RISK FACTOR MODIFICATION AND LEFT ATRIAL REMODELLING IN PATIENTS WITH EMBOLIC STROKE

John Leonard Fitzgerald

M.B.,B.S. (Hons.), F.R.A.C.P.

Centre for Heart Rhythm Disorders

Discipline of Medicine

University of Adelaide

and

Royal Adelaide Hospital

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To my parents Tony and Margaret,
my wife Marielle,
and our children Céleste and Blaise

Abstract

Stroke, the second-leading cause of death and third-leading cause of disability worldwide, is a condition with an ongoing recurrence rate in large part attributable to underlying medical and lifestyle risk factors. These include hypertension, hyperlipidaemia, diabetes mellitus, smoking, alcohol use, obstructive sleep apnoea, obesity and physical inactivity. Embolic stroke causes include further mechanisms such as general increased thrombotic tendency related to underlying inflammatory, auto-immune or neoplastic processes; specific intracardiac thrombus formation or passage such as that associated with prosthetic heart valves, severe left ventricular dysfunction with associated relative intracardiac haematologic stasis and veno-arterial passage through cardiac shunts such as patent foramen ovale. The majority of both incident and recurrent embolic stroke is related to the influence of underlying medical and lifestyle risk factors leading to large (or small) vessel atherosclerosis with associated plaque rupture, thrombosis and embolism, or to left atrial thrombus formation in the presence of an underlying left atrial cardiomyopathy, with or without the manifestation of clinical or sub-clinical ('silent') atrial fibrillation.

In the secondary prevention of embolic stroke, national and international guidelines strongly emphasise the benefit of control of these risk factors, each of which has an underlying scientific literature showing varying levels of evidence for reduced recurrence related to isolated risk factor control.

Despite attempts to date, what has not been seen, however, is a successful model for modifying these same risk factors comprehensively and thoroughly to achieve the reduction in recurrent stroke and cardiovascular events aimed for in the stroke guidelines. Fortunately, a model of controlling these very same risk factors has shown success in improving outcomes

for atrial fibrillation. Atrial fibrillation is a cardiac arrhythmia shown to be significantly contributed to by the effect of the same risk factors causing mechanical, structural, electrical, pro-inflammatory and pro-thrombotic changes in the left atrium. These same changes are thought to underlie the stroke risk associated with atrial fibrillation, and the risk associated with myopathic changes in the left atrium which could occur prior to the detection of atrial fibrillation.

Chapter 2 of this thesis focuses on a key sub-group known as embolic stroke of undetermined source (ESUS). With an underlying literature detailing the myopathic process thought to occur in the left atrium, this chapter proposes a protocol for a randomised, controlled trial to test the effect of aggressive risk factor modification on this process, powered for the primary outcomes of reduced incident atrial fibrillation and reduced embolic stroke recurrence.

Chapter 3 of this thesis focuses on expansion of application for risk factor modification to all patients with embolic stroke or transient ischaemic attack (TIA) thought to be related to unknown causes, atrial fibrillation, or large vessel atherosclerotic disease. These causes, which make up the majority of embolic stroke, stand to benefit from risk factor modification, and the same model of care delivery as in chapter 2 will be applied in a second randomised trial, this time with primary outcomes of recurrent embolic stroke and other major cardiovascular events.

Chapter 4 of this thesis includes a detailed outline of the effect of aggressive risk factor modification on the risk factors themselves, by comparing an intervention group randomised to aggressive risk factor control, with a control group who receive the usual current routine

management involving intermittent primary care follow-up of unspecified frequency following embolic stroke.

Chapter 5 includes a study of left atrial substrate, thought to be a key underlying cause of embolic stroke in the group with ESUS. Cardiac magnetic resonance imaging is performed to characterise left atrial myocardial scarring via demonstration of late gadolinium enhancement, left atrial volumes and surface area. Comparison is made between patients developing atrial fibrillation and those not developing this arrhythmia during follow-up with continuous cardiac monitoring, to explore the predictive value of these left atrial parameters as measured at baseline.

Chapter 6 includes a study of comparison of left atrial function and exercise performance between participants with ESUS, those with known atrial fibrillation and a control group without either of these conditions. Left atrial and left ventricular function are compared in terms of ejection fraction, strain-rate myocardial deformation imaging, and exercise capacity is compared using cardiopulmonary exercise testing according to a standardised protocol.

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

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John Fitzgerald

Centre for Heart Rhythm Disorders

University of Adelaide and Royal Adelaide Hospital

Adelaide, Australia

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Table of Contents

Abstract II

Declaration V

Acknowledgements VI

Chapter 1 1

RISK FACTORS UNDERLYING EMBOLIC STROKE AND EVIDENCE FOR MODIFICATION 1

Literature review 1

EMBOLIC STROKE: BACKGROUND 1

TOAST CRITERIA 2

Mechanisms and pathophysiology 3

RISK FACTORS AND STROKE 3

MODIFIABLE RISK FACTORS AND PRIMARY PREVENTION OF STROKE 4

Hypertension 4

Hyperlipidaemia 5

Diabetes Mellitus 6

Obesity 7

Physical Inactivity 7

Obstructive Sleep Apnoea 8

Smoking 9

Alcohol Intake 10

Atrial Fibrillation 11

STROKE RECURRENCE 13

Acute and Subacute Stroke Specific Therapies 14

Anti-Thrombotic Therapy 15

Antithrombotic Therapy and Embolic Stroke of Undetermined Source 16

Implantable Cardiac Monitoring-Guided Anticoagulation in ESUS 18

STROKE RISK FACTORS AND SECONDARY PREVENTION 22

Hypertension 22

Hyperlipidaemia 22

Diabetes Mellitus 25

Smoking 25

Obstructive Sleep Apnoea 26

Alcohol 28

Physical Inactivity 28

Obesity 29
SEX AND GENDER SPECIFIC RISK FACTORS IN STROKE 30
RISK FACTOR MODIFICATION FOR STROKE 30
Delivery of stroke risk factor modification 30
ATRIAL CARDIOMYOPATHY AND STROKE 33
LEFT ATRIAL CARDIOMYOPATHY PATHOPHYSIOLOGICAL CHANGES 34
Left atrial dilatation and mechanical dysfunction 34
Left Atrial Inflammatory Changes 36
Left Atrial Hypercoagulability 37
Biomarkers for Ageing 37
ATRIAL FIBRILLATION AND THE EFFECT OF RISK FACTORS 37
Obesity and AF 38
Physical Inactivity and AF 38
Hypertension and AF 39
Obstructive Sleep Apnoea and AF 40
Diabetes Mellitus and AF 41
Alcohol and AF 42
Smoking and AF 42
Cholesterol and AF 43
EVIDENCE FOR RISK FACTOR MODIFICATION IN AF 43
Risk Factor Modification Delivery for AF 43
CONCLUSION 46
Chapter 2 47
The PREDICTive value of aggressive risk factor modification on the development of atrial fibrillation in Embolic Stroke of Undetermined Source trial: PREDICT-ESUS design and rationale 47
ABSTRACT 48
Background 48
Objective 48
Methods and study design 48
Conclusion 49
BACKGROUND 50
Hypothesis 51
METHODS 51
Study setting and timeline 52
Funding 52

Participant Eligibility / Study Population 52
Baseline evaluation 53
Intervention 54
Usual Care 55
OUTCOMES 55
Assessments 55
Primary Outcome 56
Secondary Outcomes 56
Outcome adjudication 57
Analyses 57
Sample size calculation 57
DISCUSSION 58
CONCLUSION 58
Table 1 PREDICT-ESUS Trial Inclusion and Exclusion Criteria 61
Table 2. PREDICT-ESUS Trial Study Follow-up Schedule 62
Figure 1: PREDICT-ESUS Trial Workflow and Timeline 63
Graphical Abstract: PREDICT ESUS study design 64
Chapter 3 65
The PREDICTive value of aggressive risk factor modification on the occurrence of major cardiovascular events in patients with embolic STROKE: PREDICT-STROKE: design and rationale 65
ABSTRACT 67
Background 67
Objective 67
Methods/design 67
Summary 67
BACKGROUND 69
HYPOTHESIS 70
OUTCOMES 71
METHODS 71
Study setting and timeline 71
Funding 72
Participant Eligibility / Study Population 72
Baseline evaluation 73
Intervention 73
Risk factor Targets 74

Usual Care 76
Assessments 77
Primary Outcome 78
Secondary Outcomes 79
Outcome adjudication 79
Analyses 80
Planned Interim analyses 80
Cost-benefit analysis 80
Data collection and management 81
Sample size calculation 81
DISCUSSION 82
Previous risk factor management trials 82
Evidence for the Risk Factor Clinic model 83
LRFM in a population with embolic stroke 83
CONCLUSION 83
Table 1. PREDICT STROKE Inclusion and Exclusion criteria 86
Table 2. PREDICT STROKE Planned follow-up schedule 87
Figure 1. PREDICT-STROKE study workflow 88
Chapter 4 89
Structured Intensive Risk Factor Modification for Secondary Prevention of Ischemic Stroke. 89
Impact of a Randomized Feasibility Study 89
ABSTRACT 91
Background 91
Methods 91
Results 91
Conclusions 92
INTRODUCTION 94
METHODS 95
Study Participants 95
Randomization 96
Usual Care 96
Risk Factor Clinic 96
Risk Factors, Measures and Targets 97
Statistical Analysis 100

RESULTS 101
Study Recruitment 101
Baseline Risk Factor Profiles 101
Risk Factor Clinic Attendance 101
Change in Risk Factor Profile 102
LRFM Compared to Usual Care 102
Participant retention and Clinic attendance 103
DISCUSSION 104
New Information 104
Risk Factors and Recurrent Stroke 104
Previous Data on Risk Factor Management 107
The Case for a Dedicated Risk Factor Clinic 108
Study Limitations 108
CONCLUSION 109
Graphical Abstract 112
Figure 1: Risk Factor Clinic structured visits and Control Arm 113
Figure 2: Consort Diagram 115
Figure 3: Lifestyle and Risk Factor Management or Usual Care 116
Table 1: Baseline Characteristics 117
Table 2: Risk Factor Modification Results 119
Table 3: Risk Factors at Target 122
Chapter 5 123
Characterization of Left Atrial Volume and Fibrosis by Cardiac Magnetic Resonance Imaging Post-Embolic Stroke: Predicting Atrial Fibrillation on Implantable Cardiac Monitoring 123
ABSTRACT 124
Background 124
Purpose 124
Methods 124
Results 124
Conclusion 125
BACKGROUND 126
METHODS 126
Standard protocol approvals, registrations, and patient consents 126
Study Population 127
Cardiac MRI with LGE 127

Statistical Analysis 128
Results 128
Atrial Fibrillation 129
Cardiac MRI LGE and LA volumes, AF detected 129
DISCUSSION 130
Empirical anticoagulation 130
Subclincial AF – how much AF is enough? 130
Predicting an Atrial Cardiomyopathy 132
Clinical implications 133
Limitations 133
Conclusion 134
Table 1: Baseline Characteristics 135
Table 2: Cardiac MRI Findings 136
Figure 1: Left Atrial Fibrosis, Volume, Surface Area, and Atrial Fibrillation Detection 136
Chapter 6 137
Left Atrial Structure and Function in Embolic Stroke of Undetermined Source compared with Atrial Fibrillation (ES-AF) 137
ABSTRACT 138
Background 138
Aim 138
Methods 138
Results 138
Conclusions 139
INTRODUCTION 140
METHODS 141
Study Design 141
Study Population 141
Echocardiography 142
Cardiopulmonary Exercise Testing 143
N-terminal pro B-type Natriuretic Peptide 144
Statistical Analysis 144
Powering 144
RESULTS 145
DISCUSSION 146
Clinical implications 148

Limitations 148
CONCLUSION 149
Figure 1: Consort Diagram of patient recruitment for each group. 150
Table 1: Baseline Characteristics. 151
Table 2: Exercise echocardiographic parameters and exercise performance. 152
Table 3: Univariable and multivariable regression analysis for predictors of resting left atrial reservoir strain. 153
Figure 2: Distribution of Left atrial ejection fraction, left atrial reservoir strain and N-terminal pro-B-type Natriuretic Peptide in the 3 groups. 154
Chapter 7 155
Final Discussion 155
Chapter 8 159
Future Directions 159
REFERENCES 161

Publications and Communications to Learned Societies

Chapter 1: Literature review

Manuscript: Fitzgerald JL, Gallagher C, Middeldorp ME, Sanders P. Risk factor management in atrial fibrillation A key pillar of care. Med Today 2021;22(9):42-49.

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Chapter 1

RISK FACTORS UNDERLYING EMBOLIC STROKE AND EVIDENCE FOR MODIFICATION

Literature review

EMBOLIC STROKE: BACKGROUND

Stroke was the second-leading cause of death and third-leading cause of death and disability combined worldwide in the most recent Global Burden of Disease Study reports, with an estimated cost of US$891 billion, and 1.12% of global gross domestic product (GDP).[1, 2] Between 1990 and 2019, incident stroke has increased in absolute number by 70% and prevalent stroke has increased by 85%, though age-standardised incidence rates have decreased by 17%, mortality has decreased by 36% and prevalence has decreased by 6%.[1] There has, however, been an increase in stroke among people younger than 70 years with incidence rates increased by 15%, and prevalence increased by 22%, with higher mortality (3.6x) and higher age-standardised disability-adjusted life-years (DALY) (3.7x) in World-Bank low income group countries compared to World-Bank high income group countries.[1] Stroke categories are broadly divided into haemorrhagic or ischaemic. Haemorrhagic stroke includes subarachnoid haemorrhage, with bleeding into the subarachnoid space, often caused by leak or rupture of arterial vessel aneurysm; or intracranial haemorrhage with bleeding within and into the brain parenchyma. Ischaemic stroke is driven by interruption of arterial blood supply to brain tissue. Each of these three dominant mechanisms have separate approaches driven by acute and chronic management of the underlying pathologies, and separate international guidelines for recommended and evidence-based approaches.[3-7]

Ischaemic stroke makes up the majority of strokes, at >62% of strokes in the 2019 Global Burden of Disease Study.[1] In order to subclassify ischaemic stroke mechanisms for more

targeted study, comparisons across cohorts and research focus, the "Trial of Org 10172 in Acute Stroke Treatment" investigators' (TOAST) criteria were published in 1993, and still provide a framework for understanding and grouping acute ischaemic stroke subtypes today.[8] The TOAST criteria define possible or probable causes of stroke based on ancillary studies.

TOAST CRITERIA

Large-artery atherosclerosis (embolus/thrombosis)
Cardioembolism (high-risk/medium-risk)
Small-vessel occlusion (lacune)
Stroke of other determined etiology
Stroke of undetermined etiology a. Two or more causes identified b. Negative evaluation c. Incomplete evaluation

Work-up recommended for stroke in the TOAST criteria included cardiac imaging via echocardiography, head and neck vessel imaging via computed tomography (CT), magnetic resonance imaging (MRI), or ultrasonography, with cerebral imaging via CT or MRI. Lacunar stroke was defined as <1.5cm lesion size in characteristic subcortical or brain-stem regions.

Cardiac imaging / history findings consistent with different levels of risk for embolic stroke in the original TOAST criteria are listed in the table below:

Features	LVD stroke	SVD stroke	CE stroke	Other cause	Cryptogenic stroke
Clinical					
Cortical or cerebellar syndrome	+	-	+	+/-	+/-
Lacunar syndrome	-	+	-	+/-	+/-
Imaging					
Cortical, cerebellar, brainstem, or subcortical infarct > 15 mm	+	-	+	+/-	+/-
Subcortical or brainstem infarct < 15 mm	-	+	-	+/-	-
Tests					
Stenosis of an appropriate extracranial or intracranial artery	+	-	-	-	-
Cardiac source of emboli	-	-	+	-	-
Other abnormality on tests	-	-	-	+	-

LVD = large vessel disease, SVD = small vessel disease, CE = cardioembolic

Table adapted from original form by Adams et al.[8]

Mechanisms and pathophysiology

Within the TOAST classification of ischaemic stroke, thromboembolism is the predominant mechanism, whether related to large artery atherosclerosis, or cardiac source, particularly as a result of atrial fibrillation. Mechanisms of ischaemic stroke which are less common, though more prevalent in younger age-groups include arterial dissection, vasculitis, haematological disorders, and patent foramen ovale (PFO). Patent foramen ovale is a normal communication between the right and left atria allowing blood to bypass the lungs in the foetal circulation, which closes in the first weeks of life, though may remain persistent in around 25% of the population.[9]

RISK FACTORS AND STROKE

Non-modifiable risk factors for stroke are increased age, sex and genetic factors. The INTERSTROKE study identified 10 key modifiable risk factors responsible for 91% of the population attributable risk (PAR) for stroke.[10] These risk factors include arterial hypertension, hyperlipidaemia (apolipoproteinB/apoplipoprotein A1 ratio in the study), raised

waist-to-hip ratio (which generally correlates with increased body mass index (BMI)), psychosocial factors, cardiac causes, diabetes mellitus, smoking, increased alcohol intake and tobacco use with higher quality diet (as measured by Modified Alternative Healthy Eating Index) and regular physical activity associated with reduced risk for stroke.[10] In the Modified Alternative Healthy Eating Index, foods associated with reduced cardiovascular and cancer risk such as vegetables and wholegrains improve scores and those associated with increased risk such as higher trans-fat and sugar intake reduce scores. Furthermore, according to recent Global Burden of Diseases study data, population-attributable fraction DALYs which can be attributed to risk factors is in excess of 85%, and is similar across all stroke subtypes, including ischaemic stroke intracerebral haemorrhage and subarachnoid haemorrhage.[1] While stroke burden is increasing disproportionately in low and middle-income countries,[1, 11] risk factor contribution also remains significant across higher income countries.[12-15]

MODIFIABLE RISK FACTORS AND PRIMARY PREVENTION OF STROKE

Modifiable risk factors have been proposed as important primary prevention priorities for stroke in previous and updated stroke primary prevention guidelines.[16-18] A summary of key primary prevention principles, evidence and recommendations follows.

Hypertension

Stroke incidence has been shown to increase in proportion to systolic and diastolic blood pressures.[19-21] Systolic blood pressure rises with increasing age in children and in adults, and even in normotensive individuals at 55 years of age, the lifetime chance of developing hypertension is 90%,[22, 23] with > two thirds of people aged >65 being hypertensive.[20]

Meta-analyses show more intensive blood pressure reduction (to SBP <130 mmHg) reduces risk more than less intensive blood pressure control, with greater benefit in those with cardiovascular disease risk factors, but without established cardiovascular disease.[24]

While blood pressure control can usually be achieved, it more often requires 2 or more agents to do so.[25, 26] Some subgroups have been shown to benefit most from BP reduction, including diabetics in the ACCORD Blood Pressure Trial,[27, 28] and blood pressure reduction benefit has been proven in the Systolic Hypertension in Europe (Syst-Eur) trial, and in the elderly in the Systolic Hypertension in the Elderly Program (SHEP) Trial and the Hypertension in the Very Elderly (HYVET) Trial.[29-31]

Overall recommendations arising from the above from the American Heart Association (AHA) include annual screening for hypertension, lifestyle modification followed by medication to target blood pressure of < 140 / 90 mmHg with a focus on blood pressure target, rather than defined combination of agents to achieve this, and self-measured BP monitoring.[18]

Hyperlipidaemia

Elevated Low Density Lipoprotein cholesterol (LDL-C) has been established as a risk factor for ischaemic stroke,[32] and ischaemic stroke may be prevented by low levels of LDL-C,[33] though this is most relevant to athero-embolic mechanism strokes.[33]

Consistent risk reduction in stroke has been shown with statin treatment in high-risk populations,[34, 35] with meta-analysis from the Cholesterol Treatment Trialists (CTT) collaboration showing a 16% (95% CI 11% – 21%) risk reduction in any stroke for each 1 mmol reduction in LDL-C.[36] A large trial of ezetimibe addition to statin therapy showed additional stroke risk reduction of 0.6%,[37] and systematic review of all ezetimibe trials showed similar results.[38] A more recent potent class of cholesterol-lowering drugs, Proprotein

convertase subtilisin/kexin type 9 (PCSK9) inhibitors has also shown modest stroke risk-reduction when added to statins in high-risk populations.[39-41]

Recommendations from the AHA are for lifestyle changes, and addition of lipid lowering medications including statins with or without the addition of ezetimibe or PCSK9 inhibitors for the primary prevention of stroke in those at high 1-year cardiovascular risk.[18]

Diabetes Mellitus

Diabetes Mellitus is an independent risk factor for stroke, with doubling of risk compared to non-diabetics, and around 1 in 5 diabetics dying of stroke.[42] Fasting hyperglycaemia is also associated with stroke.[43] Despite these findings, trials of more intensive diabetic control have failed to show reductions in stroke. In the UK Prospective Diabetes Study (UKPDS), the ACCORD study, the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) Trial, and the Diabetes Control and Complications/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Trials, there was no change shown in the incidence of stroke events.[44-47]

Among diabetic patients within various primary prevention trials, co-morbid hypertension treatment intensity has been associated with reduced stroke risk in one meta-analysis, which included 73,13 patients across 31 trials.[48]

In diabetic patients, treating with LDL-lowering, primarily with statins, in the Heart Protection Study (HPS), Collaborative Atorvastatin Diabetes Study (CARDS), Treating to New Targets (TNT) study LDL-C lowering in patients with diabetes, with or without additional vascular risk factors resulted in variable lowering of incident stroke.[49-51]

AHA Recommendations are for intensive blood pressure and LDL-C control in patients with diabetes, and recommendations are for a general target of HbA1c <7%, though with minimal evidence for this last strategy on specific stroke risk reduction.[18]

Obesity

Evidence is accumulating for increasing obesity association with increased stroke, independent of age, lifestyle and other cardiovascular risk factors, with prospective studies showing a BMI range of 25- 50 kg/m^2 conveys a 40% increase in stroke mortality for each 5 kg/m^2 increase in BMI, a relationship that does not exist in the BMI 18 – 24 kg/m^2 range.[52] Meta-analysis of 25 studies with >2.2 million participants showed a RR of 1.22 (95% CI 1.05 – 1.41) for ischaemic stroke if overweight, and 1.64 (95% CI 1.36 – 1.99) if obese,[53] results also supported by large Chinese and Japanese studies[54, 55] and the ARIC study,[56] though when adjustment for covariates such as diabetes, hypertension and hyperlipidaemia were taken into account, this association was reduced or nullified in these studies.

Studies of weight loss effect on stroke risk are limited. A 4000 patient Swedish study of bariatric surgery versus usual care with 10 – 20 year follow-up did show a significant reduction in diabetes, myocardial infarction (MI) and stroke in the surgical group,[57] and 36,000 Swedish participants followed for >13 years showed stroke incidence reduction with > 3 healthy lifestyle goals met, including normal weight.[58] Blood pressure reduction in the order of 4.4 and 3.6 mmHg in Systolic and Diastolic, respectively has been shown with 5.1kg weight loss in a meta-analysis of 25 trials.[59]

AHA Recommendations are for those with BMI > 25, weight loss to lower BP, and also to reduce stroke risk.[18]

Physical Inactivity

Two meta-analyses show a reduction in stroke in the order of 25 – 30% in those who are physically active, compared with least active.[60, 61] Sex interaction has been inconsistent among studies, with one suggesting greater exercise intensity benefit in women but not

men,[62] but another large study, the Northern Manhattan Study (NOMAS), suggesting benefit of more intense physical activity in men but not women.[63] The National Runner's Health Study showed reduced incidence of stroke with vigorous activity, regardless of sex,[64] and reduced prevalence of brain infarcts has been shown in another study with increased physical activity.[65]

The effects of physical activity on controlling blood pressure, diabetes, and other cardiovascular risk factors may be important mechanisms mediating its effects on stroke risk,[66-68] but changes in blood parameters have also been shown, including reduction in plasma fibrinogen and platelet activity, increased tissue plasminogen activator activity and elevated HDL concentrations.[69-71] Other positive effects may be through physical activity causing increased anti-inflammatory cytokines such as interleukin-1 receptor antagonist and interleukin-10, and through immune-system modulation.[72]

AHA Recommendations are for regular physical activity, as it is associated with reduced risk of stroke, and ≥ 150 minutes of moderate intensity physical activity per week.[18]

Obstructive Sleep Apnoea

Obstructive sleep apnoea (OSA) has been shown to approximately double the risk of stroke in multiple systematic reviews and meta-analyses.[73-78] This is in the presence of adjusting for confounders such as age, sex, BMI, smoking, alcohol consumption, hypertension and diabetes. Increased risk of stroke is seen in patients with OSA, particularly in young-to middle-aged patients.[79, 80] Two studies have shown an increased risk of stroke in patients with OSA and comorbid atrial fibrillation, with increased risk correlating with OSA severity,[81, 82] though another study did not show this relationship in elderly patients, though hospitalisation was more likely with OSA and AF.[83] Early observational studies of continuous positive airways pressure (CPAP) treatment for OSA showed apparent improved cardiovascular

outcomes, but more recent RCTs and meta-analyses have not shown net benefit.[84-86] The largest of these meta-analyses did show a benefit for ≥4 hours of CPAP use versus non-use in a sensitivity analysis, but risk of bias in this result was also identified.[84] Other interventions for OSA did not show benefit on stroke risk reduction, although there have been quite limited studies.[87-89]

Overall, data suggests that OSA doubles the risk of incident stroke. Treatment with CPAP, although supported by observational studies, is not well-proven in RCTs, though there may be a benefit of >4 hours versus non-use of prescribed CPAP.

Smoking

Smoking has been associated with stroke in multivariable analysis in many studies and portends a doubling of risk.[90-92] A meta-analysis of 32 studies confirmed a RR of 1.9 (95% CI 1.7-2.2) for ischaemic stroke with smoking.[93] Cigarette smoking has been shown to potentiate the effect of other risk factors such as hypertension and oral contraceptive use.[94, 95] Some studies of environmental exposure to tobacco smoke have shown a risk increase approaching the same magnitude as active smokers,[96-101] suggesting a possible smoke exposure threshold rather than a linear dose-response relationship.[102] The mechanisms of smoking increasing stroke risk include short-term increased thrombus formation in atherosclerotic vessels, and long-term increased atherosclerosis.[103] Even one cigarette has been shown to increase heart rate, mean BP and cardiac index, and decrease arterial distensibility.[104, 105] Thrombotic and embolic stroke are increased by smoking, but so is cryptogenic stroke.[106, 107]

Public health measures to reduce smoking have resulted in reduced rates of stroke. For example, an Arizona statewide ban on smoking in indoor public places resulted in a 14% stroke reduction in counties without this measure previously in place.[108] Smoking cessation rapidly reduces stroke risk to that approaching, but not reaching people who have never

smoked.[103, 109-111] Counselling and medications have been shown to be more effective than either alone,[112-114] and varenicline has been shown to be more effective than nicotine replacement therapy or buproprion,[115, 116] though all were more effective than placebo medication.[115]

AHA Recommendations are for cessation of all forms of tobacco use, or ideally ongoing abstention in those who have never smoked, and for a combination of counselling and pharmacologic therapy for assisting cessation of active smoking. Community-wide or statewide bans as have already been implemented widely internationally are strongly endorsed to reduce stroke risk.[18]

Alcohol Intake

Heavy alcohol consumption has been shown to be a risk factor for all types of stroke.[117-121] In a large study including 71,243 women from the Nurses' Health Study and 43,685 men from the Health Professionals Follow-up Study, a J-shaped association of risk of stroke has been shown. Women who were light drinkers had reduced stroke risk, but those who drank ≥30 g of alcohol per day had a 40% increased risk of stroke (RR 1.41; 95% CI 1.08 – 1.88 for ischaemic stroke and RR 1.40; 95% CI .86 – 2.28 for ICH).[122] A Chinese prospective study showed men who drank 21 or more drinks (1 drink defined as 12.5g of pure alcohol in this study) per week had a 22% increase in stroke risk, whereas the lowest stroke risk was seen in those who drank 1-6 drinks per week.[123] This J-shaped curve of risk for alcohol consumption and stroke is supported by most studies, though a meta-analysis has recently shown that overall mortality for women is higher amongst those drinking >3 drinks per day.[124] In a meta-analysis of 35 observational studies, 60 g of alcohol consumption per day was associated with 64% increase in risk of all stroke, with reduced risk associated with consumption of ≤12 g of

alcohol per day, and lower ischaemic stroke risk associated with consumption of 12-24 g of alcohol per day, (RR 0.72; 95% CI 0.57 – 0.91).[125]

Mechanisms whereby light alcohol consumption may help reduce stroke risk are association with raised HDL cholesterol,[126, 127] reduction in platelet aggregation,[128, 129] lowering of fibrinogen concentrations[130] and increasing insulin sensitivity and glucose metabolism.[131, 132] Heavy alcohol, on the other hand is associated with hypertension,[133-136] hypercoagulability and reduced cerebral blood flow,[137] and increased risk of AF.[118, 138-142] Alcohol consumption is associated with poorer blood pressure control in patients with hypertension, and particularly if the hypertension is mainly driven by heavy alcohol consumption.

AHA Recommendations are currently for reducing alcohol intake in heavy drinkers, acknowledging that ≤2 standard drinks per day in men and ≤1 standard drink per day in women might be reasonable.[18]

Atrial Fibrillation

Atrial fibrillation is associated with a 5-fold increased risk of ischaemic stroke,[143] and is also an independent predictor of increased mortality.[144] Paroxysmal AF has been shown to increase stroke risk to a similar degree as persistent AF,[145] with embolism of stasis-induced thrombi formed in the left atrial appendage believed to be the dominant mechanism of AF-related stroke.[143]

Various risk scores for AF – related stroke exist. The CHA_2DS_2-VASc score remains the most commonly used, despite some limitations.[146] Congestive Heart failure (1 point), Hypertension (1 point), Age (1 point for ≥65 years, 2 points for ≥75 years), Diabetes Mellitus (1 point), Stroke or transient ischaemic attack (TIA) (2 points), Vascular disease (peripheral arterial disease, myocardial infarction or aortic plaque 1 point), Female sex (1 point) make up the variables with a possible score of 0-9 points.[146] A study of predictive value in 45,576 patients,

showed rates of thromboembolism of 0.84 per hundred person-years for CHA_2DS_2-VASc score of 0, to 1.79, 3.67. 5.75, and 8.18 for CHA_2DS_2-VASc scores of 1, 2, 3, and 4 respectively.[146] While the recent 2023 AHA AF management guidelines continue to use CHA_2DS_2-VASc,[147] others such as the 2018 Australia/New Zealand and recent 2024 European Society of Cardiology AF management guidelines have dropped female sex, truncating to CHA_2DS_2-VA score.[148, 149] The HAS-BLED score, among others, has been used to estimate bleeding risk from anticoagulation, though it was originally designed in the context of warfarin use.[150, 151] Hypertension, abnormal renal or liver function, past stroke, past bleeding history or predisposition, labile INR on warfarin, older age (>65 years) and use of certain drugs (concomitant antiplatelet, non-steroidal or alcohol abuse) are each assigned one point.[150] In fact this HAS-BLED score involves similar variables to the CHA_2DS_2-VASc score, with the main difference being the renal/liver dysfunction or concomitant anti-platelet/non-steroidal/alcohol abuse.

Fortunately, in the current climate, direct oral anticoagulants have been proven equivalent or superior to warfarin for anticoagulation in atrial fibrillation, reducing the stroke risk by approximately 2/3rds. The RE-LY study with Dabigatran, ROCKET-AF with rivaroxaban, ARISTOTLE with Apixaban and ENGAGE AF-TIMI 48 trial with Edoxaban have proven these agents are as effective as warfarin, with an overall reduction in bleeding risk, and a particular reduction in intracranial haemorrhage.[152-155] In addition, the AVERROES trial with Apixaban versus aspirin in patients unsuitable for warfarin was terminated early after 1.1 years due to superiority of Apixaban over aspirin, with no significant increased bleeding risk.[156]

In patients who have unacceptably high ongoing bleeding risk with antithrombotic therapy, left atrial appendage closure has been shown to reduce stroke risk in trials of the WATCHMAN and AMULET devices.[157-159]

Stroke risk has not been shown to be reduced with rhythm control medication or cardioversion.[160-164] After AF ablation, which has a modest success rate of around 70% at 12 months in most studies (though varying by subtypes paroxysmal or persistent), asymptomatic episodes of AF are often discovered, and ongoing stroke risk is likely to exist,[165] though trials of cessation of anticoagulation post AF ablation to assess stroke risk are ongoing.[166]

AHA Recommendations are for anticoagulation in the case of clinically detected AF, if CHA_2DS_2-VASc score is 2 or more and bleeding risk acceptably low with or without the assistance of assessment with the HAS-BLED or other bleeding risk score. A CHA_2DS_2-VASc score of 0 is deemed low enough risk not to anticoagulate, whereas a score of 1 in the context of low bleeding risk is at patient and physician discretion regarding anticoagulation or not.

Opportunistic screening for the detection of AF is recommended by palpation of pulse +/- ECG in patients > 65 years.[18]

STROKE RECURRENCE

Following ischaemic stroke, recurrent stroke is common and accounts for significant healthcare burden. A large Danish nationwide stroke registry study with 42,182 individuals having incident ischaemic stroke revealed a 3.6% recurrence of stroke at 12-months, with even higher rate of death at 10.5% and cardiovascular events at 6.7%.[167] Five-year recurrence after ischaemic stroke was 16-18% in further studies.[168, 169] Risk of stroke or death combined following incident ischaemic stroke in 1626 patients in London was 65.3% at 5 years, with 9% of recurrences attributable to diabetes, and 4.9% to AF.[168] In a meta-analysis of 58 studies examining recurrent stroke in patients after incident stroke or TIA, annual recurrence was 4.3%, and this remained stagnant over follow-up, without decline over time.[170]

A subtype of embolic stroke, embolic stroke of undetermined source (ESUS) makes up 25 – 30% of ischaemic stroke in most cohorts. Patients with ESUS have a particularly high stroke recurrence rate in most studies. In an Argentinian cohort of 236 individuals with ischaemic stroke, 32% were identified as ESUS.[171] During a median 17-month follow-up, 15% experienced recurrent stroke, according to patient self-report. All of these individuals were on antiplatelet therapy at the time of recurrence, and 12% had AF detected on routine 24-hour holter monitoring.

The Athens stroke registry with 2735 ischaemic strokes identified over a 10-year period, classified 10% as ESUS according to the Cryptogenic Stroke/ESUS International Working Group criteria.[172] Clinical presentation of recurrent stroke over follow-up was 11.3%. In participants re-presenting with stroke, AF was highly prevalent, detected in 30% during repeat admission telemetry or on repeat ECG.

Risk factors are predicted to contribute to the majority of ischaemic stroke recurrence, including the subgroup with ESUS when this cohort is examined in isolation.[173]

Acute and Subacute Stroke Specific Therapies

Patients who have already experienced a stroke or TIA represent a higher risk cohort for further stroke and cardiac events than those known to be at high risk for incident stroke.[174] Guidelines on acute stroke management with modalities such as thrombolysis and intravascular thrombus retrieval specify the situations and timelines around these critical and potentially life and function-saving therapies.[175-177]

After the acute hours of stroke and initial urgent management, further intervention with allied health and stroke unit rehabilitation also has evidence for improvement in outcomes.[178]

Aside from these acute and subacute stroke-specific interventions, further stroke management priorities are antithrombotic therapy, treatment and control of ongoing risk factors.

Anti-Thrombotic Therapy

At the time of ischaemic stroke, initiation of anti-thrombotic therapy has been clearly shown to reduce recurrence. The European Stroke Organisation has extensively reviewed contemporary evidence for anti-thrombotic therapy in stroke secondary prevention as part of guidelines on pharmacological interventions for long-term secondary prevention after ischaemic stroke or TIA.[7] Eleven large contemporary trials with a total of 13,369 participants were reviewed, with respect to antiplatelet monotherapy versus placebo following ischaemic stroke. Included studies are the Trial of Aspirin in Transient Ischaemia (AITIA),[179] Canadian cooperative study,[180] The Accidents Ischimique Cerebraux Lies a L'Athersclerose (AICLA) trial,[181] The Danish Cooperative Study,[182] The Swedish Cooperative study,[183] The UK-TIA Trial,[184] The Swedish Aspirin Low-Dose Trial,[185] ESPS2,[186] The Canadian American Ticlopidine Study,[187] and The Cilostazol Stroke Prevention Study (CSPS).[188] Meta-analysis of nine of these trials showed reduced risk of any stroke with antiplatelet therapy (OR 0.82, 95% CI 0.73-0.92, $I^2 = 0$, $p = 0.001$), with concurrent reduction also in myocardial infarction (OR 0.77, 95% CI 0.61-0.98, $I^2 = 0$, $p = 0.56$).[7]

In terms of long-term dual antiplatelet therapy, meta-analysis of 5 major trials including The ESPS-2 trial,[186] The Management of Atherothrombosis with Clopidogrel in High-risk patients (MATCH),[189] Clopidogrel for High Athero- thrombotic Risk and Ischaemic Stabilisation Management and Avoidance (CHARISMA),[190] The SPS3 trial,[191] and The PRoFESS trial,[192] showed use of long-term dual anti-platelet therapy did not significantly reduce overall stroke risk, but with low level of certainty, it did reduce ischaemic stroke risk (OR =0.92, 95% CI 0.85 – 0.99). Unfortunately this came at a cost of significantly increased risk of haemorrhagic stroke, in the order of roughly 4 more haemorrhagic strokes per 1000 people treated.[7]

Antithrombotic Therapy and Embolic Stroke of Undetermined Source

Embolic Stroke of Undetermined Source (ESUS) was proposed as a clinical construct by Hart and colleagues in 2014, and has entered the literature as a subgroup of the original TOAST classification cryptogenic stroke group, with the exclusion of lacunar stroke.[193] Whether thrombus in this form of stroke is formed in cardiac chambers, or head and neck vessels is not clear. Major trials have assessed whether anticoagulation to prevent thrombus formation in cardiac chambers is an up-front effective strategy in this form of ischaemic stroke.

The NAVIGATE-ESUS study assessed Rivaroxaban 15mg compared to Aspirin 100mg in a multicentre, double-blinded randomised trial of 7213 people with mean follow-up of 2 years.[194] Recurrent stroke risk was not reduced (HR 1.08, 95% CI 0.87-1.34, p=0.47), major bleeding was increased (HR 2.72, 95% CI 1.68-4.39, p<0.001), and the trial was stopped prematurely due to lack of benefit and increased bleeding risk. The RESPECT ESUS study assessed Dabigatran 150mg or 110mg BD (based on standardised dose reduction parameters of age ≥75 years, and or creatinine clearance 30 to < 50 mL/minute) compared with Aspirin 100mg in people with ESUS in the previous 3 months or ESUS in the previous 6 months with an additional vascular risk factor with median follow-up of 19 months.[195] Dabigatran was not superior to aspirin in stroke reduction (HR 0.85, 95% CI 0.69-1.03, p=0.10) though it did not significantly increase bleeding risk (HR 1.19, 95% CI 0.85-1.66). An additional trial, Apixaban versus Aspirin for Embolic Stroke of Undetermined Source (ATTICUS) was recently published.[196] This was a multicentre randomised, open-label, blinded outcome trial of Apixaban 5mg BD compared with Aspirin 100mg within 28 days after ESUS in patients with at least one predictive factor for AF (CHA_2DS_2-VASc score ≥ 4, atrial high-rate episodes ≥ 20 cycles and < 30 seconds, left atrial size >45mm, spontaneous echo contrast or flow velocity ≤0.2m/s in the left atrial appendage) or a Patent Foramen Ovale. The primary outcome was any new ischaemic lesion on brain MRI during 12-month follow-up, and

secondary outcome was major and clinically relevant non-major bleeding. All participants had continuous cardiac monitoring with an insertable cardiac monitor and switching from Aspirin to Apixaban was mandated if AF was detected. Original powering was for 600 participants based on an expected 10% of participants in the Aspirin group having new ischaemic lesions, and 7.5% projected in the Apixaban group, for 90% power. Fewer than 30% of participants in the Aspirin group were expected to develop AF within the 12 months of the study. After a planned interim analysis, new trial enrolments were terminated early in 2020 by the Data Safety Monitoring Board due to futility with 353 participants enrolled, though ongoing follow-up to 12 months continued as there were no safety concerns. This trial differed from the previous 2 in that all participants had at least one cardioembolic risk enrichment factor and 36.6% had multiple factors. It also differed in mandating continuous cardiac monitoring, which occurred in 95.4% (4.5% had external cardiac monitoring). The primary outcome occurred in 13.6% in the Apixaban group and 16.0% in the Aspirin group (OR 0.79, 95% CI 0.42-1.48, p=0.57), another non-significant result. The secondary outcome of any recurrent stroke or systemic embolism occurred in 6.2% of the Apixaban group versus 7.6% of the Aspirin group, again not significantly different (HR 0.81; 95% CI, 0.36-1.80). Major and clinically relevant nonmajor bleeding was not significantly different between groups at 2.8% in the Apixaban group, and 4.0% in the Aspirin group (HR 0.68; CI, 0.22-2.16). In another recently published trial of Apixaban in ESUS, the ARCADIA study, participants with ESUS and one additional AF risk factor (raised NT-Pro-BNP, ECG markers of left atrial (LA) abnormality or LA enlargement) were randomised to anticoagulation with Apixaban, or to Aspirin.[197] The result was no difference in stroke rates of 4.4% by 18 months' follow-up in both arms and the trial was stopped early for futility after a planned interim analysis. Interestingly, only 3.3% of the 1015 participants enrolled had significant LA

enlargement as an atrial cardiomyopathy marker, with the vast majority of participants qualifying on BNP or ECG markers alone.

Taken together, in the 4 major studies to date, there is no net benefit of an up-front anticoagulation strategy in patients with ESUS, with a signal of more bleeding from this approach seen in the NAVIGATE ESUS study with Rivaroxaban.

Implantable Cardiac Monitoring-Guided Anticoagulation in ESUS

The CRYSTAL AF study showed that in a cohort with cryptogenic stroke, atrial fibrillation detection on implantable loop recorder was 12.4% at 1 year, and 30% by 3-years of monitoring.[198] This compared with 2% at 12 months and 3% at 3 years using intermittent ECG monitoring at study visits. This study was not designed or powered to investigate the effect of anticoagulation for device-detected AF in this cohort in terms of stroke recurrence or other outcomes.

The CRYSTAL AF study has led to the practice in many countries of implantable cardiac monitoring insertion (implantable loop recorder – ILR) in patients with ESUS, at least after an initial 1 month of continuous wearable cardiac monitoring has elapsed, in order to detect unknown atrial fibrillation as a likely cause of stroke, though evidence of degree of benefit from this approach is lacking.[199]

Additional studies have assessed the rate of AF in groups with mixed causes for stroke or in atherosclerotic cause. The STROKE-AF study enrolled 496 participants with stroke deemed due to large or small vessel cause.[200] Half the participants were randomly assigned to have implantable cardiac monitoring inserted 10 days after stroke, and AF detection rates were noted to be 12.1% in the ILR group, and 1.8% in the standard care group at 12 months with extended follow-up to 3 years showing 21.7% and 2.4%, respectively.[201] The PER DIEM study randomised 300 participants without known AF, within 6 months of stroke to

implantable cardiac monitoring or ECG follow-up at 30 days, 6 months and 12 months.[202] In this cohort the overall median CHA2DS2-VASc score was 4, and 66.3% had ESUS. AF was detected in 15.3% in the implantable loop recorder group, versus 4.7% in the control group. These studies variably used 30 seconds or 2 minutes of AF as the threshold for diagnosis, though with a monitor which generally requires a 2-minute EGM sample for analysis. Clearly, detection of AF with implantable loop recorders is significantly increased compared with intermittent follow-up across different stroke subtypes. The important clinical question from here is what is the appropriate threshold for anticoagulation in this situation, once AF is detected?

Three large clinical trials have examined this question. In the Implantable loop recorder detection of atrial fibrillation to prevent stroke (The LOOP Study): a randomised controlled Trial, 6004 individuals aged 70-90 years without a known history of AF, but with at least one risk factor for stroke (hypertension, diabetes, previous stroke or heart failure) were randomly assigned in a 1:3 ratio to undergo ILR monitoring, or standard care.[203] Atrial fibrillation episodes lasting 6 minutes or longer triggered recommendation for commencement of anticoagulation. Over a median follow-up of 64.5 months, atrial fibrillation was detected in 31.8% of the ILR group, with anticoagulation started in 29.7% versus 12.2% in the control group, with anticoagulation started in 13.1%. The primary outcome of stroke or other systemic arterial embolism occurred in 4.5% of the ILR group, compared to 5.6% of the control group (HR 0.80; 95% CI 0.61-1.05, p=0.11), and major bleeding occurred in 4.3% of the ILR group versus 3.5% of the control group (HR 1.26, 95% CI 0.95-1.69, p=0.11). In addition to this lack of significant difference in the overall trial, 25% of the participants in each group had suffered a previous stroke or TIA, and could effectively be thought of as a secondary prevention group. There was no significant difference even in this subgroup with

previous stroke with 7.3% in the ILR monitored group and 7.4% in the control group having stroke recurrence.

A recent trial, Anticoagulation with Edoxaban in Patients with Atrial High-Rate Episodes, the NOAH-AFNET 6 study, randomly allocated 2536 participants without a history of known AF, but with AHREs ≥ 6 minutes aged ≥65 years with at least one additional risk factor for stroke (heart failure, hypertension, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease (previous myocardial infarction, aortic plaque, or peripheral, carotid, or cerebral arterial disease), or an age of 75 years or older) 1:1 to Edoxaban or placebo.[204] The placebo contained aspirin if the patient had a separate indication for it, such as peripheral arterial disease, myocardial infarction, or stroke, and was otherwise inert. The primary efficacy outcome was cardiovascular death, stroke, or systemic embolism. Again, there was no significant difference in outcomes between groups with 3.2% in the Edoxaban group and 4% in the placebo group experiencing the primary outcome (HR 0.81, 95% CI 0.60 – 1.08, p=0.15) with stroke at 1% per patient-year in both groups. The safety outcome, a composite of death or major bleeding, was higher this time in the Edoxaban group at 5.9% per patient-year versus 4.5% per patient-year (HR 1.31, 95% CI 1.02-1.67, p=0.03). In this study 10% of participants had a history of previous stroke or TIA.

Finally, the Apixaban for Stroke Prevention in Subclinical Atrial Fibrillation (ARTESIA) study, also recently published, included 9% of participants with previous stroke.[205] In this study, 4102 participants with implanted cardiac devices and adjudicated AF detection of duration 6 minutes to 24 hours were enrolled and randomised in a double-blind, double-dummy design to Apixaban 5mg BD (with dose reduction to 2.5mg BD where indicated) or Aspirin 81mg per day. If a threshold of 24 hours of device-detected AF was reached, trial medication was discontinued and anticoagulation was routinely started. The primary endpoint was again stroke or systemic embolism. After mean follow-up of 3.5 years, stroke or systemic

embolism occurred in 0.78% per patient year in the Apixaban group, compared to 1.24% per patient year in the Aspirin group, (HR 0.63, 95% CI 0.45-0.88, p=0.007). In an on-treatment analysis of major bleeding, this was 1.71% per patient year in the Apixaban group and 0.94% per patient year in the Aspirin group (HR 1.80, 95% CI 1.26-2.57, p=0.001). Fatal bleeding occurred in 5 patients in the Apixaban group and 8 patients in the Aspirin group. The authors of this study noted that in the aspirin group, a high 45% of strokes resulted in death or clinically significant long-term disability, and that in 90% of the major bleeding events in the Apixaban group, non-procedural measures (including blood transfusion) were adequate for management. This does add some nuance to the otherwise somewhat direct comparison of reduced primary endpoint versus increased bleeding safety endpoint. Additionally, an analysis from the ARTESIA study showed participants with a CHA2DS2VASC score >4 had an increased stroke/systemic embolism risk of 2.2% per year and that the benefits of Apixaban outweighed the risks in this group.[206]

Although it was performed in a general population with pacemakers, and not specifically with prior stroke, analysis from the ASSERT trial which enrolled 2580 patients, points to minimal stroke increased risk with device-detected AF episodes between 6 minutes and 24 hours, though a significant risk increase with episodes >24 hours (hazard ratio 3.24, CI 1.51 – 6.95).[207]

In summary, these recent trials in continuous monitoring have proven that AF (or AHRE) detection is a common finding, and that the duration threshold for net benefit from anticoagulation is less and less clear. In the LOOP study with 25% having previous stroke, NOAH-AFNET 6 with 10% and ARTESIA with 9% having previous stroke, there has been no significant benefit signal from a threshold of 6 minutes. For AF episodes > 24 hours the ASSERT data suggests stroke risk is high enough to recommend anticoagulation.

STROKE RISK FACTORS AND SECONDARY PREVENTION

Hypertension

Elevated blood pressure after ischaemic stroke or TIA is a known risk factor for recurrence.[21, 208] Multiple randomised trials have evaluated blood pressure lowering after stroke. [25, 209-216] Systematic Review and Metaregression of these trials by Katsanos and colleagues in 2017 has provided needed guidance on what blood pressure target should be aimed for following stroke.[217] Systolic blood pressure reduction was linearly related to a lower risk of recurrent stroke, myocardial infarction and death from any cause. Diastolic blood pressure reduction was also linearly related to a lower risk of recurrent stroke and all-cause mortality. Although no specific blood pressure cut-off could be defined, this linear relationship continued down to a systolic blood pressure target of < 130mmHg, lending strength to more recent recommendations that this target is associated with lower risk than a higher threshold.[217] A further and more recent meta-analysis and meta-regression examining magnitude of blood pressure reduction across 10 major RCTs of anti-hypertensive treatment following stroke confirmed that more intensive versus less intensive blood pressure lowering was associated with risk reduction for recurrent stroke, major cardiovascular events, and death from cardiovascular causes.[218] Additionally, the magnitude of both differential SBP and DBP reduction were monotonically associated with lower risk of stroke.[218]

Most current stroke secondary prevention guidelines endorse a target blood pressure of <130/80 mmHg.[7, 199]

Hyperlipidaemia

While hyperlipidaemia, and particularly raised LDL-C is associated with incident stroke, most data in individuals with a history of ischaemic stroke and elevated LDL-C comes directly from trials of lipid-lowering agents for secondary prevention. Key randomised trials

include the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, with significant reduction in any nonfatal or fatal stroke with randomisation to atorvastatin 80mg vs placebo (adjusted HR 0.84, CI 0.71-0.99);[219] The Heart Protection Study Collaborative (HPSC) with 63% of participants having previous non-disabling, non-haemorrhagic stroke, and 40mg of simvastatin vs placebo reducing subsequent stroke (HR 0.75, CI 066-0.85);[220] the Japan Statin Treatment Against Recurrent Stroke (J-STARS) trial which only achieved around 50% planned recruitment at 1578 participants and did not show benefit of pravastatin 10mg vs placebo (adjusted HR 0.95, 95% CI 0.71–1.28);[221] the Cholesterol and Recurrent Events (CARE) trial comparing pravastatin 40mg to placebo following MI, with a subgroup analysis of the 100 or more participants in the treatment and placebo arms with previous stroke showing 37% relative risk reduction for stroke or TIA (95% CI 23-68);[222] and the Long-Term Intervention with Pravastatin in ischaemic Disease (LIPID) trial with a subgroup of 610 participants with previous stroke, showing a non-significant RR reduction of stroke of 0.72 (95% CI 0.46-1.12).[223]

Fortunately, a large recent RCT has been conducted in this setting to more clearly establish the role of cholesterol lowering for prevention of recurrent stroke. The Treat Stroke to Target Trial enrolled 2860 patients with atherosclerotic-cause stroke in France and South Korea with 3.5 years of follow-up. This trial showed an LDL reduction target to <1.8 mmol/L (65mg/dL) led to a reduction in recurrent stroke and major cardiovascular events, compared with a more lenient target of 2.5 mmol/L (96 mg/dL). In this study, there was no significant increase in intracranial haemorrhage or new-onset diabetes, as had been seen in previous trials such as SPARCL.[224] The target of <1.8mmol/L was achieved in 88% of participants in the treatment arm with the use of oral agents, and anti-lipid therapy escalation was required in nearly one third of patients, supporting follow-up dose titration after initiation of high-dose statin at the time of stroke. Subsequent meta-analysis of LDL-C lowering treatment for stroke secondary

prevention by Lee and colleagues included this more recent trial with previous RCTs and confirmed reduced stroke risk with more-intensive versus less-intensive lipid lowering therapies, particularly in those with stroke and evidence of atherosclerosis.[225] A slight increase in risk of intracranial haemorrhage was noted in this meta-analysis, as it was in previous ones without the treat stroke to target trial included, though the number needed to treat with high-intensity LDL-lowering to prevent a stroke at 4 years was 90, to prevent a MACE event was 35 and the number needed to harm in the same analysis for one intracranial haemorrhage was 242.[225] In a recent 2023 statement from the AHA by Goldstein and colleagues, the issue of under treatment with LDL-C lowering, reasons for this, and details of possible relationship between statin treatment and increased haemorrhagic stroke, new onset diabetes and dementia is explored in detail.[226] Systematic review and meta-analysis of 25 RCTs with 46836 patients showed no difference between statin and placebo in incidence of cognitive events or worsening cognitive scores.[227] Studies of ezetimibe and PCSK9 inhibitors evolocumab[228-230] and alirocumab[231] did not show correlation between use of these agents, lower LDL-C levels achieved and cognitive impairment. An increase in haemorrhagic stroke has not been seen with PCSK9 inhibitors alirocumab[232] or evolocumab.[40] Data for Ezetimibe are limited, but outside of its use with statins, there is no convincing evidence it causes any increased risk of haemorrhagic stroke.[233, 234]

In summary, evidence supports the strategy of more intensive LDL-C lowering in patients with atherosclerotic disease cause of stroke with a small signal for slight increase in haemorrhagic stroke though with a high number needed to harm (242 over four years of treatment) versus a low number needed to treat (35) to prevent MACE, or 90 to prevent recurrent stroke. Stroke guidelines now endorse an LDL-C target of <1.8 mmol/L for atherosclerotic-related stroke.[7, 199, 226]

Diabetes Mellitus

Although Diabetes is known to double the risk of incident stroke, with 15% increased risk for each 1% increase in HbA1c,[235, 236] intensive control of blood sugar in people with diabetes reduces microvascular complications (retinopathy, nephropathy, neuropathy), with less certain benefit on major cardiovascular adverse events, including stroke. There is a lack of randomised data to evaluate the effect of intensive blood sugar control following stroke. In the Veterans Affairs Diabetes Trial (VADT), Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial and Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, varying proportions of 9-40% enrolled had cardiovascular disease, though intensive treatment in these trials was not associated with reduced major cardiovascular events.[45, 46, 237] Seven trials of intensive glucose lowering in diabetes were included in a meta-analysis which showed major cardiovascular events to be reduced by 10% with intensive glucose control (RR 0.90, 95% CI 0.85–0.96, $p<0.001$),[238] though there was no effect on stroke, and episodes of hypoglycaemia were increased. A U-shaped relationship with HbA1c was seen with a lowest cardiovascular risk associated with an HbA1c of 7.5%, with a tendency to more benefit from intensive treatment with shorter duration of diabetes, lower HbA1c at baseline and longer follow-up. Overall, there is a lack of evidence for strict blood sugar control or an HbA1c ideal target for stroke secondary prevention. Stroke guidelines endorse a <7% goal, in agreement with the known benefits of reduced microvascular disease, but the benefits on recurrent macrovascular events remain to be proven.[7, 199]

Smoking

Smoking cessation after stroke has been shown to occur in around 50% of smokers, and is more likely with more severe stroke, insular cortex infarction, or intensive smoking cessation

intervention.[239] Smoking cessation after stroke has been associated with a relative risk reduction of 1/3rd for recurrent stroke compared with continuing to smoke.[239-241] Nationwide analyses in the USA have shown significant variation in the smoking cessation rates across different geographies, and it is noted that smoking cessation is less likely after stroke than after a cancer diagnosis.[242] Regarding behavioural and pharmacologic therapies, data on varenicline and bupropion safety following ischaemic stroke is scarce when examined across a number of studies, however a combination of behavioural and other smoking cessation therapies is more effective than a single brief behavioural intervention.[243] Cost-benefit modelling shows that combination pharmacotherapy with intensive counselling are cost-effective, though with the addition of a monetary incentive as well, could provide more quality-adjusted life years (QALYs) and reduce total cost as a combined intervention.[244]
In summary, cessation of all forms of tobacco use are strongly recommended following stroke and a combination of behavioural and pharmacological approaches if required are guideline endorsed.[199, 245]

Obstructive Sleep Apnoea

Obstructive Sleep Apnoea (OSA) is a common finding in patients with stroke, with a 2019 meta-analysis of available studies showing at least mild (apnoea-hypopnoea index - AHI >5) OSA in 71% and severe OSA (AHI >30) in 30% of cases.[246] Early neurological deterioration post-stroke has been associated with the presence of OSA in a recent study of 305 patients in Korea.[247] Post-stroke OSA is associated with recurrent stroke or TIA, increased vascular mortality and increased vascular events in various studies, with increasing severity (most frequently measured via apnoea-hypopnoea index, AHI) associated with increased risk of these outcomes.[248] Earlier studies suggested a diminishing severity of sleep disordered breathing over time post-stroke, but a recent large prospective study showed severity was

stable with repeat portable sleep apnoea testing at 3, 6 and 12 months in 414 individuals after first-time stroke and showed stable severity over the first 12 months post-stroke.[249] The gold-standard treatment for OSA post-stroke is CPAP.[250] One RCT of nasal CPAP in 140 patients with ischaemic stroke and AHI ≥20 randomised 57 patients to nasal CPAP and 69 patients served as a control group. At 5-years of follow-up cardiovascular survival was higher in the nasal CPAP group (100%) versus the non-CPAP group (89%), log-rank test 5.887, P = 0.015. Cardiovascular event-free survival was numerically higher in the CPAP group (89.5%) compared with the non-CPAP group (75.4%), though this did not reach statistical significance, log-rank test 3.565, P = 0.059.[250] An earlier publication on this same cohort at 2-year follow-up had documented improved neurological recovery at 1 month after stroke with early initiation of nasal CPAP in the treatment group.[251] A 2018 Meta-analysis of CPAP for OSA after stroke identified 10 RCTs with 564 participants and noted the presence of mainly feasibility studies with short and variable follow-up, and significant trial drop-out rates, limiting certainty about the effects of CPAP treatment after stroke.[252] Nonetheless, in this study, CPAP adherence was on average 4.5 hours per night and an overall neurofunctional improvement with CPAP was noted, albeit with considerable heterogeneity.

In summary, evidence exists that OSA is common and associated with worse acute neurological outcomes in patients with stroke. Some evidence exists that longer term mortality and vascular events are reduced with CPAP treatment, but there is heterogeneity in published studies and a marked lack of high-quality randomised data to strengthen the certainty of this relationship.

Assessment for OSA and treatment with CPAP where indicated is endorsed as a management strategy post-stroke in European guidelines.[253]

Alcohol

Alcohol intake, particularly at high levels, is associated with stroke recurrence, with a recent study highlighting this relationship in 1216 young Dutch patients with stroke.[254] This study showed ongoing alcohol intake at high levels, defined as >200g of alcohol per week, was associated with long-term (5-year) stroke risk increase, (HR 2.0, 95% CI 1.0-3.8, P=0.04). Heavy alcohol intake of >60g per day has been linked with increased stroke recurrence within 90 days in a further study.[255] There is a lack of randomised trial evidence for reducing alcohol intake after stroke. Alcohol reduction has been shown to reduce blood pressure, with greater reductions in those with high blood pressure.[256] Diabetes incidence is lower in those with low compared to heavy alcohol consumption.[257] Alcohol reduction to reduce recurrent stroke risk may therefore operate largely through modulating blood pressure reduction and reducing new onset diabetes, but data is lacking to confirm this.

Recommendations in AHA and Australian/New Zealand stroke guidelines are not to exceed alcohol intake levels classed as low risk in the general population after stroke.[6, 199]

Physical Inactivity

While physical inactivity is a well-recognised risk factor for incident stroke, most data for secondary prevention has focussed on the direct effects of exercise on performance measures, rather than stroke recurrence.[258-266] Beneficial effects shown for exercise after stroke include measures such as maximum oxygen consumption (VO2 max), 6-minute walk test and timed-up and go testing with subacute treadmill, bicycle ergometer and general aerobic exercise interventions.[258-262] For more chronic-phase stroke recovery, structured aerobic or strength training for 10-12 weeks has shown initial and sustained gains in some or all of these parameters.[263-266] One Chinese observational study showed lower stroke recurrence in a dose-

dependent fashion in patients who engaged in long-term regular mild exercise (more than 5 sessions per week of 40 minutes of more).[267]

Stroke guideline recommendations for exercise vary from AHA guidelines for moderate intensity 10 minutes 4 times per week (or vigorous activity for 20 minutes twice per week)[6] to higher levels in alignment with general population targets of 2.5 – 5 hours of moderate intensity physical activity (Australian Stroke Guidelines).[199]

Obesity

Early concerns based on historical, observational studies, pointed to a potential 'Obesity Paradox' after stroke, whereby increased BMI was associated with better outcomes.[268] More detailed recent analysis of outcomes, however, has highlighted likely confounders.[269] Obese patients tend to have strokes at a younger age and are more likely to have smaller strokes which have not been well controlled-for in previous analyses. There may be a treatment bias at play, survival bias, and other confounders.[269] Metabolic risk factors are common with stroke, and losing weight is associated with reduced severity of hypertension, sleep apnoea, insulin resistance and left atrial dysfunction in populations without stroke.[59, 270-272] One recent randomized controlled trial of a targeted diabetes prevention program post-stroke showed effective weight loss with improvement in metabolic markers, social participation and eating habits.[273]

In summary, the effects of weight loss in obese patients after stroke require more evidence for firm conclusions but would be expected to improve many metabolic markers and have a positive effect on other risk factors including hypertension, sleep apnoea and diabetic control. Guidelines recommend weight loss in patients with stroke or TIA to reduce ongoing atherosclerotic cardiovascular disease risk.[6, 199]

SEX AND GENDER SPECIFIC RISK FACTORS IN STROKE

Retrospective studies have shown that while all risk factors apply, there are sex differences in risk factor loading and contribution to risk, and additional specific risk factors in females.[274] Oral contraceptive pill use and lifetime oestrogen exposure alter the risk of stroke in females, as do adverse pregnancy outcomes and these additional risk factors for stroke are often under-recognised.[275] Women have been shown to be more likely to experience mis-diagnosis, report atypical symptoms, and experience different rates of acute thrombolysis or endovascular therapy compared with men.[276, 277] Although women experience stroke as frequently as men, they are under-represented in clinical trials for stroke. In one large retrospective Korean study of 787 patients with recurrent stroke, males were shown to have higher rates of smoking and drinking, while females had higher rates of hypertension, diabetes, hyperlipidaemia and overweight/obesity than males.[278]

RISK FACTOR MODIFICATION FOR STROKE

Although national and international stroke guidelines endorse the management of stroke risk factors for secondary prevention, there is a scarcity of evidence on the best method for achieving control of these risk factors in the medium to long term.

Delivery of stroke risk factor modification

Description of risk factor modification following stroke as an overarching strategy has been mentioned in the literature since the mid-1980s,[279] and published studies from the mid 1990s have highlighted the inadequacy of stroke risk factor control in both incident and recurrent stroke.[280, 281] In 2002, Allen and colleagues published a randomised trial on a post discharge care management model for stroke and TIA, with 96 participants in the USA randomised to an in-home biopsychosocial assessment by an advanced practice nurse at 1 month with

patient phone contact during the week before this and a patient tailored evidence-based treatment plan formulated, with outcomes assessed at 3 months.[282] Improvements were significantly more in the treatment group across a 'profile of health and prevention' with parameters measured including neuromotor function, severe complications, quality of life, risk management for post-stroke complications and recurrent stroke, and stroke knowledge. Since this time, there has been a stream of randomised trials including others with nurse-led multi-disciplinary interventions[283-296] A meta-analysis of nurse-led interventions for stroke secondary prevention in 2018 reported a significant effect on systolic blood pressure (SMD = -0.14 (95% CI = -0.23, -0.05), I^2 = 0%; p = 0.002, diastolic blood pressure SMD = -0.16 (95% CI = -0.27, -0.05), I^2 = 0%; p = 0.003, and in a subgroup of the 16 studies assessed, led to improved physical activity, diet, medication adherence and knowledge of risk factors. There was a lack of effect seen on smoking behaviour and alcohol use.[297] Other randomised trials of risk factor intervention have taken place with GP-led/facilitated care with or without structured guideline programs,[298-302] remote introduction of decision-support tools into medical practice,[303, 304] pharmacist-led additional intervention,[292, 305-308] written, web-, app-based or combination resources,[309-312] allied health input,[313, 314] standardised discharge orders, [315] specialist outpatient clinic input,[316] community health worker-delivery,[317, 318] peer-education workshops,[319] motivational interviewing,[320] medication self-monitoring and self-titrating.[321] The effects of these interventions on risk factor control parameters have been variable, with none of these studies powered for the hard outcomes of recurrent stroke or cardiovascular events. Some of these studies have shown a degree of change in surrogate measures, most frequently somewhat better blood pressure control, and higher physical activity where that was specifically targeted, though many of these studies have failed to change risk factor control at follow-up.

A Cochrane review of interventions for improving modifiable risk factor control after stroke was published in 2018.[322] This review included 42 randomised controlled trials (most of the above studies), with a total of 33,840 participants, with 26 studies of organisation interventions and 16 of educational and behavioural interventions. Outcomes assessed were mean systolic and diastolic blood pressure, mean body mass index, achievement of HbA1c target, lipid profile, mean HbA1c level, medication adherence, or recurrent cardiovascular events. Educational and behavioural interventions were not found to show any clear difference in outcomes. Organisational interventions improved blood pressure control to target (OR 1.44; 95% CI 1.09-1.90), but in the analysis, did not result in significant change in systolic blood pressure (mean difference -1.58mmHg, 95% CI -4.66-1.51) and mean diastolic blood pressure (mean difference -0.91mmHg, 95% CI -2.75-0.93). Other review outcomes were not significantly changed by organisation interventions.

This evidence clearly indicates that successful risk factor modification presents an ongoing challenge and the models of care to-date have not yielded adequate outcomes. In the ASPIRE S study it was clearly shown that many stroke survivors have poor risk factor control still by 6 months after stroke.[323] Large studies comparing coronary heart disease outcomes to patients with stroke across various populations in the USA and China have shown hypertension and other risk factor control is worse after stroke than after myocardial infarction,[324, 325] with other studies pointing out this is very much the case even in high-risk groups like those with diabetes.[326] After stroke, cardiovascular disease medications are underutilised,[325] and in a Norwegian study, risk factor control was shown to be suboptimal despite high medication persistence and adherence.[327] In addition to suboptimal risk factor control across all the populations studied, additional barriers have been identified to vary by race and ethnicity,[328, 329] and frequently medication beliefs and knowledge are a crucial issue.[330]

In separate analyses to the GBD studies, it has again been confirmed that 80% or more of all recurrent strokes are probably related to inadequate risk factor control.[331] A recent review of the National Health and Nutrition Examination Survey (NAHNES) data from the US shows that there has been no improvement in secondary prevention within the past decade.[332] In a South London study of stroke recurrence published in 2020, it was noted that stroke recurrence had reduced up until the mid-2000s, but had remained stable since,[333] and a Danish review showed stroke recurrence in Denmark has not reduced over the past 2 decades.[334] Clearly, a more effective model of risk modification for secondary prevention of stroke is very much needed.

Fortunately, another cardiovascular condition has gathered strong evidence of benefit for an approach to risk factor management which is now guideline-endorsed as best practice. Atrial fibrillation, while a risk factor itself, is the result of very similar cardiovascular pathophysiological changes that also lead to stroke. In fact, there is growing understanding of the important interlinking of AF and stroke, and the concept of an atrial cardiomyopathy as a common mechanism involved in both conditions.

ATRIAL CARDIOMYOPATHY AND STROKE

The key cardiovascular risk factors underlying stroke including hypertension, hyperlipidaemia, diabetes mellitus, smoking, excess alcohol consumption, overweight and obesity, physical inactivity and obstructive sleep apnoea are also risk factors for atrial fibrillation incidence, recurrence, and progression.[12, 164, 335] Risk travels both ways – atrial fibrillation confers 5-fold stroke risk, and in patients with stroke, there is a significant chance of detecting AF on continuous monitoring of around 12-15% at 1 year and > 20% at 3 years,

even with atherosclerotic cause of stroke, with an even higher rate of 30% with cryptogenic stroke.[198, 201] Atrial cardiomyopathy is a concept that has been well described and explored in the literature during the past decade, and is a term that encompasses the pathophysiological changes occurring in the left atrium including dilatation and remodelling as a result of the progressive effects of underlying risk factors.[335-337] These risk factors lead to stroke by atherosclerotic mechanisms, stroke via cardioembolism in the presence of AF, and are also proposed to underlie the likely atrial source of thrombus which may arise in the presence of atrial cardiomyopathy, even prior to the manifestation of AF. The concept of a left atrial thrombus threshold relates to the lead-time of atrial cardiomyopathy exceeding a critical thrombus formation threshold which could precede the point at which the threshold for AF is reached by a variable amount of time.[338] With the vast majority of ESUS patients having no cause for stroke found, it is likely that many of them experienced their original event due to thrombus formation in the context of an underlying left atrial cardiomyopathy. Given the recent findings already outlined of frequent AF detection outside of cryptogenic stroke in the STROKE-AF and PER DIEM studies, it is likely that atrial cardiomyopathy is frequent in other forms of stroke as well.

LEFT ATRIAL CARDIOMYOPATHY PATHOPHYSIOLOGICAL CHANGES

Left atrial dilatation and mechanical dysfunction

In an analysis published in 1995 from the Framingham Heart study, increased left atrial size has been shown to be predictive of stroke and death.[339] Dilation of the left atrium is known to promote stasis, with increased rates of spontaneous echocardiographic contrast, thrombus and embolic events noted in early studies with the use of trans-oesophageal echocardiography.[340-342] In this early Framingham study, which excluded patients with known atrial fibrillation at baseline, the risk of stroke was increased by increasing degree of left atrial enlargement. This

relationship persisted when excluding patients with known congestive heart failure or myocardial infarction. In this Framingham study and in a 1999 cohort drawn from the Northern Manhattan Stroke Study, this relationship was stronger in males, and was somewhat reduced though still present when controlling for increased left ventricular mass, though increase in LV mass and LA size were noted to be colinear.[339, 343]

Recurrent stroke has also been linked with increased left atrial size among the cohort in the Northern Manhattan Stroke Study in a 2015 publication.[344] Moderate-to-severe left atrial enlargement was shown to be an independent predictor of recurrent cardioembolic or cryptogenic stroke in 665 first-time ischaemic stroke patients followed for up to 5 years. This relationship was independent when controlling for variables including hypertension and history of atrial fibrillation. Increased left atrial indexed volume, a further quantification of left atrial size, has been linked with increased risk of recurrent stroke in further observational studies and has been suggested to be more sensitive than left atrial diameter.[345, 346] With increases in left atrial size, left atrial function reduction is typically seen. This can be studied through speckle tracking echocardiography to characterise left atrial wall function through the periods of the left atrial cardiac cycle known as reservoir, conduit and booster pump function.[347] In efforts to further characterise left atrial cardiomyopathy in ESUS and other stroke patients, abnormally reduced left atrial strain has been associated with ESUS more than non-cardio-embolic stroke, and is associated with increased chance of AF detection after stroke.[348] A further derived measurement of left atrial stiffness using the commonly assessed mitral peak E-wave velocity divided by mitral annular e' velocity (E/e′) and dividing this by the measured LA reservoir strain has been found to be elevated (with a cutoff of ≥0.22 used) in 150 patients with cryptogenic stroke compared to 150 age- and sex-matched controls.[349] This measure requires further testing to see if it is predictive of future ischaemic events.

Cardiac MRI use to quantify LA size, volume, function and other parameters in patients with

ischaemic stroke is beginning to be explored in the literature recently. It has been noted in one small comparison study of 44 patients with trans-thoracic echocardiograms compared to cardiac MRI, that the volumes measured are consistently lower in echocardiography compared to MRI.[350] Whether this will add predictive value in future or if it is simply reflective of known differences between these modalities remains to be seen. Interestingly another small study of 20 patients with ESUS and 20 age- and sex-matched controls, there was no significant difference in cardiac MRI-based left atrial cardiomyopathy measures including LA velocities, LA ejection fraction, and MRI-derived left atrial strain measures.[351] Left atrial scarring detected as fibrosis on cardiac MRI has been shown to reflect levels seen in patients with AF, and to be significantly more than healthy control patients.[352] Following on from this, a prospective, multicentre study including 53 patients with ESUS, 100 with AF, and 50 further participants (35 controls and 15 with lacunar stroke) showed that among ESUS patients with a left atrial scar threshold of ≥12%, there was more AF or recurrent stroke detected, over a mean follow-up of 19 months.[353]

These studies suggest that along with initial findings of left atrial size and volume increase, measurements of left atrial function require more study as potential predictive factors for recurrent stroke.

Left Atrial Inflammatory Changes

Left atrial cardiomyopathy is known to be associated with changes in biomarkers of inflammation including CRP, Interleukin-6, Tumour Necrosis Factor alpha, and aldosterone, and these biomarkers are elevated in association with AF.[354-356] Whether these biomarkers are significantly elevated in embolic stroke or could predict stroke recurrence requires further research to determine.

Left Atrial Hypercoagulability

Prothrombotic indices including D-dimer, vWF and GDF15 have been elevated in association with AF and have been shown to associate with subsequent stroke and thromboembolism.[357-359] Altered endothelial cell function has been demonstrated with AF,[360, 361] and reactive oxygen species (ROS) are believed to contribute to atrial myopathic changes through effects on ion channels and calcium-cycling proteins.[362-364]

Biomarkers for Ageing

Increasing age is associated with increased risk of AF, though when controlling for risk factors, the mechanism for this is not clear. One known marker of cellular ageing is the telomere, a region of repetitive DNA sequences at the end of a chromosome which functions to protect the chromosome from degradation, and is known to shorten with increasing age. A study of 3576 participants in the Intermountain Heart Collaborative Study showed that reduced telomere length was associated with paroxysmal AF.[365] It remains to be seen if telomere length can be predictive of recurrent stroke, with at least one recent study involving 8041 patients with ischaemic stroke or TIA in China suggesting no robust association, when controlling for other stroke risk factors.[366] One study has shown biological age as measured by DNA methylation can be predictive of stroke recurrence.[367]

ATRIAL FIBRILLATION AND THE EFFECT OF RISK FACTORS

The same risk factors that clearly increase the risk of incident and recurrent embolic stroke are well recognised to increase the risk of atrial fibrillation incidence, recurrence, and progression, by contributing to onset and progression of underlying atrial cardiomyopathy. Obesity, physical inactivity, hypertension, obstructive sleep apnoea, diabetes mellitus, alcohol consumption, and smoking have all been shown to increase the risk of AF.[368-376]

Obesity and AF

Obesity has been shown to cause increases in left atrial size, pressure and blood volume with increases in systemic vascular resistance, increased epicardial and pericardial fat deposition, as well as conduction slowing.[377-380] In a large meta-analysis, every 5-point increase in BMI was shown to cause a 29% increase in the risk of AF.[368]

Evidence shows achieving and sustaining weight loss when part of a co-ordinated comprehensive risk-factor modification approach, can reduce both pre and post-ablation atrial fibrillation, as demonstrated in the LEGACY and ARREST-AF studies.[381, 382] In both these studies, a physician-led multidisciplinary clinic was used to guide weight loss in all participants whose BMI was ≥27 kg/m^2, and in the LEGACY study, 10% weight loss led to a dramatic 50% reduction in AF burden (assessed using the atrial fibrillation symptom severity score questionnaire and measured freedom from AF)[383], with effects of reduced magnitude with smaller degrees of weight loss. In the SORT-AF trial, an intervention group randomised to weight loss after ablation had reduced AF recurrence among participants with persistent AF followed with implantable cardiac monitoring.[384] While there is likely to be reversibility, adverse left atrial remodelling with obesity may reach a point where chronic low-grade inflammatory changes have resulted in permanent fibrotic change and the key is to intervene before this point.

Physical Inactivity and AF

Physical inactivity has been clearly associated with a higher risk of developing AF,[385] as well as being associated with poorer cardiovascular health and increased obesity.[385] Among the 5446 participants in the Cardiovascular Health Study, it was shown that moderate intensity physical activity was associated with up to 24% reduction in the risk of AF.[369]

In the CARDIO-FIT study, improved cardiorespiratory fitness was shown to have an additive effect to weight loss, and an effect independent of weight loss in reducing AF burden (assessed using the atrial fibrillation symptom severity score questionnaire and measured freedom from AF).[386] The ACTIVE-AF randomised trial showed that a 6-month exercise intervention in patients with AF resulted in reduced arrhythmia recurrence and improved symptoms.[387] A U-shaped relationship with exercise and outcomes in AF is known to exist,[385] and for this reason, moderate intensity exercise is recommended, with a volume similar to that recommended in general cardiovascular disease prevention guidelines of 30 minutes 3-5 times per week, increasing to at least 200 minutes of moderate intensity exercise per week.[381, 382, 388, 389]

Hypertension and AF

Hypertension has been shown to induce various pathophysiological changes in the cardiovascular system associated with increased afterload. These include left ventricular hypertrophy and stiffening, reduced diastolic filling and increased left atrial volumes.[390-392] Left atrial dilatation results, with adverse electrophysiological changes and these are perpetuated by circulating hormones such as angiotensin II, also leading to fibrosis.[390] In the Framingham Heart Study, 40 – 50% increased likelihood of developing atrial fibrillation was shown with hypertension.[370] In a large study involving a cohort of over 300,000 patients with known atrial fibrillation, a blood pressure exceeding 130/80mmHg was associated with a significantly increased risk of major cardiovascular events.[393]

Treatment of hypertension is a key priority in the management of atrial fibrillation risk, and lowering it to <130/80mmHg has been shown to result in a reduction in AF incidence of the same magnitude as the increase seen with this risk factor in the Framingham Heart Study.[394] The recommended target blood pressure in atrial fibrillation risk factor modification is the

same as the target blood pressure for secondary prevention of stroke: <130/80mmHg, and this level is ideally attained for ≥ 80% of the time, allowing for some expected variation seen.[381, 382, 388] A hypertensive response to exercise (peak exercise systolic blood pressure above 210mmHg in men and 190mmHg in women) may indicate benefit to be obtained by intensifying anti-hypertensive treatment. Renal denervation when added to AF ablation resulted in better blood pressure control and higher freedom from AF in the ERADICATE-AF trial, and in the SMAC-AF study, patients over 60 years of age had reduced AF recurrence when randomised to more aggressive blood pressure lowering after AF ablation, though at a cost of more hypotension in the trial group randomised to strict control.[395, 396] Careful monitoring is necessary for changes in blood pressure and symptoms of postural hypertension. Resolution of left ventricular hypertrophy is a potential surrogate marker for adequate blood pressure control.

Obstructive Sleep Apnoea and AF

During episodes of obstructive sleep apnoea, hypoxaemia-associated atrial electrophysiological changes and significant haemodynamic changes increase LA pressures and lead to LA enlargement, with the ongoing recurrent pharyngeal collapse and repetitive interruption of ventilation.[397-399]

Treatment of OSA in some non-randomised studies has reduced AF recurrence after either cardioversion or catheter ablation to the level seen in those without atrial fibrillation,[400] but there is randomised data in patients with OSA and only mildly raised BMI showing minimal benefit from treatment with CPAP.[401] Further data is needed in this area.

OSA is frequently asymptomatic in patients with AF, and any symptoms experienced are known to correlate poorly with severity of OSA.[402] Screening of all patients with AF is ideal given its preponderance to independently increase the risk of recurrence, despite treatment of

other more apparent risk factors, and emerging data from implantable cardiac monitoring devices confirms that OSA severity can show significant night-to-night variability, implying repeat sleep studies are worthwhile in patients with a remaining high clinical suspicion of OSA despite an initial negative test.[403]

A sleep physician should be involved in sleep assessment and treatment via referral and CPAP is usually prescribed if OSA is severe (Apnoea-hypopnoea index >30 per hour), or >20 with resistant hypertension or daytime sleepiness. Mandibular advancement splints or sleep positional devices have less evidence of effectiveness in treating sleep apnoea, but are usually utilised in patients who cannot or will not tolerate CPAP.

Diabetes Mellitus and AF

One-third increase in the risk of developing AF has been independently attributed to diabetes mellitus.[372] Increased thromboembolism and stroke risk has been seen with diabetes in patients with AF, and poor diabetes control has been shown to increase the risk of stroke and systemic embolism.[404, 405] Following catheter ablation for atrial fibrillation, poorer diabetic control has been associated with higher AF recurrence rates.[406]

In a similar situation to embolic stroke, there is little evidence for a definite effect of treating diabetes mellitus as a risk factor in isolation in the management of AF. Generally, diabetes management in accordance with recommendations in the general population is recommended, with a target HbA1c of <7%, (52mmol/L). This target should be decided in association with a specialist diabetes team which involves an endocrinologist, and may vary depending on duration of the condition and progression to insulin requirement, prevalence of hypoglycaemic episodes, number of comorbidities and functional capacity. Generally, metformin is prescribed if HbA1c is persistently above 7% despite lifestyle measures.

Alcohol and AF

Binge-drinking was recognised as an early association with AF, a phenomenon termed 'holiday heart syndrome'.[373] Chronic alcohol use is also known to increase the risk of developing AF, and to increase the risk of recurrence, with a systematic review associating increased risk with >3 standard drinks (30 grams) of alcohol per week.[374] Variation appears to exist depending on the type of beverage consumed, with a recent UK Biobank study showing low-level beer and cider intake was more strongly associated with AF than wine or spirits.[375] A randomised trial showed that alcohol abstinence advice for atrial fibrillation led to a 20% reduction in AF recurrence in the treatment arm and a longer delay to recurrence, via an 88% reduction in alcohol intake, compared with only 20% reduction in the control arm.[407] With heavy alcohol intake associated with increased adverse events in the population with AF,[374, 408] effective risk factor modification trials have involved recommendations for ideally abstinence or ≤3 standard drinks of alcohol per week.[381, 382]

Smoking and AF

Smoking has been shown to be an independent risk factor for developing AF, with up to double the risk shown in the ARIC study.[376, 409, 410] Changes with smoking thought to promote AF include increased sympathetic tone, oxidative stress, inflammation and atrial fibrosis.[411] Former smokers have been shown to have lower risk of AF than those who currently smoke, or who have recently quit.[376]

In atrial fibrillation risk factor modification trials, and current guidelines, smoking cessation is a key component of management,[164, 381, 382] and an accepted method is utilising an approach known as the '5As': ask, advise, assess, assist, arrange follow up.[412]

Cholesterol and AF

Earlier observational studies have appeared to show a 'cholesterol paradox' with AF – lower levels of LDL-C have been associated with higher incidence of AF.[413, 414] When randomised trials are subject to meta-analysis, however, a signal of reduced AF recurrence in patients treated with statins has arisen, though the most convincing data is in patients undergoing cardiac surgery, or with myocardial infarction.[415]

In general, treatment of hyperlipidaemia in the context of AF should be guided by overall cardiovascular risk.[164]

EVIDENCE FOR RISK FACTOR MODIFICATION IN AF

Fortunately, there is evidence for the effectiveness of risk factor modification in the management of atrial fibrillation, via intensive intervention to control the very same risk factors identified as important priorities in embolic stroke.[381, 382, 386, 388, 389]

While managing one individual risk factor if it is in an extreme state has been beneficial in some studies of varying rigor for hypertension, alcohol use, and sleep apnoea,[396, 407, 416, 417] little, if any benefit from this approach is found with isolated risk factor targeting in the presence of multiple risk factors with more modest contribution to risk.[396]

Risk Factor Modification Delivery for AF

In the management of chronic diseases such as AF, better guideline adherence, enhanced patient compliance and improved clinical outcomes have been demonstrated from a structured, co-ordinated and integrated approach.[418-420] An integrated care approach is therefore optimal in the delivery of risk factor modification for atrial fibrillation,[421, 422] with a separate clinic focussed on risk factor modification in addition to usual specialist review for AF follow-up utilised in successful trials of risk factor modification for AF.[381, 382, 388, 389] This

approach has been described in recent consensus documents and summarised by the 'HEAD2TOES' approach, an acronym with a structured assessment and targeting of Heart failure, Exercise, Arterial hypertension, Diabetes type 2, Tobacco use, Obesity, Ethanol intake and Sleep apnoea.[419, 420] The team involved in individually tailored AF risk factor modification care for patients involves the primary care doctor, heart rhythm specialist, specialised nurse, and where required, exercise physiologist, sleep physician, endocrinologist / diabetes care team, and pharmacist.

AF Risk factor modification clinics are now supported as a key underlying aspect of AF care in most international guidelines including the European Society of Cardiology, the AHA / American College of Cardiology and others.[148, 149, 164]

Key elements of an effective risk factor modification clinic for AF include:

- Patient centred, individually tailored care;
- A lifestyle journal including regular recordings of blood pressure, exercise and dietary intake, which is regularly reviewed, with feedback provided;
- Incremental, goal-directed approach;
- Flexible follow-up, with access to care between appointments;
- Surveillance and titration of medication and other treatments;
- Screening of all patients with AF for the presence of OSA and review of any CPAP treatment data to ensure efficacy.

In more detail, the intervention strategy utilised is as follows.

Risk factor modification is performed in a multidisciplinary risk factor modification clinic with structured follow-up appointments and contact frequency adjusted according to the needs of the individual. These range from 3-monthly formal appointments to weekly contact

by phone or email. A structured, motivational and goal-directed program using face-to-face counselling is used for each risk factor. Patients are encouraged to utilise support counselling and schedule more frequent reviews as required. Initial weight reduction is attempted by a meal plan and behaviour modification. In any patients with a BMI ≥27 kg/m^2, the initial goal is to reduce body weight by 10%. After patients achieve the initial goal, ongoing dietary advice is provided to achieve a target BMI of ≤27kg/m^2. All patients are asked to maintain a lifestyle journal outlining all food and drink consumption, exercise undertaken and home blood pressure monitoring results to facilitate optimisation of cardiovascular risk factor profile. Patients are encouraged to increase their exercise habits progressively until they reach a minimum weekly target volume of at least 150 minutes, with a view to increasing to a final target of 250 minutes. Where progress is not satisfactory, accredited exercise physiologist input is sought. Any exercise prescription is initiated based on baseline exercise testing and physical activity profile. Patients are encouraged to increase their exercise habits progressively until they reach the target weekly volume. All patients continue to have separate standard of care medical management for AF through their treating physicians – Cardiologist, General Practitioner and where required, sleep physician and endocrinologist / diabetes care team.

While successful clinical trials of this intervention involve dedicated, specialist-led clinics,[381, 382, 388, 389] a similar approach could be set-up in primary care, given adequate resources. This would require some additional input from primary care doctors, utilisation of the skills and assistance of practice nurses if trained in risk factor modification delivery, and perhaps as a funding base, the use of a chronic disease management plan to facilitate delivery of this care.

CONCLUSION

Risk factors for the incidence and, importantly, recurrence of stroke remain majority players in contribution to ongoing stroke events. Despite much research into models of risk factor secondary prevention for stroke, there has been limited success to-date for delivering highly effective care and evidence shows risk factor control post-stroke usually remains sub-optimal. The effective risk factor modification model proven in the management of atrial fibrillation provides a logical template for exploring effectiveness in the population of patients after embolic stroke and shows promise in presenting a new method for reducing recurrent stroke and major cardiovascular events in this population. This method is ideally suited to be implemented and subjected to assessment for outcomes, and tested in a randomised controlled trial in the stroke population.

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Statement of Authorship

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By signing the Statement of Authorship, each author certifies that:

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Name of Co-Author	Mehrdad Emami		
Contribution to the Paper	Concept, editing 3%		
Signature		Date	7/28/2024

Name of Co-Author	Melissa M Middeldorp		
Contribution to the Paper	Concept, editing 2%		
Signature		Date	29/07/2024

Please cut and paste additional co-author panels here as required.

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Name of Co-Author	Adrian D. Elliott		
Contribution to the Paper	Concept, editing 3%		
Signature		Date	27/07/2024

Name of Co-Author	Timothy Kleinig		
Contribution to the Paper	Concept, editing, Supervision 2%		
Signature		Date	7/29/2024

Name of Co-Author	Celine Gallagher		
Contribution to the Paper	Concept, editing, Supervision 5%		
Signature		Date	01/08/2024

Name of Co-Author	Prashanthan Sanders		
Contribution to the Paper	Concept, editing, Supervision 5%		
Signature		Date	7/27/2024

Chapter 2

The PREDICTive value of aggressive risk factor modification on the development of atrial fibrillation in Embolic Stroke of Undetermined Source trial: PREDICT-ESUS design and rationale

Short Title: *Fitzgerald et al. PREDICT-ESUS: design and rationale*

John L. Fitzgerald, MBBS,[a,b] Mehrdad Emami, MBBS, PhD,[a,b] Melissa E. Middeldorp PhD MPH,[a,b] Adrian D. Elliott PhD,[a] Timothy Kleinig, MBBS, PhD,[a,b] Celine Gallagher, PhD,[a] Prashanthan Sanders MBBS, PhD[a,b]

From: [a]Discipline of Medicine, University of Adelaide, Adelaide, Australia; [b]Departments of Cardiology and Neurology, Royal Adelaide Hospital, Adelaide, Australia

Correspondence:

Prashanthan Sanders

Centre for Heart Rhythm Disorders

Department of Cardiology, Royal Adelaide Hospital

Adelaide, SA 5000. AUSTRALIA

Telephone: +61883139000; Facsimile: +6183622273

Email: prash.sanders@adelaide.edu.au

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ABSTRACT

Background

Stroke recurrence after embolic stroke of undetermined source (ESUS) is a significant healthcare burden. Up to 30% of patients with ESUS will develop atrial fibrillation (AF) within 3 years of continuous cardiac monitoring, likely reflecting progression of an underlying atrial cardiomyopathy substrate. Lifestyle and risk factor management (LRFM) reduces burden and progression of AF. Whether LRFM following ESUS can reduce the incidence of new AF and recurrent stroke is unknown.

Objective

To assess whether LRFM to achieve current stroke guideline-driven targets compared with usual care will achieve a significant reduction in a primary endpoint of incidence of new AF and secondary endpoint of stroke after ESUS.

Methods and study design

This multicenter, prospective, randomized, open label, blinded end-point assessment trial commenced recruitment on the 2nd of February 2021. A total of 400 patients aged >18 years with a primary diagnosis of ESUS will be randomized 1:1 to physician-led aggressive LRFM in a multi-disciplinary outpatient clinic targeting hyperlipidemia, physical inactivity, hypertension, diabetes/impaired glucose tolerance, tobacco use, obesity, alcohol use, obstructive sleep apnea, or to usual care. The primary outcome is the incidence of new AF via implantable cardiac monitoring over a period of 3 years of follow-up. Key secondary outcomes include clinical and radiological recurrence of stroke on cranial imaging, change in left atrial size and function on transthoracic echocardiography and change in inflammatory and coagulopathy markers.

Conclusion

PREDICT-ESUS will determine whether aggressive LRFM compared with usual care can reduce the incidence of new AF and reduce the recurrence of clinically overt or asymptomatic cerebral emboli.

Trial registration: ACTRN12620000771954.

Key words: Stroke, Secondary prevention, Risk factors, Randomized controlled trial, Integrated care

Non-standard abbreviations and acronyms

LRFM: lifestyle and risk factor management

BACKGROUND

Embolic stroke of undetermined source (ESUS), a subgroup of cryptogenic stroke which excludes lacunar stroke, is responsible for approximately 30% of all embolic strokes,[423] whereby no definite cause is found despite vascular imaging, cardiac imaging and initial cardiac rhythm monitoring.[193] After excluding patent foramen ovale in patients under 60 years of age, where evidence exists for the benefit of closure,[424-426] key other potential mechanisms for ESUS include left atrial thrombus formation with or without as-yet undetected atrial fibrillation (AF), and symptomatic non-stenotic carotid plaque-related events.[427-429] Although up to 30% of patients with cryptogenic stroke develop AF on implantable cardiac monitoring within 3 years,[198] oral anticoagulation for all ESUS patients has not shown net benefit over aspirin[194, 195] and clinical stroke recurrence remains significant in this population at 4-5% per year.[194, 195]

A potential underlying substrate driving cardiac thrombus formation even before AF occurs or is detected on continuous implantable monitoring, is the development of atrial cardiomyopathy.[335, 336, 338] An enlarged left atrium, which usually reflects adverse remodeling, has been associated with increased incidence of both AF and stroke.[339, 345] Intervention with aggressive risk factor modification in patients with AF, utilizing a 'HEAD2TOES' approach targeting heart failure, exercise, arterial hypertension, diabetes mellitus type 2, obesity, ethanol intake and smoking has been shown to favorably improve left atrial function and reduce further occurrence of AF in previous trials,[381, 382, 389, 420] and this approach is now guideline-endorsed for management of this condition.[147-149]

Treatment of individual risk factors for stroke such as hypertension and hyperlipidemia has been shown to reduce recurrent stroke in randomized controlled trials and subsequent meta-

analyses.[217, 218, 224] Whether aggressive risk factor modification following ESUS to comprehensively target all cardiovascular risk factors can reduce the incidence of AF and recurrent stroke is unknown. Given the shared risk factors for ESUS and AF, the PREDICT ESUS study aims to evaluate the impact of intense cardiovascular risk factor modification in patients with ESUS.

Hypothesis

The primary hypothesis is that aggressive risk factor modification targeting hyperlipidemia, physical inactivity, hypertension, diabetes/impaired glucose tolerance, tobacco use, obesity, alcohol use, obstructive sleep apnea via regular review in a physician-led clinic will reduce the incidence of AF (defined as clinical AF or 2 or more minutes of device-detected AF during continuous implantable cardiac monitoring) following ESUS when compared with usual care. Secondary hypotheses are that aggressive risk factor modification will reduce the clinical and radiological recurrence of stroke, normalize left atrial size and mechanical function, reduce levels of serum markers of inflammation and thrombosis, favorably alter left atrial voltage demonstrated on non-invasive surface ECG-based mapping (iECG), and lead to reduction in loss of telomere length on serum assay.

METHODS

Study design

The PREDICT-ESUS trial is an investigator-initiated, multicenter, 2-arm, prospective, randomized, open label, blinded end-point assessment trial. Participants are patients >18 years of age and are enrolled within 6 months of presenting to inpatient or outpatient neurology services with ESUS, and without documented history of AF or atrial flutter prior to enrolment. Eligible participants who provide written, informed consent are randomized in a

1:1 ratio to aggressive risk factor modification via a minimum 3-monthly physician-led clinic review or to usual care which consists of as-required contact with a primary health practitioner. Randomization is performed via blocks of randomly generated and varying sizes, administered via integration into a centrally administered Research Database Capture (REDCap)[430] database at the time of enrolment. Outcomes will be adjudicated by assessors blinded to the randomization of participants. Approval has been obtained from the relevant ethics committees of each institution involved and study procedures are in accordance with principles of Good Clinical Practice and the Declaration of Helsinki.

Study setting and timeline

This is a trial involving four Australian hospital and outpatient clinic sites. First participant enrolment was on the 2nd of February 2021. As of the 19th of November 2024, all sites have been activated and 76 participants have been enrolled. Each participant will be followed up for 3 years after enrolment.

Funding

This trial is partially funded through an Investigator Grant from the National Health and Medical Research Council of Australia and through the Centre for Heart Rhythm Disorders, University of Adelaide, Australia.

Participant Eligibility / Study Population

Patients >18 years of age presenting to inpatient or outpatient services with ESUS are eligible for enrolment within 6 months of their acute event. Standard criteria for a diagnosis of ESUS have been utilized: ischemic stroke detected by computed tomography (CT) or magnetic resonance imaging (MRI) that is not Lacunar Stroke; absence of extracranial or intracranial

atherosclerosis causing ≥50% luminal stenosis in arteries supplying the area of ischemia; no major-risk cardioembolic source of embolism (no history of AF or atrial flutter; no documented cardiac thrombus, no prosthetic cardiac valve); and no other specific cause of stroke identified (e.g., arteritis, dissection, migraine/vasospasm, drug misuse).[193] Patients are excluded if there is a history of serious underlying medical disorder, full anticoagulation prior to randomization, moderate-severe valvular heart disease, prosthetic heart valve or endocrinopathy including subclinical thyroid disease. The full inclusion and exclusion criteria are listed in table 1.

Baseline evaluation

As part of usual care, each enrolled participant has had a full clinically indicated ESUS workup already completed prior to consideration of eligibility. This includes cerebral MRI, carotid imaging via contrast-enhanced computed tomography or ultrasound and echocardiography. As implantable cardiac monitoring via an implantable loop recorder is indicated as part of standard clinical monitoring for this type of stroke, all ESUS patients receive this independent of study participation. Additional testing is arranged at enrolment, including cardiopulmonary exercise testing, 3-day Holter monitor, baseline blood sampling for markers of inflammation, thrombosis, telomere analysis, and fasting serum lipids, full blood count, electrolytes, creatinine, glucose, hemoglobin A1c, N-terminal pro-brain natriuretic peptide. In a subset of participants from each study group, left atrial voltage mapping projected onto a cardiac CT utilizing a 252 surface electrode vest (ECGi) will be applied at baseline and at study completion. Baseline surveys are administered electronically, or in paper form where necessary including 36-item short-form health survey (SF-36)[431, 432] and the Atrial Fibrillation Symptom Severity Scale (AFSS)[383]. Physical measurements of height, weight, waist circumference, neck circumference, blood pressure, heart rate and a 12-

lead electrocardiogram are performed as well as implantable loop recorder interrogation if this device has already been implanted prior to enrolment.

Intervention

Lifestyle Risk Factor Management

Risk factors of hyperlipidemia, physical inactivity, hypertension, diabetes/impaired glucose tolerance, tobacco use, obesity, alcohol use, obstructive sleep apnea are sought and evaluated in each person and compared with targets specified for each in current American Stroke Association, European Stroke Organisation and Australian Stroke Foundation guidelines.[6, 7, 199] Each of the relevant risk factors for that given individual is then targeted aggressively. Risk factor modification is performed using a physician-led clinic with appointments and contact frequency adjusted according to the needs of the individual. These range from 3-monthly formal appointments to weekly contact by phone or email. This approach, with goal setting and endpoints, has been demonstrated to be achievable.[381, 382, 389]

Participants receive regular physician-led consultation, regarding risk factor modification via any appropriate intensification of treatment for hyperlipidemia, physical inactivity, hypertension, diabetes/impaired glucose tolerance, tobacco use, obesity, alcohol use, obstructive sleep apnea. Intensification of treatment includes medication optimization as required, adjustment of meal plans and modified exercise programs with or without exercise physiologist input if this is required to reach target exercise volume. Face-to-face interview and/or telephone/video calls involve an initial assessment and follow-up appointments of 30-60 minutes. Anticoagulation according to standard indications for any detected AF is prescribed utilizing the appropriate oral anticoagulation agent. A structured, motivational, and goal-directed program is used for weight reduction within scheduled sessions, with

encouragement to keep an accurate food and physical activity diary. Measurements of weight, blood pressure and results from any appropriate re-assessment tests such as serum cholesterol or glucose are evaluated at each visit. Participants are encouraged to utilize support counselling and schedule more frequent reviews as required. In participants with a body mass index (BMI) greater than or equal to 27kg/m^2, a meal plan and behavior modification are utilized initially for weight reduction. The initial goal is to reduce body weight by 10%. Where participants require extra input to reach exercise targets, an accredited exercise physiologist prescribes regular exercise with a target of 180 minutes per week of moderate aerobic exercise and 30 minutes of home-based resistance training. The exercise prescription is initiated according to baseline exercise testing and physical activity profile. Participants are encouraged to increase their exercise habits progressively until they reach the weekly target volume. Adherence to treatment strategies is assessed at each visit via comparison of prescribed diet, exercise and medication changes with exercise and food diary.

Usual Care

Standard care (control) group participants are issued with once-off written and verbal advice from the physician at study enrolment regarding medical risk factor targets and healthy exercise according to current stroke guidelines.[6, 199] Standard care participants do not attend risk factor clinic and management of this group is left to the referring physician. Completion of a diet and activity diary is not requested.

OUTCOMES

Assessments

All participants undergo repeat assessments including blood testing, cardiopulmonary exercise test, 3-day Holter monitor, trans-thoracic echocardiography, cranial MRI, SF-36 and AFSS

questionnaires at 12, 24 and 36 months. All implantable loop recorders are continuously monitored remotely, as part of standard clinical care post-stroke. Participants in the control group undergo testing annually, without regular review. Speckle tracking analysis of left atrial function is performed offline on the stored two-dimensional echocardiographic images at the beginning of the study and on an annual basis until the end of the trial.

Clinical stroke recurrence is based on the history obtained from patients and their hospitalization history for stroke. Radiological recurrence of stroke is determined by repeat MRI. A new lesion on cranial MRI that is in a new territory is considered a radiological recurrence of stroke. The follow-up schedule is illustrated in table 2.

Primary Outcome

The primary outcome is AF incidence, (greater than or equal to 2 minutes in duration, based on implantable loop recorder requirements for episodes to be this length or longer to be adequately detected)[433] recorded on Implantable Cardiac Monitor over a 36-month period of follow-up.

Secondary Outcomes

Secondary outcomes include clinical and radiological recurrence of stroke assessed using cranial imaging, change in left atrial size on transthoracic echocardiography, change in left atrial function on speckle tracking echocardiography, change in inflammatory markers including hsCRP, IL-6, TNF-alpha using serum assay, change in coagulopathy markers including Thrombin-antithrombin complex, P-selectin (CD62P) and collagen using serum assay, and change in telomere length. In the subgroup with ESUS undergoing baseline and follow-up ECGi, change in left atrial electrical characteristics on ECGi will be assessed.

Outcome adjudication

An independent Clinical Events Committee will adjudicate clinical endpoints. The panel members have expertise in cardiology and neurology management. A Cardiology Subcommittee will review and adjudicate the AF incidence and burden data. A Neurology Subcommittee will adjudicate subsequent clinical and radiological stroke events. These committee members are independent and are not investigators in the trial.

Analyses

All continuous variables will be reported as mean with standard deviation (SD). Participant characteristics, including cardiovascular risk factors and echocardiography parameters, will be compared at follow-up by analysis of covariance (ANCOVA) with adjustment for baseline values. The primary and key secondary endpoint (AF incidence and Stroke recurrence) will each be compared between groups using Cox regression for survival analysis. Baseline and follow-up serum assays will be compared for markers of coagulation, inflammation and telomere analysis. Baseline and follow-up iECG voltage mapping will be compared directly.

Sample size calculation

The study is 80% powered with an alpha value of 0.05 to assess for reduction in the primary outcome of reduction of atrial fibrillation and secondary outcome of radiologic recurrence of stroke and in the intervention group. AF burden (on implantable loop recorder): allowing for 15% attrition, with a sample size of 400 participants (200 in each group), and a planned follow-up of 36-months, 50% reduction in AF burden is expected in the intervention group. Stroke recurrence: allowing for 15% attrition, with a sample size of 270 participants (135 in each group) and a planned follow-up at 36-months, 50% reduction in radiological recurrence

of stroke is expected. Thus, the overall study sample size is 400 participants, with 200 in each group and each participant is assessed for both outcomes individually.

DISCUSSION

The optimal method for achieving control of all lifestyle and medical risk factors following ESUS is currently unknown. While guidelines recommend targets underpinned by varying levels of evidence for each risk factor following stroke[6, 7, 199], there is no specific structured, unified approach with evidence for effectiveness in achieving these targets.[322]

Given there is nearly complete overlap between ESUS risk factors and those for atrial fibrillation,[434-436] we hypothesize that delivering a comprehensive risk factor modification model with evidence of effectiveness in the management of atrial fibrillation[382, 389, 419, 437] should translate to benefit in the ESUS population by modifying the underlying atrial substrate involved,[338, 438] thus leading to reduced AF and a reduction in recurrent stroke compared with usual care. While efforts to predict which ESUS patients will develop AF continue,[439] it is hoped the approach in this trial will arrest atrial substrate progression and even achieve a degree of reversal with tight control of risk factors.

CONCLUSION

The PREDICT-ESUS trial will determine if aggressive risk factor modification following ESUS, compared to usual care is effective in reducing the risk of atrial fibrillation occurrence or recurrent stroke.

Sources of funding

Dr John Fitzgerald is supported by a top-up Central Adelaide Health Network scholarship and a postgraduate research scholarship, both administered through the University of Adelaide. Dr Elliott is supported by a Future Leader Fellowship from the National Heart Foundation of Australia. Dr Gallagher is supported by a Building Leaders Fellowship from the University of Adelaide and a postdoctoral fellowship from the Australian POTS Foundation. Dr Sanders is supported by a Practitioner Fellowship from the National Health and Medical Research Council of Australia and by the National Heart Foundation of Australia.

Disclosures

Dr Sanders reports that the University of Adelaide has received on his behalf lecture and/or consulting fees from Medtronic, Boston-Scientific, and Abbott Medical. Dr Sanders reports that the University of Adelaide has received on his behalf research funding from Medtronic, Abbott Medical, Boston Scientific, and Becton Dickenson. All other authors have no disclosures.

Tables and Figures with Legends

Graphical Abstract: PREDICT ESUS study design

Table 1: PREDICT-ESUS Trial Inclusion and Exclusion Criteria

Table 2: PREDICT-ESUS Trial Study Follow-up Schedule. *Risk factor modification (treatment) group participants are reviewed 3-monthly with extra reviews as required - this may be up to weekly in frequency.

TTE, trans-thoracic echocardiography; MRI, magnetic resonance imaging; ECGi, non-invasive surface ECG voltage mapping utilizing cardiac computed tomography and 252-electrode vest; ILR, implantable loop recorder; SF 36, Short Form 36 Health Survey; AFSS, Atrial fibrillation Symptom Severity Scale

Figure 1: PREDICT-ESUS Trial Workflow and Timeline

Table 1 PREDICT-ESUS Trial Inclusion and Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Primary diagnosis of ESUS • No history of documented atrial fibrillation or flutter during 24 hours ward telemetry or ambulatory Holter monitoring • No known history of atrial fibrillation or flutter • Minimum age of 18 years	• Documented atrial fibrillation or flutter prior to randomization • Serious Underlying Medical Disorder • Age < 18 • Inability to Provide Informed Consent • Being fully anticoagulated prior to randomization • Moderate-Severe Valvular Heart disease • Prosthetic Heart Valve • Endocrinopathy including subclinical thyroid disease

Table 2. PREDICT-ESUS Trial Study Follow-up Schedule

	Initial Visit	1 Week	3 months	6 months	9 months	12 months	15 months	18 months	21 months	24 months	30 months	36 months	End of study
Enrolment and Randomization	x												
Clinical History	x			x		x		x		x		x	
TTE	x					x				x		x	
MRI – brain	x					x				x			
3-day Holter	x					x				x		x	
ECGi		x								x			
ILR Insertion		x											
ILR burden				x		x		x		x		x	x
Blood tests		x				x				x		x	
Risk factor Clinic*		x	x	x	x	x	x	x	x	x	x	x	x
Exercise Physiology*		x	x	x	x	x	x	x	x	x	x	x	x
Exercise Performance		x				x				x		x	
SF 36		x				x				x		x	
AFSS		x				x				x		x	
Phone review													x

*Risk factor modification (treatment) group participants are reviewed 3-monthly with extra reviews as required - this may be up to weekly in frequency.
TTE, trans-thoracic echocardiography; MRI, magnetic resonance imaging; ECGi, non-invasive surface ECG voltage mapping utilizing cardiac computed tomography and 252-electrode vest; ILR, implantable loop recorder; SF 36, Short Form 36 Health Survey; AFSS, Atrial fibrillation Symptom Severity Scale

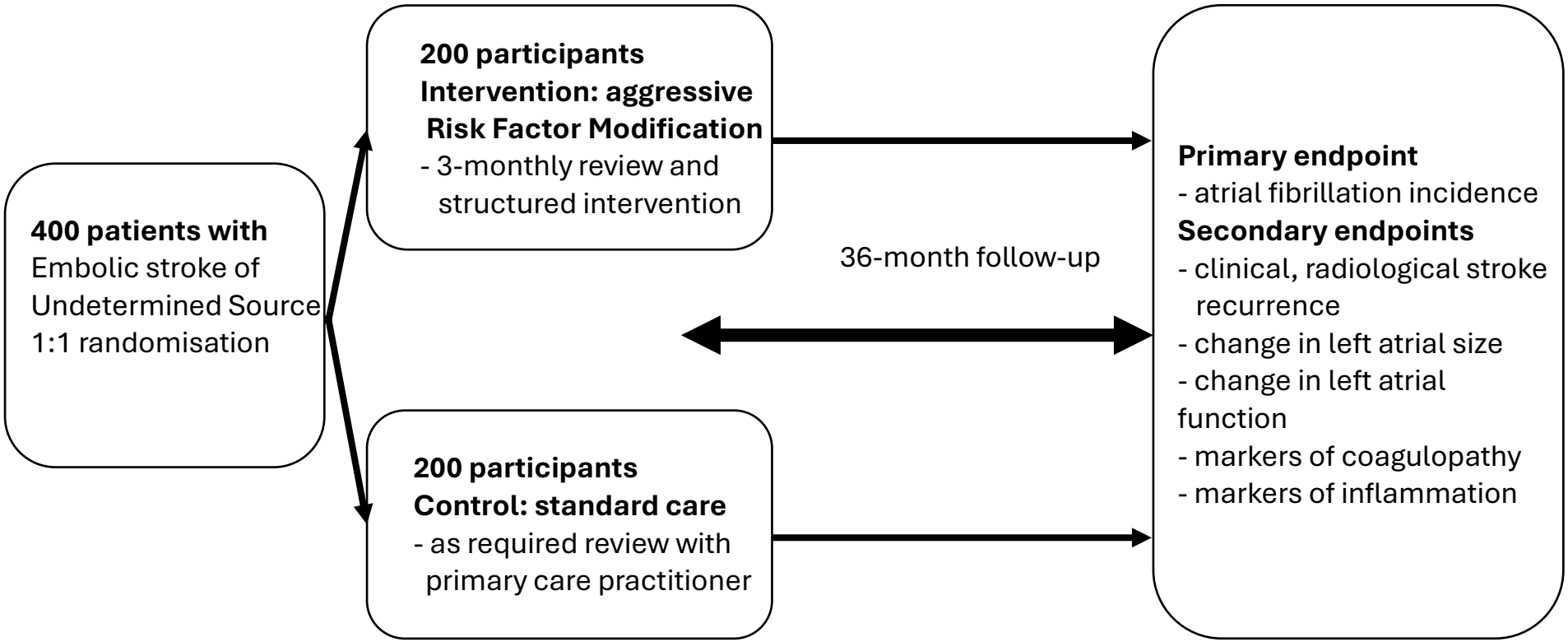
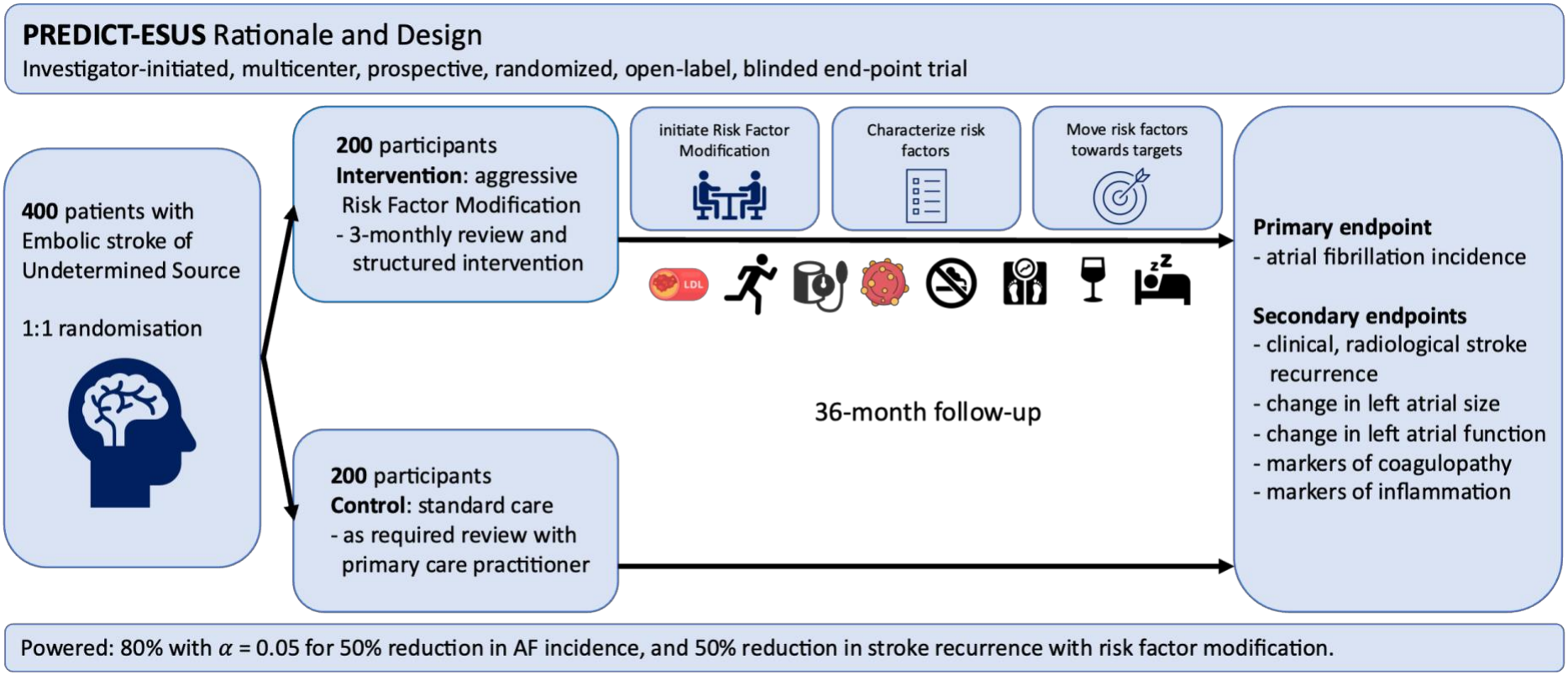


Figure 1: PREDICT-ESUS Trial Workflow and Timeline



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Principal Author

Name of Principal Author (Candidate)	John Fitzgerald		
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Overall percentage (%)	75%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	21st of July 2024

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Mehrdad Emami		
Contribution to the Paper	Concept, editing 5%		
Signature		Date	7/28/2024

Name of Co-Author	Jean Jacques Noubiap		
Contribution to the Paper	Concept, editing 3%		
Signature		Date	7/28/2024

Please cut and paste additional co-author panels here as required.

Docusign Envelope ID: 6CDB2403-D14E-42BE-B0DF-C76892B0D3D0

Name of Co-Author	Melissa M Middeldorp		
Contribution to the Paper	Concept, editing 2%		
Signature		Date	29/07/2024

Name of Co-Author	Adrian D. Elliott		
Contribution to the Paper	Concept, editing 3%		
Signature		Date	27/07/2024

Name of Co-Author	Timothy Kleinig		
Contribution to the Paper	Concept, editing, Supervision 2%		
Signature		Date	7/29/2024

Name of Co-Author	Celine Gallagher		
Contribution to the Paper	Concept, editing, Supervision 5%		
Signature		Date	01/08/2024

Name of Co-Author	Prashanthan Sanders		
Contribution to the Paper	Concept, editing, Supervision 5%		
Signature		Date	7/29/2024

Chapter 3

The PREDICTive value of aggressive risk factor modification on the occurrence of major cardiovascular events in patients with embolic STROKE: PREDICT-STROKE: design and rationale

Short Title: *Fitzgerald et al. PREDICT-STROKE: design and rationale*

John L Fitzgerald MBBS[1,2], Mehrdad Emami MBBS PhD[1,2], Jean Jacques Noubiap MD PhD[1], Melissa E. Middeldorp PhD MPH[1,2], Adrian D Elliott PhD[1], Timothy Kleinig MBBS PhD[1,2], Celine Gallagher PhD[1], Prashanthan Sanders MBBS PhD[1,2]

From: [1]Discipline of Medicine, University of Adelaide and Royal Adelaide Hospital, Adelaide, Australia; [2]Department of Cardiology and Neurology, Royal Adelaide Hospital, Adelaide, Australia.

Correspondence:

Prashanthan Sanders

Centre for Heart Rhythm Disorders

Department of Cardiology, Royal Adelaide Hospital

Adelaide, SA 5000. AUSTRALIA

Telephone: +61883139000; Facsimile: +6183622273

Email: prash.sanders@adelaide.edu.au

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Disclosures

Dr Sanders reports that the University of Adelaide has received on his behalf lecture and/or consulting fees from Medtronic, Boston-Scientific, and Abbott Medical. Dr Sanders reports that the University of Adelaide has received on his behalf research funding from Medtronic, Abbott Medical, Boston Scientific, and Becton Dickenson. All other authors have no disclosures.

Ethical Approval and informed consent

The study protocol was approved by the Human Research Ethics Committee from the Central Adelaide Local Health Network and the University of Adelaide, Adelaide, Australia to cover all participating sites. The study then underwent governance approval at each participating site. Sites included currently are Royal Adelaide Hospital, Queen Elizabeth Hospital, Lyell McEwin Hospital, Flinders Medical Centre, and the Cardiovascular Centre, all in Adelaide, Australia. Central ethics approval has also been granted for interstate sites at Austin Health and Melbourne Health in Victoria, and Canberra Hospital in Australian Capital Territory. All study procedures are conducted in accordance with principles of Good Clinical Practice and the Declaration of Helsinki. Written, informed consent is required from each study participant prior to enrolment.

ABSTRACT

Background

Recurrent stroke and other cardiovascular events occur commonly following embolic stroke, despite medical and procedural management instituted at the time of the event. Whether aggressive lifestyle and risk factor modification (LRFM) following embolic stroke can reduce the occurrence of major cardiovascular events is unknown.

Objective

To assess if LRFM can achieve a reduction in recurrent stroke and other cardiovascular events following embolic stroke compared with usual care.

Methods/design

This multicentre, prospective, randomized, open label, blinded end-point assessment trial commenced recruitment in February 2021. Patients aged between 18 and 85 years with a primary diagnosis of embolic stroke are randomised to physician-led LRFM in a multi-disciplinary outpatient clinic following the 'HEAD2TOES' format targeting hyperlipidaemia, physical inactivity, hypertension, diabetes/impaired glucose tolerance, tobacco use, obesity, alcohol use, and obstructive sleep apnoea or to usual care. The primary outcome is a composite of major adverse cardiovascular events defined as recurrent stroke, asymptomatic cerebral embolism, any acute coronary syndrome, or vascular death over a period of 2 years of follow-up. Secondary outcomes include quality of life assessed by the SF-36 questionnaire, cardiovascular and all-cause mortality, atrial fibrillation burden, cardiovascular and all-cause hospitalization, and transient ischemic attack. The calculated sample size is 1460 participants (730 per group).

Summary

The PREDICT-STROKE trial will evaluate the impact of aggressive LRFM after embolic stroke on the incidence of major cardiovascular events.

Clinical Trial Registration: ACTRN12620000704998.

Key words: Stroke, Secondary prevention, Risk factors, Randomized controlled trial, Integrated care

Non-standard abbreviations and acronyms

LRFM: lifestyle and risk factor management

BACKGROUND

Stroke remains a key healthcare priority, as the second-leading cause of death and third-leading cause of death and disability combined worldwide, with cost estimated at US$891 billion, and 1.12% of global Gross Domestic Product.[1, 2]

Despite guideline-directed medical care recommendations, stroke recurrence remains an important and common problem. Meta-analysis data shows an embolic stroke recurrence rate of 4.3% per year on average, and up to 16-18% at 5 years.[169] In addition to this, mortality and cardiovascular event rates are high, with a Danish nationwide registry showing mortality of 10.5% and cardiovascular event rate of 6.7% in the first year following stroke.[167] Recurrent events have been attributed in significant proportion to underlying cardiovascular comorbidities such as diabetes and atrial fibrillation.[168]

Cardiovascular risk factors drive the mechanisms behind most of the key classifications of ischemic stroke, as described in the original 'TOAST' criteria which include large-artery atherosclerosis, small-vessel occlusion, stroke of other determined aetiology, and stroke of undetermined etiology.[8] Recurrence rates remain high, particularly for large vessel atherosclerosis, cardioembolic (a significant proportion being attributed to atrial fibrillation) and stroke of undetermined source.[440] Links have been proposed in the literature between the mechanisms driving atrial fibrillation, and underlying preceding adverse changes in the left atrium referred to as 'atrial cardiomyopathy'.[377, 441] This atrial cardiomyopathy has been implicated as a likely underlying cause of stroke.[336, 338] and involves adverse structural remodelling, altered haemodynamics and a prothrombotic, pro-inflammatory state, which are almost certainly drivers of thrombus formation in this chamber. This thrombus formation is believed to frequently occur before AF is first detected, or at different times to episodes of AF when continuous monitoring is in place.[355, 357, 438, 442, 443] Prolonged implantable cardiac

monitoring in patients after cryptogenic stroke shows atrial fibrillation in over 12% at 1 year and 30% by 3 years, and more recent data has shown a very similar rate of AF is seen in patients with atherosclerotic disease as the cause of stroke, or in all-comer embolic stroke.[198, 200, 202]

Cardiovascular risk factors and their relationship to atrial fibrillation are almost identical to those for embolic stroke.[444, 445] Individual risk factor control to reduce stroke recurrence has strong evidence for hypertension and hyperlipidemia.[217, 224, 225, 437] National and international guideline recommendations from the AHA, European Stroke Organisation and Australian/New Zealand Stroke Foundation are to target these risk factors, as well as diabetes, sleep apnoea, physical inactivity, smoking and tobacco use.[6, 7, 199] However, an effective comprehensive model which simultaneously targets multiple risk factors to prevent recurrent events via dedicated, ongoing clinic review post stroke has not been tested. Fortunately, lifestyle and risk factor management (LRFM) for atrial fibrillation through a dedicated multidisciplinary clinic has been proven feasible and effective.[381, 382, 389, 419, 420] In The PREDICTive value of aggressive risk factor modification on the occurrence of major cardiovascular events in patients with embolic STROKE (PREDICT STROKE) study, we will apply this LRFM model to determine if this approach can reduce recurrence of major cerebrovascular and cardiac events following embolic stroke or transient ischemic attack.

HYPOTHESIS

This study tests the primary hypothesis that in patients with embolic stroke or TIA, aggressive LRFM via a dedicated, physician-led clinic will reduce recurrent stroke and major cardiovascular outcomes.

OUTCOMES

The primary outcome is a composite of major cardiovascular events (stroke, asymptomatic cerebral embolism, any acute coronary syndrome, or vascular death. Secondary outcomes are quality of life (on short-form 36 questionnaire), all-cause mortality, atrial fibrillation burden, all-cause and cardiovascular hospitalization, and occurrence of transient ischemic attack.

METHODS

The PREDICT-STROKE trial is an investigator-initiated, multicentre, 2-arm, prospective, randomized, open label, blinded end-point assessment trial. Patients aged between 18 and 85 years with embolic stroke or transient ischemic attack are eligible to enrol and are randomized in a 1:1 ratio to aggressive risk factor modification via 3-monthly cardiologist-led clinic review or to usual care with primary health practitioner review. Randomisation in blocks of various size is performed via Research Database Capture (REDCap)[430] software and administered centrally. Adjudication of outcomes will be performed by assessors blinded to participant randomization. A panel of 3 cardiologists and 3 neurologists not involved in trial design or recruitment will assess all trial outcome events and a data safety monitoring board will oversee the study, meeting annually or more frequently as appropriate. The study was approved by the Human Research Ethics Committee of the Central Adelaide Local Health Network and the University of Adelaide, Adelaide, Australia to cover all participating sites (supplement)x. All study procedures are in accordance with principles of Good Clinical Practice and the Declaration of Helsinki.

Study setting and timeline

This trial involves multiple inpatient and outpatient centres in multiple States of Australia, with central co-ordination by the Centre for Heart Rhythm Disorders at the University of

Adelaide, Adelaide, South Australia. As of the 25th of November 2024, all South Australian sites have been activated, and 156 participants have been enrolled. Sites in the Australian states of Victoria and Australian Capital Territory are yet to be activated. The follow-up duration for each participant in this study is 2 years after enrolment.

Funding

This trial is partly funded by an Investigator Grant from the National Health Medical Research Council of Australia and by the Centre for Heart Rhythm Disorders, University of Adelaide, Australia.

Participant Eligibility / Study Population

Written, informed consent is required from each participant. Eligible patients aged between 18 and 85 years with TIA or embolic stroke subtypes of large artery atherosclerosis, cardioembolism where the mechanism is AF, or undetermined source according to standard 'TOAST' trial classification aetiologies are included.[8] Participant enrolment is after full stroke workup testing by a treating neurologist via cranial imaging, head and neck-vessel imaging, and echocardiogram, neurologist confirmed diagnosis, and with a target period of 30 days to 6 months, though allowed up to 12 months after stroke or TIA. Patients are excluded if there is a current or planned pregnancy, if unable to undergo an MRI scan, if there is a history of major surgery <6 months previously, valvular disease needing intervention, left ventricular ejection fraction equal to or less than 35%, active malignancy, autoimmune or systemic inflammation, specific stroke mechanisms: Patent Foramen Ovale, vessel dissection, subacute bacterial endocarditis ; severe renal dysfunction (defined as dialysis, prior or planned transplant, Cr >2.26 mg/dl or > 200 µmol/L); severe liver dysfunction (Cirrhosis or Bilirubin > 2 x Normal or AST/ALT/ALP > 3x Normal); malabsorption disorders;

institutional living; inability to attend appointments; inability to provide informed consent. An outline of these inclusion and exclusion criteria is contained in table 1.

Baseline evaluation

Patients with embolic stroke or TIA have neurologist-adjudicated diagnoses with standard definitions guided by standard workup including cranial MRI, relevant imaging of the head, neck and aortic arch vessels, and initial cardiac rhythm monitoring prior to screening for study enrolment.[446] Once enrolled, baseline testing includes cardiopulmonary exercise testing, 3-day holter monitor, baseline blood sampling for markers of inflammation and thrombosis, serum lipids, electrolytes, renal and liver function, thyroid function, full blood count, iron studies, and N-terminal pro-brain natriuretic peptide. Surveys are administered electronically or where required in paper form at baseline including: Montreal Cognitive Assessment (MoCA),[447] 36-item short form health survey (SF-36),[431, 432] European 5-Dimension 5 Level (EQ-5D-5L) questionnaire,[448] University of Toronto Atrial fibrillation severity scale (AFSS)[383], Hospital Anxiety and Depression Scale (HADS)[449], International Physical Activity Questionnaire (IPAQ) Short Form[450], Fried-based Frailty Phenotype Score.[451, 452] Physical measurements of height, weight, waist circumference, neck circumference, blood pressure, heart rate and a 12-lead electrocardiogram are also performed. Implantable loop recorder insertion is arranged and interrogated if already in place prior to enrolment.

Intervention

Risk Factor Clinic

Risk factors including hyperlipidaemia, physical inactivity, hypertension, diabetes/impaired glucose tolerance, tobacco use, obesity, alcohol use, and obstructive sleep apnoea are

systematically evaluated in each participant. LRFM in a regular cardiologist-led clinic with minimum 3-monthly reviews and additional appointments and email contact according to individual needs are performed as per already-published methodology.[419, 422] Clinicians involved included a doctor, or doctor and nurse (depending on requirements), with additional input from exercise physiologist, sleep physician and endocrinology where indicated.

At initial baseline visit a detailed profile of the patient and family is developed to understand educational levels, value structures, behavioural motivations and medical history (Structured Patient-Centred Education (SPCE)). Structured patient diaries are commenced recording blood pressure, diet and exercise. The HEAD2TOES approach is then used to evaluate risk factors including hyperlipidaemia, exercise, arterial hypertension, type 2 diabetes mellitus, tobacco consumption, ethanol use and sleep apnoea. For each risk factor, achievable goals were defined at appointments to achieve optimization.

Graded exercise recommendations, gradual changes in eating habits and calorie intake, smoking cessation advice and planning, alcohol reduction goal setting and medication titration were utilised at clinic visits. Appointments are 30-60 minutes face-to-face with intermittent telephone/video contact, and ongoing measurements and review of weight, waist circumference blood pressure and participant diary.

Risk factor Targets

Targets for LRFM are in accordance with the published "Adelaide Model" for AF management[419], with adoption of the post-stroke low-density lipoprotein (LDL) target into this model.

Low Density Lipoprotein

The lipid target was an LDL level of <1.8 mmol/L (<70mg/dL) with nutrient intake change and medication titration to achieve this, measurement 6 weeks after changes and then 6-monthly.

Exercise

The minimum exercise target was 150 minutes of moderate intensity activity per week, recorded in participant diary and gradually increased, with exercise physiologist input requested if progress was slow.

Arterial Hypertension

Target blood pressure is ≤130/80 mmHg, to be achieved on 80% or more of home measurements, taken at rest, assessed daily and at varying times with early medication titration to achieve this.

Diabetes Mellitus type 2 and elevated Blood sugar levels

In the presence of diabetes, a hemoglobin A1c (HbA1c) <7% is targeted, and in the absence of diabetes, a normal range fasting glucose of ≤5.5 mmol/L is the aim with retesting 3-6 monthly and exercise and diet changes to achieve this.

Tobacco use

Tobacco use cessation is strongly recommended and the 5As (ask, advise, assess, assist, arrange) is utilized with or without collaboration with the general practitioner to further support quit attempts, utilizing pharmacological support where possible.

Obesity

The target body mass index (BMI) is ≤27kg/m^2, with 10% weight loss initially, and continuing progress towards this target. Methods include reducing snacking and later eating, overnight fasting, reduction in sugar, excess carbohydrate and processed food and a focus on lean protein and vegetable intake.

Ethanol

Alcohol intake recommendation is <100 grams per week, and if AF diagnosed, ≤30 grams per week, with this intake recorded in the patient diary.

Sleep apnea

If no previous assessment performed, all participants were referred to a sleep physician with an aim to perform polysomnography. Treatment recommendation with continuous positive airways pressure (CPAP) is at sleep physician recommendation, but typically suggested for moderate sleep apnea (Apnea-Hypopnea Index ≥15 events/hour) or above.

Usual Care

Participants who are randomized to the control arm receive standard medical therapy left to the discretion of their treating physician, after being provided with once-off written and verbal advice regarding medical risk factor targets and healthy exercise according to current national stroke guidelines[199] at the commencement of study participation. Completion of a diet and activity diary is not requested.

Atrial fibrillation detected during study monitoring in treatment or control groups

Any new atrial fibrillation detected during the study will result in referral to a separate, blinded cardiologist for assessment and management according to recognized AF guidelines.

Anticoagulation according to standard indications for any atrial fibrillation detected is prescribed utilizing the appropriate oral anticoagulation agent (in the absence of any contra-indication).

Assessments

Testing performed annually for all participants includes the following:

Resting transthoracic echocardiography with left atrial and left ventricular strain assessment

Speckle tracking for left atrial and left ventricular function is performed offline on the stored two-dimensional echocardiographic images at the beginning of the study and on an annual basis until the end of the trial.

Cardiopulmonary exercise test

An upright cycle ergometer (Lode Corival, Lode B.V.) and metabolic cart (Vyntus CPX, Vyaire Medical) are utilised and expired carbon dioxide and oxygen consumption averaged over 20 second intervals during continuous pulmonary gas exchange measurement. Exercise echocardiography is performed in a subgroup with ESUS utilising a supine bicycle ergometer to allow echocardiographic imaging during exercise which was commenced at a workload of 20W and increased by 20W every 2 minutes. Exercise was stopped just before E and A wave fusion on imaging, or when symptoms precluded further exercise.

3-day holter monitor

Standard wearable holter monitor, with assessment for atrial or ventricular tachy or brady arrhythmias and burden assessment for any AF detected.

Montreal Cognitive assessment

Performed using recognised published format, by clinicians trained and certified to apply this assessment.

Physical measurements

Height, weight, waist and neck circumference, blood pressure, 12-lead electrocardiograph, loop recorder or other cardiac implantable electronic device interrogation.

Blood testing.

Annual testing full blood count, electrolytes, urea and creatinine, serum lipids, thyroid function, thrombotic markers (von-Willebrand factor, D-Dimer), serum N-terminal Pro-Brain Natriuretic Peptide (NT-Pro-BNP).

Participants in the intervention group are reviewed at a minimum frequency of 3-monthly. Participants in the control group undergo testing annually, without regular review.

Clinical stroke recurrence is based on the history obtained from the participants and their hospitalization history for stroke. Radiological recurrence of stroke is determined by repeat brain magnetic resonance imaging (MRI) performed annually. A new lesion on cranial MRI that is in a new territory is considered a radiological recurrence of stroke. The follow-up schedule is illustrated in table 2.

Primary Outcome

The primary endpoint is a composite of major adverse cardiovascular events defined as recurrent stroke, asymptomatic cerebral embolism, (assessed on annual brain MRI), any acute

coronary syndrome, or vascular death, assessed by participant medical records and self-report assessment.

Secondary Outcomes

Secondary endpoints include: All-cause mortality; Cardiovascular mortality (Classified according to Hinkle-Thaler criteria[453], including: cardiac arrhythmic, cardiac non-arrhythmic, and vascular non-cardiac causes); Stroke; TIA; Asymptomatic cerebral embolism; AF burden on implantable loop recorder or with ambulatory monitoring; All-cause hospitalization; Cardiovascular hospitalization (according to MACCE classification, this includes hospitalization for: Arrhythmic events (AF, atrial arrhythmias, sustained ventricular tachycardia, cardiac arrest) confirmed on ECG; Embolic complications (ischemic stroke, Transient Ischemic Attack, peripheral, pulmonary or systemic embolism) confirmed by a neurologist based on computerized tomography or Magnetic Resonance Imaging; Major bleeding (drop in Haemoglobin level by >2 g/L, or requiring blood transfusion); Heart failure (independent of left ventricular ejection fraction, preferably confirmed by biomarker assessment using NT-pro-BNP); Acute coronary syndrome (STEMI/NSTEMI or unstable angina pectoris) documented on ECG as well as/or assessed in blood levels of key biochemical markers); Quality of Life as assessed by the SF-36 questionnaire.

Outcome adjudication

Two separate, blinded, independent Clinical Events Committees (CEC) have been established to adjudicate clinical events during the course of the trial. A neurological CEC is established to assess all recurrent clinical stroke events, cranial MRIs and neurological hospitalisations, and a cardiac CEC to assess events including heart failure, arrhythmia, major cardiovascular end-point events, death and cardiac hospitalisations. These committee members are not

investigators in the trial and meet every 3 months or as required to independently adjudicate events.

Analyses

Statistical analysis will be performed by a senior statistician with experience in managing clinical trial data. Analyses will be conducted under the intention to treat principle. Logistic regression will be used to calculate hazard ratios for the composite primary end point. Time to event data will be analysed using the Kaplan-Meier method with comparison between-groups using Log-Rank statistics with two degrees of freedom. Pre-specified subgroup analysis will be performed using Cox-proportional hazards regression specifically for participants with a diagnosis of ESUS.

Planned Interim analyses

Two formal interim analyses for the composite primary endpoint will be performed after 1/3rd and 2/3rds of total participants have been recruited and have completed full trial follow-up of at least 2 years. Stopping rules have been planned according to the method of O'Brien and Fleming.[454] The formal stopping criteria to reject the null hypothesis of no difference between treatment groups at two interim analyses are, respectively, p-values <0.0005, 0.014, and $p < 0.045$ for the final analysis of the primary outcome.

Cost-benefit analysis

Prospective approval for data linkage has been obtained to allow for a detailed cost-benefit analysis incorporating true patient healthcare service and pharmaceutical costs over the course of trial enrolment.

Data collection and management

After the enrolment visit, where randomization is performed, all participants receive baseline testing and measurement as described previously, and these measurements, along with repeat blood testing, cardiopulmonary exercise testing, 3-day holter monitor, trans-thoracic echocardiography, cranial MRI and repeat SF-36, EQ-5D, AFSS, IPAQ, HADS, Frailty and MoCA questionnaires are repeated at 12 and 24 months. Clinical trial management is through the Centre for Heart Rhythm Disorders in Adelaide. Data is collected via Research Electronic Data Capture (REDCap), a secure electronic database hosted by the Centre for Heart Rhythm Disorders. A web-based data management system is established to allow multiple researchers to enter the collected trial data simultaneously, to assist in participant tracking and generation of participant follow up schedules.

For the purposes of the study the participants remain identifiable by the treating team. However, the data is de-identified for all analytical purposes and stored on secure servers utilising a custom-made Resource and Data Capture (REDCap) database.

Sample size calculation

Sample size calculation for this trial is based on the composite primary endpoint of major adverse cardiovascular events (MACE). The following assumptions were considered: (1) 24-month minimum follow- up; (2) 27 % annual risk of composite endpoint (6% for recurrent stroke,[170] 15% for asymptomatic cerebral embolism,[455] 6% for any acute coronary syndrome or vascular death)[167]; (3) 25% reduction in MACE recurrence with our planned intervention compared to the standard care group; (4) 15% attrition rate (loss- to-follow-up or withdrawal of consent); (5) 1:1 allocation ratio.

The study will require 1240 participants (620 in each arm) with a = 0.05 and an 80% power. Allowing for a 15% attrition rate, the recruitment aim is for a total of 1460 participants (730 in each arm).

DISCUSSION

Lifestyle and Risk Factor Management targets following stroke are clearly defined in stroke guidelines[6, 7, 199], but sub-optimal risk factor control has been commonly documented in follow-up studies.[324, 325, 327] With 80% of recurrent stroke probably related to poor risk factor control according to Global Burden of Disease study analysis,[331] this is a crucial focus to improve outcomes.

Previous risk factor management trials

While risk factor modification has been recognised as an important priority for stroke secondary prevention for over 3 decades,[279] an effective model for comprehensive delivery has not yet been proven. Models of care explored to date include general practitioner-led / facilitated care,[302] , allied health-led care,[305] pharmacist-led interventions,[314] and specialist outpatient clinic models.[316] While some improvements in blood pressure and physical activity over the shorter term have been achieved with some of these interventions, many have failed to achieve significant change over follow-up. A 2018 updated Cochrane review of organization, educational and behavioural interventions for secondary prevention of ischaemic stroke showed that apart from blood pressure, other risk factor targets were not significantly impacted by trials performed to date in this area.[322]

Evidence for the Risk Factor Clinic model

In the care of atrial fibrillation, comprehensive risk factor modification with the clinic model proposed in this trial has shown proven benefit in reducing AF recurrence. [381, 388, 389] International AF guidelines have adopted lifestyle and risk factor management as a key underlying pillar of AF care, and this forms part of routine practice today for this condition.[147, 149] Aggressive risk factor modification as part of clinical management of AF leads to reverse atrial remodelling with a reduction in atrial size, and favourable change in the electrophysiological and electro-anatomical properties of the left atrium.[381, 382, 388] This has also translated beyond these surrogates into reduced AF symptoms, burden and reversal of the type of AF.

LRFM in a population with embolic stroke

Given the risk factors underlying stroke are the same as those shown to benefit from aggressive LRFM in AF, it would be expected that LRFM would favourably affect the recurrence of clinical events known to be driven principally by these risk factors. The LRFM approach stands to effect substrate for stroke in the left atrium, as well as the vasculature. Indeed, exercise and antihypertensive medications combined have been proven to give superior blood pressure control to medications alone.[456] Cardiovascular event recurrence after stroke is only likely to be partially prevented by medical management only such as aggressive blood pressure and lipid control, and with the addition of holistic lifestyle focus stands to more thoroughly alter the underlying pathophysiology driving events.

CONCLUSION

The PREDICT STROKE trial will determine whether aggressive risk factor modification delivered via a dedicated clinic compared with usual care following embolic stroke can

reduce the occurrence of major adverse cardiac and cerebrovascular events. If this proves successful, it will inform a new model of care delivery to incorporate into clinical guidelines for secondary prevention post-stroke.

References
TABLES AND FIGURES WITH LEGENDS

Table 1. PREDICT STROKE Inclusion and Exclusion criteria.

Table 2. PREDICT STROKE Planned follow-up schedule.

Figure 1. PREDICT-STROKE study workflow.

Inclusion Criteria	• At least 18 years old • Embolic Stroke or TIA
Exclusion Criteria	• Age > 85 years • Pregnancy or planned pregnancy within the next 24 months • Unable to undergo Magnetic Resonance Imaging (MRI) scan • Major surgery <6 months • Valvular Disease Needing Intervention • Left Ventricular Ejection Fraction (LVEF) ≤35% • Active Malignancy • Autoimmune or Systemic Inflammation • Specific Stroke Mechanisms: Patent Foramen Ovale, Vessel dissection, Subacute Bacterial Endocarditis • Severe Renal Dysfunction (defined as dialysis, prior or planned transplant, Creatinine >2.26 mg/dl or > 200 μmol/L) • Severe Liver Dysfunction (Cirrhosis or Bilirubin > 2 x Normal or AST/ALT/ALP > 3x Normal) • Malabsorption Disorders • Institutional Living • Inability to Attend Appointments • Inability to Provide Informed Consent

Table 1. PREDICT STROKE Inclusion and Exclusion criteria

Steps	Initial Visit#	0 M	3 M	6 M	9 M	12 M	15 M	18 M	21 M	24 M
Enrolment and Randomization	x									
Clinical History	x			x		x		x		x
Echocardiogram	x					x				x
Brain MRI	x					x				x
Cardiac MRI	x									x
3-day Holter	x					x				x
Implantable Loop Recorder Insertion		x								
Implantable Loop Recorder interrogation				x		x		x		x
Blood tests		x				x				x
Risk factor Clinic*		x	x	x	x	x	x	x	x	x
Exercise Physiology if indicated*		x	x	x	x	x	x	x	x	x
Exercise Performance		x				x				x
Short Form 36 (SF-36) questionnaire		x		x		x				x
EQ-5D-5L questionnaire		x		x		x				x
Atrial Fibrillation Symptom Severity (AFSS) questionnaire		x				x				x
Montreal Cognitive Assessment (MoCA)		x				x				x
Fried Frailty Assessment		x				x				x
Hospital Anxiety and Depression Scale		x				x				x
Internation Physical Activity Questionnaire		x				x				x

*Lifestyle and Risk Factor Management group only

Table 2. PREDICT STROKE Planned follow-up schedule

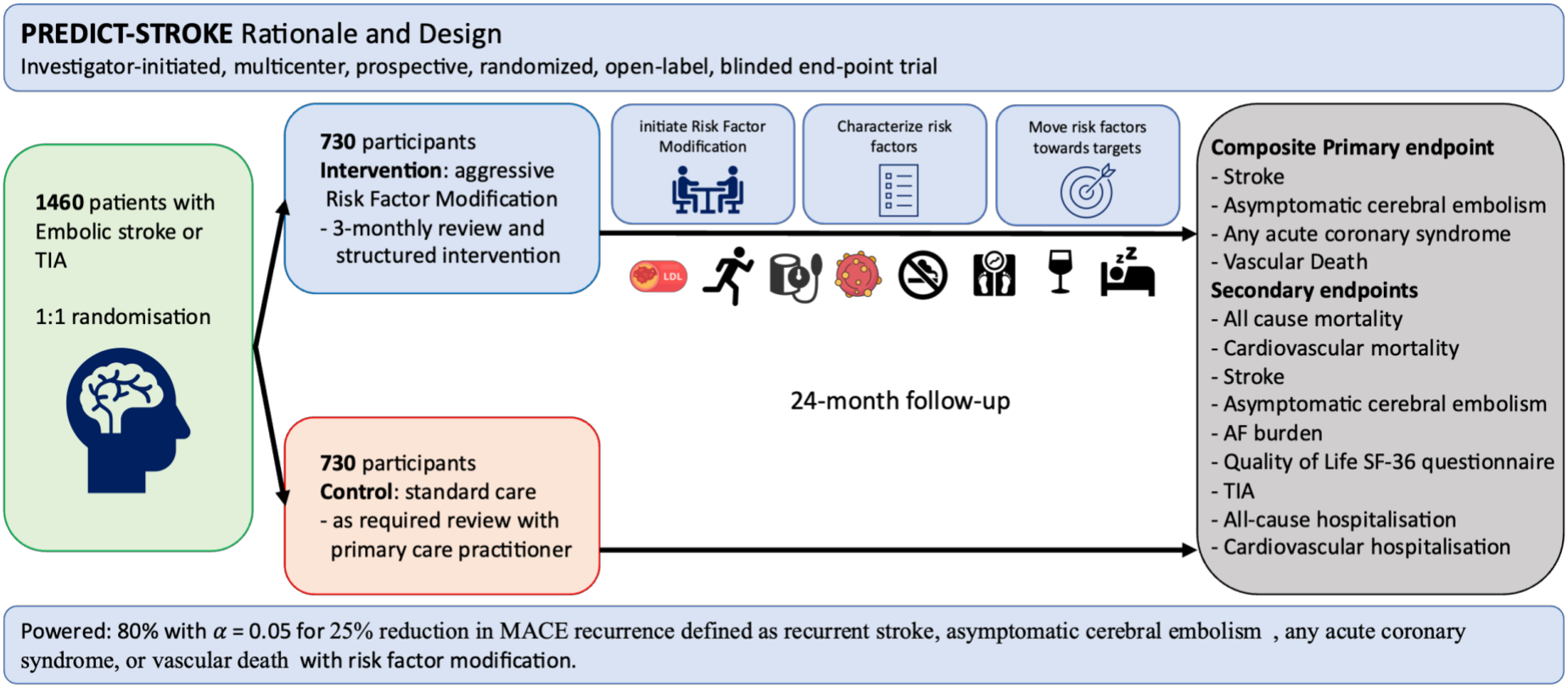

Figure 1. PREDICT-STROKE study workflow

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Principal Author

Name of Principal Author (Candidate)	John Fitzgerald		
Contribution to the Paper	Concept, writing , editing, re-drafting, illustrating		
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Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	11th November 2024

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Mehrdad Emami		
Contribution to the Paper	Concept, editing 2%		
Signature		Date	12/5/2024

Name of Co-Author	Jean Jacques Noubiap		
Contribution to the Paper	Concept, editing 2%		
Signature		Date	12/5/2024

Please cut and paste additional co-author panels here as required.

Docusign Envelope ID: 1D1FDCC7-1CE8-4855-8832-00C71DAA0524

Name of Co-Author	Melissa M Middeldorp		
Contribution to the Paper	Concept, editing 2%		
Signature		Date	06/12/2024

Name of Co-Author	Elnaz Shahmohamadi		
Contribution to the Paper	Statistical Analysis, editing 5%		
Signature		Date	12/9/2024

Name of Co-Author	Mohanaraj Jayakumar		
Contribution to the Paper	Editing 1%		
Signature		Date	12/13/2024

Name of Co-Author	Debra Rowett		
Contribution to the Paper	Editing 1%		
Signature		Date	12/14/2024

Name of Co-Author	Andrew W Moey		
Contribution to the Paper	Editing 1%		
Signature		Date	12/15/2024

Name of Co-Author	Matthew Willcourt		
Contribution to the Paper	Editing 1%		
Signature		Date	12/16/2024

Name of Co-Author	Andrew Lee		
Contribution to the Paper	Concept, Editing 1%		
Signature		Date	12/15/2024

Docusign Envelope ID: 1D1FDCC7-1CE8-4855-8832-00C71DAA0524

Name of Co-Author	Adrian D. Elliott		
Contribution to the Paper	Concept, editing 2%		
Signature		Date	14/12/2024

Name of Co-Author	Celine Gallagher		
Contribution to the Paper	Concept, editing, Supervision 5%		
Signature		Date	15/12/2024

Name of Co-Author	Timothy Kleinig		
Contribution to the Paper	Concept, editing, Supervision 2%		
Signature		Date	12/15/2024

Name of Co-Author	Prashanthan Sanders		
Contribution to the Paper	Concept, editing, Supervision 5%		
Signature		Date	12/19/2024

Chapter 4

Structured Intensive Risk Factor Modification for Secondary Prevention of Ischemic Stroke.

Impact of a Randomized Feasibility Study

Short Title: *Fitzgerald et al. Risk Factor Modification for Ischemic Stroke*

John L Fitzgerald MBBS;[1,2] Mehrdad Emami MBBS, PhD;[1,2] Jean Jacques Noubiap MD, PhD;[2] Melissa E. Middeldorp PhD, MPH;[1,2] Elnaz Shahmohamadi MD, MPH;[2] Mohanaraj Jayakumar MD;[1,2] Debra Rowett B Pharm;[3,4] Andrew W. Moey MBBS;[5] Matthew Willcourt MBBS;[6] Andrew Lee MBBS, MPH;[7] Adrian D Elliott PhD;[8] Celine Gallagher PhD;[2] Timothy Kleinig MBBS, PhD;[1,2] Prashanthan Sanders MBBS PhD[1,2]

From: [1]Departments of Neurology and Cardiology, Royal Adelaide Hospital, Adelaide, Australia; [2]Discipline of Medicine, University of Adelaide, Adelaide, Australia; [3]Drug and Therapeutics Information Service, Southern Adelaide Local Health Network; [4]University of South Australia, South Australia, Australia; [5]Department of Neurology, Lyell McEwin Hospital, Adelaide, Australia; [6]Department of Neurology, Flinders Medical Centre, Adelaide, Australia; [7]Flinders University, Adelaide, Australia; [8]School of Biomedicine, University of Adelaide, Adelaide, Australia

Correspondence:

Prashanthan Sanders

Centre for Heart Rhythm Disorders

Department of Cardiology, Royal Adelaide Hospital

Adelaide, SA 5000. AUSTRALIA

Telephone: +61883139000; Facsimile: +61883622273

Email: prash.sanders@adelaide.edu.au

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ABSTRACT

Background

Modifiable risk factors are largely responsible for stroke, but implementation of risk factor management has not been standardized. This study evaluated an intensive lifestyle and risk factor management (LRFM) clinic model following embolic stroke compared to usual care.

Methods

Eligible participants 18 to 85 years old with embolic stroke were randomized 1:1 to 3-monthly multi-disciplinary structured LRFM or to standard primary care for up to 3 years. Risk factors evaluated included hypertension, hyperlipidemia, diabetes or impaired fasting glucose, physical inactivity, overweight/obesity, sleep apnea, alcohol and tobacco use. Key elements of the LRFM intervention included structured person-centered education, shared decision making, achievable goal identification, and refinement at each visit leading to behavioral change to achieve stroke secondary prevention guideline targets.

Results

Of 140 participants enrolled (39% female, mean age 71±9 years) 100±70 days post embolic stroke, 72 were allocated to LRFM and 68 to usual care. Median follow-up was 545 (362-759) days. LRFM was associated with greater likelihood of achieving target blood pressure (Relative Risk [RR] 3.0, 95% CI 2.1-4.4, $p<0.001$), low density lipoprotein cholesterol (RR 1.4, 95% CI 1.1-1.8, $p=0.007$) and exercise volume (RR 1.8, 95% CI 1.2-2.7, $p=0.004$). Overweight or obese LRFM group patients (body mass index (BMI) of >27kg/m^2) achieved better weight reduction compared to the usual care group (7.5±5.4% vs 1.3±4.9%, $p<0.001$). Blood sugar control, alcohol intake and tobacco abstinence were not significantly different. Achievement of all risk factors to target including a BMI ≤27kg/m^2 was significantly more likely (47% versus 0%) with LRFM compared to usual care (RR 3.0, 95% CI 2.2-4.3, $p<0.001$).

Conclusions

Structured multi-disciplinary risk factor management was feasible and led to greater risk factor control than standard follow-up in patients with embolic stroke. Whether this approach reduces cardiovascular and stroke adverse outcomes requires further evaluation.

Registration: ACTRN12620000704998

Key words: Stroke, Secondary prevention, Risk factors, Randomized controlled trial, Feasibility study, Integrated care

ABBREVIATIONS

BMI: Body mass index

LRFM: lifestyle and risk factor management

RR: Relative risk

INTRODUCTION

Cardiovascular risk factors underlying embolic stroke remain crucial targets for secondary prevention,[457] as globally it is estimated that 90% of stroke is preventable by addressing modifiable risk factors.[10] Although there are established guideline targets,[6, 7] the implementation of risk factor management post-stroke has not been standardized. As a result, there remains a substantial risk of further stroke, around 4% annually, reaching up to 18% at 5-years.[170] Subtypes of stroke with the highest recurrence are driven by these risk factors, including cardio-embolism, with a majority attributed to atrial fibrillation (AF), embolic stroke of undetermined source (ESUS), and large vessel atherosclerosis.[8, 440] In addition to recurrent stroke, mortality and overall cardiovascular event rates are high following embolic stroke, at 10.5% and 6.7%, respectively in the first-year post event in a Danish nationwide registry study.[167]

Individual risk factors with strong evidence for management to target after stroke include hypertension and hyperlipidemia.[217, 224, 225] International stroke guidelines endorse treatment targets for these and other risk factors including diabetes, physical inactivity, alcohol intake, tobacco use, and sleep apnea.[6, 7] Unfortunately, there has been minimal success to date in models of delivery for comprehensive risk factor modification following embolic stroke.[322]

For the management of AF, a body of literature has demonstrated the benefit of a structured intensive comprehensive lifestyle and risk factor management (LRFM) program,[381, 386, 388, 389] which has led to consensus statements[458] and new guideline recommendations in AF.[147, 149] The mechanics of this clinic and targets for risk factor control in AF have been previously presented.[419, 422] Therefore, in this study we explore the feasibility of delivering such a structured LRFM to patients following embolic stroke. Here

we present a feasibility pilot study investigating the application of an intensive multi-disciplinary risk factor modification clinic in patients following embolic stroke.

METHODS

Study Participants

Patients aged between 18 and 85 were approached during the 12 months following embolic stroke or transient ischemic attack (TIA) and offered participation in the study. Stroke or TIA diagnosis were based on expert neurologist clinical assessment and according to recognized definitions, with stroke requiring the presence of acute infarction, and TIA being a transient episode of neurological dysfunction caused by focal brain ischemia without acute infarction.[446] Patients were recruited from 5 participating hospitals (Royal Adelaide Hospital; The Queen Elizabeth Hospital; Flinders Medical Centre; Lyell McEwin Hospital and the Calvary Adelaide Hospital, Adelaide, Australia). Patients were excluded if they had conditions that precluded participation in any aspect of the LRFM program, or if the cause of stroke was unlikely to be related to traditional cardiovascular risk factors. The following exclusions were used: pregnancy or planned pregnancy within the next 24 months; inability to undergo MRI scan; major surgery <6 months; valvular disease needing intervention; left ventricular ejection fraction (LVEF) ≤35%; active malignancy; autoimmune or systemic inflammation; patent foramen ovale; vessel dissection; endocarditis; severe renal dysfunction (defined as dialysis, prior or planned transplant, Cr >2.26 mg/dl or > 200 μmol/L); severe liver dysfunction (cirrhosis or bilirubin > 2 x normal or AST/ALT/ALP > 3 x normal); malabsorption disorders; institutional living; inability to attend appointments; and inability to provide informed consent. We considered the benchmarks of retention of participants of at least 80%, and participation in the treatment arm in > 70% of scheduled visits for >70% of participants as proof of the feasibility of this intervention model.[459]

All patients provided written informed consent to the study protocol which was reviewed and approved by the Human Research Ethics Committee of the Central Adelaide Local Health Network and the University of Adelaide. In addition, each participating hospital provided approval for the study. The study was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12620000704998).

The study was partially funded by an Investigator Grant from the National Health and Medical Research Council of Australia. The funder was not involved in the development of the study protocol or monitoring of the study.

Randomization

Following enrollment into the study, all participants were provided verbal and written advice (supplement 1) concerning guideline-directed risk-factor targets. During this visit participants were randomized in a 1:1 ratio via a computer-generated schedule with random block size, stratified by site, to undergo 3-monthly LRFM clinic follow-up or usual care for up to 3 years post-enrolment.

Usual Care

In the usual care group, participants attended an enrollment visit with detailed history taking and profiling, were provided with the same advice on risk factor targets as the control group, and then continued care with their regular general practitioner, with call back to risk factor clinic for follow-up testing only.

Risk Factor Clinic

The LRFM included regular cardiologist-led clinic review. The clinic structure and methodology of intervention have been previously described.[419, 422] In brief, multi-

disciplinary clinic reviews were scheduled at a minimum frequency of 3-monthly, with additional appointments and email contact arranged according to individual needs. Consultations involved input from a doctor or doctor and nurse (depending on requirements). Additional services of exercise physiology, sleep physician review and endocrinology were sought by referrals on an as-required basis.

The structure of the initial visit involved developing a profile of the participant and family to understand their educational levels, value structures, behavioral motivations and medical history (Structured Patient-Centered Education). Following this baseline and ongoing assessment included recording of structured patient diaries for weight, blood pressure, diet and exercise. Systematic evaluation and management was performed of each risk factor using the HEAD2TOES approach[420] and extended to include hyperlipidemia with exercise, arterial hypertension, type 2 diabetes mellitus, tobacco consumption, ethanol use, and sleep apnea. Achievable goals were set at each appointment to gradually achieve optimization of each risk factor. Intervention involved graded exercise recommendations, gradual changes to eating habits and calorie intake, smoking cessation advice and planning, alcohol reduction goal setting and medication titration. Appointments were between 30 and 60 minutes face-to-face or intermittently by telephone/video with measurements of weight, waist circumference, blood pressure and review of participant diary. The risk factor clinic structured appointment format is summarized in Figure 1.

Risk Factors, Measures and Targets

The LRFM clinic undertook comprehensive management of each risk factor that was identified in a given individual. The methods of the "Adelaide Model" in AF management have been outlined[419] and the targets for each risk factor have been presented.[422] These targets

correspond with targets specified in stroke guidelines, with the exception of a low-density lipoprotein (LDL) target, which was added.

Low Density Lipoprotein

The lipid target was an LDL level of < 1.8 mmol/L (<70 mg/dL), with nutrient intake change and medication titration used together to achieve and sustain this. Repeat testing was performed at appropriate intervals of 6 weeks after changes in treatment, and 6-monthly.

Exercise

The exercise minimum target was 150 minutes of moderate intensity per week. This was recorded in the patient diary, reviewed at each visit, and a structured approach advised to increase gradually where appropriate. Where progress was slow, review with an exercise physiologist was sought.

Arterial Hypertension

The blood pressure target was a measurement of ≤130/80 mmHg (consistent across US stroke and AF guidelines)[6, 147] with an aim to achieve this 80% or more of the time on home measurements, taken at rest and assessed daily at one or more varying times of day. Medication titration was performed to achieve this target, which was monitored ongoing with some reduction in frequency of measurements if stable and at target.

Diabetes Mellitus type 2 and elevated Blood sugar levels

A fasting glucose within the normal range (≤5.5 mmol/L) was the aim for patients without diabetes, or a hemoglobin A1c (HbA1c) <7% if established type 2 diabetes (T2DM). This

was re-tested 3-6 monthly as appropriate with key interventions of nutrient intake change, exercise increase, and body weight reduction applied.

Tobacco use

Cessation of all forms of tobacco use was recommended, and motivational interviewing implementing the '5A's' (ask, advise, assess, assist, arrange)[460] was performed. Collaboration with the local general practitioner was sought, with or without pharmacological support for quit attempts, as per patient and team preference.

Obesity

The target weight to achieve for patients who were overweight or obese corresponded with a Body Mass Index (BMI) of $\leq 27 kg/m^2$. With significantly elevated weight, the aim was to achieve up to 10% weight loss, in the first instance, and to then continue progress towards the BMI target. Methods advised were reduction and elimination of snacking and late eating, observing overnight fasting, minimizing sugar, excess carbohydrate and processed food, and focusing on lean protein and vegetable intake.

Ethanol

The alcohol intake target was <100 grams per week, or ≤30 grams if AF, and daily intake was also recorded in the patient diary, which was reviewed at each visit.

Sleep Apnea

All participants who had not been assessed were referred for sleep physician review with a view to polysomnography in all patients who would accept testing, given the high rate of underlying sleep apnea known to exist in patients with stroke, and the frequent lack of

traditional symptoms. Treatment recommendations were guided by the sleep physician, typically including CPAP recommendation for those with moderate sleep apnea (Apnea-Hypopnea Index ≥15 events/hour) or above. Participants with a pre-existing diagnosis of sleep apnea were encouraged to present for treatment review and titration of CPAP if required with their usual sleep physician / service.

Outcomes assessed in this study are the proportion of participants achieving guideline-recommended targets for control of each individual risk factor, and across all risk-factors.

Statistical Analysis

This feasibility component of risk factor management being presented in the current study did not undergo formal power analysis. Categorical variables are presented as frequencies and percentages, while continuous variables are summarized as mean ± standard deviation (SD) or median and interquartile range (IQR) if non-normally distributed. For analyzing between-group comparisons, Student's t-test was used for normally distributed continuous data, the Mann-Whitney U test was used for non-normally distributed continuous data, and the chi-square test was used for categorical data. Within-group differences between baseline and follow-up were analyzed using student t-tests, Wilcoxon signed-rank tests (for nonparametric variables) and chi-square tests. Regarding the management of risk factors, the proportion of patients achieving each risk factor was analyzed using a log-binomial regression to assess relative risk. Baseline characteristics were included as covariates in the analysis for group comparisons. All analysis was conducted using STATA 18.0 (StataCorp LLC, Texas, USA). Significance was set at $P<0.05$.

RESULTS

Study Recruitment

From 266 eligible patients identified at participating institutions, 140 participants were enrolled in the study. Figure 2 presents the CONSORT figure of enrollment. 77 patients were excluded for pre-specified exclusions and a further 49 declined participation. Participants enrolled at a mean of 100±70 days after embolic stroke or TIA. Stroke subtypes of enrolled participants were ESUS in 67 (48%), cardioembolic because of AF in 35 (25%), extracranial atherosclerotic disease (ECAD) in 23 (16%) and intracranial atherosclerotic disease (ICAD) in 10 (7%). Five participants (4%) were enrolled after TIA with embolic mechanism suggested by history, cerebral vessel territory affected and/or concomitant atherosclerotic disease detected on work-up. Median follow-up was 545 (362-759) days. Baseline characteristics of participants are shown in Table 1.

Baseline Risk Factor Profiles

Risk factors at baseline were well-balanced between the intervention and control groups, respectively. Hypertension was very common (85%) and (82%), as was hyperlipidemia (83%) and (85%). A history of tobacco use was frequent (51%) and (47%), but the vast majority were ex-smokers, with current smoking in only 2 (3%) and 5 (7%). Other risk factor details are shown in Table 1.

Risk Factor Clinic Attendance

The LRFM intervention was delivered to the 72 participants in the LRFM group with 3-monthly planned minimum frequency, and additional appointments in selected patients, for a mean of 8±5 visits. Six participants withdrew, 5 in the LRFM group and 1 in the usual care group. Reasons for withdrawal were cited as inconvenience of the study in 4, immediate

withdrawal after enrollment with no interest in risk factor modification after initial baseline testing in 1, and no specific reason given for 1 participant. Greater than 6 months of follow-up data was available for all but 4 of the active trial participants.

Change in Risk Factor Profile

Comparison of baseline risk factor status to final follow-up within and between groups is shown in Table 2 and Figure 3.

LRFM Compared to Usual Care

With no significant difference between groups in risk factor status at baseline, LRFM was associated with more frequent achievement of important guideline targets. Risk factor clinic intervention was associated with significantly more chance of blood pressure control to target of ≤130mmHg (Relative Risk [RR] 3.0, 95% CI 2.1-4.4, p<0.001): 20 participants (28%) in the treatment group had a systolic blood pressure at target of ≤130 mmHg, which rose to 96% at study completion. Low density lipoprotein cholesterol (LDL-C) control to target of <1.8mmoL/L was more likely in with LRFM (RR 1.4, 95% CI 1.1-1.8, p=0.007): in 40% of LRFM group participants LDL was at target of <1.8 mmol/L at baseline, which had risen to 88% by follow-up. Achievement of target exercise volume ≥150 minutes/week was also more likely in the LRFM group (RR 1.8, 95% CI 1.2-2.7, p=0.004): 40% of LRFM group participants exercised to target at baseline, and this rose to 72% by follow-up.

A target BMI of ≤27kg/m^2 was present in 42% of the treatment group at baseline, rising to 50% with LRFM, compared with 49% at baseline in the control group, dropping to 40% at follow-up, though this result did not reach statistical significance (RR 1.2, 95% CI 1–1.6, p=0.052). There was, however, a significant difference in the final median BMI of 26.8 (24.3-29.1) in the treatment group compared with the control group final median BMI of 27.5

(24.9-30), p<0.001, and the average weight change in participants with a BMI >27kg/m^2 of 7.5±5.4% in the treatment group compared with 1.3±4.9% in the control group (p<0.001).

Recommendation and referring for sleep apnea testing in the LRFM group achieved test completion in 38 (53%), with 18 (25%) pending testing, for a potential achievement of 78% tested, with 14 (37%) having moderate or severe OSA (apnea-hypopnea index ≥15 events per hour). Of these, 7 (50%) reported compliance with CPAP prescribed with downloads from CPAP machine checked to verify this. This compares to a total of 9 (13%) of the control arm tested during follow-up, with a similar rate (33%) of moderate or severe OSA in those tested.

HbA1c target was achieved in a higher proportion of diabetics numerically in the LRFM group, but this did not reach statistical significance (RR 1.6, 95% CI 0.8-3.2, p=0.188). Changes in alcohol consumption and smoking were not statistically different between groups (RR 1.1, 95% CI 0.9-1.2, p=0.223 and RR 1, 95% CI 0.9-1.0, p=0.212 respectively).

Finally, achievement of all risk factors to target (achieved in 47% in the LRFM group versus 0% in the control group) was significantly more likely in the LRFM group, compared to the control group (RR 3.0, 95% CI 2.2-4.3, p<0.001).

Participant retention and Clinic attendance

Participant retention in the study exceeded the 80% benchmark, with 93% of the treatment group continuing follow-up through the study and 98.5% of the control group. LRFM clinic attendance exceeded the benchmark of 70% among 70% of participants. In fact, when examined amongst all enrolled treatment arm participants (including those who withdrew), the clinic attendance was on average >77% across each 3-monthly timepoint. Common reasons for missing a time-point were medium-term holidays, respiratory or other short-term

illness and participants usually then attended the subsequent re-scheduled review, such that very few participants were reviewed at an interval of > 6 months.

DISCUSSION

New Information

Lifestyle and risk factor management is a recommendation for all patients suffering from stroke; however, its implementation and effective change is variable. This study demonstrates the feasibility and impact on risk factors of a structured intensive lifestyle and risk factor modification delivered via a multidisciplinary clinic following embolic stroke. It demonstrates the following:

1. Individuals with ischemic stroke have significant and multiple co-existent risk factors;
2. A dedicated clinic, partnered with Cardiology services, is feasible and highly effective in obtaining increased control of medical and lifestyle risk factors compared with usual care.

The implementation of guideline recommendations remains an important obstacle for the improvement of patient care. The feasibility of achieving such a change in risk factor profile is expected to translate to improved cardiovascular outcomes including recurrent stroke.

Risk Factors and Recurrent Stroke

Strict blood pressure control after stroke or TIA is a key priority, with meta-analyses and meta-regressions showing a linear reduction in risk of stroke, myocardial infarction and death with lower achieved systolic or diastolic blood pressure, a proposed systolic threshold of ≤130mmHg and a greater likely risk reduction with greater absolute magnitude of blood pressure reduction.[217, 218] This target was achieved in the vast majority of participants (96%) in the LRFM arm in this study.

In the Treat Stroke to Target study, an LDL reduction target of <1.8 mmol/L led to a reduction in recurrent stroke and major cardiovascular events in patients with atherosclerotic disease without evidence of an increase in intracranial hemorrhage or new onset diabetes.[224] Meta-analysis including this study data confirms the reduced stroke risk, though with a slight increase in risk of intracranial hemorrhage, albeit with a high number needed to harm for this outcome and a significantly lower number needed to treat for cardiovascular event reduction.[225] In our study, an LDL of <1.8 mmol/L was achieved in 88% of the LRFM group, with the use of oral lipid lowering agents. Anti-lipid therapy escalation was required nearly one third of the time, supporting the strategy of follow-up dose titration after initiation of high-dose statin at the time of stroke.

Randomized data is limited for the benefit of intensive glucose lowering and secondary prevention of stroke. Large studies including the UK Prospective Diabetes Study (UKPDS), Action to Control Cardiovascular Risk in Diabetes (ACCORD) and others have shown minimal impact on macrovascular events.[45, 461] A meta-analysis of randomized trials of intensive glucose lowering compared with usual glucose control showed 10% reduction in major cardiovascular events, but no reduction in stroke, and a U-shaped curve for lowest mortality associated with an HbA1c of 7.5%.[462] In our study we aimed for guideline-recommended HbA1c <7% in participants with T2DM,[7] and this was achieved in 86% of cases in the LRFM arm by follow-up. A numerically higher proportion reached HbA1c target and achieved normal-range fasting blood sugar in the treatment group compared to controls, though this did not reach statistical significance, likely due to low participant numbers.

Post-stroke OSA is associated with increased all-cause mortality and increased vascular events, with CPAP the gold-standard treatment post-stroke. Despite this, trials of CPAP following stroke investigating effects on cardiovascular events have been neutral, or underpowered with trends to reduced events only.[463, 464] In our study, testing for obstructive

sleep apnea was encouraged in all participants in the treatment arm, and just over one third of patients tested had moderate or severe obstructive sleep apnea, with nearly all prescribed CPAP by a sleep physician.

Metabolic risk factors are common with stroke, and losing weight is associated with reduced severity of hypertension, sleep apnea, insulin resistance and left atrial dysfunction in populations without stroke.[59, 270, 272] In our study participants were encouraged to reduce BMI to ≤27kg/m^2 in all cases, with increased intensity of effort if fasting glucose was above the upper limit of normal (5.5 mmol/L). A mean reduction of 8.1 kg (7.5% of body weight) in those with BMI >27kg/m^2 at enrolment and an increase in proportion of participants with a BMI ≤27kg/m^2 from 42% at enrolment to 50% at follow-up in the LRFM group is evidence of at least moderate effectiveness from this approach.

Exercise after stroke has shown beneficial effects on measures such as VO_2 max, 6-minute walk test and timed-up and go testing with subacute treadmill, bicycle ergometer and general aerobic exercise interventions.[260, 262] For more chronic-phase stroke recovery, structured aerobic or strength training for 10-12 weeks has shown initial and sustained gains in some or all of these parameters.[266] In cardiovascular risk reduction there is a lack of randomized data, though impacts on blood sugar regulation, blood pressure and left atrial compliance would all be expected to be positive with ongoing regular exercise. In our study, the proportion of participants exercising to target volume of 150 minutes per week or more was increased from 40% to 72% by follow-up in the LRFM arm, compared with no change at 39% in the control group.

There is a lack of randomized evidence for alcohol reduction after stroke, though alcohol reduction has been shown to decrease blood pressure, with greater reductions in those with higher blood pressures, and the incidence of diabetes is lower with low alcohol compared with heavy alcohol consumption.[256, 257] In this study alcohol intake was at or below

the recommended weekly maximum of 10 standard drinks in 90% of participants at trial enrolment, and this proportion increased slightly to 94% at follow-up in the LRFM arm, with a similar proportional increase from 84% to 87% in the control arm.

Smoking cessation after stroke has been shown to occur in around 50% of smokers,[239] and is more likely with more severe stroke, insular cortex infarction, or intensive smoking cessation intervention. Smoking cessation after a first stroke is associated with around 1/3rd relative risk reduction of recurrent stroke.[239, 240] In this study, only 2 participants in the LRFM group and 5 participants in the control group were smoking at enrolment. In the LRFM group, one participant withdrew after enrolment, one continued to smoke, and one switched to weekend vaping. In the control group one participant reported ceasing tobacco use during the study follow-up. This low ongoing tobacco use rate is an encouraging confirmation that public health interventions to reduce smoking rates have been effective (51% were ex-smokers, most having quit many years prior), but highlights the challenge of delivering effective smoking cessation intervention, and the lower likelihood of quitting with the less severe stroke / TIA seen in the ongoing smokers in this study.

Previous Data on Risk Factor Management

This LRFM feasibility study begins to address a lack of evidence for effective models of comprehensive post-stroke risk-factor care. Since the mid-1980s, the strategy of risk factor modification for stroke has been mentioned in the literature.[279] Various randomized trials of nurse-led interventions have been examined in a meta-analysis in 2018 which showed an improvement in blood pressure control, and in a subset of the studies, physical activity, diet and medication adherence.[297] Examples of other models used in studies to deliver risk factor control include general practitioner-led / facilitated care,[302] pharmacist-led interventions,[305] allied health-led care,[314] and specialist outpatient clinic input.[316] These studies have

sometimes shown improvements in blood pressure and physical activity where these were targeted, but many have failed to significantly change risk-factor control at follow-up.

One Cochrane review, updated in 2018, detailed 26 studies assessing organizational interventions and 16 assessing educational and behavioral interventions.[322] While blood pressure target was more often met, other modifiable risk factors such as lipid profile and HbA1c did not show improvement with the interventions studied. Given the predicted increased disease burden due to inadequate risk factor control in analysis of the Global Burden of Disease study,[457] effectively controlling risk factors remains a crucial priority.

The Case for a Dedicated Risk Factor Clinic

The importance and effectiveness of comprehensive risk factor modification have been demonstrated in the care of patients with AF.[381, 389] This approach to care for cardiac patients utilizing clear information, structured, patient-focused care in a multi-disciplinary integrated team setting, has shown clear evidence for reduction in AF, improvement in patient satisfaction, and is cost-effective,[465] leading to inclusion in major international guidelines.[147, 149] Further efforts to predict which patients with ESUS will go on to develop AF also remain foci for ongoing research.[439] Reduction in AF occurrence and burden through risk factor modification[437], along with positive changes in left atrial structure and function can be expected to translate into a post-stroke cohort, given the risk factors are the same. This specific clinic-based approach to secondary prevention of stroke should now be tested in randomized trials assessing recurrent stroke and major cardiovascular events.

Study Limitations

While this study recruited from multiple institutions with stroke services, the LRFM intervention was delivered by and at locations with dedicated LRFM clinics within the

Cardiology service. This study represents a feasibility evaluation in the stroke population and demonstrates effective and improved risk factor control. Whether the same results are achievable at other sites without this experience or scalable to large numbers of patients remains unknown. Finally, how such management changes future cardiovascular and stroke events has not been evaluated in this study.

CONCLUSION

Structured, intensive lifestyle and risk factor modification following embolic stroke is feasible and effective in achieving control-to-target of medical and lifestyle risk factors with significantly better risk factor control than usual care. A randomized comparison of this intervention is needed to determine whether surrogate measures of effective risk factor control translate into a significant reduction in stroke and other cardiovascular events.

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Disclosures

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TABLES AND FIGURES WITH LEGENDS

Graphical Abstract: Summary of the study findings.

Figure 1: Risk Factor Clinic structured visits and Control Arm. Acknowledgement to AF clinic figure with HEAD2TOES 'Adelaide' model described by Linz et al in the 2024 9th AFNET/EHRA consensus conference document. Emphasis shifted from heart failure to High LDL (low density lipoprotein) control in this stroke trial population, where heart failure was an exclusion criterion. BSL: blood sugar level.

Figure 2: CONSORT figure of study recruitment.

Figure 3: Lifestyle and Risk Factor Management or Usual Care

Table 1: Baseline characteristics.

Table 2: Risk factor modification results.

Table 3: Risk factors at target.

Graphical Abstract

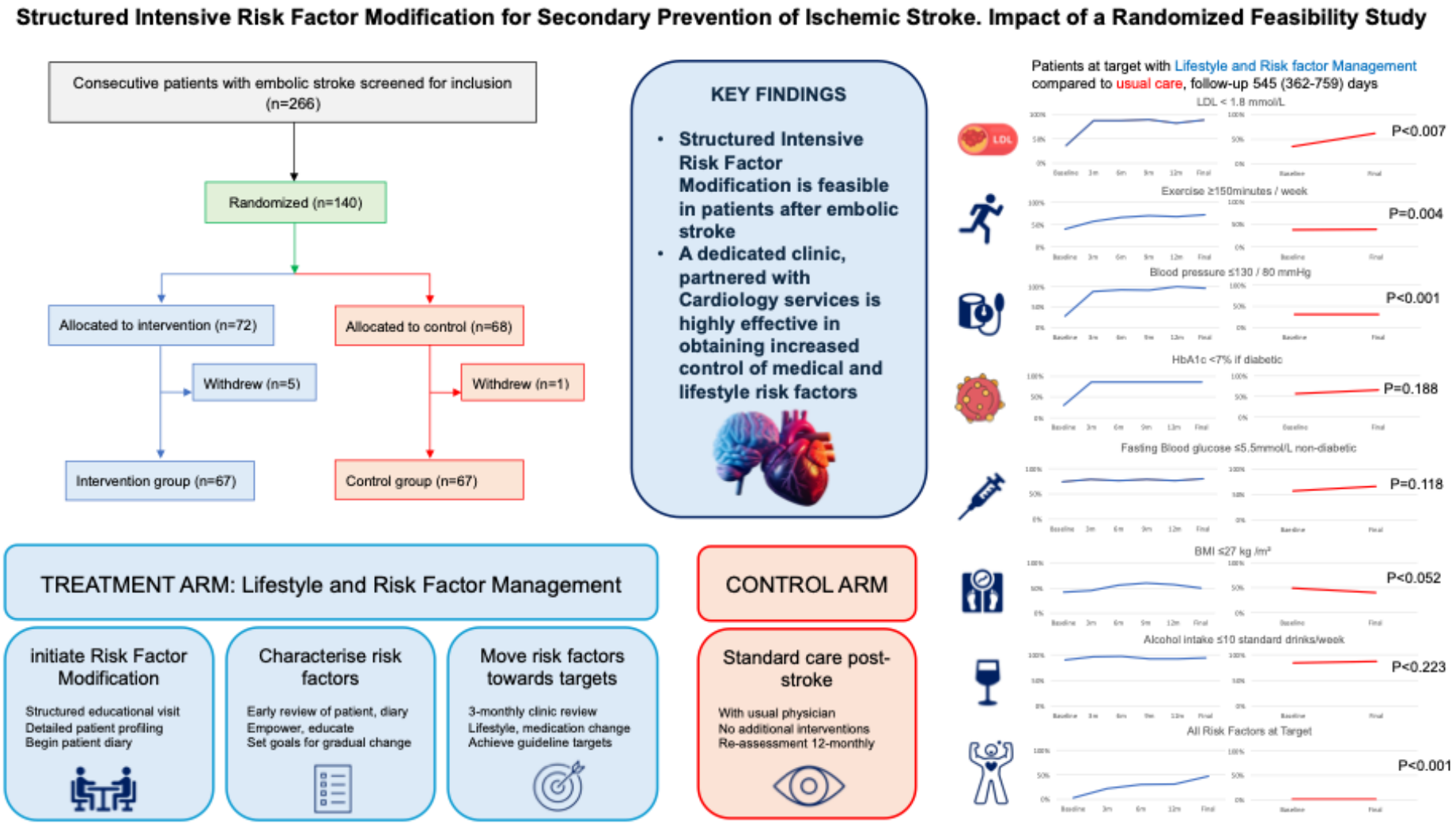
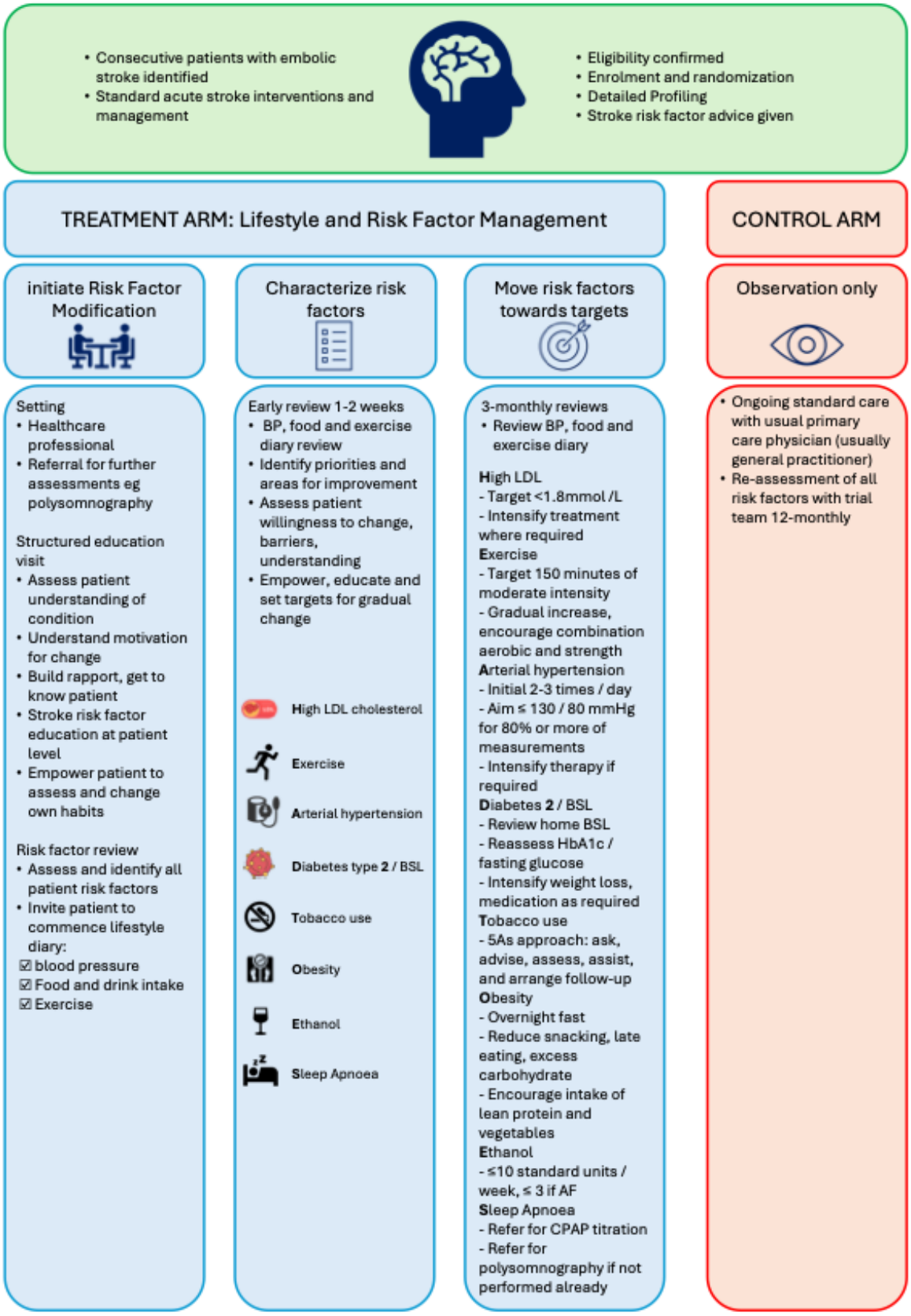


Figure 1: Risk Factor Clinic structured visits and Control Arm



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from heart failure to High LDL (low density lipoprotein) control in this stroke trial population, where heart failure was an exclusion criterion. BSL: blood sugar level.

Figure 2: Consort Diagram

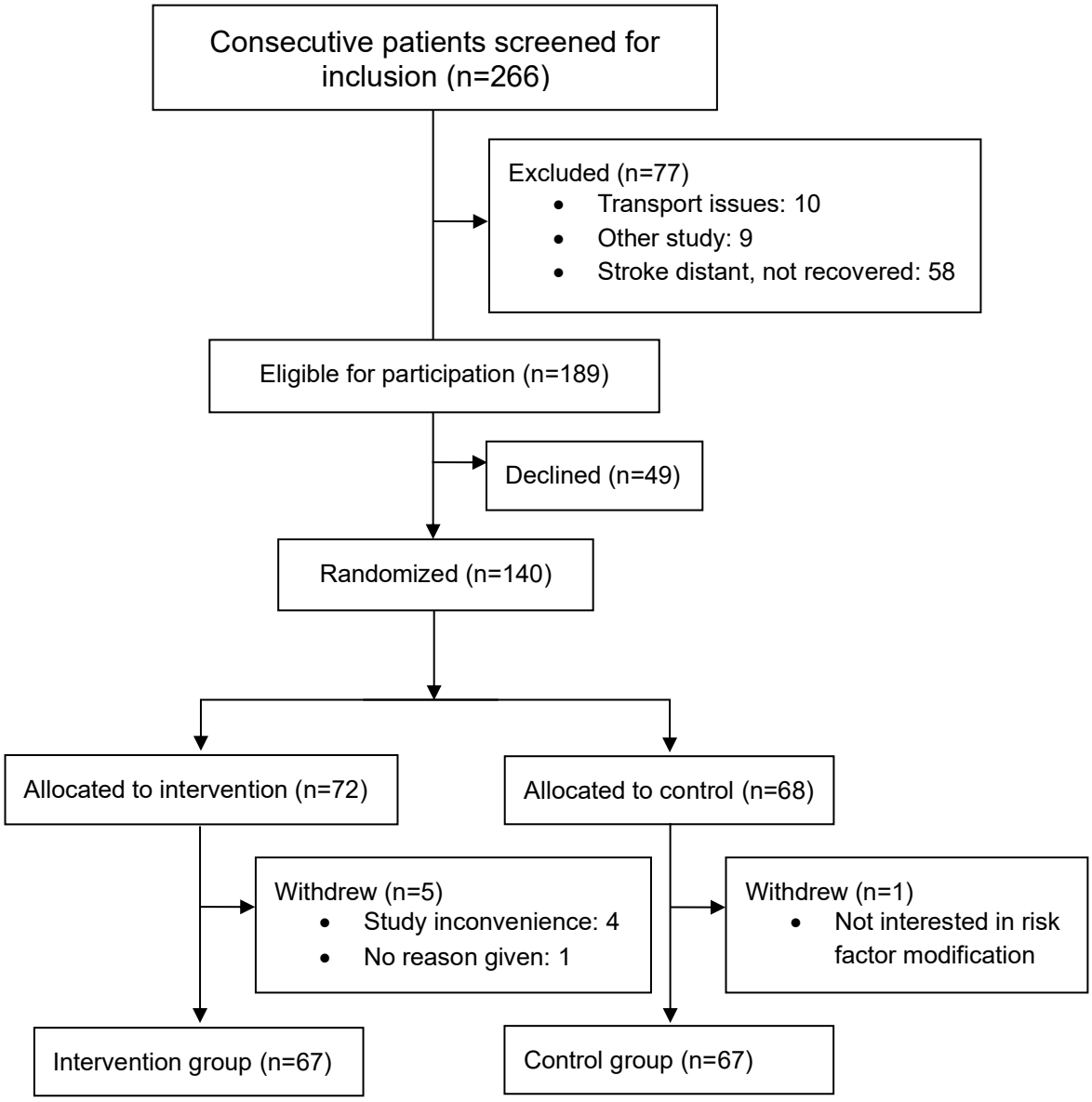

Figure 3: Lifestyle and Risk Factor Management or Usual Care

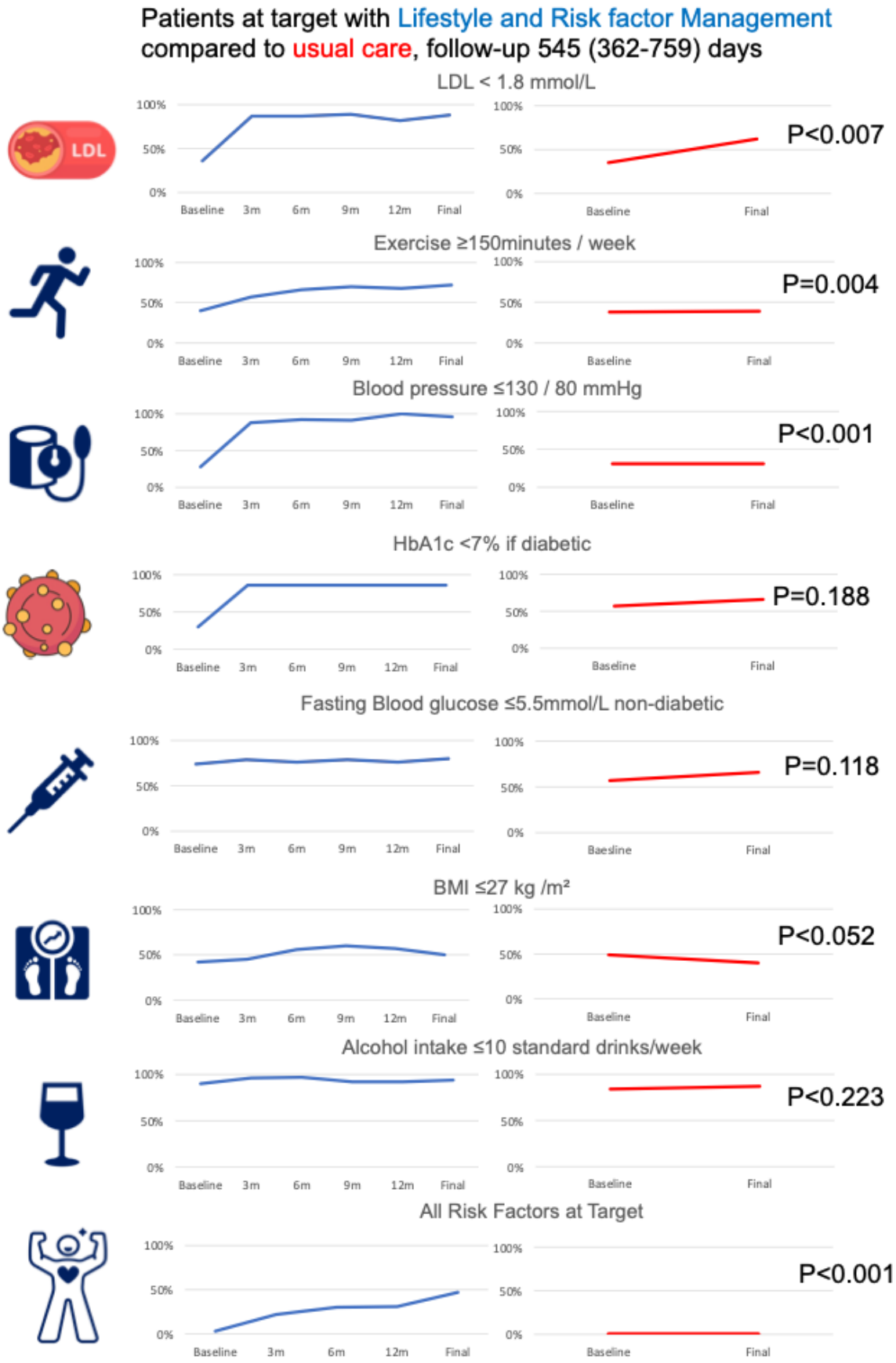

Table 1: Baseline Characteristics

	LRFM Group (n=72)	Usual Care Group (n=68)
BASELINE CHARACTERISTICS		
Age	71.5 (65-77)	74 (68.5-79)
Female Sex	30 (42%)	25 (37%)
STROKE DETAILS		
Embolic Stroke of Undetermined Source	34 (47%)	33 (49%)
Atrial Fibrillation	18 (25%)	17 (25%)
Extracranial atherosclerosis	11 (15%)	12 (18%)
Intracranial atherosclerosis	4 (6%)	6 (9%)
Transient Ischemic Attack	5 (7%)	0 (0%)
National Institutes of Health Stroke Scale	3 ± 5	3 ± 5
Days post-stroke at enrolment	79.5 (42.5-154.5)	95.5 (54-128)
STROKE RISK FACTORS		
Body Mass Index (BMI) (kg/m^2)	28.3 (25.8-31.3)	27.1 (24.8-31.2)
Number with BMI >27	42 (58%)	35 (51%)
Median BMI if >27	30.9 (29.6-33.7)	31.2 (28.7-33.2)
Hypertension	61 (85%)	56 (82%)
Systolic Blood Pressure (mmHg)	136 (127-152)	137.5 (125.5-156.5)
Diastolic Blood Pressure (mmHg)	77 (71.5-82)	77 (70.5-81.5)
Mean number of antihypertensive medications	1.3 ± 1	1.6 ± 1.2
Hyperlipidemia	60 (83%)	58 (85%)
Low Density Lipoprotein (LDL) (mmol/L)	2.1 (1.45-2.75)	2.2 (1.6-3.2)
Mean number of lipid lowering medications	1 ± 0.5	1.1 ± 0.3
Diabetic	10 (14%)	16 (24%)
If Diabetic, median Hemoglobin A1c	7.15 (6.7-7.9)	6.9 (6.4-8.6)
Median fasting glucose if diabetic	7.1 (5.9-8.5)	8 (6.8-10.7)
Glucose Intolerant (Fasting glucose >5.5 mmol/L)	16 (22%)	22 (32%)
Median fasting glucose if >5.5 mmol/L	5.9 (5.8-6)	5.85 (5.6-6.1)
Obstructive Sleep Apnea	8 (11%)	4 (6%)
Continuous Positive Airway Pressure (CPAP)	3 (4%)	2 (3%)
CPAP prescribed	5 (7%)	3 (4%)
CPAP compliance (used / prescribed)	3 (60%)	2 (67%)
Regular alcohol use	43 (60%)	33 (49%)
Median number of drinks/week (total)	2 (0-7)	0 (0-6.5)
Median number of drinks/week (drinkers)	6 (3-9)	7 (3-14)
Number of drinkers >7 per week	12 (17%)	14 (21%)
Median number of drinks/week if >7	13 (10-17.5)	14.5 (12-28)
Number of drinkers >10 per week	7 (10%)	11 (16%)

Median number of drinks/week if >10	14 (14-28)	21 (14-28)
History of Tobacco use	37 (51%)	32 (47%)
Median pack years if tobacco use history	20 (10-30)	22.5 (8.75-37.5)
Current smoking	3 (4%)	9 (13%)
Continuing to smoke after stroke	2 (3%)	5 (7%)
ECHOCARDIOGRAM PARAMETERS		
Left Ventricular Ejection Fraction (%)	61 (55.5-66.5)	60 (55-65)
Left Ventricular Septal Thickness (cm)	1.1 (0.9-1.2)	1.1 (0.9-1.3)
Left Ventricular Hypertrophy (>1cm)	38 (53%)	35 (51%)
Left Ventricular Internal Diameter End Diastole (cm)	4.6 (4.2-5.0)	4.5 (4.2-4.9)
Left Atrial Volume Indexed (mL/m^2)	32 (27-40)	32 (27-36)
Left Atrial Area (cm^2)	19 (16-23)	18 (15-23)
Left Atrial Diameter (cm)	3.8 (3.4-4.1)	3.7 (3.4-4.1)

Values are presented as mean +/- standard deviation or median (quartile 1 – quartile 3) where non-normally distributed

Table 2: Risk Factor Modification Results

	LRFM Group		p-value*	Usual Care Group		p-value*	p-value†
Risk Factor Modification Intervention results	**Baseline**	**Follow-up**		**Baseline**	**Follow-up**		
Follow-up duration to date (days)		545 (352-743)			520 (372-776)		0.998
Follow-up appointments		8 ± 5					
Body Mass Index (BMI) (kg/m^2)	28.3 (25.8-31.3)	26.8 (24.3-29.1)	**<0.001**	27.1 (24.8-31.2)	27.5 (24.9-30)	0.212	**<0.001**
Number with BMI >27	42 (58%)	33 (46%)	-	35 (51%)	34 (50%)	-	**0.018**
Median BMI if > 27 at enrolment	30.9 (29.6-33.7)	28.6 (27.3-32)	**<0.001**	31.2 (28.7-33.2)	30 (28-32)	**0.015**	**<0.001**
•Average % weight change if start BMI >27		-7.5 ± 5.4			-1.3 ± 4.9		**<0.001**
Hypertension	61 (85%)			56 (82%)			0.820
•Systolic Blood Pressure (mmHg)	136 (127-152)	120 (117-125)	**<0.001**	137.5 (125.5-156.5)	145 (126-152)	0.790	**<0.001**
•Diastolic Blood Pressure (mmHg)	77 (71.5-82)	75 (70-77.5)	**<0.001**	77 (70.5-81.5)	77 (70-82)	0.701	0.061
•Mean number of antihypertensive medications	1.3 ± 1	1.7 ± 0.9	**<0.001**	1.6 ± 1.2	1.6 ± 1	0.588	**<0.001**
•Therapy intensification		31 (43%)			7 (10%)		**<0.001**
•Therapy reduction		7 (10%)			7 (10%)		1

Hyperlipidaemia	60 (83%)			58 (85%)			0.818
•Low Density Lipoprotein (LDL) (mmol/L)	2.1 (1.45-2.75)	1.3 (1.2-1.6)	<0.001	2.2 (1.6-3.2)	1.6 (1.4-2.1)	0.011	0.233
•Mean number lipid lowering medications	1 ± 0.5	1.2 ± 0.5	0.025	1.1 ± 0.3	1 ± 0.3	0.158	**0.01**
•Therapy intensification		24 (33%)			5 (7%)		**<0.001**
Diabetic	10 (14%)			16 (24%)			0.192
•If Diabetic, median Haemoglobin bA1c	7.15 (6.7-7.9)	6.5 (6.2-6.8)	0.062	6.9 (6.4-8.6)	6.4 (6.2-8.6)	0.683	0.170
•Therapy intensification if diabetic		5 (50%)			3 (19%)		0.231
Non-Diabetic	62 (86%)			52 (76%)			0.192
Fasting blood glucose >5.5 mmol/L	16 (22%)	11 (15%)	-	22 (32%)	12 (18%)	-	0.098
Median fasting glucose if >5.5 mmol/L at enrolment	5.9 (5.8-6)	5.3 (4.9-5.6)	**<0.001**	5.85 (5.6-6.1)	5.4 (5-5.7)	0.063	0.399
Obstructive Sleep Apnoea							
•Prior known	8 (11%)			4 (6%)			0.368
•Continuous Positive Airway Pressure (CPAP)	3 (4%)			2 (3%)			-
•New Diagnosis (any) / number tested		34 / 38 (89%)			4 / 9 (44%)		**0.007**
•New Diagnosis moderate or severe / number tested		14 / 38 (37%)			3 / 9 (33%)		1
•Prescribed CPAP	5 (7%)	14 (19%)	-	3 (4%)	6 (9%)	-	0.130
•CPAP compliance (used / prescribed)	3 (60%)	7 (50%)	-	2 (67%)	4 (67%)	-	1

Drinking (any)	43 (60%)	43 (60%)	-	33 (49%)	44 (65%)	-	**<0.001**
•Median drinks per week (all)	2 (0-7)	1 (0-4)	0.002	0 (0-6.5)	0 (0-3)	0.212	0.382
•>10 drinks per week	7 (10%)	4 (6%)	-	11 (16%)	6 (9%)	-	0.417
Current smoking	2 (3%)	2 (3%)	-	5 (7%)	4 (6%)	-	1

Values are presented as mean +/- standard deviation or median (quartile 1 – quartile 3) where non-normally distributed
*P-value comparing baseline and follow-up within groups
†P-value comparing groups at follow-up

Table 3: Risk Factors at Target

Risk Factor Target	LRFM* - baseline	LRFM - follow-up	Control - baseline	Control - follow-up	Relative risk (95% CI)	p-value†
Low Density Lipoprotein <1.8 mmol/L	26 (36%)	58 (88%)	24 (35%)	28 (62%)	1.4 (1.1-1.8)	**0.007**
Exercise moderate intensity ≥150 minutes/week	29 (40%)	48 (72%)	26 (38%)	17 (39%)	1.8 (1.2-2.7)	**0.004**
Systolic Blood Pressure ≤130mmHg	20 (28%)	66 (96%)	21 (31%)	19 (31%)	3.0 (2.1-4.4)	**<0.001**
If Type 2 Diabetes Mellitus, Hemoglobin A1c <7%	3 (30%)	6 (86%)	8 (50%)	6 (60%)	1.6 (0.8-3.2)	0.188
If not Type 2 Diabetes Mellitus, Fasting glucose ≤5.5 mmol/L	45 (74%)	45 (80%)	29 (57%)	23 (66%)	1.3 (0.9-2.2)	0.118
No use of tobacco	70 (97%)	66 (97%)	63 (93%)	51 (93%)	1 (0.9-1.1)	0.212
Body Mass Index ≤27 kg/m^2	30 (42%)	36 (50%)	33 (49%)	27 (40%)	1.2 (1-1.6)	0.052
Alcohol intake ≤10 standard drinks/week	65 (90%)	64 (94%)	57 (84%)	40 (87%)	1.1 (0.9-1.2)	0.223
All Risk Factors at target	2 (3%)	34 (47%)	0 (0%)	0 (0%)	3.0 (2.2-4.3)	**<0.001**

*LRFM: lifestyle and risk factor management group
†Comparison between groups at follow-up

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Publication Details	Trial protocol paper, for submission to publication. Describes a key element of the randomised clinical trial undertaken during this PhD

Principal Author

Name of Principal Author (Candidate)	Dr John Fitzgerald		
Contribution to the Paper	Concept, writing , editing, re-drafting, illustrating		
Overall percentage (%)	75%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	24th July 2024

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Mehrdad Emami		
Contribution to the Paper	Concept, editing 2%		
Signature		Date	7/28/2024

Name of Co-Author	Melissa M Middeldorp		
Contribution to the Paper	Concept, editing 1%		
Signature		Date	29/07/2024

Please cut and paste additional co-author panels here as required.

Docusign Envelope ID: 711FC607-2549-4305-83AE-A7A89FC37533

Name of Co-Author	Adrian D. Elliott		
Contribution to the Paper	Concept, editing, analysis 5%		
Signature		Date	28/07/2024

Name of Co-Author	Timothy Kleinig		
Contribution to the Paper	Concept, editing, Supervision 1%		
Signature		Date	7/29/2024

Name of Co-Author	Celine Gallagher		
Contribution to the Paper	Concept, editing, Supervision 1%		
Signature		Date	01/08/2024

Name of Co-Author	Prashanthan Sanders		
Contribution to the Paper	Concept, editing, Supervision 5%		
Signature		Date	7/28/2024

Name of Co-Author	Patrick M Boyle		
Contribution to the Paper	Concept, Analysis, editing 5%		
Signature		Date	7/28/2024

Name of Co-Author	Nazem Akoum		
Contribution to the Paper	Concept, Analysis, editing 5%		
Signature		Date	8/4/2024

Chapter 5

Characterization of Left Atrial Volume and Fibrosis by Cardiac Magnetic Resonance Imaging Post-Embolic Stroke: Predicting Atrial Fibrillation on Implantable Cardiac Monitoring

Short Title: *Fitzgerald et al. MRI LA Volume Post Stroke Predicts New AF*

John L Fitzgerald MBBS[1,2], Mehrdad Emami MBBS PhD[1,2], Melissa E. Middeldorp PhD MPH[1,2], Adrian D Elliott PhD[1], Celine Gallagher PhD1, Timothy Kleinig MBBS PhD1,2, Prashanthan Sanders MBBS PhD[1,2], Patrick M Boyle PhD[4], Nazem Akoum MD, MS[4]

From: [1]Discipline of Medicine, University of Adelaide, Adelaide, Australia; [2]Departments of Cardiology and Neurology, Royal Adelaide Hospital, Adelaide, Australia; [4]University of Washington, Seattle, WA, United States

Correspondence:

Prashanthan Sanders

Centre for Heart Rhythm Disorders

Department of Cardiology, Royal Adelaide Hospital

Adelaide, SA 5000. AUSTRALIA

Telephone: +61883139000; Facsimile: +61883622273

Email: prash.sanders@adelaide.edu.au

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ABSTRACT

Background

Atrial fibrosis and increased volumes on cardiac magnetic resonance imaging (MRI) are seen in patients with atrial fibrillation (AF) and represent underlying atrial substrate changes. Although similar changes have been described in patients with embolic stroke of undetermined source (ESUS), whether this is associated with the development of AF or recurrent stroke is not known.

Purpose

To characterise atrial fibrosis and left atrial volumes in a cohort with embolic stroke and determine the association with AF detection during follow-up with continuous cardiac monitoring.

Methods

This is a prospective, multicentre, observational study of patients aged 18-85 years enrolled after embolic stroke undergoing cardiac MRI at enrolment with dedicated atrial fibrosis imaging and receiving continuous cardiac monitoring via implantable loop recorder.

Results

Twenty patients with ESUS, 13 (65%) females, mean age 72±6 years, were enrolled a mean of 137±58 days following stroke. During a mean follow-up of 760±252 days, 6 patients (30%) were diagnosed with AF on implantable cardiac monitoring a mean of 234±91 days post-stroke. Mean left atrial volume of 101±30mL vs 75±22mL (p=0.04) and mean left atrial surface area of 138±28cm^2 vs 116±16cm^2 (p=0.04) were significantly higher in patients who developed AF versus those who did not, respectively. Mean left atrial fibrosis was 11±7% in patients who developed AF versus 7±4% in those who did not, though this did not reach statistical significance (p=0.1). In patients with AF, median burden was low at 1% (0.3-1.4),

median longest episode was 251 minutes (113-1422), with 5 of 6 patients having AF episodes over 1 hour and 2 of 6 having episodes over 24 hours long.

Conclusion

Patients with embolic stroke and implantable cardiac monitor-detected AF in this series had increased left atrial volume and left atrial surface area on cardiac MRI when compared with those who did not. Moderate fibrosis was present, though not different between groups, and AF burden was low. Larger cohorts will be needed to refine incident AF and recurrent stroke predictors in this group, to ultimately guide tailored treatment approaches.

BACKGROUND

Atrial cardiomyopathy is a proposed mechanism leading to increased stroke risk and is thought to drive progression to atrial fibrillation (AF) detected after embolic stroke.[198, 200, 202, 335, 336, 338] Adverse atrial remodelling manifests as structural changes including increased size, changes in left atrial strain, and progression to reduced myocardial voltage and then fixed scarring.[339, 345, 348, 352, 353, 466-468] Left atrial fibrosis on cardiac magnetic resonance imaging (cMRI) in patients with embolic stroke of undetermined source (ESUS) has been demonstrated to be significantly higher than in control patients, and similar to that seen in a population with known AF.[352] In one study, increased left atrial fibrosis of ≥12% in patients with ESUS has been associated with recurrent stroke, incident AF or both, though this was with largely intermittent monitoring for AF detection.[353] In this study we employ routine continuous implantable cardiac monitoring for AF to further explore the hypothesis that incident AF can be predicted by atrial cardiomyopathy, as detected by left atrial fibrosis and volume changes on cardiac MRI.

METHODS

A prospective, multicenter, observational study design was utilised in patients aged 18-85 years receiving implantable loop recorders for detection of subclinical AF after ESUS. All patients received guideline-directed post-stroke care, with full characterisation of all cardiovascular risk factors.

Standard protocol approvals, registrations, and patient consents

Approval was obtained from the Central Adelaide Local Health Network Human Research Ethics Committee, with Human Research Ethics Committee Acknowledgement at all other clinical sites, and Human Research Ethics Approval Notification endorsed by the University

of Adelaide. The study was carried out in accordance with principles of Good Clinical Practice and the Declaration of Helsinki, and all study participants provided written informed consent.

Study Population

Patients with ESUS were recruited from sites in Adelaide including the Royal Adelaide Hospital, Lyell McEwin Hospital and Flinders Medical Centre. Patients with ESUS all met published criteria[193] with non-lacunar infarcts of embolic appearance and no apparent cause on intracranial and extracranial vessel imaging, trans-thoracic echocardiogram, initial inpatient telemetry as well as outpatient wearable event monitoring for 1 month, or blood panel for hypercoagulability or other inflammatory disorders. Implantable loop recorders were utilized in all participants after an initial period of inpatient telemetry and a standard approach of 28 days' wearable event recorder with automated AF detection. Participants with patent foramen ovale (PFO), severe claustrophobia, severe renal impairment or other contra-indication to cMRI with gadolinium, severe liver impairment, institutional living, Modified Rankin Scale (mRS) > 3 or inability to attend follow-up appointments were excluded from the study. Complete medical history was obtained by combined hospital chart review and patient face-to-face history and medication confirmation.

Cardiac MRI with LGE

Gadolinium-enhanced cMRI to quantify degree of left atrial fibrosis was obtained for all patients utilizing a previously defined Merisight delayed-enhancement MRI protocol (MARREK Inc).[469] A three-dimensional inversion-recovery, respiration-navigated, ECG-gated, gradient echo pulse sequence was used to obtain LGE-MRI imaging of the left atrium 15 to 25 minutes after contrast injection. Navigator-gated free-breathing and a transverse-

imaging volume with a voxel size of 1.25 × 1.25 × 2.5 mm (reconstructed to 0.625 × 0.625 × 1.25 mm) acquisition parameters were utilized with ECG gating to acquire a small subset of phase-encoding views during atrial diastole. Cine images of the left atrium were used to define the time interval between the R peak on ECG and the start of image acquisition. Fat saturation sequences were used to suppress fat signals. Inversion time was identified with a scout scan of the left ventricle in short axis. Typical scan time was 5 to 10 minutes on the basis of respiration and heart rate. Image acquisition was with a Siemens Magnetom Cima.X scanner. Image processing was performed offline with Corview image processing software (Merisight, Inc, Salt Lake City, UT). Processing and reporting of images was performed by personnel blinded to the clinical details and AF status of the participants.

Statistical Analysis

Analysis was performed utilizing R (version 4.3.2, R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are reported as mean ± SD, or median ± IQR for non-normally distributed parameters and categorical variables are reported as proportions. Wilcoxon rank-sum tests were used to compare LA fibrosis, volumes and surface areas between groups with and without subsequent AF detection. Univariate logistic regression was performed to identify determinants of AF detection with comparison via Wilcoxon-Mann-Whitney, Kruskal-Wallis and chi-square tests. A 2-tailed value of $p < 0.05$ was considered significant.

Results

A total of twenty consecutive eligible ESUS patients consenting to cardiac MRI were recruited, 13 (65%) female, with a mean age of 72±6 years a mean of 137±58 days following stroke. Baseline characteristics are listed in Table 1.

Atrial Fibrillation

All patients participated in continuous remote monitoring after loop recorder implant and were switched to oral anticoagulation after any AF detected. Six patients had new AF detected during study follow-up a median of 251 (113-260) days post stroke. The median detected AF burden was 1% (0.3-1.4) and the median longest episode under 6 hours (251 (113-1422) minutes). Five of 6 patients had AF episodes over 1 hour. Two of 6 patients had episodes over 24 hours long.

Cardiac MRI LGE and LA volumes, AF detected

Cardiac MRI findings for LGE proportion, LA volume and LA surface area are shown in Table 2.

During a mean follow-up of 479±210 days, 6 patients (30%) were diagnosed with AF on implantable cardiac monitoring a mean of 234±91 days post-stroke. Mean left atrial volume of 101±30mL vs 75±22mL (p=0.04) and mean left atrial surface area of 138±28cm^2 vs 116±16cm^2 (p=0.04) were significantly higher in patients who developed AF versus those who did not, respectively. Left atrial indexed volume of 51±17mL/m^2 vs 41±12mL/m^2 (p=0.1) was not significantly different between patients who developed AF versus those who did not. There was no significant difference in left atrial fibrosis with a mean of 11±7% in patients who developed AF versus 7±4% in those who did not, (p=0.1). Figure 1 shows the distribution of values for left atrial fibrosis, volume and surface area in participants who developed AF versus those who did not. In patients with incident AF, median burden was 1% (0.3-1.4), median longest episode was 251 minutes (113-1422), with 5 of 6 patients having AF episodes over 1 hour and 2 of 6 having episodes over 24 hours long.

DISCUSSION

New findings in this study include:

1) Left atrial volume and left atrial surface area were both predictive of subsequent AF detected via routine continuous implantable cardiac monitoring
2) Amount of left atrial fibrosis, Utah score, indexed left atrial volume and cardiac risk factors were not predictive of subsequent incident AF
3) Mean left atrial fibrosis percentage of 11±4 % was close to, but below the previously published cutoff of ≥ 12% seen in patients with ESUS

Empirical anticoagulation

Unfortunately, efforts to prevent recurrent stroke related to presumed underlying LA cardiomyopathy with anticoagulation for ESUS patients in randomised controlled trials have not shown net benefit to date in the NAVIGATE-ESUS, RE-SPECT-ESUS or ATTICUS studies.[194-196] A subgroup > 75 years old in the RE-SPECT ESUS study seemed to derive benefit from routine anticoagulation, and it is possible this is due to the increased rate of AF detection with increased age, though this finding is hypothesis-generating only.[470]

Subclincial AF – how much AF is enough?

A further important clinical question is the amount of subclinical atrial fibrillation required to increase stroke risk enough to warrant switching to anticoagulation. The recently published large LOOP study, involving randomisation to continuous implantable cardiac monitoring in patients without known AF or to usual care included 25% of participants with previous stroke and failed to show net benefit from anticoagulation for a threshold of 6 minutes of device-detected AF in the arm with ILR monitoring.[203] Likewise, NOAH-AFNET 6 did not show benefit of anticoagulation with Edoxaban for 6 minutes – 24 hours of device-detected Atrial

High Rate Episodes (AHREs) in a predominantly pacemaker-monitored population, with a smaller 10% having previous stroke or TIA.[204]

The recently published ARTESIA study showed a reduction in stroke risk and particularly in disabling or fatal stroke with anticoagulation versus aspirin for 6 minutes-24 hours of device-detected AF in a population with 9% having previous stroke or TIA, and predominantly pacemaker or ICD monitoring. This was offset by an increased rate of major bleeding recorded with anticoagulation, though bleeding responded to supportive care and there was no increase in fatal bleeding.[205]

In the ARCADIA study, participants with ESUS and one additional AF risk factor (raised NT-Pro-BNP, ECG markers of LA abnormality or LA enlargement) were randomised to anticoagulation with Apixaban, or to Aspirin. The result was no difference in stroke rates of 4.4% by 18 months follow-up in both arms and the trial was stopped early for futility after a planned interim analysis. Interestingly, only 3.3% of the 1015 participants enrolled had significant LA enlargement as an atrial cardiomyopathy marker, with the vast majority of participants qualifying on BNP or ECG markers alone. [197]

In summary, anticoagulation of all patients with AF or AHRE detection on implantable monitoring of 6 minutes to 24 hours, anticoagulation of all ESUS patients or those with selected risk factors for the development of AF has not shown net benefit for stroke reduction compared to increased bleeding in trials to date. The reduction in disabling or fatal stroke in the ARTESIA study with small increase in manageable bleeding and the possible subgroup benefit of patients > 75 in RE-SPECT ESUS and ATTICUS are thought-provoking and require further research. Prediction of which patients with ESUS or other forms of stroke will go on to develop AF remains a priority, even with the threshold for anticoagulation remaining unclear.

The median AF burden was low at 1% (0.3-1.4) in this study and the median longest episode under 6 hours (251 minutes (113-1422)). This finding of low AF burden is similar to that amongst non-stroke patients in other recent studies such as the ARTESiA trial and NOAH-AFNET 6 trial, though in this current study a larger proportion (5 of 6 patients) had AF episodes over 1 hour. Two of 6 patients in this study with episodes over 24 hours long is a higher proportion than in the ARTESiA trial where only around 9% of patients with incident atrial-high-rate episodes had episodes > 24 hours. This is despite the population in ARTESiA having known device-detected AF at baseline, though with a threshold of only 6 minutes for entry into the study.

Predicting an Atrial Cardiomyopathy

Patients with ESUS have been shown to demonstrate more atrial fibrosis than healthy controls, and to more closely resemble patients with known clinical AF on cardiac MRI.[352] In a multicentre study, patients with ESUS and recurrent events (AF or recurrent stroke) were found to have increased left atrial scarring compared with those who did not have recurrent events.[353] In this current study cohort, left atrial scarring showed a trend towards a higher mean in patients with incident AF detected, though with significant variability, and this did not reach statistical significance. Left atrial volume and surface area were significantly different, which is in contrast to the previous study.[353] This may be due to the difference in AF detection strategy in this study with continuous monitoring in all participants, whereas in the previous study, 26% of the 53 patients with ESUS had ILRs. This may have increased the detection of all AF in the current study, including that which is less related to a scarring process, or to the original stroke itself.

Risk factor profiles in this study showed somewhat higher rates of hypertension and hyperlipidaemia (90%) and (85%), respectively, compared to the previously mentioned ESUS

studies, where these rates are around 75% and 60%, respectively. While hypertension is a strong risk factor for AF, competing causes of stroke such as symptomatic non-stenotic carotid disease, a subset of ESUS, as the cause of the index event, are ever-present possibilities which could reduce the relationship between detected AF and recurrent stroke and might explain why despite a high AF detection rate in this cohort, there were no recurrent strokes seen. A significant detection of 30% of patients having new AF during 15 months of follow-up was quite high, given other studies such as CRYSTAL-AF, PER-DIEM and STROKE-AF have shown lower detection at this time-point.[198, 200, 202] This may have been due to the higher rate of hypertension in this cohort, though diabetes was a little lower at 15%, and has been closer to 25% in other ESUS studies.

Clinical implications

Given this study has shown that incident AF on continuous cardiac monitoring may be more related to left atrial size and surface area than left atrial scar burden, ESUS patients with these findings may also be at more risk of future stroke recurrence and could be chosen to undergo closer clinical surveillance and testing. The threshold for longest AF episode duration or overall AF burden necessary to predict clinically significant increased stroke risk, however, remains unclear.

Limitations

A key limitation of this cohort study is the limited sample size, however there was a 30% event rate of detected AF over a follow-up of just 15 months. Loop recorder implant was somewhat delayed after initial 1-month wearable monitoring, at a mean of 152±84 days, reflecting local timeframes for neurology outpatient review following initial monitoring period and for completion of procedures once referral is made. This may have led to some

early AF being missed, but if clinically significant, it would be expected to recur during the ongoing monitoring period. It was not possible to look at other harder endpoints such as stroke recurrence or major cardiovascular events due to the small sample size, and in fact no patient in this study had any stroke recurrence at the date of last data collection. This may have reflected the effectiveness of contemporary stroke secondary prevention measures employed in routine clinical care in the health districts involved, though with a stroke recurrence of 4-6% per year in most published ESUS cohorts[194, 195], only 1 – 2 recurrent strokes at most would be expected in this sample size. It is possible that some atrial substrate is missed by cardiac MRI due to limitations such as reduced spatial resolution, leading to underestimates of fibrotic burden.[471]

Conclusion

Patients with ESUS who went on to develop AF on continuous cardiac monitoring in this study had larger left atrial volumes and greater left atrial surface area on LGE-MRI compared with those who did not. Left atrial fibrosis percentage was moderate, but not statistically different in those who developed incident AF. This may be due to small sample-size, ESUS atrial cardiomyopathy substrate arrhythmogenesis variability, or competing causes of stroke outside the left atrium. Further understanding of predictors for which patients will develop AF or recurrent stroke is needed to guide tailored treatment approaches in this group.

Table 1: Baseline Characteristics

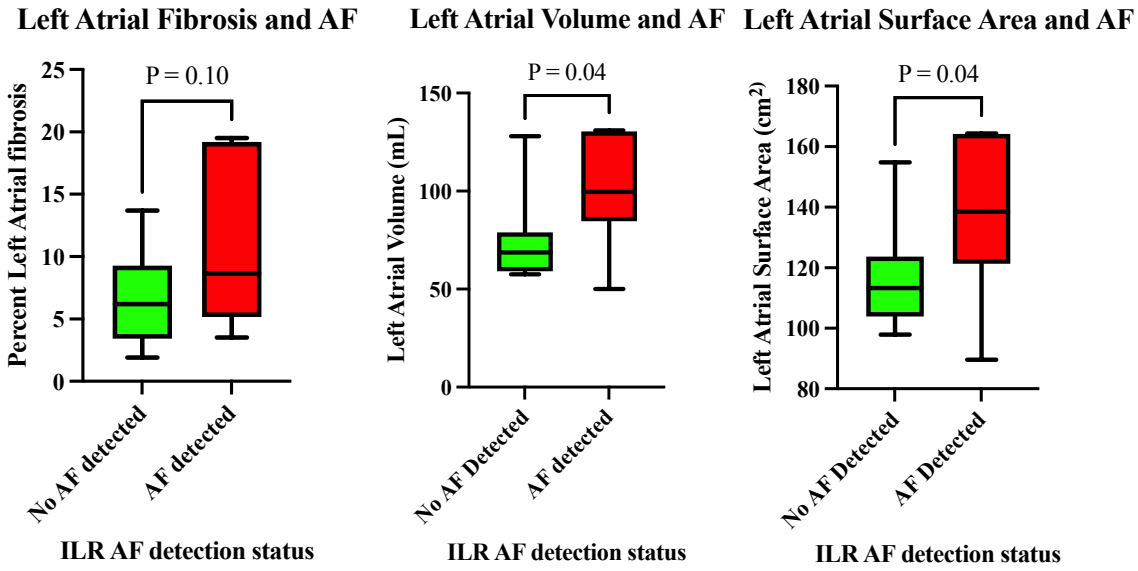
Patient Characteristics	
Participants with cardiac MRI	N=20
Age (years)	72 ± 6
Female Sex	13 (65%)
National Institutes of Health Stroke Scale	3 ± 5
Days post-stroke at enrolment	137 ± 58
Body Mass Index (BMI) (kg/m^2)	29.2 ± 5
Number with BMI >27	12 (60%)
Mean BMI if >27	32.5 ± 4
Hypertension	18 (90%)
Systolic Blood Pressure (mmHg)	138 ± 21
Diastolic Blood Pressure (mmHg)	76 ± 9
Mean number of antihypertensive medications	2 ± 1
Hyperlipidaemia	17 (85%)
Low Density Lipoprotein (LDL) (mmol/L)	2.3 ± 1.2
Mean number of lipid lowering medications	1.1 ± 0.2
Diabetic	3 (15%)
If Diabetic, mean Haemoglobin A1c	7.4 ± 1.8
Mean fasting glucose if diabetic (mmol/L)	7.6 ± 1.7
Non-Diabetic	17 (85%)
Fasting blood glucose >5.5 mmol/L	6 (35%)
Mean fasting glucose if >5.5 mmol/L	6.6 ± 2.1
Impaired Fasting Glucose (>6.0 mmol/L)	2 (12%)
Mean fasting glucose if >6.0 mmol/L)	6.7 ± 0
Known Obstructive Sleep Apnoea	3 (15%)
Continuous Positive Airway Pressure (CPAP)	1 (5%)
Regular alcohol use	7 (35%)
Mean number of drinks/week (total)	3 ± 7
Mean number of drinks/week (drinkers)	8 ± 10
Number of drinkers >10 per week	2 (10%)
Mean number of drinks/week if >10	21 ± 10
History of Tobacco use	10 (50%)
Mean pack years if tobacco use history	26 ± 14
Smoking up to stroke	2 (10%)
Continuing to smoke after stroke	2 (10%)
Echo Left Ventricular Ejection Fraction (%)	61 ± 9
Echo Left Atrial Volume Indexed (mL/m2)	32 ± 9

Table 2: Cardiac MRI Findings

Cardiac MRI findings	All N = 20	AF detected N=6 (30%)	No AF detected N=14 (70%)	AF versus no AF detected
LA fibrosis	7 ± 6	11 ± 4	7 ± 4	p = 0.10
LA volume (ml)	78 ± 38	101 ± 26	75 ± 26	**p = 0.04**
LA Surface Area (cm2)	118 ± 30	138 ± 22	116 ± 22	**p = 0.04**
LA indexed volume (ml/m2)	40 ± 19	51 ± 14	41 ± 14	p = 0.12
Utah Score	1 ± 1	2 ± 0	1 ± 0	P = 0.22

LA: Left atrial; AF: Atrial Fibrillation; Utah Score: staging system for left atrial remodelling based on extent of late gadolinium enhancement on MRI where I = <5%, II = 5-20%, III = 21 – 35%, IV = >35%[469]

Figure 1: Left Atrial Fibrosis, Volume, Surface Area, and Atrial Fibrillation Detection



AF: Atrial Fibrillation; ILR: Implantable Loop Recorder

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Principal Author

Name of Principal Author (Candidate)	Dr John Fitzgerald		
Contribution to the Paper	Concept, writing , editing, re-drafting, illustrating		
Overall percentage (%)	70%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	24th July 2024

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Jonathan P. Ariyaratnam		
Contribution to the Paper	Concept, recruitment, testing, editing, analysis 10%		
Signature		Date	31/07/2024

Name of Co-Author	Jenelle K. Dziano		
Contribution to the Paper	Reruitment, testing, editing 2%		
Signature		Date	28/07/2024

Please cut and paste additional co-author panels here as required.

Docusign Envelope ID: 602B0355-DA93-48F8-A921-70B767D5724D

Name of Co-Author	Jackson O. Howie		
Contribution to the Paper	Reruitment, testing, editing 2%		
Signature		Date	28/07/2024

Name of Co-Author	Mehrdad Emami		
Contribution to the Paper	Reruitment, testing, editing 2%		
Signature		Date	7/28/2024

Name of Co-Author	Ricardo S. Mishima		
Contribution to the Paper	Concept, editing 2%		
Signature		Date	7/29/2024

Name of Co-Author	Melissa M Middeldorp		
Contribution to the Paper	Concept, editing 2%		
Signature		Date	29/07/2024

Name of Co-Author	Elnaz Shahmohamadi		
Contribution to the Paper	Concept, editing 1%		
Signature		Date	7/28/2024

Name of Co-Author	Mohanaraj Jayakumar		
Contribution to the Paper	Editing 1%		
Signature		Date	7/28/2024

Name of Co-Author	Celine Gallagher		
Contribution to the Paper	Concept, editing, supervision 1%		
Signature		Date	01/08/2024

Docusign Envelope ID: 602B0355-DA93-48F8-A921-70B767D5724D

Name of Co-Author	Timothy Kleinig		
Contribution to the Paper	Editing, Supervision 1%		
Signature		Date	7/29/2024

Name of Co-Author	Adrian D Elliott		
Contribution to the Paper	Concept, editing, Supervision 3%		
Signature		Date	28/07/2024

Name of Co-Author	Prashanthan Sanders		
Contribution to the Paper	Concept, editing, Supervision 3%		
Signature		Date	7/28/2024

Chapter 6

Left Atrial Structure and Function in Embolic Stroke of Undetermined Source compared with Atrial Fibrillation (ES-AF)

Short Title: *Fitzgerald et al. The Left Atrium in Embolic Stroke and Atrial Fibrillation*

John L Fitzgerald MBBS[1,2], Jonathan P. Ariyaratnam MB, BChir PhD[1,2], Jenelle K. Dziano BClinExphys (Hons)[1], Jackson O. Howie MClinExphys[1], Mehrdad Emami MBBS PhD[1,2], Ricardo S. Mishima, MD PhD[1,2], Melissa E. Middeldorp PhD MPH[1,2], Elnaz Shahmohamadi MD MPH[1], Mohanaraj Jayakumar MD[1,2], Celine Gallagher PhD1, Timothy Kleinig MBBS PhD1,2, Adrian D Elliott PhD[1], Prashanthan Sanders MBBS PhD[1,2]

From: [1]Discipline of Medicine, University of Adelaide, Adelaide, Australia; [2]Departments of Cardiology and Neurology, Royal Adelaide Hospital, Adelaide, Australia;

Correspondence:

Prashanthan Sanders

Centre for Heart Rhythm Disorders

Department of Cardiology, Royal Adelaide Hospital

Adelaide, SA 5000. AUSTRALIA

Telephone: +61883139000; Facsimile: +6183622273

Email: prash.sanders@adelaide.edu.au

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ABSTRACT

Background

Patients with embolic stroke of undetermined source (ESUS) have an elevated stroke recurrence rate. Left atrial (LA) myopathy may be common, given 30% have atrial fibrillation (AF) detected by 3 years. We hypothesise that LA dysfunction may be a predictor of atrial cardiomyopathy in ESUS and may indicate higher risk of future stroke and cardiovascular events

Aim

This study compares resting and exercise LA function, serum biomarkers and exercise performance in patient groups with ESUS, known AF and healthy controls.

Methods

Eligible participants 18-85 years old with ESUS, a comparator group with AF, and healthy controls underwent transthoracic echocardiography at rest and during exercise on a supine cycle ergometer and cardiopulmonary exercise test (CPET). LA structural and functional parameters including LA volume, LA ejection fraction (EF), and LA strain and parameters of left ventricular (LV) function were assessed during rest and exercise. Serum N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) was measured.

Results

Participants included 27 with ESUS (aged 71.1±7.8 years, 26% female), 27 with AF (aged 70.6±7.1 years, 26% female) and 12 controls (aged 63.4±8.5 years, 20% female). Baseline characteristics were similar, apart from lower age ($p=0.002$) in the control group and lower prevalence of known obstructive sleep apnea ($p<0.001$) in the ESUS group. Resting echocardiography parameters were similar between groups, other than slightly higher LV EF (64.2±3.8%) in the ESUS group compared with controls (61.7±1.8%) and the AF group

(59.7±6.0%). Resting LA EF and exercise reservoir strain with ESUS were comparable to controls. Resting LA EF was lower in the AF group ($p < 0.01$). Mean NT-proBNP was elevated in the AF group ($p=0.008$) but comparable between ESUS and controls. Exercise echocardiographic parameters including LA EF and LA strain and exercise performance, measured by VO_{2peak}, were not significantly different between groups. On multivariate regression analysis, only increasing age and the presence of AF were predictive of reduced resting LA strain.

Conclusions

Mechanical LA function was not impaired in participants with ESUS compared to controls, and the only significant difference in participants with AF was a reduction in resting LA strain. These findings do not support the presence of universal mechanical LA dysfunction in ESUS, though the subset of ESUS patients with LA dysfunction should be a focus for further investigation and alternative treatment strategies.

Registration: ACTRN12623000411640

Key words: embolic stroke, atrial fibrillation, cardiopulmonary reserve, strain, implantable cardiac monitor

INTRODUCTION

Left atrial (LA) cardiomyopathy is a description encompassing various pathophysiological changes in LA size and function.[335, 338, 438] Changes in structural, mechanical and electrical function of the LA with a fibrotic, prothrombotic, proinflammatory state have been documented in the context of conditions including stroke, atrial fibrillation, hypertension, diabetes and metabolic syndrome, as well as structural heart disease.[345, 346, 348, 353-355]

In patients with stroke, a group with no underlying cause found on diagnostic workup, and imaging characteristics consistent with embolic mechanism make up around 25% of all new ischaemic stroke diagnoses.[472] This group with embolic stroke of undetermined source (ESUS) have been extensively studied in recent years and present a relatively high stroke recurrence rate of 4-5% per year, and up to 18% at 5 years.[170] Frequent, though not universal findings in this group such as LA enlargement, raised biomarkers such as n-terminal pro-brain natriuretic peptide (NT-proBNP) along with electrocardiogram (ECG) abnormalities such as increased P-wave terminal force in lead V1 (PTFV1) have been identified.[345, 346, 473-475] Unfortunately, efforts to medically manage patients with ESUS in a uniform way such as escalating anti-platelet therapy to anticoagulation have not proven to be effective strategies.[194-197] Whether this is because the markers of LA cardiomyopathy chosen in some of these studies, such as the recent ARCADIA study,[197] are inadequate indicators of the true structural and functional impairment of the left atrium, or whether this impairment is not as predictive of stroke risk from an LA thrombus mechanism as it has been thought to be remain unanswered questions.

Recent studies of LA function during exercise in patients with atrial fibrillation (AF) have shown evidence of LA impairment characterised by reduced LA ejection fraction and

reservoir strain, which are correlated with reduced exercise tolerance assessed during cardiopulmonary exercise testing (CPET).[476, 477] These findings suggest that exercise imaging may unmask LA dysfunction that may not be readily quantified at rest. This approach may be beneficial in the assessment of LA cardiomyopathy amongst patients with ESUS, although this has not been directed addressed. While other mechanisms of ESUS are possible, such as non-obstructive large-vessel atherosclerosis-driven plaque rupture events or paradoxical embolus, LA cardiomyopathy remains a strongly suspected driver.[338] We test the hypothesis that exercise echocardiography can demonstrate subtle LA dysfunction in patients with ESUS not seen on resting echocardiography. This LA dysfunction may indicate higher risk of future stroke and cardiovascular events.

METHODS

Study Design

In this prospective, multicentre, observational study we enrolled three patient groups: one with a history of ESUS, one with a history of known AF and a group of healthy controls. The trial was approved by the Central Adelaide Local Health Network Human Research Ethics Committee and the University of Adelaide. Prospective trial registration was with the Australian and New Zealand Clinical Trials Registry (ACTRN12623000411640)

Study Population

Participants with ESUS according to current accepted definitions,[193] which includes cryptogenic stroke from the original TOAST criteria, with the exclusion of those with imaging characteristics suggestive of lacunar stroke were recruited through liaison with and assistance from local metropolitan hospital stroke units.[8, 193] To exclude specific causes of stroke unlikely related to LA myopathy, patients were not approached if they had the

following exclusions: pregnancy or planned pregnancy within the next 24 months; inability to undergo MRI scan; major surgery <6 months; valvular disease needing intervention; LVEF ≤35%; active malignancy; autoimmune or systemic inflammation; specific stroke mechanisms: patent foramen ovale, vessel dissection, subacute bacterial endocarditis; severe renal dysfunction (defined as dialysis, prior or planned transplant, Creatinine >2.26 mg/dl or > 200 μmol/l); severe liver dysfunction (cirrhosis or bilirubin > 2 x normal or AST/ALT/ALP > 3x normal); malabsorption disorders; institutional living; inability to attend appointments; inability to provide informed consent.

Consecutive consenting age-matched participants with symptomatic paroxysmal or persistent atrial fibrillation who were scheduled to undergo catheter ablation were enrolled with the following exclusions: atrial fibrillation at the time of exercise testing, reduced resting LVEF (<50%); previous diagnosis of cardiomyopathy; moderate-to-severe valvulopathy; previous diagnosis of pulmonary hypertension; active malignancy; severe chronic obstructive airways disease (FEV1/FVC <70%); inability to exercise; age <18 years or inability to provide written informed consent.

A group of consenting control participants was enrolled from patients referred for exercise testing with no history of stroke or AF for comparison. The same exclusion criteria were applied to this group as the group with known AF.

Echocardiography

An experienced sonographer, blinded to patient group performed resting and exercise echocardiography according to a previously published method focussing on LA and LV structure and function.[476] A supine bicycle ergometer was utilised to allow echocardiographic

imaging during exercise which was commenced at a workload of 20W and increased by 20W every 2 minutes. Exercise was stopped just before E and A wave fusion on imaging, or when symptoms precluded further exercise. Trans-thoracic echocardiography images were taken during every second stage. Imaging was performed in parasternal and apical views by a cardiac sonographer blinded to patient group. LV ejection fraction (LVEF) was measured with Simpson's biplane method. Biplane area-length method was used, indexed to body surface area for maximum (LA_{max}) and minimum (LA_{min}) LA volumes. LA emptying fraction (LAEF) was calculated with the following formula: LAEF = (LAmax – LAmin)/LAmax x 100. LA strain and LV strain were assessed with previously validated software (GE Healthcare EchoPac, Chicago IL).[478] Echocardiography measurements were performed according to guidelines from the American Society of Echocardiography.[479, 480] Averaging over 3 cardiac cycles was performed.

Cardiopulmonary Exercise Testing

An upright cycle ergometer (Lode Corival, Lode B.V.) and metabolic cart (Vyntus CPX, Vyaire Medical) were utilised for cardiopulmonary exercise testing (CPET). Expired carbon dioxide and oxygen consumption were averaged over 20 second intervals during continuous pulmonary gas exchange measurement. After starting exercise at a power of 20W, workload was increased incrementally by 10W/minute. Peak exercise was defined as a respiratory exchange ratio of >1.05 and the participant felt the need to stop due to symptoms of fatigue. The highest VO_2 achieved during exercise (VO_{2peak}) was measured and chronotropic response was calculated using the difference between the pre-exercise resting heart rate, and that attained at peak exercise.

N-terminal pro B-type Natriuretic Peptide

A fasting blood sample prior to exercise testing was utilised for measurement of NT-proBNP.

Statistical Analysis

Variables are reported as mean ± SD for normally distributed and median (IQR) for non-normally distributed data. Categorical variables are expressed as frequencies and percentages. The Shapiro-Wilk test was used to test normality of each continuous variable. Comparisons between all three groups were performed using one-way ANOVA. If significant differences were detected, between group differences were performed with Student t-tests or Mann Whitney U tests depending on normality. Categorical variables were compared using chi-square or Fisher's exact test. Binary logistic regression was used to investigate univariable and multivariable predictors of LA function. $P \leq 0.05$ were considered significant.
All statistical analysis was performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Powering

Assuming a normal Exercise Left Atrial Emptying Fraction (LA EF) as shown in previous studies of 67 +/-10%[481], to determine 10% difference in LA EF during exercise between embolic stroke of undetermined source and control groups, 27 participants per group gives 90% power with alpha 0.025. Target recruitment is 30 participants in each group to allow for 10% inadequate imaging acquisition in each group. Comparison is made with exercise LAEF in an additional 30 participants with known Atrial fibrillation.

RESULTS

A total of 27 participants with ESUS completed all testing with adequate imaging quality for analysis, after screening 37 patients for inclusion. The mean age in the ESUS group was 71.1±7.8, 26% female, mean BMI 26.2±2.6 kg/m^2, mean LA volume 31.6±6.4 mL/m^2. Figure 1 details recruitment for each subgroup with ESUS, AF and controls, and reasons for non-inclusion.

A further 27 participants with AF were analysed, from a screened 32 eligible participants, with a mean age of 70.7±6.7 years, 26% female, 48% paroxysmal, mean BMI 27.9±4.7 kg/m^2, mean LA volume 32.9±8.5 mL/m^2.

Finally, 12 control participants were included in the analysis from a total of 20 screened, mean age 62.4±6.5 years, 20% female, mean BMI 26.4±6.0 kg/m^2, mean LA volume 27.0±7.4 mL/m^2.

Table 1 shows patient characteristics in the 3 groups. Main between-group differences for baseline characteristics were for age (younger in the control group, P=0.002) and obstructive sleep apnoea (more common in the AF group, P <0.001).

Baseline imaging parameters are outlined in Table 1. Resting LVEF was slightly lower in the AF group at 59.7±6.0%, (P=0.03), compared to the control group (61.7±1.8%) and ESUS group (64.2±3.8%). LV global longitudinal strain (GLS), was similar across all groups (P =0.51). The LA EF was significantly lower in the AF group (P<0.01) at 39.2±13.0%, compared to the control group (52.3±3.3%) and ESUS group (50.8±9.3%). Baseline NT-proBNP was similar in the control group and ESUS group (90(54-126) pg/mL and 106(54-180) pg/mL), and higher in the AF group (219(110-512) pg/mL) (P=0.008).

Table 2 shows exercise echocardiography and exercise performance parameters. Exercise ejection fraction showed some augmentation in the AF group, such that there was no

difference between groups (P=0.73). In this cohort, exercise LV GLS was numerically lower in the control group (17.1±3.2%), and ESUS group, (17.6±3.7%) compared with the AF group (20.1±3.9%), though this did not reach statistical significance (P=0.05). With exercise, LA function as measured by LA EF and LA strain, was not significantly different between groups. Peak oxygen consumption was numerically higher in the control group (26.1±6.8) compared with the ESUS (21.9±6.2) and AF (21.2±8.0) groups, though this did not reach statistical significance (P=0.13).

Table 3 shows univariable and multivariable linear regression analysis for predictors of LA strain at rest. Only increasing age and the presence of AF were predictive, and this was across both models.

Figure 2 shows the distribution of LA EF, LA reservoir strain and NT-proBNP in the three groups.

DISCUSSION

The main findings from the cohort in this study are:

- Compared to patients without a history of stroke or AF, ESUS patients did not exhibit evidence of LA dysfunction at rest or during exercise imaging.
- Patients with AF showed some signs of LA dysfunction, compared with the other 2 groups at rest, though this was only in left atrial ejection fraction, influenced by a larger left atrial minimum indexed volume.
- The subtle difference in the AF group disappeared with exercise.

Although LA myopathy is a proposed mechanism of thrombus formation and resulting embolic stroke in patients with ESUS,[335, 338, 438] the results of this study do not show significant impairment of LA function in this ESUS group, when compared with a control

group. This could indicate that LA functional impairment is not a prerequisite for thrombogenicity, and that other parameters such as pro-inflammatory or pro-thrombotic markers may be important. Another possibility is that the source of stroke in these ESUS patients is not thrombus formed in the LA, but is due to other mechanisms such as plaque rupture events in symptomatic non-stenotic carotid plaques (SyNC), or occasional paradoxical embolism, even in this group which is outside the age-range of the trials showing benefit for closure of PFO.[482-487]

There was significant heterogeneity in the extent of LA mechanical function amongst the ESUS group in this study. It is possible that ESUS patients within the lower range of LA function present a specific phenotype of ESUS patients with more extensive atrial cardiomyopathy, and subsequent higher risk of thrombogenicity than those with LA function within the normal range. This hypothesis would require further evaluation in a larger cohort of ESUS patients with extended follow-up.

The failure of anticoagulation to significantly reduce ESUS recurrence in clinical trials compared with aspirin,[194-196] may be reflective of the heterogeneity in thrombus risk across populations with ESUS. It is still possible that a subgroup who would benefit from this approach could exist. Whether those with reduced LA mechanical function as measured in this study with LAEF and reservoir strain impairment could benefit from this approach would require further selective testing and recruitment within a general ESUS population, and then randomised treatment allocation. In the recently published ARCADIA study, the markers of LA myopathy chosen were raised NT-proBNP, P-wave terminal force greater than 5000 μV x ms and indexed LA diameter > 3 cm/m^2 on echocardiography. The majority of patients met the first 2 criteria, with only 3.3% being randomised based on LA diameter measurement.

The study showed no difference in embolic events between groups, as measured on MRI brain over 1.8 years of follow-up. It remains unclear if using left atrial size in the majority of patients, or left atrial function, as measured in this current study, would make a difference to this outcome.

Clinical implications

Patients with ESUS show a range of left atrial function rather than uniform reduction, and those demonstrated on exercise stress echocardiography to have lower left atrial function may be a higher-risk group warranting further study and close follow-up.

Limitations

Differences between the groups were present at baseline as a limitation of comparisons in this study, principally with a lower mean age in the control group, though the LA strain and other parameters were comparable in the ESUS group, despite increased age.

The ESUS population recruited in this study were required to be high-functioning and mobile to participate in the exercise testing, so it is unclear if the results of this study are generalisable to a broader ESUS population with lower function. The control group was reduced in number compared to the target powering, which may have altered results, though this group had a spread of atrial function similar to normal values found in the literature, making this unlikely. Exercise echocardiography may be limited by suboptimal image acquisition in some patients, and inter and intra-observer variability have been noted, though reduced with more modern imaging analysis software.[488] An alternative imaging modality such as cardiac MRI might provide more optimal imaging in patients with poor echocardiographic imaging windows, though it is more resource and cost-intensive.

CONCLUSION

In this study participants with ESUS showed similar LA function, NT-proBNP and exercise performance to control participants. Participants with AF had more left atrial impairment, as measured by reduced resting LA strain, and increased NT-proBNP, though exercise LA function and LA strain were not different across groups. These findings do not support the presence of significant mechanical left atrial dysfunction as a key underlying feature in the majority of ESUS patients to explain the increased risk of stroke, though they do not exclude other potential mechanisms such as pro-thrombotic and pro-inflammatory changes.

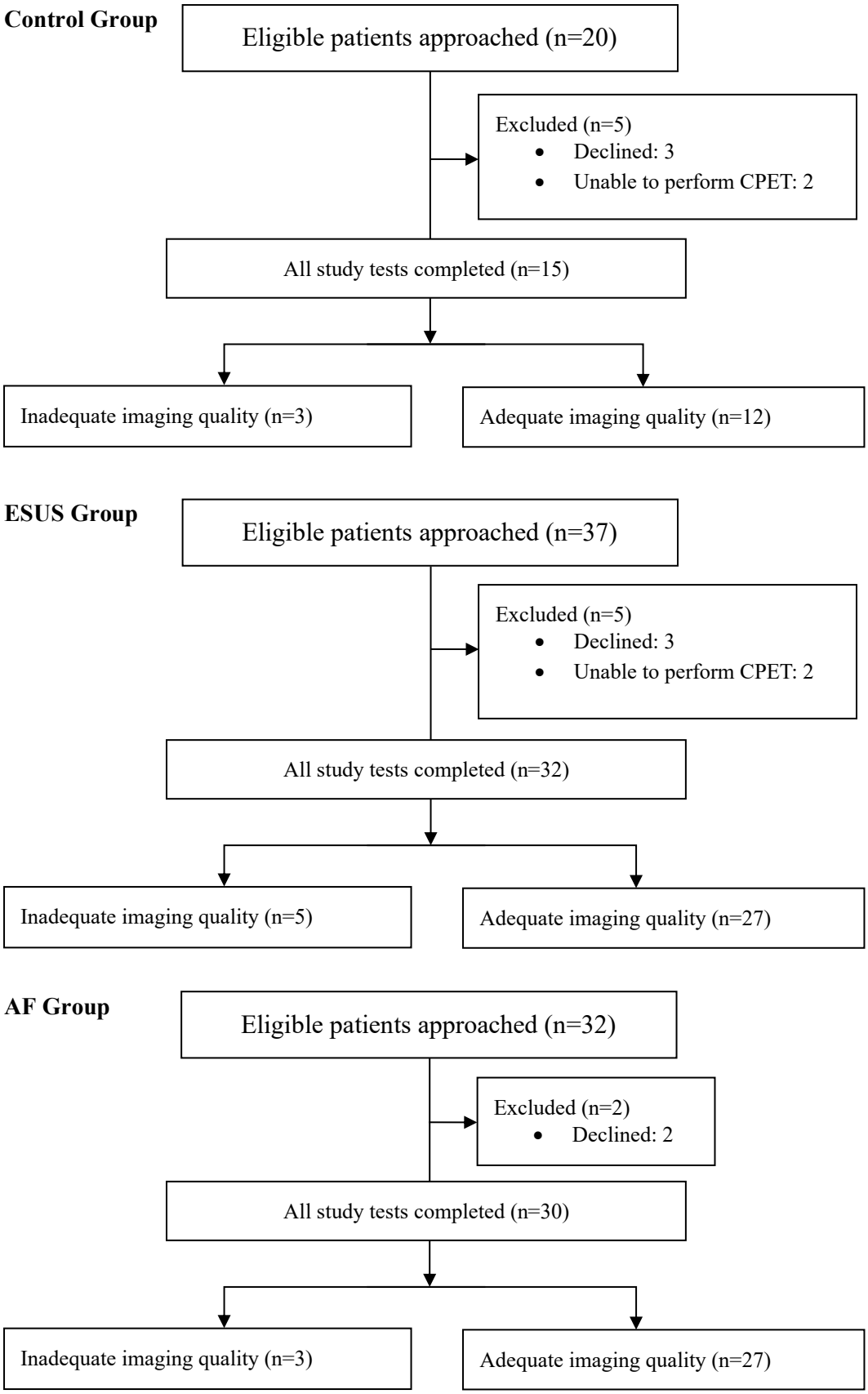

Figure 1: Consort Diagram of patient recruitment for each group.

CPET = cardiopulmonary exercise testing; AF = atrial fibrillation

	Controls (12)	ESUS (27)	AF (27)	P value
Baseline Characteristics				
Age, yrs	62.4±6.5	71.1±7.8[a]	70.7±6.7[a]	**0.002**
Female, %	2 (20)	7 (25.9)	7 (25.9)	0.86
Hypertension, %	6 (50)	23 (85.2)	22 (81.5)	0.10
Body mass index, kg/m^2	26.4±6.0	26.2±2.6	27.9±4.7	0.34
Diabetes, %	1 (8.3)	5 (18.5)	6 (22.2)	0.64
Obstructive sleep apnoea, %	3 (25)	2 (7.4)	15 (55.6)[ab]	**<0.001**
Alcohol use, %	2 (16.7)	13 (48.1)	11 (40.7)	0.23
Smoking, %	0 (0)	1 (3.7)	4 (14.8)	0.18
Coronary artery disease,%	1 (8.3)	2 (7.4)	3 (11.1)	0.90
Resting echocardiographic parameters				
LV ejection fraction, %	61.7±1.8[b]	64.2±3.8	59.7±6.0[b]	**0.03**
LV GLS, %	17.4±3.2	16.6±2.8	16.3±1.4	0.51
Indexed LV Mass, g/m^2	165±50	166±53	164±44	0.99
Indexed LA_{max}, mL/m^2	27.0±7.4	31.6±6.4	32.9±8.5	0.09
Indexed LA_{min}, mL/m^2	12.9±6.9	16.6±6.9	22.3±16.9 [ab]	**0.04**
LA Ejection Fraction, %	52.3±3.3	50.8±9.3	39.2±13.0 [ab]	**<0.01**
LA Reservoir strain, %	27.1±9.2	27.5±4.9	22.2±8.6	0.07
Cardiac biomarker				
NT-proBNP, pg/mL	90(54-126)	106(54-180)	219(110-512)[ab]	**0.008**
[a]p<0.05 vs controls in pairwise comparison [b]p<0.05 vs ESUS in pairwise comparison				

Table 1: Baseline Characteristics.

Comparison between the three groups performed using one-way analysis of variance (ANOVA) or Kruskal-Wallis test where appropriate.

LV = left ventricular; GLS = global longitudinal strain; LA_{max} = left atrial maximum volume; LA_{min} = left atrial minimum volume.

Exercise echocardiographic parameters				
LV ejection fraction, %	61.8±3.5	62.8±2.8	63.3±8.2	0.76
LV GLS, %	17.1±3.2	17.6±3.7	20.1±3.9	0.05
Indexed LA_{max}, mL/m^2	30.6±9.7	32.7±5.3	35.3±9.6	0.23
Indexed LA_{min}, mL/m^2	14.6±6.1	16.8±3.6	17.8±6.2	0.25
LA Ejection Fraction, %	53.9±5.4	48.4±9.5	47.8±13.0	0.31
LA Reservoir strain, %	27.7±5.3	27.9±8.8	24.4±11.9	0.40
Exercise performance				
VO2Peak, mL/kg/min	26.4±6.6	21.9±6.2	21.3±8.2	0.13
Peak HR, bpm	150±17	140±20	136±24	0.20

Table 2: Exercise echocardiographic parameters and exercise performance.

Comparison between the three groups performed using one-way analysis of variance (ANOVA) or Kruskal-Wallis test where appropriate.

LV = left ventricular; GLS = global longitudinal strain; LA_{max} = left atrial maximum volume; LA_{min} = left atrial minimum volume.

Variable	Univariate Regression Analysis		Multivariate Regression Analysis	
	Slope (95% CI)	**p-value**	**Slope (95% CI)**	**p-value**
Age	**-0.33 (-0.60 – -0.06)**	**0.02**	**-0.29 (-0.55 - -0.29)**	**0.03**
Gender	-2.90 (-7.85 – 2.05)	0.25		
BMI	-0.37 (-0.90 – 0.16)	0.17		
Hypertension	-2.80 (-7.99 – 2.40)	0.29		
Diabetes	-1.12 (-6.67 – 4.24)	0.69		
Alcohol	-0.005 (-4.40 – 4.39)	0.99		
Smoking	-0.67 (-8.75 - 7.42)	0.246		
ESUS	3.33 (-0.96 -7.62)	0.13		
AF	**-5.00 (-9.19 - -0.81)**	**0.02**	**-4.37 (-8.47 - -0.26)**	**0.04**
Control	2.88 (-2.82 – 8.59)	0.32		

Table 3: Univariable and multivariable regression analysis for predictors of resting left atrial reservoir strain.

BMI = body mass index, kg/m^2; ESUS = embolic stroke of undetermined source; AF = atrial fibrillation.

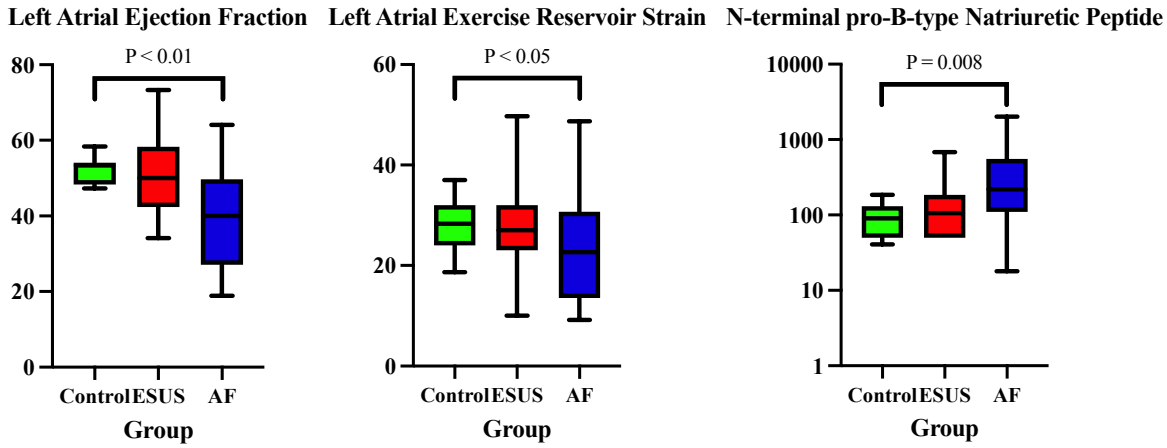

Figure 2: Distribution of Left atrial ejection fraction, left atrial reservoir strain and N-terminal pro-B-type Natriuretic Peptide in the 3 groups.

ESUS = embolic stroke of undetermined source.

Chapter 7

Final Discussion

In this thesis, the key elements of risk factor association with stroke are examined, with a strong focus on the impact of cardiovascular and lifestyle risk factors on recurrent embolic stroke. Evidence for the effects of modifying individual risk factors including hypertension, hyperlipidaemia, diabetes, smoking, obstructive sleep apnoea, obesity, and physical inactivity is explored, and efforts to date to address these risk factors comprehensively is outlined, with limited effectiveness demonstrated in models of care to date.

The strong evidence for effectiveness of a comprehensive, multi-disciplinary, physician-led clinic to deliver intensive risk factor modification for atrial fibrillation is reviewed, and this model was proposed as a logical step forward to deliver comprehensive risk factor modification to patients after embolic stroke to improve the effectiveness of secondary prevention. Left atrial pathophysiological changes known to occur in atrial fibrillation including mechanical, electrical and structural adverse remodelling as well as pro-thrombotic and pro-inflammatory changes and accelerated cellular ageing stand to be favourably impacted by risk factor modification. Embolic stroke, and particularly that of undetermined source, are proposed to occur frequently in a situation with underlying left atrial cardiomyopathy, and it is proposed that modifying this same substrate as seen in atrial fibrillation, albeit at an earlier clinical stage, could reduce the risk of thrombosis and embolization hypothesised to lead to stroke recurrence.

Chapter 2 lays out the full design of a randomised clinical trial to investigate the effect of aggressive risk factor modification on the co-primary end-points of incident atrial fibrillation and recurrent embolic stroke. Through the delivery of care in the same model as that proven

for atrial fibrillation, these outcomes are measured with continuous cardiac monitoring via implantable loop recorder, and via annual magnetic resonance imaging, for a planned follow-up of 3 years to examine silent and clinically apparent recurrent embolic events.

Chapter 3 details a design for a second, much larger randomised controlled trial to examine the effect of aggressive risk factor modification expanded to all embolic stroke inclusive of ESUS, AF and large-vessel athero-embolic causes. Investigation of the effect of risk factor modification this time is on a combined primary endpoint of recurrent imaging-detected embolic stroke, together with major cardiovascular events inclusive of any acute coronary syndrome, or vascular death. The risk factor delivery model is the same as in the previous trial design with extensive secondary endpoints and sub-studies proposed.

In chapter 4, the results are presented of a feasibility study with randomised comparison of intensive risk factor modification to usual care, examining the surrogate outcome of risk factor control itself. In the intensive risk factor modification group, control to target of many risk factors was significantly greater than control, including hypertension, hyperlipidaemia, and achievement of target exercise volume of 150 minutes per week. Amongst participants with a BMI > 27 kg/m^2, a significantly greater amount of weight was lost in risk the factor modification group (7.5 ±5.4%) versus the control group (1.3 ±4.9%), (P<0.001). Achievement of all risk factors to target, including a BMI ≤27 kg/m^2, was significantly more likely with risk factor modification than standard care (RR 3.0 (95% CI 2.2-4.3, P =0.001) and was achieved in 47% of the risk factor modification group versus 0% of the control group. This success with these important management priorities supports the efficacy of this approach and provides evidence that further evaluation of this model with outcomes outlined in Chapter 2 and Chapter 3 of this thesis should be performed in future work.

In chapter 5, left atrial substrate in patients with ESUS is explored further through cardiac magnetic resonance imaging assessment of left atrial scarring via late gadolinium enhancement, and left atrial volume and surface area measurements. The hypothesis was that left atrial structural changes likely underlie ESUS in a significant number of cases, and may predict subsequent incident AF. In this study of 20 participants with ESUS undergoing cardiac MRI, numerical differences in left atrial fibrosis were seen, but these were not statistically significant. This may be in part due to the small sample size, or it could be that the atrial myopathy responsible for embolic stroke is not necessarily manifest as the advanced changes seen with scarring and thrombogenesis may be occurring at an earlier stage. Previous studies have suggested a cutoff in scar volume was associated with incident AF or recurrent stroke as a combined endpoint. This was not seen in this cohort, though left atrial volume and surface area were associated with incident AF.

Chapter 6 of this thesis explores the hypothesis that LA functional changes could underlie ESUS and may be predictive of the known increased cardiovascular risk associated with this condition. This is a comparative study of resting and exercise LA function, serum biomarkers and exercise performance among separate patient groups with ESUS, known AF and healthy controls. Resting echocardiography parameters were compared and a main key difference at baseline was left atrial ejection fraction, which was reduced in the group with AF, compared to the other 2 groups. Mean NT-proBNP was also elevated in the AF group. These findings did not support a global picture of reduced LA resting function in ESUS as a contributor to the stroke substrate, and the parameters of LA function were not significantly different between ESUS and control groups. On exercise, left atrial reservoir strain was reduced in the group with known AF, though other parameters were not significantly different between

groups. Likewise, this finding does not support a significant dynamic LA mechanical dysfunction as a key factor in patients with ESUS. It is possible that the increased spread of LA function seen both at rest and with exercise in the ESUS group, compared to the control group, might identify patients at more risk who have LA function parameters towards the lower range within this ESUS group. This study was not, however, powered or designed to be sensitive enough to show this, or to examine a difference in clinical outcomes.

Chapter 8

Future Directions

The studies presented in this thesis show important insights into the efficacy of aggressive risk factor modification for the secondary prevention of embolic stroke. This preliminary work has demonstrated improvement in the surrogate outcomes of risk factor control. The further studies of left atrial changes on MRI and left atrial structure and function, exercise and biomarker comparison of patients with ESUS to those with AF and controls, raise many questions that require further investigation.

The proposed studies in Chapter 2 and Chapter 3 in patients with ESUS, and the broader group with ESUS, AF or large vessel athero-embolic stroke now need to be taken forward to confirm whether the improved risk factor control achieved translates into proposed clinical outcomes of reduced incident AF, embolic stroke and major adverse cardiovascular events.

If significant improvements in these outcomes are confirmed with the approach of intensive lifestyle and risk factor management, then this should serve as a model for standardisation of post-stroke care. To offer this approach routinely to patients after embolic stroke would require stroke guideline endorsement for this approach, in the same way this exists in AF guidelines. Coordinated training for other centres to deliver the required risk factor management clinics would be required, along with policy changes to divert funding to such clinics and services.

Regarding left atrial fibrosis changes on MRI, this reporting approach currently requires input from trained imaging cardiologists. Further training for AI models with large datasets may lead to the semi-automation of much of this reporting, and open up the scalability of readily

imaging and analysing more patients both in and outside clinical studies. Generative AI could also play a role in identifying novel structural and functional markers of risk in broader stroke populations to better tailor care to those at the highest risk of ongoing cardiovascular events. The question of whether risk factor modification can impact the substrate shown on cardiac MRI will hopefully be answered with the PREDICT STROKE cohort undertaking repeat cardiac MRI imaging after 3 years of this approach.

The ultimate goal of preventing strokes and facilitating policy change required to provide necessary resources for lifestyle and risk factor management to achieve this are key outcomes to be achieved in taking this area of research forward.

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