td>
</tr>
<tr>
<td>MI, n (%)</td>
<td>4 (1.1%)</td>
<td>1 (0.8%)</td>
<td>3 (1.2%)</td>
<td>0.752</td>
</tr>
<tr>
<td>TVR, n (%)</td>
<td>3 (0.8%)</td>
<td>1 (0.8%)</td>
<td>2 (0.8%)</td>
<td>1</td>
</tr>
<tr>
<td>CVA, n (%)</td>
<td>2 (0.5%)</td>
<td>0 (0%)</td>
<td>2 (0.8%)</td>
<td>1</td>
</tr>
<tr>
<td>MACE, n (%)</td>
<td>18 (4.9%)</td>
<td>1 (0.8%)</td>
<td>17 (6.8%)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

MI = myocardial infarction, TVR = target vessel revascularisation, CVA = cerebrovascular accident, MACE = major adverse cardiovascular event. *p is for comparison between patients ≤55 years of age and patients >55 years of age.
4.4 Discussion

We found that approximately one-third of all patients admitted to our institution with acute MI who have at least 50% angiographic stenosis demonstrated in at least one epicardial coronary were aged $\leq 55$ years. This is unexpectedly high compared to the literature. Fournier et al demonstrated only 4% of their patients admitted with MI were young although their cut off age for young patients was $\leq 40$ years which is considerably less than our definition (16). In addition, the younger cohort in our study had higher prevalence of diabetes mellitus, hypertension and dyslipidaemia compared to the young cohort in the study conducted by Fournier et al (16). Loughnan et al reported approximately 20% of patients admitted with MI were below the age of 55 years (18). The high proportion of young patients found in our study could possibly be explained by the fact that we only included patients proceeding onto coronary angiography. This potentially may have excluded older patients in whom coronary angiography may have been contraindicated due to comorbidities. Another potential explanation for the discrepancy is the low socioeconomic status of the cohort in our study.

The finding of our study conforms with other studies that have shown young MI patients are more likely to be male, have a family history of premature CHD, be current smokers (6,11,21,22,24-26) and with evidence that they are less likely to have previous history of CHD, type 2 diabetes mellitus or hypertension (6,24,25,27). We found a higher proportion of ex smokers among the older group, which is also supported by previous data (6). The fact
that approximately two-thirds of the younger patients were current smokers at the time of their presentation with MI is a major public health concern. The low socioeconomic environment of the catchment area of our hospital is a likely major contributing factor for this finding (64). Prior studies also describe an association between dyslipidaemia and young MI (25,26). The rate of dyslipidaemia in our study was numerically higher in the younger group but this did not reach statistical significance. This maybe due to under reporting, under diagnosis or under treatment of this particular condition in the younger group, which has been described in other studies (21).

There was no difference with respect to the proportion of patients presenting with STEMI in each group. Contemporary data suggests most young MI patients will present with NSTEMI but the proportion of patients presenting with STEMI appears to be rising (14). The mean peak serum troponin I was higher in the younger group. This is an unexpected finding given previous reports of the presence of higher troponin levels in older patients (66). Our finding maybe partially explained by the fact that our laboratory only reports troponin values up to 50 micrograms/L. Hence, the older group may have had potentially higher troponin values that were not reported. Left ventricular systolic function was more likely to be severely impaired in the older group, which is supported by the literature (11,24). Only older patients were found to be in Killip class IV and all of them presented due to out of hospital cardiac arrest. This was despite no statistical difference being found with respect to arrhythmia between the two groups.
As demonstrated previously in the literature, multivessel and three-vessel disease were found to be less frequent in the younger cohort (16,24). This is likely due to a number of factors including age and comorbidities such as increased prevalence of hypertension and diabetes in the older cohort. Even though multivessel disease was less common in the young it was still found in approximately 50% of patients, which is considerably higher than in previous reports (16,24). Our data agrees with previous reports that among the young, men are more likely to have multivessel disease as compared to women (24) but we were also able to show an association with dyslipidaemia. As illustrated in previous reports we found an association between type 2 diabetes mellitus and multivessel disease (67) but only in the older cohort. This is likely due to increasing susceptibility for multivessel disease with a longer exposure to type 2 diabetes mellitus (68).

Only a single patient in the younger cohort had MACE, which is in keeping with the literature (16). This was due to a proximal edge dissection of a stented right coronary artery, which caused reinfarction and required further PCI. MACE in patients aged >55 years was mainly driven by in-hospital deaths. These were all cardiac deaths and were only recorded among patients from the older cohort. The cause of this was likely to be multifactorial. Firstly only patients in the older group presented in Killip class IV, which is known to be associated with higher in-hospital mortality (69). In addition, a higher proportion of patients in the older group exhibited severe left ventricular systolic dysfunction that has also been associated with increased in-hospital mortality (70). In addition the older cohort had higher proportion of type 2
diabetes mellitus that is also known to increase in-hospital mortality (71). Finally, there were likely other contributing comorbidities, which were not recorded as part of this study.

4.5 Study limitations

Our study was a single centre, retrospective and observational analysis. This can be associated with selection bias and missing information. As highlighted already, our design of only including patients who proceeded onto coronary angiography may have potentially excluded more older patients. No follow up data was presented as this study was based only on in-hospital records. Telephone follow up could be a potential way to obtain short and long term outcome data in the future.

4.6 Conclusion

In this study covering a low socioeconomic Australian population, one-third of patients presenting with acute MI were young. These young patients were more likely to be male, have a family history of premature CHD and be current smokers. The rate of smoking among the young cohort exceeded 60%. Multivessel disease was discovered in approximately 50% of young MI patients but was more common in the older group. In-hospital outcomes in young MI patients were excellent with no deaths demonstrated and MACE
rate of <1%. This was in stark contrast to the older cohort that had an in-hospital mortality and MACE rate of approximately 5% and 7% respectively.
CHAPTER 5: SCREENING FOR ASYMPTOMATIC CORONARY HEART DISEASE IN THE YOUNG ‘AT RISK’ POPULATION: WHO AND HOW?

5.1 Background

Coronary heart disease (CHD) remains the primary cause of death worldwide (2). There is general agreement regarding the need for investigation of symptomatic patients suspected of CHD and subsequent instigation of therapies (72,73). Screening asymptomatic individuals, however, is controversial but potentially allows early detection and more accurate risk estimation (74). Estimating risk in any one individual is important not only for implementation of effective management strategies but also for reassurance and psychosocial security. In some cases, the first presentation of CHD maybe myocardial infarction (MI) or worse, sudden cardiac death (SCD) (75). Screening may allow detection of occult CHD prior to such catastrophic events. That said, while these catastrophic events are often associated with CHD, silent or asymptomatic ischaemia may account for more than 75% of ischaemic episodes (76).

Wilson et al, on behalf of the World Health Organization, have described the principles that should underlie any potential screening program (5). This includes screening for health problems that are important, have accepted treatment, have available acceptable diagnostic tools and have an early asymptomatic stage (5). Identifying asymptomatic disease is only useful if
disease progression can be altered (5). Dietary and pharmacological interventions have been shown to reduce morbid cardiovascular events in asymptomatic individuals (77-80) although the published data did not specifically focus on a young cohort. Both the PREDIMED and the JUPITER studies enrolled participants without known CHD and were able to demonstrate a reduction of major cardiovascular events with administration of a Mediterranean diet and a statin respectively (77,79). The current U.S. preventive services task force recommends low-to-moderate-dose statins in asymptomatic adults aged 40 to 75 years who have one or more risk factors for CHD and a calculated 10-year event risk of 10% or greater (81).

Screening of the general population is not cost effective (5) hence a mechanism is required to identify ‘at risk’ individuals. Risk of CHD can be estimated in any individual via risk scores and this can be further refined with functional and non-functional investigations. Here we review existing risk estimation tools, potential screening modalities and the appropriateness of implementing them in estimating risk of CHD in the young.

5.1.1 CHD in the ‘young’

20% of men as young as 34 have been shown to have advanced coronary artery lesions (15). The Framingham Heart Study demonstrated a rate of MI in men and women between the ages of 30-44 of 51.1/1000 and 7.4/1000 respectively (4). A higher rate of MI of between 4% and 10% among those aged ≤45 years was reported in other studies with the vast majority of them aged ≤45 years was reported in other studies with the vast majority of them aged ≤45 years was reported in other studies with the vast majority of them aged ≤45 years was reported in other studies with the vast majority of them aged ≤45 years was reported in other studies with the vast majority of them.
being male (16,17,82). 20% of MI have been demonstrated to occur in the young in an urbanized Australian population (18). It of course stands to reason that the prevalence of asymptomatic CHD in the young is higher.

There is some evidence to suggest that the prevalence may be even higher in a socio economically deprived area (37). Despite this there is paucity of data on the prevalence of CHD and MI of the young.

The manifestation of developing heart disease at a young age can be psychologically and economically challenging not only for the individual but also for family members and especially siblings who may fear for their own health. Family history of premature CHD is known to be a risk factor for CHD (26,83) but is lacking in the widely accepted risk scores. The prevalence of family history of CHD in young MI patients has been reported as high as 64% (11,24,82). In the Framingham Offspring Study, presence of sibling CHD increases the risk of a cardiovascular event in young adults by almost two fold (84). It can therefore be hypothesized that siblings of patients who experience MI at a young age maybe at increased risk of asymptomatic CHD and future premature MI. Yusuf et al demonstrated the importance of family history as a risk factor for MI particularly in young patients (26). They quoted the population attributable risk of MI in the young compared with older individual to be 14.8% (26). With the aid of an effective screening tool premature CHD could potentially be identified in these individuals.

Screening asymptomatic patients for subclinical CHD could be equally important in young and old populations at risk. This paper, however,
specifically focuses on a younger population because of significant socioeconom
impact from the consequences of CHD in this sub-group. The application of an effective screening strategy to the young is likely to lead to large clinical and social successes due to their increased potential life expectancy. As we have already discussed, screening an entire population to identify this group is neither cost effective nor feasible. Hence identification of the ‘at risk’ group is paramount in implementation of any screening tool.

5.2 Estimating risk

The contemporary “gold standard” for detection of CHD is the catheter-based coronary angiogram. Catheter based selective coronary angiography, however, is an invasive procedure that is associated with a small but significant risk of life threatening complications such as stroke, bleeding and MI (85). Hence, catheter-based coronary angiography is not suitable as a screening tool or a method of estimating risk of CHD.

The concept of screening requires not only a cost-effective strategy but also clearly established treatment or disease modifying tools for the pathology being screened for (5). It must also be safe and accurate, with high sensitivity in order to detect disease (5). Screening must be targeted at disorders with high prevalence (5) and CHD appears to be perfectly positioned in this respect. Existing screening programs such as strategies aimed at detecting colorectal carcinoma via faecal occult blood testing (FOB) (86) and breast carcinoma via mammography (87) demonstrate many of these qualities.
Controversies do exist regarding the use of FOB and mammography, however, overall they are regarded beneficial and potentially helpful in mitigating the risk of late detection and its consequences.

5.2.1 Risk scores

Risk scores are based on the premise that an individual’s total burden of risk factors for CHD is more predictive than the level of any one particular risk factor. They predict a statistical population attributable risk but lack sensitivity or specificity in identifying an individual’s risk (88).

Perhaps the most well known risk scoring system in the field of CHD originated from the Framingham Heart Study (89). This study utilized observational data to formulate a risk estimation system based upon categorical variables where an individual’s risk of having a CHD event is predicted at 10 years. The variables incorporated are age, presence of diabetes, smoking, blood pressure and total and LDL cholesterol. The receiver-operating characteristic (ROC) curve c-statistic of the model (using total cholesterol as a variable) is 0.73 and 0.76 in men and women respectively. A c-statistic of greater than 0.7 typically suggests a reasonable model (90). There are a number of factors associated with this tool that may not necessarily make it universally applicable however. It was a single centre study, based in the United States of America, and focused on a middle-aged white cohort with data from the early 70s.
The contemporary Interheart study sought to overcome some of these limitations (26,91). It was a large case-control study of acute MI in 52 countries that attempted to represent every inhabited continent. The risk factors required for estimation of risk are age, apolipoprotein B:A1 ratio, smoking, passive smoking, presence of diabetes and hypertension. Validation of the score was demonstrated across an international population with consistent results across ethnic groups and geographic regions (91). An area under the ROC curve c-statistic of 0.71 was established.

A risk scoring system developed specifically for Europe was published in 2003. The Systemic Coronary Risk Evaluation (SCORE) project was established due to concerns of applying the Framingham Risk Score to a European cohort (92). Data was derived from 12 European countries and comprised over 200,000 people. Variables of the score are age, sex, blood pressure, smoking and either total cholesterol or cholesterol/HDL ratio. Contrary to the other two risk factors described above, SCORE aims to predict fatal cardiovascular risk rather than CHD risk. Areas under the ROC curve for this risk scoring system are between 0.71 and 0.84 (92) over the differing geographical locations studied.

5.2.2 Exercise stress test

The simple exercise stress test (EST) or exercise electrocardiograph (ECG) is a mainstay of investigating patients suspected of CHD but it has also been utilized as a screening tool due to the correlation demonstrated between...
asymptomatic or silent ischaemia and CHD mortality (93,94). Rautaharju et al (93) and Ekelund et al (94) showed the potential of a positive EST to predict the risk of cardiac death. It appears, however, that the exercise capacity of an individual during exercise rather than ST changes, which is usually the factor used to discriminate between a normal and abnormal test, maybe the better discriminator of outcome (95).

Presence of risk factors strongly affects the pretest probability of an EST (96,97). The relative risk of CHD mortality if an individual has 3 or more risk factors and an abnormal EST is 80 (96) with a 5.9 fold increased in CHD mortality for a smoker with silent ischaemia (97). EST can predict CHD death with high specificity of 89% but this is countered against relatively poor sensitivity of 61%, as demonstrated by Gibbons et al (96).

The published literature is biased when describing the diagnostic accuracy of EST as most of the studies include symptomatic rather than asymptomatic individuals. The EST studies discussed above focus on mortality and hence cannot be used to evaluate the sensitivity and specificity of EST in detecting asymptomatic CHD. For this one would require all patients with a negative EST to undergo coronary angiography. A review suggests specificity and sensitivity of approximately 80% and 50% respectively of EST in an asymptomatic cohort (98). Data from a meta-analysis, not exclusively looking at asymptomatic individuals, reports wide variability with sensitivity and specificity of 68±16% (SD) and 77±17% (SD) respectively (99).
EST is usually only viable if the underlying ECG is normal and is dependent on an individual being able to exercise. Hence it is not suitable for all individuals.

5.2.3 Exercise myocardial perfusion imaging

Radionuclide myocardial perfusion imaging (MPI) may be utilized for the detection of CHD and thereby to estimate individual risk. The uptake of tracer by the myocardium can be detected and acts as a surrogate for the presence and magnitude of CHD. It can therefore also be used to identify ischaemia of specific myocardial territories. Similar to EST, however, the ability of MPI to detect ischaemia is dependent on an adequate level of exercise and therefore heart rate being achieved (100). Also, as with EST, certain ECG abnormalities can impair the predictive value of MPI. In particular left bundle branch block can provide false positives indicating myocardial ischaemia of the septum (101).

Meta-analysis of weighted pooled results has demonstrated 87% (95% CI, 86%-88%) sensitivity of MPI for diagnosis of CHD but relatively poor specificity of 64% (95% CI, 60%-68%) (102). This could potentially lead to further unnecessary invasive investigations due to false positives. If one restricts the positive definition of this modality to multiple myocardial distributions rather than single territories then the specificity increases to 87% (95% CI, 85%-89%) but at the cost of a much lower sensitivity of 44% (95% CI, 38%-49%) (102). Conversely however the accuracy of MPI in detecting left
main and triple vessel coronary artery disease is low (103). Kwok et al (104) demonstrated 26% of patients had triple vessel or left main coronary artery disease where the MPI was abnormal in only a single coronary territory.

The balance of evidence for the usefulness of MPI is weighted in the direction of symptomatic rather than asymptomatic individuals due to lack of data. Blumenthal et al (105) however conducted a study concentrating on asymptomatic siblings of persons with documented CHD. They demonstrated a high false positive rate of MPI with only 25% of participants who had a positive MPI having angiographically significant disease as defined by coronary stenosis greater than 70%.

As with any modality utilizing radiation the exposure to the patient always needs to be taken into consideration. This is of particular importance with the cumulative exposure of repeated studies. Radiation doses between 8 mSv and 30 mSv have been reported for MPI (106) depending on the isotope and protocol choices.

5.2.4 Exercise stress echocardiography

CHD may be detected by demonstration of wall motion abnormalities with the aid of two-dimensional stress transthoracic echocardiography. Myocardial stress is typically induced with exercise or pharmacotherapy using agents such as adenosine, dipyridamole or dobutamine. Use of dobutamine has been associated with achieving the optimum combination of sensitivity and specificity.
specificity (107).

Meta-analysis data, not exclusively concentrating on asymptomatic patients, suggests sensitivity and specificity of 85% (95% CI, 83%-87%) and 77% (95% CI, 74%-80%) respectively (102). Marwick et al (108) have validated a high positive predictive value of 89% for stress echocardiography but this was offset with a relatively low negative predictive value of 61%. In addition Marwick et al (108) reported reduced sensitivity of stress echocardiography in patients unable to tolerate dobutamine and therefore unable to reach target heart rate. The negative predictive value of stress echocardiography for prediction of MI and cardiac death however appears to be better at 98% (109).

Once again data on the asymptomatic cohort is lacking. In a small study conducted by Bacci et al (110), on 35 asymptomatic patients with type 2 diabetes mellitus, the sensitivity and specificity of stress echocardiography was demonstrated to be 21% and 94% respectively. This may not be applicable to a non diabetic cohort however and the diagnostic accuracy of stress echocardiography in an all comer asymptomatic cohort is unknown.

Unlike MPI which can be semi automated, the interpretation of stress echocardiography is subjective and dependent on the experience of the clinician (111). Certain patient characteristics such as presence of left ventricular hypertrophy, left bundle branch block and high body mass index may be associated with erroneous results and therefore preclude its use in
certain patient groups (108).

The use of stress echocardiography as a screening test for CAD may be appropriate given the relative high sensitivity and specificity that have been demonstrated. Also it has been shown to be at least as cost effective as MPI (112) but without the added potential risk of radiation that would be associated with MPI.

5.2.5 Coronary artery calcium scoring via computer tomography (CT)

Currently 64-detector multidetector row computer tomography (MDCT) can be used to quantify coronary artery calcification (CAC) and allow representation via the Agaston score (113). The sensitivity of CAC for detection of coronary stenosis ≥50% has been demonstrated to be as high as 91% but with a high variance of between 68-100% (114). Specificity in the literature is reported to be as low as 49% but again with a wide range between 21-100% (114). Similarly high negative predictive values of up to 100% and 97% with low positive predictive values of 66% and 62% in females and males respectively have been reported although this was for a low threshold score of between 0-20 (115). As with many modalities the sensitivity drops with increasing threshold cut off CAC scores and Budoff et al (116) have shown a sensitivity of 98% for CAC score > 0 and as low as 60% for CAC score of >400. There is a correlation between age and degree of coronary calcium with higher CAC scores found in higher age groups (115). Haberl et al (115) demonstrated an area under the ROC curve of >0.75 for all age groups for coronary stenosis.
CAC has been shown to predict CHD events in an asymptomatic cohort with a relative risk of 10.5 and 2.6 in men and women respectively (117). The accuracy of prediction for future CHD events appears to be related to the degree of coronary calcification with a sensitivity of 89% and 53% for CAC threshold cut off score of 100 and 680 respectively (118). CAC appears a better predictor of mortality over the traditional risk scores described above and is also able to accurately reclassify risk from intermediate to low and high risk (119,120). In an analysis of risk markers for incident CHD, CAC was found to be superior in comparison to ankle-brachial index, high sensitivity CRP and family history (HR 2.60, 0.79, 1.28, 2.18 respectively) (121).

5.2.6 Coronary CT angiography (CCTA)

CT can be utilized not only to determine the amount of calcium burden but also allows indirect visualization of the coronary arteries and therefore filling defects. Although MDCT scanners have high temporal resolution image acquisition, and therefore quality, it is still dependent on achieving a low enough heart rate, typically around 60-70 beats/min. It involves injection of iodinated contrast and therefore maybe contraindicated in certain individuals such as those with history of contrast allergy.
When considering the sensitivity and specificity of CCTA it is common for the literature to include evaluation at the patient level (i.e. patient has significant CHD or not) and at the segment level (accuracy of identifying site of CHD). For asymptomatic patients, the literature concentrates on patient level evaluation. With respect to patient level evaluation, Budoff et al demonstrated high sensitivity for CCTA of 95% (95% CI, 85%-99%) with modest specificity of 83% (95% CI, 76%-88%) for detection of ≥50% coronary artery stenosis (122). Positive and negative predictive values were 64% and 99% respectively. Miller et al however established a lower sensitivity of 85% (95% CI, 79%-90%) with a higher specificity of 90% (95% CI, 83%-94%) (123). Meanwhile Meijboom et al revealed the highest sensitivity of 99% (95% CI, 98%-100%) but with a correspondingly low specificity of 64% (95% CI, 55%-73%) (124). A systemic review published in 2008 confirms the high sensitivity of CCTA at 98% with comparatively low specificity of 88% (125).

CCTA has been utilized to detect asymptomatic CHD in young adults. Ha et al demonstrated CHD in a population of adults under the age of 40 years with a prevalence of >10% (126). They also illustrated increasing prevalence in higher risk groups that were determined via a risk scoring tool.

The utility of CCTA extends beyond the detection of ≥50% coronary artery stenosis as even the detection of nonobstructive (≤50% coronary artery stenosis) plaque allows risk to be predicted due to the relationship between nonobstructive coronary plaque and increased mortality (127,128). Other imaging modalities such as intravascular ultrasound and optical coherence...
tomography have been demonstrated to be useful in predicting the vulnerability of these mild plaques and thereby allow prediction of future acute coronary syndromes (129,130). These complementary imaging modalities are, however, invasive and therefore not suitable for screening.

Limitations of this modality include patient factors such as tachycardia, arrhythmias and inability to breath hold. As with many modalities increasing age can reduce the effectiveness and in the case of CCTA severe coronary calcification, which often coexists in the elderly, can interfere with image reconstruction. Radiation dose was an initial concern in the previous generations of MDCT scanners with effective doses up to 10.5mSv (131). With contemporary technology, however, the radiation dose can be reduced to well below 2mSv, which approximates to the Australian annual background radiation dose (132). That level of radiation exposure is estimated to result in an excess lifetime cancer risk of approximately 42/100 000 men and 62/100 000 women (131).

5.3 Current Practice Guidelines

5.3.1 American College of Cardiology Foundation/American Heart Association (ACC/AHA)

The 2010 ACC/AHA Task Force Practice Guidelines discuss screening for asymptomatic cardiovascular disease using the modalities described above.
The use of EST is suggested for intermediate-risk (6-10% 10-year risk) adults but only with a class IIb recommendation and importance is given to non-ECG markers as a surrogate for a positive test such as exercise capacity. Stress echocardiography is not recommended and the use of MPI is suggested only for those with diabetes or for those with a strong family history of CHD but again with a relatively weak class IIb recommendation. They suggest CAC to guide risk assessment in individuals at intermediate (10-20% 10-year risk) risk (class IIa recommendation) and low to intermediate (6-10% 10-year risk) risk (class IIb recommendation) but not for low (<6% 10-year risk) risk. CCTA was not recommended as a screening tool due, mainly, to a lack of evidence.

5.3.2 European Society of Cardiology (ESC)

The recommendation for the use of EST in cardiovascular risk assessment by the ESC is comparable to that of the ACC/AHA with a class IIb recommendation and similar emphasis focused on non-ECG markers (134). The 2012 ESC guidelines suggests use of CAC for cardiovascular risk assessment in asymptomatic adults at moderate (SCORE risk assessment 1 - <5% 10-year risk) risk with a grade IIa recommendation and alludes to the use of CCTA in the same group (134). ESC guidelines also suggest the use of clinical risk predictors and imaging tests in general are not given strong recommendation.
5.4 Discussion

Here we have presented various potential modalities and tools that can be used to estimate the risk of CHD and related mortality of an individual. Most of the data discussed however was not derived from studies aimed at screening asymptomatic patients and concentrates on patients aged over 50 years of age. As a result of this lack of data it is difficult to objectively review the modalities discussed above when considering their use for potential risk estimation in an asymptomatic cohort and therefore if the aim is to define the risk of CHD in a young ‘at risk’ group the application of this data to formulate a screening tool may not be appropriate.

If we hypothesize that a substantial number of patients with a strong family history of MI have significant CHD despite being asymptomatic then early detection of disease by imaging and non invasive functional tests may have a significant role in primary prevention and thereby lead to improved long term outcome. Currently available risk predictive algorithms may not be accurate in predicting the presence of CHD as detected on CCTA. Risk scores are a good tool in predicting population attributable risk but poor at demonstrating individual risk.

The anxiety associated with discovering premature CHD in a sibling should not be underestimated. Nor should the reassurance of knowing one does not have critical CHD. In order to do this however a screening modality is required which has a high sensitivity and hence a low false negative rate but at the
same time must also have sufficient specificity and therefore a low false positive rate. As we have illustrated above CCTA appears to be well positioned in this respect with very high sensitivity and negative predictive value, but without sacrificing specificity.

EST remains the most widely used and accessible non-invasive preliminary investigation but due to the poor relative sensitivity, with a wide variability, warrants further scrutiny. In any case it is usually performed as part of exercise stress echocardiography and exercise MPI. The high sensitivity of MPI appears to lend itself well to screening purposes but it exposes the individual to radiation without the benefit of the high specificity of CCTA. Stress echocardiography has a comparable sensitivity to MPI, at least in a symptomatic cohort, but has the advantage of a lack of radiation.

Currently CCTA does not have a strong recommendation by the AHA or ESC for the purposes of CHD screening but there is increasing momentum for its use in this cohort which is likely being driven by reducing radiation exposure and costs. As a result there is varying practices with the use of CCTA. In the past, screening via CCTA or CAC was discouraged in view of concern regarding the radiation dose. As discussed above, however, the radiation dose of this modality has decreased significantly in recent times due to advances of CT technology and better scanning protocols making it more attractive as an investigational tool.
5.5 Summary

The prevalence of CHD in the young is not insignificant and is higher among those with a family history of MI. Assessing these individual further with risk score estimation and screening investigations may allow the identification of a high risk group in whom the risk can be modified and future adverse events prevented. The screening tools chosen for this task should abide by the requirements of a suitable screening strategy. Currently available clinical risk score lacks specificity and sensitivity while functional stress tests lack strong clinical data for its sensitivity and specificity. CAC has emerged as a more reliable risk predictor in comparison with conventional risk assessment modality. CCTA is also a potential screening tool but it lacks clinical data and it comes with ionizing radiation, which has been a concern in the past.
CHAPTER 6: PREVALENCE OF ASYMPTOMATIC CORONARY HEART DISEASE IN THE SIBLINGS OF YOUNG MYOCARDIAL INFARCTION PATIENTS AS DETECTED BY CORONARY COMPUTER TOMOGRAPHY ANGIOGRAPHY: A PILOT STUDY (SACHSMI STUDY)

6.1 Introduction

Despite improving trends, coronary heart disease (CHD) remains the leading cause of death in the world (63). Often the initial presentation of patients with CHD is myocardial infarction (MI) with a sizeable proportion presenting catastrophically due to sudden cardiac death (75). In addition silent myocardial ischemia has been demonstrated to be a strong predictor of future CHD related morbidity and mortality (97). Implementation of an effective screening strategy therefore has the potential to reduce a substantial proportion of future CHD related events (5,74). Current data does not support mass screening of the general population for occult CHD and therefore it is imperative to identify an appropriate cohort who have the greatest to benefit from a screening program (5). The prevalence of CHD increases with age (135) but contemporary data appears to show a considerable proportion of the young are also affected (17,18). A CHD screening strategy directed at the young may yield higher rewards due to the potential for increased life expectancy and the socioeconomic impact from the consequence of CHD in this subgroup. It is not feasible to screen all young individuals hence an ‘at risk’ cohort needs to be identified (5). Family history of premature CHD has...
been identified as one of the major risk factors for CHD (11,13,26). This risk is not only restricted to parental history but also includes siblings with history of CHD (84). Hence family history and in particular sibling history of premature CHD could potentially be used to identify an ‘at risk’ cohort.

Coronary computer tomography angiography (CCTA) allows non-invasive detection of CHD with high sensitivity and specificity (122). It has been used in the past to demonstrate asymptomatic CHD in a young cohort but with a relatively low yield that likely suggests under-estimation of the prevalence due to indiscriminate screening (126). Exposure to radiation has been a concern with the use of CCTA. Due to advances in computer tomography technology, however, the radiation dose of CCTA has decreased significantly below 5 mSv and is approaching 1 mSv (136).

The Screening for Asymptomatic Coronary Heart disease in the Siblings of young Myocardial Infarction patients (SACHSMI, Australian New Zealand clinical trial registry number ACTRN12614000105640) study aims to demonstrate the feasibility of a screening program for CHD in a young ‘at risk’ group. The primary aims of this study are to estimate the prevalence of asymptomatic CHD in young siblings of young MI patients as detected by CCTA and to evaluate the reliability of cardiovascular risk scores for prediction of CHD.

6.2 Methods
6.2.1 Participant selection

Patients aged 55 years or younger presenting with acute MI and at least 50% stenosis demonstrated in at least one epicardial coronary artery on diagnostic coronary angiography to a tertiary community based hospital in Melbourne, Australia were prospectively identified. This group comprised the index MI cohort. Those less than 18 years of age were excluded. Patients presenting with spontaneous coronary artery dissection or stent thrombosis were excluded. The purpose of this was to ensure the cause of MI was coronary atherosclerosis.

These patients were then contacted to determine if they had siblings aged between 30 and 55 years if male and 30 and 60 years if female. Subsequently the siblings were invited to participate in the study following informed consent. The siblings comprised the participants for our study. Exclusion criteria included symptoms of CHD, known history of CHD, refusal to consent, intolerance to intravenous contrast, chronic renal impairment, atrial fibrillation, thyrotoxicosis, pregnancy, ventricular pacing, left bundle branch block, severe valvular heart disease and malignancy. The institutional human research ethics committee approved the study.

6.2.2 Screening tools

All participants were invited to undergo CCTA, which were performed with a low radiation dose (<5mSv) algorithm in compliance with the Australian Screening for asymptomatic coronary heart disease in the siblings of young myocardial infarction patients (SACHSMI).
National Health and Medical Research Council guidelines (137). All CCTA were performed with the General Electric™ 64 slice volume computed tomography (VCT) scanner using low radiation dose scanning protocol with prospective gating step and shoot scanning mode with 100kvp. Agatston coronary calcium score and CCTA reformatted images were obtained from the CCTA study for further analysis. Two Society of Cardiovascular Computerised Tomography level II equivalent (or higher) CCTA reporters read all studies. CHD by CCTA was considered present if there was at least one epicardial coronary artery with stenosis. Severity of CHD by CCTA was defined as none (0% luminal stenosis), mild (<50% luminal stenosis), moderate (50-69% luminal stenosis) and severe (≥70% luminal stenosis) in at least one epicardial coronary artery. Obstructive CHD by CCTA was defined as the presence of either moderate or severe stenosis in at least one epicardial coronary artery.

On a separate, earlier, occasion all participants underwent stress echocardiography. A standard protocol for conducting stress echocardiography was followed (138). Stress was induced either via graded treadmill exercise according to the Bruce protocol or with intravenous dobutamine to achieve target heart rate. A cardiologist subspecialising in echocardiography interpreted all stress echocardiography studies. A positive stress echocardiography was defined as the presence of a new or worsening regional wall motion abnormality in one or more segments.
In order to calculate cardiovascular risk scores fasting blood samples were obtained and analysed for total cholesterol, high-density lipoprotein (HDL) cholesterol, calculated low-density lipoprotein (LDL) cholesterol and triglycerides. Framingham (89), HeartScore (139) and InterHeart (140) risk score calculations were conducted for all participants.

6.2.3 Safety measure

Participants with luminal stenosis of ≥50% in the left main coronary artery or of ≥70% in the proximal left anterior descending coronary artery, proximal right coronary artery or proximal dominant circumflex coronary artery on CCTA were invited to undergo invasive coronary angiography. Further management was at the discretion of an independent cardiologist in consultation with the participant.

6.2.4 Outcomes of interest

The primary outcome was the number of participants who had evidence of obstructive CHD by CCTA. We also wished to know the predictive strength of the Framingham, HeartScore and InterHeart cardiovascular risk scores for prediction of obstructive CHD by CCTA. In addition we wished to identify if any of the traditional risk factors for CHD that were investigated were predictors of obstructive CHD by CCTA.
6.2.5 Statistical analysis

Categorical variables were expressed as numbers and percentages, while continuous variables were expressed as mean with standard deviation or median with first and third quartiles. Odds ratios (OR) were calculated using binary logistic regression. Statistical tests were performed using Minitab 17 Statistical Software (2010) and a 2 sided p value ≤ 0.05 was considered statistically significant. Data capture was complete with no missing information.

6.3 Results

Over a period of eighteen months we identified 167 patients admitted with acute MI who satisfied the study criteria. The recruitment process is illustrated in Figure 1. From this cohort of index MI patients, 50 sibling participants were recruited. Participant demographics, clinical risk factors and medications are listed in Table 1. The majority of participants were female, had dyslipidaemia and were either current or ex-smokers. Prevalence of prescribed medications for cardiovascular disease was low.

Framingham, HeartScore and InterHeart risk score calculations for the participants are listed in Table 2. The vast majority of the participants were low risk for future adverse CHD events according to Framingham and HeartScore predictions. Participant InterHeart scores however were more evenly spread with the largest proportion being in the high risk group.
Figure 6.1: Recruitment process

167 young index MI patients

87 (52.1%) index MI patients had eligible siblings

- No siblings or too young/old 53 (31.7%)
- Unable to contact index MI patient 25 (15.0%)
- Siblings already had CHD 2 (1.2%)

38 (43.7%) index MI patients with eligible siblings wished to participate

49 (56.3%) index patients with eligible siblings did not wish to/could not participate

51 siblings agreed to participate
(some index MI patients had multiple siblings)

- Lost to follow up 1

50 siblings participated

- Does not want to know 39 (79.6%)
- Unable to contact 7 (14.3%)
- Phobia to needles 1 (2.0%)
- Contrast allergy 1 (2.0%)
- Malignancy 1 (2.0%)

CHD = coronary heart disease, MI = myocardial infarction.
Table 6.1: Participant demographics, clinical risk factors and medications

<table>
<thead>
<tr>
<th></th>
<th>n=50</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years ± SD)</td>
<td>47.5</td>
<td>45.6 – 49.5</td>
</tr>
<tr>
<td>Mean BMI (kg/m² ± SD)</td>
<td>28.9</td>
<td>27.2 – 30.6</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>20 (40%)</td>
<td>26% - 55%</td>
</tr>
<tr>
<td>Mean waist/hip ratio (cm ± SD)</td>
<td>0.89</td>
<td>0.87 – 0.92</td>
</tr>
</tbody>
</table>

Clinical risk factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>n (%)</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>4 (8%)</td>
<td>2% - 19%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8 (16%)</td>
<td>7% - 29%</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>26 (52%)</td>
<td>37% - 66%</td>
</tr>
<tr>
<td>Smoking current</td>
<td>20 (40%)</td>
<td>26% - 55%</td>
</tr>
<tr>
<td>Smoking ex</td>
<td>10 (20%)</td>
<td>10% - 34%</td>
</tr>
<tr>
<td>PVD</td>
<td>1 (2%)</td>
<td>0% - 11%</td>
</tr>
<tr>
<td>CVA</td>
<td>0 (0%)</td>
<td>0% - 6%</td>
</tr>
</tbody>
</table>

Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>n (%)</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>2 (4%)</td>
<td>1% - 14%</td>
</tr>
<tr>
<td>Statin</td>
<td>6 (12%)</td>
<td>5% - 24%</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>0 (0%)</td>
<td>0% - 6%</td>
</tr>
<tr>
<td>ACE inhibitor/ARB</td>
<td>6 (12%)</td>
<td>5% - 24%</td>
</tr>
</tbody>
</table>

ACE = angiotensin converting enzyme, ARB = angiotensin II receptor blocker, BMI = body mass index, CI = confidence interval, CVA = cerebrovascular accident, PVD = peripheral vascular disease.
Table 6.2: Participant cardiovascular risk scores

<table>
<thead>
<tr>
<th></th>
<th>Low risk</th>
<th>Moderate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire cohort (n=50)</td>
<td>43 (86%)</td>
<td>6 (12%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Framingham, n (%)</td>
<td>49 (98%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>HeartScore, n (%)</td>
<td>17 (34%)</td>
<td>13 (26%)</td>
<td>20 (40%)</td>
</tr>
<tr>
<td>InterHeart, n (%)</td>
<td>7 (77.8%)</td>
<td>1 (11.1%)</td>
<td>1 (11.1%)</td>
</tr>
<tr>
<td></td>
<td>8 (88.9%)</td>
<td>1 (11.1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>2 (22.2%)</td>
<td>1 (11.1%)</td>
<td>6 (66.7%)</td>
</tr>
</tbody>
</table>

Participants with obstructive CHD by CCTA only (n=9)

<table>
<thead>
<tr>
<th></th>
<th>Low risk</th>
<th>Moderate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham, n (%)</td>
<td>7 (77.8%)</td>
<td>1 (11.1%)</td>
<td>1 (11.1%)</td>
</tr>
<tr>
<td>HeartScore, n (%)</td>
<td>8 (88.9%)</td>
<td>1 (11.1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>InterHeart, n (%)</td>
<td>2 (22.2%)</td>
<td>1 (11.1%)</td>
<td>6 (66.7%)</td>
</tr>
</tbody>
</table>

CCTA = coronary computer tomography angiography, CHD = coronary heart disease.
The findings on CCTA are listed in Table 3. Interestingly the majority of participants (31/50 (62%; 95% confidence interval (CI): 47% to 75%)) had some degree of CHD detected by CCTA. Given 9/50 (18%) participants had obstructive CHD detected by CCTA the number needed to screen to detect a single participant with obstructive CHD by CCTA is 5.6. Most participants (27/50 (54%; 95% CI: 39% to 68%)) had an Agatston score of 0 with 11/50 (22%; 95% CI: 12% to 36%) with an Agatston score >100. There was a trend for participants who had obstructive CHD by CCTA to have a higher mean Agatston score compared to those who did not, 334 versus 62 respectively, although this did not reach statistical significance (95% CI for difference in mean: 66 to 611, \( p = 0.100 \)). The overall radiation exposure to participants was low (median radiation dose 3.9 mSv) fulfilling the Australian National Health and Medical Research Council guidelines of <5 mSv for research purpose.
### Table 6.3: Participant CCTA results

<table>
<thead>
<tr>
<th>Stenosis Type</th>
<th>n=50</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No stenosis, n (%)</td>
<td>19 (38%)</td>
<td>25% – 53%</td>
</tr>
<tr>
<td>Mild/non-obstructive stenosis (&lt;50%), n (%)</td>
<td>22 (44%)</td>
<td>30% – 59%</td>
</tr>
<tr>
<td>Moderate stenosis (50-69%), n (%)</td>
<td>6 (12%)</td>
<td>5% - 24%</td>
</tr>
<tr>
<td>Severe stenosis (≥70%), n (%)</td>
<td>3 (6%)</td>
<td>1% – 17%</td>
</tr>
<tr>
<td>Obstructive CHD (≥50%), n (%)</td>
<td>9 (18%)</td>
<td>9% - 31%</td>
</tr>
<tr>
<td>Obstructive 1 vessel disease, n (%)</td>
<td>6 (12%)</td>
<td>5% - 24%</td>
</tr>
<tr>
<td>Obstructive 2 vessel disease, n (%)</td>
<td>2 (4%)</td>
<td>1% - 14%</td>
</tr>
<tr>
<td>Obstructive 3 vessel disease, n (%)</td>
<td>1 (2%)</td>
<td>0% - 11%</td>
</tr>
<tr>
<td>Obstructive LMCA disease, n (%)</td>
<td>0 (0%)</td>
<td>0% - 6%</td>
</tr>
<tr>
<td>Calcified plaque, n (%)</td>
<td>24 (48%)</td>
<td>34% - 63%</td>
</tr>
<tr>
<td>Median radiation dose (mSv, 25-75% IQ range)</td>
<td>3.9 (2.9-4.8)</td>
<td>3.6 – 4.3</td>
</tr>
<tr>
<td>Median Agatston score (HU, 25-75% IQ range)</td>
<td>0 (0-85)</td>
<td>0 - 27</td>
</tr>
</tbody>
</table>

CCTA = coronary computer tomography angiography, CHD = coronary heart disease, CI = confidence interval, HU = Hounsfield unit, LMCA = left main coronary artery, mSv = millisievert.
Only a single participant out of fifty (2%; 95% CI: 0.1% to 10.6%) had a positive stress echocardiogram. This was a female with apical regional wall motion abnormality. Her CCTA demonstrated moderate calcified stenosis of the proximal left anterior descending coronary artery. Hence only one of nine participants with obstructive CHD by CCTA had a positive stress echocardiogram (11%; 95% CI: 0.3% to 48.2%).

In line with our safety parameter the 3 participants with severe stenosis detected on CCTA were offered invasive coronary angiography. Severe multivessel CHD was detected in 2 of these participants on invasive coronary angiography. Both were recommended by our heart team to undergo surgical revascularization and proceeded to successful procedures. The remaining participant with severe stenosis detected on CCTA only had mild disease of the left anterior descending coronary artery and right coronary artery on invasive coronary angiography. Given 3/50 (6%) participants had severe stenosis detected by CCTA the number needed to screen to detect a single participant with severe stenosis by CCTA is 16.7.

Results of analysis of cardiovascular risk scores of the 9 participants who exhibited obstructive CHD by CCTA are provided in Table 2. Framingham and HeartScore had poor correlation with the presence of obstructive CHD. The majority of participants with obstructive CHD had a high InterHeart score but the association was not statistically significant (low versus high risk OR: 0.31; 95% CI: 0.05 to 1.81, p = 0.193). All participants with obstructive CHD were either a current or an ex-smoker. The age range of those with obstructive
CHD by CCTA was between 36 years and 57 years (mean 48.3 ± 7.7 years; 95% CI: 42.4 to 54.3). Multivariate analysis revealed male gender and current smoking among participants were strong independent predictors for the presence of any stenosis (Table 4). For the presence of obstructive CHD by CCTA current smoking among participants was the only independent predictor among all of the traditional risk factors for CHD investigated.
Table 6.4: Predictors of stenosis by CCTA

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Any stenosis (n=31)</th>
<th>Obstructive stenosis* (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td>Multivariate(^{\ddagger})</td>
</tr>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Age</td>
<td>1.06 (0.97, 1.15)</td>
<td>0.217</td>
</tr>
<tr>
<td>Male</td>
<td>6.48 (1.56, 26.84)</td>
<td>0.010</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.59 (0.08, 4.55)</td>
<td>0.610</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.04 (0.37, 11.33)</td>
<td>0.415</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>0.96 (0.31, 3.01)</td>
<td>0.944</td>
</tr>
<tr>
<td>Smoking (current)</td>
<td>11.77 (2.31, 60.04)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

CCTA = coronary computer tomography angiography CI = confidence interval. *Obstructive stenosis is defined by ≥50% luminal stenosis. \(^{\ddagger}\)Multivariate analysis is adjusted for age, sex, diabetes mellitus, hypertension, dyslipidaemia and current smoking.
6.4 Discussion

Our study suggests approximately two thirds of young siblings of young MI patients have asymptomatic CHD detected by CCTA. A third of this (18% of the total cohort) is obstructive CHD with a third of that being severe (6% of the total cohort). In a similar study, Ha et al demonstrated asymptomatic CHD prevalence of only 11% in young adults, regardless of family history of premature CHD, by CCTA with no obstructive CHD identified (126). The participants in Ha et al’s study however were all below 40 years of age, which is considerably younger than the participants in our study who had a mean age of approximately 48 years. Others have demonstrated a prevalence of asymptomatic obstructive CHD by CCTA of approximately 5% with a mean age as low as 50 years and as high as 54 years (141,142). There was a high proportion of males in these studies (126,141,142) but the majority of our participants were female and it could be contended that the prevalence we detected could be higher with a more equal gender distribution.

The majority of participants with CHD detected on CCTA had mild stenosis. Recent data suggests that even mild or non-obstructive CHD is an important prognostic finding (143). Statins appear to reduce mortality in patients with non-obstructive CHD identified by CCTA and have also been demonstrated to reduce mortality in other primary prevention settings (143,144).

Our finding of a low Agatston coronary calcium score in this young asymptomatic cohort is in keeping with previous literature (145). The likely

Screening for asymptomatic coronary heart disease in the siblings of young myocardial infarction patients
(SACHSMI).

Dr. Nadim Mohammed Shah, 22 May 2017.
reason for this is the shorter duration for coronary plaque maturity in the young. Tota-Maharaj et al demonstrated a relatively high mortality rate among the young with Agatston scores above 100 (145). Approximately one fifth of the participants in our study had Agatston scores above 100, which is higher than previous studies (145-147) although the mean age of our participants was higher.

Cardiovascular risk scores are proposed to be effective for the estimation of population attributable risk but poor at an individual level (88). This was suggested by the poor predictive accuracy of Framingham and HeartScore calculations with obstructive CHD by CCTA for the participants in our study. It is a concern regarding prediction of CHD as Framingham is arguably the most widely used cardiovascular risk score. There was a trend for participants with obstructive CHD to have high InterHeart scores but the association was not found to be statistically significant likely due to small sample size. A probable explanation for this is that Framingham and HeartScore calculations are restricted by traditional cardiovascular risk factors of age, sex, smoking status, presence of hypertension and lipid levels. InterHeart, however, in addition to incorporating these risk factors also take into consideration presence of diabetes, family history, stress levels, presence of depression, physical activity, diet and waist to hip ratio.

Approximately two thirds of participants in our study were either a current or an ex-smoker, which is a major public health concern. Smoking was associated with more than an eight-fold increase of detecting asymptomatic
CHD by CCTA in our study. Choi et al investigated independent predictors for asymptomatic CHD by CCTA in a larger study but did not find smoking to be among them (142). It is possible that siblings who smoked were more likely to volunteer for our study, which may have resulted in our current findings. An important factor for ethics approval for our study was to offer the results of all investigations to the participants. Whether knowledge of CCTA findings is associated with change of smoking status is currently being investigated as part of a sub study.

The median radiation exposure to the participants of our study was below 5 mSv. With the introduction of newer generation scanners there is potential to reduce this even further. This may make CCTA acceptable as a screening tool for a young ‘at risk’ population and in particular for those who smoke.

The stress echocardiography results in our study appear to suggest weak correlation with CCTA findings. This maybe due to potential overestimation of CHD by CCTA but functional assessment in this cohort generally appears to have weak correlation with obstructive CHD. This was found in a similar study by Blumenthal et al who investigated young siblings of patients with premature CHD via exercise stress test, exercise thallium scintigraphy and invasive coronary angiography (105). They demonstrated abnormal functional assessment in approximately one fifth of participants who went on to have only predominantly mild CHD via invasive coronary angiography. This is in stark contrast to the two participants we discovered with severe multivessel CHD requiring surgical revascularization that would have otherwise been over
looked if we had restricted invasive coronary angiography to only those with abnormal stress echocardiography.

6.5 Study limitations

This was a small single centre observational study. Extension of this study to recruit a larger sample size with long term follow up would allow assessment of the statistical significance of other clinical predictors and correlation between clinical risk score and presence of CHD, and the long term outcomes of asymptomatic CHD. The current follow up period is too short for any major adverse cardiovascular event to be statistically significant. There was a higher proportion of female participants and unusually high number of current and ex-smokers.

Invasive coronary angiography is traditionally regarded as the gold reference standard in this setting. Using CCTA as the referenced standard was a limitation of this study. CCTA is known to overestimate the degree of coronary stenosis in comparison with invasive coronary angiography. In a screening study such as this one, it would be impractical and unethical to perform invasive coronary angiography for all participants.

6.6 Conclusion
The majority of asymptomatic young siblings of young MI patients had CHD by CCTA. Furthermore approximately one fifth were found to have obstructive CHD by CCTA, all of whom were current or ex-smokers. No statistically significant association was found between the cardiovascular risk scores investigated and obstructive CHD by CCTA with the vast majority of participants having low Framingham and HeartScore risk scores. Hence screening for CHD in asymptomatic young siblings of young MI patients warrants further investigation, particularly for those with a history of smoking.
CHAPTER 7: PREVALENCE OF OCCULT CORONARY HEART DISEASE IN ASYMPTOMATIC SUBJECTS AS DETECTED ON CORONARY COMPUTER TOMOGRAPHY ANGIOGRAPHY

7.1 Introduction

Routine screening for coronary heart disease (CHD) is currently not recommended by the American Heart Association or European Society of Cardiology guidelines due to lack of evidence (133,134). There is however increasing evidence that asymptomatic CHD may be underestimated with a significant prevalence even among the young (126,148-150). In addition CHD in general has high prevalence with clearly established disease modifying tools that lends itself to the goals required of a screening program (5). Considering CHD remains the highest cause of global mortality (63) there is a potential for great benefit from an effective screening strategy. Coronary computer tomography angiography (CCTA) has high sensitivity for the detection of CHD and is increasingly being utilised for screening for CHD, particularly in high risk groups (125,148). Traditional concerns exist regarding the use of CCTA due to radiation exposure. The use of novel CCTA technology however allows significant reduction in radiation exposure to below 5 millisieverts (mSv) (136).

A screening program for CHD utilising CCTA has been established in Epworth Hospital, Richmond, Victoria, Australia, which is a large tertiary referral centre.
for cardiovascular disorders. The aim of this was to estimate the prevalence of occult CHD in asymptomatic subjects as detected by CCTA.

### 7.2 Methods

This was a retrospective analysis of all CCTA performed on asymptomatic subjects between January 2011 and June 2015. The subjects were identified from the local CCTA database and were referred for screening CCTA by general practitioners and cardiologists. This referral was performed via referral forms that clearly indicated the asymptomatic status of the subjects. Individuals less than 18 years of age, with prior history of CHD or symptoms suggestive of CHD were excluded. All scans were performed on a Siemens Dual Source Scanner with a low radiation dose (<5mSv) algorithm in compliance with the Australian National Health and Medical Research Council guidelines (137). CCTA reformatted images and Agatston coronary calcium scores were obtained from the CCTA study for further analysis. A Society of Cardiovascular Computerised Tomography level II equivalent CCTA reporter interpreted all studies. The institutional human research ethics committee approved the study and waived the requirement for subjects’ consent. Data collected included age, gender, indication for CCTA and CCTA results.

Coronary heart disease by CCTA was defined by the presence of stenosis in at least one epicardial coronary artery. The severity of CHD by CCTA was defined as none (0% luminal stenosis), mild (<50% luminal stenosis), moderate (50-69% luminal stenosis) and severe (≥70% luminal stenosis).
Obstructive CHD by CCTA was defined as the presence of either moderate or severe stenosis in at least one epicardial coronary artery. Multivessel disease was defined as obstructive CHD by CCTA of more than one epicardial coronary artery. The outcome of interest was the number of subjects who had evidence of obstructive CHD by CCTA.

7.2.1 Statistical analysis

Categorical variables were expressed as numbers and percentages, while continuous variables were expressed as mean with standard deviation or median with first and third quartiles. Statistical tests were performed using Minitab 17 Statistical Software (2010) and a 2 sided p value ≤ 0.05 was considered statistically significant. Imaging data capture was complete with no missing information.

7.3 Results

Four hundred and eleven subjects met the criteria for inclusion. Of these 304 (74%, 95% confidence interval (CI) 69%-78%) were male. The mean age of the subjects was 58 ± 9 years (95% CI 57-59 years).

Table 1 demonstrates the CCTA findings. Some degree of CHD was found on CCTA in the majority of subjects (264/411 (64%)). Calcified plaque was present in the vast majority of subjects but despite this the median Agatston
score was low. Males however had higher Agatston scores than females and were more likely to have calcified plaque (Table 2). Radiation exposure to the subjects overall was only 1.9 mSv, fulfilling the Australian National Health and Medical Research Council guidelines.

Obstructive CHD was found in approximately one fifth of the studies. Males were more likely to have obstructive CHD than females and females were more likely to have no stenosis (Table 2). A higher proportion of subjects above the age of 55 years of age had obstructive CHD compared to younger subjects, 58/246 (24%, 95% CI 18%-29%) versus 17/165 (10%, 95% CI 6%-16%) respectively (p<0.001).

Multivessel disease was present in approximately one tenth of the subjects. Numerically a higher proportion of males had multivessel disease than females but this did not reach statistical significance (Table 2). Subjects older than 55 years of age however were more likely to have multivessel disease as compared to their younger counterparts, 22/246 (9%, 95% CI 6%-13%) versus 6/165 (4%, 95% CI 1%-8%) respectively (p=0.023).
Table 7.1: Subject CCTA results

<table>
<thead>
<tr>
<th>Subject CCTA results</th>
<th>n=411</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No stenosis, n (%)</td>
<td>147 (36%)</td>
<td>31% – 41%</td>
</tr>
<tr>
<td>Mild/non-obstructive stenosis (&lt;50%), n (%)</td>
<td>189 (46%)</td>
<td>41% – 51%</td>
</tr>
<tr>
<td>Moderate stenosis (50-69%), n (%)</td>
<td>61 (15%)</td>
<td>12% - 19%</td>
</tr>
<tr>
<td>Severe stenosis (≥70%), n (%)</td>
<td>14 (3%)</td>
<td>2% – 6%</td>
</tr>
<tr>
<td>Obstructive CHD (≥50%), n (%)</td>
<td>75 (18%)</td>
<td>15% - 22%</td>
</tr>
<tr>
<td>Obstructive 1 vessel disease, n (%)</td>
<td>46 (11%)</td>
<td>8% - 15%</td>
</tr>
<tr>
<td>Obstructive 2 vessel disease, n (%)</td>
<td>18 (4%)</td>
<td>3% - 7%</td>
</tr>
<tr>
<td>Obstructive 3 vessel disease, n (%)</td>
<td>10 (2%)</td>
<td>1% - 4%</td>
</tr>
<tr>
<td>Obstructive multivessel disease, n (%)</td>
<td>28 (7%)</td>
<td>5% - 10%</td>
</tr>
<tr>
<td>Obstructive LMCA disease, n (%)</td>
<td>3 (1%)</td>
<td>0% - 2%</td>
</tr>
<tr>
<td>Calcified plaque, n (%)</td>
<td>328 (80%)</td>
<td>76% - 84%</td>
</tr>
<tr>
<td>Median radiation dose (mSv, 25-75% IQ range)</td>
<td>1.9 (1.4-2.9)</td>
<td>1.9 – 2.0</td>
</tr>
<tr>
<td>Median Agatston score (HU, 25-75% IQ range)</td>
<td>17 (1-134)</td>
<td>11 - 29</td>
</tr>
</tbody>
</table>

CCTA = coronary computer tomography angiography, CHD = coronary heart disease, CI = confidence interval, HU = Hounsfield unit, LMCA = left main coronary artery, mSv = millisievert.
Table 7.2: Subject CCTA results by gender

<table>
<thead>
<tr>
<th></th>
<th>Male n=304</th>
<th>Female n=107</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No stenosis, n (%)</td>
<td>94 (31%)</td>
<td>53 (50%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mild/non-obstructive</td>
<td>148 (49%)</td>
<td>41 (38%)</td>
<td>0.060</td>
</tr>
<tr>
<td>stenosis (&lt;50%), n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate stenosis (50-69%), n (%)</td>
<td>51 (17%)</td>
<td>10 (9%)</td>
<td>0.036</td>
</tr>
<tr>
<td>Severe stenosis (≥70%), n (%)</td>
<td>11 (4%)</td>
<td>3 (3%)</td>
<td>0.672</td>
</tr>
<tr>
<td>Obstructive CHD (≥50%), n (%)</td>
<td>62 (20%)</td>
<td>13 (12%)</td>
<td>0.035</td>
</tr>
<tr>
<td>Obstructive 1 vessel disease, n (%)</td>
<td>37 (12%)</td>
<td>9 (8%)</td>
<td>0.251</td>
</tr>
<tr>
<td>Obstructive 2 vessel disease, n (%)</td>
<td>15 (5%)</td>
<td>3 (3%)</td>
<td>0.292</td>
</tr>
<tr>
<td>Obstructive 3 vessel disease, n (%)</td>
<td>9 (3%)</td>
<td>1 (1%)</td>
<td>0.132</td>
</tr>
<tr>
<td>Obstructive multivessel disease, n (%)</td>
<td>24 (8%)</td>
<td>4 (4%)</td>
<td>0.083</td>
</tr>
<tr>
<td>Obstructive LMCA disease, n (%)</td>
<td>3 (1%)</td>
<td>0</td>
<td>0.082</td>
</tr>
<tr>
<td>Calcified plaque, n (%)</td>
<td>258 (85%)</td>
<td>70 (65%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean Agatston score (HU, ± SD)</td>
<td>162 ± 391</td>
<td>52 ± 139</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CCTA = coronary computer tomography angiography, CHD = coronary heart disease, HU = Hounsfield unit, LMCA = left main coronary artery, SD = standard deviation.
7.4 Discussion

In our study approximately two thirds of subjects were found to have occult CHD on CCTA. Of these, approximately one third had obstructive CHD. In a similar study conducted by Choi et al the prevalence of any CHD by CCTA was approximately 20% with a similar proportion of these subjects exhibiting obstructive disease (142). In a further similar study performed by Bachar et al approximately one half of subjects had CHD by CCTA of which approximately 10% had obstructive disease (141). One of the likely explanations for the higher prevalence in our study is the higher mean age of our subjects compared to these other studies (58 ± 9 years in our study compared to 50 ± 9 years and 54 ± 8 years in the studies by Choi et al and Bachar et al, respectively). The subjects in our study also had relatively high prevalence of multivessel disease on CCTA. In the study by Choi et al the prevalence of multivessel disease was less than our study by a factor of five (1.4% versus 7%) (142). Again, the probable reason is suggested not only by the relative higher age of our subjects, but also the higher proportion of males in our study (74% versus 63%) (142). Both Choi et al and Bachar et al demonstrated higher prevalence of obstructive CHD in males similar to the findings of our study (141,142). The finding of gender difference in our and other studies may indicate greater potential benefit of using CCTA for CHD screening in men than women.

The majority of our subjects who had CHD on CCTA only had mild or non-obstructive stenosis (189/264, 72%) but this is an important prognostic
finding. Chow et al have demonstrated that subjects with even mild or non-obstructive CHD on CCTA have a 6% higher risk of mortality over a period of approximately 27 months (143). In the same study statins were shown to be effective in reducing this risk (143). Obstructive CHD on CCTA has been shown to be a mortality predictor and carries a worse prognosis than non-obstructive CHD (151).

The low median Agatston coronary calcium score of the subjects in our study is likely explained by the relatively young age of the cohort and is consistent with previous data (145). A plausible explanation for this is the young have a shorter duration of coronary plaque maturity compared to their older counterparts. A high Agatston coronary calcium score correlates with poor prognosis even among the young particularly if the score is above 100 (145). Approximately one third of our subjects had an Agatston score above 100.

A potential disadvantage of CCTA is overestimation of coronary stenosis that may lead to exaggeration of the severity of CHD when compared to invasive coronary angiography (123). This overestimation may lead to unnecessary invasive coronary angiography and may bring into question the cost effectiveness of a screening strategy using CCTA. Nonetheless, it still reflects burden of disease and has the potential for increasing the accuracy of risk estimation (152).

The subjects of our study were exposed to minimum radiation with the median exposure well below 5 mSv in keeping with the Australian National Health and
Medical Research Council guidelines (137). There is potential to reduce the radiation exposure even further with the advent of newer generation scanners. Hence CCTA may emerge as an acceptable screening modality for the detection of occult CHD.

7.5 Study limitations

This was a single centre observational study with a modest number of subjects. The findings may not be applicable to other cohorts due to age, ethnic or cultural differences. Data regarding the risk factor profile of our subjects was limited and sporadic hence this has not been presented but this raises the possibility of selection bias. In addition we were not able to present outcome data as this was not available. We aim to extend this study to address these issues in the future.

7.6 Conclusion

The majority of middle-aged asymptomatic subjects had CHD demonstrated on screening CCTA. Approximately one fifth were found to have obstructive CHD by CCTA. Their exposure to radiation was minimal. Coronary CT angiography warrants further investigation to evaluate its potential use as a screening tool for detecting occult CHD in an asymptomatic, middle-aged male population.
CHAPTER 8: EFFECTS OF CORONARY COMPUTER TOMOGRAPHY ANGIOGRAPHY SCREENING ON SMOKING HABITS IN ASYMPTOMATIC INDIVIDUALS WITH FAMILY HISTORY OF PREMATURE CORONARY HEART DISEASE: REFLECTIONS FROM THE SACHSMI STUDY

8.1 Background

Coronary computer tomography angiography (CCTA) is being increasingly used as a non-invasive diagnostic test for coronary heart disease (CHD) with similar clinical outcome predictions when compared with stress testing (153). The Screening for Asymptomatic Coronary Heart disease in the Siblings of young Myocardial Infarction patients (SACHSMI, Australian New Zealand clinical trial registry number ACTRN12614000105640) study investigated the prevalence of obstructive CHD as detected by CCTA in the siblings of young myocardial infarction (MI) patients. Fifty asymptomatic participants underwent CCTA and the results described a statistically significant association between obstructive stenosis as detected by CCTA and smoking, as described above in chapter 6. The methodology and results of the SACHSMI study are described in detail in chapter 6 above.

A considerable proportion of the young is affected by CHD (17,18) and cigarette smoking has been reported in 73% of patients younger than 45 years versus 46% of older patients with MI (154). With high prevalence of tobacco smoking in young populations worldwide and a phenomenon of...
unrealistic optimism whereby “people have an optimistic bias concerning personal risk” (155), it becomes a necessity to investigate effective means of modifying smoking behaviour in the primary prevention setting to reduce the burden of CHD. Previous studies have linked patients’ perception of their own illness and clinical outcomes (156,157), calcium scoring and composite measure of risk (158), psychosocial interventions and smoking cessation (159). Lederman et al described the influence of CCTA on cardiac risk reduction in postmenopausal women (160), however, little is known about the effects of CCTA screening on the individual’s health perception and smoking habits in young individuals.

The aim of this study is to demonstrate any association that exist between individuals with family history of ischaemic heart disease undergoing cardiac risk assessment using CCTA and their smoking habits pre and post screening. We predicted that participants who underwent CCTA would report significant change in their smoking habits.

### 8.2 Methods

#### 8.2.1 Participant selection

Patients aged 55 years or younger presenting with acute MI due to primary coronary atherosclerosis and at least 50% stenosis demonstrated in at least 1 epicardial coronary artery via diagnostic coronary angiography to Western
Health, Melbourne, Victoria, Australia were prospectively identified. This group comprised the index MI cohort. Those less than 18 years of age were excluded.

These patients were then contacted to determine if they had siblings aged between 30 and 55 years if male and 30 and 60 years if female. Subsequently the siblings were invited to participate in the study following informed consent. The siblings comprised the participants for our study. Exclusion criteria included symptoms of CHD, known history of CHD, refusal to consent, intolerance to intravenous contrast, chronic renal impairment, atrial fibrillation, thyrotoxicosis, pregnancy, ventricular pacing, left bundle branch block, severe valvular heart disease and malignancy.

The current smokers were identified from this group and we investigated the effects of undergoing screening CCTA on smoking habits in this asymptomatic group via telephone call 1 and 12 months after inclusion. The local human research ethics committee approved the study.

8.2.2 Screening

The participants underwent CCTA but were not blinded to the results of each of the studies. Each participant was shown and explained the results of their CCTA. Low radiation dose (<5mSv) CCTA algorithm was performed in compliance with the National Health and Medical Research Council guidelines (137). All CCTA was performed with the General Electric 64 slice Volume CT
(VCT) scanner using low radiation dose scanning protocol with prospective gating step and shoot scanning mode with 100kvp. Coronary calcium score and CCTA reformatted images were obtained from the CCTA study for further analysis. Two level II (or higher) CCTA reporters (verified by the Society of Cardiac Computer Tomography) reported all studies.

8.2.3 Definitions

Current smoking was defined as having smoked at least 100 cigarettes during the participants’ lifetime and in the 30 days prior to inclusion. CHD by CCTA was considered present if there was at least 1 epicardial coronary artery with stenosis. Severity of CHD by CCTA was defined as none (0% luminal stenosis), mild (<50% luminal stenosis), moderate (50-69% luminal stenosis) and severe (≥70% luminal stenosis) in at least 1 epicardial coronary artery. Obstructive CHD by CCTA was defined as the presence of either moderate or severe stenosis in at least 1 epicardial coronary artery.

8.2.4 Outcomes of interest

The primary outcome of interest was to identify any change in smoking habit among the participants of the SACHSMI study undergoing CCTA 1 and 12 months post scanning. In addition we wished to know whether there was any association between the results of screening CCTA and change in smoking habit.
8.2.5 Statistical analysis

Categorical variables were expressed as numbers and percentages, while continuous variables were expressed as mean with standard deviation or median with first and third quartiles. Odds ratios (OR) were calculated using binary logistic regression. Statistical tests were performed using Minitab 17 Statistical Software (2010) and a 2 sided p value ≤ 0.05 was considered statistically significant. Data capture was complete with no identifiable missing information.

8.3 Results

We identified 167 acute MI patients who met inclusion criteria over a period of 18 months. Fifty asymptomatic siblings of these patients were recruited and were included as participants in the SACHSMI study. Twenty (40%) of the participants had a history of current smoking. Table 1 lists participant demographics, clinical risk factors and medications. Among the smokers males were more predominant. There was equipoise with respect to the clinical risk factors among the total cohort, smokers and non-smokers. In keeping with an asymptomatic cohort, prevalence of prescribed cardiovascular medications was low.
Table 8.1: Participant demographics, clinical risk factors and medications

<table>
<thead>
<tr>
<th></th>
<th>Total cohort n=50</th>
<th>95% CI</th>
<th>Smokers n=20</th>
<th>95% CI</th>
<th>Non-smokers n=30</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years ± SD)</td>
<td>48 ± 7</td>
<td>46 - 50</td>
<td>47 ± 6</td>
<td>44 - 50</td>
<td>48 ± 7</td>
<td>45 - 51</td>
</tr>
<tr>
<td>Mean BMI (kg/m² ± SD)</td>
<td>29 ± 6</td>
<td>27 - 31</td>
<td>27 ± 6</td>
<td>24 - 30</td>
<td>30 ± 6</td>
<td>28 - 32</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>20 (40%)</td>
<td>26% - 55%</td>
<td>12 (60%)</td>
<td>36% - 81%</td>
<td>8 (27%)</td>
<td>12% - 46%</td>
</tr>
<tr>
<td>Mean waist/hip ratio (cm ± SD)</td>
<td>0.89 ± 0.10</td>
<td>0.87 - 0.92</td>
<td>0.93 ± 0.10</td>
<td>0.87 - 0.98</td>
<td>0.87 ± 0.09</td>
<td>0.83 - 0.90</td>
</tr>
</tbody>
</table>

Clinical risk factors

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total cohort n=50</th>
<th>95% CI</th>
<th>Smokers n=20</th>
<th>95% CI</th>
<th>Non-smokers n=30</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>4 (8%)</td>
<td>2% - 19%</td>
<td>1 (5%)</td>
<td>0% - 25%</td>
<td>3 (10%)</td>
<td>2% - 27%</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>8 (16%)</td>
<td>7% - 29%</td>
<td>3 (15%)</td>
<td>3% - 38%</td>
<td>5 (17%)</td>
<td>6% - 35%</td>
</tr>
<tr>
<td>Dyslipidaemia, n (%)</td>
<td>26 (52%)</td>
<td>37% - 66%</td>
<td>9 (45%)</td>
<td>23% - 68%</td>
<td>17 (57%)</td>
<td>37% - 75%</td>
</tr>
<tr>
<td>PVD, n (%)</td>
<td>1 (2%)</td>
<td>0% - 11%</td>
<td>1 (5%)</td>
<td>0% - 25%</td>
<td>0 (0%)</td>
<td>0% - 10%</td>
</tr>
<tr>
<td>CVA, n (%)</td>
<td>0 (0%)</td>
<td>0% - 6%</td>
<td>0 (0%)</td>
<td>0% - 14%</td>
<td>0 (0%)</td>
<td>0% - 10%</td>
</tr>
</tbody>
</table>

Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Total cohort n=50</th>
<th>95% CI</th>
<th>Smokers n=20</th>
<th>95% CI</th>
<th>Non-smokers n=30</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin, n (%)</td>
<td>2 (4%)</td>
<td>1% - 14%</td>
<td>1 (5%)</td>
<td>0% - 25%</td>
<td>1 (3%)</td>
<td>0% - 17%</td>
</tr>
<tr>
<td>Statin, n (%)</td>
<td>6 (12%)</td>
<td>5% - 24%</td>
<td>3 (15%)</td>
<td>3% - 38%</td>
<td>3 (10%)</td>
<td>2% - 27%</td>
</tr>
<tr>
<td>Beta-blocker, n (%)</td>
<td>0 (0%)</td>
<td>0% - 6%</td>
<td>0 (0%)</td>
<td>0% - 14%</td>
<td>0 (0%)</td>
<td>0% - 10%</td>
</tr>
<tr>
<td>ACE inhibitor/ARB</td>
<td>6 (12%)</td>
<td>5% - 24%</td>
<td>2 (10%)</td>
<td>1% - 32%</td>
<td>4 (13%)</td>
<td>4% - 31%</td>
</tr>
</tbody>
</table>

ACE = angiotensin converting enzyme, ARB = angiotensin II receptor blocker, BMI = body mass index, CI = confidence interval, CVA = cerebrovascular accident, PVD = peripheral vascular disease.

Screening for asymptomatic coronary heart disease in the siblings of young myocardial infarction patients (SACHSMI).

Dr. Nadim Mohammed Shah, 22 May 2017.
The CCTA findings of the participants of the SACHSMI study are listed in table 2. The overwhelming majority of smokers had some degree of CHD detected by CCTA. Five times more smokers had obstructive CHD compared to non-smokers. Calcified plaque was more evident among the smokers by approximately a factor of four compared to non-smokers.

One month following their screening CCTA 12 (60%; 95% confidence interval (CI): 36% to 81%) participants either stopped smoking or reduced the number of cigarettes smoked daily. Seven (35%; 95% CI: 15% to 59%) participants stopped smoking altogether and 5 (25%; 95% CI: 9% to 49%) reduced. None of the 30 participants who were not current smokers commenced smoking 1 month following their screening CCTA.

At 12 months post screening CCTA 11 out of the original 20 participants who smoked either stopped smoking or reduced the number of cigarettes smoked daily (55%; 95% CI: 32% to 77%). Of these 6 (30%; 95% CI: 12% to 54%) participants stopped smoking altogether and 5 (25%; 95% CI: 9% to 49%) reduced. At 12 months post screening CCTA 10 (83%; 95% CI: 52% to 98%) out of the 12 participants who either stopped or reduced the number of cigarettes smoked daily at 1 month maintained this status. Two (17%; 95% CI: 21% to 48%) out of the 12 participants and relapsed, both of who had stopped smoking altogether at 1 month but had returned to smoking.

There was a trend for those participants who had obstructive CHD detected on their CCTA to stop or reduce smoking at 1 month (OR 7.0; 95% CI: 0.6 to
75.7, p=0.109) and 12 months (OR 9.6; 95% CI: 0.9 to 105.2, p=0.064) although this did not achieve statistical significance. There was a weaker trend demonstrating the presence of having any stenosis on CCTA and the likelihood of stopping or reducing smoking at 1 month (OR 1.6; 95% CI: 0.1 to 29.4, p=0.762) and 12 months (OR 1.3; 95% CI: 0.1 to 23.3, p=0.881) but again this did not reach statistical significance. A trend for males being more likely to stop or reduce smoking at 1 month was detected but this again was not statistically significant (OR 2.0; 95% CI: 0.3 to 12.5, p=0.459).
### Table 8.2: Participant CCTA results

<table>
<thead>
<tr>
<th></th>
<th>Total cohort</th>
<th></th>
<th>Smokers</th>
<th></th>
<th>Non-smokers</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=50</td>
<td>95% CI</td>
<td>n=20</td>
<td>95% CI</td>
<td>n=30</td>
<td>95% CI</td>
<td>p’</td>
</tr>
<tr>
<td>No stenosis, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19 (38%)</td>
<td>25% – 53%</td>
<td>2 (10%)</td>
<td>1% – 32%</td>
<td>17 (57%)</td>
<td>37% - 75%</td>
<td>0.001</td>
</tr>
<tr>
<td>Mild/non-obstructive stenosis (&lt;50%), n (%)</td>
<td>22 (44%)</td>
<td>30% – 59%</td>
<td>11 (55%)</td>
<td>32% – 77%</td>
<td>11 (37%)</td>
<td>20% - 56%</td>
<td>0.251</td>
</tr>
<tr>
<td>Moderate stenosis (50-69%), n (%)</td>
<td>6 (12%)</td>
<td>5% - 24%</td>
<td>5 (25%)</td>
<td>9% - 49%</td>
<td>1 (3%)</td>
<td>0% - 17%</td>
<td>0.032</td>
</tr>
<tr>
<td>Severe stenosis (≥70%), n (%)</td>
<td>3 (6%)</td>
<td>1% - 17%</td>
<td>2 (10%)</td>
<td>1% - 32%</td>
<td>1 (3%)</td>
<td>0% - 17%</td>
<td>0.556</td>
</tr>
<tr>
<td>Obstructive CHD (≥50%), n (%)</td>
<td>9 (18%)</td>
<td>9% - 31%</td>
<td>7 (35%)</td>
<td>15% - 59%</td>
<td>2 (7%)</td>
<td>1% - 22%</td>
<td>0.021</td>
</tr>
<tr>
<td>Obstructive 1 vessel disease, n (%)</td>
<td>6 (12%)</td>
<td>5% - 24%</td>
<td>5 (25%)</td>
<td>9% - 49%</td>
<td>1 (3%)</td>
<td>0% - 17%</td>
<td>0.032</td>
</tr>
<tr>
<td>Obstructive 2 vessel disease, n (%)</td>
<td>2 (4%)</td>
<td>1% - 14%</td>
<td>1 (5%)</td>
<td>0% - 25%</td>
<td>1 (3%)</td>
<td>0% - 17%</td>
<td>1.000</td>
</tr>
<tr>
<td>Obstructive 3 vessel disease, n (%)</td>
<td>1 (2%)</td>
<td>0% - 11%</td>
<td>1 (5%)</td>
<td>0% - 25%</td>
<td>0 (0%)</td>
<td>0% - 10%</td>
<td>0.400</td>
</tr>
<tr>
<td>Obstructive LMCA disease, n (%)</td>
<td>0 (0%)</td>
<td>0% - 6%</td>
<td>0 (0%)</td>
<td>0% - 14%</td>
<td>0 (0%)</td>
<td>0% - 10%</td>
<td>1.000</td>
</tr>
<tr>
<td>Calcified plaque, n (%)</td>
<td>24 (48%)</td>
<td>34% - 63%</td>
<td>17 (85%)</td>
<td>62% - 97%</td>
<td>7 (23%)</td>
<td>10% - 42%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median Agatston score (HU, 25-75% IQ range)</td>
<td>0 (0-85)</td>
<td>0 - 27</td>
<td>44 (2-238)</td>
<td>8 - 183</td>
<td>0 (0 - 6)</td>
<td>0 - 0</td>
<td>-</td>
</tr>
</tbody>
</table>

CCTA = coronary computer tomography angiography, CHD = coronary heart disease, CI = confidence interval, HU = Hounsfield unit, LMCA = left main coronary artery.

*p is for comparison between smokers and non-smokers.
8.4 Discussion

The majority of the participants of the SACHSMI study who smoked, all of who underwent screening CCTA, either reduced smoking or stopped smoking both at 1 and 12 months. Previous studies investigating the role of CCTA in changing smoking habits have been neutral at best (158,160). Data investigating this particular topic is lacking however. Computer tomography is also used for lung cancer screening and there is some data to suggest it may influence smoking habits in this group (161,162). It was of interest that none of the participants who were not current smokers commenced smoking following their screening CCTA especially considering the vast majority of them did not have obstructive CHD detected by CCTA. This finding is interesting but not particularly surprising given the motivation required to participate in such a study likely also indicates a strong willingness to avoid risks of developing or increasing CHD.

Specific therapies are available to increases smokers’ chances of reducing or even stopping smoking. Nicotine replacement therapy is widely available and has been extensively investigated. Treatment with nicotine replacement therapy for 6 - 18 months is estimated to achieve a reduction rate of approximately 22% for a follow up period of between 12 – 26 months (163). This is far below the rate achieved in our study but of course our follow up period of up to 12 months may account for relapses that may occur beyond this period.
Nearly half of the study participants were active smokers. This is alarming considering the prevalence of smoking in Australia was only 14.5% in those aged 18 years and above between 2014 – 2015 (164). Even in the young, defined as aged between 18 – 44 years the prevalence was only 16.3% between 2014 – 2015 (164). Hence any strategy that can identify such a high prevalence and may help in its reduction should be investigated further. The potential for gain in such a young and high-risk group should not be underestimated.

The prevalence of any stenosis, obstructive CHD and calcified plaque was higher among smokers compared to non-smokers but despite this no statistically significant association was found between the severity of disease on CCTA and a participant’s likelihood of reducing or stopping smoking. The small numbers of smokers in our study may explain the lack of statistical significance. Alternatively, motivation is required to participate in such a study and it maybe hypothesized that this makes our participants more likely to reduce their modifiable risk factors for CHD irrespective of undergoing CCTA or knowledge of the results. To investigate this further a case control study would be required. It is known however, from previous data investigating screening for lung cancer via computer tomography, the rate of abstinence is increased among smokers with abnormal findings (161). Participation in it self in general cardiovascular screening appears to be an important factor in helping smokers quit irrespective of the results of the screening program (165).
The majority (60%) of the smokers in our study were male but men only comprised 40% of the entire cohort. There was trend for males to stop or reduce smoking at 1 month compared to females but this did not reach statistical significance likely due to our small sample size. Previous data however does not appear to highlight an association between gender and smoking cessation (166).

8.5 Study limitations

Given the single centre observational nature of this study it is prone to multiple confounders. Extending the study by recruiting more participants could potentially improve the findings of some of the outcomes that are currently not statistically significant.

8.6 Conclusion

Two fifths of the young asymptomatic participants of the SACHSMI study, who have a family history of premature CHD, were smokers. The majority of these participants either reduced or stopped smoking at 1 and 12 months following their screening CCTA. Hence screening CCTA may have the added benefit of motivating participants to reduce or stop smoking. This potential benefit however requires further investigation.
CHAPTER 9: COMPARISON OF RADIATION DOSE AND IMAGE QUALITY OF CORONARY CT ANGIOGRAPHY IN THE LATEST GENERATION OF MULTI-DETECTOR CT SCANNERS

9.1 Introduction

Coronary CT Angiography (CCTA) has become a useful diagnostic modality in scanning patients with low to intermediate risk for coronary artery disease. It has been shown to have high negative predictive value, sensitivity and specificity (167-170) while it is easily accessible and has low cost (171-174). Radiation exposure, however, is a major healthcare concern, particularly in younger patients undergoing CCTA who are susceptible to an increased lifetime risk of cancer (175,176). Advancement in technology of multidetector row computer tomography (MDCT) scanner allows lower radiation dose and better image quality of CCTA. Various dose reduction techniques and image enhancement methods are implemented in CT scanners by different vendors. Recently, dual energy CT (DECT) method has been introduced to improve tissue characterization (177). Siemens Somatom Definition Flash, GE Revolution and Toshiba Aquilion One ViSION scanners are all new generation MDCT scanners. All three scanners are capable of performing cardiac CT study in a single rotation. Previous studies have compared radiation dose and image quality in different generations of MDCT. Limited literature, however, is available that has directly compared the radiation dose and image quality in patients scanned using new generation of scanners by different vendors. The current study was performed to compare the radiation dose of
Siemens Somatom Definition Flash, GE Revolution and Toshiba Aquilion One ViSION MDCT scanners, and to assess the study image quality of CCTA scans between the three scanners.

9.2 Methods

This was a retrospective observational study of consecutive cases of CCTA performed at three major sites of cardiac CT services in Melbourne, Australia. For the purpose of keeping the sites anonymous we have named them site A, B and C. The cases were collected consecutively for a set of 126 studies per site. Site A cases were collected between 28 October 2014 to 18 June 2015, site B cases were collected between 1 February 2015 and 12 May 2015, and site C cases were collected between 11 May 2015 to 1 September 2015. Inclusion criteria were all CCTA performed within the specified study period and CCTA performed for evaluation of native coronary arteries. CCTA for bypass graft assessment, triple rule-out, and transcatheter aortic valve implantation (TAVI) assessment scans were excluded. The study was approved by the local human research ethics committee and patient consent was exempted.

9.2.1 CCTA acquisition

All patients at three centres were prepared using a similar pre-scanning protocol in terms of pre-medication with beta-blockers or Ivabradine (Servier...
Pharmaceuticals, France) if beta-blockers were contraindicated to achieve heart rate (HR) of less than 60 - 65 beats/min prior to CCTA if possible. Patients at site A were scanned using Siemens Somatom Definition Flash CT scanner (Siemens Healthcare, Erlangen, Germany). Patients at site B were scanned using GE Revolution CT scanner (General Electric (GE) Healthcare, Waukesha, WI, USA). Patients at site C were scanned using Toshiba Aquilion One ViSION (Toshiba Corporation Medical System, Otawara, Japan). All cardiac studies were routinely started with scout scans, followed by non-contrast CT scan for calcium scoring, contrast bolus timing scan and finally contrast enhanced scan. Prior to the contrast enhanced scan, sublingual Nitroglycerine spray or tablet was used for coronary artery vasodilation to enhance the images of coronary arteries. All scans were performed using prospective ECG-triggered scanning. All studies were preferably performed with tube voltage of 100 kVp or less if possible. Tube voltage of 120 kVp was used in the following circumstances: when the patient was obese, non-contrast scan revealed calcification of coronary arteries and in the presence of coronary stent(s). Image acquisition was performed during a single heartbeat. In the Somatom cohort imaging was performed using dual source dual energy CT scanner. Acquisition parameters were 2 x 128 x 0.6-mm detector collimation, gantry rotation time 0.25s, temporal resolution 75ms and spatial resolution 0.33 mm. Data sets were acquired using ECG-triggered spiral acquisition with high pitch of 3.0. In the Revolution cohort, patients were scanned using GE Revolution CT scanner with 256 x 0.625-mm detector collimation, gantry rotation time of 0.28s-0.35s, temporal resolution 140ms and spatial resolution 0.23 mm. Scanning parameters in the Aquilion cohort...
were 320 x 0.5-mm detector collimation, gantry rotation time 0.275s, temporal resolution of 137.5ms and spatial resolution 0.39 mm. The tube current was adjusted by automatic exposure control (SURE Exposure 3D, Toshiba Medical Systems) based on the X-ray attenuation on scout images.

9.2.2 Data collection

Data was collected from the information archived in picture archiving and communication system (PACS). All studies were subcategorised into three cohorts: studies performed using the Siemens Somatom Definition Flash CT scanner (Somatom cohort), GE Revolution CT scanner (Revolution cohort) or Toshiba Aquilion one Vision CT scanner (Aquilion cohort). Patient’s demographics details, including patients’ age, gender, weight and height were collected. Patients’ body mass index (BMI) was calculated using formula BMI = weight/height squared (kg/m²). Scanning data included HR during scan, scanning tube potential (kVp), tube current and dose length product (DLP). Dose length product was used to indicate the radiation dose of cardiac CT inclusive of scout scans, non-contrast scan, bolus timing run and contrast enhanced scan per study. Effective radiation dose for CCTA was calculated as DLP multiplied by the conversion factor of 0.014 mSv x mGy/cm (178).

9.2.3 Definitions of Image Quality
The quality of scan was determined by the reporters based on visual assessment. Data sets were reviewed by the reporters on Inspace workstation (Somatom cohort) an Advantage Workstation (Revolution and Aquilion cohorts). Axial image sets and curved multiplanar reformats on PACS were reviewed by reporters to define the image quality of the CCTA scans. Studies were evaluated using a standard 18-segment model (179). The image qualities of the CCTA scans were defined as follows:

1- Excellent: excellent attenuation of the vessel lumen and clear delineation of vessel walls, excellent diagnostic quality without artifact
2- Good: good attenuation of the vessel lumen and clear delineation of vessel walls, good study quality with minor artifacts
3- Adequate: reasonable attenuation of the vessel lumen and vessel wall delineation, reduced image quality due to some artifacts, but still diagnostic study
4- Poor: impaired image quality due to poor vessel wall delineation, poor attenuation of the vessel lumen or major artifact rendering study non-diagnostic.

CCTA studies with excellent, good and adequate image quality were considered as diagnostic, whereas CCTA studies with poor image quality were considered as non-diagnostic (180).

9.2.4 Statistical Analysis
Data were analysed with statistics program Minitab 17 (Minitab Inc., State College, PA, USA). Numeric data were expressed in mean ± standard deviation (SD) if data had normal distribution or median (Interquartile range (IQR)) if data had skewed distribution. Categorical data were expressed in counts (%). Continuous variables with normal distribution were compared using One-Way ANOVA test or two sample t-test, while continuous variables with skewed distribution were compared using non-parametric Kruskal–Wallis test. Categorical variables were compared using Chi-Square analysis. Fit regression model was used to perform multivariate analysis of interaction of radiation dose with patient and scanning factors. A p value of 0.05 was used as a threshold of statistically significant level.

9.3 Results

9.3.1 Patient demographics and CCTA scan characteristics

A total of 378 patients were included in this retrospective study; 126 patients were included in the Somatom, the Revolution and the Aquilion cohorts, respectively. Age of patients varied significantly, the youngest patient being 27 years old and the eldest patient being 91 years old. Patients in Revolution cohort were older than in the Aquilion or the Somatom cohorts with mean age of 62 ± 11 years vs 54 ± 12 and 58 ± 10 years, respectively (p<0.001). 29% of patients were female in the Somatom cohort; this was significantly lower compared with the Revolution and the Aquilion cohorts. There was no
difference in the patients’ weight, BMI and HR between the cohorts; the mean weight was 80 ± 20.2 kg; mean BMI was 28.7 ± 6.4 kg/m²; and the mean HR was 59 ± 8 bpm. Data on patients’ weight, BMI and scan HR was not available for patients in the Somatom cohort. 235 patients (62%) were scanned using 100 kVp. Four patients were scanned with tube voltage of 80 kVp; two patients in the Somatom and two patients in the Aquilion cohorts. 120 kVp used in the majority of patients in the Revolution cohort (65%) whereas 100 kVp was used in the majority of patients in the Somatom and the Aquilion cohorts, 90% and 62% (p<0.001), respectively. Tube current used in the Somatom cohort was significantly higher than in the Revolution or the Aquilion cohorts, 1131.5 mA vs 475.5 mA and 535.0 mA, respectively (p<0.001) (Table 1).
Table 9.1: Patient characteristics, CCTA factors and radiation dose

<table>
<thead>
<tr>
<th></th>
<th>Somatom cohort</th>
<th>Revolution cohort</th>
<th>Aquilion cohort</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number, n (%)</td>
<td>126</td>
<td>126</td>
<td>126</td>
<td></td>
</tr>
<tr>
<td>Mean age (years ± SD)</td>
<td>58±10</td>
<td>62±11</td>
<td>54±12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>36 (29%)</td>
<td>59 (47%)</td>
<td>65 (52%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (kg ± SD)</td>
<td>N/A</td>
<td>77.73 ±19.19</td>
<td>82.85±21.16</td>
<td>0.064</td>
</tr>
<tr>
<td>Mean BMI (kg/m² ± SD)</td>
<td>N/A</td>
<td>28.18±5.94</td>
<td>29.39±6.89</td>
<td>0.293</td>
</tr>
<tr>
<td>Heart Rate (beat/ min ± SD)</td>
<td>N/A</td>
<td>59±9</td>
<td>60±7</td>
<td>0.309</td>
</tr>
<tr>
<td>Tube Potential, 100 kVp, n (%)</td>
<td>113 (90%)</td>
<td>44 (35%)</td>
<td>78 (62%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tube Current (mA) (25-75% IQR)</td>
<td>1131.5 (925.8-1271.3)</td>
<td>475.5 (334.8-535.3)</td>
<td>535.0 (387.5-700.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DLP (mGy-cm) (25-75% IQR)</td>
<td>126.0 (110.0-290.5)</td>
<td>180.0 (122.5-247.1)</td>
<td>280.5 (188.5-401.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Effective Dose (mSv) (25-75% IQR)</td>
<td>1.76 (1.54-4.07)</td>
<td>2.52 (1.72-3.46)</td>
<td>3.93 (2.64-5.62)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BMI = body mass index, CCTA = coronary computer tomography angiography, DLP = dose length product, IQR = interquartile range, kVp = peak kilovoltage, N/A = not available, SD = standard deviation.
9.3.2 Radiation Dose

The median DLP and effective dose in the Somatom cohort were significantly lower compared with the Revolution and the Aquilion cohorts; 126 mGy-cm (1.76 mSv) vs 180 mGy-cm (2.52 mSv) and 280.5 mGy-cm (3.93 mSv), respectively (p<0.001). Median DLP (effective dose) was significantly lower in CCTA scans performed using 80 kVp vs 100 kVp and 120 kVp, 57 mGy-cm (0.8 mSv) vs 139.0 mGy-cm (1.95 mSv) and 263.0 mGy-cm (3.67 mSv), respectively (p<0.001). Multivariate regression analysis of interaction of radiation dose with patient and scanning factors revealed that scan HR, tube potential (120 kVp) and tube current were independently associated with radiation dose. Whereas patients’ age, gender, weight and BMI were not associated with radiation dose they were exposed to after controlling other factors (Table 2).
Table 9.2: Multivariate analysis of factors affecting radiation dose

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>SE</th>
<th>T- Value</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.532</td>
<td>0.828</td>
<td>1.85</td>
<td>0.066</td>
</tr>
<tr>
<td>Female Gender</td>
<td>-42</td>
<td>108</td>
<td>-0.39</td>
<td>0.699</td>
</tr>
<tr>
<td>Male Gender</td>
<td>-55</td>
<td>110</td>
<td>-0.50</td>
<td>0.618</td>
</tr>
<tr>
<td>Weight</td>
<td>1.39</td>
<td>1.10</td>
<td>1.26</td>
<td>0.210</td>
</tr>
<tr>
<td>BMI</td>
<td>-2.71</td>
<td>3.43</td>
<td>-0.79</td>
<td>0.431</td>
</tr>
<tr>
<td>Scan heart rate</td>
<td>6.29</td>
<td>1.01</td>
<td>6.23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tube current</td>
<td>0.4741</td>
<td>0.0757</td>
<td>6.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>120 kVp</td>
<td>103.8</td>
<td>22.4</td>
<td>4.64</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
9.3.3 Image Quality

All scans were of diagnostic quality. Analysis of image quality revealed that the Siemens Somatom Flash CT scanner produced a better image quality than the GE Revolution CT scanner or Toshiba Aquilion ONE ViSION CT scanner. There were more studies classified as “Excellent” and less studies classified as “Good” or “Adequate” in Somatom cohort than in Revolution or Aquilion cohorts (p<0.001) (Table 3). In patients scanned with 100 kVp there were 175 (75%) studies with “Excellent” image quality compared with 87 (63%) “Excellent” studies in the 120 kVp group (p=0.049).
<table>
<thead>
<tr>
<th>Study Image Quality</th>
<th>Somatom cohort</th>
<th>Revolution cohort</th>
<th>Aquilion cohort</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent, n (%)</td>
<td>123 (97.6%)</td>
<td>95 (75.4%)</td>
<td>47 (37.3%)</td>
<td>265 (70.1%)</td>
</tr>
<tr>
<td>Good, n (%)</td>
<td>2 (1.6%)</td>
<td>27 (21.4%)</td>
<td>67 (53.2%)</td>
<td>96 (25.4%)</td>
</tr>
<tr>
<td>Adequate, n (%)</td>
<td>1 (0.8%)</td>
<td>4 (3.2%)</td>
<td>12 (9.5%)</td>
<td>17 (4.5%)</td>
</tr>
<tr>
<td>Poor, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total, n</td>
<td>126</td>
<td>126</td>
<td>126</td>
<td>378</td>
</tr>
</tbody>
</table>

Table 9.3: Study image quality

p<0.001
9.4 Discussion

With advancement of technology substantial reduction in radiation dose of cardiac CT scans has been achieved from median estimated dose of 11 mSv in 64-slice MDCT (181) to as low as less than 1 mSv in newer CT scanners (182-184). Median effective dose in our study ranged between 1.76 - 3.93 mSv. Our results are lower compared with previously reported results of 3.0 ± 1.9 and 7.6 ± 1.6 mSv in 256 and 320 slice CT scanners, respectively (185). Multiple dose reduction techniques were utilized during cardiac CT scans in the CT scanners by the three vendors with aim to accomplish “as low as reasonably achievable” (ALARA principle) radiation exposure to the patient without jeopardizing the image quality of the scans. Dose reduction techniques used include prospective ECG triggered sequential scanning (181,186-190), body size adjusted tube current modulation (191,192), BMI based tube voltage reduction (168,180,192,193), automated tube voltage selection (194), high pitch spiral prospective triggering (182,195-197), increased spatial resolution with higher number of slices, shortening scan duration by increased gantry rotation speed (198), reduction in Z-axis length (199,200), noise reduction filters (201), automatic exposure control system (202) and iterative image reconstruction (203-208).

Our study demonstrated that despite higher tube current used, the Siemens Somatom Definition flash CT scanner with implementation of multiple dose-saving strategies had markedly lower radiation dose in comparison with GE Revolution and Toshiba Aquilion ONE ViSION CT scanners in CCTA studies. Screening for asymptomatic coronary heart disease in the siblings of young myocardial infarction patients (SACHSMI). Dr. Nadim Mohammed Shah, 22 May 2017.
The median DLP (effective dose) of cardiac CT scanning was 126.0 mGy-cm (1.76 mSv) vs 180.0 mGy-cm (2.52 mSv) and 280.5 mGy-cm (3.93 mSv), in the Somatom vs Revolution and Aquilion cohorts, respectively. The Siemens Somatom Definition flash CT scanner, a new generation dual source MDCT achieves significant decrease of radiation exposure by reducing the overall exposure time and avoiding overlapping slices with combination of prospectively ECG-triggered acquisition and the use of high pitch (182). The difference in radiation dose in the three cohorts could be confounded by higher kVp used in the Revolution cohort, and differences in tube current and scan HR between the cohorts.

The radiation dose in the Somatom cohort in our study is higher compared to other studies which used dual-source CT where patients were exposed to less than 1 mSv of effective dose (170,182,209). Higher pitch of 3.2 and/or 3.4 was used in those studies compared to pitch of 3.0 in our study. Also, Achenbach et al. included highly selected group of patients with body weight <100kg and low and stable HR and used fixed tube potential of 100kVp and tube current of 320mAs/rot (182). In our study automated tube current modulation was utilized and some patients in the Somatom cohort were scanned with 120 kVp based on their body habitus. Effective dose in our study was lower compared with study by Cao et al. where dual source CT was used for CCTA using 120 kVP and 80 kVp with effective dose of 6.4 mSv and 2.7 mSv respectively (193). All our patients were scanned using prospective ECG gated technique compared to routine retrospective ECG gated technique used in Cao’s study. This reiterates importance of combination use of various

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dose-saving techniques to achieve lower radiation exposure from CCTA. Effective dose in the Revolution cohort in our study were comparable with results reported by Latif (210). It was higher compared with the Somatom cohort. This could be potentially explained by the rapid switching of the tube potentials leading to hindrance in tube current modulation resulting in higher radiation dose. Compared with our results, Chen et al. have demonstrated much lower effective dose of 0.93 mSv utilizing 320- detector row Aquilion One CT scanner (136). In Chen’s study, greater proportion of patients were scanned using 100kVP (90.6% vs 62% in our Aquilion cohort), and their patients’ mean HR was lower than in our cohort (57 bpm vs 60 bpm) (136). Furthermore, Oda et al. reported lower effective doses of 1.5 ± 0.5 mSv vs 2.4 ± 1.0 using 80 kVp vs 120 kVp without image quality compromise (211). These results are lower than in our study. Compared to our study, Oda’s study was performed in patients with significantly lower body weight allowing the use of lower tube potential. In patients with larger body size, 80 kVp CCTA tends to yield images of poorer quality because of the increased image noise attributable to radiation scattering and absorption, hence higher kVp is required to achieve diagnostic image quality resulting in higher radiation exposure (211). Di Cesare et al. reported effective dose of 2.8 - 2.89 mSv which is again lower than in our study but Di Cesare et al. excluded patients with HR > 65 bpm and their patient weight was lower than in our study cohort (212). In contrast to Di Cesare’s study, in the current study, there was significant difference in effective radiation dose between groups scanned with 100 kVp vs 120 kVp.
In our study, multivariate regression analysis revealed patients’ scan HR, tube current and tube potential (120 kVp) were independently associated with the effective dose. Pontone et al. have demonstrated in their meta-analysis that age, dual-source MDCT, BMI adapted scanning protocol and prospective ECG gating were independent predictors of overall effective dose reduction (168). In our study, although there was significant age difference in the three cohorts, after correlation with other factors, age was not associated with radiation dose. Consistent with previous studies that have demonstrated significant effective radiation dose reduction with use of lower tube voltage of 100 kVp compared with 120 kVp (180), our results showed significantly lower effective dose when 100 kVp was used versus 120 kVp. However, use of lower kVp may affect the image quality by increasing the image noise (194). Nonetheless, it is feasible to achieve diagnostic image quality with lower tube potential of 70 kVp to 80 kVp using a combination of iterative image reconstruction and higher tube current that offset the increased image noise, and higher pitch in dual-source CT in selected patients with lower BMI and lower HR whilst exposing patients to ultra-low radiation dose of < 1 mSv (193,209,213). In patients with BMI > 30 kg/m², Pan et al. demonstrated feasibility of low dose CCTA using low voltage in combination with iterative reconstruction and low concentration contrast agent with preserved image quality (214).

9.5 Study limitations
Our study has several limitations. Only subjective qualitative assessment of the image quality was performed. However, the 4-point-scale image quality assessment used in the current study is a well-established assessment tool in CCTA. Different CT specialists reported cardiac CTs at different sites. Although all scans were performed with the lowest tube potential, determination of kVp use was at the discretion of CT radiographers. Given the scans were performed at three different sites; scanning bias based on individual performance of CT radiographers cannot be excluded.

9.6 Conclusion

In our local multicentre study on the radiation dose of CCTA, the Siemens Somatom Definition flash CT scanner appears to produce the least radiation dose in comparison with the GE Revolution or the Toshiba Aquillion One scanners without compromising the quality of the study.
CHAPTER 10: CONCLUSION, LIMITATIONS AND FUTURE DIRECTIONS

10.1 Conclusions

Current practice guidelines do not support the routine use of CCTA (coronary computer tomography angiography) as a screening modality for the detection of asymptomatic coronary heart disease (CHD). This is largely due to a lack of evidence supporting its use for this purpose and concerns of the use of ionising radiation. The findings of this thesis have advanced our knowledge in this regard. It has demonstrated a relatively high prevalence of asymptomatic CHD in an at-risk cohort via CCTA. The feasibility of using CCTA as a screening tool for CHD in such a cohort has been demonstrated. The possibility of modifying risk factors for CHD by partaking in a screening program has also been highlighted. In addition the low radiation exposure associated with the latest generation of CCTA scanners has been ascertained.

10.1.1 Myocardial infarction in young versus older adults

This study looked at the proportions, demographics, risk profile, angiographic data and in-hospital outcomes of young versus older myocardial infarction (MI) patients presenting to a community teaching hospital in Melbourne, Australia. It was a retrospective study of patients presenting prospectively, with acute MI between August 2013 and July 2014, who demonstrated

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coronary stenosis ≥50% on invasive coronary angiography in at least one epicardial coronary artery. Patients were divided into two groups by age; those who were aged 55 years or younger and those who were older.

Approximately a third of patients with acute MI admitted to a tertiary Australian hospital, covering a low socioeconomic population, over a 12-month period were aged ≤55 years. This younger cohort was more likely to be male, have a family history of premature CHD and be current smokers but were less likely to have multivessel disease. In addition the younger cohort had less in-hospital major adverse cardiovascular outcomes.

10.1.2 Prevalence of asymptomatic CHD in siblings of young MI patients as detected by CCTA (SACHSMI pilot study)

The study aimed to estimate the prevalence of asymptomatic CHD in siblings of young patients with MI using CCTA. Prospective observational data was collected on siblings of patients’ aged ≤55 years presenting with acute MI and having coronary stenosis ≥50% on invasive coronary angiography in at least one epicardial coronary artery. Inclusion criteria included age of 30-55 and 30-60 years for males and females respectively. Outcome of interest was obstructive CHD by CCTA, which was defined by either moderate (50 - 69% stenosis) and/or severe (≥70% stenosis). In addition to CCTA the participants were also invited to undergo stress echocardiography. The Framingham,
HeartScore and InterHeart cardiovascular risk scores were calculated for all of the participants.

Of the 50 participants 40% were male and 60% were current or ex-smokers. Obstructive CHD by CCTA was detected in 9 (18%, 95% CI 9%-31%) participants and 3 (6%, 95% CI 1%-17%) participants were found to have severe luminal stenosis. Non-obstructive stenosis was found in 22 (44%, 95% CI 30%-59%) participants. Current smoking was found to be a strong predictor for the presence of obstructive CHD and all of the participants with obstructive CHD were either a current or an ex-smoker. The median radiation does the participants were exposed to was low at 3.9 (IQR 0.9) mSv.

Only 1 (2%; 95% CI: 0.1% to 10.6%) participant had an abnormal stress echocardiogram and there appeared to be poor correlation between the findings of this modality and obstructive CHD as detected by CCTA.

Framingham and HeartScore cardiovascular risk calculations were found to be poor for predicting the presence of obstructive CHD by CCTA. The InterHeart score however faired better with a trend for participants with obstructive CHD to have a high InterHeart score. No statistically significant association was demonstrated however likely due to small sample size.
10.1.3 Prevalence of asymptomatic CHD in all comers as detected by CCTA

The aim of this study was to estimate the prevalence of occult CHD in asymptomatic subjects as detected by CCTA in a tertiary Australian referral centre. Retrospective data was collected from all CCTA performed on asymptomatic subjects between January 2011 and June 2015. The outcome of interest was obstructive CHD by CCTA, which was defined by either moderate (50 - 69% stenosis) and/or severe (≥70% stenosis) in at least one epicardial coronary artery.

Four hundred and eleven subjects were included in the study. The mean age was 58 ± 9 years. Obstructive CHD was detected in 75 (18%) subjects. Non-obstructive stenosis was found in 189 (46%, 95% CI 41%-51%) subjects. Males were more likely to have obstructive CHD than females (20% versus 12%, p=0.035). Subjects above the age of 55 years were more likely to have obstructive CHD (24% versus 10%, p<0.001). Fourteen (3%) subjects were found to have severe CHD. The median radiation dose the participants were exposed to was low at 1.9 (IQR 1.5) mSv.

10.1.4 Effects of CCTA screening on smoking habits of participants of the SACHSMI pilot study

The results of the SACHSMI pilot study described a statistically significant association between smoking and prevalence of obstructive CHD as detected by CCTA. The aim of this study was to elucidate whether partaking in a
cardiac screening program using CCTA has effects on smoking habit. As noted above, fifty asymptomatic siblings of prospectively identified index myocardial infarction patients, aged 55 years or younger, were screened. These 50 sibling participants were shown and explained their CCTA results. The participants were followed using telephone call at 1 and 12 months after screening to assess any change in their smoking habits. The primary outcome of interest was to identify any change in smoking habit among the participants of the SACHSMI study undergoing CCTA 1 and 12 months post scanning.

Of the 50 participants, 20 (40%) had a history of smoking. One month post CCTA, 12 (60%; 95% confidence interval (CI): 36% to 81%) participants either stopped smoking (7/20 (35%; 95% CI: 15% to 59%)) or reduced (5/20 (25%; 95% CI: 9% to 49%)) the number of cigarettes smoked daily. At 12 months post CCTA, 11 (55%; 95% CI: 32% to 77%) participants either stopped smoking (6/20 (30%; 95% CI: 12% to 54%)) or reduced (5/20 (25%; 95% CI: 9% to 49%)) the number of cigarettes smoked daily.

10.1.5 Comparison of radiation dose of latest generation CCTA scanners

The main aim of this study was to assess the radiation dose of the latest generation of multi-detector CT scanners. It was a retrospective observational study of 378 consecutive cases of CCTA performed at three major cardiac CT centres between October 2014 and September 2015. Patients were divided
into three cohorts based on the scanner used to perform the CCTA scans: Siemens Somatom Definition Flash CT scanner (Somatom cohort), GE Revolution CT scanner (Revolution cohort), and Toshiba Aquilion ONE ViSION CT scanner (Aquilion cohort). One hundred and twenty six patients were included in each cohort. 120 kVp used in 65% of patients in the Revolution cohort, whereas 100 kVp was used in 90% and 62% of patients in the Somatom and Aquilion cohorts, respectively. Significantly lower radiation dose was observed in the Somatom cohort compared with Revolution or Aquilion cohorts, with median dose length product (DLP) (effective dose) of 126.0 mGy-cm (1.76 mSv) vs 180.0 mGy-cm (2.52 mSv) and 280.5 mGy-cm (3.93 mSv), respectively (p<0.001). Regression analysis revealed scan HR, tube potential of 120kVp and tube current were independently associated with radiation dose. All three scanners however exposed patients to relatively low amounts of radiation.

10.2 Limitations

As with any study our studies have limitations. With reference to our main SACHSMI study it was single centre and observational with the inherent bias associated with these factors. The sample size in this study was small and there was no case control cohort to assess the significance of the association of smoking and obstructive CHD as detected by CCTA. Only 12 months follow up data regarding clinical events was presented and this is likely too short to pick up any adverse events given the asymptomatic status of the cohort being
investigated. A larger multi centre study with a case control cohort and longer follow up period would be required to address these shortcomings.

The referral process confirmed the asymptomatic status of the subjects of the study investigating the prevalence of asymptomatic CHD in all comers. There was however lack of robust clinical information that may have lead to a selection bias. In addition outcome data was not available, which would have increased the significance of the findings. A prospective design would overcome these limitations and should be considered for any similar future study.

The study focusing on change in smoking habits of the participants of the SACHSMI trial is limited by the same factors as the main study. The findings demonstrated a large reduction in smoking pre and post scanning but the significance in blunted by the small sample size. In addition lack of randomization reduces the impact this finding has and the general applicability.

10.3 Future directions

The finding of stenosis on CCTA is important irrespective of the degree of severity. Both obstructive and non-obstructive stenosis have significant influence on the long term outcome of subjects (143). Previous published registry data appears to suggest the benefit of statin therapy in those with non-obstructive CHD as detected by CCTA (143). Approximately one half of Screening for asymptomatic coronary heart disease in the siblings of young myocardial infarction patients (SACHSMI).

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the participants of both the SACHSMI and the all comer studies were found to have non-obstructive stenosis. None of the participants of the SACHSMI study with non-obstructive stenosis had abnormal stress echocardiography demonstrating the disadvantage of traditional cardiac functional assessment for this purpose. The binary outcome provided by stress echo (absence or presence of regional wall motion abnormality) revealed no information about possible subclinical CHD and hence does not allow for risk mitigation in these patients. Other disadvantages of functional studies include equivocal results and relatively high rates of false positive and negative findings.

Cardiovascular risk scores are commonly used in clinical practice. These risk scores, however as in our studies, may fail to correctly stratify the actual cardiovascular risk in this cohort. A large randomised controlled trial however is required to change clinical practice and demonstrate the utility of CCTA in identifying those individuals who will profit from statin therapy. The SACHSMI study participants who had non-obstructive stenosis could be randomised to statin therapy but we would require a larger number of participants for the findings to be statistically significant.

An important point of clarification is what cohort cardiac screening will be a target for. With reference to this thesis, the participants of the SACHSMI study were young and had a family history of premature CHD. As demonstrated however all of the participants with obstructive CHD were current or ex-smokers. Hence any future case control study should try and clarify whether the presence of family history, smoking or perhaps even both increases the risk of obstructive CHD as detected by CCTA sufficiently for screening to be
effective. This can be performed by choosing a control group without family history and one with no smoking history.

A large proportion of the index patients in the SACHSMI study that had eligible siblings did not wish to participate in the study. The reasons behind this decision require further investigation to improve compliance with any potential screening program. A possible way to do this would be to educate young MI patients and their family members on the high prevalence of CHD in asymptomatic individuals, particularly in those with additional risk factors such as smoking. This will hopefully increase the likelihood of participation in a screening program.

To make it financially viable, screening for subclinical CHD by using CCTA has to be affordable. The authority and clinicians should work together to provide guidelines on effective screening for CHD, including selection criteria for using CCTA. The American College of Cardiology/American Heart Association (ACC/AHA) 2013 guideline on the assessment of cardiovascular risk does not discuss CCTA (215). The earlier 2010 ACC/AHA guideline for the assessment of cardiovascular risk in asymptomatic adults does not recommend CCTA as a screening tool (133). The European Society of Cardiology (ESC) 2016 guidelines on cardiovascular disease prevention provides a class IIb recommendation for coronary artery calcium scoring only as a risk modifier in cardiovascular risk assessment but does not discuss the role of CCTA (216). The underlying reason for not recommending CCTA as a screening tool in these guidelines is lack of evidence supporting its role. There
was also concern about radiation, particularly in the use of older generation multidetector row CT scanners. With current technology, as shown in one of the studies here, the dose of radiation is relatively low and almost equivalent to the annual background radiation in our environment. This is why research, such as presented in this thesis, is crucial to help explore and hopefully justify the role of CCTA as an effective screen tool for asymptomatic CHD.

The factors discussed above need to be addressed for CCTA to become a viable screening modality for asymptomatic CHD. Any future study aiming to demonstrate the utility of screening CCTA has to be more selective and choose participants who are more likely to have CHD. This thesis has demonstrated the high prevalence of CHD in male smokers with sibling history of premature CHD that appear to be a suitable target for future studies. Ultimately any screening program has to demonstrate benefit for the cohort being investigated. This of course will require a large multi centre study with relatively long follow up that is able to demonstrate favourable cardiovascular outcomes.
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