Improving ablation outcomes in atrial fibrillation: improving procedural efficacy, safety, and patient selection

A thesis submitted for the Degree of Doctor of Medicine (Research)
The National Heart and Lung Institute
Imperial College London

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ABSTRACT

Atrial fibrillation (AF) is a major health problem, affecting 1-2% of the population. AF reduces quality of life (QoL) and increases morbidity and mortality. Catheter ablation (CA) is the most efficacious means of restoring sinus rhythm but is not always successful and is occasionally associated with serious complications. Several questions are currently unanswered. True procedural effectiveness, particularly long-term, remains uncertain, especially in more advanced disease. The best technique for achieving success remains an issue of considerable debate and as yet, few, if any, means exist to predict when acute electrical success will translate into sustained clinical benefit. CA is indicated for symptomatic relief but QoL, both as a treatment outcome and as a guide to patient selection, has generally been overlooked in the published literature. Finally, although the maxim, “First, do no harm” may often be ascribed erroneously to Hippocrates, it remains a central tenet of medical practice. However, little previous research has focussed on improving the safety of CA.

I have attempted to tackle these issues from a number of angles. I have performed a comprehensive literature review and a retrospective analysis of ablation outcomes at Liverpool Heart and Chest Hospital, the largest and longest such data from the UK, to ascertain a comprehensive, up-to-date assessment of practice. In an effort to improve procedural success, I carried out a multicentre randomised controlled trial testing two ablation strategies. A sub-study tests the hypothesis that clinical outcomes can be predicted by a novel measure of effective ablation. Two further studies aim to improve safety, through use of ultrasound to guide venous access, and to better understand QoL in AF – a theme throughout the thesis – which may help improve selection of appropriate patients for CA. Together, I hope these studies will help physicians improve the outcomes of CA for their patients.
# Table of Contents

Abstract ................................................................................................................................. 2

Table of Contents .................................................................................................................. 3

List of Tables ......................................................................................................................... 11

List of Figures ......................................................................................................................... 13

Publications arising from this thesis .................................................................................. 16

National awards for work contained in this thesis .............................................................. 17

Declaration of originality ...................................................................................................... 18

Copyright declaration ........................................................................................................... 19

Acronyms and abbreviations used in this thesis ................................................................. 20

Acknowledgements ............................................................................................................... 23

1. Improving ablation outcomes in atrial fibrillation: introduction and review of the literature .......................................................................................................................... 24

   1.1. Atrial fibrillation in perspective .................................................................................. 24

   1.1.1. Atrial fibrillation as a public health problem ......................................................... 24

   1.1.2. The effect of AF on the individual ......................................................................... 24

   1.1.3. Atrial fibrillation as a disease ................................................................................ 25

   1.1.4. Current treatment strategies for AF ....................................................................... 29

   1.1.5. Rate versus rhythm control .................................................................................. 30

   1.1.6. Pharmacological therapy ....................................................................................... 30

   1.1.7. Non-pharmacological (interventional) therapy .................................................... 32

   1.2. Questions I hope to answer through this thesis ......................................................... 34

   1.2.1. Theme .................................................................................................................. 34

   1.3. Efficacy of catheter ablation for persistent atrial fibrillation: a systematic review and meta-analysis of evidence from randomised and non-randomised controlled trial .. 36
1.3.1. Methods.................................................................................................................. 36
1.3.2. Results....................................................................................................................... 40
1.3.3. Discussion................................................................................................................. 67
1.3.4. Conclusions .......................................................................................................... 73

2. Improving patient outcomes by better understanding current practice: Real life long
term outcomes after persistent AF ablation; Six year data from a high volume UK centre.. 74

2.1. Background ............................................................................................................. 74
2.2. Methods .................................................................................................................... 74
2.2.1. Patients .................................................................................................................. 75
2.2.2. Follow-up ............................................................................................................. 75
2.2.3. Electrophysiological study .................................................................................. 76
2.2.4. Statistical analysis .............................................................................................. 77
2.3. Results ..................................................................................................................... 78
2.3.1. Patients and baseline characteristics ................................................................. 78
2.3.2. Patient journey ................................................................................................... 79
2.3.3. Follow-up ............................................................................................................. 82
2.3.4. Procedural complications .................................................................................... 82
2.3.5. Ablation procedures ........................................................................................... 83
2.3.6. Outcomes after a single procedure ..................................................................... 84
2.3.7. Outcomes after multiple procedures .................................................................. 87
2.3.8. Longstanding PeAF ............................................................................................ 90
2.3.9. Effect of CT integration on freedom from recurrent AF ................................... 90
2.3.10. Quality of life (QoL) after CA of PeAF ................................................................. 92
2.4. Discussion ............................................................................................................. 93
2.4.1. Implications for clinical practice ....................................................................... 95
2.4.2. Limitations ................................................................. 95
2.4.3. Conclusion ................................................................. 96

3. Methods of the Substrate Modification with Ablation and antiarrhythmic drugs in Non-Permanent Atrial Fibrillation (SMAN-PAF) Randomised controlled trial ........................................ 97

3.1. Introduction.................................................................. 97
3.2. Original hypotheses/ research question............................. 98
3.3. Design........................................................................... 98
3.4. Study duration.............................................................. 98
3.5. End Points..................................................................... 99
3.5.1. Primary endpoint......................................................... 99
3.5.2. Secondary endpoints:.................................................... 100
3.6. Safety............................................................................ 102
3.6.1. Expected complication rates......................................... 102
3.6.2. Reporting of Adverse events........................................ 102
3.7. Blanking period.............................................................. 103
3.8. Patients.......................................................................... 103
3.9. Inclusion criteria............................................................ 104
3.10. Exclusion criteria.......................................................... 105
3.11. Randomisation.............................................................. 106
3.12. Study visits and investigations .......................................... 106
3.13. Follow up..................................................................... 107
3.15. Quality of life assessment............................................... 109
3.15.1. AFEQT questionnaire.................................................. 109
3.16. Anti-arrhythmic drug protocol......................................... 109
3.17. Anticoagulation ........................................................................................................110
3.18. Ablation procedure ..................................................................................................111
3.19. Lesion description and definition of success .........................................................113
3.20. Recurrence of AF ...................................................................................................114
3.21. Repeat ablation .......................................................................................................115
3.22. Sample size calculation ..........................................................................................115
3.23. Statistical analysis ..................................................................................................116
3.24. Assessment of primary endpoint ...........................................................................117
3.25. Recruitment ............................................................................................................117
3.25.1. CONSORT diagram ...............................................................................................118
3.25.2. Progress ................................................................................................................119
3.26. Ethical considerations ..............................................................................................119
3.26.1. Good Clinical Practice .........................................................................................119
3.26.2. National Research Ethics Service (NRES) .........................................................119
3.26.3. Confidentiality ....................................................................................................120
3.27. Flow chart ...............................................................................................................120
3.28. Trial registration .....................................................................................................122
3.29. Case record form ....................................................................................................122
3.30. Sponsor ..................................................................................................................123

4. Improving patient outcomes though better ablation strategies: Results of the Substrate Modification with Ablation and antiarrhythmic drugs in Non-Permanent Atrial Fibrillation (SMAN-PAF) Randomised controlled trial .........................................................................................................................124

4.1. Introduction ..............................................................................................................124
4.2. Methods ...................................................................................................................125
4.3. Results .....................................................................................................................125
5. improving patient outcomes by better understanding ablation lesion quality: A novel marker to predict early recurrence after atrial fibrillation ablation; The Ablation Effectiveness Quotient

5.1. Introduction

5.2. Methods

5.2.1. Patients

5.2.2. Ablation procedure

5.2.3. Ablation Effectiveness Quotient (AEQ)

5.2.4. Follow-up and arrhythmia monitoring

5.2.5. Study endpoint

5.2.6. Statistical analysis

5.3. Results

5.3.1. Patient characteristics

5.3.2. Primary outcome

5.3.3. Comparison of ablation strategies

5.3.4. Comparison with contact force readings
7. Improving patient outcomes by better understanding quality of life in atrial fibrillation: Validation and Improvement of The European Heart Rhythm Association Symptom Classification

7.1. Background

7.2. Methods

7.2.1. Phase One

7.2.2. Phase Two

7.2.3. Phase Three: AFEQT questionnaire

7.2.4. AFEQT questionnaire (3 Level version)

7.2.5. Visual analogue scale (VAS)

7.2.6. Statistical analysis

7.3. Results

7.3.1. Phase One

7.3.2. Phase Two

7.3.3. Reproducibility of the mEHRA class

7.3.4. Phase 3: Prospective validation of mEHRA

7.4. Discussion

7.4.1. Limitations

7.5. Conclusions

8. Final Discussion

8.1. To what extent did I achieve my aims?

8.2. What problems were encountered and how were they overcome?

8.2.1. Chapter 4: Use of a modified intention to treat analysis

8.2.2. Chapter 4: Recruitment and retention
8.2.3. Duration of follow up in AF trials .................................................................201
8.3. Areas for future research .....................................................................................202
8.4. Final conclusions .................................................................................................204
9. Reference List .........................................................................................................205
10. Appendices ............................................................................................................231
   10.1. Appendix 1: Funnel plots for analyses carried out in Chapter 1 .....................231
   10.2. Appendix 2: Patient information sheet for the SMAN-PAF Trial ..................234
   10.3. Appendix 3: AFEQT QoL form (Chapters 3,4 &7) .........................................239
   10.4. Appendix 4: SF-36 QoL questionnaire (Chapters 3 & 4) ..............................241
   10.5. Appendix 5: EQ-5D QoL questionnaire (Chapter 7) ....................................246
   10.6. Appendix 6: Permissions information for published work ............................248
LIST OF TABLES

Table 1-1: Studies included in the review................................................................. 45
Table 1-2: Assessment of study quality...................................................................... 49
Table 1-3: Sensitivity analysis examining the effect of inclusion of non-randomised trials in meta-analyses.................................................................72
Table 2-1: Baseline characteristics of patients undergoing catheter ablation for PeAF ....... 79
Table 2-2: Logistic regression analysis for freedom from recurrent AF after a single procedure........................................................................................................... 86
Table 2-3: Logistic regression analysis for freedom from recurrent AF after multiple procedures........................................................................................................... 89
Table 3-1: Study visit schedule. ......................................................................................... 106
Table 3-2: Ablation lesions (and definitions of success) used as part of study protocol.....114
Table 4-1: Baseline characteristics of patients enrolled in the SMAN-PAF randomised controlled trial ...........................................................................................................126
Table 4-2: SMAN-PAF Procedural details.........................................................................129
Table 4-3: Binary logistic regression analysis of SMAN-PAF results...............................131
Table 4-4: Overall AFEQT score at baseline and at the six month follow up visit.......... 133
Table 5-1: Baseline characteristics for AEQ analysis..........................................................147
Table 5-2: Univariate logistic regression analysis for predictors of recurrence of atrial tachyarrhythmia after atrial fibrillation ablation.........................................................149
Table 6-1: Studies of the use of vascular ultrasound to assist cannulation of the Femoral (FV) or Internal Jugular Vein (IJV). W ................................................................. 161
Table 6-2: Baseline Characteristics for the two groups in the study of ultrasound use......168
Table 6-3: Univariate regression analysis for predictors of a BARC2+ bleed ......................171
Table 6-4: Multivariable logistic regression analysis for predictors of a BARC2+ Bleeds ..172
Table 7-1: Modified EHRA (mEHRA) classification..........................................................180
Table 7-2: Baseline Characteristics by EHRA Class..............................................................184
Table 7-3: Mean (and standard deviation) for each EHRA Class........................................185
Table 7-4: Mean (and standard deviation) shown for each mEHRA Class.............................187
Table 7-5: Comparison of retrospective and prospective Quality of Life scores, for each of
the two proposed additional mEHRA classes ....................................................................190
List of Figures

Figure 1-1: An illustration of how I envisage the areas of research presented in this thesis overlap .......................................................... 35

Figure 1-2: PRISMA diagram showing the search strategy results and exclusion steps and reasons .................................................................................................................. 41

Figure 1-3: Forest plot showing ORs and 95%CIs for studies comparing catheter ablation with medical therapy .................................................................................................................. 52

Figure 1-4: Forest plot showing ORs and 95%CIs for studies comparing encircling lesions of the pulmonary veins with other techniques in which the veins were not encircled .......... 54

Figure 1-5: Forest plot showing ORs and 95%CIs for studies comparing electrical isolation of the pulmonary veins with techniques in which isolation was not a procedural goal or endpoint .................................................................................................................. 55

Figure 1-6: Forest plot showing ORs and 95%CIs for studies comparing circumferential pulmonary vein isolation with a segmental technique .................................................................................................................. 56

Figure 1-7: Forest plot showing ORs and 95%CIs for studies comparing ablation strategies using linear ablation lesions against strategies of pulmonary vein isolation without linear ablation .................................................................................................................. 58

Figure 1-8: Forest plot showing ORs and 95%CIs for studies in which a comparison was made between one strategy using less extensive linear ablation against a strategy of more extensive lesions .................................................................................................................. 59

Figure 1-9: Forest plot showing ORs and 95%CIs for studies reporting the effect of adding complex fractionated atrial electrogram ablation to other techniques .................................................................................................................. 61

Figure 1-10: Forest plot showing ORs and 95%CIs for studies comparing a left atrial ablation strategy against a strategy using bi-atrial ablation .................................................................................................................. 63
Figure 2-1: The procedural journey for our cohort of patients with persistent atrial fibrillation.

Figure 2-2: Recurrence curve showing number of patients remaining free from documented recurrence over time after a single procedure.

Figure 2-3: Recurrence curve showing number of patients remaining free from documented recurrence over time after their last procedure.

Figure 2-4: Kaplan-Meier curve showing AF-free survival after a single procedure for patients grouped according to use of CT integration.

Figure 2-5: Kaplan-Meier curve showing AF-free survival after the final procedure for patients grouped according to use of CT integration.

Figure 3-1: Antiarrhythmic treatment algorithm.

Figure 3-2: Study CONSORT diagram.

Figure 3-3: Study flow diagram.

Figure 3-4: Screen shot of eCRF database.

Figure 5-1: Box and Whisker chart of AEQ and early recurrence of atrial tachyarrhythmia in patients with paroxysmal atrial fibrillation.

Figure 5-2: Receiver Operating Characteristic (ROC) curve for AEQ as a predictor of freedom from recurrence of atrial tachyarrhythmia over 12 month follow up in patients with paroxysmal atrial fibrillation.

Figure 6-1: Two-handed technique for gaining venous access under ultrasound guidance and representative image of the femoral vasculature.

Figure 7-1: Quality of Life scores (mean ± SD) by EHRA Class.

Figure 7-2: Quality of Life scores (mean ± SD) by mEHRA Class.
Figure 7-3: AFEQT sub-domain scores (mean ± SD) by mEHRA Class ........................................189

Figure 8-1: Copy of Figure 1-1 ........................................................................................................196
PUBLICATIONS ARISING FROM THIS THESIS


In addition, thirteen abstracts have been presented and published in peer-reviewed journals.
National Awards for Work Contained in this Thesis

2014    British Heart Rhythm Society   Young Investigator Award Winner (Clinical)

Long term outcomes after persistent AF ablation: six year data from a high volume UK centre.

2013    British Cardiovascular Society    Highest scoring abstract

Modification of the European Heart Rhythm Association AF symptom score improves discriminative ability: a validation study
DECLARATION OF ORIGINALITY

The work contained within this thesis is that of the author, produced with the aid and guidance of his supervisors. All experimental work and statistical analyses were performed by the author, with statistical support and guidance provided by Dr Laura Bonnett, University of Liverpool. Where work has been published in the literature, co-authors of that work have provided editorial commentary, but final responsibility has remained with the author at all times.
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## Acronyms and Abbreviations Used in this Thesis

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full text</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAD</td>
<td>Anti-Arrhythmic Drug(S)</td>
</tr>
<tr>
<td>ACT</td>
<td>Activated Clotting Time</td>
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<td>AEQ</td>
<td>Ablation Effectiveness Quotient</td>
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<td>AF</td>
<td>Atrial Fibrillation</td>
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<td>AFEQT</td>
<td>Atrial Fibrillation Effect on Quality Of Life Tool</td>
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<td>ANOVA</td>
<td>Analysis of Variance</td>
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<td>ARR</td>
<td>Absolute Risk Reduction</td>
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<td>Arterial</td>
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<td>AUC</td>
<td>Area Under the Curve</td>
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<td>Atrioventricular</td>
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<td>BARC</td>
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<td>BD</td>
<td>Twice daily</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<td>CA</td>
<td>Catheter Ablation</td>
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<td>CFAE</td>
<td>Complex Fractionated Atrial Electrogram(S)</td>
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<td>CI</td>
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<td>CMR</td>
<td>Cardiac Magnetic Resonance</td>
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<td>Cardiopulmonary Resuscitation</td>
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<td>DAP</td>
<td>Dose-Area Product</td>
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<td>DC (CV)</td>
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</tr>
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<td>Abbreviation/Description</td>
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</tr>
<tr>
<td>FIRM</td>
<td>Focal Impulse and Rotor Modulation</td>
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<td>Fluoroscopy</td>
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<td>g</td>
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<td>High Frequency Stimulation</td>
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<tr>
<td>INR</td>
<td>Internationally Normalised Ratio</td>
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<td>Litre</td>
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<td>PVI/ PVAI</td>
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<td>QALY</td>
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<td>Receiver Operating Characteristic</td>
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<tr>
<td>WACA</td>
<td>Wide Area Circumferential Ablation</td>
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ACKNOWLEDGEMENTS

Firstly, I would like to thank Dr Dhiraj Gupta for his unwavering guidance and enthusiasm through every step of my research endeavour. He has acted as supervisor, mentor and friend and helped me through the many highs and lows of clinical research. Without his invaluable leadership none of this would have been possible.

Secondly, I thank Professor Sian Harding for guiding me through and, most importantly, for extending a hand of friendship and support to a stranger. In doing so she had much to lose and little to gain, but I hope her investment in me is now deemed worthwhile, and that she has enjoyed our association as much as I.

My thanks also go to the various colleagues who have made this process possible. To Sharon Ngai, without whose organisation and help I may never have got out of the starting blocks, and to Dr Sandeep Panikker, who worked tirelessly and with amazing good grace to help turn an idea in Liverpool into a multi-centre trial. To Maureen and Ben, my research nursing team, and all the cardiac physiologists and cath lab staff at Liverpool Heart and Chest Hospital, especially the electrophysiology team, who often worked late or fitted in extra tasks for my benefit rather than their own. To Dr Laura Bonnet for her statistical tutelage, and to all of the consultant Electrophysiologists who have put up with me, and the needs of my various studies, throughout my time with them.

Finally thank you, to my darling wife, Anna, and my children, Lara, Emmy and Richie: without whom nothing else has any meaning.
1. IMPROVING ABLATION OUTCOMES IN ATRIAL FIBRILLATION: INTRODUCTION AND REVIEW OF THE LITERATURE

1.1 ATRIAL FIBRILLATION IN PERSPECTIVE

1.1.1. ATRIAL FIBRILLATION AS A PUBLIC HEALTH PROBLEM

Atrial fibrillation (AF) is the most common cardiac arrhythmia occurring in 1-2% of the general population\(^1\)-\(^4\). AF approximately doubles mortality rates\(^5\). The incidence of AF rises with age and it is an important risk factor for stroke\(^6\)-\(^8\).

Direct treatment of AF consumes 2% of the total NHS budget, of which half is due to hospital admissions\(^9\). This calculation does not include the cost of stroke rehabilitation and other secondary complications. Patients with complications of AF account for \(\frac{1}{3}\) million hospital bed days every year in England and Wales alone (Patient Episode Database for Wales and Hospital Episode Statistics – personal communication). The current NICE guidance on AF recommends referral of such patients to a ‘specialist’ for consideration of interventional treatments such as catheter ablation or pacemaker and AV node ablation\(^7\).

1.1.2. THE EFFECT OF AF ON THE INDIVIDUAL

Many patients suffer considerable symptoms associated with a reduced quality of life (QoL)\(^10\). This is accompanied by reduced exercise capability\(^11\). The effect of AF on QoL is as severe as in patients with significant structural heart disease\(^12\). Treatment for AF aims to
minimise or abolish these symptoms and to avoid the development of complications and improve QoL\textsuperscript{13}.

1.1.3. **ATRIAL FIBRILLATION AS A DISEASE**

1.1.3.1. **PATHOGENESIS OF AF**

In AF there is chaotic, rapid electrical activity within the atria resulting in disorganised local contraction and ineffective transit of blood to the ventricles\textsuperscript{14}. Generally, AF cycle lengths are shorter in the left atrium than the right, suggesting this as the chamber driving the arrhythmia\textsuperscript{15}. Multiple hypotheses have been proposed to explain the pathogenesis of atrial fibrillation and it remains unclear whether one, true, hypothesis predominates or whether a combination of mechanisms can exist, either within a population or an individual\textsuperscript{16}. Evidence for initiation of AF by ectopic foci within the pulmonary veins provided the basis for the development of strategies for percutaneous catheter ablation (CA) of AF\textsuperscript{17}. Maintenance of AF may be due to a critical number of self-propagating wavelets and/or to areas of localised microreentry\textsuperscript{18,19}. Each of these proposed mechanisms has been shown to exist experimentally and treatment strategies based on the proposed models have been shown to be clinically effective\textsuperscript{20-24}. On a cellular level, changes in ionic currents occur, either due to genetic mutations or in response to cellular stress. Abnormalities in cellular calcium handling can occur, particularly due to down regulation of the $I_{\text{ca,L}}$ current\textsuperscript{25}. Combined with down regulation of other depolarisation currents, such as $I_{\text{to}}$ and $I_{\text{Na}}$, there is a reduction of conduction velocity and shortening of the atrial cardiac action potential resulting in heterogeneous shortening of effective refractory periods\textsuperscript{26}. This dispersion of abnormal electrical conduction properties creates a mechanism by
which either re-entry or wavelet propagation can occur. Interestingly, it seems to be the 
alteration of normal myocardial conduction properties or patterns that promotes AF more 
than the specific mechanism. This is evidenced by the fact that some models have shown 
that AF susceptibility can also be increased by ionic changes that are the opposite to those 
described above, such as up regulation of \( I_{\text{ca,L}} \) in postoperative or hyperthyroidism-
associated AF.\(^{27,28}\)

1.1.3.2. GENETIC ASPECTS OF AF

The genetics of AF are complex and incompletely understood. Occurrence of atrial 
fibrillation in childhood is rare, and usually associated with congenital structural or 
electrical abnormalities (such as an accessory atrio-ventricular pathway) within the 
heart.\(^{29,30}\) However, certain familial forms seem to exist in which multiple relatives develop 
atrial fibrillation, often in young adulthood, without any clear precipitating comorbidities.\(^{31}\) 
Several genes have been identified which appear to be associated with AF development.\(^{32}\) 
These can be seen to cause ion channel dysfunction, structural remodelling or abnormal 
cytoskeletal interactions.\(^{33}\) A gain-of- function mutation of the \( KCNQ1 \) gene, which encodes 
a subunit of the \( I_{\text{Ks}} \) channel, was the first to be identified as having an association with atrial 
fibrillation.\(^{34}\) Since then abnormalities in several other genes encoding for potassium 
channels, as well as the sodium channel gene, \( SCN5A \). As with \( I_{\text{ca,L}} \) described above, both 
gain-of- function and loss-of-function mutations have been described associated with 
increased susceptibility to AF.\(^{33}\)
One particular non-ion channel locus, which has been studied extensively, is 4q25 which encodes PITX2. PITX2 is critical for left/right asymmetry, including specification of the left atrium (LA) and pulmonary myocardium and suppression of a default program for sinoatrial node formation in the left atrium. Mutations in genes encoding PITX2 may prevent normal differentiation and development of the LA to developing AF.\textsuperscript{35} As well as compatible cellular level abnormalities found in animal/tissue models, strong associations have been seen in population studies.\textsuperscript{36} Two studies found polymorphisms at 4q25 were implicated in both early and late recurrence after CA.\textsuperscript{37,38} A number of mutations can occur and risk, with increasing number of mutations, may be cumulative.\textsuperscript{39}

Polymorphisms of the gene encoding the intercellular gap protein, connexin40, have been shown by several groups to be associated with increased risk of AF.\textsuperscript{40-42} Expression of connexin40 is associated with atrial conduction velocities, providing a mechanism by which the genotype may be linked with the AF phenotype.\textsuperscript{43} However, this promising early work has been hampered by difficulties obtaining reliable samples and inconsistencies in connexion quantification.\textsuperscript{32,33}

A major complicating factor in understanding a potential genetic basis for AF is the late-onset, acquired nature seen most frequently. Whether genetic predisposition plays a role in increasing susceptibility to the disease-inducing effects of associated conditions is hard to determine, and incompletely studied, due the considerable confounding that cannot be adequately controlled for in older patients. For example, a number of studies have looked at genetic components of the rennin-angiotensin system with particular attention paid to
the ACE gene, the D(eletion) allele of which seems particularly strongly associated with development of AF.\textsuperscript{44} Associated mutations in the angiotensinogen and angiotensin receptor genes have also been shown.\textsuperscript{45} Abnormalities in any of these aspects of the renin-angiotensin system can lead to the development of hypertension and pre-existing hypertension is strongly associated with occurrence of AF. Classically, hypertension has been thought to increase intra-atrial pressure, causing atrial stretch and resultant abnormal remodelling is thought to explain this association but it's possible that both diseases can be manifestations of the same genetic abnormality(ies).

It is likely that there is no simple “AF gene” rather a number of genotypes which increase risk and, at least in some cases, have an additive risk. It may be that some abnormalities (particular ion channel) may be sufficient to be considered monogenic AF whereas other abnormalities are polygenic. In some cases AF would seem to be a direct consequence of the genetic abnormality (e.g. abnormal connexion, ion channel loss or gain in function) and in others it may be that AF is either a direct genetic consequence or a secondary effect of the phenotype. A “two-hit” hypothesis has been proposed in which both genetic and acquired risk factors are required for AF to develop.\textsuperscript{46}

\begin{itemize}
\item \textbf{1.1.3.3. Classification of AF}
\end{itemize}

Atrial fibrillation may occur intermittently (in paroxysms) or may be present continuously. In practice the terms paroxysmal AF (PAF) and persistent AF (PeAF) are widely used. The definitions of these terms have changed over recent years suggesting that the distinctions are not clear cut.\textsuperscript{14,47-49} Longstanding PeAF (LsPeAF) describes AF that has been present
continuously and without significant interruption for at least twelve months. Although the time period of twelve months is an arbitrary cut off the relevance of this subcategory is that it tends to represent a point at which a rhythm control strategy may well be significantly less successful than in less advanced disease states. There is no accepted consensus as to what duration of sinus rhythm can occur after an attempt at cardioversion or ablation before AF is no longer considered longstanding. The term permanent AF is also used and differs from the other subcategories in that it is defined by a treatment decision rather than a disease state. Permanent AF is present when patient and treating clinician have decided to accept atrial fibrillation and to no longer pursue attempts to restore sinus rhythm. The term is usually used when AF is present continuously. If a later decision is made to try to restore sinus rhythm, permanent AF should be reclassified.

1.1.4. Current treatment strategies for AF

Treatment of atrial fibrillation focuses on the avoidance of complications, mainly in the form of stroke, and reduction in symptoms. As stated previously, the incidence of AF rises with age and it is an important risk factor for stroke.6-8 Thromboembolism occurs in AF due to a combination of abnormal blood stasis in the hypocontractile left atrium, and in particular the left atrial appendage; abnormal activation of circulating platelets and the coagulation cascade; and endothelial dysfunction due various mechanisms such as inflammation, abnormal turnover of extracellular matrix and myocytic hypertrophy.50 Thankfully, there are now well established guidelines for the effective prevention of stroke with anticoagulation47,51. In addition to the vitamin K antagonist, warfarin, a number of new and effective therapeutic agents are now available.52-55 For patients unable to take
pharmacological anticoagulation, percutaneous closure of the left atrial appendage is a potential alternative.\textsuperscript{56,57}

The second significant issue with AF is that many patients suffer considerable symptoms associated with a reduced quality of life (QoL).\textsuperscript{10} This is frequently accompanied by reduced exercise capability\textsuperscript{11}. Symptoms may include palpitations, lethargy, dyspnoea, chest pain and even personality change.\textsuperscript{7} The effect of AF on QoL is as severe as in patients with significant structural heart disease\textsuperscript{12}. In addition to the need to avoid embolic stroke, treatment of AF aims to minimise or abolish these symptoms and improve QoL.\textsuperscript{13} There are two broad categories of treatment. One option is to accept atrial fibrillation and focus simply on controlling the ventricular rate (rate control) and the second is to attempt to restore and maintain sinus rhythm (rhythm control).

\subsection*{1.1.5. Rate versus rhythm control}

There have been five large trials performed to try to establish the optimum treatment strategy, rate or rhythm control, for patients with A.F\textsuperscript{58-62} These trials recruited over 5000 patients and focussed on important hard endpoints, including mortality, but none showed an advantage of one strategy over the other. The management of AF in these trials was principally focussed on pharmacological means to control heart rate or rhythm, with a limited number of patients moving to interventional (ablation) treatments. Sub analysis of these trials showed no difference in quality of life between the treatment strategies\textsuperscript{63,64} although successful maintenance of sinus rhythm did appear to confer an improvement.\textsuperscript{65}

\subsection*{1.1.6. Pharmacological therapy}
Pharmacological treatments can be grouped according to whether they predominately work by controlling rate or rhythm. Because of the negative results of the abovementioned studies, rate control medications are generally advocated for first line use, with rhythm control medications (antiarrhythmic drugs) reserved for those who remain symptomatic despite adequate rate control.\(^7\) Beta-blockers are the mainstay of pharmacological rate control with alternatives predominantly being the negatively chronotropic non-dihydropiridine calcium channel blockers, verapamil and diltiazem, or digoxin.\(^66\) Antiarrhythmic (rhythm control) drugs licenced for use in the UK include flecainide, procainamide, propafenone, sotalol, dronedarone, and amiodarone. These agents are classified according to the predominant action they exert on the cardiac action potential due to the variety of cell membrane ion channels on which the individual drug acts. Unfortunately, these changes may have the unintended side-effect of increasing the likelihood of re-entrant tachyarrhythmia, either by increasing the period during which a cell is vulnerable to after-depolarisations, or by stabilising re-entry when it occurs.\(^67\) This tendency is termed pro-arrhythmia and is potentially life-threatening. Pro-arrhythmia may help explain why, at least in AFFIRM – by far the largest of the rate v rhythm studies discussed above, the overall beneficial survival effects of sinus rhythm appeared negated when it was achieved with antiarrhythmic drugs.\(^68\) In addition, anti-arrhythmic drugs are limited in the efficacy in which they actually achieve sinus rhythm. At the five year follow-up point of AFFIRM, 34.6% of patients in the rate control group were nonetheless in sinus rhythm, increasing to only 62.6% in the rhythm control arm, an absolute difference of only 28%.\(^60\)
1.1.7. Non-pharmacological (interventional) therapy

In contrast to the studies of rate v rhythm with medication studies of interventional management of AF have shown considerable improvements in QoL. The dramatic improvement seen in QoL when it is possible to “cure” AF has been confirmed in studies of catheter ablation\(^{69-71}\). It appears that if AF can be controlled, without the potentially deleterious side effects and pro-arrhythmic risks of anti-arrhythmic medication, there is a significant resulting improvement in quality of life\(^{72}\). As interventional treatments for AF are both more effective at controlling the rate and rhythm and associated with fewer side effects there is a good rationale for presuming that they should produce greater improvements in QoL than achieved with medication\(^{73-75}\).

1.1.7.1. Palliative ablation (pace and ablate)

Permanent pacemaker implantation and atrioventricular (AV) node ablation (Pace and Ablate, P&A) is a strategy that is designed to definitively control and regulate the heart rate without attempting to restore normal (sinus) rhythm. This is achieved by destroying (ablating) the AV node which is the electrical connection between the atria and the ventricles. Therefore, whilst the atria continue to fibrillate, this is not conducted to the ventricles. Because the ventricles’ own intrinsic ability to contract is both unreliable and slow: a pacemaker is implanted prior to AV node ablation to ensure an adequate heart rate. As such it is sometimes considered as the “ultimate” means of rate control. P&A has been shown to improve quality of life, increase exercise capacity and, in patients with impaired left ventricular (LV) function initially, to improve LV function\(^{76,77}\). However, because of the irreversible nature of the procedure, the life-long dependency on a pacemaker –
replacement of which is required periodically with each procedure carrying an inherent risk of infection or other complication, and the potential deleterious effect of permanent loss of atrioventricular synchrony and non-physiological pacing. P&A is usually reserved for patients in whom other treatment options have failed or are considered unsuitable due to advanced age or comorbid conditions.47

1.1.7.2. Catheter Ablation

CA, often called pulmonary vein isolation or PVI, is an attempt to cure AF. In >95% of patients AF is triggered by rapid electrical beats within the pulmonary veins which stimulate the heart thereby causing AF17. The ablation procedure is designed to prevent these pulses of electricity from entering the heart by forming a line of electrical insulation between the mouth of the veins and the heart78. Additional burns may also be performed at other critical points for AF initiation or maintenance, or in a pattern that attempts to compartmentalise the atria to prevent abnormal electrical “short circuits” (re-entry) from occurring. When compared to pharmacological rhythm control therapy CA significantly and consistently produces greater freedom from AF.73-75,79-81

1.1.7.2.1 Effect of Catheter Ablation on Quality of Life

Although in the previously mentioned studies of rate versus rhythm control no QoL difference was seen between the groups, this may relate to the pharmacological strategies employed in these trials. CA has been shown to improve QoL and it appears that rhythm control with CA produces a quality of life benefit whereas pharmacological rate control does not.69,70,75,80 Even when CA does not “cure” AF, there can still be an important
improvement in quality of life.\textsuperscript{82} Recent work by Reynolds et al showed that patients with drug-resistant paroxysmal AF treated with AF ablation showed significant and sustained improvements in QoL measured with the SF-36 instrument.\textsuperscript{83} This improvement was shown in the physical component score, mental component score, symptom frequency and symptom severity. The magnitude of improvement was greater than the 2 to 3 point improvement that defines a minimum, clinically meaningful difference.\textsuperscript{11,84} In contrast, patients randomised to drug therapy showed little symptomatic improvement. Furthermore, those patients who crossed over from drugs to catheter ablation showed similar QoL gains to those initially randomised to catheter ablation.

1.2 Questions I hope to answer through this thesis

1.2.1 Theme

The use of CA to treat AF is a relatively new and developing procedure, having only initially having been described in the last few years of the twentieth century.\textsuperscript{17,78,85} Despite the advantages of CA over pharmacological therapy, many areas for improvement remain. The theme of this thesis will be to investigate how CA, the most advanced of the available treatments for AF, can be improved to the benefit of patients. The central aim is that the new knowledge gained through the research undertaken will provide novel insights into how patient outcomes can be improved. I believe that the outcome for the patient is a multi-factorial concept. Freedom from recurrent AF after a CA is undeniably important, but is not the “90be all and end all”. Therefore whilst some of the work presented in subsequent Chapters will focus on arrhythmic success, others will explore issues of patient safety, patient selection and a novel means of assessing ablation effectiveness, potentially allowing
prediction of appropriate follow up. I will focus on areas where current research is either limited of lacking. For example, therefore, when looking at arrhythmic outcomes I will focus on PeAF, and/or substrate-based AF. QoL will be a prevalent theme throughout several Chapters. In Chapter two I will investigate how heath status, as a surrogate for QoL, is linked with arrhythmic outcome and investigate how CA affects both aspects. Later, I will describe and report a randomised trial in which QoL is an important secondary outcome measure. Finally, I will show how assessment of QoL can help to select appropriate patients with AF for CA. Together, I hope to present a coherent and complimentary body of work which moves scientific knowledge forward towards the goal of optimum patient outcome, as illustrated in Figure 1-1, below.

![Figure 1-1: An illustration of how I envisage the areas of research presented in this thesis overlap, with a key central goal of optimising the overall outcome for patients undergoing catheter ablation](image)
1.3 Efficacy of catheter ablation for persistent atrial fibrillation: A systematic review and meta-analysis of evidence from randomised and non-randomised controlled trial

1.3.1 Methods

1.3.1.1 Search strategy and study eligibility

I aimed to systematically review the literature for evidence of the clinical effectiveness of CA of PeAF in randomised, quasi-randomised or other controlled trials following recommendations for the reporting of meta-analysis of observational studies. The initial search was performed on 21 June 2012 and was repeated periodically until 20 October 2013. The searches were performed with the assistance of an information specialist librarian. We searched PubMed/MEDLINE (1/1/1995 until October 2013), EMBASE (1950 until October 2013) and the Cochrane Central Register of Controlled trials (CENTRAL - up until and including Issue 9, September 2013) using the search terms (((atrial) OR auricular) AND fibrillation) AND (ablation OR isolation) We cross-checked this search using wildcards (((Auric*) OR Atrial) AND Fibrillat*) AND (ablat* OR isolat*) and the MESH Headings ATRIAL FIBRILLATION and CATHETER ABLATION mapped to the thesaurus. For the EMBASE search we additionally searched using the Heading HEART ATRIUM FIBRILLATION. We excluded those not published in English unless an English version of the article was accessible, and applied the filters: Humans AND (Clinical Trial OR Controlled Clinical Trial OR Randomized Controlled Trial). In order to attempt to access the grey literature we searched using the OpenGrey Database (http://www.opengrey.eu) using the terms (Atrial Fibrillation AND (Isolation OR Ablation)) and searched for studies with
results available on the online trial registry www.clinicaltrials.gov. We attempted to contact authors to clarify any areas of uncertainty regarding study data. Where data for patients with PeAF were presented graphically but explicit figures were not provided in the published manuscript we used graphic digitization software (DigitizeIt, Braunschweig, Germany). Potentially eligible studies were assessed independently by two investigators with differences resolved by consensus including a third investigator and statistician.

We included studies of ablation against medical therapy and also those which compared one ablation strategy with another. We excluded studies which did not report outcome data or where the outcome data was limited to immediate procedural success. We also excluded studies which did not contain a comparator group but allowed a wide range of comparators such as placebo, randomised control arm, quasi-randomised or non-randomised contemporary control or historical cohort. Studies needed to have a comparator group in which treatment was different. Studies in which two groups were formed based on the outcome of an earlier procedure but then analysed as separate groups (i.e. long term success comparing acute procedural failure vs. acute procedural success) were not included. We also excluded studies of surgical ablation, and studies of ablation techniques other than AF ablation.

Because of well documented weaknesses in the methodology, accuracy, and completeness of conference abstracts we excluded studies published only in abstract form. We supplemented our database searches with hand searches of the reference lists of published studies and major review articles. We included one study only available online ahead of print and one which was available only on clinicaltrials.gov at the time of our literature
search and data analysis, both of which have subsequently been published in peer-reviewed journals.\textsuperscript{89,90}

Few studies differentiated between persistent and longstanding PeAF and fewer still provided a breakdown of results based on this distinction. In addition, the definition used was inconsistent and rarely stated explicitly. Therefore, throughout this manuscript we use “PeAF” as a single encompassing term. Only four studies exclusively recruited patients with longstanding (>12 months) PeAF.\textsuperscript{91-94} These studies were included in the pooled analyses along with a discussion about any impact this may have had on the results.

\section*{1.3.1.2 Areas for analysis}

We grouped studies according to the following analysis areas for patients with PeAF.

1. Efficacy of CA compared to medical therapy
2. Effect on efficacy of encircling ablation and isolation of the PVs
3. Efficacy of circumferential versus segmental pulmonary vein isolation (PVI)
4. Efficacy of linear atrial ablation lesions
5. Efficacy of ablation of Complex Fractionated Atrial Electrograms (CFAEs)
6. Efficacy of other peri-ablation techniques and strategies

Studies were assessed individually as to the most appropriate analysis area but were permitted to contribute to more than one if appropriate to the study design (e.g. multi-arm study or 2x2 factorial design).
1.3.1.3  **Statistical analysis**

A qualitative analysis is provided unless there is sufficient data (at least three comparable studies) to perform a meta-analysis. Meta-analysis was performed using random-effects modelling, checked against fixed-effects to avoid undue influence of small studies. Heterogeneity was assessed using the $I^2$ statistic. We followed the recommendations of the Cochrane Handbook, grading significant heterogeneity as moderate (30-60%), substantial (50-90%) or considerable (>75%).

Statistical analysis was performed using Comprehensive Meta Analysis software, version 2.2 (Biostat, Englewood, New Jersey, USA) and StatsDirect version 2.7.8 (StatsDirect Ltd, Cheshire, UK). Where studies enrolled patients with both paroxysmal and PeAF and provided details of outcomes split by AF type but did not perform their own analysis we compared proportions using the $\chi^2$ test. Funnel plots were used as a graphical assessment for publication bias. These are provided in Appendix 1. Individual studies which caused a marked increase in the heterogeneity and publication bias were assessed for a clinical explanation for the differences observed (e.g. substantial differences in the intervention or control group), in which case they were described individually rather than pooled with other studies. If studies were excluded on this basis we performed and reported a sensitivity analysis. Where sufficient data were available we also performed sensitivity analyses for outcomes after single or multiple ablation procedures. We found insufficient data to perform any sub-group analyses.
1.3.2 RESULTS

1.3.2.1 LITERATURE SEARCH

Of the 967 potential eligible unique studies identified, 921 were excluded leaving 46 full text articles for analysis. Details of our inclusion and exclusion process are given in Figure 1-2.
Figure 1-2: PRISMA diagram showing the search strategy results and exclusion steps and reasons
1.3.2.2. **Study and Patient Characteristics**

We identified 46 studies containing 6085 patients. Thirty two were RCTs, and 14 were NRCTs of which the study design was a cohort study in 12 and case-control in two. Twenty three studies included only patients with PeAF and 23 contained a mixed patient population with results split by AF type. The median proportion of PeAF in the mixed studies was 39% (range 19-72%). The total number of patients with PeAF was 3819. Mean follow-up was 13.5±6 months (range 3–36). Five non-randomised studies were of sequential cohort design with uneven follow-up between groups. We did not analyse individual patient characteristics as most studies reporting results for patients with both paroxysmal and PeAF reported these only for the study population as a whole. All studies used radiofrequency (RF) alternating current as the ablation energy source. Details of the included studies are shown in Table 1-1.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study type</th>
<th>N</th>
<th>AF Type</th>
<th>% PeAF</th>
<th>Control group</th>
<th>Treatment group</th>
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<tr>
<td>Arentz, 2007</td>
<td>RCT</td>
<td>110</td>
<td>Mixed</td>
<td>39</td>
<td>Segmental PVI</td>
<td>WACA</td>
</tr>
<tr>
<td>Bansch, 2013</td>
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<td>Mixed</td>
<td>35</td>
<td>No waiting period after PVI</td>
<td>Prolonged waiting period (1 hour)</td>
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<td>RCT</td>
<td>80</td>
<td>Persistent</td>
<td>100</td>
<td>PVI + MIL + CTI</td>
<td>As control + SVCI + intercaval septal and posterior lines</td>
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<tr>
<td>Corrado, 2010</td>
<td>RCT</td>
<td>320</td>
<td>Mixed</td>
<td>54</td>
<td>PVAI</td>
<td>PVAI + SCVI</td>
</tr>
<tr>
<td>Della Bella, 2009</td>
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<td>290</td>
<td>Mixed</td>
<td>29</td>
<td>Fluoroscopy-guided CA</td>
<td>Image integration-guided CA</td>
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<td>Di Biase, 2009</td>
<td>Cohort</td>
<td>390</td>
<td>Mixed</td>
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<td>Manual ablation</td>
<td>Robotic navigation-delivered ablation</td>
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<tr>
<td>Di Biase, 2010</td>
<td>Cohort</td>
<td>267</td>
<td>Mixed (repeat CA)</td>
<td>71</td>
<td>LAA not ablated</td>
<td>LAA ablation (focal/LAA isolation)</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Study type</td>
<td>N</td>
<td>AF Type</td>
<td>% PeAF</td>
<td>Control group</td>
<td>Treatment group</td>
</tr>
<tr>
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<td>----</td>
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<tr>
<td>Dixit, 2012</td>
<td>RCT</td>
<td>156</td>
<td>Persistent</td>
<td>100</td>
<td>PVI + ablation of non-PV triggers</td>
<td>As control + CFAE ablation</td>
</tr>
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<td>Elayi, 2008</td>
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<td>Longstanding PeAF</td>
<td>100</td>
<td>PVAI</td>
<td>PVAI + CFAE</td>
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<td>Cohort</td>
<td>77</td>
<td>Persistent</td>
<td>100</td>
<td>CFAE</td>
<td>PVI + CFAE</td>
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<td>116</td>
<td>Persistent</td>
<td>100</td>
<td>PVI + CFAE</td>
<td>PVAI + lines (1-3 of roof, MIL, CTI)</td>
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<td>Mixed</td>
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<td>PVI + MIL</td>
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<td>PVI + lines (MIL, roof, CTI)</td>
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<td>Persistent</td>
<td>100</td>
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<td>Propafenone AND amiodarone for 2 months post-PVI</td>
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<td>100</td>
<td>AAD +/- DCCV</td>
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<td>Persistent</td>
<td>100</td>
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1.3.2.3. STUDY QUALITY

In keeping with previous work we assessed study quality using a modified version of published quality assessment criteria for case series, combined with guidance from the Cochrane Handbook. Standard measures of quality such as randomisation method and blinding were of limited relevance due to the inclusion of non-randomised trials, but were variably reported in the included RCTs. No studies adjusted for multiple hypothesis testing when reporting outcomes at sequential time points or results of both single and multiple procedures. Indicators of potential bias, such as loss to follow-up, were variably reported and explained. Only four RCTs achieved all of the required quality criteria. Ignoring randomisation and blinding, only two NRCTs were assessed positively for all remaining criteria. Overall, therefore, the quality of included studies was generally poor.
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<td>Eligibility criteria reported</td>
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Table 1-2: Assessment of study quality. RCT: Randomised Controlled Trial
1.3.2.4.  **Definitions of success**

For all studies, except for the two specifically assessing CA against medical therapy in patients with heart failure, the outcome measure used was recurrence of atrial fibrillation or other atrial tachyarrhythmia. The most frequent definition used was documented atrial arrhythmia lasting >30 seconds (22 studies). Other definitions used were arrhythmia lasting 3 seconds (one study), 32 seconds (one study), 60 seconds (four studies), 10 minutes (two studies) and 24 hours (one study). One study stated symptom-free status off anti-arrhythmic drugs and sinus rhythm on ECG. Fourteen studies didn’t state how they defined recurrence. Rhythm monitoring was performed using ambulatory ECG devices in 35 studies, trans-telephonic monitoring or daily ECGs in four and resting ECG in four. One study used implanted loop recorders. The means of monitoring heart rhythm was not clear in two studies. The two heart failure studies used left ventricular ejection fraction as a measure of success. In one it was the study’s primary endpoint and for the other it was a secondary endpoint with peak VO$_2$ as the primary endpoint. Of all 45 eligible studies, only four reported the effect of the investigational technique on patients’ quality of life.

1.3.2.5.  **Complications**

Four studies did not report procedural complication rates. Of the remaining 42 studies, four reported no complications although often failed to define what they considered a complication. Of those reporting complications, the definitions used were frequently unclear and varied greatly between studies. Overall, the median reported complication rate was 3% (range 0-15%). None of the studies with mixed populations provided a breakdown of complications by AF type. Of the total population (6085) there were 20 reported arterial thromboembolic events and four deaths.
Four studies tested the efficacy of ablation against medical therapy in a general patient population. Oral et al. showed a borderline significant improvement in freedom from atrial fibrillation or flutter without the need for anti-arrhythmic drugs (AAD) (74% vs. 58%, p=0.05) after 12 months. The medical management strategy employed oral therapy with amiodarone for three months combined with either one or two electrical cardioversions. The authors stated the control group was designed to control for confounding variables rather than as a true comparison of CA and medical therapy. In the CACAF study, Stabile achieved sinus rhythm with CA in 50% of the sub-group with PeAF but in none of those treated with AAD. Two recently published RCTs compared catheter ablation, each using a different technique, to AAD therapy in patients with PeAF. The primary endpoint for Mont was 24 hours of AF which was significantly less common with CA than with AAD (30% vs 66%, p=0.002) as was a secondary endpoint of 30 seconds of AF (40% vs 70%, p<0.001). Similar results were found in a second study, this time using phased RF ablation (TTOP AF), that showed that a significantly higher proportion of patients undergoing CA achieved a >90% reduction in atrial tachyarrhythmia episodes at 6 months compared to treatment with Class I or III AAD (56% vs. 26%, p<0.001). Heterogeneity was low to moderate (32%). Overall, CA significantly reduced the risk of recurrent AF compared to medical therapy (OR 0.32, 95% CI 0.20-0.53, p<0.001 (Figure 1-3)).
1.3.2.6.1. **Patients with heart failure**

Two studies have assessed the efficacy of CA in patients with heart failure (MacDonald 2011 and Jones 2013). Both studies defined heart failure as New York Heart Association Class II-IV symptoms with a left ventricular ejection fraction (LVEF) <35%. In both studies the medical therapy arm was treated according to a rate-control strategy, rather than with anti-arrhythmic drugs. Primary endpoints for these studies therefore assessed functional parameters such as change in LVEF and change in peak VO\textsubscript{2} on cardiopulmonary exercise testing. Neither study assessed efficacy in terms of maintaining sinus rhythm. MacDonald studied 41 patients and found a non-significantly greater improvement in LVEF when measured by cardiac magnetic resonance (CMR) imaging (+4.6±11.1% with CA vs. +2.9±6.7%, p=0.06) but a more significant difference when measured by radionuclide ventriculography (+8.3±12.0% with CA vs. +1.4±5.9%, p=0.03). Of note, sinus rhythm was successfully maintained in only 50% of patients. A post hoc analysis showed the improvement in LVEF was significantly greater for those
who remained in sinus rhythm by both CMR and radionuclide ventriculography (+10.5±10.4% vs. +1.6±7.7%, p=0.008 and +13.3±15.0% vs. +2.2±5.6%, p=0.045, respectively). Jones et al randomised 58 patients to either CA or pharmacological rate-control. A greater proportion (88%) achieved sinus rhythm with CA by the end of the study (after a mean of 1.2 procedures, single procedure success rate 68%). Nonetheless, the difference in LVEF improvement after 12 months, again measured by radionuclide ventriculography, was also non-significant between treatment arms (+10.9±11.5% with CA vs. +5.4±8.5%, p=0.06). However, the primary endpoint of the study was change in peak VO₂ after 12 months which showed a significantly greater improvement with CA than with rate-control therapy (mean difference between groups +3.07 ml/kg/min (95%CI 0.56-5.59), p=0.018).

1.3.2.7. **ANALYSIS 2: EFFECT ON EFFICACY OF ENCIRCLING ABLATION OF THE PVs**

Three studies provided data to assess the effect of ablation lesions that encircled the PVs. Oral tested encircling PV ablation against left atrial linear lesions (non-encircling left atrial ablation). This study found the two strategies were equally efficacious (prevalence of AF after 9 months 28% vs. 25%, p=0.8). Two studies included an analysis of CFAE ablation with and without PVI. Both found the addition of PVI improved procedural success rates. Heterogeneity between studies was only moderate (I²=42%). Overall, adding ablation lesions that encircled the PVs significantly reduced recurrence rates (OR 0.26, 95%CI 0.09-0.74, p=0.01 (Figure 1-4)).
1.3.2.8. **Importance of Electrical Isolation**

Two studies looked specifically at the effect of electrical isolation of the PVs. Stabile performed a cluster-cohort study in patients treated at one of three centres, one of which (36 patients) performed an anatomical ablation with a procedural endpoint of loss of local electrograms. The other two centres (n=61) used a circular mapping catheter to assess electrical isolation of the PVs from the left atrium. After 15 months they found no difference in the rate of AF recurrence between the two groups (58% vs. 56%, p=0.9). A subsequent randomised study allocated patients to a procedure in which a single catheter was used to both map and ablate (again using local electrogram attenuation as the acute endpoint) or to the additional use of a circular mapping catheter to assess isolation. The latter strategy was associated with a significantly lower rate of AF recurrence (29% vs. 55%, p=0.02). The reason for the discordance between these studies is not clear, but the design of the study by Stabile may have introduced considerable bias dependent on the skill and experience of the operators in the different centres. Two of the studies in the previous analysis also confirmed
electrical isolation of the PVs.\textsuperscript{104,130} Looking at these four studies together, in which one arm had confirmed electrical isolation and the other either had solely anatomical or no encircling PV ablation, electrical isolation of the PVs produced significantly lower recurrence rates (OR 0.33, 95%CI 0.13-0.86, p=0.02 (Figure 1-5)). Heterogeneity was moderately high (59%). Removal of the study by Stabile would have eliminated heterogeneity but not affected the direction or significance of the pooled analysis and therefore was included in the analysis.

<table>
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**Figure 1-5:** Forest plot showing ORs and 95%CIs for studies comparing electrical isolation of the pulmonary veins with techniques in which isolation was not a procedural goal or endpoint

1.3.2.9. **Analysis 3: Efficacy of Circumferential Versus Segmental PVI**

Originally, PVI was performed by isolating each vein individually (segmentally), usually at the level of the vein ostia. Subsequently a technique by which ipsilateral veins are isolated together in two pairs using a wide ring of ablation lesions performed in the PV antra (wide area circumferential ablation, WACA) has been used. Three studies have assessed WACA against segmental ostial PVI techniques.\textsuperscript{96,115,118} One study was non-randomised and this was the only study which permitted the use of anti-arrhythmic drugs. This study by Mansour followed-up patients who underwent segmental PVI for
considerably longer than patients treated with circumferential ablation (21 vs. 11 months).\textsuperscript{115} There was no heterogeneity between studies. Considered together, these studies showed a non-significant trend towards improved outcomes with WACA (OR 0.41, 95\%CI 0.15-1.10, p=0.08 (Figure 1-6)). Only a single study (Nilsson) reported outcomes from multiple procedures.\textsuperscript{118} This study reported better outcomes with WACA from both a single and multiple procedures, although the difference was only significant for the latter (OR 0.16, 95\%CI 0.04-0.63, p<0.01).

![Meta analysis comparing circumferential and segmental pulmonary vein isolation](image)

**Figure 1-6:** Forest plot showing ORs and 95\%CIs for studies comparing circumferential pulmonary vein isolation with a segmental technique

One further study (Elayi 2008) was considered but was not included as all three treatment arms involved a form of wide area antral PV isolation (typical circumferential PVI in one arm and a novel lesion set named PV antral isolation in the other two).\textsuperscript{91} Its inclusion would have created considerable heterogeneity (I\textsuperscript{2}=77.5) and a marked shift in the funnel plot. Sensitivity analysis showed that its inclusion would not have altered the overall significance (OR 0.80, 95\%CI 0.14-4.51, p=0.80). The study contained three arms and the main finding was the additional effect of CFAE ablation over PV antral ablation and so was included in Outcome 5.
1.3.2.9.1. **OTHER PVI TECHNIQUES**

A single non-randomised study of patients with paroxysmal or PeAF assessed whether antral or ostial ablation was better for segmental PVI. After a mean of 1.4 procedures, AF recurrence in patients with PeAF was less common with antral ablation (22% vs. 52%, p=0.03), although follow-up in that group was also markedly shorter (647±197 vs. 1,015±257 days) making the results difficult to interpret.\(^\text{132}\)

1.3.2.10. **ANALYSIS 4: EFFICACY OF LINEAR ABLATION LESIONS**

Three eligible studies looked at the impact of adding additional linear ablation to PVI.\(^\text{106,107,131}\) One study tested the effect of an ablation line between the mitral annulus and left inferior PV (“mitral line”).\(^\text{106}\) Two studies tested a combination of a mitral line and a left atrial roof line connecting contralateral superior PVs.\(^\text{107,131}\) One further study, containing patients with both paroxysmal and PeAF, had a 2x2 factorial design including a comparison with and without mitral isthmus ablation.\(^\text{112}\) However, the study authors did not provide results split by AF type for this comparison, although they did for the other (included in the analysis of more or less extensive ablation, below). Heterogeneity was acceptable (moderate) between eligible studies (\(I^2=36\%\)). Pooled single procedure success rates were significantly higher in patients receiving additional linear ablation (OR 0.22, 95%CI 0.10-0.49, p<0.001 (Figure 1-7)). Only the study by Gaita reported multiple procedure success rates and the outcomes were again significantly better in the linear ablation group (OR 0.22 95%CI 0.08-0.64, p=0.005).\(^\text{24}\)
Figure 1-7: Forest plot showing ORs and 95% CIs for studies comparing ablation strategies using linear ablation lesions against strategies of pulmonary vein isolation without linear ablation

1.3.2.10.1. **More or Less Extensive Linear Ablation**

Three studies looked at the effect of fewer or extensive linear lesions, in addition to PVI. Mikhaylov added a septal line and Tamborero added a left atrial floor line, both to left atrial roof and mitral lines.\(^94,127\) Lim added box isolation of the posterior wall to a mitral line.\(^112\) Despite the slight differences in lesions deployed and the fact that Mikhaylov enrolled patients only with longstanding PeAF, there was no statistical heterogeneity between studies and no evidence of publication bias from visual analysis of the funnel plot. Overall there was no benefit seen from more extensive linear ablation (OR 0.77, 95% CI 0.41-1.43, p=0.40 (Figure 1-8)).
Figure 1-8: Forest plot showing ORs and 95% CIs for studies in which a comparison was made between one strategy using less extensive linear ablation against a strategy of more extensive lesions.

Pak studied outcomes for a group with a mitral line against a group who had a more extensive anterior wall line. Because the number of linear lesions in both groups was the same, although one was longer than the other, it was not included in the previous analysis. This showed a significantly higher success rate with a line across the anterior wall of the left atrium compared to a standard lateral mitral line. Of note, bidirectional conduction block across the anterior wall line was significantly more common than for the mitral line (69% vs. 32%, p<0.001). It may have been this, rather than the line itself, that accounted for the difference between study arms, as failure to achieve bidirectional block across an ablation line increases the risk of iatrogenic macro re-entrant left atrial tachycardia. The authors did not undertake a regression analysis to look at this possibility.

1.3.2.11. Analysis 5: Efficacy of Complex Fractionated Atrial Electrogram (CFAE) Ablation

Seven studies looked at the effect of additional CFAE ablation. There was substantial heterogeneity between studies when looking at single procedure success
rates ($I^2=61\%$) mainly due to the inclusion of the most recent RCT (the RASTA study) by Dixit\textsuperscript{103} However, heterogeneity was low when looking at AF recurrence after multiple procedures, even with the RASTA study included, and the study was within the expected funnel plot. In addition, we did not consider there to be any valid clinical reason for exclusion. Four studies showed no benefit of CFAE ablation, including one by Oral (2008) in which right atrial CFAE ablation was added, in a randomised manner, to a cohort who remained in AF after left atrial ablation including left atrial CFAEs.\textsuperscript{93} Although slightly different in this regard to the other studies in this analysis, the clinical effect being measured in each is that of adding CFAE ablation. Exclusion of this study would have actually increased heterogeneity ($I^2=68\%$ from 61\%) and sensitivity analysis showed no effect on the significance of the pooled analysis. We therefore included both the RASTA study and the study by Oral in our analysis. Two studies showed a statistically significant benefit and one, the RASTA study discussed above, showed worse outcomes with CFAE ablation. One study, by Lin, reported results both on and off anti-arrhythmic drugs but this had only a negligible effect on the overall study findings.\textsuperscript{113} We therefore used the results off drugs for the analysis as all the other eligible studies required the patients to be off medication. The study found in favour of CFAE ablation but with shorter follow-up in that group. The study by Elayi had three arms (CPVI, PVAI, and PVAI+CFAE). For this analysis we compared the latter two (PVAI vs. PVAI + CFAE) due to the consistent form of PVI used in both arms. Overall, CFAE ablation showed no additional benefit over other ablation techniques after a single procedure (OR 0.64, 95\%CI 0.35-1.18, $p=0.15$) or multiple procedures (OR 0.67, 95\%CI 0.42-1.08, $p=0.10$ (Figure 1-9)).
Figure 1-9: Forest plot showing ORs and 95% CIs for studies reporting the effect of adding complex fractionated atrial electrogram ablation to other techniques

Three of the included studies in this analysis enrolled only patients with longstanding PeAF. Sensitivity analysis showed that results for these studies in isolation did not differ from the overall result (OR 0.64, 95% CI 0.38-1.07, p=0.09) and removal of the studies would not have altered the direction or significance level of the overall pooled result (OR 0.57, 95% CI 0.18-1.88, p=0.36).

1.3.2.11.1. **Comparison of CFAE ablation and linear lesions**

Only a single study has compared CFAE ablation against linear lesions. Estner randomised 116 patients to one or other treatment in addition to PVI. The proportion of patients in each group with a recurrence of AF during 12 months' follow-up without antiarrhythmic drugs was the same in both groups (39% vs. 37%, p=0.88).
1.3.2.12. **Analysis 6: Efficacy of Other Peri-ablation Management and Strategies**

1.3.2.12.1. **Peri-ablation Management**

Two studies looked at aspects surrounding the CA procedure, not directly related to the actual ablation itself. Gu randomised 123 patients with PeAF to either a single AAD or a combination of Propafenone and amiodarone for 2 months post-CA but showed no significant difference in AF recurrence over 1 year (36% vs. 33.9%, p=0.78). Rivard looked at the effect of restoring sinus rhythm prior to ablation in 40 patients against 40 case-matched controls, all with PeAF. They found this strategy decreased the extent of ablation performed but did not alter either single (55% vs. 45%, p=0.28) or multiple procedure (90% vs. 70%, p=0.28) success rates.

1.3.2.12.2. **Left Atrial or Bi-atrial Ablation**

Three randomised studies looked at the effect of adding right atrial ablation in addition to left atrial ablation and reported conflicting results. Corrado tested the addition of superior vena cava isolation (n=73) to PVI alone (n=87) and found no difference in recurrence rates (27% vs. 29%, p=0.9). Calo used a more extensive lesion set and found a 39% (n=41) recurrence rate in a group treated with PVI plus cavotricuspid and mitral isthmus ablation compared to 15% (n=39) when intercaval posterior line, intercaval septal line, and electrical disconnection of the superior vena cava was also performed (p=0.02). Notably, completeness of these linear lesions, rather than block across them, was determined as the lesion endpoint, which may have adversely affected outcomes. Oral evaluated the addition of right atrial CFAEs (or nothing) to patients still in AF after left atrial ablation that included left atrial CFAEs. They found no difference in the proportion of patients remaining free from recurrent AF after a single (30% vs. 24%, p=0.8) or multiple procedures (58% vs. 52%, p=0.6) over 17 months’ follow-up.
Combining the three studies showed no significant benefit of performing bi-atrial, rather than isolated left atrial ablation (OR 0.62, 95%CI 0.31-1.24, p=0.17 (Figure 1-10)). Heterogeneity was only moderate (I²=40%).

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**Meta analysis comparing left atrial and biatrial ablation**

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*Figure 1-10: Forest plot showing ORs and 95%CIs for studies comparing a left atrial ablation strategy against a strategy using bi-atrial ablation*

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**1.3.2.12.3. MAPPING TECHNIQUES**

A recent non-randomised study looked at the effect of adding a newly developed mapping and ablation technique, Focal Impulse and Rotor Modulation (FIRM), to a conventional WACA. Of 107 procedures performed in the complete study, 76 had PeAF, although three were lost to follow-up. Of those remaining, the addition of FIRM significantly increased the proportion of patients free of AF after a mean follow-up of 9 months (82% vs. 38%, p<0.001).

Two studies looked at the effect of integrating computed tomography imaging data into an electroanatomical mapping system (CartoMerge, Biosense Webster, Diamond Bar, California, USA). One RCT with 83 patients with PeAF (from a total cohort of 290) showed that an ablation guided by image-integration was more effective at maintaining
sinus rhythm than an ablation guided by conventional fluoroscopy (75% vs. 52%, p<0.01). A second non-randomised study found a similar magnitude of improvement but, with only 48 patients with PeAF, appears to have been underpowered for the difference to reach statistical significance (62% vs. 42%, p=0.2). A single quasi-randomised cohort study assessed freedom from AF off AAD or with previously ineffective AAD after either ablation using the Hansen Robotic Medical System or conventional manual ablation. One hundred and twenty seven patients out of 390 studied had PeAF and statistically similar rates were found with both treatment strategies (76% vs. 72%, p=0.64).

1.3.2.12.4. Steerable vs Non-steerable Sheath

Three randomised studies looked at the effect of using a steerable sheath. As each study assessed the effect on a different and non-comparable lesion set (PVI alone, PVI with extensive linear lesions and mitral isthmus line alone), a meta-analysis was not performed. Matsuo achieved bidirectional conduction block across the mitral isthmus line more often with a steerable sheath (98% vs. 78%, p=0.02) but, interestingly, this did not affect freedom from recurrent AF (53% vs. 43%, p=0.41). A standardised additional left atrial ablation protocol, including segmental PVI, was performed in both groups. A second study, in which patients underwent extensive left atrial ablation, contained 44 patients with PeAF from a total sample size of 130. Although freedom from atrial tachyarrhythmias during 6 months’ follow-up of a single procedure was significantly higher with the use of a steerable sheath in the group as a whole, the difference failed to reach statistical significance in patients with PeAF (67% vs. 39%, p=0.07). It is likely that a large type II error was present due to the small number of patients with PeAF. Although this was also true of the third study by Rajappan, there
was no trend seen when the lesion set was PVI alone (with additional CFAE ablation if required); with success rates after 6 months of 40% (4/10) with a non-steerable and 41% (7/17) with a steerable sheath.\textsuperscript{123}

\textbf{1.3.2.12.4. Other Strategies}

One study looked at the difference between isolating the veins by making a series of spot ablations (point-by-point) and continuously dragging the ablation catheter along the ablation lines. Although usually considered of limited clinical importance, the primary endpoint was recurrence of AF within the first 3 months post-ablation. A high proportion of patients had an early recurrence and although the recurrence rate for the group overall was lower for continuous dragging, the difference was not significant for the subgroup of patients with PeAF (58\% (n=12) vs. 81\% (n=16), p=0.2).\textsuperscript{133} By 12 months, the difference seen in the overall cohort was no longer significant but 12 month data by AF type was not provided.

One non-randomised study looked at the effect of catheter design and RF power on clinical outcomes. In a mixed cohort they found that, compared to a catheter with an 8mm non-irrigated ablation tip (Group 1, 55W 50°C), arrhythmia-free survival after 12 months was lower with a cooled 4mm tip at low power (Group 2, 30W 45°C) but not for a cooled 4mm tip at high power (Group 3, 40W 45°C). The authors communicated that a similar trend was seen for patients with PeAF between the first two groups (72\% vs. 25\%, p<0.01) despite a longer follow-up time for the first group that would normally be expected to be associated with lower success rates (20±10 vs. 14±6 months). Unfortunately the authors did not provide data for the subgroup of patients with PeAF in Group 3.\textsuperscript{116}
One small RCT (30 patients) found no significant difference in medium term (15 months) freedom from recurrent AF with the use of high-frequency stimulation of the atria in addition to WACA (33% vs. 27%, p=0.73).\textsuperscript{125}

A waiting period at the end of the procedure before checking for persisting isolation is generally recommended after PVI but this was questioned by a study that randomised patients to a wait of an hour after vein isolation versus immediate check and termination of the procedure. In 47 patients with PeAF out of a total of 107 they found no difference in the clinical success rates over 10 months between the two groups (52% vs. 55%, p=0.77) which mirrored the result of the larger, mixed cohort.\textsuperscript{13}

One further study randomised 100 patients still in AF after PVI and left atrial linear ablation to receive either an intravenous does of the antiarrhythmic drug nifekalant or nothing before CFAE ablation. They found nifekalant shortened the procedure and reduced the amount of ablation performed without affecting success rates over 12 months after a single procedure (74% vs. 76%, p=0.82).\textsuperscript{111}

Finally, in 217 patients with PeAF from a cohort of 266 undergoing a repeat CA with frequent premature atrial contractions or an atrial tachyarrhythmia originating from the left atrial appendage (LAA), electrically isolating the LAA in addition to a standard ablation procedure appeared to produce considerably greater freedom from AF (83%) in the 12 months following ablation than either performing focal LAA ablation (15%) or not performing any LAA ablation (6.5%) (P<0.001).\textsuperscript{102}
1.3.3. **Discussion**

Each of the analysis areas has produced results worthy of further discussion. Most importantly, in a general population of patients with PeAF, our analysis has shown a clear benefit in terms of freedom from recurrent AF with CA when compared to medical therapy. However, for patients with heart failure the picture is less clear. Unlike all other studies in this review, neither heart failure study assessed freedom from recurrent AF as an endpoint as both used rate-control in their medical therapy group. Whilst peak VO\textsubscript{2} is improved with CA compared to rate control medication, the effect on LVEF is uncertain and may depend on the ability to maintain sinus rhythm and/or the imaging modality used.

In terms of ablation technique, PVI has long been considered the cornerstone of AF ablation and our analysis confirms that encircling and electrically isolating the PVs both appear to improve procedural success rates. WACA showed a non-significant trend toward better results than segmental PVI but further study is needed to clarify this. The addition of linear ablation lesions within the left atrium significantly reduces the risk of AF recurrence, although there appears to be a limit to the extent of linear ablation that provides incremental improvement. The lack of benefit for more extensive linear lesion sets may be due to the cumulative risk of deploying an incomplete linear lesion, potentially creating a zone of slow conduction and pivot point which then allows macro-reentrant atrial tachycardia to occur. It is worth noting that two of the three studies testing more extensive lesion sets added non-anchored lesions. Lines, such as LA roof or mitral isthmus lines, that are deployed between two sites of anatomical or functional block can be tested and confirmed as having bidirectional block across them. In contrast, non-anchored lines (such as septal or inferior left atrial lines) cannot be tested.
for continuity in the same way and bidirectional conduction block is not relevant in this situation. Counter intuitively, Matsuo found that higher rates of mitral line block achieved with a steerable sheath did not translate into better clinical results.\textsuperscript{17} In our opinion, the optimum left atrial linear lesion set is not clear from this analysis. Adding linear ablation within the right atrium produces variable results.

From our analysis of Analysis 5, CFAE ablation does not appear to significantly improve procedural success rates when added to other ablation strategies and is inadequate as a solo strategy. An important problem to consider when comparing CFAE studies is the variability in how CFAE ablation was performed. Although there was a degree of similarity between how the included studies defined CFAEs there was not complete uniformity and mapping techniques also varied. Crucially the definition of successful CFAE ablation was not described in three studies and different in each of the remaining four. Before publication of the most recently published study (Dixit 2012),\textsuperscript{103} the pooled odds would have favoured CFAE ablation as an adjunctive strategy (OR 0.52, 95%CI 0.35-0.79). It is possible that the end point used for CFAE ablation (CFAE abolishment using a power of ≥20 W for at least 20 seconds with a concomitant 5- to 10-Ω decrease in impedance) in the RASTA study was less robust than that used in other trials. In addition, the lack of significant difference in a study comparing CFAE ablation to linear lesions suggests it may be an effective strategy in some patients. For Analysis 6 the included studies were highly variable and it was only possible to produce a single pooled analysis showing that bi-atrial ablation appeared to offer no benefit over sole left atrial ablation. In addition, there is a weak message that steerable sheaths may produce better outcomes for linear ablation but not for PVI. The role of rotor ablation and the FIRM technique is attracting considerable interest but so far has only been
demonstrated in a single non-randomised study. Should the results of the CONFIRM trial be replicated in other studies this will add considerably to the debate as to what ablation in addition, or possibly even instead of, PVI should be performed for patients with PeAF. One final point of note is that for none of the outcomes of interest did it make any statistical difference whether clinical results were analysed after a single or multiple procedure(s).

1.3.3.2. Comparison to other meta analyses

We are aware of few other studies that have looked at the efficacy of CA and CA techniques in patients with PeAF. As mentioned earlier, the Cochrane review found few eligible studies and by failing to either treat chronic and PeAF uniformly or to extract results for the sub-group of patients with PeAF from mixed trials (apart from in one case where the results were explicitly presented in that format) they were unable to reach a conclusion either about overall efficacy or which ablation strategy may be most effective. Parkash attempted to perform a more comprehensive analysis than the Cochrane review though they too limited themselves to RCTs. Predominantly because of this, their study covered fewer areas of analysis than ours. Where we and they analysed similar questions, the two reviews agreed on the comparison between CA and medical therapy and the effect of linear ablation lesions. However the results were different in other areas. In part this is because a number of recent studies were not included in their analysis as they have only been published subsequently. Additionally, some of their analyses appear to have inadvertently mixed patients with paroxysmal and PeAF and these and other discrepancies explain much of the difference in our findings. Like us, Piccini showed a considerably higher rate of freedom from AF after CA compared to a non-ablation strategy but combined 6 studies with both paroxysmal and
PeAF. Of note, removal of the single study containing only patients with PeAF increased the odds ratio dramatically (9.74 to 15.78). The same group also looked at the effect of CFAE ablation, which they found improved single procedure success (OR 2.0, 95% CI 1.04-3.8, p=0.04) but again this was in a mixed AF population and they found no evidence in patients with PeAF and no treatment effect in long-standing PeAF (OR 2.1, 95% CI 0.42-10.3). One meta-analysis found favourably for CA in heart failure but also combined paroxysmal and PeAF. Therefore, this study adds considerably to the evidence base available to clinicians and health policymakers.

1.3.3.3. LIMITATIONS

Although we have managed to assess several areas of potential interest, most analyses contained few studies, most studies were relatively small and study quality was variable. As previously stated very few studies met all of our quality criteria. Universal standards have been published for the reporting AF ablation trials, including minimum follow-up period, but these are rarely strictly adhered to. Until this becomes the norm uncertainty will remain as to how to best interpret study results. Results will have been influenced by the variable definitions of success and length of follow-up. By including both RCTs and NRCTs, we increased the available evidence for analysis. However, the meta-analysis technique was originally intended for use with RCT data and, whilst inclusion of observational data is now well accepted, additional bias may be introduced. Whilst we followed published guidance for performing such analysis, there is more chance of potential confounding in observational studies which is not necessarily detectable. However, we were mindful of this and a sensitivity analysis (Table 1-3) showed that the strategy we employed (including RCTs and NRCTs) increased power without introducing significant bias. Finally, we deliberately pooled both persistent and
longstanding PeAF. It is conceivable that treating these as separate entities may have produced different results in some analyses, however few studies made this distinction when presenting their findings.
<table>
<thead>
<tr>
<th>Analysis</th>
<th>RCTs/ NRCTs</th>
<th>Main analysis</th>
<th>RCTs only</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4/0</td>
<td>OR 0.32, 95% CI 0.20-0.53</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>2.1</td>
<td>3/0</td>
<td>OR 0.26, 95% CI 0.09-0.74</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>2.2</td>
<td>2/2</td>
<td>OR 0.33, 95% CI 0.13-0.86 OR 0.27, 95% CI 0.11-0.64</td>
<td>Inclusion of two NRCTs increased the sample size and resulting power of the meta-analysis but had very little effect on the overall effect size*</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2/1</td>
<td>OR 0.41, 95% CI 0.15-1.10 OR 0.34, 95% CI 0.11-1.05</td>
<td>Inclusion of one NRCTs increased the sample size and resulting power of the meta-analysis but had very little effect on the overall effect size*</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3/0</td>
<td>OR 0.22, 95% CI 0.10-0.49</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>4</td>
<td>3/0</td>
<td>OR 0.77, 95% CI 0.41-1.43</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>5</td>
<td>5/2</td>
<td>OR 0.64, 95% CI 0.35-1.18 OR 0.76, 95% CI 0.35-1.63</td>
<td>As there were 5 RCTs analysis could have been performed without NRCTs. However, inclusion of two NRCTs increased the sample size and resulting power of the meta-analysis but did not affect the effect size</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3/3</td>
<td>OR 0.62, 95% CI 0.31-1.24</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Table 1-3: Sensitivity analysis examining the effect of inclusion of non-randomised trials in meta-analyses

*My pre-specified criteria required at least 3 studies for meta-analysis to be performed so quantitative analysis would not have been performed using RCTs

1.3.3.4. CLINICAL IMPLICATIONS

Despite the current restrictions on funding and regulatory approval, for patients with PeAF, catheter ablation significantly reduces AF recurrence when compared with medical therapy. For those undergoing ablation, the pulmonary veins should be encircled by ablation lesions and electrical isolation confirmed. Additional limited linear ablation is likely to improve procedural success. Ablation of CFAEs may be of benefit in
some patients but the overall impact is unclear. Very extensive ablation strategies and those involving right atrial ablation appear to offer little, if any, additional benefit. In our analyses, where data were available we found the relative benefits seen held true both after a single or multiple procedure(s). Future research should be in sufficiently large studies to minimise risk of type II error and should seek to distinguish patients with persistent from longstanding PeAF as duration of AF has an important bearing on success rates with ablation. If researchers do decide to recruit mixed populations they should also report results stratified by AF duration. This would provide greater clarity when attempting to apply study findings to routine clinical practice. The international AF expert consensus document, published in 2012, provides clear standards for reporting outcomes in clinical trials. It is important that investigators strive to adhere to these standards in future studies to improve the quality of available evidence. We found a surprising dearth of procedural safety and complication data in the published studies, and these should be given greater prominence as endpoints in future studies. As CA is primarily indicated to improve symptoms of AF it is essential that future studies measure and report the effect of interventions on patients’ quality of life, something that occurred very rarely in studies included in this review.

1.3.4. Conclusions

For patients with PeAF, CA achieves significantly greater freedom from recurrent AF than medical therapy. The most efficacious ablation strategy is likely to be one combining isolation of the PVs with a limited number of additional linear lesions within the left atrium. Neither biatrial ablation nor CFAE ablation appear to provide any additional advantage. However, the ideal lesion set remains unclear and may not be the same for all patients.
2. Improving patient outcomes by better understanding current practice: Real life long term outcomes after persistent AF ablation; Six year data from a high volume UK centre

2.1. Background

Although, as we have seen, recent randomised controlled trials have shown superior efficacy of CA compared to medical therapy for patients with PeAF the follow-up for these trials is short. In Chapter One, my systematic review of randomised and non-randomised controlled trials of CA in PeAF found the mean follow-up was only 13.5±6 months. One issue for both forms of the disease is that early CA success does not always translate into long-term freedom from AF. Whilst short-term success is obviously vital, if this is not maintained longer term than the benefit to the patient is blunted. If we are seeking optimum outcomes for our patients then early improvements must be maintained long term. Whilst some long term data exist for ablation of PAF, late recurrence after CA is considered to be a particular concern when the patient was initially treated for PeAF. To investigate this further, I reviewed consecutive CA procedures performed for PeAF over a three-year period at a single, high-volume, centre in the United Kingdom and followed-up patients for a further three years in order to provide up to six years of outcome data.

2.2. Methods
2.2.1. Patients

Consecutive patients who underwent a first-time CA for PeAF at Liverpool Heart and Chest Hospital (LHCH) during a three-year period (01/01/2008 – 31/12/2010) were identified retrospectively and clinical notes reviewed for procedural data. Patients were classified as having PeAF if they had AF present continuously or had episodes of AF lasting for longer than 7 days at a time or requiring cardioversion, as specified by the published guidelines at the time the study was initiated. Comprehensive demographic, medical history and procedural details were collected from the hospital notes and electronic data storage systems. Data verification was performed for all outlying data points.

2.2.2. Follow-up

Clinical follow-up data was collected prospectively until January 2014. Two clinicians, both of whom were independent of the original procedure, reviewed the follow-up data. Missing follow-up data were obtained by contacting the patient's base hospital and/or General Practitioner. Recurrence of AF was deemed to have occurred whenever AF or atrial tachycardia was documented on resting ECG or during a period of monitoring, or – in keeping with the real world nature of this study – if the responsible clinician treated the patient for recurrence of AF without definitive proof, for example by performing repeat CA or starting new antiarrhythmic medication because of the return of the patient's typical symptoms. Mortality data was obtained from the UK’s central healthcare database (NHS Spine). For any patient who died during follow-up their General Practitioner was contacted for cause of death and further details. At the end of the study all patients were contacted by phone to invite them to provide final follow-up data. Telephone interviews were carried out using a standardised interview template.
To avoid loss of follow-up due to working patterns or holidays, initial unsuccessful daytime contact was followed up by repeated attempts in the evening and at the weekend, spread out over a several week period. The study was approved by both the hospital and regional research ethics committees.

2.2.3. Electrophysiological study

CA was performed under conscious sedation or general anesthesia. Antiarrhythmic drugs were stopped at least five half-lives prior to the procedure, except for amiodarone which was generally continued. Post procedural anticoagulation was with warfarin with bridging low molecular weight heparin (LMWH) used until the patient’s INR was ≥2. Pre-procedural transoesophageal echocardiography was carried for patients in AF without at least four preceding weeks of therapeutic anticoagulation. In general, vascular access was exclusively via the right femoral vein, with other routes only used as required. A deflectable decapolar catheter was positioned within the coronary sinus. Transseptal access was gained using a Brockenbrough or Endrys needle under fluoroscopic guidance with either a single or double puncture. A variety of long sheaths were used. Unfractionated heparin was used to maintain an activated clotting time above 250-300 seconds. In all cases, pulmonary vein isolation (PVI) was first performed, predominantly using a 3.5-4mm irrigated tip radiofrequency catheter with flow rates between 12-30mls/minute, using a segmental ostial or wide area circumferential ablation (WACA) pattern. A 20-pole circular mapping catheter was used to measure electrical activity within the pulmonary veins. The addition of linear lesions and complex fractionated atrial electrogram (CFAE) ablation was according to operator preference. Temperature limits were set to 50° Celsius and ablation power was limited to 25-30 watts on the posterior left atrial (LA) wall, 30-35 watts on the anterior wall,
roof and the intervenous carina, 25 watts in the coronary sinus and 50 watts for cavo-
tricuspid isthmus ablation. Ablation was carried out either using a continuous dragging
technique or individual point-by-point lesions of 20-40 seconds duration to achieve
>75% attenuation of the local electrogram. In three cases PVI was performed using the
HD Mesh Ablator (C.R. Bard Inc. Murray Hill, New Jersey, USA) and in one case with the
Arctic Front cryoablation system (Medtronic Inc, Minneapolis, Minnesota, USA). In
keeping with published guidance, PVI was defined as proven entrance block. For linear
lesions, excluding non-anchored lesions, the desired end point was bidirectional
conduction block, as verified with appropriate pacing maneuvers. The overall
procedural end-point was completion of the attempted lesion sets rather than
termination of AF. Patients were monitored overnight and routinely discharged the
following day.

2.2.4. Statistical analysis

Discrete variables are described in terms of the frequency and proportion and
compared using the $\chi^2$ or Fisher’s exact test. Continuous variable are described as mean
± standard deviation, and compared using unpaired t-tests, or median (interquartile
range, IQR) and compared using Mann-Whitney U test, dependent on the distribution.
Analyses were performed using IBM SPSS Statistics software version 21. Survival data
was plotted using the Kaplan-Meier estimator. The log-rank test was used to compare
survival between groups. Univariable and multivariable predictors of AF recurrence
were examined using logistic regression using forward conditional modelling. We pre-
specified that variables with a p value ≤0.1 would be included in the multivariable
model, and if necessary to maintain a minimum of 10 events per variables, selected on a
hierarchical basis\textsuperscript{146}. Where applicable, two-tailed tests were used in all analyses. A P value ≤0.05 was considered significant for all tests.

2.3. RESULTS

2.3.1. PATIENTS AND BASELINE CHARACTERISTICS

We identified 189 patients in whom first-time percutaneous CA for PeAF was attempted during the study period. Baseline characteristics are provided in Table 2-1. The mean duration of the current episode at the time of CA was 7±14 months. 37 (20\%) of patients had longstanding PeAF, defined as 12 months’ continuous AF with no period of sinus rhythm (SR) lasting >24 hours. 143 patients (76\%) had at least one attempt at electrical cardioversion prior to their CA, although only 70 (46\%) maintained SR for >1 month. The mean CHA\textsubscript{2}DS\textsubscript{2}VASc score was 1.45±1.46 (median=1). One patient did not undergo ablation as LA access was not possible, leaving 188 patients who were eligible for follow-up.
Table 2-1: Baseline characteristics of patients undergoing catheter ablation for PeAF

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, n(%)</td>
<td>157 (83%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>57.3±9.7</td>
</tr>
<tr>
<td>Time since first AF diagnosis (months)</td>
<td>48±52</td>
</tr>
<tr>
<td>Longstanding PeAF, n(%)</td>
<td>37 (20%)</td>
</tr>
<tr>
<td>Left atrial anteroposterior diameter (mm)</td>
<td>44±6</td>
</tr>
<tr>
<td>Left ventricular systolic function, n(%)</td>
<td></td>
</tr>
<tr>
<td>Good (Ejection fraction (EF) &gt;50%)</td>
<td>156 (83%)</td>
</tr>
<tr>
<td>Mildly impaired (EF 40-49%)</td>
<td>12 (6%)</td>
</tr>
<tr>
<td>Moderately impaired (EF 30-39%)</td>
<td>9 (5%)</td>
</tr>
<tr>
<td>Severely impaired (EF &lt;30%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Hypertension, n(%)</td>
<td>85(45%)</td>
</tr>
<tr>
<td>Diabetes, n(%)</td>
<td>12 (6%)</td>
</tr>
<tr>
<td>Obstructive sleep apnoea, n(%)</td>
<td>11 (6%)</td>
</tr>
<tr>
<td>Previous stroke/ transient ischaemic attack, n(%)</td>
<td>8 (4%)</td>
</tr>
<tr>
<td>Ischaemic heart disease, n(%)</td>
<td>15 (8%)</td>
</tr>
</tbody>
</table>

2.3.2. Patient journey

In total 332 CA procedures were performed or attempted. Four procedures were abandoned before any ablation was performed due to complications of transseptal puncture. Of these, three had no sequelae and one resulted in a small pericardial effusion that was managed conservatively. These procedures were included in complication data but excluded when calculating arrhythmic outcome data. Excluding
abandoned procedures, 105 (56%) patients underwent more than one CA for AF. The “patient journey” experienced in our patient cohort is illustrated in Figure 2-1. Eight patients (4%) were eventually treated by implantation of a permanent pacemaker and atrioventricular node ablation.
Figure 2-1: The procedural journey for our cohort of patients with persistent atrial fibrillation. Patients underwent a maximum of 4 ablations and these are detailed in the centre of the diagram as well as the number with post-procedural recurrence. To the left are the patients without recurrence and to the right are those with recurrence who did not have further ablation.
2.3.3. Follow-up

Clinical follow-up data was available for 186 of 188 eligible patients (98.5%). Mean follow-up time was of 46±16 months and ranged between 4-72 months. Follow-up of greater than one year was available for >95% of patients. Eight patients died during follow-up. All deaths were remote from the CA, with the earliest occurring after 121 days. Five deaths were non-cardiovascular (two from malignancy, one each from pulmonary fibrosis, pneumonia, and renal failure) and three were cardiovascular in aetiology (one each of aortic dissection, heart failure, and myocardial infarction). Three patients suffered a stroke or transient ischaemic attack (TIA) during follow-up, of whom two had complete neurological recovery. All three had had warfarin stopped prior to their event, in one because of intolerable side effects, one because of low risk profile (CHA2DS2-VASc=0) and one by the original referring physician despite a previous history of TIA. Data on antithrombotic medication was available for 139 patients (75%), of whom 75 (54%) were taking oral anticoagulation (warfarin in 69, direct thrombin/ Factor Xa inhibitor in 6), 27 (19%) an antiplatelet agent, and 37 (27%) no anti-thrombotic therapy. Mean CHA2DS2-VASc was significantly lower for those on no therapy or an antiplatelet agent (no therapy 0.65±0.75, antiplatelet 1.07±1.00, combined 0.83±0.88) compared to those or an oral anticoagulant (1.52±1.12, P<0.001).

2.3.4. Procedural complications

Seven patients experienced major complications. There were three pericardial effusions requiring percutaneous (n=2) or surgical (n=1) drainage, two inadvertent aortic punctures, one phrenic nerve paralysis and one femoral arterial pseudo aneurysm. Overall, this represents an incidence of major complications of 2.1% per procedure and 3.7% per patient. There were eighteen minor complications of which eleven related to
vascular access and four were pericardial effusions managed conservatively. One patient developed constrictive pericarditis four years after his CA, which had been felt at the time to be uncomplicated. He was found to have a calcified pericardial haematoma on pericardiectomy that may have been an unrecognised consequence of his CA procedure.

2.3.5. Ablation Procedures

Of 188 index procedures, 91% were performed under conscious sedation and 9% under general anaesthesia. Conventional radiofrequency energy was used in 98% of procedures. 90%, of cases utilised 3-dimensional mapping systems: CARTO (Biosense Webster, Diamond Bar, California, USA) in 60% and Ensite NavX (St. Jude Medical, St. Paul, Minnesota, USA) in 30%. In 96 (51%) cases, the 3-dimensional map of the LA was integrated with a pre-operative computed tomography (CT) scan. Mean procedure duration was 200±41 minutes, and mean ablation and fluoroscopy times were 57±22 minutes and 40±31 minutes respectively. Average radiation dose, in terms of Dose-Area-Product, was 5796±7634 mGycm².

PVI was performed in all cases, with additional linear lesions deployed in 146 cases (78%) and CFAE ablation in 62 (33%). PVI was by means of WACA in 109 cases, segmental isolation in 75, and a mixed approach in three. The most common LA linear lesion was a roof line (117, 62%) followed by a floor line (72, 38%). A mitral isthmus line was created in 37 (20%) cases. A right atrial flutter line was performed in 97 (52%) patients. CFAE ablation was performed in the LA in 56 (30%) cases and in the right atrium in 9 (5%).
At the start of the procedure 112 (60%) patients were in AF or flutter and a further 23 patients developed sustained AF intra-operatively. Of these 135, 28 (21%) were ablated to SR but the majority (104, 77%) were cardioverted either electrically or pharmacologically. Three patients remained in AF.

2.3.6. Outcomes after a single procedure

Antiarrhythmic medication was continued until the first follow-up appointment (median 3 (IQR 2-3) months after CA (IQR 2-3)) for 75% of patients (47% Amiodarone, 17% flecainide 8% sotalol and 3% others). Allowing for a 3-month blanking period, 139 (75%) patients experienced recurrence of AF after a single procedure during extended follow-up. The initial recurrence mechanism was paroxysmal in 55 patients (39%), persistent in 81 (58%) and unclear in four. AF was the recurrence arrhythmia in 104 (74%) patients with atrial tachycardia or flutter seen in 29 (21%). The recurrence arrhythmia was unknown for 7 patients. The median time to first recurrence was 210 days (range 91-1850). A graphical representation of recurrence over time is shown in Figure 2-2. Although first recurrence was seen to occur as late as 5 years after a hitherto successful procedure, 71% of AF recurrences occurred within the first year following CA and 91% within two years.
Regression analysis identified AF as initial rhythm at the time of CA (OR 2.05, 95%CI 1.05-4.03, P=0.037) as the only univariable predictor of AF recurrence after a single procedure, while integration of CT imaging into 3-dimensional mapping reduced the risk of recurrence (OR 0.39, 95%CI 0.19-0.78, P=0.008). Female sex (P=0.092) met the pre-specified criteria for inclusion in multivariable modelling, but was not conventionally significant. After multivariable analysis, only AF as initial in-lab rhythm (OR 2.59, 95%CI 1.27-5.31, P=0.009) remained a statistically significant predictor of recurrence, and CT integration (OR 0.33, 95%CI 0.16-0.69, P=0.003) remained an
independent predictor of success. Details of single procedure univariable and multivariable analyses are given in Table 2-2.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Age</td>
<td>0.374</td>
<td>1.02 (0.98-1.05)</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.092</td>
<td>2.59 (0.86-7.84)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.559</td>
<td>1.22 (0.62-2.39)</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>0.671</td>
<td>0.98 (0.91-1.06)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.388</td>
<td>0.57 (0.16-2.04)</td>
</tr>
<tr>
<td>LA Diameter (mm)</td>
<td>0.564</td>
<td>1.02 (0.95-1.09)</td>
</tr>
<tr>
<td>Time since diagnosis*</td>
<td>0.985</td>
<td>1.00 (0.99-1.01)</td>
</tr>
<tr>
<td>Current episode length*</td>
<td>0.406</td>
<td>1.02 (0.98-1.06)</td>
</tr>
<tr>
<td>Longstanding PeAF</td>
<td>0.776</td>
<td>0.88 (0.37-2.10)</td>
</tr>
<tr>
<td>General anaesthesia</td>
<td>0.195</td>
<td>2.72 (0.60-12.37)</td>
</tr>
<tr>
<td>3D mapping</td>
<td>0.989</td>
<td>0.99 (0.30-3.24)</td>
</tr>
<tr>
<td>CT integration</td>
<td>0.008</td>
<td>0.39 (0.19-0.78)</td>
</tr>
<tr>
<td>WACA</td>
<td>0.349</td>
<td>0.72 (0.36-1.44)</td>
</tr>
<tr>
<td>Linear ablation</td>
<td>0.775</td>
<td>1.10 (0.56-2.19)</td>
</tr>
<tr>
<td>CFAE ablation</td>
<td>0.192</td>
<td>1.64 (0.78-3.44)</td>
</tr>
<tr>
<td>AF as initial rhythm</td>
<td>0.037</td>
<td>2.05 (1.05-4.03)</td>
</tr>
<tr>
<td>Ablate to SR†</td>
<td>0.163</td>
<td>0.52 (0.20-1.31)</td>
</tr>
</tbody>
</table>

Table 2-2: Logistic regression analysis for freedom from recurrent AF after a single procedure. OR – Odds ratio, CI – Confidence interval, WACA – Wide area circumferential ablation, CFAE – Complex fractionated atrial electrogram * Time in months, †compared to those cardioverted to SR.
2.3.7. Outcomes after multiple procedures

In our cohort, patients underwent a mean of 1.75±0.79 procedures (range 1-4). Median follow-up time after patients’ last CA was 35 months (IQR 15-45). 90 (48%) had a further recurrence of AF following their final procedure. Median time to recurrence after last procedure was 301 days (range 91-1850). A graphical representation of recurrence over time is shown in Figure 2-3. Of those who remained free of recurrence, 31 (32%) remained on Class I or III antiarrhythmic drugs.

Figure 2-3: Recurrence curve showing number of patients remaining free from documented recurrence over time after their last procedure
As shown in Table 2-3, the only univariable predictor of AF recurrence after the final procedure was age (OR 1.05, 95% CI 1.01-1.08, P=0.006). Female sex (P=0.08) and time (in months) since first diagnosis of AF (P=0.07) also both met the criteria for inclusion in multi-variable modelling. CT integration (OR 0.33, 95% CI 0.18-0.61, P<0.001) and isolation of the pulmonary veins using a WACA technique (OR 0.49, 95% CI 0.27-0.88, P=0.018) were associated with a lower risk of recurrence. After controlling for confounding with multivariable modelling, only age (OR 1.05, 95% CI 1.01-1.09, P=0.018) and (lack of) CT integration (OR 0.30, 95% CI 0.15-0.60, P=0.001) remained statistically significant in terms of predicting recurrence.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable</th>
<th></th>
<th>Multivariable</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P value</td>
<td>OR (95%CI)</td>
<td>P value</td>
<td>OR (95%CI)</td>
</tr>
<tr>
<td>Age</td>
<td>0.006</td>
<td>1.05 (1.01-1.08)</td>
<td>0.018</td>
<td>1.05 (1.01-1.09)</td>
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<td>Female sex</td>
<td>0.080</td>
<td>2.03 (0.92-4.46)</td>
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<td>Hypertension</td>
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<td>BMI</td>
<td>0.645</td>
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<td>Diabetes</td>
<td>0.479</td>
<td>0.63 (0.18-2.24)</td>
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<td>LA Diameter (mm)</td>
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<td>1.01 (0.95-1.06)</td>
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<td>Time since diagnosis*</td>
<td>0.071</td>
<td>1.01 (1.00-1.01)</td>
<td>0.211</td>
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<td>Current episode length*</td>
<td>0.900</td>
<td>1.00 (0.98-1.02)</td>
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<td>Longstanding PeAF</td>
<td>0.353</td>
<td>0.68 (0.30-1.53)</td>
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<td>General anaesthesia</td>
<td>0.594</td>
<td>1.31 (0.48-3.56)</td>
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<td>3D mapping</td>
<td>0.801</td>
<td>0.88 (0.31-2.44)</td>
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<td>CT integration</td>
<td>&lt;0.001</td>
<td>0.33 (0.18-0.61)</td>
<td>0.001</td>
<td>0.30 (0.15-0.60)</td>
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<td>WACA</td>
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<td>0.48 (0.27-0.88)</td>
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<td>Linear ablation</td>
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<td>CFAE ablation</td>
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<td>Time to first recurrence#</td>
<td>0.767</td>
<td>1.00 (1.00-1.00)</td>
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</table>

Table 2-3: Logistic regression analysis for freedom from recurrent AF after multiple (mean 1.7) procedures.

OR – Odds ratio, CI – Confidence interval, WACA – Wide area circumferential ablation, CFAE – Complex fractionated atrial electrogram. *Time in months, #for those patients who had a recurrence of AF after their first procedure, †compared to those cardioverted to sinus.
2.3.8. LONGSTANDING PeAF

The presence of longstanding (>1 year) PeAF has traditionally been associated with poorer outcomes after CA but was not a predictor of recurrence after single or multiple procedures in our cohort. To investigate this further we performed a subgroup analysis and found that AF recurrence was no more likely for patients with longstanding PeAF than for those with shorter duration PeAF after either a single (73% v 74%, P=0.9) or final (41% v 48%, P=0.4) procedure.

2.3.9. EFFECT OF CT INTEGRATION ON FREEDOM FROM RECURRENT AF

As shown in Tables 2-2 and 2-3, integration of CT imaging into 3-dimensional mapping was the only significant predictor of outcome after multivariate modelling after both single and multiple procedure(s). We therefore undertook subgroup survival analysis grouping patients according to use of CT integration during their initial procedure. AF-free survival was significantly increased with CT integration after both initial (P=0.026) and final procedure (P=0.001) compared to patients whose ablation was performed without image integration, as shown in Figure 2-4 and 2-5.
Figure 2-4: Kaplan-Meier curve showing AF-free survival after a single procedure for patients grouped according to use of CT integration.
Figure 2-5: Kaplan-Meier curve showing AF-free survival after the final procedure for patients grouped according to use of CT integration

2.3.10. Quality of Life (QoL) after CA of PeAF

As a surrogate for formal QoL measurement, patients’ health status was assessed by the independent investigators for each follow-up clinic visit. We also asked patients to rate their own health state at the final telephone follow-up. Overall, 82% of patients felt better in terms of their arrhythmia with 62% of patients having considerable clinical improvement or arrhythmia cure and a further 20% gaining at least some improvement. These proportions did not differ between those cases adjudicated by the investigators and those reported directly by the patient. Although three-quarters of patients with
ongoing episodes of AF still gained a benefit in terms of their health status, patients who remained free from recurrent AF were significantly more likely to gain symptomatic improvement (75% v 93%, P <0.001).

2.4. Discussion

There are a number of conclusions to be drawn from the data presented. Firstly, CA of PeAF is safe with a low rate of complications. Our 2.1% incidence of major complications, with no thromboembolic events, compares favourably with that reported in worldwide registries and other studies147,151. Secondly, recurrence after the initial CA is the norm, rather than the exception. Although two years’ follow-up is sufficient to observe approximately 90% of AF recurrence, recurrences can occur even after five years of remission. After multiple procedures (in our cohort the mean number was 1.7 which is lower than reported in many other series151) over half of patients can be rendered free of AF. Importantly, although many patients continue to experience episodes of AF, the vast majority gain clear symptomatic benefit, especially if persisting SR is achieved. The improvement in those with recurrent AF presumably relates, in part, either to conversion of continuous persistent to paroxysmal AF or to the previously demonstrated increase in asymptomatic AF after ablation.152 Finally, there are few predictors of successful outcome. In our series, although being in AF was associated with a higher recurrence risk after the initial procedure and increased age predicted poorer long-term success, only integration of CT imaging into 3-dimensional mapping predicted both single and multiple procedure success.

Few other groups have reported long-term CA outcomes for large series of patients undergoing CA for PeAF. The largest reported study contained 676 patients with non-paroxysmal AF153 Success rates of 67% after a single procedure and 84% after multiple
procedures were reported. However, in contrast to our study they appear to have found very few recurrences occurring between 24-84 months after either single or multiple procedures, and none later than 32 months. Intensity of follow-up after the initial 12 months was unclear. Another leading European centre reported slightly lower single (20%) and multiple procedure (45%) success rates compared to our study, but that was in a population with longstanding PeAF over a slightly longer follow-up period (56 months). They found that only total AF duration, which was significant on univariate but not multivariate analysis in our study, predicted freedom from AF.

Other studies have generally been of short duration and/or contained small numbers of patients. In the largest previously published study from the UK, Hunter reported on 125 patients with PeAF as part of a larger mixed cohort. Single and multi-procedure success rates for PeAF off antiarrhythmic drugs were 20% and 60% respectively over a follow up period of 2.7 years. An important study by Bertaglia highlighted the importance of long-term follow-up in this group of patients. In patients who had already remained in SR for 12 months after their initial CA, they found an actuarial recurrence rate of 55% at 6 years. A recent meta-analysis of long-term CA outcomes for PeAF has reported 42% (95% CI, 25-61%) success after a single procedure and 78% (95% CI, 69-85%) after multiple procedures but with substantial heterogeneity between studies. One of the most striking findings from our study is the value of CT-integration into a 3-dimensional mapping system in predicting procedural success. Since its introduction, there has been much interest in image-integration due to the potential benefits of accurate anatomical visualisation, particularly of anomalous PV arrangements, leading to improved ablation delivery. A few small randomised controlled trials (RCTs) and observational studies yielded mixed results. Detailed review of these studies highlights several important limitations. In two of the RCTs in which no difference in
outcome was found, CT imaging was performed in all patients and was available for review by operators, thereby negating part of the benefit of CT-integration in recognising variant anatomy.\textsuperscript{110,157} A meta-analysis showed a non-significant reduction in risk of AF recurrence with image-integration (RR=0.76 95% CI 0.55-1.04, \(P=0.09\)).\textsuperscript{161} Crucially, the five studies included in the meta-analysis had follow-up durations of only 6-12 months. The only previous study with longer follow-up (283 patients with median 37 months follow-up), which was not included in the meta-analysis, showed a significant improvement in single procedure success with CT-integration compared with 3-dimensional mapping alone (\(P=0.018\)), in keeping with our findings.\textsuperscript{160}

2.4.1. IMPLICATIONS FOR CLINICAL PRACTICE

The term curative AF ablation is often used but, from our results, would appear to be misleading for PeAF. Patients must be aware that recurrence is the norm, rather than the exception. Operators may consider using 3-dimensional mapping techniques that combine integration of computed tomography images, as our results suggest this has a significant impact on long term success. That notwithstanding, the indication for CA is the relief of AF symptoms rather than freedom from recurrent AF and our results show this is achievable for the majority of patients. Although previously discouraged as a primary endpoint for clinical trials,\textsuperscript{162} formal assessment of QoL will help us to better inform patients and make more meaningful cost-effectiveness analyses than those based purely on arrhythmic outcome.

2.4.2. LIMITATIONS

Because the study was observational, follow-up and management was decided on clinical grounds by the responsible physician. As a result there was some inevitable
variation in the intensity of follow-up and monitoring and treatment strategies employed. ECGs were performed for all patients attending follow-up clinics, but more intense monitoring tended to be dependent on symptoms and therefore it is possible that some patients with asymptomatic paroxysms of AF were missed. However, the long duration of follow-up and broad definition of recurrence goes some way towards mitigating this risk. Our final follow-up was by telephone which may have reduced the accuracy of reports of recurrence. However, by asking if patients had had an episode of AF confirmed by a doctor, we attempted to achieve a similar degree of diagnostic certainty as required at other follow-up points. We based our QoL assessment on patients' reported clinical state rather than a formal questionnaire that would have provided more objective information. Whilst other long-term studies have employed similar techniques, it is clearly sub-optimal.\textsuperscript{151} We have since changed our practice to collect validated generic and AF-specific QoL data from all patients at each clinic visit.

Finally, the CA procedures in our study pre-dated the advent of contact force sensing technology that may result in more durable lesions and thus higher success rates for AF ablation than those found in our study. However this is an inevitable limitation while reporting long-term results of a rapidly evolving procedure such as CA for AF.

2.4.3. Conclusion

CA of PeAF is safe, with a low incidence of major complications. During long-term follow-up, recurrence of AF is common, particularly after a single procedure but considerable improvements in patient wellbeing can be achieved, especially in those who remain free of recurrent AF. Use of 3D-mapping with CT image integration is associated with improved procedural success rates.
3. Methods of the Substrate Modification with Ablation and Antiarrhythmic Drugs in Non-Permanent Atrial Fibrillation (SMAN-PAF) Randomised Controlled Trial

The following methods detail the study protocol for the central study for this thesis. The main results are presented in Chapter 4 and a substudy in Chapter 5.

3.1 Introduction

Atrial fibrillation (AF) is a continuum of disease. At one extreme are patients with a single paroxysm without accompanying comorbidity. At the other end are patients with continuous, permanent AF in whom sinus rhythm cannot be restored. These latter patients would be expected to have adversely remodelled left atria and may well have additional comorbidities, such as hypertension, known to increase susceptibility to AF. For convenience, AF is classified as either paroxysmal or persistent but, as discussed in Chapter 1, the boundary between these categories is fairly arbitrary and can be indistinct. The term permanent AF is sometimes used to describe persistent AF present continuously for longer than one year but more correctly applies to those patients in whom persistent AF has been accepted by physician and patient, irrespective of duration. Not only have there been subtle changes to the internationally accepted definitions but both AF types may be present in the same patient and it is technically possible for a patient with paroxysmal AF to have a higher burden of AF than a different patient classified as having persistent AF. Where AF is truly paroxysmal, its
occurrence may be predominantly due to “triggers”, such as pulmonary vein ectopy, which both initiate and sustain AF in an otherwise relatively normal heart.\textsuperscript{24} Removal of the trigger might be expected to prevent further recurrences. As AF progresses to more advanced, sustained disease triggers may still be important for initiation of AF but its sustained nature probably relies on a remodelled atrium that provides a substrate that favours maintenance of AF. In these patients modification of the substrate may be at least as important as removal of the trigger.

3.2. **Original hypotheses/research question**

I hypothesised that modification of the AF substrate by radiofrequency ablation would improve single procedure success rates for catheter ablation (CA) for substrate-based non-permanent AF when compared to that achieved with short-term peri-procedural anti-arrhythmic drug therapy alone.

3.3. **Design**

The study was designed as a prospective, two-way, multicentre randomised, controlled single-blinded trial. Eligible consenting patients were randomised, via a computerised randomisation procedure, in equal proportions into one of two groups.

- Pulmonary venous isolation only (PVI group), or
- PVI and linear ablation (PVI + lines group).

All patients received peri-procedural AADs as described below.

3.4. **Study duration**

Current recommendations for trials of interventions in AF are that follow up should be for a minimum 12 month duration.\textsuperscript{162,164} However, it was necessary for the study to be
performed within the time restraints of an MD (Res) research project, completed within allowed Out Of Programme (Research) Time granted from my national cardiology training programme by my employing Deanery. Therefore, a pragmatic decision was made a priori to report six month follow up data for the purpose of this thesis. In keeping with the abovementioned recommendations, study follow up was continued for a further six months to provide a total follow up period of 12 months for the purpose of reporting the study in the medical literature.

3.5. **End Points**

3.5.1. **Primary endpoint**

The primary endpoint for this thesis was defined as documented atrial fibrillation or other atrial tachyarrhythmia (including right or left atrial flutter and both focal and macro re-entrant atrial tachycardia) at six months following a single procedure. In accordance with published guidelines, to qualify as a primary endpoint an episode of AF must have met at least one of the following criteria:\(^{162,165}\):

- 30 seconds or more of symptomatic or asymptomatic atrial tachyarrhythmia captured on continuous ambulatory (Holter) ECG monitoring (Burdick Vision, Cardiac Science Holdings (UK) limited) or in situ cardiac rhythm management device (e.g. pacemaker).

- 30 seconds or more of symptomatic atrial tachyarrhythmia captured on symptom-activated ambulatory ECG monitoring (R.Test Evolution 3, Novacor UK Ltd).
• Any symptomatic episode of tachycardia lasting longer than 30 seconds with contemporaneous documentation of atrial tachyarrhythmia on resting 12 lead ECG.

3.5.2. **SECONDARY ENDPOINTS:**

The following secondary endpoints were pre-specified for analysis:

- Adverse events (death, stroke, procedural complications, cardiovascular hospitalisation).
- Mean QoL score six months after the index procedure.
- Per protocol analysis of the primary outcome
- Analysis of the primary endpoint according to AF type
- Freedom from atrial tachyarrhythmia after 12 months, following a single procedure
  - This endpoint will not be reported in this thesis for reasons given above.
  - For the purpose of reporting the study in the medical literature this was pre-defined as the primary endpoint.
- Freedom from AF/atrial tachycardia at 12 months following up to two procedures
  - This endpoint will not be reported in this thesis for reasons given above.
- Mean QoL score 12 months after the index procedure.
  - This endpoint will not be reported in this thesis for reasons given above.

3.5.2.1 **ADVERSE EVENTS**

The following definitions were used for adverse events:
• Death.
  o All-cause mortality (with no adjudication).

• Stroke (ischaemic or haemorrhagic)
  o A clinical syndrome consisting of rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death within 24 hours with no apparent cause other than that of vascular origin. \(^ {166} \)

• Procedural Complications
  o Any of the following discharge diagnoses were classified as procedural complications
    ▪ Pericardial effusion requiring percutaneous or surgical drainage.
    ▪ Bleeding requiring transfusion and/or radiological or surgical intervention.
    ▪ Transient Ischaemic Attack (with stroke counted independently).
    ▪ Symptomatic pulmonary vein stenosis (>50% reduction compared with pre-operative imaging).
3.6. **SAFETY**

3.6.1. **EXPECTED COMPLICATION RATES**

A local audit of 150 AF ablation procedures performed shortly before initiation of the study revealed the following complications and rates: significant (delaying discharge) groin haematoma (1.3%), Stroke (0.7%), pericardial effusion requiring drainage (0.7%). Total/combined incidence of significant complications was 2.7%. This was in keeping with other leading centres. A recent worldwide survey of 20,825 catheter ablation procedures for AF on 16,309 patients revealed an overall major complication rate of 4.5% including: cardiac tamponade 1.31%; stroke 0.23% (transient ischaemic attack 0.71%); major vascular complication 1.5% and death 0.15%. All other complications were reported in less than 0.3% of cases. These data made up the basis of the risks quoted in the Patient Information Sheet and in the (clinical) informed consent process on the day of ablation.

3.6.2. **REPORTING OF ADVERSE EVENTS**

The standard definition of a serious complication is an event which a) results in death, b) is life-threatening, c) requires hospitalisation or prolongation of existing hospitalisation, d) results in persistent or significant disability or incapacity, or e) consists of a congenital anomaly or birth defect.

As detailed above, CA is associated with a known risk of serious complications. Given the intended sample size, it is to be expected that those complications known to occur in greater than 1% of cases will be encountered during the course of the study. These were therefore considered Expected Serious Adverse Events (SAE). There was no additional requirement to report serious adverse events above the standard local adverse event
reporting procedure. SAEs with a known occurrence rate of less than 1% (Stroke or Death) would not be expected to be seen during the study. If these occurred in the peri-procedural period, i.e. at a time when their occurrence may have been linked to their procedure, or if any SAE was associated with peri-procedural AAD therapy (as mandated by protocol) they were regarded as Suspected Unexpected Serious Adverse Events (SUSARs). In addition to standard local reporting period, SUSARs were to be reported to the Research Ethics Committee and the Study Sponsor.

3.7 Blanking period

Episodes of atrial tachyarrhythmia occurring entirely and solely within three months (90 consecutive days) of the index ablation period were not counted as recurrence of AF for the purpose of either the primary or secondary study endpoints.¹⁶²,¹⁶⁵

3.8 Patients

Patients were recruited through the heart rhythm service at three NHS hospitals that make up the clinical partnership of the Institute of Cardiovascular Medicine and Science. Patients eligible for CA and felt to be suitable for inclusion by their cardiologist were initially contacted either by letter or in person at the time of their outpatient appointment. All patients were provided with the Participant Information Sheet (PIS) at the time of first contact.

- Patients initially contacted by letter received a follow up telephone call at least 1 week later to allow for discussion of the study. Patients provisionally agreeing to participate were interviewed in person when they next attended the department (usually for an outpatient appointment or booked investigation) at which point the consent forms were completed and signed.
• Patients initially seen in person were encouraged to take time to read the PIS and discuss it with relevant relatives and friends. It was made explicitly clear that they were free to either complete and return the consent form before they left the hospital or to return it by post at a later date if they wished to take more time to consider whether or not to participate.

3.9. **Inclusion criteria**

Patients listed for CA at were assessed for inclusion against the following criteria

- Age over 18 years.
- Able and willing to give written, informed consent.
- Non-paroxysmal atrial fibrillation, as pre-classified as
  - **Persistent AF**: AF requiring Electrical/Chemical cardioversion or that lasting >7 days.
  - **Sustained Paroxysmal AF with underlying substrate**: Patients with Individual AF episode(s) lasting >12 hours but less than 7 days plus one or more of the following:
    - Age >65 years.\(^{168}\)
    - Hypertension with left ventricular hypertrophy.\(^{169}\)
    - Significant left atrial dilatation of >45 mm on Echo (PLAX view).
    - Obesity (BMI >30), and/or confirmed diagnosis of sleep apnoea.\(^{170}\)
    - Diabetes Mellitus requiring hypoglycaemic drugs and/or Insulin.\(^{171}\)
• On-going symptoms (EHRA Class 2 or above) in spite of treatment with rate control/ antiarrhythmic medication or intolerance of these medications.

3.10. Exclusion Criteria

Presence of any of the following attributes or characteristics at the time of potential recruitment were excluded from the study

• Inability or unwillingness to receive oral anticoagulation.

• Previous ablation procedure for AF.

• Unwillingness or inability to complete the required follow up arrangements.

• Presence of long standing persistent AF with continuous AF longer than 12 months. This included patients in whom sinus rhythm may have been maintained following electrical cardioversion for a period of less than 1 week at a stretch.

• Documented typical atrial flutter (proven on 12 lead ECG)
  
  o Patients whose first documented episode of atrial flutter occurred after randomisation were not excluded from the study but, if randomised to the PVI only arm, also received linear ablation of the cavo-tricuspid isthmus (flutter line). For the purposes of Intention to Treat analysis this patients were analysed in accordance with their initial randomisation

• Prior prosthetic mitral valve replacement or severe structural cardiac abnormality

• Contraindications and/or prior intolerance to both amiodarone and flecainide

• Reversible cause for atrial fibrillation

• Known hypertrophic or infiltrative cardiomyopathy
3.11. Randomisation

Randomisation was performed using freely available computerised randomisation software (Minim, www.sghms.ac.uk/depts/phs/guide/randser.htm) incorporating a partial minimisation procedure to adjust the randomisation probabilities between groups to balance for AF type (persistent or sustained paroxysmal) and was stratified according to NHS Trust.\(^{173,174}\)

3.12. Study Visits and Investigations

The schedule of visits and investigations is given in the table below.

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<th>3 months post-procedure</th>
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<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Troponin T</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>X(^5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Stop study medication</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>X</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 3-1: Study visit schedule. \(^1\)At least 6 weeks pre-procedure for all patients unless already prescribed at time of recruitment. \(^2\)Electrograms recorded at these points as part of standard clinical care but not specifically required for the study protocol. \(^3\)Choice of modality made according to clinical requirements and availability. \(^4\)Holter monitoring not necessarily required if recurrence of AF, meeting the definitions of a trial endpoint, confirmed by alternative modality. \(^5\)Only performed on a subset of patients.
3.13. **Follow Up**

Study follow up visits were performed at 3, 6 and 12 months post-ablation as detailed above. Additional clinical visits were permitted as required. A 12 lead resting ECG was performed at all visits. 24 hour ambulatory ECG (Holter) monitoring was performed at all study visits barring the exceptions detailed above. *Ad hoc* Holter monitoring was also performed as required for patients with intercurrent symptoms suggestive of atrial tachyarrhythmia. Prolonged (7-14 day) symptom activated ambulatory monitoring was performed for patients with on-going symptoms where symptom-arrhythmia correlation was not achieved from the resting ECG or Holter recordings.

Warfarin/other oral anticoagulant agents were continued for at least three months post-ablation. At that point the decision whether or not to continue was made individually, based on CHADS$_2$/CHA$_2$DS$_2$VASc score, freedom from AF and patient preference.

3.14. **Baseline Data**

The following data were collected prior to randomisation, either at the initial consultation or during the time the patient was on the waiting list for AFA.

- Inclusion and exclusion criteria.

- **AF history**
  - AF Categorisation (SusPAF or PeAF)
  - Substrate marker for patients categorised as SusPAF.
  - Number of previous cardioversions, duration of sinus rhythm after most recent DCCV and AAD used at time of cardioversion.

- **Comorbid conditions**
  - Hypertension, previous myocardial infarction, previous stroke and/or TIA, Peripheral vascular disease, valvular heart disease, heart failure,
tachycardia induce cardiomyopathy (current or previous), diabetes mellitus (type 1 or 2), obstructive sleep apnoea (OSA), smoking history, and CHA\textsubscript{2}DS\textsubscript{2} VASc score.\textsuperscript{175}

- Possible undiagnosed OSA was also screened for using a simple screening questionnaire (with 2 or more answers suggestive of OSA)
  - Do you snore?
  - Are you excessively tired during the day?
  - Do you have a history of hypertension?
  - Is your neck size > 17in (male) or > 16in (female)?
  - Have you been told you stop breathing during sleep?

- Other Clinical data
  - Height, weight, BMI and gender.
  - Heart rhythm at time of recruitment (based on 12 lead ECG findings).
  - Prescribed medications and previously failed AADs.

- Symptom evaluation (EHRA class).\textsuperscript{162}

- 12 lead electrocardiogram (ECG).

- 24 hour ambulatory ECG (Holter), to assess mean baseline heart rate and establish the presence of persistent/ non-paroxysmal AF and overall AF burden.\textsuperscript{176}

- Quality of Life Assessment using the Atrial Fibrillation Effect on QualiTy of life questionnaire (AFEQT).\textsuperscript{177}

- Thyroid function and liver function tests
  - Any significant abnormalities in these tests were discussed with the clinical team. For patients receiving, or due to receive, amiodarone consideration was given to the use of flecainide as an alternative agent.
3.15. Quality of Life Assessment

Quality of life was assessed objectively at the time of recruitment and at 6 and 12 months after ablation. A subjective assessment was also made by the reviewing clinician at all study visits using the EHRA score.\textsuperscript{162}

3.15.1. AFEQT Questionnaire

The Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT) Questionnaire is a validated, disease-specific, self-administered QoL instrument.\textsuperscript{178} It has 20 questions with four conceptual domains and published algorithms allow calculation of domain and global scores. Each of the 20 questions is marked on a seven point Likert scale. The questionnaire specifies a recall period of the preceding four weeks. The questionnaire was used under licence from St. Jude Medical Inc, (Minnesota, USA). The raw scores are used to generate the AFEQT overall score and the component sub-scores (symptoms, activities and concerns) using algorithms supplied by the company.

3.15.2. Anti-arrhythmic Drug Protocol

A study published shortly before the commencement of this trial suggested that pre-procedural AAD therapy may improve the success rates for ablation in substrate-based AF.\textsuperscript{179} Subgroup analysis from that study suggested that the improved clinical outcome could not be predicted simply by the restoration of sinus rhythm and that the key element appeared to be reversal of the adverse remodelling that occurs in the atria of patients with AF. All patients were prescribed an AAD for a minimum of six weeks pre-procedure and exactly six weeks post procedure. Deviation from this was only permitted if mandated by clinical need.

The choice of AAD was decided according to the following algorithm:
A two week loading regime was used for patients commenced on amiodarone as part of the study. This consisted of a dose of 200mg of amiodarone three times a day for seven days followed by the same dose twice a day for a further seven days.

3.16. **Anticoagulation**

All patients not already receiving oral anticoagulation therapy were commenced on either warfarin or dabigatran. For patients on warfarin the aim target INR level was between 2 and 3 but management of warfarin dosing was not managed as part of the study protocol. The standard dose of dabigatran was 150mg twice daily.
3.17. Ablation Procedure

All patients continued oral anticoagulation peri-procedurally with an INR on the day of procedure between 2.0 and 3.5 considered acceptable for those taking warfarin.\textsuperscript{181,182} Periprocedural use of Dabigatran was allowed according to local guidelines for patients taking these agents. Transoesophageal echocardiography (TOE) was permitted to exclude left atrial thrombus prior to CA at the discretion of the operator according to their normal practice. As a guide, TOE was recommended for patients in AF at the time of their ablation if the INR readings in the previous 4 weeks are <2.0 for those taking warfarin, or if anticoagulation had been inadequate (e.g. missed doses) for those taking Dabigatran.

After successful transseptal puncture patients were anticoagulated with intravenous unfractionated heparin to maintain an Activated Clotting Time (ACT) of >250-300 seconds.

Atrial fibrillation ablation was performed under conscious sedation or general anaesthesia in a standard fashion in a similar manner to that which has been described previously.\textsuperscript{183} Single or double transseptal punctures were made using fluoroscopic guidance with additional pressure monitoring. If patients were in AF at that point, they underwent DCCV to restore sinus rhythm. An electroanatomical map of the left atrium was then created and, whenever possible, then integrated with the MR or CT reconstruction of the atrium using a 3D navigation system (CartoMerge; Biosense Webster, Diamond Bar, California, USA).\textsuperscript{110,159}

Group 1: Using a 3.5-4mm irrigated tip radiofrequency ablation catheter a series of lesions >2 mm outside PV ostia were made to encircle and electrically isolate the pulmonary veins in two ipsilateral pairs (wide area circumferential ablation, WACA).\textsuperscript{184} A 20-pole PV mapping catheter was used to confirm electrical
isolation. If the patient was in atrial fibrillation at this stage, sinus rhythm was restored with electrical cardioversion and PVI isolation of the pulmonary veins confirmed in sinus rhythm.

**Group 2:** Initially, isolation of the pulmonary veins was undertaken in an identical manner to Group 1. Once PVI had been achieved, patients received a pre-specified additional linear ablation lesion set. This consisted of a left atrial roof line, mitral isthmus line, (including ablation inside the coronary sinus if necessary), and ablation on the cavitricuspid isthmus (CTI). If the patient was in atrial fibrillation at this stage, the acute end-point would be signal obliteration at the ablated area. Once sinus rhythm was restored with electrical cardioversion, PVI was confirmed in sinus rhythm and conduction block across the LA roof line, Mitral line and CTI was then verified with appropriate pacing manoeuvres as detailed below.

In both groups a minimum waiting time of 30 minutes was allowed to elapse between complete isolation of the pulmonary veins and verification of conduction block and pulmonary vein isolation.

In either of the 2 groups, if AF became organised to a regular atrial tachycardia or sustained atrial flutter at any stage, attempts were made to map and ablate this to sinus rhythm according to the protocol described by Jais *et al.* That notwithstanding, these patients still received the pre-specified ablation lesion set according to their randomisation group. Patients who were randomised to PVI only but required a cavitricuspid isthmus line to treat induced flutter were still considered to have been treated as per their randomisation for intention to treat analysis but had this deviation from protocol recorded.
At the end of the procedure and at the discretion of the operator, administration of intravenous protamine to reverse the effects of heparin was permitted but not mandated.

### 3.18. Lesion Description and Definition of Success

The follow descriptions were used to define the ablation lesions performed as part of the study protocol and the criteria for judging those lesions as completely or partially successful when checked after the compulsory waiting period.

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Description</th>
<th>Complete success</th>
<th>Partial success</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left sided WACA</strong></td>
<td>Creation of a contiguous series of lesions &gt;2 mm outside PV ostia which encircles* and electrically isolate the pulmonary veins in two ipsilateral pairs. Ablation within the WACA is also permitted, especially across the intervenous carina.* If isolation of both veins is demonstrated before complete encirclement (e.g. by ablation of all active fascicles) then it is not mandatory to complete the entire lesion.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Right sided WACA</strong></td>
<td>Roof Line Creation of a contiguous line of ablation lesions along the LA roof, joining the superior PVs</td>
<td>Success checked with Spiral catheter within each pulmonary vein in turn, demonstrating by either (a) Elimination of all PV potentials, or (b) Entrance block into the PV with dissociated PV potentials</td>
<td>Failure of complete isolation of 1 or more veins</td>
</tr>
<tr>
<td><strong>Roof Line</strong></td>
<td>Creation of a contiguous line of ablation lesions along the LA roof, joining the superior PVs</td>
<td>Demonstration of caudocranial activation of the posterior wall and/or online corridor of double potentials along the entire length of the roof during sinus rhythm and/or during pacing of the anterior LA</td>
<td>Significant slowing of conduction but without demonstrable conduction block</td>
</tr>
</tbody>
</table>
### Table 3-2: Ablation Lesions (and Definitions of Success) Used as Part of Study Protocol

<table>
<thead>
<tr>
<th>Mitral Isthmus Line</th>
<th>Creation of a contiguous line of ablation between the lateral mitral annulus and the inferior aspect of the left-sided WACA. Where necessary this may include ablation within the coronary sinus.</th>
<th>Pacing lateral to the line through the ablation catheter placed endocardially demonstrating a proximal-to-distal activation sequence along the CS septal of the line</th>
<th>Slowing of conduction across the line but without meeting the criteria for complete success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavo-Tricuspid Isthmus Line</td>
<td>Creation of a contiguous line of ablation lesions from the ventricular aspect of the tricuspid annulus (where the atrioventricular electrogram shows a 1:1 to 2:1 ratio) and the rim of the IVC (the point at which no local electrogram can be recorded)</td>
<td>At least one of: Demonstration of bidirectional block across the line by means of differential pacing so that: When pacing from CS or MAP catheter (placed lateral to CTI) the conduction time to the other catheter DECREASES when MAP is moved to a more lateral position. The manoeuvre is then repeated whilst pacing from the other catheter. Demonstration widely split (&gt;90ms) double potentials with an intervening isoelectric interval along the entire course of the ablation line</td>
<td>Significant slowing of conduction across the line but without demonstrable block</td>
</tr>
</tbody>
</table>

### 3.19. Recurrence of AF

Recurrence of AF, or other atrial tachyarrhythmia following ablation was managed according to clinical need with repeat ablation offered to all with enduring symptoms (EHRA Class 2 or greater). Patients who developed continuous persistent AF after their ablation were offered electrical cardioversion as the first line treatment option. Patients
whose symptoms were mild and/or who declined a repeat ablation procedure were maintained on AAD as required.

3.20. **Repeat Ablation**

Patients with symptomatic PAF occurring or continuing after the pre-defined blanking period or who reverted back to PeAF following electrical cardioversion were offered repeat ablation. This was performed using the lesion set allocated at randomisation. Additional ablation was only permitted if:

- The original lesion set was found to be intact (all veins still isolated and persisting conduction block across all linear lesions), in which case additional ablation was permitted according to the operator’s standard practice. And/or
- A de novo focal or macro-reentrant atrial tachycardia or flutter was seen, in which case this was mapped and ablated as described for the index ablation procedure.

Only the initial and first repeat procedure were limited by study protocol. If a third ablation was required for any patient during the study period the choice of ablation lesions was left to the discretion of the operator.

3.21. **Sample Size Calculation**

A formal sample size calculation was performed, using StatsDirect software version 2.7.8, according to the following equation
Zp is the standard normal deviate for probability p. We accepted the more conservative continuity corrected sample size ($n_c$) having specified the number of control subjects per experimental subject (m) to be 1.

Based on local audit data we assumed a 6 month single procedure success rate of 55% in Group 1 and 80% in Group 2. Allowing for an α error of 0.05 and a β of 20% (80% power) the number of patients required was calculated as 124. Allowing for an anticipated 5% attrition rate gave a target sample size of 130.

### 3.2.2. Statistical Analysis

All end points, apart from the pre-specified per-protocol analysis, were examined by means of a modified intention-to-treat analysis. In this, patients who underwent ablation were analysed according to the allocated treatment arm, irrespective of the actual lesion set delivered. Patients who withdrew or were withdrawn after randomisation but before their procedure were excluded from analysis. Categorical variables were compared with $\chi^2$ or Fisher’s exact test where appropriate. The dependent variables were checked for normal distribution by the Shapiro-Wilk statistic and appropriate descriptive statistics generated. Continuous variables were expressed as means (±SD) and be compared with the use of the student’s t-test (if normally distributed) or Wilcoxon rank-sum and signed-rank tests (if not). All reported p values were two-sided and a value of 0.05 or lower was considered significant for all tests.
Statistical tests were performed either with either StatsDirect software version 2.7.8. or IBM SPSS Statistics software version 21.

3.23. Assessment of primary endpoint

Monitoring ECG traces were assessed initially by an experienced cardiac physiologist and then reviewed by a clinician who categorised each recording as either showing an atrial tachyarrhythmia lasting 30 seconds or longer (primary endpoint achieved) or not. If the primary reviewing clinician was uncertain, an expert secondary review was performed by an experienced electrophysiologist. Any cases in which there was uncertainty about classification of outcome (mainly due to difficulties clarifying the exact timing of an event) the decision was passed to an independent adjudication committee who were provided with all available clinical and trial data. All assessors were blinded to treatment allocation.

3.24. Recruitment

Recruitment commenced at Liverpool Heart and Chest Hospital in October 2011. The study was initially conducted as a single site study to allow testing and verification of the protocol. With the establishment of the Institute of Cardiovascular Medicine and Science, permission was granted for multi-centre involvement, and recruitment at Harefield Hospital and The Royal Brompton Hospital began in June 2012. The study closed to recruitment in June 2013 having achieved the intended recruitment target. A CONSORT diagram for the study is shown below.
3.24.1. CONSORT Diagram

Figure 3-2: Study CONSORT diagram
3.24.2. Progress

Overall the study was well received by patients with a high proportion of eligible patients agreeing to participate. However, fewer than expected patients met the study’s inclusion criteria. In addition the unexpected delay in moving the study from single centre to multi-centre status also slowed recruitment. Our original intention was that all patients would have been recruited and all index ablations performed by May 2013 but it became clear during the course of the study that this was not likely to be achieved. Although recruitment was completed in June 2013, due to the demands on the NHS waiting lists, the final ablation was not performed until November 2013.

3.25. Ethical Considerations

3.25.1. Good Clinical Practice

The study was conducted in accordance with the requirements of the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice guidelines. Institutional review and approval was provided by the Research and Development Committees at Liverpool Heart and Chest Hospital NHS Foundation Trust and The Royal Brompton and Harefield Hospitals NHS Foundation Trust. All documents intended to be made available to patients were reviewed and approved by the Service Users Research Endeavour (SURE) group at LHCH to ensure clarity and readability for patients.

3.25.2. National Research Ethics Service (NRES)

The study was reviewed by the NRES Committee North West – Greater Manchester Central, on 13 June 2011 and a Favourable Opinion was granted on 1st July. The
Research Ethics Committee reference was 11/NW/0354. In accordance with the standard requirements for monitoring of a favourable ethical opinion, a progress report was submitted annually to the Committee.

According to the NHS Health Research Authority guidance document, "After Ethical Review", a substantial amendment is defined as an amendment to the terms of the application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

1. The safety or physical or mental integrity of the subjects of the trial;
2. The scientific value of the trial;
3. The conduct or management of the trial; or
4. The quality or safety of any investigational medicinal product used in the trial.

A single Notification of Substantial Amendment was submitted on 5th July 2012 and approved on 6th August.

### 3.25.3. Confidentiality

Participants were assigned a unique code which was used to identify them throughout the trial and on all study documents. Electronic records were stored securely either on a password protected laptop or on secure Trust servers with controlled access permissions.

### 3.26. Flow Chart

The following flowchart was provided to all potential participants to illustrate graphically the requirements of involvement in the trial.
Potential participants identified at referral. Information sheet sent

Patients seen in Heart Rhythm clinic. Screened and interviewed by researcher, informed consent gained

Baseline blood tests, Echocardiogram, questionnaire(s), 24 hour ECG

Premedication with Amiodarone (or flecainide) for 6 weeks

Randomisation

Premedication with Amiodarone (or flecainide) for 6 weeks

MRI Scan

Pulmonary Venous Isolation (PVI)

Day 1: Echocardiogram, Signal Averaged ECG and blood test prior to hospital discharge

MRI Scan

PVI with additional linear lesions

Month 3: Follow up visit (clinical): Echocardiogram and Signal Averaged ECG performed. 24h ECG monitor +/- event recorder. MRI Scan

Month 6: Follow up visit (clinical): Echocardiogram and Signal Averaged ECG performed. 24h ECG monitor +/- event recorder

Month 12: End of study (final follow up visit)
24 continuous ECG monitor +/- event recorder

* Direct current cardioversion will be offered in the first instance with repeat ablation for patients failing to maintain sinus rhythm after cardioversion.

Figure 3-3: Study flow diagram
3.27. **Trial registration**

Clinical trials should be registered on a publically accessible database. The study was prospectively registered at www.clinicaltrials.gov with the registration number NCT01445925.

3.28. **Case record form**

Data were recorded on a paper Case Record Form (CRF), a copy of the final version of which is included in the appendices. This was then transferred to a purpose-built Microsoft Access 2007 database which acted as the electronic CRF (eCRF). The database is fully relational allowing for one-to-one and one-to-many relationships between tables. The design allows collection of all trial data to be performed through a single user-friendly portal. By coding elements using Visual Basic for Applications 6 (VBA6) scripting language the database was able to make simple calculations such as the patient’s age based on their date of birth and procedure date, the CHA$_2$DS$_2$ VASc score based on documented comorbidities and the required dates of follow up. Microsoft Access supports Structured Query Language (SQL) which allowed me to write queries which could then be used to check data integrity and perform initial analyses. In turn, some of these queries provided the basis for Microsoft Word 2007 mail merge documents which provided a semi-automated means of communication with participants and their GPs. By combining queries with the inbuilt report function, it was possible to maintain a rolling schedule of required appointments and investigations for all participants. A screenshot of the eCRF is shown below.
Figure 3.4: Screen shot of eCRF database

3.29. Sponsor

Liverpool Heart and Chest Hospital NHS Foundation Trust acted as the study sponsor.
4. Improving patient outcomes through better ablation strategies: Results of the Substrate Modification with Ablation and Antiarrhythmic Drugs in Non-Permanent Atrial Fibrillation (SMAN-PAF) Randomised Controlled Trial

4.1. Introduction

Initial attempts at ablation of AF targeted triggers by attempting to ablate individual ectopic foci within the pulmonary veins. Modern techniques have evolved to encirclement of ipsilateral vein pairs by creating contiguous rings of ablation lesions in the antral area between the vein ostia and the body of the left atrium (Wide Area Circumferential Ablation, WACA). Whilst the key purpose of these WACA lesions is to electrically isolate the pulmonary veins, thereby removing the most potent triggers, a relatively large area of tissue needs to be ablated to achieve this aim. This ablation may additionally modify the left atrial substrate by creating physical barriers to re-entry, interrupting potential sites of rotor activation and by modification of the autonomic innervation of the heart due to indirect ablation of ganglionic plexi which tend to be concentrated in the antral regions. Further modification of the left atrial substrate can be achieved by the use of antiarrhythmic drugs, by performing more extensive ablation within the atria or by combining both approaches.

In this study, I set out to assess whether very extensive modification of the left atrial substrate by addition of bi-atrial linear ablation lesions to a strategy combining WACA
and periprocedural antiarrhythmic drug therapy provides greater freedom from AF recurrence in the medium term.

4.2. METHODS

The trial methodology is described in detail in an earlier Chapter. In brief, I set out to randomise 130 patients with persistent or sustained paroxysmal episodes of AF to one of two ablation strategies. Treatment allocation was in a 1:1 ratio. For the purpose of the study I defined persistent atrial fibrillation as an episode of AF lasting longer than 7 days and sustained paroxysmal AF as episodes of AF lasting ≥12 hour (but less than 7 days) in patients with an additional comorbid condition previously shown to be associated with abnormal left atrial substrate. Ablation was performed at three sites (two NHS trusts) within the UK, all tertiary AF referral centres. Recruitment was stratified according to AF type and NHS trust. For the purpose if this study, patients were followed up for six months during which time they were seen clinically and had periodic ECG monitoring. The primary endpoint of the study was recurrence of AF within the follow up period after an initial blanking window.

4.3. RESULTS

4.3.1. Patient characteristics

Of 130 enrolled patients, 64 (49%) were randomised to PVI with peri-procedural pharmacological substrate modification (PVI group) and 66 (51%) to a strategy of additional substrate modification with linear lesions (PVI + lines group). Characteristics of enrolled patients are shown in the table below.
Table 4-1: Baseline characteristics of patients enrolled in the SMAN-PAF randomised controlled trial

<table>
<thead>
<tr>
<th></th>
<th>Total n =130</th>
<th>PVI n = 64</th>
<th>PVI + Lines n = 66</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>88 (68%)</td>
<td>47 (73%)</td>
<td>41 (62%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Age</td>
<td>61.9 ± 10.5</td>
<td>61.8 ± 9.7</td>
<td>61.9 ± 11.4</td>
<td>0.98</td>
</tr>
<tr>
<td>BMI</td>
<td>28.9 ± 8.7</td>
<td>29.2 ± 9.3</td>
<td>28.6 ± 8.0</td>
<td>0.71</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>79 (61%)</td>
<td>39 (61%)</td>
<td>40 (61%)</td>
<td>0.97</td>
</tr>
<tr>
<td>Hypertension</td>
<td>75 (58%)</td>
<td>33 (52%)</td>
<td>42 (64%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Previous MI</td>
<td>12 (9%)</td>
<td>5 (8%)</td>
<td>7 (11%)</td>
<td>0.58</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8 (6%)</td>
<td>6 (9%)</td>
<td>2 (3%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Smoker (or previous)</td>
<td>55 (42%)</td>
<td>28 (44%)</td>
<td>27 (41%)</td>
<td>0.74</td>
</tr>
<tr>
<td>EHRA class</td>
<td>2.8 ± 0.6</td>
<td>2.8 ± 0.6</td>
<td>2.8 ± 0.7</td>
<td>0.74</td>
</tr>
<tr>
<td>CHA₂DS₂VASc</td>
<td>1.7 ± 1.3</td>
<td>1.4 ± 1.2</td>
<td>1.9 ± 1.4</td>
<td>0.054</td>
</tr>
<tr>
<td>LV Ejection fraction (%)</td>
<td>61.1 ± 11.8</td>
<td>60.5 ± 11.0</td>
<td>61.5 ± 12.6</td>
<td>0.65</td>
</tr>
<tr>
<td>LA Diameter (mm)</td>
<td>43 ± 6</td>
<td>43 ± 6</td>
<td>43 ± 6</td>
<td>0.81</td>
</tr>
</tbody>
</table>

4.3.2. Follow up

All bar two patients who underwent ablation completed follow up as planned and thereby provided data for analysis. Of those who did not complete follow up, one patient reported freedom from symptomatic AF episodes but repeatedly failed to attend any follow up appointment after his ablation and did not undergo any ECG monitoring. A second patient, with pre-existing Crohn’s disease had a relapse shortly after his
ablation. He was hospitalised for this and later underwent extensive surgery. Unfortunately, he died from complications of his Crohn's disease approximately eight months after his ablation. Both patients had been randomised to the PVI only ablation strategy.

Six patients, three in each arm, withdrew or were withdrawn from the study after randomisation but before ablation had been performed. Of these, in three patients a decision was made to switch to medical therapy rather than undergo ablation. In two this was because their symptoms were sufficiently controlled on their periprocedural antiarrhythmic drug regime and in the other because of presence of left atrial thrombus. One patient underwent an alternative intervention. In two patients a new diagnosis of hypertrophic cardiomyopathy, an exclusion criteria, was made based on pre-procedural imaging. These patients were not included in subsequent analyses.

4.3.3. ABLATION PROCEDURES

The allocated lesion set was attempted in all but one patient according to randomisation. One protocol violation occurred where a patient randomised to PVI+ lines did not have the additional linear ablation because of a clinical decision by the operating consultant. One further patient had no linear ablation because inability to cannulate the coronary sinus meant that it would have not been possible to check line integrity using standard pacing manoeuvres, as required by protocol. Two further patients, who had there procedure under conscious sedation, had only a partial lesion set due to ongoing pain which limited the ability to deliver radiofrequency energy. In eight patients allocated to PVI only an additional cavo-tricuspid isthmus line was performed because of sustained atrial flutter induced during the procedure. All patients
described above were included in an intention to treat analysis according to their initial randomisation.

Successful isolation of all four pulmonary veins was achieved in 122 (98%) of patients. In one patient it was not possible to cannulate the lower veins to check isolation. In two patients it was not possible isolate one of the four pulmonary veins (right upper in one, and right lower in the other). For those who had additional linear ablation performed, bidirectional block was demonstrated for all attempted lines in 50 (82%). In terms of individual linear lesions, proven bidirectional block was achieved for 90% (55/61), of roof lines 83% (49/59) of mitral isthmus lines, and 96% (65/68) of cavotricuspid isthmus lines.

Details of the index procedure for all patients who underwent ablation are given in Table 4-2. No repeat procedures were performed within the six month follow up period.
## Table 4-2: SMAN-PAF Procedural details

<table>
<thead>
<tr>
<th></th>
<th>Total n = 124</th>
<th>PVI n = 61</th>
<th>PVI + linear lesions n = 63</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Procedure Time (mins)</strong></td>
<td>191 ±51</td>
<td>172 ± 44</td>
<td>209 ± 52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Ablation Time (secs)</strong></td>
<td>3435 ±1415</td>
<td>2503 ± 1061</td>
<td>4352 ± 1084</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>DAP (Gycm2)</strong></td>
<td>3065 ± 4853</td>
<td>2106 ± 1679</td>
<td>3992 ± 6496</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Fluoro Time (secs)</strong></td>
<td>1356 ± 764</td>
<td>1079 ± 527</td>
<td>1610 ± 858</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Wait Time (mins)</strong></td>
<td>62 ± 33</td>
<td>43 ± 16</td>
<td>80 ± 35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>General Anaesthetic</strong></td>
<td>49 (40%)</td>
<td>16 (26%)</td>
<td>33 (52%)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>CT/ MR Merge</strong></td>
<td>84 (68%)</td>
<td>39 (64%)</td>
<td>45 (71%)</td>
<td>0.37</td>
</tr>
<tr>
<td><strong>Sinus Rhythm at start</strong></td>
<td>89 (72%)</td>
<td>43 (71%)</td>
<td>46 (73%)</td>
<td>0.75</td>
</tr>
<tr>
<td><strong>Incomplete lesions</strong></td>
<td>16 (13%)</td>
<td>2 (3%)</td>
<td>14 (22%)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

4.3.4. **Primary endpoint**

Within the first six months after ablation, excluding events occurring solely within the pre-specified blanking period, recurrence of atrial tachyarrhythmia occurred in 11 patients (18.6%) in the PVI group and 16 patients (25.4%) in the PVI + lines group.
following a single ablation procedure. The difference between the groups was not statistically significant (p=0.37).

4.3.4.1. Predictors of AF recurrence

Univariable predictors of occurrence of the primary endpoint were sought using binary logistic regression analysis. Details of the analysis are given in Table 4-3. Only procedural duration and ablation time met the pre-specified inclusion criteria for inclusion in the multivariable model. However, neither remained significant on multivariable analysis.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable analysis</th>
<th></th>
<th>Multivariable analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>95% CI</td>
<td>P value</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>------------</td>
<td>-------------</td>
<td>-----------</td>
<td>------------</td>
</tr>
<tr>
<td>Ablation time (mins)</td>
<td>1.02</td>
<td>1.00-1.04</td>
<td>0.09</td>
<td>1.01</td>
</tr>
<tr>
<td>CHA\textsubscript{2}DS\textsubscript{2} VASc Score</td>
<td>1.14</td>
<td>0.83-1.58</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>Current/ Ex smoker</td>
<td>1.72</td>
<td>0.94-3.14</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.70</td>
<td>0.24-2.03</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>1.00</td>
<td>0.96-1.04</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>1.08</td>
<td>0.44-2.69</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>General anaesthetic</td>
<td>0.85</td>
<td>0.35-2.04</td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.97</td>
<td>0.41-2.32</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>Incomplete lesions</td>
<td>1.32</td>
<td>0.43-4.05</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>Left atrial diameter (mm)</td>
<td>1.02</td>
<td>0.94-1.10</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.29</td>
<td>0.04-2.38</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Persistent AF</td>
<td>1.09</td>
<td>0.45-2.62</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>Procedure time (mins)</td>
<td>1.01</td>
<td>1.00-1.02</td>
<td>0.03</td>
<td>1.01</td>
</tr>
<tr>
<td>Treatment allocation</td>
<td>1.49</td>
<td>0.62-3.53</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>Wait time (mins)</td>
<td>1.00</td>
<td>0.99-1.01</td>
<td>0.99</td>
<td></td>
</tr>
</tbody>
</table>

Table 4-3: Binary logistic regression analysis of SMAN-PAF results
4.3.5. **SECONDARY ENDPOINTS**

4.3.5.1. **COMPARISON OF PERSISTENT AND SUSTAINED PAROXYSMAL ATRIAL FIBRILLATION**

Of the 122 patients who completed follow up, the primary endpoint was observed in 17 of 75 patients with PeAF and 9 of 47 with SusPAF (22.7% vs 19.1%, p=0.64) after a single procedure. Although underpowered for subgroup analysis, there was no signal that occurrence of the primary endpoint differed between treatment arms according to AF type (PeAF (PVI 19.4%, PVI + linear lesions 25.6%, p=0.52) SusPAF (PVI 17.4%, PVI + linear lesions 20.8%, p=0.76)).

4.3.5.2. **PER PROTOCOL ANALYSIS**

As described in Section 0, eight patients randomised to PVI only, also had ablation of the cavotricuspid isthmus because of induced typical right atrial flutter. Two patients randomised to PVI + linear lesions had only two of the three prescribed linear lesions and two had none (effectively treated with a PVI only strategy). To evaluate whether this may have affected the primary endpoint, I performed a per protocol analysis of patients who received PVI alone against those who received a complete linear lesion set. The primary outcome occurred in 14/59 (24%) patients treated with PVI + linear lesions and 9 of 53 (17%) patients treated with PVI alone. As with the main intention to treat analysis, there was no significant difference between the groups (P=0.38) with similar proportions in both analyses.

4.3.5.3. **QUALITY OF LIFE**

The overall AFQT score for the cohort at baseline was 50.7±22.3 which improved significantly to 80.9±19.1 six months after ablation (P<0.0001). The improvement after ablation was seen in both treatment groups. No significant difference was seen between
the study groups, either at baseline (p=0.72), or at the six month follow up visit (P=0.54). These results are shown in Table 4-4.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Six months’ follow up</th>
<th>P value (Baseline – 6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall cohort</td>
<td>50.7±22.3</td>
<td>80.9±19.1</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>PVI only</td>
<td>49.8±22.9</td>
<td>82.3±18.0</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>PVI + linear lesions</td>
<td>51.6±22.0</td>
<td>79.4±20.3</td>
<td>P&lt;0.0001</td>
</tr>
</tbody>
</table>

Table 4-4: Overall AFEQT score at baseline and at the six month follow up visit

Improvement in QoL after ablation was seen both in those who remained free from the primary endpoint (50.9±21.9 - 83.1±16.6, P<0.0001) and those patients who suffered recurrence of AF (49.8±24.2 - 71.8±25.7, P=0.015). Although the magnitude of improvement was greater in those who did not have recurrence, the difference at the six month follow up period was not statistically different (71.8±25.7 v. 83.1±16.6, P=0.14).

4.3.6. Safety endpoint

4.3.6.1. Major complications

There were no peri-procedural deaths and no thromboembolic events occurred in the peri-procedural period or during follow up. One patient suffered a pericardial effusion which was successfully drained percutaneous without persisting sequala. Two femoral pseudo aneurysms occurred, both which were successfully treated with direct injection
of thrombin. The overall rate of major complications was 2.4% with no difference between treatment groups (P=0.62).

There was one non-cardiovascular death, details of which are given above in Section 0. Including this in our pre-specified safety analysis gave an incidence of major complications and all cause death of 4.9% (n=3) in the PVI only group and 1.6% (n=1) in the PVI + linear lesions group. This difference was not statistically significant (P=0.36).

4.3.6.2. Other Complications

One procedure was abandoned due to complications of transseptal access but had no clinical sequelae and the patient went on to have a subsequent successful procedure. Five patients developed haematomas relating to femoral venous access which were managed conservatively but which either delayed discharge or prompted subsequent readmission. Two patients were admitted with symptoms of heart failure follow their procedure both of whom were successfully managed medically. Including major complications, all cause death and minor complications gave an incidence of 9.7%, with no difference between the treatment groups (PVI 8.2%, PVI + linear lesions 11.1%, P=0.76).

4.4. Discussion

Our study was powered based on an assumption of freedom from the primary endpoint after a single procedure being achieved in 80% of patients in the PVI + linear lesions group and 55% of the PVI group at 6 months. Overall, 78.7% of patients remained free of AF - very close to the upper limit of what we believed possible with either strategy with a non-significant 5.2% difference in favour of the less extensive strategy (the
opposite direction to that which we had predicted). This finding was not affected by whether patients had PeAF or SusPAF.

When a study produces an unexpected non-significant result there are several important questions to ask. Firstly, was the original expectation on which the sample size was calculated reasonable and, secondly, was the study underpowered. If the answers to these questions confirm that the trial methodology was robust then we need to look back at differences with previously published studies which may explain the findings.

We designed the trial expecting that additional linear lesions would reduce recurrence of AF compared to PVI alone in patients treated with peri-procedural antiarrhythmic drugs. This assumption was derived from local audit data but was in keeping with published literature. Our trial population was patients with PeAF and those with an advanced form of PAF causing sustained episodes of PAF, likely to be associated to an abnormal left atrial substrate and therefore more akin to PeAF than purely trigger-based PAF. This specific patient group has never been studied previously. Three studies have previously trialled a pulmonary vein isolation technique with against one involving additional linear ablation in patients with PeAF.\textsuperscript{106,107,131} I performed meta-analysis of the patients with PeAF included in these studies in my introductory Chapter and found that addition of linear lesions significantly and substantially reduced the risk of recurrence (OR 0.22, 95%CI 0.10-0.49, p<0.001).\textsuperscript{142} In two of these studies which included both patients with PAF and PeAF a significant difference between treatment arms was seen in both subgroups. My initial assumption would therefore appear to have been a reasonable one.
The sample size calculation, and thus the trial’s “power” to detect a difference between groups, was made using conventional values for α and β error (5% and 20% respectively) and an expected between-group difference of 25%. Of the three studies discussed above the mean difference between treatment arms was 33%, similar to the value we used in our calculation. Looking solely at patients with PeAF, the mean difference between groups was 36%. Therefore, whilst the effect size we anticipated was large, it was entirely in keeping with the available evidence. When one talks of a trial’s power, one is referring to its ability to avoid incorrectly failing to reject the null hypothesis when, in fact, a true difference exists between the groups being studied (a type II error). From our results, if the null hypothesis is false it would appear to be because PVI alone is superior to performing additional linear lesions. Therefore, I believe our study did not find a beneficial effect of additional linear lesions because one does not exist rather than because our sample was too small.

From our study we cannot say whether the slightly lower recurrence rate seen in the PVI group (18.6% v 25.4%) represents a true difference between groups. However, the magnitude of the difference seen (7%) is sufficiently small that, if true, a study design containing over 2000 patients would be required to prove it. Given that a PVI only strategy entails shorter procedure times, ablation times, and lower radiation doses, I do not believe it is necessary to prove that the strategy is superior. If the two are equivalent then these ancillary benefits are sufficient for it to be the strategy of choice for clinicians.

Why then, do our results differ so markedly from those I reviewed in the introductory Chapter? The answer may be due to the means of pulmonary vein isolation. As
discussed in the introduction to this Chapter, isolating the veins using WACA – as we did for all patients – involves ablation of a significant amount of antral atrial, rather than venous, tissue.\textsuperscript{118} This may well have an additional substrate modification effect over and above pure venous isolation. In my earlier meta-analysis I found that studies looking at WACA compared to segmental isolation showed a non-significant trend towards lower incidence of AF recurrence with the former (OR 0.41, 95\%CI 0.15-1.10, p=0.08). Previous studies of linear lesions in addition to PVI did not use a WACA technique. Gaita \textit{et al.} performed ablation of ostial vein potentials, with encircling, segmental ablation only performed if electrical isolation not achieved.\textsuperscript{107} Similarly, Fassini performed electrical disconnection of the veins with non-encircling lesions, guided by electrogram mapping.\textsuperscript{106} Willems did isolate the veins anatomically, as well as electrically, but used segmental isolation of individual vein ostia meaning that considerably less, potentially important, antral atrial tissue was ablated.\textsuperscript{131} It may be that modifying atrial substrate with linear lesions is of benefit only when the ablation around the pulmonary veins is limited. Performing WACA of ipsilateral vein pairs may sufficiently alter the atrial substrate, nullifying any potential effect of linear lesions.

One aspect of this study, which is unique from other such studies mentioned above, is the universal use of peri-procedural AAD use. Although this strategy is common in clinical practice, AADs have been stopped at or before the time of CA in previous clinical trials of linear ablation. A benefit of continuing AAD was suggested by a number of observational studies, which contributed to our trial design.\textsuperscript{124,179} However, the recently published AMIO-CAT RCT found no benefit of 8 weeks’ amiodarone in 212 patients with either PAF or PeAF, followed up for 6 months, as in our study.\textsuperscript{190} Although the AMIO-CAT study suggests no absolute benefit from peri-procedural AAD, I cannot say whether
our use of this strategy reduced the benefit that would have been seen of one study group of the other in this trial.

Another unique aspect of my study is the inclusion of patients with SusPAF. The decision to include this group was based partly on our belief that the distinction between PAF and PeAF is not clear cut, rather that it is a continuum between predominantly trigger-based and predominantly substrate-based atrial disease. As described in Chapter 3, patients required both prolonged (>12 hours) episodes of PAF – longer than would necessarily be expected if AF is simply driven by automatic pulmonary vein ectopy, and an additional comorbid condition that has previously been shown to be associated with abnormal atrial remodelling (substrate). The Substrate and Trigger Ablation for Reduction of Atrial Fibrillation (STAR AF) trial similarly included both patients with PeAF and “advanced” PAF. Our subanalyses, presented in Section 0, did not suggest that inclusion of the SusPAF group altered the overall primary finding of our trial and the similarity of results between the groups would seem to back our assertion that patients with SusPAF have a similar disease process to those with PeAF.

The concept of time-lag bias may also apply, whereby early studies of a new intervention tend to be positive, with negative results only emerging later. This concept is well established and has been demonstrated in a number of areas of medical research. Although my results differ from those included in my earlier analysis, they tally more closely with a trial not published yet in full but recently presented at the European Society of Cardiology in September 2014, The STAR AF 2 trial is a large multicentre study of patients with PeAF. Like us they tested PVI alone against PVI + linear lesions and, in a third arm, PVI + complex electrogram ablation. Like us they found that
freedom from AF was slightly more common in the PVI only group than in the more extensive ablation groups (59% for PVI v 44% for linear ablation and 48% for PVI plus electrograms, p=0.15). Taken together, these two trials reopen the question as to whether additional ablation is of benefit in PeAF and whether any possible benefit outweighs the additional procedure time and radiation exposure.

4.4.1. LIMITATIONS

Undoubtedly a limitation of the results we present is the short duration of follow up. This is very likely to overestimate the overall long-term benefits of ablation. Gaita et al. included in their paper, study outcomes at both one and three years.\textsuperscript{107} They found that the between group effect size in patients with PeAF did not differ greatly with extended follow up (18% at one year compared to 22% at three years). Although a greater change was seen in patients with PAF (11% to 24%), the direction of the effect was unchanged, suggesting it is unlikely that longer follow up would have allowed us to reject the null hypothesis in favour of PVI plus linear lesions.

It is important to bear in mind that our results should not be extrapolated to other groups. Brooks et al. performed a comprehensive review of studies of patients with long standing PeAF.\textsuperscript{194} They found low success rates in, mainly non-randomised, studies using a PVI only strategy. Based on this review, the current international consensus document recommends the use of more extensive lesion sets than PVI alone. It was on this basis that patients with longstanding PeAF were excluded from our study.
4.5. Conclusion

Over six months' follow up, in patients with non-permanent substrate-based AF treated with peri-procedural AADs, significant QoL benefits can be achieved with approximately 80% of patients rendered free of recurrent atrial tachyarrhythmia. The addition of linear ablation lesions, to a strategy of pulmonary vein isolation with wide area circumferential ablation, requires significantly more ablation; increasing procedure duration and prolonging fluoroscopy time, but provides no clinical benefit.
5. IMPROVING PATIENT OUTCOMES BY BETTER UNDERSTANDING ABLATION LESION QUALITY:
A NOVEL MARKER TO PREDICT EARLY RECURRENCE AFTER ATRIAL FIBRILLATION ABLATION; THE ABLATION EFFECTIVENESS QUOTIENT

5.1. INTRODUCTION

In earlier Chapters of this thesis I have examined the efficacy of catheter ablation (CA) of persistent atrial fibrillation (AF), both in the published literature and from our local experience. In Chapter 2 we found that, aside from CT image integration, there were no consistent predictors of clinical success. This is in keeping with previously published literature. The inability to either reliably identify those patients who are likely to do well after ablation, or to predict when acute success will be maintained in the longer term remains the procedure’s Achilles’ Heel. When patients with recurrence return to the catheter laboratory for a repeat procedure they are almost invariably found to have electrical conduction across an ablation lesion initially thought to be intact at the original procedure. Recent data have shown that ablation lesions in any given segment are only as effective as the ‘worst’ ablation performed in that segment. Cardiac Troponin T (cTnT) is released when myocardial cell death occurs and the level detectable in the bloodstream correlates with the mass of necrotic cardiac myocytes. Serum cTnT is the most reliable marker of myocardial damage after AF ablation. The high sensitivity assay (HScTnT) is an order of magnitude more sensitive than previously-available commercial assays. Theoretically it might be
expected that there would be a strong linear relationship between the amount of ablation performed and the post-procedural release of HScTnT and other cardiac specific biomarkers. However this is not always the case and studies have produced contradictory findings in terms of the relationship between cardiac Troponin levels post-PVI and clinical outcome. We postulated that this may be because some of the ablation lesions are ineffective due to poor tissue contact or ablation of previously ablated areas, and that the ratio of post-ablation HScTnT levels to the total ablation time would be a better indicator of the ‘quality’ of radiofrequency (RF) ablation delivered during the PVI procedure. We termed this novel ratio the Ablation Effectiveness Quotient (AEQ). We hypothesized that a high AEQ would correlate directly with freedom from early (<6 months) recurrence of AT.

5.2. Methods

5.2.1. Patients

The study population consisted of a subset of 60 patients undergoing first-time AF ablation at one of the contributory centers (Liverpool Heart and Chest Hospital) of the SMAN-PAF randomized controlled trial, presented in Chapter 4. Briefly, this is a prospective, two-way, multicenter randomized controlled single-blinded trial for patients with either persistent AF (PeAF) or sustained episodes of paroxysmal AF (PAF). Patients received either PVI alone (PVI), or PVI plus additional linear ablation (PVI+). Exclusion criteria included a reversible cause for AF, prior ablation for AF, prosthetic mitral valve replacement and hypertrophic or infiltrative cardiomyopathy. Patients with documented typical right atrial flutter were excluded as it was felt to be potentially unethical to randomize them to a PVI only strategy. Although included in the main trial,
patients with moderate or severe left ventricular systolic dysfunction on echocardiography were excluded from this study because of the possible effect on troponin levels.\textsuperscript{205}

### 5.2.2. Ablation Procedure

CA was performed under conscious sedation or general anesthesia in a standard manner.\textsuperscript{183} Following transseptal access, an electroanatomical map of the left atrium was created and, where available, integrated with a magnetic resonance (MR) or computed tomography (CT) reconstruction of the atrium using a 3D navigation system (CartoMerge; Biosense Webster, Diamond Bar, California). Using a 3.5 mm irrigated-tip radiofrequency ablation catheter (Thermcool or Thermcool Smarttouch; Biosense Webster, Diamond Bar, California) a series of lesions at least 2 mm outside the pulmonary vein (PV) ostia were made to encircle and electrically isolate the PVs in two ipsilateral pairs (wide area circumferential ablation (WACA))\textsuperscript{184} using a catheter drag technique with the end-point of individual lesions being >75\% signal attenuation. A 20-pole PV mapping catheter was used to confirm electrical isolation. In keeping with published guidance, pulmonary vein isolation was defined as proven entrance block with testing for exit block permitted but not mandated.\textsuperscript{14} Testing with adenosine was not routinely performed. If the patient was in AF at this stage, sinus rhythm was restored with intra-procedural electrical cardioversion and isolation of the PVs was confirmed in sinus rhythm. For those patients randomized to receive additional linear ablation lesions, these were delivered once PVI had been achieved. These consisted of a left atrial roof line, mitral isthmus line (including ablation inside the coronary sinus if necessary), and cavotricuspid isthmus ablation. The end point was conduction block across all three lines as verified with appropriate pacing manoeuvres.\textsuperscript{206} For all patients,
a minimum waiting time of 30 minutes from last PV isolation was mandated following complete isolation of the PVs before verification of PVI could be made. Acute procedural success was defined as electrical isolation of all PVs and bidirectional block demonstrated across any linear lesions. All patients were monitored overnight and discharged the following day.

5.2.3. Ablation Effectiveness Quotient (AEQ)

HScTnT was measured in all patients between 12 and 18 hours following the ablation procedure during which time period HScTnT levels have been described as having reached a stable peak. Baseline HScTnT measurements were performed in a random selection of patients at the time of recruitment. Blood samples were analyzed using the Elecsys electrochemiluminescence immunoassay (Cobas, Roche Diagnostics GmbH, Mannheim, Germany) in an accredited on-site diagnostic laboratory. The assay employs two monoclonal antibodies specifically directed against human cTnT and provides a precise and reliable measure of cardiac myocyte necrosis. Ablation time was recorded automatically by the electrophysiology recording system (LabSystem Pro, BARD Electrophysiology, MA). AEQ was defined as the ratio of HScTnT, measured in ng/L, to total ablation time, measured in seconds.

5.2.4. Follow-up and arrhythmia monitoring

All patients received anti-arrhythmic drug therapy with either amiodarone or flecainide for at least 6 weeks before their ablation and this was continued for six weeks after, at which point it was stopped. Mandatory study follow-up visits were performed at three and six months post-ablation and additional clinical visits were permitted as required. A 12-lead resting ECG and 24 hour ambulatory ECG (Holter) monitoring were performed
at all study visits. Additional 7-14 day symptom-activated ambulatory ECG monitoring was performed as required for patients with intercurrent symptoms suggestive of AT. Monitoring ECG traces were assessed initially by an experienced cardiac physiologist and then reviewed by a clinician. In case of uncertainty, a second review was performed by an experienced electrophysiologist. All assessors were blinded to treatment allocation.

5.2.5. STUDY ENDPOINT

The primary endpoint was defined as documented AT (AF or other atrial tachyarrhythmia) at six months following a single procedure. In accordance with published guidance, an episode of AT had to last more than 30 seconds and be documented on resting or ambulatory ECG to qualify as a primary endpoint. Episodess of AT occurring entirely and solely within three months of the index ablation procedure were not counted as recurrence of AF.

5.2.6. STATISTICAL ANALYSIS

Analyses were performed using IBM SPSS Statistics software version 21 (IBM Corp., Armonk, New York). Continuous data are presented as mean ± standard deviation and compared using unpaired t-tests or median (interquartile range) and compared using Mann-Whitney U test. Categorical data are presented as number and proportions and were compared using the χ² statistic or Fisher’s exact test if expected frequencies were too small for χ² (less than 5 for any individual cell). Linear regression was used to compare the relationship between HScTnT and ablation time and logistic regression was used to compare the relationship between each of these variables and the primary outcome. Correlation was assessed using Pearson’s correlation coefficient. The
Receiver Operating Characteristic (ROC) was used to assess the potential for AEQ to predict clinical outcome. Where applicable, two-tailed tests were used in all analyses. A $P$ value of 0.05 or lower was considered significant for all tests.

5.3. Results

5.3.1. Patient characteristics

Sixty patients were included in the study. Their baseline characteristics are shown in Table 5-1. Forty-two patients (70%) were male and 22 (37%) had PAF. The mean age was 62.5 years (range 40-87). All patients were white Caucasian. All 240 pulmonary veins were successfully isolated at the time of the index ablation. It was not possible to achieve bidirectional block across the mitral isthmus line in four patients (three without recurrence, one with) nor across the left atrial roof line in two patients (neither of whom had arrhythmia recurrence). Overall the rate of acute procedural success, defined as isolation of all veins and bidirectional block across any attempted linear lesion was 90%. Within the follow up period of the study, 20 patients (33%) had a documented arrhythmia recurrence and 40 patients (67%) did not. Mean creatinine was equal in both groups ($0.99\pm0.17$ v. $0.99\pm0.22$, $P=0.97$) and no patient had an estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73m$^2$. The mean baseline HScTnT level was $6\pm2.1$ng/L and none had a level above the upper reference limit (99th percentile) for the high sensitivity assay (14 ng/L). Performance of intraprocedural DC cardioversion had no significant effect on the mean post-ablation HScTnT level ($1388\pm788$ ng/L vs. $1251\pm594$ ng/L, $P=0.45$).
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=60)</th>
<th>Recurrence (n=20)</th>
<th>No Recurrence (n=40)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.5±10.6</td>
<td>63.1±11.2</td>
<td>62.3±10.1</td>
<td>0.79</td>
</tr>
<tr>
<td>Male Sex</td>
<td>42 (70.0%)</td>
<td>14 (70%)</td>
<td>28 (70%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Paroxysmal Atrial Fibrillation</td>
<td>22 (36.7%)</td>
<td>9 (45%)</td>
<td>13 (32.5%)</td>
<td>0.34</td>
</tr>
<tr>
<td>Left Atrial size (mm)</td>
<td>42.3±6.2</td>
<td>43.9±5.8</td>
<td>41.5±6.3</td>
<td>0.17</td>
</tr>
<tr>
<td>Body Mass Index (Kg/m²)</td>
<td>29.5±4.6</td>
<td>29.8±6.0</td>
<td>29.4±3.4</td>
<td>0.76</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL)</td>
<td>0.99±0.21</td>
<td>0.99±0.17</td>
<td>0.99±0.22</td>
<td>0.97</td>
</tr>
<tr>
<td>Hypertension</td>
<td>35 (58.3%)</td>
<td>9 (45%)</td>
<td>26 (65%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3 (5.0%)</td>
<td>1 (5.0%)</td>
<td>2 (5.0%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>CHA²DS²-VASc</td>
<td>1 (1-2.5)</td>
<td>1.5 (0.5-2)</td>
<td>1 (1-3)</td>
<td>0.87</td>
</tr>
<tr>
<td>HScTnT (ng/L)</td>
<td>1307±675</td>
<td>1175±706</td>
<td>1372±658</td>
<td>0.29</td>
</tr>
<tr>
<td>Ablation time (secs)</td>
<td>3237±1245</td>
<td>3428±1336</td>
<td>3171±1205</td>
<td>0.46</td>
</tr>
<tr>
<td>PVI only</td>
<td>29 (48.3%)</td>
<td>9 (45.0%)</td>
<td>20 (50.0%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Waiting time (minutes)</td>
<td>58.3±25.2</td>
<td>53.0±20.6</td>
<td>60.0±27.4</td>
<td>0.27</td>
</tr>
<tr>
<td>Intraprocedural DCCV</td>
<td>24 (40.0%)</td>
<td>11 (55.0%)</td>
<td>13 (32.5%)</td>
<td>0.09</td>
</tr>
<tr>
<td>General anaesthesia</td>
<td>16 (26.7%)</td>
<td>6 (30%)</td>
<td>10 (25.0%)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Table 5-1: Baseline characteristics for AEQ analysis. Continuous variables are presented as mean ± standard deviation or median (interquartile range); discrete variables as n (%). PVI: Pulmonary Vein Isolation, HScTnT: High sensitivity Cardiac Troponin T, AEQ: Ablation Effectiveness Quotient, DCCV: Direct current cardioversion.
5.3.2. **Primary outcome**

Mean AEQ was significantly lower in those with recurrence (0.35±0.14 ng/L/s) than those with clinical success (0.45±0.18 ng/L/s, *P*=0.02). Although there was a positive linear relationship between HScTnT and ablation time as assessed by Pearson correlation, the correlation coefficient was only moderate (*r*= 0.512). There were no significant differences in the mean HScTnT levels and mean ablation times in patients who had AT recurrence compared to those who did not (Table 5-1). Univariate logistic regression showed that AEQ was the only significant predictor of AT recurrence (*P*=0.03) (Table 5-2).
<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.01 (0.96-1.06)</td>
<td>0.78</td>
</tr>
<tr>
<td>Body Mass Index (Kg/m²)</td>
<td>1.02 (0.89-1.18)</td>
<td>0.76</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL)</td>
<td>1.06 (0.72-15.49)</td>
<td>0.97</td>
</tr>
<tr>
<td>Paroxysmal atrial fibrillation</td>
<td>1.70 (0.57-5.11)</td>
<td>0.35</td>
</tr>
<tr>
<td>Left Atrial Size (mm)</td>
<td>1.07 (0.97-1.17)</td>
<td>0.17</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc Score</td>
<td>0.94 (0.61-1.44)</td>
<td>0.94</td>
</tr>
<tr>
<td>PVI only</td>
<td>0.82 (0.28-2.40)</td>
<td>0.72</td>
</tr>
<tr>
<td>Waiting time (mins)</td>
<td>0.99 (0.96-1.01)</td>
<td>0.26</td>
</tr>
<tr>
<td>Ablation Time (per 100 secs)</td>
<td>1.02 (0.97-1.06)</td>
<td>0.31</td>
</tr>
<tr>
<td>HScTnT (per 100 ng/L)</td>
<td>0.95 (0.87-1.04)</td>
<td>0.29</td>
</tr>
<tr>
<td>AEQ (per 0.01 ng/L/s)</td>
<td>0.96 (0.92-0.99)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Table 5-2: Univariate logistic regression analysis for predictors of recurrence of atrial tachyarrhythmia after atrial fibrillation ablation. PVI: Pulmonary Vein Isolation, HScTnT: High sensitivity Cardiac Troponin T, AEQ: Ablation Effectiveness Quotient

5.3.3. **Comparison of ablation strategies**

Patients who underwent PVI plus linear ablation (PVI+) had both higher mean ablation times (4135±980 vs. 2361±839 secs, \(P<0.001\)) and HScTnT levels (1619±733 vs. 1619±733 vs. ...
954±394 ng/L, $P<0.001$) than those who underwent PVI alone. There was no difference in mean AEQ for patients having PVI alone compared to PVI+; either overall (0.43±0.16 (PVI) vs. 0.40±0.19 (PVI+), $P=0.6$), or grouped by whether they had recurrence (0.36±0.11 (PVI) vs. 0.34±0.17 (PVI+), $P=0.7$) or clinical success (0.46±0.18 (PVI) vs. 0.45±0.19 (PVI+), $P=0.9$).

5.3.4. Comparison with contact force readings

For the 20 patients for whom contact force data was available the mean contact force during ablation was 11.2±4.3g. There was no significant correlation between average contact force and AEQ ($P=0.14$). In addition the mean contact force was not statistically different for those patients in the success group from those with recurrence (11.0 ± 5.2g vs. 11.8 ±2.8g, $P=0.69$).

5.3.5. Repeat procedures

Twelve patients with recurrence underwent repeat ablation. Of these, eleven had reconnection of at least one pulmonary vein and only one patient, who had a history of PeAF and had received PVI only, had persisting isolation of all four pulmonary veins. This patient had an AEQ of 0.47, compared to a mean AEQ of 0.36±0.16 for the 11 patients with PV reconnection.

5.3.6. Sub-group analysis

Sub-group analysis was performed by AF type. In patients with PeAF, there was no difference in mean AEQ between those with and without recurrence (0.39±0.17 vs. 0.44±0.18 ng/L/s, $P=0.44$). However, in PAF patients, mean AEQ was significantly lower for those with recurrence compared to those without (0.30±0.07 vs. 0.49±0.18 ng/L/s, $P=0.003$, Figure 5-1). Logistic regression was performed for the sub-group with PAF,
using the same range of covariates as for the full cohort. As in the full cohort, AEQ (OR [per 0.01 ng/L/s] 0.87 (95% CI 0.78-0.98) p=0.02) was the only significant univariate predictor, with all other covariates failing to show significance.

Figure 5-1: Box and Whisker chart of AEQ and early recurrence of atrial tachyarrhythmia in patients with paroxysmal atrial fibrillation. Thick line represents the median value, the box represents the interquartile range and whiskers represent inner fences (1.5x box height). Cases outlying the inner fences are marked with open circles.

5.3.7. EXTENDED FOLLOW UP

Having established that AEQ appears of value in PAF, but not in PeAF, we extended the follow up of patients with PAF to twelve months post ablation. During this medium term follow up period one additional patient had AT recurrence. Mean AEQ was significantly
lower in those with recurrence at 12 months (0.33±0.12 ng/L/s) than those with clinical success (0.48±0.18 ng/L/s, P=0.035).

5.3.8. AEQ TO PREDICT CLINICAL OUTCOME IN THE MEDIUM TERM IN PAROXYSMAL AF

For the cohort with PAF, the ability of AEQ to predict AT recurrence was assessed using ROC analysis. The area under the curve (AUC) was very high both at six months (0.88) and with extended follow up to twelve months (0.80, Figure 5-2) suggesting good discriminative ability at both time points. Nine of twelve patients with an AEQ below 0.4 ng/L/s had recurrence. In contrast, AT occurred in only one of the 10 patients with a higher AEQ. An AEQ cut-off value of >0.4 ng/L/s had a sensitivity of 75% (95% CI 0.43-0.93) and a specificity of 90% (95%CI 0.54-0.99) in predicting freedom from recurrence in PAF (positive predictive value 90% (95%CI 0.54-0.99) negative predictive value 75% (95% CI 0.43-0.93)) although the small sample size means these figures should be treated with caution.
Figure 5-2: Receiver Operating Characteristic (ROC) curve for AEQ as a predictor of freedom from recurrence of atrial tachyarrhythmia over 12 month follow up in patients with paroxysmal atrial fibrillation.

5.4. DISCUSSION

Achieving durable electrical isolation of the PVs is the goal of most AF ablation procedures. Although acute PV isolation can be achieved in almost all cases, it is unusual to find no evidence of return of PV conduction at the time of repeat procedure for patients with AT recurrence. The major contributory factor to PV recovery is thought to be ineffective ablation producing extracellular oedema that mimics tissue necrosis but produces only temporary electrical changes. In contrast, cTnT is only released following irreversible cell death. The concept of AEQ stems from the idea that effective ablation lesions are likely to be those where rapid cell death occurs before
the formation of significant edema. Such lesions would be expected to have a higher chance of being transmural and observed electrical endpoints more likely to be permanent. Our results do appear to support this novel hypothesis.

Our results strike accord with recent findings from the EFFICAS 1 study which suggested that an initial non-transmural ablation lesion may make it difficult to achieve transmurality with further ablation at the same site. At present our results can be considered only proof-of-concept and require validation in larger populations. However AEQ is a novel, simple measure which provides new insight into why AF ablation succeeds or fails and may, eventually, be a useful clinical tool.

At the time of the procedure, the integrity of any linear or encircling ablation lesion is based on the extent to which it is possible to demonstrate that electrical conduction across the lesion no longer occurs. The limitation is that it is not truly possible to test the integrity of an ablation lesion until the entire lesion set is complete. By that point edema is already likely to have developed at points of ineffective ablation and repeated attempts to re-ablate these areas may not result in true long-lasting transmurality. Indeed, the EFFICAS 1 study found that the average number of ablations per segment was inversely correlated with isolation. If the initial lesion is not transmural, edema occurs that not only mimics tissue necrosis in terms of acute electrical isolation but also increases wall thickness by up to 100%. This tissue swelling reduces the effect of tissue heating and makes it difficult to achieve full transmurality with subsequent ablations. Neuzil and colleagues recently stated that the goal of any RF ablation should be to achieve transmurality with the first attempt but as yet there is no means of ensuring or measuring this. Whilst AEQ cannot be used to ensure the quality of ablation in real time it may be a way of assessing it subsequently.
Our study shows that AEQ correlates very well with early clinical success in patients with PAF, but not in patients with PeAF. The reason for this discrepancy most probably relates to the abnormal atrial substrate that is more prevalent in the latter. In PAF, isolating the PVs effectively eliminates arrhythmia triggers. However, in PeAF even effectively delivered ablation lesions around PVs will not target the variety of extrapulmonary triggers, re-entrant wavelet circuits and rotors that may be important in this population. Only one of our patients was observed to have persisting isolation of all PVs at the time of his repeat procedure for recurrence. It is a notable observation that this patient had PeAF and a relatively high AEQ of 0.47, illustrating that even effective ablation, both in terms of AEQ and enduring lesions, in this group of patients may not guarantee freedom from recurrence.

The ablation time is a fairly crude measure of amount of RF energy delivered. The development of catheter contact force technology and software developments within electroanatomical mapping systems allow measurement of the force-power-time integral which may provide further refinement to the AEQ concept. In our study we found no relationship between average contact force and either AEQ or clinical success. This is likely to be due, at least in part, to the manner in which contact force data was recorded. Ablation markers were placed onto the electroanatomical map manually and these recorded only the contact force at the moment the marker was created. They therefore capture only a very limited snapshot of the true lesion being delivered. A more accurate mean of recording lesion contact force may well have yielded different results. Our ongoing study using a new facet of the Carto 3 mapping system, Visitag, will allow further exploration of the relationship between AEQ and both the total energy
delivered (cumulative force-power-time) as well as the quality of lesions at repeat electrophysiology study for both those with and without clinical recurrence of AF (http://clinicaltrials.gov/show/NCT01942408). In addition only a small number of patients were included in this post-hoc subanalysis which substantially reduces its power to detect a significant result. Our abovementioned prospective validation study should provide much greater clarity of this issue.

5.4.1. Potential clinical implications

The lack of durability of PVI continues to be an important issue that impacts on single-procedure success rates. At present there is no way to identify those patients acutely following ablation whose PVI is likely to endure and thus who are likely to remain arrhythmia-free on follow up. Our study provides a preliminary investigation into the potential of AEQ in this regard. However, it appears that patients with PAF with high AEQ are at considerably lower risk of AF recurrence. If our findings are confirmed in future studies, it may be that patients with high AEQs can be discharged after only limited follow-up. This would be both economically beneficial and reassuring to patient and physician alike. Conversely, it may be that patients with a low AEQ should be monitored more intensively and have a low threshold for further interventional therapy. It may be preferable to maintain anti-arrhythmic and/or anticoagulant therapy in the long-term in these patients.
5.4.2. Limitations

This was an exploratory study of a novel hypothesis regarding how we define an effective ablation lesion, in the setting of a procedure that has almost universal acute success but considerable rates of late failure in terms of arrhythmia recurrence. As such, at this stage it has to be considered as hypothesis generating until verified in larger, more uniform cohorts. That notwithstanding, the fact that such a simple measure can produce significant results seems, to us, worthy of further study and discussion. The simplicity of AEQ is also a potential weakness. If all but one of the RF lesions along the WACA are effective and transmural, the AEQ would be expected to be high even if the one suboptimal RF application subsequently resulted in vein reconnection and recurrent arrhythmia. Conversely, even if the entire WACA lesion set has been completed effectively in the ‘first-pass’, considerable unnecessary ablation could still be delivered subsequently, thereby lowering the AEQ. This might happen if there is initial failure to recognize a far-field signal as such in an isolated vein, or while performing extra-PV ablation in a patient with purely PV-trigger driven AF. This limitation may partially explain the inconsistent outcomes for patients with moderate to low AEQ levels in our study. Assessment of myocardial scar within the left atrium and of ablation lesion quality by cardiac magnetic resonance scanning may have provided additional useful information. However, at present these techniques have not been shown to be reliable or reproducible.\(^{216}\) A significant proportion of our study patients underwent electrical cardioversion during their PVI procedure. Although this may have had a minor influence on troponin levels we did not find evidence of this, in keeping with previous work.\(^ {204}\) Although we measured baseline HScTnT in only a small sample of our patients, the magnitude of the levels seen after ablation compared to the low levels found in a normal population (<14ng/L) and the levels we found at baseline (6±2.1ng/L) means
that variations in baseline levels are likely to have had negligible impact on post-procedural HScTnT level and therefore on AEQ. Our findings show that the relationship between AEQ and clinical success is much stronger in PAF than PeAF. Future work, such as the ongoing study mentioned above, which minimizes patient heterogeneity, may allow clearer understanding of the relevance of the AEQ.

5.5. Conclusion

The AEQ is a simple, novel means of assessing lesion quality after AF ablation. In patients with PAF, a high AEQ appears to correlate well with freedom from early AF recurrence. Short term results appear to be maintained to at least one year post ablation.
6. IMPROVING PATIENT OUTCOMES BY IMPROVING SAFETY: A PROSPECTIVE STUDY OF THE USE OF ULTRASOUND TO GUIDE VASCULAR ACCESS FOR CATHETER ABLATION FOR ATRIAL FIBRILLATION

6.1. INTRODUCTION

In earlier Chapters of this thesis I have concentrated on the outcome of freedom from recurrent AF. However, as discussed in the thesis introduction, this is not the only outcome of relevance to patients. In 2012 the European Society of Cardiology clearly stated in their updated guidelines on the management of AF that, “improving safety of catheter ablation should be a primary goal in the further development of this therapy”\textsuperscript{51}. As mentioned previously, two large worldwide surveys of the methods, efficacy, and safety of catheter ablation (CA)\textsuperscript{147,148} published in 2005 and 2010 showed a dramatic increase in the number of CA procedures being performed over this period. This increase in operator experience, accompanied by improved techniques and technology, led to a reduction in the overall procedural complication rate from 5.9% to 4.5%. However, complications relating to vascular access actually increased from 0.9% to 1.5% of procedures. Vascular complications were also the most frequently observed in the SMAN-PAF trial, presented in Chapter 4. Furthermore published surveys/registries reported only the most serious of vascular complications, unavoidably leading to an underreporting of the true incidence. A previous study found that physicians significantly underreported procedural complications when compared to what patients
themselves perceived (4.5% v. 24%) and that patient reported complication rate rose even further (32%) if post-discharge reporting was encouraged\textsuperscript{217}.

The use of two-dimensional ultrasound has become standard practice within fields such as anaesthesia and nephrology to improve the safety and success rates of venous cannulation\textsuperscript{218}. Three prospective studies using ultrasound compared to an anatomical approach have all showed reduced complications and improved success rates in a diverse spectrum of patients\textsuperscript{219-221}. A number of retrospective studies showed improved procedural outcomes, such as time to cannulation or successful cannulation and non-significant trends towards reduced complications\textsuperscript{222-224}. None showed any detrimental effect of ultrasound guidance. A summary of published studies is provided in Table 6-1. Vascular ultrasound has not, however, been widely adopted in interventional electrophysiology and consequently there are no studies investigating its potential safety benefits for CA.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>Population</th>
<th>N</th>
<th>Outcome</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farrell 1997</td>
<td>Retrospective</td>
<td>Dialysis (IJV)</td>
<td>69</td>
<td>First attempt</td>
<td>83% v 36% P&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dialysis (FV)</td>
<td>30</td>
<td>First attempt</td>
<td>86% v 56% P=NS</td>
</tr>
<tr>
<td>Iwashima 2008</td>
<td>Prospective, non-</td>
<td>Paeds (FV)</td>
<td>87</td>
<td>Art puncture</td>
<td>7% v 32% p&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>randomised</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kwon 1997</td>
<td>Prospective with historical</td>
<td>Dialysis (FV)</td>
<td>66</td>
<td>First attempt</td>
<td>93% v 55% P&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hilty 1997</td>
<td>Prospective RCT</td>
<td>CPR (FV)</td>
<td>20*</td>
<td>Success</td>
<td>90% v 65%, P = 0.06</td>
</tr>
<tr>
<td>Prabhu 2010</td>
<td>Prospective RCT</td>
<td>Dialysis (FV)</td>
<td>110</td>
<td>Complication</td>
<td>6% v 18% p=0.04</td>
</tr>
<tr>
<td>Dudeck 2004</td>
<td>Prospective RCT</td>
<td>Angiography</td>
<td>112</td>
<td>Complications</td>
<td>NS difference</td>
</tr>
<tr>
<td></td>
<td>(FA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weak pulse</td>
<td>42</td>
<td>Attempts</td>
<td>1.8 v 3.1 p &lt; 0.05 NNT = 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leg &gt;60cm</td>
<td>23</td>
<td>Attempts</td>
<td>1.0 v 2.3 p &lt; 0.001 NNT = 2</td>
<td></td>
</tr>
<tr>
<td>Zollo 2001</td>
<td>Retrospective</td>
<td>Dialysis (FV)</td>
<td>230</td>
<td>Art Puncture</td>
<td>2.6% v 11.2%**</td>
</tr>
<tr>
<td></td>
<td>(anat) v 38 (US)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Haematoma</td>
<td>0%</td>
<td></td>
<td>0% v 3.9%</td>
<td></td>
</tr>
<tr>
<td>NICE TAG 49</td>
<td>Review/ Guideline</td>
<td>Pooled (IJV)</td>
<td>Complications</td>
<td>57% RRR, 95% CI 13% - 78%, p = 0.02</td>
<td></td>
</tr>
</tbody>
</table>

Table 6-1: Studies of the use of vascular ultrasound to assist cannulation of the Femoral (FV) or Internal Jugular Vein (IJV). Where specific p values are stated as NS (not significant) this reflects manuscripts that did not report numeric values. RCT = Randomised controlled trial. * Patients had bilateral line insertion and acted as their own controls

We hypothesized that the conventional definition of vascular complications underestimates the true incidence of patient-reported significant vascular access events
following CA, and that the routine use of ultrasound to guide venous access would
decrease the incidence of these events.

6.2. METHODS

We prospectively studied consecutive patients undergoing CA at our centre over a 10-
month period. In the first phase of the study performed from May 2012 to Sept 2012,
vascular access was performed as per standard technique (Group S). The second phase
of the study was performed from Oct 2012 to Feb 2013 and mandated the use of
ultrasound for vascular access for all patients (Group U). In every other way the CA
technique and peri-procedural patient management was identical in the two phases.
The ablation procedures were performed under general anaesthesia or intravenous
conscious sedation (fentanyl and midazolam). After transseptal access had been
successfully achieved intravenous unfractionated heparin was administered to target an
Activated clotting time (ACT) of greater than 300 seconds. Patients with persistent AF
were routinely anticoagulated with warfarin for a period of at least four weeks pre-
procedure to ensure a stable International Normalized Ratio (INR) of between 2.0 and
3.5. Patients with a sub therapeutic INR at the time of the procedure were treated with
subcutaneous enoxaparin post procedurally using a standardized protocol (1 mg/Kg on
the day of the procedure, then 1.5mg/Kg OD) until their INR levels reached 2.0. Patients
with paroxysmal AF were either anticoagulated with warfarin peri-procedurally or
administered dabigatran postoperatively having been left anticoagulant naïve pre-
procedurally.
6.2.1. Vascular Access

Vascular access was via the right femoral vein unless this route was inaccessible or unachievable. Three sheaths were inserted for catheters in the coronary sinus, and for ablation and circular mapping catheters in the left atrium. In a small proportion of patients, a fourth sheath was inserted to allow placement of a diagnostic catheter in the right atrium. In patients in Group S, the default method for locating the femoral vein was based on conventional surface anatomical landmarks and palpation of the femoral arterial pulse. Vascular ultrasound was not routinely used, but was permitted without restriction by protocol if considered necessary by the operator because of predicted or unexpectedly encountered difficulties using the anatomical approach. The use of multiple guide wires via a single sheath was permitted but not used for any study patient. The femoral artery was not used for invasive blood pressure monitoring. This represents standard practice at our institution.

Patients in Group U received routine ultrasound-guided vascular access. It was mandated that operators used real-time 2-dimensional vascular ultrasound (SonoSite SICU™, Fujifilm Sonosite Inc, Washington, USA) to guide cannulation of the femoral vein. The ultrasound probe (10-5MHz) was covered in a sterile sheath and sterile ultrasound gel was placed both between the probe and the sheath, and the sheath and the patient’s skin. The probe was held in the operator's non-dominant hand with the ultrasound beam orientated perpendicular to the femoral vessels allowing them to be seen in cross section (Figure 6-1). Initial cannulation was performed under direct visualisation, so that the path of the modified-Seldinger needle was observed passing into the vein, accompanied by aspiration of venous blood into the syringe. Once a guide wire had been placed in the vein using ultrasound guidance, it was left to the operator's own
preference whether to use it for subsequent punctures. The reasons for this were
twofold. Firstly, the guide wire produces acoustic shadowing and, on occasion, makes it
difficult to avoid trapping air between the skin and the probe. Both of these issues
reduce the quality of the obtainable ultrasound image. Secondly, the guide wire
provides the operator with a direct, physical marker of the location of the vein that can
be used to guide subsequent punctures.

In both groups, at the end of the procedure the sheaths were removed with the patient
still on the operating table and manual pressure applied to the puncture site until
haemostasis was achieved. Reversal of anticoagulation with intravenous protamine was
permitted at the operator’s discretion.

![Figure 6-1](image)

**Figure 6-1**: Left Panel: Two-handed technique for gaining venous access under ultrasound guidance. Right
panel: Representative image of the femoral vasculature. The femoral artery (FA) is non-compressible and has
a circular cross-sectional appearance. The shape of the femoral vein (FV) is variable and can be altered by
compression. The echo-bright needle tip (arrows) can be seen entering the vein at the 2 o’clock position,
distorting the vessel wall as it enters.
Before commencing the second phase of the study operators were trained in the use of vascular ultrasound using prosthetic phantoms (simulation) and over a two-week period during live cases. Training cases were excluded from analysis. All operators were competent and experienced at gaining femoral access using an anatomical approach before the initiation of the study, with each having performed greater than 100 prior procedures.

Data on vascular complications were collected at three time points; immediately following the procedure, at the time of hospital discharge and at one month post-procedure by means of a bespoke postal questionnaire. The pre-specified primary outcome measure evaluated was overt (BARC 2 or greater) bleeding complications. Secondary measures, as assessed by the follow up patient questionnaires, were prolonged groin pain and prolonged (>2 weeks) bruising.

The BARC (Bleeding Academic Research Consortium) Criteria are standardised bleeding definitions for cardiovascular clinical trials, developed by consensus amongst an expert group and adopted by the European Society of Cardiology as an appropriate means by which to quantify bleeding complications in conditions such as acute coronary syndrome and percutaneous coronary intervention. There are 6 (0-5) BARC levels. Neither BARC 4 (Coronary Artery Bypass related) nor BARC 5 (fatal) bleeding was encountered during the study. BARC 0 indicates no bleeding, BARC 1 is bleeding that is not actionable and does not cause the patient to seek additional attention while BARC 2 bleeding is clinically overt bleeding that is actionable (requiring intervention by a health care professional, leading to or prolonging hospitalization or increased level of care, or prompting testing or treatment) but does not meet criteria for a higher category. BARC
3 bleeding for the purpose of this study represented bleeding requiring transfusion. We classified an overt bleeding complication as one meeting the criteria for either BARC 2 or greater. Patients due to have combined venous and arterial access, for example for concomitant coronary angiography were prospectively excluded.

The study received prospective institutional approval as a Quality Improvement Project, in accordance with published guidance\textsuperscript{229}. All patients gave written informed consent.

6.2.2. Statistical analysis

All data were analysed on an Intention to Treat basis. Analyses were performed using IBM SPSS Statistics software version 20. Continuous data are presented as mean ± Standard Deviation and compared using unpaired t-tests. Binary categorical data were compared using the $\chi^2$ statistic and the Mann-Whitney U test was used to compare the number of sheaths used. Univariate and multivariable predictors of bleed were examined using logistic regression. Variables with a p-value of less than or equal to 0.1 were included in the multivariable model, and if necessary to maintain a minimum of 10 events per variables, were selected on a hierarchical basis\textsuperscript{146}. Where applicable, two-tailed tests were used in all analyses. A p value of 0.05 or lower was considered significant for all tests.

6.3. Results

6.3.1. Patients

We studied 146 consecutive patients in Group S and 163 consecutive patients in Group U. Two procedures in Group U were performed without ultrasound guidance due to protocol deviation and in one case ultrasound use was abandoned in favour of an
anatomical approach. All three were included in the intention to treat analyses. Follow up questionnaires were received from 92.6\% of patients (n = 138 (Group S) v. 148 (Group U), p = 0.1).

6.3.2. Baseline characteristics

The two groups were well matched at baseline. Characteristics for each group are given in Table 6-2. The majority of patients were male (72.5\%) with a mean age of 58.9±10.2 years. A regime of uninterrupted warfarin therapy was used for 70.2\% of patients (Group S 109 (74.7\%), Group U 108 (66.3\%), p = 0.11) with a mean INR of 2.2 and was not either statistically or clinically different between the study groups (Δ 0.15, p = 0.07). Bridging therapy for Enoxaparin was used for only two patients and all other patients were anticoagulated only post-procedure (Group S 37 (25.3\%), Group U 53 (32.5\%), p = 0.17). Patients with persistent AF accounted for 29.8\% of the study population.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Group S (n=146)</th>
<th>Group U (n=163)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (n, % male)</td>
<td>100 (68.5%)</td>
<td>121 (74.2%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Age, years (mean, SD)</td>
<td>58.7 (±11.0)</td>
<td>59.1 (±9.6)</td>
<td>0.78</td>
</tr>
<tr>
<td>BMI (Mean, SD)</td>
<td>28.9 (±5.5)</td>
<td>29.1 (±4.3)</td>
<td>0.76</td>
</tr>
<tr>
<td>Redo Procedure (n, % yes)</td>
<td>49 (33.3%)</td>
<td>50 (30.9%)</td>
<td>0.64</td>
</tr>
<tr>
<td>Number of sheaths (median, range)</td>
<td>3 (2-4)</td>
<td>3 (2-4)</td>
<td>0.35</td>
</tr>
<tr>
<td>Uninterrupted warfarin (n, % yes)</td>
<td>109 (74.7%)</td>
<td>108 (66.3%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Protamine Use (n, % yes)</td>
<td>126 (85.7%)</td>
<td>147 (90.7%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Pre-procedure INR (Mean, SD)</td>
<td>2.15 (±0.44)</td>
<td>2.28 (±0.61)</td>
<td>0.07</td>
</tr>
<tr>
<td>Periprocedural LMWH use (n, % yes)</td>
<td>24 (16.4%)</td>
<td>28 (17.2%)</td>
<td>0.86</td>
</tr>
<tr>
<td>Peak ACT (mean, SD)</td>
<td>367 (±83)</td>
<td>382 (±114)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Table 6-2: Baseline Characteristics for the two groups in the study of ultrasound use

6.3.3. PRIMARY OUTCOME MEASURE

A BARC 2+ bleed was significantly less common in Group U (n=17, 10.5%) as compared to Group S (n=29, 19.7%) p=0.023. This absolute risk reduction (ARR) of 9.2% equated to a relative risk reduction (RRR) of 47.0%, and a number needed to treat (NNT) of 11 to prevent one bleeding event. There were no fatal (BARC 5) bleeds. BARC 3 complications occurred in two patients in Group S and in one patient in Group U.
Ultrasound use was permitted in Group S when access was either expected or found to be more difficult. Despite the fact that this was a selected high-risk group, none of the Primary Outcomes in Group S occurred whilst using ultrasound.

Of the 46 BARC 2+ bleeding complications seen in the study, 3 patients required blood transfusion (one retroperitoneal haemorrhage, two large localized haematomas within the adductor muscle group), 4 patients required hospital re-admission, 2 had unscheduled medical care following discharge but were not admitted to hospital and 36 patients required additional, unplanned and unanticipated intervention to achieve haemostasis after leaving the catheter laboratory. Of these, 13 required a mechanical adjunct (e.g. Femostop device) and 23 required manual compression to suppress hematoma. One had a significant hematoma but no additional intervention. Where patients had more than one qualifying event they were categorized according to the above hierarchy. Non access site related bleeding complications were not included in any analysis.

6.3.4. Secondary outcome measures

Group U patients were significantly less likely to suffer groin pain after discharge (n=39, 27.1%) as compared to patients in Group S (n=59, 42.8%), p=0.006. This ARR of 15.7% and RRR of 36.7% translated to a NNT of 7. Patients in Group U were also less likely to require the use of analgesic medications after they had left hospital (n=14, 9.7%) as compared to Group S (n=34, 24.6%), p=0.001. The incidence of prolonged local bruising, lasting longer than two weeks, was also significantly lower in Group U (n=31, 20.5%) than in Group S (n=55, 40.4%) p=0.001.
Inadvertent arterial puncture, as recognised by the operator, was less common in Group U than Group S (10 (6.1%) v. 19 (13.0%), p=0.04. Patients with inadvertent arterial puncture were significantly more likely to experience a BARC 2+ bleed (p=0.002).

We did not specifically measure the time taken to gain vascular access but did retrospectively assess procedure duration using the hospital’s electronic database, supplemented by paper case notes when required. Procedures in Group U were significantly shorter than those in Group S, suggesting a potential indirect benefit of ultrasound use (184 ±53 min v. 167 ± 4 min, p=0.04).

6.3.5. Effect of learning curve

All clinicians received simulation and clinical training in the use of vascular ultrasound prior to the second phase of the study. For each procedure performed during the Ultrasound phase of the study, operators were asked their experience level with the technique (fewer than 5 cases, 5 to 10 cases, or greater than 10 cases). Nine cases in Group U were performed by operators with prior experience of fewer than 5 ultrasound-guided procedures. When compared to cases performed by operators with experience of 10 or more prior cases, there was a significant higher incidence of a BARC 2+ bleed (22.9% v. 8.0% p=0.03).

6.3.6. Predictors of BARC 2+ bleed

The results of univariate binary logistic regression to estimate the magnitude of risk of BARC 2+ bleeding associated with various patient and procedural variables are given in Table 6-3. Significant predictors of bleeding were increasing age (OR 1.05, 95%CI 1.01 – 1.09 p=0.008), inadvertent arterial puncture (OR 4.29, 95% CI 1.93 – 9.55 p<0.001) and non-ultrasound guided (i.e. anatomical) access method (OR 2.92, 95% CI 1.51 –
5.64, p=0.001). Approximately 80% of patients had 3 sheaths placed with a range of only 2-4. In two cases both groins were accessed, in other case requiring multiple sheaths these were all via a single vein. The modality of the sheath use variable precluded it from inclusion in the regression analysis. A Mann-Whitney U test confirmed that there was no significant relationship between number of sheaths used and the primary outcome.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(95% confidence</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interval)</td>
<td></td>
</tr>
<tr>
<td>Age (Years)</td>
<td>1.051 (1.013 - 1.091)</td>
<td>0.008</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>0.631 (0.327 - 1.218)</td>
<td>0.170</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>1.003 (0.938 - 1.073)</td>
<td>0.927</td>
</tr>
<tr>
<td>Paroxysmal AF (v. Persistent)</td>
<td>2.211 (0.984 - 4.966)</td>
<td>0.055</td>
</tr>
<tr>
<td>Access by Fellow (v. Consultant)</td>
<td>0.795 (0.422 – 1.498)</td>
<td>0.477</td>
</tr>
<tr>
<td>Periprocedural use of LMWH</td>
<td>1.048 (0.458 – 2.399)</td>
<td>0.912</td>
</tr>
<tr>
<td>Redo procedure (v. De novo)</td>
<td>0.543 (0.874 - 3.882)</td>
<td>0.109</td>
</tr>
<tr>
<td>Procedure Duration (mins)</td>
<td>0.998 (0.992 - 1.004)</td>
<td>0.515</td>
</tr>
<tr>
<td>Peak ACT (seconds)</td>
<td>0.998 (0.995 - 1.002)</td>
<td>0.369</td>
</tr>
<tr>
<td>Uninterrupted Warfarin use</td>
<td>0.964 (0.487 – 1.905)</td>
<td>0.915</td>
</tr>
<tr>
<td>INR (normalised units)</td>
<td>0.916 (0.420 - 1.999)</td>
<td>0.826</td>
</tr>
<tr>
<td>Post procedural Protamine use</td>
<td>0.543 (0.230 - 1.284)</td>
<td>0.165</td>
</tr>
<tr>
<td>Protamine Dose (Units)</td>
<td>0.999 (0.992 - 1.006)</td>
<td>0.798</td>
</tr>
<tr>
<td>Inadvertent Arterial Puncture</td>
<td>4.288 (1.926 - 9.550)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-ultrasound guided access</td>
<td>2.918 (1.509-5.643)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 6-3: Univariate regression analysis for predictors of a BARC2+ bleed
Multivariable regression analysis was performed using the pre-specified criteria detailed above. Results of the analysis are shown in Table 6-4. Having adjusted for potential confounding, only non-ultrasound guided access (OR 3.12, 95% CI 1.54 – 5.34, p=0.003), and increasing age (OR 1.05, 95% CI 1.01-1.09 p=0.02) remained significant predictors of a bleeding complication.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% confidence Interval)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadvertent arterial puncture</td>
<td>2.402 (0.974 - 5.923)</td>
<td>0.057</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>2.152 (0.925 - 5.008)</td>
<td>0.075</td>
</tr>
<tr>
<td>Age</td>
<td>1.046 (1.008 - 1.086)</td>
<td>0.018</td>
</tr>
<tr>
<td>Non-ultrasound guided access</td>
<td>3.121 (1.535 – 5.343)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Table 6-4: Multivariable logistic regression analysis for predictors of a BARC2+ bleeds

6.4. DISCUSSION

To our knowledge, this is the first study assessing the safety benefits of ultrasound guidance for femoral venous cannulation in CA and the largest such study in any discipline. Our data, collected in a true real-world setting, have shown the benefits of adopting a policy of using vascular ultrasound for all CA procedures. As well as significantly reducing the number of actionable (BARC 2/3) haemorrhages, there was also a clear reduction in the number of patients suffering groin pain after hospital discharge and in those with prolonged unsightly bruising, issues which may not be appreciated by physicians but may impact on a patient’s experience of the procedure. The magnitude of this protective effect of ultrasound appears to be sizeable; only 11 patients needed to be treated to prevent one bleeding complication and 7 to prevent ongoing groin pain after discharge. It is likely that the reduced risk of complications is
due to a reduction in the occurrence of inadvertent arterial puncture, some of which may not be recognized at the time. It is also possible that ultrasound allows ‘cleaner’ venous punctures through a reduced tendency to perforate the posterior venous wall with the modified-Seldinger needle. An important aspect of the use of ultrasound is to identify an access point at which the vein is most easily accessible without risk of damage to the artery so that, even if the vessels are overlying in one plane the operator can chose a different plane in which the vessels are better disassociated.

Because our endpoint included both BARC 2 and BARC 3 complications and we also included late complications that occurred in the month following discharge, our vascular complication rate, of almost 20% in Group S, seems very high at first glance. This endpoint was explicitly chosen in order to assess complications from the perspective of the patient rather than the physician. It has been described that physician-reported complication rates following PVI appear to miss the majority of vascular events considered important to patients\textsuperscript{217}. Our data in this study mirror that observation. BARC 3 complications occurred in only 3 patients (1%), in keeping with rates reported in large international registries \textsuperscript{147,148}.

We believe a universal policy of ultrasound use for all patients undergoing CA is preferable to attempts to select high risk patients. It is not possible to reliably identify those patients for whom an anatomical approach is entirely safe. Although all three patients with BARC 3 complications had a Body Mass Index (BMI) greater than 30 (with the patient in Group U having a BMI of 38), overall there was no association between BMI and the risk of a bleeding complication. Furthermore, variations in vascular anatomy cannot be predicted. This is supported by the results of our multivariable regression analysis where, apart from increasing age, only non-ultrasound guided
access was found to be significantly associated with the occurrence of a vascular complication. None of the published studies looking at ultrasound guided vascular access have reported any increased risk with use of ultrasound. These findings are in keeping with our own. In our opinion the balance of risk-benefit therefore appears firmly in favour of ultrasound use.

We did not specifically assess resource implications or cost effectiveness from our data. However, The UK National Institute for Health and Care Excellence (NICE) concluded that the additional cost of using ultrasound equipment for the CVC placement procedure is likely to be less than £10 [$16] per procedure\textsuperscript{226}. The same figure was reached in a separate cost effective analysis which concluded that ultrasound use was likely to be cost effective, with an approximate saving of £2000 ($3200) per 1000 procedures (2003 prices)\textsuperscript{230}. Furthermore, the potential for shortening the PVI procedure time by a combination of speedier vascular access at the start and shorter groin compression time at the end, as seen in our study, would be expected to have a favorable impact on precious catheter lab time.

6.4.1. LIMITATIONS

The most important limitation of this study is the non-randomised design. To mitigate this, we attempted to minimize selection bias by collecting data on 100\% of patients during the study period. However, as for any observational study we are inherently at risk of confounding and this limits the strength of conclusions that can be drawn. As a longitudinal cohort study, it is theoretically possible that the benefits seen in the ultrasound-guided phase of the study were exaggerated by a general improvement of vascular access skills. However all procedures were performed by highly experienced operators and so it is unlikely that this had a significant effect. This notwithstanding, the
use of any new tool has the potential to introduce operator bias. Second, our choice of BARC 2+ bleeding as our primary endpoint may be considered too broad. The reason for choosing this was based on the publication of standardised criteria for clinical trials. Also, although physicians may be most interested in avoiding life-threatening complications, the effect on patient wellbeing of "lesser" events can be significant. Furthermore our *a priori* calculations showed that to demonstrate a difference in potentially life-threatening (BARC 3+) complications, we would require an unfeasibly large sample size. Indeed, based on our results, an adequately powered study to look for a difference in BARC 3+ complications would require a sample size of around 5000 patients. Another possible limitation of the study is the lack of patient blinding. This was inevitable given that most procedures were performed under local anaesthesia and conscious sedation. However, in order to minimise potential bias the patient survey specifically avoided mentioning that comparison was being made between techniques. Finally, at our centre all operators perform venous access using a uniform technique. It is therefore not possible to say whether alternative techniques, such as a strategy utilizing both groins or with femoral arterial blood pressure monitoring, might have demonstrated greater or lesser benefit of ultrasound use.

6.5. **Conclusion**

In real-world practice, we found routine use of ultrasound guided vascular access during CA to be associated with a significant reduction in bleeding complications, post-procedural pain and bruising compared to standard care.
7. Improving Patient Outcomes by Better Understanding Quality of Life in Atrial Fibrillation: Validation and Improvement of the European Heart Rhythm Association Symptom Classification

7.1. Background

In the preceding chapters I have focussed on post ablation outcomes, both in times of procedural efficacy and safety. In Chapter 2 I found no pre-procedural demographic factors that predicted success after both a single and the final procedure. However, at present the indication for catheter ablation (CA) is the relief of symptoms over and above freedom from recurrent atrial fibrillation (AF).\textsuperscript{14} Because symptoms can be variable in severity, frequency and different patients may experience different combinations of symptoms, several systems have been proposed for categorisation and quantification.\textsuperscript{10,16,22,23} In this final results chapter I undertook the first retrospective and prospective validation of the most commonly used scoring system in Europe and, importantly, looked at how this may help to select appropriate patients for CA, based on the severity of their symptoms. Improving the tools available for patient selection means that those who are likely to benefit from CA are put forward for ablation, whereas those who are unlikely to benefit, but will still be exposed to the same risks, are not and thus the outcomes for both groups should improve.

In 2007 an expert group of the German Atrial Fibrillation Competence NETwork (AFNET) and the European Heart Rhythm Association (EHRA) published
recommendations for the conduct of clinical trials in AF\textsuperscript{162}. Noting that no accepted and easily applicable measure for AF-related symptoms exists, this group of experts proposed and described in their recommendations a new scoring system, the EHRA Classification, to assess and quantify symptoms related to AF.\textsuperscript{162} The EHRA classification is based on the impact of symptoms on daily activity during presumed episodes of AF. It is simple to use and has a format similar to the New York Heart Association (NYHA) symptom classification system for patients with heart failure, making it relatively intuitive for practicing clinicians whilst hopefully being more appropriate to AF-related symptoms.\textsuperscript{232} When the EHRA score was published the authors made specific mention of the need for validation.\textsuperscript{162} A similar score was thereafter validated by a Canadian group\textsuperscript{10}. Since its initial proposal, the EHRA score has entered widespread use and has even been used in European Society of Cardiology guidelines for the management of AF in the recommendations for rate and rhythm control.\textsuperscript{47,51,72,233-235}

To put the EHRA score into context with existing tools to assess disease-related quality of life in AF patients, we compared the EHRA Score to accepted and validated measures of health-related QoL. Specifically we used both a disease specific tool, the Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) questionnaire, and a general tool, the very well established EQ-5D questionnaire.\textsuperscript{178,236,237} The AFEQT is a well validated, patient-reported AF-specific symptom questionnaire and as such is very sensitive to changes in symptom burden but it cannot be compared with other conditions. EQ-5D, however, is applicable to a wide range of health conditions and provides a single index value for health status, called the health utility, which can be used to calculate ‘quality-adjusted life years’ (QALYs) for health economic evaluation.\textsuperscript{238} Previous studies have suggested that the minimal meaningful difference in EQ-5D derived health utility is 0.07.\textsuperscript{238} In line
with this, a previous study of the cost-effectiveness of catheter ablation in the UK setting found catheter ablation to be cost-effective with an estimated utility difference of 0.09 between symptomatic AF on drugs compared to sinus rhythm following ablation.\textsuperscript{239}

We aimed to validate the EHRA score using these general and disease-specific QoL measures. We hypothesised that the discriminative power of the EHRA score could be improved and attempted to achieve this through a simple modification.

7.2. Methods

7.2.1. Phase One

Consecutive patients with a diagnosis of AF attending designated heart rhythm/Electrophysiology clinics at a single specialist cardiac hospital in England (Liverpool Heart and Chest Hospital) were invited to complete the AFEQT questionnaire and EQ-5D instrument, including the VAS\textsuperscript{236,237}. At the same clinic visit, the reviewing clinician was asked to independently score the patient according to the EHRA symptom classification. In keeping with real-world practice, these assessments were completed by a range of clinicians experienced in the management of patients with AF, including consultant cardiologists, trainee physicians and arrhythmia nurses. Clinicians were provided with, and requested to complete, a classification form that listed the published definitions for each class. In order to replicate how the classification is likely to be used in routine practice, no specific training was provided beyond that described above and access to the original publication in which the EHRA score was proposed. This mirrored the methods used to validate an alternative classification system\textsuperscript{10}.

QoL was assessed by the AFEQT score (global), the health-related utility based on the EQ-5D instrument, and VAS. For each measure a higher score represents a higher
quality of life. AFEQT and VAS are scored from 0-100. Health utility (EQ-5D) ranges between 1 (perfect health) through 0 (death) to -0.59 (QoL worse than death, e.g. suffering so great that death is considered a “release”). Mean QoL scores were compared between neighbouring EHRA classes to assess the score’s accuracy in semi-quantifying QoL.

7.2.2. Phase Two

We proposed a modified EHRA (mEHRA) classification by subdividing Class 2 into 2a (mild) and 2b (moderate) according to the degree to which the patient was ‘troubled by their symptoms’ (Table 7-1). All patients categorised as Class 2 during Phase One of the study were independently re-categorised as either 2a or 2b by two clinicians (electrophysiology fellows) who were both blinded to the corresponding QoL scores. Clinic letters were reviewed with specific attention made to the extent to which the patients appeared ‘troubled by their symptoms’, given that their daily activities were not affected (which would indicate Class 3 symptoms). We sought to assess the patient’s own perception of the impact of AF on their well-being. Those suffering from anxiety, loss of confidence or symptoms that they found unpleasant were graded as 2b. There was agreement between the reviewers for all cases reclassified into mEHRA Class 2a and 2b. Where the clinical letters were lacking in detail, the hospital records were re-reviewed and a consensus agreed upon. The mEHRA score was assessed and validated using the same methods used to validate the EHRA score in the initial phase of the study.
<table>
<thead>
<tr>
<th>mEHRA Score</th>
<th>Symptoms</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>Normal daily activity not affected, symptoms not troublesome to patient</td>
</tr>
<tr>
<td>2a</td>
<td>Mild</td>
<td>Normal daily activity not affected, symptoms not troublesome to patient</td>
</tr>
<tr>
<td>2b</td>
<td>Moderate</td>
<td>Normal daily activity not affected but patient troubled by symptoms</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
<td>Normal daily activity affected</td>
</tr>
<tr>
<td>4</td>
<td>Disabling</td>
<td>Normal daily activity discontinued</td>
</tr>
</tbody>
</table>

Table 7-1: Modified EHRA (mEHRA) classification. Underlined text represents the modification to the original descriptions of EHRA classes.

7.2.3. Phase Three:

Having completed Phases One and Two we wished to verify and validate the findings from our retrospective scoring of the mEHRA score, by comparing our findings with an independent cohort in whom the mEHRA score had been used prospectively. The method of data collection for this phase matched exactly that in Phase One, except that clinicians were asked to classify symptoms according to the new, expanded, mEHRA score rather than the original EHRA score. We compared the prospective and retrospective scores, for the two new mEHRA classes, for each of the three QoL measures used in the previous two phases.

7.2.4. AFEQT Questionnaire

The Atrial Fibrillation Effect on Quality-of-Life (AFEQT) Questionnaire is a validated, disease-specific, self-administered QoL instrument. It has 20 questions with four conceptual domains: Symptoms (four questions specifically targeted to assess AF
related symptoms), Treatment Concerns (six questions that assess AF treatment concerns in patients), Daily Activities (eight questions that evaluate daily function in AF patients) and Treatment Satisfaction (two questions asking about how the well current treatment controls their AF and relieves symptoms). Each of the 20 questions is marked on a seven point Likert scale. A published algorithm exists to allow calculation of a score, between 0-100 (where higher is better), for each domain and a global score based on the first three domains. The questionnaire specifies a recall period of the preceding four weeks.

7.2.5. EQ-5D Questionnaire (3 Level Version)

EQ-5D is a standardised measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal.236 243 possible health states can be defined from the five questions and these can be converted into a single summary index called the 'health utility' based on country-specific value sets.240 The health utility measure is of particular interest as it is generalisable to other diseases and to the general population. Therefore, it allows the calculation of QALYs and therefore the cost effectiveness of interventions such as catheter ablation.

7.2.6. Visual Analogue Scale (VAS)

The VAS forms an integral but distinct part of the EQ-5D instrument. Respondents are asked to mark a single point on a linear scale that represents their health status on the day of completion. The scale extends from 0 (worst imaginable health state) to 100 (best imaginable health state). The VAS provides a quantitative measure of health state, as judged by the individual patients.
7.2.7. **Statistical analysis**

Analyses were performed using StatsDirect software version 2.7.8. Analysis of QoL scores (AFEQT score, EQ-5D derived utility and VAS) using the Shapiro-Wilk W test showed a non-Gaussian distribution that was not corrected by logarithmic transformation. However, the central limit theorem is generally taken to imply that an assumption of normality is not necessary for parametric testing to be valid if group sizes are greater than about 30. This is the case for all but one group in our analysis. In addition, presentation of data as means with standard deviation was adjudged to be of greater clinical relevance than presentation of medians with inter-quartile ranges. Continuous data are therefore presented as mean ± Standard Deviation and compared using the t-test. A similar approach has been used in previous work using QoL measures\(^{241}\). Two-tailed test were used where there was not an *a priori* expectation of the direction of difference between groups. However, where a comparison was made between two adjacent groups, resulting in assessment for a difference in a single direction only, one-tailed testing was considered more appropriate. Analysis of variance was compared using one-way ANOVA. Trend across groups was assessed using Cuzick’s test. Proportions were compared using the $\chi^2$ statistic. Intra- and inter-observer variability was calculated, and assessed using the Kappa statistic. A p value of 0.05 or lower was considered significant for all tests.

The study was performed as part of a wider institutionally-approved Patient Reported Outcome Measures (PROMs) service improvement programme at the recruiting centre.

7.3. **Results**

QoL and symptom data were collected on 362 patients attending the heart rhythm clinics during 2012. All patients received physician-allocated EHRA classification at the
same clinic visit. Baseline characteristics are given in Table 7-2. There were no clear
differences between the groups in terms of age, sex or proportion classified as having
paroxysmal, as opposed to persistent or permanent, AF. Previous studies have found
QoL to be lower in females\textsuperscript{242}. However, in our cohort patient gender did not have a
significant effect on any of the three QoL measures (EQ-5D p=0.56, VAS p=0.70, AFEQT
p= 0.14). Hypertension was by far the most common comorbid condition (48.6% of all
patients) and showed a significant trend towards increasing prevalence in higher EHRA
classes (p=0.003). Other comorbidities were infrequently present and were also similar
across Classes. However, there was a clear trend seen whereby those in less severe
symptom classes were the most likely to have previously undergone ablation and those
in the most severe classes were considerably more likely to subsequently go on to have
an ablation for atrial fibrillation (p<0.0001 for both). A small proportion of
asymptomatic patients went on to have an ablation in keeping with published data from
the EURObservation study where 13% of patients were asymptomatic, citing a desire
for drug free lifestyle, improved quality of life and/ or the maintenance of sinus
rhythm\textsuperscript{243}. 

Table 7-2: Baseline Characteristics by EHRA Class. NC = not calculated (where ANOVA revealed no significant variance between groups, a test for trend was not performed). †Predominant pattern at time of assessment.
COPD = Chronic Obstructive Pulmonary Disease, TIA = Transient Ischaemic Attack, PAF = Paroxysmal Atrial Fibrillation. * for trend

7.3.1. Phase One

Results for the three QoL measures are shown in Table 7-3 and Figure 7-1. Analysis of variance and regression analysis confirmed significant negative correlation between
EHRA Class and QoL as assessed by all three measures. To determine the ability of the EHRA classification as a semi-quantitative tool, each EHRA Class was compared with the Class immediately below in terms of QoL (i.e. EHRA 2 with EHRA 1, EHRA 3 with EHRA 2, and EHRA 4 with EHRA 3). Using the disease-specific AFEQT score, significant differences were seen at each grade boundary suggesting that the EHRA score was an effective means of categorising patients' symptoms. Likewise, using the patient-based VAS there was a significant difference between each and its immediate neighbour suggesting that the EHRA score effectively categorised patients in terms of their own assessment of their health state. However, when comparing health-related utility, derived from the EQ-5D questionnaire, although there was a significant difference of 0.12 (P<0.001) between Classes 2 & 3, the difference between Classes 1 & 2 was only 0.04 (p=0.08). This observation prompted us to develop the mEHRA classification.

<table>
<thead>
<tr>
<th>EHRA Class</th>
<th>Utility (by EQ-5D)</th>
<th>P value</th>
<th>VAS</th>
<th>P value</th>
<th>AFEQT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.85 (±0.21)</td>
<td>n/a</td>
<td>76.2(±19.9)</td>
<td>n/a</td>
<td>78.4 (±19.0)</td>
<td>n/a</td>
</tr>
<tr>
<td>2</td>
<td>0.81 (±0.17)</td>
<td>0.08</td>
<td>70.3 (±20.3)</td>
<td>0.02</td>
<td>63.6 &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.69 (±0.27)</td>
<td>&lt;0.001</td>
<td>59.6 (±21.9)</td>
<td>&lt;0.001</td>
<td>42.1 &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.59 (±0.29)</td>
<td>0.08</td>
<td>46.9 (±25.9)</td>
<td>0.03</td>
<td>31.3 0.01</td>
<td></td>
</tr>
</tbody>
</table>

Table 7-3: Mean (and standard deviation) for each EHRA Class. P values compare each Class with the next lowest Class in terms of symptom severity. VAS = Visual analogue Scale, AFEQT = AFEQT Global score.
7.3.2. **Phase Two**

Of the 99 patients originally classified as EHRA Class 2, 90 had sufficient detail in their archived clinic letters to be reclassified in accordance with the proposed modified EHRA classification into either 2a or 2b. Of these, 43 were classified as 2a and 47 were classified as 2b. The sub-division of Class 2 into 2a and 2b, resulted in clearly separate groups, with Class 2a patients having AFEQT scores and health utilities much closer to Class 1 patients and Class 2b patients having significantly more symptoms as judged by AFEQT and a significant reduction in health utility as judged by EQ-5D. The results are shown in Table 7-4 and Figure 7-2.
<table>
<thead>
<tr>
<th>mEHRA Class (by EQ-5D)</th>
<th>Utility</th>
<th>VAS</th>
<th>P value</th>
<th>AFEQT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.85</td>
<td>76.2</td>
<td>n/a</td>
<td>78.4 (±19.0)</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>(±0.21)</td>
<td></td>
<td>(±19.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2a</td>
<td>0.86</td>
<td>75.6</td>
<td>0.41</td>
<td>70.9 (±19.8)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>(±0.18)</td>
<td></td>
<td>(±19.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td>0.77</td>
<td>65.2</td>
<td>0.01</td>
<td>58.3 (±17.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>(±0.15)</td>
<td></td>
<td>(±20.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.69</td>
<td>59.6</td>
<td>0.09</td>
<td>42.1 (±21.1)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>(±0.27)</td>
<td></td>
<td>(±21.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.59</td>
<td>46.9</td>
<td>0.03</td>
<td>31.3 (±18.6)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>(±0.29)</td>
<td></td>
<td>(±25.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 7-4: Mean (and standard deviation) shown for each mEHRA Class. P values compare each Class with the next lowest Class in terms of symptom severity. VAS = Visual analogue Scale, AFEQT = AFEQT Global score.
Figure 7-2: Quality of Life scores (mean ± SD) by mEHRA Class. Classes 1,3 and 4 are as for Figure 1. Class 2 has been split into 2a (n=43) and 2b (n=47).

We also analysed the mEHRA class according to the three subdomains of the AFEQT score: Symptoms, Activities and Concerns. As can be seen in Figure 7-3, there is a clear stepwise trend to lower scores as mEHRA class increases. As these components of the AFEQT Global score are themselves not individually validated we did not seek to analyse these on a Class-by-Class basis. However, ANOVA confirmed a highly significant difference between groups for all three subdomains (P < 0.0001 for each) and Cuzick’s trend test showed a strong, and highly significant trend towards lower scores with increasing mEHRA class (P < 0.0001 for each of the three subdomains).
7.3.3. Reproducibility of the mEHRA Class

To assess the reproducibility of the mEHRA score we measured both intra-observer and inter-observer variability. Agreement between the two assessors for ratings of 2a or 2b was very good at 83.2% (kappa 0.70, 95% confidence interval = 0.53 to 0.87). Inter-observer variability was assessed by asking each assessor to re-classify a random sample of 20 of the original clinic letters used for Phase 2 of the study. This was performed after an interval of several months to avoid bias due to recall of previous classification. This demonstrated excellent repeatability, with an agreement between the original and repeat classification of 90% for one assessor and 95% for the other (combined Kappa 0.85, 95% CI for Kappa, 0.54 to 1.16).
Phase 3: Prospective validation of mEHRA

The mEHRA Score was thereafter prospectively applied to a second cohort of patients attending the heart rhythm clinics at Liverpool Heart and Chest Hospital. Using the new scoring system, 165 patients were classified as either Class 2a (n = 85) or 2b (n = 80). These data are shown in Table 7-5. Prospective scoring showed the same pattern as retrospective scoring with significantly lower AFEQT, EQ-5D and VAS scores for mEHRA Class 2b than 2a. There were no significant differences between any of the three QoL measured between this validation cohort and the initial cohort in either of the two new mEHRA classes (2a and 2b).

<table>
<thead>
<tr>
<th>QoL Measure</th>
<th>Retrospective</th>
<th>Prospective</th>
<th>P value Retro v Prospective</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Utility (EQ-5D)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2a</td>
<td>0.86 (±0.18)</td>
<td>0.81 (±0.22)</td>
<td>0.23</td>
</tr>
<tr>
<td>2b</td>
<td>0.77 (±0.15)</td>
<td>0.72 (±0.22)</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>P value 2a v 2b</strong></td>
<td>P=0.01</td>
<td>P&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td><strong>VAS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2a</td>
<td>75.6 (±19.9)</td>
<td>77.9 (±15.9)</td>
<td>0.51</td>
</tr>
<tr>
<td>2b</td>
<td>65.2 (±20.1)</td>
<td>67.0(±16.4)</td>
<td>0.60</td>
</tr>
<tr>
<td><strong>P value 2a v 2b</strong></td>
<td>P=0.01</td>
<td>P=0.009</td>
<td></td>
</tr>
<tr>
<td><strong>AFEQT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2a</td>
<td>70.9 (± 19.8)</td>
<td>67.7 (±22.2)</td>
<td>0.42</td>
</tr>
<tr>
<td>2b</td>
<td>58.3 (±17.3)</td>
<td>54.1(±20.2)</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>P value 2a v 2b</strong></td>
<td>P&lt;0.001</td>
<td>P&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Table 7-5: Comparison of retrospective and prospective Quality of Life scores, for each of the two proposed additional mEHRA classes
7.4. Discussion

This comparison of the EHRA symptoms classification with one disease-specific quality of life instrument (AFEQT) and another general measure for health-related quality of life (EQ-5D, incorporating the VAS) provides good evidence that the EHRA score can be used to assess AF-related symptoms without prior training. It is easily applied in clinical practice and has the potential to be useful in clinical trials. However, it does not discriminate sufficiently in patients with low level symptoms in terms of health related utility. We found that the EHRA classification can be improved by sub-dividing Class 2 into two separate classes (2a and 2b). Class 2b symptoms then may represent a more appropriate threshold for intervention in terms of health economics.

Phase One of this study provides evidence that the EHRA classification, in its originally proposed format correlates well with disease-related QoL, as judged by the AFEQT questionnaire and with patients’ own perception of their health state (VAS). There is a step-wise, negative association between EHRA Class and both of these measures. The EHRA score can therefore be considered as a validated tool for symptom classification. In a similar manner to the NYHA functional class for heart failure and the CCS angina scale, the EHRA score allows clinicians to broadly categorise the severity of patients’ symptoms. Where the specifics and complexities of symptoms can be considerable, this sort of categorisation provides a simple means of communicating and quantifying symptom severity. It allows cross-sectional comparison between patients and longitudinal comparison for individual patients or groups of patients.

However, using health-related utility as a measure of QoL, the EHRA score only showed significant discriminatory power at the boundary between mild (Class 2) and severe
(Class 3) symptoms. To try to improve discriminative ability for patients with mild-moderate symptoms we subdivided EHRA Class 2 patients (patients with symptoms, but symptoms that were either not limiting daily activity) into 2a and 2b, based on the degree to which the patient was ‘troubled by their symptoms’, and found the two subdivisions were significantly different from each other on all three QoL measures. Indeed, the health-related utility showed no significant difference between Class 1 (asymptomatic patients) and Class 2a (patients with symptoms but which are not troublesome and do not affect daily activity). Class 2b patients showed a significant reduction (0.09) in health utility compared to Class 2a patients (Table 7-4). As such it may be more appropriate for cost effectiveness analyses to base treatment decisions not only on the presence or absence of symptoms, but also to consider whether the symptoms cause trouble to the patient or not. A scoring system such as mEHRA is intended to provide a measure of symptoms/ QoL at a particular point in time. This can then be compared with other patients or for the same patient over time to help assess the impact of interventions.

At first sight the EQ-5D questionnaire does not obviously represent a useful QoL assessment for a patient with AF. The value in its use, however, is the assessment of a health utility score at baseline, which can then be reassessed following treatment. This allows the calculation of the cost-efficacy of the intervention, and thereby a comparison of the effectiveness of medical interventions between different disciplines. There is a growing demand in all countries to understand the cost-effectiveness of treatments used for common conditions to ensure efficient and appropriate use of health resources. This is particularly the case when considering potentially costly treatments such as catheter ablation. In addition there is an increasing focus on the patient reported health
status as the most relevant outcome of medical interventions, and as clinicians we should embrace this method of assessing outcomes.\textsuperscript{244}

The EQ-5D QoL questionnaire has previously been studied in AF, although not in association with the EHRA score. Berg et al reported the findings from the EQ-5D in the Euro heart survey.\textsuperscript{245} The EQ-5D was completed by 5,050 patients attending specialist hospital departments in 35 European countries. The population studied was somewhat older than ours with a mean age of 66 years. The mean utility was 0.75, which would suggest most patients had a symptom level around mEHRA Class 2b. A repeat survey after 1-year was completed by 3,045 patients showed only a minor (0.013) improvement in health utility. A lower health utility was associated with AF specific symptoms, but also other variables including increasing age, history of stroke and the inability to take regular exercise. Only 2.5\% of the patients enrolled into the Euro Heart Survey received treatment with catheter ablation.\textsuperscript{246} A sub-analysis of the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study, looking at an older population (mean age 82, range 75-99) showed a comparable baseline utility for males (0.77) but a lower utility for females (0.68).\textsuperscript{242}

In assessing interventions, doctors are often focussed on observable events, such as the frequency and duration of AF episodes, which may not tally with the patients’ perspective of their QoL.\textsuperscript{12,247} The motivation of the patient to seek treatment, however, is based on the hope that symptoms will improve. We propose that the reclassification of EHRA Class 2 into 2a and 2b can be of clinical use in selected patients with moderate AF-related symptoms. Should our findings be validated in other data sets, the information may also make health economic sense. The reclassification of EHRA Class 2
is focussed on the impact that AF has on the patient, by stating either that AF symptoms are 'not troublesome to patient' (Class 2a) or that the 'patient is troubled by symptoms' (Class 2b). This distinction will be intuitive for many clinicians, and appears as easily applicable as the original score. From our results we can see that this clearly differentiates 2 groups with not only a statistically significant difference in health utility, but with an absolute difference of 0.09, a clinically meaningful difference.

7.4.1. LIMITATIONS

The EHRA score, and by extension the mEHRA score, is intended to be used for patients with either paroxysmal or non-paroxysmal and we did not differentiate between the two AF types in our analyses. It is conceivable that, within an individual mEHRA class, there is a difference in QoL between the two AF types. The subdivision of EHRA Class 2 in Phase Two was performed retrospectively using clinical letters and could be considered subjective as it was based on a judgement of whether the patient was 'troubled by their symptoms'. This was however performed by 2 independent physicians who were both blinded to the QOL scores of patients in Phase 1 of the study. In a small minority of cases (n=9), subdivision was not possible because of inadequate detail in the clinical letter and therefore these patients could not be included in Phase 2. By looking at and comparing a prospective cohort we have shown that retrospective scoring is unlikely to have a significant effect on the conclusions drawn. In addition, although our assessments were made by a range of health care providers, all were experienced in the management of patients with AF. Finally, the population studied is from a specialist tertiary centre where a large proportion of patients are managed invasively. The classification may be less appropriately used in the hands of others.
groups of physicians or nurses or in other patient populations. Within these limitations, mEHRA appears a practicable and useful addition to the EHRA score.

7.5. Conclusions

The EHRA classification, as originally proposed, is a valid means of quantifying AF symptom severity and correlates well with AFEQT and with the generic EQ-5D. Subdividing EHRA Class 2 into Class 2a and Class 2b by a single additional question has the potential to discriminate two clearly separate groups, with Class 2b patients having significantly impaired QoL due to AF, whereas those with Class 2a symptoms do not differ significantly from asymptomatic patients. This simple modification may further improve the clinical usefulness of the EHRA score, particularly when considering interventions such as ablation, where Class 2b symptoms appear to be the appropriate treatment threshold.
8. Final Discussion

8.1. To what extent did I achieve my aims?

In my introduction I presented this image, to represent what I hoped to achieve through this thesis.

![Image](image.png)

Figure 8-1: Copy of Figure 1-1

Throughout the thesis I have attempted to address each of these areas that contribute to the central goal of improved patient outcome. I have looked at two ablation strategies for substrate-based AF, by means of a randomised controlled trial, and found no difference in terms of arrhythmia recurrence or quality of life between the two. However the secondary benefits of reduced procedural time, shorter duration of ablation and, importantly, lower radiation doses suggest that less may be more when it comes to selecting a lesion set likely to produce the optimum outcome overall. I was able to demonstrate a significant benefit in terms of patient safety through the use of...
ultrasound to guide vascular access with a clear likely benefit in terms of patient outcome. I also found that effective lesions appear to be those in which maximal myocardial damage is achieved through minimal application of radiofrequency energy. A measure of this relationship, the AEQ, has some potential – at least in patients with paroxysmal AF - in predicting the risk of future arrhythmia recurrence. Whilst the term “good outcome” is commonly used in the AF ablation literature as a synonym for freedom from recurrent arrhythmia, the procedure is correctly indicated for the relief of symptoms and therefore quality of life (QoL) is at least, if not more, important as a measure of a “good outcome”. Through my work on the European Heart Rhythm Association symptom score, I was able to show that patients with mild symptoms had a quality of life that was not discernably different from those who were asymptomatic and therefore concluded that selecting these patients for ablation would be unlikely to produce a meaningful improvement for them whilst exposing them to procedural risk. Therefore, by selecting only those patients most likely to benefit the outcomes for all can be improved.

8.2. What problems were encountered and how were they overcome?

8.2.1. Chapter 4: Use of a modified intention to treat analysis

Intention-to-treat (ITT) analysis for clinical trials dates back to the 1960s and can be summarised as “once randomized, always analyzed”.248 and is widely accepted as the gold standard for clinical trials, however may not always be appropriate for clinical trials in AF. The ITT principle was developed to account for the problem of incomplete compliance in drug trials, because the reasons for non-compliance may be related to
In such circumstances, a per-protocol analysis risks overestimation of the treatment effect and may provide an inaccurate estimate of the likely benefit in standard clinical practice where the reasons for non-compliance are likely to be at least as prevalent as during a closely monitored clinical trial. In a strict ITT analysis after randomisation all losses to follow up and withdrawals are ignored and events before treatment commences count towards the primary endpoint.

In my RCT (Chapters 3 & 4), I performed a modified intention-to-treat analysis. In this I excluded patients who were lost to follow up (neither of whom attended any follow up appointments) or who withdrew prior to undergoing ablation. The reasons for this were threefold. Firstly, patients in either of those groups who were not seen again in follow up are impossible to clarify in terms of our primary endpoint of AF recurrence. Secondly, and notwithstanding the first point, because our intervention was intended to “remove” a condition (AF) and our primary endpoint was recurrence of that original condition, all patients not undergoing the intervention would be expected to have the condition present continuously, i.e. to immediately meet the primary endpoint. Any situation in which this does not occur is likely to be due to confounding (e.g. increased AAD use) and therefore a strict ITT analysis may potentially risk increasing bias. These two issues may not have been relevant if we had chosen a different endpoint, most obviously mortality where death would not be routinely expected and data may still be obtainable (with appropriate consent and ethical permission) for patients lost to follow up through centralised databases. Thirdly, the difference in interventions, from a patient perspective, was relatively minor and we did not believe that any patient withdrew because of this difference per se.
Although strategies exist for mitigating the effect of unknown outcomes data due to loss to follow up, none are without some degree of unverifiable assumption, and all risk introduction of additional bias. True ITT analysis may therefore be impractical where loss to follow up occurs. In a systematic review by Abraha and Montedori, loss to follow up was the most common reason for studies adopting a modified ITT approach. If a patient who did not receive an intervention is included as a subject who received treatment, then it indicates very little about the efficacy of the treatment. Exclusion of these patients is therefore a common approach may be considered an appropriate strategy. Where modified ITT is used, sensitivity analyses are recommended. In my study, I found that both per protocol and as treated analyses yielded very similar results to my main analysis. In addition, I performed a further analysis attempting a strict application of ITT. In this, for the reasons given above, I assumed that all those who withdrew or were withdrawn from the study met the primary endpoint. Although neither patient lost to follow up attended for any follow up visits, telephone conversations with them or their relative suggested that neither had any further AF and therefore for this analysis I have treated them as being free of the primary endpoint. Interestingly, using these criteria gave an overall success rate of 74.6% with the primary endpoint occurring in 28.8% of patients randomised to PVI + linear lesions and 21.9% randomised to PVI alone. The difference between the groups was of a similar magnitude (Δ6.9 v. 7.2) to the main analysis with a near-identical level of significance (P= 0.37). If, as a worst case scenario, the two patients lost to follow up were also considered to have had recurrent AF the difference between the treatment arms remained non-significant (28.8% v. 25.0%, P=0.63). Overall, this would seem to suggest my approach was valid, although may not have been necessary.
Recruitment to my trial was good, although slower than we had originally anticipated. In retrospect, this was probably due to a lower than expected number of patients meeting criteria for SusPAF. We had expected at least half of participants to come from this subgroup but, ultimately, the proportion was only 39%. We screened 200 patients in order to recruit 130 and of the 70 not recruited, 53 (76% of non-participants and 26% of all screened) were found to be ineligible, in keeping with the comments above. Only 12 patients declined to participate (17% of non-participants and 6% of all screened) suggesting the study was well received by potential participants. Of the two patients who were lost to follow up, one had a severe relapse of an unrelated chronic condition shortly after his ablation which prevented further participation and, unfortunately, led to his death. The other repeatedly failed to attend appointments, stating pressure of work and that he felt too well to need to come to hospital.

In my sample size calculation I allowed for an attrition rate of 5%, but the rate we experienced was 6% because of a number of patients who withdrew or were withdrawn after randomisation. This problem would have been avoided by delaying randomisation until the day of the procedure. However, unfortunately we were unable to do this, partly due to the need to initiate AAD therapy at least six weeks in advance. Equally important, was the fact that one of our treatment arms entailed a significantly longer procedure than the other (a difference of 45 minutes based on as treated data) and early randomisation was required by the clinical service in order to allow efficient and adequate scheduling. If undertaking a similar trial design in the future these factors would need to be taken into consideration, but may not be possible to entirely mitigate for in which case a larger allowance could be made for attrition.
8.2.3. Duration of follow up in AF trials

It is clear from our findings in Chapter 2 that we need to continue to look beyond the short follow up generally reported in clinical trials. However, there is an inherent difficulty in presenting long-term follow up results for a rapidly developing technique such as catheter ablation. Whilst knowledge of the course of the disease several years after ablation is essential to truly understand the procedure and to allow us to select and inform our patients, long follow up data such as I have presented is at risk of being out-of-date as soon as it is available. One example of the problem is illustrated by anecdotal evidence of a move away from CT or image integration for CA, which contrasts sharply with our finding that this is the only significant predictor of success after both a single and the final procedure. This discrepancy could be due to decisions based on insufficient or misleading available evidence (I highlighted the limitations of previous studies in my discussion of Chapter 2), failure to appreciate the long term impact of the strategy (to my knowledge the data in Chapter 2 is by far the longest reported study to analyse the effect of image integration), or because our long-term data is, inherently and obligatorily, out-dated in that the strategy was previously beneficial but improvements in mapping systems have now rendered it superfluous. In addition to the ongoing accumulation of experience by operators and centres, since we performed the ablations reported in Chapter 2 there have been numerous advances in catheter and imaging technology, in methods for verifying lesion integrity and in our understanding of the mechanisms of AF to mention but a few. We will not know for several years what, if any, benefit these advances bring, by which time they too may have been superseded.
In Chapter 4 the results presented are based on only a short, six month, follow up period. The reason for this is predominantly pragmatic, with a need to complete work for this thesis within a manageable timescale. As detailed in the methods chapter (Chapter 3), I will continue to follow up study participants for a further six months in order to generate the minimum duration recommended for reporting trials in the medical literature. Until that time, the short-term data presented here should be interpreted with caution as early results may not be maintained.

In Chapter 5, I made my primary analysis at six months, again due to pragmatic reasons but also in order to identify early any trends and messages emerging from the testing of an entirely novel concept. Having discovered that the relationship between AEQ and arrhythmia recurrence was most significant for patients with PAF, I then extended follow up to 12 months and found that the early findings were maintained. In Chapter 6 the outcome of interest was acute, or sub-acute, procedural bleeding complications relating to vascular access. Again the issue of follow up duration is relevant with most previous comparable studies reporting only immediately apparent complications. In my study I extended follow up to a month post-discharge by means of a unique postal questionnaire. In doing so I believe I was able to present a much more accurate picture of the true experience of our patients, rather than the narrow view gained from looking at only a potentially short list of very major and immediate complications.

### 8.3. Areas for future research

As stated at the beginning of this chapter, I set out to provide new knowledge through my research to improve outcomes for patients undergoing AF ablation, and specifically took a more holistic definition of “outcomes” than simply arrhythmia recurrence.
Whilst I hope and believe I have achieved this aim, it is perhaps not surprising that in answering one question, other questions develop. One particular point of interest is our findings in Chapter 1 that additional linear ablation lesions appeared to reduce the risk of arrhythmia recurrence which contrasts sharply with the results presented in Chapter 4. I have discussed this dichotomy in detail earlier in the thesis so will avoid duplication here but if modern ablation techniques for substrate-based AF mean that linear ablation provides no additional benefit then we must wonder if PVI is truly the optimum strategy or if any other substrate modification techniques have a role. It is interesting to note that the most recently published study of complex fractionated electrogram ablation, the RASTA study, showed a trend towards increased harm, whereas preceding studies had suggested a neutral or non-significantly positive impact. This mirrors the chronological pattern discussed earlier for linear ablation.

In Chapter 7 I showed how a modified version of the European Heart rhythm association symptom score may help clinicians better select patients likely to benefit from AF ablation. However, I did not test this in a linear manner and future research looking at quality of life, before and after ablation, is warranted to verify that my conclusions hold true in clinical practice. My work on the Ablation Effectiveness Quotient (AEQ) has provided both new insight into what contributes to successful lesion delivery and also may turn out to be a useful clinical marker of risk of arrhythmia recurrence. Further work to externally verify and expand on my initial exploratory findings is ongoing.
8.4. Final conclusions

Catheter ablation of AF can be an effective treatment, associated with a low risk of major complications. However, long term recurrence – at least after ablation of persistent AF – remains a risk as long as 5 years after an initially successful procedure. For persistent AF, the use of CT integration with 3D mapping systems can reduce recurrence risk, and in paroxysmal AF the risk of recurrence appears to relate to the effectiveness of ablation, as measured by the AEQ. Quality of life is improved by ablation but good patient selection is important as those with non-troublesome symptoms (mEHRA Class 2a) may not gain a meaningful benefit by being rendered asymptomatic. Patient safety is paramount, and the use of vascular ultrasound significantly reduces the risk of bleeding complications. By selecting the most suitable patients, minimising the risk of complications and employing an appropriate imaging and ablation strategy optimum outcomes for our patients are hopefully a few steps closer.


112. Lim TW, Koay CH, See VA, McCall R, Chik W, Zecchin R, Byth K, Seow SC, Thomas L, Ross DL, Thomas SP. Single-ring posterior left atrial (box) isolation results in a different mode of recurrence compared with wide antral pulmonary vein
isolation on long-term follow-up: longer atrial fibrillation-free survival time but similar survival time free of any atrial arrhythmia. Circ Arrhythm Electrophysiol 2012;5(5):968-977.


134. Chambers D, Rodgers M, Woolacott N. Not only randomized controlled trials, but also case series should be considered in systematic reviews of rapidly developing technologies. *J Clin Epidemiol* 2009;62(12):1253-1260.


191. Ioannidis JP. Effect of the statistical significance of results on the time to completion and publication of randomized efficacy trials. JAMA 1998;279(4):281-286.


229. Casarett D, Karlawish JH, Sugarman J. Determining when quality improvement initiatives should be considered research: proposed criteria and potential implications. *JAMA* 2000;283(17):2275-2280.

230. Calvert N, Hind D, McWilliams RG, Thomas SM, Beverley C, Davidson A. The effectiveness and cost-effectiveness of ultrasound locating devices for central


10. Appendices

10.1. Appendix 1: Funnel plots for analyses carried out in Chapter 1

Publication bias funnel plot for Analysis 1 Catheter ablation against medical therapy

Publication bias funnel plot for encircling PV isolation
Publication Bias funnel plot for the effect of PV isolation

Publication bias funnel plot for Analysis 3 (WACA v. alternative PVI technique)

Publication bias funnel plot for Analysis 4 (Effect of linear lesions)
Publication bias funnel plot for the analysis of more extensive or less extensive linear ablation

Publication bias funnel plot for Analysis 5 (effect of Complex fractionated atrial electrogram (CFAE) ablation)

Publication bias funnel plot for studies of biatrial ablation
10.2. APPENDIX 2: PATIENT INFORMATION SHEET FOR THE SMAN-PAF TRIAL

Part One

You are being invited to take part in a research study. Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. One of the members of the research team will go through it with you. Please ask if there is anything that is not clear or if you would like more information. Please take time to decide whether or not you wish to take part.

Part 1 tells you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study.

Thank you for reading this.

Study title
Substrate modification and remodelling for patients with non-paroxysmal atrial fibrillation undergoing radiofrequency ablation

Why have I been invited to participate?
You have been invited because you are being considered for radio frequency ablation treatment for atrial fibrillation.

What is the purpose of the study?
The results of catheter ablation for atrial fibrillation are generally around 60% after 1 procedure. This study attempts to look at ways to improve that success rate. We aim to do so by comparing two different strategies for Ablation. One strategy involves performing ablation only around the areas at which the veins returning blood from the lungs attach to the heart (pulmonary vein isolation). The other involves performing additional ablation in other areas of the left atrium (the chamber of the heart most associated with atrial fibrillation). An additional purpose is to assess how the heart responds to the ablation procedure to see if any measured parameters are useful to help predict which patients remain cured of atrial fibrillation in the long term.

Do I have to take part?
It is up to you to decide whether or not to take part. If you decide to take part you will be given this participant information sheet to keep and be asked to sign a consent form. If you decide to take part you are free to withdraw at any time, and a decision not to take part will not affect your future care in any way.

What will happen to me if I take part?
Sometimes we don't know which way of treating patients is best. To find out, we need to compare different treatments. We put people into two groups, give each group a different treatment and compare the results to see which is better. In this study there is an equal (random) chance of being placed in either group. In order to reduce the potential for bias, you will not be told which group you have been put into until the end of the trial (blinded).

Many of the tests and treatments you will undergo in this study are part of the standard care anyway, and will be offered to you even if you decide not to participate in this study. All trial participants will complete a short survey and questionnaire at the beginning of the study and provide a small (5ml) sample of venous blood. They will then receive heart rhythm stabilizing
tablets for 6 weeks prior to their ablation procedure. These tablets will be discontinued 6 weeks after the ablation.

The ablation procedure will be carried out in a similar manner to what would happen if you were not taking part in the trial. The extent of ablation (either isolation of the pulmonary veins alone or in combination with additional lines of ablation) will be decided according to a randomisation procedure. Some additional measurements will be made at the time of the time of the ablation.

An ECG will be performed before and after the ablation. This will then be repeated, along with an echocardiogram (ultrasound scan of the heart) the day after the ablation prior to discharge from the hospital. A further blood test will be taken.

You will be asked to return for follow up appointments at 3, 6 and 12 months after the ablation and the echocardiogram and ECG will be repeated as well as a continuous heart rate monitor to be worn for 24 hours. You may be asked to undergo a repeat MRI scan of the heart after 3 months. If you have ongoing symptoms you may be given a heart rate monitor to use over 1-2 weeks. If you are found to have a recurrence of atrial fibrillation you will usually be offered electrical cardioversion in the first instance. If this is unsuccessful you will be offered an additional ablation procedure.

A flow chart is attached to the back of this sheet to help summarise what will happen.

What are the possible disadvantages and risks of taking part?
The risks for patients in this study are not expected to significantly differ from any other patient having an AF ablation. The procedure may last slightly longer (up to ½ hour) than would otherwise be the case but this will not affect when you are discharged from hospital.

Follow up appointments may be more frequent and slightly longer for trial participants than might be the case for non participants. In order to minimise inconvenience, every effort would be made to ensure that follow up investigations are carried out on the same day as clinic visits.

If you participate in the trial you will receive a heart rhythm stabilizing medicine (usually amiodarone) for a short period before and after your ablation. This is similar to standard practice for all AF ablation patients at Liverpool Heart and Chest Hospital.

Radiation and the Ionising Radiation (Medical Exposure) Regulations – (IRMER)
In order to perform an ablation we need to use X-rays. As well as undergoing ablation you may also be asked to undergo a cardiac CT scan (usually only if there is a reason only you cannot have a magnetic resonance (MRI) scan). Both of these procedures involve exposure to ionising radiation.

It is not expected that you will be exposed to any additional ionising radiation if you participate in the study compared to someone who has an AF ablation but is not taking part in the study.

For patients under 70 years of age the lifetime additional risk of fatal cancer from the ablation is estimated to be 1 in 4000 (1 in 2300 if a cardiac CT scan is also required). For patients over 70 years old the risks are approximately 5 times less.

For comparison the overall lifetime risk of cancer in the population is 1 in 3.

What are the possible benefits of taking part?
We hope to show through the study that additional ablation improves AF ablation success rates as compared to ‘standard’ PVI. There is a probability that you might benefit if that does turn out
to be the case. In addition trial participants will be followed more frequently in the first year after their ablation than non-participants and this may mean earlier detection of problems or relapses.

**What happens when the research study stops?**
Depending on each individual’s ongoing clinical requirement some people will continue to be followed up by the Heart Rhythm Team at Liverpool Heart and Chest Hospital whilst others will be discharged back to the care of their GP.

**What if something goes wrong?**
Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part Two.

**Will my taking part in the study be kept confidential?**
Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

*This completes Part One of the information sheet.*

*If you are interested in taking part please read Part Two which provides further information which you may find useful.*
Part Two

**What if relevant new information becomes available?**

Sometimes we get new information about the treatment being studied. If this happens, your research doctor might consider you should withdraw from study. He/she will explain the reasons and arrange for your care to continue. If the study is stopped for any other reason, we will tell you and arrange your continuing care.

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

You can withdraw from treatment but keep in contact with us to let us know your progress. Information collected may still be used. Any stored blood or tissue samples that can still be identified as yours will be destroyed if you wish.

**What if there's a problem?**

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. Contact details can be found at the end of this information sheet.

In the event that something does go wrong and you are harmed during the research and this is due to someone’s negligence then you may have grounds for a legal action for compensation against Liverpool Heart and Chest Hospital NHS Foundation Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

**What will happen to the results of the research study?**

The results of the study will be available after it finishes and will usually be published in a medical journal or be presented at a scientific conference. Results may also be made available online. They will also form part of a thesis for the degree of Doctor of Medicine at Imperial College, London. The data will be anonymous and none of the patients involved in the trial will be identified in any report or publication.

Should you wish to see the results, or the publication, please ask your study doctor.

**Will my taking part in the study be kept confidential?**

If you consent to take part in this study, the records obtained while you are in this study as well as related health records will remain strictly confidential at all times. The information will be held securely on paper and electronically at Liverpool Heart and Chest Hospital under the provisions of the 1998 Data Protection Act. Your name will not be passed to anyone else outside the research team or the sponsor, who is not involved in the trial. You will be allocated a trial number, which will be used as a code to identify you on all trial forms.

Your records will be available to people authorised to work on the trial but may also need to be made available to people authorised by the Research Sponsor, which is the organisation responsible for ensuring that the study is carried out correctly. A copy of your consent form may be sent to the Research Sponsor during the course of the study. By signing the consent form you agree to this access for the current study and any further research that may be conducted in relation to it, even if you withdraw from the current study.

The information collected about you may also be shown to authorised people from the UK Regulatory Authority and Independent Ethics Committee; this is to ensure that the study is carried out to the highest possible scientific standards. All will have a duty of confidentiality to you as a research participant.
If you withdraw consent from further study treatment, unless you object, your data and samples will remain on file and will be included in the final study analysis.

In line with Good Clinical Practice guidelines, at the end of the study, your data will be securely archived for a minimum of 10 years. Arrangements for confidential destruction will then be made.

With your permission your GP, and other doctors who may be treating you, will be notified that you are taking part in this study.

**Informing your General Practitioner (GP)**
When you agree to take part in this study a letter will be sent to your GP explaining the details of the trial and informing him/her that you are participating.

**What should I do if I want to take part?**
You will have been given this information sheet either via the post along with your clinic appointment letter, or in the outpatient department having attended a Heart Rhythm clinic.
- If you were sent the information prior to your appointment you will be seen by one of the research team when you attend clinic and asked if you want to take part. The researcher will be able to answer any questions you may have and complete the required paperwork. If you have questions you would like answered before you attend you can contact the lead researcher, Dr Gareth Wynn using the details at the bottom of this page.
- If you were given the information sheet in clinic a member of the research team is on hand to answer your questions and complete the required paperwork if you wish to take part. If you would like to take longer to think about it you may take the paperwork away and return it to us by post.

**Who is organising and funding the research?**
The study is being carried out by members of staff at the Liverpool Heart and Chest Hospital which is acting as sponsor for the study. No external funding has been provided.

**Who has reviewed the study?**
All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by The North West Research Ethics Committee.

Contact for Further Information
If you have any further questions you can get additional information from Dr Gareth Wynn, Electrophysiology Research Registrar via his email address gareth.wynn@lhch.nhs.uk or by phone by contacting the Liverpool Heart and Chest Switchboard on 0151 228 1616.

*This completes Part Two of the information sheet.*

*Thank you for taking the time to read this information*
### 10.3. Appendix 3: AFEQT QoL Form (Chapters 3, 4 & 7)

**Atrial Fibrillation Effect on Quality-of-life (AFEQT) Questionnaire**

**Section 1. Occurrence of atrial fibrillation**

Are you currently in atrial fibrillation? □ Yes □ No

If No, when was the last time you were aware of having had an episode of atrial fibrillation? (Please check one answer which best describes your situation)

- earlier today
- within the past week
- 1 month to 1 year ago
- more than 1 year ago
- I was never aware of having atrial fibrillation

**Section 2. The following questions refer to how atrial fibrillation affects your quality of life.**

**On a scale of 1 to 7, over the past 4 weeks, as a result of your atrial fibrillation, how much were you bothered by:**

(Please circle one number which best describes your situation)

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all bothered</th>
<th>Hardly bothered</th>
<th>A little bothered</th>
<th>Moderately bothered</th>
<th>Quite a bit bothered</th>
<th>Very bothered</th>
<th>Extremely bothered</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Paroxysms: Heart fluttering, skipping or racing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Irregular heart beat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. A pause in heart activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Lightheadedness or dizziness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**On a scale of 1 to 7, over the past 4 weeks, have you been limited by your atrial fibrillation in your:**

(Please circle one number which best describes your situation)

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all limited</th>
<th>Hardly limited</th>
<th>A little limited</th>
<th>Moderately limited</th>
<th>Quite a bit limited</th>
<th>Very limited</th>
<th>Extremely limited</th>
</tr>
</thead>
<tbody>
<tr>
<td>5. Ability to have recreational activities, sports, and hobbies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Ability to have a relationship and do things with friends and family</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**On a scale of 1 to 7, over the past 4 weeks, as a result of your atrial fibrillation, how much difficulty have you had in:**

(Please circle one number which best describes your situation)

<table>
<thead>
<tr>
<th>Question</th>
<th>No difficulty at all</th>
<th>Hardly any difficulty</th>
<th>A little difficulty</th>
<th>Moderate difficulty</th>
<th>Quite a bit of difficulty</th>
<th>A lot of difficulty</th>
<th>Extreme difficulty</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. Doing any activity because you felt tired, fatigued, or low on energy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Doing physical activity because of shortness of breath</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Exercising</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Walking briskly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Walking briskly up or carrying groceries or other items, up a flight of stairs without stopping</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Doing vigorous activities such as lifting or moving heavy furniture, running, or participating in strenuous sports like tennis or racquetball</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Atrial Fibrillation Effect on Quality-of-life (AFEQT) Questionnaire

**On a scale of 1 to 7, over the past 4 weeks, as a result of your atrial fibrillation, how much did the feelings below bother you? (Please circle one number which best describes your situation)**

<table>
<thead>
<tr>
<th>Feeling/worried or anxious that your atrial fibrillation can start anytime</th>
<th>Not at all bothered</th>
<th>Hardly bothered</th>
<th>A little bothered</th>
<th>Moderately bothered</th>
<th>Quite a bit bothered</th>
<th>Very bothered</th>
<th>Extremely bothered</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Feeling/worried that atrial fibrillation may worsen other medical conditions in the long run</th>
<th>Not at all bothered</th>
<th>Hardly bothered</th>
<th>A little bothered</th>
<th>Moderately bothered</th>
<th>Quite a bit bothered</th>
<th>Very bothered</th>
<th>Extremely bothered</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

**On a scale of 1 to 7, over the past 4 weeks, as a result of your atrial fibrillation treatment, how much were you bothered by? (Please circle one number which best describes your situation)**

<table>
<thead>
<tr>
<th>Worrying about the treatment side effects from medications</th>
<th>Not at all bothered</th>
<th>Hardly bothered</th>
<th>A little bothered</th>
<th>Moderately bothered</th>
<th>Quite a bit bothered</th>
<th>Very bothered</th>
<th>Extremely bothered</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Worrying about complications or side effects from procedures like catheter ablation, surgery, or pacemakers therapy</th>
<th>Not at all bothered</th>
<th>Hardly bothered</th>
<th>A little bothered</th>
<th>Moderately bothered</th>
<th>Quite a bit bothered</th>
<th>Very bothered</th>
<th>Extremely bothered</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Worrying about side effects of blood thinners such as nosebleeds, bleeding gums when brushing teeth, heavy bleeding from cuts, or bruising.</th>
<th>Not at all bothered</th>
<th>Hardly bothered</th>
<th>A little bothered</th>
<th>Moderately bothered</th>
<th>Quite a bit bothered</th>
<th>Very bothered</th>
<th>Extremely bothered</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Worrying or feeling anxious that your treatment interferes with your daily activities</th>
<th>Not at all bothered</th>
<th>Hardly bothered</th>
<th>A little bothered</th>
<th>Moderately bothered</th>
<th>Quite a bit bothered</th>
<th>Very bothered</th>
<th>Extremely bothered</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

**On a scale of 1 to 7, overall, how satisfied are you at the present time with: (Please circle one number which best describes your situation)**

<table>
<thead>
<tr>
<th>Extremely satisfied</th>
<th>Very satisfied</th>
<th>Somewhat satisfied</th>
<th>Mixed with satisfied and dissatisfied</th>
<th>Somewhat dissatisfied</th>
<th>Very dissatisfied</th>
<th>Extremely dissatisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>19. How well your current treatment controls your atrial fibrillation?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

| The extent to which treatment has relieved your symptoms of atrial fibrillation? | 1 | 2 | 3 | 4 | 5 | 6 | 7 |

**Name or ID:**

---

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*Developed by AFEQT Core Team: John Sparrow, MD, Mid America Heart Institute, Kansas City, MO; Paul Doria, MD, St. Michael's Hospital, Toronto, ON; Rosemary Bukenya, RN, University of Alabama, Birmingham, AL; Caroline Burt, PharmD, B.S., Steven Leslie, PhD, Donna Godejohn, BSN, St. Jude Medical, St. Paul, MN.*
### SF-36 HEALTH SURVEY

**INSTRUCTIONS:** This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. **In general, would you say your health is:**

   (circle one)

   - Excellent ................................................................. 1
   - Very good ....................................................................... 2
   - Good .............................................................................. 3
   - Fair ............................................................................... 4
   - Poor ............................................................................... 5

2. **Compared to one year ago, how would you rate your health in general now?**

   (circle one)

   - Much better now than one year ago .................................. 1
   - Somewhat better now than one year ago ................................. 2
   - About the same as one year ago ............................................ 3
   - Somewhat worse now than one year ago ................................. 4
   - Much worse now than one year ago ........................................ 5
3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(circle one number on each line)

<table>
<thead>
<tr>
<th>ACTIVITIES</th>
<th>Yes, Limited A Lot</th>
<th>Yes, Limited A Little</th>
<th>No, Not Limited At All</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Vigorous activities, such as running, lifting heavy objects,</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>participating in strenuous sports</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Moderate activities, such as moving a table, pushing a vacuum cleaner,</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>bowling, or playing golf</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Lifting or carrying groceries</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>d. Climbing several flights of stairs</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>e. Climbing one flight of stairs</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>f. Bending, kneeling, or stooping</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>g. Walking more than a mile</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>h. Walking half a mile</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>i. Walking one hundred yards</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>j. Bathing or dressing yourself</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

(circle one number on each line)

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Cut down on the amount of time you spent on work or other</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>activities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Accomplished less than you would like</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>c. Were limited in the kind of work or other activities</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>d. Had difficulty performing the work or other activities (for</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>example, it took extra effort)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(circle one number on each line)

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Cut down on the amount of time you spent on work or other activities</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>b. Accomplished less than you would like</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>c. Didn't do work or other activities as carefully as usual</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

(circle one)

- Not at all .................................................................1
- Slightly ...........................................................................2
- Moderately ........................................................................3
- Quite a bit .........................................................................4
- Extremely ............................................................................5

7. How much bodily pain have you had during the past 4 weeks?

(circle one)

- None ..................................................................................1
- Very mild ............................................................................2
- Mild ..................................................................................3
- Moderate ............................................................................4
- Severe ...............................................................................5
- Very severe ........................................................................6
8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

(circle one)

Not at all .............................................................................................................. 1
A little bit .............................................................................................................. 2
Moderately .......................................................................................................... 3
Quite a bit ............................................................................................................ 4
Extremely .......................................................................................................... 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks -

(circle one number on each line)

<table>
<thead>
<tr>
<th></th>
<th>All of the Time</th>
<th>Most of the Time</th>
<th>A Good Bit of the Time</th>
<th>Some of the Time</th>
<th>A Little of the Time</th>
<th>None of the Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Did you feel full of life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>b. Have you been a very nervous person?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>c. Have you felt so down in the dumps that nothing could cheer you up?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>d. Have you felt calm and peaceful?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>e. Did you have a lot of energy?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>f. Have you felt downhearted and low?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>g. Did you feel worn out?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>h. Have you been a happy person?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>i. Did you feel tired?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>
10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?  

(circle one)  

All of the time .................................................................1  
Most of the time ...............................................................2  
Some of the time ..............................................................3  
A little of the time .........................................................4  
None of the time ..............................................................5  

11. How TRUE or FALSE is each of the following statements for you?  

(circle one number on each line)  

<table>
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<tr>
<th></th>
<th>Definitely True</th>
<th>Mostly True</th>
<th>Don't Know</th>
<th>Mostly False</th>
<th>Definitely False</th>
</tr>
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<tbody>
<tr>
<td>a.</td>
<td>I seem to get ill more easily than other people</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>b.</td>
<td>I am as healthy as anybody I know</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>c.</td>
<td>I expect my health to get worse</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>d.</td>
<td>My health is excellent</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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</table>
By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

**Mobility**
- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

**Self-Care**
- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

**Usual Activities (e.g. work, study, housework, family or leisure activities)**
- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

**Pain/Discomfort**
- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

**Anxiety/Depression**
- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed
To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.
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Manuscript #: CIRCAE/2014/001759-T1
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