LEFT ATRIAL APPENDAGE OCCLUSION FOR STROKE PREVENTION

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Stroke and Left Atrial Appendage Occlusion in Cardiac Surgery

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Abstract

Stroke is a devastating event for a patient. Patients undergoing cardiac surgery are at risk of both peri-operative and delayed stroke. This thesis comprises 8 chapters that highlight the rate of stroke in cardiac surgery patients and its risk predictors. It justifies the need for a randomized controlled trial of left atrial appendage (LAA) occlusion on top of usual antithrombotic therapy for stoke prevention in patients with atrial fibrillation or flutter.

Chapter 1 is a preface that provides the rationale for undertaking each of the studies included within this thesis.

Chapter 2 presents a large cohort study that examines the predictors of early and long-term stroke in patients undergoing cardiac surgery with emphasis on the impact of atrial fibrillation as well as the CHADS$_2$ score.

Chapter 3 has been published in the journal *Circulation* in a modified form. A review of the current literature is presented, highlighting that although LAA occlusion holds promise for stroke prevention in AF, there is currently insufficient evidence that it can replace the gold standard of oral anticoagulation.

Chapter 4 is a long-term follow-up study of the first Left Atrial Appendage Occlusion Study. This trial included patients undergoing coronary artery bypass grafting with or without AF. By performing a long-term follow-up of these patients, an estimate of stroke risk and risk of developing new AF was obtained.

In Chapter 5, the results of LAAOS II are presented. This registry and pilot trial was used to assess the rate of recruitment into a novel design of a trial comparing LAA occlusion to antithrombotic therapy, LAA amputation safety, and the rate of a composite outcome of death, myocardial infarction, stroke, non-cerebral systemic emboli, and major bleeding.

Chapter 6 presents the design for the LAAOS III trial. The data presented in the previous chapters is used to create the definitive trial of LAA occlusion on top of usual antithrombotic therapy using a prospective, randomized open trial with blinded end-point study (i.e., PROBE) design.

Chapter 7 presents the health economic analysis plan for LAAOS III.

Finally, Chapter 8 presents the conclusion, limitations, and implications of the research presented in my PhD thesis

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Contributions by Others

At the end of each chapter is a full account of authors' contributions.

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List of Abbreviations

ACTIVE	Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events
AF	Atrial Fibrillation
AFFIRM	Atrial Fibrillation Follow-up Investigation of Rhythm Management
ARISTOTLE	Apixaban versus Warfarin in Patients with Atrial Fibrillation
ASA	Acetylsalicylic Acid
ATRIA	Anticoagulation and Risk Factors in Atrial Fibrillation
AVERROES	Apixaban versus Acetylsalicylic Acid to Prevent Strokes
CABG	Coronary Artery Bypass Grafting
CANNeCTIN	Canadian Network and Centre for Trials Internationally
CCN	Cardiac Care Network
CCORT	Canadian Cardiovascular Outcomes Research Team
CHF	Congestive Heart Failure
CI	Confidence Interval
CIHI	Canadian Institute of Health Information
CIHR	Canadian Institutes of Health Research
CK-MB	Creatine Kinase-Muscle and Brain
CNS	Central Nervous System
CPB	Cardiopulmonary Bypass
CT	Computerized Axial Tomography
CVA	Cerebrovascular Accident
DM	Diabetes Mellitus
DRG	Diagnosis-Related Groups
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ED	Endothelial dysfunction
FDA	Food and Drug Administration
FRACTAL	Fibrillation Registry Assessing Costs, Therapies, Adverse events and Lifestyle
HAF	History of Atrial Fibrillation
HHSC	Hamilton Health Sciences Center
HOPE	Heart Outcomes Prevention Evaluation
HR	Hazard Ratio
ICD 9	International Statistical Classification of Diseases
ICH	Intracranial Hemorrhage
INR	International Normalized Ratio
LAA	Left Atrial Appendage
LAAOS	Left Atrial Appendage Occlusion Study
LBBB	Left Bundle Branch Block
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
MI	Myocardial Infarction
MOHLTC	Ministry of Health and Long-term Care
NABOR	National Anticoagulation Benchmark and Outcomes Report

OAC	Oral Anticoagulant
OASIS	Organization for the Assessment of Strategies for Ischemic Syndromes
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
PHRI	Population Health Research Institute
PLAATO	Percutaneous Left Atrial Appendage Transcatheter Occlusion
POAF	Post-Operative Atrial Fibrillation
PROTECT AF	WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation
PVD	Peripheral Vascular Disease
QVSFS	Questionnaire for Verifying Stroke-Free Status
RAFT	Resynchronization/Defibrillation for Ambulatory Heart Failure Trial
RCT	Randomized Controlled Trial
REB	Research ethics Board
RELY	Randomized Evaluation of Long-Term Anticoagulant Therapy
RPDB	Registered Person Database
RR	Relative Risk
RRR	Relative Risk Reduction
SD	Standard Deviation
SPAF	Stroke Prevention in Atrial Fibrillation
SPINAF	Stroke Prevention in Nonrheumatic Atrial Fibrillation
TEE	Transesophageal Echocardiogram
TIA	Transient Ischemic Attack
U	Units
ULN	Upper Limit of Normal
VAD	Ventricular Assist Device
VKA	Vitamin K Antagonist

Thesis Chapter 1: Preface

1.1 Background

Stroke is the third leading cause of death in North America. When not fatal, a stroke event is often disabling and also has enormous social and economic impact. Atrial fibrillation (AF) is responsible for at least one sixth of all strokes in Canada. Therefore, stroke prevention in AF has been a high priority for health care researchers, governments, funding agencies and industry, as evidenced by the multitude of antithrombotics, antiarrythmics, and devices that are already available or are currently being studied for stroke prevention in patients with AF.

To date, three approaches for stroke prevention in AF have been proposed: 1) elimination of AF, itself; 2) prevention of clot formation by medical therapy (either antiplatelet or anticoagulant); and 3) occlusion of the left atrial appendage (LAA) to prevent formation and hence the embolization of clots from the left atrium. The elimination of AF has not been effective in preventing stroke likely because antiarrhythmic therapy has not been able to suppress all episodes of AF or that restoration of sinus rhythm may not eliminate the risk of stroke. Antithrombotic therapy has been very successful in stroke prevention, but is limited by the risk of bleeding, poor adherence to therapy, and costs of prolonged treatment. LAA occlusion has been performed since the 1950s during surgery on the mitral valve.[1] Although the occlusion of the LAA is a logical idea, as yet there is no clear evidence for its efficacy. Cardiac surgery via median sternotomy provides easy access to this structure and permits for safe removal. This makes it an opportune moment to perform LAA occlusion and if conducted in the context of an RCT, to assess whether it is beneficial for stroke protection in AF patients. My thesis provides the background work necessary to conduct a definitive trial of left atrial appendage occlusion in patients undergoing cardiac surgery.

1.2 Stroke Risk after Cardiac Surgery and its Predictors

In preparing for a study to examine the impact of LAA occlusion in cardiac surgery patients, one must understand the risk profile of this specific population. Studies of stroke prevention in atrial fibrillation to date have focused on non-valvular AF, and thus there is a knowledge gap on the longer-term stroke outcomes of patients who have undergone cardiac surgery with pre-existed AF and new postoperative AF. In chapter 2, Ontario databases are linked to determine predictors of short- and long-term stroke, estimate their prevalence, and specifically examine the impact of AF in this population. The data acquired assists in identifying the target population for trials, estimating event rates for statistical considerations, and identifying other groups that may be of interest for inclusion in future trials of stroke prevention (for example; elevated $CHADS_2$ score independent of cardiac rhythm).

1.3 Current Evidence for Left Atrial Appendage Occlusion

The AHA guidelines have supported LAA occlusion as a supplementary procedure during mitral valve surgery.[2] At the crux of this thesis is the theory that left atrial appendage occlusion for stroke protection in AF patients is promising, but as yet the evidence is lacking for its efficacy. Chapter 3 provides an overview of the current knowledge regarding the left atrial appendage in AF, its role in cardioembolic strokes, and safety and efficacy of its occlusion. This chapter highlights that LAA occlusion is a promising idea for stroke prevention with some encouraging results from small but not definitive studies. Therefore, the evidence of efficacy and safety are insufficient to recommend this approach as an alternative to antithrombotic medications. A large trial that establishes the proof of efficacy for stroke prevention is needed.

1.4 Long-term Outcomes of Participants in Prior LAAO Pilot Studies

Chapter 2 provides an estimate of the 2-year risk of stroke in patients after cardiac surgery with and without AF. Further, the data suggest that patients with elevated $CHADS_2$ score are at elevated stroke risk, independent of their cardiac rhythm. The first Left Atrial Appendage Occlusion Study (LAAOS) pilot was completed in 2002[3] and included patients with AF and without AF but with an elevated $CHADS_2$ score. This provides an opportunity to obtain estimates of long-term stroke risk in the population of interest for a future LAA occlusion trial in cardiac surgery and provides an estimate of the risk of developing new atrial fibrillation in elevated $CHADS_2$ patients. Chapter 4 reports the 8-year follow-up of patients randomized at the Hamilton Health Sciences Center who had participated in the original LAAOS pilot.

1.5 The Feasibility of a Trial of LAA Occlusion Versus Oral Anticoagulation

The PROTECT AF trial in which patients were randomized to a percutaneously placed intravascular LAA occlusion device was published in 2009.[4] The results of this trial, while inconclusive, were promising as a proof of concept that LAA occlusion may benefit in stroke prevention.[5] These results generated great enthusiasm in the field and resulted in the development of the Left Atrial Appendage Occlusion Study II pilot study (LAAOS II) by myself and the CANNeCTIN cardiac surgery working group. Chapter 5 reports the results of this feasibility study that randomized AF patients with an elevated $CHADS_2$ score to left atrial appendage occlusion and aspirin versus optimal antithrombotic therapy.

1.6 Left Atrial Appendage Occlusion in Addition to Usual Care

From the knowledge accumulated and presented in chapters 2 through 5, chapter 6 presents the rationale, design, and organization of an international RCT which we have initiated that is evaluating LAA occlusion in addition to usual antithrombotic. The advantages of this design over the "versus OAC" design are discussed, and strategies to overcome methodological challenges are presented.

1.7 Conclusions and Future Directions

Chapter 7 provides conclusions of the body of work, describes its limitations, and outlines future research that I plan to conduct in this field.

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Thesis Chapter 2

Title: Predictors of Early and Late Stroke Following Cardiac Surgery

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Abstract

Background: While much is known about the short-term risk of stroke following cardiac surgery, little is known about the long-term risk and its predictors.

Methods and Results: A cohort study of patients undergoing CABG or valve surgery in Ontario Canada between1996 and 2006 was assembled with linked clinical and administrative databases. Data on stroke and mortality up to 2 years after surgery were analyzed with Cox modeling. Of 108,722 patients, 3.6% (95% CI 3.5% -3.7%) suffered a stroke over the next 2 years, with half occurring in the peri-operative period. The strongest predictors of both early and late stroke were a prior history of a transient ischemic attack or stroke (HR 2.0, p<0.0001), increasing age (HR 1.9, p<0.0001), combined surgery (HR 1.7, p<0.0001) or valve surgery (HR 1.5, p<0.0001), and peripheral vascular disease (HR 1.6, p<0.0001). New post-operative atrial fibrillation (OR 1.5, p <0.0001), and preoperative dialysis dependence (OR 1.9, p<0.0001) predicted early but not late stroke.

A CHADS$_2$ score $\geq$2 increased the risk of stroke and death at 2 years from 9.9% to 18.4% in individuals with pre or post-operative AF (n=27,600) and from 6.2% to 12.5% in those without this condition (n=81,102).

Conclusions: Cardiac surgery patients are at highest risk of stroke in the early post-operative period and have ongoing hazards over the ensuing 2 years with similar risk predictors over these periods suggesting that the risk of stroke persists beyond this period. New post-operative AF increases early stroke risk, particularly with elevated CHADS$_2$ score. Finally, the CHADS$_2$ score predicts the 2 year stroke risk in patients with and without atrial fibrillation.

Background

Stroke remains a devastating complication following cardiac surgery, with substantial functional and economic impact.[46-48] Stroke research in cardiac surgery has focused on the immediate post-operative period[49-54]; however, most patients having cardiac surgery have risk factors such as hypertension, diabetes and atrial fibrillation (AF) which place them at long-term risk of stroke.

The early and late outcomes of patients having cardiac surgery could be improved if the precise risk of post-operative stroke was defined and characteristics which increase this risk were identified. With this information, clinicians could take advantage of the peri-operative period to optimize medical therapy for stroke risk factors like hypertension[55, 56], improve the evidence-based use of empiric oral anticoagulation in patients with AF, and consider future studies to examine intra-operative surgical strategies, such as removal of the left atrial appendage[1], in patients whose clinical characteristics predict an increased risk of stroke. The current study seeks to describe the incidence of stroke from the time of surgical admission to 2 years after surgery and define the risk factors that predict this outcome.

Methods

Patients

All patients 18 years of age and older who underwent coronary artery bypass grafting (CABG), isolated valve surgery, or combined CABG and valve surgery in the province of Ontario from 1996 until 2006 were identified with the Cardiac Care Network (CCN) database. If a person had more than one cardiac surgical procedure on the same admission, only data from the first procedure was considered.

Databases

Three linked databases were examined: the Cardiac Care Network of Ontario, the Canadian Institute of Health Information (CIHI) database for patients' discharge disposition, and the Registered Person Database (RPDB) were used to identify deaths that occurred outside of hospitals. These databases have been used extensively to examine health outcomes as anonymised healthcare records can be analyzed using encrypted identifiers to track individuals over time.[57-59] Where possible patient characteristics, surgery characteristics, and outcomes were captured prospectively in the CCN clinical registry and are proven to be reliable when compared to manual chart review. However, the history of atrial fibrillation and hypertension were poorly captured within the CCN database, thus the presence of these two conditions was ascertained by reviewing the corresponding ICD 9 (before 2002, AF = 4273, hypertension = 401, 402, 403, 404, 405) or ICD 10 (after 2002, AF = I480, I481, hypertension = I10, I11, I12, I13, I15) codes for the preceding 10 years in all patients. Post-operative AF (POAF) was defined by an absence of a history of AF and the appearance of AF diagnosis code during the cardiac surgical admission.

Outcomes

The primary outcome was stroke occurring up to 2 years after surgery. Secondary outcomes were peri-operative stroke or death (occurring during the same admission as the surgical procedure) and late stroke or death (from time of being discharged alive from surgical admission to 2 years after surgery).

Statistical Analysis

The prevalence of plausible risk factors[16,17] for stroke was examined in all patients and then compared between: 1) patients with a history of AF (group HAF) versus those with no

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history of AF (group noHAF) and 2) patients with no history of AF but new onset post-operative AF (group noHAF/POAF) versus those with no history of AF and no post-operative AF (group noHAF/noPOAF), using a chi-square test and student's t-test where appropriate. Plausible risk factors for stroke examined in this analysis included: age, gender, diabetes mellitus, congestive heart failure, left ventricular systolic function, cerebrovascular disease, valvular surgery, CABG surgery, creatinine, dialysis, hypertension, prior TIA/CVA, hyperlipidemia, peripheral vascular disease, reoperation, history of myocardial infarction, left main disease, history of AF, and new post-operative AF.

Crude and risk adjusted rates of stroke were then analyzed in 6 month intervals and by AF group. Next, univariate analysis was performed for the outcomes. Those risk factors with a $p<0.2$ were then entered into multivariable analysis with no further selection. A multivariable Cox model was used for the primary outcome as well as for late stroke, while the outcome of early stroke was analyzed with logistic regression. For the outcome of overall stroke, the precise timing of stroke events that occurred during the same hospital admission as the surgery was not available. Therefore, it was assumed that all of these strokes occurring in the first 48 hours post-operatively based on previous findings supporting that the majority of strokes occur within this timeframe.[60, 61] Collinearity diagnostics were not assessed. Proportionality for Cox models were tested visually via Kaplan-Meier Curves. Analyses were performed using SAS software (SAS Institute Inc).

Results

Population Characteristics

A total of 108,722 patients were identified for analysis in the study. Table 1 presents the prevalence of risk factors in the cohort divided by the presence of HAF and POAF. The cohort represents well the variety of cardiac surgical procedures performed with 77% the patients undergoing isolated CABG, 13% having isolated valve procedure, and 10% undergoing combined CABG/valve surgery. In all, 8.8% of the cohort had a history of AF and were older, more likely to be female, and more likely to have valvular or re-operative surgery than those without a history of AF. Post-operative AF developed in 16.6% of those without a history of AF. These patients were older, had more CHF and CVD or PVD in their history, and were more likely to have undergone valvular surgery with or without CABG than those who did not develop POAF.

Crude and Risk adjusted rates of Stroke and Death

The in-hospital risk of stroke is 1.8% (95% CI 1.7%-1.9%) and 2.8% (95% CI 2.7% to 2.9%) for death. Over the next 2 years, there is a 3.6% (95% CI 3.5% to 3.7%) risk of stroke (figure 1) and 6.8% (95% CI 6.6% to 7.0%) risk of death.

Predictors of Stroke

Table 2 presents the adjusted odds ratios and hazard ratios for the predictors of stroke at various times from surgical admission to 2 years post-operative with their respect 95% confidence intervals. The strongest predictor of stroke at any time from operation to 2 years is a history of stroke or TIA (OR 2.0, 95% CI 1.8-2.2) and advanced age ≥ 65 years (OR 1.9, 95% CI

1.7-2.0). Other strong predictors include dialysis dependence, PVD, and valvular surgery versus isolated coronary bypass grafting.

Comparing peri-operative to late stroke, the risk factors are similar with a few exceptions (table 3). The strongest independent predictors of peri-operative stroke are: advanced age ≥ 65 years (OR 2.1, 95% CI 1.9-2.3), history of transient ischemic attack or stroke (OR 2.0, 95% CI 1.7-2.4), preoperative dialysis dependence (OR 1.9, 95% CI 1.4-2.5), combined surgery (OR 1.7, 95% CI 1.6-2.3) or valve surgery (1.4, 95% CI 1.2-1.7), peripheral vascular disease (OR 1.6, 95% CI 1.4-1.7), and new onset post-operative AF (OR 1.5, 95% CI 1.3-1.6). For late stroke occurring up to 2 years post-operative, several important predictors are shared with peri-operative stroke such as prior stroke/TIA (HR 2.1, 95% CI 1.8-2.4), advanced age (HR 1.7, 95% CI 1.6-1.9), combined surgery (HR 1.6, 95% CI 1.4-1.8) or valve surgery (and 1.5, 95% CI 1.3-1.7), peripheral vascular disease (HR 1.5, 95% CI 1.4-1.7), and a pre-operative history of AF (HR 1.4, 95% CI 1.2-1.6). However, post-operative AF and dialysis are not associated with later stroke once a patient is discharged stroke free and alive.

The Impact of CHADS$_2$ and AF on Stroke and Death

Figure 2a and 2b illustrates the 2-year crude rate of stroke and stroke or death by CHADS$_2$ score and AF group, respectively. The data highlight that an increasing CHADS$_2$ score predicts a higher risk of stroke in patients with any AF (preoperative or new postoperative AF) and in patients with no preoperative of post-operative AF. The additional relative risk of AF on top of CHADS$_2 \geq 2$ is approximately 1.8. There is a high risk of stroke and stroke or death in patients with elevated CHADS$_2$ score, with rates greater than 20% for CHADS$_2 \geq 3$ in all AF categories. Specifically, the rate of stroke or death in the absence of any AF is 5.8% for patients with a CHADS$_2$ of 0 or 1 compared to 20.3% for those with a CHADS$_2$ score of greater than 3. If

a patient has a history of AF, the rate of stroke or death at 2 years is 13.0% for a CHADS$_2$ of 0 or 1 compared to 28.8% for those with a CHADS$_2$ score of greater than 3. Finally, if a patient suffers from new post-operative AF, the rate of stroke or death at 2 years is 7.8% for a CHADS$_2$ of 0 or 1 compared to 21.2% for those with a CHADS$_2$ score of greater than 3.

Discussion

This study has three key findings. First, patients undergoing cardiac surgery are at highest risk of stroke in the early post-operative period, but also have ongoing risk over the subsequent 2 years. Second, the risk factors predicting a peri-operative versus a late stroke event are similar except for new post-operative AF which only predicts early stroke. Third, in the cardiac surgical population, the CHADS$_2$ score predicts the 2 year stroke and stroke or death risk in patients with atrial fibrillation and in those without atrial fibrillation.

This study presents the largest cohort data used to examine long-term stroke risk in this population. It is a large sample of patients undergoing cardiac surgery in the province of Ontario, Canada, over a 10-year period. It defines the risk of stroke and its predisposing characteristics in cardiac surgical patients over the first 2 post-operative years in this population (tables 2 and 3). The strongest predictors of in-hospital stroke are similar to those of later stroke (advanced age, history of CVA, peripheral vascular disease, and valvular surgery). The results extend the observations made by others who have described similar predictors of early stroke.[50-53, 62, 63] Bucerius et al. studied 16,184 patients and found that cerebrovascular disease, preoperative infection, and high transfusion requirement were the strongest independent predictors of peri-operative stroke.[64] Similarly, Roach et al. found proximal aortic atherosclerosis, history of neurologic disease, use of intraaortic balloon pump, and age (amongst

others) to be strong predictors of early adverse cerebral outcomes amongst 2108 patients.[52]

However, the current study is the first to demonstrate that risk factors for peri-operative stroke

continue to predict later stroke risk.

The finding that new onset post-operative AF is an independent predictor of early stroke

(OR 1.5) but not of late stroke suggests that patients with POAF should be considered for a short

course of anticoagulation initiated early. We believe that the in-hospital mortality rate in POAF

group appeared less because of ascertainment bias: those patients who die early do not have the

opportunity to develop POAF. POAF as a predictor of post-operative stroke has been debated

within the literature. In a study of 2972 cardiac surgery patients, Hogue et al. found that POAF

had no impact in postoperative stroke rate unless it was accompanied by low cardiac output

syndrome, with a resultant OR of 1.7 (1.0-2.9).[51] Creswell et al., on the other hand, found that

POAF was associated with an increased incidence of postoperative stroke (3.3% versus 1.4%,

p<0.0005) in their study of 4,507 adult patients.[49] Most recently, Tarakji et al. in a prospective

cohort study of 45,432 CABG patients found that POAF did not increase the risk of post-

operative stroke but actually lowered it.[54] The authors suggest that this is the result of an

aggressive approach to POAF involving anticoagulation that is taken at the single center where

the patients were recruited. The current study adds over 100,000 patients to this literature, with

18, 046 (18.2%) developing POAF in whom there is a strong association with increased early

stroke risk. Creswell's data collected prospectively demonstrated an incidence of POAF ranging

from 31.9% to 63.6% depending on the surgery type. It is, therefore, very likely that this

administrative dataset is under-reporting POAF and thus is likely underestimating the true risk

attributable to POAF.

The CHADS$_2$ score is a validated clinical prediction rule for stroke risk in non-rheumatic atrial fibrillation[65] who were not prescribed warfarin and now is used to guide when antithrombotic therapy in AF patients. Figures 2a and b highlight that the CHADS$_2$ score is an important predictor of stroke or death even in the absence of any known atrial fibrillation, with a RR of 3.5 for CHADS$_2 \geq 3$ versus CHADS$_2 = 0,1$. This raises the question of stroke source in the non-AF patients: is the elevated CHADS$_2$ score a marker of vascular disease and the strokes are all thrombotic, or are these patients having occult AF and resultant embolic events? It is likely that what we are observing is a combination of the both. A prospective observational study of cardiac surgery patients that closely tracks these events is needed to determine the relative frequencies of stroke subtypes and assist in planned therapies to reduce the stroke risk. Possible therapeutic approaches to be examined include optimization of antihypertensive therapy, optimization of antithrombotic therapy, and intraoperative strategies such as left atrial appendage occlusion.

This study has several limitations. Firstly, some variables included within the study were not validated within the CCN database (e.g. hypertension and history of AF). However, our method of looking back 10 years for ICD 9 or 10 codes for these diagnoses did yield incidences that one would expect to see in this population. Second, the incidence of post-operative atrial fibrillation is under-captured within the dataset. The most plausible effect of this is that the impact of this variable on stroke is underestimated. Finally, the dataset contained no information on post-operative anticoagulation use, in-hospital or on discharge and so we are unable to examine the impact of OAC on outcomes.

Conclusion

Patients undergoing cardiac surgery are at significant risk of stroke, both peri-operatively and in the subsequent years. The predictors of stroke are similar for these two time periods and include previous cerebrovascular accident, peripheral vascular disease, and advanced age. New onset postoperative atrial fibrillation, however, predicts early but not late stroke and thus, early initiation of a short course of anticoagulation should be considered, particularly in the presence of elevated CHADS$_2$ score. Finally, elevated CHADS$_2$ score also predicts for increased risk of stroke or death in patients with atrial fibrillation and in patients without. Patients with elevated CHADS$_2$ score should be a focus for preventive strategies in future research irrespective of heart rhythm.

Acknowledgements

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Contributorship Statement

Richard Whitlock originated the idea for this paper and brought together the authors to formulate and debate the points in the text. He developed the study design, participated in the statistical analysis, interpretation of the data, wrote the first draft of the manuscript, and provided critical revisions to the manuscript.

Stuart Connolly contributed significantly to the manuscript design, interpretation of data, and provided critical revisions to the manuscript.

Jeff Healey contributed significantly to the manuscript design, interpretation of data, and provided critical revisions to the manuscript.

Julie Wang contributed significantly to the statistical design, interpretation of data, and provided critical revisions to the manuscript.

Jack V. Tu contributed significantly to the manuscript design, interpretation of data, and provided critical revisions to the manuscript.

Richard Novick contributed significantly to the manuscript design, interpretation of data, and provided critical revisions to the manuscript.

Stephen Fremes contributed significantly to the manuscript design, interpretation of data, and provided critical revisions to the manuscript.

Kevin Teoh contributed significantly to the manuscript design, interpretation of data, and provided critical revisions to the manuscript.

Vikas Khera contributed significantly to the manuscript design, interpretation of data, and provided critical revisions to the manuscript.

Salim Yusuf contributed significantly to the manuscript design, interpretation of data, and provided critical revisions to the manuscript.

Tables

Table 1: Baseline Characteristics of Patients (n=108,722) by History of AF and by New Post-

Operative AF

VARIABLE	History of AF	No History of AF	P	New Post-operative AF	No AF*	P
	n=9,574	n=99,148		n=18,046	n=81,102	
Patient Demographics						
Age ≥ 65 years	72.7%	51.7%	<0.001	68.1%	48.0%	<0.001
Female	35.7%	25.2%	<0.001	26.4%	24.9%	<0.001
Risk Factors						
Congestive Heart Failure	47.0%	18.2%	<0.001	23.9%	17.0%	<0.001
Creatinine	93.8±32.4	91.7±25.4	<0.001	92.4±22.8	91.5±25.9	<0.001
Cerebrovascular Accident/Transient Ischemic Attack	7.4%	3.6%	<0.001	4.6%	3.4%	<0.001
Cerebrovascular Disease	16.9%	10.3%	<0.001	12.5%	9.7%	<0.001
Diabetes	27.9%	30.2%	<0.001	29.3%	30.4%	0.003
Dialysis	1.8%	1.1%	<0.001	1.0%	1.1%	0.526
Hypertension	47.3%	33.7%	<0.001	35.4%	33.3%	<0.001
Left Main Disease	13.1%	19.7%	<0.001	19.9%	19.7%	0.46
Previous MI	19.3%	23.0%	<0.001	22.7%	23.1%	0.22
LV grade 2-4	51.8%	49.6%	<0.001	48.3%	49.9%	<0.001
Reoperation	7.5%	3.3%	<0.001	3.5%	3.2%	0.054
Peripheral Vascular Disease	16.6%	14.0%	<0.001	16.5%	13.5%	<0.001
$CHADS_2$ (mean±SD)	1.63±1.17	1.03±1.02	<0.001	1.20 ± 1.08	0.99 ± 1.01	<0.001
Surgery type						
CABG	48.1%	79.6%	<0.001	71.0%	81.5%	<0.001
Valve	31.8%	11.2%	<0.001	14.8%	10.4%	<0.001
CABG + Valve	20.1%	9.2%	<0.001	14.2%	8.1%	<0.001

AF Atrial Fibrillation, MI Myocardial Infarction, CABG Coronary Artery Bypass Grafting,

SD Standard Deviation

*No history of AF and no post-operative AF

Table 2: Predictors of stroke by time period for all patients

Variable	Early Stroke* OR (95% CI, p)	Late Stroke¶ HR (95% CI, p)	All Stroke HR (95% CI, p)
Age>=65 years	2.1 (1.9-2.3, <0.001)	1.7 (1.6-1.9, <0.001)	1.9 (1.7-2.0, <0.001)
Previous CVA or TIA	2.0 (1.7-2.4, <0.001	2.1 (1.8-2.4, <0.001)	2.0 (1.8-2.2, <0.001)
Dialysis	1.9 (1.4-2.5, <0.001)	1.2 (0.8-1.6, 0.39)	1.5 (1.2-1.9, <0.001)
Peripheral vascular disease	1.6 (1.4-1.7, <0.001)	1.5 (1.4-1.7, <0.001)	1.6 (1.4-1.7, <0.001)
Post-operative AF	1.5 (1.3-1.6, <0.001)	1.0 (0.9-1.1, 0.90)	1.2 (1.1-1.3, <0.001)
Valve†	1.4 (1.2-1.7, < 0.001)	1.5 (1.3-1.7, <0.001)	1.5 (1.4-1.7, <0.001)
CABG and Valve†	1.7 (1.6-2.3, <0.001)	1.6 (1.4-1.8, <0.001)	1.7 (1.6-1.9, <0.001)
Congestive heart failure	1.3 (1.2-1.5, <0.001)	1.1 (1.0-1.2, 0.10)	1.2 (1.1-1.3, <0.001)
Diabetes	1.3 (1.1-1.4, <0.001)	1.3 (1.2-1.5, <0.001)	1.3 (1.2-1.4, <0.001)
Hypertension	1.2 (1.1-1.3, <0.001)	1.4 (1.2-1.5, <0.001)	1.3 (1.2-1.3, <0.001)
Left main disease	1.2 (1.1-1.4, <0.001)	1.0 (0.9-1.1, 0.58)	1.2 (1.1-1.3, 0.001)
History of AF	1.2 (1.0-1.4, 0.01)	1.4 (1.2-1.6, <0.001)	1.3 (1.2-1.4, <0.001)
Female	1.1 (1.0-1.2, 0.04)	1.3 (1.2-1.4, <0.001)	1.2 (1.1-1.3, <0.001)
LV dysfunction	1.1 (1.0-1.2, 0.03)	1.2 (1.1-1.3, <0.001)	1.2 (1.1-1.6, <0.001)

*Stroke occurring during surgical admission

¶Stroke occurring between discharge from surgical admission to 2 years post-operative

Figures

Figure 1: Stroke free survival in patients from time of surgery
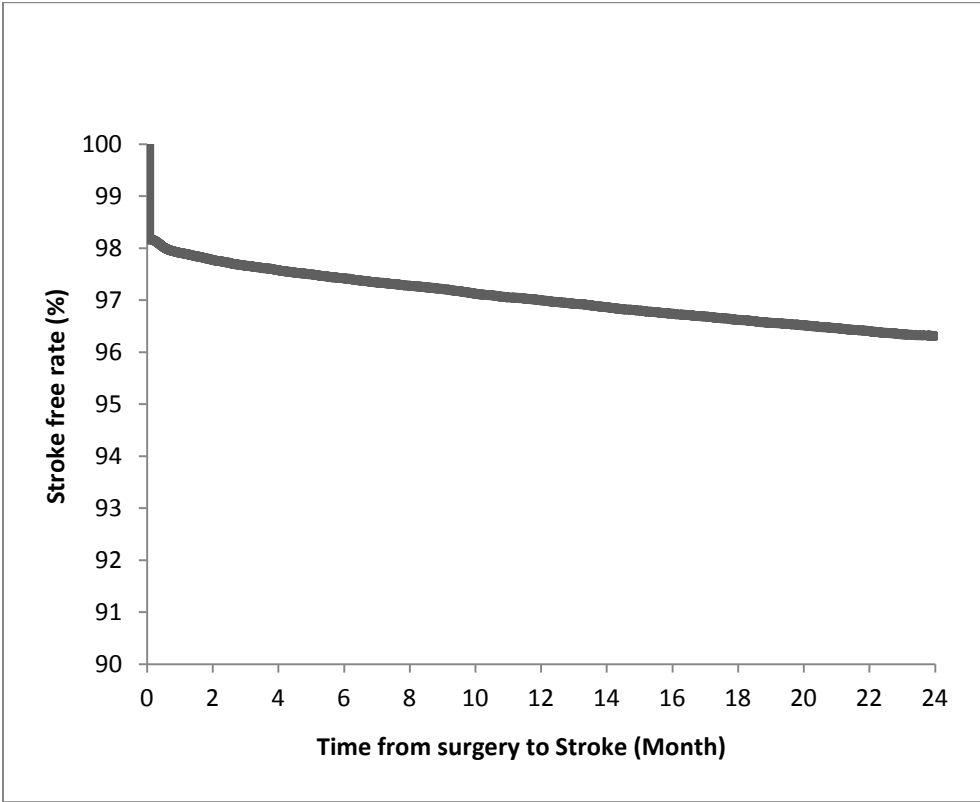
Figure 2a: Crude rate of stroke by CHADS$_2$ score and by AF category
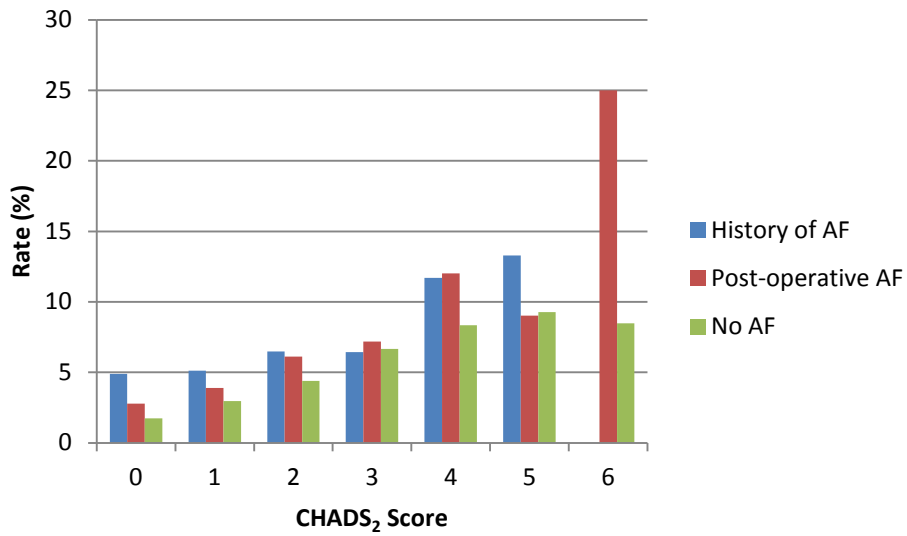
Figure 2b: Crude rate of stroke or death by CHADS$_2$ score and by AF category
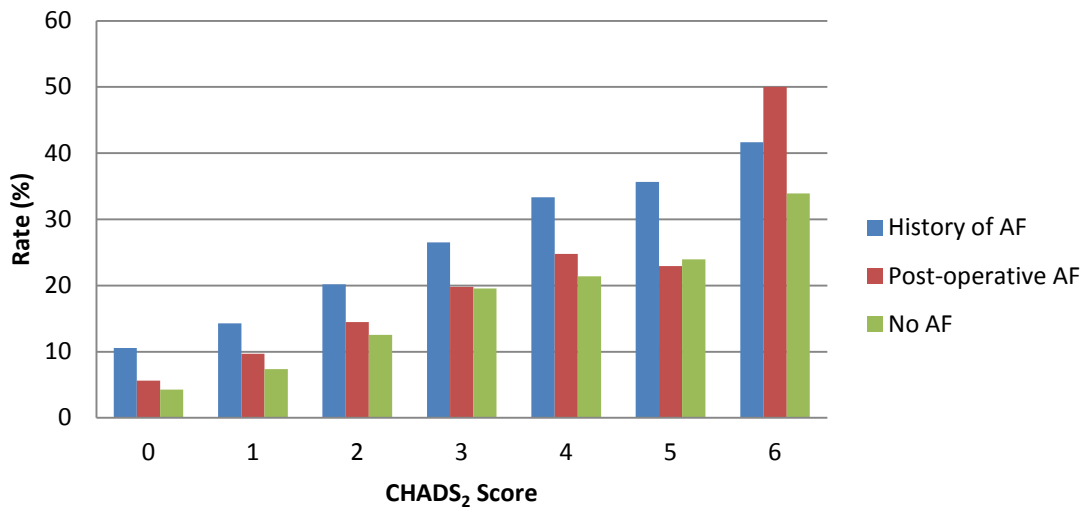
Thesis Chapter 3

Title: Does Left Atrial Appendage Exclusion Eliminate the Need for Warfarin?

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Introduction

Atrial fibrillation is the most common sustained heart rhythm disorder. It is increasing in incidence, which has major societal implications for our aging population.[3-5] It is estimated to affect 1-1.5% of the developed world, and the incidence increases with age to a rate of 19.2 per 1000 patient years in those 65 years of age and over. The most important aspect of the treatment of patients with atrial fibrillation is the prevention of stroke. The average annual stroke rate across risk groups is 5%, and AF associated strokes confer worse outcomes than those occurring in the absence of AF.[3, 6] Furthermore, SPINAF data suggest that 15% of patients with atrial fibrillation suffer silent cerebral infarctions on computed tomography, the implications of which are unknown.[7]

Oral anticoagulant (OAC) therapy with warfarin has been established as the standard for stroke prevention in patients with AF who have more than one risk factor for stroke.[8] Hart et al. have summarized this literature in meta-analyses that include twenty-nine trials and 28,044 patients.[9, 10] Compared to placebo, warfarin reduced the rate of stroke by 64% (95% CI, 49% to 74%) and in trials of warfarin versus antiplatelet, warfarin reduced the rate of stroke by 37% (95% CI, 23% to 48%). This is a large treatment effect when compared to other drug therapies in cardiovascular medicine. Further, even with an absolute risk increase in ICH and major hemorrhage of 0.2% per year over anti-platelet therapy, warfarin still produces a statistically significant 26% reduction in overall mortality compared to placebo.[9]

Despite its demonstrated benefit, warfarin therapy is administered to as few as 25% of patients with AF and only 70% of patients who are felt to be "ideal" candidates for warfarin.[11-17] In the CCORT AF study, using prescription claims databases in Alberta, British Columbia and Ontario from 1997 to 2000 (pre-AFFIRM), less than one-half of AF patients filled a prescription

for warfarin within 90 days of discharge for an AF hospitalization.[15] Also concerning is the rate

of warfarin discontinuation, which has been documented in the FRACTAL registry as 20% over

a 2.5-year period.[16] Many patient, prescriber and systems related barriers have been identified.

However, the main limitation of warfarin is concern about bleeding and this often prevents its

use in potentially suitable patients.[18, 19] In study patients assigned to warfarin therapy, it has been

noted that patients are in therapeutic range on only 50% to 68% of monitored days.[20] The

relationship between INR and outcomes has been well documented, and a low INR results in an

increased risk of stroke and high INR is associated with increased risk of bleeding.[21] This is even

a greater issue in routine medical care where time in therapeutic range has been documented to

be even lower.[22, 23] An effective, low risk therapy that could eliminate the need for oral

anticoagulants and their associated risks to the patient is therefore very attractive.

The left atrial appendage (LAA) is a 2 to 4 cm tubular structure attached to the left

atrium, and has been deemed by some "our most lethal attachment".[24] The failure of the

fibrillating atrium to contract results in atrial stretch and dilation, promoting stasis and thrombus

formation in the LAA (Figure 1). Transesophageal echocardiogram (TEE) allows for clear

imaging of the LAA and several studies have examined the formation of thrombus in the hearts

of patients with AF. In one study of 233 patients with AF who were not taking warfarin, 34

patients (15%) had left atrial thrombus. All but one of these were located in the LAA.[25] In a

similar study, 272 non-rheumatic AF patients had an 8% incidence of left atrial clot, all of which

were in the left atrial appendage. A review of these and other studies concluded that at least 90%

of left atrial thrombi are found in the LAA.[26] These observations have lead to the concept of

LAA exclusion as a means of reducing stroke and other embolic events in AF.

To determine the current role of LAA exclusion in the management of patients with atrial fibrillation, we must consider the following questions: Does the pathophysiology of stroke in AF implicate LAA thrombus as the sole or predominant cause? Can the LAA be reliably and safely excluded or eliminated? And lastly, what is the evidence that LAA occlusion reduces stroke compared to either no treatment or warfarin?

Methodology

In considering a meta-analysis of LAA occlusion on embolic outcomes, it was apparent that insufficient data existed to pool. We, therefore, undertook a narrative review of the available literature.

Pathophysiology of Stroke in Atrial Fibrillation

The echocardiographic evidence suggests that many strokes originate from the left atrium in AF patients. However, investigators have come to recognize that important factors other than stasis leading to thrombus formation in the LAA are involved, including systemic atherosclerosis, disorders of coagulation, and increased platelet activation. In a study of 72 nonvalvular AF patients with completed ischemic stroke undergoing echocardiography, Okura et al. demonstrated that other sources of embolism including patent foramen ovale, atrial septal aneurysm, and particularly proximal aortic atherosclerotic plaque, can be found in over 50% of patients.[27] The clinical relevance of these findings is suggested by a post-hoc analysis of the SPAF I-III trials.[28] The 217 strokes that occurred within these trials were classified as cardio-embolic versus non-cardioembolic according to clearly stated criteria. Of the classifiable strokes, 32% were presumed to be non-cardioembolic. Further, Blackshear's echocardiographic sub-study of 770 patients in the SPAF III trial highlighted the burden of atherosclerosis in AF

patients. Fifty-seven percent of these patients were noted to have plaque within the thoracic aorta.[29] The absence of such plaque in AF patients who are considered high-risk for thrombo-embolism is associated with a lower than expected stroke risk, even without adequate anticoagulation (1.2%/yr, 95%; CI 0.2% to 8.7%).[30]

AF patients who are at elevated risk of thrombo-embolism have been demonstrated to have systemic factors that increase the risk of thrombo-embolism. Endothelial dysfunction (ED) has been associated with AF as documented by reduced plasma nitrite/nitrate levels and impaired increase in acetylcholine-mediated blood flow.[31] ED is associated with oxidative stress and pro-inflammatory agents. AF is also associated with a systemic hypercoagulable state. Platelet function is enhanced with increased plasma levels of β-thromboglobulin and platelet factor 4.[32] Systemic markers of activation of the coagulation cascade, such as thrombin-antithrombin II complex, D-dimers, fibrinogen, and prothrombin fragments 1 and 2 are also increased.[33] In summary, AF patients have significant atherosclerotic burden and a systemic prothrombotic state that increases the risk of thrombosis and embolism from multiple sources in addition to the LA, such as aorta, left ventricle and cerebral vasculature.

From these data, one can speculate that in patients with AF, the LAA likely accounts for much less than 90% of strokes, suggested by echo studies. As the efficacy of LAA occlusion therapy for stroke prevention in atrial fibrillation will depend on the proportion of strokes that are actually caused by LAA thrombus, the uncertainty surrounding the etiology of stroke in AF requires that the concept of LAA occlusion for prevention of stroke must be proven in well-designed trials before it is utilized in routine practice.

Technical Issues and Safety

Two different general approaches are being developed for excluding the LAA from circulation: a surgical approach that amputates or externally occludes the LAA and a percutaneous approach that uses devices to occlude the appendage (Figure 2). The success and safety of both approaches are incompletely understood. In our own pilot study, the Left Atrial Appendage Occlusion Study (LAAOS), over-sewing the appendage without amputation produced successful exclusion in only 45% of patients. This rate increased to 72% if a stapler device was used; however, failure was secondary to the presence of a residual stump and not due to leaks.[2] Schneider et al. reported on a small number of patients in whom the LAA was suture-closed from within the atrium. TEE demonstrated complete closure in only 1 of 6 patients at a mean of 51 days post-operative.[34] The incomplete closure was observed to result in increased blood stagnation and higher velocity at the appendage os, which might actually increase the risk of stroke. This is supported by a case report of a patient with stroke in whom the only source identified was an incompletely occluded LAA containing clot.[35] Kanderian et al. reported no leaks with excision and suture closure of the appendage in a series of 137 patients, but 27% were left with residual stump > 1 cm.[36] The clinical implications of leaving a residual stump are unknown.

Blackshear et al. have published on the thoracoscopic obliteration of the LAA using loop snares or staples as an isolated procedure in 15 patients.[37] This series raised safety concerns in that 3 of the 15 patients suffered serious adverse events related to the procedure. One patient required an urgent thoracotomy to control bleeding, one suffered a prolonged air leak and one developed refractory cardiac failure. Within the LAAOS pilot, 15% (8/52) of patients having the LAA occluded experienced a tear necessitating additional sutures; not causing any major

morbidity in an on-pump setting, but raising concerns about the safety of off-pump procedures. These procedural risks, combined with evidence suggesting the LAA elimination may decrease cardiac function, impair hemodynamic response to volume and pressure changes, impede thirst, and promote heart failure suggests that the effects of removing the LAA may not be benign.[38] From the surgical standpoint, the most reliable and safe way to exclude the LAA has not yet been established.

The percutaneous approach to LAA exclusion is a newer technique and, to date, little evidence exists around their efficacy. The PLAATO device was a self-expanding nitinol frame with fixation barbs and a polytetrafluoroethylene covering that faces the left atrium. It was placed through a trans-septal approach via a catheter-based delivery system using ultrasound, fluoroscopic, and angiographic guidance. This device has been assessed within two prospective, non-randomized, multi-center pilot trials including 111 patients. Three patients did not receive the device due to presence of LAA thrombus, access issues, and tamponade. There were 7 major adverse events in 5 patients, and 9 procedure-related serious adverse events including 4 pericardial effusions, 3 requiring pericardiocentesis. The study defined implant success as mild to no leak. Eighty-seven percent showed trace or no leak and 13% showed mild leak at implant. By 6 months, of 50 patients, 64% showed trace or mild leak.[39] Whether such leaks are benign has not been demonstrated. Further, placement of these intravascular devices necessitates post-intervention ASA, clopidogrel, or OAC for a short time, which may limit its use. Concerns have also been raised around appropriate device deployment. Schwartzman et al. have raised concerns around the geometric complexity and inter-individual variation in the LAA.[40] They suggest, based on CT imaging, that current assessment of echocardiograhic information for detection of peri-device leak may be inadequate.

Results from Non-randomized Clinical Trials

No conclusive evidence exists to demonstrate that LAA exclusion reduces stroke in AF patients. Results from case series of Maze procedure patients have been cited to support the amputation of the LAA.[41] The Maze procedure attempts to eliminate AF through a series of cuts in the right and left atria, suturing them closed, and excising both atrial appendages in a similar fashion. Cox et al. published a case series of 306 patients who underwent a "cut and sew" Maze procedure.[42] The peri-operative stroke rate was 0.7% and 0.4% in the follow-up of 11.5 years, which was low. However; about half the patients in this series had lone atrial fibrillation and no risk factors for stroke (n=162) and thus had a very low anticipated rate of stroke. In the absence of randomization, it is difficult to conclude that the Cox-Maze surgery actually reduced the risk of stroke. Furthermore, the low rate of stroke could in part be the result of the restoration of sinus rhythm, rather than from the removal of most of the LAA.

LAA occlusion is often performed in association with mitral valve surgery. In another retrospective study examining 205 patients post mitral valve surgery, the success rate of closure when attempted approached 90%. Multivariate analysis demonstrated the absence of LAA ligation as an independent predictor of the occurrence of an embolic event (OR 6.7, 95% CI 1.5-31.0). When incomplete ligation was grouped with no ligation, the OR increased to 11.9.[43] However, in another similar observational cohort of 137 patients published by Almahameed et al. it was reported that 12% of patients suffered a thromboembolic event over 3.6 years.[44] Ultimately, these and several other small observational studies have failed to show consistent results. Thus, there may be promise in surgical closure, however; the best approach to accomplish this is not yet established and the definitive demonstration of efficacy for stroke protection does not exist.

Randomized Controlled Trials

There are no large surgical randomized trials of LAA closure published that examine stroke as the primary outcome in the surgical literature. The Left Atrial Appendage Occlusion Study (LAAOS) randomized 77 patients to demonstrate the efficacy and safety of LAA closure at the time of open heart surgery. The study suggested that surgical occlusion could be safely performed, however; with so few patients randomized, no conclusions could be made about clinical benefit of LAA occlusion.[2] The first RCT within the interventional literature has recently been presented at the 2009 American College of Cardiology and commented on following a FDA advisory committee review. The PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation, ClinicalTrials.gov NCT00129545) Trial was a randomized, prospective, multi-centered study that sought to evaluate WATCHMAN device closure of the LAA compared with warfarin in patients nonvalvular AF. The WATCHMAN device is a self-expanding, covered nitinol cage that is placed into the LAA via a transeptal approach using femoral access (Figure 2). There were 707 patients randomized 2:1 between device and warfarin. Two-thirds of the patients had a CHADS2 score of 1 or 2. In the device arm, 87% of patients stopped warfarin at 45 days, with 10% subsequently restarting for clinical reasons.[45]

With mean follow up of just over a year, the rates of the primary efficacy outcome of cardiovascular death, stroke, or systemic embolism were 3.4 events per 100 patient-years in the device group versus 5.0 in the warfarin group (RR 0.68 95% CI 0.37, 1.41). Stroke (hemorrhagic and ischemic) event rates were 2.6 events per 100 patient-years versus 3.5, respectively (RR 0.74 95% CI 0.36,1.76). Implantation of the WATCHMAN device was challenging. Of 449 attempted procedures, 408 were successful, with12.3% of patients

experiencing serious procedural complications, including pericardial effusions requiring drainage or surgery (5%) and acute stroke due to air or thrombus (1.1%). Four patients subsequently had to have the device removed because of device embolization or sepsis. The rate of ischemic stroke was 50% higher in the device group (3.0% versus 2.0%), in part due to events occurring early after implantation in the device group. [45]

As pointed out by Maisel, PROTECT AF trial is too small to conclusively claim non-inferiority to warfarin, reflected by the wide 95% confidence interval (0.36, 1.76) for the outcome of greatest interest, stroke. [45] A definitive randomized trial is still required.

Another way of evaluating the concept that LAA occlusion reduces stroke in AF is to perform LAA occlusion at the time of routine cardiac surgery (either CABG or valve surgery). Antithrombotic therapy would not be required or prohibited. A pilot study has been performed to assess the feasibility of randomizing adult patients undergoing any cardiac surgical procedure who have ECG-documented paroxysmal or permanent AF with a CHADS2 score of 2 or greater (Clinicaltrials.gov NCT00908700). Excluded patients are those undergoing the Maze procedure, heart transplant, complex congenital surgery, planned ventricular assist device insertion, and re-operation. The primary outcome for the full study is stroke or non-central nervous system systemic embolism. Secondary outcomes include mortality, hospitalization for heart failure, bleeding, and need for surgical re-exploration. This study will need to randomize about 5000 patients and follow them for 2-4 years to have sufficient statistical power to determine if LAA occlusion is superior to no occlusion. The advantage of this approach is that it uses a superiority design, which is more easily interpretable compared to a non-inferiority design.

Limitations

The narrative approach taken in this review has several limitations. This approach is highly susceptible to reviewer bias as it is very subjective (in determination of which studies to include, the way that they are analyzed and presented, and the conclusions drawn). We concede that it was our intention to demonstrate that, as yet, warfarin remains the god standard for stroke prevention over LAA occlusion. Further, no formal comparison of the study quality is performed, which leads to failure to consider relationship between study characteristics and results.

Conclusions

Left atrial appendage occlusion has been a promising idea for stroke prevention in AF for decades, but it still lacks conclusive proof that it is effective and safe. Given the extent of atherosclerotic disease in some AF patients and the presence of a systemic disorder of coagulation and platelet function in most high-risk AF patients, a local approach that controls only the left atrial appendage may not be sufficient. Although recent results with the percutaneous closure device are promising, the evidence of efficacy and safety are insufficient to recommend this approach for any patients other than those in whom long-term warfarin is absolutely contra-indicated. More large randomized trials of device and surgical approaches should are required. At present, antithrombotic medications will remain the standard treatments to prevent stroke in AF.

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Contributorship Statement

The introduction of this thesis is an overview of the evidence for stroke prevention through LAA occlusion prior to commencing this PhD topic. It builds the case that evidence is yet needed to establish LAAO as an alternative to OAC. As Richard Whitlock was working on the LAAOS studies, he was invited to review this topic for the Circulation. He undertook the literature review, wrote the first draft of the manuscript, and provided critical revisions to the manuscript.

Jeff Healey and Stuart Connolly contributed significantly to the manuscript design and provided critical revisions.

Figures

Figure 1 Excised left atrial appendage with thrombus extracted from within.
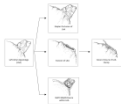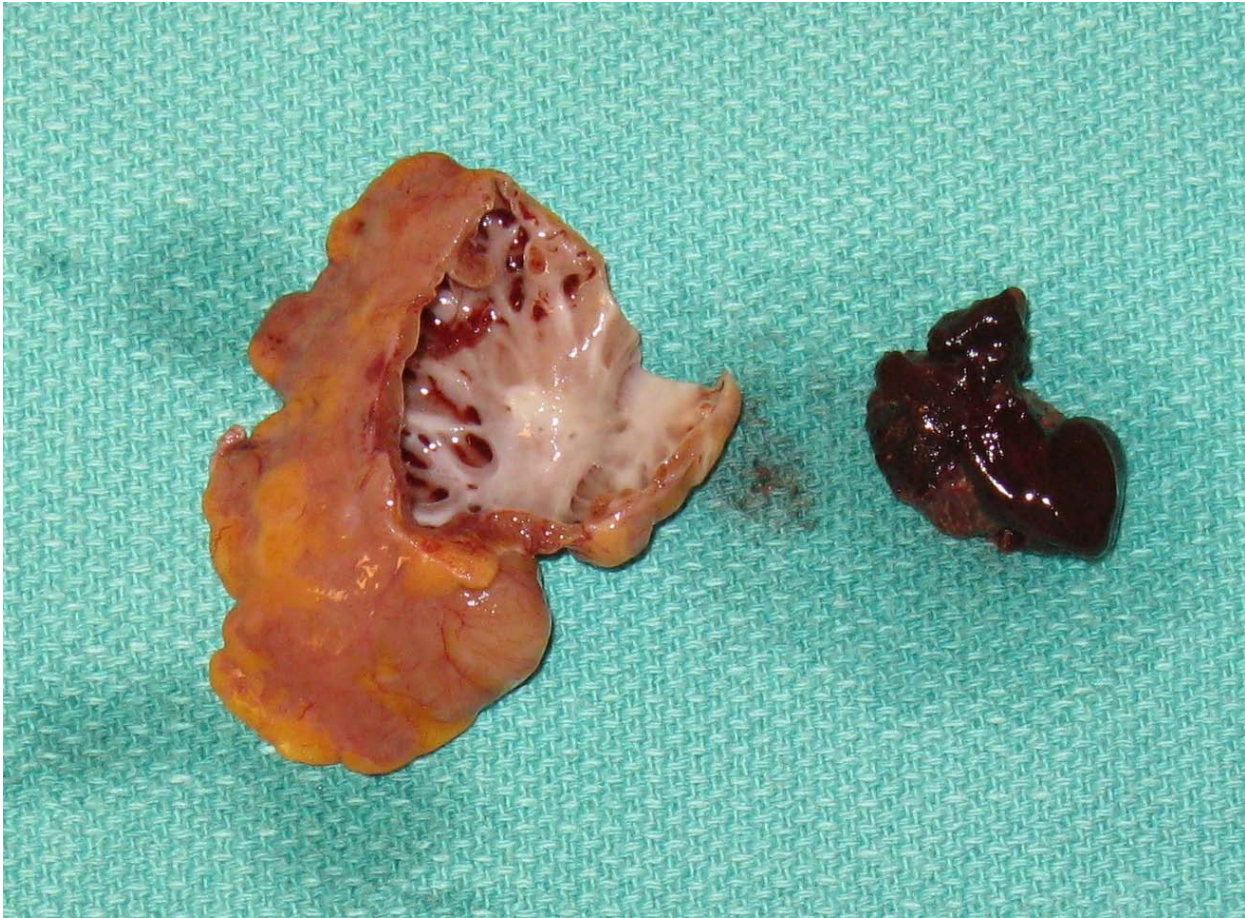
Figure 2 Methods of left atrial appendage occlusion.
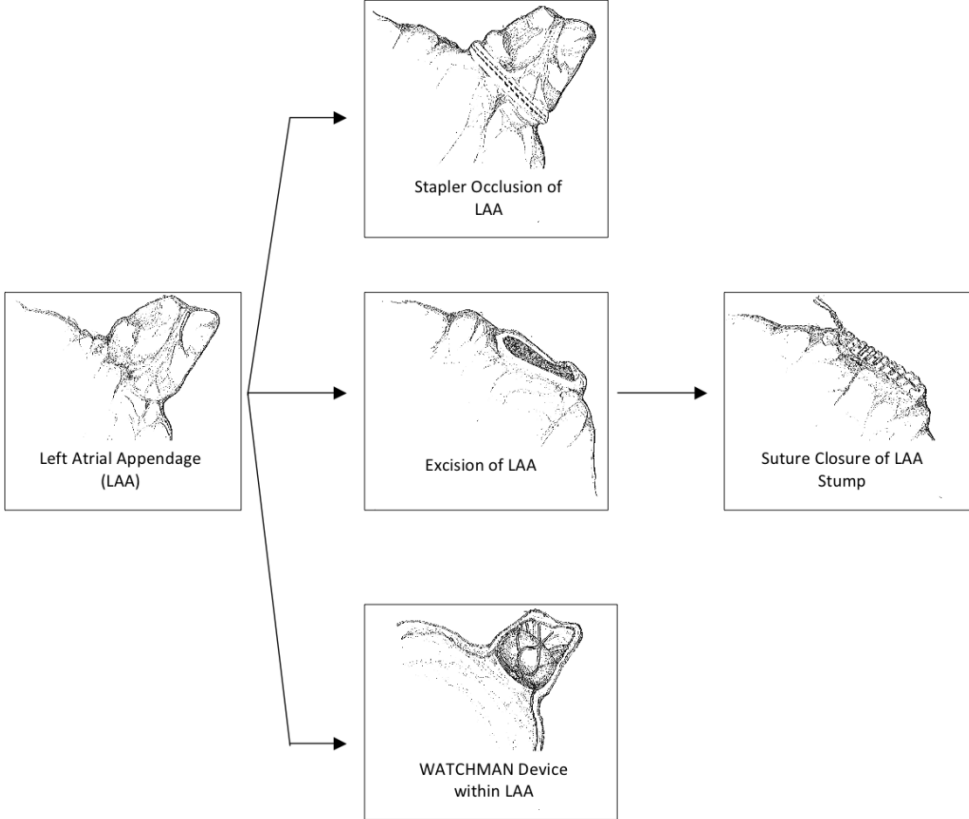
Thesis Chapter 4

Title: Left Atrial Appendage Occlusion Study (LAAOS): A randomized controlled pilot study of left atrial appendage occlusion during coronary bypass surgery in patients for stroke prevention - Long-term follow-up for stroke

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Abstract

Background

Atrial fibrillation (AF) promotes thrombus formation in the left atrial appendage (LAA) and is thus an important cause of stroke. The Left Atrial Appendage Occlusion Study was the first randomized controlled trial to study the safety and feasibility of LAA occlusion as a concomitant procedure to CABG surgery in order to reduce the risk of stroke. We now report the 8-year follow-up to examine the long-term risk of stroke and the risk of developing new AF in those without it at the time of the surgery.

Methods

Trial participants from Hamilton Health Sciences Center were contacted to complete a questionnaire which included Questionnaire for Verifying Stroke-Free Status. The primary outcome was the long-term (8-year) rate of stroke in patients that were randomized to the control or treatment group.

Results

Long-term follow-up data was acquired on all 67 patients for a median follow-up of 105 months. Nine patients (20.0%) in the occlusion group and 3 patients (13.6%) in the control group suffered stroke over the 8-year follow-up (p=0.46). Of those patients in sinus rhythm at baseline, 3.5% per year developed new atrial fibrillation. Finally, 33.3% of the occlusion arm and 18.2% of the control were on coumadin at their last known follow-up (p=0.2).

Conclusion

LAAOS long-term follow-up highlights a population with a high stroke rate, a high risk of new AF, and that a definitive trial to establish clinical benefit of left atrial appendage occlusion is still needed.

Background

Atrial fibrillation (AF) promotes thrombus formation in the left atrial appendage (LAA) and is thus an important cause of stroke, responsible for at least one sixth of all strokes in Canada. Antithrombotic medical therapy has been very effective for stroke reduction, but is limited by a risk of serious bleeding and by the problem of compliance (like all medical therapies in that they must be both prescribed and then taken continuously for years to be effective).[1,2,3,4,5] Another approach of stroke prevention is the occlusion of the site of clot formation; the left atrial appendage (LAA).[6,7] These approaches have very different mechanisms of action and it is likely that their effects are complementary and additive to medical therapy; reduction of clot formation by removal of the appendage would provide protection when antithrombotic are not prescribed, are sub-therapeutic, or are transiently interrupted.

From 2001-2002, the Left Atrial Appendage Occlusion Study was conducted at Hamilton Health Sciences and the JW Goethe University Hospital in Frankfurt, Germany; this 77 patient pilot study was the first randomized controlled trial to study the safety and feasibility of LAA occlusion as a concomitant procedure to CABG surgery in order to reduce the risk of stroke.[8] The 1-year results of this pilot trial have been previously published.[9] We now report the 8-year follow-up to examine the long-term risk of stroke and risk of developing new AF in those without at the time of surgery.

Methods

Study Population

This cohort includes 67 patients who were randomized to the control or treatment group as part of the LAAOS trial at the Hamilton Health Sciences Center, Ontario.

The rationale for and the early results of this trial have been previously published.[8,9] The trial complied with the Declaration of Helsinki and was initially approved by the local research ethics board for a 1-year follow-up. In brief, patients were considered for participation if they were undergoing elective CABG surgery with any one of the following risk factors for AF and stroke: age>75 years, hypertension and age > 65 years, previous stroke, or a history of AF. All patients signed informed consent and were randomized to LAA occlusion or control in a 2:1 fashion. Treatment was not blinded.

Between June 2001 and October 2002, 77 patients were randomized, 67 of who were local to Hamilton Health Sciences Center (HHSC). After obtaining local REB approval, HHSC trial participants were contacted by a research nurse on behalf of the patient's cardiac surgeon to determine if they verbally agree to receive a questionnaire regarding their stroke status. All patients that agreed were mailed a questionnaire which included the Questionnaire for Verifying Stroke-Free Status, QVSFS [10]). The patients were again contacted via telephone by a member of the research team to ensure the patient had received and understood the questionnaire. Data for patients that had died or had become incapacitated were obtained from the patient's medical records.

Outcomes

The primary outcome was the long-term (8-year) rate of stroke in patients that were randomized to the control or treatment group as part of the Left Atrial Appendage Occlusion Study. The most important secondary outcome was to determine the 8-year rate of new AF in patients randomized in LAAOS who did not have a history of AF at the time of surgery. Other outcomes include 8-year mortality and long-term use of OAC.

Statistical analysis

The primary analysis was designed to examine the rate of stroke by treatment group. A Kaplan-Meier survival curve for stroke-free status was generated and compared by treatment group with a Log Rank statistic. Proportional hazards were tested visually. Secondarily, for patients without a history of AF at the time of surgery, we calculated the 8-year risk (and 95% confidence internal) of developing AF. The 8-year risk of mortality and OAC were also determined. All analyses were performed on SPSS version 11.0.

Results

Long-term follow-up data was acquired on all 67 patients for a median follow-up of 105 months (96 months, 109 months). Table 1 presents the baseline characteristics of these patients. The average age of the study patients was 71 years, 30% were female, 16% had a history of AF, and 12% had a history of stroke.

Figure 1 presents the Kaplan-Meier cumulative stroke-free survival curve by treatment group. Nine patients (20.0%) in the occlusion group and 3 patients (13.6%) in the control group suffered a stroke over the 8-year follow-up, with no statistical difference by the Log Rank

statistic (p=0.46). The overall rate of stroke in the LAAOS population approximates 2% per year.

At baseline, 56 (83.6%) of the 67 patients were in sinus rhythm. Over the subsequent 8 years, 17 (30.4%) of these patients developed new atrial fibrillation; an average of 3.5% per year. The overall 8-year mortality was 22.2% in the occlusion group and 18.2% in the control arm (p=0.7). Finally, 33.3% of the occlusion arm and 18.2% of the control were on coumadin at their last known follow-up (p=0.2).

Discussion

The long-term follow-up of LAAOS has 3 key findings. First, the risk of stroke in the included population is high. Second, the long-term risk of developing AF in the included patients without AF at the time of surgery is also high. Finally, there is no clear trend for benefit nor harm of occlusion of the LAA on top of usual care.

LAAOS was the first RCT of LAAO in cardiac surgery patients. Its primary objective was to demonstrate the safety and efficacy of LAAO during cardiac surgery, which was accomplished. The long-term follow-up now completed further informs a future definitive trial to establish clinical benefit of LAAO in both AF and non-AF patients.

The long-term stroke risk of AF patients has been well described in AF registries and trials.[11,12,13] LAAOS follow-up sheds light on expected event rates if one includes patients having undergone cardiac surgery and patients at-risk of AF in a definitive trial. In this trial, patients were included if they had AF or if their CHADS$_2$ score was at least 1. Interestingly, the annual stroke rate of these patients (2%/year) exceeds those observed in the warfarin arms of AF trials such as RELY (1.57%/year) and ACTIVE W (1.4%/year); recognizing that these trials had

highly selected people with their OAC use closely monitored. [13,14] Therefore, including at-risk of AF patients appears to increase event rates compared to AF patients on standard therapy. This observation may partially be explained by the high rate of developing new overt AF. Over 80% of LAAOS patients had no history of AF when they underwent surgery. Over 8 years, the proportion free from AF fell to 58%, establishing a rate of new AF of 3.5% per year.

Currently, no adequately powered surgical randomized trial of LAA closure is published that examines stroke as the primary outcome. This is a challenging area to study. A study in excess of 15,000 patients would be required to perform a non-inferiority trial of LAA occlusion compared to best anticoagulation. Consequently, to date, only small inconclusive trials have been done. One such trial was performed with the watchman device. [3] PROTECT AF was not only underpowered but also mixed bleeding and thrombotic events in a composite outcome which although convenient, is methodologically inappropriate. In addition to its formidable cost, a definitive trial comparing LAA to OAC in high risk AF patients could pose ethical challenges. By targeting patients with AF who undergo cardiac surgery in whom the LAA could be excised or occluded safely and with a small extra effort, the LAAOS trial design overcomes many of problems presented by a direct comparison of LAA and OAC. The paradigm that LAA occlusion should replace current antithrombotic therapy must be reconsidered. The setting of cardiac surgery provides an ideal opportunity to test the concept that LAA occlusion would be complementary and adjunctive to the antithrombotic medical therapy a patient receives. LAA occlusion and antithrombotic therapy have different mechanisms of action for stroke prevention; occlusion removing the anatomic location for many potential cardiac thrombi, while antithrombotic therapy reduces the tendency for thrombi formation. Even the most effective antithrombotic therapy needs to be taken every day over years (even decades) to be fully

beneficial; a challenge even to the most compliant patient. LAA occlusion once performed could provide un-interrupted protection against thrombus formation, and potentially stroke, for life. Limited data from LAAOS long-term follow-up does not show a clear trend towards favoring LAAO. However, the data from PROTECT AF suggests much greater promise.

A positive result of an adequately powered and carefully executed clinical trial of surgical LAA occlusion versus no occlusion would be the first clear demonstration of the effectiveness of LAA occlusion and would lead to almost universal adoption of the procedure at time of cardiac surgery. It would not prove that LAA occlusion could replace anticoagulation which would have to be tested separately, but would be a tremendous encouragement to evaluate a variety of different approaches to LAA occlusion as replacements to anticoagulation. Conversely, a clear lack of benefit will definitively settle the question and allow focusing on alternative approaches. There are in access of 2 million cardiac surgical procedures performed annually world-wide, and the impact on a population level of this inexpensive, low-risk procedure could be immense. A definitive trial is a priority.

Conclusion

LAAOS long-term follow-up highlights a population with a high stroke rate, a high risk of new AF, and that a definitive trial to establish clinical benefit is still needed.

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Contributorship Statement

Richard Whitlock originated the idea for this paper and brought together the authors to formulate and debate the points in the text. He developed the study design, participated in the statistical analysis, interpretation of the data, wrote the first draft of the manuscript, and provided critical revisions to the manuscript.

Joseph Mathew contributed significantly to the manuscript design, interpretation of data, and provided critical revisions to the manuscript.

Deborah Nelson contributed significantly to the data acquisition and provided critical revisions to the manuscript.

Jeff Healey contributed significantly to the statistical design, interpretation of data, and provided critical revisions to the manuscript.

Tables

Table 1: Baseline Patient characteristics by treatment group.

Characteristics	LAA Occlusion (n=45)	Control (n=22)
Age (y, mean ± SD)	71.5 ± 6.5	70.7 ± 5.3
Women (%)	13 (28.9)	7 (31.8)
Hypertension (%)	34 (75.6)	20 (90.9)
DM (%)	13 (28.9)	6 (27.3)
History of AF (%)	9 (20.0)	2 (9.1)
History of CVA (%)	8 (17.8)	0 (0)
On Coumadin (%)	7 (15.6)	3 (30)

Figures

Figure 1: Survival without stroke by treatment group.
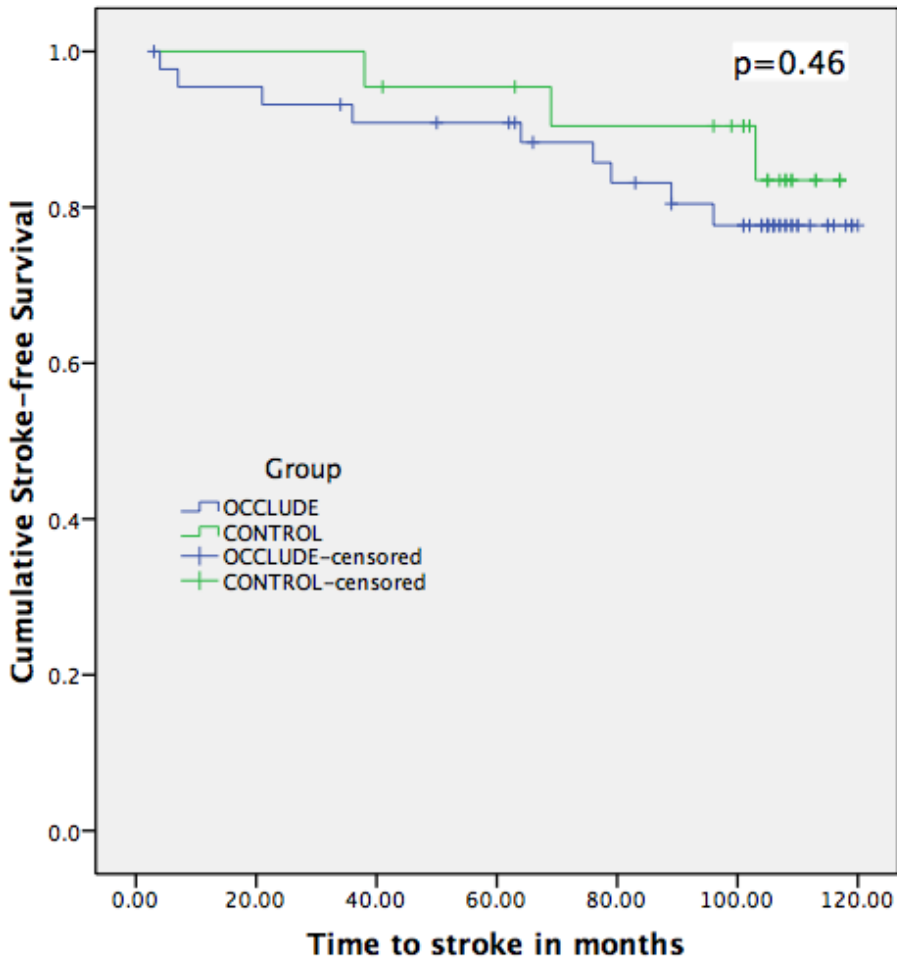
Thesis Chapter 5

Title: Left Atrial Appendage Occlusion Study II (LAAOS II)

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Abstract

Objectives: Surgical removal of the left atrial appendage (LAA) is a potential alternative to oral anticoagulation for some patients with atrial fibrillation; however evidence of its safety and efficacy are lacking. Through a cross-sectional study and a pilot trial, we explored the feasibility of a definitive randomized trial of LAA occlusion for stroke prevention in atrial fibrillation.

Methods: A cross-sectional study of 1886 consecutive patients undergoing cardiac surgery was conducted to determine the prevalence of AF and risk factors for stroke. We also randomized 51 AF patients who had increased stroke risk to LAA occlusion combined with aspirin therapy (n=26) or no occlusion and OAC (n=25) to assess: the rate of recruitment (success defined as defined as 2 patients per center per month) and the safety of LAA amputation.

Results: In the cross-sectional study, 203 patients (10.8%) had AF and 100 (5.3%) met trial eligibility. Fifty-one patients were recruited into the pilot trial over 14.5 months. No LAA occlusion patient suffered significant bleeding at the LAA site. At 30 days, 3 patients (11.5%) in the occlusion arm and 5 patients (20.5%) in the no occlusion arm experienced the composite outcome (relative risk [RR] 0.69, 95% CI 0.2 to 2.6). The predominant component of the composite was stroke with 1 in the occlusion arm and 3 in the no occlusion arm.

Conclusion: LAAOS II demonstrates that LAA occlusion can be safely performed at the time of cardiac surgery. A large trial to evaluate the clinical efficacy of LAA occlusion in cardiac surgery patients is possible in committed centers with some modifications to the design of LAAOS II.

Background

Oral anticoagulant (OAC) therapy is effective and is the standard for stroke prevention in atrial fibrillation (AF). OAC therapy does, however have well-recognized limitations which results in its underutilization; being administered to as few as 25% of patients with AF and only 70% of patients who are felt to be "ideal" candidates for warfarin.[1-7] Based on the limitations of OAC therapy, physicians and patients continue to seek an effective, low risk therapy that could eliminate the need for oral anticoagulants and their associated risks.

Most strokes in AF are embolic and are thought to originate from the thrombi in the left atrial appendage (LAA).[8] In a post-hoc exploratory analysis of the SPAF I-III trials 68% of the classifiable strokes were judged to be embolic. The proposed site of origin of embolic strokes from the LAA in AF patients is based on echocardiographic evidence. In one study of 233 patients with AF, not taking warfarin, 34 patients (15%) had left atrial thrombus, and all but 1 were located in the LAA. In another study of 272 non-rheumatic AF patients, the incidence of thrombi in the left atrial appendage was 8%. Based on a review of these and other studies it was concluded that at least 90% of left atrial thrombi are found in the LAA.[9] Based on this information it is reasonable to propose that the occlusion of the LAA would greatly reduce the risk of stroke in AF patients.[10] To date no conclusive evidence exists that LAA exclusion is effective in preventing stroke in AF patients. Patients undergoing open heart surgery are an ideal population to test the hypothesis that excluding the LAA from circulation is safe and effective for stroke prevention.

We have undertaken two pilot investigations to determine the feasibility of performing of a large RCT of LAA occlusion versus anti-coagulation in AF patients undergoing cardiac surgery. First, we performed a cross-sectional study of consecutive patients undergoing cardiac

surgery to examine the prevalence of AF in these patients and their characteristics. Second, we performed a pilot trial of LAA occlusion versus antithrombotic therapy to examine the feasibility of, and barriers to, performing an adequately powered randomized study these patients. We herein report the results of the LAAOS II study.

Materials and Methods

LAAOS II Cross-sectional Study

A cross-sectional study of 1886 consecutive patients undergoing cardiac surgery at 4 centers was generated to determine the prevalence of AF and risk factors for stroke. Variables collected included: history of AF, CHADS$_2$ score if history of AF was present, warfarin therapy, eligibility for LAAOS II and reasons not eligible, and reasons not enrolled in LAAOS II if eligible.

LAAOS II Pilot Trial Design

We undertook a 4-center prospective, randomized open trial (n=51) with blinded end-point pilot study designed to establish feasibility of recruiting into a larger RCT of LAA occlusion versus optimal antithrombotic therapy in AF patients at elevated risk of stroke undergoing cardiac surgery. The study complies with the Declaration of Helsinki and was approved by the local research ethics boards. The pilot trial and the cross-sectional study only partly overlapped; the cross-sectional data collection was stopped before the end of the pilot trial. LAAOS II was registered with ClinicalTrials.gov; NCT00908700.

Trial Participants

Adult patients were considered eligible for the randomized trial if they were undergoing any cardiac surgical procedure with the use of cardiopulmonary bypass and had a history of AF with either 1) prior stroke or TIA or 2) at least 2 of the following 4 risk factors: age >65 years, hypertension, diabetes mellitus, or heart failure/left ventricular ejection fraction <50%. Patients were excluded if they were to undergo redo surgery, planned atrial ablation procedure, planned implantation of mechanical valve, planned aortic arch repair, heart transplant, complex congenital heart surgery, planned ventricular assist device insertion, or presence of an absolute contraindication to transesophageal echocardiography; e.g. esophageal tumor, stricture, perforation, diverticulum, advanced varices, or active gastrointestinal bleeding.

Procedures

After obtaining informed consent, trial participants were randomly assigned to the occlusion arm or the no occlusion arm via a central 24 hours automated interactive voice activated randomization system. Treatment allocation was performed according to a computer generated randomization list and was stratified based on pre-operative OAC use. The occlusion arm consisted of the occlusion of the left atrial appendage along with aspirin therapy. Occlusion had to be performed using either amputation and closure (http://www.youtube.com/watch?v=aPoeoAhIjGw) or stapler device. Intraoperative TEE was required to demonstrate successful occlusion (when applicable), defined as absence of Doppler flow across the closure line and residual stump less than 1 cm. Oral anticoagulation for AF within this arm was discouraged but could be utilized if other indications arose, e.g. deep vein thrombosis, short-term for bioprostheses. The comparator was optimal antithrombotic therapy as per best evidence (no occlusion arm). This pragmatic approach was adopted with the knowledge

of the imminent approval of dabigatran and other new OACs when the pilot trial was being developed.

Objectives

The primary study objective was an assessment of feasibility of performing a large trial of LAA occlusion for the prevention of stroke and major bleed events. This was to be assessed by i) the proportion of cardiac surgery patients with preoperative atrial fibrillation who were potentially eligible for the study and ii) the ability to randomize eligible patients into an RCT in a timely fashion, defined as 2 patients per center per month. Secondary objectives were i) to assess the safety of LAA amputation and closure (as indicated by the rate of life threatening atrial tears and the need for re-exploration for hemorrhage) and ii) to estimate the rate of death, myocardial infarction, stroke, non-cerebral systemic emboli, and major bleeding. Major bleeding was defined as bleeding occurring greater than 48 hours post-operative and associated with any of the following: death, drop in hemoglobin of at least 2 g/dL, significant hypotension with the need for inotropic agents, bleeding requiring surgical intervention (other than vascular site repair), intracranial hemorrhage, intraocular hemorrhage (excluding subconjunctival hemorrhage), or the requirement for a transfusion of at least 2 U of blood. A central adjudication committee adjudicated all strokes, other embolic event events, bleeding events, and deaths.

Statistical Analysis

The target sample size of 50 patients for this pilot was one of convenience to give us enough experience to assess the ability to recruitment 2 patients per center per month into a larger multicenter study. Assessment of the secondary clinical outcomes was based on the intention to treat principle, in which all participants are included in their assigned treatment

groups regardless of actual surgical procedure performed. Group baseline characteristics were compared between the groups via a t-test, chi-square test, Fischer's exact test, or non-parametric tests where appropriate. Secondary clinical outcomes at 30 days are presented as rates and the relative risk for the occlusion arm to no occlusion arm, with 95% confidence intervals.

Results

Cross-sectional Study

The LAAOS II cross-sectional study was closed prior to the LAAOS trial's completion. A total of 1886 patients from 4 Canadian centers were entered into the study over an average of 7 months (Table 1). Of these, 203 patients (10.8%) had a history of AF and 100 patients (5.3%) were eligible for the trial. Of the 1786 patients not eligible for the trial, the most common reason was the absence of AF (93.9%), followed by planned off-pump surgery (6.7%) and planned mechanical valve implantation (3.6%). Of the eligible patients in the cross-sectional study, 39% were successfully randomized into the trial. The most common reasons for not randomizing eligible patients were patient refusal (n=24, 39.3%), physician refusal (n=16, 26.2%), and participation in another study (n=11, 18.0%). Exploring the physicians' reasons for refusal, the most common reasons cited were the belief that the appendage should be excluded and the desire to perform an atrial ablation procedure which was under captured in the eligibility assessment as these surgeons did not want their patients considered.

Characteristics of the Trial Patients

A total of 51 patients were enrolled into the trial between August 2009 and October 2010; 26 were randomized to the occlusion arm and 25 to the no occlusion arm. The baseline

characteristics were well-balanced between the groups with the exception that there was more valvular disease (p=0.01) and a trend towards more valve surgery (p=0.06) in the occlusion arm (Table 2). The mean age of the trial patients was 76 years and 76% were male. The majority had paroxysmal AF (74%) and was on pre-operative oral anticoagulation (67%).

Primary Objective

Recruitment within the trial was primarily achieved in the lead center with 46 patients enrolled over 14.5 months; 3.2 patients/month. Three additional centers were open for 6 months and recruited only 5 patients.

Secondary Objectives

Thirty-day data was available on 100% of the LAAOS II trial patients. Table 3 presents the 30-day clinical outcome data by group.

Need for Reoperation and Left Atrial Tears

Three patients in the study were re-explored for bleeding; 2 in the occlusion arm and 1 in the no occlusion arm. Neither reoperation among the occlusion patients was deemed secondary to bleeding at the appendage occlusion site. Further, within the 26 occluded patients, there were no instances of left atrial tears that were deemed to be life threatening during the procedures. The trial required demonstration of LAAO success by intraoperative TEE, defined as defined as absence of Doppler flow across the closure line and residual stump less than 1 cm. This was accomplished in all occlusion patients.

Rate of Death, MI, Stroke, Non-CNS Embolism, and Major Bleeding

At 30 days, 8 patients had experienced the primary composite efficacy outcome; 3 patients in the occlusion arm, and 5 patients in the no occlusion arm. The predominant component of the composite was stroke with 1 in the occlusion arm and 3 in the no occlusion arm. (3 were ischemic, 1 was type uncertain). Two patients in the no occlusion arm experienced a major bleed (both gastrointestinal) and 1 in the occlusion arm (gastrointestinal).

Discussion

Overall at all 4 LAAOS II sites, the recruitment was below what was expected. However, the recruitment rate was excellent in one site which was the lead center. Therefore LAAOS II suggests that a definitive trial of LAAO for stroke prevention in AF is possible in the cardiac surgical population with some modification to this LAAOS II pilot trial design and if committed centers participate. This conclusion is supported by: 1) the cross-sectional study illustrating that preoperative AF is common in patients undergoing cardiac surgery, 2) the observation that amputation and closure technique of occlusion can be accomplished safely as a concomitant procedure, and 3) a trial of rigorous inclusion criteria was successful in a motivated center.

LAAOS II cross-sectional study showed that pre-operative AF in patients undergoing cardiac surgery is common, being present in 10.8%. This rate is consistent with data from Ngaage et al. who reported from their institutional database that, between 1993 and 2002, 8.7% of CABG patients and 9.8% of AVR patients had preoperative atrial fibrillation.[11,12] Therefore, the cardiac surgery population is ideal to establish proof of concept that LAA occlusion provides clinical benefit in AF.

The results of the LAAOS II pilot trial suggests that LAA amputation and closure can be performed safely at the time of on-pump cardiac surgery performed via sternotomy. There were no instances of left atrial tears that were felt to be life threatening. The procedure adds little surgical time; in this pilot trial, the occlusion group had more patients undergoing combined procedures, explaining the slightly longer cross-clamp and bypass times observed. The experience at the lead center was that the time required to perform this procedure was equivalent to adding an additional distal coronary anastomosis (approximately 10 minutes). A requirement of the LAAOS II trial was the demonstration by intraoperative TEE of successful closure in occlusion patients which was achievable in all patients when the surgeons and echocardiographers were targeting this result and revised if necessary (although, no cases of revision were reported). In a direct comparison of occlusion methods, Kanderian et al. also previously demonstrated this method to be superior to suture exclusion and stapler techniques.[13]

The inclusion and exclusion criteria for the LAAOS II pilot were rigorous. In requiring additional risk factors for stroke, only 5.3% of patients undergoing cardiac surgery were eligible. The lead center, being the most motivated, exceeded recruitment targets set. However, recruitment at the 3 other sites was slow for several reasons including: 1) the low percentage (5.3%) of patients that were eligible for the trial based on the current design, 2) other competing studies for the patients as well as study team resources, and 3) the incomplete "buy-in" of some of the surgeons at these sites (1/3 of eligible patients were lost due to surgeon refusal), because of the desire to perform the ablation procedure and the concern about denying patients access to proven therapy for stroke prevention: anticoagulation. Opening the study to all cardiac surgical patients with a history of atrial fibrillation would double the number of patients that are eligible. As yet, the evidence that atrial ablation procedures reduce stroke risk is poor and based on non-

randomized data.[14] Furthermore, if real, it is not possible to determine if the reduced stroke risk is the result of the restoration of sinus rhythm or the removal of the most the LAA. In a future definitive RCT, we propose to include patients undergoing atrial ablation procedures, stratifying for this subgroup, and further randomize to LAA exclusion or not as a part of the procedure. We anticipate that this will increase surgeon willingness to enter patients into the study. Finally, a design on removing the left atrial appendage or not on top of usual care is to be considered. It is highly probable that benefit would still be seen if present given the limitations of OAC with respect to compliance.

LAAOS II is the second study performed by our group to examine the safety of LAAO in AF patients. The first pilot RCT, LAAOS, included CABG patients in a lower risk population than LAAOS II. [15] In that first pilot trial, two of 77 patients suffered a stroke at 1 year. In contrast, a follow-up survey of eligible non-enrolled patients showed a 5.6% stroke rate at one year. Like LAAOS II, the first pilot study also suggested safety of LAA occlusion at the time of on-pump surgery with 52 patients having their LAA stapled or over-sewn.

Study Limitations

The main limitation of this study is its small sample size.

Conclusion

LAAOS II cross-sectional study and pilot trial demonstrates that a definitive study to evaluate the clinical efficacy of LAA occlusion in cardiac surgery patients with AF is possible with modifications to the LAAOS II design. Preoperative AF is common amongst patients

undergoing cardiac surgery, occlusion techniques can be safely performed as a concomitant procedure, and randomizing the patients has been shown to be achievable. A future trial will include all AF patients and allow atrial ablation procedures with and without LAA occlusion to be performed.

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Contributorship Statement

Richard Whitlock originated the idea for this paper and brought together the authors to formulate and debate the points in the text. He developed the study design, participated in the statistical analysis, interpretation of the data, wrote the first draft of the manuscript, and provided critical revisions to the manuscript.

Stuart Connolly contributed significantly to the manuscript design, interpretation of data, and provided critical revisions to the manuscript.

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Michel Carrier contributed significantly to the manuscript design, interpretation of data, and provided critical revisions to the manuscript.

Salim Yusuf contributed significantly to the manuscript design, interpretation of data, and provided critical revisions to the manuscript.

Jeff Healey contributed significantly to the manuscript design, interpretation of data, and

provided critical revisions to the manuscript.

Tables

Table 1: Characteristics of LAAOS II cross-sectional study patients.

Total number of patients entered	1886
Total number of patients with AF or history of AF	203/1886 (10.8%)
Total number of patients NOT eligible	1786/1886 (94.7%)
Number of patients NOT eligible due to*:	
No AF	1677/1786 (93.9%)
Absence of previous stroke/TIA or 2 listed risk factors	36/1786 (2.0%)
Planned off-pump	119/1786 (6.7%)
Planned mechanical valve	64/1786 (3.6%)
Heart transplant, VAD or complex congenital surgery	7/1786 (0.4%)
Reoperation	48/1786 (2.7%)
Planned Atrial Ablation	44/1786 (2.5%)
Total number of eligible patients	100/1886 (5.3%)
Total number of patients eligible but NOT randomized	61/100 (61.0%)
Number of patients eligible but NOT randomized due to**:	
Patient refusal	24/61 (39.3%)
Health care provider refusal	16/61 (26.2%)
Participation in another study	11/61 (18.0%)
Nurse unavailable to consent	5/61 (8.2%)
Language barrier	3/61 (4.9%)
Reason unknown	2/61 (3.3%)
Cognitive impairment	1/61 (1.6%)
Total number of patients randomized	39/100 (39.0%)

* 210 patients were not eligible because of 2 or more reasons
** 2 patients were eligible but not enrolled due to 2 or more reasons

Table 2: Characteristics of LAAOS II trial patients.

Baseline Characteristics	Left Atrial Appendage Occlusion (n=26)	Standard Surgery/No Occlusion (n=25)
Age – yr (mean±SD)	77.4 ± 6.8	74.6 ± 7.6
Male – n(%)	20 (76.92)	19 (76)
Type of atrial fibrillation n(%)		
Permanent AF	4 (15.38)	5 (20)
Paroxysmal AF	20 (76.92)	18 (72)
Persistent AF	2 (7.69)	2 (8)
Previous stroke -- n(%)	6 (23.08)	5 (20)
TIA -- n(%)	3 (11.54)	6 (24)
Heart failure/LVEF < 50% -- n(%)	7 (26.92)	10(40)
Diabetes mellitus -- n(%)	7 (26.92)	7 (28)
Hypertension -- n(%)	24 (92.31)	23 (92)
Prior myocardial infarction -- n(%)	12 (46.15)	9 (36)
Atrial fibrillation at time of surgery -- n(%)	13 (50)	12 (48)
Valvular heart disease -- n(%)	21 (80.77)	12 (48)
Significant coronary artery disease -- n(%)	21 (80.77)	21 (84)
Medications in use at baseline -- n(%)		
ASA	17 (65.38)	14 (56)
Long-term VKA therapy	17 (65.38)	17 (68)
Clopidogrel	6 (23.08)	2 (8)
ARB of ACE inhibitor	14 (53.85)	14 (56)
Beta-blocker	18 (69.23)	18 (72)
Statin	19 (73.08)	18 (72)
Calcium Channel Blocker	15 (57.69)	12 (48)

Operating Room		
Number of cross-overs, n (%)	1 (3.8)	1 (4.0)
Method used for LAA occlusion, n (%)		
Stapler	1 (3.8)	0 (0)
Cut and sew	24 (92.3)	1 (4.0)
Completed using CPB, n (%)	26 (100)	25 (100)
Type of surgery, n (%)		
Isolated CABG	9 (34.6)	15 (60.0)
Valve	14 (53.8)	7 (28.0)
Other	3 (11.5)	3 (12.0)
Total CPB time (mean±SD)	132.8 ± 48.4	115.5 ± 40.3
Cross-clamp time (mean±SD)	108.0 ± 43.6	86.5 ± 39.3

Table 3: Secondary Outcomes at 30 days of follow-up.

Outcome at 30 days	Occlusion Arm (n=26)	No Occlusion Arm (n=25)	RR (95% CI)
Death, MI, stroke, non-CNS embolism, or major bleeding, n (%)	3 (11.5)	5 (20.5)	0.69 (0.2 to 2.6)
Death, n (%)	1 (3.8)	0 (0.0)	2.9 (0.1 to 67.8)
Stroke, n (%)	1 (3.8)	3 (12.0)	0.3 (0.0 to 2.9)
Non-CNS embolism, n (%)	0 (0.0)	0 (0.0)	1.0 (0.0 to 46.8)
Major bleeding, n (%)	1 (3.8)	2 (8.0)	0.5 (0.0 to 5.0)
Re-operation for bleeding, n (%)	2 (7.6)	1 (4.0)	1.9 (0.2 to 19.9)

MI-myocardial infarction, CNS-central nervous system

Thesis Chapter 6

Title: Rationale, design, and organization of the Left Atrial Appendage Occlusion Study III; LAAOS III

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Abstract

Background: Atrial fibrillation (AF) promotes thrombus formation in the left atrial appendage (LAA) and is thus an important cause of stroke, responsible for at least one sixth of all strokes in Canada. It is well established that most strokes in AF are cardio-embolic, originating from the LAA. Three approaches of stroke prevention in AF have been formulated: 1) Elimination of AF, itself, 2) Prevention of clot formation by medical therapy (either antiplatelet or anticoagulant) and 3) Occlusion of the site of clot formation, the LAA. To date, elimination or suppression of AF has not been effective against stroke, probably because no AF suppressive therapy has been able to suppress all AF episodes. Antithrombotic medical therapy has been very effective, but is limited by a risk of serious bleeding and by the problems of non-prescription, non-compliance, anticoagulation control and treatment withdrawal. A third approach, occlusion or removal of the LAA, is a logical idea that has received considerable recent attention due to positive results from a small trial of device closure, but for which there is still no definitive evidence of effectiveness. Cardiac surgery provides an excellent opportunity to remove the atrial appendage at very low risk and examine the clinical benefit of doing so.

Methods: LAAOS III is a blinded multicenter trial randomizing adult patients undergoing a cardiac surgical procedure with a history of atrial fibrillation/flutter to surgical LAA removal or not. All patients will receive antithrombotic therapy according to best local practice. Patients will have clinic visits annually with telephone follow-up every 6 months for an average of 4 years. The primary outcome is composite of stroke or non-CNS systemic embolism. Secondary outcomes include death, operative safety outcomes, major bleeding, and readmission for heart failure.

LAAOS III is a 5 year study including 2 years of recruitment with average follow-up of 4 years. 4700 patients will allow us to detect a 25% RRR with 80% power, accounting for a 2%/year loss of patients due to competing death. If the event rates are lower than expected, follow-up can be extended at low cost with this study design.

Conclusion:

LAAOS III will test if opportunistic surgical removal of the LAA at the time of other routine cardiac surgery can reduce stroke in patients with AF and is a high priority for 2 reasons: 1) A positive trial will immediately change clinical surgical practice making LAA occlusion a standard part of cardiac surgery which in turn will lead to a very large reduction in the stroke burden of patients undergoing cardiac surgery, 2) It will for the first time provide conclusive evidence that LAA occlusion reduces stroke, greatly stimulating the agenda of further research in this promising area.

Introduction

Embolic Stroke in Atrial Fibrillation and the Left Atrial Appendage

Atrial fibrillation is a risk factor for stroke, a common cause of serious disability and death.[1-3] The percentage of strokes attributable to AF varies according to age, but overall approximates 15%. AF associated stroke is associated with worse outcomes than those occurring in the absence of AF.[4, 5] Furthermore, the results of the SPINAF trial suggests that 15% of patients with atrial fibrillation suffer silent cerebral infarctions on computed tomography, the implications of which are unknown.[6]

Clinical and diagnostic imaging evidence indicates that at least 70% of all strokes in patients with atrial fibrillation are cardio-embolic from the left atrium.[7] Trans-esophageal echocardiogram (TEE) provides clear imaging of the LAA.[8] Several studies show that most atrial clots form in the appendage. For example TEE evaluation of 233 patients with AF, not taking warfarin, showed that 34 patients (15%) had left atrial thrombus, and all but 1 of these were located in the LAA. In a similar study, 272 non-rheumatic AF patients had an 8% incidence of left atrial clot, all of which were in the left atrial appendage. A review of echocardiographic and autopsy studies of atrial thrombus location concluded that 90% of left atrial thrombi are found in the LAA.[9]

The left atrial appendage (LAA) is a 2 to 4 cm tubular structure, which is attached by a narrow junction to the left atrium. It has pulsatile flow in sinus rhythm; this disappears in AF resulting in greatly reduced appendage emptying. Reduced emptying of the appendage together with increased atrial fibrosis typical of AF, and activation of blood coagulation underlie thrombus formation in AF (Virchow's triad). Removal or occlusion of the LAA removes a key component of this triad which should in turn reduce thrombus formation and embolic stroke in

AF patients.[10] However, currently no adequately powered randomized trial of LAA removal has been done. The PROTECT AF trial was reported last year. It evaluated the Watchman device which is designed to occlude the LAA by delivery of an occluding device over a trans-venous, trans-septal approach.[11] PROTECT AF investigators chose to compare device therapy to warfarin in an unblinded non-inferiority trial using a composite outcome that included bleeding, thrombotic and fatal outcomes. This trial claimed non-inferiority to warfarin but the due to the weak design (small size, unconventional primary outcome and wide non-inferiority margins) it has failed to lead to regulatory approval. An on-going study is enrolling patients but using the same design. This trial design has provided some proof of concept to the occlusion approach but will continue to be limited by the complexity of the non-inferiority design against effective active therapy (warfarin). Recent non-inferiority trials of new oral anticoagulants against warfarin have required enrolments of between 14,000 and 20,000 patients to demonstrate non-inferiority. Prior to the publication of PROTECT AF, this literature was dominated by observational studies. It was upon these observational data that the America Heart Association based its recommendation to occlude the LAA in AF patients undergoing mitral valve surgery.[43, 44] In a retrospective study examining 205 patients post mitral valve surgery, the success rate of LAA closure when attempted approached 90%. Multivariate analysis demonstrated the absence of LAA ligation as an independent predictor of occurrence of an embolic event (OR 6.7, 95% CI 1.5-31.0). When incomplete ligation was grouped with no ligation, the OR increased to 11.9.[45] In another observational cohort of 137 similar patients published by Almahameed et al. reported that 12% of patients suffered a thromboembolic event over 3.6 years.[46] Results from case series of Maze procedure patients are also often cited to support the amputation of the LAA.[47] The Maze procedure attempts to eliminate AF through a

series of cuts in the right and left atria, suturing them closed, and excising both atrial appendages in a similar fashion. Cox et al. published a case series of 306 patients who underwent a "cut and sew" Maze procedure.[48] The peri-operative stroke rate was 0.7% and 0.4% in the follow-up of 11.5 years, which was low. However; the majority of patients in this series had lone atrial fibrillation and no risk factors for stroke (n=162) and thus had a very low anticipated rate of stroke. In the absence of randomization, it is difficult to conclude that the Cox-Maze surgery actually reduced their risk of stroke. Furthermore, the low rate of stroke could in part be the result of the restoration of sinus rhythm, rather than from the removal of the most the LAA. Ultimately, these and several other small observational studies cannot provide the level of evidence needed to profoundly change practice.

If a complex procedure is required to occlude the LAA, it may be most appropriate to do this to replace warfarin, but if the LAA occlusion can be performed at time of routine surgery with almost no risk, then considering that surgical and medical therapies are almost certain to be complementary, it makes most sense to evaluate surgical LAA occlusion as an adjunct to usual medical therapy. Not only does the proposed design of our study overcome the significant limitations and obstacles of an unblinded non-inferiority trial but it innovates in testing the value of combined surgical and medical therapy which has a strong rationale. LAA occlusion and antithrombotic therapy have completely different mechanisms; occlusion removes the anatomic location for most potential cardiac thrombi, while antithrombotic therapy reduces the tendency for thrombi formation. It is a strong hypothesis that the two approaches will additive or synergistic against stroke. Even the most effective antithrombotic therapy needs to be taken once or twice every day over years (even decades) to be fully beneficial; a challenge even to the most

compliant patient. LAA occlusion once adequately performed will never re-form and thus will provide un-interrupted protection against thrombus formation, and potentially stroke, for life.

Oral Anticoagulation

Oral anticoagulant (OAC) therapy reduces the risk of stroke in AF and is recommended for stroke prevention in patients with AF and risk factors for stroke.[12] A meta-analyses that included twenty-nine trials and 28,044 patients[13, 14] reported that warfarin reduced the rate of stroke by 64% (95% CI, 49% to 74%) compared to no treatment and by 37% (95% CI, 23% to 48%) compared to aspirin. Aspirin is also effective, reducing stroke in AF by 20%. Anticoagulation is now recommended for all higher risk patients with AF, the remainder receiving aspirin. New oral anticoagulants are being introduced which also reduce stroke in AF; the direct thrombin inhibitor dabigatran and the Factor Xa inhibitors rivaroxaban and apixaban. These agents have been evaluated in large clinical trials and have been shown to be non-inferior, and in some cases superior, to warfarin for stroke reduction; with similar or less bleeding.

There are many limitations to oral anticoagulant therapy which can be summarized in the following list: 1) increased risk of bleeding; 2) need for monitoring of coagulation (INR) for warfarin; 3) patient non-compliance, a problem with all chronic medications (see next section below); 4) physician reluctance to prescribe especially to elderly patients; and 5) frequent need for therapy discontinuations for surgery, procedures and diagnostic tests.

1) Increased bleeding, both major and minor is inherent in all antithrombotic therapy. For example, in the recent RE-LY Trial, the annual rates of major bleeding were 3.4%, 2.7% and 3.1% for dabigatran 110 mg BID, 150 mg BID and warfarin, respectively; and minor bleeding rates were 13%, 15% and 16% per year. Major bleeding is serious. In both ACTIVE and RE-LY trials, major bleeding increased the adjusted risk of death several fold compared to those without

bleeding. One of the biggest problems with bleeding is that even minor bleeding may lead to discontinuation of antithrombotic therapy and exposure to stroke risk; a problem that would be mitigated by concomitant LAA occlusion.

2) The need for monitoring of warfarin therapy makes it very unattractive to patients and because warfarin is difficult to control, it is a major limitation of therapy. Keeping patients in the therapeutic range of the INR is achieved only about half to two thirds of the time even in clinical trials where patients and centres are selected.[15] In typical community practice, the time in therapeutic range falls to about 50% as demonstrated by a recent overview of studies.[16, 17] A low time in range is strongly associated with an increased risk of both stroke and bleeding.[18] Thus a concurrent therapy such as LAA occlusion that reduces stroke and is continuously effective is likely to be beneficial in patients receiving warfarin. LAA occlusion would theoretically provide protection to patients when their INR is non-therapeutic.

3) Patient non-compliance is a major limitation inherent to OAC therapy. In a major review of medication compliance for cardiovascular disease, Ho and colleagues estimated that 25–55% of patients do not take their chronic cardiac medications as prescribed.[19] Medication adherence for asymptomatic or chronic conditions is typically lower than that for acute or symptomatic conditions, and drops substantially after the initial months of therapy.[19-22] The reasons for this include patient-related factors (e.g., health illiteracy, forgetfulness, socio-economic barriers), medication-related factors (e.g., cost, complexity of the regimen, side effects) and provider-related factors (e.g., a lack of coordinated care and follow-up).[22-25] Non-adherence is strongly skewed towards under- rather than over-dosing, and is associated with an increased risk of death, disability, hospitalization, and avoidable health care costs.[19, 26-29] A recent study of point of care testing in 53 Australian general practices is instructive. The study included patients who

required OAC and only 43% of patients on anticoagulants reported consistent adherence to therapy during the study.[30] There is also substantial evidence that physicians under-estimate the degree of medication non-compliance even in patients who they 'know well'.[31] Compliance issues continue to be a problem with all medications and may be more of a problem with new anticoagulants than with warfarin, due to short half-lives and lack of need to regular monitoring. Clearly LAA occlusion could provide benefit to many patients on medical therapy who are sometimes non-compliant.

4) The under-use of anticoagulants is widely documented in virtually every country where this has been studied (Table 1).[32-38]. Many patients (up to half) are unsuitable for warfarin for a variety of reasons and some will remain unsuitable for the new anticoagulants. In the CCORT AF study, using prescription claims databases in Alberta, British Columbia and Ontario from 1997 to 2000, less than one-half of AF patients filled a prescription for warfarin within 90 days of discharge for an AF hospitalization.[36] After initiation of warfarin, discontinuation is very common. In one large administrative database registry from the United Kingdom, Gallagher et al reported warfarin discontinuation rates of 50% within a 4 year follow-up period (Figure 1). A very recent analysis of Ontario Drug Benefit claims data in 125,195 patients >65 years with atrial fibrillation who initiated warfarin therapy, found that almost one third (31.8%) discontinued warfarin within 1 year of initiation, and the median time to discontinuation was 2.9 years (Tara Gomes, University of Toronto, personal communication). The main limitation of warfarin is concern about bleeding and this often prevents its use in otherwise suitable patients.[39, 40] This suggests that even with the new anticoagulants, non-use and discontinuation of anticoagulants will be a problem; one that can be mitigated potentially by LAA occlusion.

5) Interruption of anticoagulant therapy for surgery, procedures and diagnostic tests is very common in patients with AF. In the RE-LY Trial, dabigatran and warfarin patients were off of their anticoagulant study medication 13.6% of the time during the two years of follow up. Considering that these patients were being followed very closely by a dedicated study nurse and investigator who encouraged study medication compliance and re-initiation of therapy after a discontinuation, it is likely that rates of anticoagulation non-compliance are much greater in usual clinical practice; and LAA occlusion can potentially be very useful in this situation.

We have detailed the fundamental limitations of OAC therapy and how LAA occlusion might mitigate these. It is also important to recognize that LAA occlusion is not a panacea and that it might not be a suitable stand-alone therapy. AF is associated with a systemic hyper-coagulable state. Platelet function is enhanced with increased plasma levels of thromboglobulin and platelet factor 4. Systemic markers of activation of the coagulation cascade, such as thrombin-antithrombin II complex, D-dimers, fibrinogen, and prothrombin fragments 1 and 2, are also increased. Although most thrombi form in the left atrial appendage, some likely come from aortic plaque, the left ventricle and elsewhere. Thus a systemic antithrombotic therapy is likely a very good complement to a focused surgical intervention that targets only one source of embolism, albeit the most important one.

In summary we hypothesize that LAA occlusion will reduce stroke and will benefit virtually all AF patients if it can be performed at very low-risk at the time of routine cardiac surgery. A positive result of an adequately powered and carefully executed clinical trial of surgical LAA occlusion versus no occlusion would also be the first unequivocal demonstration of the effectiveness of LAA occlusion. A positive trial would likely lead to almost universal adoption of this procedure at time of cardiac surgery, because it takes little time to perform and it

is an easy procedure for any cardiac surgeon. It would NOT prove that surgical LAA occlusion could replace anticoagulation, something that would have to be tested separately at a future time, but it would result in a major reduction in stroke and it would be a tremendous encouragement to evaluate a variety of different approaches to LAA occlusion as an additive intervention AND as a replacement to anticoagulation.

Methods

Trial Design

LAAOS III is a multicenter randomized blinded trial of surgical left atrial occlusion in patients with atrial fibrillation/flutter who are undergoing cardiac surgery. Occlusion or not will occur in addition to usual care including oral anticoagulation. Patients, health care providers (except the operating surgeon, who will not collect data for the trial), data collectors, and outcome adjudicators will be blind to treatment allocation.

Trial Population

Inclusion Criteria

a. Patients 18 years of age or older undergoing a clinically indicated cardiac surgical procedure with the use of cardiopulmonary bypass, AND

b. A documented history of atrial fibrillation or atrial flutter, AND

c. Signed informed consent

Exclusion Criteria

a. Off-pump surgery, heart transplant, complex congenital heart surgery, and ventricular assist device insertion as sole indication for surgery, reoperation,

b.   Previous placement of a percutaneous LAA closure device.

Trial Intervention

The intervention being tested is surgical occlusion of the LAA in addition to usual medical care including oral antithrombotic therapy. The trial will permit the following techniques of LAA occlusion: 1) amputation of the LAA and closure or 2) stapler closure of the LAA. Intraoperative TEE is to be utilized to determine successful closure of the appendage. Successful occlusion is defined as TEE Doppler assessment demonstrating an absence of flow across the suture line and a stump of <1 cm. If the closure is not successful by this definition, additional maneuvers should be performed to rectify (e.g. additional sutures, additional staple line) as long as the surgeon feels that it is safe to do so. In patients with pre-operative appendage thrombus, the LAA must be opened to surgically remove the thrombus prior to the occlusion. No off-pump cases will be allowed. An atrial ablation procedure can be performed; however, if randomized to non-occlusion, the LAA must not be occluded.

The control group will not have the LAA occluded and will receive usual care including antithrombotic therapy.

Randomization

Consenting patients will be randomized by a web-based randomization system after patient identification and key clinical data have been provided. This system has been used to randomize more than 300,000 patients in several trials that Population Health Research Institute (PHRI) has conducted. An email identifying the allocated treatment will be automatically generated to the operating surgeon. Randomization will be stratified by site.

Blinding Strategy and Reducing Bias

This trial will blind relevant groups to the intervention allocation data; patients, cardiologists, family doctors, PHRI Project Office, and outcome adjudicators. The surgeon will know the allocation but will agree not be involved in the ongoing antithrombotic management or data collection. The dictated surgical report will only note that the patient has been enrolled in the LAAOS III trial and randomized to LAA occlusion or not. The patient's written physician notes will however indicate whether the LAA was occluded or not as this information is potentially required post-operatively in case of bleeding. Surgeons typically have little say in the on-going antithrombotic therapy of patients on whom they operate for reasons unrelated to the AF. This approach has been used successfully in previous trials such as the CIHR-funded Resynchronization/Defibrillation for Ambulatory Heart Failure Trial (RAFT).[50] RAFT compared two types of implantable cardioverter-defibrillators (with and without cardiac-resynchronization therapy). Central unblinding of the treatment allocation will be available 24/7 through a study specific 1-800 phone number.

An international team of adjudicators, blinded to group allocation, will adjudicate all strokes, major bleeds, and other vascular events. We will use validated procedures to mitigate bias and the underreporting of events used in trials such as ACTIVE-A and W and most recently, RELY. Documents will be reviewed in local languages after independent blinding. All transient ischemic attacks will be reviewed to ensure a stroke has not been missed. To detect possible unreported events, symptom questionnaires will be regularly administered to patients and adverse events and hospitalization reports were scrutinized for unreported primary or secondary outcomes. The will be no review of summary statistics by treatment group and thereby, no knowledge of emerging treatment effect.

Patient Follow-up

1-Perioperative follow-up (at hospital discharge and at 30 days)

2-Long term follow-up: Clinic visits alternating with telephone follow-up will occur every 6 months. During the follow-up visits and calls, the validated questionnaire for verifying stroke free status (QVSFS) will be administered which has been validated for telephone use.[51] With cardiac surgery being centralized in many regions, in person clinic follow-up for some patients may be impossible. For example, Hamilton Health Sciences in southern Ontario operates on patients who live in the far north of Ontario. In such circumstances, telephone follow-up for all visits will be permitted.

Antithrombotic management

Because the surgeon is not blinded to the occlusion intervention, they are encouraged to leave the management of antithrombotic therapy for AF to the primary cardiologist or thrombologist, ensuring the usual pattern of care for the patient in this regard. All patients will receive usual antithrombotics/antiplatelet.

Trial Outcomes

Primary Outcome

The primary outcome of LAAOS III is the first occurrence of stroke or non-CNS systemic embolism (definitions below which have been used in ACTIVE-A, ACTIVE-W, and RELY)[52, 53].

1) Stroke: Diagnosis of stroke will require focal neurological symptoms with rapid onset, lasting at least 24 hours. All strokes will be classified as definite ischemic, definite hemorrhagic or type uncertain.

2) Non-CNS Systemic Embolism: Non-CNS systemic embolism will be judged to occur where there is a clinical history consistent with an acute loss of blood flow to a peripheral artery (or arteries), which is supported by objective evidence of embolism.

Secondary Outcomes

1. Occurrence of death

2. Operative Safety Outcomes:

   a. 30 day mortality

   b. Chest tube output in mL in the first post-operative 24 hours

   c. Rate of post-operative re-exploration for bleeding.

   d. Transfusion requirements: autologous blood, homologous processed red blood cells, whole blood, plasma, platelets, cryoprecipitate will be recorded for 24 hours after surgery.

   e. Rate of left atrial tears deemed by the surgeon to be life-threatening

3. Myocardial Infarction. Perioperative MI (<48 hours) is defined as the presence of new Q-waves or a new left bundle branch block on electrocardiogram, combined with a biomarker (CK-MB or troponin) elevation of more than 5 times the upper reference limit. Late MI (>48 hours) is defined as ischemic symptoms, changes consistent with myocardial infarction (new significant Q waves in two contiguous leads) or evolving ST-segment or T-wave changes in two contiguous leads signifying ischemia or new left bundle branch block (LBBB) or ST segment elevation and elevated cardiac markers (troponins or CK-MB) in the necrosis range. Myocardial injury occurring after a percutaneous coronary intervention (PCI) are included in the late perioperative Myocardial Injury group but are defined as elevation of cardiac

markers ≥ 3 times upper limit of normal (ULN) within 24 hours of percutaneous coronary

intervention (PCI) or characteristic evolution of new ECG changes.

4. Readmission for heart failure. The definition of new heart failure requires both clinical (i.e.

any of the following signs: elevated jugular venous pressure, respiratory rates, crepitations,

or presence of S3) and radiographic evidence (e.g. vascular redistribution, interstitial

pulmonary edema, or frank alveolar pulmonary edema).

5. Major bleed: Bleeding that is defined as bleeding greater than 48 hours post-operative and is

associated with any of the following: death, drop in hemoglobin of at least 2 g/dL, significant

hypotension with the need for inotropic or vasopressor agent, bleeding requiring surgical

intervention [other than vascular site repair], intracranial hemorrhage, intraocular

hemorrhage (excluding subconjunctival hemorrhage), or the requirement for a transfusion of

at least 2 U of blood. We recognize that this outcome is unlikely to be effected by the

proposed intervention. However, tracking of this event is seen as important for possible

future studies.

Health Service Research Outcomes

The economic analysis of LAAOS III will include the assessment of surgical costs and

resource consumption over the long-term follow-up. (Appendix) Our hypothesis is that left atrial

appendage occlusion will be a dominant strategy i.e. clinically effective and with minimal

increase in overall costs. Therefore, the economic analysis will focus on the cost of each surgical

procedure in the participating countries (which can vary depending on the choice of occlusion

method; suture versus device) and the cost of stroke in each group.

Statistical Considerations

Proposed sample size

This study will enroll 4,700 patients with an average follow-up of 4 years which will allow us to detect a 25% relative risk reduction (RRR) in the primary outcome with an expected control event rate of 2.5% per year. This trial would have 80% power, accounting for a 2%/year loss of patients due to competing death. This sample size is contingent on reasonable assumptions about the patient risk and the types of antithrombotic therapy that patients will receive during follow up. If the event rates are lower than expected, follow-up can be extended with this study design. Table 2 presents required sample size by effect size and power.

The enrolment requirement of this trial depends primarily on two parameters: the expected event rate in the control arm and the treatment effect expected from LAA occlusion. We can estimate the event rate in the control arm of the study from the event rates on various antithrombotic treatments in recent trials (Table 3) if we have a good estimate of the $CHADS_2$ score. We have performed a registry of 1886 patients in which we observed that the mean $CHADS_2$ score of patients with AF coming to cardiac surgery was 2.3.

Table 4 shows the expected treatment effects of LAA occlusion in different sub-groups of patients expected to be enrolled into the study. As can be appreciated from Table 4, to properly estimate the control event rate we also need to estimate the rate of use of different antithrombotic medications during follow up. Numerous surveys indicate that oral anticoagulants are used in only about 50% to 60% of high-risk patients with AF due to difficulties with control of the INR, bleeding risk, patient reluctance and physician behavior. The use of oral anticoagulants will tend to increase over the next few years as the new anticoagulants are introduced; however, there will still remain a substantial number of patients who either take aspirin or no therapy due to refusal

to take an anticoagulant, difficulty with INR management, high cost of new anticoagulants, development of renal failure which increases the risk of anticoagulation. Therefore we estimate that the number of patient-years of follow on aspirin or no antithrombotic therapy will be 35% ±5%. We have very good estimates of the rate of stroke or systemic embolism for these patients from ACTIVE A and AVERROES (3.7% per year on aspirin and 5.1% on no antithrombotic therapy).

Because of cost issues and familiarity, we estimate that warfarin and other Vitamin K antagonists will remain the most common oral anticoagulants used (45% of patient-years of follow up). There will be gradually increasing use of dabigatran and the Factor 10a inhibitors over the next 5 years. It is estimated that 20% of patient years of follow-up will be on dabigatran, rivaroxaban, or apixaban. We estimate, based on the recent large trials, that the primary event rate in control patients taking warfarin will be 1.7% per year and in those taking one of the new anticoagulants it will be 1.5% per year. Thus the overall annual event rate in the control arm without LAA occlusion is estimated at 2.5% per year.

This study is powered to have 80% power to detect a 25% relative risk reduction. This treatment effect is reasonable because the PROTECT AF trial of device closure suggests that the effect of LAA occlusion is similar to that of warfarin, although the mechanism is obviously different and the effect of LAA occlusion will be additive to that of medical therapy. Table 4 shows that the largest effect will likely occur in those receiving no therapy or aspirin. The most recent data comparing an oral anticoagulant to aspirin in AF patients comes from AVERROES, where the reduction in ischemic stroke with apixaban compared to aspirin was 63% (HR = 0.37 (95% CI 0.25–0.55) p <0.001. For patients prescribed an oral anticoagulant, the treatment effect of LAA occlusion will be more modest but not trivial. The benefit of the surgical removal of the

LAA will occur during warfarin therapy when patients are out of target therapeutic range (30-50% of time) and during therapy with any oral anticoagulants when there is non-compliance (which is very common); and interruptions for procedures and surgery, which are also common. In RE-LY, 25% of patients had at least one interruption of therapy for procedures. Overall in RE-LY patients were off study medication 14% of time. Based on these considerations a 25% relative reduction in stroke or systemic embolism with LAA occlusion in patients prescribed with oral anticoagulants is reasonable. The overall treatment effect of LAA occlusion on top of usual care is the blended total of these rates which is a 36% relative risk reduction. For the purpose of this trial, we plan to have sufficient statistical power to detect a reduction of 25%.

Planned recruitment rate

We plan to recruit 4700 patients over 2 years across 70 centers globally, expecting an average of 3 patients randomized per center per month. Our group has completed a pilot study (LAAOS II) to explore the feasibility of these recruitment targets. LAAOS II began screening patients at HHSC on August 10th, 2009. With more rigorous entry criteria than those proposed, HHSC recruited 46 patients over 14.5 months; 3.2 patients/month.

PHRI has led many successful international clinical trials. Recruitment amongst the centers will be tracked closely by the central study team. Initiation visits to the participating centers will be performed to ensure efficient and proper process across the sites. Our intent is to involve 60 centers world-wide with established investigators from Canada, the United States, China, Australia, Holland, Philippines, Belgium, South Africa, Italy, and Germany.

Data Analysis

Main Analysis

The reporting of the analysis results will follow the CONSORT guidelines (www.consort-statemet.org). We will tabulate the number outcomes by treatment group using the intention to treat principle. A time-to-event analysis will be used to test the primary outcome variable. The primary outcome (stroke or peripheral systemic embolism) will be presented using Kaplan-Meier survival curves and the treatment effect as measured by the hazard ratio and 95% confidence interval will be derived by the Cox proportional hazards model. A p-value of <0.05 for the proportional hazards model will be considered as significant. The proportional hazards assumption will also be tested by graphical means. This analysis will also be performed on the secondary outcome of 'death or primary outcome'. To check on our assumption that the effect on death will not distort the intervention effect on stroke, the 'proportional subdistribution hazards' regression model will be fitted. This Competing Risk Regression model considers the intervention effect on the subhazard function accounting for the competing risk of death. All other secondary outcomes will be compared via a t-test, chi-square test, or non-parametric tests where appropriate. The primary outcome will be analyzed at a median follow-up of 4 years.

Secondary Analysis

We will tabulate the number of secondary outcomes by treatment group. The main analysis will be performed on the secondary outcome of 'death or primary outcome' and its components. The other secondary outcomes of readmission for heart failure, operative safety outcomes, and major bleed will be compared via a t-test, chi-square test, or non-parametric tests where appropriate. Additional Cox models will be used to evaluate interactions between treatment and subgroups of interest (Table 5): antithrombotic used, amputation and closure

technique versus other, CHADS$_2$ score, atrial ablation procedure, and rheumatic heart disease. We will infer a subgroup effect if the interaction term of treatment and subgroup is statistically significant.

Interim Analysis

The independent Data Safety Monitoring Board (DSMB) will ensure patient safety, receive and review interim analyses of efficacy data, provide feedback to the Steering Committee, and ensure the study follows the highest standards of ethics. Over the median follow-up of 4 years, we expect 376 primary outcome events. Two formal interim analyses will be undertaken when 50% (188 events) and 75% (282 events) of the expected events have occurred. Conservative statistical guidelines for data monitoring have been developed and will follow the modified Haybittle-Peto rule (which has been used in trials such as HOPE, OASIS-2, 3, 4, 5, and 6 trials and several other ongoing trials that we are conducting). For efficacy, reductions in events of ≥ 4 SD in the first interim analysis and ≥ 3 SD in the second will be used. To be considered significant these predefined boundaries will have to be exceeded in two consecutive analyses performed three or more months apart. Given the extremeness of the monitoring boundaries and the paucity of interim analyses, no adjustment will be made to the final p-value at the trial end. The DSMB in making a recommendation for early stopping will also consider the consistency of the secondary endpoints and any relevant external data. For safety, increase in the rates of the primary outcome of ≥ 3 SD (first look) and ≥ 2 SD (second look) will be used as a trigger for discussion of early stopping and reporting. A decision to continue or stop the trial would be based on a number of factors in addition to the statistical significance of the main results, including consistency of the pattern of the data over time and an assessment of net benefit-risk ratios. At any time during the study, if safety concerns arise the

DSMB chairperson will assemble a meeting of the full committee. The DSMB will make their recommendations to the steering committee after considering all the available data and any external data from relevant studies.

Trial Organization and Funding

The Population Health Research Institute (PHRI) at McMaster University and Hamilton Health Sciences is the study coordination center and is primarily responsible for the, organization of the study, development of the randomization scheme, the study database, data internal consistency checks, data analysis, and coordination of the centers. The trial structure includes the following groups: the operations committee, coordinating centers, national coordinators, the adjudication committee, the data monitoring and safety board, and the investigators. Table 6 lists the key members.

Seed funding had been acquired from the McMaster University Surgical Associates. Additional seed funding is being sought from the Canadian Network and Center for Trials Internationally (CANNeCTIN). Finally, shared full funding for LAAOS III is being sought from the Canadian Institutes for Health Research and the Medical Research Council/National Institute for Health Research.

Discussion

LAAOS III will provide a clear answer to whether left atrial appendage occlusion, performed as a concomitant procedure in adult AF patients undergoing cardiac surgery, reduces the risk of stroke. AF affects approximately 10% of patients undergoing cardiac surgery; during which time it is safe to remove thissite of thrombus formation. There are in excess of 2 million cardiac

surgical procedures performed annually world-wide. LAAOS III, if positive, would result in a major reduction in stroke or systemic embolism. Further, the trial will provide the first definitive proof-of-concept and greatly stimulate this field of research.

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Contributorship Statement

Richard Whitlock originated the idea for this paper and brought together the authors to formulate and debate the points in the text. He developed the study design, established the network of investigators, wrote the first draft of the manuscript, and provided critical revisions to the manuscript.

Stuart Connolly contributed significantly to the study design, and provided critical revisions to the manuscript.

Jessica Vincent contributed significantly to the protocol design and provided critical revisions to the manuscript.

Jeff Healey contributed significantly provided critical revisions to the manuscript.

Jack Hirsh contributed significantly to the study design and provided critical revisions to the manuscript.

Salim Yusuf contributed significantly to the study design and provided critical revisions to the manuscript.

Tables

Table 1: Use of Oral Anticoagulant Therapy to Prevent Stroke in AF: Results of Recent Surveys.

Year	Study	Published Survey Population	Treated With Warfarin, % (Patient Status)
1999	ATRIA Study[54]	11 082 US patients large health maintenance organization without contraindications	60 (high-risk patients)
2005	NABOR Study[55]	945 US patients from teaching, community, and VA hospitals	55 (high-risk patients)
2006	Euro Heart Survey[56]	2706 outpatients in 35 European countries	64
2006	Hylek et al[57]	402 US patients, _65 years old, not on warfarin at admission to teaching hospital	51 (discharged on warfarin)
2006	Birman-Deych et al[58]	16 007 US Medicare patients	49
2007	Glazer et al[59]	437 newly detected AF patients at high risk of stroke	59%
2011	Mercaldi et al[60]	119 764 nonvavlular AF Medicare patients	58.5%

ATRIA indicates Anticoagulation and Risk Factors in Atrial Fibrillation; NABOR, National Anticoagulation Benchmark and Outcomes Report.

Table 2: Sample Size for Primary Outcome Assuming Control Arm Event Rate of 2.5%/year.

Reduction in Hazard Ratio	Power		
	80%	85%	90%
25%	4700	5380	6300
30%	3170	3630	4240
35%	2260	2580	3020

Assumes proportional hazards model with control arm outcome rates of 2.5% per year, 2 year enrollment and total 5 year follow up period, 2% per year mortality/lost rate

Table 3: Annual rate of stroke or systemic embolism in current antithrombotic trials.

Agent, Trial, (n of arm)	Stroke or systemic embolism (annual rate)
Aspirin, ACTIVE A, (3782)	3.7%
Aspirin, AVERROES, (2791)	3.5%
Aspirin and Plavix, ACTIVE A, (3772)	2.8%
Apixaban, ARISTOTLE, (9120)	1.3%
Apixaban, AVERROES, (2808)	1.6%
Warfarin, ACTIVE W, (3371)	1.5%
Warfarin, RELY, (6022)	1.7%
Warfarin , ARISTOTLE, (9081)	1.6%
Dabigatran 150 mg, RELY, (6076)	1.1%
Dabigatran 110 mg, RELY, (6015)	1.5%

Table 4: Expected event rates for primary outcome and relative risk reduction with LAA occlusion on top of usual care

Therapy Component of usual care	% patients years on therapy component	Control rate of primary outcome per year	Expected relative risk reduction with LAA occlusion	Treatment rate of primary outcome per year
No antithrombotic	5	5.1	63%	1.9
Aspirin	30	3.7	63%	1.4
Warfarin	45	1.7	25%	1.3
Novel anticoagulant	20	1.5	25%	1.1
Overall Usual Care	100	2.5	36%	1.6

Table 5: Subgroups to be Analyzed in LAAOS III and Hypotheses

Subgroup	Hypothesis
Antithrombotic used	Great risk reduction will be seen in those patients not on OAC. Effect size will not differ by type of OAC.
LAA occlusion technique	Amputation and closure will have a greater risk reduction than stapler occlusion.
$CHADS_2$ score	Great benefit will be observed in patients with higher $CHADS_2$ score.
Atrial ablation procedure	The performance of atrial ablation procedure will not impact on the effect of LAA occlusion.
Rheumatic heart disease	Patients with rheumatic heart disease will see less benefit from LAA occlusion; some evidence has suggested that these patients have a great propensity to form thrombi outside of the LAA.

Table 6: Left Atrial Appendage Occlusion Study III Investigators.

Investigator	Role	Description
Dr. Richard Whitlock	Principal Applicant	Protocol development, day to day runnings of trial
Dr. Stuart Connolly	Steering Committee Chair	Protocol development, day to day runnings of trial
Dr. Jeff Healey	Co-Principal Applicant	Protocol development, day to day runnings of trial
Dr. Robert Hart	Co-Applicant	Stroke Expert, PI of INTERSTROKE
Dr. Jack Hirsh	Co-Applicant	Anti-coagulant Expert, methodologist
Dr. Salim Yusuf	Co-Applicant	Protocol development, methodologist
Dr. Kevin Teoh	Co-Applicant	Protocol development
Dr. Andre Lamy	Co-Applicant	Health Economist
Dr. Rohit Singal	Co-Applicant	Protocol development, methodologist
Dan Sessler	Co-Applicant	National lead USA
Alistair Royce	Co-Applicant	National lead Australia
Marco Alings	Co-Applicant	National lead Netherlands
Wilko Reents	Co-Applicant	National lead Germany
Domenico Paparella	Co-Applicant	National lead Italy
Yunxia Zuo	Co-Applicant	Co-National lead China
YQ Guo	Co-Applicant	Co-National lead China
Dr. Andrea Colli	Co-Applicant	National lead Spain

Figures

Figure 1

Warfarin Use in General Practice: Discontinuation

Gallagher AM, et al. *J Thromb Haemost.* 2008;6:1500-1506.
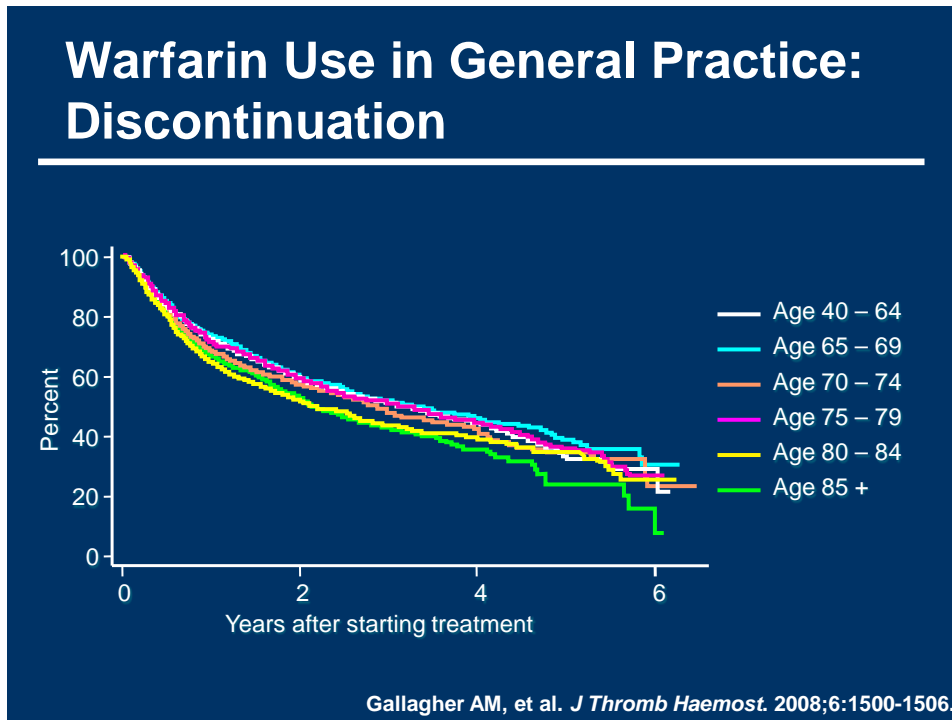
Thesis Chapter 7

Title: Left Atrial Appendage Occlusion Study III (LAAOS III) Health Economic Assessment

Principle Investigator: Dr. Richard Whitlock

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Abstract

Background: Atrial fibrillation (AF) promotes thrombus formation in the left atrial appendage (LAA) and is thus an important cause of stroke, responsible for at least one sixth of all strokes in Canada. Occlusion of the LAA is a logical idea that has received considerable recent attention due to positive results from a small trial of device closure, but for which there is still no definitive evidence of effectiveness. The Left Atrial Appendage Occlusion Study III will be a large trial that explores the risks and benefits of LAA occlusion in addition to usual medical care in patients undergoing cardiac surgery. An economic analysis will be important to assess the cost implications of this trial.

Methods: The viewpoint of a third party payer will be used for the health services assessment. Data pertaining to LAA occlusion, transesophageal echocardiogram use, systemic embolic events, bleeding events, and anticoagulant use will be collected to generate unit costs. Unit costs will be applied to patient-level utilization to arrive at a cost per patient, and the average cost within each treatment group will be compared. A stochastic cost-effectiveness analysis will be performed with the patient-level data for both clinical outcomes and costs.

Conclusion:
LAAOS III will test if opportunistic surgical removal of the LAA at the time of other routine cardiac surgery can reduce stroke in patients with AF. The economic analysis will shed important light on the cost implications of this intervention.

Introduction

Strokes due to atrial fibrillation (AF) are a significant problem, responsible for one-sixth of all strokes in Canada. Current preventative measures may take the form elimination of AF itself, which is frequently ineffective at preventing all AF episodes or pharmacological antiplatelet / anticoagulant therapy, which is often limited by side effects inherent to the medication or issues with patient compliance. A third option which has garnered much attention recently is the occlusion or removal of the left atrial appendage (LAA) in order to prevent atrial thrombi formation. To date there have been no sufficiently powered randomized trials that have investigated this option, however small trials have shown promising results. The Left Atrial Appendage Occlusion Study III (LAAOS III) will be a large trial that explores the risks and benefits of LAA occlusion/removal in conjunction with usual medical care. Because of the implications this trial may have in addressing stroke prevention in patients with AF, an economic analysis will be important to assess the cost implications of this trial.

Design

The primary outcome is the first occurrence of stroke or non-CNS systemic embolism. The secondary outcomes are: a composite outcome of death, stroke or non-CNS systemic embolism; operative safety outcomes (chest tube output in mL in the first post-operative 48 hours; rate of post-operative re-exploration for bleeding; rate of left atrial tears deemed by the surgeon to be life-threatening or 30 day mortality) or readmission for heart failure.

The primary clinical hypothesis is that patients who have had their LAA occluded / removed will benefit over those on usual care alone.

Because the method of LAA occlusion could have a significant impact on the cost implications of this intervention, analyses of different scenarios exploring these differences will be conducted. Our analysis will consider the following three situations:

1) The cost implications based on actual resource use in the LAAOS III trial (base case).

2) The cost implications if all surgical occlusions of the LAA were achieved with amputation or closure of the LAA using inexpensive surgical sutures.

3) The cost implications of using stapler closure or medical device like the ATRICURE clip to achieve occlusion of the LAA.

Although the cost of occlusion technique could vary, it is likely that LAA removal / occlusion together with usual care will be cost-saving over the study period.

Study horizon

The follow up period of the study will be 5 years, with an anticipated median follow-up period of 4 years.

Study perspective

The viewpoint of a third party payer will be used in this trial. In-hospital data pertaining to the occlusion of the LAA, perioperative transesophageal echocardiogram (TEE) use, strokes and non-CNS embolisms and oral-anticoagulant use at discharge will be collected during the trial.

Discounting

Costs will be reported in Canadian dollars (2012). Because follow-up for each patient is longer than a year, a discounting rate of 3% will be used.

Unit costs

Large multinational trials involving many countries add a new level of complexity for health economists as the sample size is fragmented and distributed between countries with different health care systems. Thus any economic analysis of a multinational trial is invariably limited by the intrinsic design of the study. The inevitable problem of variation of resources consumed[1] and unit costs from one country to the other (inter-country variations) and also within a single country (intra-country variations) could be described as "system effect". This "system effect" limits the applicability of the analysis to any of the participating countries. The approach we used in HOPE[2], CURE[3-6] and ACTIVE-A[7] was to aggregate results of resources consumption (events) from all patients in all countries and multiply them with the unit costs from specific countries of interest to calculate the total costs of the intervention and control arms. As the sample size in each country does not allow a country specific analysis, this approach is based on the assumption that there is no difference in resource utilization between these countries. This approach provides some answers but with 2 serious limitations: they are restricted to the countries of interest and these results are based on a fragment of the study population. This approach has been challenged recently and a new consensus on the best way to handle this problem within the constraints of a large multi-center international trial is starting to emerge in the literature[8] and we will adhere to its general principles.

This study will ultimately recruit 4700 patients from at least 9 countries (Canada, China, Germany, the United States, Italy, Spain, Australia, the Netherlands, and the Philippines). The issue of inter-country variation is enormous as patients are recruited from countries with different health care system such as those in this study. Given the current design of this grant, as we cannot increase the sample size to account for the variations in resource utilization between countries, we are proposing a systematic approach i.e. collecting relevant resources associated with clinical events of interest from the CRFs and collect all unit costs from <u>all</u> participating countries. Although this approach represents a significant endeavor, it is the simplest way to deal with the methodological problem we are facing and we have demonstrated the feasibility of this approach in the recently published economic analysis of the ONTARGET[9] trial.

Development of unit costs

This analysis will not focus on capturing all costs and resources consumed during this trial. Instead we will limit our focus to the cost of surgical occlusion of the LAA, and the outcomes of stroke, and non-CNS systemic embolism since these are the only anticipated differences in outcomes and procedures between the two groups. Perioperative TEE use will also be recorded. The cost of reoperations due to bleeding will also be included, as bleeding is a possible adverse event of this procedure. The cost of surgical occlusion of the LAA will be determined based on the technique chosen by the operating surgeon. Since all patients, regardless of their randomization, are undergoing a clinically indicated cardiac surgical procedure, only the cost of the LAA closure method will be taken into account. The additional time (5 minutes) required by the surgeon to surgically occlude the LAA is anticipated to be insignificant.

During the follow up period, this economic analysis will consider hospitalization due to non-CNS systemic embolism and the yearly cost of stroke. We feel that using an annual cost of stroke is a better reflection of the actual economic implications of stroke rather than a cost that reflects just the cost of the resources consumed during the index hospitalization and have use this approach in our economic analysis of the ACTIVE-A trial as well[7]. Oral anti-coagulant use during the trial period will also be captured in our analysis.

Canada

Supplies costs for the occlusion of the LAA will be obtained from HHS. As no DRG system exists in Canada, we rely on a detailed case-costing system developed at the Hamilton Health Sciences for hospitalization events[1]. This allows us to determine with precision, for cardiac diseases, the unit cost per location (a day in CCU or ICU, step-down unit, and regular ward), pharmacy costs, radiology tests, nuclear medicine investigations, and other interventions. From this system we will have detailed costs for non-CNS systemic embolism, including periprocedural costs (holding area, angiography suite). Professional fees (Ontario Fee Schedule) are added. Ontario Drug Benefit program prices will be used to establish drug costs.

Other countries

The economic team will prepare a list of unit costs needed for the analysis. These costs include the cost of the same key variables mentioned above. The national coordinator (or a

delegate) for each country will have the task of providing these costs. This can be accomplished relatively easily when a working collaboration with local hospital administrators is possible. Many investigators already have a set of unit costs available. We believe that we can develop unit costs in all countries as we are working with experienced investigators who have participated in similar trials before. We have recently completed a similar analysis in a large multinational study (44 countries) ONTARGET and see no difficulties in obtaining the costs applicable to this study. Missing cost data will be estimated by using regression analysis similar to the technique used by Reed and Schulman but using local cost data rather than DRG to perform the regression. The total cost per patient will be translated into a single currency (CAD or USD) by using PPP (power purchasing parity) ratios.

Health care utilization

Resources consumed in the occlusion of the LAA will be recorded. This will consist of the method of the occlusion and quantity of the occlusion device used. Oral anti-coagulant use will also be recorded. All resources consumed in the treatment of strokes or non-CNS systemic embolism during this study will be included in the analysis. Other health care resources unrelated to the study i.e. cancer, orthopedic surgery, etc. would be ignored unless a significant difference between randomization groups is detected. Resources utilization is divided into 5 categories: oral anti-coagulants, stroke, non-CNS systemic embolism and occlusion devices. Each category (average cost per patient) will be individually analyzed and a total average cost per patient will be provided.

Oral anti-coagulants

All oral anti-coagulants consumed by patient out of hospital will be recorded and a unit cost will be attributed. We will use the generic cost when available; otherwise the brand name cost will be used.

Analysis plan

Unit costs will be applied to patient-level utilization data to arrive at a cost per patient, and the average cost within each treatment group will be calculated. Since the cost data will not be normally distributed, a bootstrap analysis will be used to calculate standard errors and 95% confidence intervals for the difference in average costs. The bias corrected and accelerated (BCa) method will be used to obtain confidence intervals for average costs. With patient-level data for both clinical outcomes and costs available, a stochastic cost-effectiveness analysis will be performed. Comparisons between the two groups will be conducted using t-tests based on these estimates of standard error. We expect a very complete data set with the LAAOS III study. Nevertheless, some data could be missing. Patients with missing data will not be excluded from the analysis. Missing data will be replaced by the mean cost for the missing item (mean imputation).

Economic team

Dr. Andre Lamy, health economic scientist will be the project leader. He will be assisted by a health economic analyst (Wesley Tong). Statisticians from PHRI will also assist in the

analysis. These statisticians have also helped in the economic analysis of HOPE, CURE,

ONTARGET, ACTIVE-A, TIMACS, CORONARY and ORIGIN.

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Contributorship Statement

Richard Whitlock originated the idea for this paper and brought together the authors to formulate and debate the points in the text.

Andre Lamy contributed significantly to the study design, and provided critical revisions to the manuscript.

Wesley Tong contributed significantly to the study design, and provided critical revisions to the manuscript.

Stuart Connolly contributed significantly to the study design, and provided critical revisions to the manuscript.

Thesis Chapter 8

Title: Conclusions and Future Directions

7.1 Background

This doctoral thesis explored issues related to developing the evidence for left atrial appendage occlusion for stroke prevention in atrial fibrillation (AF). The literature review and original studies in this thesis highlight that oral anticoagulation remains the gold standard for stroke prevention in AF, informs the longer-term stroke rate after cardiac surgery, the incidence and impact that AF has on this risk, the rate of new AF in this population, the feasibility of a trial of LAA occlusion versus oral anticoagulation, and presents the rationale and design of a large-scale trial that will answer whether LAA occlusion results in stroke protection for AF patients having undergone cardiac surgery.

7.2 The Need for an RCT

Oral anticoagulation for stroke prevention in atrial fibrillation is a very effective therapy. However, as discussed in this thesis, it suffers from limitations including 1) increased risk of bleeding; 2) need for monitoring of coagulation (INR) for warfarin; 3) patient non-compliance; 4) physician reluctance to prescribe; and 5) frequent need for therapy discontinuations for surgery, procedures and diagnostic tests. An alternative therapy that overcomes these limitations while remaining efficacious in stroke prevention is desirable. As described in Chapter 3, the left atrial appendage (LAA) is thought to be the dominant source of thrombus in AF. If this is the case, then its exclusion from the circulation should eliminate the majority of strokes in AF

patients. Despite cardiac surgeons performing this procedure for decades(1), there is no strong evidence that it is effective. The WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation trial randomized 707 patients 2:1 between device occlusion and warfarin, and showed promise in the direction of the results.(2) However, the trial is too small to claim non-inferiority to warfarin with wide 95% confidence intervals for the stroke outcome (0.36, 1.76). Thus, oral anticoagulation remains the gold standard for stroke prevention in AF.

The Left Atrial Appendage Occlusion Study, published in 2005, was the first randomized trial of left atrial appendage occlusion during cardiac surgery.(3) This study suggested that feasibility of performing such a trial and the safety of occluding the appendage while performing cardiac surgery through a sternotomy. Further, the results showed that successful occlusion of the appendage can be achieved in 90% of cases performed by an experienced surgeon using a stapler device. The 8-year follow-up of a subset of these trial patients presented in chapter 4 highlights that the annual stroke rate of these patients (2%/year) exceeds those observed in the warfarin arms of AF trials such as RELY (1.57%/year) and ACTIVE W (1.4%/year).(4, 5) Examining the stroke outcomes by treatment group, there is no trend in any direction in this subset of trial patients.

Given the lack of evidence supporting or refuting LAA occlusion for stroke prevention in AF, a definitive trial is needed. Chapters 2 and 5 demonstrate that approximately 10% of patients undergoing cardiac surgery have a history of AF. This appears to be a safe environment to remove the LAA from circulation and provide opportunity to establish proof of clinical benefit.

7.3 What is the Optimal Design for LAAOS III?

There are several designs that may be considered to determine the efficacy to LAA occlusion in cardiac surgery for stroke prevention. The other main design that was considered to evaluate surgical LAA occlusion was that of LAAOS II; a trial which would randomize AF patients coming to cardiac surgery between LAA occlusion and anticoagulant therapy. In such an alternate design, patients having the LAA occlusion would **not** receive an oral anticoagulant. From the experience in LAAOS II, we concluded that we must first answer the question of whether the occlusion procedure adds value, irrespective of the on-going medical therapy. For the surgeon, the critical question is whether or not to do the procedure when the chest is open. Once the value of surgical appendage occlusion has been demonstrated, a subsequent study can evaluate whether or not anticoagulant therapy can be discontinued in patients after surgical LAA occlusion. Another factor favoring a trial of LAA occlusion versus no occlusion in addition to usual medical care is a practical one. This trial will be much easier to execute, will have greater acceptance from patients and surgeons, will be less expensive, and will not pose the ethical issues of asking patients to forego proven beneficial medical therapy to test a new but unproven approach. Patients will have little difficulty in agreeing to be randomized to LAA occlusion which is known to be safe, because they will not need to agree to forgo known beneficial medical therapy. Furthermore the trial we are proposing can easily be blinded (the operating surgeon will not be involved in patient study follow up). On the other hand, the trial of LAA occlusion versus best anticoagulant therapy cannot be blinded and will have significant challenges in enrolment and in long-term compliance (patients and physicians will have difficulty keeping high risk AF patients off of anticoagulants if they were randomized to LAA occlusion). Finally, the trial we are proposing will be a superiority trial which is much easier to conduct and interpret, whereas a

trial of LAA occlusion would need to use a non-inferiority design. It is generally accepted that non-inferiority of a new therapy compared to warfarin can only be reliably claimed if the new therapy preserves at least 50% of a conservative estimate (i.e. half the lower CI limits) of the benefits of VKA versus control therapy. This yields a null hypothesis that the hazard ratio of LAA occlusion versus oral anticoagulation is larger than or equal to 1.38.(6) To have 90% power and conclude non-inferiority at α of 0.025 (1-sided) level, 7,500 patients would be required assuming an annual event rate of 1.6% in the control arm. This would be a far more difficult and expensive study than a trial of establishing the superiority of LAO versus no occlusion against a background of usual care.

Another alternate approach to the non-inferiority design is another superiority design in which major bleeding is included in composite primary outcome with stroke and other systemic embolism. The hypothesis is that the LAA occlusion arm will have similar or only slightly higher embolic rates with much lower major bleeding events. The importance of major bleed is highlighted by the ACTIVE trials from which the relative risk of death from an extra-cranial bleed is 4.85, approaching the risk associated with non-hemorrhagic stroke, 7.13. Similar findings were reported by the OASIS 5 investigators. Over 25% of the patients who developed major bleeding in OASIS 5 experienced death, MI, or stroke during follow-up to 180 days.(7) Compounding the issue within AF patients, once the patient has had a major bleed and survives, the OAC is frequently stopped and the patients risk for future embolic events is increased. Therefore, bleeding is a powerful determinant of fatal and non-fatal outcomes. However, the results of such a trial may pose additional challenges in interpretation as one may have to weigh the values or preferences of major bleeding versus stroke which may vary by the perspectives of

different individuals. This is not desirable in a study that will be the first definitive evaluation of proof of concept.

The trial of LAA occlusion as an adjunct to usual antithrombotic care tests the question most directly relevant to surgeons. It is practical to perform; it can use the most rigorous clinical trial methodology and it can be done at moderate cost. If positive, it would be the first adequately powered trial to prove conclusively that LAA occlusion works, it would immediately change surgical practice, it would prevent considerable disability and death from stroke and it would greatly advance the research agenda on non-medical approaches to stroke prevention. The major challenge will be if the use of oral anticoagulation exceeds our expectations. If this occurs, some may consider the results difficult to interpret. However, I feel that the trial would provide the important information that LAA occlusion on top of optimal care is of no added benefit. A future trial of non-inferiority versus anticoagulation would not be precluded.

One could consider running both the "versus" design and the "on top of" designs concurrently as a three arm study; Arm A=OAC and no occlusion, Arm B=OAC and LAA occlusion, and Arm C=ASA only and LAA occlusion. There is no question that this design would be the most informative, demonstrating whether there is synergism of LAA occlusion and OAC, and determining whether LAA occlusion could replace OAC therapy in these patients. However, the disadvantages of this design are substantial. The complexity of running a 3 arm trial that plans for one comparison to be a superiority approach and the other a non-inferiority comparison is great and unprecedented. The sample size of such a trial would exceed 10,000 patients given the need for alpha-splitting, which creates feasibility issues with respect to recruitment and cost. Further, the experience in LAAOS II highlighted that patients would prefer to not be randomized to an arm in which the treatment includes OAC, whereas the physicians

were of the opposing view. We therefore have concern that the refusal rate for participation by both the patients and the physicians will be increased by this design. Finally, with one arm not receiving OAC, blinding becomes a major concern. To keep the trial fully blinded would come at major cost, prohibitive in a trial the will require public funding.

As described in Chapter 4, the original LAAOS pilot included patients that were deemed "at risk" for developing atrial fibrillation. This group included patients without AF and any one of the following risk factors: age>75 years, hypertension and age > 65 years, or previous stroke. The majority of the patients were of CHADS$_2$ score 2 or greater and the annual rate of new AF was 3.5%. Further, Chapter 2 highlights that elevated CHADS$_2$ score predicts stroke or death independent of heart rhythm; a CHADS$_2$ score ≥ 2 increased the risk-adjusted rate of stroke and death at 2 years from 9.9% to 18.4% in individuals with pre or post-operative AF (n=27,600) and from 6.2% to 12.5% in those without this condition (n=81,102). The CHADS$_2$ score is a validated clinical prediction rule for stroke risk in non-rheumatic atrial fibrillation(8) who were not prescribed warfarin and now is used to guide when antithrombotic therapy in AF patients. This data highlights that CHADS$_2$ is an important predictor of stroke or death even in the absence of any known atrial fibrillation, with a RR of 3.5 for CHADS$_2 \geq 3$ versus CHADS$_2$=0,1. Given this, should patients with elevated CHADS$_2$ score be included independent of heart rhythm? A major criticism is that as yet we are unable to answer if elevated CHADS$_2$ score a marker of vascular disease and the strokes are all thrombotic, or are these patients having occult AF and resultant embolic events. Without this data, we risk producing a negative trial because the intervention was not targeting the pathophysiology in this particular subgroup. Thus, in this first proof of concept trial, these patients are not included.

7.4 Limitations of the Work Done

Chapter 2 presents predictors of early and late stroke after cardiac surgery. The chapter highlights the high early hazard, the risk incurred by having post-operative new atrial fibrillation, and that the CHADS$_2$ score predicts stroke risk independent of heart rhythm. However, the study is retrospective in nature, using linked databases within Ontario, and thus has inherent limitations. First, the accuracy of codes for patient related health information can be questioned in these databases. We strived to use database codes with the best validation possible but were limited for variables such as hypertension and history of AF. Our method of looking back 10 years for ICD 9 or 10 codes for these diagnoses did yield incidences that one would expect to see in this population, which suggests that it is valid. Second, the timing of stroke relative to new post-operative atrial fibrillation during the surgical stay is unknown; claiming causality is not possible. It is possible that cardiac surgery patients who suffer post-operative stroke are at greater risk of AF and thus, POAF is not causative of stroke. Third, we are limited to variables collected within the databases. These issues can only be resolved with an appropriately designed prospective study which is described in section 7.5.

Chapter 4 presents the long-term follow-up of patients from the Hamilton General Hospital who participated in the first left atrial appendage occlusion study. This subset represents 67 of the 77 patients randomized. The study is severely limited by the small sample size and the fact that the balance obtained by randomization is damaged. No conclusion can thus be made regarding the efficacy of LAA occlusion on long-term stroke outcome. However, the chapter provides important information on the rate of stroke and of developing new atrial fibrillation in at-risk patients.

Chapter 5 presents a second pilot trial of LAA occlusion versus optimal antithrombotic therapy as well as a registry of 1886 patients undergoing cardiac surgery. Due to funding limitations, it was impossible to have the registry and the trial completely overlap. This would have provided a clearer picture regarding eligibility and recruitment success. The trial is limited by its sample size and conclusions regarding benefit of LAA occlusion cannot be made. However, important data regarding feasibility of a "versus" design was gathered.

Chapter 6 and 7 provided the rationale and design of LAAOS III; a definitive trial to establish whether there is clinical benefit to removing the LAA in patients with AF undergoing cardiac surgery. The trial design is currently limited by 5 key assumptions that need validation in a vanguard phase (to be described in section 7.5):

1) The rate of patient enrollment achievable in a global trial. In our other cardiac surgery trials including Steroids In cardiac Surgery (SIRS) and Coronary Artery Bypass Surgery Off or On Pump Revascularization Study (CORONARY), we have established a network of cardiac surgical centers that are able to recruit into clinical trials. We need to establish whether 60 to 70 of these centers can enroll 4700 patients over 2 years. This will require entry of 2 patients per center per month.

2) The rates of use of antiplatelet, vitamin K antagonist and new oral anticoagulant therapy during follow up and the CHADS$_2$ risk profile of enrolled patients. The sample size of LAAOS III is dependent on the control arm event rate. We can estimate the event rate in the control arm from the event rates on various antithrombotic therapies in recent trials if we have a good estimate of the CHADS$_2$ score and the distribution of the agents used globally.

4) The rate of successful occlusion of the LAA. Our estimates of effect size are contingent on the ability to successfully occlude the LAA. The PROTECT AF trial of device closure suggests that

the effect of successful LAA occlusion is similar to that of warfarin. We need to demonstrate that this can be accomplished in at least 90% of patients.

5) The rate of use of an atrial ablation procedure at time of surgery. Surgeons are interested in atrial ablation procedure and it potential to reduce stroke by reduced AF burden. It is important to establish what proportion of these patients will undergo this procedure to allow for potential loss of effect and to explore the feasibility of an ablation substudy, examining it effectiveness in stroke prevention.

7.5 Future directions

In addition to the work already performed or planned, two studies will developed to clarify or further knowledge gained in these thesis: 1) a prospective cohort study, VISION Cardiac Surgery, that will examine new post-operative atrial fibrillation (POAF) and its relationship to stroke risk in a prospection manner; and 2) a vanguard phase of LAAOS III to validate key assumptions made within the full trial.

7.5.1 VISION Cardiac Surgery: New Post-operative Atrial Fibrillation Substudy

Our group is in the process of developing a large multicentre, international, prospective cohort study in 15,000 patients undergoing isolated CABG, isolated valve or combined CABG + valve surgery with the primary objective of determining the incidence of death and combined major vascular events, the optimal clinical model to predict major perioperative vascular events, and relationship between postoperative troponin measurements and the risk of early and late death, vascular events, and quality of life. We call this study the Vascular events In Surgery patIents cOhort evaluatioN (VISION) Cardiac Surgery Study. A substudy of VISION Cardiac will examine the incidence of new onset post-operative atrial fibrillation (POAF) in a

representative sample of patients undergoing cardiac surgery globally. We will examine the risk of stroke incurred by the occurrence of POAF during the in-hospital period as well as over the ensuing year follow-up. The impact of antithrombotic therapies in the setting of POAF will be assessed. Finally, the risk of conversion to paroxysmal, persistant, or permanent AF in those patients developing POAF will be compared to those who did not develop PAOF.

7.5.2 LAAOS III Vanguard

LAAOS III vanguard has an identical design to the full trial. This phase will recruit the first 300 patients to validate assumptions about 5 key parameters that affect the design of the full trial, providing the following estimates within the listed margin of error, 95% of the time(9):

1) Patient enrolment. For the Vanguard to be successful, we need to be able to enroll suitable patients at a rate of 2 per month per center consistently. This will be assessed at 12 centres selected to represent the global nature of the planned Full trial. A one year recruitment period in 12 centres distributed evenly across Canada, USA, Western Europe, Australia and Asia will provide a very good assessment of whether a global cohort of 60-70 centres can enroll the additional 4400 patients required in the two subsequent years. Successful recruitment must be achieved in 90% +/- 16% of sites.

2) Rate of use of oral anticoagulation and of antiplatelet therapy during follow up after surgery. As seen in the statistical assumptions for the full trial (chapter 6), the rate of use of these agents is important to estimate the expected treatment effect of LAA occlusion, a driver of the necessary patient enrollment. We seek to validate the assumption that ASA therapy alone will be used for stoke prevention in 30% +/- 5.2% of patient years of follow up and oral anticoagulant therapy will be used in 65% +/- 5.4%.

3) Risk profile of the enrolled patients. CHADS$_2$ risk is a well validated predictor of the rate of stroke and systemic embolism. We have very good estimates of event rates according to CHADS$_2$ risk for patients on various antithrombotic therapies from the recent randomized trials. The score of enrolled patients should 2.3 +/- 0.2.

4) Rate of successful LAA conclusion, defined as absence of leak across the LAA closure line and a residual stump less than 1 cm. We seek to validate our assumption that the rate is at least 90% +/- 3.4%.

5) Rate of the performance of atrial ablation procedures for AF ablation is <10% +/- 3.4%.

If this vanguard phase validates its assumptions and shows feasibility, vanguard phase patients will be retained in the trial, and we will expand the trial to enroll an additional 4400 participants.

7.6 Summary

The chapters in this thesis provide insight into the stroke risk in cardiac surgical patients with and emphasis on atrial fibrillation. The randomized trial presented in chapter 6 will conclusively answer whether left atrial appendage occlusive in protective against stroke in atrial fibrillation. Finally, my future research agenda will further elucidate our understanding of new onset atrial fibrillation after cardiac surgery, and will provide insight into mechanism of stroke in atrial fibrillation.

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