Evaluating Cardiac Surgery Outcomes in the Context of a High-Risk Patient Population and its Implications for the Training of Future Surgeons

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DECLARATION

This thesis is submitted to the University of Sydney in fulfilment of the requirement for the degree of Doctor of Philosophy (PhD).

I, Akshat Saxena, hereby declare that the work presented in this thesis is, to the best of my knowledge and belief, original except as acknowledged in the text. I have not submitted this material, either in full or in part, for a degree at this or any other institution

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ABBREVIATIONS

ACC	American College of Cardiology
ACSD	Adult Cardiac Surgery Database
AF	Atrial fibrillation
AHA	American Heart Association
ANZSCTS	Australian and New Zealand Society of Cardiac and Thoracic Surgeons
AS	Aortic stenosis
AVR	Aortic valve replacement
BAV	Bicuspid aortic valve
BMI	Body mass index
CABG	Coronary artery bypass grafting
CCTR	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CORONARY	CABG Off or On Pump Revascularization Study
CPB	Cardiopulmonary bypass
CRISP	Coronary artery bypass grafting in high-RISk patients
EACTS	European Association for Cardio-Thoracic Surgery
ESC	European Society of Cardiology
EuroSCORE	European System for Cardiac Operative Risk Evaluation
FREEDOM	Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease
HR	Hazard ratio
HRQOL	Health-related quality of life
IABP	Intra aortic balloon pump
ICU	Intensive care unit
LIMA	Left internal mammary artery
LMD	Left main disease
LVEF	Left ventricular ejection fraction
MACCE	Major adverse cardiac and cerebrovascular events

MR	Mitral regurgitation
MV	Mitral valve
NYHA	New York Heart Association
ONCAB	On pump coronary artery bypass surgery
ONS	UK Office of National Statistics
OPCAB	Off pump coronary artery bypass surgery
OD	Odds ratio
PARTNER	Placement of Aortic Transcatheter Valves
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
AF	Pre-existing atrial fibrillation
PVD	Peripheral vascular disease
QOL	Quality of life
RA	Radial artery
RBC	Red blood cell
RCT	Randomised controlled trial
RIMA	Right internal mammary artery
ROOBY	Randomised On/Off Bypass
RR	Relative risk
sAVR	Surgical aortic valve replacement
SCTS	Society for Cardiothoracic Surgery
SD	Standard deviation
STS	Society of Thoracic Surgery
SURTAVI	Surgical Replacement and Transcatheter Aortic Valve Implantation
SYNTAX	Synergy between PCI with Taxus and Cardiac Surgery
TAVI	Transcatheter aortic valve implantation
U.S.	United States of America
USD	U.S. Dollar
VHD	Valvular heart disease

ABSTRACT

Modern cardiac surgery was facilitated by the introduction of the cardiopulmonary bypass machine in the 1950's. Since then it has become an indispensable tool in the armamentarium against congenital and acquired cardiovascular disease. In the past two decades, however, there has been a fundamental shift in the population of patients undergoing cardiac surgery, towards the elderly and high-risk. This has reflected the general ageing of populations in the developed world and the concurrent increase in the incidence of co-morbidities such as diabetes, obesity, atrial fibrillation (AF), heart failure, renal disease and chronic pulmonary disease. This trend is set to continue. As such, cardiac surgeons are operating on older and sicker patients and this has significant clinical implications. The overall objective of this thesis was to evaluate the risks associated with cardiac surgery in a high-risk population and to determine the implications of these changed demographics on the training of future cardiac surgeons.

Our thesis demonstrated the important role cardiac registries have played in the monitoring of outcomes of high-risk patients. Most importantly, they have enabled the development of sophisticated risk assessment tools. These have allowed clinicians to objectively measure a patients' risk and evaluate their suitability for various cardiovascular interventions. Furthermore, risk assessment tools have facilitated research in high-risk patients, allowing, in particular, comparative analyses to be performed between surgery and minimally invasive percutaneous interventions. These tools, however, are imperfect. Given that they are derived from historical series; risk scores have often been shown to overestimate peri-operative mortality in high-risk patients undergoing cardiac surgery. Furthermore, many variables, such as AF, are not

included in most risk assessment tools. Our thesis demonstrated, through a series of meta-analysis, the negative early and mid-term prognostic implications of pre-existing atrial fibrillation (AF) across a spectrum of cardiac surgery procedures. It highlighted the need to consider inclusion of AF into future risk models This finding is also significant because AF can be potentially treated at the time of cardiac surgery through concomitant AF surgery with minimal additional morbidity. One of the potential implications of an increasingly high-risk patient population is a reduced opportunity to train junior surgeons. This has been amplified in recent years by the increased scrutiny on outcomes due to the more widespread reporting of outcomes-based data. Our thesis, however, highlighted that, even in the contemporary era, carefully supervised trainees achieve equivalent outcomes to consultant surgeons. It emphasises the importance of training future cardiac surgeons to be adept at treating the high-risk patient population that they will more frequently encounter.

Section II of the thesis evaluated the utility of clinical registries (Chapter II) and risk stratification tools (Chapter III) for prognostication in cardiac surgery. These are critically important in cardiac surgery where only a fraction of interventions have randomized support. In an era where patients are increasingly high risk, our thesis discussed the importance of collecting, analysing and publishing data on high-risk patients where the benefit-risk relationship is not immediately apparent. Perhaps more then any other specialty, we found that cardiac surgery has benefitted from the widespread utilization of clinical registries as they have enabled the quantification of the outcomes of high-risk patients and established the safety and efficacy of surgery in a real life setting. We found that this has subsequently facilitated increased acceptance of surgical intervention in

these patients with data subsequently demonstrating that this has translated into superior long-term survival. We also found that clinical registries have been used to evaluate surgical education; they have demonstrated that cardiac surgery can be safety performed by surgeons in training. Overall, our thesis showed that the utility of clinical datasets has had a profound impact on the practice of cardiac surgery worldwide. Our research, however, did show that registries have significant limitations. They are subject to treatment bias, missing data, sampling errors and require significant human and financial resources.

It is not well understood that well maintained datasets have enabled cardiac surgeons to develop perhaps the most sophisticated risk assessment tools in clinical medicine. Chapter III showed that this has in itself afforded the opportunity to optimize the outcomes of high-risk patients. Risk assessment tools allow clinicians to provide patients a thorough explanation of their risk rather then relying on the “end of the bed” test. This is particularly relevant in high-risk patients, where there may be non-surgical approaches available that modify risk. In addition, risk assessment tools can optimize outcomes of high-risk patients through their role in guiding treatment allocation. For example, surgical aortic valve replacement (AVR) remains the gold-standard intervention for patients with symptomatic, severe aortic stenosis. In patients adjudged to be ‘‘high risk’’ as per risk assessment tools, however, transcatheter aortic valve implantation (TAVI) may be more appropriate. Our study also demonstrated that risk assessment tools may improve patient outcomes by enabling data benchmarking (allowing identification of underperforming units) and by facilitating research. It may also facilitate surgical education, through identification of suitable cases for trainees.

Risk assessment tools also have significant limitations which we discussed. They are derived from a dataset developed over a particular period of time and may not be contemporaneous from the outset. The most commonly used tool, EuroSCORE, was shown to overestimate the expected mortality of high-risk patients, particularly in an Australian context. This led to the development of the AusSCORE. Moreover, they may be subject to confounding by unknown variables which were not collected in the dataset from which they were derived. For example, scoring systems do not take into account factors which may predicate a poorer outcome such as atrial fibrillation and frailty. They may also be inappropriately applied to patient populations in whom they are not appropriate. This may theoretically lead to an incorrect assessment of risk and potential treatment misallocation.

Registries and risk stratification tools not only allow identification of high-risk patients but allow research on their outcomes. The efficacy of different treatment approaches can then be compared. Off-pump coronary artery bypass (OPCAB) differs from conventional CABG in that it avoids the use of an extra-corporeal circuit and minimizes aortic manipulation. Theoretically this should reduce the risk of mortality, embolic stroke and the morbidity associated with the systemic inflammatory response syndrome that accompanies cardiopulmonary bypass. Our hypothesis is that the use of clinical datasets and risk-assessment tools have improved the care of high-risk patients undergoing cardiac surgery.

Chapter IV consists of a review of the Australian and New Zealand Society of Cardiac and Thoracic Surgeons' (ANZSCTS) registry for high-risk (AusSCORE > 5) patients (n=7822) undergoing isolated CABG surgery and compared the on-pump

coronary artery bypass (ONCAB) (n=7277) with the OPCAB (n=545) technique. Preoperative and intraoperative risk factors, and postoperative outcomes were analysed. Survival analysis was performed after cross-matching the registry with the national death registry to identify long-term mortality. The data demonstrated that the ONCAB and OPCAB groups had similar risk profiles based on the AusSCORE. There was a trend towards reduced 30-day mortality (2.4% vs 3.9%, p=0.067) and stroke (1.3% vs 2.4%, p=0.104) in the OPCAB group but this did not reach statistical significance. OPCAB patients received fewer distal anastomoses than ONCAB patients (2.5±1.2 vs 3.3±1.0, p<0.001). The rates of new postoperative atrial arrhythmia (28.3% vs 33.3%, p=0.017) and blood transfusion requirements (52.1% vs 59.5%, p=0.001) were lower in the OPCAB group, while duration of ICU stay in hours (97.4±187.8 vs 70.2±152.8, p<0.001) was longer. There was a non-significant trend towards improved 10-year survival in OPCAB patients (74.7% vs. 71.7%, p=0.133). Overall, the study demonstrated in a high-risk population, CABG surgery has a low rate of mortality and morbidity, regardless of the revascularization method employed. Our data did not show a definitive survival benefit for OPCAB patients but it demonstrated that this technique may reduce postoperative morbidity and is a safe procedure for 30-day mortality, stroke and long-term survival in high-risk patients.

Atrial fibrillation (AF) is the most common arrhythmia in the adult population and its causative relationship with embolic stroke and premature death is well established. The incidence of AF increases with age and co-morbidities; as such it will be increasingly encountered by the cardiac surgeon. Over the last 3 decades several surgical techniques

have been evaluated for the treatment of AF and there is substantial evidence that they are effective in restoring sinus rhythm and reducing the need for anti-coagulation.

There have been several studies, including some by our group, on the short- and mid-term implications of AF on cardiac surgery. Many have shown that AF is independently associated with poorer outcomes. Nevertheless, many surgeons treat AF merely as a nuisance or just a marker of a sick patient. One reason for this is there is the belief that there is insufficient evidence about the implications of AF on outcomes after cardiac surgery; it is not a risk factor on most risk assessment tools. A second important reason is that many surgeons believe that AF surgery increases the invasiveness of procedures which patients may not be able to tolerate. As such, only a minority of patients (<40%) who are suitable for AF surgery undergo this procedure. This may compromise their long-term outcomes.

Section III of the dissertation evaluated the short- and long-term implications of AF on outcomes after coronary artery bypass graft (CABG) surgery, aortic valve and mitral valve surgery and percutaneous mitral valve repair through a series of systematic reviews and meta-analyses. For this, Medline, EMBASE and CENTRAL databases were systematically searched for studies that reported outcomes according to the presence or absence of AF; meta-analyses were then conducted according to predefined clinical endpoints.

Chapter 5 evaluated the impact of AF on early and mid-term outcomes after CABG. Twelve observational studies (n=389,998) met criteria for inclusion, with eight studies (n=381,479) reporting propensity-matched or adjusted analyses. Peri-operative mortality was higher overall in patients with AF (odds ratio [OR] 1.64; 95% confidence interval [CI],

1.29–2.09; p<0.001). Subgroup analysis demonstrated that AF was associated with mortality in patients undergoing on-pump (OR 1.53; 95% CI, 1.21–1.94; p<0.001) and off-pump CABG (OR 2.75; 95% CI, 1.35–5.59; p=0.005). AF was also associated with increased incidence of four other peri-operative complications: stroke (OR 1.50; 95% CI, 1.06–2.11; p=0.02), acute renal failure, re-operation and prolonged ventilation. Mid-term mortality was significantly higher in patients with AF (hazard ratio [HR] 1.74; 95% CI, 1.42–2.13; p<0.001). This was true regardless of whether patients underwent on-pump (HR 1.69; 95% CI, 1.34–2.15; p<0.001) or off-pump (HR 1.97; 95% CI, 1.26–3.08; p=0.003) revascularization.

Chapter 6 evaluated the impact of AF on early and mid-term outcomes after AVR. Six observational studies with 8 distinct AVR cohorts (AVR ± concomitant surgery) met criteria for inclusion, including a total of 6693 patients. Of these, 1014 (15%) presented with AF. Overall, peri-operative mortality was increased in patients with AF (OR 2.33; 95% CI, 1.48 – 3.67; p<0.001). Subgroup analysis of patients undergoing isolated AVR also demonstrated AF as a risk factor for peri-operative mortality (OR 2.49; 95% CI, 1.57-3.95; p<0.001). AF was also associated with acute renal failure (OR 1.42; 95% CI, 1.07-1.89; p=0.02) but not stroke (OR 1.11; 95% CI, 0.59 – 2.12; p=0.74). Mid-term mortality was significantly higher in patients with AF (HR 1.75; 95% CI, 1.33-2.30; p<0.001). This relationship remained true when only patients who underwent isolated AVR were analyzed (HR 1.97; 95% CI, 1.11-3.51; p=0.02).

Chapter 7 evaluated the impact of AF on early mortality and mid-term outcomes after mitral valve surgery (MVS). Ten observational studies met criteria for inclusion, including a total of 4279 patients. Of these, 1896 (44%) presented with AF. There was a

non-significant trend towards increased peri-operative mortality in patients with AF (OR 1.61; 95% CI, 0.97 – 2.67; p=0.07). Analysis of long-term outcomes demonstrated that pre-AF was associated with a higher incidence of stroke at follow-up (HR, 3.70; 95% CI, 1.36 – 10.06; p=0.003), cardiac death (OR, 4.29; 95%, CI, 1.28 – 14.37; p=0.02) and mid-term mortality (HR, 1.84; 95%, CI, 1.40 – 2.42; p<0.001).

Chapter 8 evaluated the impact of AF on early and 12-month outcomes after percutaneous mitral valve repair with MitraClip. Eight studies met criteria for inclusion, including a total of 8704 patients. Of these, 5201(60%) presented with AF. AF was associated with an increased risk of peri-procedural mortality (OR 1.35; 95% CI, 1.02 – 1.78; p=0.03) and longer hospital stay (Mean difference [MD] 0.65; 95% CI, 0.36 – 0.93; p<0.001) but not early stroke (OR, 0.94; 95% CI, 0.46 – 1.95; p=0.88). At 12 months, AF was associated with an increased risk of mortality (HR, 1.45; 95% CI, 1.27 – 1.66; p=0.03) and hospitalization for heart failure (HR, 1.18; 95% CI, 1.03 – 1.35; p=0.02) but not stroke (HR, 1.01; 95% CI, 0.32 – 3.20; p=0.99). Cumulatively, the data from Chapters 5 – 8 demonstrated the negative prognostic short and long-term implications of AF across a spectrum of cardiac surgery procedure. They support the more widespread application of concomitant AF surgery or ablation as a means of improving patient outcomes. Moreover, our data strongly suggests that AF should be incorporated as a risk factor in future risk models (for both early and mid-term mortality).

This is particularly important in the contemporary era where percutaneous cardiovascular interventions such as transcatheter aortic valve implantation (TAVI) are being increasingly applied in low and mid-risk patient cohorts with severe aortic stenosis. AF can be effectively treated at the time of surgery through a variety of surgical techniques

such as the Cox-Maze procedure. There is, however, no data validating the efficacy of concomitant percutaneous ablative procedures during TAVI. In this regard, patients with AF who undergo treatment with TAVI may have an inferior outcome than if they underwent AVR and concomitant AF surgery.

The changing demographic of patients undergoing cardiac surgery has implications not only on patients but the training of future cardiac surgeons. Traditionally, the apprenticeship model of surgical training dictates that trainees start with easy cases and then progress to more difficult ones. The increased complexity of cases now encountered has raised concerns that patient outcomes may be compromised by allowing trainees to do cases. On the other hand, it is argued that surgical training is being progressively diluted by the increased risk profile of patients as well as the increased scrutiny on surgeon outcomes and the trend towards more technically involved minimally invasive procedure. Section IV of the dissertation critically evaluated the published literature to determine whether cardiac surgery can be safely performed by supervised trainees through a series of systematic reviews and meta-analysis. Again, Medline, EMBASE and CENTRAL databases were systematically searched for studies that reported outcomes according to; meta-analyses were then conducted according to predefined clinical endpoints.

Chapter 9 demonstrated that equivalent outcomes can be attained after CABG performed by consultant and trainee surgeons. Sixteen observational studies involving a total of 52966 patients met the criteria for inclusion. Trainee cases were associated with increased aortic cross-clamp (weighted mean difference [WMD] 4.80; 95% confidence interval [CI], 0.76-8.83) and cardiopulmonary bypass (WMD 4.24; 95% CI, 0.00-8.47)

durations. Peri-operative mortality was similar whether CABG was primarily performed by trainees or consultants (OR 0.98; 95% CI, 0.81-1.18;). There was no significant difference in the incidence of peri-operative stroke, myocardial infarction, acute renal failure, re-operation for bleeding or wound infection. Trainee operator status was not associated with increased mid-term mortality (HR 1.00; 95% CI, 0.90-1.11). Subgroup analysis of off-pump CABG cases and sensitivity analysis by study quality did not impact upon these findings.

Chapter 10 further showed that valvular surgery cases performed by trainees were not associated with adverse peri-operative outcomes. Eleven observational studies met the inclusion criteria, reporting on five patient cohorts undergoing mitral valve surgery (n=3975), six undergoing aortic valve replacement (AVR) (n=6236) and three undergoing combined AVR and coronary artery bypass grafting (CABG) (n=3495). MV surgery performed by trainees had significantly longer pooled CPB (WMD 9.37; 95% CI, 5.54 – 13.21, $p < 0.001$) and aortic cross-clamp (WMD 10.59; 95% CI, 3.74 – 17.45, $p = 0.002$) durations. For AVR, trainees and consultants had similar CPB (WMD 4.70; 95% CI, -5.73 – 15.13; $p = 0.38$) and aortic cross-clamp (MD 3.17; 95% CI, -5.91 – 12.25; $p = 0.49$) times. Aortic cross-clamp (MD 6.25; 95% CI, 0.44 – 12.06; $p = 0.04$) duration was significantly higher when trainees performed concomitant AVR and CABG, but the difference in CPB duration was not statistically significant (MD 4.96; 95% CI, -7.98 – 17.89; $p = 0.45$). Peri-operative mortality was not significantly different between trainee and consultant cases for mitral valve surgery (OR 0.92; 95% CI, 0.62–1.37), AVR (OR 0.67; 95% CI, 0.37–1.24), or combined AVR and CABG (OR 1.07; 95% CI, 0.40–2.85). The incidences of peri-operative stroke, myocardial infarction, arrhythmias, acute renal

failure, re-operation or wound infection were not significantly different between trainee and consultant cases. Chapters 8-9 both demonstrated that trainee cases have longer operative times but a structured approach to training can sufficiently mitigate trainee deficiencies. These data are reassuring, particularly give that fear of poorer outcomes may reduce training opportunities to residents particularly in an era where the complexity of cases has increased and there is extensive reporting of outcomes based data. Even in technically challenging procedures, such as OPCAB, which are particularly useful in high-risk cases, the meta-analysis did not show that training status predicated a poorer outcome. There is an urgent need, however, to address the deficiencies in training current and future cardiothoracic surgeons in novel endovascular cardiac interventions and AF surgery for which there is currently a paucity of data. Studies with longer follow-up duration and echocardiographic data are also required to assess long-term durability and safety of trainee outcomes. Finally, we believe that, given our study demonstrated that surgeons-in-training can safely perform cardiac surgery in reputed institutions with a strong teaching culture, a structured training programme for high-risk patients would be beneficial. Trainee surgeons can be mentored by recognized experts to manage the pre-operative, intra-operative and peri-operative issues associated with high-risk patients. This has the real potential to improve patient outcomes.

In summary, this dissertation has provided an improved understanding in evaluating the risks associated with cardiac surgery in a high risk population and addresses how outcomes can be optimized through careful risk assessment and proper treatment allocation. This includes adopting an individualized approach to treating high-risk patients with application of risk assessment tools to calculate risk and consideration

of alternative approaches to mitigate risk such as OPCAB. The changing demographic of patients will increasingly expose cardiac surgeons to atrial fibrillation; our data unequivocally showed that it was associated with poorer outcomes and concomitant ablative surgery should be considerable wherever feasible. An unintended consequence of the increasingly high-risk nature of cardiac surgery and the public availability of outcomes data is decreased training opportunities for junior surgeons. Reassuringly, our data demonstrated that outcomes of supervised trainees are equivalent to those of consultants and mitigates concerns that trainee outcomes are inferior. The paucity of data on trainees performing novel endovascular cardiothoracic interventions such as TAVI and MitraClip represents an avenue for further research particularly in the context of an increasingly complex subset of patients.

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SECTION I

GENERAL INTRODUCTION AND LITERATURE REVIEW

CHAPTER I

LITERATURE REVIEW: EVALUATING THE IMPACT OF HIGH-RISK PATIENTS ON OUTCOMES AFTER CARDIAC SURGERY

1.1 HISTORY OF CARDIAC SURGERY

The contemporary practice of cardiac surgery emerged after the traumatic events of World War II(1). In 1946, Dwight Harken used his wartime experience to describe techniques for the removal of foreign bodies from chambers of the heart in injured soldiers(2). Contemporaneously, in 1944, Blalock and Taussig described the creation of the “Blalock-Taussig” shunt to restore pulmonary circulation in patients with pulmonary stenosis/atresia(3). These landmark events sparked an enthusiasm in the medical community to develop techniques for the treatment of patients with congenital and acquired heart disease who previously had no potential treatment options.

Initial progress was slow and cumbersome. Most procedures until the 1960s were palliative extra-cardiac operations(1). Nevertheless, several innovative approaches were devised in an attempt to achieve a definitive intra-cardiac repair. Gross and colleagues(4) described a technique known as the “Gross atrial wall” whereby atrial septal defects could be repaired in heparinised patients through a rubber funnel sutured to the atrial wall. The importance of interrupting the blood flow through the heart during intra-cardiac operations was also recognized. Methods involving hypothermia were proposed, whereby circulation was interrupted by snaring the superior and inferior vena cava after cooling the patients to 26˚F (-3˚C)(1). The success of this technique was predicated on a quick operative time (under 10 minutes) to avoid cerebral complications. This technique, however, had a high risk of air entrapment and it was unsuitable for complex intra-cardiac repairs.

A landmark publication by John Gibbon in 1953 further facilitated the development of contemporary cardiac surgery(5). For over a decade, Gibbon had worked to design an extra-corporeal device that allow both oxygenation and circulation. He evaluated his technique of open heart surgery and total cardiopulmonary bypass in 4 patients and whilst

only 1 survival it represented a powerful proof of concept. In the following decade, dramatic advances were made in every aspect of cardiopulmonary bypass from the development of more simple oxygenators through to the recognition that the extracorporeal circuit could be be primed with crystalloid rather than blood(1). With these refinements, the operative indications for cardiac surgery significantly expanded and surgeons were able to repair most intra-cardiac abnormalities(6). By the end of 1956, Cooley and colleagues(7) themselves had performed 134 open heart procedures including a repair of a post-infarct ventricular septal defect. Further refinement in surgical technique and the development of prosthetic valve replacement also enabled surgeons to definitively treat aortic and mitral valve disease(1, 8).

1.2 HISTORY OF CORONARY ARTERY BYPASS GRAFT SURGERY

Today the most commonly performed cardiac surgery operation worldwide is coronary artery bypass graft (CABG) surgery. Approximately 200,000 isolated cases are performed in the United States every year with an average incidence rate of 50-60 per 100,000 inhabitants in developed countries(9). Conceptually, CABG was described over 100 years ago when Alexis Carrel provided a theoretical rationale for the operation and himself performed intra-thoracic aortic and cardiac anastomosis in dogs(10). Nevertheless, it was not until the inadvertent development of coronary angiography in 1958 by Sones and colleagues(11) that CABG was attempted by surgeons. Prior to this surgeons attempted other techniques to treat angina including the placement of muscle pedicles, omentum and pericardial fat tissue within the pericardium in an attempt to increase myocardial blood supply(12). In the 1960's, armed with knowledge of a patients coronary vasculature and the then novel techniques of cardiopulmonary bypass and cardioplegic arrest, cardiac

surgeons were able to construct coronary bypass grafts in a relatively bloodless field using conduits including the saphenous vein and internal mammary artery(1, 13, 14). The volume of CABG surgery has since declined with the introduction of percutaneous transluminal coronary angioplasty by Gruentzig and colleagues(15). Nevertheless, it represents an important treatment in the armamentarium against coronary artery disease and there is Class IA evidence that it is superior to percutaneous coronary intervention in patients with complex triple vessel disease and diabetes mellitus(16).

1.3 NEW TREATMENTS FOR STRUCTURAL HEART DISEASE

In the past two decades, the landscape of cardiac interventions has been transformed by the introduction of new, minimally invasive techniques to address structural heart abnormalities. The impetus for the development of these techniques was the increasingly frail and elderly nature of patients requiring cardiac intervention. The “traditional” treatment for severe, symptomatic aortic stenosis (AS) has been surgical aortic valve replacement (AVR). Unfortunately, however, up to 50% of patients were denied surgery because of advanced age or co-morbidities(17, 18). This limitation stimulated clinicians to develop a minimally invasive approach to addressing AS. In 2002, Cribier and colleagues(19) demonstrated the feasibility of transcatheter aortic valve implantation (TAVI). This technology has since evolved with robust improvements in valve design, durability and ease of deployment. The efficacy of this approach was initially established in a high-risk cohort(20, 21); however, it has now been more broadly applied to lower risk patients with excellent results(22). Similarly, percutaneous mitral valve repair with MitraClip was developed for patients with severe mitral regurgitation (MR) deemed to be at a high or prohibitive surgical risk. This technique is derived from a surgical repair

technique developed by Alfieri and colleagues in the 1990s where a suture is used to anchor the free edge of the prolapsed leaflet to the opposite leaflet(23). Several studies have demonstrated the efficacy of this technique in the context of severe MR although randomized evidence is required(24). Overall, the increased complexity of patients with cardiovascular disease and the increased array of potential therapeutic options has highlighted the need for a multi-disciplinary approach to patient care, centred around the "Heart Valve Team".

The development of new approaches and techniques in cardiac surgery and interventional cardiology continues to accelerate. It is important, in this context, to continue to review the efficacy of these treatments in a real world sense and to ascertain the impact of risk factors, such as atrial fibrillation, on patient outcomes after intervention.

1.4 AGEING POPULATION AND ITS IMPLICATIONS FOR HEART DISEASE

The population of the world is ageing and this trend is set to accelerate. In the U.S., the proportion of people aged 65 years and older increased from 4.1% to 12.9% over the past century (1910-2010)(25). In Australia, the proportion of the population over 65 years increased from 5% in 1927 to 15% in 2017; it is expected to increase to 22% by 2057(26). Even more dramatic is that proportion of the population who are "very elderly" (> 85 years) is expected to increase from 1.6% in 2006 to between 4.9 and 7.3% by 2056(26). This demographic shift is even more pronounced in countries with low fertility rates and high life expectancy such as Japan and Germany.

The impact of advanced age on the cardiovascular system has been extensively studied and is beyond the scope of this thesis. Ageing changes the morphology of the heart, mostly through alterations of intracellular molecular and biochemical pathways(27,

28). This ultimately results in decreased mechanical and contractile efficiency, decreased myocyte count, increased myocyte size, blunted beta-adrenoceptor-mediated contractile and inotropic response and stiffening of myocardial cells, mural connective tissue and valves(29, 30). Ageing affects the morphology and function of the vasculature and increases vascular stiffness(31, 32). The large arteries dilate, their walls thicken, the wall matrix changes, elastolytic and collagenolytic activity increases and smooth muscle tone increases(31). This translates into an increased aortic impedance and elevated left ventricular afterload(28). The compensatory increase in left ventricular wall thickness ultimately leads to decreased left ventricular compliance and impaired diastolic function(27). Moreover, ageing causes progressive dysfunction of the coronary circulation(33, 34) and the autonomic nervous system(27) through a variety of mechanisms.

In addition to this, advanced age affects cardiovascular risk factors and itself increases the incidence of cardiovascular diseases. Data from the U.S. showed that the prevalence of cardiovascular disease increases from 50% at age 45 to 80% at age 80. For valvular heart disease, the prevalence increased from 0.3% of the 18-44 year olds to 11.7% of those aged 75 years and older(35). In fact, the final presentation of most cardiovascular patients reflects a complex interplay between cardiovascular disease and age-related changes in cardiovascular physiology(27).

Consistent with the elderly population of developed countries is the high morbidity and mortality associated with cardiovascular disease. In Australia, 30% of all deaths were attributed to cardiovascular disease and ischaemic heart disease remained the single largest cause of death (11.6%)(36). Moreover, ischaemic heart disease was a

contributing factor in an additional 22% of deaths(36). Similarly, in the U.S., heart disease is the leading cause of mortality in both males and females, comprising 25% of all deaths. The economic burden of cardiovascular disease is very substantial and growing; in the United States it is expected to grow from $555 billion in 2016 to $1.1 trillion in 2035(37).

1.5 CHANGE IN RISK PROFILE OF PATIENTS UNDERGOING CARDIAC SURGERY

The ageing of the world's population combined with the increased utilization of percutaneous coronary intervention in patients with less extensive coronary artery disease has changed the demographic profile of patients undergoing cardiac surgery towards the elderly. Numerous studies have shown an increase in the average age and comorbidity profile of patients undergoing a spectrum of cardiac surgery procedures(38-41). Early reports showed that cardiac surgery in these patients was associated with in-hospital mortality rates of more than 10%(42, 43) with one study reporting early mortality as high as 24%(44). However, continuous refinements in surgical technique and peri-operative mortality have resulted in significantly improved outcomes recently. There is now widespread acceptance that selected elderly patients may benefit from both a symptomatic and prognostic viewpoint from open heart surgery. In our previous multi-institutional report on 1664 octogenarians who underwent isolated CABG, the observed 30-day mortality was 4.2% (45). Five-year survival (73%) was comparable to an age-matched Australian population. We reported similar results for patients undergoing isolated AVR and concomitant AVR-CABG(46, 47). The benefits of cardiac surgery in restoring functional status and health-related quality of life (HRQOL) in elderly patients has also been established(48, 49).

The improved outcomes observed after cardiac intervention in elderly and high-risk groups largely reflects the extensive utilization of clinical registries. Cardiac surgery has benefitted from the widespread utilization of clinical registries more than any other specialty. These have allowed clinicians to quantify the early and mid-term outcomes of high risk patients and established the safety of surgery in a real life setting. This has subsequently facilitated increased acceptance of surgical intervention in these patients which has translated into superior long-term survival. Data from the multi-institutional ANZSCTS dataset, for example, allows us to show that elderly patients (> 80 years) have an age-adjusted survival similar to that of the general Australian population(47, 50). Analysis of these datasets has also demonstrated that mortality rates after cardiac surgery remain stable despite a sicker patient cohort.

The development of risk assessment tools such as the STS score, EuroSCORE and the AusSCORE has also improved our ability to manage high-risk patients. They allow clinicians to identify high-risk patients and allocate them the most appropriate treatment (e.g. surgical AVR vs. TAVI). Moreover, current European and U.S. guidelines frequently employ registry-derived risk assessment tools to categorize the risk profile of patients. For example, surgical aortic valve replacement (AVR) remains the gold-standard intervention for patients with severe aortic stenosis. In patients adjudged to be ‘‘high risk’’ as per risk assessment tools, however, surgical AVR may not be appropriate. In these ‘‘high risk’’ patients, cardiology guidelines stipulate that trans-catheter aortic valve implantation (TAVI) may improve symptoms and survival(51). Risk-adjusted analysis of clinical datasets also enables clinicians to evaluate the relative efficacy of different treatment options. In this thesis, for example, we used both the ANZSCTS registry and

the AusSCORE to address whether there was a difference in outcomes between two types of surgical revasularization (OPCAB vs ONCAB) in high-risk patients.

In addition to this, these tools may facilitate patient counselling, allow benchmarking of performance and drive quality improvement initiatives. Despite this, there are few studies which address the clinical utility of registries or risk tools themselves. A key theme of this dissertation is exploring the role of clinical registries and risk assessment tool in evaluating high-risk patients.

1.6 IMPACT OF ATRIAL FIBRILLATION ON CARDIAC SURGERY OUTCOMES

The shift in the demographic profile of patients undergoing cardiac surgery towards the elderly and high-risk has increased the proportion who present with arrhythmias. Atrial fibrillation (AF) is the most common supraventricular arrhythmia in adults and its incidence steadily increases with age; the prevalence in those older than 80 years is up to 15%(52). This reflects age-related increases in left atrial size and workload, and a higher incidence of age-associated electrolyte imbalances, clinical or subclinical hyperthyroidism, electrolyte imbalances and digoxin toxicity(27). The incidence of AF also increases with co-morbid conditions including congestive heart failure, anaemia, impaired ventricular function, renal disease and peripheral vascular disease(27, 53). In an epidemiological study carried out in the United States, the incidence of age- and gender-adjusted AF increased from 3.04 to 3.68 per 1000 person-years between 1980 and 2000(54). The same authors reported a prevalence model which estimated a three-fold increase in the number of patients with AF in the next 50 years. Annual hospitalizations in the United States from AF are predicted to rise from 376,000 in 1999 to over 3.3 million by 2025(55).

The majority of patients with AF report symptoms but a significant proportion (12-42.5%) remain asymptomatic(56). A significant portion of AF patients experience an increased perception of the heartbeat (palpitations)(57). This is often associated with anxiety. The sensory pathways underlying palpitations have not been defined. Chest pain often occurs during AF, even in the absence of structural heart disease(57). This may be attributed to impaired myocardial perfusion(58) as well as increased coronary vascular resistance(59), irregularity of the ventricular response and alteration of both the sympathetic nervous system activation and the renin-angiotensin system(58). More then half of AF patients also report reduced exercise capacity as measured by the New York Heart Association (NYHA) class(60). It has known that cardiac output is compromised during AF secondary to the reduced diastolic filling that accompanies rapid ventricular rates. This manifests in reduced exercise tolerance in the order of 15-20%(58, 61). Moreover, diastolic dysfunction in AF may increase left-sided intracardiac pressures predisposing patients to episodes of subclinical pulmonary oedema and causing dyspnea(62). Dizziness, syncope and presyncope may also be present in AF and have been associated with sympathovagal imbalance(63). Other mechanisms proposed are sinus node dysfunction with pauses upon conversion of AF into sinus rhythm or rapid ventricular rates in patients with underlying conditions such as valvular stenosis, hypertrophic cardiomyopathy, or an accessory pathway(64). Overall, the symptoms attributed to AF cause lower functional status and health related quality of life (HRQOL)(65, 66).

The deleterious affects of AF are well understood. The loss of coordinated atrial activity predisposes patients to thrombus formation and, subsequently, embolic

stroke(67). AF increases the risk of stroke by a factor of 3 to 5, and is responsible for an estimated 15% to 20% of all strokes(68). Moreover, AF doubles the risk of premature death(67). Priebe and colleagues(27) argued that the impact of AF on elderly patients is particularly profound because they become progressively dependent on atrial contribution to diastolic filling. As such, any compromise in cardiac output or arterial pressure may critically depress cerebral perfusion secondary to a blunted beta-adrenoceptor response, increased vascular stiffness and greater likelihood of pre-existing cerebrovascular disease(27).

AF is common in the cardiac surgery population with an incidence of up to 40% in patients undergoing mitral valve surgery(69, 70). In the context of cardiac surgery, however, there is debate as to whether AF is a negative prognostic factor in its own right or whether it is a marker for a worse physiological milieu. It has been regarded by many surgeons as a “nuisance” which does not warrant surgical correction.

The most commonly used risk stratification tool, EuroSCORE, does not include AF as a risk factor. We previously published several series addressing the impact of AF on outcomes after cardiac surgery. All studies demonstrated that AF was associated with a higher incidence of early complications and reduced long-term survival(53, 71, 72). Nevertheless, the current surgical literature is sparse and contradictory. Determining the prognostic implications of AF is also important because it can be potentially treated at the time of surgery with the Cox-Maze procedure. Since its introduction in 1987, the Cox-Maze procedure has been continually refined and new techniques have been developed which have minimized the invasiveness of the procedure without compromising its efficacy(73). The most recent iteration (Cox Maze IV) replaced the “cut and sew”

technique of original procedure with lines of ablation using a combination of radiofrequency ablation and cryotherapy. There is substantial evidence to indicate that atrial fibrillation surgery is effective at restoring sinus rhythm and can be concomitantly performed without an increase in morbidity or mortality (74, 75). Henn and colleagues(76) reported the outcomes of 576 patients who underwent Cox-Maze IV between 2002-2014 at the Washington University School of Medicine. At five years, overall freedom from AF was 78% and freedom from AF off anti-arrhythmic drugs (AAD) was 66% despite the fact that median duration of preoperative AF was 42 months. Ad and colleagues(77) demonstrated a 5-year freedom from AF of 85% and freedom from AF off AAD was 71% in a group of 120 patients. There is also evidence that it may improve long term survival and decrease mid-term stroke (78-81). Cox and colleagues(81) reported a long-term stroke rate of only 0.1% per year in patients who underwent the Cox-Maze III procedure despite the fact that the majority were able to discontinue anticoagulation medication. Impressively, although 19%(58/306) patients had experienced a neurologic event before surgery, there were only two minor strokes on long-term follow-up (mean 3.9 ± 2.7 years). A Japanese study showed that patients who had a concomitant Cox-Maze procedure with their mitral valve replacement were 99% stroke-free at 8-year follow-up, whereas the cohort that did not were 89% stroke free(80).

Furthermore, whilst newly published guidelines have made a Class IIa recommendation advocating the concomitant treatment of AF, reluctance in the surgical community remains high and the number of patients treated with ablation is less than 30%(82). As mentioned above, the primary cause for reluctance amongst surgeons to treat AF concomitantly is the perception that it is may not be a negative prognostic

indicator in itself(83). Our thesis seeks to address this notion by evaluating the impact of AF on outcomes across a variety of cardiovascular interventions using meta-analysis of adjusted data. There are also other reasons why adoption has been limited. Firstly, AF surgery is technically complex and invasive as it involves multiple additional incisions in the heart(84). This results in an increased cardiopulmonary bypass and ischaemic time which in themselves may compromise outcomes. The Maze procedure is also associated with chronotropic incompetence and a higher incidence of permanent pacemaker implantation(85). The original maze procedure was modified twice because of concerns that the sinus node was unable to generate a sufficient heart rate during maximal exercise(86, 87). Reassuringly, the manifestations of sinus node dysfunction are time dependent with decrease in frequency and intensity 12 months after surgery(86).

There is also concern that it is not possible to identify the exact propagation pathway for AF in an arrested heart thereby compromising the efficacy of the ablative procedure(88). Finally, AF surgery is not a focus of most contemporary cardiothoracic training programs and so surgeons may not have had sufficient exposure to the procedure(89). This deficiency in training needs to be rectified. Addressing the implications of AF is important given that will be encountered more frequently by surgeons in the future and the fact it is potentially amenable to cure.

1.7 BALANCING RESIDENT TRAINING AND PATIENT SAFETY IN THE CONTEXT OF A HIGH-RISK PATIENT POPULATION

The changing demographic of patients undergoing cardiac surgery has implications not only on patients but the training of future cardiac surgeons. Cardiac operations are now more complex and the patients undergoing them are theoretically less able to cope

with the complications associated with aortic cross clamping and cardiopulmonary bypass. It is intuitive that trainee cases should take a longer time than consultant cases. The increased cardiopulmonary bypass and aortic cross clamp time in these cases may affect patient outcomes by predisposing patients to complications such as microemboli, increased transfusion requirements, coagulation defects and immunosuppression(90, 91). Hence, it is imperative to evaluate whether cardiac surgery can be safely performed by surgeons-in-training.

The increased complexity of cases has coincided with the extensive collection and reporting of outcomes data, which has subsequently been used for physician and institution financial compensation(92). As such, complications are heavily scrutinized and many surgeons may be reluctant to provide their trainees with the autonomy and operative opportunities that they were afforded in their training(93).

On the other hand, it is important to ensure that the future generation of surgeons are equipped to deal with a high-risk patient cohort. Historically, surgical training operated on the basis of an apprenticeship model where a trainee steadily improves their skill by starting with easy cases and then progressing to more difficult ones. The increased complexity of cases has raised concerns that the quality of training is being diluted because consultants are less able to provide suitable cases. This has been exacerbated by the increased scrutiny of registry-reported outcomes and the introduction of work hour limits in some countries(94). Moreover, the introduction of minimally invasive techniques in an effort to mitigate surgical risk may have reduced training opportunities; these cases tend to be more technically difficult and have a longer learning curve. Efforts have been made to compensate for this through the introduction of surgical simulation and virtual

reality training(95, 96). There has also been a paradigm shift in what constitutes a good training program. There is now more focus on the non-technical skills associated with being a surgeon and greater emphasis on research, higher degrees and teaching. Again, whilst this provides a more balanced approach to training it may compromise exposure to surgical procedures and operative cases(97).

Hence, there is a real need to critically evaluate the safety and efficacy of cardiac surgery operations performed by trainee surgeons. This will establish whether our current expectation that cardiac surgery remains safe in training institutions in being met. It may also mitigate concerns amongst some surgeons that training compromises patient outcomes in an era where high-risk patients are the norm. One component of this dissertation involved addressing this important clinical issue with a series of meta-analyses.

1.8 SPECIFIC AIMS

The overall objective of this dissertation is to evaluate the outcomes of patients undergoing cardiac surgery in the context of a high-risk population. The dissertation has several broad themes and aims which are summarized below.

1.8.1 Specific aim 1: Evaluate the implications of the use of clinical registries and risk stratification tools in improving the care of high-risk patients undergoing cardiac surgery.

Our hypothesis is that the use of clinical datasets and risk-assessment tools have improved the care of high-risk patients undergoing cardiac surgery. This is because clinical registries have allowed clinicians to monitor the outcomes of patients undergoing

surgery over time and to identify trends. By identifying underperforming centers, they may improve outcomes through a system of constructive feedback. The prospective collection of a large body of data allows clinicians to identify which pre-operative, intra-operative or post-operative characteristics may modify risk. These may include, but are not limited to, cardio-protective medications or alternative procedures. Clinical datasets enable research that can not be performed in a randomized fashion such as volume-outcome relationships which may result in health policy changes such as centralization of certain procedures into “centers of excellence”. This may further reduce risk in high-risk patients. Risk assessment tools further allow clinicians to objectively define a patients’ risk and to test strategies which may mitigate risk. Although both clinical registries and risk assessment tools have merit, they have several limitations which may preclude their usefulness in certain situations. Our aim was to evaluate the benefits and limitations associated with the use of robust clinical datasets and risk assessment tools.

1.8.2 Specific aim 2:

a) Primary aim: Evaluate whether OPCAB, compared to ONCAB, improves peri-operative outcomes (30-day mortality, myocardial infarction, take-back for graft occlusion, re-bleeding, new renal failure, new atrial fibrillation/flutter, ventilation > 24 hours, infection, neurological events, length of hospital stay, length of intensive care unit stay) in high-risk patients (AusSCORE > 5) undergoing CABG.

b) Secondary aim: Compare mid-term survival outcomes between OPCAB and ONCAB in high risk patients (AusSCORE > 5).

The working hypothesis is that OPCAB, compared to ONCAB, reduces peri-operative mortality and morbidity and improves mid-term survival in high-risk patients because it avoids the use of an extra-corporeal circuit and minimizes aortic manipulation. To test this hypothesis, we used the ANZSCTS registry to compare peri-operative mortality, peri-operative morbidity and mid-term survival of high-risk patients (AusSCORE > 5) who underwent either OPCAB or ONCAB. Preoperative and intraoperative risk factors, and postoperative outcomes were compared and analyzed. Survival analysis was performed after cross-matching the registry with the national death registry to determine long-term mortality.

1.8.3 Specific aim 3:

a) Primary aim: Evaluate the impact of AF on peri-operative and mid-term (> 12 months) mortality after CABG.

b) Secondary aims:

i) **Evaluate the impact of AF on peri-operative morbidity (stroke, acute renal failure, prolonged ventilation, re-operation, re-operation for bleeding, wound infection, myocardial infarction, and re-operation for bleeding).**

ii) **Evaluate the impact of AF on early and mid-term outcomes, stratified by revascularization strategy (on-pump vs off-pump).**

The working hypothesis is that AF is associated an increased incidence of peri-operative mortality, morbidity and poorer mid-term survival after CABG. To test this hypothesis, we

performed a systematic review and meta-analysis of eligible studies which reported the clinical outcomes of isolated CABG according to the presence or absence of baseline AF. All meta-analyses in the thesis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

1.8.4 Specific aim 4:

a) Primary aim: Evaluate the impact of AF on peri-operative and mid-term (> 12 months) mortality after AVR

b) Secondary aims:

i) **Evaluate the impact of AF on peri-operative morbidity (stroke, acute renal failure, prolonged ventilation, re-operation for bleeding).**

ii) **Evaluate the impact of AF on peri-operative and mid-term (> 12 months) outcomes in patients undergoing isolated AVR.**

The working hypothesis is that AF is associated an increased incidence of peri-operative mortality, morbidity and poorer mid-term survival after AVR. To test this hypothesis, we performed a systematic review and meta-analysis of eligible studies which reported the clinical outcomes of AVR according to the presence or absence of baseline AF.

1.8.5 Specific aim 5:

a) Primary aim: Evaluate the impact of AF on peri-operative and mid-term (> 12 months) mortality after MVS

b) Secondary aim: Evaluate the impact of AF on the mid-term (> 12 months) incidence of stroke, cardiac death and poor functional status (NYHA III/IV) after MVS.

The working hypothesis is that pre-operative atrial fibrillation is associated an increased incidence of peri-operative mortality and poorer mid-term outcomes (mortality, stroke, cardiac death, poor functional status) after MVS. To test this hypothesis, we performed a systematic review and meta-analysis of eligible studies which reported the clinical outcomes of MVS according to the presence or absence of baseline AF.

1.8.6 Specific aim 6:

a) Primary aim: Evaluate the prognostic impact of AF on peri-procedural and 12-month mortality after percutaneous mitral valve repair with MitraClip implantation. The secondary aims were:

i) **Evaluate the association of AF with peri-procedural outcomes (length of hospital stay, stroke, acute renal failure, major bleeding, procedural success)**

ii) **Evaluate the association of AF with 12-month outcomes (hospitalization for heart failure, stroke).**

The working hypothesis is that AF is associated with an increased risk of peri-procedural and 12-month mortality as well as poorer peri-procedural and 12-month morbidity outcomes after MitraClip implantation. To test this hypothesis, we performed a systematic review and meta-analysis of eligible studies which reported the clinical outcomes of MitraClip according to the presence or absence of baseline AF.

1.8.7 Specific aim 7:

a) Primary aim: Evaluate the impact of training status (trainee vs consultant) on peri-operative and mid-term (> 12 months) mortality after CABG

b) Secondary aims:

i) **Evaluate the impact of training status on peri-operative outcomes (stroke, myocardial infarction, acute renal failure, re-operation for bleeding, wound infection, length of hospital stay, and length of ICU stay)**

ii) **Evaluate the impact of training status on technical outcomes (aortic cross-clamp time, cardiopulmonary bypass time)**

iii) **Evaluate the impact of training status on peri-operative and mid-term outcomes after OPCAB**

The working hypothesis is that training status does not compromise peri-operative or mid-term outcomes in patients undergoing CABG. To test this hypothesis, we performed a systematic review and meta-analysis of eligible studies which reported the clinical outcomes of patients undergoing CABG, stratified by training status.

1.8.7 Specific aim 8:

a) Primary aim: Evaluate the impact of training status on peri-operative and mid-term (> 12 months) mortality after aortic and mitral valve surgery

b) Secondary aims:

i) **Evaluate the impact of training status on peri-operative outcomes (stroke, myocardial infarction, acute renal failure, re-operation, re-operation for bleeding, wound infection, permanent pacemaker implantation) after aortic and mitral valve surgery**

ii) **Evaluate the impact of training status on technical outcomes (aortic cross-clamp time, cardiopulmonary bypass time) after aortic and mitral valve surgery**

The working hypothesis is that training status does not compromise outcomes in patients undergoing valvular heart surgery. To test this hypothesis, we performed a systematic review and meta-analysis of eligible studies which reported the clinical outcomes of patients undergoing valvular heart surgery, stratified by training status.

SECTION II

THE UTILITY OF CLINICAL REGISTRIES AND RISK STRATIFICATION FOR PROGNOSTICATION IN CARDIAC SURGERY

CHAPTER 2

APPLICATION OF CLINICAL REGISTRIES TO CONTEMPORARY CARDIAC SURGERY: WHERE ARE WE NOW?

2.1 BACKGROUND

In clinical medicine, prospective and well-conducted randomized controlled trials (RCTs) are regarded as the gold standard for establishing safety and efficacy of an intervention. Unfortunately, RCTs often cannot be conducted for ethical, financial or practical reasons(98, 99). This is particularly true in surgery; only 24% of the main treatment interventions in surgical patients are supported by randomized evidence(100). For thoracic surgery, only 14% of treatments are supported by randomized evidence(101). Consequently, the effects of new devices and techniques are often based on observational data obtained from large registries. Registry studies can also be used to study rare outcomes, risk factors, and side effects, and to examine whether results from RCTs translate into effective treatment in routine practice. Support from randomized trials cannot and should not be demanded of all treatment interventions used in clinical practice(102). Performing high-quality observational studies requires the availability of large datasets with clinically important variables.

Cardiac surgery has embraced and encouraged the use of large, multi-institutional datasets in clinical practice. Beyond their value for research, these datasets are often used for quality assurance and clinical governance (103, 104). Moreover, these datasets have been employed to generate risk assessment tools which have significant utility for patient counseling, operative decision-making and treatment allocation(105-108). Overall, the widespread adoption of datasets in cardiac surgery has facilitated improved outcomes (40, 109). Herein are discussed various aspects of large registries relevant to cardiac surgery clinical research and practice.

2.2 ADVANTAGES OF CLINICAL REGISTRIES

The research utility of large registries cannot be denied. The robust outcomes data from the Society of Thoracic Surgeons (STS) registry has itself led to over 150 peer-reviewed publications.

One particular advantage is the large sample size available for analysis. This generally represents a larger proportion of the population of interest, thereby reducing sampling error and improving external validity(110). Large registries also capture data on patients with rare diseases (such as primary cardiac sarcomas) or those undergoing an infrequently performed procedure(111).

Often, in clinical medicine, RCTs cannot be performed because low disease incidence or uncommon adverse outcomes would require extremely large sample sizes. In these situations, large observational registries may allow us to infer causal relationships or relate outcomes between variables if good study design and statistical modeling (e.g. propensity matching techniques) are employed (102, 112, 113). For example, the Framingham Heart Study, an ongoing epidemiological heart study has provided substantial insight into the epidemiology of cardiovascular disease and its risk factors. One of its most important contributions was the demonstration that both hypertension and AF were potent risk factors for stroke(114). Wolf and colleagues(115) used the Framingham data to demonstrate that non-rheumatic AF was associated with a > 5 fold excess risk of stroke. This prompted the authors to recommend controlled trials of anticoagulation in patients with AF. These trials were subsequently performed and led to anticoagulation becoming the standard of care.

Furthermore, RCTs are expensive; one study showed a mean cost of $USD 12 million per RCT(116). Also, the conduct of a RCT takes several years until being published, thus data is restricted from the medical community for many years and may be less relevant at the time of publication. In light of these disadvantages, a good registry study, rather than a randomized controlled trial, may represent a more appropriate research tool for in certain clinical circumstances(102).

Registries have other advantages. The inclusion of large number of patients from multiple centers reduces procedure selection biases and difference among groups that would otherwise reduce the validity of single center studies. Furthermore, because of the heterogeneity of the population captured in datasets, the focus is on effectiveness (the effect of intervention in general clinical situations) rather than efficacy (the effect of intervention in ideal circumstances). As such, the collection and analysis of large, population-based datasets reflects real world practice(110). Moreover, because registries utilize data that has already been collected, studies based on registries are usually less expensive, less obtrusive, less likely to be ethically questionable, and quicker to perform. As emphasized by Nguyen and colleagues, registries also allow for ongoing review of disease incidence, disease mortality, volume-outcome relationships, national trends in the use of procedures, and disparities in health care(110). In cardiac surgery, the ongoing assessment of patient data has demonstrated to clinicians and healthcare policy makers the shifting profile of patients undergoing cardiac surgery. They have shown that surgical patients are older and have more co-morbidities(40). Concurrently, analysis of data from registries has been critical in demonstrating the improved outcomes in high-risk groups, such as the elderly(45, 53). We previously used the Australian and New Zealand Society

of Cardiac and Thoracic Surgeons (ANZSCTS) Registry to evaluate the outcomes of octogenarians (> 80 years) undergoing CABG(45). Our data showed that 30-day mortality (4.2%) was significantly lower than historical controls and the 5-year survival of these patients (73%) was comparable with the age-matched Australian population. We reported similarly encouraging results in octogenarians undergoing isolated AVR and concomitant AVR-CABG(47, 50). These data have subsequently facilitated increased acceptance of surgical intervention in these patients which has translated into superior long-term survival. The fact that trainee surgeons can safely perform cardiac surgery was demonstrated through registry analysis(117-119). Shi and colleagues(120) analysed the outcomes of mitral valve surgery performed by surgeons-in-training using the ANZSCTS registry. The authors derived 142 propensity-score-matched patient pairs and demonstrated that trainee cases experienced longer cross-clamp times (137 ± 52 vs 121 ± 58 mins, p=0.023), but there was similar 30-day mortality (3.5% vs 4.2%, p=1.00) and any mortality/morbidity (24% vs 28%, p=0.52). Six-year survival between matched pairs was also similar (80% vs 74%, p=0.64). We used the ANZSCTS registry to demonstrate similar results for patients undergoing AVR and AVR-CABG(47, 117). Moreover, the impact of surgical volume on outcomes, disparities in outcomes on the basis of socioeconomic status and comparisons in outcomes on the basis of operative techniques have all been facilitated by registry analyses(121).

Well-conducted cardiac surgery registries have also facilitated the development of clinically useful risk-assessment tools. In cardiac surgery, risk tools such as EuroSCORE, Society of Thoracic Surgeons Score and AusScore have all been developed using well-designed, prospective datasets(105-108). These tools are useful for several reasons.

Firstly, they provide relatively objective information to patients regarding the risks and benefits of surgical procedures(103). In clinical practice, this risk is estimated from the clinicians' knowledge and experience, but risk-prediction models can provide an objective and individualized probability estimate of an adverse outcome, such as operative mortality. Accordingly, risk models, derived from registries, are often used to facilitate informed patient consent(103, 122). Secondly, risk models contribute to quality assurance and improvement(121). Operative mortality is often used as a surrogate marker for surgical quality. The use of this marker alone, however, is confounded by the fact that demographic, comorbidity, and disease-severity profiles are highly variable among patients, within and between institutions(123). Consequently, comparison of operative outcomes without adjusting for prognostically influential variables will lead to an invalid evaluation of the efficacy of a surgical procedure. Using risk models at an institutional or population level and comparing the estimated risk with actual outcomes is useful for quality assurance and identifying underperforming centers(124). Thirdly, risk scores assist with surgical and interventional decision-making. In particular, risk models are increasingly used to determine whether patients might be better suited for transcutaneous aortic valve implementation (TAVI) rather than surgical aortic valve replacement (AVR)(103, 125).

Aside from their obvious research utility, clinical registries are important tools for clinical governance and quality control. As stated earlier, operative mortality is often used as a surrogate marker for surgical quality(103, 126). Since the widespread implementation of registry reporting, several studies have demonstrated a decreased rate of operative mortality despite an increase in the predicted mortality of patients(40). This

likely represents, at least to some degree, active interventions implemented at the national and institutional level to improve the quality of care provided to patients undergoing cardiac surgery. The transparent reporting of mortality outcomes makes it incumbent on health providers to improve the quality of pre-operative, intra-operative and post-operative care of patients undergoing surgery. In the ANZSCTS registry(127), units are evaluated against key parameters of performance. Five clinical outcomes (mortality, reoperation for bleeding, deep sternal wound infection, derived new renal failure and permanent stroke) are used for peer review while the remaining administrative data points are used in online and annual reports to compare unit activity at a national level. Selection bias is minimized because the data completeness of these key indicators is greater than 95%.

Moreover, in the United States, perceived quality of surgical care might affect a patient's choice of health-care provider and this choice is made possible by public reporting of institutional performance. One of the first programmes that used "provider profiling" in cardiac surgery arose in the late 1980s with collection of clinical data from all patients undergoing CABG surgery in New York State, USA(128). This registry was used to derive data on surgeon-specific and institutional-specific operative mortality that were publically disclosed. After the introduction of public reporting, a 41% decline in risk-adjusted mortality between 1989 and 1992 was reported. Furthermore, Medicare patients in New York experienced a 22% decline in CABG surgery mortality between 1989 and 1992 compared with a 9% decline in the USA overall(129). Several states including California, Massachusetts, New Jersey, and Pennsylvania have also provided institutional 'report cards' reflecting surgical outcomes with the rationale that these will

stimulate health-care providers to improve quality of care to attract patients to their institutions(130). Some evidence suggests that this strategy might reduce provider-specific mortality in cardiac surgery, but its success has been variable(131). For example, some researchers reported that only 10% of patients interviewed in Pennsylvania, USA were aware of the existence of institutional report cards, and <1% were familiar with the performance of their chosen care provider(132). Public reporting of cardiac surgery performance, although offering transparency, may also have unintended negative consequences. For example, institutions might erroneously code patients in a high operative risk category to improve their apparent surgical performance(133).Aversion to treating a high-risk patient is another potential concern with public reporting. Surgeons might decline to treat high-risk surgical candidates to maintain a low publicized operative mortality for marketing purposes(132, 134). Some organizations, such as the Veterans Administration, have embraced the notion that provision of feedback to health-care providers might improve quality of care, but have opted to provide such feedback confidentially. In doing so, participating institutions are privately informed of their performance relative to overall national benchmarks, with the intent of stimulating continuous enhancement in surgical quality. In this way the improvement in quality is not necessarily a function of public reporting, but rather a consequence of a structured programme of feedback provision. Regardless of what strategy is employed, it is accepted that provision of ongoing feedback to institutions in comparison to national and international benchmarks improves healthcare delivery.

The most prominent example of where the introduction of a registry has improved outcomes is in paediatric cardiac surgery in the United Kingdom. The impetus for this was

a public inquiry into high mortality rates at the Bristol Royal Infirmary(135). A subsequent report emphasized the importance of collating clinical data and all paediatric units were required to be involved in the Central Cardiac Audit Database (CCAD)(136). The data was analysed at regular intervals by a collaborative team comprising the Royal College of Surgeons, professional societies and the Department of Health with provision of feedback to underperforming units The improvement in results was reflected by a 75% in mortality rates between 1985 and 2002(136).

Nag and colleagues(124) reported that a combined performance report and structured feedback improved performance in under-performing units in Australia and New Zealand. Furthermore, Grover and colleagues(137) argued that the regular and systematic feedback of data at an institutional and national level heightens awareness and leads to self-examination and more prudent practice, thereby improving outcome.

Another utility of clinical registries has been in establishing the link between surgical volumes and outcomes. Such analyses have influenced the reorganization of healthcare systems and have been used to audit the results following reorganization(121). Gammie and colleagues(138) used the STS National Cardiac Database to evaluate the outcomes of 13614 patients who underwent elective surgery for mitral regurgitation. The authors demonstrated that annual mitral valve volumes varied widely from 22 cases per year in the lowest-volume quartile to 394 in the highest. The risk-adjusted odds ratio for mortality in the highest-volume category compared to the lowest was 0.48 and the rate of mitral valve repair increased from 47.7% to 77.%. Such findings have led, in some cases, led to a rationalization of healthcare resources such

that certain complex procedures are more routinely performed at recognized “centers of excellence”(139).

A summary of the advantages of clinical registries is provided below (Table 2.1).

Table 2.1: Advantages of Clinical Registries	
1	Research utility -Large sample size -Study rare disease or uncommon adverse outcomes -Study infrequently performed procedures -Studies less expensive, obtrusive than RCTs -Studies less ethically questionably than RCTs -Studies are quicker to perform
2	Facilitate development of risk-assessment tools
3	Drive quality improvement and clinical governance
4	Ongoing review of disease incidence, disease mortality, volume-outcome relationships, national trends in the use of procedures and disparities in health care

2.3 DISADVANTAGES OF CLINICAL REGISTRIES

Despite their utility, registries have several disadvantages. Firstly, they are subject to treatment bias(110). The observed treatments were not randomly assigned, but rather the decisions were made based on patient’s characteristics, provider preference, and other clinical factors. Procedural selection is problematic as it confounds direct comparisons between groups(140). For research studies, several techniques can be employed to improve the ability to infer causal relationships or relate outcomes between variables in non-randomized studies. The most commonly employed method is multivariate analysis, where various forms of regression models (logistic regression, liner regression, or Cox proportional hazards models) are used to estimate the effects of

multiple variables on a given outcomes variable(110). Case-control matching, propensity scoring methods, and instrumental variables have also been employed to correct for treatment bias(112). While these techniques are effective, they cannot eliminate other sources of selection bias due to unmeasured and unidentified variables. Hence, observational studies do not allow firm causal conclusions from being drawn due to the potential for bias and confounding when compared with randomized controlled trials.

Registries are also subject to sampling error and missing data. Large registries often represent incomplete samples of the cohorts they represent(110). If sampling is random, the dataset can still serve as a good estimate of the population with an appropriate sampling error(110). If patients or data elements are missing because of systemic causes, however, the registry is susceptible to systemic bias. For example, if data from patients in particular institutions is consistently underreported due to a lack of registry administrative staff, then the frequency of disease and procedures that may be associated with those institutions will be underrepresented. Many registries only subsample the population by design because of cost or logistic concerns(110). In doing so, registry administrators must ensure that the sampling algorithms will result in a subset of patients' representative of the entire population of interest. Sampling error decreases as sample size increases and approaches the true population size. Special care must be taken to adequately sample small subgroups, such as racial minorities, or rare diseases of interest(110). Their small numbers make them more susceptible to sampling error. In practice, cardiothoracic surgery registries usually capture a large proportion of the procedures performed in a given unit.

Patients and their related data elements may also be missing from the registry due to clerical or logistic reasons.(110) Whilst data entry errors are to some degree inevitable, it is more concerning that systematic inconsistencies and omissions in the coding may lead to misleading findings(141). The accuracy of diagnostic coding can vary significant between different categories and coding of secondary diagnoses is often inferior to primary coding(142). Furthermore, although it would be ideal for trained and dedicated staff to be responsible for data entry, this is not always feasible. Black and colleagues(143) in a cross-sectional survey of 105 multicenter clinical registries in the United Kingdom also demonstrated that the accuracy and completeness of data is influenced by the purpose for which the dataset was created.

In addition, missing data may not be randomly distributed among the registry sample but is rather specific to the patient (i.e., different sets of variables collected at different study sites)(121). Missing data may introduce statistical error and bias results(144). In general, a variable should be included in a multivariate analysis only if <5% of its values are missing(110). Methods do exist to replace missing values, such as using mean value or using logistic regression formulas to compute a value, but such methods should be limited to cases in which no more than 5% to 15% of the values of a variable are missing(145). With regards to risk stratification, it has been shown that much of the predictive power of surgical risk models is derived from a limited number of critical clinical variables which are sometimes missing in administrative registries(121). Cook and colleagues(121) emphasized the importance of clear and easily understood coding structures when establishing a data collection system. This, together with the ongoing

monitoring of the appropriateness of the coding structures to changes in healthcare can minimize inconsistencies and missing data.

Maintenance of registries also requires significant human and financial resources(121). Usually a dedicated registry manager is required at each site to facilitate the collection, tabulation and evaluation of data. Dixon and colleagues(146) from Baylor Health in the United States reported that the cost of registry participation at their institute was >$125,000 USD with an additional cost of 6.5 full-time employees for registry management. In 1990, the collection of detailed hospital outcomes data was estimated to cost US$61 million in California alone(147).

For multi-institutional registries, a supervising registry manager is needed to provide feedback and ensure consistency of reporting across sites(124, 148). Linkage with other datasets (such as birth and death data) is required and this represents a complex undertaking(144). Regular meetings by a dedicated multi-disciplinary team of surgeons, biostatisticians and registry managers are required to ensure that the registry remains relevant(127). In practice, registry custodians invest substantial time and effort in refining variable definitions when updating versions of the clinical registry, with the goal of optimizing clarity and data accuracy(127). These changes, however, can be problematic, owing to the fact that data gathered using previous registry versions are not reabstracted. The implications of these dynamic variable definitions on outcomes have not been clarified but nevertheless represent a limitation. Finally, ensuring that registries function effectively requires an ongoing funding source(127).

Table 2.2 summarizes the disadvantages of clinical registries.

Table 2.2: Disadvantages of Clinical Registries	
1	Subject to treatment bias
2	Sampling error and missing data
3	Significant human and financial resources required
4	Regular reviews and updates to ensure registry remains contemporaneous

2.4 CLINICAL REGISTRIES IN CURRENT CARDIOTHORACIC SURGERY PRACTICE

Clinical registries which capture data on patients undergoing cardiothoracic surgery have been present for several decades. The largest, and arguably, most robust, registry is the Society of Thoracic Surgery (STS) Adult Cardiac Surgery Database (ACSD) from the United States. Established in 1989, the STS-ACSD has gathered data on more than 5 million surgical records representing 95% of cardiac surgery programmes in the USA(149). The latest STS-ACSD edition collects information on >600 individual data points per patient. The data is subject to a comprehensive audit by the STS Audit Task Force to ensure its completeness and accuracy. The audit has demonstrated a <1% error rate in the documentation of major operative complications in an institutional STS dataset(150) .

Since its inception, the STS-ACSD has also emerged as a powerful tool for clinical research. More than 100 publications have been derived from registry outcomes(149). These studies have been published in a variety of professional journals and textbooks and have contributed to improvements in knowledge in cardiothoracic surgery. Moreover, the data collected by STS-ACSD has allowed the derivation of numerous risk models to predict outcomes—including operative mortality, early postoperative permanent stroke, renal failure, prolonged ventilation, deep sternal wound infection, and reoperation in patients undergoing CABG surgery or valvular heart surgery(103, 108). The STS risk

assessment tools have been applied worldwide in the pre-operative evaluation of patients and their utility has been shown in numerous studies. A significant advantage of the STS registry is that independent subsets of patients (for example, only those undergoing CABG surgery or AVR) were used to develop procedure-specific score, thereby enhancing risk-prediction accuracy. In contrast, the European System for Cardiac Operative Risk Evaluation (EuroSCORE) was derived from a repository consisting predominantly of patients undergoing isolated CABG but has been applied to non-coronary surgery.

The Society for Cardiothoracic Surgery (SCTS) registry is an analogous registry to the STS registry used in the UK and Ireland. The SCTS registry was established in 1994, and includes information on >400,000 operative records, including data from all National Health Service hospitals that undertake adult cardiac surgery in the UK with input from some private providers and hospitals in Ireland. In addition, long-term mortality data from the UK Office of National Statistics (ONS) is linked to the registry offering long-term tracking. Like the STS registry, the SCTS registry has facilitated the continuous evaluation of performance in cardiac surgery units across the country. Moreover, it has served as an excellent research useful tool in its own right.

In 2001 the Australasian Society of Cardiac and Thoracic Surgeons (now the Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS), together with the Victorian Department of Health developed a program to collect data on, cardiac (heart) surgery in Victorian hospitals. The program has since expanded to include 19 of 25 public Hospitals and 6 private hospitals Australia-wide. At present, the program contains over 100,000 records. The ANZSCTS data definitions manual were developed

based on adaptions from the STS and the SCTS registry but have been refined since then(127). Registry data has been linked to mortality data obtained from the Australian National Death Index allowing for evaluation of long-term survival. The ANZSCTS registry was used in the derivation of several risk stratification tools including the “AusScore” which estimates the risk of 30-day mortality in patients undergoing isolated CABG(107). More recently, the “AusScore II” was derived from the dataset with the benefit of greater patient numbers and longer follow-up(151). In addition, outcomes-based studies have been published using the ANZSCTS registry; these have demonstrated the safety and efficacy of cardiac surgery in several “high-risk” groups and addressed the impact of certain variables on outcomes (45, 47, 53, 118, 152, 153). A promising initiative in Australia is the possible integration of the ANZSCTS registry with a nationwide registry on interventional cardiology procedures. A dedicated registry on percutaneous coronary intervention exists in Australia and it is managed by the same body as the ANZSCTS registry under the auspices of different steering committees. The integration of both registries has been envisaged and discussions are continuing(154).

The ongoing success of these nationwide registries from a clinical governance, quality improvement and research standpoint has encouraged other countries to develop their own registries(155, 156). Specialized adult cardiothoracic surgery datasets for novel procedures such as transcatheter aortic valve implantation (TAVI) and mitral clip implantation have also been devised and may soon see widespread application (157).

2.5 FUTURE ENDEAVOURS

The last 20 years have seen a significant increase in the application of clinical registries to cardiothoracic practice. Moreover, they have been refined through the process of continuous quality improvement. Nevertheless, there is considerable room for improvement. Many registries have not been linked to provide access to long-term survival. Even those that do often lack data on the cause of mortality(127). Moreover, angiographic follow-up is absent in almost all large clinical registries. The possible integration of more detailed long-term clinical data in the future will significantly improve the utility of. It is increasingly accepted that quality of life (QoL) outcomes are an important measure of procedural success after cardiac surgery. Unfortunately, few registries contain any information of QoL outcomes. Integration of these data into existing cardiothoracic registry or linkage with current QoL registries will facilitate increased understanding of the impact of cardiac surgery on QoL(158). Similarly, linkage with cost, intensive care unit stay and re-admission data will allow increased understanding of the resource utilization associated with cardiac surgery, particularly for high-risk groups. An ongoing initiative in some countries is the integration of cardiac surgery registries with registries evaluation non-surgical cardiac interventions such as PCI and TAVI. Several registries have already included these procedures in prospective datasets whilst discussions are ongoing in other countries(159).

2.6 CONCLUSIONS

Clinical registries are important for the purposes of clinical governance, quality control and research, among others. They have facilitated an increased understanding on the

impact of cardiac surgery on patient outcomes. Important findings regarding the incidence or prevalence of cardiac risk factors in a population, disease and procedure-specific mortality, volume-outcome relationships, national trends, disparities in healthcare delivery, and other important insights will continue to be reported through large registry studies. Nevertheless, clinical registries are imperfect and require substantial financial and human resources for ongoing maintenance. Improved linkage with other registries will increase the utility of clinical registries in the future.

SECTION II

THE UTILITY OF CLINICAL REGISTRIES AND RISK STRATIFICATION FOR PROGNOSTICATION IN CARDIAC SURGERY

CHAPTER 3

THE BENEFITS AND PITFALLS OF THE USE OF RISK STRATIFICATION TOOLS IN CARDIAC SURGERY

3.1 BACKGROUND

From its experimental background, cardiac surgery has become an indispensable tool in the armamentarium against congenital and acquired cardiovascular disease. In the last two decades, the continuous improvements in all aspects of health care have transformed cardiac surgery from a relatively morbid undertaking to a safe and effective treatment for cardiac disease. This has been reflected by improved peri-operative and long-term outcomes in patients despite an increase in mean age and co-morbidities(39). A review of Australian data showed a 30-day mortality of only 1.7% and 1.9% in patients undergoing isolated coronary artery bypass graft (CABG) surgery and aortic valve replacement (AVR), respectively(160, 161). In contrast, high-volume institutions in the 1980 and 1990s routinely reported 30-day mortality of between 3-6%(40, 162). A review of American data as collected by the Society of Thoracic Surgeons (STS) shows a continuous reduction in operative risk over time. Ferguson and colleagues(40) demonstrated that observed operative risk decreased by 23.1% (3.9% to 3.0%) from 1990 to 1999 ($p<0.001$) despite a 30.1% increase in predicted risk. A subsequent analysis on American patients undergoing isolated primary CABG showed that observed mortality decreased from 2.4% to 1.9% from 2000 to 2009 (relative risk reduction of 24.4%) despite no change in predicted risk.

3.2 IMPORTANCE OF RISK ASSESSMENT IN CARDIAC SURGERY

Despite these improvements, it must be noted that cardiac surgery induces a vigorous stress and inflammatory response in the body, particularly in older, more vulnerable patients(163). Vulnerable patients are at higher risk for complications after surgery and

will be less likely to return to function post-operatively(163). There is a substantial body of evidence that combination of physiological function, co-morbidity, and inflammation contribute to a patient's vulnerability for negative outcomes after cardiac surgery(106, 163, 164). Holmes and colleagues(164) demonstrated that cardiopulmonary bypass is associated with a dramatic rise in inflammatory markers with levels that can be over 100 times the baseline level. This is amplified in vulnerable patients who often have a pre-existing low level inflammation and contributes to complications such as vasoplegia, new-onset AF and delirium(165, 166). It is imperative to pre-operatively assess a patient's suitability for surgery by objectively evaluating their risk profile. Standardized risk assessment for invasive procedures is important and useful for three main tasks in cardiac surgery (Table 3.1).

Table 3.1: Summary of potential uses of risk scoring systems	
1	Inform patients and clinicians about risk
2	Benchmark performance of particular units against general population
3	Monitor impact of innovative new therapies
4	Evaluate the efficacy on investment of health promotion strategies
5	Improved data management

The first is to inform patients and clinicians about risk(103). It is essential to provide a thorough explanation of potential risks to patients, particularly given that there may be non-surgical approaches available to them and to their clinicians that modify risks, especially in high-risk patients. This is particularly important in the contemporary era,

where there is an increased expectation for clinicians to provide information to patients on potential risks and more non-surgical treatments are available. In fact, in current clinical practice, the allocation of patients to treatment is largely guided by risk-benefit assessment. For example, surgical aortic valve replacement (AVR) remains the gold-standard intervention for patients with severe aortic stenosis. In patients, adjudged to be "high risk" as per risk assessment tools, however, surgical AVR may not be appropriate. In these "high risk" patients, studies have shown that transcutaneous aortic valve implantation (TAVI) may improve symptomatology and survival(47, 167). Overall, risk assessment assists clinicians and patients in choosing the most suitable treatment option.

Moreover, the use of risk-prediction models can help clinicians to understand the contribution of risk factors to post-operative outcomes(168). Systematic use of these tools can identify at-risk patients and lead to interventions to modify risk. Chronic respiratory disease is a risk factor for operative mortality and a complicated postoperative recovery(168). In these patients, a strategy that addresses modifiable risk factors including weight loss, smoking cessation 30 days prior to surgery and optimizes lung function with pre-operative pulmonary rehabilitation, exercise, patient education, and treatment of bronchospasm and bronchorrhea may improve outcomes(169). Post-operative lung dysfunction can also be minimized by reducing time on mechanical ventilator support, and avoiding crystalloid and blood product transfusions(170). A strategy of early extubation, particularly in patients with pre-existing lung disease, is also associated with improved outcomes(171). A similar systematic approach can be adopted for patients with other co-morbidities.

Secondly, collection of risk assessment data allows us to benchmark the performance of particular units against the general population(104). Arguably, the improved outcomes in cardiac surgery in recent decades largely reflect the increased scrutiny on patient outcomes by registries and risk assessment tools(103). Improvements in outcome can be correlated with changes in clinical practice through registries which are used to collect risk assessment data; for example, reductions in observed mortality versus predicted mortality has been traced to the increased use of internal mammary artery for revascularization(172, 173). Risk assessment data may identify underperforming units and thereby lead to internal or external audit of clinical practice with a view to improving patient outcomes(103, 124). Thalji and colleagues(103) also suggested that risk assessment tools may drive improve outcomes via the "Hawthorne effect" – that is, operators aware of the scrutiny associated with their outcomes may have improved performance, resulting in favorable operative mortality, which is lower than pre-operative estimates.

Thirdly, risk assessment is an important research tool. It allows us to monitor the impact of innovative new therapies on performance. In cardiac surgery, for example, the safety of novel operative techniques such as off-pump cardiac surgery has been established by comparing the safety and efficacy of this procedure in patients with a similar risk profile who underwent conventional on-pump surgery(174, 175). Risk assessment allows us to determine whether improvements in clinical practice have been made through comparison of observed morbidity and predicted morbidity over time. Moreover, risk assessment allows identification of patient subgroups in whom it may be useful to evaluate alternative treatments, for example, "high risk" patients with valvular

heart disease(168). Simply put, risk assessment facilities innovation and scientific discovery.

3.3 APPLICATION OF RISK ASSESSMENT TOOLS IN CARDIAC SURGERY

Given the considerable benefits of both the collection and analysis of risk assessment data, several risk assessment scoring systems have been developed for cardiac surgery. The majority were developed to predict risk of operative mortality(176). Non-fatal outcomes have been difficult to accurately assess because of the low incidence of some outcomes for patients undergoing cardiac surgery. The most common significant non-fatal outcomes after cardiac surgery include permanent stroke (0.5-2%), acute myocardial infarction (0.5-2%), new renal failure (4-6%) and return to theatre (6-10%)(160, 161, 177). Early studies used single institution data to generate a risk prediction algorithm, while more recent studies have used multi-institutional data with larger patient samples(108, 178-180). This explains why there is significant variation in the clinical factors incorporated for the assessment of risk in the various scoring systems, because of variations in the patients being studied (Table 3.2). Some factors, however, such as advanced age, non-elective procedures, acute renal failure and impaired left ventricular function have ubiquitously been associated with poorer outcomes(108, 176, 178-180).

Table 3.2: Summary of variables included in risk assessment tools

	Parsonnet	**Cleveland**	**EuroSCORE I**	**Pons**	**STS**	**EuroSCORE II**	**AusScore I**	**AusScore II**
Patient Data								
Age	+	+	+	+	+	+	+	+
Body weight	+	+	-	-	+	-	-	-
Cardiac								
Unstable angina	-	-	+	+	-	+	-	-
Aortic stenosis	+	+	-	+	-	-	-	-
Active endocarditis	-	-	+	+	-	+	-	-
Congenital heart defect	+	-	-	-	-	-	-	-
Hypertension, arterial	+	-	-	-	-	-	-	-
Hypertension, pulmonary	+	-	+	-	-	+	-	-
Left ventricular aneurysm	+	-	-	-	+	-	-	-
Left ventricular ejection fraction	+	+	+	+	-	+	+	+
Mitral valve insufficiency	-	+	-	-	+	-	-	-
Myocardial infarction	-	-	+	+	+	+	-	+

NYHA	-	-	-	+	+	+	+	+
Post MI VSD	-	-	+	-	-	-	-	-
Ventricular tachycardia/fibrillation	-	-	+	-	+	-	-	-
Pulmonary								
Asthma	+	-	+	-	-	-	-	-
COPD	-	+	+	+	-	+	-	-
Renal								
Dialysis	+	-	-	-	+	+	-	+
Creatinine	-	+	+	+	+	+	-	+
Acute renal failure	+	-	+	-	-	-	-	-
Other								
Anemia	-	+	-	-	-	-	-	-
Diabetes	+	+	-	-	+	+	-	-
Liver disease	-	-	-	+	-	-	-	-
TIA/Stroke History	-	+	+	-	+	+	-	-
Paraplegia	+	-	-	-	-	-	-	-
Pacemaker	+	-	-	-	-	-	-	-
Vascular						-	-	-
Peripheral arterial disease	-	+	+	-	+	+	+	+
History of vascular surgery	-	+	-	-	-	-	-	-
Preoperative								

Ventilation	-	-	+	+	-	-	-	-
Intra-aortic balloon pump	+	-	+	-	+	-	-	-
Inotropes	+	-	+	-	+	-	-	+
Resuscitation	-	-	+	-	-	-	-	-
Cardiogenic shock	+	-	-	-	+	-	+	+
Operation								
Combined surgery	+	-	+	+	+	+	-	-
Urgent/Emergency	+	+	+	+	+	+	-	-
Reoperation	+	+	+	+	+	+	-	-

The most commonly used scoring systems are the European System for Cardiac Operative Risk Evaluation (EuroSCORE) and the American Society of Thoracic Surgeons (STS) risk score(105, 108, 180). Both of these can be easily accessed online and provide a near immediate assessment of a patient's risk of peri-operative mortality provided their co-morbidities are accurately known. Studies have validated both scoring systems(181, 182). These scoring systems, however, must be used with caution (Table 3.3). Studies have also shown that they may overestimate the risk of operative mortality, especially in high-risk groups(183, 184). A study on the applicability of the EuroSCORE in an Australian patient cohort, for example, showed that it over-estimated the risk of operative mortality by a factor of 2(183). If the EuroSCORE alone was used to select patients for surgery, many patients who would have a reasonable outcome may be inappropriately excluded. Scoring systems have also been developed using data from the Australian registry (provided by the Australian and New Zealand Society of Cardiothoracic Surgery [ANZSCTS]) for cardiac surgery procedures(107, 185, 186). The most recent development was the development of the AusSCORE II for the estimation of 30-day mortality after isolated CABG surgery; this model demonstrated improved prediction compared to the original AusSCORE(187). Whilst this tool is likely to be more applicable to an Australian patient population, further studies are required to evaluate its validity.

Table 3.3: Disadvantages of Risk Scoring Systems	
1	Over-estimation of risk for patients, especially for high-risk patients
2	Confounding by unknown variables
3	Infrequent updates
4	Variation in use of variables between scoring systems
5	Demographic differences in patients across countries

3.4 LIMITATION OF RISK ASSESSMENT TOOLS

Risk scoring systems are developed at a particular time and are infrequently updated; as such, they frequently over-estimate operative risks(183). The EuroSCORE, in particular, has been shown to dramatically overestimate the risk of operative mortality. Brown and colleagues(188) in a series of 1177 patients undergoing isolated AVR reported that the predicted operative mortality with the logistic EuroSCORE (10.9%) was more than four times greater than the observed mortality (2.5%). The greatest discrepancy was in high-risk patients, in whom estimated mean mortality was 23.6% versus an observed mortality of 5.7%(188). As cardiac surgery continues to evolve with improvements in operative technique, anesthesia and both pre-operative and post-operative care, operative mortality will, presumably, continue to decline. In the past decade alone, cardiac surgery has evolved such that minimally invasive techniques including robotic and endoscopic CABG surgery and valve replacements are being performed routinely in some centers. This trend is set to continue. Concurrently, the patient population undergoing cardiac surgery is getting older and sicker given the increased efficacy of medical therapies and utilization of percutaneous interventions in patients with less advanced disease(39, 177, 189). As such, contemporary scoring systems need to be continuously updated to reflect the changes in operative techniques and patient demographics. In 2011, the new EuroSCORE II algorithm was released to correct for the overestimation of hospital mortality by the original EuroSCORE(106). It has shown improved performance in more contemporary series(190). Nevertheless, the EuroSCORE II has also been shown to overestimate operative mortality in high-risk subjects(191).

Risk scoring systems are also derived and validated from a specific population (e.g. isolated first-time CABG) but applied more broadly. The EuroSCORE, for example, was derived from a sample of patients undergoing first-time CABG surgery but has been applied for risk assessment in patients undergoing transcatheter aortic valve implantation(192, 193), mitral valve replacement(194), aortic valve replacement(195), percutaneous coronary intervention(196, 197), among others. This tool has been validated for use in different patient subgroups but this is clearly not the main intention of its use. The European Society of Cardiology wrote a position paper in 2012 discussing the widespread use of risk scores derived from CABG patients to assess risk in patients with valvular heart disease(194). As part of their assessment, they reviewed the most widely used risk score (EuroSCORE, STS, and Ambler score), analysed the variables included and their predictive ability when applied to patients with valvular heart disease. They found that the scores provided a relatively good discrimination, i.e. a gross estimation of risk category, but could not be used to estimate the exact operative mortality in an individual patient because of unsatisfactory calibration. The authors advised that these models should be interpreted with caution and only used as a part of an integrated approach, which incorporates other patient characteristics, the clinical context, and local outcome data. Whilst use of risk assessment tools in non-target populations is not a major concern if it used in the gross estimation of patient risk, it is concerning if it influences patient management. This has undoubtedly been the case. For example, a quick search of the literature demonstrates that numerous institutions allocated patients to TAVI based on EuroSCORE(198-200). The allocation of patients with valvular heart disease to an experimental treatment based on risk assessment tools derived from patients with a

different disease altogether (coronary artery disease) is clearly concerning. Inadvertently, it may compromise patient care through improper treatment allocation. For example, in the multi-institutional, randomized trial comparing TAVI using the CoreValve® with conventional AVR, 30-day mortality in the surgical arm (4.5%) was substantially lower than that predicted using the STS model (7.5%). Similar results have been reported elsewhere. Hence, overestimation of surgical risk may result in patients being stratified for TAVI when conventional AVR is more appropriate. The development of disease and treatment specific risk-models is necessary to optimize patient safety and guide appropriate treatment.

It must also be noted that many clinical and patient-related factors which cannot be accounted for may influence outcomes. Additionally, factors which can be accounted for may not have been measured in the various datasets from which these risk assessment scoring systems are derived. In geriatrics, frailty assessments have been developed as a tool in determining physiologic functioning capacity. A recent systematic review demonstrated that frailty had a strong positive relationship with the risk of major adverse cardiac and cerebrovascular events (MACCE) (odds ratio 4.89; 95% confidence interval, 1.64-14.60)(201). Despite this, risk scores are yet to include frailty assessments in the preoperative assessment of risk. They remain heavily reliant on chronological age as a predictor of health. Other variables have also been proposed that warrant consideration in future risk assessment tools which may have particular utility in treatment allocation. These include AF(71), chest deformities(202), previous mediastinal radiation(103, 203), liver failure or cirrhosis(204) and porcelain aorta(205). Slow gait speed has also been independently associated with poorer outcomes(206). Even the

definition of co-morbidities in scoring systems needs to be reviewed before treatment allocation. For example, identifying the burden of peripheral vascular disease is important in the assessment of vascular access prior to TAVI but the majority of patients with PVD were classified on clinical rather than radiological grounds(103). This may also contribute to improper treatment allocation. The negative prognostic implications of AF across a spectrum of cardiac surgery procedures is discussed in depth in the later chapters of this thesis. The independent association of AF with poorer early and mid-term outcomes highlights both the deficiencies of many risk assessment tools and the opportunity to improve them further. The lack of inclusion of AF in risk assessment tools, has contributed, in our opinion, to its under treatment at the time of cardiac surgery. Many surgeons merely regard AF as a "nuisance" and a marked for a poorer physiological milieu(83). Our data strongly suggested that this is not the case. The fact that most contemporary risk assessment tools only predict the risk of an adverse early outcome (usually peri-operative mortality) is also misleading given that risk obviously extends beyond the peri-operative period and one of the primary goals for cardiac surgery is to prolong life. In this regard, the negative long-term implications of AF are underappreciated by contemporary scoring systems. We believe that future risk assessment tools should consider inclusion of AF as a risk factor particularly given that it can be potentially cured through concomitant AF surgery.

How much a patient can, or should, rely on risk estimates is also debatable, because mode accuracy and performance can be variable, particular between different patient populations(207, 208). Some investigators, in fact, proposed that during patient counseling, operative risk should be quoted as a range between two confidence intervals,

rather than an exact number. Hence, whilst risk stratification tools help to delineate risk in patient populations it is important for clinicians to recognize their limitations(123).

Alternatives to formal “risk stratification” tools have been proposed. Laurent and colleagues(209) developed a simple bedside clinical evaluation based on consensus of cardiologist who examined patients and ordered the preoperative preoperative workup. It consisted of classifying patients on a four-grade scale of estimated mortality risk: grade I (0-3.9%), grade II (4-6.9%), grade III (7-9.9%), or grade IV (≥10%), based on the result of all diagnostic investigations. The authors found that the beside clinical evaluation was as reliable as the various established scores for predicting operative risk. Whilst this tool may be useful in a clinical setting, however, it would undoubtedly lack the reproducibility or validity of established scoring systems. Moreover, the utility of this tool for research or quality assurance purposes would be limited. In patient selection for TAVI, most centers select patients after thorough risk assessment and review by a multi-disciplinary “heart team” consisting of a general cardiologist, interventional cardiologist, cardiothoracic surgeon, anesthetist and radiologist. This clinical approach, which is mandatory in many institutions, may decrease the inaccuracies associated with using risk assessment tools alone.

3.5 CONCLUSION

In summary, cardiac surgery in the contemporary era is reproducible, effective and increasingly safe. Outcomes have improved significantly over time and this trend is set to continue. Nevertheless, there are significant risks associated with cardiac surgery. Risk

stratification tools may allow clinicians to identify patients most likely to have an adverse outcome and tailor their management accordingly. Nevertheless, they should be interpreted with caution.

SECTION II

THE UTILITY OF CLINICAL REGISTRIES AND RISK STRATIFICATION FOR PROGNOSTICATION IN CARDIAC SURGERY

CHAPTER 4

OUTCOMES OF ON-PUMP (ONCAB) VERSUS OFF-PUMP (OPCAB) CORONARY ARTERY BYPASS GRAFT SURGERY IN THE HIGH RISK (AusSCORE > 5)

Statement from Corresponding author and Supervisor

confirming Authorship contribution of the PhD candidate

As co-authors of the paper "Outcomes of on-pump (ONCAB) versus off-pump (OPCAB) coronary artery bypass graft surgery in the high risk (AusSCORE > 5)", we confirm that Akshat Saxena has made significant contributions to the following:

- Conception, organization and execution of the research
- Literature search
- Writing the paper and critical appraisal of content
- Analysis and interpretation of data
- Participated in drafting and revising the paper and provided important intellectual contributions
- Revising the paper for important intellectual content

Vikrant Dhurandhur _____ Date: 11/07/2019

Paul G. Bannon _____ Date: 11/07/2019

4.1 INTRODUCTION

There is now a significant body of randomized evidence that has confirmed that coronary artery bypass graft (CABG) surgery is the standard of care of patients with complex coronary artery disease and comorbidities such as diabetes, peripheral vascular disease and left main disease(210, 211). The prevalence of these “high risk” patients will increase given the ageing population of developed countries. In Australia, the median age has increased by 4.8 years over the last two decades and the proportion of people aged 65 years and over will increase from 14.4% in 2003 to 24% in 2056(212). Advanced age is associated with diminishing physiological reserve and increasing comorbid illnesses, including diabetes, chronic obstructive pulmonary disease, cerebrovascular disease, and peripheral vascular disease (213).

Cardiopulmonary bypass (CPB) and cardioplegic arrest have formed the basis of CABG surgery for over three decades. However, the association of CPB with systemic inflammation and multi-organ dysfunction has led some surgeons to adopt off-pump (OPCAB) techniques(214). Several authors have reported that OPCAB reduces mortality and morbidity, specifically stroke rates, transfusion requirements, atrial arrhythmia rates and renal dysfunction(215, 216). Puskas and colleagues showed that the high-risk population benefits in terms of mortality from the OPCAB approach (217). This enthusiasm, however, has been tempered by concerns that OPCAB may compromise graft patency, lead to incomplete revascularization and compromise long-term survival(218, 219). A meta-analysis of 27,623 octogenarians showed that OPCAB was associated with a reduced in-hospital mortality, stroke rate and length of hospital stay(220).

We evaluated real life registry data collected by the Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) registry, and compared the 'on-pump' (ONCAB) and OPCAB approach in the high-risk population. High-risk status was determined by an additive AusSCORE greater than 5. The AusSCORE risk prediction model has shown greater accuracy at predicting operative mortality than the EuroSCORE in the Australian cohort (221).

The primary aim of this study was to evaluate whether OPCAB, compared to ONCAB, improves peri-operative outcomes (30-day mortality, myocardial infarction, take-back for graft occlusion, re-bleeding, new renal failure, new atrial fibrillation/flutter, ventilation > 24 hours, infection, neurological events, length of hospital stay, length of intensive care unit stay) in high-risk patients (AusSCORE > 5) undergoing CABG. The secondary aim was to compare mid-term survival outcomes between the two groups. The working hypothesis is that OPCAB, compared to ONCAB, reduces peri-operative mortality and morbidity and improves mid-term survival in high-risk patients because it avoids the use of an extra-corporeal circuit and minimizes aortic manipulation.

4.2 MATERIALS AND METHODS

4.2.1 Patient selection

Patient data collected at hospitals in Australia and New Zealand participating in the ANZSCTS registry between January 2001 and January 2012 was included. The Ethics Committee of each participating hospital had previously approved the use of de-identified patient data contained within the registry for research and waived the need for individual patient consent. High-risk status was defined by an additive AusSCORE greater than 5.

A total of 7822 high-risk patients underwent isolated CABG within 19 public and 6 private hospitals in Australia. Of these, 93% had an ONCAB procedure and 7% an OPCAB procedure. End points included 30-day mortality and morbidity, one-year mortality and, five- and 10-year survival. Long term mortality was identified by cross-matching the ANZSCTS registry with the Australian Institute of Health and Welfare's National Death Index which has displayed a 93.7% sensitivity and 100% specificity for the identification of deaths(222). The date of survival follow-up used is 12 January 2012.

The reported results place patients according to the surgery type they ultimately received and do not take into account conversions in either direction as this data is not collected by the ANZSCTS registry.

The quality control activities associated with the ANZSCTS registry have previously been described(154). The ANZSCTS registry is an established quality assurance program which is subject to strict quality control and employs systematic measures to ensure registry accuracy and validity. The program is a declared activity under Commonwealth Legislation. As such, no patient was lost to follow-up during the peri-operative period as legislation maintains that accurate data be maintained for all patients in participating institutions. Central to this is an independent, comprehensive data validation process. This includes site audits performed at two random cardiac units per annum by the ANZSCTS Registry Program Audit Team to evaluate for completeness and accuracy of data. Identifying information of 5% of the procedures performed by the unit were provided to the onsite manager two weeks prior to the audit date to permit medical record retrieval. The auditors are given a printout of each patient's data fields recorded on the central ANZSCTS registry to be checked/verified against the medical records. Any

discrepancies between the registry and medical records are queried, validated and amended on both onsite and aggregated registries. The results of the audit are then used to assist in the further development of appropriate standards. Overall, the current auditing process is rigorous and robust which is reflected in the high degree of accuracy of data (96.7%) collected at participating hospitals. These data are comparable or better than other major cardiac surgical and interventional registries(223, 224). Missing data elements constituted less than 1% of the overall dataset although one or more missing predictor variables were present in 15.8% of the patients in the dataset(225). The "multiple imputation" method was used where possible to improve the validity of the dataset when missing values were present. The use of this method has been previously described within the context of the ANZSCTS registry(225)

4.2.2 Definition of terms

Definitions of the preoperative risk factors and postoperative complications were made according to the ANZSCTS Data Definitions Manual version 4.0 (226). This has been provided as an appendix to the thesis (Appendix H). Chronic renal failure was defined as a preoperative creatinine level of 200μmol/l or more and/or preoperative dialysis requirement. This is consistent with previous reports evaluating outcomes in patients with chronic renal failure utilizing the ANSCTS registry(227) but other definitions have been used in the literature(228, 229).

Fifteen post-operative outcomes were analysed. These were a) 30-day mortality, defined as death within 30 days of operation; b) 12-month mortality, defined as death within 12 months of surgery; c) Postoperative acute myocardial infarction, defined as at

least two of the following: enzyme level elevation, new cardiac wall motion abnormalities, or new Q waves on serial electrocardiograms; d) Graft occlusion take-back, defined as return to theatre for graft refashion, or grafting of a previously ungrafted coronary artery; e) Re-bleeding, defined as return to theatre for bleeding; f) New renal failure, defined as at least two of the following: serum creatinine increased to more than 200 μmol/L, doubling or greater increase in creatinine *vs* preoperative value, or new requirement for dialysis or haemofiltration; g) New atrial fibrillation/flutter; h) Prolonged ventilation (> 24 hours); i) infection, defined as infection of sternal bone, muscle and/or mediastinum; j) transient major neurological event, defined as a new transient central neurologic deficit that was resolved completely within 72 hours; k) permanent major neurological event, defined as a stroke or new central neurologic deficit (persisting for > 72 hours) peri- or post-operatively; l) blood transfusion, defined as allogeneic red blood cells (RBC) transfused during the intra-operative or post-operative period; m) hospital stay in days; and n) length of intensive care unit (ICU) in hours. Multiple events were recorded separately as no composite outcome (such as Major Adverse Cardiovascular Events) was evaluated.

4.2.3 Surgical technique

The surgical technique selected (ONCAB or OPCAB) was based on individual surgeon preference and the preoperative and postoperative work up of patients was based on individual hospital protocols. The ONCAB technique generally involved aortic and right atrial cannulation and the application of an aortic cross clamp and intermittent cardioplegic

solution for cardioplegic arrest. Proximal anastomoses to the aorta and distal coronary anastomoses were then performed in a relatively bloodless field.

The OPCAB technique differs by minimizing aortic manipulation. This avoids aortic cannulation as well as the cross clamp and instead, uses a side-biting aortic clamp to perform proximal aortic anastomoses, or avoids the aorta altogether by the use of a composite or "T" graft based on internal mammary artery inflow approach. Distal anastomoses are then performed on the beating heart with or without the use of coronary stabilisation devices and/or intravascular shunts.

4.2.4 Statistical analysis

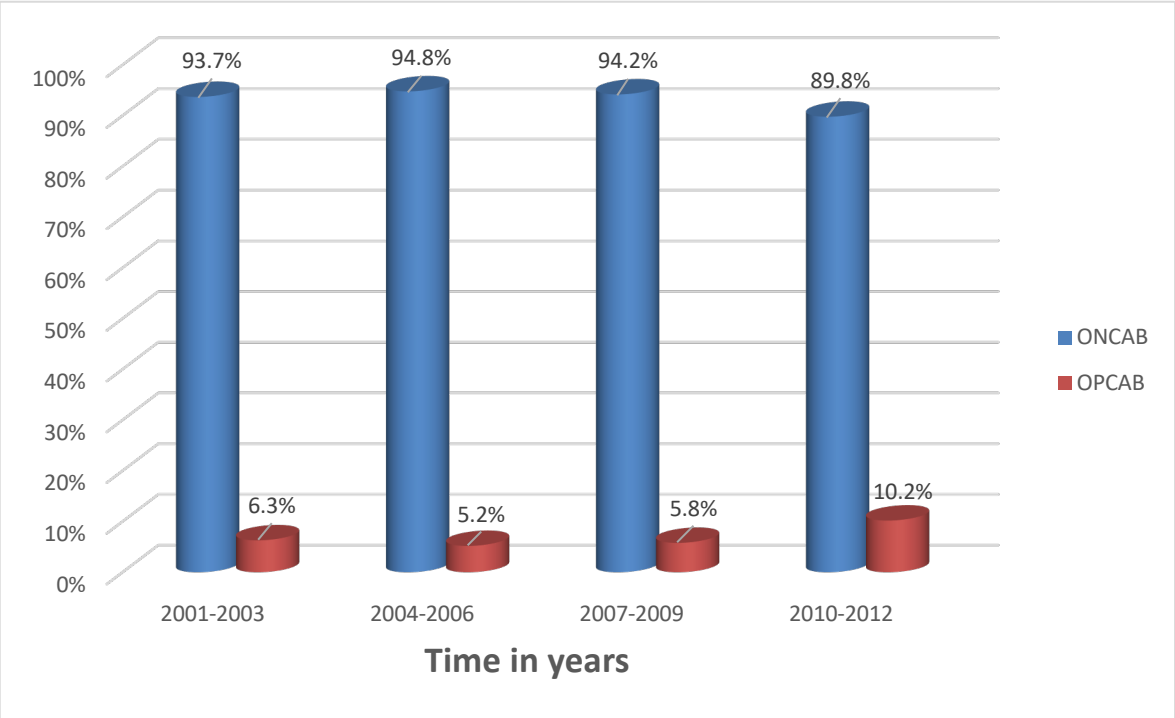
Statistical analyses were performed using SPSS v20 (SPSS Inc., Chicago, Illinois). Categorical data are presented as percentages and were analysed using the Chi square test or Fisher's exact test. Continuous data are presented as the mean and standard deviation if normally distributed and median (interquartile range) is not normally distributed. Continuous variables were analysed using the Mann-Whitney test. Long term survival was estimated by Kaplan Meier curves and analysed with the log-rank test. Additionally, unadjusted and adjusted hazard ratios were calculated using the Cox proportional hazards model. A level of significance $\alpha<0.05$ was considered significant. Propensity matching was attempted by the two groups could not be matched due to the disparity in the types (cardiac versus non-cardiac) of co-morbidities between the two groups in addition to the low event rates (mortality and stroke) and small numbers in the OPCAB group. All pre-operative variables in Table 4.1 were included in the adjusted analyses. These were selected in the adjusted analysis on the basis that they could

introduce confounding of outcomes data if not accounted for. Intra-operative variables were not included as they can not be used in the pre-operative assessment of risk. To ensure the statistical precision of the study, we calculated the minimum sample size required to achieve 50% power to detect a 67% difference in the early mortality rate (3% OPCAB; 5% ONCAB) using a one-side type I error rate of 0.05(230). The enrolment ratio for the calculation reflected that observed in the current study (14 ONCAB: 1 OPCAB). Based on this, the sample size required for demonstration of an early mortality difference was 476 and 6664 for the OPCAB and ONCAB groups, respectively.

4.3 RESULTS

A total of 31345 patients underwent isolated CABG during the study period; of these, 2759(8.8%) were OPCAB. Overall, 7822 (25.0%) patients were classified as high-risk (AusScore > 5%). The prevalence of OPCAB surgery was significantly lower in the high-risk group [545(7%) vs 2214(9.4%); p<0.001). The proportion of OPCAB procedures was broadly consistent across the timeframe of the study (5.2% - 6.3%) except for an increase in 2010-2012 to 10.2% (Figure 4.1).

Figure 4.1: Proportion of ONCAB and OPCAB surgeries performed over the 12-year period



4.3.1 Pre-operative characteristics

A summary of the pre-operative characteristics of the groups is provided in Table 4.1. Patients who underwent the OPCAB procedure were more often older, females, with a family history of coronary artery disease and with atrial fibrillation/flutter preoperatively. Patients with myocardial infarction, triple vessel disease, an ejection fraction less than 30%, and preoperative intra-aortic balloon pump (IABP) insertion were more prevalent in the ONCAB group. All other preoperative risk variables were equally distributed between the two groups. The predicted mortality calculated by the AusSCORE was not significantly different between the two groups.

Table 4.1: Pre-operative characteristics					
Variable	**On-pump**		**Off-pump**		**p**
	n	**%**	**n**	**%**	
Overall	7277	93	545	7	-
Additive score (Median)(IQR)	8(7-10)	-	8(6-10)		0.273
Predicted Risk (AusScore†)(Median)(IQR)	4(1-7)	-	4(0-8)		0.366
Age (Median) (IQR)	72 (66-77)	-	73(67-80)		0.02
Female gender	1820	25	161	29.5	0.019
Smoking history	4789	65.9	345	63.5	0.266
Hypercholesterolemia	4890	67.2	375	68.8	0.44
NYHA‡ class IV	1147	15.8	91	16.7	0.564
Cardiogenic shock	426	5.9	25	4.6	0.221
Hypertension	5741	78.9	440	80.7	0.308
Diabetes mellitus	2575	35.4	184	33.8	0.444
Obesity (BMI≥30)	1947	26.8	128	23.7	0.12
Creatinine ≥200μmol/L	277	3.8	29	5.3	0.079
Dialysis	145	2	13	2.4	0.53
Chronic renal disease	314	4.3	31	5.7	0.132
Chronic lung disease	1223	16.8	98	18	0.48
Atrial fibrillation/flutter	754	10.4	76	13.9	0.009
Myocardial infarction	5033	69.2	327	60	<0.001
Peripheral vascular disease	1861	25.6	156	28.6	0.118
Family history	2248	30.9	191	35.2	0.018
Elective surgery	2245	30.9	168	30.8	0.99
Emergency surgery	5032	69.1	377	69.2	0.99
Ejection fraction <30%	1003	13.8	56	10.3	0.021
Left main disease	2533	34.8	175	32.2	0.21
Triple vessel disease	5845	80.4	273	50.1	<0.001
Cerebrovascular disease	1208	16.6	100	18.3	0.291
Preoperative IABP insertion	782	10.7	40	7.4	0.013

Previous cardiac surgery	851	11.7	53	9.7	0.165
p <0.05 was considered significant BMI: body mass index ‡New York Heart Association functional classification					

4.3.2 Operative characteristics

Operative factors for each group are shown in Table 4.2. The average number of distal anastomoses per patient was significantly lower in the OPCAB group (2.5±1.2 vs 3.3±1.0, p<0.05). Use of right internal mammary artery (RIMA) grafts and bilateral internal mammary artery (BIMA) grafts were significantly higher in the OPCAB group while the use of radial artery (RA) grafts and saphenous vein grafts were significantly higher in the ONCAB group.

Table 4.2: Operative characteristics

Variable	**On-pump**		**Off-pump**		**p**
	n	**%**	**n**	**%**	
Overall	7277	93	545	7	-
Cross clamp time (minutes)(Median)(IQR)	67(50-87)	-	-	-	-
Pump time (minutes)(Median)(IQR)	94(75-94)	-	-	-	-
Average distal grafts (Median)(IQR)	3(3-4)	-	2(1-3)	-	<0.001
Use of LIMA	6429	97.7	500	96.3	0.06
Use of RIMA	620	9.4	113	21.7	<0.001
Use of bilateral IMA	542	7.4	100	18.3	<0.001
Use of Radial artery	3452	47.5	204	37.8	<0.001
Use of Saphenous vein	5423	74.5	170	31.3	<0.001
p <0.05 was considered significant					

4.3.3 Post-operative outcomes

Postoperative outcomes are shown in Table 4.3. There was no significant difference between the two groups in terms of 30-day and 1-year mortality (ONCAB vs OPCAB: 3.9% vs 2.4%; 7.4% vs 5.6%). Major neurological event rates (temporary and permanent) were higher in the ONCAB group but this difference did not reach significance. ONCAB significantly increased the rates of new-onset atrial fibrillation and need for blood transfusions. OPCAB, on the other hand, significantly prolonged the duration of ICU stay.

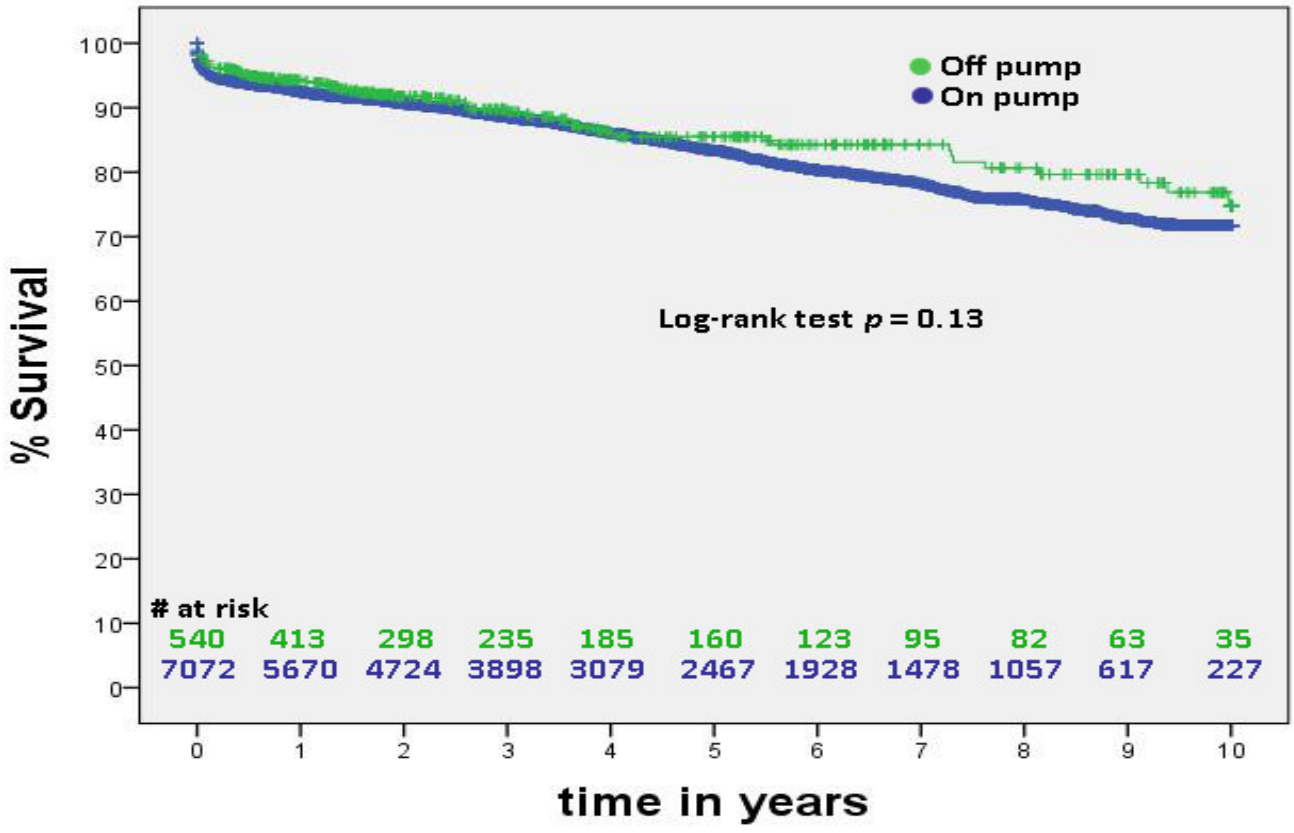
Table 4.3: Postoperative outcomes

Variable	**On-pump**		**Off-pump**		**p**
	n	**%**	**n**	**%**	
Overall	7277	93	545	7	-
30 day Mortality	287	3.9	13	2.4	0.067
1 year Mortality	521	7.4	30	5.6	0.117
Myocardial infarction	74	1	7	1.3	0.554
Graft occlusion take-back	10	0.2	2	0.4	0.202
Re-bleeding	214	2.9	11	2	0.214
New renal failure	445	6.1	22	4	0.048
New atrial fibrillation/flutter	2420	33.3	154	28.3	0.017
Prolonged ventilation (>24 hours)	1181	16.3	73	13.4	0.082
Infection	182	2.5	16	2.9	0.533
Major neurological event	172	2.4	7	1.3	0.104
Transient	57	0.8	2	0.4	0.437
Permanent	121	1.7	6	1.1	0.316
Blood transfusion	4327	59.5	284	52.1	0.001
Hospital stay in days (mean ± S.D.)	14(9-23)	-	14(10-19)	-	0.638
ICU stay in hours (mean ± S.D.)	47(23-96)	-	66(23-94)	-	<0.001
p <0.05 was considered significant					

4.3.4 Survival outcomes

The median follow-up for this study was 44 months (range, 0 – 132). The Kaplan Meier survival estimates at 3-, 5-, 7- and 10- years for ONCAB were 88.5%, 83.3%, 78.2% and 71.7% while those for OPCAB were 89.4%, 85.5%, 84.3% and 74.7%. The difference in survival estimates did not reach significance. (Figure 4.2) The unadjusted hazard ratio (0.83; 95% confidence interval 0.65-1.06; *p*=0.14) and adjusted hazard ratio (0.86; 95% confidence interval 0.67-1.11; *p*=0.26) for OPCAB surgery at 10 years were similar.

Figure 4.2: Ten-year survival, stratified by on-pump and off-pump CABG



4.4 DISCUSSION

One of the major challenges facing cardiothoracic surgeons is achieving good outcomes in high-risk patients undergoing coronary revascularization (231-235). There is substantial evidence from observational studies that OPCAB maybe efficacious in this setting. (231, 236-240). Theoretically, OPCAB should decrease the incidence of organ-specific morbidity in high-risk patients by eliminating the systemic inflammatory response and global hypoxia caused by the CPB and cardioplegic arrest(233, 241). OPCAB has been shown to decrease postoperative morbidities such as, ventilation time, atrial fibrillation, transfusion requirements, stroke rates, renal dysfunction, hospital and ICU stay (233, 241-243).

There is considerable debate about which patients should be categorized as “high risk”(244-247). As explored in the previous chapter, many risk stratification models have been developed that aim to quantify the surgical risk profile of patients undergoing CABG. The most widely and most accessible tool is the EuroSCORE(246). However, Sergeant and colleagues found that the EuroSCORE overestimates the risk between 0-8, is accurate between 9 and 11, and underestimates the risk when the score was 12 or higher (248). For this reason, a new score was developed for the general Australian population called the AusSCORE, which is derived from the ANZSCTS registry. This score is based on 8 preoperative variables and is a better predictor of 30-day mortality than the EuroSCORE in the Australian cohort. Based on this score, “high-risk” is defined as an additive score more than 5 and we used this definition in our study (221).

Our data is a reflection of the actual cardiothoracic practice in Australia and New Zealand, derived from the ANZSCTS registry. While previous observational cohorts have demonstrated that OPCAB may reduce mortality in high-risk patients the widespread adoption of this technique has been precluded by its technical difficulty and conflicting evidence regarding its efficacy (217, 231, 240) The. The ROOBY trial randomized 2203 patients to either on-pump or off-pump procedures(249). The primary short-term end point was a composite of death or complications (reoperation, mechanical support, cardiac arrest, coma, stroke or renal failure) before discharge or within 30 days after surgery. The authors demonstrated that there was no significant difference between off-pump and on-pump CABG in the rate of the 30-day composite endpoint (7.0% and 5.6%, respectively; p=0.19). Of concern was also that a higher proportion of OPCAB patients had fewer grafts than originally planned (17.8% vs 11.1%, p<0.001) and follow-up overall graft patency was lower in the OPCAB group (82.6% vs. 87.8%, p<0.01). This trial, however, has been criticized for several reasons and its results may not be broadly applicable to a high-risk population. It largely included a lower risk population which may not derive significant additional benefit from OPCAB. Additionally, the experience of the OPCAB surgeons was low (12% conversion to ONCAB and 18% incomplete revascularization) for a technically challenging procedure. Data from other randomized trials has also been equivocal; both the CORONARY trial in the population aged > 70 years and the BEST Bypass Surgery trial in the high risk population (EuroSCORE ≥ 5) showed no difference between ONCAB and OPCAB with respect to 30-day mortality (250, 251)..

In our study, even though the 30-day and 1-year mortality were lower in the OPCAB group, this difference was not significant. This could be explained by the low

event rates and the relatively low numbers in the OPCAB arm, reducing the power of the study. It could also be due to inadequate surgical experience or a propensity to perform OPCAB on patients with diseased aortas or increased frailty. Conversely, CPB may have been selectively employed in technically difficult or acute/high risk patients. Unfortunately, this data was not collected. The observed 30-day mortality of 3.9% and 2.4% in the ONCAB and OPCAB group respectively was similar to the predicted mortality of 3.6% and 3.4%, thus validating the predictive power of the logistic AusSCORE in the high-risk Australian population.

OPCAB has also been shown to reduce stroke rates, even in the high risk population (221). However, the prospective randomized CORONARY trial and the Best Bypass Surgery trial both showed no difference in stroke rates between OPCAB and ONCAB in the perioperative period (250, 251). In the ANZSCTS registry the OPCAB group showed a lower stroke rate in the high-risk population but this was not significant. Again, this may reflect that the study is insufficiently powered to detect differences. Moreover, although not specifically evaluated, a lack of experienced operators of this technique may have confounded the results. This may be particularly true in the high-risk context given that only 7% of procedures in the ANZSCTS dataset were OPCAB. The degree of aortic manipulation used also has been shown to significantly affect the stroke rates following OPCAB surgery with the anaortic technique having superior outcomes (252-254). Unfortunately, the ANZSCTS dataset does not provide this information. A previously Australian study evaluated the outcomes of 1135 patients elderly patients (> 70 years) who underwent anaortic OPCAB across three experienced centers(215). The authors reported a low rate of 30-day mortality (70-79 y: 1.8%; ≥ 80 y: 2.8%) and permanent

stroke (70-79 y:0.2%; ≥ 80 y:0.9%) in the patient cohort. Contrastingly, in both aforementioned randomized trials, the OPCAB technique involved the use of side-biting aortic clamps.

The average number of grafts performed per patient was significantly less in the OPCAB group which could be due to the technical challenges involved in performing anastomoses on the lateral and inferior cardiac walls, or due to the surgeon preference for using cardiopulmonary bypass for multi-vessel disease. This observation has been made by other studies as well and has been one of the main criticisms of OPCAB in terms of inadequate revascularization and postoperative residual ischaemia (251, 255, 256). However, the rates of perioperative graft occlusion and myocardial infarction were similar between the two groups in our study. Moreover, as mentioned earlier, the number of patients with triple vessel disease was significantly more in the ONCAB group making surgeon preference a more likely assumption.

Maximum benefit of the OPCAB procedure was observed in terms of the reduction in perioperative incidence of new-onset atrial arrhythmias and the need for blood transfusions. This has been observed in other studies as well (231, 240). This difference could be due to the property of the CPB and cardioplegic arrest to alter the physiologic milieu in the ONCAB procedure resulting in electrolyte imbalance causing AF, and affecting platelets and coagulation factors causing excessive blood loss.

Another advantage of the OPCAB procedure has been the reduction in the duration of total ICU and hospital stay (231, 240). However, both hospital and ICU stay were longer in the OPCAB group with the difference in ICU stay reaching significance.

This discrepancy could be the result of individual hospital protocols for ICU management rather than a real difference. However, we could not clearly determine this.

OPCAB and ONCAB have been shown to have similar long term survival so far. A 10-year study showed that ONCAB had no long term advantage over OPCAB (217). There is a paucity of long term data in the high-risk population. A retrospective study showed no difference in the five-year actuarial results in terms of freedom from all-cause and cardiac death (231). The BEST Bypass Surgery trial on the other hand, showed a significant difference in terms of all-cause mortality, favouring ONCAB. However, the difference in cardiac death was not significant (251). The ANZSCTS data did not show any difference between ONCAB and OPCAB in 10-year survival. With an adjusted hazard ratio of death of 0.86 (C.I. 0.67-1.11, p=0.261), OPCAB seems to be an efficacious for long-term survival after CABG in the high-risk population.

4.5 LIMITATIONS

The ANZSCTS registry collects data prospectively and this review is a retrospective analysis of the registry and may suffer from the limitations applicable to registry studies. The reported results place patients according to the surgery type they ultimately received and do not take into account conversions in either direction. Finally, the numbers in the OPCAB group could be considered inadequate as compared to the ONCAB group resulting in an issue of adequate power associated with the study. Thus, it was difficult to eliminate all confounding factors and biases associated with such a study.

4.6 CONCLUSION

Even in the high risk group CABG surgery is associated with low mortality and stroke rates irrespective of surgery type. OPCAB surgery has equivalent mortality and stroke rates as ONCAB with maximum benefit seen in terms of lower blood transfusion and postoperative atrial arrhythmia rates. However higher risk patients are more frequently operated on using cardiopulmonary bypass. Long term survival is comparable in both groups. There is a need for reporting of anaortic data to identify the real benefit of OPCAB regarding postoperative neurological complications. While OPCAB is as safe option in high risk patients in the short and long term, meticulous patient selection is essential and further prospective randomized trials are required to affirm the best surgical strategy in this patient group.

SECTION III

THE IMPACT OF PRE-OPERATIVE ATRIAL FIBRILLATION ON OUTCOMES AFTER CARDIAC INTERVENTIONS

CHAPTER 5

PRE-OPERATIVE ATRIAL FIBRILLATION PORTENDS POOR OUTCOMES AFTER CORONARY ARTERY BYPASS GRAFT SURGERY: A SYSTEMATIC REVIEW AND META-ANALYSIS

5.1 INTRODUCTION

Atrial fibrillation (AF) is the most common abnormal cardiac rhythm with an estimated prevalence of 4% in the Australian population over the age of 30(257). The incidence of AF steadily increases with age; the prevalence in those older than 80 years is up to 15%(52). The clinical impact of AF is described in Section 1.6.

The demographic profile of patients undergoing coronary artery bypass graft (CABG) surgery has significantly changed in the past two decades due to the increased utilization of coronary stents and the ageing population of developed countries. Increasingly, older patients with a greater incidence of comorbidities including valvular disease, diabetes and impaired ventricular function are undergoing CABG(39, 40, 45). These factors are all associated with an increased risk of AF(258). Hence, it is imperative to understand the clinical implications of AF for patients undergoing CABG. Some cohort studies have demonstrated that AF may be an independent risk factor for poorer peri-operative outcomes and reduced long-term survival(259-263). However, there has only been a limited evaluation of AF in the context of CABG surgery and the EuroSCORE has not recognized preoperative AF as a risk modifier. Moreover, the impact of AF on clinical outcomes according to revascularization strategy (on-pump or off-pump CABG) remains largely unexplored.

The primary aim of this systematic review and meta-analysis was to evaluate the impact of AF on early and mid-term (> 12 months) mortality after CABG. The secondary aims were:

iii) Evaluate the impact of AF on peri-operative morbidity (stroke, acute renal failure, prolonged ventilation, re-operation, re-operation for

bleeding, wound infection, myocardial infarction, and re-operation for bleeding).

iv) Evaluate the impact of AF on early and mid-term outcomes, stratified by revascularization strategy (on-pump vs off-pump).

Our hypothesis is that AF has an adverse impact on early and mid-term mortality after CABG surgery and pre-disposes patients to poorer peri-operative outcomes, regardless of revascularization strategy. We performed a systematic review and meta-analysis of relevant studies to test our hypothesis.

5.2 METHODS

This systematic review and meta-analysis was conducted and presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines(264). The study was approved by the local ethics committee. The quality of included studies was assessed with the Newcastle-Ottawa scale for observational studies(265). The Newcastle-Ottawa scale (NOS) criteria are split into 3 sections: selection, comparability, and outcome. Each study is designated a number of stars for each section, based on predetermined queries. The thresholds for converting the NOS criteria to Agency for Healthcare Research and Quality (AHRQ) standards (good, fair and poor) are as follows:

a) Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
b) Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

c) Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

5.2.1 Search strategy and Study Selection

Electronic searches were performed using Ovid Medline, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) from their dates of inception to January 2016. The search terms “coronary artery bypass” OR “CABG” were combined with “atrial fibrillation” AND (“baseline OR “pre-operative”) as keywords and MeSH terms. This was supplemented by hand searching the reference lists of key reviews and all potentially relevant studies.

Two reviewers (A.S; S.V) independently screened the title and abstract of records identified in the search. Full-text publications were subsequently reviewed separately if either reviewer considered the manuscript as being potentially eligible. We appropriately excluded previous review articles on this topic. Disagreements regarding final study inclusion were resolved by discussion and consensus. Unavoidable in this kind of review is that the validity of their interpretation can be no better than the initial data published in each study.

5.2.2 Eligibility Criteria

Eligible studies were those reporting on clinical outcomes of isolated CABG according to the presence or absence of baseline AF. Non-comparative studies lacking a control group of patients without AF were excluded. Studies presenting mixed data for different cardiac surgeries were only included if clinical outcomes for the isolated CABG cohort were

separately reported. Studies reporting outcomes of patients undergoing concomitant atrial fibrillation surgery were excluded.

All publications were limited to those involving human subjects and written in English. Abstracts, case reports, conference presentations, editorials and expert opinions were excluded. Review articles were omitted because of potential publication bias and duplication of results. When institutions published duplicate studies with accumulating numbers of patients or increased lengths of follow-up, only the most complete reports were included for quantitative assessment. For this study, outcomes were defined as short-term if they occurred during hospital stay. Mid-term outcomes included mid-term mortality which was defined as mortality beyond 12 months after surgery.

5.2.3 Data Extraction

All data were independently extracted from text, tables and figures by two investigators (S.A.V and S.B). The final results were reviewed by the senior reviewer (A.S.). For each study, the following information was extracted: study period, institution, study design, patient characteristics and risk factors, procedural details and clinical outcomes.

The pre-determined primary endpoint was peri-operative all-cause mortality, defined as death occurring within 30 days of surgery or during the same hospitalization and mid-term survival. Secondary endpoints included peri-operative morbidity (stroke, acute renal failure, myocardial infarction, wound infection and re-operation for bleeding). We also evaluated the impact of AF on clinical outcomes, stratified by revascularization strategy (on-pump vs off-pump).

The definition of wound infection was inconsistent between studies; some studies reported on sternal wound infection whilst others reported any surgical site infection (e.g. leg and sternal).

5.2.4 Statistical Analysis

The odds ratio (OR) or hazards ratio (HR) were used as summary statistics, and reported with 95% confidence intervals (CI). When available, multivariable adjusted or propensity-matched ratios were extracted from individual studies. Otherwise, unadjusted ratios were computed from the exposure distribution given in the papers.

Meta-analyses were performed using random-effects models to take into account he anticipated clinical and methodological diversity between studies. The I^2 statistic was used to estimate the percentage of total variation across studies due to heterogeneity rather than chance, with values exceeding 50% indicative of considerable heterogeneity. Subgroup analysis was conducted to specifically examine the impact of AF on outcomes following conventional and off-pump CABG. In all manuscripts that were analyzed, the groups of stratified based on the presence or absence of AF.

A sensitivity analysis aims to determine the robustness of the observed outcomes to the assumptions made in performing the analysis. As stated by Bown and colleagues(266), they are an important part of quality control in meta-analysis. There is no set strategy for performing a sensitivity analysis but the underlying principle is to repeat the primary analysis with an altered dataset/statistical method to determine whether these changes have any effect on the combined outcome estimate(266). When altering the dataset, the choice of studies to add or remove is often based on assumptions of quality

of study size and is at the authors discretion. In this meta-analysis, our primary aim was to evaluate whether AF was an independent predictor of poorer short and long-term outcomes after CABG surgery. To best test this, a sensitivity analysis was performed by excluding studies that did not report propensity-matched or multivariable adjusted ratios. This is acknowledged as an acceptable strategy for hypothesis testing(267). The Forrest plots were generated using adjusted ratios, whenever available. Otherwise, unadjusted ratios were computed from the exposure distribution given in the papers. In the current study, only one study did not report adjusted or propensity matched ratios(268) (Table 5.1). The Forrest plot generated from the sensitivity analysis only included studies which report propensity matched or adjusted ratios.

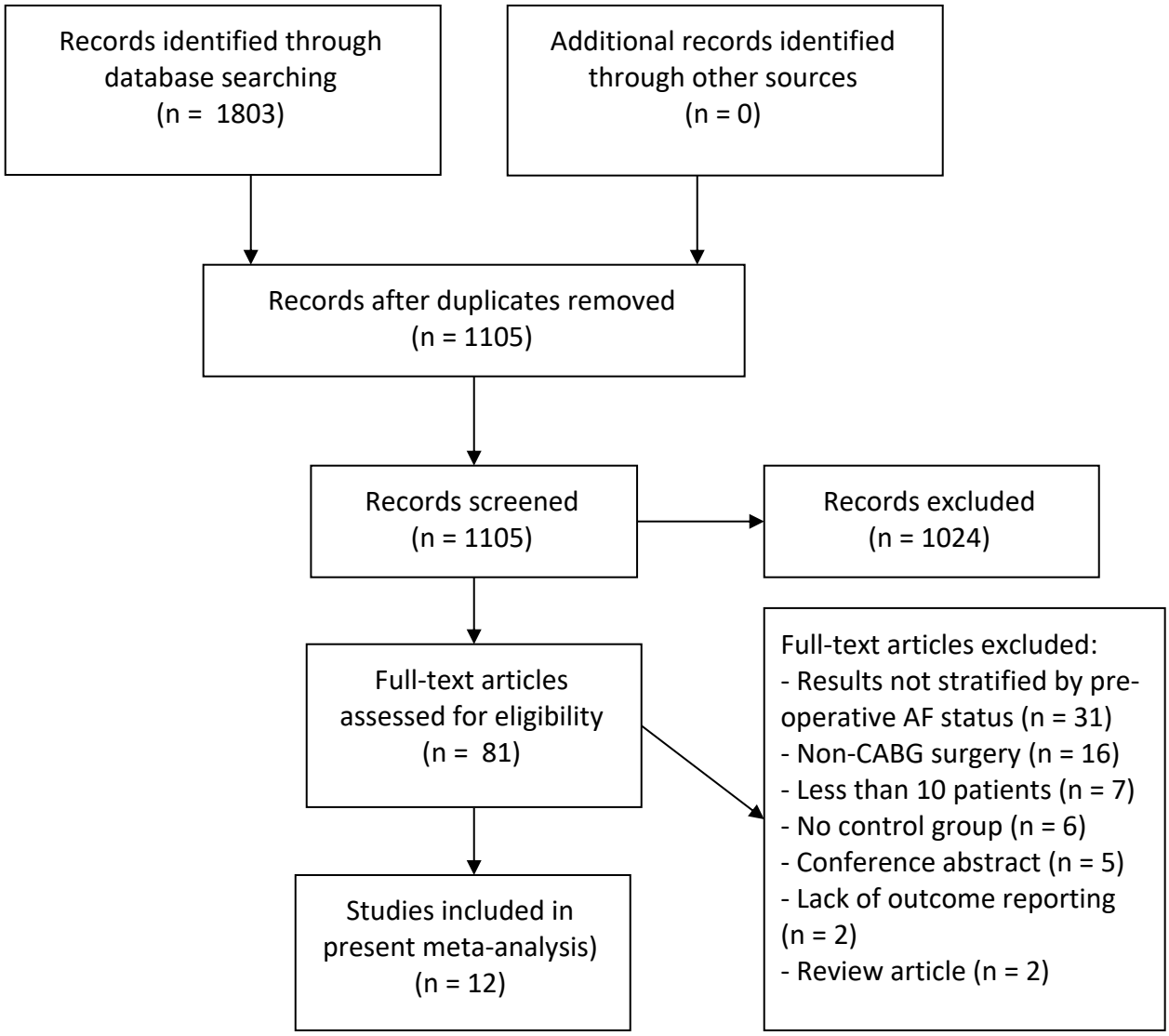
Publication bias was assessed using funnel plots comparing log odds ratios with their standard error. Egger's linear regression method(269) and Begg's rank correlation test(270) were used to detect funnel plot asymmetry, and the Trim-and-Fill method was used to explore the impact of studies potentially missing due to publication bias(271). Statistical analysis was conducted with Review Manager Version 5.1.2 (Cochrane Collaboration, Software Update, Oxford, UK) and Comprehensive Meta-Analysis v2.2 (Biostat Inc, Englewood, NJ, US). All p-values were two sided, and values < 0.05 were considered statistically significant. We previously published reported a series which used the ANZSCTS registry to evaluate the impact of AF on early and mid-term outcomes after CABG (Appendix I).

5.3 RESULTS

5.3.1 Study Characteristics

A total of 1105 unique records were identified through the database and bibliographic searches. After considerable filtering, 1024 were excluded on the basis of title and abstract content. After the full text of the remaining 81 articles was screened, 12 studies met the inclusion criteria(259-263, 268, 272-277) (Figure 5.1)

Figure 5.1: Summary of PRISMA flowchart



All included studies were retrospective observational reports (Table 5.1). These included data on a total of 389,998 patients who underwent CABG; 370,292 patients did not have pre-operative AF and 19,706 had pre-operative AF. The median study sample size was 5240 (range: 513 – 281,569). In three studies, outcome reporting was limited to the peri-operative period(260, 268, 272). In the remaining studies, the mean or median follow-up time ranged from 3 to 12.6 years. Baseline demographic characteristics and risk-factor profiles of study participants are summarized in Table 5.2.

Table 5.1: Study characteristics

First author	Study Period	Institution	Surgery type	Study design	Follow up (years)	Number of patients			Adjusted/ propensity patching	NOS
						AF	No AF	Total		
Ad 2009	2002-2003	Multiple (Society of Thoracic Surgeons National Adult Cardiac Surgery Database)	ONCABG	Retrospective OS	Peri-Operative	15,755	265,814	281,569	Adjusted analysis	S4C2O2
Al-Sarraf 2012	2000-2008	St James's Hospital	ONCABG	Retrospective OS	Peri-Operative	413	3,364	3,777	Adjusted analysis	S4C2O2
Attaran 2011	2000-2010	Liverpool Heart and Chest Hospital	ONCABG + OPCABG	Retrospective OS	10^{M}	477	9,984	10,461	Propensity matched	S4C2O3
Banach 2008	2000-2004	Department of Cardiac Surgery, Medical University Lodz, Poland	ONCABG	Retrospective OS	3^{M}	174	2,826	3,000	Adjusted analysis	S4C2O3
Boning 2015	2008-2011	Multicentre	ONCABG + OPCABG	Retrospective OS	Peri-Operative	232	2,071	2,303	Univariate analysis with raw data	S4C0O2
Bramer 2001	1998-2007	Catharina Hospital, Eindhoven	ONCABG	Retrospective OS	4.6 $\pm$ 2.9	221	8,630	8,851	Adjusted analysis	S4C2O3
Fukahara 2010	2000-2005	University of Toyama, Japan	OPCABG	Retrospective OS	3.3 $\pm$ 2.7	26	487	513	Adjusted analysis	S3C2O3
Ngaage 2007	1993-2002	Mayo Clinic College of Medicine	ONCABG	Retrospective OS	6.7^{M}	257	269	526	Adjusted analysis	S4C2O3
O'Neal 2013	2002-2011	East Carolina Heart Institute	ONCABG	Retrospective OS	4.2 [1.85 – 6.55]	263	5,175	5,438	Adjusted analysis	S4C2O3
Quader 2004	1972-2000	The Cleveland Clinic Foundation	ONCABG	Retrospective OS	12.6 $\pm$ 7.3	451	46,533	46,984	Propensity matched	S4C2O3
Rogers 2006	1996-2002	Multiple (Patient Activity Tracking System Database)	ONCABG	Retrospective OS	5^{M}	125	4,917	5,042	Adjusted analysis	S4C2O3
Saxena 2015	2001-2009	Multiple (Australasian Society of Cardiac and Thoracic Surgeons)	ONCABG	Retrospective OS	3.08^{m}	1,312	20,222	21,534	Adjusted analysis	S4C2O3

Data presented as mean $\pm$ standard deviation or median [interquartile range], unless otherwise stated. M, median; m, mean; NOS -Newcastle-Ottawa score**;** S – Selection component of Newcastle-Ottawa score; C – Comparability component of Newcastle-Ottawa Score; O – Outcome component of Newcastle-Ottawa Score

Table 5.2: Baseline patient characteristics

Study	Age (years)		Male (%)		Diabetes (%)		Prior MI (%)		PVD (%)		CVD (%)		LVEF % (%)		NYHA III/IV (%)		HTN (%)	
	AF	**No AF**	**AF**	**No AF**	**AF**	**No AF**	**AF**	**No AF**	**AF**	**No AF**	**AF**	**No AF**	**AF**	**No AF**	**AF**	**No AF**	**AF**	**No AF**
Ad 2009	NR	NR	72	72	38*	36*	53*	45*	23*	16*	21*	13*	NR	NR	66*	58*	81*	76*
Al-Sarraf 2012	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Attaran 2011																		
- ONCABG	70.1 [64.8-74.9]	70.4 [65.5-75.0]	89	89	26	25	NR	NR	17	18	NR	NR	15 (<30%)	14 (<30%)	NR	NR	69	68
- OPCABG	70.7 [65.5-75.3]	71.3 [65.5-75.6]	88	88	32	30	NR	NR	18	16	NR	NR	18 (<30%)	18 (<30%)	NR	NR	75	75
Banach 2008	64.4 ± 7.9*	59.7 ± 9.5*	58*	70*	18*	15*	NR	NR	NR	NR	NR	NR	39.4 ± 6.7*	43.7 ± 9.6*	NR	NR	NR	NR
Boning 2015																		
- ONCABG	78.8	78.4	70	67	18	14	39	38	35	33	9	8	3* (<30%)	7* (<30%)	55	42	NR	NR
- OPCABG	78.8	78.6	80	67	22	14	37	36	35	32	11	10	5* (<30%)	2* (<30%)	60	44	NR	NR
Bramer 2010	69.8 ± 7.8	70.2 ± 7.7	76	74	24	19	NR	NR	15	15	8	11	33.5 (<50%)	30.8 (<50%)	NR	NR	48	41
Fukahara 2010	69.9 ± 10.1	67.0 ± 9.8	85	78	8	14	35	40	8	6	27	20	50.0 ± 14.6*	56.1 ± 12.2*	NR	NR	58	56
Ngaage 2007	71 ± 8	70 ± 8	79	79	35	26	55	52	NR	NR	11	10	53.0 ± 14	56.0 ± 16	92	87	74	71
O' Neal 2013	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Quader 2004	66.2 ± 9.0	66.6 ± 9.0	81	80	22	20	54	55	27	28	NR	NR	NR	NR	39	38	73	74
Rogers 2006	68 [64-73]*	64 [57-70]*	85	81	24*	16*	53*	43*	17*	9*	19*	8*	45 (<50%)*	27 (<50%)*	50*	34*	67*	58*
Saxena 2015	71.1 ± 8.6*	65.2 ± 10.5*	77	78	36	33	33*	25*	18*	12*	17*	11*	8 (<30%)*	4 (<30%)*	32*	21*	82*	77*

Data presented as mean ± SD, median [IQR] or % of patients. * $p < 0.05$; AF, pre-existing atrial fibrillation; CVD, cerebrovascular disease; HTN, hypertension; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PVD, peripheral vascular disease;

5.3.2 Clinical Outcomes

5.3.2.1 Entire cohort

The impact of AF on peri-operative and mid-term outcomes following isolated CABG is summarized in Table 5.3. There was a statistically significant association between AF and peri-operative mortality (OR 1.64; 95% CI, 1.29 – 2.09; p<0.001; I^2 = 54%). AF was also associated with stroke (OR 1.50; 95% CI, 1.06 – 2.11; p=0.02; I^2 = 63%), acute renal failure (OR, 1.50; 95% CI, 1.23 – 1.83; p<0.001; I^2 = 48%), prolonged ventilation (OR 1.40; 95% CI, 1.16 – 1.68; p<0.001; I^2 = 53%) and re-operation for bleeding (OR 1.22; 95% CI, 1.07 – 1.40; p=0.003, I^2 = 19%). AF was not associated with an increased incidence of infective complications, re-exploration for bleeding, myocardial infarction or peri-operative blood transfusion.

Nine studies reported sufficient data for quantitative analysis of mid-term mortality (45, 259, 261, 263, 273-277). Analysis of pooled data from these studies indicated that AF was independently associated with mid-term mortality (HR 1.74; 95% CI, 1.42 – 2.13; p<0.001; I^2 = 76%).

Table 5.3: Meta-analysis on the impact of pre-operative AF on early and mid-term outcomes

Outcome	**No. of Cohorts**	**OR/HR**	**95% CI**	**P-value**	**I^2 (%)**
Early Mortality	13	1.64	1.29 – 2.09	< 0.001	54
Stroke	11	1.50	1.06 – 2.11	0.02	63
Acute Renal Failure	11	1.50	1.23 – 1.83	< 0.001	48
Prolonged Ventilation	9	1.40	1.16 – 1.68	< 0.001	53
Re-Operation	5	1.22	1.07 – 1.40	0.003	19

Wound infection	7	1.30	0.98 – 1.73	0.07	0
Re-operation for Bleeding	7	1.05	0.72 – 1.53	0.80	43
Myocardial Infarction	7	0.76	0.49 – 1.19	0.24	0
Blood Transfusion	3	0.94	0.83 – 1.06	0.31	0
Mid-term Mortality	9	1.74	1.42 – 2.13	< 0.001	76

5.3.2.2 Sensitivity analysis

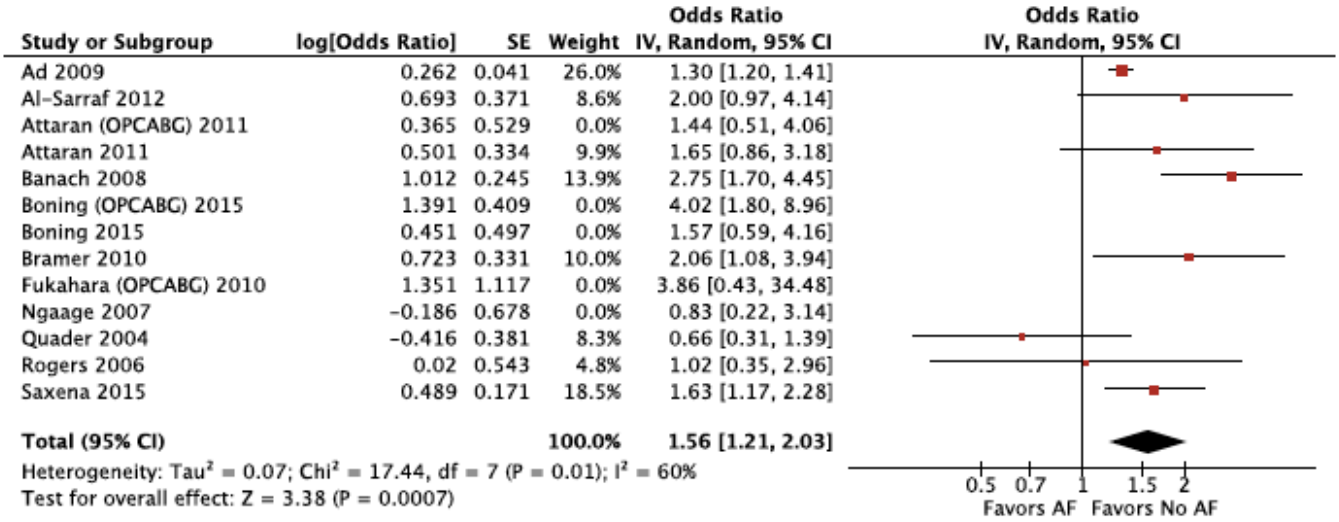
Eight studies(260-263, 272, 273, 276, 277), involving a total of 381,218 patients, reported propensity-matched or adjusted ratios for the primary endpoint of peri-operative mortality. The impact of AF on early and mid-term outcomes in this study cohort is provided in Table 5.4. A sensitivity analysis including only these studies still demonstrated a significant association between AF and peri-operative mortality (OR 1.56; 95% CI, 1.21 – 2.03; $p<0.001$; $I^2 = 60\%$; Figure 5.2). AF also remained significantly associated with an increased risk of stroke, acute renal failure, prolonged ventilation and re-operation for bleeding. Sensitivity analysis confirmed that AF was a risk factor for mid-term mortality (HR 1.47; 95% CI, 1.32 – 1.63; $p<0.001$) and eliminated heterogeneity ($I^2 = 0\%$).

Table 5.4: Sensitivity analysis on the impact of pre-operative AF on early and mid-term outcomes

Outcome	**No. of Cohorts**	**OR/HR**	**95% CI**	**P-value**	**I^2 (%)**
Early mortality	8	1.56	1.21 – 2.03	< 0.001	60
Stroke	6	1.18	1.07 – 1.31	< 0.001	0
Acute Renal Failure	6	1.43	1.13 – 1.82	0.003	59
Prolonged Ventilation	6	1.34	1.09 – 1.65	0.005	62

Re-Operation	3	1.24	1.09 – 1.42	0.001	30
Wound infection	5	1.33	0.99 – 1.79	0.06	0
Re-operation for Bleeding	3	1.32	0.79 – 2.22	0.29	65
Myocardial Infarction	4	0.69	0.39 – 1.22	0.20	0
Blood Transfusion	3	0.94	0.83 – 1.06	0.31	0
Mid-term Mortality	6	1.47	1.32 – 1.63	< 0.001	0

Figure 5.2: Meta-analysis of the association of pre-operative AF with peri-operative mortality after CABG (adjusted studies).



5.3.2.3 Subgroup Analysis: On-pump CABG

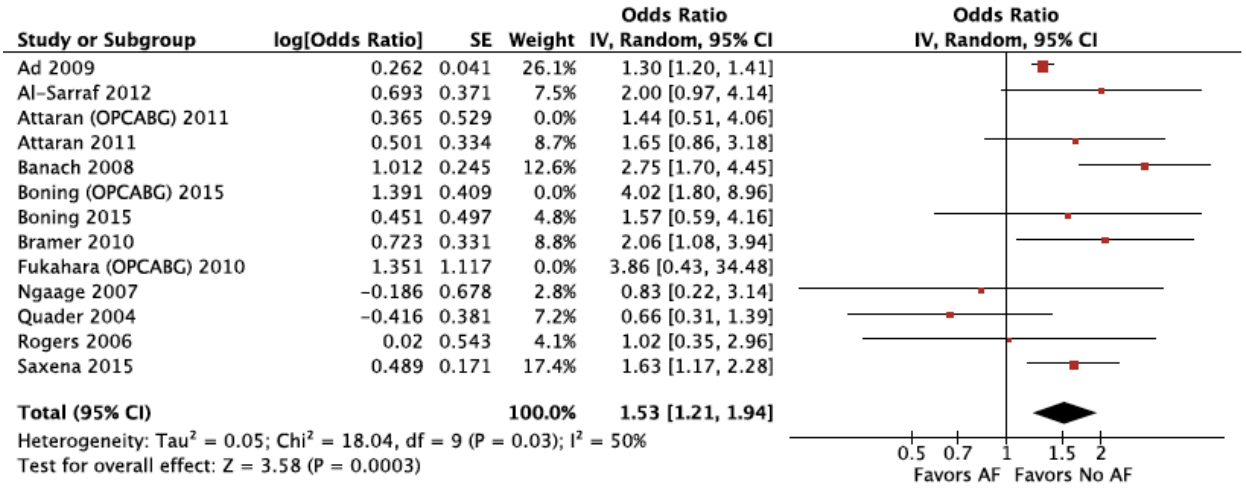
Eleven studies(259-263, 268, 272, 273, 275-277), involving a total of 384,666 patients, examined patients undergoing on-pump CABG surgery. Of these, 19,402 patients presented with AF and 365,264 did not present with AF. A summary of the impact of AF

on early and mid-term outcomes in this study cohort is provided in Table 5.5. In sub-group analysis of on-pump CABG patients, AF was associated with an increased risk of four peri-operative complications including mortality (OR 1.53; 95% CI, 1.21 – 1.94; p<0.001; I^2 = 50%, Figure 5.3), acute renal failure (OR 1.41; 95% CI, 1.17 – 1.69; p<0.001; I^2 = 39%), prolonged ventilation (OR 1.34; 95% CI, 1.13 – 1.60; p<0.001; I^2 = 49%) and re-operation for bleeding (OR 1.23; 95% CI, 1.04 – 1.46; p=0.01; I^2 = 38%). AF was associated with mid-term mortality (OR 1.69; 95% CI, 1.34 – 2.15; p<0.001; I^2 = 81%) following on-pump CABG.

T*able 5.5: Meta-analysis of the impact of pre-operative AF with outcomes after on-pump CABG*

Outcome	No. of Cohorts	OR/HR	95% CI	P-value	I^2 (%)
Mortality	10	1.53	1.21 – 1.94	< 0.001	50
Stroke	9	1.22	0.98 – 1.51	0.08	18
Acute Renal Failure	9	1.41	1.17 – 1.69	< 0.001	39
Prolonged Ventilation	8	1.34	1.13 – 1.60	< 0.001	49
Re-Operation	4	1.23	1.04 – 1.46	0.01	38
Wound infection	6	1.31	0.98 – 1.76	0.07	0
Re-operation for Bleeding	5	1.13	0.75 – 1.72	0.56	50
Myocardial Infarction	5	0.66	0.38 – 1.15	0.15	0
Blood Transfusion	3	0.94	0.83 – 1.06	0.31	0
Mid-term Mortality	7	1.69	1.34 – 2.15	< 0.001	81

Figure 5.3. Meta-analysis of the association of pre-operative AF with peri-operative mortality after on-pump CABG

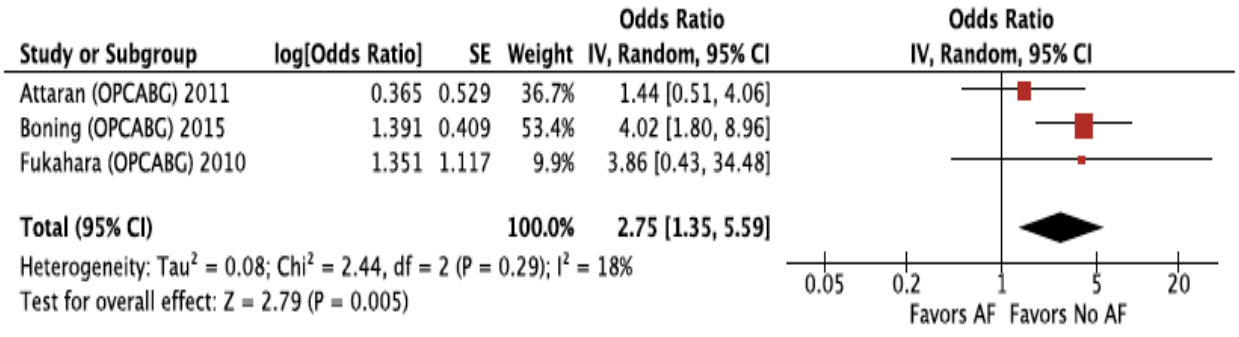


5.3.2.4 Subgroup Analysis: Off-pump CABG

Three studies(261, 268, 274), involving a total of 5322 patients, examined patients undergoing off-pump CABG surgery. Of these, 305 patients presented with AF and 5027 did not present with AF. A summary of the impact of AF on early and mid-term outcomes in this study cohort is provided in Table 5.6. In sub-group analysis of off-pump CABG patients, AF was associated with an increased risk of peri-operative mortality (OR 2.75; 95% CI, 1.35 – 5.59; p=0.005, I^2 = 18%, Figure 5.3). There was a trend towards an increased incidence of acute renal failure (OR 2.29; 95% CI, 0.98 – 5.35; p=0.06; I^2 = 63%). AF was associated with an increased risk of mid-term mortality (HR, 1.97; 95% CI, 1.26 – 3.08; p=0.003, I^2 = 33%) following off-pump CABG.

Table 5.6: Meta-analysis of the impact of pre-operative AF with outcomes after off-pump CABG					
Outcome	**No. of Cohorts**	**OR/HR**	**95% CI**	**P-value**	**I^2 (%)**
Mortality	3	2.75	1.35 – 5.59	0.005	18
Stroke	2	3.71	2.21 – 6.22	< 0.001	0
Acute Renal Failure	2	2.29	0.98 – 5.35	0.06	63
Prolonged Ventilation	1	-	-	-	-
Re-Operation	1	-	-	-	-
Wound infection	1	-	-	-	-
Re-operation for Bleeding	2	0.72	0.27 – 1.95	0.52	36
Myocardial Infarction	2	0.99	0.46 – 2.13	0.99	0
Blood Transfusion	0	-	-	-	-
Mid-term Mortality	2	1.97	1.26 – 3.08	0.003	33

Figure 5.4: Meta-analysis of the association of pre-operative AF with perioperative mortality after off-pump CABG.



5.3.2.5 Subgroup Analysis: Studies excluding STS

A subgroup analysis was performed of studies excluding the large STS study (Table 5.7)(272). In this analysis, AF was associated with an increased risk of peri-operative mortality (OR, 1.74; 95% CI, 1.33 – 2.28; p<0.001), acute renal failure (OR, 1.60; 95% CI, 1.23 – 2.08; p<0.001) and prolonged ventilation (OR, 1.52; 95% CI, 1.15 – 2.00; p=0.003). There was a clear association of AF with mid-term mortality (HR, 1.74; 95% CI, 1.42 – 2.13).

Table 5.7: Subgroup analysis (excluding the STS study)

Outcome	**No. of Cohorts**	**OR/HR**	**95% CI**	**P-value**	**I^2 (%)**
Early mortality	12	1.74	1.33 – 2.28	< 0.001	37
Stroke	10	1.55	0.99 – 2.41	0.05	60
Acute Renal Failure	10	1.60	1.23 – 2.08	< 0.001	44
Prolonged Ventilation	8	1.52	1.15 – 2.00	0.003	54
Re-Operation	4	1.30	0.98 – 1.73	0.07	9
Wound infection	7	1.30	0.98 – 1.73	0.07	0
Re-operation for Bleeding	7	1.05	0.72 – 1.53	0.80	43
Myocardial Infarction	7	0.76	0.49 – 1.19	0.24	0
Mid-term Mortality	9	1.74	1.42 – 2.13	< 0.001	76

5.3.2.6 Subgroup Analysis: Excluding studies enrolling patients before 2000

A subgroup analysis of studies that recruited patients after 2000 is presented in Table 5.8. Four studies were excluded(259, 263, 276, 277). In this analysis, AF was associated with an increased risk of peri-operative mortality (OR, 1.83; 95% CI, 1.39 – 2.43; p<0.001), stroke (OR, 1.54; 95% CI, 1.02 – 2.32; p=0.04), acute renal failure (OR, 1.52; 95% CI, 1.20 – 1.93; p<0.001), prolonged ventilation (OR, 1.44; 95% CI, 1.14 – 1.83, p=0.002), re-operation for bleeding (OR, 1.19; 95% CI, 1.13 – 1.26) and infective complications (OR, 1.42; 95% CI, 1.02 – 1.97; p=0.04). There was a clear association of AF with late mortality (HR, 1.91; 95% CI, 1.43 – 2.55; p<0.001).

Table 5.8: Subgroup Analysis (Excluding Studies Enrolling Patients Before 2000)

Outcome	**No. of Cohorts**	**OR/HR**	**95% CI**	**P-value**	**I^2 (%)**
Mortality	9	1.83	1.39 – 2.43	< 0.001	60
Stroke	8	1.54	1.02 – 2.32	0.04	73
Acute Renal Failure	8	1.52	1.20 – 1.93	< 0.001	62
Prolonged Ventilation	6	1.44	1.14 – 1.83	0.002	69
Re-Operation	4	1.19	1.13 – 1.26	< 0.001	0
Wound infection	4	1.42	1.02 – 1.97	0.04	0
Re-operation for Bleeding	5	1.14	0.67 – 1.92	0.63	54
Myocardial Infarction	5	0.76	0.45 – 1.30	0.32	0
Mid-term Mortality	9	1.97	1.43 – 2.55	<0.001	84

5.3.2.7 Publication Bias

Both Egger's linear regression method (p = 0.13) and Begg's rank correlation test (p = 0.30) suggested publication bias was not an influencing factor when peri-operative mortality was selected as an endpoint. Accounting for potentially missing studies using the imputed Trim-and-Fill method did not alter the result obtained for peri-operative mortality.

5.4 DISCUSSION

The present meta-analysis demonstrated the AF is an independent risk factor for poorer peri-operative outcomes and reduced overall survival after CABG. There has been considerable debate amongst clinicians as to whether AF independently predisposes patients to a poorer outcome or whether it is simply a marker of a more complex physiological milieu. Certainly, AF is associated with age, cardiovascular comorbidities, impaired ventricular function and critical peri-operative state(258, 262).

Nevertheless, our study demonstrated an independent association between AF and poorer peri-operative outcomes. A cumulative analysis of the 13 studies demonstrated that AF increased the risk of peri-operative mortality by 64% (OR 1.64; 95% CI 1.29 – 2.09, p<0.001). Even when only studies that included propensity-matched or adjusted ratios were analyzed, AF was independently associated with a 56% increase in the risk of peri-operative mortality (OR 1.56; 95% CI, 1.21 – 2.03; p<0.001). This is an important clinical finding particularly given that previous cohort studies may have been underpowered to detect a clinical difference(259, 263).

After mortality, the most significant sequelae of AF is an increased risk of stroke. Our analyses demonstrated that AF increased the risk of peri-operative stroke by 50% (OR 1.50; 95% CI 1.06 – 2.11; p=0.02). Off-pump CABG has been shown to reduce the incidence of peri-operative stroke(278). Theoretically then, an off-pump revascularization strategy may reduce the incidence of stroke in patients with AF. Attaran and colleagues(261) performed a matched analysis which compared the outcomes of patients with and without AF based on revascularization strategy (on-pump or off-pump). The authors demonstrated that, in patients undergoing on-pump CABG, AF was associated with a significantly higher risk of stroke (5.4% vs 1.6%, p<0.001). In contrast, in patients undergoing off-pump CABG, AF was not associated with stroke (0% vs 0.5%, p>0.99). Our analyses, however, demonstrated that AF was associated with a greater than threefold increase in the risk of stroke in patients undergoing OPCAB (OR 3.71; 95% CI, 2.21 – 6.22; p<0.001). The optimal revascularization strategy for patients with AF, therefore, remains unclear and further prospective investigation is required. It must be noted that confounding factors may have influenced the observed outcomes. For example, the presence or absence of aortic cross clamping can influence the incidence of postoperative stroke. Unfortunately, we are unable to determine on a case-by-case basis precisely what proportion of the study population had aortic cross-clamping.

AF was also associated with an independently increased risk of acute renal failure, prolonged ventilation and re-operation for bleeding. Several mechanisms have been proposed to explain the association between pre-operative AF and poorer early outcomes. It has been suggested that reduced ventricular filling due to atrial fibrillation results in hypoperfusion of end organs such as the brain and kidneys, rendering patients

susceptible to stroke and renal impairment(263). Encouragingly, however, we found no association between AF and peri-operative myocardial infarction. Moreover, our study showed no association between AF and the rate of bleeding or blood transfusion between the two groups. This is an interesting observation given that it is probable that a higher percentage of patients in AF were on pre-operative anticoagulants. The lack of a significant difference in the rate of bleeding may reflect good clinical management of pre-operative anticoagulants in patients with AF. It may also relate to good intraoperative management of coagulopathy/bleeding.

Our study demonstrated a strong association between AF and mid-term mortality. A cumulative analysis of the 9 studies showed that AF increased the risk of mid-term mortality by up to 74% (HR 1.74; 95% CI, 1.42 – 2.13; p<0.001). Even when only propensity-matched or adjusted studies were analyzed, mid-term mortality was increased by 47% (HR 1.47; 95% CI, 1.32 – 1.63; p<0.001) with excellent homogeneity across studies (I^2 = 0). Our results were consistent with several of the studies included in the meta-analysis. Banach and colleagues(273) evaluated 3000 patients who underwent isolated CABG and demonstrated that 3-year survival was 20% lower in patients who had AF (71% vs 91%, p<0.001). Rogers and colleagues(263) similarly showed an absolute survival difference of 20% after 3 years (70% vs 90%; HR 1.49; 95% CI, 1.06 – 2.08; p=0.020). The cause for increased mid-term mortality in patients with AF is multifactorial. Firstly, AF may predispose patients to thromboembolic or hemorrhagic events(279). Secondly, long-term AF may induce tachycardia-related cardiomyopathy(280). Thirdly, long-term AF exacerbates congestive heart failure(281). Finally, potentially fatal anticoagulation-related complications are more common in patients with AF due to the

high use of warfarin(261).

Given the implications of AF on poorer peri-operative and long-term outcomes, some investigators have advocated to role of adjunct strategies to treat AF. European guidelines suggest that all cardiac surgery patients with symptomatic AF should be offered concomitant peri-operative ablation (recommendation Class IIa, Level A(282)). They also recognize that surgical ablation should be considered in asymptomatic patients with AF (Class IIb, Level C)(282). Cheng and colleagues(283) performed a meta-analysis of 33 studies including 10 randomized controlled trials (RCT) which compared the outcomes of patients who underwent concomitant AF surgery with those that did not. The authors demonstrated a higher rate of sinus rhythm in RCT and non-RCT studies compared with cardiac surgery alone, and this effect remained robust over the long term (5 years). There is evidence that patients with successful sinus restoration had improved survival who were treated but remained in atrial fibrillation(284). Concomitant left atrial occlusion has also been advocated as a treatment strategy to reduce stroke and perioperative mortality in patients with AF but further evidence is required to validate its clinical efficacy(284).

Despite this evidence, the uptake of concomitant AF surgery has been inconsistent. An analysis of data from the Society of Thoracic Surgeons Adult Cardiac Surgery Database (2005 – 2010) showed that only 27.5% of patients undergoing CABG underwent ablation compared to 61.5% of patients undergoing mitral valve repair(285).As discussed by Le Meir and colleagues(286), there are several reasons why concomitant ablation has not been universally adopted. Firstly, there is a lack of large RCTs demonstrating the prognostic benefit of restoring sinus rhythm. Secondly, many surgeons

do not believe that the additional technical complexity of AF ablation justifies the future benefits of sinus rhythm, particularly in patients that do not require an atriotomy. Overall, given the negative implications of AF on both short and long term outcomes, there is a need for further investigate the impact of concomitant ablative strategy in patients with AF undergoing CABG.

5.5 LIMITATIONS

Our study has several limitations. First, all included studies were retrospective, observational reports. Sensitivity analyses were performed, whenever possible. In all cases, the sensitivity analysis were concordant with the general results of the thesis. Some studies only reported unmatched data and in this context the availability of a larger pool of unmatched data did not necessarily confer additional validity to the analysis. Second, considerable heterogeneity was detected in the analysis of several peri-operative complications including mortality, stroke, prolonged ventilation and acute renal failure. This may reflect differences in reporting standards, data collection, endpoint definitions or peri-operative management across institutions. For example, the incidence of AF varied between studies. Whilst, to some degree, this reflects real variation across centers, it is likely that there were differences in screening practices across institutions. Third, due to the nature of the included studies, we could not determine the impact of the type or duration of AF on clinical outcomes. Fourth, our analysis of off-pump CABG was limited by the small number of studies reporting clinical endpoints. Fifth, AF is associated with primary or secondary structural and physiologic derangements that can have a direct

influence on outcomes following cardiac operations that would not be possible to account for in the study design of a meta-analysis. Finally, the analysis of early and mid-term mortality was limited to an assessment of overall mortality rather than disease-specific or event-specific mortality. Moreover, we were unable to gather sufficient data to evaluate the impact of AF on mid-term stroke, which is an important clinical endpoint.

5.6 CONCLUSION

In conclusion, this meta-analysis demonstrated that AF was associated with poorer peri-operative outcomes and reduced long-term survival after CABG. Our study does not prove causality but it does suggest that there is an ongoing need to evaluate the role of concomitant AF surgery. Our data supports the inclusion of AF in risk assessment tools.

SECTION III

THE IMPACT OF PRE-OPERATIVE ATRIAL FIBRILLATION ON OUTCOMES AFTER CARDIAC INTERVENTIONS

CHAPTER 6

SYSTEMATIC REVIEW AND META-ANALYSIS ON THE IMPACT OF PRE-OPERATIVE ATRIAL FIBRILLATION ON SHORT- AND LONG-TERM OUTCOMES AFTER AORTIC VALVE REPLACEMENT

6.1 INTRODUCTION

The clinical impact of AF is described in Section 1.6.

Aortic valve replacement (AVR) is the most commonly performed valvular surgery and remains the gold-standard treatment for patients with severe, symptomatic aortic stenosis and regurgitation(287, 288). The ageing demographic of developed counties has led to an increasingly older cohort with greater co-morbidities undergoing cardiac surgery(289). Commensurate with this the advent of minimally invasive transcatheter aortic valve implantation (TAVI) in the past 15 years has led to a renewed interest in identifying “high risk” patients who may be more suitable for a conservative treatment approach(290). Most recently, the randomized PARTNER 3 trial demonstrated that TAVI can be used in patients with low surgical risk and achieve excellent results(22).

Up to 20% of patients undergoing AVR present with AF(53, 69, 71). Given the association of AF with poorer outcomes, the increased utilization of TAVI and the older population undergoing cardiac surgery, it is imperative to determine the impact of AF on early and mid-term outcomes after AVR. This is particularly true given the evolution of surgical techniques to potentially curatively treat AF in the intraoperative setting(283, 286). Unfortunately, only a few cohort studies have addressed this topic (53, 69, 71, 291).

As TAVI becomes more commonly used in low and moderate risk patients, it is even more important to establish the impact of AF. This is because whilst AF is potentially amenable to surgical cure at the time of AVR, there is currently no effective treatment for AF at the time of TAVI(77). A previous meta-analysis demonstrated that AF was associated with a 68% increased risk of mid-term all-cause mortality after TAVI(292).

Hence, treating a patient with AF with TAVI may not be as appropriate as an approach combining conventional AVR and AF surgery.

The primary aim of this study was to synthesis the available evidence and evaluate the impact of AF on peri-operative and mid-term (> 12 months) mortality after AVR. The secondary aims were:

iii) Evaluate the impact of AF on peri-operative morbidity (stroke, acute renal failure, prolonged ventilation, re-operation for bleeding).

v) Evaluate the impact of AF on early and mid-term (> 12 months) outcomes in patients undergoing isolated AVR.

Our hypothesis is that AF is associated with an increased incidence of peri-operative mortality, morbidity and poorer mid-term survival after AVR. We performed a systematic review and meta-analysis of relevant studies to test our hypothesis.

6.2 METHODS

This systematic review and meta-analysis was conducted and presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines(264). The quality of included studies was assessed with the Newcastle-Ottawa scale for observational studies(265). A detailed description is provided in Section 5.2.

6.2.1 Search Strategy and Study Selection

Electronic searches were performed using Ovid Medline, Embase and Cochrane Central Register of Controlled Trials (CENTRAL) from their dates of inception to January 2016. The search terms “aortic valve replacement” OR “AVR” were combined with “atrial

fibrillation" AND ("baseline OR "pre-operative") as keywords and MeSH terms (Supplementary Table 1). This was supplemented by hand searching the reference lists of key reviews and all potentially relevant studies. A description of the search strategy is provided in Section 5.2.1.

6.2.2 Eligibility Criteria

Eligible studies were those reporting on clinical outcomes of AVR according to the presence or absence of baseline AF. A description of the process by which studies were screened for eligibility is provided in Section 5.2.2.

6.2.3 Data Extraction

A description of the process by which data was extracted is provided in Section 5.2.3.

6.2.4 Statistical Analysis

A summary of the techniques used for statistical analysis is provided in Section 5.2.4. We previously published reported two series which used the ANZSCTS registry to evaluate the impact of AF on early and mid-term outcomes after AVR (Appendix J) and AVR-CABG (Appendix K).

6.3 RESULTS

6.3.1 Study characteristics

A total of 492 unique records were identified through the database and bibliographic searches. Of these, 465 were excluded on the basis of title and abstract content. After

screening the full text of the remaining 27 articles, 6 studies met the inclusion criteria (Figure 6.1).

All included studies were retrospective observational reports (Table 6.1). These included data on 6693 patients who underwent CABG; 5679 patients did not have AF and 1014 had AF. The median study sample size was 501 (range: 83 – 2789). The mean or median follow-up time ranged from 2.4 to 6.6 years. Baseline demographic characteristics and risk-factor profiles of study participants are summarized in Table 6.2.

Figure 6.1: Summary of PRISMA flowchart

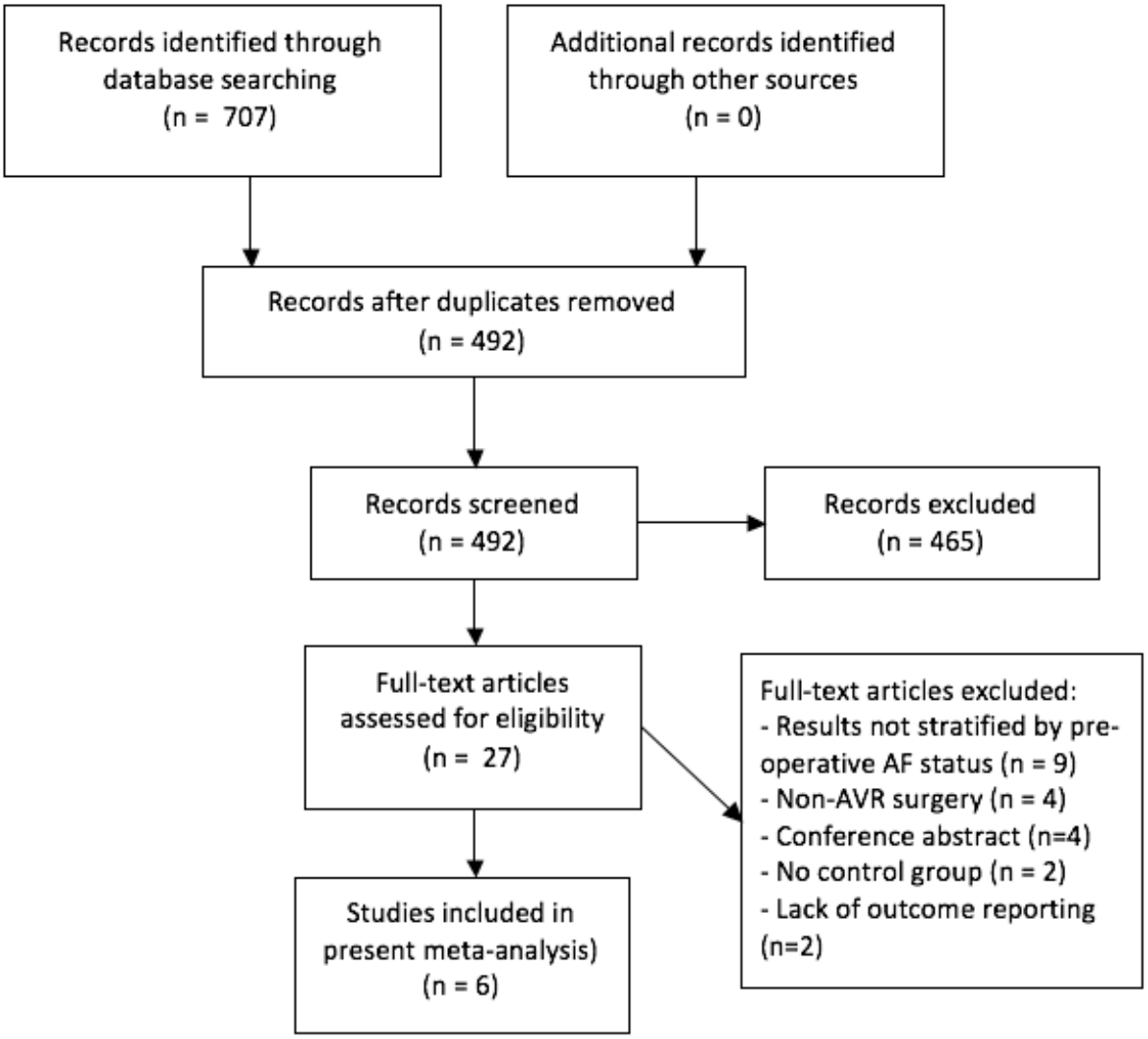


Table 6.1: Study characteristics

First Author (Year)	Study Period	Institution	Type of Surgery	Study Design	-Up)	Number of Patients			NOS
						AF	No AF	Total	
Levy 2006	1988 - 2003	University Hospital, Amiens, France	AVR ± CABG	Retrospective OS	3.2 ± 2.3	29	54	83	S4C2O3
Ngaage 2006	1993 – 2002	Mayo Medical Centre, Rochester, USA	AVR	Retrospective OS	4.5	129	252	381	S4C2O3
Saxena 2013	2001 – 2009	Multicentre, Australia	AVR	Retrospective OS	3.1	380	2409	2789	S4C2O3
Saxena 2013	2001 – 2009	Multicentre, Australia	AVR-CABG	Retrospective OS	2.4	322	2241	2563	S4C2O3
Schulenberg 2010	2008 - 2011	John Radcliffe, Oxford, UK	AVR/AVR-CABG/AVR-MVR	Retrospective OS	6.6	35	222	257	S4C0O3
Wang 2014	1998-2007	Auckland City Hospital, Auckland, New Zealand	AVR	Retrospective OS	3.8 ± 2.4	119	501	620	S4C2O3

AF- pre-existing atrial fibrillation; NOS -Newcastle-Ottawa score**;** S – Selection component of Newcastle-Ottawa score; C – Comparability component of Newcastle-Ottawa Score; O – Outcome component of Newcastle-Ottawa Score

Table 6.2: Baseline patient characteristics

Study	Age (years)		Male %		Diabetes %		Prior MI %		PVD %		CVD %		LVEF %		NYHA III/IV %		HTN %	
	AF	*No AF*	*AF*	*No AF*	*AF*	*No AF*	*AF*	*No AF*	*AF*	*No AF*	*AF*	*No AF*	*AF*	*No AF*	*AF*	*No AF*	*AF*	*No AF*
Levy 2006	68 ± 10	72 ± 7	76	82	21	17	4	17	NR	NR	NR	NR	30 ± 5	30 ± 4	NR	NR	55	33
Ngaage 2006	74 ± 10	73 ± 9	67	66	18	14	8	4	NR	NR	5	4	NR	NR	72	63	NR	NR
Saxena 2013	73 ± 10	68 ± 13	61	58	30	21	NR	NR	10	6	14	10	7 (<30%)	4(<30%)	57	42	76	64
Saxena 2013	76 ± 8	74 ± 8	67	68	33	31	NR	NR	17	15	23	17	9 (<30%)	5(<30%)	51	44	80	80
Schulenberg 2010	56 ± 12 (AVR) 64 ± 7 (AVR-CABG) 66 ± 10 (AVR-MVR)		74(AVR) 89(AVR-CABG) 41(AVR-MVR)		NR		NR		NR		NR		NR		NR		NR	
Wang 2014	71 ± 13	63 ± 16	65	65	22	16	9	9	8	6	11	5	8 (<30%)	4 (<30%)	55	37	52	48

6.3.2 Clinical Outcomes

6.3.2.1 Entire cohort

The association of AF with outcomes is summarized in Table 6.3. There was a statistically significant association between AF and peri-operative all-cause mortality (OR 2.33; 95% CI, 1.48 – 3.67; p<0.001; I^2 = 15%; Figure 6.2). AF was also associated with acute renal failure (OR 1.42; 95% CI, 1.07 – 1.89; p=0.02; I^2 = 0%). AF was not associated with an increased risk of stroke (OR 1.11; 95% CI, 0.59 – 2.12; p=0.74; I^2=0), prolonged ventilation (OR 1.38; 95% CI, 0.89 – 2.14; p=0.15, I^2=81%) or re-operation (OR 1.11; 95% CI, 0.83 – 1.48; p=0.48; I^2=0%).

Five studies reported sufficient data for quantitative analysis of mid-term mortality. Analysis of pooled data from these studies indicated that AF was independently associated with mid-term mortality (HR 1.75; 95% CI, 1.33 – 2.30; p<0.001; I^2 = 39%) (Figure 6.3).

Table 6.3 Meta-analysis on the impact of pre-operative AF on early and mid-term outcomes

Outcome	**No. of Cohorts**	**OR**	**95% CI**	**P-value**	**I^2 (%)**
Early mortality	8	2.33	1.48 – 3.67	< 0.001	15
Stroke	4	1.11	0.59 – 2.12	0.74	0
Acute Renal Failure	4	1.42	1.07 – 1.89	0.02	0
Prolonged Ventilation	3	1.38	0.89 – 2.14	0.15	81
Re-Operation for bleeding	3	1.11	0.83 – 1.48	0.48	0
Mid-term mortality	5	1.75	1.33 – 2.30	<0.001	39

Figure 6.2 Meta-Analysis of the association of pre-operative AF with peri-operative mortality after AVR.

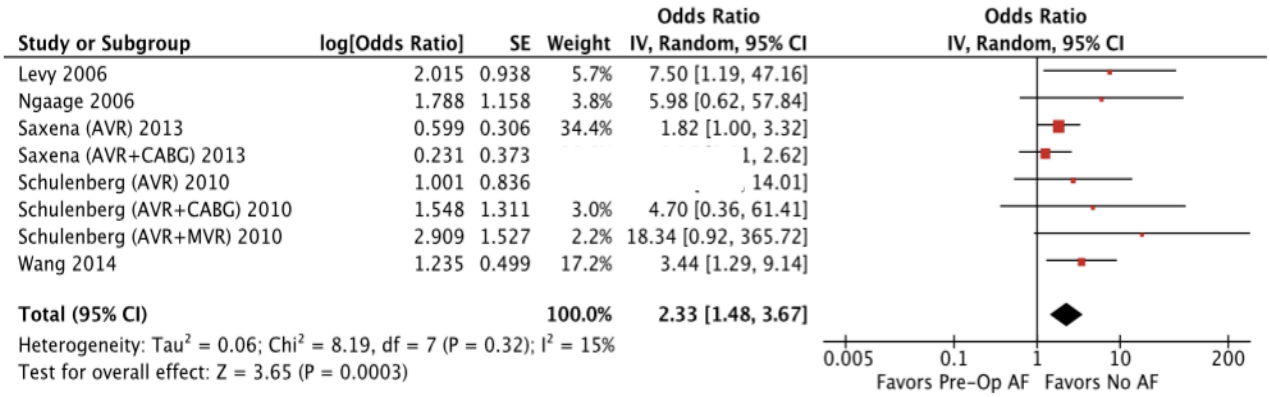
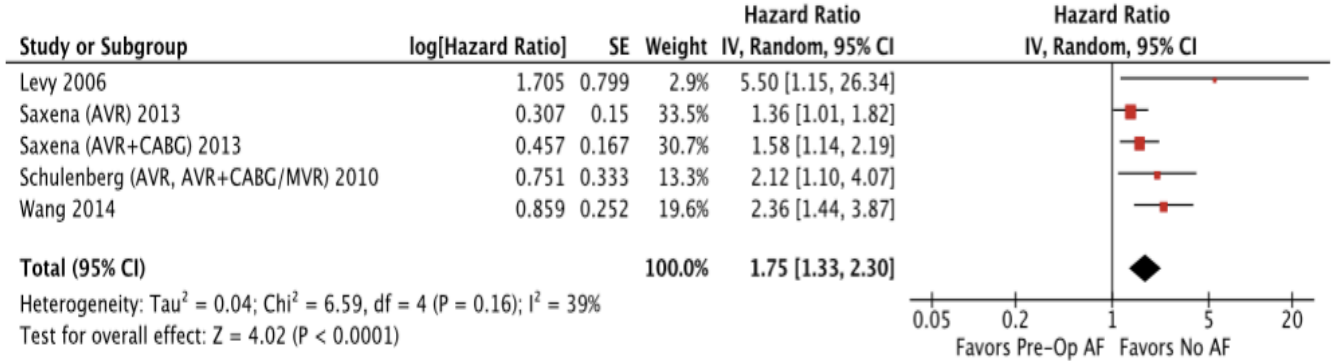


Figure 6.3 Meta-Analysis of the association of pre-operative AF with mid-term mortality after AVR.



6.3.2.2 Subgroup analysis

Isolated AVR

The association of AF with outcomes after isolated AVR surgery is summarized in Table 6.4. Five studies, involving a total of 4,043 patients, examined patients undergoing isolated AVR surgery. Of these, 671 presented with AF and 3373 did not present with AF. In sub-group analysis of isolated AVR, AF was associated with an increased risk of peri-operative all-cause mortality (OR 2.49; 95% CI, 1.57-3.95; p<0.001, I^2 = 0; Figure 6.4) and acute renal failure (OR 1.47; 95% CI, 1.04 – 2.07; p=0.03, I^2 = 0%). There was also a trend towards increased risk of prolonged ventilation (OR 1.75; 95% CI, 1.00-3.05; p=0.05; I^2 =58%). AF was not associated with stroke (OR 1.98; 95% CI, 0.66-5.96; p=0.23; I^2 =0%) or re-operation (OR 1.14; 95% CI, 0.76-1.70; p=0.53; I^2 =19%).

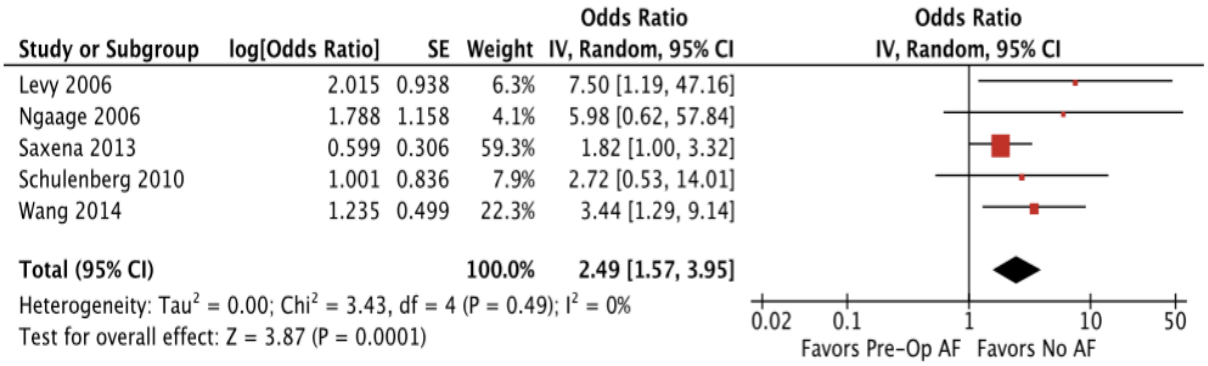
Four studies examining outcomes after isolated AVR reported sufficient data for quantitative analysis of mid-term mortality. Analysis of pooled data from these studies indicated that AF was independently associated with mid-term mortality (HR 1.97; 95% CI, 1.11-3.51; p=0.02; I^2 = 66%).

Table 6.4. Meta-Analysis on the association of pre-operative AF on outcomes after isolated AVR

Outcome	No. of Cohorts	OR	95% CI	P-value	I^2 (%)
Mortality	5	2.49	1.57 – 3.95	< 0.001	0
Stroke	2	1.98	0.66 – 5.96	0.23	0
Acute Renal Failure	3	1.47	1.04 – 2.07	0.03	0

Prolonged Ventilation	2	1.75	1.00 – 3.05	0.05	58
Re-Operation for bleeding	2	1.14	0.76 – 1.70	0.53	19
Mid-term mortality	4	1.94	1.27 – 2.96	0.002	54

Figure 6.4. Meta-Analysis of the association of pre-operative AF with peri-operative mortality after isolated AVR.



6.3.2.3 Publication Bias

Egger's linear regression method (p = 0.005) and Begg's rank correlation test (p = 0.08) suggested publication bias may have been an influencing factor for the primary outcome of peri-operative all-cause mortality. However, accounting for potentially missing studies using the imputed Trim-and-Fill method, AF remained a significant risk factor for peri-operative mortality (OR 1.92; 95% CI, 2.67 – 1.74).

6.4 DISCUSSION

The impact of AF on outcomes after aortic valve surgery has been spare and inconclusive.

This is surprising given the widespread understanding of the mechanism by which AF increases the risk of thromboembolic events, cardiac-related hospitalization and death(67). The present meta-analysis, to our knowledge, the first of its kind, demonstrated that AF increased the risk of peri-operative and mid-term mortality. A cumulative analysis of 8 cohorts demonstrated that AF more than doubled the risk of peri-operative mortality (OR 2.33; 95% CI 1.48-3.67; p<0.001). The same relationship was observed when only patients undergoing isolated AVR were analyzed (OR 2.49; 95% CI, 1.57-3.95; p<0.001). This is an important clinical finding particularly given that the small sample sizes of some previous studies may have precluded them from demonstrating a clinical difference(53, 71).

There is debate in the surgical community about the “true” impact of AF on outcomes. It has been suggested that AF may just be a marker of cardiovascular co-morbidities which predispose patients to poorer outcomes. A previous multi-institutional Australian analysis evaluated 2789 patients undergoing isolated AVR of whom 380(14%) presented with AF(71). The authors demonstrated that patients with AF were older (p<0.001), with a greater incidence of diabetes (p<0.001), cerebrovascular disease (p<0.001), peripheral vascular disease (p=0.002), and severely impaired left ventricular function (p<0.001). Correspondingly, the additive EuroSCORE was higher in AF patients (10.0 ± 3.1 vs. 8.5 ± 3.0, p<0.001). The unadjusted 30-day mortality was significantly higher in patients with AF (5.6% vs 1.8%, p<0.001). When confounding factors were accounted for, however, the relationship between AF and early mortality was more equivocal (OR 1.82; 95% CI, 1.00-3.32; p=0.051). Hence, the more complex comorbidity profile of AF patients does account for some of the variance observed in clinical

outcomes. Similar results have been expressed elsewhere(53, 69).

Nevertheless, our study does suggest that there is a real association between AF and poorer early outcomes. Unless definitively treated, the majority of patients in AF sustain this rhythm peri-operatively and on long-term follow-up. In the peri-operative period, AF may predispose patients to complications through several ways. Intuitively, the loss of sustained contraction of the atria in AF reduces ventricular filling which culminates in reduced cardiac output. This subsequently results in hypoperfusion of end organs, rendering patients susceptible to renal impairment and stroke. Peterson and colleagues demonstrated over 25 years ago that atrial fibrillation impaired cerebral blood flow. Fortunately, our study did not show an association between AF and stroke (OR 1.11; 95% CI, 0.59 – 2.12; p=0.74) although this may reflect the small number of studies which evaluated this outcome. There was, however, an association between AF and acute renal failure (OR 1.42; 1.07-1.89; p=0.02). The association between AF and acute kidney injury has been consistently reported in the cardiac surgery literature, particularly for patients undergoing coronary artery bypass graft (CABG) surgery. There was also a trend toward increased ventilation times in patients with AF undergoing isolated AVR, perhaps reflecting a more conservative approach adopted by intensive care physicians and cardiac surgeons in extubating patients with rhythm abnormalities.

AF compromises long-term survival after AVR. Our adjusted analysis showed that the incidence of mid-term mortality was 75% higher in patients with AF (OR, 1.75; 95% CI, 1.33-2.30; p<0.001). A subgroup analysis of patients undergoing isolated AVR demonstrated that AF almost doubled the risk of mid-term mortality (OR, 1.97; 95% CI, 1.11-3.51). These data are commensurate with those reported for CABG and mitral valve

surgery suggesting that the association of AF with thromboembolic and cardiovascular complications compromises long term outcomes in patients undergoing concomitant surgery.

The impact of AF on poorer clinical outcomes after cardiac surgery has several clinical implications. Firstly, in an era where transcatheter aortic valve implantation (TAVI) is becoming increasingly utilized it may be argued that select patients with AF may be more suitable for a less invasive procedure. TAVI is the gold-standard treatment for non-surgical candidates with aortic stenosis and it is being increasingly deployed in patients with a moderate risk profile(288). A meta-analysis evaluated the impact of AF on short and long-term outcomes after TAVI(293). It showed that 30-day all-cause mortality in patients with AF was similar to patients in sinus rhythm. Conversely, however, AF significantly increased the risk of long-term all-cause mortality (OR 1.68; $p<0.001$) and cardiovascular mortality (OR 2.07; $p=0.01$). Hence, TAVI does not necessarily alleviate the additional risks conferred by AF. Allocating patients for treatment on a case-by-case basis as part of a dedicated heart term remains the best way to improve outcomes in high-risk patients.

Secondly, there may be a need to consider inclusion of AF in risk scoring algorithms. Currently, the only widely employed risk stratification tool which acknowledges that AF may be portend a poorer outcome is the American Society of Thoracic Surgeons (STS) score(180). Other contemporary scoring systems including the EuroSCORE and the AusSCORE do not incorporate AF(105, 151, 185). The short and long term implications of AF suggest that this needs to be re-examined.

Finally, these data suggest that patients may benefit from concomitant AF ablation surgery. European guidelines already stipulate that all patients with symptomatic AF who are undergoing cardiac surgery should be considered for concomitant AF ablation (Class IIa, Level A)(282). Moreover, they suggest that surgical ablation has a role in asymptomatic patients (Class IIb, Level C)(282). The potential benefit of concomitant ablation, however, needs to be balanced by the risk of an additional procedure. Fortunately, there is much evidence that, in the contemporary era, concomitant ablation does not increase the risk of surgery(294). This reflects the continuous improvement in techniques for surgical ablation; the old invasive “cut and sew” Cox-Maze procedure has been gradually replaced by a variety of less invasive epicardial and endocardial techniques(286). There is randomized data suggesting that concomitant ablation improves long-term survival outcomes in patients undergoing cardiac surgery(283). Our data supports the more widespread application of concomitant AF ablation given that it can, to some degree, improve the prognosis of patients with AF.

6.5 LIMITATIONS

Our study has several limitations. First, all included studies were retrospective and observational in nature. Second, many included studies only presented data on all-cause mid-term mortality precluding us from performing an analysis on cardiac-death free survival or cardiac-event free survival. This represents an important avenue for future research. Third, there is significant heterogeneity between studies reflecting differences in endpoint definitions, peri-operative management and reporting standards. In particular,

we are not able to determine the anticoagulation profile of patients in each of the cohorts on discharge or during follow-up. This could affect long-term survival outcomes. Fourth, the number of studies in this meta-analysis was limited; moreover, some studies did not report all the clinical endpoints which we intended to evaluate. Finally, there was publication bias detected for the primary outcome of peri-operative mortality. However, after accounting for potentially missing studies using the imputed Trim-and-Fill method, AF remained a significant risk factor for peri-operative mortality.

6.6 CONCLUSIONS

In conclusion, AF is associated with an increased risk of both peri-operative and long-term mortality. Our data supports the more widespread utilization of concomitant AF surgery. Further study is required to address the impact of AF on cardiac-event free survival and cardiac-specific mortality. Our study also highlights the need to consider the inclusion of AF as an independent risk factor in future risk assessment scores.

SECTION III

THE IMPACT OF PRE-OPERATIVE ATRIAL FIBRILLATION ON OUTCOMES AFTER CARDIAC INTERVENTIONS

CHAPTER 7

THE IMPACT OF PRE-OPERATIVE ATRIAL FIBRILLATION ON OUTCOMES AFTER MITRAL VALVE SURGERY

7.1 INTRODUCTION

The clinical implications of AF are described in Section 1.6.

European guidelines recommend that patients with AF undergoing MVS have a concomitant AF ablation procedure, such as pulmonary vein isolation or the Cox-Maze procedure, particularly if symptomatic(295). Nonetheless, up to 40% of such patients do not receive an AF ablation(285). The possible reasons for this treatment gap include uncertainty about the peri-operative and long-term implications of AF in the context of MVS and concern that the risks of an additional procedure in these patients outweighs the advantage of potentially curing AF(83). It has also been argued that the poorer outcomes in patients with AF are more likely due to the more complex physiologic milieu in these patients rather than a true association with AF(272). Finally, understanding the impact of AF on outcomes is complicated by the fact that, in the postoperative setting, approximately one-third of patients who were in sinus rhythm pre-operatively, develop late AF(296).

A first step in evaluating the risk/benefit of AF ablation procedures with MVS is the description of the impact of AF upon patient outcomes. To our knowledge, no previous systematic review and meta-analysis has quantified the impact of AF on short- and long-term outcomes of patients undergoing MVS without concomitant ablation.

The primary aim of this study was to evaluate the impact of AF on peri-operative and mid-term (> 12 months) mortality after MVS. The secondary aim was to evaluate the impact of AF on the mid-term incidence of stroke, cardiac death and poor functional status (NYHA III/IV) after MVS. The hypothesis was that AF was associated with poorer early

and mid-term outcomes after MVS. We performed a systematic review and meta-analysis of relevant studies to test our hypothesis.

7.2 METHODS

A description of the Methods used is provided in Section 5.2.

7.2.1 Search Strategy and Study Selection

Electronic searches were performed using Ovid Medline, Embase and Cochrane Central Register of Controlled Trials (CENTRAL) from their dates of inception to December 2018. The search terms “mitral valve replacement” OR “mitral valve repair” or “mitral valve surgery” or “MVR” were combined with “atrial fibrillation” AND (“baseline OR “pre-operative”) as keywords and MeSH terms (Supplementary Table 1). This was supplemented by hand searching the reference lists of key reviews and all potentially relevant studies. A description of the search strategy is provided in Section 5.2.1.

7.2.2 Eligibility Criteria

Eligible studies were those reporting on clinical outcomes of MVS according to the presence or absence of baseline AF. A description of the process by which studies were screened for eligibility is provided in Section 5.2.2.

7.2.3 Data Extraction

A description of the process by which data was extracted is provided in Section 5.2.3.

7.2.4 Statistical Analysis

A summary of the techniques used for statistical analysis is provided in Section 5.2.4.

7.3 RESULTS

7.3.1 Study Characteristics

A total of 530 unique records were identified through the database and bibliographic searches. Of these, 504 were excluded on the basis of title and abstract content. After screening the full text of the remaining 26 articles, 10 studies met the inclusion criteria (Figure 7.1).

All included studies were retrospective observational reports (Table 7.1). These included data on 4279 patients who underwent MVS; 2383 patients did not have AF and 1896 had AF. The median study sample size was 393 (range: 91 – 1026). The mean or median follow-up time ranged from 2.0 to 8.7 years. Baseline demographic characteristics and risk-factor profiles of study participants are summarized in Table 7.2.

Figure 7.1. Summary of PRISMA flow chart

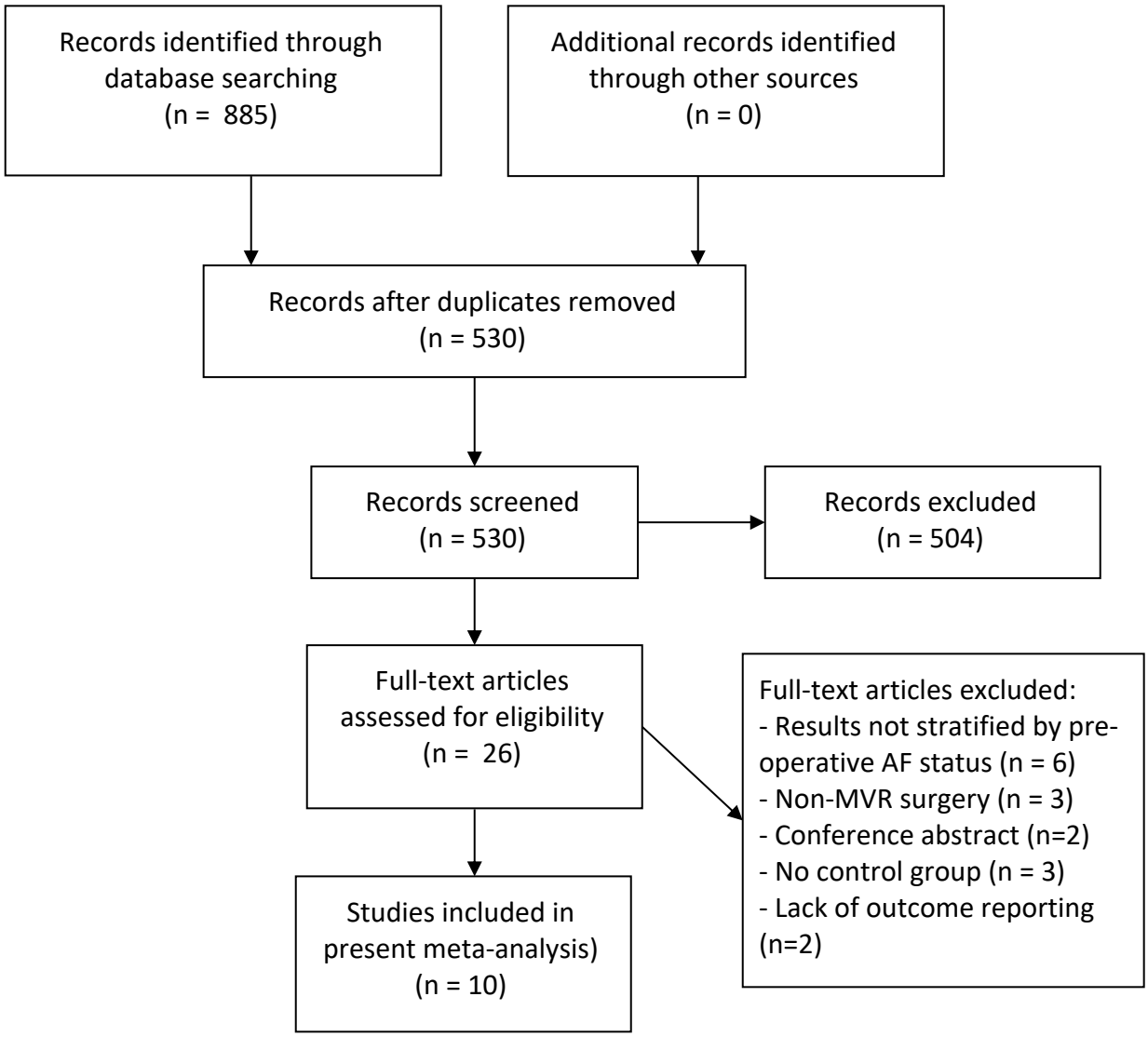


Table 7.1: Study characteristics

First Author (Year)	Study Period	Institution	Type of Surgery	Study Design		Jp	Number of Patients			Type of AF		
							AF	No AF	Total	PAR	PERS	PERM
Alexiou 2007	1997 - 2003	University Hospitals of Leicester, Leicester, UK	MVr	Retrospective OS	S4C2O3	4.5 ± 1.6	152	197	349	31	121	
Bando 2005	1991 - 2003	Multicentre, Japan	MVr	Retrospective OS	S4C2O3	4.3	363	663	1026	25	28	310
Chua 1994	1979 - 1991	Mayo Clinic, Rochester, USA	MVr	Retrospective OS	S4C1O3	2.6	97	215	312	NR		
Eguchi 2005	1991 - 2002	Sakakibara Heart Institute, Tokyo, Japan	MVr	Retrospective OS	S4C2O3	4.7 ± 3.3	129	154	283	NR		
Lim 2001	1987 - 1990	Papworth Hospital, Cambridge, UK	MVr	Retrospective OS	S4C2O3	2.0 [0.9 – 5.1]	152	241	393	NR		
Ngaage 2007	1993 – 2002	Mayo Medical Centre, Rochester, USA	MVr	Retrospective OS	S4C2O3	5 ± 3	231	229	460	134		48
Schulenberg 2010	1994 - 2006	John Radcliffe, Oxford, UK	MVR	Retrospective OS	S4C2O3	6.8 ± 3.8	44	85	129	NR		
Sims 2006	1993 - 2005	Baylor University Medical Centre, Dallas, USA	MVR	Retrospective OS	S4C2O2	NR	38	53	91	NR		
Szymanski 2015	1991 – 2012	University Hospital Amiens, Amiens, France	MVr	Retrospective OS	S4C2O3	8.7 ± 5.3	187	256	443	86		101
Wang 2013	1998-2005	Changhai Hospital, Shanghai, China	MVR	Retrospective OS	S4C2O3	8.6 ± 2.4	503	290	793	NR		

PAR: paroxysmal; PERS: persistent; PERM: permanent; NOS -Newcastle-Ottawa score; **S – Selection component of Newcastle-Ottawa score; C – Comparability component of Newcastle-Ottawa Score; O – Outcome component of Newcastle-Ottawa Score**

Table 7.2: Baseline patient characteristics

Study	Age		Male(%)		Diabetes(%)		Prior MI(%)		CVD(%)		LVEF %		NYHA III/IV(%)		HTN(%)		Mitral Valve Pathology(%)	
	AF	No AF	AF	No AF	AF	No AF	AF	No AF	AF	No AF	AF	No AF	AF	No AF	AF	No AF	AF	No AF
Alexiou 2007	66 ± 7*	62 ± 9*	68	66	7	5	NR	NR	7	3	NR	NR	NR	NR	34	32	NR	NR
Bando 2005	62 (19-78)*	56 (18-82)*	60	60	3	2	7	3	7	3	NR	NR	46	30	15	9	D(81%), E (9%), R(9%), C(2%)	D(74%), E(9%), R(4%), C(3%)
Chua 1994	68 ± 11	63 ± 14	69	65	NR	NR	NR	NR	3	5	56 ± 13	57 ± 14	75	72	NR	NR	NR	NR
Eguchi 2005	59 ± 13*	52 ± 14*	60	67	NR	NR	NR	NR	NR	NR	NR	NR	70	87	NR	NR	NR	NR
Lim 2001	67 ± 9	62 ± 12	63	66	NR	NR	NR	NR	NR	NR	NR	NR	78	66	NR	NR	D(80%), R(13%), E(5%), I(3%),	D(82%), R(3%), E(9%), I(6%), T(0.5%)
Ngaage 2007	65 ± 12	65 ± 12	64	64	5	3	5	1	3	0.4	2(<35%)	1(<35%)	66	45	NR	NR	NR	NR
Schulenberg 2010	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sims 2006	62 (42-800	59 (33-78)	11	15	24	11	13	6	NR	NR	NR	NR	79	62	53	53	NR	NR
Szymanski 2015	69 ± 10*	63 ± 12*	67	75	7	6	NR	NR	NR	NR	66 ± 9	69 ± 9	59	42	39	37	NR	NR
Wang 2013	50 ± 12*	46 ± 14*	35	38	NR	NR	NR	NR	NR	NR	59 ± 9*	63 ± 9*	87	74	NR	NR	NR	NR

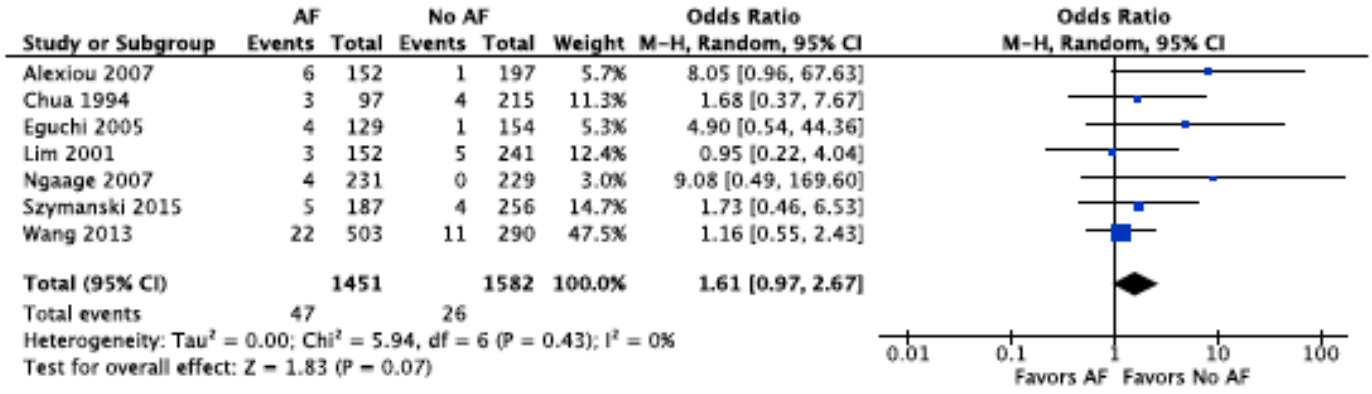
Data presented as mean ± SD, median [IQR] or % of patients. * p < 0.05; AF, pre-existing atrial fibrillation; CVD, cerebrovascular disease; HTN, hypertension; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PVD, peripheral vascular disease; D, degenerative; E, endocarditis; I, ischaemic; R, rheumatic; T, traumatic; C,

7.3.2 Clinical Outcomes

7.3.2.1 Peri-Operative Mortality

In 8 studies involving a total of 3033 patients, there was a trend towards increased peri-operative mortality in patients with AF (OR, 1.61; 95% CI, 0.97 – 2.67; p=0.07; I^2 = 0%; Figure 7.2) but it did not reach statistical significance.

Figure 7.2. Forest plot displaying odds ratio (OR) of peri-operative all-cause mortality for mitral valve surgery cases in patients with and without pre-operative atrial fibrillation.



7.3.2.2 Mid-term Outcomes

In 5 studies involving a total of 2261 patients, AF was associated with significantly increased mid-term mortality (HR, 1.84; 95%, CI, 1.40 – 2.42; p<0.001; I^2 = 0%; Figure 7.3). Similarly, AF was also associated with significantly increased incidence of stroke (HR, 3.70; 95% CI, 1.36 – 10.06; p=0.003; I^2 = 78%; Figure 7.4) and cardiac death (HR, 4.29; 95%, CI, 1.28 – 14.35; p=0.02; I^2 = 77%) at follow-up. There was no association

between AF and NYHA III/IV at follow-up (HR, 1.07; 95% CI, 0.64 – 1.81; p=0.79; I^2=39%).

Figure 7.3. Forest plot displaying hazard ratio (HR) of mid-term all-cause mortality for mitral valve surgery cases in patients with and without pre-operative atrial fibrillation.

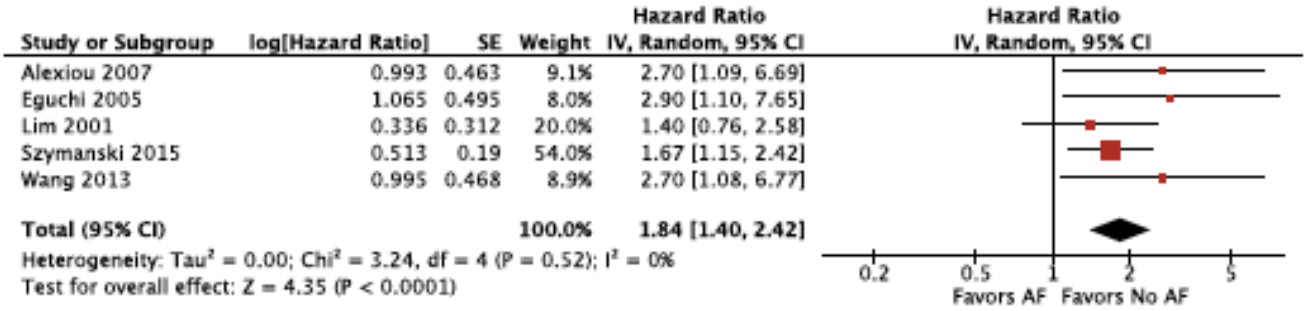
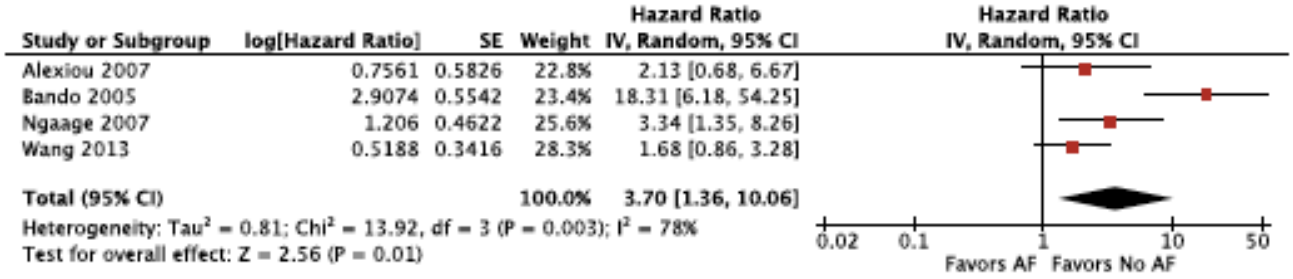


Figure 7.4. Forest plot displaying hazard ratio (HR) of mid-term stroke for mitral valve surgery cases in patients with and without pre-operative atrial fibrillation.



7.4 DISCUSSION

Although AF has been consistently associated with an increased risk of morbidity, stroke and mortality in the general population there has been only sporadic assessment of its impact after MVS. Data from the Society of Thoracic Surgeons (STS) registry shows that the majority of patients with AF who underwent MVS also undergo concomitant ablation.

Nevertheless, 40% did not undergo any potentially curative procedure for AF(285). What is clear is that the decision to treat AF is highly dependent on institutional and surgeon-related factors.

Our study demonstrated that there was a trend towards increased risk of peri-operative mortality after MVS but this did not reach statistical significance. Studies have been inconsistent on the association of AF with early mortality. Wang and colleagues(69) evaluated 793 patients who underwent MVS between 1998 to 2005. The authors showed that peri-operative mortality in patients with AF was comparable to that of patients in SR (4.4% vs 3.4%, p=0.579). In contrast, Ngaage and colleagues(297) showed that patients with AF had a longer postoperative hospitals stay (9 ± 7 vs 7 ± 4 days, p<0.001) and higher in-hospital mortality (2% vs 0%, p=0.05). Unfortunately, many studies did not report data on other early complications preventing a meta-analysis from being performed. This represents a limitation in the current literature. Data from other studies, however, which have evaluated the impact of AF on outcomes in patients undergoing a spectrum of cardiac surgery procedure have shown associations with early mortality(69, 262, 268), peri-operative stroke(262), new renal failure(298), prolonged ventilation(69, 260, 298), return to theatre(262) and prolonged overall hospital stay(262, 276). Hence, clinicians need to be vigilant about the potential implication of AF in the peri-operative setting.

Almost all studies showed an association between AF and poorer mid-term outcomes. Patients with AF had an 84% increased risk of mid-term mortality (OR, 1.84; 95% CI, 1.40 – 2.42; p<0.001). Alexiou and colleagues(299) showed that the difference in mid-term mortality was sustained; at 7 years survival in the AF and SR group was 75 ± 6% versus 90 ± 3%, respectively (p=0.005). This difference was significant on

multivariate analysis (OR, 2.70; 95% CI 1.09 – 6.68; p=0.03). A more critical analysis of the data supports the fact that this difference, is at least partially, attributed to cardioembolic complications. Our study demonstrated that the incidence of cardiac related death was more than 4 times higher in the AF group (OR, 4.29; 95% CI, 128 – 14.37; p=0.02). Eguchi and colleagues(70) evaluated 392 patients with moderate to severe MR who underwent mitral valve repair between 1991 – 2002. At 5 years, the authors observed that patients in SR had better survival than those with AF (96% vs 87%, p=0.002). Similarly, cardiac event-free survival was higher in the SR group (96% vs 75%, p<0.001). Multivariate regression demonstrated that AF was an independent risk factor for reduced overall survival (OR, 2.9; p=0.027) and cardiac event-free survival (OR, 3.1; p=0.002). Further, the authors analysis of cause of death during follow-up provided evidence for a causal relationship between AF and poorer long-term outcomes. Of the 27 patients who died at follow-up, 21 had AF and 6 were in SR. In the AF group, 9 patients died of cardioembolic causes. In comparison, no patients in the SR group died from cardioembolic complications. These data supported the notion that AF reduced survival by predisposing patients to cardioembolic sequelae.

Even beyond its negative implications on overall survival, AF may translate into poorer quality of life outcomes by increasing the risk of stroke. Our data showed that the risk of stroke on follow-up was more than tripled by the presence of AF (OR, 3.70; 95% CI, 1.36 – 10.09; p=0.003). This is a notable finding, especially given that stroke is associated with a significantly worse quality of life and morbidity burden. Ngaage and colleagues(297) reported a significantly higher rate of stroke in patients with AF after a mean duration of 5 years (12% vs 5%, p=0.03). This was despite the fact that a

significantly higher proportion of patients with AF were anticoagulated (48%vs 13%, p<0.001) and commenced on beta-blockers (49% vs 32%, p=0.002). The incidence of late hospital readmissions was almost triple in the AF group (46% vs 17%, p=0.001).

Our study did not suggest any association between AF and poor functional status (NYHA III/IV) on follow-up. While this suggests that MVS may produce functional benefits in patients with AF there is evidence that AF may reduce the improvement in left ventricular function that occurs after surgery. Wang and colleagues(300) showed that freedom from thromboembolism at 13 years was lower for patients with AF compared with that for patients in SR (76.3% vs 94.8%, p=0.001). Moreover, the degree of left ventricular improvement was markedly lower in the AF group (1.2% vs 5.3%, p=0.028). In this regard, the equivocal data from the current meta-analysis may reflect inadequate power and follow-up in the studies evaluated. Future studies evaluating the long-term implications of AF on cardiac function are required.

The association of AF with poorer long-term clinical outcomes after cardiac surgery has many implications. Firstly, in an era where percutaneous techniques for mitral valve repair are being increasingly employed, it may be argued that select patients with AF may be more suitable for a less invasive procedure, particularly those at high surgical risk. There is currently, however, only spare data on the impact of AF on outcomes after percutaneous mitral valve repair. Most importantly our data emphasizes that these patients may benefit from concomitant AF ablation surgery. European guidelines already stipulate that all patients with symptomatic AF who are undergoing cardiac surgery should be considered for concomitant AF ablation (Class IIa, Level A)(282). Moreover, they suggest that surgical ablation has a role in asymptomatic patients (Class IIb, Level

C)(282). The potential benefit of concomitant ablation, however, needs to be balanced by the risk of an additional procedure. Fortunately, there is much evidence that, in the contemporary era, concomitant ablation does not increase the risk of surgery(294). This reflects the continuous improvement in techniques for surgical ablation; the old invasive "cut and sew" Cox-Maze procedure has been gradually replaced by a variety of less invasive epicardial and endocardial techniques(286). There is randomized data suggesting that concomitant ablation improves long-term survival outcomes in patients undergoing cardiac surgery(283). Nevertheless, the use of concomitant ablation remains inconsistent between surgeons and across institutions.

7.5 LIMITATIONS

Our study has several limitations. First, all studies were observational and retrospective in nature. Second, there is significant heterogeneity between studies reflecting differences in endpoint definitions, peri-operative management and reporting standards. In particular, we are not able to determine the anticoagulation profile of patients in each of the cohorts on discharge or during follow-up. This could affect long-term survival outcomes. Third, the number of studies in this meta-analysis was limited; moreover, some studies did not report all the clinical endpoints which we intended to evaluate. Fourth, the studies did not compare outcomes between the different types of AF. Finally, there was publication bias detected for several of the primary outcomes.

7.6 CONCLUSIONS

Nevertheless, our study demonstrates with conviction that AF portends poorer outcomes in the context of MVS. Most importantly, it impairs long-term survival by increasing the risk of cardioembolic complications. These data support the more routine use of concomitant AF surgery during MVS. Future studies should also thoroughly evaluate the impact of AF in the peri-operative setting.

SECTION III

THE IMPACT OF PRE-OPERATIVE ATRIAL FIBRILLATION ON OUTCOMES AFTER CARDIAC INTERVENTIONS

CHAPTER 8

THE IMPACT OF PRE-OPERATIVE ATRIAL FIBRILLATION ON OUTCOMES AFTER PERCUTANEOUS MITRAL VALVE REPAIR

8.1 INTRODUCTION

Mitral regurgitation (MR) is the most common heart valve disorder(35). It is an age-related disease and predominantly affects patients over 65 years old. The prevalence in people over the age of 75 years is approximately 10%(35). As such, the incidence of MR has increased with the ageing of the population and this trend is set to continue. Atrial fibrillation (AF) commonly develops in patients with MR with a reported rate as high as 5% per year and an overall incidence of 31.7-67.7% at the time of intervention(301-303).

Whilst open mitral valve surgery is the gold-standard treatment for patients with severe MR or those with left ventricular dysfunction or dilatation(304) up to 50% of patients are denied because of advanced age and extensive co-morbidities(305). The percutaneous edge-to-edge mitral valve repair with MitraClip (Abbott, Menlo Park, CA, USA) reduces mitral regurgitation by approximating the edges of mitral valve leaflets to create a double orifice. It is based on a surgical technique first described by Alfieri(306). Since the first human case was described in 2003, a substantial body of evidence supporting the utility of MitraClip in high-risk patients has been published (303, 307-309). The EVEREST II study, a multi-center, randomized controlled trial demonstrated no difference in mortality (17% vs 18%, p=0.9) or the incidence of MR grade ≥ 3 (22% vs 25%, p=0.745) between patients undergoing MitraClip or surgery(310). A meta-analysis previously demonstrated the MitraClip was a safe and efficacious treatment in high-risk patients with severe MR(309).

Although the negative impact of AF on outcomes after cardiac surgery has been demonstrated, there is conflicting evidence on its impact after MitraClip(311-313). The primary aim of this systematic review and meta-analysis was to evaluate the prognostic

impact of AF on peri-procedural and 12-month mortality after MitraClip implantation. The secondary aims were:

iii) Evaluate the association of AF with early peri-procedural outcomes (length of hospital stay, stroke, acute renal failure, major bleeding, procedural success)

iv) Evaluate the association of AF with 12-month outcomes (hospitalization for heart failure, stroke)

Our hypothesis is that AF is associated with an increased risk of peri-procedural and 12-month mortality as well as poorer peri-procedural and 12-month morbidity outcomes after MitraClip implantation. To test this hypothesis, we performed a systematic review and meta-analysis of eligible studies which stratified the clinical outcomes of MitraClip according to the presence or absence of baseline AF.

8.2 METHODS

A description of the Methods used is provided in Section 5.2.

8.2.1 Search Strategy and Study Selection

Electronic searches were performed using Ovid Medline, Embase and Cochrane Central Register of Controlled Trials (CENTRAL) from January 2003 to April 2019. The search terms “percutaneous mitral valve repair” OR “Transcatheter mitral valve repair” OR “MitraClip” were combined with “atrial fibrillation” AND (“baseline” or “pre-operative) as keywords and MeSH terms. A description of the search strategy is provided in Section 5.2.1.

8.2.2 Eligibility Criteria

Eligible studies were those reporting on clinical outcomes of percutaneous mitral valve repair with MitraClip according to the presence or absence of baseline AF. A description of the process by which studies were screened for eligibility is provided in Section 5.2.2.

8.2.3 Data Extraction

A description of the process by which data was extracted is provided in Section 5.2.3.

8.2.4 Statistical Analysis

A summary of the techniques used for statistical analysis is provided in Section 5.2.4.

8.3 RESULTS

8.3.1 Study characteristics

A total of 72 unique records were identified through the database and bibliographic search. Of these, 64 were excluded after screening and application of our inclusion and exclusion criteria (Figure 8.1).

There was 1 randomized controlled trial (RCT) and 7 retrospective observational reports (Table 8.1). These included data on 8704 patients who underwent MitraClip; 3503 did not have AF. The median sample size was 601 patients (range: 116 – 5613). Baseline demographic and risk-factor profiles of study participants are summarized in Table 8.2.

Figure 8.1 Summary of PRISMA flow chart

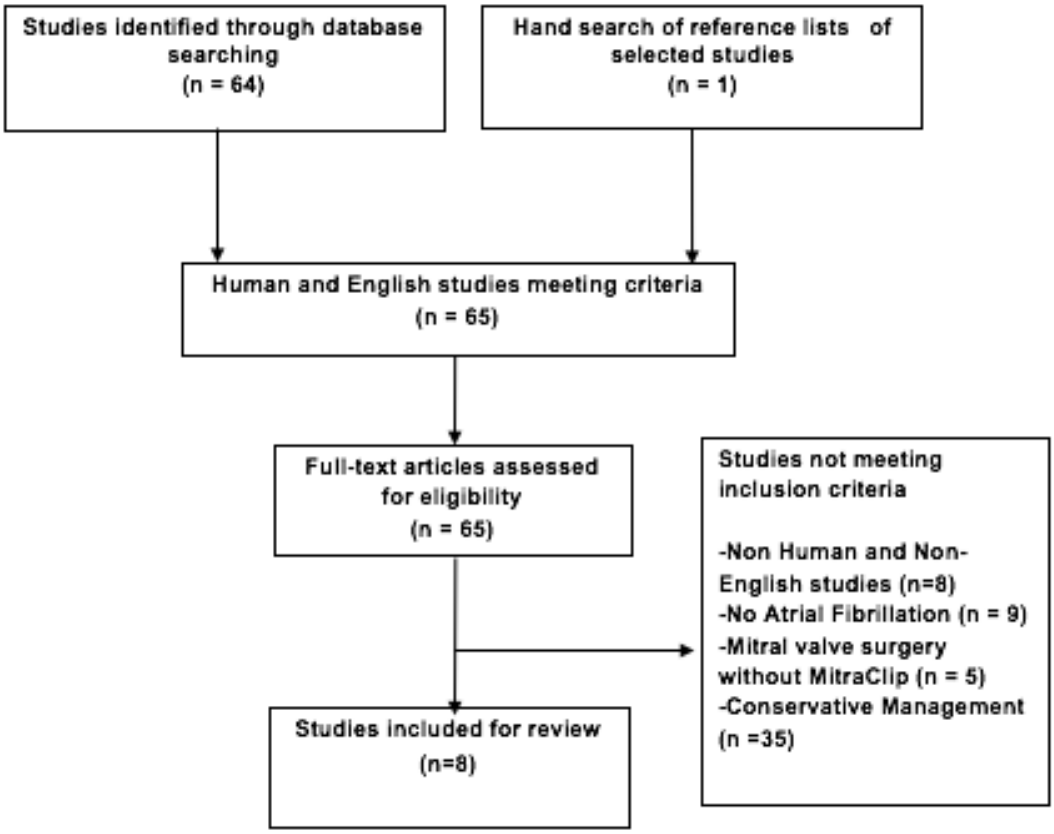


Table 8.1: Study characteristics

Study (Year)	Study Period	Institution	Country	Registry	Study Design	Number of Patients			NOS
						Total	AF	NAF	
Keßler 2018	2010 - 2016	University of Ulm	Germany	MiTraUlm Registry	Retrospective OS	355	239	116	S4C2O3
Arora 2019	2013 - 2016	Multicenter	USA	Transcatheter Valve Therapy Registry	Retrospective OS	5613	3555	2058	S4C2O3
Velu 2017	2009 - 2016	Multicenter	Netherlands	NA	Retrospective OS	618	326	292	S4C2O3
Spieker 2018	2014 - 2019	Heinrich Heine University	Germany	MitraClip Registry	Retrospective OS	200	112	88	S4C2O3
Subahi 2018	2011 - 2014	Multicenter	USA	National Inpatient Sample Registry	Retrospective OS	1026	577	449	S4C2O3
Herrmann 2012	2005 - 2008	Multicenter	USA/Canada	NA	Randomised Control Trial	175*	45*	130*	+8#
Jabs 2017	2009 - 2013	Multicenter	Germany	Transcatheter Mitral valve Interventions (TRAMI) registry	Retrospective OS	601	286	315	S4C2O3
Giordano 2015	NR	Multicenter	Italy	NR	Retrospective OS	116	61	55	S4C2O3
Total						8704	5201	3503	

***Sample receiving MitraClip intervention (ITT cohort); NR, not recorded; OS, observational study; #Jadad scale score (randomized trial); NOS -Newcastle-Ottawa score; S – Selection component of Newcastle-Ottawa score; C – Comparability component of Newcastle-Ottawa Score; O – Outcome component of Newcastle-Ottawa Score**

Table 8.2: Baseline characteristics

Study	Age Mean(SD) Median(IQR)		Male n(%)		DM n(%)		HTN n(%)		Stroke n(%)		AMI n(%)		MR Grade Mean (±SD)/n(%)		MR Gradient Mean (SD)(mmHg)		TR Grade III/IV n(%)	
	AF	NAF	AF	NAF	AF	NAF	AF	NAF	AF	NAF	AF	NAF	AF	NAF	AF	NAF	AF	NAF
Keßler	78(8)	76(9.8)	149(62)	67(58)	66(28)	38(33)	nr	nr	25(11)	11(10)	52(22)	29(25)	4 (±1)	3.5 (±1)	2(2)	1.8 (1.3)	118(56)	31(33)
Arora	80(9)	77(11)	1969(55)	1029(50)	924(26)	558(27)	3032(85)	1733(84)	398(11)	194(9)	928(26)	626(30)	nr	nr	nr	nr	nr	nr
Velu	76(9)	71(11)	185(57)*	168(58)	69(21)	73(25)	176(54)	146(50)	33(10)	38(13)	nr	nr	203(62)¥	203(70)¥	nr	nr	40(12)¥	22(8)¥
Spieker	77(9)	72(12)	61(54)	63(72)	37(33)	28(32)	105(94)	80(91)	nr	nr	nr	nr	112(100)£	88(100)£	2.3(1)	2.2(1)	63(56)	28(32)
Subahi	77(11)	72(14)	325(56)*	253(56)	150(25)	119(27)	419(73)	315(70)	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr
Herrmann	72(11)*	65(13)*	48(67)*	121(63)*	9(13)*	14(7)*	59(82)*	136(71)*	nr	nr	24(33)*	30(16)*	43(96)€	125(96)€	nr	nr	nr	nr
Jabs	78(71)	75(70-80)	161(56)	182(58)	92(32)	109(35)	220(77)	247(78)	28(10)	25(8)	65(23)	102(33)	292(92)ł	301(95)ł	nr	nr	nr	nr
Giordano	76(72-79)	74 (68-79)	32(53)	25(45)	14(23)	21(39)	40(66)	35(64)	nr	nr	23(38)	31(56)	36(59)£	42(76)£	nr	nr	nr	Nr

AF – pre-existing atrial fibrillation; NAD – no pre-existing atrial fibrillation; DM – Diabetes mellitus; AMI – acute myocardial infarction; MR – mitral regurgitation; TR – tricuspid regurgitation

Table 8.2: Baseline characteristics - continued

Study	CAD n(%)		PVD n(%)		CABG n(%)		PCI n(%)		ICD n(%)		NYHA III/IV Mean(±SD)/n(%)		EF (%±SD)/n(%)		EuroSCORE I %(SD/IQR)		EuroSCORE II n(SD/IQR)	
	AF	NAF	AF	NAF	AF	NAF	AF	NAF	AF	NAF	AF	NAF	AF §	NAF §	AF	NAF	AF	NAF
Keßler	169(71)	89(77)	63(27)∞	37(33)∞	37(16)	25(22)	nr	nr	40(17)	24(21)	3.2(0.7)	3(0.8)	44%(±18)	EF42%(±17)	nr	nr	8.6(8)	8.9(9)
Arora	nr	nr	654(18)	387(19)	1027(29)	628(31)	1038(29)	687(33)	572(16)	251(12)	3075(87)	1716(84)	EF<45% 1020(29%)	EF <45% 601(29%)	nr	nr	nr	nr
Velu	174(53)	183(63)	nr	nr	94(29)	91(31)	88(27)	90(31)	98(30)	94(32)	288(88)	250(86)	EF <30% 97(30%)	EF <30% 30(45%)	20(14)	19(14)	nr	nr
Spieker	73(65)	63(72)	nr	nr	33(29)	33(38)	nr	nr	20(18)	20(23)	100(89)	76(86)	EF 42%(±13%)	EF 38%(±13%)	22(15)	21(15)	nr	nr
Subahi	361(63)	254(57)	74(13)	51(11)	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr
Herrmann	42(59)*	76(40)*	9(13)*	13(7)*	16(22)*	33(17)*	19(26)*	35(18)*	10(14)*	6(3)*	40(56)*	90(47)*	EF58%(±10%)€	EF62%(±9%)€	nr	nr	nr	nr
Jabs	226(79)	258(82)	nr	nr	70(25)	72(23)	51(18)	60(19)	125(44)	204(65)	259(91)	281(89)	EF <30% 64(22%)	EF <30% 106(34%)	20(13-33)	18(11-30)	nr	nr
Giordano	nr	nr	nr	nr	nr	nr	nr	nr	8(15)	9(17)	21(33)¿	7(13)¿	35%(nr)	35%(nr)	nr	nr	8(3-22)	4(2-15)

CAD – coronary artery disease; PVD – peripheral vascular disease; CABG – previous coronary artery bypass graft surgery; ICD – previous implantable cardioverter defibrillator; NYHA – New York Heart Association score; EF – Ejection fraction; Values are either expressed as mean ± SD, median with IQR or n(%), * Both control and treatment cohorts of RCT, § Ejection fraction either mean ± SD or the number of cohort (EF<30%/EF<45%) affected and percentage is displayed, € Both control and treatment intent to treat cohorts, ∞ Report combined peripheral and cerebral vascular disease, ¥ Grade 4 only, £ Reported moderate/severe. Ł Reported Severe, ¿Class IV only

8.3.2 Follow-up

Table 8.3 summarizes the follow-up period for each of the included studies. All studies presented data on baseline and post-procedure follow-up. Five studies reported outcomes at or beyond 12 months.

Table 8.3: Overview of follow up period											
Study	**Baseline**	**Post procedure**	**1m**	**3 m**	**6 m**	**9 m**	**1 Y**	**2Y**	**3 Y**	**4 Y**	**5 Y**
Keßler 2018	Y	Y					Y	Y	Y		
Arora 2019	Y	Y	Y	Y	Y	Y	Y				
Velu 2017	Y	Y	Y		Y		Y	Y	Y	Y	Y
Spieker 2018	Y	Y					Y				
Subahi 2018	Y	Y									
Herrmann 2012	Y	Y	Y				Y				
Jabs 2017	Y	Y	Y			Y					
Giordano 2015	Y	Y	Y	Y	Y	Y					

8.3.3 Overall mortality and morbidity

Table 9.4 summarizes the incidence of mortality at various time points in patients with and without AF. The incidence of in-hospital mortality in patients with and without AF ranged from 2-5% and 1-5%, respectively. At 12 months, the incidence of overall mortality in patients with and without AF ranged from 5-27% and 5-19%, respectively. One study reported mortality outcomes at 5 years and showed a trend towards increased mortality

in the AF group (66% vs 53%, p=0.006). A summary of the incidence of morbidity outcomes in patients with and without AF at the final study

time-point is summarized in Table 8.5.

Table 8.4: Overview of mortality Incidence n(%)

Study	Hospital		30d		1y		3y		5y		P Value Ω
	AF	NAF	AF	NAF	AF	NAF	AF	NAF	AF	NAF	
Keßler	7(3)	4(5)	nr	nr	47(21)	13(12)	74(50)	22(32)	nr	nr	0.036
Arora	96(3)	41(2)	nr	nr	294(26)	395(19)	nr	nr	nr	nr	<0.0001
Velu	nr	nr	nr	nr	59(18)	44(15)	nr	nr	215(66)	155(53)	0.006
Spieker	nr	nr	nr	nr	19(17)	14(16)	nr	nr	nr	nr	0.842
Subahi	8(2)	12(3)	nr	nr	nr	nr	nr	nr	nr	nr	0.487
Herrmann	nr	nr	1 (2)	1 (1)	2(5)	7(5)	nr	nr	nr	nr	0.9650
Jabs	11(3)	2(1)	18(6)	9(3)	80(25)	47(17)	nr	nr	nr	nr	0.002
Giordano	3(5)	1(2)	nr	nr	11(27)*	4(10)*	nr	nr	nr	nr	nr

AF – pre-existing atrial fibrillation; NAF – no pre-existing atrial fibrillation; Ω P Value at final point of measurement
*6-7month follow up

Table 8.5: Overview of secondary outcomes at final study point n(%)

Study	CV mortality		Stroke		MACCE		Readmission		Renal failure		Infection		Bleeding		Valve Reintervention	
	AF	NAF	AF	NAF	AF	NAF	AF	NAF	AF	NAF	AF	NAF	AF	NAF	AF	NAF
Keßler	45(35)	14(24)	4(2)*	2(2)*	120(67)	39(47)	56(35)	25(28)	nr	nr	9(4)*	7(6)*	6(3)*	2(2)*	4(1.5)	0(0)
Arora	nr	nr	127(4)	66(3)	nr	nr	453(22)	675(19)	nr	nr	nr	nr	nr	nr	nr	nr
Velu	nr	nr	6(1.8)	3(1)	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr
Spieker	8(9)	10(11)	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr
Subahi	nr	nr	3(1)*	5(1)*	nr	nr	nr	nr	81(14)*	70(16)*	nr	nr	nr	nr	nr	nr
Herrmann	nr	nr	1(2)	1(1)	nr	nr	nr	nr	1(2)	0(0)	0(0)	0(0)	nr	nr	0(0)	0(0)
Jabs	74(26)	93(30)	nr	nr	88(31)	77(25)	188(66)	187(59)	nr	nr	nr	nr	31(11)	25(8)	nr	nr
Giordano	nr	nr	nr	nr	nr	nr	2(7)	1(3)	2(3)	2(4)	nr	nr	2(3)	0(0)	0(0)	1(2.6)

AF – pre-existing atrial fibrillation; NAF – no pre-existing atrial fibrillation; CV – cardiovascular; MACCE – major adverse cardiovascular events; *Post procedural

8.3.4 Meta-Analysis

8.3.4.1 Peri-procedural outcomes

Table 8.6 summaries the results of the meta-analysis on the association of pre-existing AF with peri-procedural outcomes after MitraClip. AF was associated with an increased risk of peri-procedural mortality (RR, 1.35; 95% CI, 1.02 – 1.78; p=0.03; I^2=0%, Figure 8.2) and longer hospital stay (Mean difference [MD] 0.65; 95% CI, 0.36 – 0.93; p<0.001; I^2=0%, Figure 8.3). There was no association of AF with early stroke (RR, 0.94; 95% CI, 0.46 – 1.95; p=0.88; I^2=0%, Figure 8.4), acute renal failure (RR, 0.99; 95% CI, 0.66-1.49; p=0.97; I^2=0%), major bleeding (RR, 0.91; 95% CI, 0.18 – 4.61; p=0.91, I^2=69%) or procedural success (RR, 1.00; 95% CI, 0.99-1.01; p=0.73, I^2=6%, Figure 8.5).

Table 8.6: Impact of pre-existing AF on MitraClip outcomes

Peri-Procedural Outcomes	**No. of Studies**	**RR/MD***	**95% CI**	**P-value**	**I^2 (%)**
Mortality	6	1.35	1.02 – 1.78	0.03	0
Stroke	5	0.94	0.46 – 1.95	0.88	0
Acute Renal Failure	3	0.99	0.66 – 1.49	0.97	0
Major Bleeding	3	0.91	0.18 – 4.61	0.91	69
Length of Hospital Stay*	4	0.65	0.36 – 0.93	< 0.001	0
Procedural Success (MR Grade ≤ 2+)	5	1.00	0.99 – 1.01	0.73	6

Figure 8.2 Forest plot displaying relative risk ratio (RR) of peri-procedural all-cause mortality for patients with and without pre-existing AF

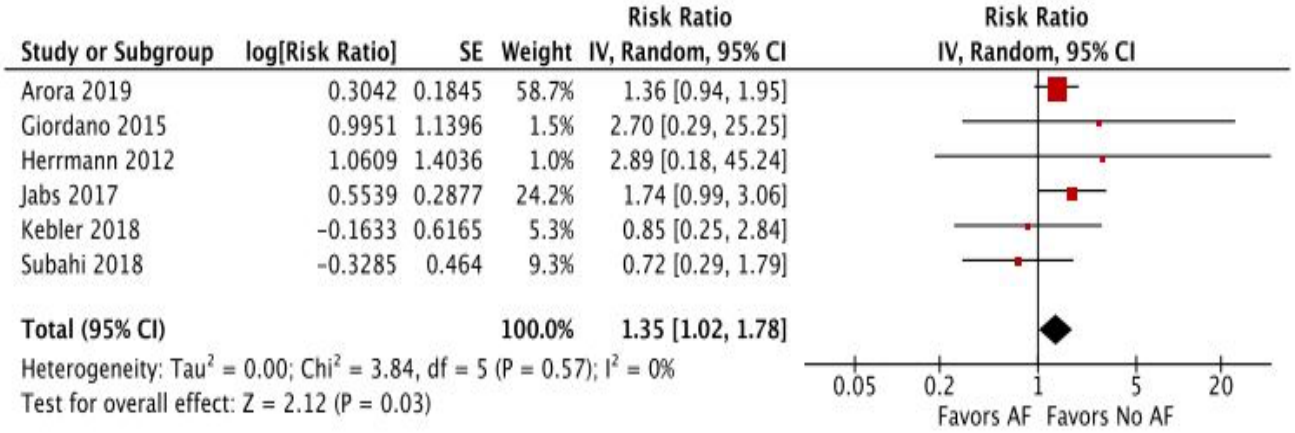


Figure 8.3 Forest plot displaying mean difference (MD) in hospital length of stay in patients with and without pre-existing AF

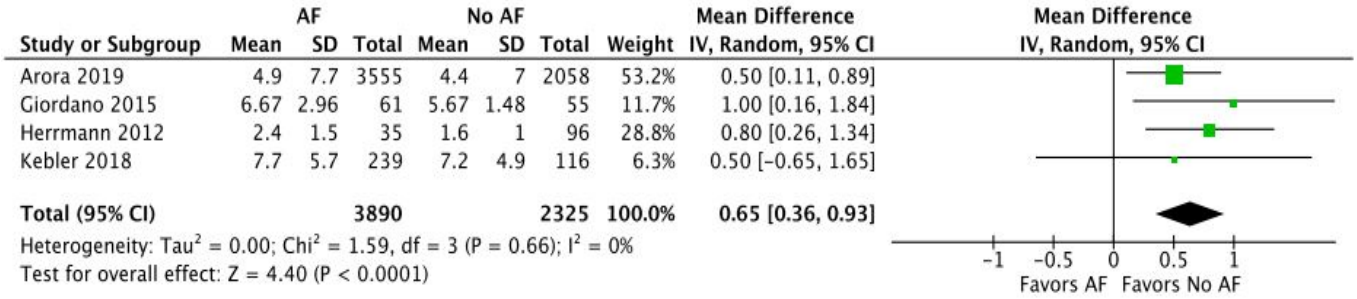


Figure 8.4 Forest plot displaying relative risk ratio (RR) of peri-procedural stroke in patients with and without pre-existing AF

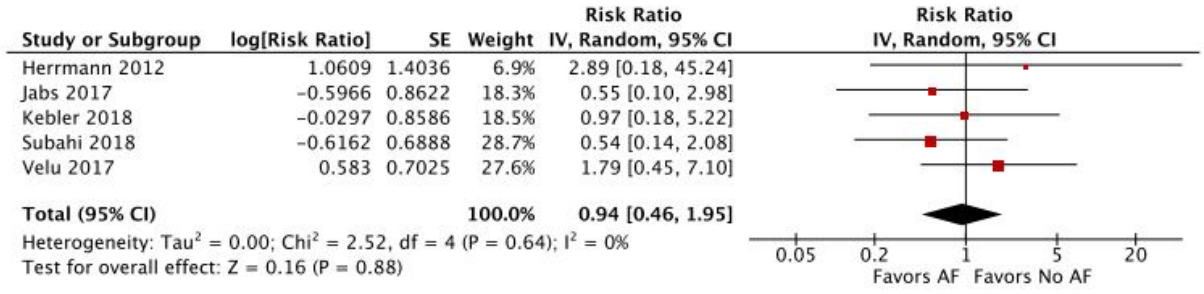
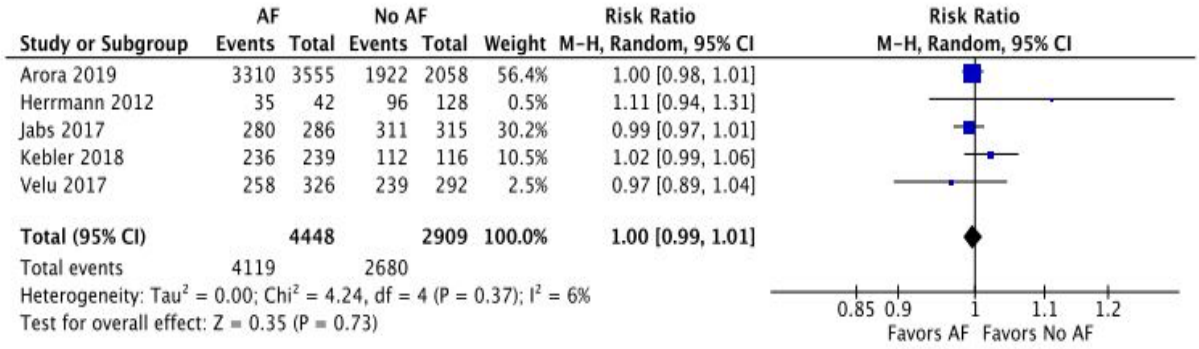


Figure 8.5 Forest plot displaying relative risk ratio (RR) of procedural success in patients with and without pre-existing AF



8.3.4.2 12-month outcomes

Table 8.7 summarizes the results of the meta-analysis on the association of AF with 12-month outcomes after MitraClip. AF was associated with an increased risk of 12-month mortality (Hazard Ratio [HR], 1.45; 95% CI, 1.27 – 1.66; p=0.03; I^2=0%, Figure 8.6) and 12-month hospitalization for heart failure (HR, 1.18; 95% CI, 1.03 – 1.35; p=0.02; I^2=0%, Figure 8.7). There was no association of AF with 12-month stroke (HR, 1.01; 95% CI, 0.32 – 3.20; p=0.99; I^2=71).

Table 8.7: Impact of pre-existing AF on 12-month outcomes after MitraClip

1-Year Outcomes	No. of Studies	HR	95% CI	P-value	I^2 (%)
Mortality	6	1.45	1.27 – 1.66	0.03	0
Stroke	3	1.01	0.32 – 3.20	0.99	71
Re-hospitalization for HF	4	1.18	1.03 – 1.35	0.02	0

Figure 8.6 Forest plot displaying hazard risk ratio (HR) of 12-month mortality for patients with and without pre-existing AF

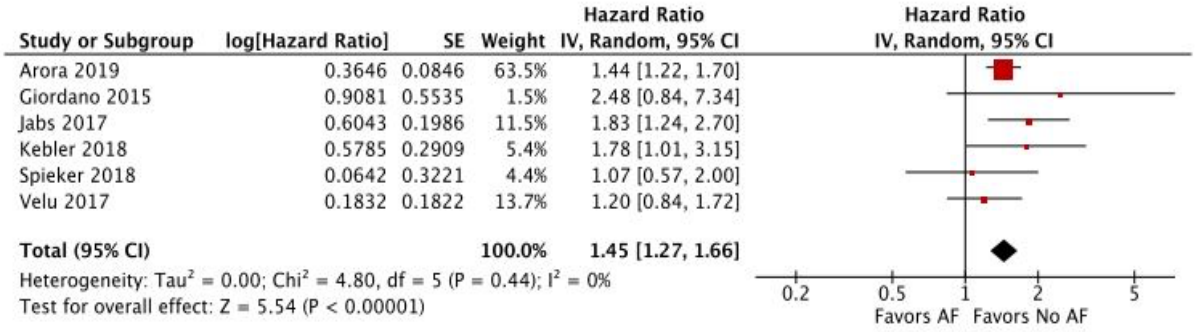
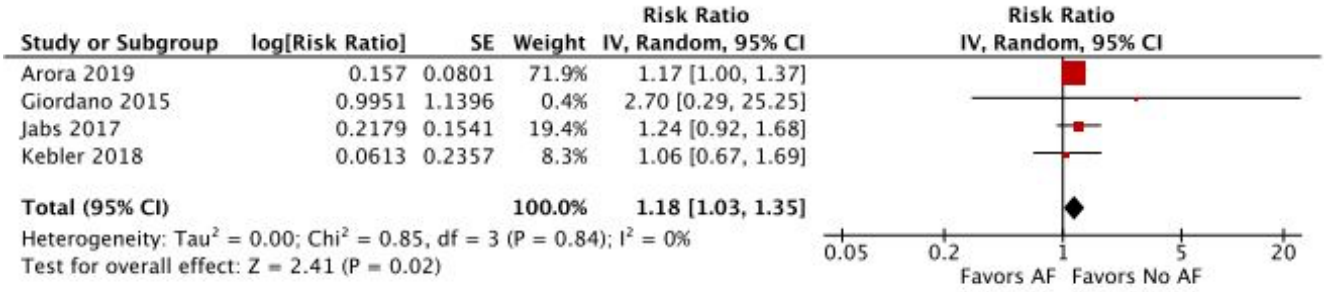


Figure 8.7 Forest plot displaying hazard risk ratio (HR) of 12-month hospitalization for heart failure for patients with and without pre-existing AF



8.4 DISCUSSION

Valvular heart disease is an independent risk factor for the development of atrial fibrillation(295). AF has been consistently shown to portend a poorer prognosis in patients undergoing intervention for valve disease including surgical aortic valve replacement(71, 314), transcatheter aortic valve implantation(315) and open mitral valve surgery(297, 300). The prevalence of AF among patients undergoing MitraClip is particularly high at up to 68%(301-303). This reflects the advanced age and comorbidity profile of these patients who are generally not surgical candidates. Despite this there is a paucity of data

on the early and late implications of AF on outcomes after MitraClip. Moreover, given that many studies are not sufficiently powered to detect potentially significant associations between AF and outcomes, the current literature is conflicting and fragmentary.

Our study included 8 studies with a total study population of 8704 patients; of these, 5201(59.8%) had AF. Studies ranged in size from 115–5613 patients. Our study reiterated that MitraClip implantation is safe regardless of initial rhythm; the overall in-hospital mortality rate was only 1-5% across all studies in both groups. Our meta-analysis, however, demonstrated that AF increased the risk of early mortality by 35% (RR, 1.35; 95% CI 1.02–1.78). This contrasts with findings of all individual series suggesting that they were underpowered to detect a difference. Jabs and colleagues(312) analyzed the multi-center German TRAMI registry and showed a non-significant trend towards increased in-hospital mortality in the AF group (3.2% vs 1.95%, p=0.055). Similarly, Arora and colleagues(316) analyzed of 5613 patients (63% AF) recruited in the Transcatheter Valve Therapy (TVT) registry and showed a trend towards higher in-hospital mortality in the AF group (2.7% vs 2.0%, p=0.12). The association of AF with increased peri-operative mortality has been extensively reported in the cardiac surgery literature.

Several studies have demonstrated the AF increases length of stay and resource utilization after cardiac intervention. This relationship is also observed after MitraClip. Of the four studies which reported this outcome, three showed that AF significantly increased length of stay with a mean increase of 0.65 days (95% CI, 0.36-0.93). A subset analysis of the EVEREST II trial showed that AF added 0.8 days to the total length of stay and 10 hours to ICU stay(311). An increased incidence of hemodynamic instability (e.g. due to rapid ventricular response) requiring active treatment and the use of Vitamin K

antagonists requiring international normalized ratio (INR) monitoring partially explains these findings. Subahi and colleagues(317) also showed that AF patients undergoing MitraClip are at an increased risk of non-routine discharge including home health care and short- and long-term care facilities. There is a paucity of data on the impact of AF on cost during hospitalization and this represents a future avenue for research.

Concerns have been raised that technical success of MitraClip may be compromised by AF. Intuitively, it could be argued that it may be more difficult to grasp the mitral leaflets in patients with an irregularly irregular rhythm. Fortunately, our meta-analysis showed that AF did not affect the rate of procedural success (MR grade ≤ 2+) (RR, 1.00; 95% CI, 0.99-1.01). These data, however, may understate the inherent difficulties that may be encountered in implanting MitraClip in these patients. The EVEREST II trial showed that procedure and device time were similar in patients with and without AF(311). Device attachment to a single leaflet, however, was significantly more common in AF patients (13% vs 3%). The authors suggested that this may reflect a greater difficulty in assessing leaflet insertion echocardiographically during AF and underscored the importance of an even more careful assessment of leaflet insertion in these patients prior to clip release. Whether conversion to sinus rhythm prior to the procedure may mitigate this risk remains unknown.

A previous report highlighted the risk of thrombus formation after MitraClip implantation given both the utilization of a pro-thrombotic intra-cardiac device and the dramatic hemodynamic changes after MitraClip (from severe mitral regurgitation to mild mitral stenosis)(318). Theoretically, this should translate into an increased risk of stroke, particularly in patients with AF. Our study, however, demonstrated no association of AF

with peri-procedural stroke (RR, 0.94; 95% 0.46-1.95) or 12-month stroke (HR, 1.01; 95% CI, 0.32-3.20). Although there was insufficient data to perform a meta-analysis it is conceivable that the lack of association of AF with stroke persists beyond 12 months. Velu and colleagues(313) reported a stroke incidence of only 2.1% in patients with AF after a median follow-up of 22 months (p=0.40). Kessler and colleagues(319) also showed a low stroke rate at three-year follow-up in patients with and without AF (6.4% vs 4.9%, p=0.72). These data may reflect the judicious and consistent use of anticoagulants in the AF group. Although not reported in all studies, Kessler and colleagues(319) showed a consistently high rate of anticoagulation use in patients with AF (72.6% at baseline and 72.4% at three years). There was a non-significant trend towards increased bleeding at three-years in the AF group (3.8% vs 0.8%, p=0.09). In our analysis of peri-procedural outcomes, AF did not increase the risk of major bleeding (RR, 0.91; 95% CI, 0.18-4.61).

Studies in the surgical literature addressing mid- and late-term outcomes have consistently demonstrated that AF increases mortality. Our study reaffirms these findings. A meta-analysis of 6 studies showed that AF increased 12-month mortality by 45% (HR, 1.45; 95% CI 1.27-1.66). Moreover, AF was associated with an increased rate of heart failure related re-hospitalization (HR, 1.18; 95% CI, 1.03-1.35). In addition to the possible embolic complications of AF, this may be driven by the selective impact of an elevated mitral valve pressure gradient (MVPG) after MitraClip implantation in patients with AF. Spieker and colleagues(320) evaluated outcomes of patients with and without AF, stratified by a MVPG > 4.0mmHg. The authors showed no correlation between MVPG and 12-month mortality in patients without AF. In contrast, the authors demonstrated a significantly reduced survival in AF patients with a post-procedural MVPG > 4.0mmHg.

The authors argued that pathophysiologically, the combination of elevated MVPG and AF created an unfavorable combination as AF leads to tachycardia, an irregular RR interval, and a lack of atrial contraction(320). In the setting of mitral stenosis (MS) where there is dysfunctional ventricular filling, adequate ventricular filling is more dependent on proper atrial contractions. In fact, up to 19% of cardiac output in patients with AF can be attributed to atrial contraction(321). This amount of filling is substantial and would be compromised by an elevated MVPG. Moreover, in patients with AF and MS, an increased heart rate impairs diastolic ventricular filling by decreasing diastolic filling time and by the common presence of ineffective ventricular contractions(322). As such, patients with AF and MS have a reduced cardiac output and higher left atrial and pulmonary pressures, compared to patients with MS who are in sinus rhythm(323). Thus, it is plausible that patients with AF and elevated MVPG may suffer from more advanced heart failure symptoms. Hence, measuring the MVPG during MitraClip implantation and not allowing it to increase above 4mmHg may facilitate clinical benefit in patients with AF. Regardless, further study is required to determine the mechanism by which AF confers a poorer prognosis after MitraClip, particularly given the lack of association identified with stroke.

8.5 LIMITATIONS

Our study has several limitations. First, the validity of our analysis depends on the quality of the included studies; all but one study were observational series derived from registries. As such they would be subject to residual confounding. Second, most studies could not differentiate outcomes based on the type of AF (permanent, persistent or paroxysmal) which precluded us from including it as a variable in our analysis. Third,

many studies lacked information on the use of anticoagulation, rate control medication and echocardiographic parameters (e.g. ejection fraction). Forth, mid- and long-term meta-analysis on several important variables could not be performed because of a paucity of data. Fifth, there is likely to be significant variation between centers regarding the management of AF and the indications for re-hospitalization. Sixth, our 12-month survival data was limited to an analysis of all-cause mortality rather than cardiovascular-specific mortality because insufficient data.

8.6 CONCLUSIONS

Our study demonstrates that AF is associated with an increased risk of peri-procedural and 12-month mortality and hospitalization for heart failure after MitraClip implantation. There was no association of AF with stroke. These data underscore the importance of aggressively managing AF and implementing strategies to reduce its deleterious impacts in the context of MitraClip intervention. Further studies are required to quantify the impact of AF on cost and resource utilization and the impact of strategies aimed at mitigating its impact.

SECTION IV

CAN TRAINEE SURGEONS SAFELY PERFORM CARDIAC SURGERY?

CHAPTER 9

EQUIVALENT OUTCOMES AFTER CORONARY ARTERY BYPASS GRAFT SURGERY PERFORMED BY CONSULTANT AND TRAINEE SURGEONS: A SYSTEMATIC REVIEW AND META-ANALYSIS

9.1 INTRODUCTION

Coronary artery bypass graft (CABG) surgery is the most common cardiac surgical procedure, with over half a million operations performed worldwide every year.(324) Despite an ageing population and increasing case complexity, the peri-operative mortality of CABG has remained relatively stable (<2%) in recent years.(325) This has been attributed to improved surgical and anesthetic techniques, as well as increased monitoring of outcomes through a greater emphasis on public reporting and registry participation.(324, 325)

However, there are concerns that the increased scrutiny of institutional and individual surgeon outcomes may be adversely impacting the quality of education provided to surgical trainees.(326) In the current climate, influenced by pay-for-performance and medico-legal issues, senior surgeons may be reluctant to facilitate trainee exposure and involvement(92). Moreover, in several countries, learning opportunities of surgical trainees have been further curtailed by the introduction of legislation capping trainee working hours.(327, 328)

Although patient outcomes must remain the primary focus of cardiac surgical units, the training needs of the next generation of operators must also be met. Hands-on experience in the operative setting is essential for trainees to develop both the technical skills and clinical judgment required to independently perform CABG. Given the perceived conflict between trainee education and patient safety, it is imperative that surgical training policies be guided by robust clinical data and high-level evidence. The present systematic review and meta-analysis was thus conducted to assess the impact of trainee operator status on the safety and efficacy of CABG.

The primary aim of the study was to evaluate the impact of training status (trainee vs consultant) on peri-operative and mid-term (> 12 months) mortality after CABG. The secondary aims were:

iv) Evaluate the impact of training status on peri-operative outcomes (stroke, myocardial infarction, acute renal failure, re-operation for bleeding, wound infection, length of hospital stay, and length of ICU stay)

v) Evaluate the impact of training status on technical outcomes (aortic cross-clamp time, cardiopulmonary bypass time)

i) Evaluate the impact of training status on peri-operative and mid-term outcomes after OPCAB

The hypothesis was that training status was not associated with an increased risk of early or mid-term mortality or poorer peri-operative outcomes. We also hypothesized that training status would be associated with longer operative times. To test this hypothesis, we performed a systematic review and meta-analysis of eligible studies which reported the clinical outcomes of patients undergoing CABG, stratified by training status.

9.2 METHODS

A summary of the methods used is provided in Section 5.2

9.2.1 Search Strategy and Study Selection

Electronic searches were performed using Ovid Medline, Embase and Cochrane Library from their dates of inception to March 2015. The search terms “coronary artery bypass” OR “CABG” were combined with “education, medical” OR “residency” OR “resident” OR

("clinical OR surge*" AND "trainee OR training") as either keywords or MeSH terms. This was supplemented by hand searching the reference lists of key reviews and all potentially relevant studies.

A summary of the search strategy is provided in Section 5.2.1.

9.2.2 Eligibility Criteria

Eligible studies were those reporting on clinical outcomes of CABG according to the training status of the primary operator (consultant or trainee). To be eligible for inclusion, studies were required to report on peri-operative (30-day) mortality. Non-comparative studies, and those that only compared outcomes between trainees themselves, were excluded. Studies presenting mixed data for different cardiac surgeries were only included if clinical outcomes for the CABG cohort were separately reported.

A description of the process by which studies were screened for eligibility is provided in Section 5.2.2.

9.2.3 Data Extraction

All data were independently extracted from text, tables and figures by two investigators (S.V. and S.R.). The final results were reviewed by the senior reviewers (A.S. and L.C.). For each study, the following information was extracted: study period, institution, study design, number of trainee and consultant cases, patient characteristics and risk factors, procedural details and clinical outcomes.

The pre-determined primary endpoint was peri-operative all-cause mortality and mid-term mortality (beyond 12 months). Secondary endpoints included peri-operative

stroke, myocardial infarction, re-operation for bleeding, acute renal failure, wound infection, length of hospital or intensive care unit (ICU) stay, and aortic cross-clamp and cardiopulmonary bypass (CPB) durations.

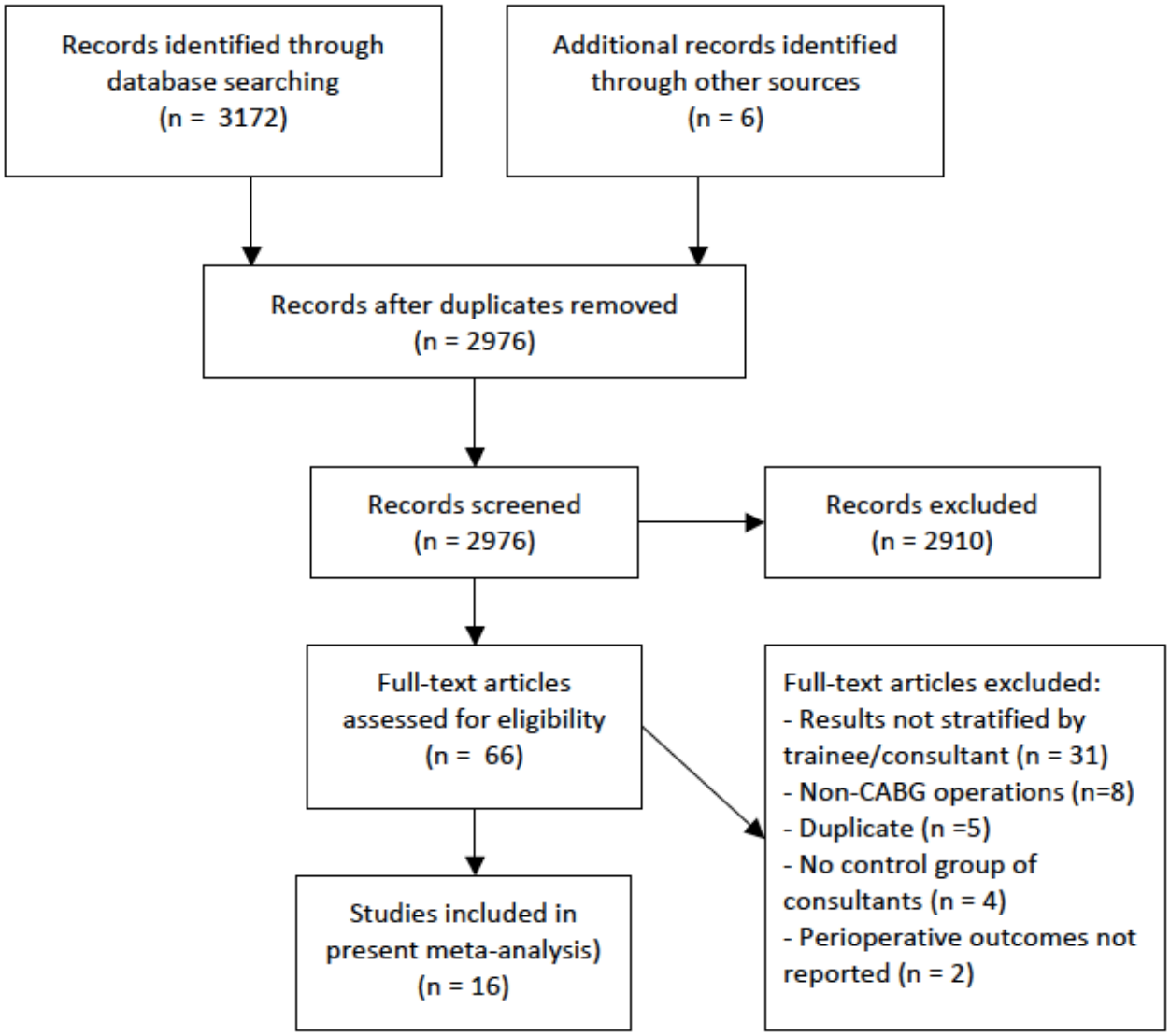
9.2.4 Statistical Analysis

A summary of the techniques used for statistical analysis is provided in Section 5.2.4.

9.3 RESULTS

A total of 2,976 unique records were identified through the database and bibliographic searches. Of these, 2,910 were excluded on the basis of title and abstract content. After screening the full text of the remaining 66 articles, 16 studies met the criteria for inclusion,(329-344) as summarized in Figure 9.1.

Figure 9.1. PRISMA flow chart for literature search and study selection



All included studies were retrospective observational reports (Table 9.1). These included data on 52,966 patients who underwent CABG, with the primary operator being a consultant in 40,746 cases and a trainee in 12,220 cases. The median study sample size was 2037 (range, 200 – 10,431). Five studies only reported on outcomes during the peri-operative period.(331, 332, 334, 335, 337) In the remaining studies, the mean or median follow-up ranged from 1.4 – 5.1 years. Baseline demographics characteristics and risk factor profiles of study participants are summarized in Table 9.2.

Table 9.1: Summary of studies examining trainee versus consultant outcomes of coronary artery bypass graft surgery

First Author (Year)	Study Period	Institution	Study Design	NOS	Follow-Up (Years)	Sample Size			OPCABG (%)	
						Trainee	Consultant	Total	Trainee	Consultant
Roberts 1999	1995-1998	UNC School of Medicine, Chapel Hill, USA	Retrospective OS	S4C1O2	NR	100	100	200	0	2
Caputo 2001	1997-2000	Bristol Heart Institute, Bristol, UK	Retrospective OS	S4C2O3	1.4 ± 0.9	124	429	553	100	100
Goodwin 2001	1996-1998	Papworth Hospital, Cambridge, UK	Retrospective OS	S3C0O2	Peri-operative	1216	1524	2740	NR	NR
Oo 2004	1997-2002	The Cardiothoracic Centre, Liverpool, UK	Retrospective OS	S4C2O3	2.9 ± 1.6	559	5119	5678	26	16
Karagounis 2006	2002-2004	St George's Hospital, London, UK	Retrospective OS	S4C2O2	Peri-operative	125	198	323	100	100
Gulbins 2007	1994-2006	Heart Institute, Lahr, Germany	Retrospective OS	S3C0O2	NR	1706	8725	10431	0	0
Guo 2008	1999-2006	London Health Sciences Center, London, Canada	Retrospective OS	S4C1O2	Peri-operative	743	2163	2906	0	0
Stoica 2008	1998-2005	Maritime Heart Center, Halifax, Canada	Retrospective OS	S4C2O3	2.7 [1-4.7]	835	5113	5948	10	5
Bakaeen 2009	1997-2007	Veteran Affairs Medical Center, Houston, USA	Retrospective OS	S4C2O3	4.1 ± 2.8	995	47	1042	NR	NR
Chen 2009	NR	Peking University People's Hospital, Beijing, China	Retrospective OS	S4C2O2	Peri-operative	200	50	250	100	100
Yap 2009	2001-2006	Hospitals in Melbourne, Australia	Retrospective OS	S4C2O3	3.5^{M}	983	6762	7745	NR	NR
Hosseini 2010	2006-2009	St George's Hospital, London, UK	Retrospective OS	S4C2O2	Peri-operative	142	349	491	9	30
Messina 2010	1998-2006	Poliambulanza Foundation Hospital, Brescia, Italy	Retrospective OS	S4C2O3	4 [3-4]	356	977	1333	100	100
Murzi 2012	1996-2009	Bristol Heart Institute, Bristol, UK	Retrospective OS	S4C2O3	5.1 ± 3.2	1589	3977	5566	100	100
Jones 2013	2003-2011	UK National Database	Retrospective OS	S4C2O3	4 [2.1-5.9]	1968	4722	6690	NR	NR
Peng 2014	2003-2010	Northern General Hospital, Sheffield, UK	Retrospective OS	S4C2O3	3.2^{M}	579	491	1070	NR	NR

Data presented as mean ± SD or median [interquartile range]. M, median; OS, observational study; NOS -Newcastle-Ottawa score; S – Selection component of Newcastle-Ottawa score; C – Comparability component of Newcastle-Ottawa Score; O – Outcome component of Newcastle-Ottawa Score

Table 9.2: Baseline patient characteristics in studies examining trainee versus consultant outcomes of coronary artery bypass graft surgery

Study	Age		Male		Diabetes		Previous MI		PVD		CVD		EuroSCORE		Left Main Disease		Triple Vessel Disease	
	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C
Roberts 1999	62 ± NR	61 ± NR	63	100	20*	17*	56	54	NR	NR	17	11	NR	NR	18	26	56	50
Caputo 2001	62.0 ± 8.5	62.8 ± 9.4	81	82	3*	7*	42	45	NR	NR	NR	NR	NR	NR	NR	NR	47	52
Goodwin 2001	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Oo 2004	63.5 [58.1-69.0]	64.3 [58.0-70.2]	84	80	15	17	46	51	11	13	6	8	2 [1-4]	3 [2-5]	17	19	69	83
Karagounis 2006	69 [61-74]	67 [57-74]	79	74	22	23	46	54	9	13	13	11	4 [2-4]	4 [2-6]	NR	NR	73	79
Gulbins 2007	65.5 ± 11.8	68.4 ± 11.8	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	4.1 ± 2.6	4.1 ± 2.7	NR	NR	NR	NR
Guo 2008	65.6 ± 9.3	64.4 ± 10.0	80	80	33	29	NR	NR	13	11	10	9	NR	NR	32	30	NR	NR
Stoica 2008#	65.2 ± 11.2	65.0 ± 10.8	72	74	36	35	53	54	18	17	14	15	NR	NR	NR	NR	NR	NR
Bakaeen 2009	61.9 ± 8.3	63.2 ± 8.4	99	100	41	36	66	47	33	15	22	23	NR	NR	36	45	72	75
Chen 2009	63.9 ± 6.9	65.2 ± 8.2	74	64	28	30	NR	NR	NR	NR	6	10	NR	NR	28	28	NR	NR
Yap 2009	65.7 ± 9.6	65.8 ± 10.4	77	76	30	33	NR	NR	13	14	10	12	NR	NR	25	23	67	75
Hosseini 2010[#]	67.4 ± 10.4	66.1 ± 13.6	73	68	25	20	41	29	7	5	8	8	NR	NR	NR	NR	NR	NR
Messina 2010	65.2 ± 15.3	65.3 ± 13.2	78	79	27	25	NR	NR	NR	NR	NR	NR	2 [1-2]	2 [1-3]	28	32	62	64
Murzi 2012	64.8 ± 9.0	65.4 ± 9.0	82	81	20	21	46	48	8	10	7	8	3.5 ± 2.0	3.9 ± 2.3	22	25	NR	NR
Jones 2013	66.7 ± 9.8	66.4 ± 10.3	81	81	34	33	42	50	10	13	3	4	3.7 [1.4-4.3]	5.4 [1.5-5.7]	27	29	NR	NR
Peng 2014	65.5 ± 10.0	66.5 ± 9.7	79	76	24	24	45	42	NR	NR	NR	NR	3.5 ± 2.7	4.1 ± 3.0	NR	NR	NR	NR

Data presented as mean ± SD, median [IQR] or % of patients. CVD, cerebrovascular disease; MI, myocardial infarction; PVD, peripheral vascular disease; *, insulin-dependent diabetes only; #, data includes patients undergoing other cardiac surgeries

9.3.1 Technical Outcomes

Seven studies involving 30,827 participants reported on aortic cross-clamp and CPB times.(329, 332, 334, 336, 341, 343) Surgeries performed by trainees had significantly longer pooled aortic-cross clamp duration (WMD 4.80; 95% CI, 0.76 - 8.83; p = 0.02; I^2 = 98%; Figure 9.2), and there was a trend towards increased CPB duration (WMD 4.24; 95% CI, 0.00 – 8.47; p = 0.05; I^2 = 95%; Figure 9.3).

Figure 9.2. Forest plot displaying the weighted mean difference (WMD) in aortic cross-clamp duration between trainee and consultant coronary artery bypass graft (CABG) cases.

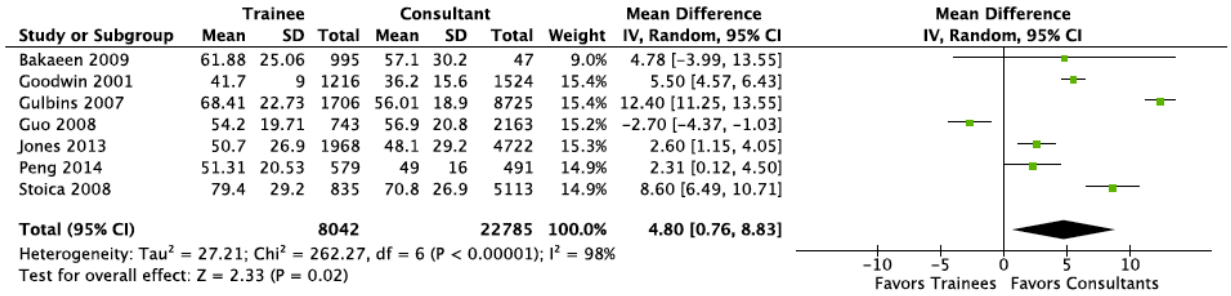
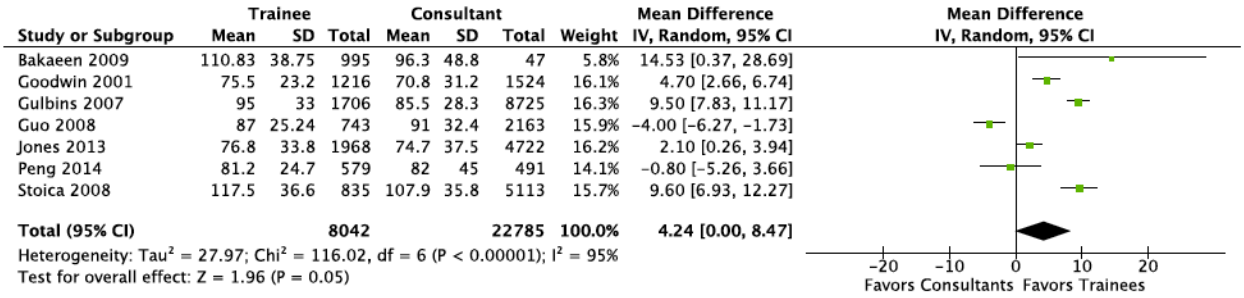


Figure 9.3. Forest plot displaying the weighted mean difference (WMD) in cardiopulmonary bypass (CPB) duration between trainee and consultant coronary artery bypass graft (CABG) cases



9.3.2 **Peri-operative Outcomes**

Overall, peri-operative mortality was similar between trainee and consultant cases (OR 0.98; 95% CI, 0.81 – 1.18; p = 0.79; I^2 = 21%; Figure 9.4). There was no statistically significant difference between trainee and consultant cases with regards to the incidence of peri-operative stroke, myocardial infarction, acute renal failure, re-operation for bleeding or wound infection (Table 9.3). The pooled length of hospital (WMD -0.12; 95% CI, -0.41 – 0.18; p = 0.43; I^2 = 54%) and ICU stay (WMD -0.09; 95% CI, -0.26 – 0.08; p = 0.28; I^2 = 72%) was also similar between the two groups.

Figure 9.4. Forest plot displaying odds ratio (OR) of peri-operative all-cause mortality for trainee versus consultant coronary artery bypass graft (CABG) cases.

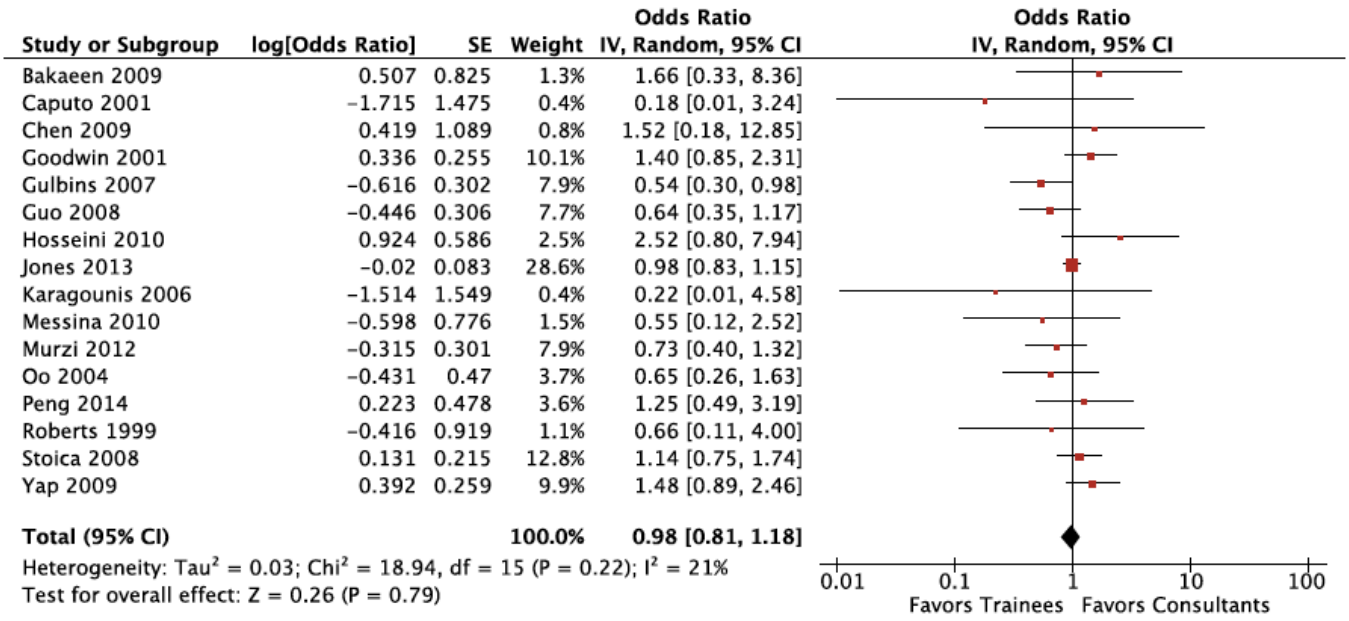


Table 9.3: Meta-analysis on the impact of trainee status on mortality and morbidity after coronary artery bypass surgery

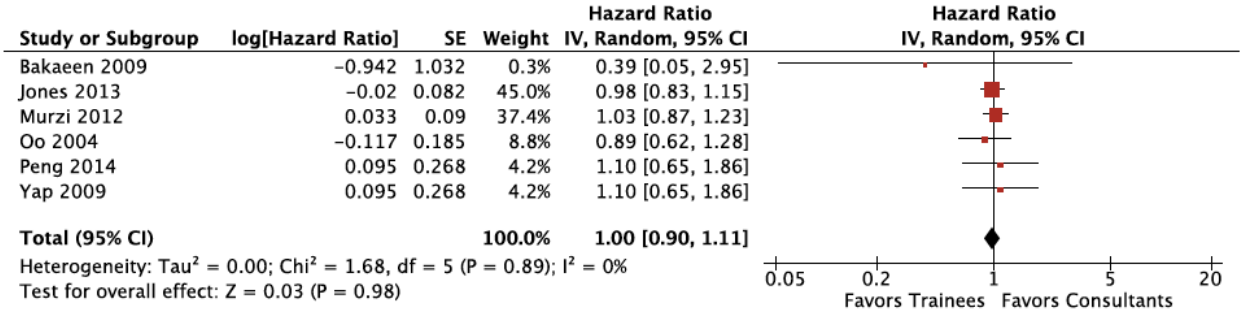
Outcome	No. of Studies	No. of Patients	OR/WMD	95% CI	P-value	I^2 (%)
Mortality	16	52 966	0.98	0.81 – 1.18	0.79	21
Stroke	12	42 537	0.98	0.77 – 1.25	0.87	0
Acute Renal Failure	10	26 340	0.96	0.74 – 1.26	0.78	0
Myocardial Infarction	9	35 324	0.96	0.68 – 1.36	0.82	54
Re-operation for Bleeding	12	34 806	0.93	0.77 – 1.11	0.43	73
Wound Infection	6	17 537	1.23	0.50 – 3.01	0.66	73
Length of Hospital Stay	4	10 192	-0.12	-0.41 – 0.18	0.43	54
Length of ICU Stay	5	10 442	-0.09	-0.26 – 0.08	0.28	72

OR, odds ratio; WMD, weighted mean difference; I^2 statistic is measure of variation across studies due to heterogeneity

9.3.3 Mid-term Survival Outcomes

Although eight studies reported mortality data beyond the peri-operative period, only six reported sufficient data for quantitative synthesis.(329, 336, 339-341, 344) Pooling survival data from these six studies, trainee operator status was not associated with increased mid-term mortality (HR 1.00; 95% CI, 0.90 – 1.11; p = 0.99; I^2 = 0%; Figure 9.5).

Figure 9.5. Forest plot displaying hazards ratio (HR) of mid-term mortality for trainee versus consultant coronary artery bypass graft (CABG) cases.



9.3.4 Subgroup Analysis

Five studies involving a total of 10,212 patients presented specific data on off-pump CABG operations performed by consultants (n = 7,818) and trainees (n = 2,394).(330, 331, 337-339) Overall, in 1.2% of both trainee and consultant cases, conversion to conventional CABG was necessary (OR 0.95; 95% CI, 0.47 – 1.95; p = 0.90; I^2 = 32%). In subgroup analysis of off-pump CABG cases, no significant difference in peri-operative mortality was detected between patients primarily operated on by trainees or consultants (OR 0.68; 95% CI, 0.41 – 1.14; p = 0.14; I^2 = 0%). Likewise, subgroup analyses of morbidity outcomes did not elicit any significant impact of trainee operator status. It was not possible to perform a meta-analysis evaluating changes in trainee outcome over time because only one study stratified outcomes according to time period(339). Moreover, more recent studies tended to have longer follow-up periods with some reporting outcomes of patients operated > 12 year before (Table 9.1). A review of the publication date of studies and the trainee outcomes reported in them, however, showed no evidence of a trends towards more adverse trainee outcomes in recent series.

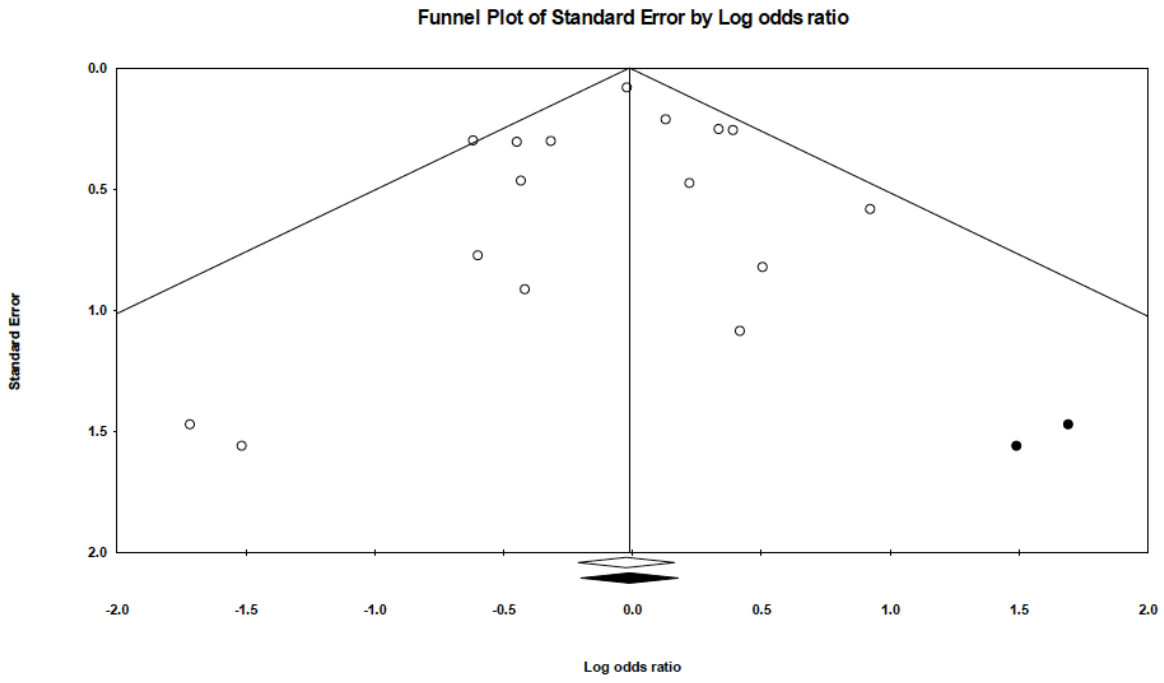
9.3.5 Sensitivity Analysis

Eight studies involving 36,479 patients reported propensity-adjusted ratios for the primary endpoint of peri-operative mortality.(329, 332, 336, 339-341, 343, 344) Sensitivity analysis only including these studies did not significantly impact upon the main result (OR 1.03; 95% CI, 0.91 – 1.18; p = 0.62; I^2 = 0%). Sensitivity analyses by study quality could not be performed for other endpoints due to insufficient number of studies reporting propensity-adjusted ratios.(340, 344)

9.3.6 Publication Bias

Both Egger's linear regression method (p = 0.57) and Begg's rank correlation test (p = 0.56) suggested publication bias was not an influencing factor when peri-operative mortality was selected as an endpoint. Accounting for potentially missing studies using the imputed Trim-and-Fill method yielded no significant difference in peri-operative mortality between trainee and consultant cases (OR 0.99; 95% CI, 0.82 – 1.19; Figure 9.6).

Figure 9.6. Funnel plot for assessment of publication bias. Open circles represent studies included in the present meta-analysis while black-filled circles represent potential missing studies. The white diamond represents the pooled logit odds ratio for peri-operative mortality in included studies while the black diamond represents the adjusted ratio after accounting for potential missing studies.



9.4 DISCUSSION

The present meta-analysis, reporting on data from 16 studies and 52 966 patients, analyzed the relationship between primary operator status (consultant or trainee) and clinical outcomes following CABG. Trainee as primary operator was not significantly associated with increased peri-operative mortality, morbidity or poorer mid-term survival.

Furthermore, subgroup analysis also demonstrated there was no significant difference between trainee and consultant outcomes in patient undergoing off-pump CABG.

There are several possible explanations for these findings. In many institutions, trainees are preferentially allocated lower-risk and non-urgent CABG cases so as not to compromise patient safety.(336, 340) However, in the present meta-analysis, sensitivity analyses including only studies reporting propensity-adjusted risk estimates did not reveal any significant difference in peri-operative or mid-term mortality. This suggests other factors may also contribute to the safety and efficacy demonstrated by trainees, such as pre-operative planning and discussion, quality of consultant supervision and the performance of other theatre staff.(345) Indeed, in their analysis of over 4 000 CABG procedures, Elbardissi and colleagues found that the cumulative experience of a consultant-trainee pairing and their familiarity with one another were more significant predictors of outcomes than individual surgeon experience(346). As such, the results of this meta-analysis should not be interpreted as suggesting operator status is irrelevant to patient outcomes; rather, they demonstrate that trainees can safely perform CABG as primary operator in the context of a well-structured training program and appropriate supervision.

With regard to technical outcomes, aortic cross-clamp and CPB durations were found to be higher in cases primarily performed by trainees (Figure 1). This is an intuitive finding as operative and perfusion times have been shown to be inversely proportional to the level of surgical experience.(329) Aortic cross-clamping and CPB have been linked with a number of complications, including microemboli, increased transfusion requirements, coagulation defects and immunosuppression.(91, 347, 348) However, in

the present meta-analysis, the increased cross-clamp and CPB durations did not translate to an increased incidence of stroke, myocardial infarction, re-operation for bleeding or wound infection (Table 3). Importantly, from a cost-effectiveness and resource utilization standpoint, trainee cases were not associated with an increased length of hospital or ICU stay. Thus, despite being statistically significant, the difference in trainee and consultant operative times is unlikely to be of sufficient magnitude to pose clinical significance.

Although conventional CABG using CPB and cardioplegic arrest is a staple component of most training programs, the teaching of off-pump CABG is far more sporadic. Off-pump CABG has been associated with reduced long-term graft patency, and less than a quarter of all CABG operations are performed using this technique.(349) Given the technical difficulties associated with operating on a beating heart, concerns have also been raised about the extent to which off-pump CABG should be incorporated in the trainee curriculum.(350) In our subgroup analysis of off-pump CABG procedures, we found no significant difference between trainee and consultant outcomes, suggesting the procedure can be safely taught to trainees. However, it must be emphasized that the included studies assessing off-pump CABG training were largely from institutions with high case volumes and senior surgeons proficient in the use of this technique. Hence, these results may have limited generalizability and should be judiciously extrapolated to individual training programs.

9.5 LIMITATIONS

The present meta-analysis has several limitations. Firstly, all included studies were retrospective observational reports, and none specifically employed an intention-to-treat analysis. This means cases that were initially assigned to trainees may have been classified as consultant surgeries if intra-operative complications or difficulties required the supervising consultant to assume the role of primary operator. Although this confounding could theoretically have biased our analysis towards a null value, it also provides a more real-world clinical assessment of surgical training programs. Secondly, considerable heterogeneity was detected in the analysis of several peri-procedural complications, including wound infection, re-operation for bleeding and length of hospital or ICU stay (Table 3). This may reflect differences in endpoint definitions, reporting standards and post-operative policies between different institutions. Other potential sources of heterogeneity include differences in training program structure, quality and experience of trainees, and degree of consultant supervision. Lastly, analysis of mid-term outcomes was limited to an assessment of mortality. Further studies with long-term follow-up are required to investigate impact of trainee status on other endpoints, such as freedom from revascularization, recurrence of angina and angiographic outcomes.

9.6 CONCLUSIONS

In conclusion, the present meta-analysis demonstrated CABG cases primarily performed by trainees were not associated with adverse peri-operative outcomes or poorer mid-term

survival. These findings suggest that the process of training can be conducted safely by a careful selection process which is appropriate to the experience and technical capability of the trainee. These data are encouraging, particularly given the concerns that training may compromise outcomes in a high-risk patient population.

SECTION IV

CAN TRAINEE SURGEONS SAFELY PERFORM CARDIAC SURGERY?

CHAPTER 10

HEART VALVE SURGERY PERFORMED BY TRAINEE SURGEONS: META-ANALYSIS OF CLINICAL OUTCOMES

10.1 INTRODUCTION

Surgical units are increasingly facing the challenge of balancing the need to train junior staff with the duty to provide the highest standard of patient care. In recent years, the level of exposure and quality of education provided to cardiac surgical trainees in particular has come under considerable scrutiny. In the context of increasingly complex patients, restrictions on trainee working hours and greater public reporting of outcomes, concerns have been raised about learning opportunities for trainees being potentially compromised(94, 136, 351).

In most cardiac surgical training programs, coronary artery bypass graft (CABG) surgery comprises the majority of operations. A number of large studies have demonstrated equivalent outcomes following CABG performed by consultants and supervised trainees(352-358). However, the impact of trainee operator status on outcomes following valvular surgery is less clear given the lower volume and increased complexity of these procedures. Given the perceived conflict between trainee education and patient safety, it is imperative that surgical training policies be guided by robust clinical data and high-level evidence. The present systematic review and meta-analysis was thus conducted to assess the impact of trainee operator status on mortality and morbidity following valvular surgery.

The primary aim of the study was to evaluate the impact of training status on peri-operative and mid-term (> 12 months) mortality after aortic and mitral valve surgery. The secondary aims were:

iii) Evaluate the impact of training status on peri-operative outcomes (stroke, myocardial infarction, acute renal failure, re-operation, re-

operation for bleeding, wound infection, permanent pacemaker implantation) after aortic and mitral valve surgery

iv) Evaluate the impact of training status on technical outcomes (aortic cross-clamp time, cardiopulmonary bypass time) after aortic and mitral valve surgery

The hypothesis was that training status was not associated with an increased risk of early or mid-term mortality or poorer peri-operative outcomes. We also hypothesized that training status would be associated with longer operative times. To test this hypothesis, we performed a systematic review and meta-analysis of eligible studies which reported the clinical outcomes of patients undergoing valvular heart surgery, stratified by training status.

10.2 METHODS

A description of the Methods used is provided in Section 5.2.

10.2.1 Search Strategy and Study Selection

Electronic searches were performed using Ovid Medline, Embase and Cochrane Central Register of Controlled Trials from their dates of inception to September 2015. The search terms (“mitral” OR “aortic” OR “pulmonary” OR “tricuspid”) AND “valve” were combined with “education, medical” OR “residency” OR “resident” OR (“clinical OR surg*” AND “trainee OR training”) as keywords and MeSH terms. This was supplemented by hand searching the reference lists of key reviews and all potentially relevant studies.

A summary of the search strategy is provided in Section 5.2.1.

10.2.2 Eligibility Criteria

Eligible studies were those reporting on clinical outcomes of valvular surgery according to the training status of the primary operator (consultant or trainee). To be eligible for inclusion, studies were required to report on the primary endpoint of peri-operative (30-day) mortality. Non-comparative studies, and those that only compared outcomes between trainees themselves, were excluded. Studies presenting mixed data for different cardiac surgeries were only included if clinical outcomes for specific cohorts were separately reported.

A description of the process by which studies were screened for eligibility is provided in Section 5.2.2.

10.2.3 Data Extraction

A description of the process by which data was extracted is provided in Section 9.2.3.

10.2.4 Statistical Analysis

A summary of the techniques used for statistical analysis is provided in Section 5.2.4.

We previously published a series which used the ANZSCTS registry to evaluate the impact of training status on early and mid-term outcomes after isolated AVR (Appendix L) and AVR-CABG (Appendix M).

10.3 RESULTS

10.3.1 Study characteristics

A total of 466 unique records were identified through the database and bibliographic searches. Of these, 431 were excluded on the basis of title and abstract content. After screening the full text of the remaining 35 articles, 11 studies met the criteria for inclusion. The study selection process is summarized in Figure 10.1. A summary of study characteristics is displayed in Table 10.1. Baseline patient characteristics and risk factor profiles are summarized in Table 10.2.

Figure 10.1 PRISMA flow chart for literature search and study selection

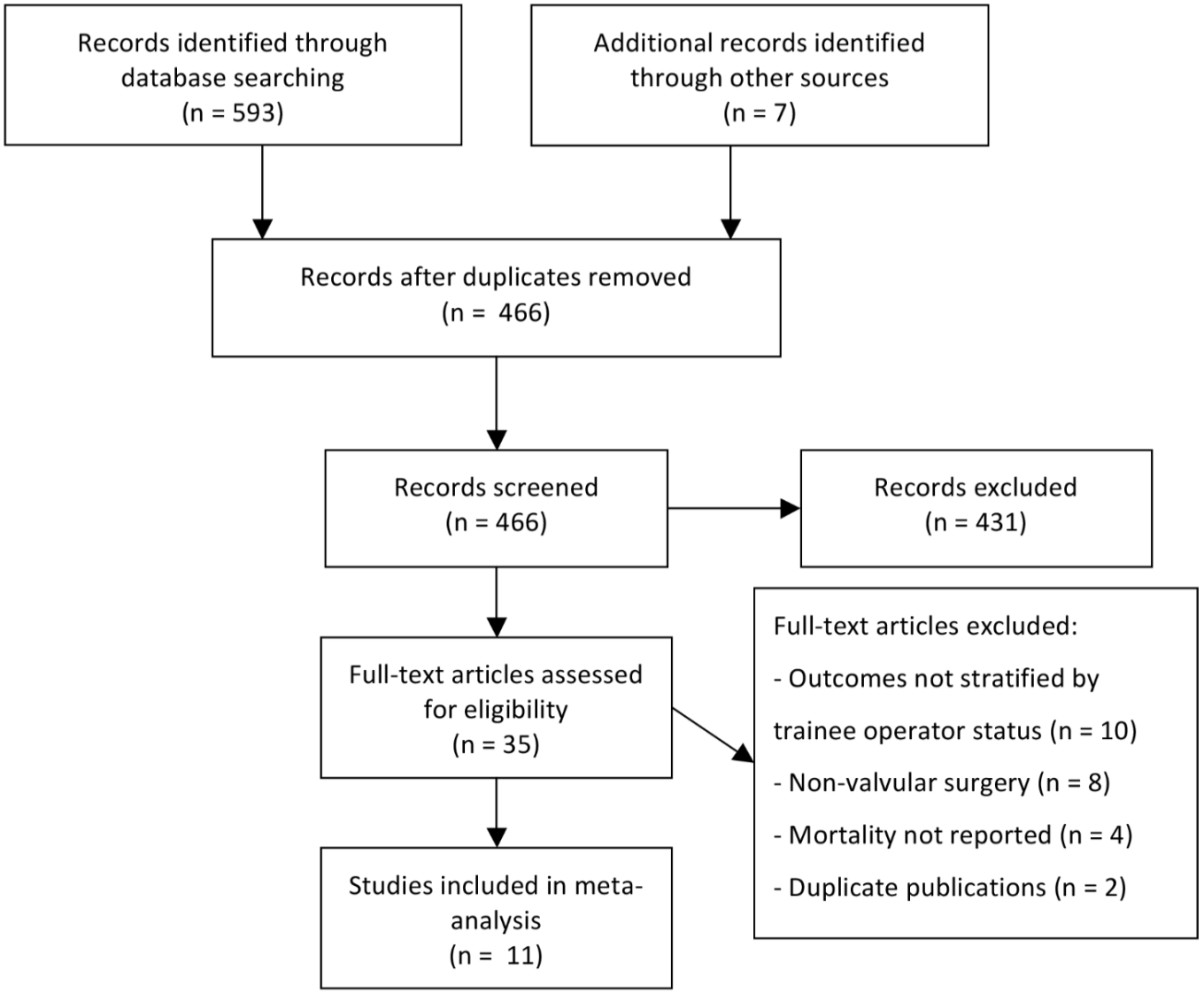


Table 10.1: Summary of studies comparing trainee versus consultant outcomes following valvular surgery								
Study	**Surgery**	**Study Period**	**NOS**	**Country**	**Number of Cases**			**Definition of "Trainee Case"**
					Trainee	Consultant	Total	
Soppa 2015	AVR	2005–2012		UK	74	131	205	Performed by trainee under direct consultant supervision
Saxena 2014	AVR	2001–2009	S4C2O3	Australia	369	2378	2747	Entire operation (or majority of the critical parts) performed by trainee with variable consultant supervision, ranging from assistance throughout to consultant being absent but available if required
Murzi 2014	MVr	2007–2013	S4C2O3	Italy	240	355	595	Performed by trainee with consultant either scrubbed in as first assistant or available for assistance if required
Chen 2013	AVR	1999–2010	S4C2O2	Canada	123	501	624	Performed by trainee under direct consultant supervision
	AVR+CABG				84	394	478	
Saxena 2013	AVR+CABG	2001–2009	S4C2O3	Australia	290	2250	2540	Entire operation (or majority of the critical parts) performed by trainee with variable consultant supervision, ranging from assistance throughout to consultant being absent but available if required
Shi 2011	MVr/MVR	2001–2008	S4C2O3	Australia	168	2048	2216	Performed by trainee under variable consultant supervision, ranging from assistance throughout to consultant being absent but available if required
Stoica 2008	AVR	1998–2005	S4C2O3	Canada	118	388	506	Performed "skin to skin" by trainee with consultant acting as first assistant or directly supervising
	AVR+CABG				101	376	477	
Gulbins 2007	AVR	1994–2006	S4C2O3	Germany	191	1273	1464	"Carried out" by trainee

Alexiou 2005	MVr	1997–2004	S4C2O3	UK	171	300	471	Performed by trainee under direct consultant supervision
Baskett 2004	MVr/MVR	1998–2003	S4C2O2	Canada	165	261	426	Performed entirely by trainee with consultant assisting or directly supervising
Sethi 1988	MVR	1977–1982	S4C2O2	USA	125	142	267	Performed by trainee under direct consultant supervision
	AVR, aortic valve replacement; CABG, coronary artery bypass graft; MVr, mitral valve repair; MVR, mitral valve replacement; OS, observational study							

Table 10.2. Summary of baseline patient characteristics in studies comparing trainee versus consultant outcomes following valvular surgery

Study	**Age**		**Male**		**DM**		**HTN**		**PVD**		**CVD**		**Renal Failure**	
(Surgery)	*T*	*C*	*T*	*C*	*T*	*C*	*T*	*C*	*T*	*C*	*T*	*C*	*T*	*C*
Soppa 2015 (AVR)	68 (32-85)	67 (29-86)	60	58	28	25	NR	NR	11	10	NR	NR	NR	NR
Saxena 2014 (AVR)	68.5 ± 13.3	68.2 ± 11.4	58	58	20	22	68	66	5	7	10	10	1	4
Murzi 2014 (MVr)	64.3 ± 12*	58.4 ± 14*	50*	59*	7	7	57*	48*	5	4	5	3	3	2
Chen 2013 (AVR)	68.7 ± 11.3	66.4 ± 13.4	63	63	20	20	NR	NR	6	6	20	12	13	13
Chen 2013 (AVR+CABG)	73.0 ± 7.3	72.9 ± 8.4	68	76	37	29	NR	NR	11	15	12	14	19	21
Saxena 2013 (AVR+CABG)	73.0 ± 7.8	74.2 ± 8.3	68	68	36	31	81	80	14	16	16	18	3	4
Shi 2011 (MVr/MVR)	NR	NR	59	53	15	16	53	49	6	8	9	8	NR	NR
Stoica 2008 (AVR)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Stoica 2008 (AVR+CABG)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Gulbins 2007 (AVR)	65.5 ± 11.8	68.4 ± 11.8	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Alexiou 2005 (MVr) 9	66 ± 7	65 ± 8	61	68	14	16	39	35	NR	NR	8	6	5	7
Baskett 2004 (MVr/MVR)	NR	NR	45	49	16	15	41	41	12	11	17	18	9	13
Sethi 1988 (AVR)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sethi 1988 (MVR)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

***p < 0.05 for comparison of trainee and consultant cases; AVR, aortic valve replacement; C, consultant; CABG, coronary artery bypass graft; CVD, cerebrovascular disease; DM, diabetes mellitus; HTN, hypertension; MVr, mitral valve repair; MVR, mitral valve replacement; NR, not reported; PVD, peripheral vascular disease; T, trainee**

10.3.2 Mitral Valve Surgery

Five studies involving a total of 3975 patients reported outcomes following mitral valve (MV) repair or replacement. In two studies, endpoint reporting was confined to the peri-operative period(359, 360). In the remaining three studies, the duration of follow-up ranged from five to six years(120, 361, 362). Degenerative mitral valve disease was the most common indication for MV surgery (59.0 - 87.6%), followed by ischemic (7.6 - 29.0%) and rheumatic (1.4 - 8.0%) mitral valve disease (Table 10.3). In one study, all patients underwent minimally invasive mitral valve repair(339).

Table 10.3. Etiology of mitral valve disease in studies comparing trainee versus consultant outcomes for valvular surgery

Study	Etiology of Mitral Valve Disease							
	Degenerative		Ischemic		Rheumatic		Infective	
	Trainee	Consultant	Trainee	Consultant	Trainee	Consultant	Trainee	Consultant
Murzi 2014	84.6%	87.6%	11.7%	7.6%	0.8%	1.4%	3.0%	3.4%
Shi 2011	28%	20%	10%	11%	28%	20%	4%	6%
Alexiou 2005	59%	60%	29%	28%	8%	8%	3%	3%
Baskett 2004	41.8%	38.3%	14.6%	16.9%	30.3%	31.0%	6.7%	6.9%
Sethi 1991	NR	NR	NR	NR	NR	NR	NR	NR

NR, not reported

10.3.3 Aortic Valve Surgery

Six studies involving a total of 6236 patients reported outcomes following aortic valve replacement (AVR)(117, 360, 363-366). In four studies, follow-up was limited to the peri-operative period(360, 363-365). In the remaining two studies, follow-up duration ranged

from 5 to 7 years(117, 343). In one study, all patients underwent minimally invasive AVR(365). Three studies presented specific outcome data for patients undergoing concomitant CABG and AVR (n = 3495)(118, 343, 363).

10.3.4 Technical Outcomes

MV repair/replacement performed by trainees had significantly longer pooled CPB (MD 9.37; 95% CI, 5.54 – 13.21; I^2 = 0%; p < 0.001) and aortic cross-clamp (MD 10.59; 95% CI, 3.74 – 17.45; I^2 = 69%; p = 0.002) durations. For AVR, trainees and consultants had similar CPB (MD 4.70; 95% CI, -5.73 – 15.13; I^2 = 95%; p = 0.38) and aortic cross-clamp times (MD 3.17; 95% CI, -5.91 – 12.25; I^2 = 97%; p = 0.49). Aortic cross-clamp (MD 6.25; 95% CI, 0.44 – 12.06; I^2 = 59%; p = 0.04) duration was significantly higher when trainees performed concomitant AVR and CABG, but the difference in CPB duration was not statistically significant (MD 4.96; 95% CI, -7.98 – 17.89; I^2 = 83%; p = 0.45).

10.3.5 Peri-Operative Mortality

Peri-operative mortality was not significantly different between trainee and consultant cases for MV surgery (OR 0.92; 95% CI, 0.62 – 1.37; I^2 = 18%; p = 0.67; Figure 10.2), AVR (OR 0.67; 95% CI, 0.37 – 1.24; I^2 = 44%; p = 0.20; Figure 10.3) or combined AVR and CABG (OR 1.07; 95% CI, 0.40 – 2.85; I^2 = 68%; p = 0.90).

Figure 10.2. Forest plot displaying odds ratio (OR) of peri-operative all-cause mortality for mitral valve (MV) surgery cases completed by trainees or consultants.

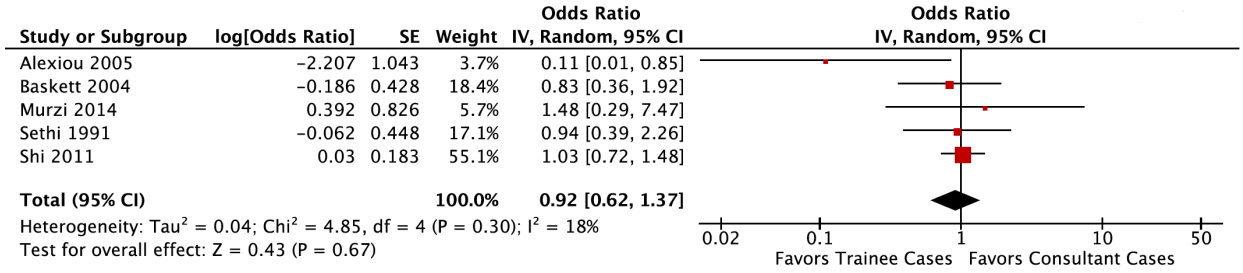
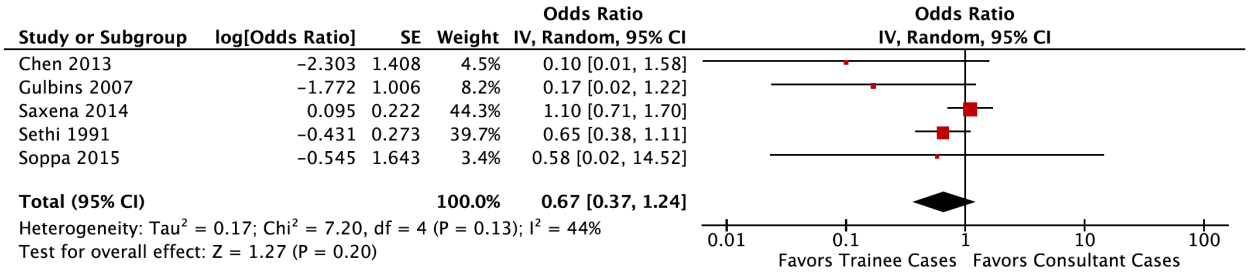


Figure 10.3. Forest plot displaying odds ratio (OR) of peri-operative all-cause mortality for aortic valve replacement (AVR) completed by trainees or consultants.



10.3.6 Peri-Operative Morbidity

For both MV surgery and AVR, there was no statistically significant difference between trainee and consultant cases with regards to the incidence of peri-operative stroke, myocardial infarction, acute renal failure, re-operation, re-operation for bleeding, wound infection or arrhythmias requiring permanent pacemaker implantation. These results are presented in Table 10.3 and Table 10.4. There were insufficient studies to perform meta-analyses for morbidity outcomes following combined AVR and CABG.

Table 10.4: Meta-analyses of peri-operative morbidity outcomes following mitral valve surgery performed by trainee and consultant surgeons

Peri-Operative Outcome	No. of Studies	No. of Patients	OR	95% CI	P-value	I^2
Stroke	5	3975	0.77	0.41 – 1.47	0.43	0%
Acute Renal Failure	3	3282	1.32	0.63 – 2.74	0.47	5%
Myocardial Infarction	3	1288	0.64	0.21 – 1.96	0.44	0%
Wound Infection	4	1320	0.84	0.32 – 2.19	0.73	0%
Re-Operation	2	551	0.89	0.52 – 1.52	0.67	0%
Re-Operation for Bleeding	4	1759	0.70	0.43 – 1.14	0.15	0%
Permanent Pacemaker Implantation	2	738	0.77	0.32 – 1.84	0.55	26%

CI, confidence intervals; I^2, measure of variation across studies due to heterogeneity rather than chance; OR, odds ratio

Table 10.5: Meta-analyses of peri-operative morbidity outcomes following aortic valve replacement performed by trainee and consultant surgeons

Peri-Operative Outcome	No. of Studies	No. of Patients	OR	95% CI	P-value	I^2
Stroke	4	4899	0.69	0.28 – 1.67	0.41	0%
Acute Renal Failure	2	3437	0.60	0.35 – 1.03	0.06	0%
Myocardial Infarction	2	3437	1.69	0.13 – 22.20	0.69	89%
Wound Infection	3	3642	0.74	0.30 – 1.84	0.51	0%
Re-Operation	3	4901	0.93	0.59 – 1.45	0.73	35%
Re-Operation for Bleeding	3	3642	1.36	0.92 – 2.01	0.12	0%
Permanent Pacemaker Implantation	2	895	1.32	0.61 – 2.83	0.48	0%

CI, confidence intervals; I^2, measure of variation across studies due to heterogeneity rather than chance; OR, odds ratio

10.3.7 Mid-term Outcomes

Mid-term survival was reported in three studies examining MV surgery(120, 361, 362). Two studies reported 5-year survival ranging from 88-90.2% for trainee cohorts and 88-92% for consultant cohorts(361, 362).Five-year freedom from reoperation ranged from 91.8-95.7% and 95-95.6% for the trainee and consultant groups, respectively. An additional study reported equivalent six-year survival following MV repair (78% vs. 79%; p = 0.73), with no association between trainee operator status and mid-term mortality in multivariable analysis (HR 0.88; 95% CI, 0.57 – 1.37; p = 0.58)(120).

Mid-term survival following isolated AVR was only reported in one study(117). Although trainee cases displayed higher 5- and 7-year survival (89.9% vs. 84.8% and 83.0% vs. 76.9%, respectively; p = 0.028), there was no significant difference between the two groups in multivariable analysis (HR 0.82; 95% CI, 0.57 – 1.17; p = 0.27). For combined AVR and CABG, pooled mid-term mortality from two studies demonstrated no significant impact of trainee operator status (HR 1.07; 95% CI, 0.97 – 1.19; I^2 = 0%; p = 0.20)(118, 343).

10.3.8 Publication Bias

Using Egger's linear regression method, publication bias was not detected for the primary endpoint of peri-operative mortality following MV surgery (p = 0.33), AVR (p = 0.13) or combined AVR and CABG (p = 0.92). Likewise, publication bias was not detected using Begg's rank correlation test for either MVR (p = 0.33), AVR (p = 0.62), or combined AVR and CABG (p = 0.60).

10.4 DISCUSSION

The present meta-analysis analyzed the relationship between primary operator status (consultant or trainee) and clinical outcomes following valvular surgery. MV repair/replacement and AVR cases primarily performed by trainees were not associated with increased peri-operative mortality or morbidity. Furthermore, trainee operator status was not associated with increased peri-operative or mid-term mortality for combined AVR and CABG. Our results are congruent with a previous meta-analysis reporting equivalent outcomes following isolated CABG performed by trainee and consultant surgeons(367). The present study extends these earlier findings by demonstrating similar trainee outcomes can be achieved for MV surgery and AVR, despite the increased complexity and lower volume of these procedures. However, it should be noted that favorable mid-term survival outcomes have been extensively reported for trainee CABG cases(367). Although several studies included in the present meta-analysis reported encouraging mid-term survival(71, 343, 361, 362), further data is required before concluding long-term safety for valvular surgery performed by trainees.

In the present meta-analysis, aortic cross-clamp and CPB durations were not significantly longer in trainee AVR cases. Furthermore, although the difference in procedural times reached statistical significance for MV surgery, the absolute differences were small. This was an unexpected finding as operative times for complex procedures tend to be inversely related to the level of surgical experience(368). The absence of a larger difference in procedural times may reflect careful allocation of trainee cases, biased selection of high-level trainees and/or mid-procedure crossovers resulting in consultants completing more difficult and complex “trainee cases.” Aortic cross-clamp and CPB

durations have been linked to complications such as microemboli, increased transfusion requirements, coagulation defects and immunosuppression(90, 347, 369). As such, it remains unclear whether equivalent peri-operative mortality and morbidity would be achieved in the absence of potential confounders suppressing differences in consultant and trainee procedural times.

In recent years, minimally invasive approaches to mitral and aortic valve surgery have been increasingly adopted(370). Compared to conventional sternotomy, minimally invasive techniques have been associated with reduced bleeding and transfusion requirements, shorter hospital and intensive care unit stay, faster functional recovery and better cosmesis(371, 372). However, these potential benefits may come at the expense of increased technical demands that could predispose to higher risk of complications and a steeper learning curve. In the present meta-analysis, only two studies specifically examined minimally invasive aortic and mitral valve surgery, reporting favorable trainee outcomes(362, 365). These results may reflect the steep learning curve of minimally invasive surgery being at least partially offset by the improved supervision and teaching opportunities provided by superior thoracoscopic valve visualization(363). However, given the paucity of current data, this remains conjecture and further studies are required to better delineate the learning curve for minimally invasive approaches, and their impact on patient outcomes.

10.5 LIMITATIONS

The findings of the present meta-analysis must be interpreted within the context of several key limitations. Firstly, in most institutions, high-risk and emergent cases tend to be

allocated to consultant surgeons, hence biasing results in favor of trainees. We attempted to account for this by preferentially extracting propensity-adjusted ratios, but these are not a substitute for randomization and potential confounders were likely omitted. This is demonstrated by the extremely high ratio of consultant to trainee cases in several included studies, which is indicative of a profound selection bias in favor of trainees(117, 120, 365). Although statistical tests conducted to assess publication bias were negative, these do not account for the indication bias that likely influenced allocation of trainee cases. Secondly, none of the studies included in the present meta-analysis employed an intention-to-treat analysis. Hence, cases that were initially assigned to trainees were likely classified as consultant cases if intra-operative complications or technical difficulties required the supervising consultant to take over. However, although such classification may have biased outcomes in favor of trainees, it also provides a more real-world assessment of surgical training programs. Thirdly, due to the paucity of reporting in individual studies, the present meta-analysis was not able to assess follow-up echocardiographic findings of valvular surgery cases performed by trainees. This remains a key area for future research, particularly in the case of MV surgery given the adverse impact of residual mitral regurgitation on mortality and risk of heart failure(373). Similarly, the present meta-analysis was not able to quantitatively assess measures of cost-effectiveness or resource utilization, such as length of hospital or intensive unit care stay, despite these being increasingly key considerations in clinical practice. Lastly, due to the limited number of studies and lack of raw data available, it was not possible to perform sensitivity analyses or meta-regression to quantitatively explore potential sources of

heterogeneity, such as differences in trainee seniority, degree of consultant supervision or study time period.

10.6 CONCLUSIONS

In conclusion, aortic and mitral valve surgery performed by trainees was not associated with adverse peri-operative outcomes. Despite the observational nature of the data, these findings suggest cardiac surgical training programs are rigorously designed so as to sufficiently mitigate trainee deficiencies. With careful case allocation, appropriate trainee assessment and adequate supervision, valvular surgery can be safely performed by trainee surgeons.

SECTION V

GENERAL CONCLUSIONS

This dissertation evaluated cardiac surgery outcomes in the context of an increasingly high-risk patient population. Section I – Chapter I (literature review) provided a background on the history of cardiac surgery and highlighted the changing nature of the specialty. It highlighted the deficiencies in understanding within the contemporary cardiac surgery literature, and elucidated, through a series of specific aims, how our thesis would address these.

Section II discussed the use of registries and risk stratification tools in optimizing the outcomes of high-risk patients in the contemporary era. Chapter 2 specifically evaluated the importance of collecting, analysing, and publishing data on high-risk patients where the benefit-risk relationship is not immediately apparent. It highlighted that, compared to any other specialty, cardiac surgery has benefitted from the widespread utilization of clinical registries as they have enabled clinicians to quantify the outcomes of high-risk patients and demonstrated its efficacy in a real-life setting(45). This has subsequently facilitated increased acceptance of surgery in these patients which has translated into improved peri-operative outcomes and superior long-term survival(137). Beyond this, registries also facilitate clinical research and are important tools for clinical governance and quality control(121). The chapter also discussed the limitations of clinical datasets; they are subject to treatment bias, sampling error and missing data(141). Maintaining registries also require significant expenditure of human and financial resources(146). Furthermore, they may not collect all clinically relevant data (e.g. angiographic data)(121). Nevertheless, the widespread availability of data on high-risk

cohorts in cardiac surgery has been facilitated by the ready accessibility to quality registry data in many countries.

Perhaps the least appreciated benefit of maintaining large clinical registries in cardiac surgery has been the development of risk-assessment tools. This was explored in Chapter 3. Risk assessment tools are critical in the contemporary practice of cardiac surgery and in most institutions treatment allocation is based on a patient's risk profile(103). Both European and U.S. guidelines highlight the importance of cardiac surgery derived risk tools in allocating patients to different treatments(304, 374). Risk assessment data may also improve outcomes in high-risk patients by allowing the performance of particular units to be benchmarked to others. This potentially allows identification of underperforming units, who can then by reviewed with a view to improve performance(123, 172). Risk assessment tools, however, also have limitations. Commonly used scoring systems such as the EuroSCORE have been shown to overestimate risk in high-risk patients; this had led to the development of the AusSCORE and EuroSCORE II(103, 188, 375). They are subject to confounding by unknown variables and may be inaccurate because they are derived from a specific population but applied more widely(103). In fact, it is being increasingly recognized, particularly in a high-risk cohort, that frailty is an important risk factor, independent of the risk assessment score(103). Afilalo and colleagues(206) demonstrated that the addition of frailty and disability to cardiac surgery risk scores more accurately identified elderly patients at high risk of mortality or major morbidity. Nevertheless, the clinical utility of risk assessment tools cannot be denied in the context of an increasingly high-risk patient population. Furthermore, with the rapid development of minimally invasive strategies to treat cardiac

disease, the utility of risk assessment tools will become more important for treatment allocation.

Chapter 4 built upon the concepts of the previous two chapters by using ANZSCTS registry data to evaluate the outcomes of high-risk patients (AusSCORE >5%) who underwent CABG. The safety and efficacy of two different strategies of surgical coronary revascularization (OPCAB vs ONCAB) were compared in this high-risk context. OPCAB was developed 40 years ago as a strategy to avoid the systemic inflammatory response and coagulopathy associated with contact of blood with an extracorporeal circuit(376). Moreover, OPCAB, particularly when performed in a manner which avoids instrumentation or manipulation of the thoracic aorta should theoretically reduce the incidence of peri-operative stroke(377). Enthusiasm for this technique, however, has been tempered by concerns that the technical difficulty for OPCAB translates into poorer graft patency and a less complete revascularization(378, 379). This has been reinforced by randomized trials (ROOBY and CORONARY) demonstrating no clear advantage with a OPCAB strategy(249, 250). There are studies, however, that show that the selective use of OPCAB in high-risk patients may improve patient outcomes(380, 381). Puskas and colleagues(382) stratified patients in the STS registry by Predicted Risk of Mortality (PROM) quartiles and demonstrated that whilst there was no difference in operative mortality between OPCAB and CPB for patients in the lower two quartiles, in the higher risk quartiles there was a mortality benefit for OPCAB (odds ratio, 0.62 and 0.45 for OPCAB in the third and fourth risk quartiles).

Our study showed of 7822 high-risk patients showed that CABG is an excellent option for revascularization in high-risk patients with 30-day mortality under 4%,

regardless of the strategy employed. Our comparison of the two revascularization strategies showed several interesting findings. Firstly, our data confirmed that the average number of grafts performed per patient was significantly lower in the OPCAB group (2 vs 3, $p<0.05$), reflecting concerns that this technique may result in undergrafting. A review of peri-operative outcomes, however, showed a trend towards reduced 30-day mortality (2.4% vs 3.9%, $p=0.067$) and a decreased incidence of new renal failure (4% vs 6.1%, $p=0.048$), new atrial fibrillation (28.3% vs 33.3%, $p=0.017$), blood transfusion (52.1% vs 59.5%, $p=0.001$) but increased length of ICU stay (66 vs 47 hours, $p<0.001$). There was no significant difference in the incidence of major neurological events (1.3% vs 2.4%, $p=0.104$) or mid-term survival ($p=0.26$). A limitation of the ANZSCTS registry is the lack of information on aortic manipulation; studies have shown that an anaortic approach to OPCAB may reduce stroke risk by preventing dislodgement and embolization of atheromatous plaque in the aorta associated with a partial occlusion clamp(383).

These data confirm other findings that OPCAB may potentially ameliorate some of the deleterious consequences of cardiopulmonary bypass in a high-risk setting but it was associated with increased length of ICU stay. This may reflect the relative unfamiliarity in managing these patients in a postoperative setting particularly in Australia where OPCAB is performed less frequently then other countries such as Japan where 65% of procedures are OPCAB(384). It may also reflect the fact that patients selectively chosen for OPCAB often have a high burden of non-coronary disease such as a porcelain aorta. Our data also suggested that OPCAB may be underutilized. The prevalence of OPCAB surgery was significantly lower in the high-risk group (7% vs 9.4%) and was broadly consistent over time. This suggests that the high-risk patients who are most likely to benefit from

OPCAB are the least likely to undergo this procedure. This reluctance amongst surgeons may reflect ongoing uncertainty with the benefits of this procedure particularly given that previous randomized studies which included lower risk patients did not show a difference(249, 250). It may also reflect the increased technical difficulty of the procedure and the fact that revascularization of the lateral and inferior walls requires vertical displacement of the heart which can cause hemodynamic compromise which high-risk patients are less able to handle(385). It also reflects, to some degree, inadequate training in this specialized technique(386). Of concern, data across the world has been consistent in showing that OPCAB is being performed less often thereby depriving trainees of potential learning opportunities(387, 388). Moscarelli and colleagues(389), argued that the reduced use of OPCAB largely reflects the lack of established training programs, the perception that success with the technique is limited to more proficient surgeons, and a fear of poor outcomes, especially during the learning curve.

Given that key to adoption of this technique is appropriate patient selection, it may be helpful to develop a risk algorithm using current registries to identify patient subsets most likely to benefit from OPCAB and to stratify patients accordingly. Current guidelines that define the indications and contraindications for OPCAB are sparse. The International Society for Minimally Invasive Cardiothoracic Surgery (ISMICS) issued a consensus statement that OPCAB should be considered in patients with EuroSCORE > 5, age > 75 years, diabetes, renal failure, left ventricular dysfunction, and in patients undergoing reoperation(390). Other key elements to optimizing outcomes include peer-to-peer training of the entire team and graded clinical experience for trainee surgeons such that the trainee progresses from performing distal anastomosis initially to the anterior wall

vessels, followed by the inferior wall vessels and then lateral wall vessels(356). Careful early case selection with later progression to more complex procedures under the guidance of experienced trainees has been demonstrated to allow effective training and excellent patient outcomes, even in a high risk cohort(337).

Novel surgical techniques have also been developed, usually involving off-pump techniques, which avoid the need for a sternotomy in high-risk patients undergoing CABG. Hybrid approaches to revascularization, which combines the performance of a single LIMA-LAD graft via a small anterolateral thoracotomy, with percutaneous coronary intervention to other myocardial territories, have been proposed. Early data has been encouraging(391, 392). More recently, the role of robotic beating heart totally endoscopic coronary artery bypass surgery has been explored in higher-risk patients with excellent outcomes(393, 394).

One of the implications of an ageing patient population in cardiac surgery is an increased incidence of AF. Studies have demonstrated that up to 40% of cardiac surgery patients have AF(395, 396). AF is not a benign rhythm; as discussed previously, it is associated with significant mortality and morbidity.

The importance in delineating the prognostic implications of AF in the context of cardiac surgery, particularly with an ageing population, lies in the fact that it a rhythm that is potentially amenable to surgical cure. Moreover, surgical treatment of concomitant AF may also obviate the need for permanent anticoagulation. Since the first description of the surgical treatment of drug-refractory AF by Seally and colleagues(397) in 1981, many surgical procedures have been devised to treat AF. These include, but are not limited to, the left atrial isolation procedure by Williams and colleagues(398), the Corridor procedure

by Guiraudon and colleagues(399) and most importantly the Maze procedure by Cox and colleagues(84). The Maze procedure has undergone several iterations and is regarded as the gold standard surgical procedure for the treatment of AF. Cox and colleagues performed intra-operative mapping studies of AF induced by pacing and showed that AF was based on randomly migrating waves of macro-rentry circuits(400). They subsequently reported a procedure involving multiple “cut-and-sew” incisions that could block all possible macro-reentry circuits and facilitate the propagation of normal sinus impulses from the sinoatrial node to the atrioventricular node through both atria(84). Subsequent iterations of this procedure, most recently the Cox-Maze IV procedure (CMIV), have employed energy-based ablation devices to replace the original cut-and-sew technique(401). These iterations have simplified the original procedure with a consequent decrease in cardiopulmonary bypass times and morbidity(401).

Despite their effectiveness, the adoption of these techniques has been limited. Data from the North American STS registry showed that whilst the incidence of AF increased from 10.0% to 12.2% between 2005 to 2010, the frequency of concomitant ablation actually decreased from 43% to 39% despite an increased body of evidence verifying its safety and efficacy(285). For patients undergoing isolated CABG the use of concomitant ablative strategies was only 26% despite the fact that these patients are less likely to have structural pathology of the heart such as left atrial dilation which may preclude a successful procedure(285). Registry studies across the world have consistently shown that AF ablation is used in less then 50% of patients in whom it may be indicated(285, 402). Hence, although many studies have demonstrated clearly superior outcomes in patients who underwent concomitant ablation, this has not shifted

the perception of many cardiac surgeons and institutions(76, 78). There are several reasons for this underutilization.

Firstly, the Maze procedure is technically complex and inherently invasive as it involves several additional incisions in the heart(83). In 2010, an independent survey of U.S cardiac surgeons at the American Association of Thoracic Surgery showed that the reason why most ignored the opportunity to treat concomitant AF was because of the increased perceived risk(83).

However, a comprehensive review of the STS Registry demonstrated that the addition of a corrective procedure only increased cardiopulmonary bypass and ischaemic time by an average of 9 minutes and was not associated with increased morbidity or mortality(75). Moreover, the advent of less invasive strategies to treat AF including the development of energy sources such as radiofrequency ablation have significantly shortened the operation significantly, dropping mean cross-clamp times for patients undergoing a lone Cox-Maze III procedure from 92 ± 26 minutes to 44 ± 21 minutes for patients undergoing the Cox-Maze IV(403).

Secondly, Maze procedure has been associated with chronoscopic incompetence with alternating bradyarrhythmias and tachyarrhythmias described especially with exercise and other forms of stress(85). Reassuringly, these symptoms improve with autonomic re-innervation over time(59). Thirdly, there is concern that the atrial scarring that this procedure entails means that the restoration of synchronized atrial contraction does not lead to functional atrial contraction and is ineffective in patients with diastolic dysfunction(88). Another criticism of all ablative strategies on an arrested heart, is the inability to identify the exact propagation pathways in specific patients(88). This

necessitates an extensive full set of empiric lesions to ensure interruption of any potential substrate. Most importantly, however, the reluctance from the surgical community reflects concerns that the prognostic implications of AF on outcomes after cardiac surgery have not been clarified(83).

In Section III we performed a series of meta-analyses to address the impact of AF in patients undergoing cardiac surgery. This represents a unique contribution to the literature given no previous meta-analysis has addressed the implications of AF across a spectrum of cardiac surgery procedures and most studies have been restricted to single center case series.

Chapter 5 evaluated the impact of AF on outcomes after CABG. It showed that AF was independently associated with an increased risk of early mortality (OR 1.64; 95% CI, 1.29 – 2.09; p<0.001), stroke (OR 1.50; 95% CI, 1.06 – 2.11; p=0.02), acute renal failure (OR, 1.50; 95% CI, 1.23 – 1.83; p<0.001), prolonged ventilation (OR 1.40; 95% CI, 1.16 – 1.68; p<0.001) and re-operation for bleeding (OR 1.22; 95% CI, 1.07 – 1.40; p=0.003). Moreover, the risk of mid-term mortality was 74% higher in patients with AF. Subgroup analyses demonstrated AF was associated with poorer early and mid-term outcomes after on-pump and off-pump CABG.

In Chapter 6, we performed a meta-analysis to evaluate the impact of AF on outcomes after AVR. Again, our data showed that AF increased the risk of early complications including peri-operative mortality (OR 2.33; 95% CI, 1.48 – 3.67; p<0.001) and acute renal failure (OR 1.42; 95% CI, 1.07 – 1.89; p=0.02). The risk of mid-term mortality was 75% higher in patients with AF. The detrimental prognostic impact of AF in patients undergoing AVR must be considered particularly given that an increasing number

of patients are undergoing TAVI. This treatment is considered gold-standard for high-risk patients with severe aortic stenosis but is being increasingly used in low to mid risk patients(22). A previous meta-analysis demonstrated that AF was associated with a markedly worse prognosis after TAVI(293). Unfortunately, whilst AF can be potentially cured at the time of surgical AVR, there is no effective concomitant treatment for AF during TAVI. Hence, the outcomes of patients with AF who are allocated to TAVI may be compromised than if they underwent conventional AVR with a concomitant AF surgery procedure. To our knowledge, no previous study has compared the outcomes of patients with AF undergoing either AVR and AF surgery or TAVI alone. This represents an avenue for further research.

Patients with mitral valve disease have the highest incidence of AF at up to 50%(70). Our data (Chapter 7) showed a trend towards increased early mortality in the AF group (OR: 1.61; 95% CI, 0.97-2.67) but it did not reach statistical significance (p=0.07). However, on follow-up AF was associated with an increased risk of mid-term mortality (HR, 1.84; 95%, CI, 1.40 – 2.42; p<0.001), stroke (HR, 3.70; 95% CI, 1.36 – 10.06; p=0.003) and cardiac death (cardiac death (HR, 4.29; 95%, CI, 1.28 – 14.35; p=0.02) after MVS. Given that our data showed that AF was associated with a greater than fourfold increased risk of cardiac death in patients undergoing MVS, it strongly emphasizes the need to consider concomitant AF surgery. Hwang and colleagues(404) evaluated the outcomes of 362 patients who underwent concomitant MVS-CMIV procedure. The authors demonstrated that freedom from atrial tachyarrhythmia off anti-arrhythmic drugs was 83% at 5-years. The majority of patients (85%) had warfarin discontinued during follow-up. Despite this, of the patients in whom warfarin was stopped,

there were only 4 cases of stroke or transient ischaemic accident at 21 deaths during 1577 patient-years of follow-up. The linearized rates for thromboembolic event and death without warfarin therapy was only 0.06% and 0.12% per patient-year, respectively, and these rates were not significantly different from patients receiving warfarin therapy. These encouraging data highlight the potential prognostic benefit of aggressively treating AF at the time of MVS.

Finally, Chapter 8 evaluated the impact of AF on outcomes after percutaneous mitral valve repair. There was a clear association of AF with peri-procedural mortality (OR, 1.35; 95% CI, 1.02 – 1.78; p=0.03), and increased length of hospital stay (Mean difference [MD] 0.65; 95% CI, 0.36 – 0.93; p<0.001). At 12-months, AF was associated with a 45% increased risk of mortality and 18% increased risk of hospitalization for heart failure. Overall, our thesis underscores the negative prognostic implications of AF across a variety of cardiac interventions. It supports current recommendations that AF should be treated with concomitant ablation at the time of surgery, whenever possible. Unfortunately, despite the prevalence of AF and its negative prognostic implications it remains undertreated. Our thesis also highlight that AF is a high-risk factor in its own right and should be considered for inclusion in future risk assessment tools.

The increasingly high-risk nature of patients undergoing cardiac surgery has implications on the training of future surgeons. It is intuitive that the current apprenticeship model of surgical training relies on trainees developing their skills with “easy” cases and then progressing to more difficult ones. This exposure may be reduced with the increased complexity of cases. On the other hand, there is concern that patient safety may be compromised by training surgeons in the context of a high-risk patient cohort(363). This

is particularly relevant in cardiac surgery given intuitively trainees have longer operative times which may translate into an increased incidence of complications associated with aortic cross-clamping and cardiopulmonary bypass(405). Other shifts in the healthcare landscape have further reduced surgical training opportunities. In Europe, the application of stringent working time directives (maximum 48-hour workweek) has led to concern that working hours are insufficient to meet training needs (406). In North America, meanwhile, academic institutions have increasingly focused their efforts on activities that generate clinical and research revenue given that measures of institutional reputation place less emphasis on resident experiences of teaching. Coupled with this lack of financial incentives to teach is the disincentive to teach from the increasing public scrutiny on clinical outcomes(407). Indeed, in the United Kingdom, the Association of Surgeons in Training (ASiT) relayed concerns that outcome reporting may lead to inappropriately cautious case selection and limit the breadth and complexity of the case mix to which surgical trainees are exposed(408). Whilst in Chapter 2 we discussed how the development of registries in cardiac surgery has driven improved outcomes, the unintended side effect of this may have been reduced training opportunities. In this context, we believe that for improvements in cardiac surgery education to be made, faculty incentives must be provided. Vaporciyan and colleagues(407) emphasized that if education is to grow in importance, there must be a way to measure its value and reward it in a scholarly manner. Two methods were proposed by the authors. Firstly, to reward high-quality education in itself and secondly to use the existing system of publications and produce conventional scholarly work in education. These suggestions have been

partially implemented in the United States where both flagship cardiothoracic journals have committed to publishing articles addressing educational issues(409).

It is imperative to establish the safety and efficacy of cardiac surgery performed by trainee surgeons in the contemporary era. There are some reassuring studies that have been published to this effect. Murzi and colleagues(356) evaluated trainee outcomes after off-pump CABG from 1996 – 2009 at the Bristol Heart Institute. They showed a significant increase in the pre-operative risk profile of the patients operated on by trainees, over time with increases in mean age ($p=0.001$), EuroSCORE ($p<0.001$), and extent of coronary artery disease ($p=0.001$). Despite this, post-operative mortality and morbidity remained similar during the study period and the proportion of procedures performed by trainees actually increased.

Section IV used two meta-analyses to evaluate early and mid-term outcomes of cardiac surgery performed by surgeons in training. This is a unique contribution to the literature given that there has been no meta-analysis on trainee outcomes after cardiac surgery.

In Chapter 9, we evaluated the impact of training status on outcomes after CABG. Expectedly, our data showed longer operative times for trainees. However, there was no difference between the groups with regards to the incidence of peri-procedural stroke, myocardial infarction, renal failure, re-operation or wound infection. Pooled data analysis also showed that trainee status did not confer a poorer long-term prognosis. A subgroup analysis demonstrated the safety of trainees performing off-pump CABG. This is a more technically demanding procedure because it entails performing microvascular anastomosis on moving target arteries and temporary coronary artery occlusion. In

Chapter 4, we found that OPCAB is associated with a lower incidence of blood transfusion and post-operative atrial arrhythmia. It is effective for certain high-risk populations, such as elderly patients with a heavily calcified ascending aorta and contraindications to cardiopulmonary bypass(217, 410). Moreover, OPCAB may facilitate minimally-invasive surgical revascularization via hybrid approaches(411). Given the changing demographic of patients undergoing cardiac surgery, the deleterious impact of atrial arrhythmia and the shift towards minimally invasive approaches, our findings are reassuring by showing that residents can safely trained to perform this technically demanding procedure.

Chapter 10 evaluated the outcomes of trainee surgeons performing valve surgery. Here, the data showed that trainee cases had longer operative times for mitral valve, but not aortic valve, surgery. Again, there was no difference in the incidence of peri-operative mortality or morbidity between the two groups. Similarly, mid-term mortality was similar between the two groups. Our data demonstrated that training residents did not compromise outcomes after cardiac surgery. It supports the fact that with careful case allocation, appropriate trainee assessment and adequate supervision, cardiac surgery can be safely performed by junior surgeons.

Despite our data demonstrating the safety and efficacy of trainees performing cardiac surgery, a reduction in the exposure of trainees to certain procedures in cardiac surgery in inevitable. This not only reflects the aforementioned factors (increased scrutiny, higher risk cases) but the increased uptake of non-surgical strategies to treat diseases previously managed by conventional open surgical techniques. For example, improved medical management of diabetes, hypertension and hypercholesterolaemia has decreased the need for surgical coronary revascularization as has the increased

utilization of endoluminal approaches such as percutaneous coronary intervention(412). More recently, the PARTNER 3 trial demonstrated the safety and efficacy of transcatheter aortic valve implantation in low risk patients with aortic stenosis(22). There is a host of new techniques being evaluated for the endovascular treatment of mitral and tricuspid valve diseases and proximal aortic aneurysm(413-415). These endovascular techniques may portend a decrease in the number of open surgical procedures performed. Contemporaneous with this is a shift in the paradigm of cardiac surgery from being a specialty which principally involved the open surgical management of cardiovascular disease to one where clinicians are increasingly required to be facile in endovascular techniques. Han and colleagues(416) reported that cardiothoracic trainees are currently in a state of “transition within a transition” in that within this endovascular transformation, they must learn to learn to interpret and predict changes in the landscape of cardiovascular surgery to set the correct career choice. Nevertheless, the authors argued, that this paradigm shift may be advantageous by bringing together momentum and resources that would not exist during times of stasis. The emergence of transcatheter techniques and the heart team approach, for example, provides the opportunity to benefit trainees through a more diverse and enriched curriculum and by promoting inter-specialty collaboration(416). Until now, however, there is sparse data on the implications of these techniques on training in cardiac surgery. Hence, evaluating both the impact of these novel approaches on cardiac surgery training and formulating strategies to train current and future residents in them is imperative.

There have been several proposed strategies to remedy the projected decline in surgical volume. These range from the incorporation of high-fidelity simulation technology

into cardiothoracic training to the development of dedicated “boot camps” to jump start training(417, 418). These have been shown to expedite the acquisition of technical skills and understanding of operative procedures. Specific training models have been developed that simulate complex skills like coronary anastomosis in OPCAB(419). Simulations have also been developed to evaluate non-technical skills like clinical judgment and communication(420). Ramphal and colleagues(418) developed a high-fidelity, computer-controlled cardiac surgery training system that simulated entire surgical cases across the spectrum of cardiac surgery. As well as technical skills, the simulation included adverse clinical scenarios requiring communication and clinical judgment. The model has been demonstrated as a valid training tool by external investigators(421). Such simulations offer an opportunity to improve patient safety in an era of higher scrutiny and the increased risk profile of patients. As such, several institutions have formally developed a cardiac surgery simulation curriculum(422). Reflecting the experience in other surgical specialties, minimally invasive cardiac surgery has also been proposed as a means of reducing risk in high-risk patients(423). These procedures are more technically demanding but are associated with improved post-operative recovery and health-related quality of life(424, 425). Murzi and colleagues(362) demonstrated that trainee surgeons can safely perform minimally invasive mitral valve surgery. The authors demonstrated in a multivariable analysis that the incidence of in-hospital mortality, stroke, conversion to sternotomy, 5-year survival and freedom from reoperation was similar between the trainee and consultant groups. There data provide further impetus to train future surgeons in minimally invasive techniques which may mitigate risk in a high-risk patient cohort.

We also believe that an active approach to addressing contemporary surgical training issues with open discussion amongst all involved parties is pivotal to improving training experience. The Improving Surgical Training (IST) project developed by the Royal College of Surgeons of England (RCS) provides a suitable framework(426). It proscribed a series of recommendations after noting high dissatisfaction rates in trainees.

Key to these recommendations is establishing a healthy relationship between the trainee, the "trainer" and the local institution. Central to this is a recognition that properly supervised trainees, as our thesis highlighted, achieve good outcomes. Further benefits may be attained by developing structured programmes to assist trainee attain skills in managing high-risk patients. No previous study, to our knowledge, has addressed the potential impact of such a programme and it represents an area for future research.

Overall, cardiac surgery is currently in a state of flux with the rapid development of minimally invasive techniques. Maintaining the adequate exposure of trainees to conventional open surgical procedures whilst developing their catheter-based skills is a challenge, particularly in the contemporary "high risk" era. Our dissertation highlights the good patient outcomes that properly supervised trainees can attain and emphasizes the need for further development of a structured training program to optimize future patient care.

FINAL REMARKS

Our dissertation evaluated the outcomes of cardiac surgery in the context of an increasingly high-risk patient cohort. It demonstrated the utility of clinical registries and risk-assessment tools in optimizing the outcomes of high-risk patients undergoing cardiac

intervention. Apart from allowing clinicians to identify and address modifiable risk factors, these tools have allowed comparative analyses to be performed which have demonstrated the safety and efficacy of novel percutaneous techniques and alternative surgical approaches in high-risk patients. Our dissertation also established the increased risk of early and mid-term mortality associated with AF across a spectrum of cardiac surgery procedures. There are two major implications of this finding. Firstly, AF warrants consideration as an independent risk factor in future risk stratification tools. Secondly, surgeons should give strong consideration to treating AF at the time of cardiac surgery with a concomitant AF surgery procedure. The safety and efficacy of this procedure has been demonstrated in many studies but it is currently underutilized. This strategy has the potential to improve early and mid-term outcomes in high-risk patients and also reduce the likelihood they will require therapy with anticoagulants and anti-arrhythmic drugs. Finally, we demonstrated the safety and efficacy of cardiac surgery performed by trainee surgeons. This is particularly relevant finding in the contemporary era where surgeons may be reluctant to provide training opportunities to junior surgeons because of the increased scrutiny on outcomes and the perception of increased risk. Our data strongly suggests that properly supervised trainees achieve equivalent outcomes to their consultant peers. Nevertheless, given the gradual shift of cardiac surgery into a specialty which incorporates more minimally invasive procedures and percutaneous interventions, there is an urgent need to train junior surgeons in these approaches. Moreover, the training deficit in AF surgery needs to be rectified. Through these actions, we can ensure that the future generation of cardiac surgeons is best equipped to deal with the increasingly high-risk patient population that they will encounter.

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