Contributing factors and clinical relevance of early arrhythmia recurrence and electrical reconnection of the pulmonary veins following pulmonary vein isolation for atrial fibrillation

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Abstract

Pulmonary vein isolation (PVI) is the cornerstone of ablation for paroxysmal atrial fibrillation (AF). However, success rates from AF ablation are not as high as would be hoped and this body of work focussed on improving outcomes from this procedure.

Late PV reconnection following PVI is very common and is strongly associated with atrial tachyarrhythmia (AT) recurrence. The primary study of this work involved a randomised controlled trial comparing standard care with a strategy of early repeat electrophysiology study, irrespective of symptoms, to assess for and treat PV reconnection. Patients were followed-up for 12 months with daily ECG monitoring using a portable monitor. This study demonstrated a reduction in AT recurrence and burden and an improvement in quality-of-life in the repeat study group.

At present, a 3-month blanking period following PVI is recommended, during which AT recurrences are not deemed indicative of procedure failure. In a secondary study, the relationship between episodes of AT recorded within this 3-month blanking period and PV reconnection was studied. Early recurrence beyond 4 weeks after PVI was associated with PV reconnection, whereas recurrence within the first 4 weeks was not.

Force-Time Integral is a commonly-used ablation lesion quality marker but has limitations. Ablation Index is a novel marker incorporating power along with contact force and time in a weighted formula. In a further study, the relationship between Ablation Index and late PV reconnection was examined. Reconnected segments had significantly lower minimum Ablation Index values than non-reconnected segments, and higher values were required to avoid reconnection in anterior/roof segments compared to posterior/inferior segments.

In the final part of the work, the relationship between sites of acute PV reconnection that underwent re-ablation and sites of late reconnection was studied, as the effectiveness of such re-ablation is unclear. No difference was found in the rates of late reconnection between areas with and without acute reconnection.
Taken together, the findings from these studies provide insights into the potential success rates that can be achieved from durable PVI in patients with paroxysmal AF, and techniques that may help to achieve this. Furthermore, assessment for early recurrence may allow better identification of those patients at higher risk of later recurrence.
Declaration of Originality

I, Moloy Das, declare that the work described within this thesis is my own and where others have contributed or collaborated, this has been appropriately acknowledged. All other work that has not been undertaken by me or in collaboration with others has been duly referenced. I confirm that this work is original and has not been submitted previously or concurrently to this or any other university towards the award of a degree.

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Publications

Work from this thesis that has previously been published in a peer-reviewed journal or presented as an abstract or oral presentation at a scientific conference is detailed below:

Chapter 1: Introduction

Manuscript

Chapter 3: Pulmonary vein re-isolation as an early routine strategy: a success rate evaluation (PRESSURE)

Manuscript

Abstract

Chapter 4: The relationship between early recurrence of atrial tachyarrhythmia and pulmonary vein reconnection

Manuscript


Chapter 5: The relationship between Ablation Index and pulmonary vein reconnection, and regional differences in target values

Manuscript


Abstracts


Chapter 6: The relationship between sites of acute and late pulmonary vein reconnection

Manuscript


Abstract

1 INTRODUCTION

1.1 Abbreviations

AF – atrial fibrillation
Al – Ablation Index
AT – atrial tachyarrhythmia
CI – confidence interval
ERAT – early recurrence of atrial tachyarrhythmia
ERP – effective refractory period
FTI – Force-Time Integral
NOAC – non-vitamin K oral anticoagulant
OR – Odds Ratio
PV – pulmonary vein
PVI – pulmonary vein isolation
RS – Repeat Study
SC – Standard Care
WACA – wide area circumferential ablation
1.2 Atrial fibrillation

Atrial fibrillation (AF) is the most commonly-occurring cardiac arrhythmia, affecting 1-2% of the general population but with increasing prevalence with advanced age\textsuperscript{1-3}. AF can present in a variety of patterns, from short self-terminating episodes lasting minutes to days (paroxysmal AF), to incessant episodes that do not self-terminate but can be converted to sinus rhythm by pharmacological or electrical intervention (persistent AF), to chronic AF that is resistant to conversion attempts, including situations where this is not attempted (permanent AF). The characteristic feature of AF is chaotic electrical activity affecting the atria, resulting in loss of concerted atrial contraction and rapid, irregular transmission of electrical impulses to the ventricles via the atrioventricular node. These effects in turn lead to typical symptoms of palpitations, dyspnoea, fatigue, light-headedness or chest pain, which are present singly or in combination in the great majority of patients, with only 12-21% of patients in registry studies being entirely asymptomatic.\textsuperscript{4-6} As a consequence, quality of life indices have been found to be significantly reduced in patients with AF compared to healthy individuals,\textsuperscript{7} though a further study found no difference in older patients.\textsuperscript{8}

Beyond symptomatic effects, AF has a number of other important health consequences. It increases the risk of stroke almost five-fold and is reported to be the cause of around one in four of all strokes.\textsuperscript{9-12} It also increases the risk of hospital admissions with heart failure,\textsuperscript{13} and can lead to severe impairment of left ventricular function through uncontrolled ventricular rates (tachycardiomyopathy).\textsuperscript{14} Finally, AF independently increases the risk of death, with data from the Framingham Heart Study population demonstrating adjusted Odds Ratios (OR) of 1.5 (95% Confidence Interval (CI) 1.2 - 1.8) in men and 1.9 (95% CI 1.5 - 2.2) in women.\textsuperscript{15}

There are multiple risk factors for the development of AF, with several well-established conditions and others that have only recently been recognised as being associated. Hypertension remains one of the most commonly associated conditions, with other associated co-morbidities
including ischaemic heart disease, left ventricular systolic dysfunction, diabetes mellitus, hypertrophic cardiomyopathy, thyrotoxicosis, obstructive sleep apnoea, gastro-oesophageal reflux disease, chronic kidney disease, obesity and alcohol excess. Valvular heart disease, particularly mitral stenosis or significant mitral regurgitation, is a major risk factor for both the development of AF and stroke-risk in AF, but has become much less common in the developed world due to the effective disappearance of rheumatic fever. AF is also commonly seen in the context of acute conditions such as sepsis and surgical procedures, particularly cardiothoracic surgery but also following procedures on other areas of the body.

Due to a combination of factors, including an ageing population and increasing levels of lifestyle-associated co-morbidities, both the prevalence and the incidence of AF are increasing.18 Through its effects on quality of life and risk of stroke and other complications, AF therefore represents a major health concern in terms of utilisation of health resources. In addition to this, a 2004 economic analysis estimated that the direct costs of healthcare for AF amounted to £244 million in 1995 (0.62% of total NHS expenditure), and was projected to rise to £459 million in 2000 (0.97% of total 1995 NHS expenditure).19 With the rising prevalence of AF as described above and increasing costs of modern interventions for its treatment, AF also represents a growing economic burden.

1.3 Pathophysiology of AF

The mechanisms leading to AF remain incompletely understood and the subject of considerable debate. In part, this can be attributed to a lack of reliable models upon which to examine the nature of the arrhythmia. For the most part, an initiating trigger and substrate for maintenance are required for AF to occur.20,21 Triggers mostly originate from the muscular sleeves extending into the pulmonary veins (PVs), particularly in patients with paroxysmal AF,22 and it has previously been shown that the effective refractory periods (ERP) of PV myocytes in patients with AF are shorter than in those without.23 The ERPs of PVs in patients with AF are shorter than those of left atrial
myocytes,\textsuperscript{23,24} creating the potential for rapid firing to initiate AF, whereas the reverse is true in patients without a history of AF.\textsuperscript{23,25} AF may then be maintained by the same mechanism, with repetitive focal ectopic firing or local microre-entry from the PVs perpetuating the arrhythmia. Exposure to AF results in further shortening of the PV and left atrial ERP,\textsuperscript{25} a form of electrophysiological remodelling which aids maintenance of the arrhythmia. However, other areas of the atria may play a greater role in more persistent forms of AF, and other re-entrant mechanisms can also maintain AF following initiation from either rapid focal firing from the PV or simply from an ectopic beat.\textsuperscript{26} In these scenarios, alteration of the left atrial substrate, either electrophysiological or structural, can play a significant role in AF perpetuation. Different types of abnormalities that promote ectopic firing and re-entrant mechanisms include: ion channel dysfunction, cellular calcium regulation abnormalities, autonomic nervous system dysregulation, and structural remodelling.

\subsection*{1.3.1 Ion channel dysfunction}

Electrophysiological remodelling and shortening of the ERP of both PV and left atrial myocytes is primarily due to induced ion channel dysfunction caused by atrial tachyarrhythmia at very high rates. Ion channels whose activity is decreased by this include the ultrarapid delayed rectifier potassium current (\(I_{Kur}\)), the outward potassium current (\(I_{to}\)) and the L-type calcium current (\(I_{Ca,L}\)). Conversely, other ion currents increase, including the inward rectifier potassium current (\(I_{K1}\)), the slow component of the delayed rectifier potassium current (\(I_{ks}\)), and the acetylcholine-dependent potassium current (\(I_{K,ACh}\)). Collectively, these ion channel effects result in shortening of the atrial and PV action potentials and, as a consequence, their ERPs.\textsuperscript{26} This remodelling occurs at variable rates, depending on the specific ion channels involved, with the time-course varying between hours to weeks, but may be reversed during periods of sinus rhythm.\textsuperscript{27,28}

\subsection*{1.3.2 Cellular calcium regulation abnormalities}

The electrophysiological remodelling described above may additionally involve abnormalities of
cellular calcium regulation. This can lead to an increase in the frequency of releases of calcium from the sarcoplasmic reticulum, which can be responsible for triggered atrial activation leading to the initiation and subsequent maintenance of AF.\textsuperscript{28-31}

1.3.3 Autonomic nervous system dysregulation

As discussed above, AF triggers commonly originate from the PV muscle sleeves. However, a further factor may be required to initiate these triggering events, and one possible cause may be variation in the autonomic nervous system. It is well-recognised that the atria are richly innervated with autonomic fibres.\textsuperscript{32} Autonomic effects on the heart can be assessed by measures such as heart rate variability, and a large number of studies have demonstrated alterations in autonomic tone in the minutes preceding the initiation of AF, as well as immediately following AF termination.\textsuperscript{33-38} Furthermore, direct high frequency stimulation of the cardiac autonomic nervous system has also been shown to induce PV ectopy and trigger AF.\textsuperscript{39} It is thought that activation of the autonomic nervous system simultaneously extends intracellular calcium transit and shortens the action potential duration, thereby aiding the initiation of early after-depolarisations and triggered activity.\textsuperscript{40}

As a result, ablation of the autonomic ganglionic plexi located on the epicardial surface of the left atrium has been investigated and mooted as a potential therapeutic strategy,\textsuperscript{41-43} and clinical trials have shown this, in combination with pulmonary vein isolation (PVI), to have beneficial results.\textsuperscript{44-46}

1.3.4 Structural remodelling

In addition to electrophysiological remodelling, AF also causes structural remodelling of the atrial wall. This is predominantly in the form of fibrosis but can also be hypertrophic change,\textsuperscript{27,47} and has a longer time-course than electrophysiological remodelling in terms of months to years. The pathologic process behind the development of fibrosis has not been fully elucidated, but is thought to include the differentiation from fibroblasts into myofibroblasts (which are greater producers of collagen), and the interaction between myofibroblasts and cardiac myocytes.\textsuperscript{48}

Causative factors for the development of fibrosis include many of the conditions commonly-
associated with AF, as well as age. A recent study found that a risk score calculated from the presence of hypertension, diabetes and renal dysfunction, as well as older age (>65 years), persistent AF, greater left atrial size (>45mm), and female gender, was predictive of both left atrial scar identified at the time of a PVI procedure as well as the clinical response to ablation consisting solely of PVI.\textsuperscript{49} This therefore provides a strong rationale for the early treatment of such associated conditions to slow or prevent the development of these left atrial structural changes.\textsuperscript{50} Attempts to identify left atrial fibrosis using imaging techniques such as magnetic resonance imaging have shown promising results,\textsuperscript{51,52} but have been difficult to replicate.

1.4 Management of AF

Medical therapy for AF is targeted towards three main areas: stroke prevention, rate-control and rhythm-control. Of these, thromboembolic prophylaxis has the strongest evidence base, with a clear and marked reduction in stroke risk of almost two-thirds demonstrated with the use of vitamin K antagonist agents (most commonly warfarin) in appropriate patients.\textsuperscript{53} The release in recent years of non-vitamin K oral anticoagulants (NOACs), each of which has been shown to provide equivalent or better stroke prevention than warfarin without an increase in bleeding risk, has expanded the therapeutic options available.\textsuperscript{54-56} Selection of appropriate patients at high risk of stroke has also been simplified by the widespread use of validated risk scoring systems, initially the CHADS2 score,\textsuperscript{57} followed more recently by the CHA\textsubscript{2}DS\textsubscript{2}-VASc score.\textsuperscript{58}

Rate-control strategies primarily utilise atrioventricular nodal blocking agents such as beta-blockers, rate-limiting calcium channel-blockers and digoxin to limit the ventricular rate during episodes of AF. This provides symptomatic and quality of life improvement in the majority of cases, and reduces the risk of heart failure and tachycardiomyopathy.\textsuperscript{59} A sub-study analysis combining data from the rate-control arms of two large randomised controlled trials comparing rhythm-control with rate-control, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study and the Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE)
trial, demonstrated that control of the ventricular rate below 100bpm is of prognostic benefit. However, results from the RACE II study showed that stricter rate-control (controlling the resting heart rate to <80bpm) does not appear to provide any additional improvement. In situations where adequate rate-control cannot be achieved with pharmacologic agents, such as due to drug intolerance or the presence of sino-atrial node dysfunction (“tachy-brady syndrome”), an alternative strategy is to implant a permanent pacemaker followed by ablation of the atrioventricular node. This provides definitive rate-control, as the ventricular rate becomes solely under the control of the pacemaker and its programming.

Rhythm-control strategies have traditionally involved use of anti-arrhythmic drugs in an attempt to restore and maintain sinus rhythm. These agents act on the cardiac action potential, by blocking sodium channels and thereby decreasing the speed of depolarisation (Class Ic in the Vaughan Williams classification), blocking β-receptors and decreasing sympathetic tone (Class II) or prolonging the action potential duration, thereby increasing refractoriness (Class III). The intended effect of these actions is to lower the likelihood of rapid automatic firing, microre-entry or rotational activation that may be responsible for the initiation and maintenance of AF. The medications primarily utilised for this purpose in the United Kingdom include flecainide, propafenone, sotalol, amiodarone and dronedarone, of which amiodarone is the most efficacious. Other agents, such as procainamide, ibutilide and dofetilide, have been used more extensively in North America. More recently, vernakalant, an intravenous agent, has been shown to be effective for chemical cardioversion, and has a higher rate of successful conversion that intravenous amiodarone. Unlike the other anti-arrhythmic drugs, this agent has been specifically designed to target potassium channels that are particular to the atrium (predominantly Kv1.5, which carries $I_{Kur}$, and Kir3.1/3.4, which carries $I_{K(ACh)}$). An oral formulation of this drug was developed, but has subsequently not been brought to market. In addition to pharmacological agents, electrical direct current cardioversion can also be used to restore sinus rhythm, and the success rate of this procedure can be improved by concomitant anti-arrhythmic drug therapy.
The potential benefits of restoring and maintaining sinus rhythm with a rhythm-control strategy are relatively apparent, including an improvement in symptoms and a reduced risk of stroke, heart failure, tachycardiomyopathy and death. However, randomised controlled trials comparing rhythm-control with rate-control strategies have consistently shown no benefit for the former. These studies included the Pharmacological Intervention in Atrial Fibrillation (PIAF) trial, the AFFIRM study, the RACE trial, and the Strategies of Treatment of Atrial Fibrillation (STAF) study. In all four studies, no substantial benefit of a rhythm-control approach was identified, with no difference in mortality or composite end-point incorporating death seen between the two treatment groups. Furthermore, rhythm-control did not confer a greater improvement in symptoms or quality of life (though a greater increase in walking distance was seen in the PIAF trial), but did increase hospital admissions and adverse drug events. Indeed, a meta-analysis incorporating all these studies demonstrated a lower risk of death or thromboembolic stroke with a rate-control strategy (OR 0.84 [95% CI 0.73 - 0.98], P=0.02), with trends towards reduced risks of death (OR 0.87 [95% CI 0.74 - 1.02], P=0.09) and thromboembolic stroke (OR 0.80 [95% CI 0.60 - 1.07], P=0.14). A post-hoc on-treatment analysis of the AFFIRM study showed that mortality was increased by 49% by the use of anti-arrhythmic drugs, and it is likely that these adverse meta-analysis findings were largely due to this combined with a tendency to stop anticoagulation after sinus rhythm was achieved in rhythm-control group patients. Furthermore, it is important to note that the ability to maintain sinus rhythm was highly limited, with only 23% (PIAF and STAF) and 39% (RACE) remaining in sinus rhythm at the end of follow-up. AFFIRM reported a considerably higher rate of 63% of the rhythm-control group being in sinus rhythm at the last follow-up, but it is unclear what method of assessment for AF recurrence was used. It seems likely that such limited ability to achieve sinus rhythm may be one of the keys reasons underpinning the lack of expected benefit from a rhythm-control strategy, and this is supported by the post-hoc analysis of the AFFIRM study which showed a significant reduction in mortality for those patients achieving sinus rhythm. The authors concluded by stating, “If an effective method for maintaining sinus rhythm with fewer adverse effects were available, it might be
beneficial.”

### 1.5 Catheter ablation of AF

With the development of radiofrequency catheter ablation techniques for other arrhythmia types, there was much interest in the potential for ablative therapy for AF. In 1998, Haïssaguerre et al investigated the spontaneous initiation of AF in paroxysmal AF patients using multi-electrode catheters and identified the PVs as the source of the majority (94%) of triggering atrial ectopy. Following this, ablative strategy for paroxysmal AF has evolved from targeting PV foci to encirclement of the superior PVs (where the majority of foci were identified) to individual encirclement of all four PVs to elliptical encirclement of ipsilateral PV pairs with confirmation of electrical PVI. As discussed in the section on the pathophysiology of AF, autonomic neural dysregulation and structural remodelling can also contribute to the initiation and maintenance of AF in certain patients, and additional atrial ablation may also be required, particularly in patients with more persistent forms of AF, evidence of structural disease or where PVI has not been of benefit.

Given the relatively limited ability of pharmacological treatment to maintain sinus rhythm along with the issues of drug toxicity, a number of randomised controlled trials have compared catheter ablation with medical therapy. As these studies were undertaken during the evolution of catheter ablation of AF, the ablation end-points for PV ablation were varied, including anatomic encirclement only, diminution of PV electrogram amplitude, or electrical isolation of the PVs. Studies included patients with paroxysmal AF only, persistent AF only, or a mixed cohort. Three of these studies randomised anti-arrhythmic drug-naïve patients, while the remainder enrolled patients with drug-refractory AF. Despite these differences, catheter ablation was consistently shown to reduce AF recurrence compared to medical therapy in each of these trials, with a meta-analysis showing an OR for recurrent AF of 0.37 (95% CI 0.29 - 0.48) for drug-refractory patients and 0.52 (95% CI 0.30 - 0.91) for drug-naïve patients. This effect is further enhanced when considering studies exclusively or predominantly consisting of patients with
paroxysmal AF, with a meta-analysis demonstrating an OR for freedom from recurrent AF of 15.8 (95% CI 10.1 - 24.7),\textsuperscript{92} and the subsequent ThermoCool trial giving an OR of 9.9 (95% CI 4.5 - 21.8).\textsuperscript{88} Nevertheless, there remains a benefit of catheter ablation in patients with persistent AF, with a meta-analysis specifically for these patients showing an OR for freedom for AF recurrence of 3.0 (95% CI 2.1 - 4.5).\textsuperscript{93}

In addition to reduced AF recurrence, quality of life, as assessed by both general health and AF-specific questionnaires, has also been shown in several studies to be improved by catheter ablation.\textsuperscript{94-96} As a result of this, current international guidelines now recommend catheter ablation for symptomatic paroxysmal AF refractory to at least one antiarrhythmic drug, and ablation for persistent AF in this scenario is deemed reasonable.\textsuperscript{97} Furthermore, catheter ablation is also reasonable for symptomatic paroxysmal AF prior to initiation of an anti-arrhythmic drug, and can be considered for persistent AF.

Notably, there is a requirement in these guidelines that patients are symptomatic, and this relates to the fact that, to date, there is no robust, randomised evidence that catheter ablation is of benefit in other areas, such as reducing stroke-risk.\textsuperscript{59} This is largely due to the relative infrequency of cerebrovascular events, particularly in the era of effective anticoagulation options, but it is hoped that clearer data will be obtained from two very large studies that are currently underway. The Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial (ClinicalTrials.gov Identifier: NCT00911508) has completed recruitment, with 2204 patients randomised to catheter ablation or medical therapy (rate-control or pharmacological rhythm-control), with a composite endpoint of total mortality, disabling stroke, serious bleeding, or cardiac arrest. The Early Treatment of Atrial Fibrillation for Stroke Prevention (EAST) trial (ClinicalTrials.gov Identifier: NCT01288352) has a target recruitment of 2745 patients, and is different in that it is comparing “usual care”, specified as initial rate-control with progression to rhythm-control if symptoms remain uncontrolled, with an early rhythm-control strategy encompassing antiarrhythmic drug therapy, catheter ablation and electrical cardioversion. In this study, the primary endpoint is a
composite of cardiovascular death, stroke and hospitalisation due to worsening of heart failure or an acute coronary syndrome.

While the outcomes of these randomised controlled trials are awaited, some circumstantial evidence is emerging that catheter ablation may lower the risk of stroke. A large study of 37,908 registry patients enrolled in the Intermountain Atrial Fibrillation Study compared the stroke-rate in patients who had undergone ablation for AF (n=4212) with the rates in patients with AF but without ablation (n=16,848) and in individuals without a history of AF (n=16,848). Patients were age- and sex-matched in 1:4:4 ratios. The authors found that after 12 months of follow-up, 893 (2.4%) of patients had suffered a stroke. The rate in patients with AF who had undergone ablation was significantly lower than in those with AF without ablation, but was no different to that for patients without AF (1.4% vs. 3.5% vs. 1.4%, P trend <0.0001). After stratifying long-term stroke risk (mean follow-up 2.9±2.9 years) by age and by CHADS2 score, these findings remained consistent, though were no longer statistically significant at extremes of age (≥80 years) or CHADS2 score (≥5), likely due to relatively smaller numbers in these strata combined with an increasing risk of non-AF-related strokes. These findings were mirrored by a further study which examined 801 propensity-matched pairs of patients with AF, with one patient treated with catheter ablation and one managed with antiarrhythmic drugs without ablation making up each pair. Again, the rate of stroke or transient ischaemic attack was significantly lower in the catheter ablation patients (3.4%) compared to medically-managed patients (5.5%), with a hazard ratio of a cerebrovascular event following catheter ablation of 0.62 (95% CI 0.44 - 0.86, P=0.005). While, in both studies, these data are not derived from randomised trials, they provide a potential indicator that improved maintenance of sinus rhythm may be of relevance to one of the major risks associated with AF.

1.6 Efficacy of catheter ablation

While catheter ablation has been consistently shown to provide improved freedom from AF compared to medical management, nevertheless, success rates following a single procedure remain
recurrently poor and are significantly lower than those for ablation procedures for most other supraventricular arrhythmias.\textsuperscript{100,101} Recurrence of atrial tachyarrhythmia (AT; comprising AF, atrial flutter or atrial tachycardia), either symptomatic or asymptomatic, has been reported to occur in more than 1 in 2 patients in long-term follow-up after ablation.\textsuperscript{102,103} Outcomes for paroxysmal AF are better than for persistent AF,\textsuperscript{104} and although success rates have gradually increased as procedural techniques have evolved, even in contemporary studies of paroxysmal AF patients ablated using radiofrequency energy, freedom from AF at one-year follow-up after a single procedure has only approached 70%.\textsuperscript{105} These disappointing success rates may contribute towards the difficulty in establishing clear prognostic benefits, such as stroke-reduction, of catheter ablation over medical therapy.

Recurrence of AT can occur at any time following catheter ablation of AF. While the majority occur in the first 6 months after ablation, first recurrences have been seen more than four years later.\textsuperscript{103} AT recurrence in the immediate aftermath of left atrial ablation is particularly common,\textsuperscript{106-108} and the frequency and extent of episodes can exceed those experienced prior to ablation in around 15% of patients.\textsuperscript{109}

### 1.7 Early recurrence of AT

It has long been recognised that early recurrences of AT (ERAT) occurring soon after ablation may not necessarily portend longer-term arrhythmia recurrence,\textsuperscript{109,110} with up to 60% of patients experiencing ERAT going on to have a successful outcome in the longer-term.\textsuperscript{97} Accordingly, international consensus guidelines recommend a three-month ‘blanking period’ following AF ablation during which AT recurrences “should not be classified as treatment failure”.\textsuperscript{97} However, data have also shown that individuals with ERAT have lower long-term success rates than those without early recurrence,\textsuperscript{106,111-114} and that patients with ERAT who undergo early re-ablation have improved freedom from AF at 12 months,\textsuperscript{115,116} suggesting that ERAT may be of clinical relevance.

The mechanisms leading to ERAT are not fully understood but are commonly attributed to a
number of transient pro-arrhythmic factors. These include: post-ablation inflammation,\textsuperscript{117,118} temporary autonomic imbalance,\textsuperscript{42,119} or the time taken for the lesion set deployed to mature.\textsuperscript{120} Whilst PV reconnection has been shown to be associated with long-term arrhythmia recurrence in paroxysmal AF,\textsuperscript{121-123} these transient factors would not be expected to lead to late AF recurrence. However, the time point at which these transient causes of ERAT give way to arrhythmia episodes related to PV reconnection has not been clearly established.

1.7.1 Post-ablation inflammation

Inflammation has been identified as an important cause for the initiation and maintenance of AF, including after major inflammatory insults such as cardiac surgery.\textsuperscript{118,124} Radiofrequency catheter ablation of cardiac tissue also stimulates a strong inflammatory response, with histological examination demonstrating infiltration of inflammatory cells into the ablated area and measurement of serum markers of inflammation showing an increase following ablation.\textsuperscript{117,125,126} As the time-course of the inflammatory phase following AF ablation was unclear, a recent study set out to determine this using serum markers of inflammation and myocardial injury.\textsuperscript{127} Lim and colleagues serially tested 90 patients undergoing radiofrequency AF ablation at baseline and at one day, two days, three days, seven days and one month after ablation for serum levels of high-sensitivity C-reactive protein, Troponin T, creatine kinase-MB, as well as white cell and neutrophil counts. The authors found that the inflammatory markers (high-sensitivity C-reactive protein, white cell count and neutrophil count) all peaked by three days following ablation, remained elevated compared to baseline at seven days, but had returned to baseline levels by one month. For markers of myocardial injury (Troponin T and creatine kinase-MB), a peak was seen at day one post-ablation, with a return to baseline by day seven. Ablation time was identified as an independent predictor of Troponin T release, in keeping with previous studies.\textsuperscript{126,128} They also sought to determine the time-course of the pro-thrombotic state following AF ablation using measurement of fibrinogen and D-Dimer, and found that these markers peaked at seven days post-ablation, and although fibrinogen had returned
to baseline by one month, D-Dimer levels remained slightly elevated at this time point.

These data suggest that the inflammatory phase following AF ablation resolves within the first month. Of note, the extent to which high-sensitivity C-reactive protein was raised was the only independent predictor of ERAT in the first few days after ablation, but none of the markers of inflammation or myocardial injury were predictive of post-blanking period AT recurrence.

1.7.2 Autonomic imbalance

As discussed in the section on the pathophysiology of AF, autonomic dysregulation can be a potential trigger for AF and has therefore been mooted as a potential ablation target. However, even in the absence of specific targeting of autonomic ganglionated plexi, the autonomic nervous system is known to be affected by standard PVI ablation. Hsieh et al examined heart rate variability changes in 37 patients with paroxysmal AF, 30 of whom underwent a PVI procedure and seven of whom had a transseptal puncture performed but no ablation. Heart rate variability measures included time-domain (standard deviation of RR intervals and root-mean-square of differences of adjacent RR intervals) and frequency-domain (low frequency, high frequency, and low-frequency/high-frequency ratio) parameters, and were obtained pre-ablation and one week, one month, and six months after ablation. The authors found a significant decrease in measures of sympathetic and, particularly, parasympathetic activity, with a corresponding increase in the mean sinus rate, one week after ablation in patients who underwent PVI. However, these changes had resolved back to baseline by one month post-ablation. There were no changes in heart rate variability parameters in the patients who underwent transseptal puncture but no left atrial ablation. This study of the time-course of autonomic dysfunction therefore suggests that this phase resolves within one month.

1.7.3 Maturation of ablation lesions

The time-course of maturation of ablation lesions has been studied in animal models through
pathological examination at various time-points after ablation. Huang and co-workers performed catheter ablation in the ventricles of dogs and undertook pathological examinations of the ablated areas four to five days later. This showed that the lesions had a well-demarcated margin, and microscopic examination demonstrated “circumscribed areas of coagulation necrosis with a peripheral zone of cellular infiltration.” Similarly, a study by Wittkampf and colleagues in another canine model identified homogeneous lesions with a distinct margin after seven days. Collectively, these data suggest that ablation lesions mature to their fully-developed state within approximately one week.

1.8 **Rationale for and duration of the 'blanking period'**

From the studies described above, there are compelling reasons for the application of a blanking period. Recurrence of arrhythmia due to any of these transient factors should not lead to later recurrence, and it is therefore appropriate not to deem ERAT occurring during the time-course of these factors to be clinically relevant as this ensures that unnecessary re-interventions are avoided. However, current international consensus guidelines recommend a three-month blanking period, whereas the studies of transient pro-arrhythmic factors described above have demonstrated that these resolve with the first month after AF ablation. The rationale for a blanking period duration of three-months is based on clinical studies of the relationship between recurrence within the first three months and subsequent recurrence. Although such studies have shown that a significantly greater proportion of patients with ERAT in the first 3 months post-PVI go on to have later recurrence compared those without ERAT, the main concern regarding taking ERAT to signify later recurrence has been the poor positive predictive value of this finding. Studies have shown that between 30% and 60% of patients with ERAT in the first three months post-ablation do not experience further AT recurrence during post-blanking period follow-up, and the authors of the consensus statement have accordingly deemed three months to be the most appropriate duration for the blanking period. However, given that some early episodes of AT post-
PVI are likely to be related to transient pro-arrhythmic factors that do not cause later recurrence, this is to be expected. The primary issue, therefore, is not whether the blanking period should exist at all, but rather how long it should be.

1.9 Timing of ERAT within the blanking period

While several studies have examined the overall relationship between ERAT and later AT recurrence, relatively few have explored the relevance of the timing of these occurrences within the blanking period. One study that did do this, by Themistoclakis et al, included 1298 patients undergoing PVI and classified patients with ERAT by the month of the first occurrence. The proportion of patients going on to suffer post-blanking period recurrences was 44% if the first episode of ERAT was in month 1, 69% if in month 2 and 98% if in month 3, indicating a high likelihood of later recurrence if ERAT began in months 2 or 3. A further study, by Bertaglia et al, found that the rate of late recurrence was significantly higher in those with a first recurrence in month 2 or 3 (80%) compared to first ERAT in month 1 (56.7%). As with the study by Themistoclakis et al, the main focus was on the timing of the first recurrence, rather than the time period in which ERAT episodes persisted. As it is entirely conceivable that an individual might have ERAT related to transient pro-arrhythmic factors in the first month post-ablation followed by ERAT related to PV reconnection in month 2 onwards, the timing of the last episode of ERAT would seem to be more valuable than that of the first episode. Added to this is the fact that the incidence of first AT recurrences is known to be highest in the first month, with diminishing levels in months 2 and 3, making analysis of outcomes for these small numbers of patients difficult.

There are only three studies that have provided data regarding timing of ERAT episodes regardless of whether this was the initial episode or a subsequent recurrence. In a re-analysis of data from Bertaglia et al, 29 patients had on-going ERAT in months 2-3 having had their first episode in month 1, and 5 patients had their first ERAT episode in months 2-3. Of these 34 patients with ERAT in months 2-3 (regardless of the timing of the first episode), 30 (88%) went on to have AT
recurrence beyond the blanking period, compared to 11 of 109 (10%) patients without month 2-3 ERAT ($P<0.0001$). In contrast, a study by Joshi et al using external loop recorders for automatic detection of AF recurrences in the first 3 months post-PVI (divided into 2-week time periods) did not show AF recurrence in each 2-week period to be predictive of post-blanking AF recurrence up to 12 months post-PVI in a multivariate model.$^{107}$ However, specific data on the proportion of patients with AF recurrence in each 2-week period that went on to suffer post-blanking AF was not presented and therefore cannot be analysed further. As the study only comprised a total of 72 patients and utilised narrow time-periods, such that only between 22% ($n=16$) and 54% ($n=39$) of subjects experienced ERAT within each time-period, the study may well have been underpowered to detect a difference between groups.

More recently, a larger study of 300 AF patients was conducted by Liang and co-workers.$^{134}$ In this study of the first six weeks following ablation, ERAT episodes were classified into ‘early’ (weeks 1-2), ‘intermediate’ (weeks 3-4) and ‘late’ (weeks 5-6). The authors found that ERAT at any time in this six-week period was predictive of treatment failure, but particularly if there were multiple episodes extending into the ‘late’ period. A re-analysis of these data shows that 50 of 59 (85%) patients with ERAT in weeks 5-6 went on to have later recurrence, compared to 82 of 241 (34%) patients with either no ERAT or ERAT confined to the first four weeks ($P<0.0001$). These findings are similar to those of Bertaglia et al, and imply that recurrences that occur beyond the first four weeks after ablation are clinically relevant. This is also consistent with the notion that transient pro-arrhythmic factors resolve within the first month after ablation, and therefore the true blanking period should be four weeks rather than three months.

### 1.10 Later (post-blanking period) recurrence of AT

Recurrence of AT beyond the three-month blanking period is deemed under current guidelines to be clinically relevant and merits re-evaluation of the treatment strategy.$^{97}$ This may include re-initiation of anti-arrhythmic medications or consideration of a repeat ablation procedure. In patients with
paroxysmal AF, the great majority of later AT recurrence is due to electrical reconnection of one or more PVs, despite initial isolation at the original PVI procedure. This has been demonstrated in a number of studies, with reconnection of multiple PVs of particular importance.\textsuperscript{121-123} This would be intuitive, as the greater the number of PVs that reconnect, the higher the likelihood of an arrhythmic PV resuming electrical contact with the left atrium. AF triggers originating from outside the PVs can also occur, but are thought to be relevant in only around 10% of cases in paroxysmal AF.\textsuperscript{22,135}

1.11 PV reconnection

In the early development of PVI procedures, PV reconnection was extremely common. In one 2003 study, 79% (88/112) of PVs that were successfully isolated at the index procedure were found to have reconnected at follow-up electrophysiology study.\textsuperscript{77} However, despite improvements in technology, the proportion of PVs remaining chronically isolated following radiofrequency ablation has remained disappointingly low. In the EFFICAS I trial, published in 2014, 39 of 80 (49%) ipsilateral PV pairs affecting 65% of patients were found to be reconnected at a protocol-driven repeat electrophysiology study three months after the index PVI procedure.\textsuperscript{136} Similarly, in the arm of the 2013 GAP AF study in which circumferential circles around ipsilateral PV pairs were completed, 70% of patients exhibited late reconnection.\textsuperscript{137}

The mechanism of PV reconnection is related to delivery of inadequate ablation at sites within the encircling lesion set, resulting in only temporary or non-transmural tissue damage. After tissue healing, this results in residual conduction of electrical activity from the PV to the left atrium, thereby allowing triggers originating within the PVs to initiate AF in the atria once again. Accordingly, this has led to much interest in the delivery of effective, transmural ablation lesions.

1.12 Ablation lesion formation

Ablation lesions are created by the delivery of high frequency alternating current from a catheter tip to tissue, causing resistive heating as the current passes through the tissue. Resistive heating only
occurs immediately adjacent to the catheter tip, as it decreases with the 4\textsuperscript{th} power of the distance from the tip. From this zone of resistive heating, heat spreads further into the tissue by conduction, and tissue coagulation occurs when the local temperature reaches 48-50\degree C. However, thrombus formation, which increases the risk of thromboembolic complications, has been shown to occur when the electrode-tissue interface temperature rises above 73\degree C\textsuperscript{138} and therefore careful attention must be paid to tissue temperature during ablation.

The size of the lesion created is determined by the energy entering the tissue. The total energy delivered, measured in Joules, is in turn dependent on the rate of energy delivery, known as the power (measured in Watts or Joules per second), and the duration of the application, measured in seconds. Additionally, energy delivered from the tip of the ablation catheter is divided between the tissue and passing blood, and the relative proportions are largely dependent on the contact between the catheter tip and the tissue.

1.12.1 Power

Power represents the rate of energy delivery to tissue, measured in Watts (W). As total energy delivery, which is a product of power and time, is an independent predictor of transmural lesion formation,\textsuperscript{139} power plays a vital role in the formation of ablation lesions. Power is also related to the size and depth of the lesion created,\textsuperscript{130,140} though this relationship is not linear. In a study by Guerra et al, ablation lesions were created in porcine ventricular myocardium in an in-vitro set-up with a variety of irrigated ablation catheters using a range of power settings and application durations with a fixed contact force (10g).\textsuperscript{141} Lesion volumes were then calculated for each application by cross-sectioning the myocardial tissue. For application durations of 30 seconds, increasing the power delivery from 20W to 35W approximately trebled the lesion volume for all six catheters tested.

From a clinical outcome perspective, it might be expected that increased power settings would result in improved lesion formation and consequently better patient outcomes. However, it
must also be taken into consideration that larger, deeper lesions may also expose the patient to the risk of complications. This was examined in a systematic review of studies investigating power settings in AF ablation. This identified 6 efficacy studies and 13 safety studies, although study heterogeneity prevented a meta-analysis from being performed. The authors found that efficacy improved with increasing power output, with low efficacy for powers of <30W, good efficacy for a power range of >30 to <45W, and better efficacy for higher powers of ≥45W. However, while power settings of <45 were found to be safe, a higher risk of complications was identified for power of ≥45W, unless application durations were shortened to 15-20secs. This last finding is in keeping with the concept of total energy delivery, where the rate of energy delivery (power) and duration of energy application (time) combine to determine the energy delivered to that tissue site.

1.12.2 Time

Duration of energy application contributes to total energy delivery and is therefore an important factor in lesion creation. However, it is not in itself an independent predictor of transmural lesions. It has previously been demonstrated in an animal model that application duration contributes little to lesion size beyond 20 seconds, and therefore increasing the duration is likely to have a lesser impact than increasing other parameters that contribute to lesion formation by the same factor. Indeed, in the study of lesion volumes by Guerra et al, doubling the application duration from 30 seconds to 60 seconds with a fixed power output of 20W resulted in an approximate doubling of lesion volume, as compared to an approximate trebling of lesion volume with a less than two-fold increase in power (20W to 35W), as discussed above.

1.12.3 Contact force

The force applied by the catheter tip on the myocardium and the resultant degree of contact between these two surfaces influences the proportion of energy that is directed into the tissue rather than into the passing bloodstream. This was a subject of interest from the early stages of the
evolution of radiofrequency ablation, and studies in animal models demonstrated that good catheter contact resulted in significantly greater tissue heating and lesion size compared to average or poor contact. However, it was not possible to translate this knowledge into clinical practice until the last few years, during which time the advent of contact force-sensing took place. One of the earliest reports of a contact force-sensing catheter was by Yokoyama and colleagues in 2008, using a catheter which integrated three optical fibres to measure microdeformation of its tip (TactiCath, Endosense SA, Geneva, Switzerland). This study validated the accuracy of the catheter’s contact force measurement, and went on to demonstrate that increasing contact force plays a significant role in lesion size, but also in thrombus formation and steam pops. Subsequently, a further contact force-sensing catheter has been developed that detects tissue contact via a precision spring mounted towards the tip of the catheter (SmartTouch, Biosense Webster, Inc., Diamond Bar, California, USA).

More recently, clinical studies have demonstrated that contact force during radiofrequency application affects ablation outcomes. The TOCCATA study, published in 2012, confirmed the safe use of the TactiCath catheter, and a further analysis of 12-month follow-up data was performed for 32 patients with paroxysmal AF undergoing PVI in that study. Average contact force was found to correlate with outcome, with all 5 patients with an average contact force <10g experiencing AF recurrence compared to only 20% of the 10 patients with an average contact force >20g. These findings were supported by the EFFICAS I study, in which PVI using a circumferential PVI technique was performed using the TactiCath catheter with the operator blinded to contact force data. Study participants were then brought back for a repeat electrophysiology study after 3 months and were assessed for the presence of PV reconnection according to an eight-segment model (four segments per circumferential PVI circle). Average and minimum contact force values were identified for each segment, and the authors found a significant difference in the average and minimum contact force between segments with and without reconnection. The minimum value \( P<0.0001 \) was more predictive than the mean \( P=0.022 \), in keeping with the concept that a line of ablation is
only as strong as its weakest link. As the relationship between PV reconnection and arrhythmia recurrence has been well-established, these findings provided a logical explanation for the inferior outcomes seen with lower average contact force in the TOCCATA study.

A number of further clinical studies have subsequently demonstrated the benefit on clinical outcomes of using contact force technology\textsuperscript{150,151}, culminating in a recent meta-analysis that showed a 37\% reduction in AF recurrence compared to standard technology after a median of 12 months of follow-up.\textsuperscript{152}

1.13 Markers of lesion quality

In order to improve the efficacy of PVI, there has been an increasing focus on obtaining real-time feedback on the quality of delivered ablation lesions. While the gold-standard may eventually involve real-time visualisation of tissue changes during ablation using, for example, ultrasound, this technology remains some way off and therefore surrogate measures of lesion quality are commonly utilized. Given the roles of contact force, time and power in lesion creation, recent developments in this area have focussed on a combination of these factors.

1.13.1 Force-Time Integral

With the emerging role of contact force as an important determinant of lesion size and the known contribution of time, these two factors have been combined in a parameter termed the “Force-Time Integral” (FTI).\textsuperscript{149,153} FTI, measured in gram-seconds (gs), provides a simple estimate of lesion quality and has been adopted increasingly in clinical practice. In addition to examining contact force data, the EFFICAS I study also sought to establish the relationship between FTI and PV reconnection.\textsuperscript{136} The authors found that lower minimum FTI for a segment was also predictive of segment reconnection ($P=0.0007$), with a trend seen for average FTI ($P=0.090$). In further analysis, it was found that segments with a minimum FTI of more than 400gs had a significantly higher probability of remaining isolated (95\%) than those with a minimum FTI less than 400gs (79\%) ($P=0.0004$).
Accordingly, the authors recommended positioning the ablation catheter to achieve a contact force of at least 10g and preferably 20g, and continuing energy application for each ablation lesion until a FTI value of at least 400gs has been achieved.

This “target value” was tested prospectively in the EFFICAS II study, in which 24 patients underwent PVI guided by a target contact force of 20g (range 10-30g) and minimum FTI value of 400gs, followed by a repeat electrophysiology study after 3 months to assessment for PV reconnection. Using this strategy resulted in a reduction in the proportion of reconnected PVs to 15% compared to 28% in EFFICAS I, and in the proportion of patients with reconnection to 37.5% from 65%. Such target-guided ablation may therefore be a promising strategy for the future.

However, FTI as a marker of lesion quality suffers from two significant limitations. Firstly, it ignores the important role of power delivery in lesion creation. Indeed, in EFFICAS I, power settings used by operators varied between 10 and 40W, which makes interpretation of the derived FTI target very difficult, as a 400gs radiofrequency application using 40W will create a much larger lesion compared to one produced with the same FTI value using 10W. Secondly, calculation of FTI relies on simple multiplication of contact force by application time, whereas it is known that the relationship between these parameters is dynamic, with both making differing contributions to lesion formation.

1.13.2 Generalizability of the FTI target value

As the FTI target value of 400gs was derived from the EFFICAS I study, which used the TactiCath contact force-sensing catheter, it may not be appropriate to extrapolate these data to SmartTouch, the other catheter with contact force-sensing capability. The mechanism of contact force-sensing is intrinsically different between these two catheters, and there are data to suggest differences in lesion creation, as estimated by impedance changes, for the same apparent contact force applied.

Furthermore, only a single FTI target value for all segments of the circumferential PVI circle was identified in EFFICAS I. This assumes that tissue thickness, and therefore the ablation depth
required, is the same for all areas of the left atrium. However, it is well-recognized from anatomical studies that tissue thickness varies considerably between different regions of the left atrium, and therefore applying a “one size fits all” approach may result in unnecessarily excessive ablation on the thin posterior wall with an associated risk of oesophageal fistula formation, a major complication with an extremely high fatality rate.

### 1.13.3 Ablation Index

Recently, a novel lesion marker has been described which differs from FTI by both incorporating power delivery and combining this with contact force and time in a “weighted” logarithmic exponential equation. This formula, termed “Force-Power-Time Index” in the index abstracts, was shown to accurately predict lesion depth in both the atrium and ventricle in canine models. It has now been incorporated into the CARTO 3 Version 4 3-dimensional mapping system (Biosense Webster, Inc.), where it is termed “Ablation Index”. Despite its potential advantages over FTI, the relationship between Ablation Index and PV reconnection has not yet been prospectively studied.

### 1.14 Areas requiring further investigation

As discussed in this section, delivering enduring PVI with radiofrequency energy remains a goal that has, to date, been difficult to achieve. If durable PVI could be performed, it would be expected that success rates for PVI would improve significantly. However, until operators are able to consistently achieve enduring PVI at the index procedure, it is conceivable that the optimal strategy at present is to bring all patients back for a routine repeat electrophysiology study with re-isolation of reconnected PVs as required. In light of relatively recent studies demonstrating that 65-70% of patients have reconnection of one or more PVs, the majority of patients remain vulnerable to AF recurrence related to PV reconnection. However, the effect of assessment and re-isolation of reconnected PVs in all patients at two months following their index procedure during the first year of follow-up, in terms of both freedom from AF and quality of life, is currently unknown.
It may also be possible to better predict those patients who develop PV reconnection, and therefore focus a strategy of early re-intervention on those who are most likely need it. One area very relevant to this is the relevance of ERAT, and particularly ERAT occurring beyond the four-week time-span of the transient factors that promote arrhythmia following radiofrequency PVI. However, the relationship between ERAT and PV reconnection has never previously been investigated.

In moving towards the goal of enduring PVI lesions, use of a FTI target value has made some progress. However, as discussed in this section, FTI has its limitations and although very recent data have shown that use of a FTI target reduced the proportion of patients with PV reconnection, more than one third of patients remained at risk of reconnection-related AF recurrence. The Force-Power-Time Index formula incorporated into Ablation Index offers several potential advantages over FTI, but its relationship to PVI segment reconnection or potential target values have not been studied. Furthermore, regional differences in target values for either FTI or Ablation Index have not previously been identified despite the known variation in left atrial wall thickness.

Linked to the first-time delivery of enduring ablation lesions is the role of re-ablation at sites within the encircling PVI line that reconnect acutely within the waiting period that is recommended following achievement of PVI in the international consensus statement. Controversy exists over whether further ablation is truly effective at sites showing either spontaneous acute reconnection or reconnection that is unmasked by the administration of adenosine. This is because oedema is known to develop rapidly following radiofrequency energy application, which may preclude the subsequent delivery of effective ablation at the same site. While previous studies have compared acute reconnection sites with sites of late reconnection identified at repeat procedure for clinical arrhythmia recurrence, this has never previously been investigated prospectively and systematically.

1.15 Aims of the work

In light of the areas requiring further investigation described above, this work aimed to examine a
number of topics relevant to these. Firstly, since consistent durable PVI with radiofrequency energy remains elusive, we planned to test the hypothesis that a routine repeat electrophysiology study with re-isolation of reconnected PVs after two months, irrespective of symptoms, provides better outcomes than current standard care. We aimed to do this by performing a randomised controlled trial of the two strategies, with outcome measures including freedom from AF, quality of life and complication rates.

Secondly, as the association between ERAT and PV reconnection is unknown, we aimed to investigate the relationship of the presence and timing of ERAT with PV reconnection by studying ECG data recorded during the three-month blanking period by patients undergoing protocol-mandated repeat electrophysiology study two months after their initial PVI.

Thirdly, in light of the potential advantages offered by Ablation Index in the delivery of enduring lesions, we aimed to examine the relationship between this novel lesion quality marker and PVI segment reconnection, and to identify target values for different regions of the left atrium. We planned to do this by comparing Ablation Index values recorded at the time of the initial PVI with PV reconnection information obtained in patients returning for repeat electrophysiology study after two months.

The final aim of this study was to systematically investigate whether further ablation at sites of acute PV reconnection following successful PVI is truly effective, by comparing such sites with sites of late reconnection in patients undergoing repeat electrophysiology study two months after their initial PVI.
2 METHODS

As individual studies were performed using the same study population, many of the methods used were common to all studies and are described in this section. Specific methods and statistical analyses performed for individual studies are presented in the relevant study results sections.

2.1 Study population

Patients were recruited from the heart rhythm clinics at Liverpool Heart and Chest Hospital. Patients listed for radiofrequency ablation of paroxysmal AF and felt to be suitable for inclusion by their responsible Consultant were approached and offered information regarding the study. Those interested in taking part were then provided with the Participant Information Sheet (PIS) by a member of the research team, either in person with the opportunity to take this literature home to review it, or by post. The PIS contained contact phone numbers and an email address for the research team should the patient have wished to get in contact with any queries. A follow-up phone call was arranged for one week later to provide a further opportunity for discussion. If the patient wished to enrol, they were approached again at the time of their Pre-admission visit or attendance for cardiac imaging and were asked to review the study consent form and provide written consent if they wished to participate.

Specific inclusion and exclusion criteria were as follows:

Inclusion criteria:

- Aged over 18 years
- Current pattern of paroxysmal AF (defined as ECG proven episodes of AF which are self-limiting and last less than seven days on each occasion, or which were cardioverted electrically or pharmacologically less than 48 hours from onset)
- Due to undergo PVI by radiofrequency ablation

Exclusion criteria:

- Inability or unwillingness to receive oral anticoagulation with warfarin or alternative
• Anticoagulant drug

• Previous ablation procedure for AF

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

• Current pattern of persistent (episodes of AF which last longer than seven days or which last longer than 48 hours but require electrical or pharmacological cardioversion) or permanent AF

• Prior prosthetic mitral valve replacement

• Severe structural cardiac abnormality (significant congenital heart disease likely to affect cardiac haemodynamics, including atrial septal defect with a significant shunt)

• Reversible cause for AF

• Known infiltrative cardiomyopathy

• Known severe left ventricular systolic function (ejection fraction <35%)

• Pregnancy

2.2 Study design

The primary study was designed as a prospective randomised, controlled, non-blinded trial. Eligible consenting patients were randomised, via a computerised randomisation process, in a one-to-one ratio to one of two groups:

• Repeat study group: Following an initial PVI procedure, all patients (regardless of early AF recurrence) underwent a repeat electrophysiology study at eight to ten weeks post-initial PVI, with re-isolation of any PV reconnection identified

• Standard care group: Patients underwent an initial PVI procedure as the only planned procedure. Further management was determined by post-blanking period AF recurrences at the responsible Consultant’s discretion as per standard care
2.3 Initial PVI procedure

2.3.1 Pre-procedure management

Patients taking Amiodarone had this drug stopped a minimum of 2 months prior to their PVI procedure in view of the long half-life of this drug. Where possible, it was replaced with another anti-arrhythmic drug. Other anti-arrhythmic drugs, including beta-blockers, were stopped five days prior to the procedure. All patients anticoagulated pre-procedurally with warfarin continued this in the peri-procedural period. An INR level between 2.0 and 3.5 was considered acceptable. For patients taking novel oral anticoagulants (direct thrombin or Factor Xa inhibitors), peri-procedural use was according to local guidelines and/or operator preference.

Echocardiographic data was collected as part of routine care, including left atrial diameter and left ventricular ejection fraction. Where possible, patients also underwent detailed cardiac imaging prior to the ablation procedure to produce a three-dimensional reconstruction of the left atrial anatomy as part of routine care. Where possible, this was in the form of a cardiac magnetic resonance imaging (MRI) scan as this has no associated radiation exposure, but where cardiac MRI was not possible, a cardiac computed tomography (CT) scan was performed instead.

Trans-oesophageal echocardiography was not performed routinely, but was undertaken at the discretion of the operator prior to the procedure to exclude left atrial thrombus as per routine care (indications included sub-therapeutic INR readings in the four weeks prior to the ablation procedure for those taking warfarin, or missed doses for those taking alternative oral anticoagulants).

In addition to data on baseline characteristics, co-morbidities, medications and cardiac imaging, patients had their quality of life and general health perceptions recorded at recruitment using the validated AF-specific AFEQT questionnaire. Their functional status was also assessed according to EHRA and CCS classifications.
2.3.2 PVI procedure

PVI was performed in a standard fashion under general anaesthesia (in the majority of cases) or conscious sedation, as previously described. Vascular access was gained under direct ultrasound guidance, as is standard in our institution. One or two transseptal punctures were made using fluoroscopic guidance with additional pressure monitoring, following which intravenous unfractionated heparin boluses were administered to maintain an Activated Cloting Time of approximately 300 seconds.

An electroanatomical map of the left atrium was created using a three-dimensional navigation system (CARTO 3, Biosense Webster, Inc.) and, whenever possible, integrated with the MRI or CT reconstruction of the left atrium (CartoMerge, Biosense Webster, Inc.). Patients then underwent PVI in a wide area circumferential ablation (WACA) pattern using a ThermoCool SmartTouch irrigated tip contact force-sensing radiofrequency ablation catheter (Biosense Webster, Inc.). Non-steerable sheaths were used for all cases; the choice of sheath was as per operator preference and therefore varied between cases. The default power setting was 30W, with limited ranges of 25-30W for the posterior wall and 30-35W for other regions of the left atrium. A contact force of between 5 and 40g with radiofrequency application duration of 20-40s was targeted at each site, aiming for local signal attenuation of >80%. Automated lesion tagging (VisiTag, Biosense Webster, Inc.) was used to mark the location of each lesion, with the following settings: Catheter Position Stability: Minimum time 10sec, Maximum range 2mm; Force Over Time: Time 30%, Minimum force 5g; Lesion tag size: 2mm. Point-by-point focal ablation was predominantly used, though “drag” lesions (a new lesion location marked based on catheter movement during a continuous burn) were allowed. As most procedures were performed under general anaesthesia, the improved catheter stability afforded by this allowed a relatively restrictive catheter position stability range of 2mm. A deliberate movement of the catheter tip of the operator of >2mm would therefore be recognised by the system and a new lesion would be created. However, this was noted to have limitations in terms of the time taken for the system to reset to a new lesion and a “drag” technique
was used less in later cases. Contiguous lesions around the WACA circle were aimed for. FTI, Ablation Index or minimum impedance drop targets were not used prospectively to guide ablation to allow for subsequent blinded analysis of association of these variables with late reconnection. No additional ablation to create left atrial linear lesions or of complex fractionated atrial electrograms was performed, and no attempt was made to look for extra-PV triggers. Cavo-tricuspid isthmus ablation was permitted if atrial flutter had been documented and was either proven to be cavo-tricuspid isthmus-dependent or appeared typical on ECG. AF that persisted after PVI was terminated with electrical cardioversion. PVI was confirmed with a circular mapping catheter (Lasso NAV Eco, Biosense Webster, Inc.) placed sequentially in each of the PVs.

2.3.3 Assessment for acute PV reconnection

After a minimum of 20 minutes following isolation of that ipsilateral PV pair, individual PVs were re-checked for spontaneous reconnection by positioning the 20-pole circular catheter at the PV ostium and recording the presence or absence of PV signals, as per the recommendations of the international consensus statement. If PV signals were identified in both ipsilateral PVs within a WACA circle, activation timings (relative to a reference site) were compared to establish which PV was activated earliest.

Each WACA circle was divided into 6 segments (Figure 2.1). The segment containing the electrode bipole with the earliest activation was taken to be the most likely site of reconnection. Re-ablation on the WACA circle within this segment that resulted in isolation of the PV or a significant change in the activation pattern within the PV was required to confirm that segment as a reconnection site (Figure 2.2).
Figure 2.1  12-segment WACA model

Figure 2.1: Diagram showing the model used, with 6 segments per WACA circle

Figure 2.2  Example of re-ablation for acute PV reconnection

Figure 2.2: Screenshot showing the ablation lesions in a 3-dimensional map with integrated CT imaging from a patient with adenosine-mediated acute reconnection in the roof segment of the right superior pulmonary vein. A superior view is shown on the left and a cut-away view looking from the left atrium into the right pulmonary veins is shown on the right. The additional lesions added to the WACA line which re-isolated the pulmonary vein are marked with yellow arrows.
If no spontaneous reconnection was identified in a PV, intravenous adenosine (12-18mg) was then administered to unmask sites of dormant conduction, and the likely reconnected segment was again identified by the electrode bipole with earliest activation. Further ablation applications were performed on the WACA circle within the likely segment for all sites of unmasked reconnection. Where sustained PV reconnection was induced by adenosine, PV isolation or activation pattern shift with re-ablation was again required to confirm that segment as a reconnection site. For transiently unmasked PV reconnection, administration of further adenosine boluses after re-ablation to confirm successful re-isolation was required to establish that segment as a site of reconnection. No further waiting period was applied following re-isolation of reconnected sites.

Acute complete procedural success was defined as electrical isolation of all PVs. Partial procedural success was defined as electrical isolation of three or more, but not all, PVs. Procedural failure was defined as electrical isolation of less than three PVs.

2.3.4 Post-procedure management

Intravenous protamine was given at the discretion of the operator to reverse the effects of heparin at the end of the procedure. Oral anticoagulation was continued or restarted post-procedure as per hospital protocol and/or the operator’s preference, and was continued for a minimum of four weeks. The subsequent decision of whether or not to continue anticoagulation was made individually by the responsible clinician, based on the patient’s CHA2DS2-VASc score and patient preference. If patients were taking anti-arrhythmic medications pre-procedure, these (other than amiodarone), along with any rate-limiting agents, were restarted post-procedure and were stopped after 4 weeks. Beta-blockers and rate-limiting calcium channel-blockers were also stopped after 4 weeks unless required for another clinical indication. Re-initiation of therapy was permitted in the event of symptomatic documented recurrences of atrial tachyarrhythmia after cessation of anti-arrhythmic medication at 4 weeks.
2.4 Randomisation

Patients were enrolled prior to their initial ablation but randomization was delayed until immediately after the procedure in order to avoid possible bias or influence on the ablation.

Randomization was in a 1:1 ratio using a custom-written two- and four-block randomization program to either the Repeat Study (RS) or Standard Care (SC) group.

2.5 Repeat study group

A repeat electrophysiology study was arranged for 8-10 weeks after the initial PVI procedure. The repeat study was performed in the same way as outlined above for the initial procedure. Any anti-arrhythmic medications restarted since the initial procedure were stopped again 5 days prior to the repeat study. Peri-procedural and intra-procedural anticoagulation management were identical. As before, an electroanatomical map of the left atrium was created using the CARTO 3 three-dimensional navigation system and integrated where possible with the original MRI or CT reconstruction of the left atrium.

Each PV was assessed in turn for late reconnection with a 20-pole circular mapping catheter. All identified sites of reconnection were re-ablated using a ThermoCool SmartTouch ablation catheter, with ablation parameters as for the initial procedure. Once PV re-isolation had been successfully achieved, the procedure was ended. No additional left atrial ablation was performed. Heparin-reversal and post-procedural anticoagulation was as per the initial procedure. Anti-arrhythmic medications (other than amiodarone) could be restarted after the procedure at the operator’s discretion, but all were discontinued by 3 months following the initial PVI.

2.6 Standard care group

A three-month blanking period was applied as per current international recommendations. Patients with documented AT recorded during this period who were suffering significant symptoms could have an anti-arrhythmic medication (other than amiodarone) restarted or undergo electrical
cardioversion at the discretion of their responsible Consultant, as per current standard care. Repeat PVI was not performed during the blanking period as per international guidelines. Any reinitiated anti-arrhythmic drugs were stopped again at the end of the three-month blanking period. Patients who continued to suffer from symptomatic AT beyond three months were eligible to undergo repeat PVI, re-initiation of anti-arrhythmic drugs or direct current cardioversion as per standard clinical care at the discretion of their responsible clinician.

2.7 Follow-up

To maximise the likelihood of documenting AT recurrences following the PVI procedure(s), all patients were provided with a validated handheld ECG monitoring device (Omron HCG-801-E, Omron Healthcare, Kyoto, Japan) approximately 1 week prior to their initial PVI procedure, to be kept for the 12-month duration of the study. Patients were taught how to use this device and were instructed to self-record a 30-second ECG each day until the end of the study, with additional recordings whenever they experienced symptoms, however minor. Recordings were checked at the time of the initial PVI for compliance and ECG trace quality. All ECG recordings recorded during the primary outcome period were analysed by one of two experienced clinicians, who were blinded to patient randomisation. Where further review was required, the other observer provided an independent analysis. In rare cases where there was disagreement between observers, an anonymised recording was reviewed by the lead investigator for final adjudication. Recurrence of AT was defined as any documented AT (AF, atrial flutter or atrial tachycardia) lasting ≥30 seconds.

A 30-second recording showing AT throughout its duration would therefore constitute a documented recurrence. The number of separate days on which AT was documented was also recorded.

Clinical review appointments were arranged at approximately six weeks and three, six and twelve months after the initial PVI procedure. Data from the portable ECG monitors were downloaded at these visits and participants were asked to complete AFEQT quality of life questionnaires at the time of the six- and twelve-month visits. A study visit diagram is presented in
Figure 2.3 and a study time-line is shown in Figure 2.4:

Figure 2.3 Study time-line

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Time-point</th>
</tr>
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<tr>
<td></td>
<td>Recruit</td>
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</tr>
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<td>QOL form</td>
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<td>Cardiac MRI/CT</td>
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<tr>
<td>PVI procedure</td>
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</table>

* ”Repeat study” patients only

Figure 2.4 Graphical representation of study time-points

Figure 2.4: Graphical representation of procedure time points, blanking periods and recurrence periods during the study. For both randomized groups, the primary endpoint period began three months after the date of the initial ablation, and recurrence prior to this did not contribute to the primary endpoint. ERAT during the three-month blanking period was categorised into the first four weeks after the initial PVI procedure (month 1), and from this point until three months (SC group - months 2-3) or to the repeat study (RS group - month 2).
2.8 Safety and complications

All major complications and other adverse events were recorded. Definitions for major complications were derived from the international Expert Consensus Statement published in 2012.97

A major complication was defined as a complication that resulted in permanent injury or death, required intervention for treatment, or prolonged or required hospitalization for more than 48 hours. Definitions of individual complications were as follows:

- Cardiac tamponade – the development of a significant pericardial effusion, resulting in hemodynamic compromise, requiring elective or urgent pericardiocentesis, during or within 30 days of undergoing an AF ablation procedure.

- Stroke – rapid onset of a focal or global neurological deficit of ≥24 h duration, or <24 h duration if therapeutic interventions were performed (e.g. thrombolytic therapy or intracranial angioplasty), or available neuroimaging documents a new haemorrhage or infarct, or the neurological deficit results in death, where there is no other readily identifiable non-stroke cause for the clinical presentation.

- TIA – development of a new focal neurological deficit with rapid symptom resolution (usually 1 to 2 h), always within 24 h, without tissue injury documented on neuroimaging.

- Myocardial infarction – the presence of any one of the following criteria: (1) detection of ECG changes indicative of new ischemia (new ST-T changes or new LBBB) that persist for more than one hour; (2) development of new pathological Q waves on an ECG; (3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

- Severe pulmonary vein stenosis – a ≥70% reduction of the diameter of a PV or PV branch.

- Phrenic nerve paralysis – absent phrenic nerve function as assessed by a sniff test; considered to be permanent when it is documented to be present 12 months or longer following ablation.

- Oesophageal perforation or atrio-oesophageal fistula – perforation of the oesophagus or a connection between the atrium and the lumen of the oesophagus.
• Major vascular complications – a vascular access complication, including development of a hematoma, an AV fistula, or a pseudoaneurysm, which requires intervention such as surgical repair or transfusion, prolongs the hospital stay, or requires hospital admission.

• Death – within 30 days of the procedure

Any suspected major complication (as defined above) or other serious adverse event occurring in the course of the study, either whilst in hospital or during the period of follow-up, was reported as per the standard local Adverse Event Reporting procedure, and a data monitoring committee was convened to review interim safety data from the trial.

2.9 Endpoints

The primary endpoint was AT recurrence occurring after a three-month blanking period following the initial PVI. Pre-specified secondary endpoints were: time to first AT recurrence following the blanking period; total AT burden during the primary outcome period; quality of life six and twelve months after initial ablation, as quantified by the AFEQT questionnaire; and comparison of rates of major complications, as defined above.

2.10 Sample size calculation

A formal sample size calculation was performed assuming a 12-month single-procedure success rate of 64% in the “standard care” group and 90% in the “repeat study” group.

The single-procedure success rate of 64% was derived from the ThermoCool AF trial, in which the rate of freedom for atrial arrhythmia at 12 months follow-up (including a 3 month blanking period) was 63%.\(^8\) However, 12.6% of the ablation group in this trial underwent a repeat procedure within 80 days of the initial PVI, which will have elevated the overall success rate above that expected for a single-procedure. Conversely, this trial used the ThermoCool irrigated catheter, which does not feature contact force sensing technology. Use of the ThermoCool SmartTouch ablation catheter in our study, which does provide contact force information, would be expected to improve
the success rate, and this benefit is likely to slightly outweigh the overestimation related to repeat procedures in the ThermoCool AF study. Hence an estimate of 64% was reached.

The projected success rate for the “repeat study” group was harder to estimate as this is a novel strategy. However, a previous study in which up to 2 additional PVI procedures were allowed within a 90 day blanking period for patients with early recurrence resulted in 89% freedom from AF at 12 months after a mean of 1.8±0.8 (median 2) procedures. As we felt that success rates would be further improved by treating PV reconnection in patients who had not had an early recurrence (but were at risk of having a subsequent one), a conservative success rate of 90% was estimated. With these estimates, an alpha error set at 0.05 and a beta of 20% (80% power), the number of patients required for a one-sided test was 64 (32 in each group). Allowing for 20% of patients who may be lost to follow-up gave an intended sample size of 80 (40 per group).

The study was therefore underpowered to detect a smaller difference between group outcomes. This was done intentionally, as the additional expected complications and healthcare costs associated with a routine repeat procedure strategy could only be justified by a major improvement in success rate at 12 months. The study was therefore only powered to detect a benefit of 25% or greater.

2.11 Statistical analysis

All end points were examined by means of an intention-to-treat analysis. Numeric variables were checked for normal distribution and appropriate descriptive statistics were generated. Continuous variables that were normally distributed are expressed as mean (± standard deviation) and were compared using Student’s t-test. Variables that were not normally distributed are expressed as median [interquartile range] and were compared with Mann-Whitney, sign or Wilcoxon signed-rank tests as appropriate. All categorical variables were compared with χ² or Fisher’s exact test as appropriate. All tests were two-sided and a P-value <0.05 was considered statistically significant. All statistical analysis was performed using SPSS (version 22, IBM Corp., Armonk, NY).
3 RESULTS - Pulmonary vein re-isolation as an early routine strategy: a success rate evaluation (PRESSURE)

3.1 Introduction

The primary sources of initiating triggers of paroxysmal AF were first identified as the PVs in 1998, and, since then, PVI has become the cornerstone of AF ablation. Creating durable PVI is difficult to achieve, however, with studies published in the recent past demonstrating that up to two-thirds of patients have PV reconnection at protocol-mandated repeat electrophysiology study despite an initially successful PVI procedure. It is now well-recognised that, following AF ablation in patients with paroxysmal AF, PV reconnection is the leading cause of AT recurrence, which occurs in around 30-40% of patients after a single procedure. Such AT recurrences can have a significant impact upon quality of life.

Patients who re-present with AT recurrence commonly undergo repeat ablation, which has been shown to increase success rates. However, quality of life can suffer, as there can be a significant delay between the recurrence of symptoms and the second procedure. Although clinical success rates have remained relatively static over recent years, the safety of AF ablation has improved significantly. In view of the high rates of late PV reconnection seen in contemporary studies, we designed the Pulmonary vein RE-isolation as a routine Strategy: a SUccess Rate Evaluation (PRESSURE) study to investigate whether a strategy of assessment and re-isolation of all PV reconnection in all patients two months after an initial AF ablation, regardless of symptoms, would reduce the recurrence of AT and provide improvements in quality of life.

3.2 Methods

The main methods used for this study were as described in the Methods chapter. Specific methods used are described below.
3.2.1 Statistical analysis

Statistical analyses were as described in the Statistical Analysis paragraph of the Methods section. Additional analyses used in this study are detailed here. Time to first AT recurrence was assessed via Cox’s Proportional Hazard model, and a comparison was made between groups using the log-rank test.

3.3 Results

3.3.1 Study participants

A CONSORT diagram showing recruitment to the study is shown in Figure 3.1. One hundred and thirteen patients were approached to take part in the study over a 13-month period (October 2013 to November 2014), of whom 16 (14%) were ineligible and 14 (12%) declined to take part. A total of 83 patients gave informed written consent to participate, with two withdrawn as they did not go on to have PVI performed and one withdrawn due to the development of a complication during his PVI procedure. The remaining 80 patients were randomised, 40 to each group, and all received their treatment allocation as planned. Patient demographics for the 80 randomised subjects are provided in Table 3.1. The median CHADS-VASc score was higher in the SC group, though this will have been influenced in part by the higher proportion of females in this group. There were no other statistically significant differences between groups at baseline.
Figure 3.1: Screening, enrolment, randomisation and follow-up of all randomised patients.

“Amiodarone” under ineligibility criteria denotes a patient whose ablation procedure was scheduled too soon after screening to allow the protocol-mandated two-month amiodarone withdrawal period.
### Table 3.1 Patient demographics by randomisation group

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=80)</th>
<th>Standard Care (n=40)</th>
<th>Repeat Study (n=40)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
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<td>64 [57-69]</td>
<td>58 [53-67]</td>
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<tr>
<td>Male gender, n (%)</td>
<td>42 (53%)</td>
<td>18 (45%)</td>
<td>24 (60%)</td>
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</tr>
<tr>
<td>LA diameter (AP), mm</td>
<td>38.5±5.8</td>
<td>38.2±6.5</td>
<td>38.8±5.2</td>
<td>0.63</td>
</tr>
<tr>
<td>LVEF &gt;55%, n (%)</td>
<td>78 (98%)</td>
<td>39 (98%)</td>
<td>39 (98%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>36 (45%)</td>
<td>22 (55%)</td>
<td>14 (35%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Ischaemic heart disease, n (%)</td>
<td>6 (8%)</td>
<td>4 (10%)</td>
<td>2 (5%)</td>
<td>0.68</td>
</tr>
<tr>
<td>Obstructive sleep apnoea, n (%)</td>
<td>4 (5%)</td>
<td>1 (3%)</td>
<td>3 (8%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Prior stroke/TIA, n (%)</td>
<td>3 (4%)</td>
<td>2 (5%)</td>
<td>1 (3%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>3 (4%)</td>
<td>3 (8%)</td>
<td>0 (0%)</td>
<td>0.24</td>
</tr>
<tr>
<td>CHA$_2$DS$_2$-VASc score</td>
<td>1 [1-3]</td>
<td>2 [1-3]</td>
<td>1 [0-2]</td>
<td>0.01</td>
</tr>
<tr>
<td>Anti-arrhythmic drugs, n (%)</td>
<td>48 (60%)</td>
<td>26 (65%)</td>
<td>22 (55%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Flecainide</td>
<td>36 (45%)</td>
<td>18 (45%)</td>
<td>18 (45%)</td>
<td></td>
</tr>
<tr>
<td>Sotalol</td>
<td>11 (14%)</td>
<td>8 (20%)</td>
<td>3 (8%)</td>
<td></td>
</tr>
<tr>
<td>Dronedarone</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Beta-blockers, n (%)</td>
<td>54 (68%)</td>
<td>26 (65%)</td>
<td>28 (70%)</td>
<td>0.81</td>
</tr>
<tr>
<td>Calcium channel blockers, n (%)</td>
<td>5 (6%)</td>
<td>3 (8%)</td>
<td>2 (5%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>ACE-I/ARB, n (%)</td>
<td>23 (29%)</td>
<td>12 (30%)</td>
<td>11 (28%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Anticoagulation, n (%)</td>
<td>53 (66%)</td>
<td>31 (78%)</td>
<td>22 (55%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Warfarin</td>
<td>39 (49%)</td>
<td>26 (65%)</td>
<td>13 (33%)</td>
<td></td>
</tr>
<tr>
<td>NOAC</td>
<td>14 (18%)</td>
<td>5 (13%)</td>
<td>9 (23%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.1: Patient demographics for the total cohort of subjects and by randomisation group.

LA - left atrial; AP - anteroposterior; LVEF - left ventricular ejection fraction; TIA – transient ischaemic attack; ACE-I - angiotensin converting enzyme inhibitor; ARB - angiotensin receptor blocker; NOAC - non-Vitamin K oral anticoagulant

### 3.3.2 Initial procedural characteristics

Procedural characteristics are show in Table 3.2 and there were no significant differences between groups. The right inferior PV could not be safely isolated at the posterior aspect in two patients due to a rise in oesophageal temperature, but all other PVs were successfully isolated. The overall PVI rate was therefore 99.4%. Of the successfully isolated PVs, spontaneous or adenosine-mediated acute reconnection was seen in 52 (16.4%) PVs in 37 (46.2%) patients. All identified sites of acute
reconnection were successfully ablated.

Table 3.2 Initial procedure details

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=80)</th>
<th>Standard Care (n=40)</th>
<th>Repeat Study (n=40)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure duration, mins</td>
<td>165±38</td>
<td>166±38</td>
<td>164±38</td>
<td>0.81</td>
</tr>
<tr>
<td>Ablation time, mins</td>
<td>43.9±11.5</td>
<td>44.3±11.5</td>
<td>43.5±11.5</td>
<td>0.72</td>
</tr>
<tr>
<td>General anaesthesia, n (%)</td>
<td>60 (75%)</td>
<td>29 (73%)</td>
<td>31 (78%)</td>
<td>0.80</td>
</tr>
<tr>
<td>Radiation dose, cGy/m²</td>
<td>1155 [732-1510]</td>
<td>1158 [726-1441]</td>
<td>1153 [733-1624]</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Table 3.2: Initial procedure details for the total cohort of subjects and by randomisation group.

3.3.3 Repeat study procedural characteristics

The 40 patients randomised to the RS group all had a repeat study performed as per their treatment allocation. This was at a mean interval of 62±6 days after the initial ablation. The median duration of the repeat study procedures was 80 [61-109] minutes, with a fluoroscopy time of 8.3 [6.8-12.0] minutes and a radiation dose of 918 [498-1756] cGy/m² respectively. The two patients in whom the right inferior PV could not be isolated at the initial procedure were both randomised to the RS group. Including these two patients, PV reconnection was identified in 25 (62.5%) patients, affecting 41 (26%) PVs at repeat study. All these PVs were successfully re-isolated, including the two right inferior PVs that had not been isolated initially as similar issues with oesophageal temperature rise were not encountered at repeat study. The median ablation time to achieve PV re-isolation in these 25 patients was 5.1 [3.6–9.6] minutes.

In the SC group, 9 (22.5%) patients went on to undergo a redo procedure for symptomatic arrhythmia recurrence after a median interval of 210 [173-233] days from the initial PVI. In one of these cases, a redo procedure was performed for frequent symptomatic bursts of atrial ectopy but no sustained AT continuing for ≥30s was recorded on ECG monitoring. This patient was therefore categorised as not having experienced the primary endpoint. Eight (89%) of these patients (including the patient without sustained AT) had PV reconnection, affecting 18 (50%) PVs. The median
procedure time was 115 [76-170] minutes and the ablation time was 12.3 [6.9-15.6] minutes. The fluoroscopy time and dose were 9.9 [6.0-14.8] minutes and 1024 [254-1709] cGy/m², respectively.

During the follow-up period, no patient in either group underwent a third left atrial ablation procedure.

### 3.3.4 Patient follow-up

The duration of clinical follow-up was 382 [372-402] days (12.6 [12.2-13.2] months), and there was no difference between groups (Table 3.3). ECG follow-up was defined as the number of days from the initial ablation to the date of the last self-recorded ECG, and was 380 [367-400] days. This also did not differ between groups.

Patients recorded a total of 32,203 ECGs (380 [335-447] per patient) during follow-up. Of these, 22,789 ECGs were recorded during the primary outcome period, again with no difference between groups (SC: 278 [222-326] vs. RS: 274 [242-315] ECGs per patient, P=0.81).

#### Table 3.3 Follow-up details

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=80)</th>
<th>Standard Care (n=40)</th>
<th>Repeat Study (n=40)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up duration to last clinical review, days</td>
<td>382 [372-402]</td>
<td>382 [271-402]</td>
<td>382 [374-402]</td>
<td>0.86</td>
</tr>
<tr>
<td>Follow-up duration to last self-recorded ECG, days</td>
<td>380 [367-399]</td>
<td>379 [366-401]</td>
<td>380 [373-399]</td>
<td>0.60</td>
</tr>
<tr>
<td>ECG recordings in primary outcome period</td>
<td>276 [231-318]</td>
<td>278 [222-326]</td>
<td>274 [242-315]</td>
<td>0.81</td>
</tr>
<tr>
<td>Anti-arrhythmic drugs continued in initial 4 weeks, n (%)</td>
<td>43 (54%)</td>
<td>23 (58%)</td>
<td>20 (50%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Additional anti-arrhythmic drugs in blanking period, n (%)</td>
<td>19 (24%)</td>
<td>10 (25%)</td>
<td>9 (23%)</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>

Table 3.3: Follow-up details for the total cohort of subjects and by randomisation group

### 3.3.5 Primary Endpoint
Over one year of follow-up, significantly fewer patients in the RS group (7 (17.5%)) experienced the primary endpoint when compared to the SC group (17 (42.5%), \( P=0.03 \), Figure 3.2).

**Figure 3.2** Bar chart of % freedom from AT

![Bar chart showing the proportion of patients free from AT recurrence during follow-up](image)

**Figure 3.2**: Bar chart showing the proportion of patients free from AT recurrence during follow-up

### 3.3.6 Time to first recurrence

Kaplan-Meier curves for the two groups are shown in Figure 3.3. For censored cases, the final follow-up date was taken as the date of the last self-recorded ECG. The log-rank test was statistically significant (\( P=0.02 \)). With the inclusion of a time-dependent covariate for randomisation group, the proportional hazards assumption required for the Cox proportional hazards model was shown to be valid (\( P \)-value for interaction term 0.78), and RS group patients were found to be 65% less likely to have AT recurrence than those in the SC group (Hazard Ratio 0.35, 95% confidence interval 0.15-0.86, \( P=0.02 \)).

As CHA₂DS₂-VASc score and left atrial diameter are known to be associated with AF ablation outcomes, these factors were assessed as co-variants. Using forward and backward selection methods, via Akaike’s Information Criteria,¹⁸⁰ resulted in a model which only included randomisation group (which was forced into the model) and there was no significant change to the effect of the randomisation group (Hazard ratio 0.36, 95% confidence interval 0.15-0.88, \( P=0.02 \)).
3.3.7 AT burden

Total group AT burden, defined as the number of patient-days on which AT was documented, was markedly lower in the RS than the SC group (91 vs. 127 days), and the median number of days per patient was significantly lower (RS group: 0 [0–0] vs. SC group: 0 [0–3], *P*=0.03).

3.3.8 Procedure-related adverse events

No participants died or suffered a stroke related to a procedure or during the study as a whole. One patient who had given written consent to participate in the study developed cardiac tamponade.
during their initial procedure. This was successfully drained percutaneously and there were no clinical sequelae. This patient was withdrawn from the study prior to randomisation but this complication is included in the overall rate. A further patient developed right phrenic nerve palsy following the initial PVI. This resolved completely during the follow-up period, as confirmed by chest X-ray and sniff test. The overall serious complication rate associated with 81 initial procedures was therefore 2.5%.

There were no adverse events related to the 40 repeat procedures in the RS group. One patient in the SC group who underwent repeat ablation for clinical recurrence suffered a transient ischaemic attack shortly after this procedure. It was felt that this may have been related to non-absorption of her oral anticoagulant due to vomiting in the post-procedural period. Considering all procedures, there were no differences in the overall serious complication rates for the two groups (RS group: one in 40 patients (2.5%) in 80 procedures (1.25%) vs. SC group: one in 40 patients (2.5%) in 49 procedures (2.0%), \( P > 0.99 \) for both).

### 3.3.9 Quality of life measures

AFEQT quality of life scores at baseline were not different between groups (RS group: 46.3 [36.1-69.1] vs. SC: 47.7 [30.1-73.3], \( P = 0.90 \)). At six months after the initial PVI procedure, AFEQT scores were significantly higher in the RS group than the SC group (88.0 [79.6-96.3] vs. 65.7 [49.5-82.9], \( P < 0.001 \)), indicating better quality of life in the RS group. This difference was maintained at twelve months (91.9 [79.5-99.1] vs. 77.3 [67.6-94.5], \( P = 0.02 \), Figure 3.4).
3.3.10 Re-initiation of medication

All anti-arrhythmic medication, including beta-blockers and rate-limiting calcium-channel blockers, were stopped during or at the end of the three-month blanking period. During the primary endpoint period, significantly more patients in the SC group had these re-initiated for symptomatic clinical recurrence (either on a regular or “pill-in-the-pocket” basis) than in the RS group (13 of 40 (32.5%) vs. 4 of 40 (10%), \( P=0.03 \)).

3.4 Discussion

3.4.1 Main findings

The main finding of the PRESSURE randomised controlled trial is that a strategy of re-assessment and re-isolation of PV reconnection two months after an initial PVI procedure, regardless of symptoms, reduces AT recurrence, reduces AT burden and improves quality of life in patients with paroxysmal AF when compared to standard care. Previous studies have demonstrated benefit from early re-intervention in symptomatic patients,\(^{115,181}\) but patients have not previously been randomised to PV
re-assessment and re-intervention irrespective of symptoms.

3.4.2 Freedom from AT

This study involved intensive daily ECG monitoring, which is recognized to result in higher AT detection rates,\(^1\) as well as the arrhythmia duration criterion of ≥30 seconds as set out in international guidelines for clinical trials in AF.\(^9\) \(^7\) 57.5% of SC group patients remained free of AT during one year follow-up, in keeping with single-procedure success rates reported in other recent trials.\(^1\)\(^7\),\(^1\)\(^7\) In comparison, 82.5% in the RS group had no AT recurrence using the same intensive monitoring. Of the remaining 17.5%, it is likely that many had non-PV triggers, which have been identified in 10-25% of patients.\(^2\)\(^2\),\(^1\)\(^8\)-\(^1\)\(^8\) This study did not involve looking for or ablating such extra-PV sources. Since patients who underwent re-ablation for PV reconnection at repeat study were not brought back for a third time to confirm enduring PVI, it is also possible that further PV reconnection following re-ablation may have contributed to recurrence in some cases. Nevertheless, early re-intervention conferred an absolute improvement in freedom from AT of 25%.

3.4.3 Context of our results

PVI remains the cornerstone of AF ablation, particularly in paroxysmal AF but also, in light of recent data, in persistent AF.\(^1\)\(^8\),\(^1\)\(^7\) However, recent studies have shown that durable PVI is only achieved relatively infrequently with a single procedure,\(^1\)\(^3\),\(^1\)\(^7\) and a similar rate of PV reconnection was found in this study. A very recent study which sought to improve PVI durability by aiming for a FTI target of 400gs for each lesion reduced this proportion somewhat, but more than one-third of patients still had late reconnection and, additionally, a high complication rate was reported.\(^1\)\(^8\)

The association between PV reconnection and AF recurrence is well-recognised,\(^1\)\(^2\)-\(^1\)\(^3\),\(^1\)\(^7\) and the goal for operators at the initial procedure is therefore to deliver durable PVI, although it is acknowledged that complete PVI is not essential in all cases.\(^1\)\(^8\) Nevertheless, the only way to achieve certainty that PV trigger-driven AF will not recur is through complete durable PVI. It may
therefore be a natural extension of the current treatment strategy to perform additional intervention to make up for the limitations of the initial procedure.

3.4.4 Implications for clinical practice

It would ideally be possible to identify patients with PV reconnection in order to direct re-intervention towards those who would benefit from it but, at present, imaging modalities such as cardiac MRI cannot identify PV reconnection with sufficient precision. Therefore, we tested in this study a strategy of invasive re-assessment for PV reconnection in all patients and this has demonstrated a marked improvement in outcomes in terms of freedom from AT, AT burden and quality of life.

Nevertheless, the concept of undertaking an invasive repeat left atrial study in all patients carries a significant burden in terms of costs to healthcare systems and the risk of procedure-related complications. Although there were no serious complications associated with elective repeat procedures in this study, this was a relatively small sample size to detect these. Furthermore, procedures in this study were undertaken by experienced operators in a high-volume centre, and a similarly low rate of adverse events could not be guaranteed in all centres. On the basis of these issues, it is unlikely that a routine “two-shot” strategy would ever be adopted into clinical practice. Nevertheless, the improved outcomes demonstrated in this study give an indication of the results that potentially could be obtained if rates of durable PVI from a single procedure can be substantially and safely improved, and therefore highlight the need to focus on this goal.

3.5 Limitations

The study has some important limitations. Firstly, the size of the study is small, having been powered to detect only a large absolute difference between groups. This was a deliberate decision, as it was felt that the potential additional risk associated with a routine repeat procedure strategy could only be justified by a marked improvement in success rates. However, whilst none of the repeat studies were associated with a serious complication, the size of this study means our ability to detect rare
complications is limited. Secondly, this study assessed point-by-point radiofrequency ablation performed by experienced operators, and the results cannot be extrapolated to alternate energy sources such as cryoablation, nor is it possible to be certain that the results would be replicated if performed by less experienced operators. Thirdly, we used validated hand-held ECG monitors to document AF recurrence as we felt these provided the most comprehensive non-invasive option for arrhythmia monitoring. Although patients were asked to provide recordings each day and when experiencing symptoms, it is possible that asymptomatic episodes lasting less than 24 hours may not have been detected. Follow-up was relatively short at 12 months, though in line with minimum guideline recommendations. Finally, due to the nature of the study, it was not possible to blind patients to treatment allocation, which could have influenced quality of life scores.

3.6 Conclusions

A strategy of routine repeat electrophysiology study to assess for and treat PV reconnection in patients with paroxysmal AF provides significant improvements in freedom from AT recurrence, AT burden, and quality of life compared to current standard care, and could be considered a reasonable option to improve outcomes.
4 RESULTS - The relevance of early recurrence of atrial tachyarrhythmia to pulmonary vein reconnection and later arrhythmia recurrence

4.1 Introduction

A 3-month blanking period following PVI for AF is recommended in current international guidelines. ERAT during this blanking period is thought not to be necessarily indicative of longer-term AF recurrence and repeat intervention is accordingly not recommended. Suggested causes for this phenomenon include pro-arrhythmia related to inflammation following ablation or transient autonomic dysfunction, or the time taken for the deployed lesion set to mature. These transient factors would not be expected to lead to late AF recurrence, whereas PV reconnection has been clearly associated with long-term arrhythmia recurrence in paroxysmal AF.

However, it remains unclear as to what time point these transient causes of ERAT give way to arrhythmia episodes related to PV reconnection. Recent data from biochemical studies have shown that the inflammatory phase following ablation is usually limited to the first month after PVI, and a study of heart rate variability changes has also demonstrated spontaneous recovery of temporary autonomic imbalance by 1 month. Furthermore, histological studies have described the formation of well-demarcated homogenous lesions by 1 week post-ablation. In previous studies of clinical outcomes, ERAT has been shown to be a strong predictor of post-blanking period AF recurrence, with more delayed onset (second and third months post-ablation) being more predictive.

In light of these factors, we hypothesized that ERAT occurring beyond 4 weeks is associated with both PV reconnection and post-blanking period AT recurrence. We sought to test this hypothesis by studying the relationships between ERAT and PV reconnection at mandatory repeat electrophysiology study 2 months after PVI and, in a separate cohort, between ERAT and AT recurrence after the 3-month blanking period.
4.2 Methods

The main methods used for this study were as described in the Methods chapter. Specific methods used are described below.

4.2.1 Monitoring for ERAT

As described in the Methods section, all patients were provided with a validated handheld ECG monitoring device (Omron HCG-801-E, Omron Healthcare, Kyoto, Japan) approximately 1 week prior to their initial PVI procedure. Patients were instructed to self-record a 30-second ECG each day, with additional recordings whenever they experienced symptoms, however minor. Recordings were checked at the time of the initial PVI for compliance and ECG trace quality. Analysis of the ECG recordings was performed by an observer who was blinded to the outcome of the repeat electrophysiology study.

Recordings during the 3-month blanking period were divided into those taken during the first 4 weeks (“month 1”) post-PVI, and those recorded from day 29 to the end of the blanking period for the SC group (“month 2-3”) or to the date of the repeat electrophysiology study for the RS group (“month 2”). ERAT was defined as any documented AT lasting ≥30 seconds during these periods. The number of separate days on which ERAT was documented was also recorded.

4.2.2 Repeat electrophysiology procedure

The operator performing the repeat electrophysiology study was blinded to the presence and timing of any ERAT. All identified sites of reconnection were re-ablated to re-isolate the PV(s), regardless of the presence or absence of ERAT.

4.2.3 Statistical analysis

Statistical analyses were as described in the Statistical Analysis paragraph of the Methods section.
4.3 Results

Demographic information for the 80 study participants, as a total cohort and by randomisation group, is provided in Table 3.1 (Chapter 3).

4.3.1 Repeat Study group portable ECG monitor recordings and ERAT

The 40 Repeat Study group patients recorded a total of 3348 ECG recordings between their initial PVI procedure and repeat electrophysiology study. The quality of the ECG recordings was good enough to be interpretable in 3293 (98%): 1507 recordings in month 1 (32 [28-41] ECGs per patient), and 1786 in month 2 (38 [30-50] ECGs per patient). The remaining 55 (2%) recordings, from 15 (38%) patients, were affected by artefact and were excluded from analysis.

ERAT was documented in 17 (42%) patients. Demographic details for patients with and without ERAT in the RS group are given in Table 4.1. Patients with ERAT were of older age but there were no other significant differences between the two groups. Four (10%) patients had ERAT only in month 1 with no further episodes beyond this, 2 (5%) patients had ERAT in month 2 only, and 11 (28%) patients experienced ERAT in both months 1 and 2. The 15 patients with month 1 ERAT had this recorded on 3 (2-6) separate days each, with the highest number of separate days being 11. The 13 patients with month 2 ERAT had this documented on 4 (2-6) separate days each, with the highest number being 12 days. These data are presented graphically in Figure 4.1.
### Table 4.1 Demographic data by presence of ERAT in the RS group

<table>
<thead>
<tr>
<th></th>
<th>Repeat Study group (n=40)</th>
<th>ERAT (n=17)</th>
<th>No ERAT (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>24 (60%)</td>
<td>7 (41%)</td>
<td>17 (74%)</td>
</tr>
<tr>
<td>Left atrial diameter, mm</td>
<td>39±5</td>
<td>37±5</td>
<td>40±5</td>
</tr>
<tr>
<td>Ejection fraction &gt;55%, n (%)</td>
<td>39 (98%)</td>
<td>17 (100%)</td>
<td>22 (96%)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>14 (35%)</td>
<td>7 (41%)</td>
<td>7 (30%)</td>
</tr>
<tr>
<td>Ischaemic heart disease, n (%)</td>
<td>2 (5%)</td>
<td>0 (0%)</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>Obstructive sleep apnoea, n (%)</td>
<td>3 (8%)</td>
<td>2 (12%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Prior stroke/TIA, n (%)</td>
<td>1 (2%)</td>
<td>1 (6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Anti-arrhythmic drugs, n (%)</td>
<td>22 (55%)</td>
<td>10 (59%)</td>
<td>12 (52%)</td>
</tr>
<tr>
<td>Flecainide</td>
<td>18 (45%)</td>
<td>8 (47%)</td>
<td>10 (43%)</td>
</tr>
<tr>
<td>Sotalol</td>
<td>3 (8%)</td>
<td>2 (12%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Beta-blockers, n (%)</td>
<td>28 (70%)</td>
<td>13 (76%)</td>
<td>15 (65%)</td>
</tr>
<tr>
<td>Calcium channel blockers, n (%)</td>
<td>2 (5%)</td>
<td>1 (6%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>ACE-I/ARB, n (%)</td>
<td>11 (28%)</td>
<td>5 (29%)</td>
<td>6 (26%)</td>
</tr>
<tr>
<td>Anticoagulation, n (%)</td>
<td>22 (55%)</td>
<td>12 (71%)</td>
<td>10 (43%)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>13 (32%)</td>
<td>6 (35%)</td>
<td>7 (30%)</td>
</tr>
<tr>
<td>NOAC</td>
<td>9 (22%)</td>
<td>6 (35%)</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>Procedure time, minutes</td>
<td>164±34</td>
<td>157±32</td>
<td>170±36</td>
</tr>
<tr>
<td>Ablation time, minutes</td>
<td>43.5±9.1</td>
<td>43.7±10.1</td>
<td>43.3±8.6</td>
</tr>
<tr>
<td>General anaesthesia, n (%)</td>
<td>31 (78%)</td>
<td>11 (65%)</td>
<td>20 (87%)</td>
</tr>
<tr>
<td>Interval between procedures, days</td>
<td>62±6</td>
<td>61±5</td>
<td>62±6</td>
</tr>
</tbody>
</table>

*Table 4.1: Patient demographics for Repeat Study group subjects, and for those with and without ERAT. TIA – transient ischaemic attack; ACE-I - angiotensin converting enzyme inhibitor; ARB - angiotensin receptor blocker; NOAC – non-Vitamin K oral anticoagulant.*
Figure 4.1 Graphic of ERAT and PV reconnection in the RS group

Figure 4.1: Graphic showing the days on which AT was recorded and the number of reconnected PVs (PVrc) for each Repeat Study group participant (ordered by timing of the latest ERAT episode). The blue box indicates month 1 and the pink box indicates month 2.

4.3.2 PV reconnection at repeat electrophysiology study

PV reconnection was identified in 25 (62%) patients at repeat electrophysiology study, affecting a total of 41 (26%) PVs. Twelve (30%) patients had reconnection of 1 PV and 13 (32%) had reconnection of 2 or more PVs. Demographic data for patients with and without PV reconnection are shown in Table 4.2.
Table 4.2: Demographic data by presence of late PV reconnection

<table>
<thead>
<tr>
<th></th>
<th>Late PV reconnection</th>
<th>No late PV reconnection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=25)</td>
<td>(n=15)</td>
</tr>
<tr>
<td>Age, years</td>
<td>57 [51-66]</td>
<td>61 [53-68]</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>15 (60%)</td>
<td>9 (60%)</td>
</tr>
<tr>
<td>Left atrial diameter, mm</td>
<td>39±5</td>
<td>38±6</td>
</tr>
<tr>
<td>Ejection fraction &gt;55%, n (%)</td>
<td>25 (100%)</td>
<td>14 (93%)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>7 (28%)</td>
<td>7 (47%)</td>
</tr>
<tr>
<td>Ischaemic heart disease, n (%)</td>
<td>0 (0%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Obstructive sleep apnoea, n (%)</td>
<td>3 (12%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Prior stroke/TIA, n (%)</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Anti-arrhythmic drugs, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flecainide</td>
<td>15 (60%)</td>
<td>7 (47%)</td>
</tr>
<tr>
<td>Sotalol</td>
<td>13 (52%)</td>
<td>5 (33%)</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>2 (8%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td></td>
<td>0 (0%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Beta-blockers, n (%)</td>
<td>17 (68%)</td>
<td>11 (73%)</td>
</tr>
<tr>
<td>Calcium channel blockers, n (%)</td>
<td>1 (4%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>ACE-I/ARB, n (%)</td>
<td>5 (20%)</td>
<td>6 (40%)</td>
</tr>
<tr>
<td>Anticoagulation, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>12 (48%)</td>
<td>10 (67%)</td>
</tr>
<tr>
<td>NOAC</td>
<td>5 (20%)</td>
<td>8 (53%)</td>
</tr>
<tr>
<td></td>
<td>7 (28%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Procedure time, minutes</td>
<td>169±36</td>
<td>156±30</td>
</tr>
<tr>
<td>Ablation time, minutes</td>
<td>44.3±9.9</td>
<td>42.1±7.8</td>
</tr>
<tr>
<td>Fluoroscopy time, minutes</td>
<td>11.8 [8.3-19.0]</td>
<td>10.7 [7.8-14.4]</td>
</tr>
<tr>
<td>General anaesthesia, n (%)</td>
<td>22 (88%)</td>
<td>9 (60%)</td>
</tr>
<tr>
<td>Interval between procedures, days</td>
<td>61±6</td>
<td>62±5</td>
</tr>
</tbody>
</table>

Table 4.2: Patient demographics for subjects with and without PV reconnection at repeat electrophysiology study. Abbreviations as for Table 4.1.

### 4.3.3 Relationship between ERAT and PV reconnection

ERAT taken as a whole (ERAT occurring at any time in month 1 or 2) was found not to be associated with PV reconnection (11 of 17 (65%) with ERAT vs. 14 of 23 (61%) without ERAT, \( P>0.999 \)).

However, when the timing of the last episode of ERAT was taken into account, a relationship was seen. Of the 4 patients with ERAT limited to month 1, none had PV reconnection. In contrast,
patients with ERAT starting or continuing in month 2 was strongly associated with PV reconnection (11 of 13 (85%) patients, \(P=0.006\) compared with month 1 ERAT).

4.3.4 Relationship between ERAT and extensive PV reconnection

Extensive PV reconnection was defined as electrical reconnection of 2 or more PVs, which was seen in 13 (32%) patients. The number of reconnected PVs for patients with and without ERAT in month 2 is shown in Figure 4.2. By the nature of WACA of PV pairs, there is an increased likelihood of PV reconnection occurring in twos due to reconnection of both ipsilateral PVs via single reconnection site, thereby favouring 0, 2 or 4 reconnected PVs. Indeed, the majority of instances of 2 reconnected PVs in this study involved ipsilateral PVs, though in most cases 2 distinct reconnection sites were identified. The presence of ERAT in month 2 was found to be strongly related to extensive PV reconnection when compared to its absence (10/13 (77%) vs. 3/27 (11%), \(P<0.0001\)). For predicting extensive PV reconnection, ERAT in month 2 had a sensitivity of 77%, specificity of 89%, positive predictive value of 77% and negative predictive value of 89%.

Figure 4.2: Dot plot showing the number of reconnected PVs for patients with and without ERAT in month 2.
4.3.5 Standard Care group portable ECG monitor recordings and ERAT

Patients in the SC group recorded a total of 4802 ECG recordings between their initial PVI procedure and the end of the three-month blanking period. The quality of the ECG recordings was good enough to be interpretable in 4738 (99%): 1322 recordings in month 1 (31 [26-38] ECGs per patient), and 3416 in months 2-3 (68 [58-86] ECGs per patient). The remaining 64 (1%) recordings, from 20 (50%) patients, were excluded from analysis. ERAT was documented in a total of 15 (37.5%) patients.

Demographic details for patients with and without ERAT are given in Table 4.3.

Table 4.3 Demographic data by presence of ERAT in the SC group

<table>
<thead>
<tr>
<th></th>
<th>Standard care group (n=40)</th>
<th>ERAT (n=15)</th>
<th>No ERAT (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>64 [57-69]</td>
<td>64 [56-70]</td>
<td>64 [58-68]</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>18 (45%)</td>
<td>5 (33%)</td>
<td>13 (52%)</td>
</tr>
<tr>
<td>Left atrial diameter, mm</td>
<td>38±6</td>
<td>37±7</td>
<td>39±6</td>
</tr>
<tr>
<td>Ejection fraction &gt;55%, n (%)</td>
<td>39 (98%)</td>
<td>14 (93%)</td>
<td>25 (100%)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>22 (55%)</td>
<td>6 (40%)</td>
<td>16 (64%)</td>
</tr>
<tr>
<td>Ischaemic heart disease, n (%)</td>
<td>4 (10%)</td>
<td>1 (7%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Obstructive sleep apnoea, n (%)</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Prior stroke/TIA, n (%)</td>
<td>2 (5%)</td>
<td>0 (0%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>3 (8%)</td>
<td>0 (0%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Anti-arrhythmic drugs, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flecainide</td>
<td>26 (65%)</td>
<td>12 (80%)</td>
<td>14 (56%)</td>
</tr>
<tr>
<td>Sotalol</td>
<td>18 (45%)</td>
<td>7 (47%)</td>
<td>11 (44%)</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>8 (20%)</td>
<td>5 (33%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Beta-blockers, n (%)</td>
<td>26 (65%)</td>
<td>8 (53%)</td>
<td>18 (72%)</td>
</tr>
<tr>
<td>Calcium channel blockers, n (%)</td>
<td>3 (8%)</td>
<td>0 (0%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>ACE-I/ARB, n (%)</td>
<td>12 (30%)</td>
<td>1 (7%)</td>
<td>11 (44%)</td>
</tr>
<tr>
<td>Anticoagulation, n (%)</td>
<td>31 (78%)</td>
<td>12 (80%)</td>
<td>19 (76%)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>26 (65%)</td>
<td>8 (53%)</td>
<td>18 (72%)</td>
</tr>
<tr>
<td>NOAC</td>
<td>5 (13%)</td>
<td>4 (27%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Procedure time, minutes</td>
<td>166±38</td>
<td>165±48</td>
<td>167±32</td>
</tr>
<tr>
<td>Ablation time, minutes</td>
<td>44.3±11.5</td>
<td>48.2±11.4</td>
<td>42.0±11.2</td>
</tr>
<tr>
<td>Fluoroscopy time, minutes</td>
<td>10.0 [6.6-15.5]</td>
<td>8.7 [6.3-14.8]</td>
<td>12.2 [6.7-16.3]</td>
</tr>
<tr>
<td>General anaesthesia, n (%)</td>
<td>29 (73%)</td>
<td>9 (60%)</td>
<td>20 (80%)</td>
</tr>
</tbody>
</table>

Table 4.3: Patient demographics for Standard Care group subjects, and for those with and without ERAT. Abbreviations as for Table 4.1.
One (2.5%) patient had ERAT only in month 1, with no further episodes beyond this. Six (15%) patients experienced ERAT in both month 1 and months 2-3 and 8 (20%) patients had ERAT in months 2-3 only. The 7 patients with month 1 ERAT had this recorded on 2 [1-3] separate days each, with the highest number of separate days being 10. The 14 patients with ERAT in months 2-3 had this documented on 4 [2-6] separate days each, with the highest number being 13 days. These data are presented graphically in Figure 4.3.

Figure 4.3 Graphic of ERAT in the SC group

![Figure 4.3: Graphic showing the days on which AT was recorded for each Standard Care group participant (ordered by timing of the last ERAT episode). The blue box indicates month 1 and the pink box indicates months 2-3.](image-url)
4.3.6 Post-blanking period AT recurrence

The 40 patients in the SC group recorded a total of 11,806 ECGs (278 [220-329] ECGs per patient) from the end of the blanking period to the end of follow-up. Seventeen (42.5%) patients had documented AT recurrence in this period. Demographic data for patients with and without late recurrence are shown in Table 4.4. As patients were asked to take ECG recordings whenever they experienced symptoms, those with AT recurrence took more recordings than those without (283 [262-439] vs. 251 [207-285] ECGs, \( p=0.020 \)).

<table>
<thead>
<tr>
<th>Table 4.4 Demographic data by late recurrence in the SC group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late recurrence (n=17)</td>
</tr>
<tr>
<td>Age, years</td>
</tr>
<tr>
<td>Male, n (%)</td>
</tr>
<tr>
<td>Left atrial diameter, mm</td>
</tr>
<tr>
<td>Ejection fraction &gt;55%, n (%)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
</tr>
<tr>
<td>Ischaemic heart disease, n (%)</td>
</tr>
<tr>
<td>Obstructive sleep apnoea, n (%)</td>
</tr>
<tr>
<td>Prior stroke/TIA, n (%)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
</tr>
<tr>
<td>Anti-arrhythmic drugs, n (%)</td>
</tr>
<tr>
<td>Flecaïnide</td>
</tr>
<tr>
<td>Sotalol</td>
</tr>
<tr>
<td>Dronedarone</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Beta-blockers, n (%)</td>
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<tr>
<td>Calcium channel blockers, n (%)</td>
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<tr>
<td>ACE-I/ARB, n (%)</td>
</tr>
<tr>
<td>Anticoagulation, n (%)</td>
</tr>
<tr>
<td>Warfarin</td>
</tr>
<tr>
<td>NOAC</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Procedure time, minutes</td>
</tr>
<tr>
<td>Ablation time, minutes</td>
</tr>
<tr>
<td>Fluoroscopy time, minutes</td>
</tr>
<tr>
<td>General anaesthesia, n (%)</td>
</tr>
<tr>
<td>Number of post-blanking period ECGs recorded</td>
</tr>
</tbody>
</table>
Table 4.4: Patient demographics for subjects with and without post-blanking period AT recurrence during follow-up. Abbreviations as for Table 4.1.

4.3.7 Relationship between ERAT and post-blanking period AT recurrence

Of the 14 patients with ERAT in months 2-3, 12 (86%) went on to experience later recurrence beyond the 3-month blanking period. The single patient with ERAT only in month 1 did not have post-blanking period recurrence and of the remaining 25 patients without ERAT, five had later recurrence. ERAT occurring beyond 4 weeks after PVI was significantly associated with post-blanking period AT recurrence (12/14 (86%) vs. 5/26 (19%), \( P=0.0001 \)).

4.4 Discussion

4.4.1 Main findings

In order to avoid unnecessary repeat procedures for ERAT that may in fact be due to transient pro-arrhythmic factors, current international guidelines recommend a three-month blanking period following PVI. Nevertheless, it is also important to offer timely re-intervention to patients with recurrence due to PV reconnection, making it important to be able to identify those in whom ERAT within the blanking period is secondary to this. The main findings of this study are that ERAT beyond 4 weeks is predictive of both PV reconnection at repeat electrophysiology study and post-blanking period AT recurrence, whereas ERAT confined to the first 4 weeks post-PVI is not associated with PV reconnection.

4.4.2 Previous investigations of ERAT and later recurrence

Previous studies have shown that a significantly greater proportion of patients with ERAT in the first 3 months post-PVI go on to have later recurrence compared those without ERAT.\(^{106,107,111-114,134}\) However, ERAT has poor positive predictive value for post-blanking period recurrence, with up to 60% of patients with ERAT not experiencing further AT recurrence during subsequent follow-up.\(^{97,133}\)
As many early episodes of AT following PVI are likely to be related to transient pro-arrhythmic factors including post-ablation inflammation, the time taken for lesions to develop or temporary autonomic dysfunction,\textsuperscript{42,117-120} this is not an unexpected finding. It is therefore clear that a blanking period should exist, but its true duration remains more uncertain.

### 4.4.3 Duration of transient pro-arrhythmic factors following PVI

A number of previous studies have examined the time-course of the transient factors that are thought to promote ERAT but are not associated with longer-term recurrence. A study of biochemical markers showed that a range of markers of inflammation (high-sensitivity C-reactive protein, white cell count and neutrophil count), myocardial injury (Troponin T, creatinine kinase and creatinine kinase-MB) and pro-thrombotic state (fibrinogen and D-dimer) are elevated in the days immediately following PVI, but all had returned to baseline within 30 days.\textsuperscript{127} As might be expected, the extent of inflammatory marker elevation was related to ERAT but not to post-blanking period recurrence.

Prior studies of the histological characteristics of radiofrequency ablation lesions have described the formation of well-demarcated, homogenous lesions by one week after ablation.\textsuperscript{129,191} Lastly, ablation to achieve PVI also affects the autonomic nervous system, which may in itself be a relevant ablation target.\textsuperscript{42,43,119} Hsieh et al examined heart rate variability changes as a marker of autonomic function following PVI and demonstrated significant dysfunction at one week, with spontaneous recovery by one month.\textsuperscript{119} The consistent finding from all of these studies is that transient factors promoting ERAT in the immediate post-ablation period resolve within one month.

### 4.4.4 Timing of ERAT within the blanking period

Although a number of studies have examined the overall relationship between ERAT and post-blanking period recurrence, relatively few have explored the relevance of the timing of these occurrences within the three-month blanking period. Themistoclakis et al reported one such study,
which enrolled 1298 patients undergoing PVI and classified patients with ERAT by the month of the first occurrence.\textsuperscript{106} The proportion of patients going on to suffer post-blanking period recurrences was 44% if the first episode of ERAT was in month 1, 69% if in month 2 and 98% if in month 3, demonstrating a high likelihood of later recurrence if ERAT first occurs in the latter part of the blanking period. Bertaglia et al performed a further study, which found that the rate of late recurrence was significantly higher in those with first ERAT in month 2 or 3 (80%) compared to a first episode in month 1 (56.7%).\textsuperscript{112} As with the study by Themistoclakis et al, the main focus was on the timing of the first ERAT episode, rather than the time period in which these recurrences persisted. This approach may miss important information, as it is entirely conceivable that an individual might have ERAT related to transient pro-arrhythmic factors in the first month post-ablation but then have on-going ERAT related to PV reconnection in month 2 onwards. The timing of the last episode of ERAT would therefore seem to be more valuable than that of the first episode. Added to this is the fact that the incidence of first AT recurrences is known to be highest in the first month, with diminishing levels in months 2 and 3,\textsuperscript{106,107,112} making analysis of outcomes for these small numbers of patients difficult.

More recently, a larger study of the first six weeks following AF ablation in 300 patients has shown that ERAT at any time in this six-week period was predictive of treatment failure, but particularly if there were multiple episodes extending into the ‘late’ period (defined as weeks 5-6).\textsuperscript{134} A re-analysis of these data shows that 50 of 59 (85%) patients with ERAT in weeks 5-6 went on to have later recurrence, compared to 82 of 241 (34%) patients with either no ERAT or ERAT confined to the first four weeks ($P<0.0001$). Furthermore, a very recent sub-study from the ADVICE trial identified 179 patients (44.6% of the total cohort) with ERAT, who were classified according to the timing of their last episode.\textsuperscript{192} The rate of post-blanking period recurrence was significantly higher for those with their last episode of ERAT in month 2 (63.6%) or month 3 (92.2%) when compared to those with the last episode in month 1 (37.4%) or no ERAT at all (22.8%).

With these findings in mind, a re-analysis of data from Bertaglia et al shows that in their
cohort, 29 patients had on-going ERAT in months 2-3 having had their first episode in month 1, and 5 patients had their initial ERAT episode in months 2-3. Of these 34 patients with ERAT in months 2-3 (regardless of the timing of the first episode), 30 (88%) went on to have AT recurrence beyond the blanking period, compared to 11 of 109 (10%) patients without month 2-3 ERAT ($P<0.0001$). In our study, 77% of RS group patients with month 2 ERAT were found to have PV reconnection of more than one PV compared to 11% of those without month 2 ERAT, and 86% of SC group patients with month 2-3 ERAT had later recurrence compared to 19% of those without. These previous studies, together with our findings, are therefore consistent in the suggestion that AT recurrences beyond the first four weeks are clinically relevant. One study that provided discordant results utilised external loop recorders for automatic detection of ERAT (divided into two-week time periods) and did not show AF recurrence in each two-week period to be predictive of post-blanking AF recurrence in a multivariate model.\textsuperscript{107} However, only 47 patients with ERAT were studied and it is therefore likely that the study was underpowered to detect differences between two-week periods.

### 4.4.5 Clinical relevance of reconnection of more than 1 PV

In this study, ERAT in month 2 following PVI was specifically found to be associated with reconnection of two or more PVs. Previous studies have shown a relationship between this degree of PV reconnection and post-blanking period AT recurrence. Verma et al assessed PV reconnection in 107 patients following PVI: 26 without AF recurrence (Group 1), 37 with AF recurrence controlled by anti-arrhythmic medication (Group 2), and 44 with AF recurrence which could not be medically controlled (Group 3).\textsuperscript{121} Sixty-one patients had reconnection of two or more PVs, and all had had AF recurrence (Group 2 or 3). Conversely, none of the patients without recurrence (Group 1) had reconnection of more than one PV. These data indicate that more extensive PV reconnection is of relevance to the on-going risk of AT recurrence.

Statistically, reconnection of two or more PVs greatly increases the likelihood of an arrhythmogenic PV being able to conduct to the atria. As an example, if only one of four PVs is
arrhythmogenic and only one PV reconnects, the likelihood of it being the arrhythmogenic PV is 25%, whereas if two PVs reconnect, this risk is increased to 50%. If there are two arrhythmogenic veins, the risk of an arrhythmogenic PV reconnecting is 50% if only one PV reconnects compared to 83% if two PVs reconnect. Clearly, the combination of factors that eventually lead to clinical AF recurrence are far more complex than these simple proportions, but the number of reconnecting PVs is likely to play an important role.

4.5 Limitations

The sample size of this study was small due to the invasive nature of the assessment for PV reconnection, and this limits the strength of the observations. Anti-arrhythmic medications were continued for four weeks post-PVI, which may have affected the incidence of ERAT in month 1. It may therefore have been preferable to discontinue all anti-arrhythmic medications post-PVI but, given the existing data regarding the presence and duration of transient pro-arrhythmic factors post-PVI and the known high prevalence of ERAT in month 1, it was felt that keeping patients entirely drug-free over this immediate post-PVI period would expose them to unnecessary inconvenience and arrhythmia. A further limitation of our study is that, as we did not implant an implantable loop recorder in study participants, it is possible that some asymptomatic AT episodes may have been missed during the monitoring period. However, PVI for paroxysmal AF is largely offered for symptomatic relief, and recommendations on repeat PVI are also likely to be made only on symptom grounds. As such, it was not felt that exposing study participants to additional invasive procedures for implant and explant of loop recorders merely to identify asymptomatic AT was likely to be worthwhile in terms of guiding future practice.

4.6 Conclusions

ERAT occurring beyond four weeks following PVI is predictive of PV reconnection at repeat electrophysiology study and, in particular, more extensive reconnection of two or more PVs, with a
high specificity (89%) and positive predictive value (77%). ERAT during this period is also associated with later AT recurrence. ERAT limited only to the first four weeks post-PVI is unrelated to underlying PV reconnection and therefore appears to be due to transient factors.
5 RESULTS - The relationship between Ablation Index and pulmonary vein reconnection, and regional differences in target values

5.1 Introduction

The creation of enduring ablation lesions during PVI is of vital importance in order to prevent late PV reconnection, which is responsible for the great majority of arrhythmia recurrences in paroxysmal AF patients. Despite improvements in technical aspects of the procedure, the proportion of PVs remaining durably isolated following radiofrequency ablation has remained disappointingly low, leading to significant research into the delivery of enduring ablation lesions.

In the absence of real-time assessment of lesion creation and transmurality, surrogate measures of lesion quality are commonly utilised. The fall in local impedance during radiofrequency application has been shown to relate to lesion size, and is therefore commonly used as a marker of the direct effect of ablation on cardiac tissue. More recently, the minimum FTI within a PVI segment has been shown to be predictive of segment reconnection at repeat electrophysiology study. Prospective use of a minimum FTI target during each ablation application improved rates of durable PV isolation but, nevertheless, more than one in three patients still had reconnection of one or more PVs at protocol-mandated repeat study. This may be because FTI is derived from a simple multiplication of contact force by time and does not take into account the important role of power delivery, whereas it is likely that these factors along with power provide differing contributions to lesion formation. Furthermore, only a single FTI target value has been suggested for all segments of the circumferential PVI circle. This assumes that tissue thickness, and therefore the ablation depth required, is the same for all areas of the left atrium, whereas it is known from anatomical studies that tissue thickness varies considerably between different left atrial regions.

Ablation Index (AI) (CARTO 3 V4, Biosense Webster, Inc.) is a novel marker of lesion quality
that incorporates contact force, time and power in a logarithmic exponential weighted formula (Figure 5.1), and has been shown to accurately estimate lesion depth in canine studies.\textsuperscript{156,157} We hypothesized that a lower minimum AI within a WACA segment would predict acute PV reconnection and reconnection at repeat electrophysiology study. We also hypothesized that different AI and FTI targets would be required to prevent late reconnection in different segments of the circumferential PVI circle.

**Figure 5.1 Formula for Ablation Index**

\[
Ablation \text{ Index} = \left( k \times \int_{0}^{\tau} CF^a(\tau) P^b(\tau) d\tau \right)^c
\]

*Figure 5.1: Formula for calculating Ablation Index (due to proprietary restrictions, letters have been used to replace the constants in the formula)*

**5.2 Methods**

The main methods used for this study were as described in the Methods chapter. Specific methods used are described below.

**5.2.1 AI and FTI analysis**

Ablation maps from the initial PVI procedures were analysed offline. For assessment of the relationship between AI and acute reconnection, ablation maps from all 80 patients were analysed. Each ablation lesion tag has a unique number. At the time of the initial procedure, tag numbers of the ablation lesions delivered to re-isolate the PV following identification of acute reconnection (either spontaneous or adenosine-mediated) were recorded. These re-isolation lesions were disregarded for analysis of acute reconnection, thereby ensuring that only AI values from the initial encirclement were analysed. Each WACA circle was divided into 6 segments (Figure 5.2, upper panel), and within each segment, the minimum AI value was identified (Figure 5.2, lower panel).
Where lesion tags significantly overlapped (centre-to-centre distance ≤2mm), the greatest of the values was taken. Segments in which acute reconnection was documented during the initial procedure were then also identified. By the nature of the re-isolation lesions appearing on the same left atrial map, it was not possible to blind the observer to sites where acute reconnection occurred.

A more detailed analysis was performed for late PV reconnection and this study only involved the 40 patients returning for repeat electrophysiology study after 2 months. For each individual ablation lesion, the AI value (no unit of measurement), FTI value (grams-seconds (gs)), maximum impedance drop (ohms) (Figure 5.3) and maximum percentage impedance drop (%) were recorded. Drag lesions, where a second automated lesion tag was created during a single radiofrequency application, were excluded from correlation analysis with impedance drop (as the impedance drop may be unreliable for these), but were included for all other analyses. AI and FTI values calculated by the CARTO system were used for these drag lesions, but it is recognised that these values are likely to have been affected by the time taken for the system to recognise a deliberate catheter movement and initiate a new lesion tag, thereby introducing measurement error.

Within each of the 12 WACA segments, the number of lesions, minimum AI value, mean AI value, minimum FTI value and mean FTI value were calculated. All lesion analysis was performed independently at Liverpool Heart & Chest Hospital.

5.2.2 Statistical analysis

Statistical analyses were as described in the Statistical Analysis paragraph of the Methods section. Additional analyses used in this study are detailed here. Pearson’s r correlation coefficient was used to assess the correlation between variables. Univariable and multivariable logistic regression modelling was used to assess the relationship between lesion quality markers (AI and FTI) and WACA segment reconnection. Univariable predictors with $P<0.05$ were entered into a multivariable model. Receiver operating characteristic curve analysis was performed for independent predictors of WACA segment reconnection.
Figure 5.2: Diagram of 12-segment WACA model and identification of minimum AI value

(Upper panel) Diagram showing the 12-segment WACA model used.

(Lower panel) Screenshots showing VisiTags colour-coded by Ablation Index value. The lesion with the minimum Ablation Index value within the inferior segment of the right WACA circle is marked with a yellow arrow.
5.3 Results

5.3.1 Demographic information

Demographic data for the 80 study participants and 40 patients randomised to repeat electrophysiology study are given in Chapter 3 (Table 3.1).

5.3.2 Acute PV reconnection

In two patients (both in the Repeat Study group), the posterior segment of the right inferior PV could not be safely isolated due to oesophageal temperature rise. Including these two segments, 66 (7%) WACA segments exhibited acute reconnection after the 20-minute waiting period, affecting 39 (49%) patients. Demographic data for patients with and without acute PV reconnection are shown in Table 5.1.
Table 5.1 Demographic data by presence of acute PV reconnection

<table>
<thead>
<tr>
<th></th>
<th>Acute PV reconnection (n=39)</th>
<th>No acute PV reconnection (n=41)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>61±9</td>
<td>60±13</td>
<td>0.644</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>21 (54%)</td>
<td>21 (51%)</td>
<td>0.827</td>
</tr>
<tr>
<td>Left atrial diameter, mm</td>
<td>38±6</td>
<td>39±6</td>
<td>0.636</td>
</tr>
<tr>
<td>Ejection fraction &gt;55%, n (%)</td>
<td>38 (97%)</td>
<td>40 (98%)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>14 (36%)</td>
<td>22 (54%)</td>
<td>0.122</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>1 (3%)</td>
<td>5 (12%)</td>
<td>0.202</td>
</tr>
<tr>
<td>Obstructive sleep apnoea, n (%)</td>
<td>1 (3%)</td>
<td>3 (7%)</td>
<td>0.616</td>
</tr>
<tr>
<td>Prior stroke/TIA, n (%)</td>
<td>1 (3%)</td>
<td>2 (5%)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>1 (3%)</td>
<td>2 (5%)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Anti-arrhythmic drugs, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flecainide</td>
<td>24 (62%)</td>
<td>24 (59%)</td>
<td>0.823</td>
</tr>
<tr>
<td>Sotalol</td>
<td>18 (46%)</td>
<td>18 (44%)</td>
<td></td>
</tr>
<tr>
<td>Dronedarone</td>
<td>6 (15%)</td>
<td>5 (12%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Beta-blockers, n (%)</td>
<td>28 (72%)</td>
<td>26 (63%)</td>
<td>0.480</td>
</tr>
<tr>
<td>Calcium channel blockers, n (%)</td>
<td>1 (3%)</td>
<td>4 (10%)</td>
<td>0.360</td>
</tr>
<tr>
<td>ACE-I/ARB, n (%)</td>
<td>7 (18%)</td>
<td>16 (39%)</td>
<td>0.049</td>
</tr>
<tr>
<td>Anticoagulation, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>25 (64%)</td>
<td>28 (68%)</td>
<td>0.814</td>
</tr>
<tr>
<td>NOAC</td>
<td>18 (46%)</td>
<td>21 (51%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 (18%)</td>
<td>7 (17%)</td>
<td></td>
</tr>
<tr>
<td>Procedure time, minutes</td>
<td>176±37</td>
<td>155±32</td>
<td>0.007</td>
</tr>
<tr>
<td>Ablation time, minutes</td>
<td>48±11</td>
<td>40 ±8</td>
<td>0.001</td>
</tr>
<tr>
<td>Fluoroscopy time, minutes</td>
<td>11 [8-17]</td>
<td>10 [7-15]</td>
<td>0.220</td>
</tr>
<tr>
<td>General anaesthesia, n (%)</td>
<td>28 (72%)</td>
<td>32 (78%)</td>
<td>0.609</td>
</tr>
</tbody>
</table>

Table 5.1: Patient demographics for patients with and without acute PV reconnection.

TIA – transient ischaemic attack; ACE-I – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; NOAC – non-vitamin K antagonist oral anticoagulant.

5.3.3 Relationship between AI and acute reconnection

Ablation Index data were not available for one patient in the Standard Care group. The 66 acutely reconnected WACA segments (including the two that could not be isolated) had significantly lower minimum AI values than non-reconnected segments (322 [268-371] vs. 365 [314-416], P<0.0001).
5.3.4 PV reconnection at repeat electrophysiology study

Including the two posterior right inferior PV segments that could not be isolated at the initial procedure, PV reconnection was identified in 53 (11%) WACA segments in 25 (62%) patients. The 53 reconnected segments were distributed regionally as follows: right posterior 16, left anterior 13, inferior (right and left) 12, left posterior 7, right anterior 4, and roof (left and right) 1. Demographic data for patients with and without PV reconnection are shown in Table 4.2 (Chapter 4).

5.3.5 Relationships between AI, FTI and maximum impedance drop

In total, 3239 ablation lesions were performed during the initial PVI procedures in the 40 Repeat Study group patients (81±16 lesions per patient). After drag lesions were excluded, 2350 (73%) of these lesions (59±21 lesions per patient) were analysed for AI, FTI, maximum impedance drop and maximum percentage impedance drop values. The relationships between AI and impedance drop, FTI and impedance drop, and AI and FTI are shown in Figure 5.4. AI data were found to be normally distributed, whereas FTI and impedance drop data were positively skewed and were therefore logarithmically transformed to base 10 for correlation analysis. AI was found to have a highly significant but weak correlation to logarithmic maximum impedance drop (Pearson $r=0.313$, $P<0.0001$) and logarithmic maximum percentage impedance drop ($r=0.314$, $P<0.0001$). Logarithmic FTI also correlated highly significantly but weakly with impedance drop ($r=0.347$, $P<0.0001$) and percentage impedance drop ($r=0.336$, $P<0.0001$). A very strong correlation was seen between AI and logarithmic FTI ($r=0.901$, $P<0.0001$).
Figure 5.4 Scatter plots of relationships between FTI, AI and impedance drop

*Figure 5.4:* Scatter plots showing the relationships between Force-Time Integral and maximum impedance drop (top panel), Ablation Index and maximum impedance drop (middle panel), and Ablation Index and Force-Time Integral (bottom panel).
5.3.6 AI and FTI as a marker of WACA segment reconnection

The 53 reconnected WACA segments had significantly lower minimum AI values than non-reconnected segments (308 [252-336] vs. 373 [323-423], \( P<0.0001 \), Figure 5.5 left panel). This difference was also seen for minimum FTI values (137 [92-182] vs. 228 [157-334] gs, \( P<0.0001 \), Figure 5.5 right panel). In receiver operating characteristic analysis, the area-under-the-curve for minimum AI for predicting no reconnection of a segment was 0.77 and for minimum FTI was 0.76. The mean AI and mean FTI for reconnected segments were also statistically lower than for non-reconnected segments (mean AI: 395 [350-429] vs. 422 [380-464], \( P=0.002 \); mean FTI: 311 [225-373] vs. 371 [260-502] gs, \( P=0.003 \)), but these did not perform as well as minimum values in receiver operating characteristic analysis. The number of ablation lesions in segments with and without reconnection was not different (5 [4-6] vs. 5 [4-6], \( P=0.860 \)).

In univariable logistic regression analysis, both minimum AI and minimum FTI were predictive of WACA segment reconnection (both \( P<0.0001 \)). In a multivariable model using logistic ridge regression (to account for the highly significant correlation between AI and FTI), both minimum AI and minimum FTI remained independently predictive (\( P<0.0001 \)).

**Figure 5.5** Box plots of minimum AI and FTI values for segments with and without reconnection

![Box plots showing minimum AI values (left panel) and minimum FTI values (gs) (right panel)](image)

*Figure 5.5*: Box plots showing minimum AI values (left panel) and minimum FTI values (gs) (right panel).
panel) for reconnected and non-reconnected segments. The thick line indicates the median, the box represents the interquartile range and the whiskers represent the inner and outer fences.

5.3.7 Regional differences

Minimum AI and FTI values for reconnected and non-reconnected segments in the 4 regions of the left atrium (roof, anterior, posterior and inferior) are shown in Table 5.2. As anterior and roof segments were found to have similar values, these were grouped together, as were posterior and inferior segments.

Table 5.2 Minimum AI and FTI values by left atrial region

<table>
<thead>
<tr>
<th>Region</th>
<th>Ablation Index value</th>
<th>Force-Time Integral value (gs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-reconnected</td>
<td>Reconnected</td>
</tr>
<tr>
<td>Roof</td>
<td>402 [346-441]</td>
<td>294*</td>
</tr>
</tbody>
</table>

*n=1

Table 5.2: Minimum Ablation Index and Force-Time Integral values for non-reconnected and reconnected segments by left atrial region.

Anterior/roof segments with reconnection had significantly lower minimum AI values than those without (332 [287-385] vs. 409 [350-447], P=0.001), with a similar difference seen for posterior/inferior segments (295 [249-322] vs. 344 [302-392], P<0.0001, Figure 5.6 Upper panel). In non-reconnected segments, minimum AI values for anterior/roof segments were significantly higher than those for posterior/inferior segments (409 [350-447] vs. 344 [302-392], P<0.0001).

Analysis of minimum FTI values showed very similar findings. Reconnected anterior/roof segments had significantly lower minimum FTI values compared to non-reconnected segments (180 [90-257] vs. 273 [186-372]gs, P=0.001), which was mirrored for posterior/inferior segments (127 [91-165] vs. 188 [138-284]gs, P<0.0001). As for AI, non-reconnected anterior/roof segments had significantly higher FTI values than non-reconnected posterior/inferior segments (273 [186-372] vs.
Figure 5.6: Box plots showing minimum AI values (upper panel) and minimum FTI values (gs) (lower panel) for reconnected and non-reconnected segments by left atrial region. The thick line indicates the median, the box represents the interquartile range and the whiskers represent the inner and outer fences.
5.3.8 Discriminatory values for AI and FTI

For Ablation Index, no late reconnection was seen in anterior/roof segments where the minimum AI value was ≥480 or in posterior/inferior segments where the minimum AI value was ≥370. For FTI, the equivalent values were ≥420gs for anterior/roof segments and ≥230gs for posterior/inferior segments.

5.4 Discussion

5.4.1 Main findings

AI is a novel ablation quality marker incorporating contact force, power and time in a weighted formula. The main findings of this study are that AI correlates with impedance drop, and the minimum AI value within a WACA segment is predictive of reconnection of that segment at repeat electrophysiology study. AI correlates strongly with FTI, and in a multivariable model incorporating minimum AI and minimum FTI, both remained independently predictive of WACA segment reconnection. Furthermore, higher AI and FTI values are required to prevent reconnection in anterior and roof segments of the WACA circle compared to posterior and inferior segments.

5.4.2 FTI as a marker of ablation lesion quality

In the recent past, FTI has been used with greater frequency to guide point-by-point radiofrequency ablation for PVI. FTI and impedance drop have previously been shown to be correlated, although the strength of this correlation has varied between studies.196,197 In EFFICAS I, the minimum FTI value within a WACA segment was shown to be predictive of PV reconnection at repeat electrophysiology study,136 and a target FTI value derived from this investigation (400gs) was used prospectively to guide ablation in the subsequent EFFICAS II study.158 Although this resulted in a reduction in the rate of PV reconnection when compared to EFFICAS I, 15% of PVs in 37.5% of patients were still found to have PV reconnection at follow-up electrophysiology study. There is therefore further scope for improvement.
There are two significant limitations regarding FTI as a marker of lesion quality. Firstly, FTI ignores the significant role of power delivery in lesion creation.\textsuperscript{141,142} In EFFICAS I, power settings of 10-40W were used in the study,\textsuperscript{136} making interpretation of the derived FTI target very difficult. In a study reported by Guerra et al, lesions with a FTI value of 300gs (a contact force of 10g for a duration of 30secs) created with 35W had more than three times greater volume than lesions with the same FTI value created with 20W,\textsuperscript{141} and accordingly, the difference between lesions of the same FTI value created with 40W or 10W would be even greater. Secondly, FTI is calculated by simple multiplication of contact force by application time, whereas it is known that the relationship between these parameters is more complex, with each making differing contributions to lesion formation.\textsuperscript{139} It has been shown previously in an animal model that application duration contributes relatively little to lesion size beyond 20 seconds,\textsuperscript{191} and therefore doubling the duration is likely to have a lesser impact than doubling the contact force despite an equivalent FTI value.

Irrespective of the deficiencies of FTI, it also may not be appropriate to extrapolate a target value derived for the TactiCath contact force-sensing catheter to the SmartTouch catheter.\textsuperscript{136,158} The mechanism of contact force-sensing for the TactiCath catheter involves microdeformation of optical fibres, as compared to a precision spring for the SmartTouch catheter. These mechanisms are intrinsically different and there are data to suggest differences in lesion creation for the same apparent contact force applied.\textsuperscript{154}

### 5.4.3 Clinical utility of AI

This study has evaluated AI, a novel ablation lesion quality marker which tackles the main deficiencies of FTI, firstly by incorporating power delivery, and secondly by incorporating this into a weighted equation along with contact force and time. AI has been demonstrated to be significantly correlated to impedance drop and has also been shown to be independently predictive for reconnection at repeat electrophysiology study. As in the EFFICAS I study, the minimum value within a WACA segment was more predictive for reconnection than the mean,\textsuperscript{136} in keeping with the
concept that the chain of ablation lesions is only as strong as its weakest link. Minimum FTI was also found to be independently predictive of WACA segment reconnection. Of note, a very narrow range of power settings was used in this study (25-35W, and predominantly 30W), which would be expected to largely neutralise one of the key advantages of AI over FTI. It is possible that if a wider range of power settings had been used, such as that used in EFFICAS I (10-40W), a greater difference may have been seen.

### 5.4.4 Regional differences in ablation target values

From morphological studies of the human heart, it is clear that the thickness of the left atrial wall varies in different regions of the chamber. A particularly pertinent further finding from this study is that there is a significant difference in both AI and FTI values required to avoid reconnection in the anterior and roof segments of the WACA circle compared to the posterior and inferior segments. This finding is suggestive of thicker atrial tissue in the anterior and roof regions, therefore requiring additional energy delivery to achieve a transmural lesion. Application of a single target FTI value of 400gs throughout the left atrium has been widely adopted following publication of EFFICAS I, but this may well result in excessive energy delivery to the thin posterior wall, which could in turn increase the risk of oesophageal fistula formation, a major complication with an extremely high fatality rate. In our study, a FTI threshold of only 230gs was required to avoid reconnection in posterior and inferior segments, with a FTI value of 420gs needed only for anterior and roof segments. The equivalent AI target values were 370 and 480 respectively. In line with refinements to ablation technique that have evolved over the years to improve the efficacy and safety of PVI procedures, applying these regional target values provides a more tailored approach to left atrial ablation. This is achieved by avoiding unnecessary ablation in thin-walled areas such as the posterior wall where the risks of collateral damage are higher, whilst avoiding compromising on efficacy at areas of thicker tissue such as the PV/appendage ridge.
5.5 Limitations

As all PV reconnection identified at repeat electrophysiology study was re-isolated, the relationship between AI and AT recurrence is not interpretable; however, our focus for this work was purely to study the relationships between ablation lesion quality markers and late reconnection.

5.6 Conclusions

AI, a novel ablation quality marker incorporating contact force, time and power in a weighted formula, has a significant correlation with impedance drop. The minimum AI and FTI in a WACA segment are both independently predictive of reconnection of that segment at repeat electrophysiology study, but minimum AI has a smaller $P$ value. Higher AI and FTI values are required to prevent reconnection of anterior and roof segments than posterior and inferior segments.
6 RESULTS - The relationship between re-ablated sites of acute reconnection after pulmonary vein isolation and sites of late reconnection at repeat electrophysiology study

6.1 Introduction

While a very high rate of acute electrical isolation of the PVs is currently achieved, it has been observed that electrical reconnection of the PVs to the left atrium occurs frequently in the minutes to hours following initial isolation. Identification of this phenomenon potentially allows the opportunity to deliver further ablation at these sites to re-isolate the PV. This re-ablation should in turn improve the chances of achieving enduring PVI and, as PV reconnection is known to be responsible for the majority of recurrences in paroxysmal AF patients, consequently should improve clinical outcomes. Accordingly, the current international expert consensus statement suggests re-assessing the PVs after a waiting period of a minimum of 20 minutes following isolation. Furthermore, intravenous adenosine administration has been used to unmask dormant conduction between the PV and left atrium. It has previously been shown that sites of adenosine-mediated acute reconnection that are left untreated predict sites of subsequent reconnection. Adenosine administration and re-ablation at sites exhibiting dormant PV conduction is therefore a strategy that is frequently employed.

However, there remains controversy over whether further ablation at sites of acute reconnection is truly effective as oedema is known to develop quickly following the delivery of radiofrequency energy. This may limit the subsequent delivery of energy at the same site, making transmural ablation extremely difficult to achieve. A comparison of sites of acute reconnection to late reconnection sites identified from redo procedures for clinical arrhythmia recurrence has been made in a number of previous studies, but this has never been investigated systematically. The aim of this study was therefore to determine prospectively whether re-ablated sites of acute reconnection are predictive of sites of late reconnection at repeat
electrophysiology study two months following PVI.

6.2 Methods

The main methods used for this study were as described in the Methods chapter. Specific methods used are as described below.

6.2.1 Patient population

The study population for this investigation was the 40 patients enrolled to the PRESSURE trial who were randomised to undergo a protocol-mandated repeat electrophysiology study at 2 months, regardless of symptoms.

6.2.2 Repeat electrophysiology procedure

The operator was blinded to the presence and location of acute reconnection sites seen at the initial procedure. All identified sites of late reconnection were re-ablated to re-isolate the PVs.

6.2.3 Comparison of acute and late reconnection sites

Sites of acute and late reconnection were classified according to the 12-segment model (6 segments per WACA circle) and were compared.

6.2.4 Statistical analysis

Statistical analyses were as described in the Statistical Analysis paragraph of the Methods section.

6.3 Results

6.3.1 Acute PV reconnection

After the minimum 20-minute waiting period, acute spontaneous reconnection was seen in 14 (3%) WACA segments and adenosine-induced reconnection was seen in a further 14 (3%) segments. This
affected 24 (15%) PVs and 21 (26%) WACA circles in 20 (50%) patients. The two patients in whom the right inferior PV could not be safely isolated at the posterior aspect due to oesophageal temperature rise did not exhibit acute reconnection elsewhere. Demographic data for patients with acute reconnection (including the two patients with non-isolation) and without acute reconnection are presented in Table 6.1. As might be expected, the total ablation time was longer for patients who exhibited acute reconnection and received additional ablation to re-isolate the PVs compared to those without reconnection.

The distribution of sites of acute reconnection is shown in Figure 6.1 (upper panel). Reconnection was most frequently seen in left and right roof segments (n=9), followed by right posterior segments (n=8). All 28 acutely reconnected segments were successfully re-isolated.

Following cessation of anti-arrhythmic and rate-limiting drugs four weeks after PVI, medications were required to be restarted in nine patients due to arrhythmia recurrence in the ERAT period. Of these patients, five had exhibited acute reconnection and four had not.
Table 6.1: Demographic data for study participants with and without acute reconnection

<table>
<thead>
<tr>
<th></th>
<th>Acute PV reconnection (n=22)</th>
<th>No acute PV reconnection (n=18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>58±10</td>
<td>59±14</td>
<td>0.801</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>14 (64%)</td>
<td>10 (56%)</td>
<td>0.748</td>
</tr>
<tr>
<td>Left atrial diameter, mm</td>
<td>40±6</td>
<td>38±4</td>
<td>0.337</td>
</tr>
<tr>
<td>Ejection fraction &gt;55%, n (%)</td>
<td>21 (95%)</td>
<td>18 (100%)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>7 (32%)</td>
<td>7 (39%)</td>
<td>0.744</td>
</tr>
<tr>
<td>IHD, n (%)</td>
<td>0 (0%)</td>
<td>2 (11%)</td>
<td>0.196</td>
</tr>
<tr>
<td>OSA, n (%)</td>
<td>1 (5%)</td>
<td>2 (11%)</td>
<td>0.579</td>
</tr>
<tr>
<td>CVA, n (%)</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Anti-arrhythmic drugs, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flecainide</td>
<td>12 (55%)</td>
<td>10 (56%)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Sotalol</td>
<td>2 (9%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>Dronedarone</td>
<td>0 (0%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>Beta-blockers, n (%)</td>
<td>16 (73%)</td>
<td>12 (67%)</td>
<td>0.738</td>
</tr>
<tr>
<td>Calcium channel blockers, n (%)</td>
<td>0 (0%)</td>
<td>2 (11%)</td>
<td>0.196</td>
</tr>
<tr>
<td>ACE-I/ARB, n (%)</td>
<td>5 (23%)</td>
<td>6 (33%)</td>
<td>0.498</td>
</tr>
<tr>
<td>Anticoagulation, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>12 (55%)</td>
<td>10 (56%)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>NOAC</td>
<td>8 (36%)</td>
<td>5 (28%)</td>
<td></td>
</tr>
<tr>
<td>Procedure time, minutes</td>
<td>171±39</td>
<td>156±27</td>
<td>0.151</td>
</tr>
<tr>
<td>Ablation time, minutes</td>
<td>46±10</td>
<td>40±7</td>
<td>0.042</td>
</tr>
<tr>
<td>Fluoroscopy time, minutes</td>
<td>14±8</td>
<td>12±6</td>
<td>0.237</td>
</tr>
<tr>
<td>General anaesthesia, n (%)</td>
<td>17 (77%)</td>
<td>14 (78%)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Interval between procedures, days</td>
<td>62±6</td>
<td>60±4</td>
<td>0.246</td>
</tr>
<tr>
<td>Cardiac rhythm drugs restarted for AT, n (%)</td>
<td>5 (23%)</td>
<td>4 (22%)</td>
<td>&gt;0.999</td>
</tr>
</tbody>
</table>

Table 6.1: Demographic data for study participants with and without acute reconnection
Figure 6.1: Diagram of sites of acute and late PV reconnection

Figure 6.1: Diagram showing the number of reconnection sites identified within each of the 12 segments acutely (upper panel) and at repeat electrophysiology study (lower panel).
6.3.2 PV reconnection at repeat electrophysiology study

Fifty-one (11%) segments in 25 (62%) patients were identified as having late PV reconnection. This affected 41 (26%) PVs and 28 (35%) WACA circles. In the two patients in whom the posterior segment of the right inferior PV could not be isolated at the initial procedure, this segment remained electrically connected at repeat study and both patients were also found to have further sites of late PV reconnection. Demographic data for patients with and without PV reconnection at repeat study are shown in Table 4.2 (Chapter 4).

The distribution of sites of late reconnection is shown in Figure 6.1 (lower panel). As was the case for acute reconnection, late reconnection was frequently seen in right posterior segments (n=14), but, in contrast, was also commonly seen in left anterior (n=13) and left and right inferior (n=12) segments.

6.3.3 Relationship between sites of acute and late PV reconnection

After excluding the two segments that were not isolated at the initial PVI procedure, the numbers and proportions of segments showing acute reconnection, late reconnection, neither or both are shown in Table 6.2.

Table 6.2 Proportions of WACA segments with acute and late reconnection

<table>
<thead>
<tr>
<th></th>
<th>WACA segments with late reconnection (n)</th>
<th>WACA segments without late reconnection (n)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>WACA segments with acute reconnection (n)</td>
<td>4 (1%)</td>
<td>24 (5%)</td>
<td>28 (6%)</td>
</tr>
<tr>
<td>WACA segments without acute reconnection (n)</td>
<td>47 (10%)</td>
<td>403 (84%)</td>
<td>450 (94%)</td>
</tr>
<tr>
<td>Total</td>
<td>51 (11%)</td>
<td>427 (89%)</td>
<td>478 (100%)</td>
</tr>
</tbody>
</table>

*Table 6.2: 2x2 table of the number and proportions of WACA segments exhibiting acute and late reconnection*
The proportion of segments with acute reconnection that exhibited late reconnection was not significantly different when compared to segments without acute reconnection (14% (4/28) vs. 10% (47/450), \(P=0.524\), Figure 6.2, left panel). In addition, there was no difference in the rate of late reconnection between acute reconnection segments that reconnected spontaneously and those that were unmasked by adenosine (14% (2/14) vs. 14% (2/14), \(P>0.999\)). The vast majority of segments exhibiting late reconnection at repeat electrophysiology study (47 of 51 (92%)) had not demonstrated acute reconnection at the initial procedure.

### 6.3.4 Acute reconnection as a marker of late reconnection

With regard to acute reconnection as a marker of late reconnection, reconnection of WACA circles was analysed. After excluding the two circles that could not be isolated at the initial procedure, 8 (38%) of 21 circles with acute reconnection exhibited late reconnection compared to 18 (32%) of 57 circles that had not acutely reconnected. This was not statistically different (\(P=0.599\), Figure 6.2, centre panel), and the majority of WACA circles with late reconnection (69%) had not demonstrated acute reconnection.

In a per patient analysis, the proportion of patients with acute reconnection demonstrating late reconnection was also not statistically different to those without acute reconnection (70% (14/20) vs. 50% (9/18), \(P=0.320\), Figure 6.2, right panel).
Figure 6.2: Bar chart showing the proportion of WACA segments, WACA circles and patients with and without acute reconnection exhibiting late reconnection at repeat electrophysiology study.

6.4 Discussion

6.4.1 Main findings

This study systematically examined the relationship between re-ablated sites of acute reconnection and sites of late reconnection by using mandated repeat electrophysiology studies to avoid the bias inherent in only collecting data from patients undergoing for a clinical redo procedure for arrhythmia recurrence. The main finding is that the proportion of WACA segments re-ablated for spontaneous or adenosine-mediated acute reconnection that go on to demonstrate late reconnection is no different to that for segments without acute reconnection. This implies that re-ablation at these sites is effective in the great majority of instances. In the remaining 14% of acutely reconnected segments that did go on to exhibit late reconnection, it cannot be determined whether this was due to ineffective re-ablation due to oedema or late reconnection at another site within that segment.
Furthermore, the presence of acute reconnection within a WACA circle or an individual patient is not associated with late reconnection elsewhere within that circle or within that patient. If acute reconnection was an indicator of generalised sub-optimal lesion creation, it would be expected that late reconnection would occur more frequently in patients with acute reconnection, even if not at the same location. These findings suggest that acute reconnection is more likely to be a localised phenomenon than a marker of generalised sub-optimal ablation.

6.4.2 Acute PV reconnection and the role of adenosine

Data have been published previously on the high prevalence of acute PV reconnection and the time-course of this phenomenon in the minutes to hours following initial isolation of the PVs.\textsuperscript{198,199} In addition to spontaneous acute reconnection, intravenous adenosine has also been shown to unmask sites of dormant conduction between the left atrium and PV.\textsuperscript{159} This has been demonstrated to be due to hyperpolarisation of PV myocytes by adenosine, and it is hypothesised that this action temporarily allows restoration of electrical conduction across myocytes that have been partially, but not permanently, damaged.\textsuperscript{204,205} Previous studies have found that PVs with transient adenosine-mediated reconnection have a very high probability of translating into subsequent reconnection if left untreated, with 94% exhibiting spontaneous reconnection after a 30 minute waiting period, and 90% having recovered conduction at repeat procedure for clinical arrhythmia recurrence.\textsuperscript{202,203}

6.4.3 Potential limitations of re-ablation at sites of acute reconnection

Given the likelihood of longer-term reconnection at sites of spontaneous or adenosine-mediated reconnection, the potential advantages of delivering further ablation lesions at these sites during the same procedure is relatively clear. However, concerns have been raised as to how efficacious these additional lesions are. Imaging studies in animal models have shown that oedema develops in the first 15 minutes following ablation,\textsuperscript{161} with almost doubling of the atrial wall thickness seen by 1 minute.\textsuperscript{162} Additionally, in the EFFICAS I study, the number of lesions applied to a segment of a PVI
circle was found to be inversely correlated to persistent isolation of that segment at repeat study 3 months later. One suggested explanation for this was that additional ablation lesions delivered following initial non-transmural ablation may be ineffective due to the presence of oedema. However, this study has demonstrated that re-ablation at sites of both spontaneous and dormant acute reconnection is effective in the great majority of cases.

6.4.4 Previous studies of the relationship between re-ablated acute reconnection sites and late reconnection sites

While this is the first study to examine the relationship between re-ablated acute and late reconnection sites systematically using protocol-mandated repeat studies, previous investigations have provided data from redo procedures for clinical arrhythmia recurrence. As in this study, Matsuo and colleagues found no difference in the rate of late reconnection between PVs with and without adenosine-mediated acute reconnection (54% vs. 59%, \( P=0.53 \)), with the majority of chronically reconnected PVs (74%) having not exhibited acute reconnection. In contrast, another study identified a trend towards a higher rate of late reconnection at redo ablation for PVs with dormant conduction (82%) compared to those without (49%). Of note, however, the site of late reconnection was concordant with the site of adenosine-mediated reconnection in only 55% of acutely reconnected PVs. This was very similar to the rate for PVs without dormant conduction, and therefore is consistent with our findings.

6.4.5 Previous studies of the clinical impact of re-isolating sites of acute reconnection

With regard to spontaneous reconnection, conflicting data have been reported. A 3-arm randomised trial of no waiting period versus a 30 minute waiting period versus a 60 minute period showed a significant improvement in freedom from arrhythmia in the latter 2 groups (60.7% vs. 84.3% vs. 86.7%). However, a subsequent similar trial of no waiting period versus a 60 minute wait showed no difference in arrhythmia freedom (43.4% vs. 44.4%), suggesting no benefit of re-ablation
of acute reconnection in the 50% of patients in the waiting period group who demonstrated this.\textsuperscript{207} Notably, no blanking period was applied in this study, which is likely to have lowered the success rates and may have affected the outcome. In contrast, a further study showed equivalent outcomes for patients who underwent re-ablation for acute reconnection after 20-60 minutes compared to those without acute reconnection.\textsuperscript{200}

A greater number of studies have investigated the clinical benefits of adenosine administration. Studies looking at the clinical impact of giving adenosine versus not giving adenosine have consistently found in favour of the former,\textsuperscript{207-209} and a systematic review combining all 3 demonstrated a relative risk of freedom from AF of 1.25 (95% Confidence Interval 1.12-1.40) with adenosine administration.\textsuperscript{210} Furthermore, a study of repeated adenosine administration and re-ablation at 30, 60 and 90 minutes post-isolation resulted in freedom from AF without anti-arrhythmic drugs in 92% of patients.\textsuperscript{199} These data are in keeping with our findings, in that re-ablation at sites of acute reconnection is effective and therefore will be of benefit compared to not identifying such sites and missing the opportunity to treat them. However, a very recent trial exploring this subject found no significant reduction in atrial tachyarrhythmia recurrence at 1 year with adenosine administration.\textsuperscript{211} Notably, the proportion of patients with dormant conduction was markedly lower in this study (27.6%) compared to previous studies (41-56%), and there will be less clinical benefit to be gained from seeking and re-ablating dormant conduction as its frequency falls. However, studies of outcomes for patients with and without adenosine-mediated reconnection have produced mixed results, with several indicating lower rates of freedom from AF for those with dormant conduction,\textsuperscript{212-214} and others showing equivalent outcomes.\textsuperscript{164,207,215} A systematic review incorporating most of these studies showed a non-significant trend towards poorer outcomes for patients with dormant conduction, though the reasons for this were unclear.\textsuperscript{210} Our study shows that re-ablated acute reconnection sites are no more likely to reconnect later than areas without acute reconnection. A slightly higher proportion of patients with acute reconnection developed late reconnection (70% vs. 50%), but this difference was not significant, though limited by
the sample size. These varying results from previous studies led to a large, multi-centre randomised trial, which demonstrated significantly improved freedom from atrial arrhythmias for patients with re-ablated dormant conduction compared to those with dormant conduction that was left untreated and also to those with no dormant conduction. These findings demonstrate that re-ablation at sites of dormant conduction provides clinical benefit, which could only be the case if that re-ablation is effective. In that regard, our results support that assumption.

6.4.6 Prevalence of late PV reconnection

The main aim of a PVI procedure is to deliver durable ablation lesions that result in persisting isolation of the PVs. Studies in which patients return for a protocol-mandated left atrial study allow the opportunity to assess for durable PVI regardless of symptoms, and a disappointingly high proportion of patients in this study (62.5%) were found to have PV reconnection. This figure is in keeping with two other contemporary studies of radiofrequency PVI involving protocol-driven repeat studies, in which 65% (EFFICAS I) and 70% (GAP AF - completed circles arm) of patients were found to have late reconnection.

The first of these studies, EFFICAS I, demonstrated that the minimum FTI value in a PVI segment is predictive of reconnection of that segment and identified a minimum FTI threshold value of 400gs, above which 95% of segments did not reconnect. In a follow-up study, EFFICAS II, the proportion of patients with PV reconnection at repeat study was reduced to 37.5% by utilising this FTI target, though a relatively high complication rate was also reported. A more tailored form of target-guided ablation may therefore be a promising strategy for the future, as discussed in Chapter 5. Comparatively, improvements in cryoballoon technology have also lowered the rate of PV reconnection, with PV reconnection seen in 21% of patients with the second-generation cryoballoon compared to 33% with the first-generation device. There therefore remains much work to do before durable PV isolation after the index procedure can be assured.
6.5 Limitations

While the sample size of 40 patients allowed examination of a total of 480 WACA segments examined, the prevalence of acute segment reconnection was relatively low, thereby limiting the strength of the observations. Additionally, no further waiting period was applied after re-isolation of acutely reconnected sites, and this may have limited the yield of acute reconnection sites as it has previously been shown that further sites become apparent with more prolonged waiting periods.\textsuperscript{176,199}

6.6 Conclusions

The great majority of segments that undergo further ablation for spontaneous or adenosine-mediated acute reconnection at the initial PVI procedure show persistent isolation at repeat study after two months, and the rate of late reconnection for these segments is no different to that for segments that did not reconnect acutely. This implies that effective re-ablation is delivered at acute reconnection sites and supports a strategy of seeking and treating acute reconnection.
7 CONCLUSIONS

7.1 Main conclusions

PVI remains the cornerstone of catheter ablation for paroxysmal AF. However, despite improvements in ablation technique and technology, there remain significant challenges to the delivery of effective, durable radiofrequency ablation lesions that result in persisting isolation of the PVs in the longer-term. The results of the studies described above, however, provide some insight into strategies that may help in this regard.

Firstly, we have demonstrated that despite contact force-guided ablation, a high proportion of patients still develop PV reconnection, and a strategy of routine repeat electrophysiology study to assess for and treat PV reconnection provides significant improvements in freedom from AT recurrence, AT burden, and quality of life compared to current standard care.

Secondly, we found that ERAT occurring beyond 4 weeks post-PVI is associated both with PV reconnection at repeat electrophysiology study (and, in particular, more extensive reconnection of 2 or more PVs) and also with post-blanking period AT recurrence. In contrast, ERAT limited only to the first 4 weeks post-PVI is unrelated to underlying PV reconnection and therefore appears to be due to transient factors.

Thirdly, use of Ablation Index (AI), a novel ablation quality marker incorporating contact force, time and power in a weighted formula, has the potential to provide benefit. AI correlates with impedance drop, a marker of tissue effect during ablation, and the minimum AI in a WACA segment is independently predictive of conduction recovery of that segment at repeat study. Furthermore, this study demonstrated that higher AI values are required to prevent reconnection of anterior/roof segments than posterior/inferior segments, allowing more tailored ablation within the left atrium. Use of AI target-guided ablation therefore has the potential to reduce PV reconnection, while maintaining safety.

Finally, we have shown that re-ablation at sites of spontaneous or adenosine-mediated acute
reconnection at initial PVI appears to be effective, as the great majority of segments that undergo such re-ablation show persistent isolation at repeat electrophysiology study. The rate of late reconnection for these segments is also no different to that for segments that did not acutely reconnect. These findings suggest that seeking and treating acute reconnection is a worthwhile strategy that can help minimise subsequent PV reconnection and therefore improve clinical outcomes, as has been shown in other studies.105

7.2 Implications for current clinical practice

It is clear that PV reconnection rates remain high despite the use of modern technology, including contact force-sensing catheters, and in turn freedom from AT is significantly lower than might be achieved if more durable PVI could be realised. Although a strategy of routine repeat electrophysiology study in all patients to assess for and treat PV reconnection was found to significantly improve outcomes, it is unlikely that this strategy would ever be adopted into routine clinical practice. This is because of both the major cost implications of such a strategy and also the potential risk of complications. Although there were no complications related to the repeat procedures in this study, complication rates can be very variable depending on the experience of the operator and centre,218 and this would therefore be a significant concern, especially in asymptomatic patients.

Accordingly, strategies to improve durability of PVI following the initial procedure are of critical importance, as the results of this study imply that enduring PVI would translate into improved outcomes. In this regard, better utilisation of the data provided by contact force-sensing catheters by incorporating this information into lesion quality markers may be beneficial. Although AI has several theoretical advantages over FTI, both were found to be independently predictive of segment reconnection at repeat study, and values for anterior/roof segments and posterior/inferior segments above which no reconnection was seen have been defined for both markers. Where AI is used, a strategy of aiming for AI values of ≥480 in anterior/roof segments and ≥370 in
posterior/inferior segments should be deployed. Alternatively, FTI values of ≥420gs and in anterior/roof segments and ≥230gs in posterior/inferior segments should be aimed for, with the caveat that these values relate to the SmartTouch catheter and power range settings of 25-30W on the posterior wall and 30-35W elsewhere. It would be expected that this strategy would improve durability of PVI while maintaining safety, but this would need to be demonstrated prospectively.

As part of the initial procedure, it would also be recommended that if acute reconnection is identified, whether spontaneous or adenosine-mediated, further ablation should be performed to re-isolate these areas with the expectation that this will be effective in the majority of instances.

Finally, the strong association identified in this work between ERAT beyond 4 weeks post-PVI and PV reconnection, particularly of 2 or more PVs, is suggestive that the blanking period following PVI for paroxysmal AF should be reduced from 3 months to 1 month. This assertion is supported by increasing clinical data demonstrating a very high likelihood of later AT recurrence in patients with ERAT in months 2 and 3 post-PVI, a finding that was also seen in this work.

If the blanking period is reduced to 1 month, then patients with AT recurrence beyond this time-point would automatically be eligible for consideration of re-intervention. However, even if the blanking period remains at 3 months, patients with AT recurrence beyond 4 weeks should still be considered for early re-intervention. In a further analysis of randomised groups in relation to ERAT, 12 (86%) of 14 in the SC group with ERAT beyond 4 weeks went on to experience the primary endpoint. This proportion was significantly reduced in the RS group (5/13 (38%), P=0.02). Comparatively, for those without early recurrence (either no recurrence or recurrence confined only to the first four weeks), the risk of reaching the primary endpoint was low (7/53 (13%)), and the difference between groups did not reach significance (SC: 5/26 (19%) vs. RS: 2/27 (7%), P=0.25). The addition of ERAT beyond 4 weeks to the multivariable model was significant, with patients experiencing this being nearly ten times more likely to reach the primary endpoint than those without ERAT (Hazard ratio 9.75, 95% confidence interval 3.94-24.15, P<0.001). The addition of ERAT beyond 4 weeks also increased the significance of the randomisation group in the model (P=0.005).
Therefore, the greatest benefit from an early re-intervention strategy is seen in patients with ERAT beyond 4 weeks post-PVI. Even if the repeat procedure is scheduled following identification of ERAT in month 2 or 3, rather than pre-planned at 2 months following the initial PVI procedure, this would reduce the time to the second procedure compared to waiting for AT recurrence beyond 3 months and is therefore likely to impact positively on overall AT burden and quality of life.

7.3 Plans for future work

The findings from these studies raise a number of questions for future investigation:

1. With regard to improving outcomes from radiofrequency ablation in patients with paroxysmal AF using current techniques, a prospective study of early re-intervention in patients with ERAT beyond 4 weeks could be undertaken. This would involve intensive ECG monitoring, as performed in the PRESSURE study, in the second month following PVI. Patients without ERAT in this period would not undergo further invasive assessment, whereas those with ERAT would be randomised to either a repeat electrophysiology study with re-isolation of reconnected PVs, or to no further intervention within the blanking period. Participants would be followed-up clinically for 12 months for AT recurrence. The hypothesis being tested in this study is that selective re-intervention only in patients with ERAT beyond 4 weeks improves outcomes, and to a level similar to that of patients without ERAT.

2. With regard to the clinical utility of Ablation Index-guided ablation, the following studies would provide further information on its value:
   a. A prospective study involving repeat electrophysiology study after two months following Ablation Index-guided PVI (using the target values identified in Chapter 5) to assess the proportions of patients and PVs with reconnection. These rates could be compared to those from the PRESSURE study (historical controls). This study has
already been designed, secured funding and obtained ethical approval, and is currently recruiting (ClinicalTrials.gov Identifier: NCT02628730).

b. A prospective study randomising patients with paroxysmal AF to undergo either Ablation Index-guided PVI using the identified target values or PVI without Ablation Index guidance (this arm could either be contact force-guided or, given the lack of data supporting clinical benefit from use of contact force, without contact force).
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