Do Clinically Relevant Differences In Outcomes Exist Between Women And Men Undergoing Treatment For Cardiovascular Disease?

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Abstract

Introduction

Throughout my own clinical practice, I became aware that differences may exist between men and women in the decisions for treatment and the outcomes after intervention for cardiovascular disease. Clinical trials have corroborated this with women typically presenting at an older age and studies have suggested there are innate differences between the sexes with women believed to have worse outcomes than men. However, historically women have been poorly represented in clinical trials, which has led to biased result interpretation, despite cardiovascular disease remaining the leading cause of death in women. Therefore, extrapolation of results to women may lead to differences in expected outcomes.

The aim of this thesis was to explore the question: 'Do outcomes differ between women and men in the treatment of cardiovascular disease?'

Methods

The over-arching research question was addressed by integrating results from 5 individual datasets. Following the literature review, the areas identified for investigation were: 1) The role of female sex in the treatment of the left main coronary artery; 2) Bleeding risk in women undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction; 3) Does sex play a role in the activated clotting time during angioplasty; 4) The role of sex on outcomes following transcatheter aortic valve implantation; and 5) Sex differences in the perceived intensity of symptoms in patients with aortic stenosis.

Each of these studies involved observational data from real world patients and allowed for assessment of matched populations to allow for a comparison when appropriate. The datasets were then analysed utilising the constructivist paradigm to identify themes that contribute to robust and generalisable new knowledge in this field.

Results

The treatment of the complex left main coronary artery is first addressed and demonstrates no differences between the sexes in those undergoing percutaneous coronary intervention,

however there was an advantage in women undergoing coronary artery bypass grafting. In patients presenting with ST-elevation myocardial infarction, women have more episodes of bleeding, however despite this have the same good outcome as men in hospital and therefore require the same access to treatment. The anti-coagulation regime during percutaneous coronary intervention is then considered and demonstrates that for a similar dose of unfractionated heparin, women are more likely to have a very high activated clotting time which may explain the increased risk of bleeding in the prior chapter.

In the assessment of aortic stenosis, in symptomatic patients undergoing transcatheter aortic valve implantation, women again appear to have an advantage over men, with male sex a predictor of mortality at long-term follow-up. However, finally addressing the symptomatology of aortic stenosis, there were no differences between sexes in the symptoms of breathlessness or in NT-pro-BNP levels.

Conclusions

The analysis demonstrated that despite an older presentation in women who underwent treatment, women can do as well as men (in coronary artery disease) or even fare better (for transcatheter aortic valve implantation) despite more bleeding and vascular complications. This may impact significantly regarding the multi-disciplinary discussion regarding intervention for these patients and needs to be considered by the clinicians involved in the treatment of cardiovascular disease.

The limitations of the studies are that the data are non-randomised and in 2 of the data sets there are small sample sizes. Additionally, there are the difficulties associated with the analysis of mixed methods research in analysing quantitative data qualitatively.

In summary, when determining if patient sex should be a factor when deciding upon the management of acquired cardiovascular disease, the triangulation of data from across a number of data sets in this thesis suggests that sex should not be the primary consideration. Further research is needed to refine clinical understanding of which factors should be taken into account.

Table of Contents

List of Tables

List of Illustrations

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Declaration

I confirm that this work is original and that if any passage(s) or diagram(s) have been copied from academic papers, books, the internet or any other sources these are clearly identified by the use of quotation marks and the reference(s) is fully cited. I certify that, other than where indicated, this is my own work and does not breach the regulations of HYMS, the University of Hull or the University of York regarding plagiarism or academic conduct in examinations. I have read the HYMS Code of Practice on Academic Misconduct, and state that this piece of work is my own and does not contain any unacknowledged work from any other sources. I confirm that any patient information obtained to produce this piece of work has been appropriately anonymised.

1. Introduction

Cardiovascular disease remains the leading cause of death amongst women in the Western world.(1) In the United Kingdom in 2012, cardiovascular disease accounted for 28% of all deaths in women.(2) The proportion of women with coronary artery disease (CAD) has risen markedly as life expectancy has increased, with a 32% estimated lifetime risk in women over the age of 40 years.(3) This problem is significant, as the annual mortality rate from CAD alone is greater than that of breast cancer, even amongst younger female patients.(3-6) Furthermore, in addition to CAD, with the ageing of the general population and the increased longevity of females, a greater number of elderly female patients are presenting with symptoms secondary to valvular heart disease.(7)

Despite this increasing knowledge, there has been a historical perception which remains that overall cardiovascular disease is a 'man's disease'.(8) During my training within interventional cardiology, I frequently observed that women appeared to have worse clinical outcomes when presenting with acquired cardiovascular disease and sustain more in hospital complications. I therefore developed an interest in the reasons for this, which led to the question for my literature review: 'Are the outcomes worse in women following intervention for cardiovascular disease and are my beliefs founded in evidence?' I planned to encompass both CAD and aortic valve disease, as these were the more common areas of practice encountered on a daily basis. I wanted to assess the available evidence to determine if there were any underlying scientific explanations for my individual perceptions.

CAD is caused when plaque builds up in the coronary arteries and can partially or totally impede coronary blood flow, causing the symptoms of angina or a myocardial infarction (MI) respectively. These narrowings can be treated with percutaneous coronary intervention (PCI), which is a non-surgical procedure whereby the coronary arteries are visualised under x-ray guidance and a balloon catheter is taken to stretch open the stenosis with a stent used to scaffold the artery open. The alternative option is coronary artery bypass grafting (CABG) which is a more invasive surgical procedure, performed through a sternotomy where vessels are grafted from elsewhere in the body to bypass the stenosed arteries.

Aortic stenosis (AS) is thickening of the aortic valve which can restrict blood flow from the left ventricle to the aorta, which can be treated only with a replacement aortic

valve. This can be done surgically (SAVR) via a sternotomy with extraction of the diseased valve and replacement with a new valve or less invasively with transcatheter aortic valve implantation (TAVI). This is a more recent advancement whereby the old valve is crushed against the side of the aortic wall and a new valve deployed in its place under x-ray guidance.

This thesis will comprise of 9 individual chapters, starting with a literature review which will present a number of studies which aim to understand these differences in more detail. There is then a chapter describing the methodology used for the thesis, following which there are 5 individual data sets, each addressing a different question raised from the literature review. A discussion and critical analysis of the data is then presented, with finally a discussion about the implications for practice and future research in this field.

1.1 Narrative Literature Review

In this first chapter of this thesis, a broad evaluation of all publications relating to this subject area was performed to take into account the abundance of information reported in this area of cardiovascular disease or 'virtual knowledge', which is scientific knowledge in journals that no one entirely remembers but can easily acquire.(9) A literature review uses a database search to retrieve results of research into a specific topic, which was planned for this thesis to include the evidence base that is available and how these studies could potentially help devise my research hypotheses.

There are generally two main types of literature review with distinct goals and characteristics. A narrative literature review describes and discusses a specific topic from a theoretical viewpoint, with a critical analysis of the literature available. This type of review does not typically list the types of databases and methodological approaches which are used or the evaluation criteria for inclusion into the review. This seeks to address a broad question with variable evaluation. As a limitation, there can be a degree of bias in selecting and assessing the literature.(10-12) Conversely, a systematic review is a well-planned review to answer a specific research question with explicit methodology to identify, select and rigorously critically evaluate the results of the included studies. The limitations of this approach are that there are narrowly defined review questions providing only specific answers to these specific questions. A full systematic review could however be considered as an original piece of work.(10, 13, 14)

I chose to perform a narrative literature review for this thesis to identify and appraise what has already been published and to help devise my research hypotheses. This method is a recognised way of identifying new study areas that have not yet been addressed.(15) This was chosen over a systematic review, as it was felt with a specific well-defined question, such as in a systematic literature review, this would be too focussed and not allow the inclusion of a broad range of aspects of cardiovascular disease. The aim was to identify gaps in our knowledge within this topic rather than develop answers, with the aim of being broad and inclusive. This chapter did also include review articles to ensure that all relevant studies were captured in order to reduce bias. Moreover, such specific analyses in systematic literature reviews can sometimes be difficult to extrapolate to daily practice (16) and can also exclude relevant studies which are deemed to be of lower quality, such as observational studies, which were important in the development of my research questions.

The question raised by the literature review was: 'Are the outcomes worse following intervention for cardiovascular disease in women?' and subsequently: 'Are my beliefs that outcomes are worse based on the available evidence?'

For this narrative literature review, a search was performed by myself utilising PubMed, EMBASE and Google Scholar. The following Medical Subject Headings (MeSH) were used: 'women', 'sex' and 'gender' in conjunction with 'cardiovascular', 'coronary artery disease', 'percutaneous coronary intervention', 'aortic stenosis', 'transcatheter aortic valve implantation', 'transcatheter aortic valve replacement' and 'heart failure'. The inclusion criteria were all types of articles, articles indexed in PubMed and those related only to humans, published from January 1992 to December 2016. The exclusion criteria were papers for which the full text was not available and those which were not published in English. A large number of publications were identified, and this involved also selecting other publications that were cited in the articles reviewed during the initial index search. The limitations of this review are that studies were not included if they were not deemed to have impact upon clinical outcomes or the full manuscript was unable to be obtained, which may have led to a bias in the findings. However, the review did give a broad overview of the current literature in the field, which was appraised and deemed to contribute to the development of the research question.

The narrative literature review focussed on both CAD and AS, alongside the common interventions for these in the form of PCI and TAVI. The next sections will take

each of these areas in turn to describe the findings and help identify the gaps in knowledge within this field. The question raised for this thesis overall is ‘are there clinically relevant differences between women and men undergoing treatment for cardiovascular disease?’

1.1 Coronary Artery Disease

1.1.1 Under Representation of Women in Clinical Trials

There is a wealth of literature describing how historically women have been extremely poorly represented in coronary artery clinical trials, typically comprising only approximately 30% of the overall patient population.(8, 17-19) It must be noted however, that this has increased from 24% inclusion rates in the 1980’s.(18, 20) Randomised controlled trials are widely accepted in the scientific community as the best measure of the effectiveness of a new treatment and the results of such studies provide evidence to develop new guidelines to allow optimum patient care. However, in order for such results to be generalised to the whole population, the study participants should be representative of the real world. Due to underlying physiological differences between women and men, testing mainly in men can both deny women the full benefit of treatments and also cause them to suffer from more adverse side effects.(21-23) This way may also raise concerns about the applicability of guidelines to minority populations, such as women. Nevertheless, the required costs and ethical approval required for such large-scale studies mean that most treatments are tested for efficaciousness in middle aged men alone.(22)

There are a number of factors which have to be taken into account which contribute to this. It may be considered that such widespread exclusion of women was not fully intentional as it was initially believed that the treatment effects would be the same when applied to women. Initially in phase one studies, women are excluded due to sex hormones, menstruation and pregnancy,(24, 25) with such frequent hormonal changes interacting with potential outcomes. In addition, in the 1950’s and 1960’s, there were widespread safety concerns for pregnant women with the thalidomide controversy, with the FDA issuing guidance that women should not be included in Phase I or early Phase II trials.(26) This was misinterpreted by the research community and was applied to all stages of research, thereby limiting the inclusion of women. For clinical studies, the inclusion criteria such as age, clinical presentation and timing of onset of symptoms negatively

impact upon the ability to recruit the female patient.(19) As women typically present with disease symptoms later with other interacting co-morbidities, often they do not fit the strict recruitment criteria such as age, for inclusion into large scale randomised controlled trials.

In addition, psycho-social factors should also be considered, such as a lesser likelihood for women to participate in clinical studies. Often women may be less aware of the ability to participate in clinical trials and also less willing to give consent without reliance on their partner, especially in the age groups which develop cardiovascular disease. Women do not understand fully the need for the study, or indeed they may perceive they are a nuisance. Inclusion may interfere with work and family obligations, with travel and testing proving a burden for women on top of child care and family commitments.(27, 28)

Finally, the inadequate reporting of clinical trial results according to the sex of the patient limits the identification of important differences in sex related outcomes. In 2001, sex was recognised as an important variable in research by the Institute of Medicine,(25) however over 15 years later this area is still under addressed. Hence, the under-representation of women in clinical trials clearly may lead to an important bias in the interpretation of the results and subsequently extending these findings for management of CAD to the female population.

1.1.2 Stable Coronary Artery Disease

Stable angina is a very common presentation of CAD, a condition that has an important and often intrusive effect on the quality of life of the individual patient. In the literature, there have been limited large intervention trials that have specifically studied women with stable CAD.(29) (30)

There are many issues regarding the sex disparities in the initial identification and treatment of CAD, both physiological and psychological. Firstly, females are typically older at presentation with more associated co-morbidities.(31) With regards to CAD, females are thought to be protected by the anti-atherosclerotic properties of oestrogen prior to the seventh decade, following which the incidence of CAD then equalizes between the sexes.(32, 33) In addition, females have different risk factors which differ across the age spectrum; if these are not considered, it may lead to the false belief that the female sex poses a continuous protective element for the development of CAD.(34-37)

Both sexes have been demonstrated to benefit from evidence based treatment for stable CAD, which includes both aspirin(38) and statin therapy. The 'Scandinavian Simvastatin Survival Study'(4S)(39), the 'British Heart Protection Study' (HPS)(40), the 'Cholesterol and Recurrent Events' (CARE) Trial(41), the 'Long-Term Intervention with Pravastatin in Ischaemic Disease' (LIPID) Study(42) and the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) Trial(43), all included a substantial proportion of women (25% overall). In these well designed, large scale randomised controlled trials, sex-specific analyses revealed a statistically significant benefit in women as well as in men.

Despite these results, in reality women are less likely to receive evidence based optimal medical therapy. One observational study of 3,779 patients (42% female) from the Euro Heart Survey assessed the effects of patient sex on the management and subsequent outcomes in chronic stable angina.(44) This study demonstrated that compared with women, more men were prescribed aspirin (81% vs. 73%; $p<0.001$) and statin therapy (51% vs. 45%; $p<0.001$). These differences persisted even following the angiographic diagnosis of CAD, with the fact that women were less likely to undergo diagnostic coronary angiography (49% vs. 31%; $p<0.001$) further confounding the situation. However, even in those with proven CAD, revascularisation was performed in significantly fewer women (adjusted Odds Ratio [OR] 0.70; 95% Confidence Interval [CI] 0.52-0.94; $p=0.019$) than men. Amongst the patients with confirmed CAD, women were more likely to suffer death (1.5% vs. 2.9%) or myocardial infarction (MI) (2.7% vs. 5.8%) during follow-up. It must however be taken into account that there are variations across Europe in both the facilities available and also the rates and timings of investigations which may have impacted upon the results.

However, as in the EuroHeart Survey, a number of other reports have shown the included women with CAD less likely to receive percutaneous coronary intervention (PCI), for which there is no clear indication given as to the reasons for this in the studies.(4, 34, 37, 45-47) One postulated reason for this may be that traditionally, analyses have demonstrated poorer outcomes in females undergoing PCI.(48, 49) During the past several decades however, there have been numerous studies evaluating sex-based differences in patients undergoing coronary revascularisation across the clinical spectrum of CAD, reporting remarkably consistent findings. Notably, in the more recent studies, the sex difference in-hospital mortality has nearly disappeared, even in large-scale registries,

which are less likely to be underpowered (only 25% to 30% of patients who are women). The use of first generation sirolimus-eluting and paclitaxel-eluting stents have demonstrated similar results to male patients with regards to target vessel revascularisation (TVR) and major adverse cardiovascular events (MACE) at one year.(50-52) The use of second generation drug-eluting stents (DES) has furthermore been assessed in females in the Xience V SPIRIT Woman study, which was first presented in 2010 at the European Society of Cardiology Scientific Sessions by Dr Marie-Claude Morice.(29) This study of 1,573 women undergoing PCI with the Xience V everolimus-eluting stent (Abbott Vascular, Illinois, USA) showed an acceptable rate of death, MI and TVR of 12% at one year and 15% at 2 years in women. Interestingly however, it must be noted in this study that the total referral time for PCI in women was 4 days longer than that for the male patients included (p=0.0003). This may be attributed to the fact that women were more likely to have atypical angina (9% vs. 6%) or indeed no chest pain (17% vs. 13%) compared with men. (29)

The difference in symptom presentation between the sexes was addressed in a more recent prospective study.(53) In total, 305 patients (39.7% women; mean age of 63.9 years) had pre-procedure descriptions of pre-existing symptoms assessed using open-ended questioning. The PCI proceeded in a standard fashion, except balloon inflation was prolonged to a maximum of 2 minutes so as to produce symptomatic and / or electrocardiographic evidence of cardiac ischaemia. Throughout balloon inflation, subjects were re-questioned about active symptoms using the same questioning tool. Concurrent ECG data were also collected. The data showed that no sex differences were found in the rates of chest or typical ischaemic discomfort, regardless of the ischaemic status. Women were significantly more likely to report throat / jaw discomfort (OR 2.91; 95% CI 1.58–5.30) even after statistical adjustment for both clinical and demographic variables. This is the first study that prospectively examined sex-specific ischaemic cardiac symptoms caused by intentional transient reduction in regional coronary blood flow. At the baseline interview, prior to the procedure, women recalled more previous symptoms than men. Moreover, the differential observed between recalled and prospectively triggered symptoms implies that women are more likely to report symptoms that are not actually part of their true ischaemic symptom array. It is possible though that the statistically significantly greater number of reported symptoms by women at baseline would have also been evident during balloon inflation if women had been exposed to inflations of equal

duration. Psychosocial factors (e.g. research assistants in this study were predominantly women, different coping mechanisms, higher levels of anxiety, and higher prevalence of depression) may influence the tendency of women to report higher pain intensity and may similarly explain the greater number of reported symptoms in this group.

Furthermore, from a psychological perspective, women tend to be caregivers for others and thus may postpone their own health concerns and increase the delay until presentation to medical services.(27, 28) In addition, women do not perceive heart disease as a risk to their own health, indeed only 30% of women surveyed thought that cardiovascular disease was the leading cause of death in women.(54, 55) This leads to a significant interval prior to diagnosis, leading to more advanced disease at presentation with therefore more associated problems.

However, despite the documented delays, when women do present with angina they are still less likely to be offered evidence-based treatments, including coronary angiography and revascularisation. The reasons for this remain unknown, although older studies have suggested poorer outcomes.(48, 49) Over recent years, there have been advances in PCI techniques, including intravascular imaging and adjuvant equipment, which has led to an enthusiasm from operators to treat more complex CAD. There remains no data from large scale trials which reports clinical outcomes in women utilising these contemporary techniques and hence it is unclear whether we are treating women in the most effective way with stable CAD.

1.1.2.1 Ischaemia and No Obstructive Coronary Artery Disease

From the literature, a reason given for performing less diagnostic coronary angiography in women may indeed be a consequence that female patients may have a more atypical presentation, sometimes even with no symptoms of chest pain at all as discussed above (4, 32, 47, 56-58). However, it is also of interest and has been postulated in recent publications that women are less likely to have obstructive CAD and diagnostic coronary angiography in this setting can appear visibly normal and hence reassuring.(59-62) These findings are universally similar and reproducible across this host of large observational studies.

It is becoming increasingly recognised as a separate clinical entity, or so called ‘Ischaemia and No Obstructive Coronary Artery Disease’ (INOCA), (63, 64) and up to 4 million patients (both women and men) from the ‘Women’s Ischaemic Syndrome

Evaluation' databases have been shown to have this.(65) This was a National Heart, Lung and Blood Institute sponsored 4 centre study, conducted with rigorous methodology to evaluate those with suspected CAD, and hence is deemed to be reliable data. Such 'normal' angiographic findings may however lead to false reassurance that there is not an underlying problem with the woman, and also result in the premature discontinuation of evidence based medical therapy for their disease, (32, 64, 66, 67) which could be detrimental to the health of the individual. Additionally, as symptoms are disregarded as being non-cardiac, increased healthcare costs can ensue due to hospital readmissions for the patient and repeat investigations including diagnostic coronary angiography.(32, 66)

However, it is important to appreciate that atheroma free epicardial vessels does not actually preclude angina, with other large observational studies demonstrating that women are statistically more likely to suffer from coronary artery vasospasm and microvascular endothelial dysfunction than their male counterparts.(32, 68, 69) In addition, importantly, if a coronary angiogram is reported as appearing normal but symptoms are persistent, the morbidity and mortality for the patient have been shown to be increased, and the prognosis in this group is not as benign as previously thought. The WISE study evaluated 673 patients overall and found that women with non-obstructive CAD but persistent chest pain at one year had more than twice the number of cardiovascular events, including MI, stroke, heart failure, and cardiovascular death compared to women without persistent symptoms.(70) However, those with normal coronary angiography were less likely to be on risk factor modifying medication and furthermore, medical therapy for ischaemia was not considered which is a flaw of the study. It does however emphasise the importance of initiating and maintaining optimal medical therapy despite seemingly normal coronary anatomy.

A number of pathophysiological processes are considered for the cause of symptoms including hypertension, coronary artery spasm, myocardial bridging and coronary microvascular dysfunction. The latter can lead to reduced coronary flow reserve (CFR) which is an integrated measure of both large and small vessel CAD as myocardial ischaemia. This has itself been shown to be a risk factor for cardiac events.(71) A recent study evaluated 329 patients (43% women) who were referred for diagnostic coronary angiography following myocardial perfusion scanning. The baseline CFR was similarly impaired amongst women and men ($p=0.30$) however in those with a low CFR, men had a higher frequency of severely obstructive CAD whereas women had a higher frequency of

non-obstructive CAD (p for trend = 0.002). At a median of 3 years' follow-up, only women with a severely impaired CFR and not actual obstructive CAD were shown to have a significantly increased risk of cardiovascular events (p<0.0001).(72) This is likely as at baseline this group were not amenable for intervention to modify their risk. It must be noted that this was a single centre observational study, which does require reproducibility of the results and there may also have been some confounding factors which were not considered at baseline.

In order to assess this important hypothesis, the Cardiovascular Disease in Women Committee of the American College of Cardiology joined forces with interested parties from the National Heart, Lung and Blood Institute, American Heart Association and European Society of Cardiology to develop a working group to try to form a consensus on the syndrome of myocardial ischaemia with no obstructive coronary arteries. This workshop concluded and reported that there is a significant knowledge gap in this area with regards to evidence-based therapies, although statins and ACE-inhibitors are recommended to counteract oxidative stress and prevent progression of disease, hence improving endothelial and microvascular function and symptoms. The next steps will include large outcome clinical trials to address diagnostic evaluation, risk stratification and management of this patient group.(73) This work may potentially lead to a greater understanding of the management of women with symptoms of stable angina and essentially normal epicardial coronary arteries in the future.

1.1.3 Acute Coronary Syndromes

Acute coronary syndromes (ACS), encompassing unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI), represent a large portion of the clinical presentation of patients with CAD. Prompt revascularisation is essential to reduce ischaemic complications in patients with STEMI and high-risk ACS.(74) However, despite the high proportion of women developing ACS, the situation is akin to that of stable CAD. ACS in women is under-diagnosed and under-treated, with suboptimal use of both revascularisation and optimal medical therapy.(75-81)

1.1.3.1 Pathophysiology of Acute Coronary Syndromes in Women

There are believed to be three main underlying pathophysiological mechanisms for an atherosclerotic plaque to cause ACS: namely plaque rupture, plaque erosion, and calcified nodules.(82) Overall, plaque rupture is by far the most common reported cause for a patient to sustain an ACS, responsible for 76% of men and 55% of women presenting with a fatal MI in a review of the literature of 22 post mortem studies.(83) Interestingly however, plaque erosion has been shown to be more common in younger women, with plaque rupture reported to be more common in men and those women who are older than 50 years of age.(82) Plaque rupture is thought to be especially rare in women who are premenopausal, which is thought likely as a consequence of the protective effects of oestrogen in this age group (84) which may well stabilise the plaque.(85) Eroded plaques can be pathologically more organised with a lesser severity stenosis than a ruptured plaque, with more women possibly symptomatic with plaque erosion, due to their inherent smaller vessel lumen diameters. This latter mechanism of ACS is a distinctly different process to that of the inflammatory response with a rupture.(86)

The 'Providing Regional Observations to Study Predictors of Events in the Coronary Tree' (PROSPECT) study utilized quantitative coronary angiography, grayscale intravascular ultrasound (IVUS) imaging, and radiofrequency virtual histology IVUS in patients presenting to hospital with ACS. This imaging study incorporating 697 patients (24% women) from across 37 sites in the USA and Europe, demonstrated that plaque rupture was significantly less common in women compared with men (6.6% vs. 16.3%; $p=0.002$).(87) Of note, age was not an exclusion criteria in this study, with women reported as older than men (63.6 years vs. 56.9 years; $p<0.0001$) and all investigations were core lab adjudicated, with analysers blinded to the outcomes. Despite the interesting results, this has to be viewed as hypothesis generating as it was not powered to detect differences between the sexes. A further small observational study of 50 women presenting with MI and less than 50% angiographic stenosis identified utilised IVUS and cardiac magnetic resonance imaging (MRI). The use of IVUS showed plaque disruption in 38%, suggesting that coronary angiography as a stand-alone investigation may not be adequate to assess high-risk atherosclerotic lesions. (88)

Furthermore, women tend to have more diffuse atherosclerosis throughout their vessels, as compared to focal obstructive lesions in men, which can make the angiographic assessment of a stenosis more difficult to determine.(89) In addition, as discussed in the

prior section, women can also have angiographically normal coronary anatomy making treatment decisions more challenging.

1.1.3.2 Delays in Presentation of Women with Acute Coronary Syndromes

As already discussed in the stable CAD patient above, there are a number of similar reasons that women presenting with an ACS have delays in their investigations and consequent management. Firstly, there is often a lack of awareness that there is a problem by the women with the condition themselves.(27, 28) Additionally, women may present with atypical symptoms (sometimes not having any chest pain at all) leading to a delay in diagnosis, with a common misconception amongst healthcare providers of worse outcomes leading to less invasive management strategies in women. (4, 32, 47, 56-58)

As with stable CAD, women are typically reported to be older at presentation with ACS and have more associated co-morbidities compared with their male counterparts.(4, 37, 90-100) Women are often older when they present with their first MI, at an average age of 71.8 years compared with 65.0 years of age for men.(101) It has been demonstrated that women presenting with ACS had a significantly higher prevalence of diabetes mellitus, hypertension, peripheral vascular disease and cerebrovascular disease.(75) Conversely, women were less likely to be smokers, or have suffered previous MI or indeed have undergone previous revascularisation. The reasons for these differences are multi-factorial and may be a consequence of the development of CAD at a later age in women. As discussed previously, this may well be attributed to differences in endogenous sex hormone production, particularly that of oestrogen, which has a protective effect until the menopause.(74, 102)

In addition, as discussed above, it has to be taken into account that women presenting with ACS more frequently have coronary arteries without any significant lesions observed at coronary angiography.(103-106) In fact, more often women have microvascular dysfunction,(107) different plaque morphology (108, 109) and more common minor endothelial erosion.(67) Furthermore, in women presenting with ACS, different pathologies, such as spontaneous coronary artery dissection, are also more frequent.

Women may have atypical symptoms at / during the onset of ACS, including back or neck pain, pleuritic chest pain, indigestion and dyspnoea.(53, 75-80, 110) Alternative

symptoms are not widely known to the general public for whom visible advertising campaigns have shown 'typical' presentations and therefore are not promptly recognised by the individual enabling treatment to be sought.(81) This leads to the first delay in the diagnosis of ACS. Indeed, a large observational registry study in the USA of 1,143,513 patients (481,581 women) recently reported that women with ACS were more likely than men to present without any chest pain at all (respectively 42.0% vs. 30.7%; $p<0.001$).(111) Although this was a large study, there was a lack of standardisation for the collection of events and there may be unmeasured confounders. In addition, this did not take into account patients who died of an ACS prior to hospital admission.

Following presentation to healthcare providers, in view of the factors outlined above, as well as a general underestimation of the CAD risk in women, ACS may not initially be suspected. The resulting hold up in the recognition of the problem and hence subsequent ECG acquisition, therefore further delays the initiation of appropriate management.

1.1.3.3 Management of Women with Acute Coronary Syndromes

Notably, it has been reported that women more often present with UA / NSTEMI within the ACS spectrum compared with men.(75) This could explain the general overall less 'invasive' management, as the presence of STEMI on the ECG means the patient is taken directly for angiography with less time to consider other risks. However, it is important to consider that the mortality after NSTEMI at longer term follow-up is actually higher than patients presenting with a STEMI. Indeed, in a study published in 2005 of 654 patients presenting with acute MI (54% NSTEMI), the mortality of those patients with NSTEMI at one year was 30.5%, compared with STEMI at 20.5%.(112) This again did not take into account patients who may have died from a STEMI or NSTEMI prior to arrival at the hospital and may have some confounders which were not taken into account. An online survey study to assess adherence to national cardiovascular guidelines, of which the respondents included 100 cardiologists, demonstrated that despite a similar calculated risk, women were assigned by the assessing physician to be in a lower risk category for CAD than men.(113) This study however had a low response rate which may have led to bias in the results, with respondents potentially more likely to answer in accordance with guidelines than the wider treating cardiologists. Moreover, confirming this opinion, a

report combining 14,196 patients from large prospective multi-centre registry studies, stated that the most commonly cited rationale for undertaking a more conservative approach in women presenting with an ACS was the perception by healthcare providers that they were indeed at a lower risk.(114)

However, despite this common misconception of being at a lower risk, in addition to a higher mortality with NSTEMI which women are more likely to present with, it has been demonstrated that females with ACS actually present with more clinical signs of heart failure than their male counterparts.(91) In this high-risk patient group, there may therefore actually be more to gain from early invasive treatment and onward revascularisation, which women may be denied.

It has been shown in a large registry study of 199,690 patients (55,691 women with NSTEMI and 12,335 women with STEMI) that when a woman presents to hospital with a suspected ACS, they are statistically less likely to receive evidence based therapy in the form of aspirin (OR 1.16; 95% CI 1.13-1.20; $p<0.01$) or the potent glycoprotein IIb / IIIa inhibitors (OR 1.10; 95% CI 1.08-1.13; $p<0.01$).(75) A similar reduction in proven therapies for secondary prevention was demonstrated at follow-up, with less optimal medical therapy prescribed, including less beta-blockers and lipid-lowering agents, which is in accordance with the findings from studies in the stable CAD populations.(44, 75, 79, 90-92, 94, 115, 116) It is unclear from these studies the reasons why women were less likely to receive such evidence based treatments and this reason remains currently unknown, although it could be hypothesised that there is poorer tolerance. It could also be due to the costs incurred with the prescriptions of medication and women may prioritise the needs of the family over themselves.

Under-utilisation of evidence based therapies in women with ACS compared with men therefore is associated with multiple factors related to the patient (age), the consequences of the disease (congestive heart failure), and the physician's assessment of patient risk (decision to perform angiography). Female sex has been shown to remain associated with the under-utilisation of lipid-modifying agents and ACE-inhibitors despite adjustment for all these confounders in the results of the Canadian Registry of ACS I and II, comprising 6,558 patients (31.8% women).(117)

Numerous studies have demonstrated that in this high-risk population, women are offered cardiac catheterisation and PCI much less frequently than men (Table 1), therefore potentially being denied the benefits of revascularisation.

Regarding the management of patients with NSTEMI, the advantage of an early invasive strategy in women has however been less clear than in males, with prior interventional studies, including the 'Fragmin and Fast Revascularisation during InStability in Coronary artery disease' (FRISC) II and the 'Randomised Intervention Trial of unstable Angina' (RITA) 3 trials demonstrating a clear benefit with a routine early invasive strategy in men, but not in women.(104, 118) However interestingly in the FRISC II trial, a prospective, multi-centre randomised trial comprising 749 women and 1,708 men in the analysis, the higher event rate in females treated utilising an early invasive strategy seemed largely due to an increased rate of death and MI in the women who underwent coronary artery bypass grafting (CABG) as the means of revascularisation.(104) This may be explained by the differences at baseline between groups, with women more likely to be older, diabetic and with more prior MI, with the revascularisation modality based on a clinical decision rather than randomisation. Furthermore, the number of women in both of these studies were much lower than men, so although prespecified subgroup analyses, may not have been adequately powered to show the benefits of an early invasive strategy in women.

Table 1. The Percentage of Individuals with Acute Coronary Syndrome undergoing Diagnostic Coronary Angiography according to Sex.

Study	**Year**	**Number of Patients**	**% of Women**	**% Women Undergoing Angiography**	**% Men Undergoing Angiography**	**Significance**
Mahon et al (119)	2000	1,059	40.0	24.1	38.0	p<0.001
Anand et al (90)	2005	12,562	38.5	39.4	45.5	p<0.0001
Blomkalns et al (91)	2005	35,875	40.6	60.1	71.1	OR 0.70
Heer et al (120)	2006	6,358	34.1	60.7	76.9	p<0.001
Alfredsson et al (121)	2007	53,781	36.7	29.0	37.0	OR 1.44

Jneid et al (122)	2008	78,254	39.2	45.6	56.2	p<0.0001
Hvelplund et al (103)	2010	18,262	32.0	32.0	68.0	OR 0.68
Bugiardini et al (117)	2011	6,558	31.8	41.8	49.6	p<0.0001
Poon et al (ACS I) (114)	2012	3,295	33.6	34.6	41.0	p<0.001
Poon et al (ACS II) (114)	2012	1,956	32.9	57.6	68.4	p<0.001

OR = Odds Ratio; ACS = Acute Coronary Syndrome.

Conversely, the 'Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction-18' (TACTICS-TIMI 18) trial, including 2,220 patients (757 women) showed a similar benefit of an early invasive strategy between sexes in those patients with elevated biomarkers.(106) A further sex specific analysis showed a comparable benefit in both men and women if they were creatine kinase or troponin positive. However, women with a diagnosis of ACS but with negative cardiac enzymes actually had higher event rates at follow-up if proceeding to an early invasive strategy (OR 1.35; 95% CI 0.78-2.35; p for interaction = 0.08).(123)

More recently, a sub-study according to sex of the 'Organization for the Assessment of Strategies for Ischaemic Syndromes' (OASIS) 5 trial, showed no differences between routine invasive or selective invasive (coronary angiography only if symptoms or signs of severe ischaemia) strategies in the primary outcome of the composite rate of death, MI or stroke. However, of note, there was a higher rate of death with a routine invasive strategy.(124) This was suggested to be due to the fact as previously discussed that women may have less obstructive coronary stenoses, thereby diluting the treatment benefit, in addition to more risk associated with CABG as suggested in the FRISC II trial. However, even after adjustment for the extent of disease, age and co-morbidities, women with ACS have still been shown to be less likely to undergo coronary revascularisation when it is potentially indicated.(103) Another contributory factor may be

due to the evidence which shows that women have more vascular complications (discussed further in section 1.2) (74, 75, 94, 125) may then impact bias upon the cardiologists who decide not to offer women an invasive strategy.

1.1.3.4 Outcomes in Women with Acute Coronary Syndromes

A number of studies have demonstrated an increased in-hospital mortality amongst women compared with men following an ACS (Table 2).

Table 2. In-Hospital Mortality according to Sex in Acute Coronary Syndrome Trials.

Study	Year	Number of Patients	% Women	Women Mortality (%)	Men Mortality (%)	Significance
Blomkalns et al (91)	2005	35,875	41.0	5.6	4.3	OR 1.27
Elkoustaf et al (126)	2006	1,197	31.8	0.3	1.1	p=0.137
Heer et al (127)	2006	16,817	34.1	6.8	4.1	p<0.001
Alfredsson et al (121)	2007	53,781	37.0	7.0	5.0	p=NS
Radovanovic et al (128)	2007	20,290	28.0	10.7	6.3	p<0.001
Jneid et al (122)	2008	78,254	39.0	8.2	5.7	p<0.0001
Akhter et al (75)	2009	199,690	34.1	2.2	1.4	p=0.52
Al-Fiadh et al (129)	2011	2,952	27.2	3.9	2.0	p<0.001
Bugiardini et al (117)	2011	6,558	31.8	3.4	2.2	p=0.0078
Poon et al (114)	2012	14,196	34.3	2.7	1.6	p<0.001

OR= Odds Ratio; NS= Non Significant.

A large US "Get With The Guidelines Coronary Artery Disease Database" of 78,254 patients with both STEMI and NSTEMI, of which a large proportion (39.0%) were female, demonstrated an unadjusted mortality of 8.2% in women compared to 5.7% in men (p<0.0001). Following multi-variable adjustment, despite the fact that these differences were no longer observed in the overall cohort (adjusted OR 1.04; 95% CI 0.99-1.10), in the STEMI group there remained a higher mortality in women (respectively 10.2% vs. 5.5%;

p<0.0001).(122) A contemporary study of 14,196 NSTEMI patients in Canada showed again that women had a higher in-hospital mortality (adjusted OR 1.26; 95% CI 1.02-1.56; p=0.036), irrespective of age (p for interaction 0.76).(114) Of note, a large study of 1,143,513 patients (42.1% women) showed that specifically younger women (< 45 years) presenting without chest pain have a higher mortality than men of the same age group (OR 1.18; 95% CI 1.00-1.39).(111)

Conversely, in the 'Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines' (CRUSADE) registry, with women comprising 41% of 35,875 patients, no difference in adjusted in-hospital mortality was observed between women and men (5.6% vs. 4.3% respectively; adjusted OR 1.01; 95% CI 0.90-1.13).(91) This was also demonstrated in The American College of Cardiology National Cardiovascular Data Registry of 199,690 patients (34.0% women) which showed an adjusted in-hospital mortality which was similar amongst both sexes (women 2.2% vs. men 1.4%; p=0.52).(75) Each of these studies include large numbers of consecutive patients presenting to the centres included with ACS, however the effect may not be comparable to all centres, depending on where the patient presents to initially.

A mortality difference in patients less frequently treated with PCI has also been demonstrated at more long-term follow-up. The Canadian Acute Coronary Syndrome registry, demonstrated a significant difference in mortality at 12 months follow-up between sexes (women 10.47% vs. men 8.02%; p=0.0017).(117) The decision for invasive management was at the physicians preference in this study and women were less likely to be considered for this, which may have impacted upon the outcomes. However, in the majority of registry studies in which the proportion of revascularised patients is high, no differences in long-term mortality has been reported, when taking into account confounders.(129-132)

Women do therefore have different pathophysiology when presenting with ACS and also are less likely to receive evidence-based therapies, including being offered revascularisation less frequently. Recently, the Task Force of the European Society of Cardiology for the management of ACS in patients presenting without persistent ST-segment elevation acknowledged that sex disparities do exist. However, they advocated both sexes should be treated in the same way with a class I, level of evidence B

recommendation.(133) This is important to provide guidance to physicians who use their own intuitive knowledge which leads to a discrepancy in approach.

1.1.3 ST-Elevation Myocardial Infarction

The current literature demonstrates that the benefit of early reperfusion therapy in STEMI in both sexes is now unquestionable and this is reflected in current practice guidelines.(134) Nevertheless, despite this overwhelming evidence, even in patients presenting with STEMI, women are less likely than men to be admitted to a hospital which has the ability to perform PCI.(135) In a recent study from Poland of 26,035 patients (34.5% of which were female), fewer women with STEMI underwent primary PCI (PPCI) earlier than 12 hours from symptom onset (35.8% vs. 44.0%; $p<0.0001$).(94) Also interestingly, there was a significant difference in the onset of symptoms to balloon time (255 [IQR 175-375] minutes vs. 241 [IQR 165-360] minutes; $p<0.0001$), and also in the door to balloon time (45 [IQR 30-70] minutes vs. 44 [IQR 30-68] minutes; $p=0.032$) compared to men. This confirms that delays are not only due to patient presentation, but also to the identification and management decision made by the medical profession during the first contact as described above. This delay may contribute to the inferior outcomes observed in women and indeed, within one year of presentation with the first MI, irrespective of the age of the patient, more women than men will die, and the median survival time is significantly lower for women compared to men.(101)

A large national registry of 74,389 consecutive patients (30.0% women) again demonstrated a lower rate of PCI with stenting in women having an acute MI (14.2% vs. 24.4%; $p<0.001$) with a subsequent higher rate of in-hospital mortality in women (respectively 14.8% vs. 6.1%; $p<0.0001$). (115) Interestingly, women who underwent PCI within the first 48 hours after the onset of symptoms appear to benefit more from this than their male counterparts (age-adjusted mortality risk at one year after revascularisation 0.65; 95% CI 0.49-0.87; $p=0.004$). The authors do comment that a strength of the study is that it includes those patients who present after 12 hours of symptom onset in comparison to prior thrombolysis studies. Indeed, this was a robust study with all hospital admissions across France included from the national database, however it did not prove possible through coding to decipher which procedures were performed as PPCI and which were elective

interventions, which may have impacted upon the outcomes.(115) A higher degree of myocardial salvage after reperfusion in women compared to men might be a possible explanation for these findings.(136) On the contrary, some registry studies have reported a lack of sex-related differences in mortality in female patients undergoing PPCI for STEMI.(75, 131, 136) Again, it is dependent on the institution the patient presents to however, as some centres do not have the capability for intervention and are not included in these registries.

However, a recent study has shown that despite female sex being a predictor of early death, it does not actually appear to be a predictor at 12 months follow-up (OR 1.02; 95% CI 0.96-1.09; p = non-significant [NS]).(94) This may mean that the women are more unwell when presenting with STEMI and / or there are more procedural related events, however if they survive the acute event, they have just as much to gain. It is unclear in the contemporary era with modern PCI techniques and advances in anti-thrombotic and anti-platelet therapies whether women have as much to gain as their male counterparts. Further work needs to be done in this era in the PPCI era to determine the outcomes according to sex.

1.2 Access Complications

Higher rates of procedural complications, in particular vascular complications and bleeding, in patients undergoing both PCI and TAVI, have been demonstrated to be increased as much as 4-fold in the female population compared with men according to contemporary data.(74, 75, 94, 125) Female sex has been shown to be an independent predictor of bleeding in several large ACS trials with different anticoagulation strategies.(130, 137-139) These studies include randomised multi-centre trials as well as consecutive patients in large scale national registry studies. A large registry study of 24,045 patients with a diagnosis of ACS (incorporating STEMI and NSTEMI) reported from 94 hospitals in 14 countries entitled the ‘Global Registry of Acute Coronary Events’ (GRACE) registry, demonstrated the adjusted OR for bleeding was 1.71 (95% CI 1.35-2.17) in women compared with men.(140) Nevertheless, interestingly the use of the potent glycoprotein IIb / IIIa inhibitors has not been reported as an independent risk for major vascular complications in women.(74, 141, 142) A large pooled analysis from 3 trials assessing the use of glycoprotein IIb / IIIa inhibitors (Evaluation of 7E3 for the Prevention

of Ischemic Complications [EPIC], Evaluation in Percutaneous Transluminal Coronary Angioplasty to Improve Long-Term Outcome with Abciximab GP IIb/IIIa Blockade [EPILOG] and Evaluation of Platelet IIb/IIIa Inhibitor for Stenting [EPISTENT] included 6,595 patients (26.9% women) and demonstrated the benefits of these potent anti-platelets in women, despite an older age and more comorbidities. The primary composite endpoint of death, MI and urgent revascularisation at 30 days was reduced from 12.7% to 6.5% in women having the treatment ($p<0.001$).(141) It must be taken into account however, that data has shown that due to a perceived bleeding risk by the treating physician, women are actually less likely to be treated with these intensive therapies.(75) This may therefore impact upon the outcomes for women undergoing invasive treatment.

Much focus has been placed in recent years on reducing bleeding in patients requiring urgent coronary intervention, with Bivalirudin (The Medicines Company, New Jersey, USA), an intravenous direct thrombin inhibitor, emerging as a possible alternative to unfractionated heparin in STEMI patients proceeding to PPCI.(143) Furthermore, in a gender sub-analysis of the 'Randomised comparison of Bivalirudin versus Heparin in patients undergoing early invasive management for acute coronary syndrome without ST-elevation' (ACUITY) study, comprising of 13,819 patients (30.1% women), the use of bivalirudin monotherapy rather than heparin plus glycoprotein IIb / IIIa inhibitors reduced the rate of major bleeding at 30 days in women undergoing PCI (12.0% vs. 6.0%; $p<0.001$). Importantly, this was without an increase in ischaemia driven outcomes.(130) This trial may not have been adequately powered to compare the differences between the sexes and this must be taken into account.

A further patient pooled analysis of 3 randomised controlled trials (the Randomised Evaluation in PCI Linking Angiomax to Reduced Clinical Events [REPLACE-2], Acute Catheterisation and Urgent Intervention Triage strategY [ACUITY], and Harmonising Outcomes with Revascularisation and Stents in Acute Myocardial Infarction [HORIZONS-AMI]) included a total of 14,784 patients. The analysis aimed to assess the effects of bivalirudin (1,870 women) versus heparin and glycoprotein IIb / IIIa inhibitor therapy (1,910 women) on bleeding rates. Despite a significantly higher rate of bleeding in women at 30 days (7.6% vs. 3.8%; $p<0.0001$) and a consequent higher mortality rate at 12 months compared to men (3.7% vs. 2.7%; $p=0.002$), bivalirudin was shown to reduce major bleeding events in women (5.6% vs. 9.7%; $p<0.0001$) and also 12 month mortality (2.9% vs. 4.4%; $p=0.02$).(144)

In addition to the parenteral anti-thrombotic agents given during PCI procedures, in contemporary practice more potent anti-platelet agents have been developed which have been shown to have superior outcomes to the previous standard therapy of clopidogrel in conjunction with aspirin.(145, 146) Recently, a sex specific meta-analysis of 87,840 patients (27.9% women) undergoing treatment with potent $P2Y_{12}$ inhibitors (including prasugrel, ticagrelor and cangrelor) showed an increase in major bleeding in women (HR 1.28; 95% CI 0.87-1.88) as well as in men (HR 1.52; 95% CI 1.12-2.07) as compared to clopidogrel. However, these newer drugs did reduce the risk of MACE by 14% in women (HR 0.86; 95% CI 0.78-0.94), comparable with the benefits seen in men.(147) This suggests that patient sex should not be a determining factor in deciding upon the anti-platelet agent being used as both groups do have a significant benefit.(148) However, despite this knowledge, it has been shown that these newer drugs are not used as frequently in women, due to a perception of bleeding risk.(149)

There is clear evidence to demonstrate that bleeding complications are an unfavourable occurrence, which can lead to significant morbidity for the patient and woman are much more likely to develop such an event due to various inherent factors. Females have different pharmacokinetics, due to smaller body mass with relatively more fat and lower creatinine clearance.(150) This leads to a higher circulating level of common anti-thrombotic therapies administered during interventional procedures at a similar dose to men. There has also been a suggestion that there is a higher baseline platelet reactivity, which plays a role in thrombus formation, in women.(151, 152) A number of studies have addressed platelet activity, (153, 154) but have not provided clear results. Nevertheless, platelets in women have a higher number of surface receptors and bind a greater amount of fibrinogen. A number of reports have also described how differences in the vessel wall biology and platelet function can be directly related to sex hormones.(155, 156)

Further factors which may contribute to the bleeding risk are that women are, as discussed previously in the CAD section, older at presentation, with more co-morbidities such as renal impairment and diabetes mellitus. A lower body mass index, again more common in the female population, has also been shown to increase the risk of bleeding.(157-160) It is therefore essential that these factors are taken into account when deciding on the type and dose of pharmacological therapies given to female patients.

Despite clear data demonstrating that women do have more vascular and bleeding complications, it remains unclear if common dosing regimens for anti-thrombotic therapy

have the same effect in women and men. More work needs to be performed in this area, as dose adjustment may need consideration according to the sex of the patient to try to minimise bleeding and vascular complications.

1.3 Aortic Stenosis

1.3.1 Pathophysiology of Aortic Stenosis

Aortic stenosis (AS) is now the most frequently encountered acquired valvular heart disease diagnosed in the adult population in the Western world and the consensus is that individuals with severe symptomatic AS should be offered intervention for this.(161) Indeed, AS is the most common indication for surgical aortic valve replacement (SAVR) and is considered a Class I indication for such intervention.(161, 162) Apart from symptomatic relief for the individual, the operation also improves long-term survival.(163) In addition to the well-researched sex disparities in CAD, it is becoming increasingly apparent that these differences may also be evident in those patients presenting with valvular heart disease in the form of AS.

It is known that cardiac hypertrophy in elderly patients appears to develop differently between women and men, with women in general developing a more concentric form of left ventricular hypertrophy with subsequent smaller ventricular diameters and less dilatation of the left ventricle. It has also been postulated that the left ventricle of women adapt differently to the haemodynamic effects of AS, developing more pronounced hypertrophy with a preserved ejection fraction, which could therefore potentially influence the time of the diagnosis to later in the course of the disease.(164, 165) Indeed, interstitial fibrosis has been shown to be more pronounced in male hearts with AS, as is collagen I, II and matrix metalloproteinase expression, which may account for these interesting differences.(166)

More recently, data has begun to emerge that women may actually have a lower degree of aortic valve calcification than men for the same doppler severity of AS. A study of 125 patients (31.2% female) underwent assessment of their aortic valve with doppler and computed tomography (CT) scanning, prior to undergoing SAVR. The excised valves were weighed and the degree of fibrosis was determined. The median aortic valve

calcification and mean aortic valve weight were both statistically significantly lower in women compared with men and female sex was shown to be an independent risk factor for higher fibrosis scores in aortic valves which were stenosed.(167) A further study of 888 patients who underwent SAVR again showed similar mean gradients between both men and women (53±15 mmHg vs. 52±13 mmHg; p=0.11). However aortic valve weight was again lower in women (1.94±0.88 grams vs. 3.08±1.32 grams; p<0.0001) even when indexed to their body surface area (BSA) or left ventricular outflow tract (LVOT) area. Of note, hypertension, diabetes mellitus and current cigarette smoking were independently associated with aortic valve weight.(168) These studies suggest that there are underlying differences in the development of AS between the sexes, although the underlying pathophysiological processes accounting for this are currently unknown. As with CAD, there may be a protective effect from the presence of oestrogen, but further work in this area is required.

Another potential reason contributing to the differences between sexes may be due to the similar mechanisms of senile degenerative AS with atherosclerosis and those of CAD.(169-171) Again, women tend to present later to the physician for psycho-social reasons and yet again may not be referred as quickly to secondary care for consideration of intervention due to their perceived frailty and hence possible poorer outcomes, taking into account the intuitive knowledge of the referring physician. However, as discussed, the pathophysiology itself may well be different according to the sex of the patient alongside the symptoms between sexes in view of the different response of the ventricle to the disease between sexes. More research is required in this area which may help to target treatments in the future for patients with AS.

1.3.2 Surgical Treatment of Aortic Stenosis in Women

Despite being older with more co-existing medical conditions, the data demonstrates that female sex is actually an independent predictor of survival in those patients older than 79 years undergoing conventional SAVR.(172) This may be due to the knowledge that women have a greater improvement of the left ventricular function following intervention for the AS.(173, 174) Despite these documented benefits in the female population, a large database registry study found that females underwent SAVR for AS at rates significantly lower than men.(175) However, this was obtained from extrapolating from an

administrative claims database in the USA, hence may be a biased view. The result however was further demonstrated in an observational study published recently evaluating the effect of sex on operative rates and outcomes in severe AS.(176) In total, 362 patients (52% female) with a class I indication for SAVR were included. Women were typically older (78±10 years vs. 72±11 years; p<0.001) and less likely to have concomitant CAD (64% vs. 90%; p<0.001) than men. Additionally, females had better baseline left ventricular ejection fraction (69% [(IQR 60-75%] vs. 62% [IQR 54-70%]; p<0.001) and increased relative wall thickness (0.58±0.13 mm vs. 0.52±0.11 mm; p<0.001) indicating a greater degree of left ventricular hypertrophy. Of note, greater relative wall thickness was associated with an increased risk of mortality (adjusted Cox regression Hazard Ratio [HR] 1.29; 95% CI 1.12-1.50; p=0.001 for every 10% increment in relative wall thickness).

In total, 83% of men vs. 68% of women (p=0.001) with a class I indication for SAVR were referred for evaluation by a cardiac surgeon. Of those referred, 98% men vs. 93% women (p=0.07) underwent SAVR. This corresponded to an overall operative rate of 72% (females 64% vs. males 81%; p<0.001). After adjusting for multiple co-variates, women had a 2.1 fold lower odds of undergoing SAVR as compared with men (p=0.02). However, in those patients actually undergoing SAVR, the mortality was similar for both sexes (p<0.001). In the cohort of patients who did not undergo SAVR, the most common reason cited in the study was the presence of other co-morbidities. Unfortunately, it was not possible to conclude the cause of death (cardiac versus non-cardiac) which would be an important to consider as this elderly population may have other co-morbid conditions unrelated to the AS, which is therefore a limitation. This study did however demonstrate a clear difference in referral patterns to cardiothoracic surgeons and subsequent operative rates.(176) One of the reasons for this is likely a consequence that in female patients, SAVR can be more technically demanding for the cardiothoracic surgeon because of their smaller stature and hence smaller aortic root. In addition, there may also be an unconscious prejudice amongst surgeons who perceive women to be frailer and therefore a higher risk due to their older age.

A further observational study of 408 consecutive patients (52.7% female) undergoing SAVR for isolated severe AS again showed the women were older (73.7±9.3 years vs. 66.5±11.5 years; p<0.001), more symptomatic (NYHA 2.3±0.7 vs. 2.0±0.7; p<0.001) and had a higher mean gradient (67.3±19.2 mmHg vs. 62.2±20.0 mmHg; p=0.001) at referral.(172) Notably, despite these unfavourable baseline characteristics,

operative mortality did not differ between sexes, indeed after division into age quintiles, the outcome of women was significantly better than men in those patients older than 79 years (p=0.005). Contemporary data from the Euro Heart Survey has also suggested a better outcome after SAVR in women.(162) These studies do suggest that despite a perceived higher risk, and hence lower referral rates in women, the outcomes are comparable with men if SAVR is undertaken. It remains unclear however which patients would benefit from SAVR for severe AS and how those who have been turned down or not considered for SAVR should be treated.

1.3.3 Transcatheter Treatment of Aortic Stenosis in Women

Importantly, up to 33% of patients with severe symptomatic AS are not considered for conventional surgical techniques, and this group of patients who are continued on medical therapy alone are known to have a particularly poor prognosis.(177) As discussed above, this group often includes women who are older with more co-morbidities and deemed too frail by their treating physician to undergo any intervention. In this very high-risk patient group, no medical therapy is known to slow the progression of the disease or improve mortality.

Transcatheter aortic valve implantation (TAVI) was first described in 2002 by Cribier et al (178) and has been clearly demonstrated as an alternative treatment for severe AS in patients considered to be prohibitively high risk for SAVR. The landmark 'Placement of AoRTic TraNscathetER valve trial' (PARTNER B) evaluated 358 surgically inoperable AS patients randomised to TAVI or optimal medical therapy (which included the use of balloon aortic valvuloplasty [BAV]). TAVI was demonstrated to be overwhelmingly superior with one year mortality of 30.7% vs. 50.7% (HR 0.55; 95% CI 0.40-0.74; p<0.001).(179) Moreover, TAVI was reported as non-inferior to SAVR in the primary endpoint of one year mortality in PARTNER A (respectively 24.2% vs. 26.8%; p=0.62; non-inferiority p=0.001).(180) Interestingly in this study, females (N=298; 42.8%) treated with TAVI had a lower mortality at 12 months as compared to men (18.4% vs. 28.0%). Furthermore, this was lower in females treated with TAVI as compared to SAVR (18.4% vs. 27.2%), hypothesising that females may indeed do better with TAVI (HR 0.68; 95% CI 0.44-1.04; p=0.05) than conventional SAVR.(180) This was a robust and well

conducted trial, however it must be taken into account that it was sponsored by a TAVI device company.

It has also been shown on multivariate analysis that female sex is independently associated with better recovery of the left ventricular systolic function following TAVI,(181) which is in accordance with reports that left ventricular hypertrophy reverses more frequently in female patients following SAVR.(174, 182) This may be secondary as discussed to the potential favourable effect of oestrogen slowing interstitial fibrosis and subsequent reversal of hypertrophy.(183) Females therefore may be more suited to undergo TAVI in view of their co-existing conditions which render conventional SAVR high risk, and women may well have a larger benefit to gain following a successful procedure. In addition, from an economical viewpoint the cost effectiveness of TAVI procedures in women may be actually be further enhanced by their longer life expectancy compared with their male counterparts. In corroboration with this, a recent publication from the CoreValve US High Risk Pivotal Trial reported the results of the women (353 in total) from this study who were randomised to SAVR versus TAVI. This encouragingly reported that women actually undergoing TAVI had a lower mortality at 12 months compared with those undergoing conventional SAVR (12.7% vs. 21.8%; p=0.03). (184) However, this subgroup analysis was underpowered to be considered statistically significant.

The first report of TAVI outcomes according to sex included 305 patients (47.9% female) with results adjudicated using the original Valve Academic Research Consortium (VARC) definitions.(185) Baseline characteristics revealed that females had a smaller body surface area (1.84±0.16 m^2 vs. 1.70±0.16 m^2; p<0.001) and aortic annulus (24.4±1.6 mm vs. 22.6±1.7 mm; p<0.001) and reported more symptoms (New York Heart Association [NYHA] Class III/IV 61.6% vs. 73.6%; p=0.026). Conversely, men had more co-morbidities: diabetes mellitus (35.2% vs. 21.9%; p=0.010), chronic kidney disease (41.8% vs. 23.3%; p=0.001), chronic obstructive pulmonary disease (45.3% vs. 30.1%; p=0.006) and previous MI (28.3% vs. 14.4%; p=0.003) or CABG (28.3% vs. 13.0%; p=0.001).

Overall in this study population, the 30 day mortality was 4.7% with no difference according to the sex of the patient (3.8% vs. 5.6%; p=0.475). Moreover, there were no differences in the incidence of MI (0.6% vs. 2.1%; p=0.274) or stroke (1.3% vs. 0.7%; p=0.613) between the sexes at 30 days follow-up. However, there was a trend for females to develop more major vascular complications (11.9% vs. 19.9%; p=0.058); indeed female

sex was an independent predictor of major vascular complications in this study (OR 0.970; 95% CI 0.947-0.993; p=0.012). Notably, in view of the vascular complications, there was no difference between groups in the ileofemoral size (9.8±3.6 mm vs. 8.9±1.4 mm; p=0.505). Additionally, females received more blood transfusions (38.4% vs. 50.0%; p=0.041) despite no significant difference in the baseline haemoglobin (12.3±1.9 g/dL vs. 12.0±1.6 g/dL; p=0.125) or actual reduction in the haemoglobin levels (2.7±1.6 g/dL vs. 2.8±1.5 g/dL; p=0.633). Furthermore, females had a trend to longer in-hospital stays as compared to males (7.4±5.7 days vs. 9.3±12.4 days; p=0.082). Despite this, the mortality at one year post TAVI procedure was reassuringly comparable (16.3% vs. 14.3%; p=0.724). The study concluded that there were no differences in the combined safety or efficacy endpoints according to the VARC criteria following TAVI according to the sex of the patient.(186) The strengths of this study was that it included all consecutive patients using all available TAVI devices, however it did not allow for a fair comparison due to the underlying differences at baseline between women and men.

A larger Canadian study of 641 patients (51.7% female) confirmed these findings of more major vascular complications in female patients undergoing TAVI (12.4% vs. 5.4%; p=0.003) and also borderline more major / life threatening bleeds (21.6% vs. 15.8%; p=0.08). Again, men had more recorded baseline co-morbidities in this study. The adjusted OR for 30 day all-cause mortality favoured women (OR 0.39; 95% CI 0.19-0.80; p=0.01) and this benefit persisted out to 2 years follow-up (HR 0.60; 95% CI 0.41-0.88; p=0.008).(187)

A number of subsequent studies have confirmed the apparent benefit favouring women compared with men undergoing TAVI for significant AS.(188-193) A recent meta-analysis analysed the results of 6 such studies, including overall 6,645 patients and reported that at a median of 365 days follow-up, female sex was related to a significantly lower risk of death compared to men (24.0% vs. 34.0%; OR 0.82).(194) A further larger meta-analysis of individual patient level data reported outcomes of 11,310 patients undergoing TAVI for AS (48.6% women). As in previous studies, women had fewer baseline co-morbidities compared with men. However, there were no differences in 30 day mortality (women 2.6% vs. men 2.2%; p=0.24). At a median of 387 days follow-up, female sex was associated with improved survival (adjusted HR 0.79; 95% CI 0.73-0.86; p=0.001).(195)

Despite these encouraging results, large studies have conversely continued to show more vascular and bleeding complications in women. Indeed data from the 'German Aortic Valve Registry' (GARY) of 15,964 TAVI procedures (54.1% women), showed that female sex was an independent predictor for severe vital complications (defined as death on the day of the TAVI procedure, the need for conversion to sternotomy, acute PCI, need for circulatory support, cardiac tamponade, aortic dissection or annular rupture) (OR 1.37; 95% CI 1.16-1.62; p=0.0002).(196) However, in those patients who survive the hospital admission following TAVI, they appear to do well in the more longer term follow-up. These registry studies do include all-comers however procedural characteristics may not be extended to other centres who are performing TAVI, which may impact upon the results.

Indeed, favourable mortality outcomes have also been demonstrated to continue in the longer term. The FRANCE-2 registry is the largest available dataset assessing follow-up for those undergoing TAVI to a median of 3.8 years and recently published the outcomes of 4,200 patients (49.5% women) undergoing TAVI in the early stages of the French national programme (2010 to 2012), incorporating 34 centres. It is noteworthy that a predictor of 3 year all-cause mortality was that of male sex (adjusted HR 0.80; 95% CI 0.72-0.90); p<0.001).(197) Unfortunately, there was not adjudication of event rates which was a limitation of this otherwise in depth study.

These results are very encouraging for women despite the recorded increased incidence of vascular complications and are reassuring for the invasive treatment of such high-risk patients, especially women, in the future.(186, 198, 199) However, it has been noted by experts within the field, that the benefit in women may simply be a reflection of the higher co-morbidity burden amongst males.(200) The 'Women's INternational Transcatheter Aortic Valve Implantation' (WIN-TAVI) was an all-female real world registry, designed to specifically explore sex specific characteristics of those undergoing TAVI for severe AS and their impact upon clinical outcomes following the procedure. In total, 1,019 women deemed to be of intermediate risk, were enrolled from 19 countries across Europe and North America. The VARC-2 (201) early safety endpoint at 30 days was reported in 14.0% with a rate of 3.4% all-cause mortality. The independent predictors of the early safety endpoint were age (OR 1.04; 95% CI 1.00-1.08), prior stroke (OR 2.02; 95% CI 1.07-3.80), left ventricular ejection fraction < 30% (OR 2.62; 95% CI 1.07-6.40) and a history of pregnancy (OR 0.57; 95% CI 0.37-0.85).(202) Although this was a well

conducted study, with events adjudicated through a central core lab, there was not however a male cohort to allow for comparison.

It is clear that there are differences between men and women undergoing TAVI from the current data that are available, however such studies have not been randomised and do not take into account the baseline differences that are present between men and women. This remains a gap in knowledge and there is still a lot of work to do to be clear as to the role that sex does play.

1.4 This Thesis

In summary, cardiovascular disease is extremely common in both women and men. (203, 204), however women are typically older with more co-morbidities at baseline at presentation. The narrative literature review above does describe that women with cardiovascular disease are treated differently to men. This is with regards to both receiving less optimal medical therapy in both stable and acute presentations of CAD and receiving less invasive management when presenting with symptoms than their male counterparts. There are also significant baseline differences between the sexes in those being referred for TAVI for severe AS. The evidence to support these differences in approach in management between the sexes is however not conclusive and hence new research is required which addresses specifically if women do worse than men, if all other factors are taken into account.

The review has demonstrated that there does remain gaps in our knowledge in specific areas; in both the treatment and outcomes of stable CAD, the outcomes following PPCI in the contemporary era, the reasons for higher bleeding rates and vascular complications in women, the outcomes following TAVI according to sex and the underlying presentation of patients with AS.

The overall objectives of this thesis are therefore to explore issues surrounding the sex of a patient in clinical outcomes of acquired cardiovascular diseases focusing on both coronary intervention as well as patients with AS. In the next chapter I will consider further my research question and how this was developed and also the methodological and theoretical techniques that I will use to try to address this question. Additionally, I will discuss the framework I will use to assess the trustworthiness and robustness of my overall

conclusions regarding any differences between the sex of the patient in clinical outcomes for cardiovascular disease.

2. Background and Methodology

2.1 Framing the Problem

As I outlined at the beginning of this thesis, my own clinical experience is that health care professionals make different decisions with regards to the care of women and men with cardiovascular disease, due to the underlying perceptions that clinical outcomes between the sexes differ. In particular, women may be denied treatment due to a perception by physicians that it may be detrimental and cause harm, or that they have very little to gain from an intervention.

This is a vitally important and relevant area to investigate, to gain new knowledge and ensure that we are treating women (and indeed men) with acquired cardiovascular disease in the best and most effective way that is possible in this contemporary era. My own observations from clinical practice were that women had more complications than men when undergoing intervention for CAD and also in the field of structural heart disease. I held this belief as I was involved with cases throughout my own clinical practice and training and stored this specific information as my perception of the likely outcomes of women following PCI and TAVI. I felt that this was justified because of my observations and also discussion with my mentors, who corroborated the same beliefs that women do not do as well as men.

It is important that there was justification of my belief and this occurs as discussed when a belief is grounded in and based upon something that gives situational justification for the belief. Indeed, knowledge is not possible without belief justification, which provides good raw material,(9) and this was my idea for the thesis.

The literature review also provides data that women did not do as well as men in certain areas as described, therefore I expected this to be true in other identified areas of cardiovascular disease. Firstly however, it must be considered that as women do not have typical symptoms,(4, 32, 47, 56-58, 63) there persists a delay until the patient seeks medical attention.(54, 55) Nevertheless, in chapter 1, the information reported is generally supportive of my own observations from clinical practice. When women do present to the medical services, the literature reports that there remains differences with regards to the way health care professionals' approach and make decisions regarding the treatment and access to intervention for cardiovascular disease.(29, 75-81) Although accepting the

important area of decision-making, my overall plan for this thesis is to focus on the outcomes of those patients who have already been 'selected' for intervention, rather than the decision-making process leading to this.

In both stable and acute presentations of CAD, women fare worse than men with higher rates of in-hospital death and MI following intervention.(91, 114, 117, 120-122, 126, 128, 129) Contributing to this, are the higher rates of bleeding observed in women, which are directly related to poorer outcomes at follow-up.(50, 75, 94, 125, 144) A factor which must be taken into account is that women are typically under-represented in CAD trials, as discussed in chapter 1, and the majority of women presenting with CAD do not 'fit' the criteria for entry into such trials.(18, 20) Therefore, the results from published studies may not be reflective of real-world practice, with results extrapolated to the treatment of women, without considering that there may be underlying inherent differences between the sexes in treatment effect. In contrast with this, in the available evidence with regards to valvular heart disease, women are represented in equal numbers,(179, 194, 196) and although there remains baseline pathophysiological differences, women have a lower risk of death at follow-up than their male counterparts.(195-197) Women however are still perceived by clinicians to be of a higher risk due to the bleeding complications.(75)

These findings demonstrate that the treatment offered may differ for women because of such perceptions, therefore potentially not giving women equal access to treatment, especially within my chosen specialty of interventional cardiology.

The research questions arising therefore ask:

a) **'Do outcomes differ between women and men in the treatment of cardiovascular disease?'**
b) **'Is the intuitive knowledge of clinicians leading to a discrepancy in approach justified or appropriate?'**

In this chapter, I will discuss the methodological options for answering this question.

Through identification of several areas through critical appraisal of the prior literature and recognising areas where knowledge was missing or inadequate, this provided a basis for potential hypotheses and to develop ideas for the data sets. It became clear that there was minimal data observing women with complex CAD and also limited data assessing the role of bleeding and anti-coagulation regimens following PCI. Although data

did exist comparing women with men in patients undergoing TAVI for symptomatic AS, these were very small-scale studies suggesting that there may be significant differences between the sexes. Furthermore, although data existed comparing the symptoms of women and men with congestive cardiac failure no data existed with regards to those patients with AS. The literature therefore played a significant contributory role to help devise new theory underpinning sex differences in cardiovascular disease.

2.2 Methodology and Research Techniques to Answer the Question

There are several approaches which could be used in order to answer my primary research question: **'Do outcomes differ between women and men undergoing treatment for cardiovascular disease?'** One consideration could have been to perform a definitive large randomised controlled trial designed and powered to look specifically at the differences according to sex in outcomes following intervention for cardiovascular disease. The advantages of such a study would be that the characteristics of participants would be similar across both sexes with an unbiased distribution, which would also facilitate the statistical analysis.(205, 206) However, such studies would only allow one area of practice to be reviewed (post-positivist) and are typically expensive in terms of both time and cost, with some degree of volunteer bias.(14, 207) As described in Chapter 1, women are likely to be under-represented in a further randomised controlled trial due to concomitant conditions as well as the psychosocial issues of caring for the family and looking after the home. It may be possible to facilitate higher levels of female recruitment, for example considering providing transport availability or reaching out into primary care. Reducing the burden of participation, including with telephone consultations could also help with the recruitment, with the development of a good rapport with the researcher and their team of paramount importance to encourage and provide explanations. Although some reports have demonstrated these interventions can increase the level of female participants (208, 209), such intensive intervention would not have been feasible within the constraints of this thesis. It may also be possible to design a trial stratified specifically on the sex of the patient, in order to encourage sites to recruit more women, but this may not allow for a fair comparison between sexes. To answer the research question, it was important to achieve real-world data and inclusive data, which a further randomised controlled trial would not necessarily achieve.

A further alternative would have been to carry out a large cohort study, to follow groups of patients over time following an exposure to an intervention. This may result in a higher number of women, as participants are included if they undergo an intervention, without considering exclusion criteria which are present for a randomised controlled trial. This would ensure that there was less selection bias as all treated patients are included and such a study also can be useful when multiple outcomes may arise.(210) It would also be beneficial with regards to the reluctance of women to attend follow-up if surveillance was used based on national data and not dependent on the individual.(211) Again, as with a randomised controlled trial, this allows for clear statistical analysis. However, unmeasured confounders are not taken into account in a cohort study as participants may not be similar at baseline and may also undergo further interventions which remain unknown. Additionally, there requires a long follow-up period, for which drop-outs can impact negatively upon the study, and also a large sample size, which would not have been possible within the confines of my thesis. As with a randomised controlled trial, this would only allow the assessment of one area of practice.(212)

As described, multi-centre intervention studies are inherently difficult for a number of reasons and would not have suited the question raised for this thesis. This is because in practical terms, there would be high costs sustained and it would also be time-consuming with minimal resources, neither of which did I have available. In addition, in methodological terms these types of study would only allow the assessment of a single intervention, whereas my overarching interest was to look at sex differences in a variety of settings of cardiovascular disease: a) the treatment of the ULMCA, b) the bleeding risk in women undergoing PPCI for STEMI, c) the effect of sex on the ACT during PCI, d) the treatment of severe symptomatic AS with TAVI and e) the perceived intensity of symptoms in patients with AS. In either a randomised controlled trial or cohort study design, covering the breadth of areas of interest would not have been feasible.

An alternative approach, which I decided upon to answer: ‘Do outcomes differ between women and men undergoing treatment for cardiovascular disease?’ was to break this down and integrate the findings from multiple studies, with a number of data sets used to critically examine this principle research question. From the literature review, it was evident that there was minimal data assessing the outcomes for women in the setting of complex CAD, and also questions remained unanswered regarding the bleeding risk of women. Moreover, as women have historically been underrepresented in clinical trials, it

was important to consider that for the first time, women were included as equally as men in the TAVI trials, giving additional opportunity to assess outcomes. A plan was developed therefore to select a range of intervention studies that reflected the complexity of cardiovascular disease, specifically focussing on these areas of interest and subsequently describe the outcomes within each of these studies. This would include any differences observed between the sexes in each study and also any variables which may explain these observed differences. Using such observational data would also reflect real world patients, without the selection bias of a randomised trial, a definite advantage to this thesis.

Other data sets were available for the assessment of complex CAD, for example coronary bifurcation lesions or chronic total occlusions, however these were discounted as the numbers of patients included were smaller, without validation across the centres and with less period of time for follow-up, hence the treatment of the ULMCA was chosen. Bleeding is known to be more common due to potent anti-coagulation during PPCI and hence this data set was chosen since the introduction of the service in the centre, which gave large numbers of patients with a prolonged period of follow-up. With regards to choosing to measure the ACT level during PCI, this is done routinely and hence standardising the timing of this to allow direct comparison in elective PCI patients gave a population which was representative with comparable subjects at baseline in a manner that was easy to recruit to. Assessing valvular heart disease, AS is much more common than any other acquired valvular heart disease and as such the relatively recent introduction of TAVI as a treatment modality meant there were significant numbers of patients, following strict procedures with databases already in place to capture the results. Finally, the assessment of symptoms in AS was performed to give a more subjective assessment of the difference between women and men. Again, as AS is common, this gave the potential to recruit more participants than alternate valvular heart disease and was done in accordance with AS from the prior chapter.

There was a potential risk of bias within the selection of these studies, as cardiovascular disease encompasses a vast array of topics. However, the aim was to minimise this by having clearly defined outcomes within each study and ensuring the patients all originated from the same population and were consecutive in inclusion. In some of the studies (chapters 3,4 and 6) the exposure to the study intervention had already occurred at the point of inclusion, which can be a further source of bias.(213) However, the reasons that these areas were specifically chosen were that the databases were originally

designed specifically for the conditions evaluated and for prospective data collection, all data was validated independently, the follow-up period was significant with independent outcome assessments e.g. death and furthermore during the analysis it was possible to control for confounding factors through matching. This therefore led to bias being minimised within each of the studies.(214) It must also be taken into account that a number of the data sets had already published results in established peer reviewed medical journals giving a degree of validity and reliability.

Finally, the plan was to perform a critical comparison of the studies to identify any overarching patterns of sex differences in clinical outcomes, considering also any explanatory factors which might account for any differences observed between the studies.

The advantage of choosing this approach to answering my research question was that it enables comparison across the clinical spectrum of cardiovascular disease, encompassing both CAD and valvular heart disease. In addition to the breadth of the study, it was possible to have large numbers of participants more representative of the target population. The disadvantage however was that despite individual statistical analyses, the final conclusions would be drawn not from this, but through a qualitative explanation of any differences observed.(14, 215) As some of the data sets were to allow a secondary analysis, I was unable to examine the data such as the recruitment logs to see if the women represented in the data are a good or a biased sample. I was however involved in the data collection for my own centre in each of the studies in chapters 3,4 and 6.

I decided upon this latter approach for both theoretical reasons, including the breadth of study, in addition to practical reasons (time-saving and cost efficiency) and the inherent difficulties in conducting large scale new clinical trials.(216) It was also possible within the confines of cost and location for myself as the researcher to pursue this. Therefore, I aimed by systematic observation of a defined range of clinical interventions, via robust critical cross-comparison of the results, to describe a new theoretical account of the importance of sex in understanding outcomes in treatment of cardiovascular disease according to the sex of the patient. This novel approach to study required a deeper consideration of both the ontological and epistemological issues arising, in order to explain how I propose to generate robust and generalisable new knowledge from this research. Due to the nature of some of the data sets, these could then be used to generate new hypotheses and contribute to the design of future larger studies, further contributing to the knowledge in this field.

2.3 Ontological and Epistemological Considerations

It was important in the development of my thesis to have an underlying understanding and awareness of the theoretical beliefs and paradigms, which are essential to conduct informed research.(217) This section will aim to explain the reasons for the methodology used in this thesis and the framework which was felt to be most relevant for potential new knowledge to be produced.

2.3.1 Post-Positivist Paradigm

This approach from an ontology point of view claims that one reality does exist but it is only known imperfectly within a certain probability due to the limitations of the researcher and the study. The role of the researcher is therefore to use rigorous methods to establish scientific facts, for example in a randomised controlled clinical trial. The advantages to this approach are that there is less bias through randomisation, blinding researchers and with consistent and definite outcome measures. However, not all research questions are amenable to a randomised controlled trial and only those factors considered relevant are recorded due to strict protocols.(218) This is more of a traditional research approach claiming that scientific knowledge is objective and that only this is valid and the truth. (14, 219)

2.3.2 Transformative Paradigm

The transformative approach places a central importance on the lives and experiences of diverse and marginalised groups, concerned with power and imbalances.(217, 218, 220) The primary aim of the researcher is to effect change and remove social injustice,(218) for which knowledge is gained through an interactive process between the participants and the researcher. With regards to ontology, multiple realities are recognised as valid but are critically examined.(218)

2.3.3 Constructivist Paradigm

This approach is defined as the fact that knowledge is socially constructed and is the outcome of the interaction between the researcher and the participants.(217) Also, there is no single reality or truth (ontological view), therefore reality needs to be interpreted through each individuals perceptions. Moreover, the perception of reality can change throughout the process of the study and is constructed rather than set in stone. (14, 221) This epistemological view therefore requires the researcher to acknowledge their involvement in the research process and attempt to access and understand the participants' complex world as experienced and interpreted by them.(14)

2.3.4 This Thesis

The purpose of the present thesis was to explore whether patient sex has an effect on the outcomes following treatment for cardiovascular disease. The thesis aimed to focus on 5 individual data sets and then draw conclusions following a critical review of the findings. The exploratory nature of the research and the underlying emphasis on sex differences led the thesis to adopt a constructivist epistemology.

Firstly, as described earlier, randomised controlled trials and cohort studies would be the methods of choice if pursuing a post-positivist framework.(14, 222) For this thesis, I have rejected the use of both randomised controlled trial or a large cohort study and did not wish to focus on a single intervention, hence this framework does not fit for the thesis. The transformative approach could be considered as this does place a central importance on women, which could be considered the diverse group,(220) however social justice was not the aim of my thesis, for which I plan to review clinical outcomes, therefore this approach was also discounted.

The reason I selected the constructivist approach was that following my literature review, I chose one overarching, open-ended, descriptive research question ('do outcomes differ between women and men in the treatment of cardiovascular disease?') followed by a number of small sub-questions (each of my individual data sets), each of which when critically combined allows for construction of potential new knowledge in this area. Having a number of areas to investigate, fits with the constructivist approach with the

underlying idea that multiple sources of data and multiple methods used to collect the data allow for better interpretation of meaning and support the validity of any potential new knowledge.(223) Indeed the constructivist view opposes the idea that a single methodology can be used to generate knowledge.(14, 221)

My aim was to try to understand the complex interaction of sex in those individuals with acquired cardiovascular disease, by being inclusive. The epistemological view in constructivism theory is that there is an interactive link between the researcher (myself) and the datasets, which is present in this thesis. Furthermore, with this paradigm, knowledge is socially constructed. Many clinical studies are read and interpreted by clinicians individually who themselves determine whether they think that the results are valid. For example, as women are under-represented in the literature, clinicians assume women do less well and change practice based on their own clinical experience. This can impact upon patient care, hence the impact that these results will have on women is socially determined.

The constructivism approach is new to me, as I have utilised the post-positivist approach during my professional career to date. I will have a large volume of data (largely observational) which will be appraised to draw conclusions focussing on the research question. However, it is recognised that this data is not totally objective as many of the researchers whose data will be used may themselves believe that women do not fare as well as men, therefore ignore results that do not fit with their assumption, assuming this is artefact rather than a real result. It also must be taken into account that many traditional researchers operate under the paradigm of post-positivism and therefore may be less willing to accept new knowledge formation in this way. However, as the constructivism approach allows inclusion of different areas of practice which are important to try and gain an understanding of the 'bigger picture' and allows observations that demand creation of new ideas,(224) I feel it is important to move forward with this approach for the thesis.

2.4 Implications for the Trustworthiness & Robustness of my Research

As described, the constructivist approaches do not assume that an external 'true' answer exists to be discovered, but rather that knowledge ('truth') is constructed through the critical interaction between myself as the researcher and the data. The criteria for judging

the robustness of a constructivist approach differs significantly from those of a post-positivist theory, which is heavily dependent on the use of quantitative statistical analyses. However, it is important for the research to be demonstrated as trustworthy in order to gain acceptance from more traditional researchers.

In this thesis, I propose to use the framework provided by Lincoln and Guba (225) in order to critically review my work. This is a series of techniques described to assist with this important aspect. These include the assessment of credibility, which assesses how congruent are the findings of the study with the truth, which can be assessed through the use of well recognised research methods, site triangulation, debriefing sessions between myself and my supervisors, peer scrutiny of the projects and examination of prior research to frame the findings. Transferability is also reviewed which aims to show how the findings are applicable to other contexts and this is important via background data provision to determine the context of the research. The next factor is dependability which is important to show that the findings are consistent and repeatable. Finally, there needs to be evidence of confirmability, which determines investigator bias and whether similar results would be achieved by an alternate investigator. Each of these areas will be discussed and explored throughout the thesis and shown in the later discussion.

2.5 Generating my Data Sets

As outlined above, I have chosen to observe 5 differing areas of clinical practice within cardiology, in order to support the critical examination of my question as to whether the sex of the patient impacts upon the clinical outcomes. The 5 clinical scenarios I have chosen are:

a) The Role of Female Sex in the Treatment of the Left Main Coronary Artery;
b) Bleeding Risk in Women Undergoing Primary PCI for STEMI;
c) Does Sex Play a Role in the Activated Clotting Time During Angioplasty?;
d) The Role of Sex on Outcomes Following Transcatheter Aortic Valve Implantation;
e) Sex Differences in the Perceived Intensity of Symptoms in Patients with Aortic Stenosis.

For a, b and d, I have contributed to data collection, interrogated and re-analysed existing data sets and for c and e data sets were generated that allowed me to assess outcomes according to the sex of the patient; the methods used to determine the data sets are

described in the individual chapters. My aim is to undertake a quantitative re-analysis of the findings of each of these studies to answer specific questions about the outcomes according to sex in patients with cardiovascular disease and so seek to draw wider conclusions about the impact of the sex of the patient on clinical outcomes in cardiovascular disease. In order to do this, I have applied specific statistical techniques which will be explained within each of the following chapters.

2.6 Summary

In this chapter, I have outlined how my research question was developed and also the methodological and theoretical techniques I will use to try to answer this question. I have also described the framework that I will use to assess and ensure the robustness and trustworthiness of my overall conclusions regarding any differences between the sex of the patient in clinical outcomes for cardiovascular disease. In the following 5 chapters I will go on to describe each of these studies and report the data generated from each of these.

In Chapter 8, I will critically compare the findings from each of these studies to assess what they reveal about sex differences in cardiovascular disease. I will also critically examine the robustness of my analysis alongside this, before describing the implications for practice and future research in Chapter 9.

3. The Role of Female Sex in the Treatment of the Left Main Coronary Artery

3.1 Introduction

As has been discussed, CAD is underdiagnosed in women with consequent delays in their treatment, which can impact upon the outcomes in this group. In addition, it was clear from my narrative review that women undergoing intervention have previously been demonstrated to have inferior outcomes following PCI for stable CAD and often women have more complex underlying coronary anatomy. One of the most complex cardiac lesions and feared by the interventional cardiologist is that of the left main coronary artery. This subtends a large area of the myocardium and hence significant disease can often be life threatening to the patient. Significant unprotected left main coronary artery disease (ULMCA) is found in approximately 5-7% of those patients undergoing diagnostic coronary angiography(226) and such a pattern of disease has a Class IA indication for CABG in current practice guidelines. (227, 228) This is secondary to a number of factors; the majority of patients have concurrent triple vessel involvement, disease affecting the distal ULMCA bifurcation is at a high risk for restenosis and, importantly, with the significant proportion of myocardium being at jeopardy, this can lead to significant left ventricular systolic dysfunction and arrhythmias.(229)

In more recent years, the role of PCI for the treatment of the ULMCA has evolved, due to advances in coronary stent technology, anti-platelet pharmacology and adjunctive imaging techniques. A number of studies have demonstrated a significant reduction in restenosis and target lesion revascularisation (TLR) following PCI, particularly with the introduction of the drug-eluting stent (DES).(230-244) As a consequence, many operators are becoming increasingly enthusiastic regarding the treatment of the ULMCA with PCI and a number of recent landmark trials have been published assessing the role of this treatment strategy, with controversial results.(245, 246) It must be remembered however that women have been continuously under-represented in CAD trials to date and hence it remains unclear whether such trials can be extrapolated to this patient group.

Currently, there is minimal data comparing outcomes according to sex in this high risk anatomical CAD group.(247) As women are older at presentation with CAD, with more co-morbidities, there may be a difference in outcomes in this subset of advanced

disease. The aim of this chapter therefore is to compare clinical outcomes according to sex in patients undergoing PCI using DES and also CABG for ULMCA disease, from the large 'Drug Eluting stent for LefT main coronary Artery disease' (DELTA) multi-centre, international registry. Treatment of the ULMCA is not a common occurrence in daily practice (although becoming increasingly so) and hence it was necessary to include more than one site to ensure adequate numbers of patients to allow for a fair comparison. All patients undergoing such treatment were included, with the aim for a 'real-world' idea of outcomes rather than focussing on a highly selected group of patients which can happen in randomised controlled trials. The outcomes comparing women with men following PCI with DES are assessed and also outcomes according to sex in those undergoing CABG. Finally, the outcomes comparing revascularisation methods in just the female cohort are compared and presented.

3.2 Methods

3.2.1 Patients and Procedures

The DELTA Registry included consecutive 'all-comers' with ULMCA disease treated in 14 multi-national centers, by either PCI with DES or CABG between April 2002 and April 2006. The overall results have previously been published. (248) I was responsible for all data collection and validation from one site (San Raffaele Scientific Institute, Milan, Italy) and co-ordinating the data obtained from the remaining sites and forming the joint database to allow for the analysis. The overall analysis was also performed by myself.

All patients enrolled in the registry were primarily evaluated by a multi-disciplinary team, including interventional cardiologists and cardiothoracic surgeons and the choice of interventional technique was deemed suitable to ensure complete revascularisation for the patient. The decision was based upon: 1) the haemodynamic status of the patient; 2) the baseline lesion characteristics; 3) the size of the vessel; 4) the co-morbidities of the patient; 5) the quality of arterial / venous conduits available for grafting and 6) the patient and / or the referring physician preference. Coronary angioplasty and stent implantation, including the bifurcation strategy in the case of distal ULMCA disease, were performed according to the preference of the operator with the aim for complete coverage of the diseased segment of the vessels.

Dual anti-platelet therapy (DAPT) was recommended for at least 12 months in those patients undergoing PCI with DES, consisting of aspirin 100mg daily and clopidogrel 75mg daily or ticlopidine 250mg twice daily. Aspirin 100 mg daily was continued indefinitely thereafter in this group. In the Korean center, cilostazol was additionally prescribed. Information regarding compliance with DAPT was obtained in all patients. Angiographic follow-up was not mandatory in this registry unless there were clinical symptoms or subjective evidence of ischaemia demonstrated on functional testing.

All data relating to the hospital admission, interventional procedures and follow-up were collected and adjudicated in each center according to the local policy. Full written informed consent was obtained from the patient for the procedure and for all subsequent data collection.

3.2.2 Definitions

The events analysed during hospital stay and at clinical follow up were death, both all-cause and cardiovascular, MI, cerebrovascular accident (CVA), target lesion revascularisation (TLR) and target vessel revascularisation (TVR). Major adverse cardiac and cerebrovascular events (MACCE) were defined in this study as a composite of death, MI, CVA and TVR.(248)

3.2.3 Study Objectives

The primary study objective was MACCE at long-term follow-up and additional objectives were each of the individual components of death, CVA, MI and TVR at long-term follow-up.

3.2.4 Statistical Analysis

Continuous variables are expressed as mean ± standard deviation (SD) and analysed with the Student t test or Wilcoxon rank-sum test depending on the variable distribution. Categorical variables were compared with the chi-squared test with Yates correction for continuity or the Fisher-exact test as appropriate. The overall analysis was performed by myself.

It is known however that in such observational studies, that there are significant baseline differences between the treated groups of patients, which can make it difficult to separate the effect of treatment from other factors.(249) and hence it was important to take this into account in the analysis of the data set. Randomised controlled trials are felt to be the gold standard method to investigate the outcomes by minimising bias between 2 treatment types, however there can be a lack of external validity, with included patients often being younger and healthier. In studies involving CAD additionally, women are under-represented and hence outcomes of such studies are extrapolated to the treatment of women as a justified belief. Indeed, it is unclear whether such standardised treatments are beneficial to women or could actually cause harm. In this data set, a propensity score matching was therefore performed with the aim to eliminate bias and allow for a fair comparison between the groups under analysis.

Propensity score matching was chosen for this observational study, as it does have some epistemological advantages over more traditional regression modelling methods.(250, 251) Multivariable regression adjusts for confounders by modelling the relationship between the covariates and outcomes, which is done using information from one group which may be very different from the other, whereas the propensity score estimates treatment effect by modelling the relationship between the confounders and the assigned treatment. In addition, if the outcome being assessed is not common (in this study MACCE), there is not usually enough available information in a conventional regression model to estimate the association between outcome and patient characteristic, which is not the case in a propensity score matched analysis, where outcomes can be compared by treatment / group type.(252) It is also important that with a propensity score matching (compared to other propensity score analyses) that it is possible to demonstrate the recorded characteristics of each group explicitly, to enable the assessment of whether the distribution of characteristics are similar within the 2 groups. It is taken into account however that the use of propensity score matching can only allow for patient characteristics that are known and have been measured, with equal distributions of unknown potential confounding factors only achievable in true randomised controlled trials. In this analysis, all patient characteristics used as independent variables in the model were determined a priori. Moreover, patients were excluded if no matching partner was found, which resulted in overall lower-case numbers. However, the numbers involved following the matching were sufficient to allow for a clear analysis of the data.

Because of the non-randomised nature of the study as described above, to reduce the effect of treatment selection bias and potential confounding in this observational study, we decided to perform rigorous adjustment for significant differences in the baseline characteristics of patients with propensity score matching in each cohort. A propensity score was calculated by performing a parsimonious multivariable logistic regression. The following co-variants were selected to calculate the propensity score: age, family history, hypertension, hypercholesterolaemia, smoker, diabetes mellitus, unstable angina, left ventricular ejection fraction, chronic kidney disease, previous PCI, previous CABG, presence of multi-vessel disease, right coronary artery disease and distal disease. To identify matched pairs we used the following algorithm: 1:1 optimal match with a ± 0.03 caliper and no replacement.(253) Clinical outcomes in the matched population were analysed with Cox proportional hazards regression stratified on matched-pairs. Regression modelling was performed to determine the independent predictors of study endpoints using purposeful selection of covariates; variables identified at univariate analysis and deemed of clinical importance from previous literature were eligible for inclusion into the multivariable model and included age, left ventricular ejection fraction, intra-aortic balloon pump (IABP) use and European System for Cardiac Operative Risk Evaluation (EuroSCORE). These results are reported as Odds Ratio (OR) with 95% Confidence Intervals (CI). Survival was recorded by a Kaplan-Meier analysis and the log-rank method was used for comparison. Statistical analysis was performed with Statistical Package for Social Sciences Version 23.0 (SPSS Inc, Chicago, Illinois, USA). A p-value of <0.05 was considered statistically significant.

3.3 Results

The overall population of the DELTA registry, consisting of 2,775 patients, and their treatment strategies are shown in Figure 1. Overall, 817 (29.4%) were female.

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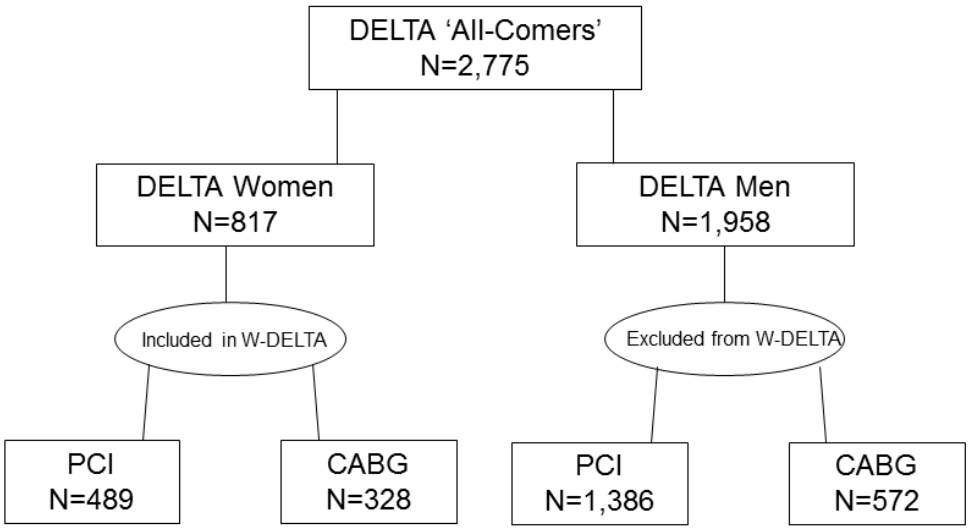


Figure 1. The overall DELTA population divided by sex and treatment strategy (PCI= Percutaneous Coronary Intervention; CABG= Coronary Artery Bypass Grafting).

3.3.1 Percutaneous Coronary Intervention Cohort

In total, 1,875 patients were included in the PCI cohort of the DELTA Registry, of which 489 (26.1%) were female and 1,386 (73.9%) were male. The baseline clinical characteristics of the PCI group are illustrated in Table 3. More women treated with PCI were older (67.4 ± 12.6 years vs. 65.3 ± 11.1 years; p=0.001), with a previous history of hypertension (73.4% vs. 60.7%; p<0.001), hypercholesterolaemia (66.1% vs. 60.4%; p=0.026) and diabetes mellitus (32.9% vs. 25.9%; p=0.003). Conversely, more men than women were smokers (24.9% vs. 52.3%; p<0.001) with a lower left ventricular ejection fraction (54.8 ± 12.2% vs. 53.5 ± 11.9%; p=0.035). Interestingly, women had a higher EuroSCORE (5.6 ± 4.0 vs. 4.7 ± 3.5; p<0.001), with men having a higher SYNTAX score (26.8 ± 13.0 vs. 29.0 ± 13.9; p=0.008). The lesion and procedural characteristics are shown in Table 4. Correspondingly, men had a longer mean stent length (20.4 ± 15.5 mm vs. 22.3 ± 18.2 mm; p=0.044) and a larger mean stent diameter (3.3 ± 0.3 mm vs. 3.4 ± 0.4 mm; p=0.003).

Table 3. The Baseline Clinical Characteristics in the Overall PCI Cohort of the DELTA Registry.

	Women N = 489	**Men N = 1,386**	**P Value**
Age	67.4±12.6	65.3±11.1	0.001
Hypertension	359 (73.4)	841 (60.7)	<0.001
Hypercholesterolaemia	323 (66.1)	836 (60.4)	0.026
Smoker	122 (24.9)	725 (52.3)	<0.001
Diabetes Mellitus	161 (32.9)	359 (25.9)	0.003
Chronic Kidney Disease	28 (5.7)	109 (7.9)	0.117
Unstable Angina	178 (36.4)	435 (31.4)	0.043
NSTEMI	79 (16.2)	193 (13.9)	0.231
STEMI	10 (2.0)	44 (3.2)	0.070
Previous CABG	51 (10.4)	151 (10.9)	0.772
Previous PCI	123 (25.2)	342 (24.7)	0.839
LVEF	54.8±12.2	53.5±11.9	0.035
EuroSCORE	5.6±4.0	4.7±3.5	<0.001

Results are expressed as N (%) or Mean ± SD as appropriate. NSTEMI = Non-ST-Elevation Myocardial Infarction; STEMI = ST-Elevation Myocardial Infarction; CABG = Coronary Artery Bypass Grafting; PCI = Percutaneous Coronary Intervention; LVEF = Left Ventricular Ejection Fraction; EuroSCORE = European System for Cardiac Operative Risk Evaluation.

Table 4. The Baseline Lesion and Procedural Characteristics of the Overall PCI Cohort of the DELTA Registry.

	Women N = 489	**Men N = 1,386**	**P Value**
Multi Vessel Disease	381 (77.9)	1,114 (80.4)	0.233
RCA Disease	150 (30.9)	533 (38.7)	0.002
SYNTAX score	26.8±13.0	29.0±13.9	0.008
Distal Location	280 (57.6)	851 (61.5)	0.133
Predilatation	230 (47.0)	590 (42.6)	0.053
Atherectomy	5 (1.0)	20 (1.4)	0.046
Rotablator	9 (1.8)	19 (1.4)	0.463
Cutting Balloon	29 (5.9)	138 (10.0)	0.022
IABP	31 (8.4)	101 (8.1)	0.871
IVUS	194 (39.7)	427 (30.8)	0.001
Mean Stent Diameter (mm)	3.3±0.3	3.4±0.4	0.003
Mean Stent Length (mm)	20.4±15.5	22.3±18.2	0.044
2 Stent Technique	126 (25.8)	362 (26.1)	0.554
Postdilatation	236 (48.3)	631 (45.0)	0.119
Maximum Diameter (mm)	3.7±0.5	3.7±0.6	0.384
Maximum Pressure (atm)	15.4±3.9	16.0±4.1	0.038
FKBI	202 (41.3)	619 (44.7)	0.314
Abciximab	60 (12.3)	141 (10.2)	0.504
Eptifibatide	11 (2.2)	18 (1.3)	0.114
Tirofiban	39 (8.0)	167 (12.1)	0.026
Bivalirudin	27 (5.5)	20 (1.4)	<0.001
Vessels Treated	1.6±0.9	1.5±0.9	0.039
Lesions Treated	1.7±1.1	1.8±1.3	0.251
Mean Hospital Stay (days)	4.1±4.0	3.4±4.7	0.131

Results are expressed as N (%) or Mean ± SD as appropriate. RCA = Right Coronary Artery; SYNTAX = Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; IABP = Intra Aortic Balloon Pump; IVUS = Intravascular Ultrasound; FKBI = Final Kissing Balloon Inflation; CABG = Coronary Artery Bypass Grafting; PCI = Percutaneous Coronary Intervention.

3.3.1.1Unadjusted In Hospital and Long Term MACCE

During the index hospitalization, all-cause mortality in women compared with men occurred in 4.1% versus 1.5%, and cardiovascular mortality in 3.5% versus 1.2% respectively. Peri-procedural MI (as defined by elevation of serum creatine kinase myocardial band exceeding 5 times the upper reference limit) was observed in 5.9% versus 3.1% and CVA 0.6% versus 0.1%. Overall in-hospital MACCE was 9.6% versus 4.4%. There were 4 (0.8%) episodes of in-hospital TVR in the PCI group and 9 (0.6%) in the CABG group.

Clinical follow-up was obtained at a median of 1,236 (interquartile range [IQR] 979-1,550) days, in 99.3% of patients. With regards to all-cause mortality, this was respectively in women compared with men 14.1% versus 14.1%, and cardiovascular mortality 7.0% versus 7.7%. With regards to MI, such an event was reported in 4.3% versus 3.8%, with TLR in 10.2% versus 10.3% and TVR rates 15.1% versus 15.6%. The occurrence of MACCE was adjudicated at 30.5% versus 30.1% at long-term follow-up.

3.3.1.2 Propensity Matched Analysis

After propensity score matching of the PCI population, there were 308 matched pairs of patients in each group. The baseline characteristics of the matched groups are shown in Table 5.

3.3.1.3 In Hospital and Long Term MACCE in the Propensity Matched Analysis

For the 308 matched pairs during hospitalization, there were no significant differences between women and men in the risk of all-cause mortality (OR 0.619; 95% CI 0.200-1.913; p=0.400) or indeed cardiovascular mortality (OR 0.596; 95% CI 0.141-2.516; p=0.477). Furthermore, there was no difference in the occurrence of MACCE (OR 0.975; 95% CI 0.437-2.178; p=0.747).

Table 5. The Baseline Characteristics in the PCI Propensity Matched Population of the DELTA Registry.

	Women N = 308	**Men N = 308**	**P Value**
Age (years)	66.1±12.6	66.4±10.4	0.762
Hypertension	209 (68.1)	208 (67.9)	0.931
Hypercholesterolaemia	188 (61.2)	187 (60.9)	0.934
Smoker	68 (22.1)	67 (21.8)	0.922
Diabetes Mellitus	92 (30.0)	100 (32.6)	0.486
Chronic Kidney Disease	12 (3.9)	16 (5.2)	0.439
Unstable Angina	115 (37.5)	109 (35.9)	0.615
Previous PCI	81 (26.4)	74 (24.1)	0.516
Previous CABG	19 (6.2)	27 (8.8)	0.220
LVEF (%)	54.5±10.9	54.9±9.7	0.576
Multi Vessel Disease	251 (81.8)	246 (80.1)	0.607
RCA Disease	104 (33.9)	116 (37.8)	0.313
Distal Location	196 (64.1)	208 (67.8)	0.334
IVUS	155 (50.5)	104 (33.9)	<0.001
IABP	25 (10.2)	16 (5.6)	0.049
Mean Stent Diameter (mm)	3.4±0.3	3.4±0.4	0.074
Mean Stent Length (mm)	22.5±18.1	23.4±20.8	0.543

Results are expressed as N (%) or Mean ± SD as appropriate. PCI = Percutaneous Coronary Intervention; CABG = Coronary Artery Bypass Grafting; LVEF = Left Ventricular Ejection Fraction; RCA = Right Coronary Artery; IVUS = Intravascular Ultrasound; IABP = Intra Aortic Balloon Pump.

At 1,197 (IQR 861-1,566) days follow-up, there was no difference between groups in the primary study objective of MACCE (OR 1.000; 95% CI 0.706-1.417; p=1.000). Additionally, there were no differences between groups in either all-cause (OR 0.828; 95% CI 0.505-1.555; p=0.452) or cardiovascular mortality (OR 0.686; 95% CI 0.340-1.384; p=0.0.290). Moreover, there were no differences between groups in the rates of MI (OR 1.342; 95% CI 0.460-3.915; p=0.589) or CVA (OR 1.342; 95% CI 0.460-3.915; p=0.589).

There were no differences in the need for repeat revascularisation between sexes with regards to both TLR (OR 3.921; 95% CI 1.422-10.811; p=1.000) and TVR (OR 5.403; 95% CI 2.315-12.610; p=0.592). Table 6 illustrates the outcomes of the matched population and Figure 2 illustrates survival curves in the PCI group according to sex.

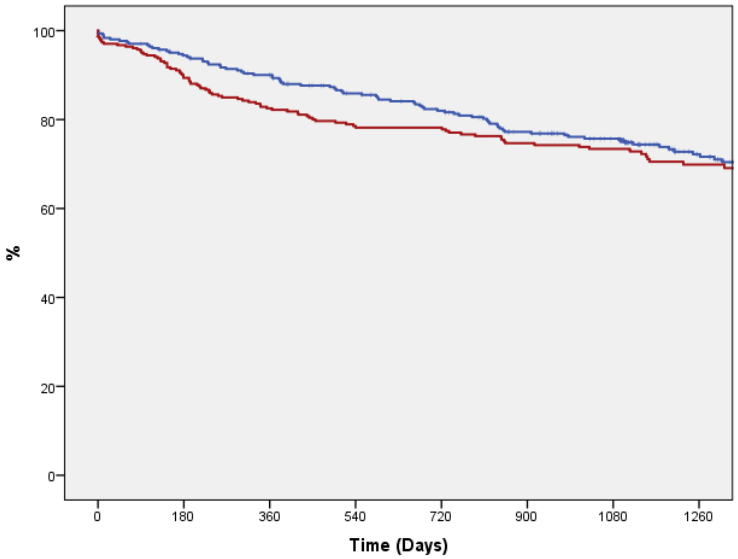
Table 6. The Outcomes of the PCI Cohort Propensity Matched Population from the DELTA Registry.

Outcome	**Number of Events (%)**				
	Women N = 308	**Men N = 308**	**OR**	**95% CI**	**P Value**
In Hospital					
All-Cause Mortality	8 (2.6)	5 (1.6)	0.619	0.200-1.913	0.400
Cardiac Mortality	5 (1.6)	3 (1.0)	0.596	0.141-2.516	0.477
MI	12 (3.9)	12 (3.9)	1.000	0.442-2.262	1.000
TVR	1 (0.3)	0			0.521
Stroke	2 (0.7)	0			0.262
MACCE	21 (6.8)	18 (5.9)	0.975	0.437-2.178	0.747
Follow-Up					
All-Cause Mortality	33(10.7)	39 (12.7)	0.828	0.505-1.555	0.452
Cardiac Mortality	14 (4.6)	20 (6.5)	0.686	0.340-1.384	0.290
MI	8 (2.6)	6 (2.0)	1.342	0.460-3.915	0.589
TLR	34 (11.1)	34 (11.1)	1.000	0.604-1.655	1.000
TVR	55 (17.9)	50 (16.3)	1.122	0.737-1.708	0.592
Stroke	8 (2.6)	6 (2.0)	1.342	0.460-3.915	0.589
MACCE	89 (29.0)	89 (29.0)	1.000	0.706-1.417	1.000

Results reported as N (%). MI = Myocardial Infarction; TLR = Target Lesion Revascularisation; TVR = Target Vessel Revascularisation; MACCE = Major Adverse Cardiovascular and Cerebrovascular Events; PCI = Percutaneous Coronary Intervention; CABG = Coronary Artery Bypass Grafting; OR = Odds Ratio; CI = Confidence Interval.

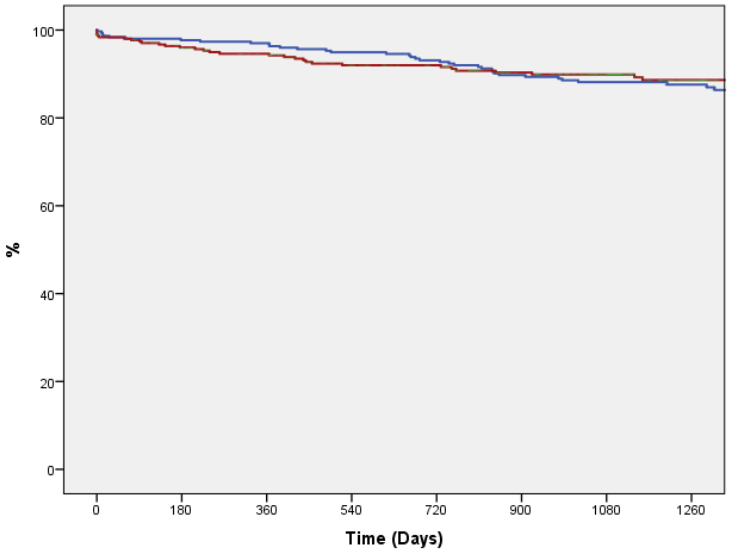
Figure 2. Kaplan Meier Curves to Illustrate MACCE (Panel A) and Death (Panel B at Follow Up According to the Sex of the Patient in the Matched PCI Cohort of the DELTA Registry. Females are depicted by the Red line and Males in Blue.

A.



Women	305	266	237	213	205	189	160	105
Men	305	283	267	244	229	210	189	125

B.



Women	305	279	261	237	227	210	182	120
Men	305	292	286	266	253	223	214	148

3.3.1.4 Predictors of the Primary and Secondary Study Objectives

In the matched PCI population, the multi-variable predictors of MACCE were the left ventricular function (Hazard Ratio [HR] 0.973; 95% Confidence Interval [CI] 0.957-0.990; p=0.002) and the SYNTAX score of the patient (HR 1.014; 95% CI 1.000-1.028; p=0.047).

Similarly, for death at follow-up, the predictors were left ventricular function (HR 0.949; 95% CI 0.928-0.972; p<0.001) and the SYNTAX score (HR 1.021; 95% CI 1.002-1.040; p=0.034), with also the age of the patient (HR 1.036; 95% CI 1.010-1.062; p=0.007) being significant.

3.3.2 Coronary Artery Bypass Cohort

In total, 900 patients were included in the CABG cohort of the DELTA Registry, of which 328 (36.5%) were female and 572 (63.5%) were male. The baseline clinical characteristics of this group are illustrated in Table 7. The women treated with CABG were as in the PCI cohort again typically older (67.9 ± 10.0 years vs. 65.9 ± 9.8 years; p=0.003) with a history of hypertension (72.9% vs. 64.6%; p=0.010) and hypercholesterolaemia (70.5% vs. 61.4%; p=0.006), in addition to diabetes mellitus (32.9% vs. 25.9%; p=0.003). As in the PCI group, more men than women were smokers (16.7% vs. 57.4%; p<0.001) with a lower left ventricular ejection fraction (54.5 ± 11.0% vs. 52.6 ± 11.7%; p=0.018). The women again had a higher baseline EuroSCORE (5.4 ± 2.6 vs. 4.8 ± 2.8; p=0.004).

3.3.2.1 Unadjusted In-Hospital Mortality and Long Term MACCE

During hospitalization, in the CABG cohort of the DELTA Registry, all-cause mortality in women versus men occurred in 2.7% vs. 3.5%, and cardiovascular mortality in 1.8% versus 2.4% respectively. A diagnosis of peri-procedural MI was observed in 18.2% versus 26.9% and CVA 1.5% versus 1.2%. Overall, the observed occurrence of in-hospital MACCE was 23.1% versus 34.9%.

Clinical follow-up was obtained at a median of 1,452 (interquartile range [IQR] 819-1,867) days, in a total of 99.8% of CABG patients. With regards to all-cause mortality, this was respectively in women compared with men 7.0% versus 14.0%, and

cardiovascular mortality 4.6% versus 8.0%. With regards to MI, such an event was reported in 1.5% versus 4.9% and MACCE was adjudicated at 15.7% versus 25.0% at long-term follow-up.

Table 7. The Baseline Clinical Characteristics in the Overall CABG Cohort of the DELTA Registry.

	Women N = 328	**Men N = 572**	**P Value**
Age (years)	67.9±10.0	65.9±9.8	0.003
Hypertension	240 (72.9)	370 (64.6)	0.010
Hypercholesterolaemia	232 (70.5)	351 (61.4)	0.006
Smoker	55 (16.7)	329 (57.4)	<0.001
Diabetes Mellitus	101 (30.7)	205 (35.8)	0.121
Chronic Kidney Disease	9 (2.7)	28 (4.9)	0.117
Unstable Angina	169 (51.4)	308 (53.8)	0.490
Previous CABG	13 (4.0)	11 (1.9)	0.068
Previous PCI	48 (14.6)	76 (13.3)	0.578
LVEF (%)	54.5±11.0	52.6±11.7	0.018
EuroSCORE	5.4±2.6	4.8±2.8	0.004

Results are expressed as N (%) or Mean ± SD as appropriate. CABG = Coronary Artery Bypass Grafting; PCI = Percutaneous Coronary Intervention; LVEF = Left Ventricular Ejection Fraction; EuroSCORE = European System for Cardiac Operative Risk Evaluation.

3.3.2.2 Propensity Matched Analysis

After propensity score matching of the CABG population of the DELTA Registry, there were in total 244 matched pairs of patients in each group. The baseline characteristics of the matched groups are shown in Table 8.

3.3.2.3 In Hospital and Long Term MACCE in Propensity Matched Analysis

For the 244 matched pairs during the initial hospitalization, there were no significant differences between women and men in the risk of either all-cause mortality (OR 0.424;

95% CI 0.446-5.549; p=0.549) or cardiovascular mortality (OR 1.695; 95% CI 0.401-7.171; p=0.469). Furthermore, there was no difference in the occurrence of MACCE (OR 1.128; 95% CI 0.748-1.702; p=0.565) between sexes.

At 1,358 (IQR 618.25-1764.75) days follow-up, there was no significant difference between groups in the primary study objective of MACCE (OR 0.691; 95% CI 0.435-1.099; p=0.117). However, there was a significant difference favoring women in the event of all-cause mortality (OR 0.035; 95% CI 0.260-0.963; p=0.035), with a trend for more MI in men (OR 0.322; 95% CI 0.086-1.205; p=0.077). Table 9 illustrates the outcomes of the matched population. Survival curves are illustrated in Figure 3.

Table 8. The Baseline Characteristics in the CABG Propensity Matched Population of the DELTA Registry.

	Women N = 244	**Men N = 244**	**P Value**
Age (Years)	67.4±9.8	67.5±9.4	0.970
Hypertension	176 (71.8)	187 (77.0)	0.195
Hypercholesterolaemia	174 (71.0)	161 (66.3)	0.257
Diabetes Mellitus	85 (34.7)	82 (33.7)	0.825
Chronic Kidney Disease	8 (3.3)	7 (2.9)	0.806
Unstable Angina	132 (53.9)	120 (49.4)	0.320
Previous PCI	36 (14.7)	36 (14.7)	0.970
Previous CABG	8 (3.3)	7 (2.9)	0.806
LVEF (%)	53.6±11.4	54.6±11.0	0.330
EuroSCORE	5.3±2.6	5.0±2.8	0.253

Results are expressed as N (%) or Mean ± SD as appropriate. PCI = Percutaneous Coronary Intervention; CABG = Coronary Artery Bypass Grafting; LVEF = Left Ventricular Ejection Fraction; EuroSCORE = European System for Cardiac Operative Risk Evaluation.

Table 9. The Outcomes of the CABG Cohort Propensity Matched Population of the DELTA Registry.

Outcome	Number of Events (%)		OR	95% CI	P Value
	Women N = 244	**Men N = 244**			
In Hospital					
All-Cause Mortality	5 (2.0)	7 (2.9)	1.424	0.446-4.549	0.549
Cardiac Mortality	3 (1.2)	5 (2.1)	1.695	0.401-7.171	0.469
MI	49 (20.0)	55 (22.6)	1.170	0.788-1.806	0.477
Stroke	5 (2.0)	4 (1.6)	0.803	0.213-3.028	0.746
MACCE	58 (23.7)	63 (25.9)	1.128	0.748-1.702	0.565
Follow-Up					
All-Cause Mortality	15 (6.1)	28 (11.5)	0.501	0.260-0.963	0.035
Cardiac Mortality	9 (3.7)	15 (6.2)	0.580	0.249-1.351	0.202
MI	3 (1.2)	9 (3.7)	0.322	0.086-1.205	0.077
Stroke	11 (4.5)	6 (2.5)	1.850	0.676-5.103	0.224
MACCE	38 (15.5)	51 (21.0)	0.691	0.435-1.099	0.117

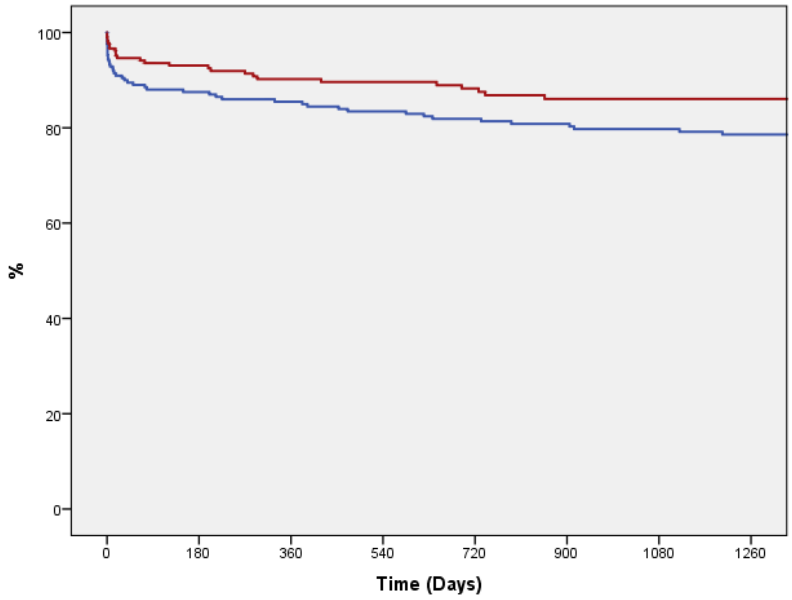
Results reported as N (%). MI = Myocardial Infarction; MACCE = Major Adverse Cardiovascular and Cerebrovascular Events; PCI = Percutaneous Coronary Intervention; CABG = Coronary Artery Bypass Grafting; OR = Odds Ratio; CI = Confidence Interval.

3.3.2.4 Predictors of Primary and Secondary Study Endpoints

The sole predictor of MACCE at follow up in the CABG cohort is male sex (HR 0.524; 95% CI 0.310-0.884; p=0.016). Similarly, male sex was a predictor of death at follow-up (HR 0.402; 95% CI 0.204-0.791; p=0.008), in addition to the EuroSCORE (HR 1.217; 95% CI 1.030-1.437; p=0.021).

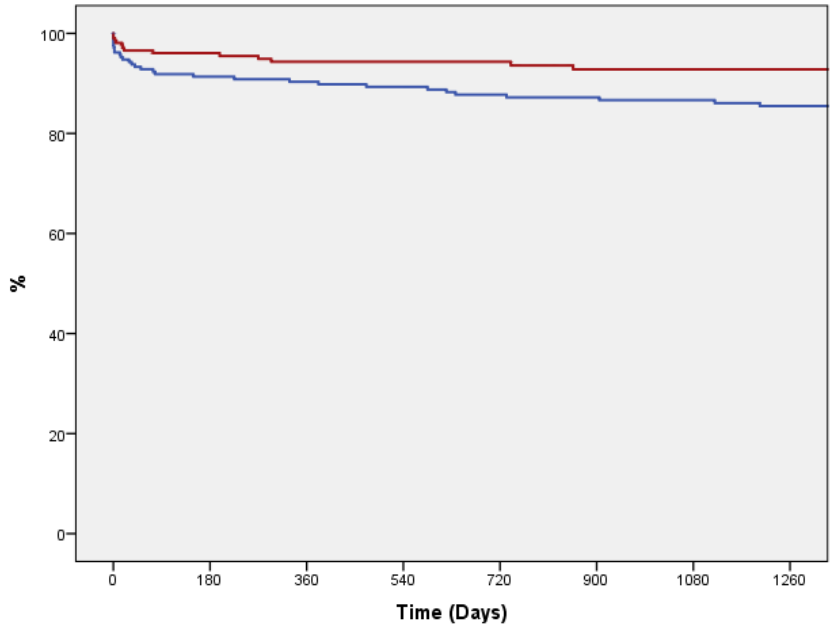
Figure 3. Kaplan Meier Curves to Illustrate MACCE (Panel A) and Death (Panel B at Follow Up According to the Sex of the Patient in the Matched CABG Cohort of the DELTA Registry. Females are depicted by the Red line and Males in Blue.

A.



Women	244	165	156	144	126	108	103	94
Men	244	173	168	162	156	149	140	129

B.



Women	244	169	156	144	126	108	103	94
Men	244	181	168	162	156	149	140	129

3.3.3 Female Cohort

In total, 817 females were included in the DELTA Registry, of which 489 (59.8%) underwent treatment with PCI with DES and 328 (40.2%) with CABG. The baseline clinical characteristics are illustrated in Table 10 and baseline lesion and procedural characteristics in Table 11.

Table 10. The Baseline Clinical Characteristics in the Overall Female Population of the DELTA Registry.

Variable	PCI (N = 489)	CABG (N = 328)	P Value
Age (Years)	67.4±12.6	67.9±11.6	0.562
Hypertension	359 (73.4%)	240 (72.9%)	0.111
Hypercholesterolaemia	323 (66.1%)	232 (70.5%)	0.680
Smoker	122 (24.9%)	55 (16.7%)	0.041
Diabetes Mellitus	161 (32.9%)	101 (30.7%)	0.504
Chronic Kidney Disease	28 (5.7%)	9 (2.7%)	0.044
Unstable Angina Pectoris	160 (32.7%)	163 (49.5%)	<0.001
NSTEMI	66 (13.5%)	34 (10.4%)	0.181
STEMI	10 (2.0%)	2 (0.6%)	0.094
Previous CABG	51 (10.4%)	13 (4.0%)	0.001
Previous PCI	123 (25.2%)	48 (14.6%)	<0.001
LVEF (%)	54.8±12.2	54.5±11.0	0.731
EuroSCORE	5.6±4.0	5.4±2.6	0.395

Results are expressed as N (%) or Mean ± SD as appropriate. NSTEMI = Non-ST-Elevation Myocardial Infarction; STEMI = ST-Elevation Myocardial Infarction, CABG = Coronary Artery Bypass Grafting; PCI = Percutaneous Coronary Intervention; LVEF = Left Ventricular Ejection Fraction; EuroSCORE = European System for Cardiac Operative Risk Evaluation.

Table 11. The Baseline Lesion and Procedural Characteristics of the Overall Female Population of the DELTA Registry.

Variable	PCI (N = 489)	CABG (N = 328)	P Value
Multi Vessel Coronary Disease	381 (77.9%)	310 (94.2%)	<0.001
Right Coronary Artery Disease	150 (30.9%)	231 (73.1%)	<0.001
Left System Coronary Artery Disease	314 (64.2%)	305 (93.0%)	<0.001
SYNTAX score	26.8±13.0	37.1±12.8	<0.001
Distal Location	280 (57.6%)	185 (58.5%)	0.794
Predilatation	230 (47.0%)		
Atherectomy	5 (1.0%)		
Rotablator	9 (1.8%)		
Cutting Balloon	29 (5.9%)		
IABP	31 (8.4%)	10 (14.3%)	0.117
IVUS	207 (42.3%)		
IVUS Guided	47 (9.6%)		
IVUS Controlled	160 (32.7%)		
Mean Stent Diameter (mm)	3.34±0.341		
Mean Stent Length (mm)	20.40±15.5		
2 Stent Technique	168 (34.4%)		
Crush	66 (13.5%)		
Mini Crush	17 (3.5%)		
Culotte	13 (2.7%)		
T Stenting	28 (5.7%)		
V Stenting	22 (4.5%)		
Other	22 (4.5%)		
Post Dilatation	236 (48.3%)		
Maximum Diameter (mm)	3.69±0.53		
Maximum Pressure (atm)	15.43±3.86		
Final Kissing Balloon Inflation	202 (41.3%)		

Table 11 continued. The Baseline Lesion and Procedural Characteristics of the Overall Female Population of the DELTA Registry.

Variable	PCI (N = 489)	CABG (N = 328)	P Value
Abciximab	60 (12.3%)		
Eptifibatide	11 (2.2%)		
Tirofiban	39 (8.0%)		
Bivalirudin	27 (5.5%)		
Vessels Treated	1.51±0.871	2.30±0.86	<0.001
Lesions Treated	1.81±1.29		
CABG Beating Heart		18 (5.5%)	
Mean Arterial Grafts		1.97±1.06	
Mean Venous Grafts		1.82±1.23	
Complete Revascularisation		276 (94.8%)	
Unintentional Incomplete		1 (0.5%)	
Mean Hospital Stay (Days)	4.1±4.0	14.5±9.4	<0.001

Results are expressed as N (%) or Mean ± SD as appropriate. SYNTAX = Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; IABP = Intra Aortic Balloon Pump; IVUS = Intravascular Ultrasound; CABG = Coronary Artery Bypass Grafting; PCI = Percutaneous Coronary Intervention.

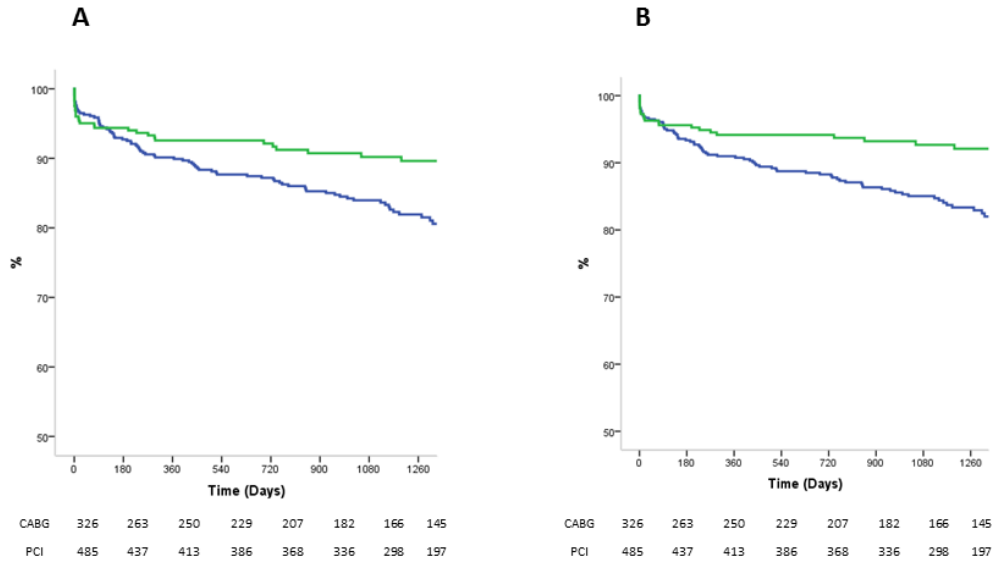
3.3.3.1 Unadjusted In-Hospital Mortality and Long-Term MACCE in the Female Cohort

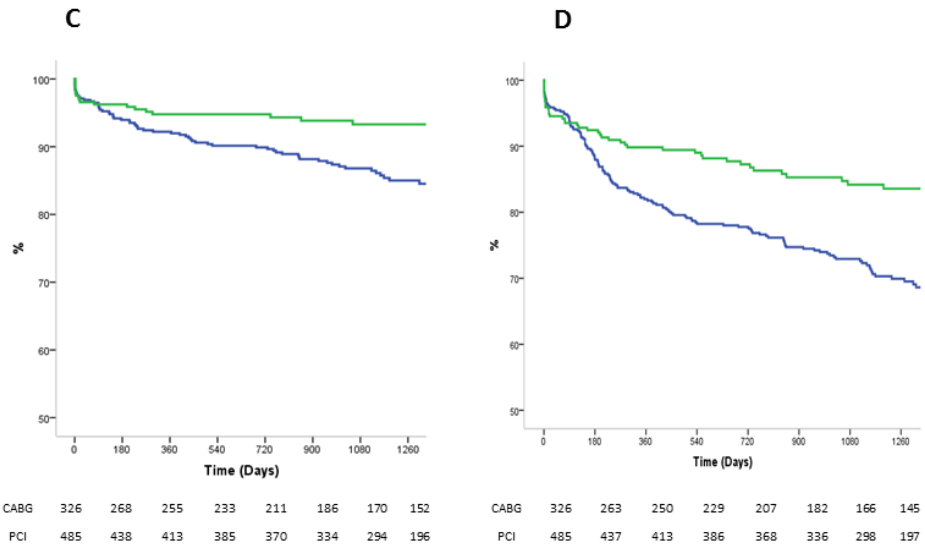
During hospitalization, all-cause mortality in PCI compared with CABG occurred in 4.1% versus 2.7%, and cardiovascular mortality in 3.5% versus 1.8% respectively. Peri-procedural MI was observed in 5.9% versus 18.2% and CVA 0.6% versus 1.5%. Overall in-hospital MACCE was 9.6% versus 22.5%. Of note, there were 4 (0.8%) episodes of in-hospital TVR in the PCI group and no such events in the CABG group. In those with distal disease treated with PCI, 55.4% underwent a single stent strategy. The in-hospital MACCE was 9.0% in those treated with a single stent strategy versus 13.0% in those undergoing implantation of 2 stents.

Clinical follow-up was obtained at a median of 1,185 (interquartile range [IQR] 628-1,548) days, in a total of 98.8% of PCI patients and 99.1% of CABG patients. With

regards to all-cause mortality, this was respectively in PCI compared with CABG 14.1% versus 7.0%, and cardiovascular mortality 7.0% versus 4.6%. The elective PCI mortality rate was 11.9% versus 20.2% for those urgent PCI cases. With regards to MI, such an event was reported in 4.3% versus 1.5%, with TLR 10.2% versus 3.8% and TVR rates 15.1% versus 5.1%. Overall, MACCE was adjudicated at 30.5% versus 15.7% at long-term follow-up. In those with distal disease treated with a single stent strategy the long term MACCE was 28.4% versus 35.2% in those requiring 2 stents. Furthermore, definite ST occurred in 6 (1.2%) of the women treated with PCI: 2 sub-acutely and 4 late. Probable ST was adjudicated in 4 (0.8%) and possible in 3 (0.6%) of patients. Figure 4 illustrates the Kaplan Meier survival curves of the overall female population.

Figure 4. Freedom from cardiac and cerebrovascular events in PCI versus CABG in the overall female population of the DELTA Registry. Freedom from death, MI and CVA (Panel A); from death and MI (Panel B; from death (Panel C) and from MACCE (Panel D) after PCI (blue line) versus CABG (green line). Patients at risk at different times reported under the graph.





3.3.3.2 Propensity Matched Analysis

After propensity score matching of the female population of the DELTA Registry, there were 175 matched pairs of patients in each of the treatment groups. The baseline characteristics of the matched groups are shown in Table 12.

3.3.3.4 In-Hospital and Long Term MACCE in Propensity Matched Analysis

For the 175 matched pairs of women during hospitalization, there were no significant differences between PCI and CABG in the risk of all-cause mortality (OR 1.333; 95% CI 0.294-6.046; p=0.709) or cardiovascular mortality (OR 0.994; 95% CI 0.198-4.995; p=0.994). A higher occurrence of MI (OR 2.145; 95% CI 1.036-4.439; p=0.040) and hence MACCE (OR 2.000; 95% CI 1.030-3.883; p=0.041) was sustained in the CABG group. However, there was no longer a difference in the incidence of CVA (OR 2.723; 95% CI 0.280-26.444; p=0.388).

At 1,148 (IQR 545-1,543) days follow-up, there was no difference between groups in the primary study objective of death, MI or CVA (OR 0.711; 95% CI 0.387-1.308; p=0.273). Additionally, there were no differences between groups in all-cause (OR 0.722; 95% CI 0.357-1.461; p=0.365) or cardiovascular mortality (OR 1.100; 95% CI 0.455-2.660; p=0.832). Moreover, there were no differences between groups in MI (OR 0.362;

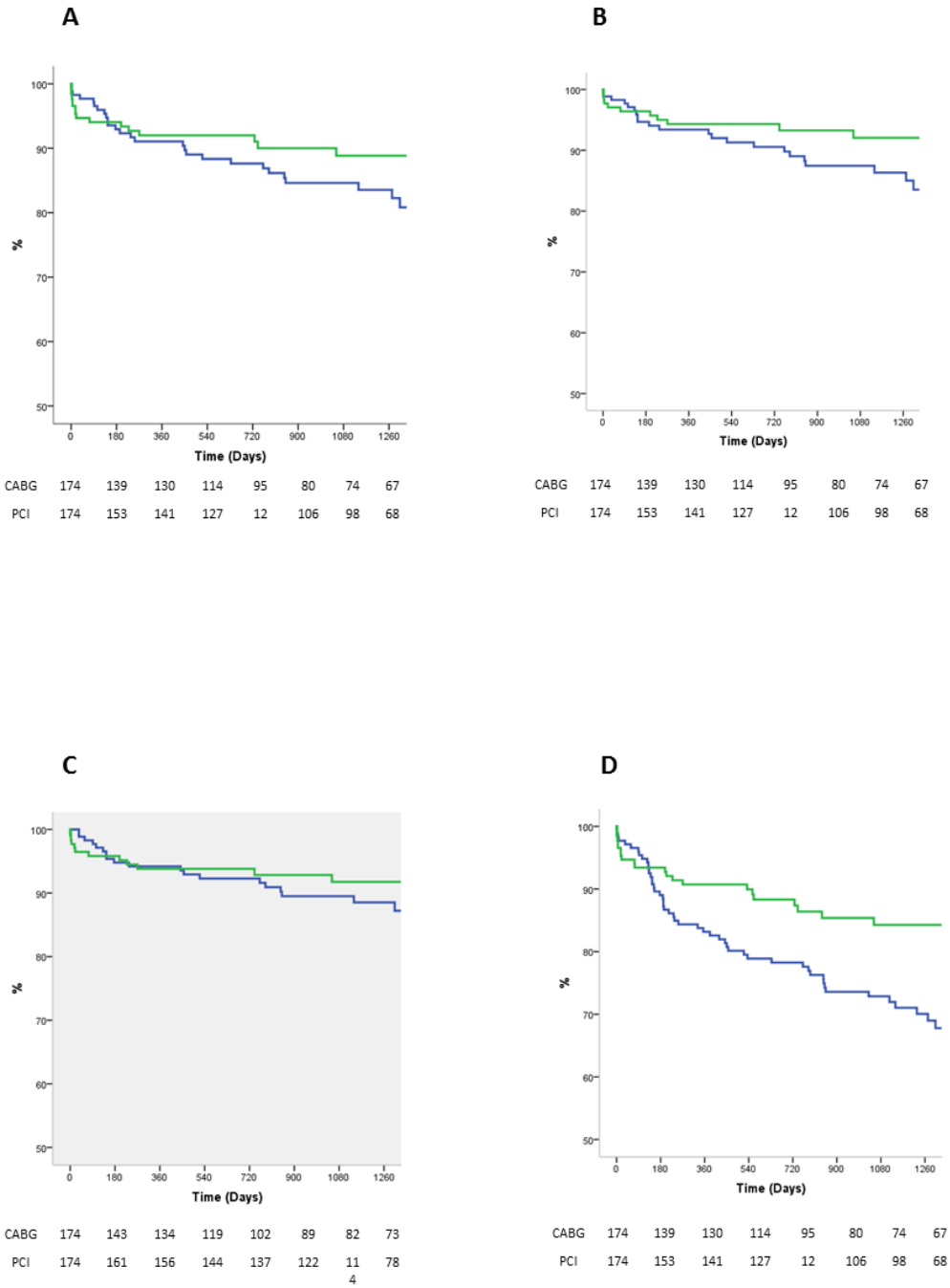
95% CI 0.094-1.388; p=0.138) or CVA (OR 1.200; 95% CI 0.359-4.007; p=0.767). However, there was an advantage of CABG over PCI in the event of TLR (OR 0.253; 95% CI 0.092-0.703; p=0.008) and TVR (OR 0.185; 95% CI 0.079-0.432; p<0.001), corresponding to an advantage in MACCE (OR 0.429; 95% CI 0.254-0.723; p=0.001). Within the PCI group, there was no difference in the occurrence of MACCE depending on whether triple anti-platelet therapy was used (triple therapy 21.2% vs. dual therapy 31.7%; p=0.235). Figure 4 demonstrates survival curves in the matched population.

Table 12. The Baseline Characteristics in the Propensity Matched Population of the Female Cohort of the DELTA Registry.

Variable	PCI (N = 175)	CABG (N = 175)	P Value
Age (Years)	67.1±12.0	67.5±10.3	0.736
Hypertension	120 (68.6%)	125(71.0%)	0.617
Hypercholesterolaemia	117 (66.9%)	127 (72.2%)	0.281
Smoker	34 (19.4%)	33 (18.8%)	0.872
Diabetes Mellitus	50 (28.6%)	55 (31.3%)	0.584
Chronic Kidney Disease	9 (5.1%)	5 (2.8%)	0.271
Unstable Angina Pectoris	72 (41.1%)	75 (42.6%)	0.780
Previous PCI	35 (20.0%)	31 (17.6%)	0.567
LVEF (%)	55.2±11.9	54.3±11.0	0.445
EuroSCORE	5.1±2.5	5.6±4.2	0.270
Multi Vessel Disease	160 (91.4%)	162 (92.0%)	0.834
Right Coronary Artery Disease	104 (59.1%)	104 (59.1%)	1.000
Distal Location	92 (52.6%)	101 (57.4%)	0.365
IABP	13 (8.8%)	2 (5.9%)	0.579
SYNTAX Score	26.6±11.1	34.0±13.5	<0.001

Results are expressed as N (%) or Mean ± SD as appropriate. PCI = Percutaneous Coronary Intervention; LVEF = Left Ventricular Ejection Fraction; EuroSCORE = European System for Cardiac Operative Risk Evaluation; IABP = Intra Aortic Balloon Pump; SYNTAX = Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery.

Figure 5. Freedom from cardiac death, myocardial infarction (MI), and cerebrovascular accidents (CVA) **(A)**; from death and MI **(B)**; from death **(C)**; and from major adverse cardiac and cerebrovascular events (MACCE) **(D)** after percutaneous coronary intervention (PCI) **(blue line)** versus coronary artery bypass grafting (CABG) **(green line)** in the propensity score matched groups. Patients at risk at different times are reported below each graph.



3.4 Discussion

The main findings of the DELTA Registry are that at long-term follow-up: 1) There were no differences between women and men in the primary study objective of death, MI or stroke in those patients undergoing PCI with DES; 2) Similarly, there were no differences between the sexes in the combined outcome of death, MI or stroke in those patients undergoing CABG; 3) Conversely, there was an advantage in all-cause mortality favouring women in those patients undergoing CABG as the revascularisation modality, indeed male sex was a predictor of MACCE and death at follow-up; 4) In the women included in the study, there were no differences in the primary study objective, all-cause or cardiovascular mortality; 5) In women , there was an advantage of CABG over PCI with DES in MACCE, exclusively driven by the need for repeat revascularisation.

There is growing data demonstrating a marked improvement in clinical outcomes following PCI of the ULMCA, in concordance with the advent of the DES.(231, 232, 234, 235, 254, 255) Indeed several non-randomised, observational registries and a number of randomised clinical trials have shown no significant differences in MACCE between CABG and PCI in patients with ULMCA disease up to a follow-up period of 5 years.(255-264) However, due to the relative under-representation of women in coronary artery trials, it is unclear whether these findings can be generalised to the female population, who due to the later age of presentation may pose more of a risk. Notably, in the SYNTAX trial women comprised only 22.3% in total and specifically women with ULMCA represented just 10.3% of the overall population.(254) The very recently published 'Evaluation of XIENCE versus coronary artery bypass surgery for effectiveness of left main revascularisation' (EXCEL) study continued to demonstrate this male preference with only 23.8% of those undergoing PCI and 22.5% of CABG patients being female. (245) Furthermore, it must be noted that women undergoing coronary revascularisation with PCI or CABG, have historically been shown to have worse outcomes compared with their male counterparts. (265-271)

The DELTA Registry is a multi-centre, multi-national registry of 2,775 patients, of which 817 (29.5%) were women, enabling a comparison of outcomes between revascularisation strategies. Due to the non-randomised nature of our study, a propensity score matching was performed to adjust for significant differences in baseline clinical

characteristics. The data enable us to compare both revascularisation strategies between sexes and then assess which strategy was best for the female patient.

At the time of writing, there was no data available comparing sexes in patients undergoing intervention in the form of PCI to the ULMCA with DES, with minimal data recently published. Previous data has suggested that women may fare less well with PCI for non ULMCA disease due to a higher rate of repeat revascularisation.(52, 272) The first study to be published assessing this specifically was the Milan and New Tokyo (MITO) Registry which directly compared outcomes of women versus men undergoing PCI with DES for ULMCA disease. Although this study demonstrated no differences between the matched groups (only 131 patients in each group) in all-cause mortality (HR 0.96; 95% CI 0.52-1.77; p=0.89) and MACE (HR 1.04; 95% CI 0.68-1.61; p=0.85), this study did demonstrate cardiac death to be higher in women than men at follow-up (HR 2.70; 95% CI 0.98-7.49; p=0.036).(247) The current study demonstrates a larger cohort of patients (308 patients in each matched group) requiring PCI with DES with comparable outcomes between sexes in all of the study end-points, including cardiovascular mortality (OR 0.686; 95% CI 0.340-1.384; p=0.290) and reassuringly TVR (OR 1.122; 95% CI 0.737-1.708; p=0.592). This is important in this high-risk group of patients, who often present later and with more co-morbidities and also often have anatomically less favourable coronary arteries with smaller vessel sizes and a higher calcification burden.

Historically, women have been demonstrated to have worse outcomes than men following isolated CABG.(273-276) To the best of our knowledge, no study has specifically evaluated the outcomes comparing women with men undergoing CABG for ULMCA disease. It is interesting in the EXCEL study, that women tended to do better following CABG with men faring better following PCI (although not statistically significant).(245) The current study demonstrates that in the matched population at long-term follow-up, there was a difference favouring women in all-cause mortality (OR 0.501; 95% CI 0.260-0.963; p=0.035). In the unmatched population, as in other studies, women have been older with more co-morbidities which is reflected in the higher baseline EuroSCORE in this group. These factors rather than the sex of the patient per se are likely the consequence for women to have had poorer outcomes in prior studies, however it must be remembered that female sex adds an additional point to the EuroSCORE, hence contributing to the perceived higher risk. The improved survival in women in this study may be a reflection of the longevity of women and once they have recovered from the

intervention, then the survival time is likely to be longer. It is encouraging that in women with coronary anatomy which would be best treated with CABG rather than PCI, the outcomes are indeed promising.

Finally, there has been no prior comparison to date specifically evaluating women undergoing PCI vs. CABG for ULMCA disease. In this study, during hospital admission there was a higher incidence of MI and subsequently MACCE in the CABG group. This is a consequence of the elevation of serum creatine kinase myocardial band observed following CABG rather than symptomatic presentation of acute MI. At a median of 1,148 (IQR 545-1,543) days, in the unadjusted as well as adjusted analysis in the propensity matched groups there was no significant difference between treatment modality in the primary study objective of death, MI or CVA This is consistent with that of the propensity matching of the entire population of the DELTA Registry (HR 0.99; 95% CI 0.73-1.33; p=0.97).(248) Of note, the p for interaction between sex and revascularisation modality was p <0.001.

Additionally, there were no differences in each of the individual components of the primary study objective. These results were similar to those reported in a ULMCA sub-analysis of the SYNTAX study comparing CABG with PCI at 3 years.(277) When the women only from the ULMCA sub-study of SYNTAX were compared (CABG n=85 and PCI n=100), there was no difference in the primary study endpoint of MACCE (CABG 21.3% vs. PCI 26.3%; p=0.47). Furthermore, there were no differences in all-cause mortality (6.3% vs. 8.1%; p=0.64), MI (2.5% vs. 6.2%; p=0.25) or CVA (6.4% vs. 2.1%; p=0.14) at 3 years (Presented at American College of Cardiology Scientific Sessions 2009, Orlando, Florida, USA). However, that analysis was limited by the small sample size of the subgroup analyzed, which inflates the risk of a false negative result.

Conversely, there was an advantage with CABG in the occurrence of MACCE, driven exclusively by the need for repeat revascularisation. It is important to take into account that in the DELTA registry mostly first-generation DES were implanted. It has been reported in a pooled analysis of the 'Clinical Evaluation of the XIENCE V® Everolimus Eluting Coronary Stent System in the Treatment of Subjects With de Novo Native Coronary Artery Lesions' (SPIRIT) II and III studies at 2 years (272) that everolimus-eluting stents are superior in women to first-generation paclitaxel-eluting stents, with regards to MACE (8.5% vs. 16.4%; p=0.02), not specifically in an ULMCA population. In addition, we cannot exclude that the low (9.6%) use of IVUS in our study

population and the routine use of angiographic follow-up in the PCI group in the DELTA Registry may have led to more angiographically driven revascularisation. However, despite other studies reporting female sex as an independent predictor or restenosis,(52, 272) this sub-study of DELTA female had similar TLR rates (10.3%) to that of the overall DELTA population.(248) It must be noted that concurrently, there have been developments in surgical technique with the advent of minimally invasive approaches and off pump CABG which may also lead to improved outcomes in this patient group.

However, clinical trials with a larger representation of women and dedicated questions for sex based issues are warranted in order to better understand the treatment for this patient population. Due to the fact women present later with more complexities, a better understanding of sex specific outcomes would potentially allow individualised revascularisation strategies to be developed for the large and growing population of women with CAD.

3.5 Limitations

The main limitation of this study is the non-randomised observational design. Furthermore, there is an assumption that the reported statistical outcomes are correct, however chance may have impacted upon the findings in this data set. There may be differences between the sexes which were not detected, however the sample size would have led to less likelihood of such a type II error.

This study does not address the impact of the physicians prejudices regarding the preferred method of treatment, or the preference of the patient in the decision-making of PCI versus CABG (or indeed medical therapy alone) which may have impacted upon the results of the study. Propensity score matching was performed to adjust for the differences at baseline to attempt to overcome the non-randomisation following the decision to treat (by whichever means).

In addition, a large proportion of patients underwent PCI with first-generation DES and treatment with first generation thienopyridines, which have been shown to be inferior to contemporary DES and anti-platelet agents. Information on menopausal state were not collected or available in a minor proportion of patients. Finally, the length of follow-up does not allow us to draw firm conclusions regarding the durability of each revascularisation option according to sex.

3.6 Conclusions

In patients with complex CAD in the form of ULMCA disease, at baseline women are older with more co-morbidities. However, after correcting for baseline characteristics, there is no difference in outcomes according to sex for those patients undergoing PCI with DES and there appears to be a benefit in all-cause mortality in women for those undergoing CABG. This provides new structured data in this area, from real-world patients undergoing intervention, with no prior similar studies performed. The significance of these findings is critically discussed in Chapter 8 of this thesis. Further large scale studies assessing the female patient with complex CAD are warranted with an aim to devise an individualized revascularisation strategy.

4. Bleeding Risk in Women Undergoing Primary PCI for STEMI

4.1 Introduction

The prior study of complex PCI does demonstrate that outcomes in women are equally as good as men and women may actually have more to benefit when CABG is deemed appropriate. Leading on from this, it was apparent that patients presenting acutely with CAD may also be at a disadvantage to men, due to delays in treatment and lack of access to both medical and interventional treatment. This chapter now attempts to look at the most acute presentation of CAD, in those patients presenting with STEMI (often extremely unstable patients and not included in the majority of prior randomised controlled trials). It must be remembered that the benefit of early reperfusion in STEMI with primary percutaneous coronary intervention (PPCI) in both sexes is now unquestionable and is reflected in current practice guidelines.(134)

Numerous studies have demonstrated an increased risk of in-hospital mortality in women presenting to hospital with STEMI.(131, 278, 279) There are a number of reasons postulated which may contribute to this, including older age of presentation and more associated co-morbidities. (4, 37, 90-100) Other studies have also demonstrated that there is a higher risk of bleeding in women undergoing PCI, which may be related to similar, higher risk, baseline clinical characteristics(74, 75, 94, 125) and it is recognised that significant bleeding is associated with a higher mortality rate.

As PPCI is the default strategy for patients with STEMI, there would be no merit from a randomised trial. The second data set therefore reviews bleeding outcomes in patients undergoing PPCI for STEMI (the most acute presentation and treatment in a group of often extremely unstable patients) dependent on sex from a large registry study from a high-volume centre. The aim of the present study is therefore to assess in-hospital bleeding complications comparing sexes from a large real life registry and assess whether this impacts upon the outcomes of the patient. It also allows us to assess whether delays to treatment which have previously been shown to occur in the female population in this contemporary cohort do actually significantly impact upon outcomes in this high-risk presentation.

4.2 Methods

4.2.1 Patients and Procedures

All unselected and consecutive patients who underwent PPCI for STEMI (default treatment) at our centre (Castle Hill Hospital, Cottingham, UK) between January 2009 to May 2015 were included in the analysis. Our centre is a tertiary referral centre for PPCI and serves a population of 1.2 million people in the North of England. This was chosen as a single centre study in comparison to the first data set as STEMI is a common presentation with the evidence-based treatment of PPCI performed to save lives occurring on a very frequent basis which allows for a significant number of patients. By including only a single centre in this, it reduced the variability which may occur amongst operators and centres with regards to the type of anti-platelet agents used and anti-coagulation regimen, in addition to the stent types, vascular access and closure devices and the medical therapy following which may provide confounding factors and impact upon the outcomes. The diagnosis of STEMI was defined as symptoms of myocardial ischaemia with associated new changes on the electrocardiogram of contiguous ST-elevation of $\geq$ 2mm in the chest leads, $\geq$ 1mm in the limb leads or new left bundle branch block. The patient demographics and angiographic details were entered prospectively into a dedicated PCI database.

All patients were pre-treated with aspirin, a thienopyridine and anti-coagulation as per the hospital policy. From the commencement of the study until June 2012, clopidogrel was the thienopyridine of choice, following which ticagrelor was used. The use of glycoprotein IIb / IIIa inhibitors and aspiration catheters were at the discretion of the individual PCI operator. Intra-aortic balloon pump counter-pulsation was used if deemed clinically necessary, dependent upon the condition of the patient.

All data relating to the hospital admission, procedures and follow up were collected and adjudicated according to the local policy. Full written informed consent was obtained from each patient.

4.2.2 Study Objectives

The primary study objective was the occurrence of bleeding as defined by grades 2 to 5 inclusive of the Bleeding Academic Research Consortium (BARC) definitions.(280) The

secondary study objectives were access site complications, acute kidney injury and all-cause mortality during the index hospital admission.

4.2.3 Statistical Analysis

Continuous variables are expressed as mean ± standard deviation (SD) and are analysed with the Student t test or Wilcoxon rank-sum test depending on the variable distribution. Categorical variables were compared with the chi-squared test with Yates correction for continuity or the Fisher-exact test as appropriate.

Again, as in Chapter 3, in order to adjust for differences in baseline characteristics, a propensity matching was also performed for the reasons described above in chapter 3 and to allow for comparison of outcomes between groups.(250, 251) Because of the non-randomised nature of the study, to reduce the effect of treatment selection bias and potential confounding in this observational study, we performed rigorous adjustment for significant differences in the baseline characteristics of patients with propensity score matching. A propensity score was calculated by performing a parsimonious multivariable logistic regression using the following co-variants: age, body mass index, hypertension, diabetes mellitus, smoker, family history, hypercholesterolaemia, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, chronic kidney disease, previous MI, previous PCI and previous CABG. The C-statistic for the propensity score model was 0.70, confirming good discrimination, and the Hosmer-Lemeshow goodness of fit was 0.45, confirming good calibration. To identify matched pairs we used the following algorithm: 1:1 optimal match with a ± 0.03 caliper and no replacement.(253) Clinical outcomes in the matched population were analysed with Cox proportional hazards regression stratified on matched pairs. Results are reported as Odds Ratio (OR) with 95% Confidence Intervals (CI).

Statistical analysis was performed with the Statistical Package for Social Sciences Version 22.0 (SPSS Inc, Chicago, Illinois, USA). A p-value of <0.05 was considered statistically significant. I was responsible for the data collection and validation of the patients and also for the full statistical analysis in this study.

4.3 Results

4.3.1 Overall Population

In total, 2,717 patients were included from the Hull Registry, of which 721 (26.5%) were women. The baseline clinical characteristics are illustrated in Table 13 with women typically being older (68.0 ± 12.8 years vs. 61.9 ± 12.0 years; p<0.001), with more co-morbidities such as hypertension (52.6% vs. 46.6%; p=0.006), cerebrovascular disease (7.9% vs. 5.6%; p=0.028) and COPD (16.3% vs. 11.9%; p=0.003). Men had a higher incidence of smoking (66.2% vs. 72.9%; p=0.001) and previous CABG (0.8% vs. 2.1%; p=0.003).

Table 13. The Baseline Clinical Characteristics in the Overall Population of the Hull STEMI Registry.

	Women N = 721	**Men N = 1,996**	**P Value**
Age (Years)	68.0±12.8	61.9±12.0	<0.001
BMI (kg / m^2)	28.0±11.0	28.9±17.1	0.279
Family History	293 (40.8)	828 (41.5)	0.731
Hypertension	378 (52.6)	930 (46.6)	0.006
Hypercholesterolaemia	700 (97.5)	1945 (97.6)	0.883
Smoking History	476 (66.2)	1453 (72.9)	0.001
Diabetes Mellitus	97 (13.4)	296 (14.8)	0.517
Insulin Dependent	30 (4.2)	53 (2.7)	0.073
COPD	117 (16.3)	238 (11.9)	0.003
PVD	69 (9.6)	149 (7.5)	0.074
Prior MI	80 (11.1)	262 (13.2)	0.163
Previous CABG	6 (0.8)	42 (2.1)	0.026
Previous PCI	62 (8.6)	220 (11.0)	0.069

Results are expressed as N (%) or Mean ± SD as appropriate. BMI = Body mass index; MI = Myocardial Infarction; STEMI = ST-Elevation Myocardial Infarction; COPD = Chronic Obstructive Pulmonary Disease; PVD = Peripheral Vascular Disease; CABG = Coronary Artery Bypass Grafting; PCI = Percutaneous Coronary Intervention.

The baseline lesion and procedural characteristics are illustrated in Table 14. Of note, less women were treated via the radial route (56.3% vs. 66.6%; p<0.001). However, the overall use of radial artery access significantly increased over time from in both women (16.7% in 2009 to 90.0% in 2015) and men (12.9% in 2009 to 85.7% in 2015). There was significantly less use of glycoprotein IIb / IIIa inhibitors in women (31.5% vs. 35.9%; p=0.035).

Table 14. The Baseline Lesion and Procedural Characteristics of the Overall Population of the Hull STEMI Registry.

	Women **N = 721**	**Men** **N = 1,996**	**P Value**
LAD Culprit Vessel	267 (36.9)	854 (42.7)	0.007
RCA Culprit Vessel	358 (49.5)	817 (40.9)	<0.001
LCx Culprit Vessel	85 (11.8)	270 (13.5)	0.229
Single Vessel Disease	317 (43.8)	800 (40.1)	0.076
Triple Vessel Disease	162 (22.4)	515 (25.8)	0.073
Cardiogenic Shock	36 (5.0)	96 (4.8)	0.852
Ventilated	14 (1.9)	32 (1.6)	0.466
GPIIb / IIIa	228 (31.5)	717 (35.9)	0.035
Thrombus Extraction	346 (47.9)	1142 (57.2)	<0.001
Ticagrelor	896 (44.8)	1102 (55.2)	0.937
IABP	12 (1.7)	34 (1.7)	0.940
Radial Access	407 (56.3)	1361 (66.6)	<0.001
2009/2010	*22 (18.6)*	*61 (19.5)*	*0.809*
2011/2012	*137 (48.1)*	*527 (66.0)*	*<0.001*
2013/2014	*203 (75.2)*	*593 (83.4)*	*0.010*
2015	*45 (90.0)*	*150 (85.7)*	*0.432*

Results are expressed as N (%) or Mean ± SD as appropriate. LAD = Left anterior decending coronary artery; RCA = Right coronary artery; LCx = Left circumflex coronary artery; GPIIb / IIIa = Glycoprotein IIb / IIIa inhibitor; IABP = Intra-Aortic Balloon Pump.

Table 15. Bleeding Academic Research Consortium (BARC) Events in the Overall Population of the Hull STEMI Registry.

	Patient Number	**BARC Event**	**Sex**	**Age**	**Access Route**	**Glycoprotein IIb / IIIa Inhibitors**	**Outcome**
Access Site Related	384	3 a	F	77	3aRadial	No	Required IABP with bleeding from site. Haemoglobin 81g/l requiring transfusion.
	671	3 a	F	64	Femoral	No	Retroperitoneal bleed
	766	5 b	F	59	Femoral	No	Retroperitoneal bleed. In hospital death
Non-Access Site Related	113	3 a	F	72	Radial	Tirofiban	Haematuria. Haemoglobin 71g/l requiring transfusion. In hospital death.
	148	3 b	M	57	Radial	No	Melaena. Haemoglobin 63g/l requiring transfusion
	260	2	F	83	Radial	No	Melaena. Haemoglobin 76g/l requiring transfusion.
	404	3 a	F	87	Femoral	Reopro	Upper gastrointestinal bleed requiring transfusion.
	590	3 a	M	65	Femoral	No	Coronary perforation and cardiac tamponade requiring transfusion.

BARC = Bleeding Academic Research Consortium; IABP = Intra-Aortic Balloon Pump; F = Female; M = Male.

Women had more presentation with right coronary artery occlusion (49.5% vs. 40.9%; p<0.001) compared with men who were more likely to have a left anterior descending artery coronary occlusion (36.9% vs. 42.7%; p=0.007). There was a trend for women to have more single vessel disease (43.8 vs. 40.1; p=0.076), in contradiction with men who had a trend for more triple vessel disease (22.4% vs. 25.8%; p=0.073).

There was no difference in the mean duration of stay between women and men (4.7 ± 5.0 days vs. 4.3 ± 5.5 days; p=0.105). During hospitalization, women had more access site complications (2.6% vs. 0.5%; p<0.001), acute kidney injury (3.6% vs. 3.5%; p=0.047), cerebrovascular events (1.0% vs. 0.5%; p=0.045) and all-cause mortality (7.1% vs. 4.4%; p=0.005). Overall, BARC bleeding episodes occurred in 2.7% of women versus 0.3% of men (p=0.001) (Table 15).

4.3.2 Propensity Matched Groups

After propensity score matching, there were 483 matched pairs of patients in each treatment group. The baseline characteristics of the matched groups are shown in Table 16. Although there was no significant difference in the onset of symptoms to arrival at hospital between groups (women 155 [IQR 98-294] minutes vs. men 126 [IQR 86-231] minutes; p=0.210), there were differences meaning delays for women in the call to hospital times (71 [IQR 56-92] minutes vs. 66 [IQR 54-82] minutes; p=0.004). The door to needle time did not lead to further delays for the women (34 [IQR 26-44] minutes vs. 31 [IQR 25-41] minutes; p=0.116). There were no differences between the groups in the incidence of cardiogenic shock (women 3.1% vs. men 3.1%; p=0.991), ventilation (4.9% vs. 5.0%; p=0.970) or the use of glycoprotein IIb / IIIa inhibitors (30.8% vs. 32.0%; p=0.709). Interestingly, there remained a higher occurrence of right coronary artery occlusion in women (49.8% vs. 42.3%; p=0.020), with a trend for left anterior descending artery occlusion in men (36.7% vs. 42.5%; p=0.063). There was also a trend for more single vessel disease in women (43.3% vs. 37.2%; p=0.053). There was less use of the radial access route in women (63.1% vs. 71.6%; p=0.016). Of note, there remained an increase in the use of radial over time in women (23.1% in 2009 to 94.6% in 2015) and men (10.0% in 2009 to 87.7% in 2015).

During hospitalization of the 483 matched pairs (Table 17), there remained a higher incidence of vascular access site complications in women (OR 0.081; 95% CI 0.011-0.626;

p=0.002) and all BARC bleeding (OR 0.971; 95% CI 0.946-0.996; p=0.018). However, this did not correspond with any difference in in-hospital mortality between the two groups (OR 1.045; 95% CI 0.567-1.927; p=0.887). There was no difference in acute kidney injury between the groups (OR 0.841; 95% CI 0.444-1.592; p=0.378).

Table 16. The Baseline Characteristics in the Propensity Matched Population of the Hull STEMI Registry.

	Women N = 483	**Men N = 483**	**P Value**
Age (Years)	66.7±12.2	66.5±12.3	0.862
BMI (kg / m^2)	28.3±11.4	27.4± 4.6	0.116
Family History	210 (43.8)	205 (42.5)	0.703
Hypertension	251 (52.3)	246 (51.0)	0.697
Hypercholesterolaemia	470 (97.9)	475 (98.3)	0.628
Smoking History	327 (68.1)	340 (70.5)	0.417
Diabetes Mellitus	72 (15.0)	70 (14.5)	0.835
COPD	79 (16.5)	73 (15.1)	0.577
PVD	43 (9.0)	46 (9.5)	0.754
Prior MI	59 (12.3)	57 (11.8)	0.824
Prior CABG	5 (1.0)	6 (1.2)	0.767
Prior PCI	51 (10.6)	50 (10.4)	0.899

Results are expressed as N (%) or Mean ± SD as appropriate. BMI = Body mass index; MI = Myocardial Infarction; STEMI = ST-Elevation Myocardial Infarction; COPD = Chronic Obstructive Pulmonary Disease; PVD = Peripheral Vascular Disease; CABG = Coronary Artery Bypass Grafting; PCI = Percutaneous Coronary Intervention.

Table 17. The Outcomes of the Propensity Matched Population of the Hull STEMI Registry.

Outcome	Number of Events (%)		OR	95% CI	P Value
	Women N = 483	**Men N = 483**			
In Hospital					
All Cause Mortality	21 (4.4)	22 (4.6)	1.045	0.567-1.927	0.887
Vascular Complication	12 (2.5)	1 (0.2)	0.081	0.011-0.626	0.002
BARC Bleeding Grade 2 - 5	5 (2.9)	0	0.971	0.946-0.996	0.018

OR= Odds Ratio; CI = Confidence Interval; BARC= Bleeding Academic Research Consortium.

4.3.3 Predictors of the Study Objectives

In the overall matched population, at Cox regression multi-variable analysis, the only independent predictor of a BARC bleeding event was the presence of peripheral vascular disease (OR 6.047; 95% CI 0.975-37.497; p=0.053).

The independent predictors of in-hospital mortality were COPD (OR 2.502; 95% CI 1.090-5.740; p=0.030), cardiogenic shock at presentation (OR 18.318; 95% CI 7.424-45.202; p<0.001) and an episode of BARC bleeding (OR 12.364; 95% CI 1.401-109.137; p=0.024).

4.4 Discussion

The main findings of this Hull Registry are that in hospital: 1) Women have more episodes of BARC bleeding following PPCI for STEMI; 2) Similarly, women have more vascular access complications following PPCI; 3) Pre-existing peripheral vascular disease appears to predict a BARC bleeding event and 4) There was no difference overall in all-cause mortality between the sexes.

Women have been consistently shown to be at a higher risk of bleeding compared with men following PCI in both randomised controlled trials and large scale registry studies, which has included those undergoing PPCI.(137, 140, 145, 281-283) This has been postulated to be secondary to the increased co-morbidities in women, including older age at presentation, lower body mass index and reduced creatinine clearance and generally is the result of a significant vascular access complication. However, interestingly, our current study continues to demonstrate an increased incidence of BARC bleeding episodes and vascular complications in women, following adjustment for differences in baseline clinical characteristics. Of note, such bleeding complications are both access site and non-access site related. This has also been demonstrated despite adjustment in the large CathPCI registry of 570,777 patients, which demonstrated a two-fold increase in bleeding in women(284) and also in a more recent analysis from the 'Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction' (HORIZONS-AMI) study of 3,602 patients (23.4% women).(285)

The reason in our study may be a consequence of the higher likelihood of a femoral procedure in women (36.9% vs. 28.4% in the matched population). Indeed, one large meta-analysis of 12 randomised trials has shown a 78% reduction in access site complications when using the radial approach.(286) Furthermore, a recent multi-centre trial randomised 8,404 patients with acute coronary syndrome (including STEMI) to radial versus femoral intervention. It was reported that radial access reduced net adverse clinical findings through a reduction in major bleeding (radial 1.6% vs. femoral 2.3%; Risk Reduction [RR] 0.67; 95% CI 0.49-0.92; p=0.013) and all-cause mortality (1.6% vs. 2.2%; RR 0.72; 95% CI 0.53-0.99; p=0.045).(287)

However, there may also be underlying differences between sexes in platelet function or responsiveness to anti-coagulant therapy used as adjuncts during the PPCI procedure.(288) There was a similar use of glycoprotein IIb / IIIa inhibitors between sexes in the matched population, therefore this was not deemed to be a causative factor. Of note, there was a significant difference in the usage of such drugs in the baseline population, which may reflect the operators concern regarding the bleeding risk in females and an underlying prejudice that this leads to worse outcomes. However, the usage in women (31.5%) in the present study, has increased since prior published data in 2008 from the same centre (26.3%)(289), with a narrowing in the gap of the usage between sexes (men 29.0% more likely in 2008 compared with 4.4% currently), which may reflect a difference

in the perception of risk by the treating clinicians and make them more likely to prescribe these evidence-based treatments for women. From 2008 to the current study, there was also the widespread introduction of more potent anti-platelet agents, which means that glycoprotein IIb / IIIa inhibitors are not used overall as commonly. Alternatively, the prior study did include all ACS patients and not STEMI alone, which may have led to the differences observed.

Despite a higher bleeding risk and incidence of complications, our study did not demonstrate any difference in in-hospital mortality between the sexes in the matched population. This is in contradiction to a number of studies which have demonstrated women to have an increased risk of in-hospital mortality when presenting with STEMI, including in contemporary PPCI studies.(131, 278, 279, 283) Indeed, number of studies have shown that major bleeding is an independent predictor of in hospital mortality.(140, 290)

A further reason postulated for the increased risk of in-hospital mortality is that women tend to present later with STEMI than men due to atypical symptoms and lack of recognition by medical professionals. There are a number of reasons as discussed which account for the delays to presentation. The first delay is a consequence of a lack of recognition by the women themselves that their symptoms are attributable to a MI.(291) Indeed, it has been recently reported that women with ACS were more likely than men to present without chest pain (respectively 42.0% vs. 30.7%; $p<0.001$).(111) Women may have only back pain or shortness of breath and subsequently these are not recognised by the general public as symptoms which require an urgent assessment. Media campaigns have emphasised the typical presentation of central crushing chest pain, like a tight belt around the chest, which is not always present in women. In addition, women often do not want to bother anyone with regards to their symptoms, feel fear or embarrassment or are alone when the symptoms commence and keep it to themselves. Women typically therefore take longer to present to hospital services.(292, 293)

It is interesting in the present study that there was no difference between sexes in the onset of symptoms to arrival at hospital, however there was a difference in the call to needle times suggesting a delay in the diagnosis and provision of treatment to women. Again, as women do not have the typical chest pain, there is often a delay to the diagnostic ECG, which does not allow the correct diagnosis to be made and hence can worsen

outcomes.(111) Hence the delay to treatment is compounded by the perceptions of medical services, in addition to the initial patient delay.(294, 295)

Despite this, in the present study, there was no difference in the mortality between women and men. It must be noted however, that in the present study, women were more likely to have single vessel disease, which suggests a lower complexity of disease compared with the men. Nevertheless, a recent study of 31, 689 STEMI patients (33.7% women), included regardless of treatment, showed a similar result to our study with no difference in adjusted in-hospital mortality (HR 1.04; 95% CI 0.97-1.12; p=0.2303).(296) Furthermore, in our study, women were more likely to have a right coronary artery occlusion, which have been shown to have a superior long term survival.(297)

4.5 Limitations

The limitations of this study are that it is a retrospective single centre observation registry. One of the main constraints is that the study does not explore the reasons behind the differences to balloon time, differences in the use of evidence-based therapies (e.g. glycoprotein IIb / IIIa inhibitors) or differences in the access site utilised. It may be with regards to the latter that radial was attempted by the operator and failed due to vessel anatomy, which is an important factor to note. Indeed, it is assumed the reported statistical outcomes are correct, however due to some of these differences, it must be considered that the findings could be due to chance or be artefactual.

In addition, our study does not include the small number of patients with STEMI who were not accepted for PPCI. The study also does not capture all the timings and reasons underlying delays to presentation, which are important, both in women and in men. During the propensity matching, there may be non-assessed co-founders, including differences in discharge medication (both secondary prevention and also dual anti-platelet regime). Also, we do not consider the time of onset of symptoms, which may impact upon the results if there were significant delays pre call to hospital. It is important to consider that several studies have assessed the impact of the door to balloon time in PPCI,(298, 299) but to date no study has considered the onset of symptoms to balloon time and how delays in this may impact upon the outcomes.

In addition, the STEMI risk stratification tools are not included and the period of follow-up is short. However, a strength of the study is that all-comers are included from a

high-volume PCI centre, performing procedures with contemporary techniques and devices, reflecting a ‘real-world’ population in the current era.

4.6 Conclusions

In this high-volume, PPCI registry study, despite more bleeding and vascular complications in women, there was no difference in in-hospital mortality in the matched population between sexes. This is important from real-world data to demonstrate the idea that women have significant benefit from high-risk PPCI in the acute setting. However, due to the potential morbidity associated with vascular complications and subsequent bleeding, measures should be taken to reduce the risk of such events, for example the use of radial access and careful use of potent anti-platelet agents. The significance of this structured data will be discussed in more depth in chapter 8 of this thesis.

5. Does Sex Play a Role in the Activated Clotting Time During Angioplasty?

5.1 Introduction

One of the underlying reasons believed to account for inferior outcomes in women in the treatment of CAD is that women may be more likely to bleed, with bleeding complications leading to a demonstrable increase in mortality in the current literature. The previous chapter demonstrated that women have more bleeding and vascular complications following PPCI for high-risk presentations with acute STEMI. This is addressed in the present chapter via a prospective observational study, where it was assessed whether the dose of weight-adjusted heparin utilized during PCI affected the activated clotting time (ACT) according to sex. The theory was that if women had a higher ACT (meaning higher anti-coagulant effects) following a similar dose of heparin to men, this would suggest why bleeding events and vascular complications may be higher.

Anticoagulation is required throughout the PCI procedure due to the risks of both significant ischaemic and thrombotic complications, which can happen when the coronary arteries are instrumented.(300, 301) Typically during PCI, a weight-adjusted dose of heparin is given at the onset of the intervention to suppress thrombin generation from the intimal injury with balloon inflation.(301) The activated clotting time (ACT) is a rapid point of care dosing test which can then be utilised within the cardiac catheterisation laboratory to monitor the level of heparin anticoagulation and ensure that it is adequate throughout the procedure.(302) It is understood that an ACT level of 250 to 300 seconds is the optimum for a coronary procedure with the use of the Hemochron system (International Techidyne Corporation, New Jersey, USA).(303) It has additionally been demonstrated that there is a significant relationship between the maximum ACT during the procedure and the consequent probability of bleeding events occurring.(304)

There are a number of factors reported which may alter the effectiveness of the weight-adjusted heparin, including the presence of impaired renal function, diabetes mellitus and elevated body mass index.(305)

Interestingly, as evident in the prior chapter assessing patients presenting with STEMI undergoing PPCI, significantly higher rates of vascular complications and bleeding, are seen in female patients, and can be increased by as much as 4-fold.(74, 75,

94, 125) Female sex has indeed been demonstrated to be an independent predictor of bleeding events in several large scale PCI trials with different anticoagulation strategies.(130, 137-139) This group of patients often have different pharmacokinetics, due to smaller body mass with relatively more fat and often lower creatinine clearance. This leads to a higher circulating level of common anti-thrombotic therapies administered throughout the PCI procedure. One study has demonstrated that both female gender and increased ACT levels were predictors of major bleeding.(306)

There does however remain limited data in this area. The aim of the present study was to identify whether the sex of the patient affected the ACT level, following administration of a weight-adjusted dose of heparin. This could therefore potentially impact on decisions regarding the anti-thrombotic regimen utilised during PCI dependent on the patient sex.

5.2 Methods

5.2.1 Patients and Procedures

This study was an exploratory pilot single centre survey carried out to assess the role of sex on the ACT value in patients undergoing elective PCI for stable CAD. This was performed in a single centre to ensure that the procedures were similar with regards to vascular access and closure, and the equipment utilised to measure the ACT level was the same, avoiding discrepancies in the data collection. The results are from my own patients where I performed the procedure and collected the data, in addition to performing the analysis. It was deemed that my own patients were representative of the population being sampled, in order to ensure any conclusions drawn were valid.

5.2.1.1 Patient Demographics

The study population consisted of consecutive eligible patients undergoing elective PCI in the Cumberland Infirmary, Carlisle, United Kingdom, from September 2013 to September 2014.

5.2.1.2 Patient Selection Criteria

All patients included had to have CAD which required PCI at the discretion of the treating interventional cardiologist / discussion with the multi-disciplinary team. Patients were excluded if there was evidence of significant renal disease (defined as an estimated GFR < 30 ml / minute), concurrent therapy with warfarin or a direct oral anti-coagulant and / or a previous documented allergy to heparin. Patients who had received low molecular weight heparin following an acute presentation were also excluded to prevent any interaction with the ACT monitoring.

5.2.1.3 Sample Size

No evidence about the expected magnitude of the effect was available when the study was designed, hence the sample size was chosen following discussion with the university statistician and myself and using the Creative Research Systems (Sebastopol, California, USA) analysis. Based on a population size of 500 patients undergoing PCI annually within my centre, with a one sided 5% significance level, 100 patients were needed to have 80% power to reject the null hypothesis if it was false. The null hypothesis was that there would be no difference between women and men in the ACT level during PCI. There was not a concern regarding allowance for attrition, as the analysis for the primary objective of the study was based on ACT readings performed during the PCI procedure. It was felt achievable to obtain this amount of participants in the study within the specified time frame and with my own resource available.

In total, follow-up was obtained on 84% of the cohort who are included in the report. The study was given approval by North Cumbria University Hospitals NHS Trust Research and Development Committee (Appendix 2). All patients provided full written consent for the interventional procedure and all subsequent data collection.

5.2.1.4 Procedures

Following enrolment into the study, the patient proceeded to PCI as per standard practice of care. Prior to the interventional procedure, the weight of the patient was measured accurately on digital scales. Heparin was administered intra arterially at a dose of 100 iu /

kg. Current guidelines from the European Society of Cardiology recommend a dose of 60-100 iu / kg (307) with a trial of stable CAD patients similar to this undergoing elective PCI that 100 iu / kg was safe and effective (308), hence this dosage was selected. The ACT was measured in all cases at 20 minutes' post heparinisation. Other than the arterial blood sample at 20 minutes, no other intervention was planned which was additional to routine care (it is standard practice to perform an ACT at this time scale), hence there was minimal additional risk to the patient by inclusion in this study.

The HAEMOCHRON® Jr Signature (International Techidyne Corporation, New Jersey, USA) whole blood micro coagulation system was used to check the ACT level. A sample of 2 ml of arterial blood was added immediately to a cuvette and filled flush to the top. This was then immediately transferred to the system and analysed. After mixing with the reagent, the sample was moved back and forth at a predetermined rate within the test channel and monitored for clot formation. The test channel was maintained at 37 °C ± 1.0 °C during the test.

The occurrence of vascular complications at hospital discharge were recorded. At 3 months' routine clinical follow-up, the patency of the radial artery was assessed manually by an experienced PCI operator. All the patient demographic data was collected and entered into a dedicated encrypted database by the co-investigators of the study.

5.2.2 Study Objectives

The primary objective of this exploratory study was to evaluate whether the sex of the patient plays a role in the obtained value of the ACT during elective PCI. The secondary objective was to assess whether the ACT level was related to the occurrence of vascular complications and / or radial artery occlusion following PCI.

5.2.3 Statistical Analysis

All continuous variables are expressed as mean ± standard deviation and were analysed with the Student t test or Wilcoxon rank-sum test depending upon the variable distribution. The categorical variables were compared with the Chi-squared test with Yates correction for continuity or the Fisher-exact test as appropriate. All data was analysed using the

Statistical Package for Social Sciences Version 23.0 (SPSS Inc, Chicago, Illinois, USA), with a p value of < 0.05 considered as statistically significant. All data collection and statistical analysis was performed by myself.

5.3 Results

In total, 84 consecutive, unselected patients with clinical follow-up were included in this exploratory study, of which 33 (39%) were female.

Table 18. The Baseline Characteristics according to the Sex of the Patient in the ACT Study.

	Women N = 33	**Men N = 51**	**P Value**
Age, years	67.0±10.7	65.8±11.8	0.626
Hypertension	20 (64.5)	24 (49.0)	0.174
Hypercholesterolaemia	13 (33.3)	26 (66.7)	0.332
Diabetes Mellitus	7 (22.6)	7 (14.3)	0.341
Creatinine, µmol / l	92.9±79.8	91.6±33.8	0.917
LVEF, %	61.9±6.9	60.0±4.4	0.401
BMI, kg / m^2	27.2±4.9	28.4±5.0	0.322
Aspirin	33 (33.0)	51 (100.0)	1.000
Clopidogrel	30 (90.9)	40 (78.4)	0.134
Ticagrelor	3 (9.1)	11 (21.6)	0.134
Radial	15 (55.6)	35 (79.5)	0.032

LVEF= Left Ventricular Ejection Fraction; BMI= Body Mass Index.

The baseline characteristics are included in Table 18, which do not demonstrate any significant differences in age (female 67 ± 10.7 years vs. male 65.8 ± 11.8 years; p=0.626), creatinine level (92.9 ± 79.8 µmol / l vs. 91.6 ± 33.8 µmol / l; p=0.917) or BMI (27.2 ± 4.9 kg / m^2 vs. 28.4 ± 5.0 kg / m^2; p=0.322).

Of note, all patients were pre-treated with routine daily aspirin with the majority prescribed clopidogrel as the additional anti-platelet agent (female 90.9% clopidogrel

usage vs. male 78.4% clopidogrel usage; p=0.134) for which the patients were loaded and treated regularly for a minimum of 30 days. Overall, less women than men were treated via the radial access route (55.6% vs. 79.5%; p=0.032).

The mean ACT result taken at 20 minutes' post heparinisation had a trend to be higher in the female group (371.3 ± 46.0 seconds vs. 351.9 ± 47.5 seconds; p=0.067). When grouped according to ACT range, more men had an ACT < 350 seconds (18.2% vs. 43.1%; p=0.018) with women more likely to have an ACT exceeding 400 seconds (54.5% vs. 33.3%; p=0.054). (Figure 6)

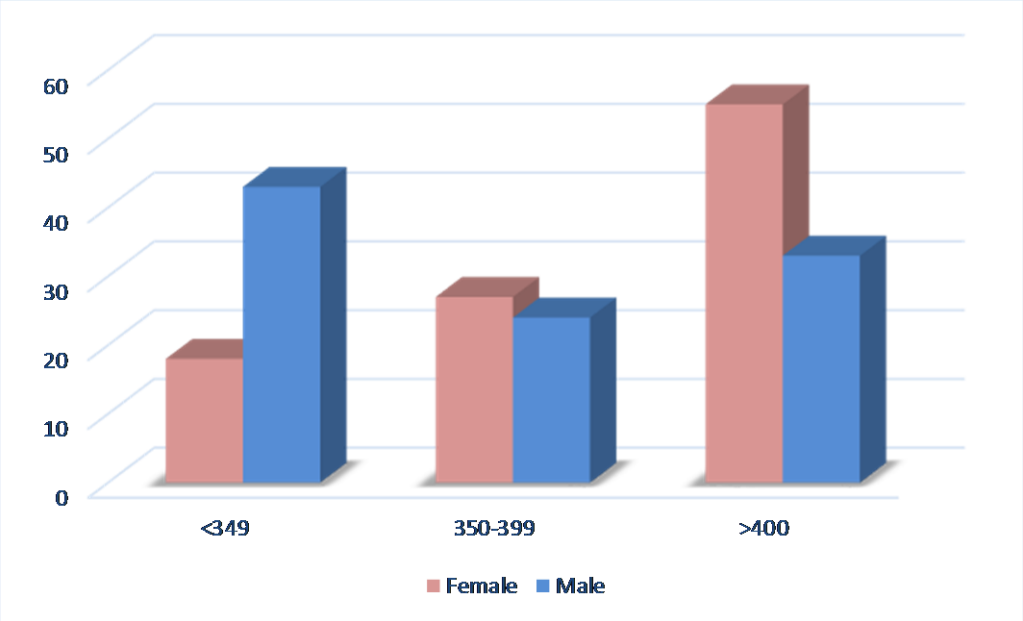


Figure 6. The distribution of ACT levels at 20 minutes following weight-adjusted unfractionated heparin in our study according to the sex of the patient.

With regards to the presence of radial artery occlusion at 3 months, overall this was noted in 3 (8.6%) men who underwent the procedure radially and no women (p=0.118). Of note, all patients undergoing radial procedures had sheath removal using patent haemostasis with a TR band according to the local protocol. There were 4 vascular complications in total (one female 3.0% vs. 3 males 6.0%; p=0.536) the nature of which are listed in Table 19. Notably, the ACT level was recorded as > 400 seconds in 3 of these documented vascular complications.

Table 19. All Recorded Bleeding Complications of the ACT Study Patients.

Patient Sex	Patient Age	Patient BMI	DAPT Regimen	Access Route	ACT	Complication
Male	39	31.4	A + C	Radial	> 400	Pseudoaneurysm
Male	72	23.8	A + T	Radial	> 400	Arm Swelling
Female	73	38.1	A + C	Femoral	> 400	Haematoma requiring compression
Male	74	24.6	A + C	Femoral	288	Small haematoma

BMI = Body Mass Index (kg / m^2); DAPT = Dual Antiplatelet Therapy; ACT = Activated Clotting Time (seconds); A =Aspirin; C = Clopidogrel; T = Ticagrelor.

5.4 Discussion

The main finding of this exploratory study is that with weight-adjusted unfractionated heparin, women are more likely to have a very high ACT than men with a value exceeding > 400 seconds. However, from this study, there does not appear to be a higher rate of vascular complications in women undergoing elective PCI. It is also notable that 3 of the 4 vascular complications had an ACT ≥ 400.

It has been demonstrated in a number of prior PCI studies that vascular complications and bleeding issues can be increased by as much as 4-fold in the female population undergoing coronary intervention.(74, 75, 94, 125) In addition, we also know that female sex has been shown to be an independent predictor of bleeding in several ACS trials with different anti-coagulation strategies.(130, 137-139) The aim of this present study therefore was to assess whether there was a difference in the ACT result according to sex in patients undergoing elective PCI, thereby evaluating whether the heparin dosing regimen actually imposes an increased risk of bleeding.

In this small cohort, women were more likely to have an ACT > 400 seconds than men, despite accurate weight-adjusted heparin administration by the operator. Interestingly, there was no significant difference in the BMI between groups, which may have been expected. This is similar to that of a previous large registry study(309) and also shown in the 'EArly discharge after Stenting of coronarY arteries' (EASY) trial(310) of

1,348 patients (22% female) undergoing PCI for ACS with reported final ACT values (female 322 ± 71 seconds vs. male 308 ± 64 seconds; p=0.003). It must be taken into account that women do have 20-25% longer bleeding times than men in prior in vitro studies.(311)

Unfractionated heparin was first discovered in 1916 (312) and despite the many benefits of this as an anti-coagulant therapy, it does pose a significant challenge for clinical practice in achieving accurate dosing and monitoring due to the variable and often unpredictable biological activity. The onset of heparin is immediate when administered intravenously, however only one third of the dose binds to anti thrombin and it is this portion which is responsible for all of the anti-coagulant effects.(313-315) It is limited by its propensity to bind to plasma proteins, macrophages, fibrinogen, lipoproteins and endothelial cells.(316) It must therefore be considered that due to the different composition of body fat between sexes, which is higher in women than men,(317) and the fact that females have less circulating blood volume than men,(318-320) the actual active dose of unfractionated heparin is different between sexes. This would account therefore for the higher ACT levels demonstrated in women in this study as a similar dose of weight-adjusted heparin therapy is more active in women. There is no difference stated in guidelines of heparin dosing according to the sex of the patient(307) A study of 698 patients comparing a fixed dose of 3,000 iu unfractionated heparin (35.0% of patients) with weight-adjusted heparin (70 iu /kg) actually showed that there were no differences in major ischaemic complications or troponin rise in hospital, suggesting that there may not be a need for such high dosages and that further research is required. The counterargument for this is that there may be more radial artery occlusion with lower dosages of heparin.(321)

Another contributory factor to the results is platelet reactivity which plays a pivotal role in thrombus formation, and the potential for differences between women and men in this. There have been a variety of studies addressing platelet activity(153, 154) which have not provided clear results however platelets in women have a higher number of surface receptors and bind a greater amount of fibrinogen. Due to the concomitant treatment in these patients investigated with dual anti-platelet therapy, this could well have impacted upon the results. A number of reports have also described how differences in the vessel wall biology and platelet function can be directly related to sex hormones.(155, 156)

The EASY study described above, also confirms that of other data which shows that female sex was associated with a higher risk of a local haematoma despite more use of

the radial access route.(310, 322) As described, this could be due to the effects of sex hormones on the vascular biology. Although notably in this current study women were less likely to undergo coronary intervention via the radial access route, there did not appear to be an increased risk of vascular complications. However, with improved technology and increased awareness by the operator of such important complications, the event rates are extremely low and hence do not therefore allow for a reliable direct comparison between groups. In this study, each patient undergoing a femoral procedure underwent haemostasis with manual compression by an experienced member of the PCI team, in order to minimise the risk of such a complication. It is interesting that half of the reported vascular complications in this study were actually following radial procedures and the use of the TR band® (Terumo, Europe, NV) radial compression device as haemostasis.

The 'Fondaparinux With Unfractionated Heparin During Revascularisation in Acute Coronary Syndromes' (FUTURA / OASIS-8) trial in the urgent patient population did not show a link between the ACT level and bleeding complications, although only 32% of patients in this study were indeed women.(323) A further pooled analysis of 8,369 patients reported only a weak correlation between the ACT value and haemorrhagic complications.(324) However, it must be taken into account that these studies reported data from strict recruitment criteria with ACT levels not taken at a pre specified time point. The benefits of the current study are the consistent dosing of heparin and the timing of the ACT measurement, in addition to the fact it was an unselected population, more representative of the real-world patients undergoing elective PCI.

A further point noted in this study is that there was a low rate of radial artery occlusion at clinical follow-up (6.0% in the population undergoing a radial procedure). The literature suggests that such an event can happen in up to 33% of patients following PCI, however a large recent meta-analysis has shown that high dose heparin can reduce the occurrence of this.(325) In our study, we did achieve high ACT levels in almost all patients, which may have contributed to our low rate, in addition to controlled haemostasis.

5.5 Limitations

The limitations of this study are that it is a small sample size and performed in a single centre however this is also a strength through the consistency of the operator, protocol and the same analyser. In clinical practice, we do not always have an accurate weight as we

rely upon the patient to inform us, whereas in this study it was accurately recorded by the investigator. Of note, it may be that the ACT is not a sensitive enough test to predict significant bleeding complications, as it takes into account only one clotting pathway and not other factors such as platelet activity, which may differ between the sexes. Larger studies are required with higher numbers of patients to further investigate this and whether there should be a reduced dose of heparin for female patients. It may be important to not only consider the actual body weight of the patient but also the body fat composition and whether this will impact ultimately on improving bleeding complications in female patients undergoing PCI.

This nevertheless does appear to show a difference between the sexes in the ACT following weight-adjusted heparin. The study was not powered to detect a difference in clinical events. In addition, the small sample size may have led to the possibility of the reported findings being due to chance with the failure to detect a difference in vascular complications which may actually be present with a larger number of participants. Another limitation is that we did not know the body fat composition of the patient or also the menopausal / hormonal status of the female patients, as this can interact with unfractionated heparin metabolism, as well as concomitant anti-platelet treatment.

5.6 Conclusions

In conclusion, in this small cohort of patients undergoing elective PCI, women appeared to have a higher ACT level at 20 minutes than their male counterparts for a similar weight-adjusted dose of heparin. However, there appeared to be no dramatic correlation between the ACT result and subsequent vascular complications or radial artery occlusion. This is the first study to report findings presented as structured data of outcomes according to the ACT in a real world population of those requiring elective PCI. The significance of these findings and potential contribution to the field will be discussed in chapter 8 of this thesis.

6. The Role of Sex on Outcomes Following Transcatheter Aortic Valve Implantation: Results from the PRAGMATIC Plus Initiative

6.1 Introduction

In the previous chapters, we have discussed CAD in women and the outcomes following coronary intervention, including the potential reasons for a higher bleeding risk in women. In addition to CAD, valvular heart disease also affects significant numbers of women and there have been shown to be differences in treatment and outcomes, with no current consensus in the evidence-based literature. It is also an exciting area to investigate as the number of women requiring intervention and becoming included in such studies is equal to men for the first time in any cardiovascular disease. This is likely due to the presentation of disease in later life and patients in such studies are of an age which is a typical exclusion factor from the CAD trials, which was a contributory factor to the high level of male participants, due to the fact women present later with CAD as discussed earlier.

Aortic stenosis (AS) is the most commonly encountered valvular heart disease in contemporary practice in the Western world, and in recent years, transcatheter aortic valve implantation (TAVI) has emerged as a safe and effective treatment option in patients who are deemed at high or prohibitive surgical risk for conventional therapies.(179, 326-328) Prior studies assessing TAVI outcomes in women have also shown more morbidity, with higher vascular and bleeding complications in this group.(186, 187, 329, 330) However, conversely, several studies which have reported sex specific complications and outcomes,(186, 187, 329-332) have suggested that females may actually have a lower mortality than men with such a procedure and have more to gain. Indeed, one such study has suggested that male sex is actually an independent predictor of mid-term mortality following a TAVI procedure for severe AS.(329) This is despite the fact that women with AS typically present at an older age, with subsequent higher surgical risk scores (similar to those with CAD).

The results therefore are inconsistent and in particular, the baseline differences in co-morbidities and indeed perceived risk, have not allowed for a fair comparison of outcomes according to the sex of the patient. Hence, the aim of this multi-centre collaborative registry study was to compare 30 days and mid-term outcomes according to the Valve Academic Research Consortium (VARC) definitions, following TAVI for severe AS comparing women with men. Chapter 6 therefore considers valvular heart disease with

the interventional treatment of symptomatic AS with TAVI, reviewing outcomes in women versus men from a large multi-centre international registry from experienced TAVI operators.

6.2 Methods

6.2.1 Patients

The PRAGMATIC Plus (Pooled-RotterdAm-MilAno-Toulouse In Collaboration) initiative is a collaboration of 4 European institutions with established TAVI experience: these comprise the San Raffaele Scientific Institute, Milan; Clinique Pasteur, Toulouse; Thoraxcenter, Erasmus Medical Centre, Rotterdam and Hôpital Rangueil, Toulouse. The baseline characteristics and clinical outcomes from a series of 1,125 consecutive TAVI patients were collected since the introduction of the respective local TAVI program in each centre. This data was collected from the early days of the TAVI experience, when this was a relatively new method of treatment. Individual centres were therefore not performing large numbers and therefore this was again a multi-centre, multi-national data set. All clinical outcomes were adjudicated according to the VARC definitions by experienced TAVI operators and all data was pooled into a dedicated database for the registry.

Patient eligibility for TAVI in each centre has been described and published previously.(333-335)

6.2.2 Procedures

Patients undergoing all accepted approaches for TAVI were included in this analysis. These are transfemoral, transapical, transaxillary and transaortic. Both of the TAVI devices which were commercially available at the onset of the TAVI experience were used: The Medtronic CoreValve® (MCV) (Medtronic Inc, Minneapolis, Minnesota), a nitinol self-expandable device and the balloon expandable Edwards SAPIEN™ / SAPIEN XT™ (ESV) (Edwards Lifesciences, Irvine, California) valve. The choice of valve was at the discretion of the operator and treating team.

6.2.3 Study Endpoints

All the study endpoints were defined according to the VARC criteria which have been previously described.(336) Of note, life-threatening bleeding was defined as fatal bleeding or bleeding in a critical area or organ (intracranial, intraspinal, intraocular), or need for pericardiocentesis, OR bleeding causing hypovolemic shock requiring vasopressors or surgery OR drop in haemoglobin of ≥ 5 g / dL or requiring packed red blood cells transfusion of ≥ 4 units. Major vascular complications were defined as access site or access related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, haematoma, irreversible nerve injury, or compartment syndrome) leading to either death, need for significant blood transfusion (≥ 4 units), unplanned percutaneous or surgical intervention, or irreversible end-organ damage (e.g. hypogastric artery occlusion causing visceral ischaemia or spinal artery injury causing neurological impairment.

All patients provided written informed consent for the TAVI procedure and subsequent data collection according to the policy of each individual treating hospital.

6.2.4 Statistical analysis

The overall analysis was performed according to the sex of the patient. All continuous variables are expressed as mean ± SD and analysed with the Student t test or Wilcoxon rank-sum test depending on the variable distribution. All categorical variables were compared with the chi-squared test with Yates correction for continuity or the Fisher-exact test as appropriate.

For reasons explained in chapter 3, a propensity score matching was also performed to allow for an equal comparison between women and men in the analysis. (250, 251) Because of the non-randomised nature of the study, to reduce treatment selection bias and potential confounding, we performed rigorous adjustment for significant differences in baseline characteristics with propensity score matching. The score was calculated by performing a multi-parsimonious multivariable logistic regression with valve type as the dependent variable. The following co-variants were selected: age, BMI, logistic EuroSCORE, Society of Thoracic Surgeons Predicted Risk of Mortality Score (STS) score,

previous MI, CABG or PCI, hypertension, COPD, DM, PVD, chronic kidney disease (CKD), cerebrovascular disease, ejection fraction and aortic annulus diameter. The C-statistic for the propensity score model was 0.75 and the Hosmer-Lemeshow goodness of fit was 0.535, confirming good calibration. To identify matched pairs we used the following algorithm: 1:1 optimal match with a ± 0.03 caliper and no replacement.(253) Clinical outcomes in the matched population were analysed with Cox proportional hazards regression stratified on matched-pairs. Multi variable Cox proportional hazards regression modelling was performed to determine the independent predictors of study objectives with purposeful selection of covariates. Variables associated at univariate analysis (all with a p value ≤ 0.1) and those judged to be of clinical importance were eligible for inclusion into the multivariable model-building process. The goodness of fit of the Cox multi-variable model was assessed with the Grønnesby-Borgan-May test. Results are reported as Hazard Ratio (HR) with associated 95% confidence interval (CI) and p value. Survival was recorded by Kaplan-Meier analysis with the log-rank method used for comparison. All statistical analysis was performed with SPSS Version 22.0 (SPSS Inc, Chicago, Il, USA). A p-value of < 0.05 was considered statistically significant.

I was again responsible for collecting all data from one site (San Raffaele Scientific Institute, Milan, Italy) and validating this data alongside data from the other sites. I devised and completed the database also performed the analysis and interpretation of the data.

6.3 Results

In total, 1,125 patients were included in this multi-centre registry study; of which 532 (47.3%) were women and 593 (52.7%) were men. The baseline characteristics of the overall population are reported in Table 20.

6.3.1 Unadjusted VARC Outcomes in the Overall Population

At 30 days, 38 (7.2%) women died following the TAVI procedure versus 42 (7.1%) men, cardiovascular death respectively occurred in 30 (5.7%) versus 32 (5.4%) patients. A

VARC major stroke occurred in 13 (2.4%) women and 13 (2.2%) men. Six (1.1%) women versus 6 (1.0%) men had a documented peri-procedural MI.

Major vascular complications and life-threatening bleeding occurred respectively in 64 (12.1%) and 78 (14.8%) of women versus 42 (7.1%) and 63 (10.6%) men. At one year, in total 120 (22.6%) women died versus 178 (30.2%) men; of these 68 (13.2%) versus 91 (16.0%) were cardiac deaths.

Table 20. The Baseline Characteristics of the Overall Population in the W-PRAGMATIC Registry.

	Women **N = 532**	**Men** **N = 593**	**P Value**
Age, years	82.0±6.8	80.4±7.3	< 0.001
MCV	261 (49.1)	327 (55.1)	0.041
BMI	26.2±5.1	25.9±3.9	0.296
NYHA III / IV	436 (82.3)	475 (80.1)	0.355
Logistic EuroSCORE	21.7±12.7	23.3±13.5	0.035
STS Score	9.4±7.2	8.5±6.4	0.036
Previous stroke	72 (13.5)	99 (16.7)	0.140
Previous MI	67 (12.6)	134 (22.6)	< 0.001
Previous CABG	51 (9.6)	192 (32.4)	< 0.001
Previous PCI	119 (22.4)	223 (37.6)	< 0.001
Diabetes Mellitus	146 (27.4)	178 (30.0)	0.341
Hypertension	372 (69.9)	421 (71.0)	0.694
GFR < 60 ml/min	312 (58.9)	377 (63.9)	0.084
COPD	148 (27.8)	212 (35.8)	0.011
PVD	103 (19.4)	175 (29.7)	< 0.001
Annulus, mm	22.0±2.0	23.9±1.9	< 0.001
LVEF, %	54.4±13.2	48.6±14.5	< 0.001

Results reported as n (%) or mean ± SD as appropriate. BMI = Body Mass Index; NYHA = New York Heart Association; Logistic EuroSCORE = European System for Cardiac Operative Risk Evaluation; STS Score = Society of Thoracic Surgeons Predicted Risk of Mortality Score; CABG = Coronary Artery Bypass Grafting; PCI = Percutaneous Coronary Intervention; CAD = Coronary Artery Disease; GFR = Glomerular Filtration Rate; COPD = Chronic Obstructive Pulmonary Disease; PVD = Peripheral Vascular Disease; AVA = Aortic Valve Area; LVEF = Left Ventricular Ejection Fraction.

6.3.2 Propensity Matched Analysis

After propensity score matching was performed, there were 344 matched pairs of patients in each group. The baseline characteristics of the matched groups are shown in Table 21.

Table 21. The Baseline Characteristics of the Propensity Matched Population of the W-PRAGMATIC Registry.

	Women N = 344	**Men N = 344**	**P Value**
Age, years	81.4±6.9	81.2±7.5	0.689
BMI	25.8±5.0	25.8±3.9	0.938
NYHA III/IV	279 (81.1)	271 (78.8)	0.446
Logistic EuroSCORE, %	22.5±13.1	22.0±13.5	0.623
STS Score, %	8.7±6.4	8.5±6.0	0.649
Previous stroke	49 (14.2)	56 (16.3)	0.458
Previous MI	55 (16.0)	53 (15.4)	0.834
Previous CABG	47 (13.7)	47 (13.7)	1.000
Previous PCI	92 (26.7)	93 (27.0)	0.931
Diabetes Mellitus	89 (25.9)	92 (26.7)	0.795
Hypertension	232 (67.4)	240 (69.8)	0.511
GFR < 60 ml/min	221 (64.2)	224 (65.1)	0.811
COPD	112 (32.6)	113 (32.8)	0.367
PVD	80 (23.3)	79 (23.0)	0.928
LVEF, %	51.6±13.4	52.4±13.6	0.447

Results reported as n (%) or mean ± SD as appropriate. BMI = Body Mass Index; NYHA = New York Heart Association; Logistic EuroSCORE = European System for Cardiac Operative Risk Evaluation; STS Score = Society of Thoracic Surgeons Predicted Risk of Mortality Score; CABG = Coronary Artery Bypass Grafting; PCI = Percutaneous Coronary Intervention; GFR = Glomerular Filtration Rate; COPD = Chronic Obstructive Pulmonary Disease; PVD = Peripheral Vascular Disease; LVEF = Left Ventricular Ejection Fraction.

6.3.2.1 VARC Outcomes for the Matched Groups (Table 22)

Table 22. The VARC Outcomes in the Propensity Matched Population of the W-PRAGMAT1C Registry.

Outcome	Number of Events (%)		HR	95% CI	P Value
	Women N = 344	**Men** N = 344			
30 Days					
All-Cause Mortality	19 (5.6)	21 (6.2)	1.116	0.589-2.115	0.737
Cardiac Mortality	14 (4.1)	16 (4.7)	1.153	0.554-2.402	0.703
Peri-Procedural MI	4 (1.2)	2 (0.6)	0.497	0.090-2.732	0.421
Spontaneous MI	7 (2.0)	0			0.008
Major Stroke	6 (1.7)	6 (1.7)	1.000	0.319-3.312	1.000
Major Vascular	50 (14.7)	23 (6.7)	0.420	0.250-0.705	0.001
Life Threatening Bleeding	64 (18.7)	32 (9.3)	0.447	0.284-0.704	0.001
Major Bleeding	59 (17.2)	69 (20.1)	1.208	0.822-1.775	0.337
AKI Stage 3	18 (5.2)	20 (5.8)	1.125	0.584-2.166	0.725
Device Success	321 (93.6)	328 (95.3)	1.405	0.725-2.724	0.314
Combined Safety	103 (29.9)	77 (22.6)	0.685	0.486-0.965	0.031
Median Follow Up					
All-Cause Mortality	120 (22.6)	178 (30.2)	1.480	1.131-1.936	0.004
Cardiac Mortality	68 (13.2)	91 (16.0)	1.246	0.880-1.750	0.204

Median follow-up 412.5 (IQR 233.3-696.0) days. Results reported as n (%). HR = Hazard Ratio, CI = Confidence Interval; MI = Myocardial Infarction; AKI = Acute Kidney Injury.

At 30 days follow-up, there were no differences in all-cause mortality (women 5.6% vs. men 6.2%; OR 1.116; 95% CI 0.589-2.115; p=0.737) or cardiovascular mortality (4.1% vs. 4.7%; OR 1.153; 95% CI 0.554-2.402; p=0.703) between women and men. In addition, both sexes had no differences in the occurrence of peri-procedural MI (1.2% vs. 0.6%; OR 0.497; 95% CI 0.090-2.732; p=0.421), stroke (1.7% vs. 1.7%; OR 1.000; 95% CI 0.319-3.132; p=1.000), stage 3 acute kidney injury (5.2% vs. 5.8%; OR 1.125; 95% CI 0.584-2.166; p=0.725) or device success (93.6% vs. 95.3%; OR 1.405; 95% CI 0.725-2.724; p=0.314) as defined by the VARC criteria.

Conversely, women had more major vascular complications (14.6% vs. 6.7%; OR 0.420; 95% CI 0.250-0.705; p=0.001) and life-threatening bleeding (18.7% vs. 9.3%; OR 0.447; 95% CI 0.284-0.704; p=0.001), corresponding to a difference in the combined safety endpoint (29.9% vs. 22.6%; OR 0.685; 95% CI 0.486-0.965; p=0.031) favouring men.

At a median follow-up of 412.5 days (IQR 233.3-696.0 days), although there was no observed difference in cardiovascular mortality (13.2% vs. 16.0%; OR 1.246; 95% CI 0.880-1.750; p=0.204), women had a lower all-cause mortality (22.6% vs. 30.2%; OR 1.480; 95% CI 1.131-1.936; p=0.004). The Kaplan Meier survival curves of the matched population are shown in Figure 7.

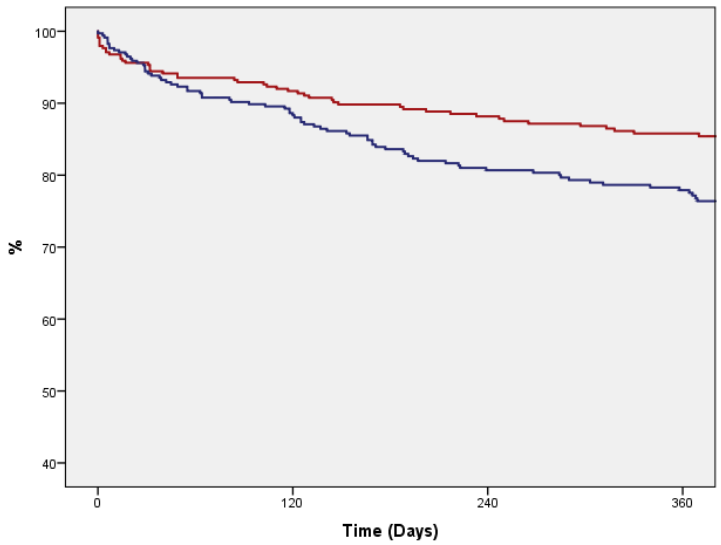
6.3.2.2 Predictors of the Study Objectives

At Cox regression multi-variable analysis, the independent predictors of all-cause mortality were male sex (1.557; 95% CI 1.095-2.214; p=0.014), left ventricular ejection fraction (0.976; 95% CI 0.964-0.989; p<0.001) and peripheral vascular disease (1.504; 95% CI 1.005-2.251; p=0.047).

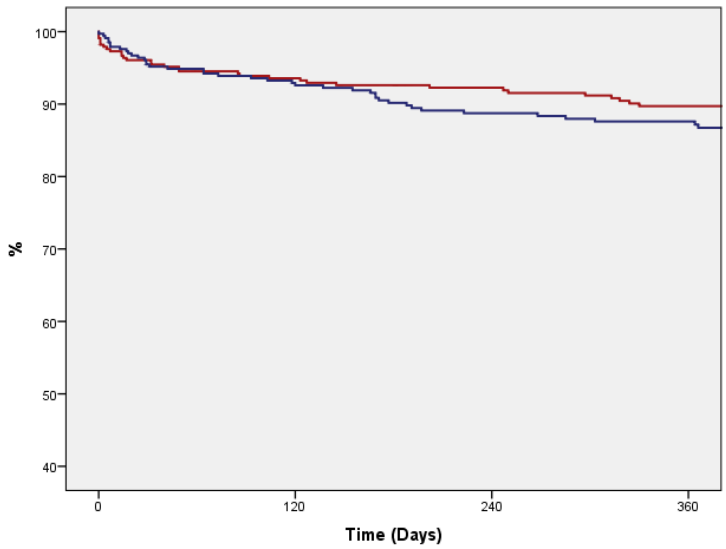
Additionally, the predictor of cardiovascular mortality was demonstrated to be left ventricular ejection fraction (0.979; 95% CI 0.964-0.994; p=0.008) alone.

Figure 7. Freedom from All-Cause (Panel A) and Cardiovascular Mortality (Panel B) at One Year in the Propensity Matched Population of the W-PRAGMATIC Registry. The Red Line represents Women and the Blue Line represents Men.

A.



Women	344	297	262	244
Men	344	286	243	212



Women	344	297	262	244
Men	344	286	243	212

6.4 Discussion

The main findings of our study are: 1) There were no differences in 30 day mortality between women and men despite more life-threatening bleeding and vascular complications in women; 2) However, at medium term follow-up, women had a survival advantage over men; 3) Moreover, male sex was an independent predictor of all-cause mortality at follow-up.

TAVI has now been accepted as an alternative solution to SAVR for patients with symptomatic AS requiring intervention.(179, 326-328). Patients undergoing such a procedure are typically deemed to be of high surgical risk, with multiple medical co-morbidities. This commonly includes women, who present at a later age. The 'Placement of AoRTic TraNscathetER valve (PARTNER) trial' was the landmark study assessing TAVI as a form of treatment for patients at high surgical risk. In this study, overall, TAVI was reported as non-inferior to SAVR in the primary endpoint of one year mortality in PARTNER A (respectively 24.2% vs. 26.8%; p=0.62; non-inferiority p=0.001)(180) and interestingly in this study, females (N = 298; 42.8%) treated with TAVI had a lower mortality at 12 months as compared to men undergoing TAVI (18.4% vs. 28.0%).(180)

Following this, a number of studies have now reported outcomes comparing the sexes following TAVI for severe AS. (186, 187, 329-332) Typically however, there are significant baseline differences which have rendered effective comparison between the groups difficult. However, reports have shown that women are more likely to develop significant bleeding and vascular complications,(186, 187, 329, 330) which have been explained by the smaller size of women (including size of vascular access) and the older age group at which they undergo treatment. Nevertheless, in this current study, which is the largest so far reported, the results in the matched population are similar, despite similar BMI and age in each group, suggesting there may be a different underlying pathology inherent to women that leads to bleeding (which is similar to that in the CAD population). Of note, we do not have available the anticoagulant regime that was utilized in each of the patients, which may have bared an impact on the findings. Interestingly however, as with other studies, these results do not relate to a difference in all-cause mortality at 30 days.

Several studies have suggested that women may have a better longer term outcome than men, but this has been explained due to differences at baseline. Importantly, our study in the matched population demonstrates a similar benefit favouring women in mortality at 412.5 days clinical follow-up. In corroboration with this, a recent publication from the CoreValve US High Risk Pivotal Trial has compared 335 patients undergoing SAVR versus TAVI. This encouragingly reported that women actually undergoing TAVI had a lower mortality at 12 months compared with those undergoing conventional SAVR (12.7% vs. 21.8%; p=0.03). (184) Our findings concur with two large meta-analyses, (194, 195) the largest of which pooled the data from 5 studies including 11,310 patients, demonstrating that female sex was independently associated with survival at a median of 387 (IQR 192-730) days (HR 0.79; 95% CI 0.73-0.86; p=0.001).(195) This in in accordance with our study which shows one of the predictors of all-cause mortality at follow-up was demonstrated to be that of male sex. Again, this has recently been suggested in a further study by Hayashida et al.(329)

There are a number of reasons postulated as to why women may do better following TAVI than their male counterparts. Women may well benefit from the protective effects of their hormones, indeed the hormone oestrogen is favourable on the myocardium, slowing the rate of interstitial fibrosis and therefore subsequent reversal of hypertrophy may happen more quickly.(183) It has been shown on multivariate analysis that female sex is independently associated with better recovery of the left ventricular systolic function following TAVI (181) and that left ventricular hypertrophy reverses more frequently in female patients following SAVR.(182) Interestingly, PARTNER A suggested that females may do better with TAVI than conventional surgery (HR 0.68; 95% CI 0.44-1.04; p=0.05). Females therefore may be more suited to undergo TAVI in view of their co-existing conditions, and may well have a larger benefit to gain. In addition, the cost effectiveness of TAVI procedures in women may be further enhanced by their longer life expectancy, enabling them to live a better quality of life with less requirement for ongoing health care costs.

Of note, the ‘Women’s INternational Transcatheter Aortic Valve Implantation’ (WIN-TAVI) all female real-world registry, designed to specifically explore sex-specific characteristics of those undergoing TAVI for severe AS and their impact upon clinical outcomes following the procedure, was recently published. In total, 1,019 women deemed to be of intermediate risk, were enrolled from 19 countries across Europe and North

America. The VARC-2 (201) early safety endpoint at 30 days was reported in 14.0% with a rate of 3.4% all-cause mortality. The independent predictors of the early safety endpoint were age (OR 1.04; 95% CI 1.00-1.08), prior stroke (OR 2.02; 95% CI 1.07-3.80), left ventricular ejection fraction < 30% (OR 2.62; 95% CI 1.07-6.40) and a history of pregnancy (OR 0.57; 95% CI 0.37-0.85).(202) Although this study does go some way to assessing features of women with severe AS undergoing TAVI, there is still a lot of work to do to be clear as to the role that sex does play. Furthermore, another factor which needs to be considered is the consideration that women may do better with TAVI as a first-line treatment rather than conventional SAVR for which work is ongoing. Women have been shown to have worse outcomes following SAVR, which has a number of contributory factors including less acute kidney injury and peri-procedural mortality. Importantly, women have a smaller aortic annulus and hence prosthesis-patient mismatch is more frequent following SAVR in women which has been shown to be associated with increased all cause and cardiovascular mortality.(337, 338) Moreover, there may be a better long-term recovery of the left ventricular function following TAVI in women due to the underlying ventricular pathology and fibrosis.

Overall, this is the largest TAVI study comparing women and men requiring treatment for severe AS and the results are encouraging for the use of TAVI in elderly high risk women with severe symptomatic AS requiring intervention. However, clearly longer term follow up in the setting of an adequately powered randomized clinical trial is needed to assess this fully, taking into account other factors which may be specific just to the female cohort.

6.5 Limitations

Due to the non-randomised and retrospective nature of this study, the findings are subject to selection bias and confounding with regards to the pre-procedural risk of the patient. In an aim to minimize these biases, a propensity score matching was performed, however hidden bias may remain due to the influences of unmeasured confounders. Selection bias does play a role as it is evident clinically that ‘frail’ patients are denied intervention, but we do not have the data on these patients for this study. Again, there may be a further

selection bias as women may be deemed more frail than their male counterparts and there is no objective frailty scoring mechanism utilised in this study.

In addition, the lack of a central core lab and adjudication committee means potential reporting bias and is a subsequently a further limitation. As in the prior data sets, there is the assumption that the presented findings are correct. It must be taken into account that the findings could be due to chance, however the larger sample size in this data set would reduce the likelihood of such a type II error.

6.6 Conclusions

At medium term follow-up, in the presentation of this structured data, women treated with TAVI for severe symptomatic AS had a survival advantage over men, despite more life-threatening bleeding and vascular complications reported during the index hospital admission. Although prior studies have reported similar findings, this is the largest such report in a real world population with similar baseline characteristics. The potential significance of these results will be discussed critically in chapter 8 of this thesis, however specific sex analyses of large randomised trials need to be reported to better understand issues relevant to treatment strategies in women.

7. Sex Differences in the Perceived Intensity of Symptoms in Patients with Aortic Stenosis

7.1 Introduction

The previous chapter demonstrated that women actually appear to have an advantage from intervention for AS by TAVI compared to men. One of the most common symptoms in patients presenting with significant AS is breathlessness, in addition to chest discomfort (angina) and dizziness / black-outs (syncope). The American Thoracic Society defines breathlessness as 'a subjective experience of breathing discomfort that is comprised of qualitatively distinct sensations that vary in intensity' (339) which can vary over time and with activity, affecting all domains of life. Often patients with AS are relatively elderly, and subsequently therefore have a number of other co-morbidities (including airways disease and anaemia), which can render the assessment of breathlessness due to their contributory valvular heart disease a challenge by the physician.

Interestingly, breathlessness related to physical activity (in those patients without AS) appears to be more common in older women compared with men of a similar age group.(340, 341) Indeed, female sex has been shown to be predictive of symptom prevalence in congestive heart failure (342) and female heart failure patients have been shown to perceive dyspnoea differently from males with a similar level of disease.(343) Population studies in patients with various cardiopulmonary conditions have indicated that when matched for disease severity, women still experience greater levels of respiratory difficulty, greater exercise intolerance and overall a poorer perceived health status than their male counterparts.(344, 345) Furthermore, women have reported greater intensity of breathlessness at a given power output during incremental cycle exercise.(346)

The mechanisms underlying the propensity for women to experience more disabling symptoms then men with similar cardiac and respiratory disease are not entirely clear. However, one study has suggested that elderly women have relatively reduced maximal ventilatory reserve compared with older men.(347) It has been demonstrated that asymptomatic women with severe AS have similar rates of abnormal exercise stress echocardiography as men despite limitations in exercise capacity amongst the women.(348) It is therefore postulated one of the reasons women with AS are diagnosed in

a similar proportion to men (unlike those with CAD) is that they are much more symptomatic with the disease process of AS and hence seek medical attention sooner.

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a 23 item, self-administered instrument that was developed with an aim to quantify physical function, physical symptoms (frequency, severity and recent change), social function, self-efficacy and knowledge, and quality of life of patients, hence allowing quantification of symptoms in the elderly population. This can be used in conjunction with the 6-minute walk test (6MWT) to measure the degree of symptoms of breathlessness in a distinct prespecified population. It is a simple, self-paced assessment to evaluate the functional status of an individual patient, which is reproducible, sensitive to changes in quality of life and is thought to mimic the general activities of daily living of the patient.(349, 350)

Finally, following all the above data sets which utilised quantitative data and analysis, a more qualitative approach was undertaken to assess the symptoms of patients with valvular heart disease. Despite reported differences between women and men in breathlessness, no study so far has assessed whether there are variances between the sexes with AS in the reported severity of shortness of breath. In addition, women are more likely to develop left ventricular hypertrophy with significant AS (and hence have diastolic dysfunction) which potentially may impact upon the symptoms of breathlessness. A prospective observational study was undertaken in a single centre to assess symptoms of breathlessness according to sex in patients with moderate AS, via a 6 minute walk test and a KCCQ questionnaire. It was hypothesised that women potentially would have more symptoms, due to the fact that they often hypertrophy the left ventricle in a greater manner than men, but also on a psychosocial level may complain more of their limitations despite a similar degree of disease severity as men with a poorer perceived health status. Hence the purpose of the present chapter is to investigate the perception of breathlessness during incremental exercise in patients with AS according to sex.

7.2 Methods

7.2.1 Patient Population

The study population consisted of patients with diagnosed moderate AS who were currently under follow up and not awaiting intervention for the AS or CAD at both the

Cumberland Infirmary, Carlisle, UK and Castle Hill Hospital, Hull, UK. Moderate AS was chosen following discussion between myself and my research supervisors, which included a Professor of Cardiology with a strong interest in 6 minute walk test assessment of patients with heart failure. Patients with severe AS were excluded as there was safety concerns in undertaking the 6 minute walk test in this population.

I applied for ethical approval for this study which was then performed across 2 sites (Cumberland Infirmary, Carlisle and Castle Hill Hospital, Cottingham). Two sites were needed to facilitate recruitment and ensure study feasibility. This related firstly to the size of the study population, as well as overcoming any issues with recruitment bearing in mind that patients with AS are often relatively old and frail and potentially less likely to consent to study participation. Moreover, many of these patients had contributing lung disease rendering them unable to be included in the study. The study was given approval by the North of Scotland Research Ethics Committee and all patients recruited provided full written informed consent for participation and data collection.

Appropriate patients were recruited through outpatient clinics and review of the respective echocardiography databases, from an existing frame with a reasonable number of these patients. In addition, the consideration was that we would review these patients at follow-up and review whether the result of the 6 minute walk test or the questionnaire could predict those patients whose disease would progress in a more rapid manner, hence this being potentially a very useful study which may help guide follow-up in the future. Participants were included if there was significant AS as determined by echocardiogram and Doppler, defined as a mean gradient of $\geq$ 20mmHg and / or an aortic valve area of $\leq$ 1.8cm^2. Patients were excluded if there was any prior history of MI, moderate to severe aortic regurgitation, moderate to severe mitral regurgitation, left ventricular ejection fraction $\leq$ 50%, unable to walk without assistance from another person and being unable to exercise due to non-cardiac limitations, e.g. osteoarthritis, COPD (defined as FEV_1 / FVC < 70%). All baseline demographics of the patients and results were recorded and entered into a dedicated encrypted database by the study investigators. To determine if COPD was present, all patients underwent a spirometry assessment with the best of three results recorded. A venous blood sample was taken from each patient to check the haemoglobin, creatinine and NT-pro-BNP levels.

The KCCQ was chosen as the questionnaire for the participants of this study following a review and discussion with my supervisors over the relative benefits of this

over other patient scoring measures. It comprises of 23 items which quantify the physical limitations, symptoms, self-efficacy, social interference and quality of life and is validated and has been shown to be reliable in patients with chronic heart failure. The benefits of this are that it also captures physical limitations, independently quantifies symptoms is sensitive to changes in clinical circumstances, but moreover is very simple to use and has been the standard used in other studies, which potentially allows for comparison with other work. This was an important consideration as often the patient population in those with AS do not wish to become involved in things which are complex and time-consuming. We also thought it was important to consider and include such patient related outcomes measures (PROMS) which are becoming more prominent as reported outcomes in clinical studies.

7.2.1.1 Sample Size

With regards to the sample size, the qualitative methodology utilised attempted to get an understanding of the theory and potentially generate more theory, with statistical inference not being the main objective. Indeed, qualitative research is about reaching saturation in the data and hence is not powered. No prior literature exists in the public domain assessing such patients in a similar fashion, with no evidence about the expected magnitude of the effect available, since symptom perception in AS has never been specifically evaluated. Hence, following review of other literature, input from my supervising Professor of Cardiology and also from the university statistician, the decision was made that a sample size of 50 patients (aiming for equal numbers of women and men, which is the case in the population of patients with AS under follow-up) would be sufficient for this explorative study. As qualitative analysis aims for depth as well as breadth, it was felt a large number of questionnaires to analyse would be difficult to complete and the current sample size would allow for any phenomenon to appear.

7.2.2 Procedures

The procedures were standardised across both sites.

7.2.2.1 Echocardiographic Assessment

Prior to entry into the study, all patients had full echocardiographic assessment by a British Society of Echocardiography (BSE) accredited operator using M-mode, 2D images and colour flow Doppler recordings utilising a Vivid 9 (GE Healthcare, Buckinghamshire, United Kingdom) echocardiography machine. All measurements were taken in accordance with American Echocardiography Society / European Association of Echocardiography guidelines. The degree of AS was evaluated using 2D transthoracic echocardiography and doppler measurements. The left ventricular function was carried out by 2D transthoracic echocardiography and left ventricular ejection fraction calculated using Simpsons formula from measurements of end diastolic and end systolic volumes on apical 2D views. When there was a lack of concordance regarding the severity of left ventricular dysfunction or degree of AS, the echo was reviewed with a third operator and a consensus achieved.

7.2.2.2 Six Minute Walk Test

The heart rate, heart rhythm, body mass index and blood pressure of the patient was measured at baseline. The 6MWT was then conducted on a 15 metre flat corridor with chairs at either end using a standardised protocol as previously reported.(351) The patient was instructed to walk as far as possible, turning 180 degrees every 15 metres in 6 minutes. During the test, the patients were able to rest if needed, however they were encouraged to resume walking as soon as they were physically able to do so. The time remaining was called by the study investigator every second minute. Patients had to walk unaccompanied, therefore there was no influence upon the speed and after 6 minutes the patient was instructed to stop and the total distance covered to the nearest metre was calculated and entered into the database. Standardized verbal encouragement was given to all patients after both 2 and 4 minutes, using the phrases ‘you are doing well’ and ‘keep up the good walk’. The peak heart rate and blood pressure of the patients were also recorded.

7.2.2.3 Kansas City Cardiomyopathy Questionnaire

The patients were then asked to independently complete the KCCQ in paper format (Appendix 10). This is 23 item questionnaire covers physical limitation of the patient, the total symptoms (symptom frequency and burden), the self-efficacy of the patient (i.e. whether the patient thinks that they have the knowledge and skills to manage their heart failure sufficiently as an outpatient), the quality of life of the patient and their social function.

7.2.3 Study Objectives

The primary study objective was to assess whether the sex of the patient had an effect on the perceived intensity of symptoms of shortness of breath in patients with moderate AS. The other study objectives were to assess the relationship between the severity of symptoms of breathlessness and the left ventricular dimensions of the patient and also the relationship between patient sex and NT-pro-BNP levels and patient sex and left ventricular dimensions in patients with moderate AS.

7.2.4 Statistical Analysis

All continuous variables are expressed as mean ± standard deviation and were analysed with the Student t test or Wilcoxon rank-sum test depending upon the variable distribution. The categorical variables were compared with the Chi-squared test with Yates correction for continuity or the Fisher-exact test as appropriate. A Spearman correlation was used to assess the correlation between the patient derived health care measures and the metabolic or echocardiographic parameters. The Student t test or Wilcoxon rank-sum test was used to examine the differences between 2 groups. All data was analysed by Statistical Package for Social Sciences Version 23.0 (SPSS Inc, Chicago, Illinois, USA), with a p-value of < 0.05 considered as being statistically significant.

I was responsible for identifying, recruiting and consenting the patients, then performing the 6 minute walk test and helping with the KCCQ questionnaire. I devised and completed the data set and performed the analysis.

7.3 Results

In total, 40 patients with moderate AS were recruited into this exploratory study, of which 19 (47.5%) were women. There were no differences in the mean age of the patients (women 70.3±7.6 years vs. men 72.2±8.4 years; p=0.464) or BMI (29.6±5.5 kg / m^2 vs. 30.3±5.7 kg / m^2; p=0.706) between the groups.

Table 23. The Baseline Characteristics and Treatments of Patients with Moderate Aortic Stenosis Undergoing a Six Minute Walk Test.

	Women (n = 19)	**Men (n = 21)**	**P Value**
Age, years	70.3±7.6	72.2±8.4	0.464
BMI, kg / m^2	29.6±5.5	30.3±5.7	0.706
Diabetes Mellitus	6 (31.6)	2 (9.5)	0.082
Hypertension	8 (42.1)	15 (71.4)	0.061
Hypercholesterolaemia	10 (52.6)	10 (47.6)	0.752
COPD	0	0	
Atrial Fibrillation	2 (10.5)	4 (19.0)	0.451
PPM	2 (10.5)	2 (9.5)	0.916
Current Smoker	2 (10.5)	1 (4.8)	0.489
Anti-platelet	6 (33.3)	10 (47.6)	0.511
Beta-blocker	7 (38.9)	11 (52.4)	0.399
ACE / ARB	6 (33.3)	14 (66.7)	0.038
Statin	13 (72.2)	11 (52.4)	0.204
Calcium Channel Blocker	3 (16.7)	6 (28.6)	0.379
Diuretic	4 (22.2)	6 (28.6)	0.651

Results reported as n (%) or mean ± SD as appropriate. BMI = Body Mass Index; COPD = Chronic Obstructive Pulmonary Disease; PPM = Permanent Pacemaker; ACE = ACE Inhibitor; ARB = Angiotensin Receptor Blocker.

The baseline characteristics and medications of the patients are illustrated in Table 23. Of note, at baseline there was a trend for more women to have a prior diagnosis of diabetes mellitus (31.6% vs. 9.5%; p=0.082) with conversely more men being on treatment for hypertension (42.1% vs. 71.4%; p=0.061). This finding explains why more men were on treatment with ACE inhibitors or angiotensin receptor blockers at baseline (33.3% vs. 66.7%; p=0.038).Women had a significantly lower haemoglobin level (127.9±14.1 g / dL vs. 144.7±12.2 g / dL; p<0.001) and a lower creatinine level (70.0±11.0 µmol / l vs.98.0±27.3 µmol / l; p<0.001). There was no statistically significant difference in the result of the NT-pro-BNP level between the sexes (343.3±359.1 pg / ml vs. 510.0±759.0 pg / ml; p=0.440).

The results of the 6MWT are shown in Table 24. Notably, there was no statistically significant difference in the distance covered during the test between the sexes.

Table 24. The Results of the Six Minute Walk Test in the Study Patients with Moderate Aortic Stenosis.

	Women (n = 19)	**Men (n = 21)**	**P Value**
Baseline HR, bpm	66.0±18.1	67.5±12.3	0.763
Baseline SBP, mmHg	152.8±28.7	145.2±22.2	0.377
Baseline DBP, mmHg	75.7±12.5	74.8±10.7	0.824
Distance covered, metres	331.5±81.5	458.7±619.7	0.437
Peak HR, bpm	84.6±28.6	72.8±18.2	0.153
Peak SBP, mmHg	152.4±29.7	150.5±22.1	0.834
Peak DBP, mmHg	77.2±12.3	75.3±9.6	0.609

Results reported as n (%) or mean ± SD as appropriate. HR = Heart Rate; bpm = beats per minute; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure.

On full echocardiographic assessment, the women had typically smaller left ventricular end diastolic dimensions (4.4±0.7 cm vs. 4.9±0.5 cm; p=0.014). However, there was no difference in the peak pressure drop across the aortic valve (46.5±8.4 mmHg vs. 45.2±8.6 mmHg; p=0.632) or indeed the peak velocity across the aortic valve (3.4±0.3 m / s vs. 3.3±0.3 m / s; p=0.654).

The results of the KCCQ calculations are shown in Table 25. There were no differences between sexes in the KCCQ Clinical Score (women 75.5±21.9 vs. men 79.1±17.2; p=0.597) or the KCCQ Overall Score (78.1±20.3 vs. 80.7±20.1; p=0.712).

Table 25. The Results of the Kansas City Cardiomyopathy Questionnaire in the Study Patients with Moderate Aortic Stenosis.

	Women (n = 19)	**Men (n = 21)**	**P Value**
Physical Limitation	72.7±22.1	79.1±24.0	0.486
Symptom Frequency	82.4±22.3	81.5±15.5	0.891
Total Symptom Score	82.4±22.3	79.9±16.4	0.717
Quality Of Life	78.6±24.2	79.6±29.2	0.916
Social Limitations	81.0±22.2	81.0±26.4	1.000
Overall Score	78.1±20.3	80.7±20.1	0.712
Clinical Score	75.5±21.9	79.1±17.2	0.597

All results reported as mean ± SD.

There was no correlation noted between the KCCQ health status measures and the left ventricular end diastolic diameter, shown in Table 26.

Table 26. Correlation Between the Kansas City Cardiomyopathy Questionnaire Measures and the Left Ventricular End Diastolic Diameters in the Study Patients with Moderate Aortic Stenosis.

	r Value	P Value
Physical Limitation	-0.267	0.218
Symptom Frequency	-0.156	0.409
Total Symptom Score	-0.187	0.321
Quality Of Life	-0.082	0.667
Social Limitations	-0.168	0.434
Overall Score	-0.103	0.590
Clinical Score	-0.116	0.541

There was however a correlation noted between the peak pressure drop across the aortic valve and the KCCQ Quality of Life outcomes measure (r=-0.402; p=0.019).

7.4 Discussion

The results of this prospective study of patients with moderate AS shows that: 1) There are no significant differences in symptoms of shortness of breath according to the sex of the patient; 2) Furthermore there are no differences in NT-pro-BNP levels between sexes in such patients; 3) Neither the left ventricular end diastolic size nor the NT-pro-BNP value are predictive of symptoms; 4) The aortic valve gradient correlates with the quality of life of patients with moderate AS.

Breathlessness related to physical activity (in those patients without AS) has been demonstrated to be more common in older women compared with men of a similar age group. (340, 341) Additionally, previous studies have demonstrated that women with heart failure perceive breathlessness differently from males (343) and indeed female sex is a predictor of symptoms in this population.(342) Furthermore, population studies in patients with various cardiopulmonary conditions have indicated that when matched for disease severity, women experience greater levels of respiratory difficulty, greater exercise intolerance and poorer perceived health status than their male counterparts.(344, 345)

However, no study so far has assessed the perception of breathlessness dependent on patient sex in patients with aortic stenosis.

The release of NT-pro-BNP from the ventricular myocardium has been shown to be associated with ventricular dilatation and pressure overload.(352) In the current study, the women had smaller left ventricular end diastolic dimensions (4.4±0.7 cm vs. 4.9±0.5 cm; p=0.014) than men. However, despite this, the NT-pro-BNP value did not differ according to the sex of the patient and moreover was not correlated with the severity of symptoms reported by the patient using the KCCQ score. Previous studies have shown that NT-pro-BNP levels are higher in women with no cardiac disease compared with men who are similarly well.(353) A study of 460 men and 175 women with stable CAD has previously shown that even in a multi-variable corrected analysis, there was no reported difference in the value of NT-pro-BNP between sexes (women 42.7 pmol / ml vs. 35.7 pmol / ml; p=0.104).(354)

In the setting of AS, it has been suggested that the measurement of NT-pro-BNP can be utilised as a prognostic tool. A prospective study of 237 patients (51% women) with moderate / severe AS (mean aortic valve gradient 43.2 mmHg) showed that if the NT-pro-BNP level was elevated, which was defined as > 515 pg /ml, at 1 year the event free survival was reduced to 50% compared with those with a NT-pro-BNP < 515 pg / ml of 93%.(355) Other studies have shown a similar result suggesting that this biomarker is related to the severity of AS,(356-358) even in asymptomatic patients (359) and also the severity of symptoms.(360) Conversely, other studies have demonstrated that caution should be utilised when using NT-pro-BNP as a diagnostic tool in patients with AS. A study of 361 patients found an important overlap between the value of NT-pro-BNP and grade of AS and also NYHA class (area under receiver operator curve 0.73).(361)

In the current study, there were no differences noted in any of the KCCQ domains between sexes. Men did appear to walk further (458.7 metres vs. 331.5 metres), though this was not statistically significant in this study with a relatively small sample size. Previously it has been reported that women with AS have a greater impairment of their functional status than men and a poorer exercise capacity, despite a similar degree of severity of AS.(164, 362) In our study, it must be stated that at baseline, the patients were similar with regards to age, BMI and range of co-morbidities. It is important also that all patients included did not have anaemia, had good left ventricular function and there were no participants with evidence of COPD. Often these co-morbidities can render the assessment

of breathlessness due to their heart disease difficult. Overall, the patients were therefore relatively well matched which may account for the lack of difference between the groups. Also, the KCCQ does not specifically address other symptoms which may be manifest in AS, e.g. angina or light headedness. However, a secondary analysis of a series of clinical trials has addressed the validity of the KCCQ in AS patients.(363) Furthermore, in the PARTNER study, in patients with severe AS medically treated, those with low KCCQ scores had a nearly 4-fold higher risk of death at 12 months than those with higher KCCQ scores.(364) It must be taken into account that survey responses are dependent on the state of mind of the patient at the time and / or can be exaggerated. The patients in this study were all willing to participate and hence may have been more likely to have a more positive outlook on their disease process.

Interestingly, the aortic valve gradient of the patient did correlate with the Quality of Life domain in the KCCQ, but none of the other domains. This is important for screening reasons as if a patient were to develop a change in their symptomatology, it may be the first sign that the disease process is progressing. As discussed, it may be a reflection that heart failure symptoms may not predominate until the disease severity worsens and the questionnaire is not able to show other symptoms the patient may have.

7.5 Limitations

There are a number of inherent limitations with this exploratory study. Firstly, the sample size was small and perhaps does not allow any significant differences to be demonstrated. It may be that there was a failure to detect an effect which is present due to this, with the findings presented not 'real'. It could also be that the method chosen was not sensitive enough to detect perceived differences i.e. too crude. Secondly, we were unsure as to the presence of CAD in the individual patients, which although asymptomatic could have affected the results. Also, it may be that the degree of AS was not significant enough to warrant reporting of symptoms in the patient population.

The severity of AS can worsen over time so a follow-up study would be of interest, hence finally, it would have been interesting to obtain clinical follow-up for the patients, to assess the prognostic value of the KCCQ and whether this, along with other parameters, could help determine the timing of aortic valve intervention in asymptomatic patients.

7.6 Conclusions

In this pilot exploratory study of symptoms of breathlessness in patients with moderate AS, the structured data presented reports that there are no differences according to sex in degree of breathlessness or NT-pro-BNP levels. As the aortic valve gradient worsens, this does appear to correlate with the quality of life of the patient as depicted by the KCCQ score.

The findings will be discussed critically in the following chapter, however further research is necessary with sex specific analyses of biomarkers to try to unveil any biological differences in the pathophysiology of AS between women and men.

8. Discussion and Critical Analysis

8.1 Critical Comparison of the Data Sets and Analysis

The unifying aim of this thesis was to explore the differences between women and men in the clinical outcomes for both CAD and AS, for which previous data has suggested that there are significant differences in outcomes following intervention. Previous studies have reported that men do better following revascularisation for CAD (48, 49, 114, 120, 122, 128, 129) with conversely women potentially having more to gain following TAVI, despite more bleeding complications.(329-332) In this thesis, I have collated and undertaken secondary analyses of 5 individual data sets to try and address my research question in chapters 3 to 7. In this chapter, I will critically analyse the results and explain any overarching differences between the sexes in clinical outcomes for cardiovascular disease and also critically discuss any explanatory factors which potentially may account for the differences observed.

To summarise the results from each of the data sets, chapter 3 was performed to highlight the results from intervention for complex coronary anatomy, in the form of ULMCA disease, the most challenging anatomic subset as a presentation of CAD. The results were compared in individuals undergoing PCI using DES or CABG. Although there was no difference observed using a statistical analysis in the primary composite end-point of death, MI and stroke in the matched population undergoing PCI with DES or CABG, there was a benefit favouring women in all-cause mortality in those revascularised by CABG. In addition, women with complex coronary anatomy requiring intervention in this data set had better MACCE (driven by repeat revascularisation) with CABG than PCI with DES. This does suggest that if the co-morbidities are discounted, women may actually do better with surgery, which is contradictory to the prior view that a risk factor for surgery (as defined in the EuroSCORE) is female sex.(365)

Chapter 4 highlights the outcomes following PPCI for acute STEMI and despite women developing more BARC bleeding complications and vascular access site complications, shows that there is no difference between sexes in all-cause in-hospital mortality. From clinical practice I have observed, the interventional cardiologist often perceives that women are at higher risk of bleeding and may deny potent anti-platelet evidence-based therapies. Leading from this, chapter 5 does demonstrate that following a

weight-adjusted dose of unfractionated heparin, women are more likely to have a very high ACT level at 20 minutes. Although not statistically significant, this may therefore be considered to be a potential contributory factor to the higher level of BARC bleeding complications observed in chapter 4.

The diagnosis and treatment of AS are examined in chapters 6 and 7. In patients undergoing TAVI for severe symptomatic AS, the study has similar results to the prior chapters in that women have more bleeding and vascular access site complications. However, overall, the results suggest that women may actually fare better in the mid-term than men, despite these complications initially. Finally, in patients with moderate AS, there did not appear to be any differences in symptoms or NT-Pro-BNP levels according to the sex of the patient.

A number of issues were identified from the results of each of these data sets, which I will discuss in turn to assess what can be concluded about sex differences in clinical outcomes of patients with cardiovascular disease. Firstly, whilst assessing the raw data from the data sets, it is apparent that when women present with cardiovascular disease they are typically older than men at baseline in the intervention studies, which are reported in Chapters 3, 4 and 6. Moreover, in the CAD studies (Chapters 3 and 4) women have more hypertension, which is consistent with prior published data (366) and deemed to be due to the effects of sex hormones, in addition to oxidative stress and weight gain as women get older (367). As women are older with risk factors, this can explain why clinicians have an underlying preconception that women will fare less well with intervention, as both increasing age and co-morbidities are perceived by clinicians to confer an added risk due to frailty. It is known that frailty has an adverse effect on outcomes after cardiac intervention.(368, 369) and hence the clinician may feel that this group are less likely to benefit from intervention. Female sex itself does not contribute to a higher frailty score, however as women are older, there may be more of a requirement for social support alongside functional support and performance, which can be indicative of frailty.(370) This is an important strength of the current secondary analysis, as in randomised controlled trials, women are not included due to their older age being an exclusion factor. As women do present later, it is important to analyse the outcomes to ensure they are not being denied treatment and in the analyses in chapters 3, 4 and 6, due to matching of the populations, this allows for a fairer comparison than otherwise has been reported in the literature.

Interestingly, at baseline men appear to have lower left ventricular function in the datasets in chapters 3 and 6. This suggests that the left ventricle adapts differently in women and men to cardiovascular disease and fits with prior data that reports women have a different response to pressure overload in the left ventricle, developing hypertrophy compared to dilatation and subsequent dysfunction.(164) It is interesting that the knowledge that men are more likely to have left ventricular dysfunction, does not deter the clinician from intervention for CAD or indeed AS, despite impaired left ventricular function being a crucial part of the risk scoring systems for cardiac surgery.(365) Of course, the men are a younger group, with less other concomitant co-morbidities, whereby the clinicians may feel that they have to do something invasive to treat, rather than rely upon medical management alone. Often clinicians rely on personal opinion and experience rather than research evidence when making clinical judgements. Indeed, confirmation bias, whereby research is favoured that confirms pre-existing belief and other literature is disregarded, can impact upon decision-making within medicine.(371) This is especially important in the assessment of patients with AS, when both SAVR and TAVI are being considered.

It is also clear from prior studies that women do have more vascular access site and bleeding complications.(74, 75, 94, 125) The vascular access site complications are likely to be related to the smaller access vessel size in women, however, there may be a difference in underlying pathophysiology between women and men which accounts for the bleeding risk. It is evident that clinicians again use their experiential knowledge and clinical judgement, as in the previously published CAD studies, women were overall less likely to be prescribed evidence-based treatment in the form of more potent intravenous anti-platelet therapy (glycoprotein IIb / IIIa inhibitors) whilst undergoing CAD intervention, both as an elective case or acutely during PPCI for STEMI.(75)

Despite this prior evidence suggesting that women are more likely to develop bleeding complications (74, 75, 94, 125), the secondary analyses from the current data sets which matched patients to adjust for possible confounding factors, shows that women do well (Chapters 3 and 4) or better from intervention (Chapter 6), even in the presence of higher rates of bleeding. This is evident in the treatment of CAD, which contradicts prior published data in stable patients which suggested inferior outcomes (265-268) in women. However, in these previous studies, direct comparisons were made at baseline and it was noted that there were significant differences in co-morbidities which rendered women

higher risk. The analysis in Chapter 3 of this thesis reports results from patients with complex CAD and matched patients in a sample representative of the entire population undergoing PCI for ULMCA disease, unlike any of the prior studies, to allow for a fairer comparison. This is important as if these differences are taken into account, women do as well as men, which includes in the treatment of complex CAD, which has limited prior published data. Unfortunately, despite a number of large landmark studies in recent years reporting outcomes following PCI with DES for the treatment of the ULMCA (245, 246), the numbers of women recruited remained low (due to exclusion factors) and the studies were not adequately powered to assess the differences between the sexes. However, more recently, a further study has demonstrated no difference between men and women (albeit in a smaller population of 131 patients in each group) in all cause mortality or MACE.(247) This is comparable to the study results in this thesis and adds credibility and also dependability to the data, contributing to the robustness of the data. Furthermore, the present study included a large number of consecutive patients, hence, the results of chapter 3 demonstrate that PCI should be considered in women as the mode of revascularisation for complex CAD, which adds new knowledge to this field.

There has been no prior published data comparing the outcomes of both revascularisation strategies (PCI and CABG) in a cohort of women. It was an interesting finding that in the matched population, when known confounders had been taken into account, that women actually did better with CABG than PCI. Women are often deemed to be higher risk and are less likely to be put forward for surgery for complex CAD. In surgical risk scoring methods, female sex is included to add to the risk of the intervention. The standard EuroSCORE (European System for Cardiac Operative Risk Evaluation), first published in 1999,(365) is a model widely used which calculates the risk of death after cardiac surgery, taking into account 17 factors about the patient, the nature of the heart disease and the proposed surgery. Indeed, even women at a lower surgically stratified risk may be put forward for PCI due to the intuitive knowledge of the surgeons who think that women do less well, again demonstrating how this could potentially impact upon outcomes. This study therefore contributes to the knowledge in this area, with more work needed to clarify the best treatment strategy for women with complex CAD, taking into account co-morbidities.

Similar findings with regards to outcomes comparing men and women with stable CAD were reported in Chapter 4, in the setting of more acute presentations. In-hospital

outcomes in women were comparable to those of men presenting with STEMI and undergoing PPCI. This contradicts prior published data in this area (131, 278, 279) where women have had poorer outcomes. This is a difficult area to perform a randomised controlled trial as current practice guidelines state that PPCI in the setting of STEMI is gold standard (134) and therefore recommended for all patients. However, prior studies have not adjusted for baseline differences and as such the strength of the current analysis in this thesis is that the patients are matched at baseline (unlike any other study in this area), providing knowledge that women do benefit from PPCI in the setting of STEMI, despite a high incidence of bleeding complications. The limitations of this are that it was a single centre study and it may be that procedures cannot be standardised across all institutions performing PPCI, however they were 'all comers' with no exclusion criteria undergoing the procedure using contemporary devices and techniques, which is a definite strength of this data, alongside the large study size.

The experiential knowledge used by clinicians leading to the use of less potent anti-platelet agents and anti-coagulation, may however be well founded as in chapter 5, it was demonstrated that for similar dosages of weight-adjusted heparin for PCI, women did have higher ACT levels. The study sample size was determined to address the primary objective which was to assess whether the sex of the patient plays a role in the ACT measured during PCI. Although this was not demonstrated in the re-analysis of these data (chapter 5), it could be hypothesized that the elevated ACT levels in women could correlate to an increased rate of bleeding complications, though to demonstrate this would require a larger study size than we analysed. The lack of a clear difference between sexes in the current study does not impact upon the results as the study was not designed to address this. Hence, the findings of the current study do appear robust to assess the difference in ACT levels between the sexes, with the observation in concordance with a prior study in ACS patients. (310) Bleeding and vascular complications are now increasingly rare with contemporary vascular access and closure techniques, hence to accurately study such events, a larger patient sample size would be required to identify such a difference. The conclusion does however suggest that the response to anti-coagulation may be more pronounced as depicted in the ACT levels and may require dose adjustment dependent on the sex of the patient. It has been postulated that as women have lower BMI than men this contributes to the bleeding risk,(157-160) however, in the current analysis, the differences in ACT between sexes is still apparent even when allowing for a weight-adjusted dose of

anticoagulation. This is an important finding as it shows that other factors, which are dependent on the sex of the patient, do contribute to the ACT level. Awareness of this is necessary for the operator in an aim to reduce bleeding risk which is associated with poorer outcomes.(74)

The results from the analysis in Chapter 6 do concur with prior data that reports women do better with TAVI than men at medium term follow-up.(184, 194, 195, 329) However, the analysis in this thesis is the only report to match the patients at baseline from a real-world population and is the largest series of patients from dedicated TAVI databases, comparing outcomes according to sex following TAVI. This is important knowledge as women do have a significant amount to gain from undergoing TAVI when previously, due to clinician preference, the risks of intervention may have been felt to be prohibitive with women denied invasive treatment. It must be taken into account that women have a smaller aortic annulus and hence prosthesis-patient mismatch is more frequent following SAVR in women. This has been shown to be associated with increased all cause and cardiovascular mortality,(337, 338) hence this is an important consideration when considering the treatment options in women, especially the smaller women.

However, it must be noted that the current datasets in this thesis only include those patients who have actually undergone intervention for their cardiovascular disease and does not include those who have been reviewed and deemed unsuitable for a procedure, which will include both women and men. Indeed, there may be a large volume of male patients who were not considered for PCI for ULMCA disease or TAVI for severe AS, as they would have been referred for a straightforward CABG or SAVR by the investigating clinician. There is therefore an inherent bias within the studies, which is a known limitation of studies with a secondary analysis.(372) Indeed, it is unknown what happened to the individuals with both CAD and AS who did not undergo any interventional treatment and it may be that the potential benefits for women with regards to revascularisation or TAVI may be over-estimated if such results are extrapolated to the entire population. Nevertheless, it is important that when an individual is deemed to be appropriate for discussion within the multi-disciplinary team for intervention (not committing them to any approach) that the options are considered alongside the potential benefits. Chapters 3, 4 and 6 include patients who would not be included in a randomised controlled trial and hence the secondary analyses in this thesis have allowed for a comparison of outcomes

according to the sex of the patient when the intervention was felt to be necessary by the clinician and the team.

Chapter 7 assessed whether there were any differences in symptoms of shortness of breath between women and men in the presence of a diagnosis of moderate AS. This did not show any differences, despite prior studies showing that women with heart failure have more symptoms than men.(342, 343) It may be that the KCCQ questionnaire that was used was not sensitive to detect any differences, or that the degree of AS chosen was not significant enough to render the patients symptomatic. In addition, the sample size may not have allowed for any differences to be observed, which was a limitation of this study. A population with moderate AS severity was chosen, as it would have been difficult to get a cohort who had more severe AS, as typically these patients are awaiting intervention for their aortic valve and there would be safety considerations for the patient with more severe AS.

There are a number of explanatory factors which may account for the differences observed between women and men. It has clearly been documented in the literature that women have the protective effects of their hormones, with oestrogen in particular being favourable upon both the coronary arteries and the myocardium, slowing the rate of interstitial fibrosis. (84, 85, 183) This explains why women may present at an older age to their male counterparts as the process of developing heart disease has been delayed. It may also be that as the female ventricle adapts differently, (181-183) that this maintains the blood pressure at a higher level whereas the ventricle of the male patient may dilate and therefore appear impaired. It is possible that smoking may impact upon this and men were likely to be smokers. This may contribute to a more rapid progression of heart disease in men and hence presentation at a younger age than women.

It is clear from both prior literature (130, 137-140) and the current secondary analyses in chapters 4 and 6 that women do bleed more and again this may be contributed to by the underlying hormonal differences between the sexes. In addition, the older age of women may contribute to this with a different percentage of body fat allowing for absorption. Moreover, the current analysis in chapter 3 does show that the coronary artery vessel size is smaller in women, who required smaller stents. Similarly, the arteries used for vascular access (both radial and femoral) are also smaller.(373-375) Despite advancements in technology and vascular access approaches, when manipulating the larger pieces of kit which are required for complex percutaneous cardiac interventions, and

indeed TAVI, in the smaller arteries of women, damage can occur which may result in more vascular access and bleeding complications.

With regards to the idea that women do as well as men in the matched data sets, this may be due to the fact that women do have a longer life expectancy than men. (376) Therefore, it may be that the men developed other conditions which were causal in their death, rather than the intervention performed. This means that women may have more to gain from intervention if this is successful, as they have more years to live, hence it is important in studies to consider the cause of death and differentiate between cardiac and non-cardiac when reporting outcomes.

Therefore, in providing a critical analysis of the data sets, it is apparent from these current studies that there are differences in clinical outcomes between men and women which may impact upon the decision-making process for clinicians. The data does differ as discussed above from some prior studies in the narrative literature review where women did not do as well as their male counterparts. However, it is important to emphasise that the results reported in this thesis used real world data and populations who were matched at baseline. There are benefits from using real world data in this manner, which reflects valuable information about the safety and effectiveness of a treatment in a large heterogeneous population without the strict inclusion and exclusion criteria of a randomised controlled trial. Indeed observational studies can address important clinical questions that randomised controlled trials cannot address and potentially accelerate the expansion of approved therapies to more wide spread groups.(377) Moreover, the data sets from chapters 3, 4 and 6 included large numbers of patients and contained data suitable for such a secondary analysis, hence examining data that hasn't been looked at in previous studies allows us to reach new conclusions.

Using each of the data sets in a constructivist manner and generalising the results in this way leads to a justified belief that differences do exist and hence have addressed some gaps in our understanding and contribute to new robust and generalisable knowledge in this area. Specifically:

1) Women do as well as men when undergoing PCI or CABG for complex ULMCA disease;
2) Women appear to do better with CABG than PCI for complex ULMCA disease;
3) Women do as well as men when undergoing PPCI for STEMI in the contemporary era;

4) Women fare better than men when undergoing TAVI for severe AS;
5) Women respond differently to weight-adjusted heparin, and
6) Women have more bleeding and vascular complications than men.

8.2 Critical Analysis of the Trustworthiness / Robustness of the Analysis

It is essential that I am able to defend my own critical analysis and ensure that this can be accepted amongst the field as trustworthy and contribute to the literature. The methods I am going to use to describe this are in alignment with the descriptors by Lincoln and Guba (225) and the following section will describe each of the components of this.

8.2.1 Credibility

The first area which is necessary to demonstrate that there should be confidence in the validity of the findings, is to interrogate the credibility of the research. My research comprises a number of data sets, each of which were collected and analysed separately, with the results then incorporated together to explain the new findings which are apparent. The data sets in chapters 3, 4 and 6 were large with consecutive patients included from the treated real-world populations, which was a strength of the thesis. The statistical analyses are described within each of the chapters and those used are valid to allow for comparison across groups. (250, 251) The consistency of the findings across the data sets allows us to conclude that women do as well as men with CAD following intervention, but also there is a higher rate of bleeding within these samples. Multiple data sets revealing the same results facilitate a deeper understanding and contribute to the credibility of the research.

A further method to assess the credibility of the research is that of peer debriefing.(225) Throughout the period of my thesis, I had regular meetings with my thesis advisory panel, which consisted of my supervisor, a professor of non-invasive cardiology and a professor of gender studies. Each of these individuals had their own beliefs with regards to cardiovascular intervention and underlying ideas of the likely benefit of each of these, which were not always favourable. During these meetings, I was regularly challenged with analytical probing which did help me overcome any internal biases that I may have had when approaching the analyses. Alongside peer debriefing, I had regular

peer scrutiny of each aspect of the project by physicians who work in the field and had been involved in different data sets. Also, manuscripts from this thesis were submitted for peer review to established medical journals and were accepted for publication, which helps with demonstrating the credibility of the overall findings.

8.2.2 Transferability

The domain of transferability is important to explain that the findings of the research can be applied to a wider population, rather than just the population upon which my research was based, hence a form of external validity. The main technique I used in my study to ensure transferability was that of thick description (225, 378) and this was done in each individual data set by explaining in significant detail the methods used to obtain the data set, perform and report the statistical analysis. It should therefore be possible for the reader to begin to form their own conclusions regarding whether the analysis techniques used can be extrapolated to other groups.

8.2.3 Dependability

Dependability means that if work is repeated again in a similar setting in the same way, then the same results would occur. This therefore is a strong component of the trustworthiness of research as if results are to be extrapolated to other patient groups then this is an essential requirement.

Inquiry audit is the method for which I aimed to show the dependability of my thesis to the reader.(379) I used an independent colleague, who has a strong background in research to reanalyse the data in each of the data sets and evaluate my interpretations and conclusions and whether these fitted the results of the data analyses. This is similar to peer scrutiny, which I utilised throughout the duration of my thesis to ensure that my findings were robust.

8.2.4 Reflexivity

Demonstrating confirmability or reflexivity in the setting of qualitative research is essential, as it may be believed there are underlying biases from myself as the researcher

which may impact upon the way the results have been reported in the thesis. It is important to show the conclusions are due to the data obtained and not due to my own opinions and preferences.(225, 380) One of the first techniques that was used in my research is that there is an audit trail from the outset of the thesis to the conclusion. This includes collection of all the raw data, including that when performed in other centres, alongside any explanatory notes from these. My own personal notes have been taken into account and also instrumental developmental information is available, for example, pilot data capture forms and consent forms.

In addition, methods triangulation, as described when referring to credibility does demonstrate confirmability, as multiple data sets within my thesis do report similar findings. My own background as the researcher may be believed by the reader to affect the framing of the conclusions drawn and therefore this is important to show that the findings are appropriate. I have shown this by performing research which has included multiple investigators. For example, both chapter 3 and chapter 6 are multi centre studies which used a number of different individuals to collect the data prior to my analysis. In continuing to have dialogue with these investigators, I had my ideas challenged and strengthened. Chapter 7 involved a more questionnaire based analysis and this again was done on 2 separate sites by different investigators, hence not relying on myself only as the one to interact with the patients and potentially causing bias. I aimed to minimise bias at the analysis stage by including all variables across each of the data sets to ensure the results were the most valid. I have also throughout the thesis discussed my own underlying beliefs in this area that may have come into play during the research process and been open about these.

Through the above techniques I have described, I have demonstrated a strong base that the conclusions drawn from my research are trustworthy and robust and can therefore be reliably considered to be new knowledge to help change opinions and strategies in the treatment of women (and men) with acquired cardiovascular disease in the future. In my final chapter, I will discuss the implications of my research for clinical practice and ideas for future research within this area.

9. Implications for Practice and Future Research

The initial research question developed for this thesis was 'Do outcomes differ between women and men in the treatment of cardiovascular disease?' Prior data have reported that women with CAD have worse outcomes following revascularisation (48, 49, 114, 120, 122, 128, 129) although fare better than men when undergoing TAVI for severe AS, despite more bleeding complications.(329-332)

As described in chapter 8, the use of a number of datasets for this thesis has resulted in new generalisable knowledge, which contributes to this important field within the treatment of cardiovascular disease. Importantly, women do have similar outcomes to men when undergoing PCI or CABG for complex CAD; indeed women do better with CABG than PCI for complex CAD. Women also have similar outcomes when undergoing PPCI for STEMI in the contemporary era. In addition, the current data confirms prior publications that women do better than men following TAVI at medium term follow-up. The current data also shows that women do have more bleeding and vascular complications than men and respond differently to weight-adjusted heparin during PCI. In this chapter, I will discuss how the findings may impact upon clinical practice for the treatment of both women and men with cardiovascular disease in the future and also discuss how some of the new knowledge gained in the generation of this thesis can be used to generate ideas for future research within this field.

The present studies demonstrate that women can fare as well as men with complex CAD, despite the presence of more bleeding and vascular complications. This is important for individual clinicians to be aware of and take this into account when considering the best treatment options for women following a multi-disciplinary team discussion. Indeed, in clinical practice, women may be discussed at multi-disciplinary meetings and determined not for CABG despite having a high-risk pattern of disease. Part of the initial research question of this thesis asked: 'is the intuitive knowledge of clinicians leading to a discrepancy in approach justified or appropriate?' In the area of complex CAD, clinicians can discount individuals from appropriate evidence-based treatments on the grounds of perceived higher risk or frailty. The results presented in chapter 3 of this thesis suggest therefore that the intuitive knowledge may not be the best approach for the patient and this needs to be further quantified in larger future studies. In order to 'challenge' individual

clinicians, further research and education is required to allow them to develop 'new' experiential knowledge that women can do well and have benefit from such intervention.

In a similar fashion, women with severe AS may not even be considered for intervention at all, as the intuitive knowledge of clinicians can be that women fare badly, due to advanced age and co-morbidities. Chapter 6 reports in a large data set of the entire population of individuals undergoing TAVI that women may do better with this and this is in concordance with prior studies.(329-332) It is again important that individual clinicians are aware that women may actually do better than men with TAVI, moving away from the intuitive knowledge, and ensure the multi-disciplinary team discussions are thorough to determine the treatment choice in the best interests of the patient in the longer term.

The studies did demonstrate an increased incidence of vascular complications and bleeding in women. From an individual interventional cardiologists' viewpoint, with regards to vascular access and bleeding complications, the operator needs to be scrupulous in vascular access management and ensure safe punctures and the management following sheath removal to try to minimise the occurrence of such events. This should of course be essential in all patients, but a greater awareness by the treating team can help reduce the likelihood of any issues developing or bring them to the attention of the operator as soon as is possible.

In addition to demonstrating new knowledge to help the clinicians in decision making in high risk patients with cardiovascular disease, the exploratory nature of some of the datasets do raise further questions which do require investigation to help further contribute to knowledge in the treatment and outcomes following intervention for cardiovascular disease. The findings of chapter 5, which show that women have a higher ACT following weight-adjusted heparin during PCI, are not conclusive but do suggest that women may require a different dosage regimen of heparin compared to men. Not enough is known about the impact of body fat on outcomes to draw firm conclusions, so more research is needed using a much larger sample to include an assessment of the body fat composition of the individual prior to the procedure.

The present analysis of the clinical implications is also limited as the sample size did not allow for the assessment in any differences between the sexes in the occurrence of vascular complications, as these are now inherently uncommon in contemporary PCI. Therefore, in future research it would also be important to repeat this with a larger cohort of patients to assess whether the ACT level did impact upon the presence of vascular

complications, which did not become statistically apparent in this thesis due to the low event rate within this study. Understanding this problem more clearly will allow the optimum use of anti-coagulation during interventional procedures to ensure safety from bleeding and vascular complications, whilst ensuring that no ischaemic complications develop. Following on from these proposed areas of study, it may be possible to determine a dosing regimen for women as compared with men and this could then be investigated to assess for the safety of bleeding and vascular complications and ensure this does not result in an increase in ischaemic complications for the patient.

Another exploratory study was Chapter 7, with regards to patients with AS under surveillance. This did not demonstrate any differences between the sexes in the symptoms of shortness of breath nor in NT-pro-BNP levels. The current dataset did not allow for following the patient up over time, serial echocardiography or the inclusion of more sex specific biomarkers or alternative blood tests, including Troponin T, C Reactive Protein and mean cell volume. Hence it would be important in the consideration of future studies to repeat with follow-up and include these other blood tests, to try to assess underlying biological differences and means to predict the timing of deterioration in patients with AS and potential optimal timing of intervention for the often elderly patients.

A main consideration throughout this work are the inherent differences between women and men, with regards to the influences of hormones and underlying pathophysiology. A huge step in research in this field would be to include sex specific information in large scale studies, for example, the age at menarche, the age at menopause, prior pregnancies, pre-term delivery, gestational diabetes mellitus, gestational hypertension, pre-eclampsia, eclampsia, use of hormone replacement therapy, etc. These sex-specific factors are emerging as important predictors of future cardiovascular risk (381) and hence essential to be aware of to enable awareness and modifications to the lifestyles of women deemed to be at risk, to prevent the development of problems in the future. Such information have already been reported in the WIN TAVI study (202), which did demonstrate that a history of pregnancy was an independent predictor of the Valve Academic Research Consortium 2 (382) early safety endpoint at 30 days.(202) Interestingly however this did not convert to any differences at one year follow-up.(383)

Nevertheless, this information needs to be included in further trials, including large-scale CAD trials and also in younger patients. Furthermore, sex specific results from ongoing studies can be reported to endeavour to show either sex related differences or

show that treatments are an option for women. Such sex-specific variables are essential to understand associations with cardiovascular disease progression and outcomes as well as to minimise any disparities in treatment between the sexes.

Another important piece of information to gather would be the outcomes of those deemed not for inclusion or intervention, for example, patients with significant ULMCA disease deemed unsuitable for any intervention or those with AS who have been discussed and decided inoperable. Formal risk scoring mechanisms that are available need to be utilised for such studies and indeed there may be scope to have 'new' scoring systems in certain areas, taking into account the sex of the patient (not necessarily negative upon women as currently is the case in surgical scoring systems).(365)

In addition, due to the questions that have been raised with regards to the likely benefit of TAVI over SAVR in women with AS (as a consequence of less prosthesis-patient mismatch), there is a need for a large adequately powered randomised trial to assess this in women. Such a study should be undertaken not only those deemed high-risk, but also those who are intermediate or lower risk. Male participants have typically been the mainstay of subjects in randomised controlled trials, for reasons as discussed in the introductory chapter, hence further research is required to address this important issue in a large cohort of patients, addressing the inequality and promoting large scale research in women.

In conclusion, the thesis does demonstrate inherent differences between the sexes in both CAD and AS and more work needs to be done to try to give each sex the best and most effective treatment option available. This requires individuals who are involved in research within interventional cardiology (many of whom are themselves male) to understand that there are disparities and be committed to addressing these issues. Women may well have been under-diagnosed and under-treated previously, but with education and increasing awareness, this group of patients may well benefit from more tailored individual therapies in the future.

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Appendices

Appendix 1. W-DELTA Publication American Journal of Cardiology

Comparison of Percutaneous Coronary Intervention (With Drug-Eluting Stents) Versus Coronary Artery Bypass Grafting in Women With Severe Narrowing of the Left Main Coronary Artery (from the Women—Drug-Eluting stent for LefT main coronary Artery disease Registry)

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Women typically present with coronary artery disease later than men with more unfavorable clinical and anatomic characteristics. It is unknown whether differences exist in women undergoing treatment for unprotected left main coronary artery (ULMCA) disease. Our aim was to evaluate long-term clinical outcomes in women treated with percutaneous coronary intervention (PCI) with drug-eluting stents versus coronary artery bypass grafting (CABG). All consecutive women from the Drug-Eluting stent for LefT main coronary Artery disease registry with ULMCA disease were analyzed. A propensity matching was performed to adjust for baseline differences. In total, 817 women were included: 489 (59.8%) underwent treatment with PCI with drug-eluting stents versus 328 (40.2%) with CABG. Propensity score matching identified 175 matched pairs, and at long-term follow-up there were no differences in all-cause (odds ratio [OR] 0.722, 95% confidence interval [CI] 0.357 to 1.461, p = 0.365) or cardiovascular (OR 1.100, 95% CI 0.455 to 2.660, p = 0.832) mortality, myocardial infarction (MI; OR 0.362, 95% CI 0.094 to 1.388, p = 0.138), or cerebrovascular accident (CVA; OR 1.200, 95% CI 0.359 to 4.007, p = 0.767) resulting in no difference in the primary study objective of death, MI, or CVA (OR 0.711, 95% CI 0.387 to 1.308, p = 0.273). However, there was an advantage of CABG in major adverse cardiovascular and cerebrovascular events (OR 0.429, 95% CI 0.254 to 0.723, p = 0.001), driven exclusively by target vessel revascularization (OR 0.185, 95% CI 0.079 to 0.432, p <0.001). In women with significant ULMCA disease, no difference was observed after PCI or CABG in death, MI, and CVA at long-term follow-up. **(Am J Cardiol 2014;113:1348—1355)**

Only a few reports have evaluated optimal revascularization strategies in women with coronary artery disease,[1,2] who typically present later than men with potentially more co-morbidities and unfavorable angiographic characteristics. Data are even more limited on outcomes of percutaneous coronary intervention (PCI) versus coronary artery bypass grafting (CABG) in women with complex coronary anatomy, including unprotected left main coronary artery (ULMCA)

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See page 1354 for disclosure information.

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Table 1
Baseline clinical characteristics in the overall population

Variable	PCI (n = 489)	CABG (n = 328)	p Value
Age (yrs)	67.4 ± 12.6	67.9 ± 11.6	0.562
Hypertension	359 (73.4)	240 (72.9)	0.111
Hypercholesterolemia	323 (66.1)	232 (70.5)	0.680
Smoker	122 (24.9)	55 (16.7)	0.041
Diabetes mellitus	161 (32.9)	101 (30.7)	0.504
Chronic kidney disease	28 (5.7)	9 (2.7)	0.044
Unstable angina pectoris	160 (32.7)	163 (49.5)	<0.001
Non–ST elevation myocardial infarction	66 (13.5)	34 (10.4)	0.181
ST elevation myocardial infarction	10 (2.0)	2 (0.6)	0.094
Previous CABG	51 (10.4)	13 (4.0)	0.001
Previous PCI	123 (25.2)	48 (14.6)	<0.001
Left ventricular ejection fraction	54.8 ± 12.2	54.5 ± 11.0	0.731
EuroSCORE	5.6 ± 4.0	5.4 ± 2.6	0.395

Results are expressed as n (%) or mean ± SD as appropriate.
Hypertension is defined as a sustained systolic pressure of >140 mm Hg or a diastolic pressure of >90 mm Hg, requiring antihypertensive therapy. Hypercholesterolemia is defined as total cholesterol >240 mg/dl, requiring lipid-lowering treatment.
EuroSCORE = European System for Cardiac Operative Risk Evaluation.

disease.[1,2] In general, women are largely underrepresented in randomized clinical trials; specifically, in the Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial, in the ULMCA subgroup, women made up 10.3% of the overall population.[3] Registries are hence the ideal setting to appraise the comparative effectiveness of different procedures in patients who are not adequately represented in randomized clinical trials. The aim of the present study was to evaluate if women had improved long-term clinical outcomes after ULMCA revascularization using PCI with drug-eluting stents (DES) compared with CABG, from the large Drug-Eluting stent for LefT main coronary Artery disease (DELTA) registry.

Methods

The DELTA registry included consecutive "all comers" with ULMCA disease treated in 14 multinational centers, by either PCI with DES or CABG, from April 2002 to April 2006.[4] The W-DELTA is a subset analysis focusing on women from the DELTA registry.

Patients enrolled in the registry were evaluated by a multidisciplinary team including interventional cardiologists and cardiothoracic surgeons, and the choice of technique was deemed suitable to ensure complete revascularization. The decision was based on (1) the hemodynamic state, (2) lesion characteristics, (3) vessel size, (4) co-morbidities, (5) quality of arterial and/or venous conduits for grafting, and (6) patient and/or referring physician preference. Coronary angioplasty and stent implantation, including bifurcation strategy in the case of distal disease, were performed according to the operator's preference with the aim of complete coverage of the diseased segment.

The use of dual antiplatelet therapy was recommended for at least 12 months in all patients undergoing PCI, consisting of aspirin 100 mg/day and clopidogrel 75 mg/day or ticlopidine 250 mg twice daily. Aspirin 100 mg/day was continued indefinitely thereafter. In the Korean center, cilostazol was additionally prescribed. Information regarding compliance was obtained in all patients. Angiographic follow-up was not mandatory unless there were clinical symptoms or subjective evidence of ischemia on functional testing.

All data relating to hospital admission, procedures, and follow-up were collected and adjudicated in each center according to local policy. Full written informed consent was obtained for the procedure and for subsequent data collection.

The events analyzed during hospital stay and at clinical follow-up were death, both all-cause and cardiovascular, myocardial infarction (MI), cerebrovascular accident (CVA), target lesion revascularization (TLR), and target vessel revascularization (TVR). Major adverse cardiovascular and cerebrovascular event (MACCE) was defined as a composite of death, MI, CVA, and TVR.[4] The primary study objective was the composite of death, MI, and CVA at long-term follow-up (1,185 days). The secondary study objectives were MACCE and each of the individual components of death, CVA, MI, and TVR at long-term follow-up.

Continuous variables are expressed as mean ± SD and were analyzed with the Student *t* test or Wilcoxon rank sum test depending on the variable distribution. Categorical variables were compared with the chi-square test with Yates' correction for continuity or Fisher's exact test, as appropriate.

Because of the nonrandomized nature of the study, to reduce the effect of treatment selection bias and potential confounding in this observational study, we performed rigorous adjustment for significant differences in the baseline characteristics of patients with propensity score matching. A propensity score was calculated by performing a parsimonious multivariate logistic regression using the following covariants: age, family history, hypertension, hypercholesterolemia, smoker, diabetes mellitus, unstable angina, left ventricular ejection fraction, chronic kidney disease, previous PCI, previous CABG, multivessel disease, right coronary artery disease, and distal disease. The C-statistic for the propensity score model was 0.77,

Table 2
Baseline lesion and procedural characteristics of the overall population

Variable	PCI (n = 489)	CABG (n = 328)	p Value
Multivessel coronary disease	381 (77.9)	310 (94.2)	<0.001
Right coronary artery disease	150 (30.9)	231 (73.1)	<0.001
Left system coronary artery disease	314 (64.2)	305 (93.0)	<0.001
SYNTAX score	26.8 ± 13.0	37.1 ± 12.8	<0.001
Distal location	280 (57.6)	185 (58.5)	0.794
Predilatation	230 (47.0)		
Atherectomy	5 (1.0)		
Rotablator	9 (1.8)		
Cutting balloon	29 (5.9)		
Intra-aortic balloon pump	31 (8.4)	10 (14.3)	0.117
Intravascular ultrasound	207 (42.3)		
Intravascular ultrasound guided	47 (9.6)		
Intravascular ultrasound controlled	160 (32.7)		
Mean stent diameter	3.34 ± 0.341		
Mean stent length	20.40 ± 15.5		
2-Stent technique	168 (34.4)		
Crush	66 (13.5)		
Mini crush	17 (3.5)		
Culotte	13 (2.7)		
T stenting	28 (5.7)		
V stenting	22 (4.5)		
Other	22 (4.5)		
Postdilatation	236 (48.3)		
Maximum diameter	3.69 ± 0.53		
Maximum pressure	15.43 ± 3.86		
Final kissing balloon inflation	202 (41.3)		
Abciximab	60 (12.3)		
Eptifibatide	11 (2.2)		
Tirofiban	39 (8.0)		
Bivalirudin	27 (5.5)		
Vessels treated	1.51 ± 0.871	2.30 ± 0.86	<0.001
Lesions treated	1.81 ± 1.29		
CABG beating heart		18 (5.5)	
Mean arterial grafts		1.97 ± 1.06	
Mean venous grafts		1.82 ± 1.23	
Complete revascularization		276 (94.8)	
Unintentional incomplete		1 (0.5)	
Mean hospital stay	4.1 ± 4.0	14.5 ± 9.4	<0.001

Results are expressed as n (%) or mean ± SD as appropriate.

confirming good discrimination, and the Hosmer-Lemeshow goodness of fit was 0.36, confirming good calibration. To identify matched pairs, we used the following algorithm: 1:1 optimal match with a ±0.03 caliper and no replacement. Clinical outcomes in the matched population were analyzed with Cox proportional hazards regression stratified on matched pairs. Results are reported as odds ratio (OR) with 95% confidence intervals (CI). Survival rate was recorded by Kaplan-Meier analysis and the log-rank method was used for comparison. The p for interaction between gender and revascularization modality assessed by chi-square analysis was p <0.001.

Statistical analysis was performed with Statistical Package for the Social Sciences, version 18.0 (SPSS Inc., Chicago, Illinois). A p value of <0.05 was considered statistically significant. The investigators had full access to and take full responsibility for the integrity of the data. All investigators have read and agree to the manuscript as written.

Results

In total, 817 women were included in the W-DELTA registry, of which 489 (59.8%) underwent treatment with PCI with DES and 328 (40.2%) with CABG. The baseline clinical characteristics are illustrated in Table 1 and baseline lesion and procedural characteristics in Table 2.

During hospitalization, all-cause mortality in PCI versus CABG occurred in 4.1% versus 2.7% patients and cardiovascular mortality in 3.5% versus 1.8% patients, respectively. Periprocedural MI (as defined by elevation of serum creatine kinase-myocardial band exceeding 5 times the upper reference limit) was observed in 5.9% versus 18.2% patients and CVA in 0.6% versus 1.5% patients. Overall in-hospital MACCE was 9.6% versus 22.5%. Of note, there were 4 episodes (0.8%) of in-hospital TVR in the PCI group and none in the CABG group. In those patients with distal disease treated with PCI, 55.4% underwent a single-stent strategy. The in-hospital MACCE was 9.0% in patients treated with a single-stent strategy versus 13.0% in those who underwent implantation of 2 stents.

Clinical follow-up was obtained at a median of 1,185 days (interquartile range [IQR] 628 to 1,548) in 98.8% of patients in the PCI group and 99.1% in the CABG group. With regard to all-cause mortality, this was 14.1% versus 7.0%, and cardiovascular mortality was 7.0% versus 4.6% in the PCI versus CABG group, respectively. Elective PCI mortality rate was 11.9% versus 20.2% for urgent PCI cases. With regard to MI, such an event was reported in 4.3% versus 1.5%, with TLR 10.2% versus 3.8%, and TVR rates 15.1% versus 5.1%. MACCE was adjudicated at 30.5% versus 15.7% at long-term follow-up. In patients with distal disease treated with a single-stent strategy, the long-term MACCE was 28.4% versus 35.2% in those requiring 2 stents. Figure 1 illustrates survival curves. Furthermore, definite stent thrombosis (ST) occurred in 6 of the women (1.2%) treated with PCI: 2 subacutely and 4 late. Probable ST was adjudicated in 4 (0.8%) and possible in 3 patients (0.6%).

After propensity score matching, there were 175 matched pairs of patients in both treatment groups. The baseline characteristics of the matched groups are listed in Table 3.

For the 175 matched pairs during hospitalization, there were no significant differences between PCI and CABG in the risk of all-cause mortality (OR 1.333, 95% CI 0.294 to 6.046, p = 0.709) or cardiovascular mortality (OR 0.994, 95% CI 0.198 to 4.995, p = 0.994). Higher occurrence of MI (OR 2.145, 95% CI 1.036 to 4.439, p = 0.040) and hence MACCE (OR 2.000, 95% CI 1.030 to 3.883, p = 0.041) were sustained in the CABG group. However, there was no longer a difference in the incidence of CVA (OR 2.723, 95% CI 0.280 to 26.444, p = 0.388).

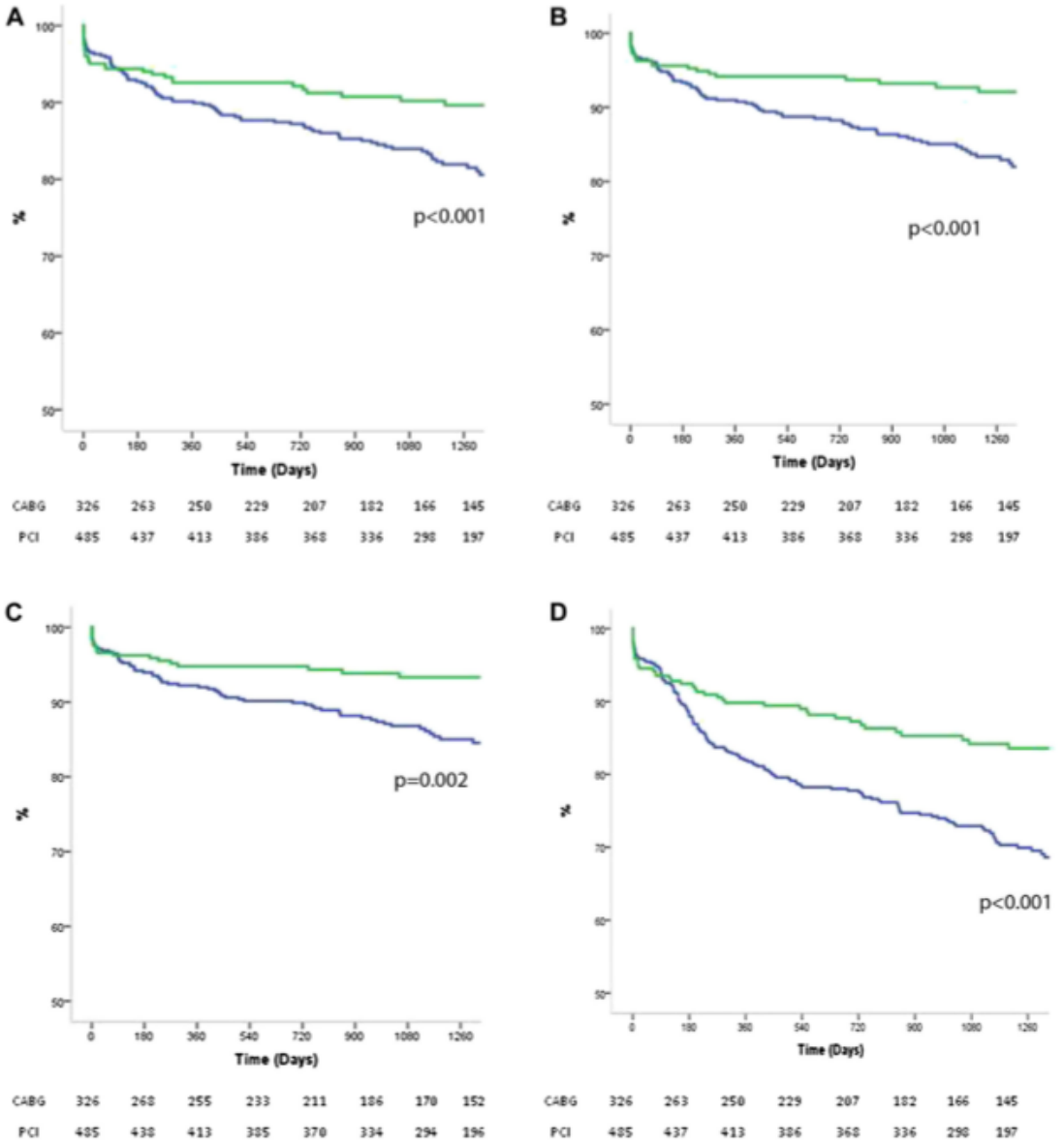

Figure 1. Freedom from cardiac and cerebrovascular events in PCI versus CABG in the overall population. Freedom from death, MI, and CVAs *(A)*; from death and MI *(B)*; from death *(C)*; and from MACCEs *(D)* after PCI *(blue line)* versus CABG *(green line)* in the overall population. Patients at risk at different times are reported below each graph.

At 1,148 days (IQR 545 to 1,543) follow-up, there was no difference between groups in the primary study objective of death, MI, or CVA (OR 0.711, 95% CI 0.387 to 1.308, p = 0.273). Additionally, there were no differences between groups in all-cause (OR 0.722, 95% CI 0.357 to 1.461, p = 0.365) or cardiovascular mortality (OR 1.100, 95% CI 0.455 to 2.660, p = 0.832). Moreover, there were no differences between groups in MI (OR 0.362, 95% CI 0.094 to 1.388, p = 0.138) or CVA (OR 1.200, 95% CI 0.359 to 4.007, p = 0.767). However, there was an advantage of CABG over PCI in the events of TLR (OR 0.253, 95% CI 0.092 to 0.703, p = 0.008)

Table 3
Baseline characteristics in the propensity-matched population

Variable	PCI (n = 175)	CABG (n = 175)	p Value
Age (yrs)	67.1 ± 12.0	67.5 ± 10.3	0.736
Hypertension	120 (68.6)	125 (71.0)	0.617
Hypercholesterolemia	117 (66.9)	127 (72.2)	0.281
Smoker	34 (19.4)	33 (18.8)	0.872
Diabetes mellitus	50 (28.6)	55 (31.3)	0.584
Chronic kidney disease	9 (5.1)	5 (2.8)	0.271
Unstable angina pectoris	72 (41.1)	75 (42.6)	0.780
Previous PCI	35 (20.0)	31 (17.6)	0.567
Left ventricular ejection fraction	55.2 ± 11.9	54.3 ± 11.0	0.445
EuroSCORE	5.1 ± 2.5	5.6 ± 4.2	0.270
Multivessel disease	160 (91.4)	162 (92.0)	0.834
Right coronary artery disease	104 (59.1)	104 (59.1)	1.000
Distal location	92 (52.6)	101 (57.4)	0.365
Intra-aortic balloon pump	13 (8.8)	2 (5.9)	0.579
SYNTAX score	26.6 ± 11.1	34.0 ± 13.5	<0.001

Results are expressed as n (%) or mean ± SD as appropriate.
EuroSCORE = European System for Cardiac Operative Risk Evaluation.

and TVR (OR 0.185, 95% CI 0.079 to 0.432, p <0.001), corresponding to an advantage in MACCE (OR 0.429, 95% CI 0.254 to 0.723, p = 0.001). Within the PCI group, there was no difference in the occurrence of MACCE depending on whether triple antiplatelet therapy was used (triple therapy 21.2% vs dual therapy 31.7%, p = 0.235). Figure 2 demonstrates survival curves in the matched population.

Discussion

The main findings of the W-DELTA registry are that at 1,148 days (IQR 545 to 1,543) clinical follow-up, (1) no difference in the primary study objective of death, MI, and CVA between PCI and CABG was observed in women with ULMCA disease; (2) similarly, there were no differences in the occurrence of all-cause or cardiovascular mortality, MI, or CVA; and (3) conversely, there was an advantage of CABG over PCI in MACCE, exclusively driven by the need for repeat revascularization.

There are growing data demonstrating a marked improvement in clinical outcomes after PCI of the ULMCA, in concordance with the advent of DES.[3,5–9] Indeed, several nonrandomized observational registries and a number of randomized trials have shown no significant differences in MACCE between CABG and PCI in patients with ULMCA disease up to a follow-up period of 5 years.[9–18] However, because of the relative underrepresentation of women in coronary artery trials, it is unclear whether these findings can be generalized to the female population, who, because of the later age of presentation, may pose more of a risk. Notably, in the SYNTAX trial, women made up only 22.3% in total and, specifically, women with ULMCA represented just 10.3% of the overall population.[3] Furthermore, women undergoing coronary revascularization with PCI or CABG have historically been shown to have worse outcomes compared with men.[19–25]

Despite a few reports examining which of the revascularization techniques is associated with a greater benefit in women, limited data are available on the outcomes of PCI versus CABG in women with more complex disease. To the best of our knowledge, no study has specifically evaluated women undergoing PCI versus CABG for ULMCA disease. The DELTA registry is a multicenter multinational registry of 2,775 patients, of which 817 (29.5%) were women, enabling a comparison of outcomes between revascularization strategies. The objective of this substudy (W-DELTA) therefore was to assess whether women had improved long-term outcomes with PCI in comparison with CABG.

Because of the nonrandomized nature of our study, a propensity score matching was performed to adjust for significant differences in baseline clinical characteristics. During hospital admission there was a greater incidence of MI and subsequently MACCE in the CABG group. This is a consequence of the elevation of serum creatine kinase-myocardial band observed after CABG rather than symptomatic presentation of acute MI. At a median of 1,148 days (IQR 545 to 1,543), in the unadjusted and adjusted analysis in the propensity matched groups there was no significant difference between treatment method in the primary study objective of death, MI, or CVA. This is consistent with that of the propensity matching of the entire population of the DELTA registry (hazard ratio 0.99, 95% CI 0.73 to 1.33, p = 0.97).[4] Of note, the p for interaction between gender and revascularization method was p <0.001.

Additionally, there were no differences in each of the individual components of the primary study objective. These results were similar to those reported in a ULMCA subanalysis of the SYNTAX study comparing CABG with PCI at 3 years.[26] When the women only from the ULMCA substudy of SYNTAX were compared (CABG n = 85 and PCI n = 100), there was no difference in the primary study end point of MACCE (CABG 21.3% vs PCI 26.3%, p = 0.47). Furthermore, there were no differences in all-cause mortality (6.3% vs 8.1%, p = 0.64), MI (2.5% vs 6.2%, p = 0.25) or CVA (6.4% vs 2.1%, p = 0.14) at 3 years (presented at the American College of Cardiology Scientific Sessions 2009, Orlando, Florida). However, that analysis was limited by the small sample size of the subgroup analyzed, which inflates the risk of a false-negative result.

Conversely, there was an advantage with CABG in the occurrence of MACCE, driven exclusively by the need for repeat revascularization. It is important to take into account that in the DELTA registry mostly first-generation DESs were implanted. It has been reported in a pooled analysis of the "Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Subjects With de Novo Native Coronary Artery Lesions" II and III studies at 2 years[27] that everolimus-eluting stents are superior in women to first-generation paclitaxel-eluting stents, with regard to MACE (8.5% vs 16.4%, p = 0.02), not specifically in a ULMCA population. In addition, we cannot exclude that the low (9.6%)

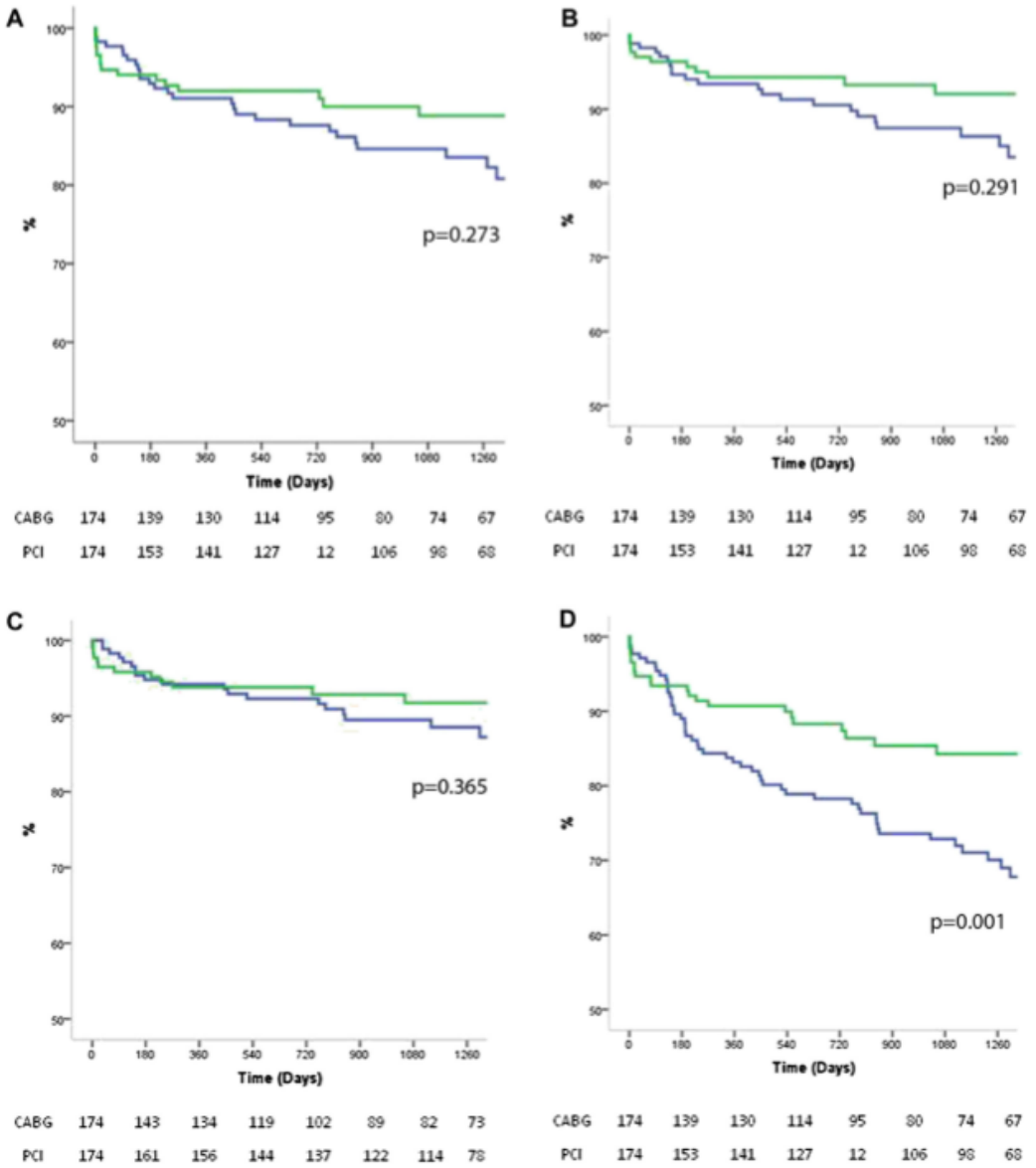

Figure 2. Freedom from cardiac and cerebrovascular events in PCI versus CABG in the propensity score–matched groups. Freedom from cardiac death, MI, and CVAs *(A)*; from death and MI *(B)*; from death *(C)*; and from MACCEs *(D)* after PCI *(blue line)* versus CABG *(green line)* in the propensity score–matched groups. Patients at risk at different times are reported below each graph.

use of intravascular ultrasound in our study population and the routine use of angiographic follow-up in the PCI group in the DELTA registry may have led to more angiographically driven revascularization. However, despite other studies reporting female gender as an independent predictor of restenosis,[27,28] this substudy of DELTA women had similar TLR rates (10.3%) to that of the overall DELTA population.[4] It must be noted that,

concurrently, there have been developments in surgical technique with the advent of minimally invasive approaches and off-pump CABG, which may also lead to improved outcomes in this patient group.

However, clinical trials with a larger representation of women and dedicated questions for gender-based issues are warranted to better understand the treatment for this patient population. Because women present later with more complexities, a better understanding of gender-specific outcomes would potentially allow individualized revascularization strategies to be developed for the large and growing population of women with coronary artery disease.

The main limitation of this study is the nonrandomized observational design. A propensity score matching was performed to adjust for the differences at baseline. In addition, a large proportion of patients underwent PCI with first-generation DES and treatment with first-generation thienopyridines. Information on menopausal state was not collected or available in a minor proportion of patients. Finally, the length of follow-up does not allow us to draw firm conclusions regarding the durability of each revascularization option in women.

Disclosures

Dr. Mehran is a consultant to Abbott (Abbott Park, Illinois), The Medicines Company (Parsippany, New Jersey), Janssen (Titusville, New Jersey), and Regado (Durham, North Carolina) and has received research grant support from BMS/Sanofi (Bridgewater, New Jersey), The Medicines Company, and Lilly/Daiichi Sankyo (Chuo-ko, Tokyo, Japan). Dr. Makkar is a consultant to Medtronic (Minneapolis, Minnesota) and Abiomed (Danvers, Massachusetts), has received speaker's fees from Eli Lilly and Medtronic, and has received equity from Entourage Medical Technologies (Menlo Park, California). Dr. Naber is a speaker for Abbott, Cordis (East Bridgewater, New Jersey), Biotronik (Lake Oswego, Oregon), Biosensors (Singapore), Medtronic, Stentys (Princeton, New Jersey), Daiichi Sankyo, and The Medicines Company, has received research support from Abbott, Biotronik, Sadra Medical (Campbell, California), Stentys, and Icon (Dublin, Ireland), and is on the advisory board of Biotronik and Abbott. Dr. Capodanno has received speaker's honoraria from Eli Lilly and AstraZeneca (Wilmington, Delaware). Dr. Moses is a consultant for Cordis and Boston Scientific (Natick, Massachusetts). All other authors have reported that they have no relations relevant to the contents of this report to disclose.

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Appendix 2. The Role of Sex in the Activated Clotting Time During Percutaneous Coronary Intervention Trust R&D Approval.

North Cumbria University Hospitals NHS

NHS Trust

R&D Department

Our ref: SPE063/13

Date: 2 September 2013

Dr L Buchanan
Consultant cardiologist
Cumberland Infirmary
louise.buchanan@ncuh.nhs.uk

Postal address:
Cumberland Infirmary
Education Centre
Newtown Road
Carlisle
Cumbria
CA2 7HY

Dear Dr Buchanan

Re. Project acknowledgement — ACT & PCI survey

This is to inform you that North Cumbria University Hospitals NHS Trust hereby gives you permission to conduct your educational project entitled: "The Role of Patient Sex in the Activated Clotting Time During Percutaneous Coronary Intervention"

Because this concerns a survey, collating and analysing readily available data, it does not constitute research and there is no requirement for ethics approval. As part of this approval it is assumed that patient data will be anonymised and that the blood sample for ACT measurement is conducted as part of regular clinical practice.

The document reviewed as part of this governance review:

- Protocol v3 Aug2013

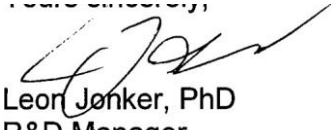
Permission is granted on the understanding that the study is conducted in accordance with the Research Governance Framework, ICH Good Clinical Practice (if applicable), and also Data Protection Act 1998 & Human Tissue Act 2004 (if applicable).

I would be grateful if you could supply us with any future amendments to the study, annual safety reports, and any other changes to the status of the study.

Please note that North Cumbria University Hospitals NHS Trust is required to monitor research to ensure compliance with the Research Governance Framework and other legal and regulatory requirements. This is achieved by random audit of research.

Please do not hesitate to contact the R&D Department if you have any queries, tel 01228 523444 ext 3445 or 01946 523410.

Yours sincerely,



Leon Jonker, PhD
R&D Manager

The Role of Patient Sex in the Activated Clotting Time During Percutaneous Coronary Intervention

An Exploratory Pilot Survey

Principal Investigator: Gill Louise Buchanan

Co-Investigators: Angela Hoye

Table Of Contents

1. Synopsis

Title	The Role of Sex in the Activated Clotting Time During Percutaneous Coronary Intervention
Principal Investigator	Gill Louise Buchanan
Overall Design	This is a single-centre, exploratory pilot survey.
Study Population	All patients undergoing elective percutaneous coronary intervention
Study Objectives	To determine if the ACT performed after heparinisation during percutaneous coronary intervention is dependent on the sex of the patient
Number of Patients	In total, 100 patients undergoing elective percutaneous coronary intervention
Start Date	September 2013
Anticipated End Date	December 2013
Primary Objective	To assess differences in ACT value according to the sex of the patient
Secondary Objectives	Occurrence of in hospital vascular complications Occurrence of radial artery occlusion at follow-up

2. Investigators

Principal Investigator: Gill Louise Buchanan

Co-Investigators: Angela Hoye

3. Background

Due to the risks of ischemic and thrombotic complications during percutaneous coronary intervention (PCI), anticoagulation is maintained throughout the procedure.(300, 301) Typically, weight-adjusted heparin in given at the onset of the intervention. The activated clotting time (ACT) is then utilised within the catheterisation laboratory to monitor the level of heparin anticoagulation.(302) It has been demonstrated there is a significant relationship between maximum ACT and the probability of bleeding events.(304)

Interestingly, higher rates of vascular complications and bleeding, are seen in female patients, and can be increased as much as 4-fold.(74, 75, 94, 125) Female sex is indeed an independent predictor of bleeding in several PCI trials with different anticoagulation strategies.(130, 137-139) This group of patients have different pharmacokinetics, due to smaller body mass with relatively more fat and lower creatinine clearance. This leads to a higher circulating level of common anti-thrombotic therapies administered throughout the PCI procedure. One study has demonstrated that both female gender and increased ACT levels were predictors of major bleeding.(306)

4. Aims

The objectives of this exploratory survey therefore are to evaluate:

1) Whether the sex of the patient plays a role in the ACT during PCI;

2) Whether the ACT is related to the occurrence of vascular complications and/or radial artery occlusion following PCI.

5. Study Design

This study is an exploratory pilot single centre survey to assess the role of sex in the ACT value in patients undergoing elective PCI for coronary artery disease.

A total of 100 consecutive patients undergoing elective PCI will be included.

6. Subjects/Patients

6.1 Demographics and Clinical Characteristics

The study population will consist of patients undergoing elective PCI.

6.2 Patient Selection Criteria

Consecutively identified candidates for this study must meet **all** of the inclusion and **none** of the exclusion criteria.

6.2.1. Inclusion Criteria

ALL candidates for the study must meet the following inclusion criteria:

1. Coronary artery disease requiring PCI;

6.2.2 Exclusion Criteria

Candidates will be excluded from the study if any of the following criteria are present:

1. Severe renal disease (eGFR<30)
2. Concurrent therapy with Warfarin
3. Allergy to Heparin

6.3 Sample Size

No evidence about the expected magnitude of the effect was available when the study was designed, therefore, no formal sample size calculation could be done. However, we expected a sample of 100 patients would be sufficient for our exploratory survey.

7. Interventions

Following enrolment into the study, the patient will proceed to PCI as per standard practice of care. Heparin will be administered at 100iu/kg. A check ACT will be taken at 20 minutes post heparinisation.

Other than the venous blood sample, no intervention is planned that is additional to routine care, with minimal risk to the patient.

8. Measurements

The HAEMOCHRON® Jr Signature (International Techidyne Corporation, New Jersey, USA) whole blood microcoagulation system will be used used to check the ACT. A sample of 2 ml of blood is added immediately to a cuvette and filled flush to the top. This

is then immediately transferred to the system and analysed. After mixing with the reagent, the sample is moved back and forth at a predetermined rate within the test channel and monitored for clot formation. The test channel is maintained at 37 °C ±1.0 °C during the test.

9. Study Plan

1. The baseline clinical characteristics will be recorded on a case report form.
2. An ACT measurement 20 minute following heparinisation will be obtained and analysed.
3. At discharge, the occurrence of vascular complications will be recorded.
4. The patency of the radial artery will be assessed manually at clinic follow-up.
5. All data will be entered into an encrypted database.

10. Analysis

The data will be entered into an encrypted database by the co-investigators of the study. All data will be analysed by Statistical Package for Social Sciences Version 18.0 (SPSS Inc, Chicago, Illinois, USA), with a p-value of <0.05 considered as statistically significant. Descriptive data summaries will be used to present and summarize the collected evaluation data. For categorical variables frequency distributions will be given. For numeric variables (e.g. patient age) minimum, maximum, mean, median and standard deviation will be calculated.

11. Ethical Issues

The study does not involve the use of any new or unusual techniques/treatments and is based on standard care for the treatment of the patient undergoing PCI. Additionally, no treatment will be withheld from the patient as a consequence of this study.

If the study investigators become aware of an adverse event, this will be immediately reported.

The Principal Investigators are dedicated to maintaining the confidentiality and privacy of patients who are enrolled in the study. Passwords are issued to appropriate personnel to insure confidentiality and protection of the database by allowing variable levels of access to the computer system. All study documents will only identify the patient by an assigned patient study identification number and in cases where applicable, the patient's initials.

There is no financial payment/reward for participation to the subject/investigator or host organization.

12. Resource Requirements

There are no resource implications to the host organisation or involved departments as the study is part of routine care for patients undergoing PCI.

The study procedures will be undertaken by Dr G. L. Buchanan within dedicated research time and will not affect any peripheral staff or service department personnel. The cost of the blood sample is with standard practice of care for the patient.

13. Supervision

The research project will be supervised by Dr Angela Hoye.

14. Dissemination and Outcome

The aim is to prepare the data for publication in a peer reviewed journal. If the data is positive, the ACT and the interaction of sex may help to predict which patients will develop vascular complications.

Appendix 4. Sex Differences in the Perceived Intensity of Symptoms in Patients with Aortic Stenosis Ethical Approval

North of Scotland Research Ethics Committee

Summerfield House
2 Eday Road
Aberdeen
AB15 6RE

Telephone: 01224 558458
Facsimile: 01224 558609
Email: nosres@nhs.net

05 November 2015

Dr Gill Louise Buchanan

Consultant Interventional Cardiologist

North Cumbria University Hospitals NHS Trust

Cumberland Infirmary

Newtown Road

CARLISLE

CA2 7HY

Dear Dr Buchanan

Study title:	**Sex Differences in the Perceived Intensity of Symptoms in Patients with Aortic Stenosis**
REC reference:	**15/NS/0108**
IRAS project ID:	**187437**

Thank you for your letter of 1 November 2015, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the Lead Reviewer.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all

studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager, Sarah Lorick, nosres@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" above).

Approved documents

The documents reviewed and approved by the Committee are:

Document	Version	Date
IRAS Checklist XML: Checklist 01112015		01 November 2015
Non-validated questionnaire: The Kansas City Cardiomyopathy Questionnaire		07 October 2015*
Angela Hoye CV		10 August 2015

Review Response	1	01 November 2015
Participant consent form		31 May 2015*
Participant information sheet (PIS)		31 May 2015*
REC Application Form: REC Form 07102015		07 October 2015
Referee's report or other scientific critique report		05 October 2015
Research protocol or project proposal: Amended - tracked changes	4	31 October 2015
Research protocol or project proposal		31 May 2015*
Summary CV for Chief Investigator (CI): Gill Louise Buchanan	1	05 August 2015

*date received

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

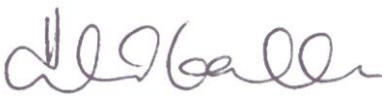
You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

15/NS/0108	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely



Professor Helen Galley Chair

Enclosures: "After ethical review – guidance for researchers" SL-AR2

Copy to: Dr Leon Jonker, North Cumbria University Hospitals NHS Trust

Appendix 5. Sex Differences in the Perceived Intensity of Symptoms in Patients with Aortic Stenosis Protocol

Sex Differences in the Perceived Intensity of Symptoms in Patients with Aortic Stenosis

Prospective, Observational Study

Principal Investigator: Gill Louise Buchanan

Co-Investigators: Angela Hoye

Table Of Contents

9. Synopsis

Title	Sex Differences in the Perceived Intensity of Symptoms in Patients with Aortic Stenosis (AS)
Principal Investigator	Gill Louise Buchanan
Overall Design	This is a multi-centre, prospective, observational study.
Study Population	All patients with moderate AS identified from the echocardiographic database.
Study Objectives	To determine if the perceived severity of symptoms in patients with moderate AS differs according to the sex of the patient.
Number of Patients	In total, 50 patients undergoing routine echocardiography for monitoring of aortic stenosis.
Start Date	October 2015
Anticipated End Date	March 2016
Primary Endpoint	Whether the sex of the patient has an impact on the perceived severity of symptoms in those with moderate AS.
Secondary Endpoints	The relationship between severity of symptoms and left ventricular dimensions. The relationship between sex and NT-pro-BNP in patients with AS.

10.Investigators

Principal Investigator: Gill Louise Buchanan

Co-Investigators: Angela Hoye, Matthew Balerdi, Mardi Hamra

11.Background

3.1 Aortic Stenosis

Aortic stenosis (AS) is the most common valvular heart disease in developed countries with the incidence increasing with age.(384, 385) Senile degenerative calcific AS, typically occurring in individuals ≥ 65 years of age, involves progressive calcification of the aortic valve leaflets which limits the opening of the cusps during systole. It is generally diagnosed by echocardiographic examination following a detectable murmur, as the disease typically remains latent for many years.

The table below demonstrates the criteria for determining severity of AS as defined by the 2006 American College of Cardiology/American Heart Association guidelines.(386)

Criteria	**Mean gradient (mm Hg)**	**Jet Velocity (m/sec)**	**Aortic valve area (cm^2)**
Mild	<25	<3	>1.5
Moderate	25-40	3-4	1-1.5
Severe	>40	>4	<1

The average increase in gradient is 7 to 10 mmHg per year(387), however there is a large and unpredictable individual variation and it can worsen by up to 25 mmHg per year.(388)

Typically, patients with AS are free from cardiovascular symptoms until late in the course of the disease when the classical trial of symptoms may emerge: breathlessness, angina and syncope.

3.2 Assessment of Dyspnoea

The American Thoracic Society defines breathlessness as ‘a subjective experience of breathing discomfort that is comprised of qualitatively distinct sensations that vary in intensity’ (339) which can vary over time and with activity, affecting all domains of life. Often patients with AS are elderly, and subsequently have a number of other co-morbidities, which renders the assessment of breathlessness due to their valvular heart disease difficult.

The Kansas City Cardiomyopathy Questionnaire is a 23-item, self-administered instrument that quantifies physical function, symptoms (frequency, severity and recent change), social function, self-efficacy and knowledge, and quality of life and can allow quantification of symptoms in the elderly population. This can be used in conjunction with the 6 minute walk test (6MWT) in an aim to quantify the degree of symptoms of breathlessness in a distinct population. It is a simple self-paced assessment to evaluate the functional status of a patient, which is reproducible, sensitive to changes in quality of life and mimics activities of daily living.(349, 350)

3.3 Dyspnoea & Women

Breathlessness related to activity (in those patients without AS) appears to be more common in older women than in older men.(340, 341) Indeed, being female has been shown to be predictive of symptom prevalence in congestive heart failure(342) and female heart failure patients perceive dyspnoea differently from males.(343) Population studies in patients with various cardiopulmonary conditions have indicated that when matched for disease severity, women experience greater levels of respiratory difficulty, greater exercise intolerance and poorer perceived health status than their male counterparts.(344, 345) Furthermore, women have reported greater intensity of breathlessness at a given power output during incremental cycle exercise.(346)

The mechanisms underlying the propensity for women to experience more disabling symptoms then men with similar disease staging are not entirely clear, however, one study has suggested that elderly women have relatively reduced maximal ventilator reserve compared with men.(347) It has been demonstrated that asymptomatic women with severe AS have similar rates of abnormal exercise stress echocardiography as men despite limitations in exercise capacity amongst the women.(348)

No study so far has assessed whether there are differences between the sexes with AS in the severity of breathlessness. Hence the aim of the study is to investigate the perception of breathlessness during incremental exercise in patients with AS.

12.Aims

The objectives of the study are to evaluate:

1) Whether the sex of the patient has an effect on the perceived severity of symptoms in patients with AS and;

2) The relationship between severity of symptoms and left ventricular dimensions and;

3) The relationship between sex and NT-pro-BNP in patients with AS.

13.Study Design

This study is a prospective, observational multi-centre study to assess whether the sex of the patient has an effect on the perceived severity of symptoms in patients with AS.

A total of 50 consecutive patients, undergoing echocardiographic follow-up with moderate AS, will be enrolled.

14. Subjects/Patients

6.1 Demographics and Clinical Characteristics

The study population will consist of patients with diagnosed moderate AS who are currently under follow-up and not awaiting intervention for the AS.

Patients will be recruited through outpatient clinics and echocardiographic database and will be evaluated for enrollment in the study at the time they are undergoing echocardiographic assessment of AS. If, based on pre-screening, the Investigator determines that patient would be a good candidate for the study given the inclusion/exclusion criteria, then he/she will be approached regarding participation in the study. The patient will be approached by the treating physician, independent of the study, (in person or by telephone) and a Patient Information Sheet will be provided. The patient will be given the contact details of the research team whom they can contact to discuss any issues further and determine whether or not they wish to be a participant.

6.2 Patient Selection Criteria

Consecutively identified candidates for this study must meet **all** of the inclusion and **none** of the exclusion criteria.

6.2.1. Inclusion Criteria

ALL candidates for the study must meet the following inclusion criteria:

2. Significant AS determined by echocardiogram and Doppler, defined as a mean gradient of $\geq$ 20mmHg and/or an aortic valve area of $\leq$1.8cm^2
3. Patient has been informed of the nature of the study and has provided full written informed consent.

6.2.2 Exclusion Criteria

Candidates will be excluded from the study if any of the following criteria are present:

4. Previous myocardial infarction
5. Moderate to severe aortic regurgitation
6. Moderate to severe mitral regurgitation
7. Left Ventricular Ejection Fraction ≤50%
8. Unable to walk without assistance from another person (not including mobility aids).
9. Unable to exercise due to non-cardiac limitations, e.g. osteoarthritis, chronic obstructive pulmonary disease (FEV_1/FVC <70%).
10. Unable to give informed consent.
11. A lack of understanding of the English language.

6.3 Sample Size

No evidence about the expected magnitude of the effect was available when the study was designed since symptom perception in AS has never been specifically evaluated. Therefore, no formal sample size calculation based on the primary end point could be done. However, we expected a sample of 50 patients would be sufficient for our explorative study.

15.Interventions

Following enrolment into the study, the patient will have blood results checked for NT-pro-BNP, by one of the study investigators. The past medical history, drug history, smoking status, echocardiographic data and symptomatic status of the patient will also be recorded at this time. To determine if COPD is present, patients will perform a spirometric assessment and the best of three manoeuvres will be recorded. In order to exclude respiratory disease, patients will be excluded if their FEV_1/FVC ratio is <70%.

The heart rate, heart rhythm, body mass index and blood pressure of the patient will be measured and the patient will then perform a 6-MWT under clinical supervision by the study investigator. This has been proven to be safe in patients with AS and can aid in clinical decision making.(389) Other than the 6-MWT, no intervention is planned that is additional to routine care, with minimal risk to the patient.

16.Endpoints

8.1 Primary Endpoint

- Whether the sex of the patient has an effect on the perceived severity of symptoms in patients with AS.

8.2 Secondary Endpoints

- The relationship between severity of symptoms and left ventricular dimensions.
- The relationship between sex and NT-pro-BNP in patients with AS.

17.Measurements

Echocardiographic assessment was performed on all patients using M-mode, 2D images and colour flow Doppler recordings using a Vivid 9 (GE Healthcare, Buckinghamshire, United Kingdom) echocardiography machine. Measurements will be taken in accordance with American Echocardiography Society/European Association of Echocardiography guidelines. The degree of AS will be evaluated using 2D transthoracic echocardiography. Left ventricular function will be carried out by 2D transthoracic echocardiography and carried out by a British Society of Echocardiography (BSE) accredited operator. Left ventricular ejection fraction will be calculated using Simpsons formula from measurements of end-diastolic and end systolic volumes on apical 2D views. When there is disagreement regarding the severity of left ventricular dysfunction or AS severity, the echo will be reviewed with a third operator and a consensus achieved.

A 6-MWT will be conducted using standardised protocols. A 15 m flat corridor with chairs at either end will be used and patients will be allowed to familiarise themselves with the course prior. The patient will be instructed to walk as far as possible, turning 180 degrees every 15 m in 6 minutes. During the test, patients can rest if needed however will be encouraged to resume walking as soon as physically able. The time remaining will be called every second minute. Patients are to walk unaccompanied therefore not influencing speed and after 6 minutes the patient will be instructed to stop and the total distance covered to the nearest metre will be calculated. Standardized verbal encouragement will be given to patients after 2 and 4 minutes, using phrases ‘you’re doing well’ and ‘keep up the good walk’. The patient will then be asked to complete the Kansas City Cardiomyopathy Questionnaire.

10. Study Plan

1. The patient will be identified as having AS, not currently planned for any intervention and will be invited into the study. The patient will be approached by the treating physician (by person or by telephone) and given a patient information sheet. The patient will be given at the details of the research team to contact if they wish to be included in the study. If the patient is agreeable a time will be arranged for the study and at this point the patient will sign an informed consent form (see Appendix).

2. The past medical history, drug history, smoking status, baseline echocardiographic parameters and clinical symptoms will be recorded on a case report form (see Appendix).

3. A baseline NT-pro-BNP venous blood sample will be obtained from the blood results prior.

4. The patient will perform a 6-MWT conducted following a standardized protocol.

5. The patient will then complete a Kansas City Cardiomyopathy Questionnaire (see Appendix).

6. All data will be entered into an encrypted database.

11. Analysis

The data will be entered into an encrypted database by the co-investigators of the study. All data will be analysed by Statistical Package for Social Sciences Version 18.0 (SPSS Inc, Chicago, Illinois, USA), with a p-value of <0.05 considered as statistically significant. Continuous variables will be described as mean ± standard deviation and categorical variables as percentages of the total population. Continuous variables will be compared between groups by the Students t test or the Mann-Whitney U test, according to whether they form a normal distribution or not. Categorical variables will be compared using a chi-squared test. Linear regression analysis will be performed to investigate for potential relationships between variables. To identify independent predictors of health

status as assessed by the KCCQ questionnaire, multi-variate and univariate linear regression analysis will be performed.

12. Ethical Issues

The study does not involve the use of any new or unusual techniques/treatments and is based on standard care for the treatment of the patient with AS. The 6MWT has been demonstrated to be safe in patients with severe symptomatic AS; no treatment will be withheld from the patient as a consequence of this study.

If the study investigators become aware of an adverse event, this will be immediately reported.

Once the Investigator has determined the patient's potential eligibility for the study based on pre-screening, the background of the proposed study and the benefits and risks of the study and procedures will be explained to the patient. It is the responsibility of the investigator before inclusion in the study, to provide each patient (or the patient's legally authorized representative), with full and adequate verbal and written information regarding the objectives of the registry. Written patient information will be given to each patient prior to enrollment. It is the responsibility of the contributor to obtain a signed informed consent from all patients enrolled in the study. If the patient refuses to sign the informed consent, this renders the patient ineligible for the study. Written informed consent must be recorded appropriately by means of the patient's dated signature prior to study procedures. The patient will receive a signed and dated copy of the informed consent form.

The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later versions. The site is responsible for

adhering to the rules and regulations of its institution, ethics committee and local and national authorities regarding releasing patient data. The study will undergo full ethical committee review prior to commencement of enrolment into the study.

The Principal Investigators are dedicated to maintaining the confidentiality and privacy of patients who are enrolled in the study. Passwords are issued to appropriate personnel to insure confidentiality and protection of the database by allowing variable levels of access to the computer system. All study documents will only identify the patient by an assigned patient study identification number and in cases where applicable, the patient's initials.

The Informed Consent Forms that are used are in accordance with the current guidelines as outlined by the GCP guidelines, ISO 14155, Declaration of Helsinki, and the ICH, as well as, all local regulations and requirements. The Ethics Committee (EC) must approve of the final informed consent form used at each investigational site prior to its implementation in the clinical trial. Documentation of informed consent is mandatory and must be obtained in writing from all patients prior to participation in the clinical trial. Informed consent must be obtained in accordance with institution's policies, procedures and regulations.

There is no financial payment/reward for participation to the subject/investigator or host organization.

13. Resource Requirements

The study procedures will be undertaken by Dr G. L. Buchanan and Dr A. Hoye within dedicated research time and will not affect any peripheral staff or service department personnel.

14. Supervision

The research project will be supervised by Dr Angela Hoye.

15. Dissemination and Outcome

The aim is to prepare the data for publication in a peer reviewed journal. If the data is positive, the use of 6 minute walk tests to assess the perception for the monitoring of disease progression in patients with asymptomatic AS may help to predict which patients will benefit from early intervention in the future.

Appendix 6. Sex Differences in the Perceived Intensity of Symptoms in Patients with Aortic Stenosis Consent Form

Study Number:

Patient Identification Number for this trial:

CONSENT FORM

Title of Project: Sex Differences in the Perceived Intensity of Symptoms in Patients with Aortic Stenosis

Name of Researcher: Dr Gill Louise Buchanan

Please initial box

1. I confirm that I have read and understand the information sheet dated May 2015 (version 1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by the researching team, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to take part in the above study. ☐

_____	_____	
Name of Patient	Date	Signature
_____	_____	
Name of Person taking Consent	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes

Appendix 7. Sex Differences in the Perceived Intensity of Symptoms in Patients with Aortic Stenosis Patient Information Sheet

PATIENT INFORMATION SHEET

Sex Differences in the Perceived Intensity of Symptoms in Patients with Aortic Stenosis

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. We'd suggest this takes about five minutes.

Talk to others about the study if you wish.

Ask us if there is anything that is not clear.

What is the purpose of the study?

Aortic stenosis (narrowing of the aortic valve of the heart) is the most common heart valve disease. A common symptom of this condition is shortness of breath. However, as patients with aortic stenosis are often (but not always) older, this symptom is difficult to assess as often there are other illnesses present, such as lung disease. It is believed that

shortness of breath related to activity is more common in women than in men. The purpose of this study is to assess what influence the sex of the patient has on the degree of shortness of breath. This is educational, to provide us with more information to allow us to better inform future patients with aortic stenosis.

Why have I been invited?

All patients with moderate aortic stenosis who are able to walk independently are to be approached to participate in the study.

Do I have to take part?

It is up to you to decide to join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

What will happen to me if I take part?

We will invite you to attend the hospital, where we will perform a brief history and physical examination. A sample of blood will be obtained. We will then ask you to walk on the flat for 6 minutes, while calculating the distance you are able to walk.

Following this we will provide you with a simple questionnaire to complete. This should take only a few minutes, and will not have any impact on your care. If you find any questions embarrassing or do not want to answer them, that does not matter. Following the questionnaire, there will be no further need for you to do anything. All information will remain entirely confidential.

What will I have to do?

The study will involve one visit to the hospital. A 6 minute walk test will be performed and a questionnaire will be provided. This should not take long and you do not need to think about the answers in great depth.

What are the alternatives for diagnosis or treatment?

The 6 minute walk test and questionnaire will have no influence on your diagnosis or treatment.

What are the possible disadvantages and risks of taking part?

There are no risks involved in taking part in the study. There is the time involved in attending for a hospital visit.

What are the side effects of any treatment received when taking part?

There are no additional side-effects from participation in the study. The 6 minute walk test is known to be safe in patients with aortic stenosis.

What are the possible benefits of taking part?

We cannot promise the study will help you, but the information that we get from this study will help us better inform future patients with aortic stenosis.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. Any complaint about the way you have been dealt with during the study will be addressed.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in part 2 before making any decision.

What if relevant new information becomes available?

The study does not have any impact on diagnosis or treatment, therefore advances in treatment will not be changed by this.

What will happen if I don't want to carry on with the study?

You can withdraw from the study at any time. This will not affect your future management in any way.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. If you remain unhappy and wish to

complain formally, you can do this via the hospital PALS service.

Will my taking part in this study be kept confidential?

If you join the study, some parts of your medical records and the data collected for the study will be looked at by the authorised researchers. They may also be looked at by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

What will happen to the results of the research study?

When the results have been analysed, the intention is to publish these results in a medical journal. The data will also help us guide future patients regarding their symptoms.

Who is organising and funding the research?

The study is being sponsored by the Research and Development team of North Cumbria University Hospitals NHS Trust.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect

your interests. This study has been reviewed and given favourable opinion by the North of Scotland Research Ethics Committee.

Further information and contact details

General information about research can be obtained from the NRES website www.nres.npsa.nhs.uk.

Specific information about the research project and advice can be obtained via the research team, contacted via Dr L Buchanan's secretary, telephone number 01228 814033.

Appendix 8. The Kansas City Cardiomyopathy Questionnaire

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. Heart failure affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by heart failure (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Place an **X** in one box on each line

Activity	**Extremely Limited**	**Quite a bit Limited**	**Moderately Limited**	**Slightly Limited**	**Not at all Limited**	**Limited for other reasons or did not do the activity**
Dressing yourself	❑	❑	❑	❑	❑	❑
Showering/Bathing	❑	❑	❑	❑	❑	❑
Walking 1 block on level ground	❑	❑	❑	❑	❑	❑
Doing yardwork, housework or carrying groceries	❑	❑	❑	❑	❑	❑
Climbing a flight of stairs without stopping	❑	❑	❑	❑	❑	❑
Hurrying or jogging (as if to catch a bus)	❑	❑	❑	❑	❑	❑

2. Compared with 2 weeks ago, have your symptoms of **heart failure** (shortness of breath, fatigue or ankle swelling) changed? My symptoms of **heart failure** have become …

Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks
❑	❑	❑	❑	❑	❑

3. Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when

1. Heart failure affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by heart failure (shortness of breath or fatigue) in your ability to do the following activities <u>over the past 2 weeks</u>.

---

you woke up in the morning?

Every morning	3 or more times a week, but not every day	1–2 times a week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑

4. Over the <u>past 2 weeks</u>, how much has **swelling** in your feet, ankles or legs bothered you? It has been …

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no swelling**
❑	❑	❑	❑	❑	❑

5. Over the <u>past 2 weeks</u>, on average, how many times has **fatigue** limited your ability to do what you want?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1–2 times per week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑	❑	❑

6. Over the <u>past 2 weeks</u>, how much has your **fatigue** bothered you? It has been …

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no fatigue**
❑	❑	❑	❑	❑	❑

7. Over the <u>past 2 weeks</u>, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1–2 times per week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑	❑	❑

8. Over the <u>past 2 weeks</u>, how much has your **shortness of breath** bothered you? It has been …

Extremely	**Quite a bit**	**Moderately**	**Slightly**	**Not at all**	I've had **no**

1. Heart failure affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by heart failure (shortness of breath or fatigue) in your ability to do the following activities <u>over the past 2 weeks</u>.

---

bothersome	bothersome	bothersome	bothersome	bothersome	**shortness of breath**
❑	❑	❑	❑	❑	❑

9. Over the <u>past 2 weeks</u>, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

Every night	3 or more times a week, but not every day	1–2 times a week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑

10. **Heart failure** symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your **heart failure** gets worse?

Not at all sure	**Not very** sure	**Somewhat** sure	**Mostly** sure	**Completely** sure
❑	❑	❑	❑	❑

11. How well do you understand what things you are able to do to keep your **heart failure** symptoms from getting worse? (for example, weighing yourself, eating a low salt diet, etc.)

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
❑	❑	❑	❑	❑

12. Over the <u>past 2 weeks</u>, how much has your **heart failure** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life at all
❑	❑	❑	❑	❑

13. If you had to spend the rest of your life with your **heart failure** the way it is <u>right now</u>, how would you feel about this?

Not at all	Mostly	Somewhat	Mostly	Completely

1. Heart failure affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by heart failure (shortness of breath or fatigue) in your ability to do the following activities <u>over the past 2 weeks</u>.

---

	satisfied	dissatisfied	satisfied	satisfied	satisfied
	❑	❑	❑	❑	❑

14. Over the <u>past 2 weeks</u>, how often have you felt discouraged or down in the dumps because of your **heart failure**?

	I felt that way **all of the time**	I felt that way **most of the time**	I **occasionally** felt that way	I **rarely** felt that way	I **never** felt that way
	❑	❑	❑	❑	❑

15. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities <u>over the past 2 weeks</u>.

Please place an **X** in one box on each line

Activity	**Severely** limited	Limited **quite a bit**	**Moderately** limited	**Slightly** limited	**Did not** limit at all	Does not apply or did not do for other reasons
Hobbies, recreational activities	❑	❑	❑	❑	❑	❑
Working or doing household chores	❑	❑	❑	❑	❑	❑
Visiting family or friends out of your home	❑	❑	❑	❑	❑	❑
Intimate relationships with loved ones	❑	❑	❑	❑	❑	❑

Appendix 9. Kansas City Cardiomyopathy Questionnaire Study Licence Agreement

LICENSE AGREEMENT

THIS LICENSE AGREEMENT is made as of this 02 March 2017, by and between Outcomes Instruments, LLC, a for-profit organization in Missouri, whose address is 18 W. 52nd Street, Kansas City, Missouri, 64112, United States ("Licensor") and North Cumbria University Hospitals NHS Trust, a not-for-profit organization in , whose address is Newtown Road, Carlisle, CA2 6RY, United Kingdom ("Licensee").

RECITALS

A. Licensor has rights in certain research methodologies, technical developments, know-how, discoveries, works of authorship, questionnaires, registries, study protocols, processes, datasets and other useful art, whether or not protected by patents, copyrights, trademarks, trade secrets or other laws protecting intellectual property rights, as more particularly described on Schedule A attached hereto and incorporated herein by this reference (the "Licensed Properties").

B. Licensee is engaged in that certain study more particularly described on Schedule B attached hereto and incorporated herein by this reference (the "Subject Study").

C. Licensor desires to grant Licensee the right to use the Licensed Properties solely in connection with the Subject Study, and Licensee desires to use the Licensed Properties in connection therewith, subject to all of the terms and conditions hereof.

NOW, THEREFORE, in consideration of the premises and the mutual promises and undertakings contained herein, the parties hereto agree as follows:

1. Grant of Limited License. Subject to the terms and conditions hereof, Licensor grants to Licensee a non-exclusive, non-transferable, non-assignable limited license to use the Licensed Properties solely in connection with the conduct of the Subject Study.
2. Ownership of Licensed Properties. As between Licensor and Licensee, Licensee acknowledges that Licensor retains all ownership rights in and to the Licensed Properties, and any improvements, modifications and derivatives thereof (whether prepared by Licensor or Licensee or otherwise), and that except for the rights granted hereunder, Licensee has no right, title or interest in and to the Licensed Properties. Licensee agrees to reproduce the appropriate copyright legends and/or trademark symbols on all written or displayed versions of the Licensed Properties and/or the results attributed to the use thereof. Licensee further acknowledges and understands that Licensor reserves the right to (i) grant others the license to use the Licensed Properties and (ii) use the Licensed Properties in its own research and investigations, without the need to account to Licensee in connection with such activities.
3. Fees. In consideration for the license granted hereunder, Licensee shall pay Licensor the license fees set forth on Schedule C attached hereto and incorporated herein by this reference, at the times, and in the manner, set forth on such Schedule.
4. Licensor's Representations and Covenants. Licensor represents and warrants to Licensee that Licensor has the full power and authority to execute and deliver

this Agreement and to perform its obligations hereunder without need to obtain the consent of any third party.

5. Site Visits. Licensor shall have the right to inspect and observe from time to time through such agents or representatives as Licensor may designate, on Licensee's site, the activities conducted by or for Licensee with respect to the Licensed Properties to determine whether Licensee is using the Licensed Properties in a proper fashion as provided hereunder. To the extent Licensor is granted access to a patient's "protected health information" ("PHI"), as such term is defined in the Health Insurance Portability and Accountability Act of 1996 and the regulations promulgated thereunder, the parties agree to negotiate and execute a Business Associates Agreement containing customary covenants regarding the confidentiality and limited use of such PHI.
6. Reports. Licensee shall keep and maintain comprehensive and accurate records pertaining to its use of the Licensed Properties, and the status and progress of the Subject Study. Such reports shall be available for examination by Licensor and its agents or representatives at any time upon reasonable advance notice.
7. Licensee's Conduct. Licensee agrees that it shall use the Licensed Properties only as permitted hereunder and further agrees to refrain from modifying, altering or amending the Licensed Properties or taking any action which could adversely affect the validity, goodwill and reputation thereof. Upon the termination or expiration of this Agreement, Licensee shall immediately discontinue all use of the Licensed Properties.
8. Litigation. As between Licensor and Licensee, only the Licensor shall have the right to commence or prosecute any claims or litigation to protect or enforce its rights in and to the Licensed Properties. Licensee agrees that it will immediately provide notice to Licensor upon learning of any litigation, whether actual or threatened, against Licensee in connection with Licensee's use of the Licensed Properties. Licensee further agrees that it will cooperate fully with Licensor by providing any information requested by Licensor in any litigation arising in connection with Licensee's use of the Licensed Properties.
9. Disclaimers; Limitations of Liability. LICENSEE ACKNOWLEDGES THAT THE LICENSED PROPERTIES ARE LICENSED "AS IS", WITH ALL FAULTS. LICENSOR HAS MADE NO REPRESENTATION OR WARRANTY THAT THE LICENSED PROPERTIES ARE SUITABLE FOR LICENSEE'S USE IN CONNECTION WITH THE SUBJECT STUDY. LICENSEE SHALL RELY ON ITS OWN JUDGMENT IN EVALUATING ITS USE OF THE LICENSED PROPERTIES AND ANY OUTCOMES ATTRIBUTABLE THERETO, WITHOUT RELYING ON ANY MATERIAL OR INFORMATION PROVIDED BY LICENSOR. LICENSOR DISCLAIMS ANY REPRESENTATIONS OR WARRANTIES, EXPRESS OR IMPLIED, INCLUDING WITHOUT LIMITATION ANY REPRESENTATIONS OR WARRANTIES AS TO THE LICENSED PROPERTIES' MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. IN NO EVENT SHALL LICENSOR BE LIABLE FOR SPECIAL, CONSEQUENTIAL, EXEMPLARY OR PUNITIVE DAMAGES. LICENSOR'S LIABILITY HEREUNDER SHALL BE LIMITED TO LICENSEE'S DIRECT DAMAGES RESULTING FROM LICENSOR'S BREACH OF ANY OF ITS OBLIGATIONS HEREUNDER WHICH CONTINUES UNREMEDIED FOR THIRTY DAYS AFTER WRITTEN NOTICE BUT SHALL IN NO EVENT EXCEED THE AMOUNT OF THE FEES ACTUALLY PAID BY LICENSEE TO LICENSOR HEREUNDER.
10. Indemnification of Licensor. Licensee hereby agrees to hold Licensor harmless of and from and indemnifies it against any and all losses, liabilities, claims, damages and expenses (including attorneys' fees and expenses) which Licensor may incur or be obligated to pay, or for which it may become liable or be compelled to pay in any action, claim or proceeding for or by reason of any acts, whether of omission or commission, that may be claimed to be or are actually committed or suffered by Licensee arising out of Licensee's use of the Licensed Properties. The provisions of this paragraph and Licensee's obligations hereunder shall survive the expiration or termination of this Agreement.

11. Indemnification of Licensee. Subject to Section 9 hereof, Licensor hereby agrees to hold Licensee harmless of and from and indemnifies it against any and all losses, liabilities, claims, damages and expenses (including attorneys' fees and expenses) which Licensee may incur or be obligated to pay, or for which it may become liable or compelled to pay in any action, claim or proceeding for or by reason of any breach of any representation, warranty or agreement on the part of Licensor under this Agreement.
12. Nondisclosure. During the term of this Agreement, the parties may have access to trade secrets, proprietary information, or other sensitive materials belonging to the other which are not generally known to the public ("Confidential Information"). During the term of this Agreement and for a period of five (5) years after termination or expiration hereof, the receiving party ("Recipient") agrees to maintain in trust and confidence all Confidential Information of the other party (the "Disclosing Party"). The Recipient agrees to safeguard the Confidential Information using the same standard of care it uses to protect its own Confidential Information. The Recipient will not disclose any Confidential Information to any third party, or make any use thereof other than as expressly permitted hereby, without the prior written consent of the Disclosing Party. As used herein, Confidential Information does not include any information which the Recipient can demonstrate (i) was known to the Recipient or to the general public at the time of disclosure; (ii) was independently developed by the Recipient without the use of any of the Confidential Information; or (iii) was disclosed by a third party without violating any restriction or duty to the Disclosing Party.
13. Publications. Notwithstanding the general restrictions set forth in Section 12 above, the parties agree that publication of the results of research activities serves their mutual interests in improving the quality of health care. Accordingly, Licensee shall be free to publish the results of its research and development activities carried out with respect to the Licensed Properties and the Subject Study. Licensee agrees to refer to Licensor and the Licensed Properties in the bibliography section of the publication.
14. Term. Subject to the provisions of Section 15 hereof, this Agreement shall remain in effect from 03/01/2017 to 03/01/2018. Subsequent renewal of this Agreement shall be optionally available through application through the web site.
15. Licensor's Right to Terminate. Licensor shall have the right to immediately terminate this Agreement by giving written notice to Licensee in the event Licensee: (i) fails to perform any of its duties and obligations set forth herein, and the continuation thereof for thirty (30) days after notice; (ii) files a petition in bankruptcy or is adjudicated a bankrupt or insolvent, or makes an assignment for the benefit of creditors; (iii) makes any use of the Licensed Properties not otherwise expressly permitted herein or (iv) the Subject Study is cancelled, abandoned, withdrawn or suspended. In such event, Licensee shall immediately cease and terminate its use of any of the rights granted hereby and shall, upon the request of Licensor, return to Licensor all records, copies, documents, media and files making use of the Licensed Properties, or furnish evidence, satisfactory to Licensor, of the destruction thereof.
16. Equitable Remedies. The parties further acknowledge that the breach, whether threatened or actual, of any of the terms hereof by Licensee shall result in immediate, irreparable injury to Licensor and its goodwill and that accordingly, Licensor shall be entitled to apply for a preliminary and/or permanent injunction to restrain the threatened or actual violation of the terms hereof by the Licensee or to compel specific performance of the terms and conditions of this License Agreement. Nothing set forth herein shall be construed as prohibiting the Licensor from pursuing any other remedies available for such breach or threatened breach, including the recovery of damages and costs incurred, together with attorneys' fees.

17. Miscellaneous.

a. This Agreement together with the exhibits hereto constitutes the entire understanding between the parties with respect to this Agreement. No change or modification of any of the provisions of this Agreement shall be effective unless memorialized by an instrument in writing signed by the parties hereto. All notices required or permitted to be given hereunder shall be given in writing, to the parties at their addresses set forth herein, or to such other address with respect to which notice has been given in accordance herewith. Whenever possible, each provision of this License Agreement shall be interpreted in such a manner as to be effective and valid under applicable law. If any covenant or other provision of this Agreement, or portion thereof, under circumstances not now contemplated by the parties, is invalid, illegal or incapable of being enforced, by reason of any rule of law, administrative order, judicial decision or public policy, all other conditions and provisions of this Agreement shall, nevertheless, remain in full force and effect, and no covenant or provision shall be deemed dependent upon any other covenant or provision unless so expressed herein. The parties desire and consent that the court or other body making such determination shall, to the extent necessary to avoid any unenforceability, so reform such covenant, term, condition or other provision or portion of this Agreement to the minimum extent necessary so as to render the same enforceable in accordance with the intent herein expressed.

b. This Agreement shall inure to the benefit of Licensor, its successors and assigns. Licensee shall not have the right to assign this Agreement, or delegate its duties, by operation of law or otherwise, without first obtaining the written consent of Licensor.

c. This Agreement shall be governed by and construed in accordance with the laws of the State of Missouri.

IN WITNESS WHEREOF, the parties hereto have caused this Agreement to be duly executed as of the day and year first above mentioned.

Outcomes Instruments, LLC	**North Cumbria University Hospitals NHS Trust**
By: John Spertus	By:
Title: President	Title:
"Licensor"	"Licensee"

Appendix 10. The Kansas City Cardiomyopathy Questionnaire Scoring Instructions

The Kansas City Cardiomyopathy Questionnaire Scoring Instructions

There are 10 summary scores within the KCCQ, which are calculated as follows:

1. Physical Limitation

- Code responses to each of Questions 1a-f as follows:

  Extremely limited = 1

  Quite a bit limited = 2

  Moderately limited = 3
  Slightly limited = 4

  Not at all limited = 5

  Limited for other reasons or did not do = <*missing value*>

- If at least three of Questions 1a-f are not missing, then compute

  Physical Limitation Score = 100*[(mean of Questions 1a-f actually answered) – 1]/4

  (see footnote at end of this document for explanation of meaning of "actually answered")

2. Symptom Stability

- Code the response to Question 2 as follows:

  Much worse = 1

  Slightly worse
  = 2 Not
  changed = 3

  Slightly better = 4

Much better = 5

I've had no symptoms over the last 2 weeks = 3

- If Question 2 is not missing, then compute

  Symptom Stability Score = 100*[(Question 2) – 1]/4

3. Symptom Frequency

- Code responses to Questions 3, 5, 7 and 9 as follows:

  Question 3
  Every morning = 1

  3 or more times a week but not every day = 2

  1-2 times a week = 3

  Less than once a week = 4

  Never over the past 2 weeks = 5

3. Symptom Frequency (cont.)

  Questions 5 and 7
  All of the time = 1

  Several times a day = 2

  At least once a day = 3

  3 or more times a week but not every day = 4

  1-2 times a week = 5

  Less than once a week = 6

  Never over the past 2 weeks = 7

  Question 9
  Every night = 1

  3 or more times a week but not every day = 2

  1-2 times a week = 3

  Less than once a week = 4

Never over the past 2 weeks = 5

- If at least two of Questions 3, 5, 7 and 9 are not missing, then compute:

  S3 = [(Question 3) – 1]/4

  S5 = [(Question 5) – 1]/6

  S7 = [(Question 7) – 1]/6

  S9 = [(Question 9) – 1]/4

  Symptom Frequency Score = 100*(mean of S3, S5, S7 and S9)

4. Symptom Burden

- Code responses to each of Questions 4, 6 and 8 as follows:

  Extremely bothersome = 1

  Quite a bit bothersome = 2

  Moderately bothersome = 3

  Slightly bothersome = 4

  Not at all bothersome = 5

  I've had no swelling/fatigue/shortness of breath = 5

- If at least one of Questions 4, 6 and 8 is not missing, then compute

  Symptom Burden Score = 100*[(mean of Questions 4, 6 and 8 actually answered) – 1]/4

5. Total Symptom Score

  = mean of the following available summary scores:

  Symptom Frequency Score

  Symptom Burden Score

6. Self-Efficacy

- Code responses to Questions 10 and 11 as follows:

  Question 10 Not at all sure = 1 Not very sure = 2

  Somewhat sure = 3 Mostly sure = 4

  Completely sure = 5

  Question 11
  Do not understand at all = 1

  Do not understand very well = 2

  Somewhat understand = 3 Mostly understand = 4

  Completely understand = 5

- If at least one of Questions 10 and 11 is not missing, then compute

Self-Efficacy Score = 100*[(mean of Questions 10 and 11 actually answered) – 1]/4

7. Quality of Life

- Code responses to Questions 12, 13 and 14 as follows:

  Question 12
  It has extremely limited my enjoyment of life = 1 It has limited my enjoyment of life quite a bit = 2

  It has moderately limited my enjoyment of life = 3 It has slightly limited my enjoyment of life = 4

  It has not limited my enjoyment of life at all = 5

Question 13
Not at all satisfied = 1

Mostly dissatisfied = 2

Somewhat satisfied =
3 Mostly satisfied = 4

Completely satisfied = 5

Question 14
I felt that way all of the time = 1

I felt that way most of the time = 2

I occasionally felt that way = 3

I rarely felt that way = 4

I never felt that way = 5

7. Quality of Life (cont.)

- If at least one of Questions 12, 13 and 14 is not missing, then compute

  Quality of Life Score = 100*[(mean of Questions 12, 13 and 14 actually answered) – 1]/4

8. Social Limitation

- Code responses to each of Questions 15a-d as follows:

  Severely limited = 1

  Limited quite a bit = 2

  Moderately limited = 3
  Slightly limited = 4

  Did not limit at all = 5

  Does not apply or did not do for other reasons = <*missing value*>

- If at least two of Questions 15a-d are not missing, then compute

  Social Limitation Score = 100*[(mean of Questions 15a-d actually answered) – 1]/4

9. Overall Summary Score

= mean of the following available summary scores:

Physical Limitation Score
Total Symptom Score
Quality of Life Score

Social Limitation Score

10. Clinical Summary Score

= mean of the following available summary scores:

Physical Limitation Score

Total Symptom Score

_____

Note: references to "**means of questions actually answered**" imply the following.

③ If there are *n* questions in a scale, and the subject must answer *m* to score the scale, but the subject answers only *n-i*, where *n-i* >= *m*, calculate the **mean of those questions** as

(sum of the responses to those *n-i* questions) / (*n-i*) **not**

(sum of the responses to those *n-i* questions) / *n*

If doing these calculations seems like too much trouble, consider using one of our tools – available at www.cvoutcomes.org: ③ SAS or SPSS code

③ Excel spreadsheets ③ Web data services

Appendix 11. Sex Differences in the Perceived Intensity of Symptoms in Patients with Aortic Stenosis Data Collection Form

Demographics

Patient Identifier	_____						
Patient DOB	_____						
Patient Age	_____						
Patient Sex	Male	□			Female	□	

Baseline Characteristics

Height	_____ m						
Weight	_____ kg						
BMI	_____						
NYHA Class	I	□	II	□	III	□	IV □
CCS Class	I	□	II	□	III	□	IV □
Creatinine	_____						
Creatinine Clearance	_____						
Haemoglobin	_____						
NT Pro BNP	_____						
QRS Duration	_____						

Past Medical History

Diabetes Mellitus	Yes	□	No	□		
If Yes;	Diet	□	Tablet	□	Insulin	□
Hypertension	Yes	□	No	□		
Hypercholesterolaemia	Yes	□	No	□		
COPD	Yes	□	No	□		
Atrial Fibrillation	Yes	□	No	□		
Permanent Pacemaker	Yes	□	No	□		
Smoker	Yes	□	No	□		

Medication

Antiplatelet therapy	□
Beta blocker	□
ACE inhibitor/ARB	□
Statin	□
Calcium channel blocker	□
Diuretic	□

Echocardiographic Data

LVIDD	_____cm			
EDV (Teich)	_____ml			
LALs A4C	_____cm			
MV E Vel	_____m/s			
MV DecT	_____ms			
MV Dec Slope	_____m/s^2			
MV A Vel	_____m/s			
AV Vmax	_____m/s			
AV maxPG	_____mmHg			
LVEF (Simpsons)	_____%			
AR	I □	II □	III □	IV □
MR	I □	II □	III □	IV □
TR	I □	II □	III □	IV □

6 Minute Walk Test

Date of Test	_____
Baseline Heart Rate	_____
Baseline Blood Pressure	_____
Total Distance	_____
Peak Heart Rate	_____
Peak Blood Pressure	_____
KCCQ Score	_____

Abbreviations

6MWT = 6 Minute Walk Test

ACS = Acute Coronary Syndrome

ACT = Activated Clotting Time

AS = Aortic Stenosis

BARC = Bleeding Academic Research Consortium

BAV = Balloon Aortic Valvuloplasty

BMI = Body Mass Index

CABG = Coronary Artery Bypass Grafting

CAD = Coronary Artery Disease

CI = Confidence Interval

COPD = Chronic Obstructive Pulmonary Disease

CVA = Cerebrovascular Accident (Stroke)

DES = Drug Eluting Stent

ECG = Electrocardiogram

EuroSCORE = European System for Cardiac Operative Risk Evaluation

FKBI = Final Kissing Balloon Inflation

HR = Hazard Ratio

IABP = Intra-Aortic Balloon Pump

IQR = Inter Quartile Range

IVUS = Intra Vascular Ultrasound

KCCQ = Kansas City Cardiomyopathy Questionnaire

LAD = Left Anterior Descending Coronary Artery

LCX = Left Circumflex Coronary Artery

LVEF = Left Ventricular Ejection Fraction

LVOT = Left Ventricular Outflow Tract

MACE = Major Adverse Cardiovascular Event

MACCE = Major Adverse Cardiovascular and Cerebrovascular Event

MI = Myocardial Infarction

NS = Non Significant

NSTEMI = Non ST Elevation Myocardial Infarction

NYHA = New York Heart Association

OR = Odds Ratio

PCI = Percutaneous Coronary Intervention

PPCI = Primary Percutaneous Coronary Intervention

PVD = Peripheral Vascular Disease

RCA = Right Coronary Artery

RR = Relative Risk

SAVR = Surgical Aortic Valve Replacement

SD = Standard Deviation

STEMI = ST Elevation Myocardial Infarction

STS = Society of Thoracic Surgeons

SYNTAX = Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery

TAVI = Transcatheter Aortic Valve Implantation

TLR = Target Lesion Revascularisation

TVR = Target Vessel Revascularisation

UA = Unstable Angina

ULMCA = Unprotected Left Main Coronary Artery

VARC = Valve Academic Research Consortium