Evaluation of Arrhythmia Recurrence and Electrical Reconnection of The Pulmonary Veins following Ablation Index Guided Pulmonary Vein Isolation for Persistent Atrial Fibrillation

A Thesis by

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Declaration of Originality

I, Ahmed Hussein, 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 myself 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.

Copyright Declaration

Abstract

Introduction

Ablation Index is a novel ablation quality marker that incorporates contact force (CF), power and application time (Force-Power-Time Index Formula). We hypothesised that the prospective use of Ablation Index previously published targets would result in better AF ablation outcomes compared to the commonly used contact-force guided ablation.

Methods and Results

Our research on Ablation Index was the first to investigate the prospective use of Ablation Index targets, 550 for anterior and 400 for posterior left atrial (LA) regions, to guide AF ablation. We investigated that in two studies; the first was a retrospective analysis and compared the acute procedural and long-term clinical outcomes with those of a propensity matched group in which AF ablation was contact force-guided. The study showed significant improvements in the incidence of acute pulmonary vein (PV) reconnection and in the freedom from recurrence atrial tachyarrhythmia (ATA), defined as atrial fibrillation, atrial flutter or atrial tachycardia, at 12 months compared to CF -guided ablation.

The second study, the PRAISE (Pulmonary vein Reconnection following Ablation Index-guided ablation: Success Evaluation) study, was a multicenter prospective study of 40 patients with persistent AF of less than 12-month duration, and no significant structural heart disease who underwent a protocol-mandated repeat procedure after 2 months. Patients were monitored for atrial tachyarrhythmia recurrence using daily ECG recordings

for 12 months. In that study Ablation Index-guided ablation resulted in a low rate of PV reconnection at repeat electrophysiology study, with 93% of PVs found to remain durably isolated. We then compared the AF ablation outcomes form the 40 patients who form the PRAISE study cohort with those of the 40 paroxysmal AF patients of the PRESSURE (Pulmonary vein RE-isolation as a routine Strategy: a SUccess Rate Evaluation) study who were also randomised to a repeat procedure 2-months following the initial CF-guided PVI. Acute and late reconnections were significantly lower in the PRAISE cohort when compared to CF-guided ablation in the PRESSURE cohort, despite significantly shorter ablation times, lower average CF values, and significantly larger left atria in the former cohort compared to the later cohort. No major complications occurred with Ablation Index-guided ablation in our research studies.

We then studied the potential occurrence of LA structural and electrical reverse remodelling following Ablation Index-guided PVI, and found that both structural and electrical remodelling became evident two months following Ablation-Index guided PVI. We also found that factors known to be associated with less likelihood for development of left atrial fibrosis in persistent AF patients, rather than durable PVI alone, were associated with LA structural reverse remodelling. We then studied the relation between LA reverse remodelling and Ablation Index-guided AF ablation outcomes, and found that the occurrence of all three types of LA reverse remodelling together; structural, conduction velocity and LA voltage, was associated with a low likelihood for ATA recurrence.

Finally, we studied the factors associated with late PV reconnection at repeat electrophysiology study and found that the occurrence of either absent first pass isolation or acute reconnection in a wide area circumferential ablation (WACA) circle predict late reconnection in the same WACA circle. A larger WACA circle transverse diameter was also found to be associated with a higher incidence of late PV reconnection. Late PV reconnection was also found to correlate with lower temperature and lower CF in the thicker anterior LA segments, and with lower impedance drop in the thinner posterior segments.

Conclusion

Ablation Index-guided ablation is associated with significant improvements in AF ablation outcomes with significant reduction of late reconnection and more freedom from atrial tachyarrhythmia at 12 months compared to CF-guided ablation, potentially due to the creation of more durable lesions as evidenced by higher impedance drop.

LA structural and electrical reverse remodelling becomes evident two months following Ablation Index guided-PVI. Factors known to be associated with less likelihood for development of left atrial fibrosis in persistent AF patients, rather than durable PVI alone, are associated with LA structural reverse remodelling. The occurrence of both structural and electrical reverse remodelling together is associated with a low likelihood for ATA recurrence.

The use of Ablation Index-guided ablation allowed the identification of factors associated with late PV reconnection in general as well as in the various LA regions.

Late PV reconnection correlates with lower temperature and lower CF in the thicker anterior LA segments, and with lower impedance drop in the thinner posterior segments.

Publications (Appendix A)

This section lists the publications, papers in peer-reviewed journals and abstract presentations at scientific conferences, which have arisen from the research work presented in this thesis.

Chapter 3 The clinical experience at Liverpool Heart and Chest Hospital with the use of ablation index to guide atrial fibrillation ablation

- **Hussein A**, Gupta D, De Potter T, Paul Spin, Eaton K, Goldstein L, Velleca M, Costa G, Grima D, Patel L, Stabile G.Treatment of Atrial Fibrillation Using Ablation Index-guided Contact Force Ablation: a Matching-adjusted Indirect Comparison to Cryoballoon Ablation.

  This publication is a peer reviewed paper the manuscript of which has been accepted by Advances in Therapy Journal in December 2019. Manuscript number: ADTH-D-19-00470R1.

- **Hussein A**, Das M, Chaturvedi V, et al. Prospective use of Ablation Index targets improves clinical outcomes following ablation for atrial fibrillation. J Cardiovasc Electrophysiol. July 2017. http://doi.wiley.com/10.1111/jce.13281.

  This publication is a peer reviewed paper published in the Journal of Cardiovascular Electrophysiology in July 2017.

- **Hussein**, M. Das, V. Chaturvedi, I. Asfour, M. Morgan, C. Ronayne, M. Shaw, R. Snowdon, D. Gupta; Prospective use of ablation index targets improves clinical outcomes following ablation for atrial fibrillation. Europace 2017; 19 (suppl 3): iii264-iii265. doi: 10.1093/ehjci/eux157.002.

This is an abstract that was presented as an oral presentation in the Rapid-Fire session, exclusively assigned to the top ten abstracts, in the European Heart Rhythm Association meeting in Vienna, Austria in June 2017.

- **Hussein, A**., Das, M., Chaturvedi, V., Asfour, I. K., Morgan, M., Ronayne, C., Shaw, M., Snowdon, R. and Gupta, D. Prospective use of ablation index targets improves clinical outcomes following ablation for atrial fibrillation. Heart Rhythm. 2017; 14 (suppl 5): S366. http://dx.doi.org/10.1016/j.hrthm.2017.04.008

  This is an abstract that was presented as a moderated poster presentation in the Heart Rhythm Society annual meeting in Chicago, Illinois, US in May 2017.
- **Hussein**, M. Das, I. Asfour, M. Morgan, C. Ronayne, M. Shaw, R. Snowdon, and D. Gupta. Ablation Index-Guided Pulmonary Vein Isolation for Atrial Fibrillation may Improve Clinical Outcomes in Comparison to Contact Force-Guided Ablation. Europace (2016) 18 (suppl 2): ii13-ii17 DOI: http://dx.doi.org/10.1093/europace/euw272

  This is an abstract that was presented as a poster presentation in the Heart Rhythm Congress, Birmingham, UK 2016.

Chapter 5 Use of AI-guided ablation results in high rates of durable pulmonary vein isolation and freedom from arrhythmia in persistent AF patients: the PRAISE Study Results

- **Hussein A**, Riva S, Morgan M, Sahni A, Shaw M, Todd D, Hall M, Modi S, Natale A, Dello Russo, A, Snowdon, R, Gupta, D. Use of Ablation Index-Guided Ablation Results in High Rates of Durable Pulmonary Vein Isolation and Freedom from Arrhythmia in Persistent Atrial Fibrillation Patients. Circ Arrhythm Electrophysiol. 2018;11(September):1-11. doi:10.1161/CIRCEP.118.006576.

This publication is a peer reviewed paper published in the Circulation: Arrhythmia and Electrophysiology Journal in September 2018.

Chapter 5-III Reverse remodelling of the left atrium occurs early after catheter ablation for persistent atrial fibrillation in the presence of durable pulmonary vein isolation

- **Hussein A**, Maille B, Das M, Morgan M, Ronayne C, Gupta A, Shaw M, Snowdon R, Gupta D. Relationship Between Left Atrial Bipolar Voltages and Pulmonary Vein Reconnection Following Ablation Index-Guided Ablation in Patients with Persistent Atrial Fibrillation. Heart Rhythm. 2019;16(5):S283. doi:10.1016/j.hrthm.2019.04.016.

  This is an abstract that was presented in the Heart Rhythm Society annual meeting in San Francisco, California, US in May 2019.
- Maille B, Das M, **Hussein A**, Shaw M, Chaturvedi V, Williams E, Morgan M, Ronayne C, Snowdon RL, Gupta D. Reverse electrical and structural remodeling of the left atrium occurs early after pulmonary vein isolation for persistent atrial fibrillation. JICE. 2019. doi: 10.1007/s10840-019-00576-1.

  This publication is a peer reviewed paper that was accepted for publication in the Journal of Invasive Cardiac Electrophysiology in May 2019.
- Maille B, Das M, **Hussein A**, Shaw M, Chaturvedi V, Morgan M, Ronayne C, Snowdon RL, Gupta D. Accuracy of left atrial bipolar voltages obtained by ConfiDENSE multielectrode mapping in patients with persistent atrial fibrillation. J Cardiovasc Electrophysiol. 2018;(March). doi:10.1111/jce.13472.

  This is a peer reviewed paper that was published in the journal of Cardiovascular Electrophysiology in March 2018.

- B Maille, M Das, **A Hussein**, M Shaw, V Chaturvedi, M Morgan, C Ronayne, R Snowdon, D Gupta. Accuracy of left atrial bipolar voltages obtained by ConfiDENSE multielectrode mapping in patients with persistent atrial fibrillation. EP Europace, Volume 19, Issue suppl 1, 1 October 2017, Pages i15, doi: 10.1093/europace/eux283.042

  This publication is an abstract that was presented as poster presentation in the Heart Rhythm Congress, Birmingham, UK in October 2017.

- B. Maille, **A. Hussein**, V. Chaturvedi, M. Morgan, C. Ronayne, R. Snowdon, D. Gupta; Reverse remodelling of the left atrium occurs early after catheter ablation for persistent atrial fibrillation. *EP Europace*, Volume 19, Issue suppl_3, 1 June 2017, Pages iii55. doi: 10.1093/ehjci/eux141.057

  This publication is an abstract that was presented as a poster in the European Heart Rhythm Association annual meeting in Vienna, Austria in June 2017.

Chapter 5-IV Factors Associated with Regional Late Pulmonary Vein Reconnection after Ablation Index-Guided Ablation in Patients with Persistent Atrial Fibrillation

- **Hussein**, M. Das, B. Maille, S. Riva, M. Morgan C, Ronayne, A. Gupta, M. Shaw, A. Natale M, A. Dello Russo, MD, R. Snowdon M, and D. Gupta. Incidence and Predictors of Late Pulmonary Vein Reconnection after Ablation Index-Guided Ablation in Patients with Persistent Atrial Fibrillation. Heart Rhythm. 2018;15(5):S488-S589. doi: 10.1016/j.hrthm.2018.03.028.

  This publication is an abstract was presented as a poster presentation in the Heart Rhythm Society annual meeting in Boston, MA, US in May 2018.

Abbreviations

AF: Atrial fibrillation

AI: Ablation Index

ARC: Acute reconnection

CFAE: Complex fractionated atrial electrograms

CF: Contact Force

CT: Computed Tomography

CI: Confidence Interval

DE-MRI: Delayed enhancement MRI

DF: Dominant frequency

EGM: Electrogram

ERP: Effective refractory period

FTI: Force Time Integral

FPTI: Force Power Time Integral

HR: Hazard Ratio

LAA: Left atrial appendage

LA: Left atrium

LLR: Left lateral ridge

LRC: Late reconnection

MDCT: Multidetector Computed Tomography

MRI: Magnetic Resonance Imaging

PAF: Paroxysmal AF

PeAF: Persistent AF

PV: Pulmonary Vein

PVI: Pulmonary vein isolation

QoL: Quality of life

SR: Sinus Rhythm

WACA: Wide area circumferential ablation

Chapter 1 Introduction

Persistent Atrial Fibrillation Definition and Pathophysiology

The 2017 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation (AF) defined persistent atrial fibrillation (PeAF) as continuous AF that is sustained beyond 7 days, and long-standing persistent AF as continuous AF of greater than 12 months' duration. In addition the statement introduced the new term, early persistent AF, to define continuous AF of more than 7 days' but less than 3 months' duration. [1]

AF is initiated by triggers from the pulmonary veins (PVs), or much less commonly from other non-PV triggers such as vein of Marshall, superior vena cava, and coronary sinus.[2,3]

Early in the course of AF the atrial tissue is relatively healthy and as a result sinus rhythm is spontaneously restored, but as the atrial substrate remodels over time AF no longer terminates spontaneously and becomes persistent. [3]

Computational mapping of human AF suggested the presence of two types of stable drivers within the atria, reenterant circuits known as rotors, and focal triggers.[4]

Compared to paroxysmal AF, more drivers are present in persistent AF and are thought to be the main contributors to the AF maintaining substrate.[5] In a study of 101 patients with sustained AF using a 64-pole basket catheter (Constellation, Boston Scientific, Natick,

Massachusetts) to map the left atrium, these drivers were found to be located in specific areas of the atria mainly in the regions of PV antra, adjacent to the septum, and the left atrial appendage.[6]

In the early months of persistent AF, the arrhythmia is sustained by few driver domains but later the substrate disseminates making AF electrically and structurally more complex. [5] Therefore, more electrophysiologists are opting to perform AF ablation early in the course of the AF in an attempt to limit AF-induced atrial damage and reduce AF burden.[7,8]

In addition, MRI studies have shown an association between reenterant drivers and the patchy zones bordering dense fibrosis. [9]

Structural and Electrical Remodelling in Persistent Atrial Fibrillation

Structural remodelling in persistent AF is characterized by atrial enlargement and fibrosis. Both large atrial dimensions and fibrosis, through interrupting fibre-bundle continuity and causing local conduction disturbances, are determinants of the persistence of AF-maintaining re-entry.[10] While atrial fibrosis appears to be a common endpoint of several of AF-promoting conditions, AF also appears to promote atrial fibrosis that in turn predicts AF recurrence and therapeutic resistance. [11,12]

While electrical remodelling in persistent AF entails changes in the atrial electrophysiological properties including decreased L-type Ca_{2+}-current (ICa_L), increased inward-rectifier K_+ current (IK_1 and IK_{ACh}), and abnormal expression and distribution of the gap junction

connexin hemichannels that connect cardiomyocytes electrically. Electrical remodelling also promotes AF by creating a reentry-prone substrate. [11]

Drug Therapy versus Catheter Ablation for Persistent Atrial Fibrillation

The SARA study, a multicentre study that compared catheter ablation with cardioversion and antiarrhythmic drugs as first-line therapy for persistent AF, demonstrated that patients who were randomized to catheter ablation had better maintenance of sinus rhythm, and better quality of life. [13]

In addition, systematic reviews also demonstrated that catheter ablation in persistent atrial fibrillation patients achieved significantly greater freedom from atrial fibrillation recurrence compared with medical therapy.[7,14]

Recently, the large international multicenter Catheter Ablation versus Antiarrhythmic Drug therapy for Atrial Fibrillation (CABANA) study, Clinicaltrial.gov registration: NCT00911508, has been reported. [15] The study included patients with paroxysmal (43%), persistent (47%) and longstanding persistent (10%) atrial fibrillation. The study patients were randomized in a 1:1 fashion to either catheter ablation (n = 1,108) or drug therapy (n = 1,096). Catheter ablation was performed with standard techniques; pulmonary vein isolation / wide area circumferential ablation, and ancillary ablations as needed. Drug therapy was either for rate or rhythm control, and all patients received anticoagulation. With intention to treat analysis, the primary composite outcome of death, disabling stroke, serious bleeding, or cardiac arrest at 5 years for ablation versus drug therapy was similar (8% vs. 9.2% (HR 0.86, 95% CI 0.65-

1.15, *P*= 0.3). However, there was a significant reduction of the secondary composite outcome of death or cardiovascular hospitalization with ablation compared to drug therapy (51.7% vs. 58.1%, HR 0.83, CI 0.74-0.93, *P*<0.001).[15,16]

Persistent Atrial Fibrillation Ablation: A Historical Perspective

In 1987, Cox et al. introduced the maze procedure (CMP) for the surgical treatment of AF that was designed to block the multiple macro-reenterant circuits that were considered as the putative cause of AF. [17] That was followed by another version of the surgery that involved cut-and-sew technique of both atria and proved to be highly efficacious, termed the CMP-III.[18] However, this procedure was not widely adopted because of its complexity and invasiveness. [19] With the development of alternative energy sources such as radiofrequency (RF) and cryoenergy, surgeons became able to create lines of ablation to replace the incisions of the original CMP-III and that shortened and simplified the procedure, which was then called CMP-IV.[20]

In 1994, Swartz et al. reported successful percutaneous ablation of AF with multiple long linear lesions that was regarded as a replication of the surgical maze procedure.[21] During the procedure, fluoroscopically guided sequential RF applications were made along a predetermined set of lines in both atria. Subsequently, a long-term follow-up of 40 patients with chronic AF who underwent this procedure demonstrated marked efficacy of the procedure , but with prolonged procedure times and a high incidence of major complications including stroke, significant pericardial effusion/tamponade, and PV stenosis.[22]

In 1998, Haissaguerre et al published a study that showed that ectopic beats from the pulmonary veins (PVs) are important in the initiation of AF, and that AF recurrence could be prevented by catheter ablation at the site of these PV triggers.[23]

However, because the sites of AF initiation and/or maintenance were frequently located within the PV antrum and because of the recognition of PV stenosis as a complication of RF delivery within a PV, there was a shift in ablation strategies to target the atrial tissue located in the antrum rather than in the PV itself.[24,25]

That strategy was pioneered by Pappone et al. who achieved PV isolation by encircling point-by-point RF lesions placed in atrial tissue outside the LA-PV junction and utilizing electroanatomical mapping. The end point of the procedure was the recording of only delayed far-field electrograms (EGMs) from within the isolated area. [26]

Left atrial anatomy in relation to AF ablation

The walls of the left atrium are muscular and can be described as roof, anterior, posterior, inferior, left lateral, and septal. The roof is in close proximity to the bifurcation of the pulmonary trunk and the right pulmonary artery, the anterior wall is located behind the ascending aorta and the transverse pericardial sinus, and the posterior and inferior walls are related to the oesophagus, the vagal nerve and the descending thoracic aorta.[27] Usually the roof, anterior, posterior and inferior walls are the walls involved in the wide antral circumferential ablation (WACA) isolation during left atrial ablation.

In a cadaveric study of the left atrial wall thickness, the mean thickness from the epicardium to endocardium was 4.5 $\pm$ 0.6 mm for the superior wall, 3.3 $\pm$ 1.2 mm for the anterior wall, and 2.3 $\pm$ 0.9 mm for the posterior and inferior walls.[28] In another study using multidetector computed tomography (MDCT) the thickest part of the left atrium was the left lateral ridge (LLR) with a mean thickness of 4.42 ± 1.28 mm.[29]

Therefore, the roof and anterior walls are thicker and hence need higher RF energy delivery to prevent PV reconnection,[30] while the posterior and inferior walls are thinner with subsequent possible risk of collateral oesophageal injury during AF ablation. [31]

Current AF Ablation Strategies for Persistent Atrial Fibrillation

Currently, AF catheter ablation is considered an effective treatment that aims to restore and maintain sinus rhythm in patients with symptomatic AF. [32]

However, compared to paroxysmal AF ablation, persistent AF ablation is more challenging with less favourable outcomes and less available data on the safety and efficacy.[7,32,33] Nevertheless, all studies that compared the outcomes of catheter ablation for persistent AF to those of antiarrhythmic drugs found less recurrence rates and better maintenance of sinus rhythm with the former. [13,34,35]

The best documented target for catheter ablation is pulmonary vein isolation (PVI) at the antral level, with complete isolation showing superior outcomes compared to incomplete isolation.[36]

Pulmonary Vein Isolation Only as an Adequate Strategy for Persistent Atrial Fibrillation Ablation

As most triggers for PAF were found to originate from the pulmonary veins, PVI was initially tested in patients with PAF [23], and was eventually used to treat both PAF and persistent AF. [37] According to the 2014 AHA/ACC/HRS guidelines for the management of patients with atrial fibrillation, PVI has been considered as the cornerstone for radiofrequency catheter ablation strategies because of the common observation of rapidly firing foci initiating paroxysmal AF arising from LA myocardial sleeves extending into the PVs.[38] To improve outcomes of persistent AF ablation, more extensive ablation in the left atrium has been proposed. However, the value, extent and location of that ablation remained uncertain. [39]

In the last decade and early in this decade, several "PVI only" versus "PVI plus adjunctive ablation strategies" for persistent AF have been studied in relatively small studies including linear RF lesions in the left and right atrium, ablation of complex fractionated atrial electrogram (CFAE), ablation of non-PV foci, isolation of the left atrial appendage (LAA), ablation of scar identified by voltage mapping or MRI, ablation of autonomic ganglia and/or ablation of rotational activity. Metanalysis of some of these studies demonstrated the superiority in ablation outcomes when substrate ablation, such as linear ablation or CFAE ablation, was added to PVI. [40,41]

More recently however, the randomised Catheter Ablation of Persist End Atrial Fibrillation Study (CHASE-AF), in which stepwise approach aimed at AF termination consisting of PVI,

ablation of CFAE, and additional linear ablation lines, did show additional benefit over PVI alone in patients with persistent AF, but was rather associated with significantly longer procedural, fluoroscopic and RF ablation times. [42]

Subsequently, the landmark randomized Substrate and Trigger Ablation for Reduction of AF Trial Part II (STAR AF II) trial failed to demonstrate any reduction in AF recurrence by adding either linear or CFAE ablation to PVI in patients with persistent AF. [33]

A recent systematic review and metanalysis of studies in which persistent AF patients underwent PVI only ablation strategy using mainly contact force (CF)-sensing catheters or second-generation cryoballoon, and included PVI only patients from the CHASE-AF and STAR AF II studies, showed outcomes comparable to those for paroxysmal AF ablation historically. Of the 956 patients included in the metanalysis, 419 (45.2%) underwent PVI alone with RF, whereas 509 (54.8%) underwent cryoballoon PVI. Pooled single-procedure 12-month arrhythmia-free survival was 66.7% (95% confidence interval 60.8%–72.2%), with the majority of patients (80.5%) off antiarrhythmic drugs. [43]

The reason why PVI alone strategy in persistent AF showed lower success rates in the earlier studies and metanalysis is likely to have resulted from unrecognised late PV reconnections related to the use of prior technologies, as compared to the advanced ones that became available later such as contact force-sensing catheters, advanced mapping systems, and second-generation cryoballoon. Moreover, the earlier ablation procedures were more

frequently ostial and segmental, [44,45] compared to the more recent wide antral approach that often incorporates a significant part of the posterior LA wall. [43]

In the light of the above study findings, the 2017 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation recommended against the routine use of these adjunctive strategies in the persistent AF ablation procedures until their safety, efficacy, and true clinical value have been demonstrated in well-designed and adequately powered prospective randomized clinical trials.[1]

Biophysics of Radiofrequency Ablation

In 1996, the work of Simmers et al. made the assumption that tissue injury with radiofrequency (RF) ablation is exclusively thermally mediated. [46]

That was followed by several assumptions made by Haines regarding the heat transfer in tissue based on the results of in vitro and in vivo studies, as discussed below (Figure 1-1).[47]

The assumptions were as follows:

- The Exposure of the myocardium to heating results in a reproducible biological response

  The relationship between the resting membrane depolarization and rise in temperature was studied by Nath et al. who found little tissue injury occurs at temperatures below 45°C, while a temperature above 50°C results in a reproducible irreversible injury.[48]

- Heat transfer in tissue is a predictable biophysical phenomenon

  The thermal transfer originates from the source and then spreads out in a radial fashion with temperature drop in an exponential fashion. That phenomenon was shown in an in vitro setting with a fairly predictable decrease in the tissue temperature with increasing the distance from the source.[49]

- Lesion size is proportional to the electrode-tissue interface

In a controlled in vitro setting temperature was the best predictor of the depth of the lesion when compared to other ablation parameters including current, power, and energy. However, that was not found to translate directly to the in vivo setting because of the cooling effect of regional blood flow. [49]

- Lesion size is proportional to the radius of the catheter-tip electrode

  If a small electrode is used, less energy transfers to the tissue with an anticipated smaller lesion size, and vice versa. In a controlled in vitro setting lesion size was found to be directly proportional to the diameter of the electrode used. [50]

- Temperatures reaching or exceeding a critical temperature at the electrode–tissue interface result in coagulum formation with sudden rise in impedance

  A sudden impedance rise occurred fairly uniformly at a temperature threshold of 100◦C, as demonstrated by in vitro and in vivo data on the relationship between the temperature at electrode–tissue interface and the resultant effect on impedance.[51]

- Dissipation of RF energy into the circulating blood pool from poor contact results in a smaller lesion size

  This occurs due to the convective cooling that results in energy being carried away in the blood and less energy delivered to the tissue. However, a cooled-tip catheter with good tissue contact allows the power to be turned up without the risk of coagulum and char formation. Also, the increased power delivery means that resistive heating occurs deeper in the tissue resulting in deeper lesions.[52] With cooled-tip catheters, however, the monitored temperature at the catheter tip is less accurate in

representing tissue temperature, and thus one loses some feedback about lesion formation. [47]

Convective cooling can occur because of blood flow in vessels, as in the case of coronary perfusion. Because they act as a heat sink, coronary arteries complications with RF ablation are rare. On the other hand, when there is a large perforating artery going through an area of tissue that is a target for RF ablation, heat sink becomes a potential problem that may lead to failure to reach the target tissue temperature required for effective ablation.[53]

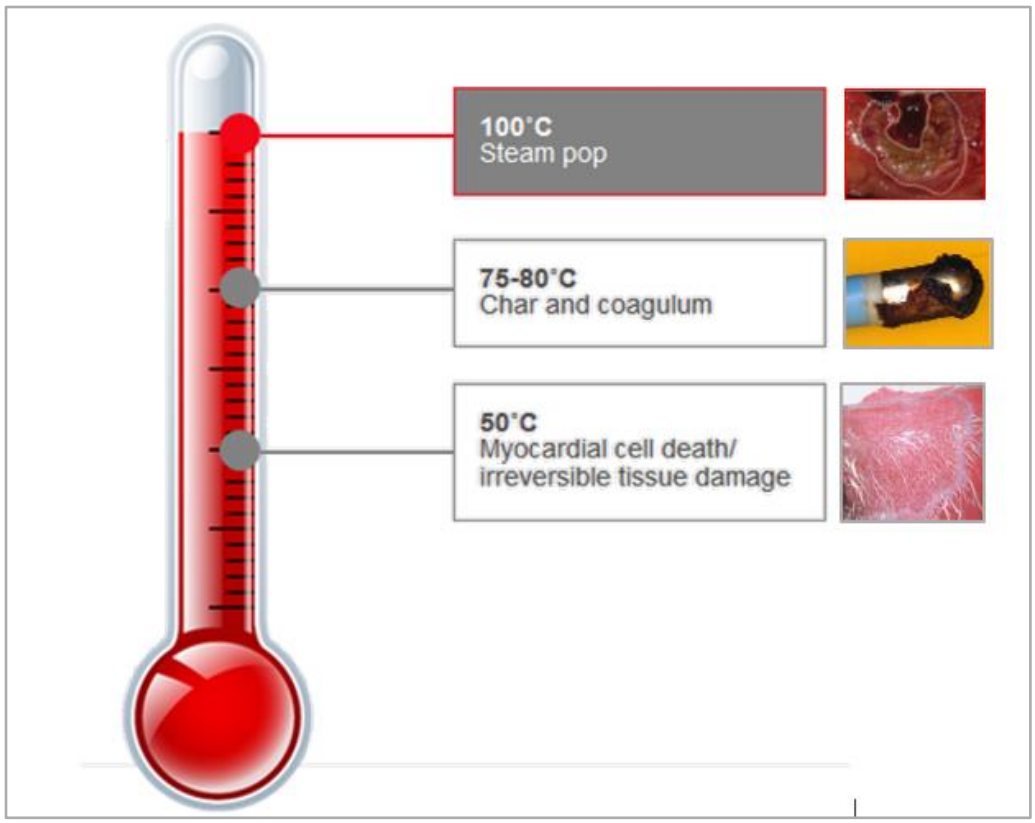


Figure 1-1 A schematic diagram showing the temperatures at which irreversible cell damage, char and coagulum formation and steam pop occur.

Chapter 2 Prediction of the Durability of Pulmonary Vein Isolation Lesions Produced during Catheter Ablation of Atrial Fibrillation

Introduction

Radiofrequency catheter ablation (RFCA) of atrial fibrillation has developed into a common treatment to prevent AF recurrence in patients with symptomatic paroxysmal and persistent AF, [32] especially for those who are refractory or intolerant to antiarrhythmic medication. [54] Several AF ablation strategies were advocated, with complete PVI widely regarded as the cornerstone in most of these strategies [36,54].

Recurrence of atrial tachyarrhythmia following catheter ablation

Unfortunately, the recurrence of atrial tachyarrhythmia, defined as atrial fibrillation, atrial flutter or atrial tachycardia, after RFCA leading to repeat ablation occurs in 20% to 40% of patients [55]. Some studies suggested risk factors that predict AT recurrence such as older age, female sex, larger left atrial size, non-paroxysmal AF, longer AF duration, hypertension, hyperlipidaemia and lower power delivery during AF ablation. [35]

Early recurrence of atrial tachyarrhythmia (ERAT) occurs within the initial three months after catheter ablation, known as the "blanking period", and is assumed to be related to sterile pericarditis or proarrhythmic effects of the ablation procedure rather than PV reconnection.[56] ERAT is common during the blanking period with an incidence that ranges between 35% and 46%.[57,58] Some studies suggested ERAT, especially when it occurs late in the blanking period, predicts later recurrence of AT. [58,59] However, because it may resolve spontaneously, there is a consensus that, except for highly symptomatic patients, repeat

ablation for patients with ERAT should be deferred during the three-month blanking period.[54]

On the other hand, late recurrence of atrial tachyarrhythmia (LRAT) that occurs after the blanking period has been largely attributed to pulmonary vein (PV) reconnection. [60,61] That view is supported by the observation of the reconnection of one or more PVs in the majority of patients who return for a repeat AF catheter ablation procedure.[54] Because LRAT after a single ablation procedure has been a common problem, with a range of 15–60%, strategies to maximise the durability of ablations lesions are considered critical to reduce recurrence rates and improve outcome after catheter ablation of AF.[62]

Improving RF catheter ablation of AF lesion durability

To achieve durable PVI, a wide area circumferential ablation needs to be carried out using a series of focal lesions that must be both transmural and contiguous. This is because non-transmural lesions can lead to oedema that heals and results in PV reconnection with subsequent AF recurrence.[63]

Although a multicentre randomised trial showed that complete is superior to incomplete pulmonary vein antral isolation (PVAI) with respect to late AF recurrence, the rate of late PV reconnection 3 months after PVAI was still high even in patients with initially complete PVAI isolation [36].

Recently new tools and techniques were developed to improve durability of ablation lesions, such as the use of steerable sheaths, CF monitoring, identification of dormant conduction with adenosine administration and direct visualization by intracardiac echocardiography

(ICE).[62] Others strategies such as the use of general anaesthesia to minimize both patient motion and respiratory, and use of jet ventilation to eliminate respiratory excursions seemed to enhance RF ablation success rates.[64]

Use of steerable sheaths

A prospective randomized study comparing steerable and non-steerable sheaths showed that single procedure success, defined as freedom from LRAT after 6 months, was 76% versus 53% , P=0.008.[65] In addition, two other studies found that the use of steerable sheaths during both paroxysmal AF and persistent AF increased ablation CF and reduced PV reconnection.[62,66]

However, according to one of the two studies these benefits of the use of steerable sheaths during wide antral circumferential ablation of AF appeared to be region dependent. The study found that there were regions in the WACA that retained a predilection for reconnection despite higher CF applied with these sheaths, suggesting regional differences in the optimal parameters required for ablation.[66] Also, in this study the steerable sheaths failed to increase CF in certain WACA regions, however this may have been related to the SmartTouch catheter's reduced accuracy in measurements with parallel contact. [66,67]

Monitoring of Contact Force

Several animal studies showed that electrode-tissue CF is a major determinant of lesion size during RFCA. [68,69] This effect is likely related to the improved catheter-tissue contact leading to the reduction of energy dissipation into the circulating blood pool resulting in better

energy delivery to tissue.[70] Moreover, monitoring CF is also important to prevent excessive CF and consequently decreases the risk of steam pop and cardiac perforation.[71]

Before the advent of CF-sensing catheters, only surrogate markers were available to monitor CF to ensure better quality of ablation lesions and hence their durability. These surrogate markers include tactile feedback from catheter manipulation, catheter stability on fluoroscopy, impedance drop, tissue temperature rise, and electrogram attenuation.

The impedance drop during the RF application is thought to be the result of tissue heating.[68]However, the measurement of impedance drop has been found to be at best moderately efficacious as surrogate marker for predicting CF.[72] This may be related to the fact that impedance measurements are sensitive to the various parameters that could affect any of the components of the typically large unipolar RF energy delivery circuit.[70]

The limitation of tissue temperature rise is that it cannot be reliably measured with irrigated catheters.[73] In addition, earlier animal studies suggested that impedance drop had a better correlation to the increase in ablation lesion diameter and depth than temperature rise.[68,71]

Other animal studies demonstrated that EGM attenuation is significantly greater in transmural compared to non-transmural lesions.[74,75] In one of these studies Otomo et al. demonstrated that the elimination of the negative component of the unipolar atrial EGM during RF energy delivery was always associated with transmural lesions. Whereas bipolar atrial EGM recorded from transmural lesions consistently demonstrated elimination of a positive deflection with non-parallel catheter orientation, and predominant attenuation (≥75%) of the R wave at sites exhibiting QRS pattern preablation or complete elimination of the R’ wave at sites exhibiting RSR’ pattern preablation with parallel catheter orientation.[74]

Subsequently, Bortone et al. confirmed that the elimination of the negative component of the unipolar atrial EGM is a useful end point for RF energy delivery during PVI in patients with paroxysmal AF, with substantial midterm maintenance of sinus rhythm and decrease in the total ablation time.[76]

However, bipolar atrial EGMs by virtue of subtraction of unipolar EGMs obtained from closely spaced electrodes eliminate noise and far-field activity, and hence has been preferred to unipolar atrial EGMs in the clinical settings.[77] Several studies that included EGM-guided PVI in AF patients used the reduction of >80% or more in the amplitude of local bipolar atrial EGMs as a target for ablation[78–80]

One of the limitations of EGM monitoring is that low amplitude is present in areas of myocardial scarring, and only the measurement of CF during mapping will enable the operator to determine whether that low amplitude is due to scarring or poor catheter contact.[81]

These limitations of the surrogate markers highlight the importance of real-time measurement of CF during ablation for optimisation of efficacy and enhancement of safety.

Real-time Contact Force monitoring using Contact Force-Sensing Catheters

Recently, catheters that allow real-time measurement of contact force between the catheter tip and the target myocardium have become available. Different technologies for measuring real-time contact force exist in different types of catheters.

In 2008, the first experience of using robotic catheter ablation in humans using a novel remotely steerable sheath associated with a system that monitors ablation catheter contact

force called Intellisense™ Fine Force Technology was published. The system uses two force sensors that grip the shaft of the ablation catheter as it protrudes from the remotely steerable sheath. In their publication, the authors concluded that the system could work safely and effectively in humans and could achieve conventional ablation endpoints. However, the limitation of IntelliSense™ technology is that it works exclusively with the robotic system and cannot be used manually. [82]

Published one year later, was the first in human experience of the use of the EnSite Contact™ system that assessed catheter-tissue contact using impedance during AF ablation.[83]

In 2012, data about the use of the TactiCath® (Endosense, SA), which was the first direct contact force sensing catheter evaluated in human, were published. The data demonstrated the catheter's feasibility and safety during ablation.[81] In the TactiCath catheter, a fibreoptic sensor is mounted on a 3.5mm open irrigated-tip ablation catheter. The micro-deformation of optical fibres within the catheter tip provides real-time contact force measurements.[84]

Finally, the ThermoCool® SmartTouch™ (Biosense Webster Inc., CA, US) catheter, Figure 2-1, was developed. In that catheter, the irrigated tip electrode is connected to the shaft by a tiny precision spring, the degree of deformation of which is used to measure the CF. [84]

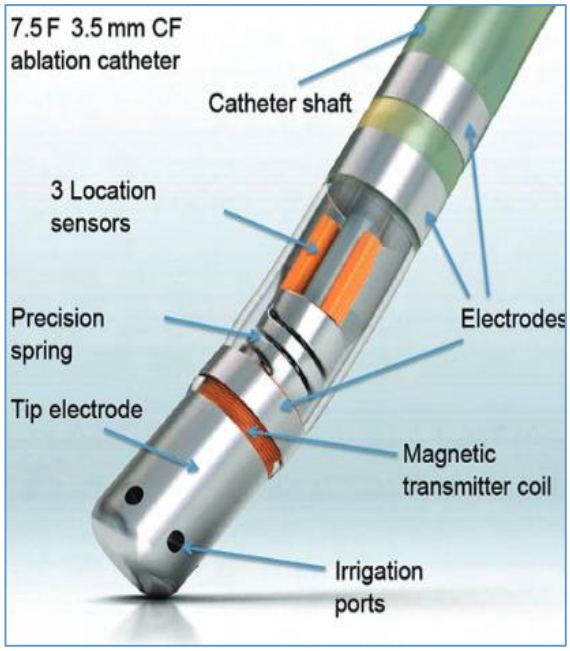


Figure 2-1 ThermoCool® SmartTouch™ (Biosense Webster Inc., CA, US).

The precision spring determines the contact force at the tip of the catheter

Some studies demonstrated that the use of real-time contact force-sensing catheters duirng AF ablation has improved long-term freedom from recurrent AF after one year.[85,86] However, other studies including a recent multicentre randomised controlled trial showed no difference in long term success rate with the use of real-time contact force-sensing catheters. [87–89]

Force Time Intergral (FTI) monitoring

The contact force–time integral (FTI) was introduced because the CF varies in the beating heart and with respiratory movements and that may result in subsequent variation in the ablation lesion quality. The preclinical study that introduced FTI found that it correlated

with lesion size, and that intermittent contact, as suggested by a lower FTI, produced smaller lesions when compared to variable contact with a higher FTI.[90]

Studies on the relation between CF and FTI and durability of ablation lesions

Several studies looked more specifically at the durability of ablation lesions that were made using real-time CF monitoring catheters during AF ablation. The TOCCATA study was the first study that used a direct CF catheter in human subjects. The study showed that CF > 20 g is most likely to result in successful PVI, defined as absence of AF recurrence or AF recurrence with durable PVI confirmed, while CF < 10 g is associated with unsuccessful PVI.[81]

That was followed by the EFFICAS I trial that evaluated the association between CF, for which operators were blinded, and the existence of gaps during PVI and at 3-month follow-up. The study provided the recommendations of a target CF of 20 g, with minimum CF > 10 g, and minimum FTI of 400 gs to achieve transmurality in a single RF application.[91]

Subsequently, the EFFICAS II trial allowed operators to utilise CF and FTI information obtained from EFFICAS I to optimize lesion creation. The EFFICAS II comprised a target CF of 20 g, range of 10 –30 g, and a minimum FTI of 400 gs. The use of these targets resulted in more durable PVI compared to EFFICAS I (85% vs. 72%, $P = 0.037$).[92]

For a noninferiority comparison between CF and non CF-sensing ablation catheters, the ToccaStar trial was designed to compare the St. Jude Medical TactiCath™ Quartz CF-sensing ablation catheter to the Biosense Webster Navistar™ Thermocool™ non CF-sensing ablation Catheter. A total of 300 patients were randomized 1:1 into either the TactiCath Catheter “CF group” or the Thermocool “control group”. Whist there was no specific recommendation in

the study protocol for the value of CF that should be used in the CF group, the manufacturer recommended that the CF should be limited to 30 g. The CF group was then subgrouped into "optimal CF" group including patients who had ≥ 90% lesions delivered at ≥ 10 g of contact force, and "non-optimal CF" group including patients who had < 90% lesions at ≥ 10 g. The need for a repeat ablation after the required 3-month blanking period was statistically lower in the "optimal CF" group vs. the "non-optimal CF" group (4.8% vs. 16.1%, respectively, P = 0.02) and vs. the control group (4.8% vs. 12.7%, P = 0.04).[88]

Safe and effective catheter contact force values as suggested by preclinical studies

In a preclinical study, catheter CF as low as 77 g was found to result in mechanical cardiac perforation and the perforating force was further reduced by 23% during ablation.[93]

Other preclinical studies were carried out to help decide on the optimum CF values that would result in adequate transmural ablation lesions whilst avoiding potential complications related to high CF. These studies found that excessive CF was frequently associated with higher tissue temperature rise resulting in higher incidence of thrombus formation and steam pops that can lead to cardiac perforation, as discussed below.[70,94]

In 2008, Okumura et al. published the results of their study in which they delivered ablation lesions to the right and left canine atria using Hansen Medical's Sensei Robotic Catheter System, the Intellisense contact force assessment system, and an irrigated tip catheter. Intracardiac echocardiography (ICE) was used to assess the effect of CF. Contact force of 10–20 and ≥20 grams produced full-thickness lesions; while smaller lesions occurred with <10 grams.[95]

In a subsequent animal study, Di Biase et al. examined ablation lesion formation and complications in relation to RF applications placed in the left atrium at different power and CF settings again using the Hansen Medical's Sensei Robotic Catheter System. They concluded that CF values in the range of 20 g to 30 g and power of 40 W were found to achieve transmurality and maintain safety. On the other hand, CF > 40 g and power of 45W were associated with steam pop and crater formation in 66.7% of lesions.[96]

Also in 2008, Yokoyama et al. reported their animal study results in which they aimed to determine safe and effective CF values using the TactiCath open-irrigated catheter. They reported that larger and deeper lesions were produced by lower RF power (30 W) at higher CF (30–40 g), than with higher power (50 W) but lower CF (2 to 10 g). However, the higher CF was associated with increased incidence of steam pop and thrombus formation.[97]

In a later study also using the TactiCath, RF was applied to ex-vivo porcine myocardium using low (20 W) and high (30 W) power; at low (2 g), moderate (20 g), and high (60 g) CF. In that study, again CF proved to be an important factor that determined the size of ablation lesion. Moderate CF was associated with reasonable lesion size with no risk of steam pop formation with low power, whilst high CF was associated with larger lesion size and high incidence of steam pop formation both with low power (30%) and high power (80%).[71]

Based on these preclinical studies, a CF target range of 10 g to 40 g has been suggested for carrying out a relatively safe and effective CF-guided RF catheter ablation. [95–97]

Force-Power-Time Index

Although the use of CF and FTI targets have resulted in improved AF ablation outcomes, up to two-thirds of patients were still found to have at least one reconnected PV at repeat procedures performed 2-3 months after the initial ablation. [59,98]

There therefore remains a need for a more effective lesion delivery strategy in order to achieve enduring PV isolation with a single ablation procedure. Controlling CF, RF power and application time: CF (grams) x Power (Watts) x Time (sec), known as Force-Power-Time Index (FPTI) was found to predict lesion size in a preclinical study. [99]

Ablation Index

Ablation Index is a novel marker of ablation lesion quality that was derived from incorporating catheter stability, RF power, catheter CF and RF delivery time in a logarithmic weighted formula, and was found to accurately estimate ablation lesion depth in pre-clinical studies.[100]

Ablation Index is calculated by a proprietary formula, depicted below, in which the constants are replaced with letters.

$$Ablation\ Index = \left(K * \int_0^t CF^a(\tau) P^b(\tau) d\,\tau \right)^c$$

CF: contact force, P: Power, t: duration of RF energy

Ablation Index was subsequently incorporated with the VisiTag module, ablation lesion tagging software, in Carto 3 V4 (Biosense Webster, Inc., Diamond Bar, CA). With real time

monitoring of CF and fixed power delivery, the Ablation Index module allows the operator to compensate for CF variability by up and down titration of the duration of RF delivery to achieve the Ablation Index target value for each segment. The Ablation Index counter will only start after preset catheter stability parameters are met, therefore ensuring adequate energy delivery to every ablation lesion. Therefore, the use of Ablation Index-guided ablation was postulated to result in fairly uniform lesions of adequate quality in all targeted left atrial regions.

Determination of Ablation Index targets

Our research group at Liverpool Heart and Chest Hospital contributed to an AF ablation multicenter study that was the first in human to retrospectively analyse the relationship between the minimum Ablation Index value along the circumferential PVI segments and spontaneous or adenosine-mediated acute reconnection. The minimum Ablation Index value for non-reconnected anterior/roof PV segments (358 [307-421]) was found to be significantly higher than for non-reconnected posterior/inferior PV segments (321 [278-372], $P<0.0001$. Subsequently, the 100% positive predictive value minimum Ablation Index thresholds that were not associated with acute reconnection were calculated, and were found to be 550 for the thick anterior/roof segments and 380 for posterior/inferior segments. [101]

The same research group then conducted another study, Pulmonary Vein Re-Isolation as a Routine Strategy: A Success Rate Evaluation (PRESSURE) that analysed the relationship between the minimum Ablation Index value values along the circumferential PVI segments and late reconnection. The study included 40 paroxysmal AF patients who underwent

contact force-guided PVI, and the minimum Ablation Index values for each segment were identified according to a 12-segment model. All patients underwent repeat electrophysiology study at 2 months, regardless of symptoms, to identify sites of late PV reconnection. The minimum Ablation Index values in late reconnected and non-reconnected segments were then compared. Reconnected anterior/roof segments had significantly lower minimum Ablation Index values than those without reconnection [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), $P < 0.0001$. 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. [102]

Excluding the PRESSURE study patients, starting from November 2014 our research group adopted the routine use of Ablation Index-guided AF ablation using an approximation of the minimum Ablation Index values that predicted absence of acute reconnection as target values, ≥550 for the anterior/roof region and ≥400 for the posterior/inferior region. The AF ablations outcomes using that strategy were compared to the corresponding outcomes of the AF ablations that were performed using the previous contact force-guided ablation strategy as discussed in Chapter 3.[103]

In the meantime, another research group that contributed to the multicentre study, conducted another study in which they used the same Ablation Index target values in addition to interlesion distance (ILD) to guide PVI, and called that strategy the CLOSE protocol.[104,105] Eventually, the group developed a new criterion to guide PVI called Ablation Line Contiguity Index (ALCI) that incorporates the Ablation Index and ILD values, as discussed in Chapter 6.[30]

An ongoing multicenter study called Pulmonary Vein Isolation Guided by Ablation Index (Ablation Index Registry Study) (AIR), ClinicalTrials.gov Identifier: NCT03277976, has been studying the outcomes of PVI using two Ablation Index settings; the first is 500 for anterior wall and 380 posterior for posterior wall, whilst the second is 450 for the anterior wall and 330 for the posterior wall, and using either Thermocool SmartTouch (ST) or Thermocool SmartTouch Surrounded Flow (STSF) (Biosense Webster, Inc., Diamond Bar, California) for RF energy delivery.

The study has already recruited 490 patients who underwent Ablation Index-guided PVI in 25 European centres, and the results that will possibly define the optimum Ablation Index target values are yet to be published.

Lesion Size Index

Lesion Size Index (LSI) is another novel marker to assess lesion size quality using the same principle of combining all 3 key ablation parameters; catheter CF, RF power and RF delivery time.

In their study, Neuzil et al. developed LSI in a preclinical setting then validated it in 40 paroxysmal AF patients recruited in the Efficacy Study on Atrial Fibrillation Percutaneous Catheter Ablation with Contract Force Support (EFFICAS I) multicenter study.[91,106] The 40 patients underwent PVI using TactiCath™ contact force-sensing ablation catheter (TactiCath, Endosense, Geneva, Switzerland) and were invasively re-evaluated at 3-months to assess for late reconnections. The lowest LSI per circumferential PVI segment was found to be the best predictor for late reconnection with very strong significance (2.9 ± 1.5 vs. 4.2 ± 1.8, p<0.00001).[106]

In the multicentre TOCCASTAR study, patients with paroxysmal AF were treated with the contact force-sensing ablation catheter (TactiCath, Endosense, Geneva, Switzerland). During the index AF ablation procedure, the following parameters were recorded for each ablation: force, FTI, LSI, and power, in relation to the circumferential PVI segments. Patients with symptomatic AF recurrence underwent a redo ablation and the location of late reconnection was determined and re-isolated.

Ablation parameters for the same location at index procedure were correlated with occurrence of late reconnection. The CF guidelines derived from previous studies, such as TOCCATA and EFFICAS I, that recommend achieving CF > 20g, minimum FTI > 400gs and minimum LSI > 5.0 showed high durable PVI rate of 80% when all criteria were fulfilled versus 46% when not all criteria were fulfilled, P=0.004. [107]

Chapter 3 The clinical experience at Liverpool Heart and Chest Hospital with the use of ablation index to guide atrial fibrillation ablation

Introduction

Even with complete PVI, which is the primary target for catheter ablation of both paroxysmal and persistent AF, high rates of late PV reconnection that lead to AF recurrence are still seen.[32,36] Several strategies have been proposed to prevent late reconnection and enhance RF ablation lesion durability, including real-time CF monitoring and using minimum CF or FTI targets during ablation.[98-92] Although the use of such targets has resulted in some improvement in AF ablation outcomes, up to two-thirds of patients were still found to have at least one reconnected PV at repeat electrophysiology procedures performed 2-3 months after the initial ablation.[59,98] Therefore, there appeared to be a need for a more effective RF delivery strategy to achieve durable PVI using a single ablation procedure.

As discussed in the previous chapter, Ablation index is a novel marker of ablation lesion quality that incorporates power in addition to CF and time in a weighted formula was found to accurately estimate ablation lesion depth in pre-clinical studies.[100] The integration of Ablation Index into the automated lesion tagging software (VisiTag ™) as an ablation lesion quality-monitoring module in the CARTO 3 V4 3D mapping system has enabled its real-time use to guide PVI.

We hypothesised that the prospective use of Ablation index-guided ablation using the derived target values from the studies discussed in Chapter 2 would result in an improvement in acute PV reconnection and clinical outcomes when compared to the previously used CF-guided ablation. We also hypothesised that Ablation index-guided lesions would demonstrate greater impedance drop compared to CF-guided lesions, which is indicative of more effective lesion creation.

To study these hypotheses, we retrospectively compared the procedural and clinical outcomes in patients who underwent Ablation Index-guided ablation versus those who underwent CF-guided ablation, as discussed below. As the study was a retrospective study no formal Ethics Review Board approval was required. Please see Appendix B.

Methods

Study patients

The study included consecutive AF patients who underwent first-time radiofrequency PVI for symptomatic drug-refractory AF by two experienced electrophysiologists at our institution, in the period between January 2013 and December 2015.

The procedures that were performed between January 2013 and October 2014 were CF-guided, whereas those that were performed between November 2014 and December 2015 were Ablation Index-guided. The first 10 patients treated with Ablation Index-guided (Ablation Index learning curve) were excluded, as well as patients who had been involved in any other research study. After exclusions, the final Ablation Index-guided cohort (AI group) was propensity-matched with the CF-guided cohort to derive a final CF-guided cohort (CF group).

AF ablation technique

The AF ablation procedures were performed under either conscious sedation or general anesthesia, and uninterrupted oral anticoagulation. Vascular ultrasound was used to guide venous access.[108] Intravenous heparin was administered at the time of transseptal puncture and as needed, targeting an activated clotting time (ACT) of ≥300 seconds.

CARTO 3, V4 3D navigation system (Biosense Webster, Inc., Diamond Bar, CA) was used in all cases to create an electroanatomical map of the LA, with possible integration with a computed tomography or magnetic resonance imaging reconstruction of the LA (CartoMerge, Biosense Webster, Inc., Diamond Bar, CA).

A fast anatomical map of the left atrium was created at baseline using the Lasso catheter. About 8-10 'Location only' points were acquired using the mapping catheter around each vein pair, with care taken to place these points ≥10 mm outside the PV ostia while ensuring that there were no near field PV signals recorded at these points.

WACA was performed around each PV pair, guided by the location-only points, using a Thermocool SmartTouch contact force-sensing RF ablation catheter (Biosense Webster, Inc. Diamond Bar, CA), advanced via a non-steerable sheath (Mullins, Cook *Inc*., Bloomington, Indiana). Point-by-point lesions were created at least 10 mm outside the PV ostia, as described above, except on the anterior ridge of the lateral PVs where lesions were delivered just inside the ridge.

The automated lesion tagging VisiTag™ (Biosense Webster, Inc.) was used to mark the location of each lesion. The VisiTag settings were as follows: minimum time 8s, maximum

range 3 mm, minimum contact force 5 g and force-over-time 30%, with the lesion tag display size of 2 mm.

The RF lesions were contiguous, with center-to-center distance <5mm, as confirmed by the overlap of the adjacent VisiTag lesions. The power settings were 25–40W depending upon the region of the LA being targeted. Oesophageal temperature was monitored continuously for cases performed under general anesthesia, and RF delivery was terminated when oesophageal temperature reached >39 degrees C.

Phase 1 of the study (CF group: January 2013 to October 2014)

During this phase, lesion creation was guided by contact force targets of 5-40 g, aiming for local signal attenuation of ≥80% at each point. These parameters were agreed on by the UK Multicentre Trials Group for a randomized trial running concurrently assessing the efficacy of CF-guided AF ablation.[87]

Phase 2 (AI group: November 2014 to December 2015)

During this phase, ablations were guided by AI target values for each lesion as follows: 550 for anterior/roof segments and 400 for posterior/inferior segments of the LA. These Ablation Index target values were rounded up from the values of 550 and 380 that had been found to have 100% positive predictive value for absence of acute reconnection in the anterior/roof and posterior/inferior segments respectively in our previous multicenter study, as discussed in Chapter 2.[101] In case of catheter displacement before an Ablation Index target could be reached, RF was recommenced at the same spot until a lesion reaching the target value was placed. If RF delivery had to be terminated because of a rise in oesophageal temperature, a sub-therapeutic Ablation Index lesion was accepted.

The broad range of CF aimed for in Phase 2 was the same as that used during Phase 1 at 5-40g. Midway during Phase 2 of the study, the operators felt comfortable to increase delivered powers from 30W to 35-40W, so as to allow the AI targets to be reached with shorter RF applications.

Impedance drop and FTI values were not monitored prospectively nor targeted during ablation in either group.

A 20-pole spiral catheter (Lasso NAV, Biosense Webster, Inc.) was positioned inside the WACA circle during ablation to check for PV isolation. First pass isolation was defined as isolation of both ipsilateral pulmonary veins that occurred either before or at completion of the WACA lesion set, without the need for ablation on the intervenous carina or for additional segmental ablation. The WACA circle was completed even in cases where first pass isolation occurred before the completion of the circle.[36] A waiting period of at least 20 minutes after the last circle was mandated,[54] and 15 mg of intravenous adenosine was administered for each WACA circle to unmask dormant PV reconnection if no spontaneous reconnection was seen.[109] Any spontaneous or adenosine-induced reconnection was addressed with further RF application.

In patients with paroxysmal AF, the lesion set in the LA was restricted to PVI only. Patients underwent cavotricuspid isthmus (CTI) ablation in addition if they had documented atrial flutter.

Conversely, in some patients with non-paroxysmal AF, the LA posterior wall was targeted with a box lesion set in addition to PVI, as this strategy was found to improve clinical

outcomes in some studies. [110–113] This seems intuitive because in patients with non-paroxysmal AF, the LA posterior wall may harbor more AF maintaining substrate. [114,115]

No additional linear lesions and no ablation of CFAEs were performed in any patient.

Clinical follow-up

All patients were followed up at 3, 6, 9 and 12-months with mandatory 12-lead ECG recordings, supplemented with symptom-determined 24-hour Holter ECG monitoring as needed. All anti-arrhythmic drugs were stopped by 3 months. Atrial tachyarrhythmia recurrence (ATA) was defined as atrial fibrillation, atrial flutter, or atrial tachycardia documented on ECG after a 3-month blanking period without anti-arrhythmic drugs. Follow-up duration was capped at 12 months for all patients, to allow for the different times of procedures in the two groups.

The study was exempted from ethical approval by the North West Research and Ethics Committee, as it did not involve any change to the normal clinical care of participants.

Ablation lesion data analysis

Although no Ablation Index targets were used to guide ablation in the CF group, an Ablation Index value for each lesion could be retrospectively calculated in the last 25 patients in that group, in whom ablation was performed using a Carto 3 system with added on Ablation Index module. Therefore, a detailed offline retrospective analysis of the WACA circle ablation lesions was limited to the last 25 patients from each of the CF and AI groups. The data for each VisiTag included: ablation duration, CF, impedance drop, FTI, and Ablation Index.

CF was defined as the mean contact force during ablation, and impedance drop as the difference between the pre-ablation and the lowest recorded impedance values during ablation. FTI and Ablation Index values were automatically calculated for each lesion by the CARTO 3 system VisiTag and Ablation Index modules. FTI was calculated by multiplication of the mean contact force during energy application by the duration of the application and is measured in gram seconds (gs). Whilst Ablation Index was calculated using a complex weighted exponential formula allocating different weights to CF, time and power. [100]

To analyse the effect of using different AI target values for the various LA regions, each WACA circle was divided into six segments (roof, 2 anterior, inferior, and 2 posterior). We then categorized the segments into two categories according to the regional AI targets used for the AI group (anterior/roof segments and posterior/inferior segments) (Figure 3-1).

Impedance drop, which is the only tissue related ablation parameter in the VisiTag module, was used as a surrogate to evaluate ablation lesion effectiveness in both CF-guided and AI-guided groups. An impedance drop cutoff of ≥10 Ω was used as a predictor of adequate lesion formation in our study based on observations from previous in vitro[116] and human studies.[117,118]

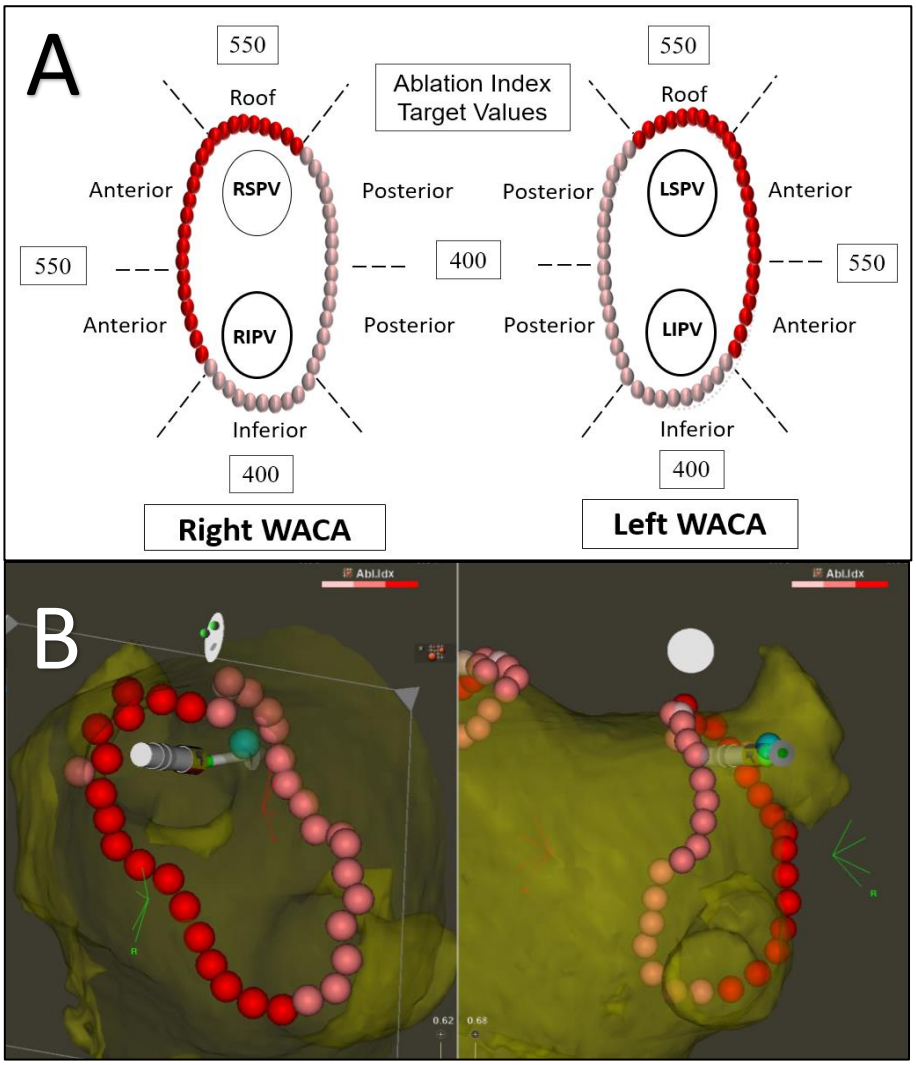


Figure 3-1: Diagram showing the 12 WACA segments and the AI target values used for each segment in the AI group. The red dots represent ablation lesions with AI target values ≥550 while the pink dots represent AI target values ≥400 but <550, B: Screenshots showing right WACA with VisiTags color-coded by AI value. The red VisiTags seen in the anterior/roof region have AI target values ≥550 while the pink VisiTags seen in the posterior/inferior region have AI target values ≥400.

Statistical analysis

Propensity matching was used to adjust for patient age, sex, LA size, and type of AF when comparing study groups. Continuous variables were expressed as mean and standard deviation if they were normally distributed, or median and quartiles (25^{th}–75^{th} percentiles) if they were not normally distributed. For continuous variables, Student's t-test, Mann–Whitney *U* test or Kruskal–Wallis test was used for unpaired group comparison. Categorical variables were presented as frequency or percentage and were compared by the x^2 test. Spearman's rank correlation coefficient was used to assess the correlation between various variables. Multivariable linear regression analysis was used to assess the relationship between ablation lesion parameters and impedance drop. Receiver operating characteristic curve (ROC) analysis was performed to determine the optimum AI values that would result in a clinically relevant impedance drop in the various LA regions. All tests were two-sided and a P value <0.05 was considered statistically significant. All statistical analysis was performed using SPSS (version 24, IBM Corp., Armonk, NY).

Results

In Phase 2 of the study, 99 patients underwent Ablation Index-guided PVI. The first 10 cases in this cohort were excluded as their procedures were considered to have been performed during the Ablation Index-guided ablation learning curve, leaving 89 patients for analysis (AI group). Whilst in Phase 1 of the study period, 168 patients underwent CF-guided AF ablation, and after propensity matching with the AI-group, only 89 patients were left for analysis (CF group) (Figure 3-2).

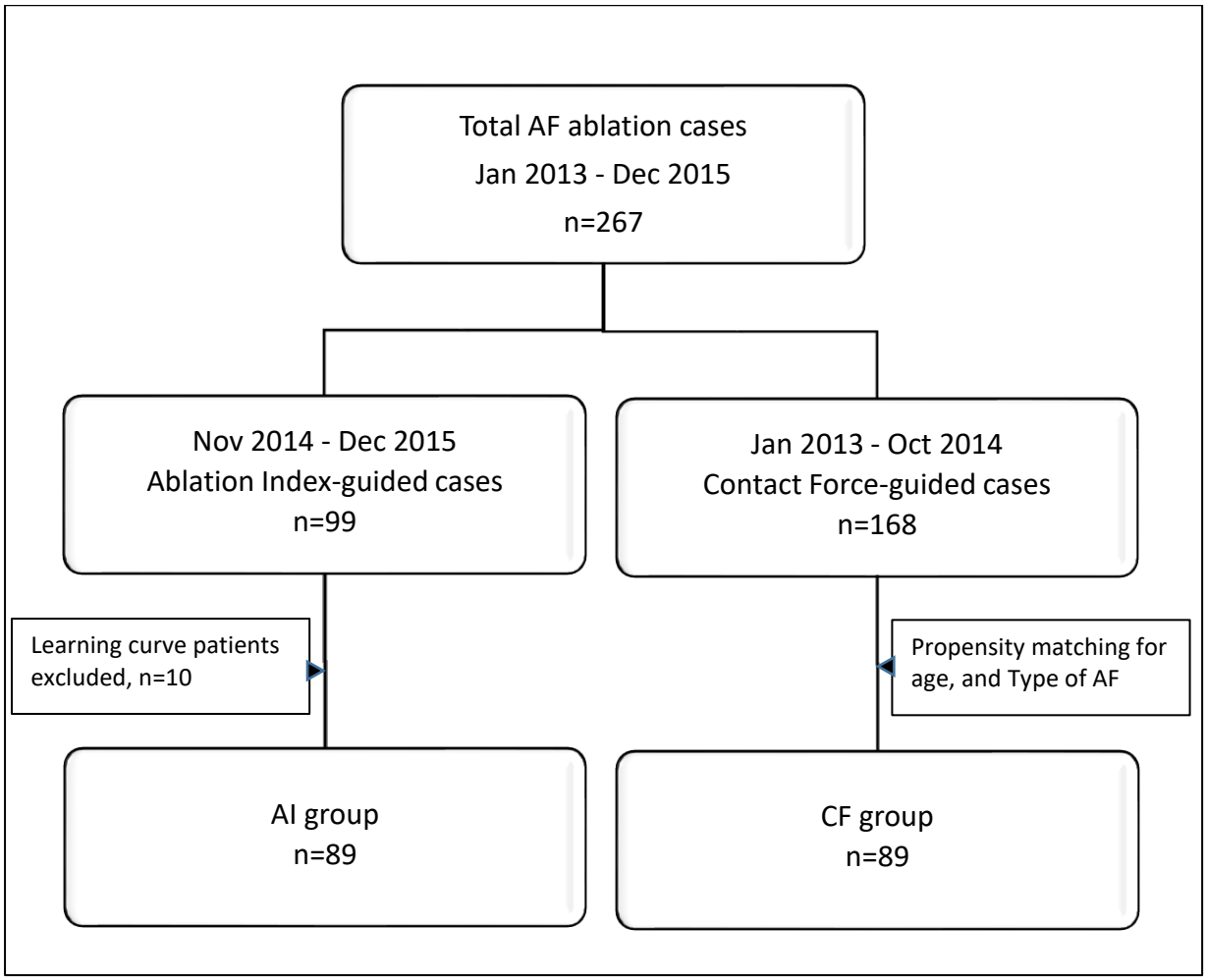


Figure 3-2 A flowchart of patients recruited to retrospective analysis of Ablation Index-guided ablation versus contact force-guided ablation study. In Phase 2 of the study, 99 patients underwent Ablation Index-guided PVI. The first 10 cases were excluded as their procedures were performed during the Ablation Index-guided ablation learning curve, leaving 89 patients for analysis (AI group). Whilst in Phase 1, 168 patients underwent CF-guided AF ablation, and after propensity matching with the AI-group, 89 patients were left for analysis.

Patient characteristics of AI and CF groups

As both groups were propensity matched, the baseline characteristics in terms of age, sex, type of AF, LA diameter and BMI were similar. Demographic information for both AI and CF groups is provided in Table 3-1.

Table 3-1 Demographic information for AI and CF groups

	AI group (N=89)	CF group (N=89)	*P* value
Age, year	62 ± 9.1	62 ± 9.1	0.88
Sex (Male/female)	67/22	65/24	0.73
LA diameter, cm	4.2 ± 0.6	4.1 ± 0.6	0.46
BMI	29 ± 4.8	29 ± 5.0	0.96
Type of AF			0.98
PAF	43	45	
PeAF	31	29	
LSPeAF	15	15	
Duration of PeAF (month)			
PeAF	7(5-10)	9 (5-12)	0.4
LSPeAF	22 (12-28)	24 (18-33)	0.8

BMI: body mass index; PAF: paroxysmal atrial fibrillation, PeAF: persistent atrial fibrillation, LSPeAF: longstanding persistent AF

Procedural results of AI and CF groups

Table 3-2 shows a comparison between the procedural data of both groups. First pass WACA circle isolation was significantly higher in the AI group compared to the CF group (173/178 (97%) vs. 149/178 (84%) circles, *P*<0.001). Of the 5 (3%) WACA circles in which there was no first pass isolation in the AI-group, 4 (80%) were right-sided affecting the right ipsilateral PVs and required further RF delivery on the right intervenous carina to achieve isolation.

After a minimum waiting period of 20-minutes, spontaneous PV reconnection was seen in 8 (4%) circles in the AI group, compared to 19 (10%) circles in the CF group, *P*=0.02. Either spontaneous or adenosine-induced PV reconnection was identified in 11 (6%) circles in the AI group (3 on the left and 8 on the right) compared to 24 (13%) circles in the CF group (12 on the left and 12 on the right) (*P*=0.02). All acute reconnections were successfully eradicated with further radiofrequency applications.

The mean PVI ablation time was similar for the two groups (AI group: 42±9 vs. CF group: 45 ± 14 mins, *P*=0.14), while the mean total ablation time was significantly shorter in the AI group compared to the CF group (48 ± 10 vs. 53 ± 13 mins, *P*=0.03). Neither the mean procedure time (AI group: 175 ± 31 vs. CF group: 163±47 mins, *P*=0.08) nor the mean fluoroscopy time (AI group: 11.9 ± 7.7 vs. CF group: 11.8 ± 5.6 mins, *P*=0.94) was significantly different between groups.

CTI ablation was performed in a higher proportion of patients in the CF group than in the AI group (27 (30%) vs. 16 (18%), *P*=0.0.5). However, none of atrial tachyarrhythmia recurrences that were accounted for in this study was due to CTI-dependent atrial flutter.

Two major complications (2%) occurred in the CF group (phrenic nerve palsy and retroperitoneal hematoma), whilst none occurred in the AI group (*P*=0.15).

Table 3-2 Procedural data of AI and CF groups

	AI group (n=89)	**CF group (n=89)**	***P* value**
Mean fluoroscopy time, min	11.9 ± 7.7	11.8 ± 5.6	0.94
Mean DAP, cGY.cm2	1656 ± 1425	1613 ± 1345	0.85
Mean PVI ablation time, min	42 ± 9	45 ± 14	0.14
LA posterior wall ablation, n (%)	25 (28%)	36 (40%)	0.08
CTI line, n (%)	16 (18%)	27 (30%)	0.05
Mean total ablation time, min	48 ± 10	53 ± 13	0.03
Mean total procedure duration, min	175 ± 31	163 ± 47	0.08
Complications, n (%)	0 (0%)	2 (2%)	0.15

DAP: Dose area product, PVI: Pulmonary vein isolation, LA: Left atrium, CTI: Cavotricuspid isthmus

Follow-up and clinical outcome results

For both the CF and AI groups, the median follow-up was identical at 12 months. Recurrence of atrial tachyarrhythmia was defined as AF, atrial flutter or atrial tachycardia recurrence after a 3-month post-ablation blanking period following a single procedure off anti-arrhythmic drugs. Atrial tachyarrhythmia recurrence was significantly lower in the AI group than in the CF group (15 vs. 33 patients), *P*=0.002.

Kaplan-Meier survival analysis showed a freedom from atrial tachyarrhythmia at 12 months of 83% in the AI-group as compared to 63% for the CF-group (log rank *P*=0.004), (Figure 3-3). Subgroup analysis showed recurrence rates were significantly lower in both the non-paroxysmal AF subgroup: (8/46 (17%) AI-group patients vs. 17/44 (39%) CF-group patients, *P*=0.02), as well as in the paroxysmal AF subgroup: (7/43 (16%) AI-group patients vs. 16/45 (36%) CF-group patients, *P*=0.04).

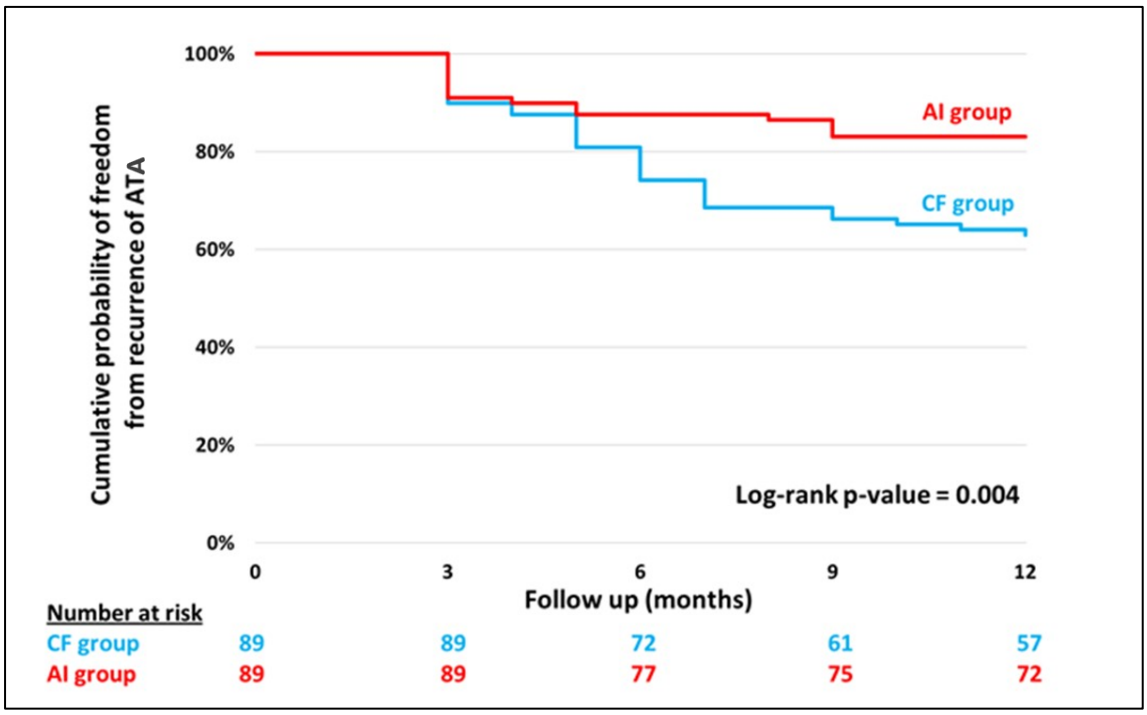


Figure 3-3 Kaplan–Meier curves of the groups' atrial arrhythmia (ATA)-free survival during the 12-month follow-up post procedure.

Ablation lesions data analysis

In total, 4018 VisiTags across both groups were analyzed, of which 146 VisiTags were excluded because of incomplete data. The mean number of analyzed WACA ablation lesions (VisiTags) for each patient was 78±17, and this was not significantly different between the two groups (73±17 for the AI group vs. 82±18, for the CF group, *P*=0.09).

The median impedance drop per VisiTag lesion was significantly higher in the AI group than in the CF group (15.2 [11.7-18.5] Ω vs. 9.5 [7.2-12] Ω, *P*<0.001, Figure 3-4A). In addition, the number of ablation lesions that were associated with impedance drop of ≥10 Ω was significantly higher in the AI group 1356 (74%), compared to 899 (44%) in the CF group, *P*<0.0001.

The median CF was also significantly higher in the AI group than in CF group (12.2 [9.3 – 17.2] g vs. 10.2 [8.0 – 14.0] g, *P*<0.001, Figure 3-4B). As CF is a component of the Ablation Index formula, multivariable linear regression was used to adjust for it as a potentially confounding variable. Even after that adjustment, AI group membership was still associated with a significantly higher impedance drop (*P*<0.001). We again used multivariable analysis that incorporated all available ablation lesion data for both AI and CF group, and this time used ablation success defined as freedom from atrial tachyarrhythmia at 12-month follow-up as an outcome.

After adjusting for time, power, impedance drop and group membership, logistic regression analysis suggested that CF was not an independent predictor for freedom from AT for 12 months. OR=1, 95% CI=0.93-1.04, *P*=0.90.

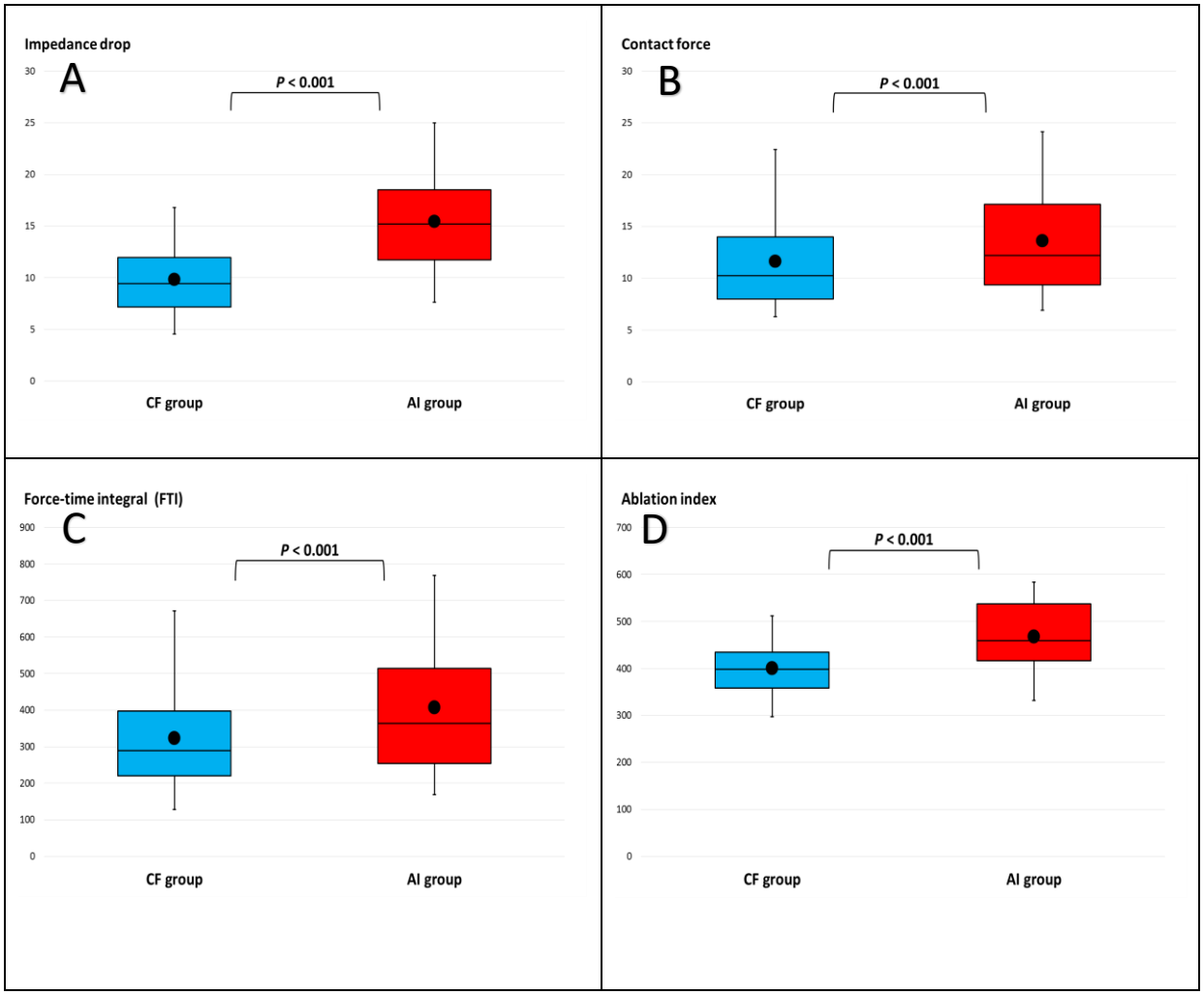
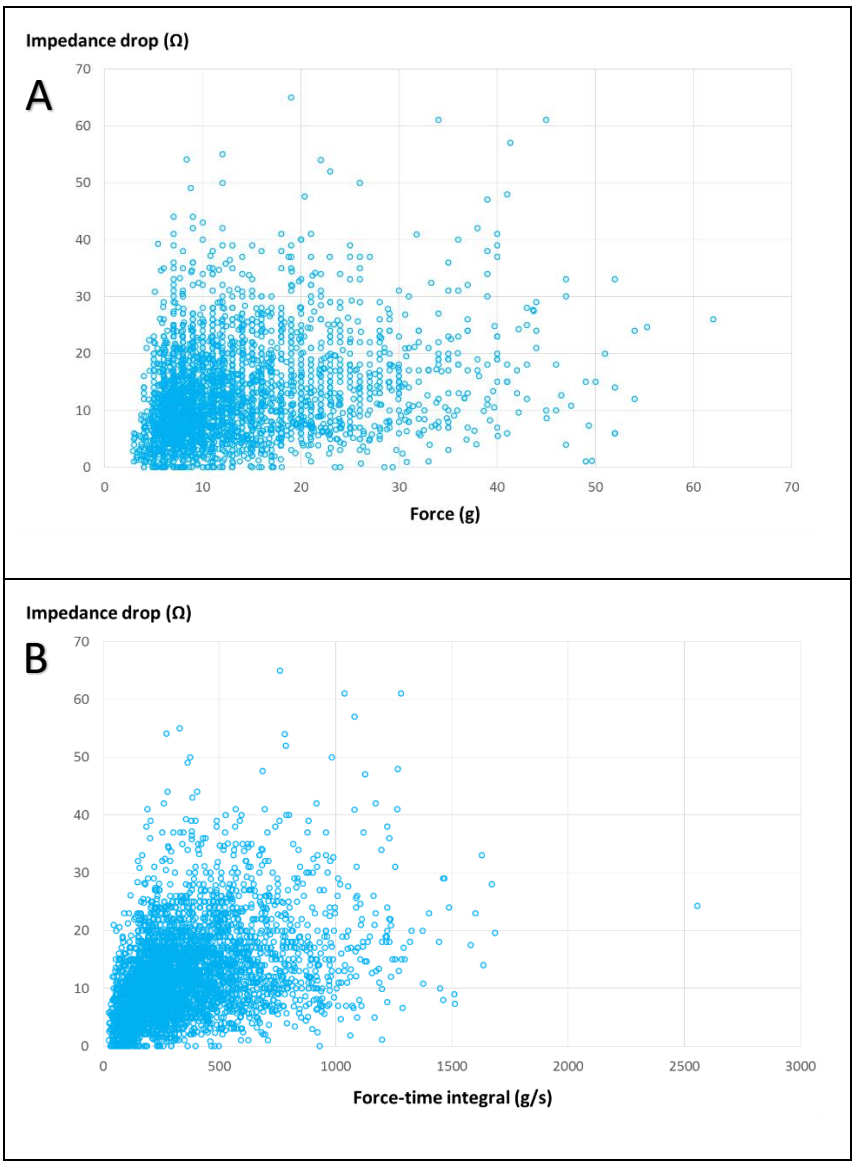


Figure 3-4 Box and whisker charts comparing A. Impedance drop in AI and CF groups, B. Contact Force in AI and CF groups, C. Force Time Integral in AI and CF groups, and D. Ablation Index in AI (prospective) and CF (calculated retrospectively) groups. Each box is bounded on the top by the third quartile and on the bottom by the first quartile. The line that divides the box is the median value and the dark dot inside the box is the mean value. The top whisker extends to the maximum value and the bottom whisker extends to the minimum value.

Relationships between Ablation Index, Contact Force, Force–Time Integral and impedance drop

Scatterplots in Figure 3-5 show the relationships between each of CF, FTI and AI with impedance drop in AI group patients. Ablation Index was found to have a significant but moderate correlation to impedance drop (Spearman r=0.42, P<0.001). Similarly, FTI correlated significantly but with moderate correlation with impedance drop (r=0.42, P<0.001). CF correlated significantly but weakly with impedance drop (r=0.29, P<0.001). A very strong correlation was seen between AI and FTI (r=0.89, P<0.001).



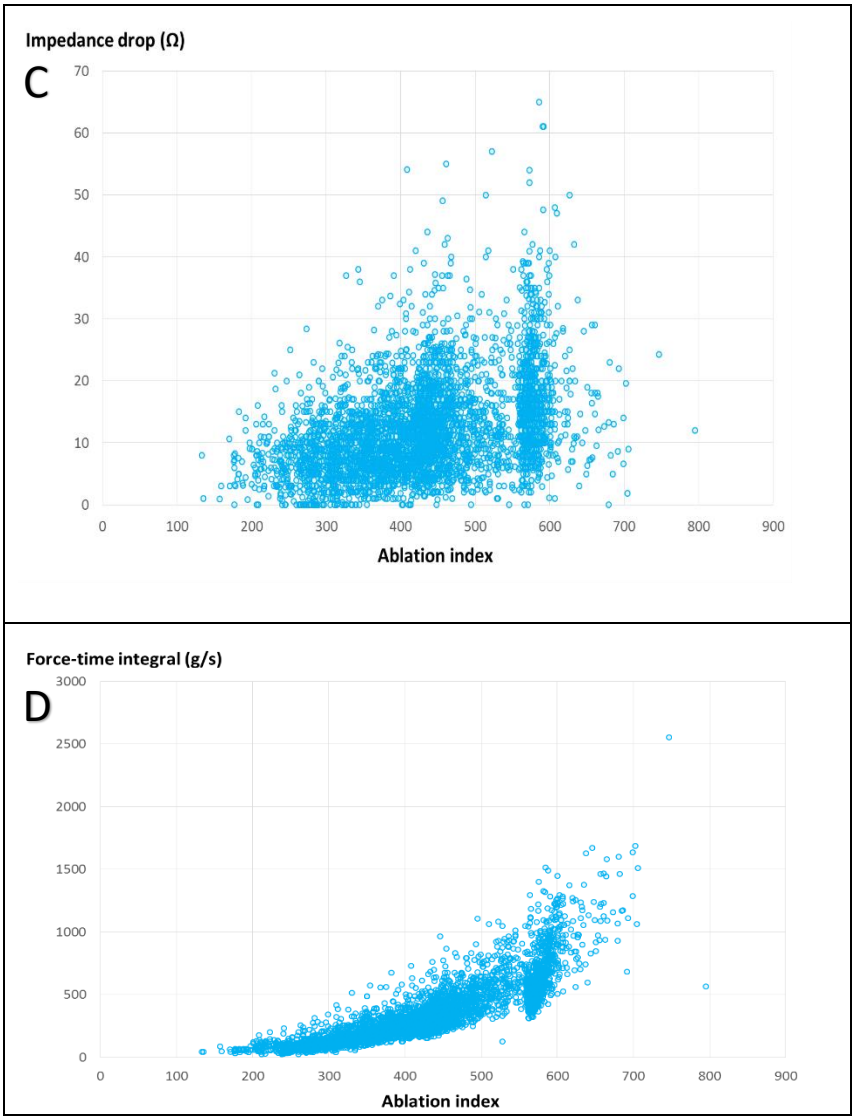


Figure 3-5 Scatter plots showing the relationships between A. CF and impedance drop, B. FTI and impedance drop, C. Ablation Index and impedance drop, and D. Ablation Index and FTI.

Regional differences in ablation lesion parameters

The regional median values of CF, FTI, Ablation Index and impedance drop in the anterior/roof and the posterior/inferior regions in both Ablation Index and CF groups are depicted in Table 3-3. In anterior/roof segments, the median ablation time, power, CF, FTI, Ablation Index and impedance drop were significantly higher in the AI group as compared to the CF group.

Conversely, for posterior/inferior segments, whilst the median power, Ablation Index and impedance drop were higher in the AI group as compared to the CF group, the ablation time, CF and FTI values were similar, suggesting better RF power delivery to the posterior wall with Ablation Index-guided ablation.

Table 3-3 Regional median values of RF times, CF, FTI, Ablation Index and impedance drop in AI and CF groups

		AI group VisiTags (N=1829)*	CF group VisiTags (N=2043)*	*P value*
Time (s)				
	Anterior/Roof	36.0 (31.0 – 42.5)	30.0 (25.1 – 37.1)	<0.001
	Posterior/Inferior	25.7 (21.1 – 29.6)	26.3 (19.9 – 30.6)	0.94
	All segments	30.0 (24.4 – 37.5)	27.8 (22.2 – 33.5)	<0.001
Power (W)				
	Anterior/Roof	35 (34 – 40)	30 (30 – 30)	<0.001
	Posterior/Inferior	35 (30 – 39)	30 (29 – 30)	<0.001
	All segments	35 (31 – 39)	30 (30 – 30)	<0.001
CF (g)				
	Anterior/Roof	14.5 (11.1 – 19.0)	10.6 (8.5 – 15.8)	<0.001
	Posterior/Inferior	10.5 (8.3 – 13.5)	9.7 (7.8 – 12.6)	0.08
	All segments	12.2 (9.3 – 17.2)	10.2 (8.0 – 14.0)	<0.001
FTI (gs)				
	Anterior/Roof	508 (416 – 626)	319 (261 – 436)	<0.001
	Posterior/Inferior	256 (208 – 335)	247 (174 – 331)	0.16
	All segments	364 (253 – 518)	289 (219 – 398)	<0.001
AI				
	Anterior/Roof	537 (483 – 575)	416 (389 – 456)	<0.001
	Posterior/Inferior	420 (379 – 448)	376 (336 – 413)	<0.001
	All segments	459 (415 – 538)	398 (357 – 435)	<0.001
Impedance Drop (Ω)				
	Anterior/Roof	16.6 (13.4 – 20.5)	10.3 (7.6 – 13.1)	<0.001
	Posterior/Inferior	13.2 (10.0 – 16.5)	8.8 (6.3 – 11.0)	<0.001
	All segments	15.2 (11.7 – 18.5)	9.5 (7.2 – 12.0)	<0.001

CF: Contact Force, FTI: Force-time integral, AI: Ablation Index
*****Derived from the last 25 patients from each group

Relation between impedance drop and regional AI target values

Receiver operating characteristic (ROC) analysis of the AI group ablation data showed that the Ablation Index cut-off (Youden Index) that predicted an impedance drop of ≥10Ω for anterior/roof segments was 444 (sensitivity 85.1%, specificity 36.9% and positive predictive value 85.5%), and for posterior/inferior segments was 382 (sensitivity 77.8%, specificity 53.6% and positive predictive value 75.7%) (Figure 3-6).

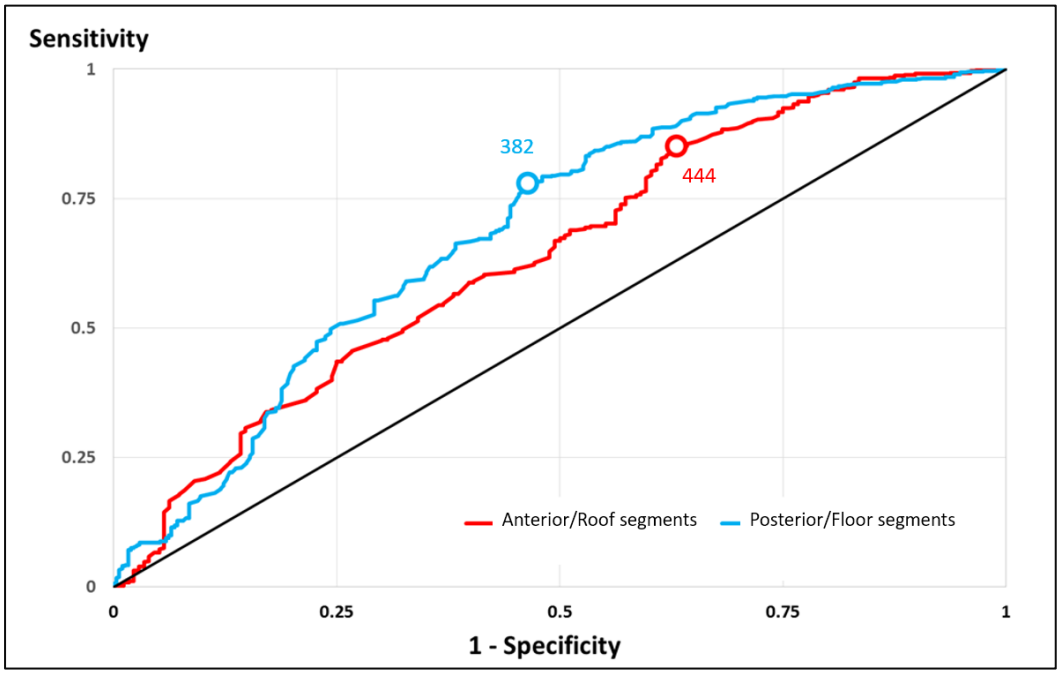


Figure 3-6 ROC curves for Ablation Index cutoff values for an impedance drop of ≥10Ω by left atrial regions.

Discussion:

Main study findings

To our knowledge, this study was the first to investigate the prospective use of tailored AI targets to guide AF ablation, and to compare procedural and clinical outcomes to the commonly used current practice of CF-guided AF ablation.

The study showed that, when compared to CF-guided ablation, tailored AI-guided ablation provided significantly improved outcomes in three important areas. Firstly, better procedural outcomes were seen, with both a much higher rate of first-pass isolation and lower incidence of acute PV reconnection, obviating the need for additional extensive ablation for PV reisolation and hence resulting in an expected shorter mean total ablation time per procedure. Secondly, with regard to clinical outcomes, the AI group experienced significantly improved freedom from arrhythmia after 12 months of follow-up. Thirdly, AI-guided ablation was associated with a significantly higher impedance drop suggesting creation of better-quality lesions.

Although all acute reconnections were eradicated by additional ablation in both groups, better clinical outcomes were noted in the AI group. This can be explained by the findings of one of our research group previous studies that although sites of acute reconnection are likely to remain isolated once ablated, other sites of PV reconnection are identified on repeat EP study. The vast majority of sites of late reconnection were not manifest acutely in spite of a 30-minute period of waiting and the use of IV Adenosine. [119]

Furthermore, although the sample size of patients who underwent Ablation Index-guided ablation was relatively small, there did not appear to be any signal of increased risk associated with this approach. This may well be related to the more tailored approach to LA ablation afforded by use of Ablation Index targets, with more ablation targeted to the thicker anterior portions of the chamber compared to that seen in the CF group (FTI value of 508 gs compared to 319 gs) but little change in posterior wall ablation (FTI 256 gs vs. 247 gs).

Furthermore, the use of Ablation Index targets allowed delivery of higher powers, especially on the LA posterior/inferior wall, resulting in achieving greater impedance drops without the need to increase either RF ablation times or CF.

Advantages of Ablation Index over CF or FTI

The advent of CF-sensing catheters was followed by a growing interest on how to utilise the real-time CF data to improve AF ablation outcomes. Some studies have suggested that certain CF thresholds are needed for durable lesion formation.[92,91] However, the availability of CF information alone to guide ablation has not necessarily translated into improved results.[87,88,89,120,121] This can be anticipated as lesion creation is not only dependent upon catheter-tissue contact, but also the duration of energy application and power delivery.

Subsequently, FTI that combines application time with CF in a linear fashion was suggested as an alternative for ablation monitoring. However, this approach was criticised as it has two significant limitations. Firstly, the interplay between CF and time in lesion creation is more complex than simple multiplication of these two factors,[122] and secondly FTI continues to omit the important role of power delivery. That latter point was clearly illustrated in an in-vitro study by Guerra et al., in which it was shown that with a fixed FTI of 300 gs, an increase from 20 W to 35 W resulted in an almost three-fold increase in lesion volume.[123] Accordingly, FTI target-guided ablation has shown some improvement in the rate of PV reconnection at repeat study, but not to hoped-for levels, with still more than one-third of patients exhibiting one or more gaps.[92,91]

The use of Ablation Index-guided ablation has the potential to overcome these limitations by not only incorporating power delivered, but also combining these three factors in a weighted formula that has been shown to correlate to lesion depth in an animal model.[100]

The rate of late PV reconnection following prospective use of AI-guided ablation was evaluated in the Pulmonary vein Reconnection following Ablation Index-guided ablation: a Success Evaluation (PRAISE) study, the results of which are discussed in Chapter 5. [124]

Regional Ablation Index target values

A significant difference in Ablation Index values that predicted an impedance drop of ≥10Ω between LA regions was demonstrated in this study (444 for the anterior/roof region compared to 382 for the posterior/inferior region). These values were notably similar to those identified by our research group for avoidance of late PV reconnection, 480 for the anterior/roof region and 370 for the posterior/inferior region as mentioned before in Chapter 2.[101,102]

These differences in Ablation Index values between the anterior/roof region and the posterior/ inferior region can be anticipated, as it is well-recognized that wall thickness varies considerably within the LA and can be particularly thick at the anterior left PV/appendage ridge.[125]

Previously used regional FTI target values

FTI target value of 400-500gs has been suggested to be necessary to create adequate ablation lesions,[126,127] and in the EFFICAS studies to avoid late PV reconnection.[92,91] While this value may well be required in some regions of the LA, there is concern that it may be excessive in more thin-walled areas, increasing the risk of damage to adjacent structures such as the oesophagus. A subsequent study has demonstrated that the optimal FTI value for achieving an effective lesion is dependent on the underlying atrial wall thickness,[128] and

our research group has previously reported that FTI values of only 230 gs were associated with no reconnection of posterior/inferior segments at repeat electrophysiology study.[102]

Clinical utility of Ablation Index-guided ablation

Taking into consideration the potential limitations of the study of a non-randomised retrospective non-parallel group study design, the study demonstrated that the prospective use of Ablation Index regional target values was associated with more effective acute PV isolation and less recurrence of atrial tachyarrhythmia during follow-up, without an associated increase in ablation time, as compared to CF ablation alone.

The study results suggest that the use of such Ablation Index regional targets, with a higher value for the thicker-walled anterior/roof region and a lower value for the thinner-walled posterior/inferior region, may be able to provide a more tailored approach to AF ablation, balancing ablation efficacy with avoidance of unnecessarily excessive ablation in the higher-risk posterior/inferior region. As such, Ablation Index-guided ablation has been proposed to be used with the intention to improve the delivery of a lesion set that effectively and durably isolate the PVs while minimizing the risk of damage to adjacent structures.

The PRAISE study, that is discussed in detail in Chapter 4, was designed to evaluate this hypothesis.

Limitations

The study was a retrospective analysis of a non-randomized consecutive series of patients who underwent CF-guided or AI-guided AF ablation. Although the two groups underwent propensity-matching resulting in similarities in their baseline characteristics, a possible

confounding effect of other unknown variables could not be excluded. Nevertheless, the study was a first and necessary step toward the design of the PRAISE study which is an adequately powered prospective study.

In addition, the possibility of temporal bias and its associated effect via institutional and operator learning curve needed to be addressed, because the two groups were recruited in a consecutive rather than parallel fashion. However, all procedures in both groups were performed by two very experienced electrophysiologists in an established high-volume center, using identical equipment and an identical ablation strategy, except for the different catheter ablation guidance, as discussed below.

The increase in RF power during the study period made it difficult to exclude the possibility that some of the benefits seen in the AI group was contributed to by this change. However, the increase in RF power during the study period highlights an important advantage of using Ablation Index target values in that it, in general, allows operators the flexibility to change any of the Ablation Index component parameters, such as power, RF ablation time and CF while being confident that the total amount of delivered RF energy will be limited by the composite Ablation Index value. However, it should be borne in mind that the quality of RF ablation lesions may vary considerably as a result of changing some or all these parameters despite having a fixed Ablation Index value. This is because the RF ablation lesion results from thermal injury that occurs in 2 consecutive phases; resistive phase that leads to immediate heating of the superficial tissue layer, and time-dependent conductive phase that extends passively from the superficial layer to deeper layers.[129] Therefore, a potential method to achieve uniform, transmural lesions during PVI is to increase the resistive phase to deliver immediate heating to the full tissue thickness, and reduce the conductive phase

to limit collateral tissue damage. This can be achieved by using higher RF power that must be delivered for a shorter duration.[130]

Another limitation was the limited intensity of ECG monitoring on follow-up that might have led to failure to detect asymptomatic AF recurrences, and thereby may have overestimated ablation success rates. However, the monitoring protocol was identical for the two study groups, and so it is unlikely that this would have been a significant source of bias affecting one study group more than the other.

Lastly, the study cohort was too small to provide definitive safety assessment of the Ablation Index-guided ablation strategy. However, the fact that the same two operators subsequently performed over 500 Ablation Index-guided AF ablation procedures with the absence of a single case of cardiac tamponade, stroke/TIA or oesophageal fistula in this cohort would appear to suggest that this strategy is likely to be at least as safe as CF-guided ablation.

In June 2018, The United States Food and Drug Administration (FDA) approved the use of Carto 3 mapping system with the Ablation Index (SURPOINT™) module. According to the approval letter, the module underwent extensive bench testing and was not found to raise concerns about safety or effectiveness. Please see Appendix C for the FDA approval letter.

A Critical Appraisal of the Use of Historical Controls for Comparison with the Ablation Index-guided Study Group

In general, retrospective cohort studies may be affected by potential confounders that can create differences in outcomes between the groups apart from those related to the interventions being assessed.[131] Nevertheless, retrospective cohort studies comparing the intervention cohort with a historical cohort are commonly employed in clinical studies,

including AF ablation studies, to evaluate new techniques and they frequently provide a useful "proof of concept" prior to development of randomized controlled trials. [132,133]

The effects of the following potential confounders in this study are being addressed here.

The cumulative experience of operators

In this study, all procedures of the two phases of the study were performed by the same two operators (DG and RS) who were already highly experienced in point-by-point RF AF ablation (having performed over 500 cases before January 2013) and had also used contact force-sensing catheters extensively since 2011. Therefore, the learning curve associated with controlling contact force for these operators, as well as for the institution, would have been passed long before the time-period from which the CF group was derived.

In a study about the initial experience with the use of SmartTouch CF-sensing catheters for AF ablation procedures in an institution, the maximum reduction in fluoroscopy time and dose, and procedure time was noted following an initial learning curve of 300 procedures.[134]

Potential changes in the clinical practice

These include potential changes in the indications for the AF ablation procedure, changes in equipment used and/or changes in the ablation procedure strategy.

For all AF patients included in the study, whether they had paroxysmal, persistent or long standing persistent AF, the indication to refer a patient for AF ablation was limited to the presence of symptomatic drug-refractory AF, and that indication did not change throughout the course of both phases of the study.

The same exact equipment was used in both phases of the procedure including SmartTouch ablation catheter, circular mapping (Lasso) Catheter and Carto 3 electroanatomical mapping system.

Also, the ablation procedures in phase 1 and phase 2 of the study were identical in terms of mapping and ablation techniques, except for using different ablation target indices to guide ablation; CF of 5-40 g aiming for local signal attenuation of ≥80% at each point in phase 1, and Ablation Index targets of 550 for the roof and anterior wall and 400 for the posterior and inferior walls in phase 2.

Conclusion

This study was the first to investigate the prospective use of Ablation Index targets to guide AF ablation. Ablation Index-guided ablation was associated with significant improvements in the incidence of acute PV reconnection and in the rate of atrial tachyarrhythmia recurrence during follow-up, without change in the mean ablation time for PV isolation, as compared to CF-guided ablation. The use of different AI regional targets, with higher values for the anterior/roof region compared to posterior/inferior region, allows for the delivery of more effective ablation to thicker-walled areas while obviating the risk of excessive ablation on thinner-walled regions such as the LA posterior wall.

Chapter 4 Pulmonary vein Reconnection following Ablation Index guided ablation: a Success Evaluation (PRAISE) Study Design

Introduction

Creation of durable ablation lesions during PVI for AF is of critical importance to prevent late PV reconnection, which is responsible for the great majority of arrhythmia recurrence in patients with paroxysmal AF.[54] Despite improvements in technology, the proportion of PVs remaining chronically isolated following radiofrequency ablation has remained disappointingly low.[36,91] This has led to much interest in the delivery of effective ablation lesions.

In the absence of real-time assessment of lesion development and transmurality, surrogate measures of lesion quality are commonly utilized. The fall in local impedance during ablation, which has been shown to relate to lesion size, [68,135]is commonly used as a marker of the direct effect of ablation on cardiac tissue. [136–139] More recently, the minimum Force-Time Integral (FTI), which multiplies contact force by radiofrequency application duration has been shown to be predictive of PVI segment reconnection at repeat electrophysiology study.[91] Prospective use of a minimum FTI-target during each ablation application improved rates of persistent PV isolation but nevertheless, over one-third of patients were still found to have at least 1 reconnected PV.[92] This may be because FTI does not take into account the important role of power delivery, and is derived from a simple multiplication of contact force by time, whereas it is likely that these factors along with power provide differing contributions to lesion formation.[122,123] Furthermore, using a single target FTI value for all

segments of the circumferential PVI circle, as has previously been suggested, [91] assumes that tissue thickness, and therefore the ablation depth required, is the same for all areas of the left atrium. However, it is known from anatomical studies that tissue thickness varies considerably between different left atrial regions.[28]

Ablation Index CARTO 3 V4, Biosense Webster, Inc., Diamond Bar, CA) is a novel marker of lesion quality that incorporates contact force, time and power in a weighted formula, and has been shown to accurately estimate lesion depth in canine studies.[140]

Hypothesis

Primary Hypothesis:

PVI achieved by point-by-point RF catheter ablation in WACA pattern, and guided by Ablation Index targets results in durable PVI, as confirmed at repeat electrophysiology study.

Secondary hypotheses:

- Durable WACA PVI, without additional left atrial ablation, results in good clinical success rates in patients with persistent AF.
- There is a significant difference between the rate and pattern of PV reconnection in patients with and those without documented early AF recurrence.
- Sites of acute PV reconnection (including those unmasked by adenosine) and late PV reconnection correlate with Ablation Index data from the initial PVI procedure.

PRAISE study design

During the study design phase, a randomized controlled trial design option was discussed at the Research and Development committee at Liverpool Heart and Chest Hospital, with an Ablation Index group compared to a group where only Contact Force data was available to the operators. However, it was felt that as the operators already had some prior experience of using AI-targets, it would be relatively easy for them to mentally guesstimate the AI values from the Contact Force and Power values even if the AI value was not available to them. This would prevent a true randomised comparison between AI and CF.

Furthermore, while randomized controlled trials are powerful tools that enable clinical researchers to evaluate the effectiveness of new therapies while accounting for the effects of unmeasured confounders and selection bias, they may be associated with high expenses and complexity, and longer time recruitment time frame.[141] On the other hand, well-designed non-randomized trials studying the effectiveness of new therapies have the advantages of lower cost and greater timeliness, and can provide results that are similar to those of randomized controlled trials.[142,143]

The PRAISE study was designed as a multicenter study that recruited patients from three centres; Liverpool Heart and Chest Hospital, Liverpool, UK, Freeman Hospital, Newcastle, UK and Centro Cardiologico Monzino, IRCCS, Milan, Italy. The aim of that design was to benefit from its advantages, which includes the accrual of an adequate number of subjects in a shorter period of time, reaching diverse populations, and benefiting from the expertise of the various centers involved.[144] Milan and Newcastle were chosen as external centres because the operators in these centres had adequate experience in Ablation Index-guided AF ablation.

The study comprised two arms were as follows:

- A prospective cohort of 40 patients with persistent AF which (Ablation Index-guided group) in whom initial PVI procedure was performed guided by Ablation Index targets of

550 for the roof and anterior wall, and 400 for the posterior and inferior walls. All patients (regardless of AF recurrence) underwent a repeat EP study at 8-10 weeks to identify and re-ablate PV reconnection.

Patients in this group were recruited all three centres in the period between February 2016 and February 2017. The majority of these patients were recruited at Liverpool Heart and Chest Hospital, as discussed in Chapter 5, because of un-anticipated delays in obtaining necessary local approvals at the two other sites.

- A historical control group (Contact Force-guided group) of 40 patients with paroxysmal AF enrolled to the repeat study arm of the PRESSURE study (ClinicalTrials.gov Identifier: NCT01942408). All 40 patients underwent contact force-guided PVI followed by a repeat EP study after 8-10 weeks. All patients in this group were recruited at Liverpool Heart and Chest Hospital.

PRAISE study End-points

Primary outcome measure:

The proportion of patients with PV reconnection seen at repeat EP study

Secondary outcome measures:

The proportion of reconnected PVs seen at repeat EP study

The proportion of patients maintaining freedom from atrial tachyarrhythmia for 12 months (after an initial 12 week blanking period)

QOL 6 and 12 months after initial ablation, as quantified by the validated AFEQT questionnaire.

Major complication rates (occurring within 60 days after a PVI procedure), to include cardiac tamponade, stroke/TIA, myocardial infarction, phrenic nerve paralysis, oesophageal perforation/atrio-oesophageal fistula, major vascular complications and death.

Patients

Patients were recruited from the heart rhythm clinics at Liverpool Heart and Chest Hospital, Liverpool, UK, Freeman Hospital, Newcastle, UK and Centro Cardiologico Monzino, IRCCS, Milan, Italy. Patients who were listed for RF ablation of persistent AF and were felt to be suitable for inclusion by their responsible consultant were approached and offered information regarding the study. Patients who were interested in taking part were provided with the Participant Information Sheet (PIS) by a member of the research team and offered the opportunity to take this literature home to discuss it with relevant relatives and friends. The PIS contained a contact phone number and email address for the research team should they wish to get in contact with any queries. A follow-up phone call may be arranged to provide a further opportunity for discussion. If the patient wished to enrol, they were invited to either return the signed consent form by post, in which case consent was then re-confirmed in person at the time of a subsequent hospital visit, or to sign the consent form at the time of their next hospital visit.

Inclusion criteria:

- Aged over 18 years old.
- Persistent AF (defined, according to the ESC/EHRA Guidelines for the Management of Atrial Fibrillation 2010, as AF episode that either lasts longer than 7 days or requires termination by cardioversion, either with drugs or by direct current cardioversion (DCC)).
- Symptomatic AF despite drug treatment.
- Due to undergo pulmonary vein isolation by RF ablation.

Exclusion criteria:

- Inability or unwillingness to receive oral anticoagulation with a Vitamin K antagonist (VKA) or non-VKA (NOAC) agent
- Previous catheter or surgical ablation procedure for AF
- Unwillingness or inability to complete the required follow-up arrangements
- Current pattern of paroxysmal AF
- Long standing persistent AF (continuous AF longer than 12 months before ablation)
- Prior prosthetic mitral valve replacement or severe structural cardiac abnormality
- Known infiltrative cardiomyopathy
- Known severe left ventricular systolic dysfunction (ejection fraction <35%)
- Pregnancy

PRAISE study Protocol (Appendix D)

Pre-procedure management:

Echocardiographic data were collected as part of routine care, including: left ventricular (LV) ejection fraction, LV end-systolic and end-diastolic dimensions, and left atrial diameter.

Some patients underwent MRI scan prior to the ablation procedure to produce a detailed 3D reconstruction of the left atrial anatomy at the operator's discretion.

Patients on VKA agents continued these in the peri-procedural period, and a pre-procedure INR of between 2 and 4 was considered acceptable. All NOAC agents were continued peri-procedurally or withheld on the morning of the procedure as per the operators' preference.

Trans-oesophageal echocardiography (TOE) was undertaken in some patients at the discretion of the operator prior to the procedure to exclude left atrial thrombus as per standard care (indications may include sub-therapeutic INR readings in the 4 weeks prior to the ablation procedure for those taking warfarin, or missed doses for those taking alternative oral anti-coagulants).

Initial ablation procedure:

The initial ablation procedure steps are summarized in this section and are discussed in more detail in Chapter 5-I.

PVI was performed under general anaesthesia or deep sedation in a standard fashion. One or two transseptal punctures was/were made following which intravenous unfractionated heparin boluses was administered.

If the patient was in AF, electrical cardioversion was performed to restore sinus rhythm if possible. A voltage map of the left atrium was be created during atrial pacing using ConfiDense mapping (Carto 3, Biosense Webster, Inc.), and where appropriate, the left atrial map was integrated with the MRI of the left atrium (CartoMerge, Biosense Webster, Diamond Bar, California, USA).

Patients then underwent PVI using point-by-point RF application in a WACA pattern using a Thermocool® SmartTouch™ irrigated RF ablation catheter. Drag lesions were not utilised. Standardised VisiTag™ settings were used for all cases (Catheter Position Stability: minimum time 10 seconds, maximum range 2 mm; force over time: 30%, minimum force 5

g; and lesion tag size: 2 mm). These VisiTag settings were the mean of the values used for cases performed at the 4 sites that contributed to the retrospective evaluation of Ablation Index.[101] Each RF lesion was guided by AI targets: 550 at the roof and anterior walls, and 400 at the posterior and inferior walls. Power settings were chosen at the operator's discretion within the range of 20-40W. Following the completion of each WACA, PVI entry and exit block were confirmed with a circular mapping catheter (Lasso® NAV Eco, Biosense Webster, Diamond Bar, California, USA) placed sequentially in each of the PVs. Intervenous carina ablation was not be performed routinely unless required to achieve PV isolation. No additional left atrial linear lesions or ablation of complex fractionated atrial electrograms was performed. Patients with documented typical atrial flutter in the past received linear ablation on the cavotricuspid isthmus until bidirectional block was achieved.

If the patient was still in AF after achieving isolation of all PVs, electrical cardioversion was performed. Left and right atrial voltage maps were then created during atrial pacing using ConfiDense mapping (Carto 3, Biosense Webster, Inc.). After a minimum of 20 minutes since the last ablation to that WACA lesion set, ipsilateral PVs were rechecked with the circular

catheter to determine if spontaneous PV reconnection has occurred. If overt PV reconnection was not detected, a bolus of intravenous adenosine (12-18mg) was given to unmask any sites of dormant conduction. Further ablation was performed at any sites of overt or unmasked reconnection to achieve PVI once again.

Oesophageal temperature monitoring was performed in all cases with an audible temperature alarm set at 38.9 degrees Celsius. RF delivery was stopped promptly as soon as the oesophageal temperature crossed this value, or earlier at the operator's discretion. Oesophageal temperature was allowed to drop below 37.5 degrees before further RF energy is delivered in the vicinity.

Acute complete procedural success was defined as electrical isolation of all PVs. Partial procedural success was defined as electrical isolation of 3 or more, but not all, PVs. Procedural failure was defined as electrical isolation of less than 3 PVs.

Post-procedure management:

All current antiarrhythmic drug therapy were continued for at least 1 month. It could then be discontinued as per physician preference.

All patients were prescribed a proton pump inhibitor (e.g. Lansoprazole 30 mg OD) for at least 1 month.

Post-PVI monitoring for AF recurrence:

The 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation task force recommended that the gold standard for reporting the

efficacy of new AF ablation techniques should remain freedom from atrial tachyarrhythmia of greater than 30 seconds in duration off all antiarrhythmic drugs.[54] According to the consensus statement, arrhythmia monitoring following AF ablation can be carried out by either continuous or non-continuous ECG monitoring methods. The non-continuous methods include scheduled or symptom-initiated standard ECGs, Holter monitor (24 hours to 7 days), transtelephonic recordings, automatically and patient activated monitoring devices, external loop recorders that can continuously record ECGs for up to 30 days, and more recently smart phone monitors that can record 30-second ECGs. [54,145]

Although more intensive ECG monitoring using any of these modalities is associated with more likelihood of detecting both symptomatic and asymptomatic AF, the use of more complex and longer methods of monitoring may be associated with lower patient compliance.[146] With adequate compliance, scheduled 7-day Holter ECG recordings or daily plus symptom activated event recordings are estimated to document approximately 70% of AF recurrences. [147]

The potential problem of low compliance with non-continuous ECG monitoring can be overcome with the use of continuous ECG monitoring, which can only be achieved by implantable loop recorders (ILRs), unless the patient has an implantable cardiac device; a pacemaker or an implantable cardioverter defibrillator. [54] However, there are several disadvantages with the use of ILRs for arrhythmia monitoring following AF ablation. These include the relatively higher cost of the device, the need for surgical implantation, and the potential risk for LR removal for erosion and infection. Moreover, ILRs are

associated with high false-positive AF detection due to noise oversensing, frequent atrial or ventricular premature beats, T wave over-sensing and/or sinus arrhythmia. [148]

For these reasons, we opted to use daily plus symptom activated event recordings using the validated handheld ECG monitor (Omron HCG-801-E, Omron Healthcare, Kyoto, Japan) (Figure 4-1). Furthermore, we already had extensive experience of using this method of arrhythmia monitoring successfully.[80] After educating the patients about how to use the handheld ECG monitor and about the importance of compliance with timely ECG recording, we provided each of them with a monitor to be kept for the duration of the study of 12 months. Patients were asked to self-record a 30-second ECG recording once a day for the duration of the study, as well as each time they experience symptoms of palpitations.

The 2007 and the 2012 Heart Rhythm Society (HRS)/European Heart Rhythm Association (EHRA) consensus documents on catheter and surgical ablation of AF, defined a sustained AF episode as lasting ≥30 seconds, with failure defined as detection of at least one sustained AF episode during follow-up.[54,149] These definitions were designed to bring consistency to the measurement of outcomes after AF ablation, therefore our research team adopted them to uniformly measure then compare the outcomes of the PRESSURE and the PRAISE studies.[80,124]

One of the limitations of the use of the HeartScan HCG-801 ECG monitor is its inability to differentiate between the routine daily and the symptom activated ECGs, because of its lack of ECG annotation capability.

Figure 4-1 ECG handheld monitor device – HeartScan HCG-801 ECG Monitor

Repeat EP study:

The repeat procedure was performed in the same way as outlined above for the initial procedure. Peri-procedural and intra-procedural anti-coagulation management was also identical to the initial procedure. As before, voltage map of the left atrium was created during atrial pacing using ConfiDense mapping and integrated with the original MRI reconstruction of the left atrium (CartoMerge, Biosense Webster, Diamond Bar, California, USA) where available.

Each PV was assessed in turn for late reconnection with a circular mapping catheter and reconnection site(s) was recorded for subsequent analysis. All identified sites of reconnection were re-ablated using a Thermocool® SmartTouch™ irrigated RF ablation catheter, with the same target Ablation Index values as before; 550 or 400 depending on location and RF power was again set at the operator's discretion until PV re-isolation was successfully achieved. If the patient was in AF after achieving isolation of all PVs, electrical cardioversion was performed. No additional left atrial linear lesions or ablation of complex fractionated atrial electrograms were performed during the repeat procedures.

Follow-up (Table 4-1 and Figure 4-2)

Continued daily, plus symptom episode, ECG recordings as described above were carried out for 12 months from the initial procedure. Clinical review appointments took place at 6 weeks, and then at 3, 6 and 12 months. Data from the handheld ECG monitors were downloaded at these visits.

Participants were asked to complete AFEQT and EQ5D questionnaires at the time of the 6 and 12-month clinic visits.

Anticoagulation with warfarin or another oral anticoagulant agent was continued for at least 3 months following the index ablation procedure. At that point the decision whether or not to continue was individually, based on the patient's CHA2DS2/CHA2DS2-VASc score and patient preference.

Any episodes of atrial tachyarrhythmia (ATA) ≥30 seconds in duration documented after the 3-month blanking period was defined as a recurrence. That signified that that the patient has reached the primary end-point of the study and offering further management including; re-initiation of anti-arrhythmic medications, electrical cardioversion or listing for repeat PVI, as per the discretion of the patient's responsible Consultant.

Table 4-1 PRAISE study schedule of events

Procedure	Recruit	Pre-admission	Procedure Day 0	6 Weeks	8 Weeks	12 Weeks	26 Weeks	52 Weeks
Clinical review	✓			✓	✓	✓	✓	✓
ECG Review	✓			✓	✓	✓	✓	✓
Handheld monitor provision		✓						
QOL forms	✓						✓	✓
PVI procedure			✓		✓			

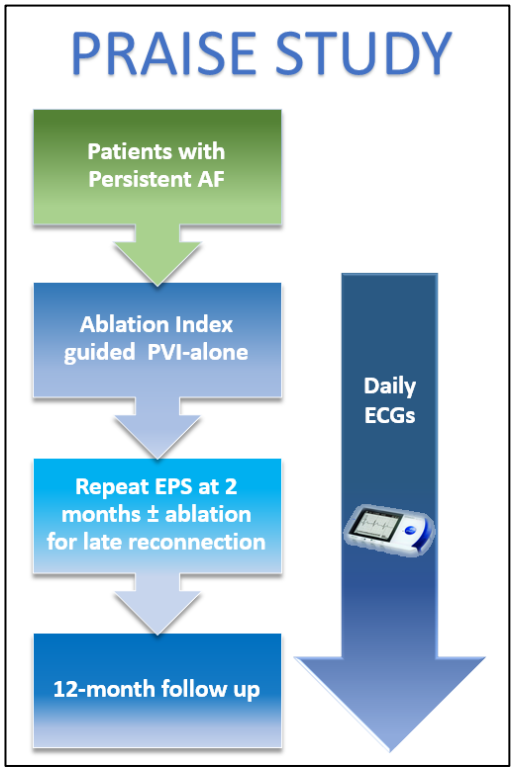


Figure 4-2 Flowchart of PRAISE study schedule of events

Safety

Major complications:

Major complications of atrial fibrillation ablation, mentioned in the HRS/EHRA/ECAS Expert Consensus Statement published in 2012, were assessed throughout the 12-month following the initial ablation procedure.[54] In general, a major complication was defined as a complication that results in permanent injury or death, requires intervention for treatment, or prolongs or requires hospitalization for more than 48 hours, such as cardiac tamponade, cerebrovascular stroke, transient Ischeamic attack, myocardial infarction, pulmonary vein stenosis, phrenic nerve palsy, oesophageal perforation or atrio-oesophageal fistula, major vascular complications that require interventions such as surgical repair or transfusion, and death.

The incidence of major complications following AF ablation in contemporary practice ranges from 3-5%. As such, it must be noted that the PRAISE study was not powered to assess the safety profile of Ablation-Index guided ablation.

Serious adverse event reporting

Any suspected major complication (as defined above) in the course of the study, either whilst in hospital or during the period of follow up, was to be reported as per the standard local adverse Event Reporting procedure.

Data monitoring committee

A data monitoring committee was appointed by the sponsor to review and monitor the PRAISE study. This committee, which is known as the Research Endeavour (SURE) group, comprised a general practitioner, a cardiologist, former patients, carers and members of the public. The committee convened and reviewed the feasibility of patients' involvement in the study, quality and clarity of the documentation, and the study safety data (Appendix H). An interim analysis of the study was carried out in February 2017 and received a favourable opinion from the Health Research Authority- North West in March 2017.

Insurance/indemnity

Indemnity was provided through the NHS indemnity scheme or professional indemnity.

Sample size calculation

Of the patients randomised to the Repeat Study arm of the PRESSURE study, 62.5% had reconnection of 1 or more PVs. We expected this rate to be at least halved when ablation was to be guided by AI targets. A formal sample size calculation was therefore performed

assuming a proportion of patients with PV reconnection of 31% in the AI-guided group and 62.5% in the CF-guided group.

With these values, an alpha error set at 0.05 and power set at 80%, the number of patients required for a two-sided test would be 36 per group. Allowing for 10% of patients who were expected to be lost to follow-up, the intended sample size was estimated to be 40 per group. That sample size requirement was already met for the CF-guided group represented by the PRESSURE study patients who had repeat ablation procedures.

Statistical analysis

All end points were examined by means of an intention-to-treat analysis. All categorical variables were compared with χ^2 or Fisher's exact test as appropriate. The dependent variables were checked for normal distribution by the Shapiro-Wilk statistic and appropriate descriptive statistics generated. Continuous variables that are normally distributed were expressed as means (±SD) and were compared using Student's t-test. Variables that were not normally distributed were expressed as a median (interquartile range) and were compared with Wilcoxon rank-sum and signed-rank tests.

For the primary outcome and the secondary outcomes, 2-sided t-test for continuous measures and Fisher's exact for categorical measures. In addition, Spearman's Rank Correlation Coefficient was used for analysis of secondary outcomes. All data were analysed using SPSS for Windows version 24 and alpha will be set at the 0.05 level.

Sponsorship and Funding

The PRAISE study was sponsored by the Liverpool Heart and Chest Hospital NHS Foundation Trust. The sponsor was responsible for obtaining all the required ethics approvals, reaching

agreements with the other sites participating in the study, and the initiation and management of the study.

The study was funded through an Investigator-Initiated Study funding agreement with Biosense Webster, Inc. (BWI-IIS-385). The funder reviewed and approved the study protocol. Subsequently, the funder provided the study monetary funding in instalments according to an agreed patient recruitment schedule, and provided the equipment required for repeat studies as described above.

Study registration

The PRAISE study was prospectively registered on the ClinicalTrials.gov database (NCT02628730), North West - Greater Manchester East Research Ethics Committee (15/NW/0930) and National Institute of Health Research (NIHR) Clinical Research Network (CRN) Portfolio (20310). Please see Appendices D-H for the PRAISE study approvals and other relevant study documents.

Chapter 5 Prospective study on the use of Ablation Index-guided ablation

This chapter is divided into four parts as follows:

5-I Use of Ablation Index-guided ablation results in high rates of durable pulmonary vein isolation and freedom from arrhythmia in persistent AF patients: the PRAISE Study Results

This part describes the results of the Pulmonary vein Reconnection following Ablation Index-guided ablation: a Success Evaluation (PRAISE) study.

5-II AI-guided ablation results in lower prevalence of PV reconnection following PVI compared to CF-guided ablation. A comparison between PV reconnections in the PRAISE and the PRESSURE studies

In this part we compared the PV reconnection data of the PRAISE study with those of the PRESSURE study, in which the RF ablation was CF-guided.

5-III Reverse remodelling of the left atrium occurs early after catheter ablation for persistent atrial fibrillation in the presence of durable pulmonary vein isolation

This part describes a substudy of the PRAISE study in which we studied the relationship between reverse remodelling of the left atrium following Ablation Index-guided ablation and the presence of durable pulmonary vein isolation.

5-IV Factors Associated with Regional Late Pulmonary Vein Reconnection after Ablation Index-Guided Ablation in Patients with Persistent Atrial Fibrillation

This part discusses the potential factors that may be associated with regional late pulmonary vein reconnection following the use of Ablation Index-guided ablation in the PRAISE study.

5-I Use of Ablation Index-guided ablation results in high rates of durable pulmonary vein isolation and freedom from arrhythmia in persistent AF patients: the PRAISE Study Results

Introduction

As discussed in Chapter 1, complete PVI has been recommended as the best established target for ablation of paroxysmal atrial fibrillation (PAF) and has been found to be non-inferior to more extensive ablation in persistent AF.[33,36,150]

Late PV reconnection has been the Achilles' heel of radiofrequency ablation, with at least one late PV reconnection reported in about 70% of patients even after complete acutely successful PVI.[36]

As discussed in Chapter 3, the introduction of CF-sensing catheters and use of FTI-targeted ablation has improved results, but not to the levels hoped for, with 38-62% of patients still showing late PV reconnection.[92,102]

Earlier this decade, Ablation Index was introduced as a novel marker of ablation lesion quality that incorporates power, CF and time in a weighted formula, and was found to accurately estimate ablation lesion depth in pre-clinical studies, as discussed before.[140] Ablation Index has been integrated as an ablation lesion quality monitoring module into the automated lesion tagging software (VisiTag™) in the CARTO 3 V4 3D electroanatomic mapping system (Biosense Webster, Inc., Diamond Bar, CA).

As previously discussed our research group contributed to two early studies on Ablation Index, the first was a multi-center study that defined the minimum regional Ablation Index target values that would be required to prevent acute PV reconnection, whilst the second defined the minimum regional Ablation Index target values that would be required to prevent late PV reconnection detected at protocol-mandated repeat procedures after 2 months.[101,102] Regional Ablation Index target values to be used prospectively were derived from these two studies as follows; 550 for anterior and roof, and 400 for posterior and inferior LA regions.

Our hypotheses were that the prospective use of these Ablation Index targets would result in a low rate of PV reconnection, and that durable PVI that alone may be adequate to achieve a high rate of clinical success in patients with persistent AF. We therefore designed the 'Pulmonary vein Reconnection following Ablation Index guided ablation: a Success Evaluation (PRAISE)' study, in which 40 patients underwent a protocol-mandated repeat electrophysiology procedure following Ablation Index -guided ablation to determine the prevalence of late PV reconnection. Patients were followed up 6 weeks after the initial ablation procedure then every three months and were monitored with daily ECGs for 12 months to determine the clinical outcomes.

Methods

As discussed in Chapter 4, the PRAISE study population comprised consecutive patients with persistent AF of less than 12 months duration and with no significant structural heart disease who underwent Ablation Index-guided PVI at 3 sites: Liverpool Heart and Chest Hospital, Liverpool, UK (co-ordinator: Ms Maureen Morgan, RN), Freeman Hospital, Newcastle, UK (co-ordinator: Miss Leanne Thompson, RN) and Centro Cardiologico Monzino, IRCCS,

Milan, Italy (co-ordinator: Ms. Catto Valentina, PhD). Ms Maureen Morgan, LHCH research nurse coordinated the study workflow among the three sites with the assistance from Dr Ahmed Hussein, LHCH primary investigator, and Prof Dhiraj Gupta, the study chief investigator. Site initiation visits to Milan and Newcastle were carried out to ensure standardisation of study protocol implementation, including standardisation of the ablation procedure, at the 3 sites.

Initial ablation procedure:

All procedures were performed under general anesthesia or deep conscious sedation. Following ultrasound-guided right femoral venous access,[151] two transseptal punctures were performed using fluoroscopic guidance with additional pressure monitoring, following which intravenous unfractionated heparin boluses were administered to maintain an Activated Clotting Time of >300 seconds. If the patient was in AF, electrical cardioversion was performed to restore sinus rhythm. CARTO 3 (Biosense Webster, Inc., Diamond Bar, California) electroanatomical mapping system was used to create a 3-D voltage map of the LA.

PVI was performed with radiofrequency energy in a point-by-point in WACA pattern using a Thermocool® SmartTouch™ irrigated tip CF-sensing ablation catheter (Biosense Webster, Inc., Diamond Bar, CA) introduced via a non-steerable sheath. The WACAs were created >10 mm outside the PV ostia, where the local electrograms did not show near-field PV signals. For the left pulmonary veins, ablation was performed just inside the ridge anterior to the veins. No ablation on the intervenous carinae, and no other ablations in the LA were delivered as part of initial lesion set unless needed to achieve pulmonary vein isolation. The

only other additional ablation permitted was cavotricuspid isthmus (CTI) ablation for documented typical atrial flutter.

The VisiTag™ settings for all 40 patients were as follows: catheter position stability: minimum time 10s, maximum range 2mm; force over time: 30%, minimum force 5g; lesion tag size: 2mm. The protocol required that the operator should aim to deliver contiguous lesions (center-to-center distance ≤6mm).[152] A CF of 5-40g was targeted at each site. Power settings were at the individual operator's discretion within the range of 20-40W depending upon the LA segment. Each lesion was guided by Ablation Index targets: 550 at the roof and anterior walls, and 400 at the posterior and inferior walls (Figure 5-1).[103] Impedance drop and FTI data were neither displayed nor targeted. Oesophageal temperature monitoring was performed in all general anesthesia cases and RF delivery was stopped as soon as the oesophageal temperature reached 39°C, even if the target Ablation Index value of 400 had not been reached. Further RF was not delivered on the posterior wall until the oesophageal temperature reached baseline level. If there was evidence of residual conduction into the PVs on the posterior wall after completion of the WACA, RF was delivered inside the WACA, i.e. further away from the oesophagus, as shown in Figure 5-3.

The acute endpoint of the procedure was complete PVI, as demonstrated by entrance block using a 20-pole circular mapping catheter (Lasso® NAV Eco; Biosense Webster, Inc.) placed sequentially in each of the PVs. After a minimum of 20 minutes from the last ablation to that WACA lesion set, ipsilateral PVs were rechecked with the Lasso catheter to determine if spontaneous PV reconnection had occurred, and these sites were tagged. If overt PV reconnection had not occurred, a bolus of intravenous adenosine (12-18mg) was

administered to unmask any sites of dormant conduction. Further ablation was performed at any sites of overt or unmasked reconnection to achieve PVI once again.

Repeat electrophysiology study:

All 40 patients underwent protocol-mandated repeat procedure, regardless of symptoms or documented AF recurrence, 8-10 weeks after the initial procedure. Peri-procedural anticoagulation management and procedural protocol were identical to the first procedure, including creation of a LA map using CARTO 3 and integration with the original computed tomography or magnetic resonance imaging reconstruction of the LA where available. Each PV was then assessed in turn for late reconnection with a Lasso catheter and reconnection sites were recorded. All reconnection sites were re-ablated using a Thermocool® SmartTouch™ irrigated ablation catheter until PVI was successfully achieved. The same Ablation Index target values as for the initial procedure (550 for the roof and anterior wall and 400 for the posterior and inferior walls) were used, as safety data for higher Ablation Index values than these are not available.

If the patient remained in AF after achieving isolation of all PVs, electrical cardioversion was performed, and no additional ablation was performed.

ECG follow up

A validated portable ECG monitor (Omron HCG-801-E, Omron Healthcare, Kyoto, Japan) was given to every patient.[153] After training them on its use, patients were instructed to self-record a 30-second ECG every day and additionally whenever they experienced symptoms. ECG recordings were downloaded at each follow-up visit and were analysed for the presence

and dates of any atrial tachyarrhythmia (ATA), defined as atrial fibrillation or any other organized atrial arrhythmia, by experienced clinicians blinded to the patient symptoms.

Patient follow-up

Follow-up visits were arranged after 6 weeks, then at 3, 6, and 12-month. Any antiarrhythmic medications, including beta-blockers, were stopped 3 months after the initial ablation unless substantial ATA continued to occur beyond 3 months.

A validated Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) questionnaire, which includes 20 questions across 3 domains (symptoms, daily activities, and treatment concerns) using a 7-point Likert scale, was completed at baseline and at 6 and 12 months.[154]

Study Outcomes

The primary outcome measure was freedom from ATA recurrence after the 3-month blanking period following the initial ablation procedure. ATA recurrence was defined as documented atrial fibrillation, atrial flutter, or atrial tachycardia lasting ≥30 seconds.[155] Secondary outcome measures were as follows: quality of life 6 and 12 months after initial ablation; time to first ATA recurrence; ATA burden during the primary outcome period; re-initiation of antiarrhythmic medication; and the occurrence of major complications.

Per-protocol analysis:

The procedural data were reviewed to rule out protocol violations, defined as a divergence from the study protocol that may potentially reduce the quality or completeness of the outcome data.

The occurrence of any of the following was regarded as a protocol violation and the relevant WACA circle/patient was excluded from PV reconnection data analysis: any technical problem that prevented the delivery of the full ablation lesion set during the initial ablation procedure; if the initial ablation lesion set was not delivered in a WACA pattern (>1 cm outside the PV ostia); or the presence of more than 8 gaps (defined as an inter-lesion distance of >6mm) in a WACA circle.[152]

Ablation lesion data analysis:

Detailed offline retrospective analyses of all WACA circle ablation lesions was carried out for all patients. The data for each VisiTag™ included ablation duration, CF, impedance drop, FTI, and Ablation Index. CF was defined as the mean CF during ablation, and impedance drop was defined as the difference between the pre-ablation impedance value and the lowest recorded value during ablation.

The FTI and Ablation Index values were automatically calculated by the CARTO 3 system for each lesion. FTI was calculated by multiplication of the mean contact force during energy application by the duration of the application and is measured in gram seconds (gs). Ablation Index was calculated using a complex weighted exponential formula allocating different weights to CF, time and power.[140]

To analyse the effect of using different AI target values for the various LA regions, each WACA circle was divided into six potential reconnection segments (roof, 2 anterior, inferior, and 2 posterior). We then categorized these 6 segments into 2 regions per WACA circle according to the regional AI targets used for AI-group: anterior and posterior regions (Figure 5-1).

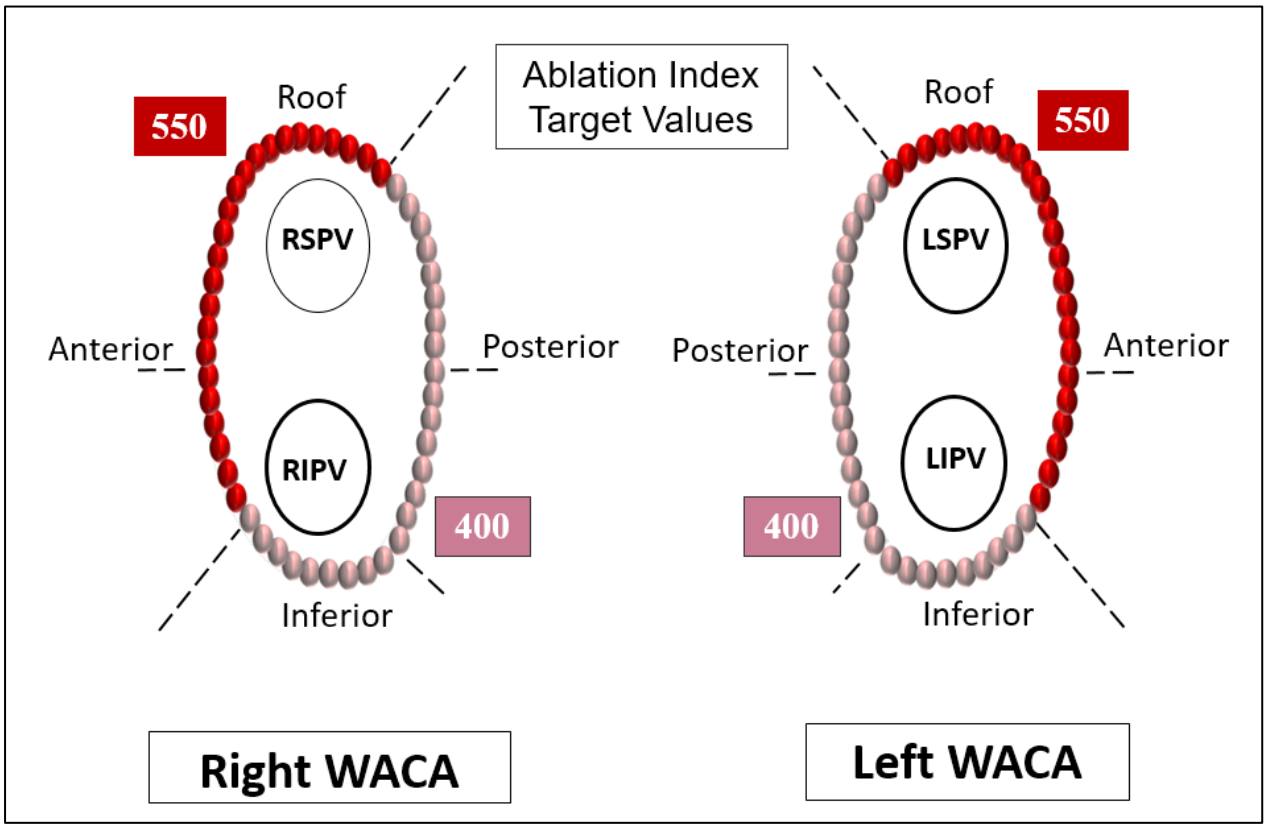


Figure 5-1 Diagram showing the anterior/roof and the posterior/inferior segments and the AI target values used for each of these segments in AI-group. The red dots represent ablation lesions with AI target values ≥550 while the pink dots represent AI target values ≥400 but <550.

Statistical analysis

Continuous variables are presented as mean and standard deviation or median and interquartile range (25th–75th percentiles) where appropriate. Student's t-test or the Mann–Whitney U-test were used for unpaired group comparison. Categorical variables were

compared by χ2 or Fisher's exact test and presented as frequency and percentage. All tests were two-sided and a $P<0.05$ was considered statistically significant.

Statistical analysis was performed using SPSS (version 24, IBM Corp., Armonk, NY).

Results

In the period between February 2016 and February 2017, 40 consecutive persistent AF patients who fulfilled the PRAISE study inclusion criteria were recruited from all three participating centres. Most patients (n=33/40 (83%)) were recruited from LHCH, 6 (15%) patients were recruited from Milan and only one patient (2%) was recruited from Newcastle. The relatively low contribution of the latter two sites occurred because of unexpected delays in the paperwork required to start recruiting from them, and at the same time there was a need to meet the patient recruitment targets in a timely manner. During the recruitment period, a total of 574 atrial fibrillation patients scheduled for AF ablation at LHCH were screened (354 (62%) paroxysmal 187 (32%) persistent and 33 (6%) longstanding persistent). The demographic and procedural data for all 40 patients are presented in Table 5-1. As the patient cohort consisted solely of persistent AF patients, the mean LA size was relatively large at 43±5 mm and LV function was impaired in 8 (20%) of patients.

The median duration of persistent AF was 9.5 (6-12) months, and 28/40 (70%) patients had undergone at least one attempt of electrical cardioversion prior to the initial PVI. All 40 patients returned for repeat study and no major complications occurred in any of the 80 procedures.

A total of 2,764 VisiTags™ were analyzed with a mean number of 69±12 VisiTags™ per patient. The mean ablation time was 36±9mins and the mean CF was 13±2g.

Four WACAs (2 left-sided and 2 right-sided), with the relevant 4 patients, 8 PVs and 24 segments, were excluded from PV reconnection analysis because of protocol violation: 2 because of the presence of >8 gaps in the WACA circle, 1 because segmental ostial (rather than WACA) PVI was performed, and 1 because of equipment failure.

Table 5-1 Demographic and procedural Data

Age, years	61±8
Male (n, %)	30 (75%)
Left atrial AP diameter, mm	43±5
LV Ejection fraction >55% (n, %)	32 (80%)
Hypertension (n, %)	12 (30%)
Diabetes mellitus (n, %)	3 (8%)
CHA_2DS_2Vasc Score	1 [0-2]
Atrial fibrillation duration, months	9.5 (6-12)
Antiarrhythmic drugs prior to ablation	36 (90%)
Procedure time, minutes	158±34
Ablation time, minutes	36±9
Number of VisiTags™ per patient	69±12
Fluoroscopy time, minutes	12 [8–14]
General anesthesia (n, %)	39 (98%)
Major complications (n, %)	0 (0%)
Interval between procedures, days	64±6
Mean CF, g	13±2
Mean FTI, gram-seconds	327±77
Mean AI	486±42
Ablation time per lesion for anterior segments, seconds	35 (27- 44)
Ablation time per lesion for the posterior segments, seconds	23 (17-28)
Patients who received CTI ablation, n (%)	3 (8%)

AP: anteroposterior, LV: left ventricular, CF: contact force, FTI: Force-Time Integral, AI: Ablation Index, CTI: cavotricuspid isthmus

Acute PV isolation and acute reconnection

Acute PV isolation was successful in all (100%) of the 147 PVs included for analysis. A carina line was required to achieve PV isolation in 9/76 (12%) WACAs in 9/36 (25%) patients. After the 20-minute waiting period and the use of adenosine, acute reconnection was seen in 10 (28%) patients affecting 14 (10%) PVs (Table 5-2).

Acute reconnection occurred in 15 (3%) segments, the majority of which (13/15 (87%)) were spontaneous. The distribution of segments of acute reconnection is shown in Figure 5-2 (Upper panel). All 15 acutely reconnected segments were successfully re-ablated and PV re-isolation was achieved.

Late PV reconnection at repeat electrophysiology study

The mean duration between the initial PVI procedure and repeat electrophysiology study was 64±6 days. Late PV reconnection was identified in 13 (3%) segments in 8 (22%) patients, affecting 11 (7%) PVs (Table 5-2). The distribution of segments with late reconnection is shown in Figure 5-2 (Lower panel).

All reconnected PVs in the 8 patients with late PV reconnection were successfully re-isolated. The median ablation time required for re-isolation was 5.6 (4.5–7.9) minutes.

*Table 5-2 Prevalence of Acute and Late Pulmonary Vein Connections in the study group**

	Acute PV reconnection at initial ablation	Late PV reconnection at repeat procedure
By Patients, n=36	10 (28%)	8 (22%)
By WACA circle, n=76	10 (13%)	8 (11%)
By WACA segment, n=456	15 (3%)	13 (3%)
By pulmonary veins, n=147	14 (10%)	11 (7%)

WACA; Wide antral circumferential ablation, PV: Pulmonary vein

* Four WACAs with their relevant 4 patients and 24 WACA segments were excluded because of protocol violation: 2 because of the presence of >8 gaps in the WACA circle, 1 because segmental ostial (rather than WACA) PVI was performed, and 1 because of equipment failure.

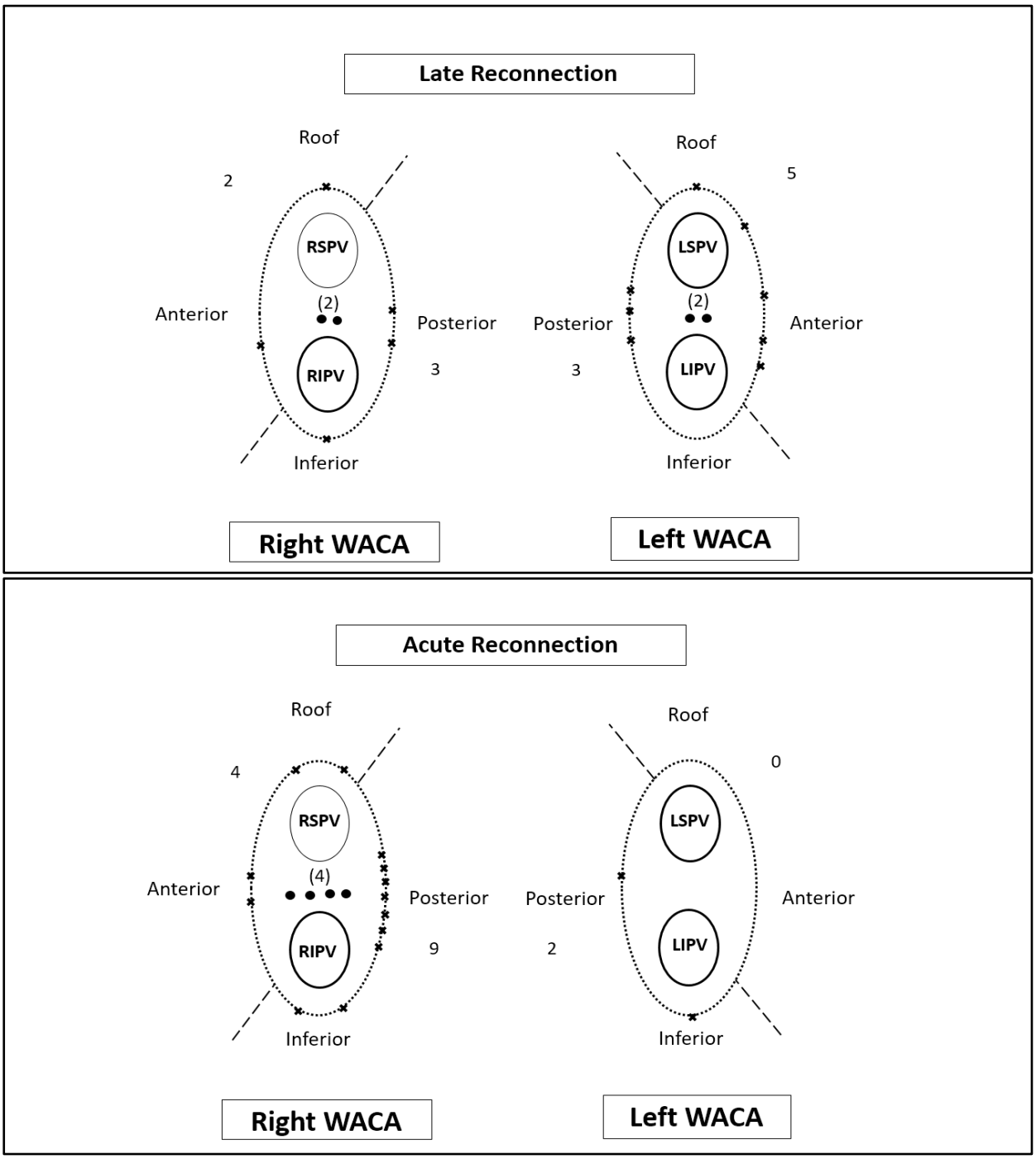


Figure 5-2 Diagram showing the number of segments with reconnection identified within each region acutely (upper panel) and at repeat electrophysiology study (lower panel). Asterisks represent sites of reconnection in segments of the WACA circle, while black dots indicate carina involvement in ipsilateral WACA reconnection requiring additional carina line ablation.

Relationship between acute and late PV reconnection

The proportion of PVs with re-isolated acute reconnection that exhibited late reconnection was significantly higher than that for PVs without acute reconnection (5/14 (36%) vs. 6/133 (5%), *P*<0.001). However, late reconnection occurred in only one segment (1/15 (7%)) that exhibited acute reconnection during the initial PVI, compared to 12 of 441 (3%) segments that did not exhibit acute reconnection during the initial PVI (*P*=0.37).

Regional variation in the pattern of acute and late PV reconnection

Acute reconnection was commonest in the right posterior/inferior segments (9/15 (60%)) (Figure 2 (Upper panel)). Conversely, segments with late reconnection were most common in the left anterior/roof regions (5/13 (38%)) (Figure 2 (Lower panel)).

Ablation Index values for reconnected versus non-reconnected segments

As expected with using Ablation Index target values, there were no significant differences in the minimum Ablation Index values for segments with acute reconnection compared to those without, either for anterior/roof regions (566 [492-573] vs. 558 [384-567], *P*=0.23) or for posterior/inferior regions (425 [414-437] vs. 417 [348-430], *P*=0.15). This was also true for segments with and without late reconnection (anterior/roof regions: 563 [424-570] vs. 557 [383-566], *P*=0.72; posterior/inferior regions: 434 [353-435] vs. 415 [348-429], *P*=0.27).

Pulmonary vein reconnection in relation to PV anatomy

Oesophageal proximity to PVs

During the initial PVI procedures, an oesophageal temperature rise of >39°C was encountered in 12 patients affecting 14 posterior segments (7 right and 7 left) compelling premature termination of radiofrequency energy application before the Ablation Index target of 400 was reached (Figure 5-3). The highest recorded peak oesophageal temperature during ablation on the LA posterior wall was 40.4°C. The incidence of acute reconnection was significantly higher in the posterior segments where oesophageal temperature rise was detected (4/14 (29%)), compared to the posterior segments where there was no such rise (4/62 (6%), *P*=0.015). Following successful re-isolation of these acutely reconnected segments, there was no significant difference in the incidence of late reconnection between posterior segments that were or were not affected by oesophageal temperature rise (1/11 (9%) vs. 4/65 (6%), *P*=0.72).

Intervenous carina ablation

In total, 16/76 (21%) WACA circles (10 right-sided and 6 left-sided) in 16/36 (44%) patients required a carina line for re-isolation at some point during the 2 procedures. A carina ablation line for re-isolation was needed in 4/10 (40%) of the acute reconnected WACAs. Similarly, there was a need for a carina ablation line at repeat study to re-isolate 4/8 (50%) of the late reconnected WACA circles (Figure 5-2).

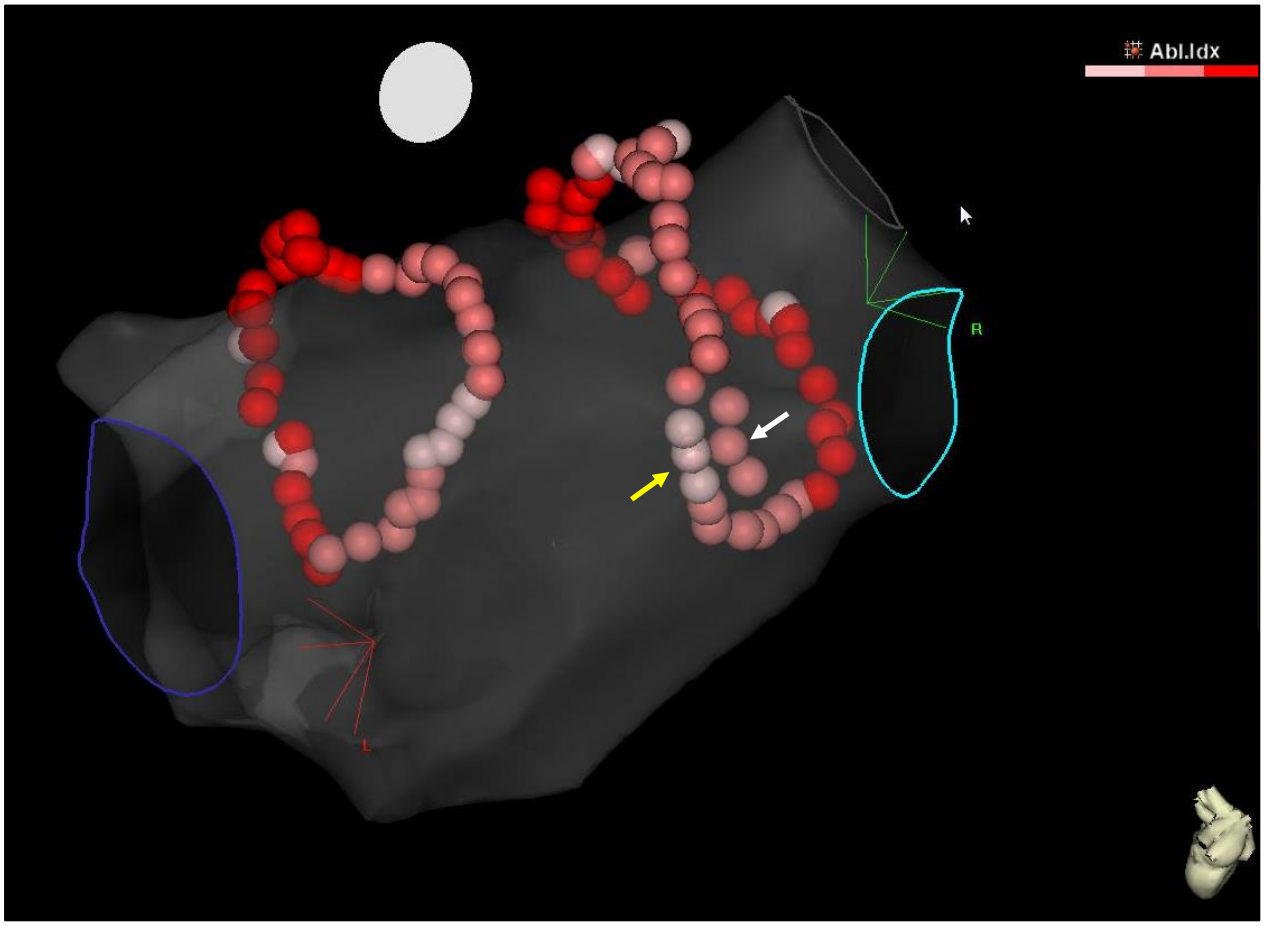


Figure 5-3 Carto 3 posteroanterior view of one of the study patients. The VisiTags™ are color coded according to the following AI target values; red for values ≥550, pink for values 400-549, and light pink for values <400. Note the sub-therapeutic VisiTags™ that were initially delivered to the posterior left atrial wall due to the associated rise in oesophageal temperature (yellow arrow). Further RF delivery was needed more distally just inside the initial WACA set to treat acute reconnection of the right lower pulmonary vein (white arrow).

Recurrence of atrial tachyarrhythmia

No patient was lost to follow up. Good patient compliance with median 7 (7-7) weekly handheld ECG recordings was achieved by 31 (78%) of patients. The remaining 9 (22%) patients had a median of 4 (4-5) weekly ECG recordings.

A total of 14,424 ECG recordings were obtained and analyzed. The median number of ECGs recorded during the 12-month follow up period was 372 (342-405) recordings per patient,

with 100 (89-107) recorded during the blanking period, and 270 (240-302) recorded during the primary outcome period.

In the period between the end of the blanking period and the end of 12-month follow-up, ATA recurrence was documented in 8/40 (20%) patients (Figure 5-4), only one of whom had late reconnection at repeat study. ATA recurrence was in a paroxysmal pattern in 5 (62.5%) patients (of whom 3 patients had ATA documented on a single day only), and in a persistent pattern requiring electrical cardioversion in 3 (37.5%) patients. The median time to first ATA recurrence 184 (133-191) days, and the ATA burden during the primary outcome period was 11 (1-48) days. By the end of the 12-month follow-up period, 38 (95%) patients were in sinus rhythm, with only four (10%) patients taking antiarrhythmic drugs (AADs) or beta-blockers.

There was no significant difference in the proportion of patients with late pulmonary vein reconnection between patients with and without ATA recurrence (1/8 (13%) vs 7/32 (22%), *P*=0.55).

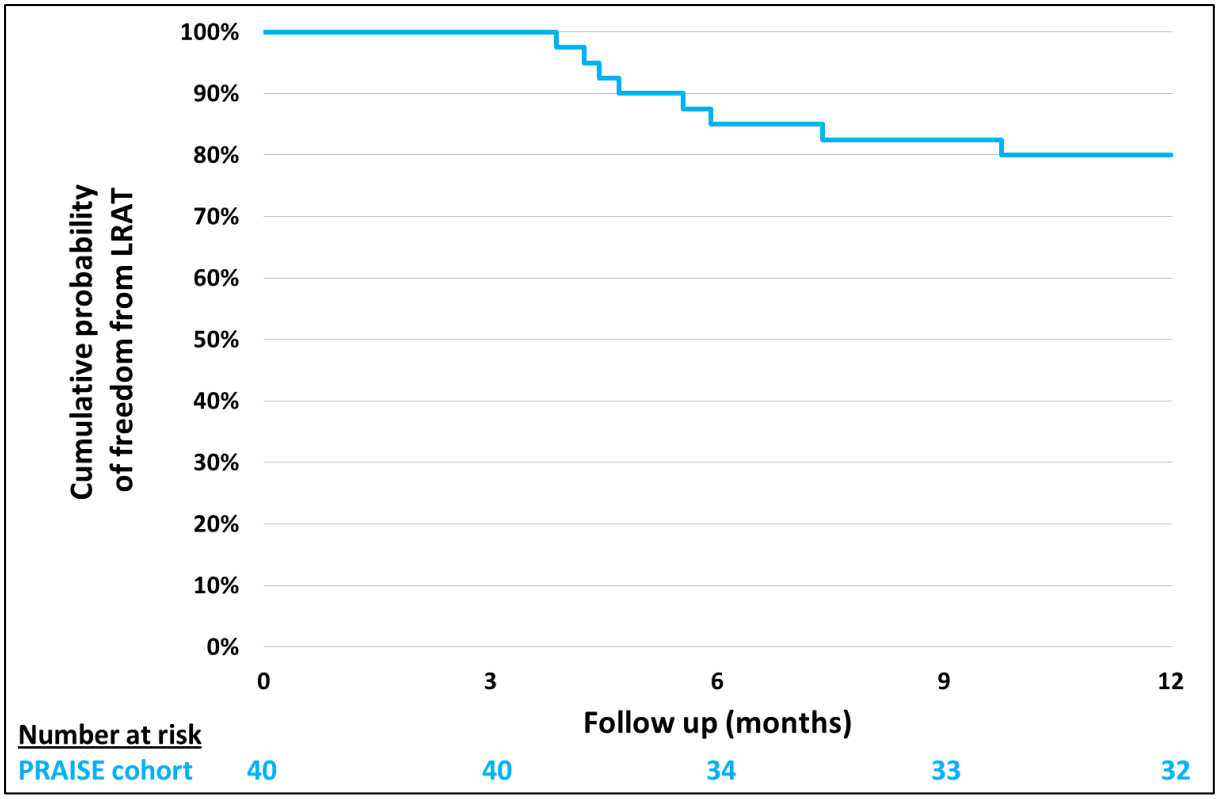


Figure 5-4 Kaplan-Meier curve of freedom from AT recurrence for all PRAISE patients.

Patient characteristics in relation to atrial tachyarrhythmia recurrence

Table 5-3 presents patient demographics and clinical characteristics of patients with and without AT recurrence. Higher body mass index (BMI) and excess alcohol intake, defined as >30g (about 4 units)/week, were the only two factors significantly associated with AT recurrence during the outcome period.

Table 5-3 Demographic and clinical characteristics in relation to AT recurrence

	No ATA recurrence (n = 32)	**ATA recurrence (n = 8)**	***P*-value**
Age, years	61 (56 - 69)	55 (49 - 68)	0.15
Male gender (n,%)	24 (75%)	6 (75%)	>0.99
BMI, kg/m^2	27.3 (25.5 - 32.1)	31.1 (29.1 - 34.0)	0.02
Duration of AF before PVI, months	10 (6 - 12)	8 (5 - 11)	0.44
CHA_2DS_2-VASc Score	1 (0 - 2)	1 (0 - 2)	0.96
Hypertension (n,%)	11 (34.4%)	1 (12.5%)	0.40
Diabetes mellitus (n,%)	1 (3.1%)	2 (25%)	0.10
Excess alcohol of >30g/week (n,%)	0 (0%)	3 (37.5%)	0.006
LVEF <40% (n,%)	6 (18.8%)	2 (25%)	0.65
LA AP diameter, cm	4.3 (4.1 - 4.6)	4.0 (4.1 - 4.9)	>0.99

ATA: Atrial tachyarrhythmia, BMI: Body mass index, PVI: Pulmonary vein isolation, LVEF: Left ventricular ejection fraction, LA: Left atrial, AP: anteroposterior.

Early recurrence of atrial tachyarrhythmia

During the blanking period, early recurrence of atrial tachyarrhythmia (ERAT) occurred in 12 (30%) patients. Only 2 patients with ERAT required redo ablation for PV reconnection at repeat study and neither had further ATA recurrence during the study follow-up period. Of the 10 remaining patients with ERAT but no PV reconnection, 4 went on to have post-blanking period ATA, indicating a non-PV driver for their recurrent ATA. The absence of ERAT during the blanking period was significantly associated with freedom from LRAT at 12 months (85.7% vs 66.7%, *P*<0.01).

AFEQT scores

For all patients at 6 months after the initial PVI procedure, AFEQT scores showed a significant improvement in patient quality of life compared to baseline (63.9 [39.1 to 69.9] vs. 91.7 [84.3 to 97.2]; *P*<0.001). This became even more evident at 12 months (98.2 [81.5 to 99.5], *P*<0.001).

Discussion

Main Findings

This study is the first to investigate the durability of PVI following Ablation Index-guided ablation, as assessed at protocol-mandated repeat electrophysiology study, and clinical outcomes at 12 months following a PVI-only strategy in patients with persistent AF. The main findings of this study are: 1) AI-guided ablation was associated with high rate of durable PVI of 93% PVs in a persistent AF population; 2) around one-third of posterior segments where therapeutic AI values could not be reached because of a rise in oesophageal temperature exhibited acute PV reconnection after the 20-minute waiting period; 3) almost half of patients in the AI-group required ablation on the intervenous carina to achieve permanent PVI; 4) an AI-guided PVI-only ablation strategy was associated with a successful outcome in the vast majority of patients over 12 months, most probably due to more durable PVI, and 5) higher BMI and excess alcohol consumption were significantly associated with AT recurrence.

Reduction of acute and late reconnection

Experiments in an animal model have suggested that AI accurately predicts the depth of ablation lesions,[140] and AI has therefore been proposed as a novel marker of ablation lesion quality. Previous retrospective analysis of VisiTag™ data in a multi-center retrospective study identified minimum AI values of 550 and 380 that were predictive of freedom from acute reconnection in the anterior/roof and posterior/inferior regions, respectively.[101] In our previously-published CF-guided paroxysmal AF ablation trial, the PRESSURE study, very similar AI values were also found to predict freedom from late reconnection at protocol-

mandated repeat procedure after 2 months.[102] Although the ablation protocol utilized in both studies was virtually identical, with the exception of the use of AI targets in this study, the fact that study populations are different and the two studies were not concurrent limits direct comparisons, though enrolment of persistent AF patients with larger LA size in the present study would be expected to confer a disadvantage. Nevertheless, the prospective use of AI target values in the current study resulted in a substantial reduction in the proportion of acutely reconnected WACA circles (13% vs. 26%), late reconnected WACA circles (11% vs. 35%) and patients with late reconnection (22% vs. 62%) compared to CF-guided ablation in the PRESSURE study.[119] These findings suggest that the use of Ablation Index-guided ablation may result in more durable PVI compared to CF-guided ablation.

These results are also consistent with our previous findings that the use of Ablation Index-guided ablation is more likely to be associated with a significant reduction in ATA recurrence compared to CF-guided ablation, possibly due to creation of better quality lesions as suggested by a greater impedance drop.[103] Recently, Taghji et al have also demonstrated improved clinical results with the use of AI-guided PVI in a cohort of patients with paroxysmal AF.[105] The wider reproducibility of this strategy is now being tested in a multicenter study of paroxysmal AF patients (ClinicalTrials.gov; Unique Identifier: NCT03062046).

Despite the reduction in acute reconnection with AI-guided ablation, a predilection for this phenomenon was still seen in the right posterior regions. This finding may be related in part to the inability to deliver therapeutic lesions (AI target of 400) on the posterior left atrial wall whenever a significant rise in the oesophageal temperature was encountered during the initial RF ablation.

Carinal ablation

There was a greater need for carinal ablation, especially on the right side, to achieve initial PVI, and the intervenous carinae were also common sites for both acute and late reconnection. This is very likely to be related to the relatively large LA size in the study group, and may also be explained by a recent study using computed tomography that demonstrated that the carinae are the thickest segments of the PV-LA junction.[156]

Since around half of WACA circles required carina ablation overall, routine ablation of the carinal regions, especially on the right side, could be considered a necessary part of the WACA lesion set in patients with persistent AF. This may be of particular importance in cases where attempts at delivering therapeutic lesions are thwarted by oesophageal temperature rise, or where the right WACA circle is particularly wide because of anatomical reasons such as presence of a dilated left atrium. We believe that the overall improvement in the acute and late reconnection rates with AI-guided ablation along the circumferential WACA lesion sets allowed identification of unablated carinae as the weak links in achieving permanent PVI. It is notable that each carinal region is obligatorily ablated twice during Cryoballoon PVI, and this may partly account for the high durable PVI rates described with this technology.[157]

The overall relationship between acute and late PV reconnection with AI-guided ablation

In keeping with previous findings,[119] the proportion of segments with acute reconnection that exhibited late reconnection at repeat study was not different from the proportion of segments that did not exhibit acute reconnection at the initial procedure, indicating effective re-ablation at these segments. However, the proportion of PVs with acute reconnection that exhibited late reconnection was significantly higher than the proportion of PVs without acute

reconnection. These findings suggest that even with the use of AI-guided ablation, there may be an additional impediment to delivering effective ablation in some persistent AF patients, such as the presence of thicker or more fibrotic tissue. This merits further investigation.

Freedom of ATA recurrence and its relation to early recurrence after AI-guided ablation

Freedom from ATA recurrence was noted in 80% of patients, and sinus rhythm was maintained at 12 months in 95%, with only 4 patients started on antiarrhythmic drugs, including beta-blockers, during the outcome period. Although this is a small sample size, these outcomes are noticeably better than the reported outcomes of catheter ablation for most persistent AF trials, some of which used additional ablation strategies to PVI. The reported freedom from ATA at 12 months in these studies were 56-70% and 60-88% with and without intensive ECG monitoring, respectively. [1,7]

As shown in table 5-4, the PRAISE study clinical outcomes are comparable to those of two other published studies that prospectively used AI with similar regional targets (550 for anterior and 400 for posterior left atrial regions) for AF ablation. This is despite the fact that the PRAISE study used a PVI-only strategy in the more challenging persistent AF population.[103,105]

Only two patients with early recurrence of ATA during blanking period had to undergo re-isolation for late PV reconnection at repeat study. These two patients did not develop late recurrence of ATA during the study follow up period. Therefore, early recurrence of ATA was not a significant predictor of late reconnection of pulmonary veins with Ablation Index-guided ablation, but rather resulted from non-pulmonary vein causes for ATA recurrence.

Relation between ATA recurrence and late PV reconnection at repeat study

The freedom from late ATA recurrence at 12 months in patients who had a single Ablation Index-guided PVI ablation was not significantly different from that of patients who had redo ablation for late ATA recurrence (81 % vs.75%, *P*= 0.69). In contrast, with CF-guided ablation we had observed that a strategy of a routine repeat electrophysiology study to assess and ablate late reconnection of pulmonary veins provided significant improvements in freedom from late ATA recurrence.[80]

Only one (13%) of the 8 patients who had ATA recurrence was found to have late PV reconnection at repeat study. This suggests that in the remaining patients with ATA recurrence, representing 7/40 (18%) of all study patients, AF at initial presentation and /or ATA recurrence may have been caused by non-pulmonary vein triggers. This percent is similar to the 11-20% prevalence of non-PV triggers of AF reported in studies involving persistent AF ablation.[158–160]

In addition, ATA recurrence in our study was associated with excess alcohol intake. It has been suggested that alcohol toxicity causes fibrotic changes in the LA myocardium that may facilitate the development of non-PV triggers. [161,162]

With durable pulmonary vein isolation ensured in all study patients at repeat study, the fact that 95% of the study patients were in sinus rhythm by the end of the 12-month follow-up period suggests that most ATA recurrences in our study were likely caused by non-PV triggers leading to paroxysmal rather than persistent pattern of recurrence. This conforms with the previously reported concept that PVs remain the dominant source of the maintenance of persistent AF, with non-PV triggers involved mainly in AF perpetuation.[163]

The 2017 HRS/EHRA expert consensus statement on atrial fibrillation ablation suggested that a strategy for identification and ablation of non-PV triggers may be considered during the

initial ablation and at repeat procedure for recurrence (Class IIb indication), but at the same time advised that the routine use of such strategy still warrants further study.[1]

Table 5-4 Studies that prospectively used Ablation Index with regional targets for AF ablation

	Type of AF	Type of ablation	Contact Force (gram)	Power (watts)	Ablation time (min)	Complication	Freedom from LRAT at 12-month off AAD
PRAISE	PeAF only	WACA only	13-15	20-40	36±9	None	81%
Hussein et al. [103]	PAF PeAF	WACA & Lines	10-14	30-40	42±9	1 phrenic nerve palsy	83%
Taghji et al.[105]	PAF only	WACA only	13-17	30-40	34±10	1 TIA	73%

WACA: Wide antral circumferential ablation, LRAT: Late recurrence of atrial tachyarrhythmia, AAD: Antiarrhythmic drug

High incidence of single procedure durable PVI with Ablation Index-guided ablation

A few previous studies have studied patients with a protocol-mandated repeat electrophysiology study 2-3 month after PVI to investigate the prevalence of late PV reconnection (Table 5-5). The percentage of patients with late reconnection of at least one PV was 60-70% in studies where CF information was not available,[36,91] or where CF-sensing catheters were used without FTI target values.[80] In the EFFICAS II study, where a minimum FTI target of 400gs globally was used to guide ablation, this was reduced to 38%, but the increased efficacy came at the expense of serious complications (tamponade) in 8.3%.[92]

Our durable PVI rate of 93% with the use of regional AI targets is the highest reported, and this was achieved without any complications. The durability of PVI in our study is comparable to the small single-center SUPIR study in which at least two 4-minute freezes were delivered to each PV with the second-generation Cryoballoon.[157] However, patients included in that study had PAF, with presumably smaller left atria, there was a 3/21 (14.3%) complication rate and 2/21 (9%) drop-out rate, and assessment for late reconnection was solely with a

circular catheter. A subsequent study of the second-generation Cryoballoon, in which a single 3-minute freeze was delivered to each PV, showed considerably higher rates of late reconnection affecting 27% of PVs in 66% of patients when assessed by both a circular mapping catheter and electroanatomical mapping, as in our study.[164]

Given the fact that a strategy of a routine repeat procedure at 2 months is not feasible in routine clinical practice, the 12-month arrhythmia-free success rate of 81% in patients who did not require ablation at the repeat procedure (n=28) was equivalent to those who required repeat ablation (n=12). This single-ablation procedure outcome is superior to the 66.7% arrhythmia-free single-procedure success rate at 12-months using PVI only in persistent AF patients seen in a recently published systematic review[43] , and likely represents an estimate of what is achievable with a durable WACA-based PVI. Moreover, these results are also consistent with our previously reported results from a wider clinical cohort, albeit in whom the intensity of ECG monitoring during follow-up was not as intensive as in this study.[9]

Table 5-5 Studies that examined late PV reconnection at mandated repeat electrophysiology study following PVI

	EFFICAS I [91]	EFFICAS II [92]	SUPIR [157]	Miyazaki et al. [164]	PRESSURE [80]	PRAISE
Patients, n	46	26	21	32	40	40
Repeat EPS, n(%)	40 (86.9%)	24 (92.3%)	19 (91%)	32 (100%)	40 (100%)	40 (100%)
Population	PAF	PAF	PAF	PAF	PAF	PeAF
Ablation Tools	Contact Force/ 3D Mapping	Contact Force/ 3D Mapping	Second-generation Cryoballoon	Second-generation Cryoballoon	Contact Force / 3D Mapping	Contact Force/ 3D mapping
Technique	Blinded to CF	CF & FTI targets	2x 4-min freezes	Single 3-min freeze	CF & EGM targets	AI targets
Complications, n(%)	0	2 (7.7%)	3 (14.3%)	1 (3.1%)	1 (2.5%)	0
Late PV Reconnection						
By Patients, n(%)	26/40 (65%)	9/24 (38%)	4/19 (21%)	21 (66%)	25/40 (62%)	8/36 (22%)
By PVs, n(%)	44/160 (28%)	14/91 (15%)	7/75 (9%)	34 (27%)	41/160 (26%)	11/147 (7%)

EPS: Electrophysiology study, PV: pulmonary vein, CF: Contact force, EGM: Electrogram, PAF: Paroxysmal atrial fibrillation, PeAF: Persistent atrial fibrillation

Factors associated with late ATA recurrence

Higher BMI and excess alcohol consumptions (>30g/week) were found to be associated with late ATA recurrence following catheter ablation. There findings are consistent with previous published work.[165,166]

Our study findings therefore support recommendations that AF patients should pursue healthy lifestyle modifications, such as weight reduction and avoidance of excess alcohol, to facilitate rhythm control following AF ablation.[161]

Limitations

The study is not a randomized controlled study and therefore direct comparisons with CF-guided ablation may not be quite straightforward. Secondly, despite the absence of complications in this study across the three centers, the study size is too small to provide definitive safety assessment of Ablation Index guided ablation strategy. However, between Jan 2015 and April 2018, our electrophysiologists at Liverpool Heart and Chest Hospital performed 542 AF ablation procedures guided by Ablation Index targets for 385 de novo and 157 redo cases. In these cases, the following major complications were observed: two cardiac tamponades (both caused by left atrial perforation with the mapping catheter before application of RF energy), two hematomas delaying hospital discharge, and one transient ischemic attack with full neurological recovery. There were no cases of phrenic nerve palsy, atrio-oesophageal fistula, or stroke. These findings are also consistent with our previously published early experience with AF ablation guided by these same Ablation Index targets.[103]

Because of protocol violation, 4 WACAs, and the corresponding 4 patients, had to be excluded from detailed CARTO analysis; however, the clinical results data for the whole cohort of 40 patients were presented.

Finally, in the absence of continuous ECG monitoring, it is possible that brief asymptomatic episodes were missed, thereby overestimating clinical success rates.

Conclusion

The use of Ablation Index regional target-guided ablation results in a low rate of PV reconnection at 22% of patients at repeat electrophysiology study, with 93% of pulmonary veins found to remain durably isolated.

The most common sites of late reconnection were encountered in carinal regions, and therefore ablating these regions pre-emptively during PVI needs to be considered.

An Ablation Index-guided PVI-only strategy in patients with persistent AF of less than 12 months duration, and with no significant structural heart disease provides a high rate of clinical success, potentially due to improved durability of PVI.

5-II AI-guided ablation results in lower prevalence of PV reconnection following PVI compared to CF-guided ablation. A comparison between PV reconnections in the PRAISE and the PRESSURE studies

In the PRESSURE study; 'Pulmonary vein RE-isolation as a routine Strategy: a Success Rate Evaluation (PRESSURE)', forty consecutive patients who were randomized to a repeat procedure two months following CF-guided PVI in the study (ClinicalTrials.gov; Unique Identifier: NCT01942408) formed the control group.[80] Please Appendix I for the PRESSURE study protocol. Whilst the PRAISE study, as previously discussed, included patients with persistent AF, the PRESSURE study included patients with PAF. In all 80 patients in both study groups the initial and the repeat ablation strategies and equipment were identical other than the use of AI targets in the former group (AI-guided group) compared to CF-guided ablation in the Later (CF-guided group).[102] As with the PRAISE study, the PRESSURE study was also approved by the individual institutional and national ethics committees, as well as monitored by Data Monitoring and Safety Committees and each patient provided written informed consent prior to participation.

Localization of sites of reconnection in the PRESSURE study patients

As in the PRAISE study, each WACA circle was divided into six potential reconnection sites (roof, 2 anterior, inferior, and 2 posterior). We then categorized these 6 sites into 2 segments per WACA circle according to the regional AI targets used for AI-group: anterior/roof and posterior/inferior segments (Figure 5-1). FTI and AI values were recorded for each site.

Results

A comparison between the demographic and procedural data for the 80 patients across the 2 groups are presented in Table 5-6. The PRAISE patient cohort was comprised of patients with persistent AF, while the PRESSURE trial involved patients with PAF,[80] accordingly, the mean LA size was larger and mean LV function was lower in AI-group as compared to CF-group.

For the PRESSURE study patients, an additional 3220 VisiTags™ were analyzed individually. The mean number of VisiTags™ per patient was significantly lower in AI-group (69±12 vs. 81±16, *P*<0.001), as was the mean ablation time (36±9 vs. 43±9 minutes, *P*<0.001). In addition, the mean CF in AI-group of 13±2g was statistically lower than that in CF-group (14±3g, *P*=0.049). No complications occurred in AI-group, whereas one complication (right phrenic nerve palsy that recovered during follow-up) occurred in CF-group (*P*=0.30). No complications occurred in any of the 80 repeat procedures across the two groups.

Per protocol analysis was carried out for the AI-group as described in Section 5-I.

Acute PV isolation and acute PV reconnection in AI and CF-groups (Table 5-7)

Acute PV isolation and acute PV reconnection in the AI-group has been previously described in Section 5-I. In the CF-group, the right lower PV in 2 patients could not be isolated at the posterior aspect due to oesophageal temperature rise. These 2 sites/WACAs/patients were excluded from acute reconnection (ARC) analysis but, as late reconnection was seen at other sites within the same WACA circle in these 2 patients,

both patients and WACAs (but not sites) were included in the late PV reconnection analysis.

Significantly fewer patients in CF-group required a carina line for initial PV isolation (3/78 (4%) WACAs in 2/38 (5%) patients, *P*=0.017).

The incidence of acute PV reconnection in AI-group was significantly lower than in CF-group in terms of proportion of patients (28% vs. 53%, P=0.0310) and WACAs (13 % vs. 27%, P=0.012), with a strong trend seen for WACA sites (3% vs. 6%, P=0.061).

Late PV reconnection in AI and CF-groups at repeat electrophysiology study (Table 5-7)

Late PV reconnection in the AI-group has been previously described in Section 5-I. The incidence of late PV reconnection in the AI-group was significantly lower than in the CF-group in terms of proportion of patients (22% vs. 62%, *P*<0.001), WACAs (11% vs. 35%, *P*<0.001), and WACA sites (3% vs. 11%, *P*<0.001).

Table 5-7 and Figure 5-5 show comparisons between the proportions of ARC and LRC in the AI and CF-groups.

Table 5-6: Demographic and procedural Data for AI-group and CF-group

	AI-group (n = 40)	CF-group (n = 40)	*P value*
Age, years	61 ± 8	58 ± 12	0.25
Male (n, %)	30 (75%)	24 (60%)	0.15
Left atrial diameter, mm	43 ± 5	39 ± 5	<0.001
LV Ejection fraction >55%	32 (80%)	40 (100%)	0.005
Hypertension (n, %)	12 (30%)	14 (35%)	0.63
Diabetes mellitus (n, %)	3 (8%)	0 (0%)	0.24
CHA2DS2Vasc Score	1.2 ± 1.3	1.6 ± 1.2	0.78
Antiarrhythmic drugs prior to ablation	20 (50%)	22 (55%)	0.82
Procedure time, minutes	158 ± 34	164 ± 34	0.4
Ablation time, minutes	36 ± 9	43 ± 9	<0.001
Fluoroscopy time, minutes	12 [8 – 14]	11 [8–16]	0.80
General anesthesia (n, %)	39 (98%)	31 (78%)	0.11
Interval between procedures, days	64 ± 6	62 ± 6	0.19
Mean FTI (gram.seconds)	327 ± 77	342 ± 106	0.5
Mean AI	486 ± 42	421 ± 43	<0.001

Table 5-7 Comparison between the Prevalence of Acute and Late Pulmonary Vein Connections in AI and CF-groups

	AI-group	CF-group	*P* value
Acute PV reconnection			
- By Patients, n (%)	10/36 (28%)*	20/38 (53%)**	0.030
- By WACA circle, n (%)	10/76 (13%)*	21/78 (27%)**	0.012
- By sites of potential reconnection, n (%)	15/456 (3%)*	28/478 (6%)**	0.061
Late PV reconnection			
- By Patients, n (%)	8/36 (22%)*	25/40 (62%)	<0.001
- By WACA circle, n (%)	8/76 (11%)*	28/80 (35%)	<0.001
- By sites of potential reconnection, n (%)	13/456 (3%)*	51/478 (11%)**	<0.001

* Four WACAs with their relevant 4 patients and 24 sites were excluded because of protocol violation.
** Two sites with their relevant WACAs and patients were excluded because of inability to isolate them during initial ablation. As these 2 patients had late reconnection at other sites within the same WACA, the 2 patients and WACAs are included in this analysis.

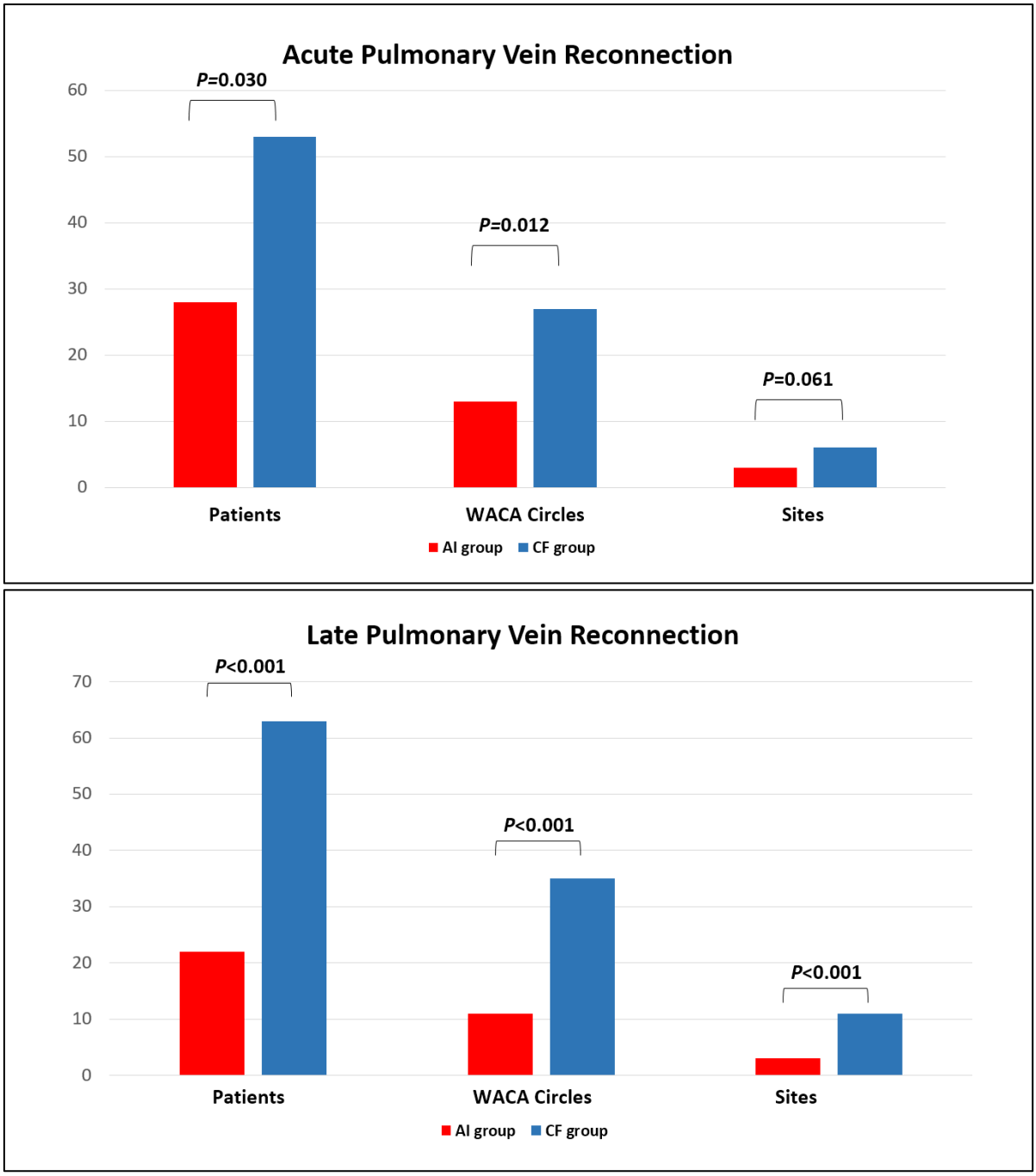


Figure 5-5 Bar charts showing comparisons between the proportions of acute (upper panel) and late (lower panel) reconnection in AI and CF-groups in terms of patients, WACAs, and sites of reconnection.

Discussion

Main Findings

Acute and late reconnection following AI-guided ablation were significantly lower compared to CF-guided ablation despite significantly shorter ablation times, lower average CF values, and significantly larger left atria.

Therefore, as we anticipated the prospective use of these AI target values in the current study resulted in a substantial reduction in both acute PV reconnection, by about half, and late PV reconnection, by about two-thirds, compared to CF-guided ablation, indicating that AI-guided ablation results in more durable PVI. These results are consistent with our previous findings that the use of this strategy is associated with a significant reduction in atrial tachyarrhythmia recurrence compared to CF-guided ablation, possibly due to creation of better quality lesions as suggested by a greater impedance drop.[103]

A recent study in which 50 consecutive paroxysmal AF patients underwent PVI using a contact force-sensing catheter targeting an interlesion distance of 6mm or less and Ablation Index of 400 or more and 550 or more at posterior and anterior walls, respectively. Results were compared to another group of 50 patients who underwent conventional contact force-guided catheter ablation. The procedure time and RF time per WACA circle were shorter, and incidence of adenosine-proof acute PVI was higher in the Ablation Index-guided group compared to the contact force-guided group. At 12 months, single-procedure freedom from AT was 94% in Ablation Index-guided group compared to 80% in the contact force-guided group ($P< 0.05$). [104]

Limitations in the comparison between AI-guided and CF-guided ablations in the PRAISE and the PRESSURE studies, respectively

The patient populations in the two groups were different with AI-group consisting of patients with persistent AF and CF-group comprising of patients with PAF. However, the superior acute and late reconnection rates observed in the AI-group, despite a significantly larger LA size in that group, suggests that the results of an AI-guided strategy may be even better in a PAF population. Because the two groups were recruited in a consecutive rather than parallel fashion, a temporal bias related to institutional and operator learning curves cannot be excluded. However, all procedures were performed by experienced electrophysiologists in established high-volume centers, using identical equipment and an identical ablation strategy, except for ablation lesion delivery guidance; Ablation Index in the AI-guided group and CF in the CF-guided group.

Conclusion

Ablation Index-guided ablation is associated with a significant reduction in both acute and late PV reconnection at repeat electrophysiology study when compared to CF-guided ablation, despite fewer ablation lesions and shorter ablation times.

Chapter 5-III Reverse remodelling of the left atrium following Ablation Index-guided catheter ablation for persistent atrial fibrillation

Introduction:

Animal studies have consistently pointed to the important role of atrial fibrosis in the development and maintenance of atrial fibrillation.[167] LA remodelling resulting from LA fibrosis, occurs more prominently in patients with persistent AF compared to patients with paroxysmal AF,[168] and is associated with increased risk of thromboembolic events.[169] In addition to LA enlargement, LA remodelling due to fibrosis is associated with changes in the electrical characteristic of the LA substrate including increase in the conduction times and decrease in the voltages. [168]

LA structural reverse remodelling following catheter ablation for persistent AF has been found to be associated with improved success rates.[170] However, the reverse remodelling time course, exact pattern and contributing factors are all poorly understood.

Research hypothesis

As discussed earlier in this chapter, the PRAISE study showed that Ablation Index-guided PVI in the persistent AF patients was associated with high incidence of durable PVI and substantial reduction in atrial tachyarrhythmia recurrence. We therefore hypothesised that the PRAISE study patients who underwent PVI in adherence to the study protocol would acheive substantial structural and electrical reverse remodelling at the 2-month follow up EP procedure, regardless of whether early recurrence of atrial tachyarrhythmia occurred or not.

Methods

Study population:

This study is aposteriori subanalysis of the 40 PRAISE study patients, in which all PRAISE study patients who underwent PVI as per the PRAISE study protocol were intended to be included. Therefore, after exclusion of the four patients with PRAISE study protocol violation and suboptimal LA Carto maps, and one patient because of corrupt electronic archive of his 3D mapping study, the remaining 35 PRAISE study patients were included in this study.

As this study is a subanalysis of the PRAISE study, the protocol of initial ablation procedure, repeat EP procedure after 2-month and follow up in this study is the same as that of the PRAISE study. All antiarrhythmic drugs were stopped four weeks after the initial ablation procedure.

The ECGs of the 35 patients (n=9,484) recorded during the follow-up period were analysed by two experienced electrophysiologists (AH, VC) who were blinded to the CARTO data.

LA volumes, linear dimensions, conduction velocities and bipolar voltages were measured from LA Carto maps both at the initial ablation procedure and the 2-month follow up EP procedure as detailed below.

Offline analysis:

Detailed offline analysis of the 70 LA maps was performed by two experienced observers (BM/AH).

The following characteristics were determined:

LA volume and dimensions:

The CARTO system provides automated assessment of the volume for each collected map. To allow for standardization across maps, respiratory data were excluded. The distal parts of the left atrial appendage (LAA) and the PVs were also excluded, retaining only the proximal 1 cm of each structure. LA dimensions were measured manually in orthogonal planes using the distance measuring tool in CARTO V3, as described in Figure 5-6. The antero-posterior (AP) dimension was measured as is the straight distance between the anterior and posterior wall midway between the left- and right-sided PVs. The LA height dimension was measured as the straight distance between the LA roof and the lowest inferior wall point midway between the left- and right-sided PVs.

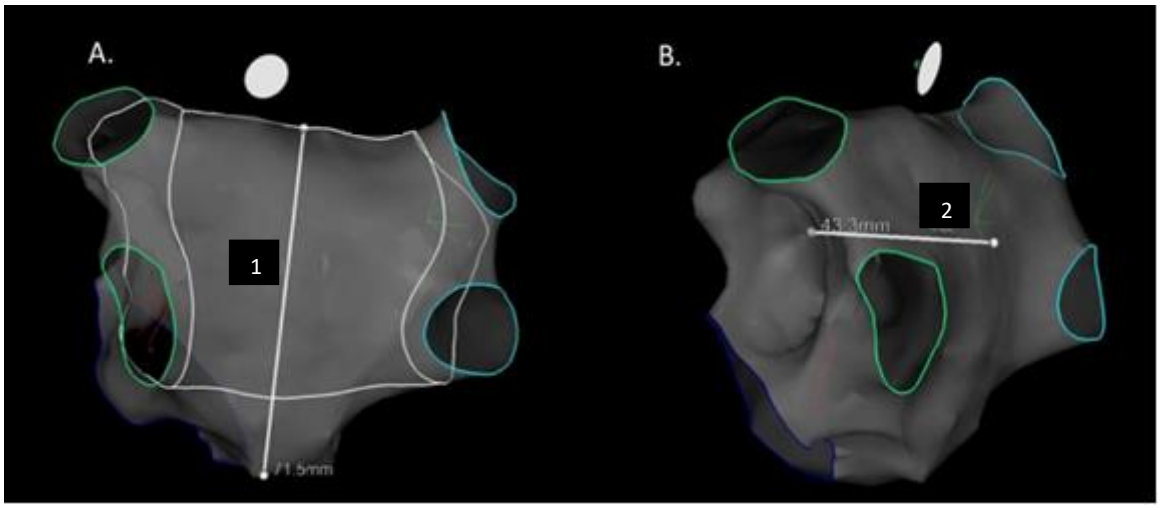


Figure 5-6 LA measurements. A: PA view B: left lateral view. 1: LA Height, 2: Antero-posterior dimension.

LA voltage:

As previously discussed in Chapter 4, LA voltage mapping was created from the points collected by the Lasso and contact force- sensing catheters using the ConfiDense (Carto 3, Biosense Webster, Inc.) mapping module.

Only LA body voltage data were analysed whilst the isolated PV areas distal to the WACA ellipse were excluded from voltage analysis. The Tissue Proximity Indicator filter was systematically applied offline, and therefore all the points collected by the circular mapping catheter that were not found to be in contact with the shell were excluded.

LA body bipolar voltages were measured at 80,612 points by automatically measuring the peak-to-peak bipolar electrogram signals, filtered at 30 to 250MHz. Moreover, in 23 patients of those included in this study each individual electrogram in the corresponding 46 maps 58,326 points were also manually assessed for quality by an experienced observer (BM), as previously published.[171]

Atrial conduction time:

Atrial conduction time was assessed along a decapolar catheter with 2-5-2mm spacing positioned within the coronary sinus. [172] The conduction times between two alternate bipoles (between 5-6 and 1-2, or between 7-8 and 3-4), during constant pacing from the coronary sinus ostium at a cycle length of 600 ms, were measured offline using on-screen digital callipers at a sweep speed of 200 mm per second. The local activation time (LAT) was manually annotated to the peak of the first deflection on bipolar electrograms. Conduction time was averaged over 3-5 beats during stable pacing capture. Conduction

velocity was calculated by dividing the distance between alternate bipoles (18 mm) by the conduction time.

Reverse LA remodelling:

For each patient, the value of each of the following LA remodelling criteria measured during the first procedure; LA volume and dimensions, LA voltage and LA conduction velocity, was compared with the corresponding value in the second procedures. Reverse remodelling was defined as ≥15% decrease in LA volume, [173] ≥5% increase in bipolar voltage and a ≥5% higher conduction velocity. Patients who exhibited reverse LA remodelling in all three criteria were called reverse remodelling super-responders.

Statistical analysis:

All continuous variables with a normal distribution are expressed as mean ± standard deviation. Variables with a skewed distribution are expressed as median (Q1-Q3). Categorical variables are expressed as number of subjects (%). Comparisons of normally distributed continuous variables were made using analysis of variance, Student's *t*-test or paired *t*-test as appropriate. Whilst, nonparametric variables were compared using a Wilcoxon test or a Fisher's exact test as appropriate. A *P* value of less than 0.05 was considered statistically significant.

Results

Patient demographics and ablation results (Table 5-8)

The mean duration of persistent AF before the initial procedure was 9 ± 3 months. Twenty (57%) patients required cardioversion to sinus rhythm before the start of the initial ablation procedure. Whilst the remaining 15 (43%) were in sinus rhythm at the start of the initial ablation, with a median of 180 (96-341) days between the last cardioversion and the ablation procedure.

During the initial ablation procedure LA body voltage mapping yielded 1,180 ± 476 points per map. Acute Isolation of all PVs was successfully achieved in all 35 (100%) patients. Four (11%) patients had additional CTI ablation for previously documented typical atrial flutter. The mean total ablation time was 36 ± 8 min.

Eleven (31%) patients experienced early recurrence of ATA, 5 (45%) of them had the recurrence in the period between the two procedures, 4 (80%) of whom required direct shock cardioversion and one reverted to sinus rhythm spontaneously.

Repeat electrophysiological studies were performed with a mean of 64 ± 6 days following the initial ablation procedures. LA body voltage mapping during the repeat procedures yielded 1,124 ± 490 points per map. Six (17%) patients were found to have evidence of late PV reconnection, all of whom underwent successfully reablation after LA mapping had been completed.

Starting from the end of the 3-month blanking until the end of 12-month follow-up period, 6 (17%) patients had evidence of late ATA recurrence in their daily ECG monitoring.

Table 5-8 Demographic data and ablation outcomes for the study group

Clinical characteristics at the first procedure	Value
Age, years	61 ± 7
Male Gender, n (%)	26 (74%)
BMI, kg/m^2	29.2 ± 4.3
CHA_2DS_2-VASc	1 (0-2)
Mild Heart dysfunction, n (%)	6 (17%)
Diabetes mellitus, n (%)	1 (3%)
Hypertension, n (%)	11 (31%)
Persistent AF duration, months	9 ± 3.1
Additional CTI ablation, n (%)	4 (11%)
Use of Antiarrhythmic drugs	12 (34%)
Amiodarone, n (%)	8 (22.6%)
Flecainide, n (%)	3 (8.6%)
Dronedarone, n (%)	1 (2.8%)
Catheter Ablation results	
Early recurrence of ATA, n (%)	11 (31%)
Late recurrence of ATA, n (%)	6 (17%)
Late PV reconnection, n (%)	6 (17%)
Radiofrequency Duration, *min*	36 ± 8

ATA: Atrial tachyarrhythmia, BMI: Body Mass Index; CTI: Cavotricuspid isthmus ablation; PV: Pulmonary vein

Left atrial electrophysiological and anatomic data (Tables 5-9)

Left atrial electrophysiological and anatomic data at baseline and at repeat procedure are shown in Table 5-9.

Table 5-9: Left atrial electrophysiological and anatomic mapping data at baseline and repeat procedure

	Baseline (n=35)	Repeat procedure (n=35)	*P* value
LA volume, ml	137 ± 32	118 ± 31	<0.001
Indexed LA volume, ml/m^2	65 ± 14	56 ± 14	<0.001
LA dimension, mm			
Antero-posterior dimension	40.4 ± 4.8	37.6 ± 6.6	0.002
Height	61.5 ± 8.9	60.2 ± 7.6	0.35
LA body voltage, mV	1.99 ± 0.63	1.95 ± 0.59	0.70
LA conduction velocity, m/s	0.79 ± 0.16	0.87 ± 0.18	0.04

LA: Left atrium

LA dimensions and volume (Tables 5-9 and 5-10)

As shown in table 5-9, the mean left atrial antero-posterior dimension was significantly reduced at the repeat electrophysiology procedure.

In addition, the mean absolute and indexed LA volumes for all study patients were significantly lower at repeat procedure compared to initial procedure (118 ± 31 vs. 137 ± 32 ml, *P*<0.001; and 56 ± 14 vs. 65 ± 14 ml/m^2, *P*<0.001, respectively). A decrease in the LA volume index between the two procedures was noted in 31 (89%) patients. In these patients there was a certain trend, that was not quite statistically significant, towards less prevalence of late PV reconnection at repeat study when compared to the 4 (11%) patients in whom there was no decrease in LA volume index (4/31 (13%) vs 2/4 (50%), *P*=0.06). There was no significant relation between the prevalence of late ATA recurrence in patients who had and those who did not have reduction of LA volume index (6/31 (19%) vs. 0/4 (0%), *P*=0.33).

Of the 31 patients who had reduction in the LA volume index between the two procedures, only 15 (43%) met the definition of reverse remodelling with ≥15% reduction

in LA volume index. Again, there was no statistically significant differences in the prevalence of either late PV reconnection or late ATA recurrence between patients who had and those who did not have LA volume reverse remodelling, as shown in table 5-10. Likewise, there was no statistical difference in the occurrence of LA volume reverse remodelling between patients with durable PVI and patients with late PV reconnection (12/29 (41%) vs. 3/6 (50%), *P*=0.70).

Patients with LA volume reverse remodelling had shorter duration since their first documented AF episode (12 (9-20) vs. 25 (19-55) months, *P*=0.045). These patients were less likely to experience early ATA recurrence (0 (0%) vs. 11 (55%) patients, *P*<0.001), and had significantly lower body mass index (27 (25-29) vs. 33 (26-35) kg/m2, *P*=0.004).

Table 5-10 Demographic and procedural parameters by volume reverse remodelling outcome

	No LA volume reverse remodelling (n = 20)	LA volume reverse remodelling (n = 15)	*P* value
Male, n (%)	7 (35%)	13 (87%)	0.16
Age, *years*	61 (56-67)	61 (54-69)	0.96
BMI, kg/m^2	33 (26-35)	27 (25-29)	0.004
CHA_2DS_2-VASc score	1(0-2)	1(0-1)	0.3
Duration since first of AF episode, *months*	25 (19-55)	12 (9-20)	0.045
Indexed LA Volume at initial procedure, ml/m^2	58 (49-72)	66 (59-82)	0.096
Indexed LA Volume at repeat procedure, ml/m^2	59 (49-66)	47 (45-57)	0.15
RF duration, *min*	34 (30-42)	36 (30-42)	0.93
Early ATA recurrence, n (%)	11 (55%)	0 (0%)	<0.001
Late PV reconnection, n (%)	3 (15%)	3 (20%)	0.71
Late ATA recurrence	4 (20%)	2 (15%)	0.62

ATA: Atrial tachyarrhythmia; LA: Left Atrium; ATA: Atrial tachyarrhythmia; BMI: Body Mass Index; SR: sinus rhythm. Volume reverse remodelling was defined as ≥15% decrease in volume; PV: Pulmonary vein.

Conduction Velocity (Table 5-11)

The mean of LA conduction velocities for all study patients was significantly greater at the 2-month repeat study (0.93 ± 0.18 vs. 0.69 ± 0.17 m/s, *P*<0.001). Even after excluding the 12 patients who had their anti-arrhythmic drug therapy changed between the two procedures, LA conduction velocity remained significantly greater at the 2-month repeat study (0.90 ± 0.16 vs. 0.74 ± 0.17 m/s, *P*=0.007).

There were no significant differences between the clinical and procedural characteristics between patients who had and those who did not have conduction velocity reverse remodelling, as shown in table 5-11.

Table 5-11 Demographic and procedural parameters by conduction reverse remodelling outcome

	No conduction reverse remodelling (n = 12)	Conduction reverse remodelling (n = 23)	*P* value
Male, n (%)	10 (83%)	20 (87%)	0.96
Age, *years*	61 (54-66)	61 (58-68)	0.49
BMI, kg/m^2	28 (26-33)	28 (26-33)	0.92
CHA_2DS_2-VASc score	1(0-2)	1(0-2)	0.67
Duration since first of AF episode, *months*	20 (12-48)	21 (13-32)	0.91
Early ATA recurrence, n (%)	2 (17%)	9 (39%)	0.17
Indexed LA Volume at initial procedure, ml/m^2	58 (52-71)	66 (57-72)	0.17
Change AAD after initial procedure, n (%)	2 (17%)	12 (52%)	0.57
Late PV reconnection, n (%)	2 (17%)	4 (17%)	0.96
Late ATA recurrence, n (%)	2 (17%)	4 (17%)	0.96

ATA: Atrial tachyarrhythmia; LA: Left Atrium; AAD: Anti Arrhythmic Drugs; BMI: Body Mass Index; SR: sinus rhythm. Conduction reverse remodelling was defined as ≥5% higher conduction velocity. PV reconnection: Pulmonary vein reconnection documented at repeat electrophysiological study at 2 months.

Left atrial body voltage (Table 5-12)

For all study patients, there was no significant difference between the mean LA body voltage values at the initial and repeat procedures (1.99 ± 0.63 vs. 1.95 ± 0.59 mV, *P*=0.70). As shown in Table 5-12, there were no significant differences between the clinical and procedural characteristics between patients who had and patients who did not have LA body voltage reverse remodelling.

Table 5-12 Demographic and procedural parameters by voltage reverse remodelling outcome

	No voltage reverse remodelling (n = 23)	Voltage reverse remodelling (n = 12)	*P* value
Male, n (%)	18 (78%)	9 (75%)	0.39
Age, *years*	61 (56-65)	64 (54-69)	0.47
BMI, kg/m^2	29 (26-33)	27 (25-33)	0.71
CHA_2DS_2-VASc score	1(0-2)	1(0-3)	0.33
Duration since first of AF episode, *months*	22 (12-49)	15 (10-32)	0.85
Early ATA recurrence, n (%)	8 (35%)	3 (25%)	0.57
Indexed LA Volume at the initial procedure, ml/m^2	59 (52-71)	66 (60-76)	0.13
Late PV reconnection, n (%)	3 (13%)	3 (25%)	0.39
Late ATA recurrence, n (%)	4 (17%)	2 (17%)	0.96

ATA: Atrial tachyarrhythmia; LA: Left Atrium; BMI: Body Mass Index; SR: sinus rhythm. Voltage reverse remodelling was defined as ≥5% increase in mean bipolar voltage, at 2 months. PV reconnection: Pulmonary vein reconnection documented at repeat electrophysiological study at 2 months.

Relationship between the various types of LA reverse remodelling

LA electrical reverse remodelling occurred in the majority (25/35 (71%)) of patients, who either had LA conduction velocity reverse remodelling (23/35 (66%)) only, LA voltage reverse remodelling (12/35 (34%)) only or both (10/35 (29%)).

There were no significant correlations between LA structural reverse remodelling and either LA conduction velocity reverse remodelling or LA voltage reverse (Pearson *r*=0.02, *P*=0.92, and Pearson *r*=0.23, *P*=0.19, respectively).

Reverse remodelling super-responders (Table 5-13)

Six (17%) patients were identified as reverse remodelling super-responders. These patients tended to have shorter duration of AF compared to the rest of the study patients (14 (9-16) vs. 21 (12-48), *P*= 0.05)

There was no significant difference in the prevalence of late PV reconnection between super-responders and non-super-responders (2 (33%) vs. 4 (14%), *P*=0.25). None (0%) of the super-responders had either early or late ATA recurrence, whilst in the remaining 29 (83%) non-super-responder patients; 11 (38%, *P*=0.15) had early ATA recurrence, 6 (21%, *P*=0.56) had late ATA recurrence, and 13 (49%, *P*=0.04) had either early or late ATA recurrence. As shown in table 5-13, super-responders tended to have shorter AF duration and less prevalence of early ATA recurrence, however, both findings did not reach statistical significance.

Table 5-13 Demographic and procedural parameters for super-responders

	Reverse remodelling non-super-responders (n=29)	Reverse remodelling super-responders (n=6)	*P* value
Age, years	64 (56-68)	61 (65-67)	0.57
Male, n (%)	24 (83%)	5 (83%)	0.97
BMI, kg/m2	29 (26-33)	26 (25-27)	0.11
CHA_2DS_2-VASc score	1 (0-2)	1 (0-1)	0.46
Duration since first of AF episode, *months*	21 (12-48)	14 (9-16)	0.05
Indexed LA Volume at the initial procedure, ml/m^2	65 (63-73)	65 (62-70)	0.09
Early ATA recurrence, n (%)	11 (38%)	0 (0%)	0.07
Late PV reconnection, n (%)	4 (14%)	2 (33%)	0.26
Late ATA recurrence, n (%)	6 (21%)	0 (0%)	0.23

ATA: Atrial tachyarrhythmia; LA: Left Atrium; BMI: Body Mass Index**;** PV: Pulmonary vein. Volume reverse remodelling was defined as ≥15% decrease in volume; Conduction velocity reverse remodelling was defined as ≥5% higher conduction velocity; Voltage reverse remodelling was defined as 5% increase in bipolar voltage. Super-responder patients were defined as patients who exhibited improvement on all LA reverse remodelling criteria.

Discussion

To our knowledge, this study is the first study to evaluate early left atrial structural and electrical reverse remodelling in persistent AF patients 2 months following Ablation Index-guided PVI procedure, in a protocol-mandated repeat electrophysiological study. The study findings suggest that 1) reduction of LA volume occurs almost invariably following Ablation-Index guided AF ablation regardless of the presence or absence of durable PVI, 2) there is a trend towards the occurrence of LA structural reverse remodelling following durable PVI 3) structural and electrical remodelling may become evident as early as 2 months following AF ablation, 4) factors that may be associated with LA structural reverse remodelling include shorter AF duration, absence of early ATA recurrence and lower BMI and 5) the occurrence of all 3 types of LA reverse remodelling; structural, conduction

velocity and voltage is associated with complete absence of both early and late ATA recurrences in these patients.

Left atrial structural reverse remodelling

Our results conform with previous studies using non-invasive modalities that showed that LA structural reverse remodelling occurs in a substantial proportion of AF patients following successful AF catheter ablation, as well as following successful electrical cardioversion. In these studies, patients who had LA reverse remodelling were likely to have had successful restoration and adequate maintenance of sinus rhythm following their rhythm restoration procedures. [173,174] Similarly, in our study patients who were found to have LA structural reverse remodelling at the repeat procedure were more likely to have had shorter AF duration, and continuously remained in sinus rhythm following the initial ablation procedure with no evidence of early ATA recurrence. This can be explained by the directly proportional relationship between the duration of AF and the development of LA fibrosis. [168]

On the other hand, 20% of patients of our study patient with LA structural reverse remodelling were found to have late PV reconnection at repeat study.

These findings suggest that the achievement and the early maintenance of sinus rhythm, rather than just the achievement of durable PVI using Ablation Index-guided ablation, were main determinants for LA structural reverse remodelling in our study. This finding may be intuitive because up to 20% of persistent AF cases can be attributed to non-PV triggers. [158–160]

Patients who achieved LA structural reverse remodelling were found to have significantly lower BMI. A study by Shoemaker *et al* found that higher BMI is associated with increased global LA voltage, supporting the concept that obesity results in LA hypertrophy and fibrosis, making reverse remodelling less likely to occur or occurs at a slower rate in obese patients. [175]

Left atrial structural reverse remodelling and ATA recurrence

As previously discussed, a significant finding in our study was the absence of early ATA recurrence in patients who achieved LA structural reverse remodelling. A metanalysis by Jeevanantham *et al* on 17 studies on the effect of radiofrequency catheter ablation of AF on LA size, and volumes found significant decreases in LA diameter and volumes after 3 months or more postablation in patients without AF recurrence, but not in patients with AF recurrence.[176]

Conversely, the achievement of LA structural reverse remodelling in our study patients was not associated with reduction of late ATA recurrence, compared to previous studies that used echocardiography and cardiac MRI to assess the LA size following AF catheter ablation and showed that LA structural reverse remodelling, with significant reduction in LA volume, was predictive of freedom from late ATA recurrence.[177–179] This is likely due to the substantially low prevalence of late ATA recurrence, despite the more intensive ECG monitoring, in our study compared to these studies. [124]

Left atrial electrical reverse remodelling

In our study patients, electrical reverse remodelling evidenced by either increase in LA conduction velocity, LA bipolar voltages or both was noted in the majority of patients 2

months following the initial ablation. However, neither of the two components of LA electrical reverse remodelling was found to have a significant relation to the occurrence of either late PV reconnection or ATA recurrence.

Relation between LA structural and electrical reverse remodelling

There was no significant correlation between LA structural and electrical reverse remodelling in our study patients. A previous study also found that there was no correlation between LA structural and substrate remodelling. [180] Nevertheless, one of the most significant findings in our study is that super-responders who achieved all three types of LA reverse remodelling; conduction velocity, bipolar voltage and structural reverse remodelling, had neither early nor Late ATA recurrence throughout the 12-month duration of the study.

Limitations

This study sample size is relatively small, being a substudy of the PRAISE study that was not powered to study the effects of LA reverse remodelling. In addition, 5 PRAISE study patients had to be excluded because of ablation protocol violation and technical problems, as discussed in the Methods section.

The use of Ablation Index-guided AF ablation in the PRAISE study was associated with substantial reduction in the number of patients with PV reconnection at repeat study. This may have contributed to the lack of a statistically significant relation between late PV reconnection and LA reverse remodelling. The PRAISE study population included patients with relatively low morbidity with less than one year duration of persistent AF, no

significant structural heart disease, and median CHA_2DS_2-VASc score of 1. Therefore, the degree of LA reverse remodelling following AF catheter ablation noted in our study may be more than what is expected to occur in patients with more extensive co-morbidities. Finally, LA reverse remodelling was looked for 2 months following catheter ablation, and this may have been too early to identify other patients who may have achieved LA reverse remodelling later in the course of the study.

Conclusion

Reduction of LA volume occurs almost invariably following Ablation-Index guided PVI. Both structural and electrical remodelling may become evident as early as 2 months following Ablation-Index guided PVI. Factors known to be associated with less likelihood for development of left atrial fibrosis in persistent AF patients including; shorter AF duration, lower BMI and absence of early ATA recurrence, rather than durable PVI alone, are associated with left atrial structural reverse remodelling following Ablation Index-guided PVI.

The occurrence of all 3 types of LA reverse remodelling; structural, conduction velocity and LA voltage, is associated with a low likelihood for ATA recurrence following Ablation Index-guided PVI.

Chapter 5- IV Factors Associated with Regional Late Pulmonary Vein Reconnection after Ablation Index-Guided Ablation in Patients with Persistent Atrial Fibrillation

Introduction

Atrial fibrillation recurrence after successful PVI is typically associated with late PV reconnection detected at repeat electrophysiology study. [1,181] Therefore, maximizing the durability of PVI is critical for prevention of late AF recurrence.[62]

The use of CF–guided PVI in paroxysmal AF patients has improved freedom from AF at 12-month follow up, from 66% to 81%, possibly by creation of more durable ablation lesions.[182] In one of our recent studies, we found a better freedom from AF at 12-month follow up with Ablation Index-guided AF ablation when compared to CF-guided ablation AF ablation (83% vs. 63%). That was supposedly due to the creation of better quality lesions as suggested by the greater impedance drop with Ablation Index-guided AF ablation.[103] Even with that substantial improvement in the clinical outcomes of Ablation Index-guided ablation there appears to be room for more improvement, conceivably by further minimising late PV reconnection.

Therefore, in this study we aimed to investigate the potential factors associated with of pulmonary vein reconnection in AI-guided ablation.

Methods

The study population comprised 40 consecutive patients who underwent AI-guided PVI at 3 sites: Liverpool Heart and Chest Hospital, Liverpool, UK, Freeman Hospital, Newcastle, UK; and Centro Cardiologico Monzino, Milan, Italy. The study was registered prospectively: 'Pulmonary vein Reconnection following Ablation Index guided ablation: a Success Evaluation (PRAISE)' (ClinicalTrials.gov Identifier: NCT02628730). The PRAISE study was approved and monitored by the individual institutional and national ethics committees, as well as Data Monitoring and Safety Committees. Each patient provided written informed consent before both procedures.

Initial ablation procedure

All procedures were performed under general anaesthesia or deep conscious sedation. Vitamin K antagonist treatment was uninterrupted while direct thrombin or Factor Xa inhibitor drugs were stopped 24h pre-procedure. Two transseptal punctures were made using fluoroscopic guidance with additional pressure monitoring, following which intravenous unfractionated heparin boluses were administered to maintain an Activated Clotting Time (ACT) between 250-300s. Trans-oesophageal echocardiography (TOE) was undertaken at the discretion of the operator prior to the procedure to exclude left atrial thrombus or to guide transseptal puncture. If the patient was in AF, electrical cardioversion was performed to restore sinus rhythm. A 3D navigation system (CARTO 3, Biosense Webster, Inc.) was used to create an electroanatomical map of the left atrium (LA) with possible integration with a computed tomography or magnetic resonance

imaging reconstruction of the LA (CartoMerge, Biosense Webster, Inc.). Pulmonary vein isolation was performed by RF delivery in a point-by-point WACA pattern using a Thermocool® SmartTouch™ irrigated tip contact force- sensing RF ablation catheter (Biosense Webster, Inc.) introduced via a non-steerable sheath. The WACAs were created at >10 mm outside the PV ostia, where the local electrograms did not show near-field PV signals. The VisiTag settings were as follows: catheter position stability: minimum time 10 s, maximum range 2 mm; force over time: time 30%, minimum force 5 g; lesion tag size: 2 mm. The RF lesions were contiguous (center-to-center distance <5mm) as confirmed by the overlap of adjacent VisiTag™ lesions. A contact force of between 5 and 40 g was targeted at each site. Power setting was at the individual operator's discretion within the range of 20-40W depending upon the LA segment. Each RF lesion was guided by AI targets: 550 at the thicker anterior wall, and 400 at the thinner posterior wall.[183]

Oesophageal temperature monitoring was performed in all GA cases and RF delivery was stopped promptly as soon as the oesophageal temperature crosses >39 degrees Celsius, even if the target AI value >400 had not been reached. After a minimum of 20 minutes from the last ablation to the WACA lesion set, ipsilateral PVs were rechecked with a circular mapping catheter (Lasso NAV, Biosense Webster, Inc.) to determine if spontaneous acute reconnection (ARC) of PV has occurred, and these sites were tagged. If overt PV reconnection has not occurred, a bolus of intravenous adenosine (12-18mg) was administered to unmask any sites of dormant conduction. Further ablation was performed at any sites of overt or adenosine-induced ARC to achieve PVI once again.

Repeat EP study

All 40 patients underwent mandated repeat procedure, regardless of AF recurrence, eight weeks after the initial procedure. Peri-procedural, intra-procedural anti-coagulation management and performing two transseptal punctures were identical to the initial procedure, as was creation of a left atrial map using CARTO and integration with the original MRI reconstruction of the LA where available. Each PV was then assessed in turn for late reconnection with a Lasso catheter and reconnection site(s) were recorded for subsequent analysis. All reconnection sites were re-ablated using a Thermocool® SmartTouch™ irrigated RF ablation catheter, until PV isolation was successfully achieved. If the patient remained in AF after achieving isolation of all PVs, electrical cardioversion was performed, and no additional ablation was performed.

Localisation of Reconnection for Studying Potential Associated factors

To analyse the effect of using different AI target values for the various LA regions, each WACA circle was divided into six potential reconnection segments (roof, 2 anterior, inferior, and 2 posterior). For each segment we obtained the following radiofrequency (RF) ablation parameters; mean time of RF application, temperature, delivered power, impedance drop, CF, FTI, and ablation index (AI). Ablation lesions with AI values < 550 for the anterior segments and <400 for the posterior segments were considered subtherapeutic.

In addition, in all patients we measured the transverse, longitudinal and circumference of all WACA circles, and the LA Carto volumes after excluding the pulmonary veins.

We then assembled the 12 segments in each patient into four regions according to the regional AI targets: right and left anterior segments and right and left posterior segments, allowing ease of comparison (Figure 5-7).

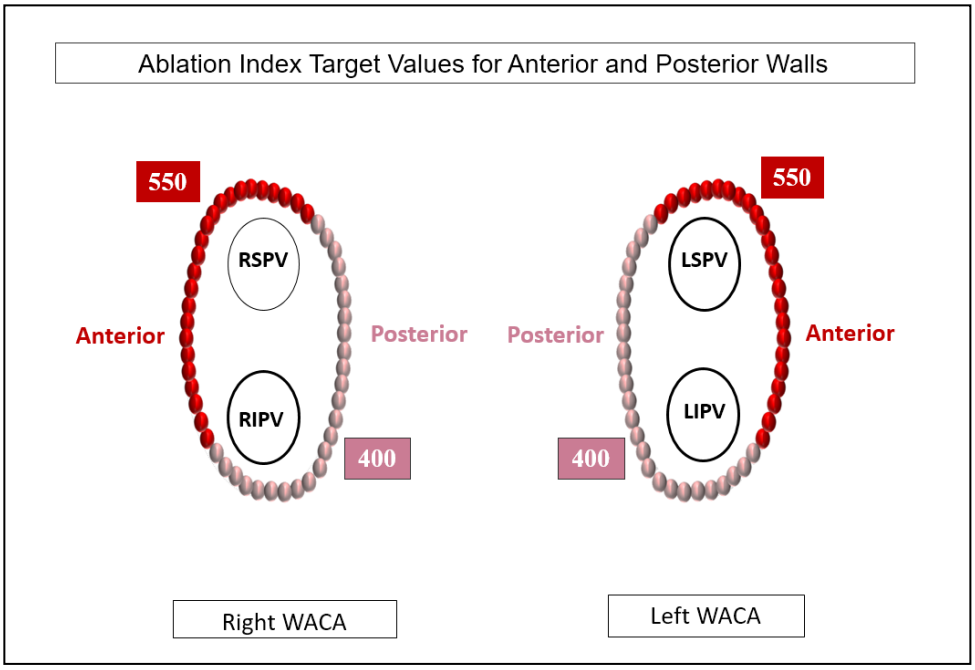


Figure 5-7 Diagram showing the anterior and the posterior segments and the AI target values used for each of these regions. The red dots represent ablation lesions with AI target values ≥550 while the pink dots represent AI target values ≥400 but <550.

Four WACAs (2 left-sided and 2 right-sided), with the relevant 4 patients, 8 PVs and 24 potential reconnection segments, were excluded from PV reconnection analysis because of protocol violation: 2 because of the presence of >8 gaps in the WACA circle, 1 because segmental ostial (rather than WACA) PVI was performed, and 1 because of the inability to deliver AI-guided ablation due to equipment failure.

Right and left WACA circumferences were calculated by the approximation of the WACA ellipse to a circle, averaging the measured transverse (d_1) and longitudinal (d_2) diameters and using the equation for the circumference of a circle as shown in the formula below.

$$WACA\ Circumference = \pi X (d_1 + d_2) / 2 = 1.57 X (d_1 + d_2)$$

In addition, the system-calculated LA volume (Carto volume) was obtained from the 3-dimensional electroanatomical map after excluding the pulmonary veins and LA appendage.

All ablation lesions underwent detailed analysis for ablation time, contact force, power, catheter-tip temperature, impedance drop, force-time integral and Ablation Index values.

Statistical analysis

Continuous variables were assessed for normality using the Kolmogorov-Smirnov test, and are presented as means ± standard deviations or medians and interquartile range (25th percentile – 75th percentile) as appropriate. Student's t-tests or the Mann–Whitney U-test were used for group comparison. Categorical variables are presented as frequency and percentage and were compared using χ 2 or Fisher's exact tests where necessary. All tests were two-sided and a $P < 0.05$ was considered statistically significant. Univariate comparisons were used to study the effect of various independent variables on the procedural outcomes. Statistical analysis was performed using SPSS (version 24, IBM Corp., Armonk, NY, USA).

Results

Demographics and Procedural Data

The demographic and procedural data for the 40 patients are included in Table 5-14. During the initial ablation procedure, first pass isolation was achieved in 63/76 (83%) WACA circles in 24/36 (67%) patients. After 20 minutes of waiting and the use of adenosine, ARC was found in 10 (28%) patients affecting 14 (10%) PVs in 10 (13%) WACAs at 15 (3%) segments. The majority of which, 13/15 (87%), were spontaneous reconnections. The remaining two (13%) segments of reconnection were adenosine-induced and were situated in the left posterior region. All 15 acutely reconnected segments were successfully re-ablated. The mean interval between the initial PVI procedure and repeat electrophysiology study was 64±6 days.

All 40 repeat electrophysiology procedures were uncomplicated. Late PV reconnection was identified at 13 (3%) segments in 8 (22%) patients, affecting 11 (7%) PVs in 8 (11%) WACAs. All reconnected PVs in the 8 patients with late PV reconnection were successfully re-isolated. The median ablation time required for re-isolation was 5.6 (4.5–7.9) minutes.

A total of 2,764 VisiTags™ were analyzed for ablation lesion parameters with a mean number of 69±12 VisiTags™ per patient.

Table 5-14 Demographic and Procedural Data

Demographic and procedural Data	Value
Age, years	61±8
Male (n, %)	30 (75%)
Left atrial diameter, mm	43±5
LV Ejection fraction >55%	32 (80%)
Hypertension (n, %)	12 (30%)
Diabetes mellitus (n, %)	3 (8%)
CHA2DS2Vasc Score	1.2±1.3
Antiarrhythmic drugs prior to ablation	20 (50%)
Procedure time, minutes	158±34
Ablation time, minutes	36±9
Fluoroscopy time, minutes	12 [8 – 14]
General anesthesia (n, %)	39 (98%)
Complications	0
Interval between procedures, days	64±6
Mean FTI (gram.seconds)	327±77
Mean AI	486±42

AI: Ablation Index, FTI: Force-time integral, LV: Left Ventricle

Distribution of Acute and Late Pulmonary Vein Reconnections

Acute PV reconnections were most common in the right posterior segments (9/15 (60%)). Whereas late PV reconnection were most common in the left anterior segments (5/13 (38%)), followed equally by right and left posterior segments, each represented 3/13 (23%) of the total late reconnected segments.

Identifying Non-RF Ablation Lesion Factors Associated with Late PV Reconnection
Left atrial size and WACA circle Size. Table 5-15.

Univariate analysis did not show a significant relation between left atrial anteroposterior diameter and late reconnection, *P*= 0.481. Similarly, there was no significant relation between initial LA Carto volume and late reconnection, *P*=0.70. The WACA circle transverse diameter was significantly greater in WACA circles with, compared to those without late PV reconnection, *P*=0.05.

As discussed in Chapter 5-III, LA volume reverse remodelling, defined as reduction of LA Carto volume by >15% at repeat procedure, was studied in 35 PRAISE patients in whom the Ablation Index-guided ablation protocol was followed and had good quality Carto maps. LA volume reverse remodelling was noted to occur in 15/35 (43%) patients in whom the median LA index volume significantly decreased from 66 (60-76) ml/m^2 at the initial to 47 (45-57) ml/m^2 at repeat procedure, *P*= 0.001. There were no statistically significant differences in the prevalence of late PV reconnection between patients who had and those who did not have LA volume reverse remodelling (3/15 (20%) versus 3/20 (15%), *P*=0.71).

First Pass Isolation and Acute Pulmonary Vein Reconnection

Absent first pass isolation was significantly more prevalent in late reconnected (5/8 (63%)) compared non-reconnected (8/68 (12%)) WACA circles at repeat study, *P*<0.001. Likewise, late reconnection at repeat study was noted to occur significantly more frequently in

pulmonary veins that were found to have acute reconnection, compared to those without acute reconnection during the initial ablation procedure (5/14 (36%) vs. 6/133 (5%) PV, *P* <0.001). Figure 5-8.

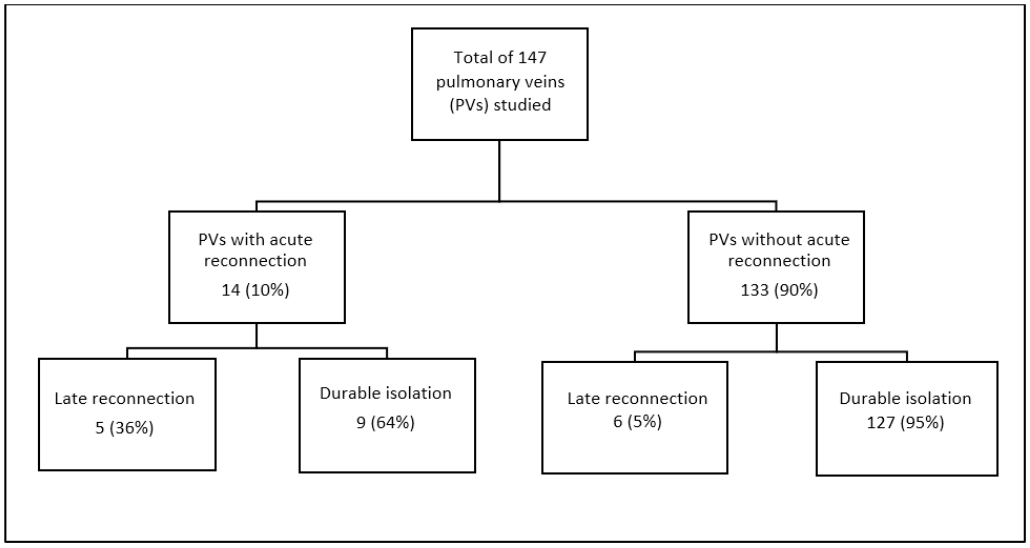


Figure 5-8: A flowchart of showing the significant relation between ***acute and late pulmonary vein reconnection in the study group***

Table 5-16 shows the incidence of acute and late PV reconnection in the study group, and the relation between them in terms of pulmonary veins, patients, WACA circles and WACA segments.

Table 5-15 Univariate analysis of non-ablation lesion related factors influencing late WACA reconnection

	Durable isolation (n = 68)	Late reconnection (n = 8)	*P* value
WACA transverse diameter (mm)	21.2 (16.5 - 23.6)	26.9 (20.1- 32.8)	0.05
WACA longitudinal diameter (mm)	35.6 (31.5- 39.1)	33.7 (31.1- 41.1)	0.87
WACA circumference (mm)	88.1 (77.0 - 96.1)	93.3 (80.1- 116.2)	0.31
Carto Volume (ml)	138 (115 - 158)	145 (126- 156)	0.70
LA AP diameter (cm)	4.3 (4.0 - 4.6)	4.3 (4.1- 4.4)	0.48

AP: Anteroposterior diameter, LA: Left Atrium, WACA: Wide antral circumferential ablation

Table 5-16 Incidence of Acute and Late Reconnection in the Study Group

	Durable isolation, n (%)	Late reconnection, n (%)	Total	*P* value
Pulmonary Veins (PVs)*				
PVs with acute reconnection, n (%)	9 (64%)	5 (36%)	14	<0.001
PVs without acute reconnection, n (%)	127 (95%)	6 (5%)	133	
Patients				
Patients with acute reconnection, n (%)	7 (70 %)	3 (30%)	10	0.36
Patients without acute reconnection, n (%)	25 (83%)	5 (17%)	30	
WACA circles *				
WACA circles with acute reconnection, n (%)	7 (70 %)	3 (30%)	10	0.03
WACA circles without acute reconnection, n (%)	61 (82%)	5 (8%)	66	
WACA segments *				
WACA segments with acute reconnection, n (%)	14 (93%)	1 (7%)	15	0.37
WACA segments without acute reconnection, n (%)	429 (97%)	12 (3%)	441	

*Four WACA circles, with their corresponding WACA segments and pulmonary veins, were excluded from analysis; three because of protocol deviation and one because of equipment failure.
WACA: Wide antral circumferential ablation

Identifying RF Ablation Lesion Factors Associated with Late PV Reconnection

Number of gaps between ablation lesions per WACA

Univariate analysis did not show a significant relation between the number of gaps of >6mm per WACA and late PV reconnection, *P*=0.39 (Figure 5-9).

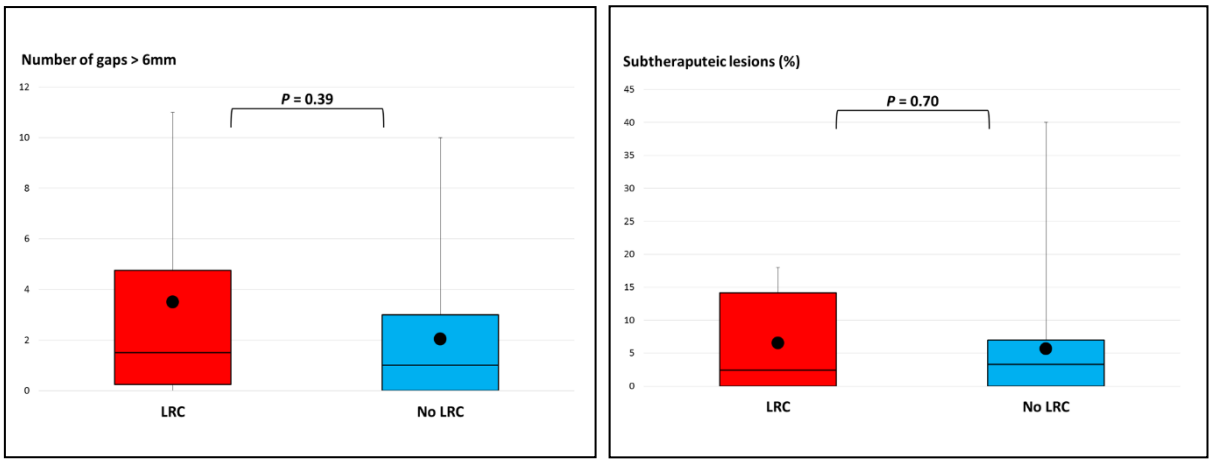


Figure 5-9 Box and whisker plots showing univariate analysis of number of ablation lesion gaps and percent of subtherapeutic lesions and late reconnection. Left panel: Univariate analysis showed non-significant increase in the number of ablation lesion gaps of >6mm per WACA with, compared to WACA without, late reconnection (LRC). Right panel: Univariate analysis showed non-significant increase in the percent of subtherapeutic lesions per WACA with, compared to WACA without, late reconnection.

Relation between mean ablation parameters and late reconnection (Table 5-17)

Ablation Index

Ablation index-guided lesions were considered to be therapeutic if their values were 550 or more for the anterior region, and 400 or more for posterior region.

For all segments, there was no statistically significant difference between the percent of late reconnections among segments with subtherapeutic lesions and segments with therapeutic lesions (3/121 [2%] vs. 10/332 [3%], *P*= 0.76). Similarly, there was no statistically significant difference between the percent of acute reconnections among segments with subtherapeutic lesions and segments with therapeutic lesions (1/121 [1%] vs. 14/332 [4%], *P*= 0.07).

A subanalysis showed that the percent of segments with subtherapeutic mean AI values in anterior regions was significantly higher than in the posterior regions (87/227 [38%] vs. 34/226 [15%], *P*<0.001. This is most likely related to the difficulty in achieving catheter

stability at the left lateral ridge on left anterior region where most late reconnections occurred.

There was a statistically significant negative correlation between acutely reconnected WACA circles and the percent of subtherapeutic lesions per WACA circle, Pearson *r* = -0.24, *P*=0.04. In contrast, a slightly negative correlation, that was not statistically significant, was noted between late reconnection of WACA circles and the percent of subtherapeutic lesions per WACA circle, Pearson *r* = - 0.04, *P*=0.72. These two correlations highlight the importance of the real time identification of subtherapeutic lesions in the prevention of PV reconnection.

Temperature

Univariate analysis showed that among all ablation parameters, mean ablation catheter tip temperature was a significant predictor for late reconnection for all segments, with mean temperature of 39±5°C for non-reconnected segments and 36±4°C for reconnected segments, *P* = 0.04.

A subanalysis showed that while mean catheter tip temperature in the segments that did not show late reconnection was significantly higher than of those that showed late reconnection in the in the anterior region (39±4 vs. 35±3 °C, *P*=0.02), the corresponding difference in mean catheter tip temperature in the posterior region was not statistically significant (38±6 vs., 36±4°C *P*=0.15).

Contact Force and Force Time Integral

For the anterior region, the mean CF value was significantly higher in the segments that were found to have durable isolation compared to those that showed late reconnection (14±5 vs. 11±4 g), *P*=0.02.

Conversely, among the posterior regions mean CF value was higher, though insignificantly, in those that showed late reconnection compared to those that did not show reconnection (11±5 vs. 14±6 g), *P*=0.57. Nevertheless, a significantly higher FTI was noted in the posterior regions that showed late reconnection compared to those that did not show late reconnection (237±74 vs. 307±99 gs, *P*=0.03). Moreover, we found that there was weak but significant correlation between FTI and catheter tip temperature that was even weaker for the posterior region (R^2=0.050 vs R^2=0.012, both *P*<0.001) (Figure 5-10).

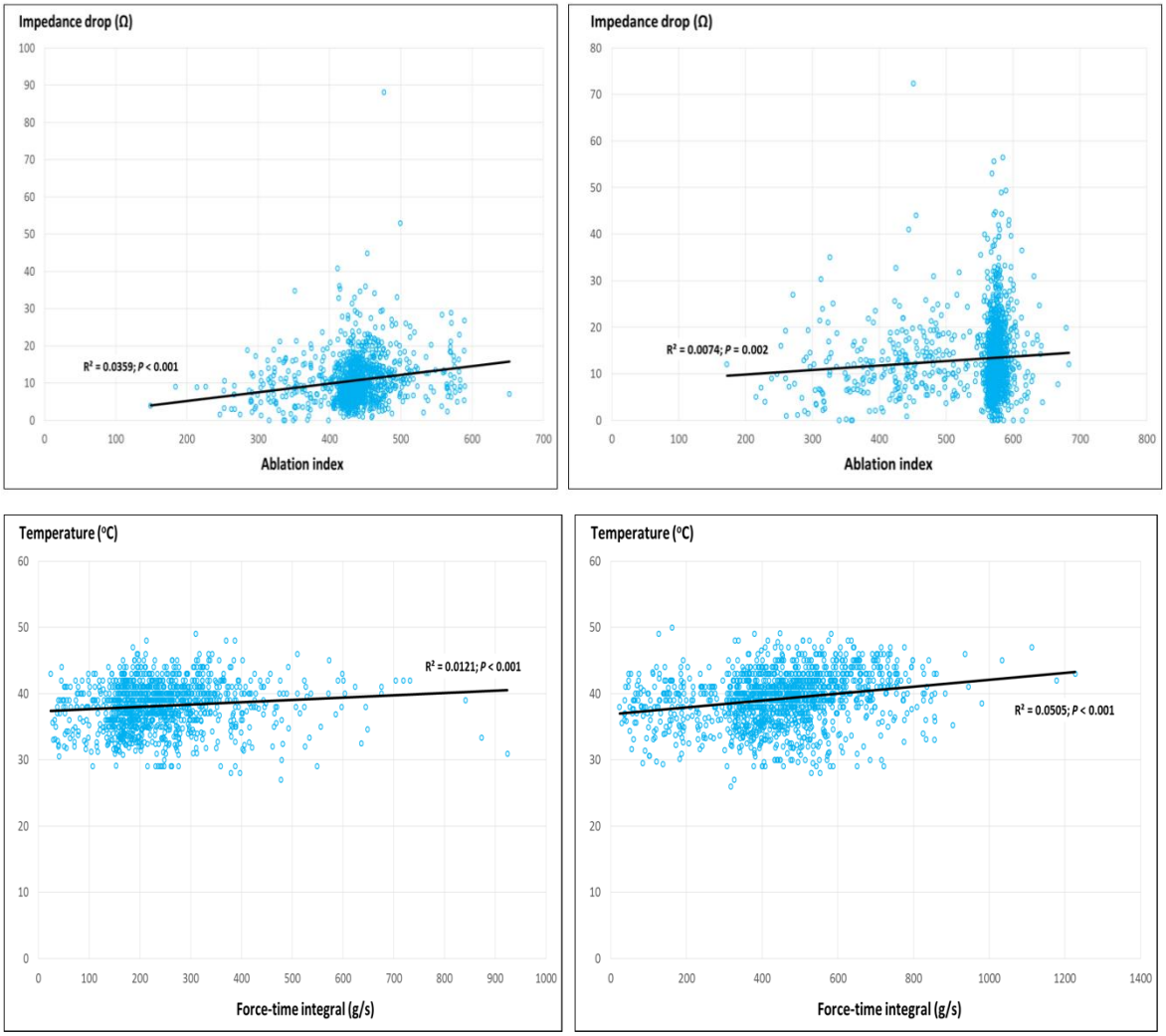


Figure 5-10 Scatterplots showing the relation between Ablation Index and FTI in relation to impedance drop and catheter-tip temperature. Top two panels show a significant positive correlation between Ablation Index and impedance drop that was slightly more evident in the posterior region (left panel) than in the anterior region (right panel). Bottom two panels show a significant positive correlation between force-time integral (FTI) and temperature that appears to be blunted in the posterior region (left panel) compared to the anterior region (right panel).

Impedance Drop

Only in the thin posterior regions, the mean impedance drop was significantly higher in the non-reconnected regions (11±4 vs. 9±3 Ω, *P*= 0.02), while in the thicker anterior region there was no significant difference between impedance drop in the reconnected and the non-reconnected segments (15±7 vs. 13±5 Ω, *P*= 0.30).

In general, we found a significant positive correlation between Ablation Index and impedance drop that was slightly more evident in the posterior region than in the anterior region (R^2=0.035, *P*= 0.002 vs R^2=0.007, *P*<0.001) (Figure 5-10).

Table 5-17 Relationship between mean RF ablation values and late reconnected WACA segments

	Durably isolated segments (n = 443)	Late reconnected segments (n = 13)	*P* value
Time (s)			
All segments	29±10	32±10	0.64
Anterior	35±10	37±9	0.23
Posterior	23±7	25±6	0.96
Force (g)			
All segments	13±5	13±5	0.76
Anterior	14±5	11±4	0.03
Posterior	11±5	14±6	0.57
Temperature (C)			
All segments	39±5	36±4	0.04
Anterior	39±4	35±3	0.02
Posterior	38±6	36±4	0.15
Impedance drop (Ohm)			
All segments	12±5	12±6	0.86
Anterior	13±5	15±7	0.30
Posterior	11±4	9±3	0.02
FTI (g.s)			
All segments	345±146	364±153	0.16
Anterior	452±117	412±181	0.06
Posterior	237±74	307±99	0.03
Ablation Index			
All segments	489±69	493±61	0.12
Anterior	546±45	530±59	0.37
Posterior	433±32	449±23	0.12

Relation between minimum ablation parameters and late reconnection (Table 5-18)

There were no statistically significant differences between minimum Ablation Index, contact force, FTI and impedance drop values in segments with late reconnection compared to segments without reconnection.

Table 5-18 Relationship between minimum RF ablation values and late reconnected WACA segments

	Durably isolated segments	Late reconnected segments	*P* value
Minimum Contact Force (g)	7 (6-10)	8 (5- 10)	0.80
Minimum FTI (g.s.)			
Anterior	333 (156-433)	361 (144- 489)	0.64
Posterior	163 (117-215)	195 (157- 235)	0.32
Minimum AI			
Anterior	557 (383-566)	563 (424-570)	0.72
Posterior	415 (348-429)	434 (353-435)	0.27
Minimum Impedance drop (Ohms)	6 (3-8)	5 (3-7)	0.98

Rise in Oesophageal Temperature

A rise in oesophageal temperature > 39° C was noted during ablation at the posterior regions of 14 /76 (18%) WACA circles, prompting premature termination of radiofrequency energy application before the AI target of 400 was reached. The highest recorded oesophageal temperature was 40.4°C. The incidence of acute reconnection in the posterior regions where oesophageal temperature rise was detected (4/14 (29%)) was significantly higher compared to the posterior regions where these was no such rise (4/62 (6%)), *P*=0.015. However, there was no significant difference in the incidence of late

reconnection between posterior regions that were or were not affected by rise in oesophageal temperature (1/11 (9%) vs. 4/65 (6%), *P*=0.72).

Discussion

Main Findings:

This is the first study to examine potential factors associated with regional late PV reconnection two months after Ablation Index-guided PVI in patients with PeAF, by means of mandated repeat electrophysiology studies to regardless the presence or absence of symptoms or documentation of AF recurrence.

The main findings of this study are as follows. Firstly, AI-guided ablation in persistent AF patients is associated with a low incidence of late PV reconnection. Secondly, the small overall incidence of late PV reconnection correlates with larger WACA circle transverse diameter. Thirdly, late reconnection best correlates with lower temperature and lower CF in the thicker anterior segments, and with lower impedance drop in the thinner posterior segments. Fourthly, there is a negative correlation between acute, and to a lesser degree late, reconnections of WACA circles and the percent of lesions with subtherapeutic Ablation Index. This can be explained by the fact that the real time Ablation Index monitoring in our study allowed for immediate identification of subtherapeutic lesions, with their distinctive VisiTag^{TM} colour in certain locations, leading to instant delivery of more therapeutic RF lesion(s) to these locations to prevent potential reconnections. This is particularly important because interstitial edema starts to develop very soon after initiation of RF ablation and lasts for 20-30 minutes.[184] Consequently, it is envisaged that

the use of AI targets may obviate the need for waiting for at least 20 minutes for edema resolution before checking for acute PV reconnections caused by under delivery of RF energy.

Finally, although Ablation Index-guided ablation significantly reduced late PV reconnection, it allowed the identification of ablation lesion parameters that are associated with late reconnection in the various LA regions as discussed below.

Relevance of temperature to lesion durability in the anterior region but not the posterior region

In this study, higher catheter tip temperature was found to be predictive of lesion durability in the anterior region but not in the posterior region. The lack of significant difference between catheter tip temperature in the late reconnected and non-reconnected segments in the posterior region indicates that catheter-tip temperature is not a good surrogate for tissue temperature at that region, probably because of extra cooling of the catheter tip by increased blood flow in the oesophageal wall producing a *heat sink* effect, with no rise in oesophageal temperature.[47] This is particularly important with the prevalence of LA dilatation in our persistent AF study group leading to closer proximity of the posterior LA wall to the oesophagus.

Moreover, it has been previously demonstrated that irrigated ablation drives the hot spot of RF ablation into the deeper tissue due to excessive cooling of the resistive heat at the endocardial surface and extension of conductive heat deeper to collateral structures.[31,185,186] That deep dissipation of energy results in teardrop shaped lesions, with a narrower lesion width subendocardially and greater width deeper below the

endocardial surface. [47,187] This may explain the frequent oesophageal heating, and the development of more acute PV reconnections in the posterior region in our study patients as reported in previous studies. [188,189]

In a study that examined the anatomic relation between the oesophagus and the LA posterior wall in individuals who had no history of AF, the oesophagus was found to pass along the middle posterior LA wall in 40% of cases, descended close to the left PV-atrial junction in 40% of cases and had a rightward course close to the right PV-atrial junction in the remaining 20% of the cases. [190] Similarly, in a study in patients with AF, 75% paroxysmal and 25% persistent, undergoing atrial fibrillation ablation there was a predilection of the oesophagus to have leftward course, with the most common location near the left PVs (54%), followed by midline (23%) and near right PVs (23%) locations.[191]

However, with significant left atrial enlargement, deviation of the oesophagus to the right and the descending aorta to the left occur due to wedging of the enlarged left atrium in between these structures. This finding was described as “posterior wedging sign”.[192] With the oesophageal deviation noted with left atrial enlargement, we presumed that the variation of the oesophageal location in relation to the LA posterior wall may be contributing to the late PV reconnection on the ipsilateral side through the heat sink effect.

To prove that concept, we studied the relation between the oesophagus and the reconnected posterior LA regions in the preablation MRI pictures, and we indeed found close proximity between the oesophagus and the ipsilateral reconnected posterior LA region as shown in Figure 5-11.

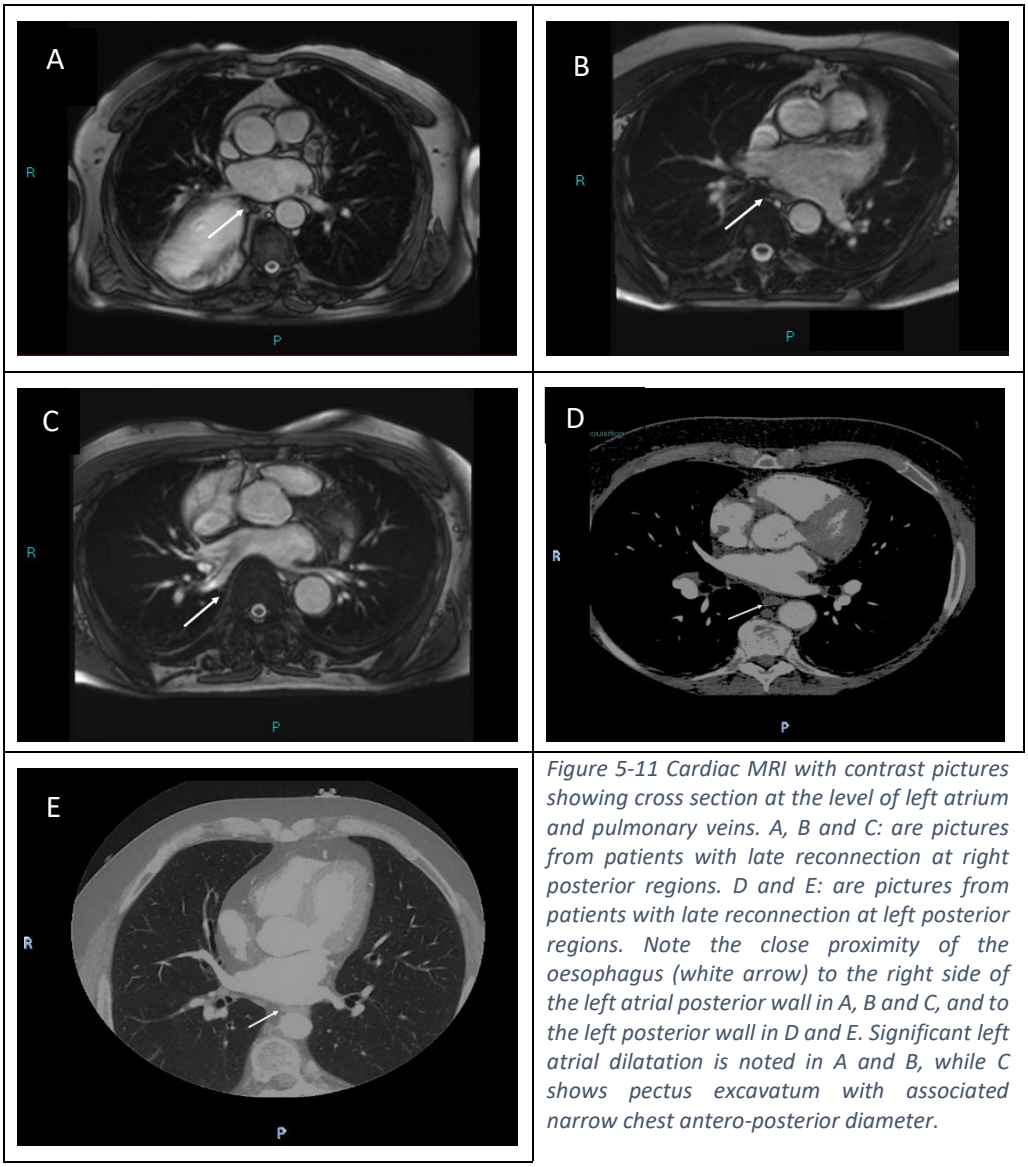


Figure 5-11 Cardiac MRI with contrast pictures showing cross section at the level of left atrium and pulmonary veins. A, B and C: are pictures from patients with late reconnection at right posterior regions. D and E: are pictures from patients with late reconnection at left posterior regions. Note the close proximity of the oesophagus (white arrow) to the right side of the left atrial posterior wall in A, B and C, and to the left posterior wall in D and E. Significant left atrial dilatation is noted in A and B, while C shows pectus excavatum with associated narrow chest antero-posterior diameter.

Contact force as a factor associated with late reconnection

Our results are consistent with a previous study that found that the majority of gaps and dormant PV reconnections were related to low ablation catheter contact force at the thick anterior LA wall, as detected by multidetector CT scan.[128]

In this study, we found that the significant correlation between FTI and catheter tip temperature was blunted for the posterior region compared to anterior region. As discussed before, left atrial dilatation brings the posterior LA wall in close proximity to the oesophagus and the descending aorta. As such, it can be anticipated that during right and left WACA ablation the longer the time and the more the force the catheter tip pushes the LA posterior wall against the oesophagus, the more the heat sink effect becomes more evident. This may explain our finding of the higher mean FTI in segments with late PV reconnection in the posterior region.

Although previous research found that higher minimum FTI is required for durable PVI isolation on the anterior compared to the posterior region [102], a negative effect of higher FTI on the posterior region has not been yet described .

Clinical implications and future prospective

This study's results suggest clear advantages for the routine use of Ablation-Index guided ablation. The study also suggests the need for real time monitoring of force and catheter tip temperature for the anterior LA region, and impedance drop for the posterior LA region.

In addition, our study results conform with the recent recommendations to increase the initial resistive heating phase by delivering higher RF energy by increasing the power to achieve transmural lesions, and at the same time to shorten the conductive heating phase by reducing RF application time to limit collateral tissue damage especially on the thin posterior wall.[130] In a recent study, this high power-short duration RF application strategy was found to be safe with short procedure time and outstanding clinical outcomes.[193] Moreover, it has been recently shown that low-flow irrigation of the posterior LA wall creates larger endocardial lesions, compared to standard irrigation that produces larger epicardial lesions with endocardial sparing and potential lesion extension to collateral structures. [31]

This study demonstrated a potential importance of catheter-tip temperature monitoring in predicting sites of potential late reconnection, especially in the anterior region. This is likely due to the ability of catheter-tip temperature to predict endocardial surface heating.[31] Novel irrigated-tip RF ablation catheters with thermocouples situated directly at the catheter tip-tissue interface were found to exhibit more accurate tissue temperature measurements during temperature-controlled AF ablation, with a resultant safe and durable PV isolation.[186]

In this study several late reconnections were thought to be related to oesophageal heat sink effect. Recently, mechanical oesophageal deviation from the PV ablation line has been found to prevent significant oesophageal heating during the delivery of RF ablation lesions to the LA posterior region.[194] We envision that the use of that strategy may also help reduction of late reconnection by abolishing the oesophageal heat sink effect.

Limitations

The limited number of the late reconnected segments, owing to the improved RF energy delivery with AI-guided ablation, may have reduced the statistical power required to optimally adjudicate some of the factors associated with late PV reconnection.

In our study we used the SmartTouch catheter open-irrigated catheter that incorporates a thermocouple temperature sensor embedded in the catheter-tip that measures the mean catheter-tip temperature. Therefore, the temperature measured during ablation is only a surrogate, rather than an accurate measurement, of the atrial tissue temperature at the catheter-tip tissue interface.[195]

Finally, although there were no complications with AI-guided ablation the number of patients in this study is too small to evaluate the incidence of serious complications that can occur with this technique.

Conclusion

Ablation Index-guided ablation is associated with a high incidence of durable PVI in patients with persistent AF. The occurrence of either absent first pass isolation or acute reconnection in a WACA circle predict late reconnection in the same WACA circle. A larger WACA circle transverse diameter is associated with a higher incidence of late PV reconnection. The significantly lower catheter tip temperature seen in late reconnected thicker anterior segments, and the prevalence of late reconnections without significant correlation with catheter tip temperature in the thinner posterior segments suggest excessive irrigation with current settings.

Lower catheter tip-temperature and contact force in the anterior segments, and lower impedance drop in the posterior segments, predict late pulmonary vein reconnection during Ablation Index-guided pulmonary vein isolation.

Chapter 6 Summary, Conclusions and Future Prospective

Summary and Conclusions

Our research on Ablation Index was the first to investigate the prospective use of Ablation Index targets to guide AF ablation. We investigated the Ablation Index-guided ablation in two studies. The first study was a retrospective analysis of the use of Ablation Index target values of 550 for anterior and 400 for posterior left atrial regions in AF ablation, and compared the acute procedural and long-term clinical outcomes with those of a propensity matched group in which AF ablation was contact force-guided. The study showed significant improvements in the incidence of acute PV reconnection and in the rate of AT recurrence during follow-up, without change in the mean ablation time for PV isolation, as compared to contact force -guided ablation. That study also showed that the use of different AI regional targets, with higher values for the anterior/roof region compared to posterior/inferior region, delivers more effective ablation to thicker-walled areas while obviating the risk of excessive ablation on thinner-walled regions.[103]

The second study, the PRAISE (Pulmonary vein Reconnection following Ablation Index-guided ablation: Success Evaluation) study, which is a multicenter prospective study of forty consecutive patients with persistent AF of less than 12-month duration, and no significant structural heart disease underwent Ablation Index-guided PVI also with target values of 550 for anterior and 400 for posterior left atrial regions, followed by a protocol-

mandated repeat procedure after 2 months. Patients were monitored for atrial tachyarrhythmia recurrence via daily plus symptom-initiated ECG recordings for 12 months. Recurrence was defined as ≥30 seconds of any atrial tachyarrhythmia (ATA) after a 3-month blanking period. In that study Ablation Index regional target-guided ablation resulted in a low rate of PV reconnection at repeat electrophysiology study, with 93% of PVs found to remain durably isolated with late reconnection was most commonly encountered in carinal regions. Eventually, 44% the PRAISE study patients required a carina ablation line at some point during the 2 procedures.

The incidence of acute reconnection was significantly higher in the posterior segments where a rise in oesophageal luminal temperature rise was detected compared with the posterior segments where there was no such rise. Moreover, there was obvious anatomical proximity between the oesophagus and the ipsilateral late reconnected posterior LA regions.

The study concluded that an Ablation Index-guided PVI only strategy in patients with persistent AF of <12 months duration, and with no significant structural heart disease provides a high rate of clinical success, potentially because of improved durability of PVI.[124]

We then compared the AF ablation outcomes form the forty patients who form the PRAISE study cohort with those of the forty paroxysmal AF patients of the PRESSURE (Pulmonary vein RE-isolation as a routine Strategy: a SUccess Rate Evaluation) study who were randomised to a repeat procedure two months following the initial CF-guided PVI.[80]

In both study groups the initial and the repeat ablation strategies and equipment were

identical other than the use of Ablation Index targets in the former group compared to the CF-guided ablation in the Later. Acute and late reconnections following Ablation Index-guided ablation in the PRAISE cohort were significantly lower when compared to CF-guided ablation in the PRESSURE cohort, despite significantly shorter ablation times, lower average CF values, and significantly larger left atria in the former cohort compared to the later cohort. These results were found to be consistent with our previous findings that the prospective use of Ablation Index-guided AF ablation was associated with a significant reduction in atrial tachyarrhythmia recurrence compared to CF-guided ablation, possibly due to creation of better quality lesions as suggested by a greater impedance drop.[103] No major complications occurred with Ablation Index-guided ablation in our research studies.

Following that we looked for the potential occurrence of LA structural and electrical reverse remodelling following Ablation Index-guided PVI. We found that reduction of LA volume occured almost invariably, and that both structural and electrical remodelling became evident two months following Ablation Index-guided PVI. We also found that factors known to be associated with less likelihood for development of left atrial fibrosis in persistent AF patients including; shorter AF duration, lower BMI and absence of early ATA recurrence, rather than durable PVI alone, were associated with LA structural reverse remodelling. Then we studied the relation between LA reverse remodelling and the Ablation Index-guided AF ablation outcomes, and found that the occurrence of both structural and electrctrical reverse remodelling together was associated with a low likelihood for ATA recurrence.

Finally, we studied the factors associated with late pulmonary vein reconnection at repeat electrophysiology study 2-month following Ablation Index-guided PVI in the PRAISE study patients. We found that the occurrence of either absent first pass isolation or acute reconnection in a WACA circle predict late reconnection in the same WACA circle. A larger WACA circle transverse diameter was found to be associated with a higher incidence of late PV reconnection. The significantly lower catheter tip temperature seen in the late reconnected thicker anterior segments, and the prevalence of late reconnections without significant correlation with catheter tip temperature in the thinner posterior segments suggested excessive irrigation with the current settings.

Moreover, we concluded that the lower catheter tip-temperature and contact force in the anterior segments, and lower impedance drop in the posterior segments, predicted late pulmonary vein reconnection.

Finally, Ablation Index-guided ablation has shortened the total duration of AF ablation procedures and improved the cardiac electrophysiology lab work-flow. This is likely related to the better RF energy delivery with that strategy. This is because even at sites where the ablation catheter had low contact, Ablation Index-target could be reached by increasing the amount of power delivered at these sites, therefore obviating the need to manipulate the catheter to get better contact. Moreover, better first pass isolation and less acute reconnections have been noticed with Ablation Index-guided ablation, therefore obviating the need for extensive additional ablation to isolate or reisolate the pulmonary veins.

Recommendations

Based on our research findings we would recommend the routine use of Ablation Index-guided, rather than contact force-guided, PVI alone for AF ablation in patients with persistent atrial fibrillation of less than 12-month duration and no significant structural heart disease. In addition, we recommend giving special consideration to pre-emptive ablation of the carinal regions to prevent late reconnection in these regions.

We also recommend the creation of WACAs with shorter transverse diameter and checking for first pass isolation and acute PV reconnections, with PV re-isolation as needed, as these all predicted late reconnection. Moreover, the real time monitoring for adequate contact force and catheter tip temperature for the anterior LA region, and impedance drop for the posterior LA region may help ensure durable PVI lesions.

Based on our research results, we recommend increasing the initial resistive heating phase enough to achieve transmural lesions by adequately increasing the power, and at the same time shorten the conductive heating phase by reducing of RF application time to limit collateral tissue damage especially on the thin posterior wall.

Moreover, high irrigation rates may result in deeper lesions whilst sparing the endocardial surface with the potential risks of causing collateral damage and late PV reconnection. We therefore recommend reducing the irrigation rate for the posterior LA region.

Future Prospective

Future Prospective of Real-time Assessment of Ablation Lesions

Ablation Index, in addition to other surrogates measures such as force-time-integral and impedance drop, have been introduced for assessment of lesion quality and transmurality during

AF ablation because of the unavailability of a reliable real-time method for such assessment.[102] During the past decade, a number of centers developed a technology to allow real-time MR-guided AF ablation. This technology allows for real-time monitoring of lesion development in the absence of ionizing radiation. However, these systems are still under development and are not available for routine clinical use because of the need for non-metallic catheters and relatively sizeable and expensive of MRI scanners, long image acquisition times, and limited spatial resolution.[1,196]

Acoustic Radiation Force Impulse (ARFI) Imaging is a novel ultrasound technique that measures tissue elasticity with high spatial and temporal resolution using standard clinical ultrasound imaging systems. An ARFI image is created by delivering a series of ultrasound pulses to mechanically displace tissue then measuring the displacement of each image pixel to assess tissue elasticity. ARFI imaging can visualize formation of an RF lesion in near real-time and distinguish between an incomplete and a complete atrial ablation lines and assess transmurality. However, clinical studies to establish the role of this technology in clinical practice are still needed.[197]

Recently, the use of near-field ultrasound (NFUS) which is a novel imaging technology that allows real-time observation of the formation and transmurality of RF ablation lesions, has enabled subsequent adjustment of ablation parameters to optimise lesion formation. Therefore, the use of NFUS to guide AF catheter ablation is anticipated to improve procedural safety and success. [188]

With the significantly low rate of acute reconnection, only 3% of WACA segments, noted in the PRAISE study, one would question the need for routine rigorous check for acute PV reconnections following PVI. Therefore, it is envisaged that the routine use of adenosine and circular mapping catheters to check acute PV reconnections may not be needed with the modern PVI technologies and strategies, such as the use of Ablation Index-guided AF ablation. A metanalysis of contemporary data suggest that there is no benefit from an adenosine- guided strategy in patients undergoing AF ablation. The benefits observed in the early studies published before 2013 could have been the result of less evolved technology, lower operator-experience leading to a higher rate of dormant vein conduction. [198] In addition, a recent study found that the use of contact force-guided single-catheter technique is feasible for PVI in patients with paroxysmal AF, leading to substantial cost-savings compared to the standard circular mapping catheter-based approach while leading to similar clinical results.[199]

Future Prospective in Catheter Pulmonary Vein Isolation Strategies and Technologies

A study found that minimal Ablation Line contiguity Index (ALCI), a novel ablation quality marker integrating both Ablation Index and interlesion distance into a weighted formula, may be a more accurate independent predictor of PV reconnection than Ablation Index.[30] This finding can be intuitively anticipated because the addition of interlesion distance to the formula accounts for the contribution of gaps in the PVI circle to reconnection.

Conforming with our recommendations above this high power-short duration RF application strategy was found to be safe with short procedure time and outstanding clinical outcomes.[193] Moreover, it has been recently shown that low-flow irrigation of the

posterior LA wall creates larger endocardial lesions, compared to standard irrigation that produces larger epicardial lesions with endocardial sparing and potential lesion extension to collateral structures. [31]

Our study demonstrated a potential importance of catheter-tip temperature monitoring in predicting sites of potential late reconnection, especially in the anterior region. Novel irrigated-tip RF ablation catheters with thermocouples situated directly at the catheter tip-tissue interface were found to exhibit more accurate tissue temperature measurements during temperature-controlled AF ablation, with a resultant safe and durable PV isolation.[186]

The PRAISE study results suggested a causative relation between the proximity of the oesophagus to either the right or left side of the LA posterior wall and the occurrence of ipsilateral acute reconnections and late reconnections at posterior LA regions. Recently, mechanical oesophageal deviation from the PV ablation line has been found to prevent significant oesophageal heating and injury during the delivery of RF ablation lesions to the LA posterior region.[194,200] We envision that the use of that strategy will not only enable adequate radiofrequency energy delivery to the posterior LA wall while circumventing the risk oesophageal temperature rise, but may reduction of acute and late reconnection by allowing for better energy delivery whilst eliminating the oesophageal heat sink effect.

Other energy sources have been investigated for AF ablation in an effort to reduce complications and improve efficacy. That has led to the development of an improved method of direct current ablation called electroporation. Electroporation involves the application of an external electric field that disrupts cellular membranes resulting in

irreversible and well-demarcated lesions by increasing cell membrane permeability, and inducing subsequent cellular apoptosis. However, it yet remains unknown if electroporation can be used successfully in cardiac ablation.[201]

Future Prospective in Other Pulmonary Vein Isolation Strategies and Technologies

Our research in conjunction with other research studies concluded that an Ablation Index-guided PVI only strategy in patients with persistent AF of <12 months duration and no significant structural heart disease provides a high rate of clinical success.[33,42,43,124] Therefore, one would expect that the utility of PVI only strategy using single-shot ablation devices, in persistent AF patients may increase in the near future, especially with the recent publications of studies that demonstrate their efficacy and safety.[202,203]

Some studies found that cryoballoon PVI, mainly using second-generation cryoballoon, appears to be an effective initial strategy in treating persistent AF especially if offered early, with a reported AF recurrence-free rate of 59%-67% at 1 year. [202,204–206] Similarly, a randomized multicenter study comparing the outcome of PVI using laser balloon-guided strategy and wide-area circumferential PVI using irrigated RF catheter in patients with persistent AF showed similar efficacy.[207]

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Appendix A Publications that Emanated from the Thesis

Advances in Therapy Journal- Manuscript ADTH-D-19-00470R1, Accepted December 2019

Treatment of atrial fibrillation using Ablation Index-guided contact force ablation: a matching-adjusted indirect comparison to cryoballoon ablation

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Abstract

BACKGROUND: Ablation Index, also known as VISITAG SURPOINT™, is a novel lesion-quality marker that improves outcomes in radiofrequency (RF) catheter ablation of atrial fibrillation (AF). There is no direct evidence on the comparative effectiveness of RF ablation with Ablation Index and cryoballoon (CB).

OBJECTIVE: To conduct a matching-adjusted indirect comparison (MAIC) using individual patient-level data (IPD) to compare the effectiveness of RF ablation with Ablation Index to that of CB on recurrence of atrial arrhythmias 12 months after catheter ablation in patients with paroxysmal AF (PAF).

METHODS: Individual patient-level data for RF ablation with Ablation Index were obtained from two studies: Solimene et al. (2019) and Hussein et al. (2017). Comparable CB studies identified from a systematic literature review were pooled. Prognostic variables for adjustment were ranked *a priori* by several practicing electrophysiologists. In the absence of a common treatment arm between the Ablation Index and CB studies, an unanchored MAIC was conducted. Primary analysis compared Solimene et al. to pooled CB studies. A secondary analysis compared pooled RF ablation with Ablation Index studies to pooled CB studies. Several scenario and sensitivity analyses were conducted.

RESULTS: Primary analyses showed statistically significant reductions in the rate of arrhythmia recurrence with RF ablation with Ablation Index compared to CB in unmatched, unadjusted (HR 0.50, 95% CI: 0.27-0.95) and matched (0.42, 0.21-0.86) analyses. Greater reductions in the rate of arrhythmia recurrence that favored RF ablation with Ablation Index were observed after matching and adjusting for age (0.41, 0.20-0.85), age and sex (0.37, 0.16-0.88), and age, sex, and left ventricular ejection fraction (0.30, 0.13-0.71). Secondary and sensitivity analyses showed similar reductions.

CONCLUSION: Radiofrequency ablation with Ablation Index was associated with reductions in recurrence of atrial arrhythmias at 12 months compared to CB in unmatched and unadjusted, matched, and matched and adjusted comparisons.

Key words: matching-adjusted indirect comparison, atrial fibrillation, catheter ablation, contact force, radiofrequency ablation, Ablation Index, VISITAG SURPOINT™ Module.

INTRODUCTION

Pulmonary vein isolation (PVI) using catheter ablation is a treatment option that is recommended by clinical guidelines and is commonly used first line or second line after antiarrhythmic drug (AAD) therapy for patients with symptomatic atrial fibrillation (AF) [1-4]. Several catheter abalation technologies for PVI are available, with evidence demonstrating that both catheter ablation using radiofrequency (RF) ablation or cryoballoon (CB) ablation technology to achieve PVI effectively reduces the recurrence of AF episodes [5-7].

Recently, a novel lesion-quality marker to guide RF ablation, Ablation Index also known as VISITAG SURPOINT™, was introduced to the market. The use of Ablation Index has been associated with significant reductions in the incidence of acute pulmonary vein reconnection and recurrence of atrial arrhythmias at 12 months when used with THERMOCOOL SMARTTOUCH™ and THERMOCOOL SMARTTOUCH™ SF contact force-guided RF ablation compared to contact force-guided RF ablation alone [8-11]. There are no studies that directly compare the effectiveness of THERMOCOOL SMARTTOUCH™/ THERMOCOOL SMARTTOUCH™ SF with Ablation Index (STAI) to that of CB in AF ablation. Naïve comparison (ie, unmatched and unadjusted) of studies of catheter ablation with STAI and CB ablation suggest that STAI may provide superior outcomes. Thus, the objective of the present study was to evaluate the impact of STAI on recurrence of atrial arrhythmias 12 months after catheter ablation compared to that with CB in patients with paroxysmal AF (PAF) using individual patient-level data (IPD) within a matching-adjusted indirect comparison (MAIC). An MAIC is a method of indirect treatment comparison (ITC) that can be used to adjust for the influence of between-study differences in protocol and trial populations on study outcomes.

METHODS

Primer on MAICs

MAICs use IPD to match the patient cohort in one study to that in another, and then to adjust for between-study differences in patient populations. The goal of matching and adjustment is to reduce differences in prognostic factors (ie, patient characteristics that are associated with AF) and treatment-effect modifiers (ie, patient characteristics that may affect the efficacy of catheter ablation on AF) between the analysis populations [12]. Matching refers to the removal of patients from one trial who would not have been included in the comparator trial. Adjusting refers to reweighting patients using inverse propensity score weighting to reduce differences in baseline characteristics (eg, sex, mean age) [12]. MAICs can be used to conduct either an "anchored" indirect comparison, when there is a common comparator arm between studies (eg, sham procedure or older technology), or an "unanchored" indirect comparison, in the absence of a common comparator arm between studies [12].

Identification of Studies for MAIC Analyses

At the initiation of this study, four studies were published on STAI in patients with PAF [8, 9, 13, 14]. Individual patient-level data on STAI were available for reanalysis for two of the investigator-initiated studies [8, 9]. The Hussein et al. [9] trial was a prospectively collected, propensity-score matched analysis comparing STAI to historical THERMOCOOL SMARTTOUCH™ control that included 43 PAF patients treated with STAI. The Solimene et al. [8] trial was a prospective, single-arm registry that included 132 PAF patients treated with STAI.

A systematic literature review was conducted to identify CB studies in patients with PAF. A search strategy was developed by an experienced medical information specialist in consultation with the review team (**Appendix S1**). A second information specialist peer reviewed the search strategy using the PRESS checklist [15]. Searches were conducted on May 23, 2019, in Ovid MEDLINE®, including Epub Ahead of Print and In-Process & Other Non-Indexed Citations, Embase, and the Cochrane Central Register of Controlled Trials. The search strategy incorporated controlled vocabulary (eg, "Catheter Ablation", "Atrial Fibrillation", "Pulmonary Veins/surgery"), keywords (eg, "cryoballoon", "paroxysmal AF", "PVI"), and relevant trade names pertaining to the CB ablation catheter (eg, Arctic Front). Vocabulary and syntax were adjusted across the databases. Animal-only studies, opinion pieces, and conference abstracts were removed, where possible, from the results. All searches were limited to the publication years 2010 to the present, and no attempts were made to contact study authors.

Screening and Selection Criteria

Study screening was conducted by two independent reviewers (TK and MH). Conflicts were resolved by consensus through discussion or a third party (LP). Cryoballoon studies were eligible for inclusion based on PICOS criteria (**Appendix S2**). Prospective studies were eligible if they had ≥50 adults with drug-refractory, symptomatic, PAF who received first-time ablation and used the Arctic Front Advance™ CB ablation catheter. A 50-patient minimum was used to limit the number of studies given the large literature base in this area. The Arctic Front advance™ ablation catheter was selected as the most relevant CB technology given that it represented the standard of care for CB at the time. Included studies reported time-to-event data on freedom from

atrial arrhythmias or recurrence of atrial arrhythmias for at least 12 months after an ablation procedure, excluding events that occurred during a 3-month blanking period. Non–English-language articles were excluded.

Data Extraction

Data were extracted by a single reviewer (KE) and verified for accuracy by a second reviewer (LP). Data items extracted (where available) included: study design, sample size, AF type (ie, paroxysmal or persistent), AAD status (ie, on or off AADs), number of catheter ablation procedures performed (ie, single or multiple), and patient baseline characteristics (eg, age, sex, left atrial diameter [LAD], left ventricular ejection fraction [LVEF], and other relevant prognostic factors and treatment-effect modifiers). The outcome of interest was freedom from atrial arrhythmias or recurrence of atrial arrhythmias at least 12 months after an ablation procedure. Atrial arrhythmias were defined as AF, atrial flutter, or atrial tachyarrhythmias, as reported in studies.

Methods for MAIC Analyses

Primary analysis was planned to compare the STAI IPD from Solimene et al. [8] to the pooled CB cohort and to compare the STAI IPD from Hussein et al. [9] to the pooled CB cohort. An MAIC using only the Hussein et al. [9] IPD data was not conducted as the small sample size of PAF patients (n = 43) was insufficient to allow robust matching to the pooled CB cohort to reduce residual imbalances with the included CB trials. Potential prognostic factors and treatment-effect modifiers reported in the STAI and CB studies were ranked *a priori* and independently by four electrophysiologists. Average rankings were calculated and used to order potential prognostic factors and treatment-effect modifiers for scenario analyses.

Patients from the STAI IPD were reweighted based on a propensity score method-of-moments estimation that incorporates prognostic factors and treatment-effect modifiers reported in all trials [12]. This process ensures balance between trials in the summary statistics (eg, means, proportions, and standard deviations) of included prognostic factors and treatment-effect modifiers (**Figure 1**). Pooled analyses were limited to the minimum set of prognostic factors and treatment-effect modifiers common to all studies pooled in each MAIC. The principal analysis for each comparison of datasets was the analysis that adjusted for the most factors and had an effective sample size of ≥50.

To estimate absolute events associated with cryoablation, reconstructed IPD representing the time-to-event outcomes from the CB studies were derived from published aggregate data (ie, Kaplan–Meier curves) using the Guyot algorithm [16]. Observations from the reconstructed IPD for the CB trials were unweighted. After matching and reweighting of STAI IPD, the CB-reconstructed IPD and STAI IPD were combined to facilitate estimating the comparative efficacy of STAI versus CB for recurrence of atrial arrhythmias. Comparative efficacy estimates were obtained by fitting Cox proportional hazards regressions using the reweighted IPD set. Estimates of absolute effects are reported as the cumulative proportion of patients who had an arrhythmia recurrence after 12-month follow-up. Estimates of relative effects are reported as a hazard ratio (HR) and confidence intervals (CIs), where CIs that do not cross unity (ie, 1) are considered statistically significant.

Scenario and Sensitivity Analyses

Scenario analyses were carried out to assess the rigor of the primary analysis by incrementally eliminating less important (based on clinical expert rankings) prognostic variables and treatment-effect modifiers from the reweighting phase. For each scenario, MAICs were estimated using a new set of weights for the STAI population. Residual imbalances in excluded prognostic factors and treatment-effect modifiers due to partial reporting of these data at baseline across the trials may bias results. To investigate any potential biases, additional factors were incorporated into pairwise MAICs, based on clinician rankings of prognostic factors and treatment-effect modifiers.

RESULTS

Literature Review Results

A total of 2,186 unique CB records were identified from the literature searches; 68 duplicates were removed (**Figure 2**). One thousand eight hundred and ninety-seven citations were excluded during title and abstract review based on PICOS criteria. Of the 221 CB citations identified for full-text review, 3 were eligible for inclusion [17-19]. The most common reasons for exclusion included incomparable study design (n = 103; eg, retrospective studies, case studies, reviews), irrelevant intervention or comparator (n = 54), and non-comparable outcomes (n = 42) (**Figure 2**).

Study Characteristics and Prognostic Factors and Treatment-effect Modifiers

Individual CB study cohorts included 50-75 patients with PAF, resulting in a pooled sample size of 175 patients (**Table 1**). The proportion of patients who were male (65%-80%) and the proportion of patients with hypertension (22%-36%) varied

across CB cohorts. Other baseline characteristics were similar among study cohorts (**Table 1**). Both STAI studies evaluated first-time ablation outcomes after a single procedure. A total of 175 patients were pooled from STAI trials. Trials differed with regard to the proportion of patients who were male, had PAF, and had diabetes (**Table 1**).

Before matching and adjusting, several differences in prognostic factors and treatment-effect modifiers (ie, patient baseline characteristics) were observed among patients in the pooled CB cohort (referred to as the pooled CB cohort) compared to those in the STAI IPD (**Table 1**). Standardized mean differences (SMDs) were used to assess imbalances between cohorts, where SMDs greater than 0.1 are considered important. After matching and adjusting, the means and proportions of prognostic factors and treatment-effect modifiers from the STAI IPD were balanced (ie, SMDs <0.1) with those in the pooled CB cohort (**Table 2**).

MAIC Results

Results of the primary analysis for STAI IPD from Solimene et al. [8] to the pooled CB cohort, and the secondary analysis for pooled STAI IPD from Solimene et al. [8] and Hussein et al. [9] to the pooled CB cohort are presented in **Figures 3-5**. Absolute efficacy (eg, cumulative proportion of patients remaining arrhythmia-free after 12 months) are reported in **Appendix S3**. Results from sensitivity analyses are presented in **Appendix S4-S6**. Individual comparison of the Hussein et al. [9] IPD to pooled CB data was not conducted because the small sample size of the PAF cohort (n = 43) was insufficient to allow robust matching and adjustment to the pooled CB cohort.

Primary analysis

Overall, estimates of comparative effectiveness between Solimene et al. [8] STAI and the pooled CB cohort are significantly in favor of STAI over CB for arrhythmia recurrence. Naïve comparison of Solimene et al. [8] STAI and pooled CB data showed lower cumulative probabilities of arrhythmia recurrence for STAI (0.09; 95% CI: 0.05-0.14) than CB (0.17; 95% CI: 0.12-0.23) at 12-month follow-up. This corresponds to a statistically significant 50% reduction in the rate of arrhythmia recurrence with STAI compared to CB at 12-month follow-up (HR 0.50; 95% CI: 0.27-0.95). A greater reduction was observed after matching patients, with STAI associated with a significant 58% reduction in the rate of arrhythmia recurrence compared to CB at 12-month follow-up (HR 0.42; 95% CI: 0.21-0.86). After increasing the equivalence of the two treatment populations by matching patients and adjusting for the common prognostic factor and treatment-effect modifier of age, STAI was associated with a significant 59% reduction in the rate of arrhythmia recurrence at 12-month follow-up compared to pooled CB (HR 0.41; 95% CI: 0.20-0.85) (**Figures 3** and **4**).

Even greater reductions in the rate of arrhythmia recurrence were observed in scenario analyses that adjust for additional common prognostic factors and treatment-effect modifiers, based on *a priori* clinical ranking (**Figure 3**). After adjusting for age and sex, STAI was associated with a significant 63% reduction in the rate of arrhythmia recurrence compared to CB at 12-month follow-up (HR 0.37; 95% CI: 0.16-0.88). When age, sex, and LVEF were adjusted, a significant 70% reduction in recurrence rate was associated with STAI when compared to CB (HR 0.30; 95% CI: 0.13-0.71).

Secondary analysis

The pooled Solimene et al. [8] and Hussein et al. [9] STAI patient-level data was associated with a lower estimate of the absolute cumulative probability of arrhythmia recurrence (0.12; 95% CI: 0.08-0.16) than the pooled CB cohort (0.17; 95% CI: 0.12-0.23) at 12-month follow-up. As a result, in the naïve comparison, ablation with STAI was associated with a 31% lower rate of arrhythmia recurrence than CB, but this was not statistically significant (HR 0.69; 95% CI: 0.41-1.15). Similar trends were observed after matching patients, (44% relative reduction in rate, HR 0.56; 95% CI: 0.31-1.01), after matching and adjusting for age and sex (39% relative reduction in rate, HR 0.61; 95% CI: 0.32-1.15), and in the scenario analysis adjusting for age (43% relative reduction in rate, HR 0.57; 95% CI: 0.31-1.05), which excluded sex based on *a priori* clinical ranking (**Figure 5**).

Sensitivity Analyses Results

Pairwise Comparison of STAI IPD to Individual CB Studies

Pairwise comparison of Solimene et al. [8] STAI IPD to individual CB cohorts showed rates of arrhythmia recurrence similar to those in the primary analysis (**Appendix S4**).

DISCUSSION

Main findings. This study, which used IPD to compare the effectiveness of STAI to that of CB on recurrence of atrial arrhythmias 12 months after catheter ablation in patients with PAF, found that: 1) ablation using STAI was associated with reductions in recurrence of atrial arrhythmias compared to CB, before, and after matching and adjusting for differences between studies and patient characteristics; 2) the results were robust across multiple scenario and sensitivity analyses.

Comparison between RF and CB. Pulmonary vein isolation is the cornerstone of all ablation strategies in AF. However, it can be challenging, and there is a significant learning curve in developing the skills needed to safely and effectively perform point-by-point RF ablation under 3D electroanatomical guidance. Therefore, novel catheter designs with alternative energy sources have been developed. Many of these novel catheter technologies are balloon-based ablation systems using various energy modalities such as cryoenergy, laser, and RF [2]. Among them, CB ablation is the widest used and recommended in the current guidelines as an alternative to point-by-point RF [1]. Several randomized trials have compared the efficacy and safety of RF and CB catheters [20-25]; however, of these published studies, few have included advanced catheter ablation technologies [25, 26]. Furthermore, the FIRE AND ICE study, which included some advanced catheter ablation technologies, was not balanced in terms of use of advanced technologies. Specifically, approximately 75% second-generation CB and only approximately 25% second-generation RF ablation catheters were used; therefore, the study was not sufficiently powered to compare advanced technologies [26, 27].

Recently, use of Ablation Index in RF catheter ablation has shown that it allows for acute and durable PVI followed by a high single-procedure arrhythmia-free survival at 12 months [8, 9, 11, 13]. One of the limitations of CB is that it is dependent upon the pulmonary vein (PV) size and anatomy, with the ablated area often being more distal in patients with tubular left common PVs, or in large funnel-shaped veins. Focal RF ablation has the advantage of versatility and is well equipped to deal with variations in PV anatomy. Prior to the advent of Ablation Index, this advantage of RF was somewhat negated by the high rate of PV reconnection; however, now that AI-guided ablation has been shown to result in high rates of durable PVI , this superiority has come to the fore.

In the absence of head-to-head trials comparing STAI and CB, we conducted an unanchored MAIC to evaluate the impact of STAI on recurrence of atrial arrhythmias compared to that with CB 12 months after catheter ablation, with corrections for differences in study protocols and populations. The present analysis provides robust, pooled, comparative evidence for the latest generations of catheter ablation devices used in the treatment of PAF, namely the THERMOCOOL SMARTTOUCH™ Catheter with Ablation Index and the Arctic Front Advance™ CB catheter. In the naïve (ie, unmatched and unadjusted) comparison, better outcomes are apparent with STAI when compared to the pooled CB cohort. Matching and adjustment to minimize differences in study populations between the Solimene et al. [8] IPD and a pooled CB cohort confirmed and strengthened the outcome difference in favor of STAI (59% relative reduction in rate; HR 0.41; 95% CI: 0.20-0.85), indicating that between-study differences in patient populations diminished the greater efficacy of STAI in naïve comparisons. When the Solimene et al. [8] and Hussein et al. [9] IPD were pooled, STAI resulted in a 39% lower rate of 12-month arrhythmia recurrence than CB (HR 0.61; 95% CI: 0.32-1.15). The reduction in the relative efficacy of STAI when both STAI datasets were pooled corresponds with the lower estimate of absolute efficacy for STAI in this dataset (cumulative probability of arrhythmia recurrence: 0.12; 95% CI: 0.08-0.16) than in the Solimene et al. [8] IPD set (cumulative probability: 0.09; 95% CI: 0.05-0.14). This result is not unexpected as the unmatched and unadjusted comparison of STAI IPD for PAF patients from Hussein et al. [9] to the pooled CB cohort showed no difference in the rate of arrhythmia recurrence between the two treatments (HR 0.98; 95% CI: 0.42-2.29). Although pooled IPD were made more similar to the CB cohort through matching on study inclusion/exclusion and adjusting for prognostic factors and treatment-effect modifiers, not all differences between the STAI studies were adjusted for due to lack of reporting or insufficient data to adjust for. For example, the method and timing for monitoring arrhythmia recurrence at discharge and throughout the follow-up period varied across studies, potentially influencing reported recurrence rates; however, data that would allow for adjustment of this variable were not available (**Appendix S10**).

Procedural outcomes were not compared in the present analysis. However, cross-study comparisons suggest that procedure time with Ablation Index-guided ablation is similar to that reported for CB. Reported mean total procedure time ranged from 95 to 175 minutes in Ablation Index-guided procedures [10], compared to 90.5 to 250.5 minutes in CB procedures [28]. On average, mean fluoroscopy time is shorter with Ablation Index-guided ablation ranging from 5 to 11.9 minutes [10], in contrast to 0 to 61 minutes with CB-guided ablation [28].

Impact of new RF lesion-quality markers. Contact between catheter tip and tissue, duration, power, impedance, and temperature have all been shown to be important determinants of lesion size and depth during point-by-point RF catheter ablation [13]. In the past 10 years several new features have been introduced to enhance our capability to monitor RF lesion formation, allowing a safe and effective PVI procedure that deploys durable, contiguous and transmural lesions. Using contemporary RF catheter ablation technologies, both re-ablation following first PVI and PV reconnection rates at second PVI procedure, have significantly decreased, as demonstrated in two large, single centre studies [29, 30]. A recently study confirmed that PV reconnection did not occur in the majority of patients after a single PVI procedure using STAI and the "CLOSE" protocol [31]. These findings may help to explain the results of our analysis which show a significantly lower 12-month recurrence rate after ablation for PAF than has previously been reported [22, 26].

Strengths & Limitations. A major strength of this study was that prognostic factors and treatment-effect modifiers reported in STAI and CB studies were ranked *a priori* and independently by electrophysiologists (**Appendix S11**), and subsequently adjusted for to reduce any potential bias due to differences in study protocol or populations. However, unanchored MAICs are subject to several inherent limitations. First, the absence of a common comparator within the IPD and comparator trials means that an

unanchored MAIC is unable to adjust for differences in prognostic factors and treatment-effect modifiers that cannot be explained by observed differences in prognostic characteristics between trials. Secondly, the ability to reduce imbalances by matching patient populations may be limited by incomplete reporting of eligibility criteria within the comparison trials of interest or by the absence of variables that might otherwise have been used to eliminate patients from the IPD sets who would not have met the eligibility criteria of the comparison study. That is, further adjustment for residual imbalances in patient characteristics is limited to baseline characteristics that are available in the IPD and reported in the comparison trial. In this study, the primary analysis adjusted for one factor (age), which was available in the Solimene et al. [8] IPD and each of the three comparison trials. Adjustment of up to four additional factors (eg, age, LVEF, diabetes, and sex) common to studies in scenario analyses comparing Solimene et al. [8] to the pooled CB cohort and pairwise comparisons of Solimene et al. [8] to individual CB studies consistently showed a lower rate of arrhythmia recurrence with STAI than with CB. Lastly, the ability to adjust for prognostic factors and treatment effect modifiers depends on having a sufficient sample size. Although a planned MAIC using only the Hussein et al. [9] IPD data was not feasible because of an insufficient sample size of PAF patients, the dataset was pooled with that from Solimene et al. [8], and results showed numerical reductions in the relative rate of recurrence that were similar to the primary analysis.

CONCLUSION

In conclusion, ablation using THERMOCOOL SMARTTOUCH™ with Ablation Index was associated with reductions in recurrence of atrial arrhythmias at 12-month follow-up compared to CB. Despite limitations inherent to conducting an unanchored MAIC, results were consistent with naïve comparison, and similar across multiple scenario and sensitivity analyses. As such, this analysis provides further evidence available for decision-makers.

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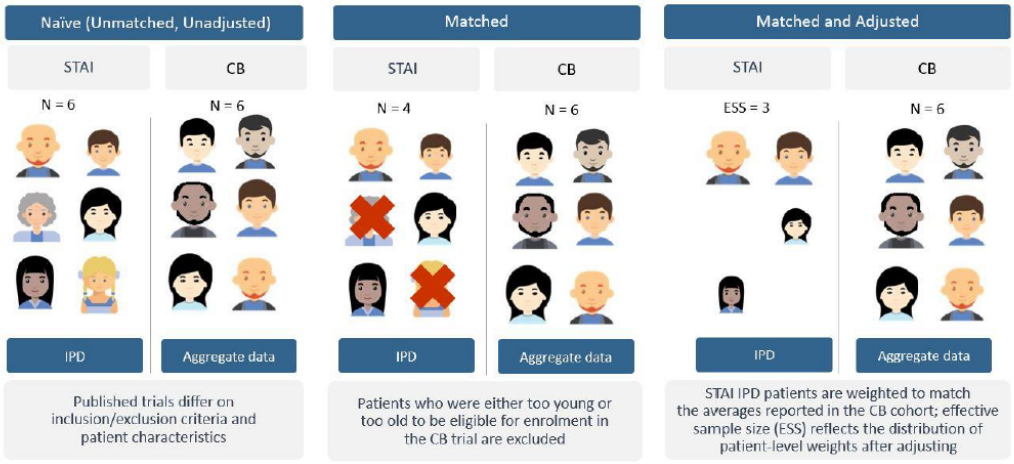
FIGURES

Figure 1: Matching and adjusting for MAIC

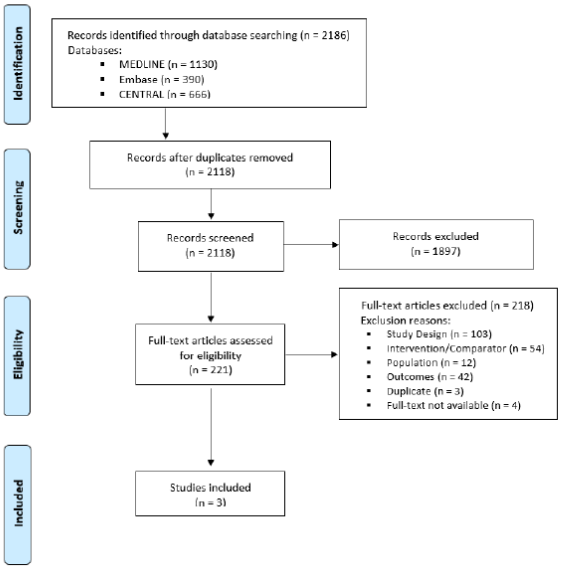


MAIC is a robust method used to reduce differences in patient cohorts from two studies, where IPD from the intervention study is matched and adjusted to aggregate data from a comparator study. **Naïve (Unmatched, Unadjusted):** Published trials differ on inclusion/exclusion criteria and patient characteristics. In a naïve comparison, outcomes from the intervention study (ie, STAI) is compared to those from the comparator study (ie, CB) without considering differences in patient cohorts. **Matched:** During matching, patients from the STAI IPD that would not have been included in the CB study are removed (eg, removal of pediatric patients and patients >90 years old from the STAI study to better match the inclusion criteria of patients 18-90 years old in the CB study). **Matched and Adjusted:** Patients in the STAI IPD are then reweighted to reduce differences in baseline characteristics with the CB study (eg, females from the STAI study can be down-weighted to simulate the same proportion of females in the CB study). This reduces the size of the effective sample (ESS) in the STAI study, which reflects a practical sample size after adjusting.

Abbreviations: CB = cryoballoon; ESS = effective sample size; IPD = individual patient-level data; MAIC= matched-adjusted indirect comparison; N = sample size; STAI = ®THERMOCOOL SMARTTOUCH™ with Ablation Index.

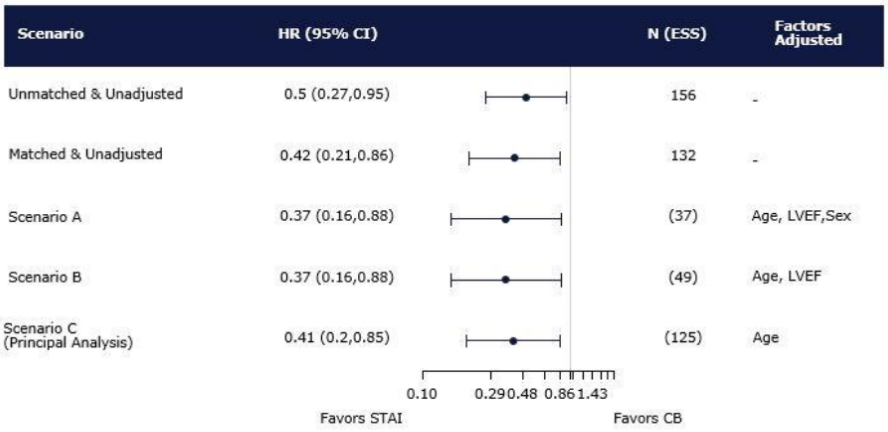
Icons altered from Freepik from www.flaticon.com

Figure 2: PRISMA flow diagram for results of the CB literature review



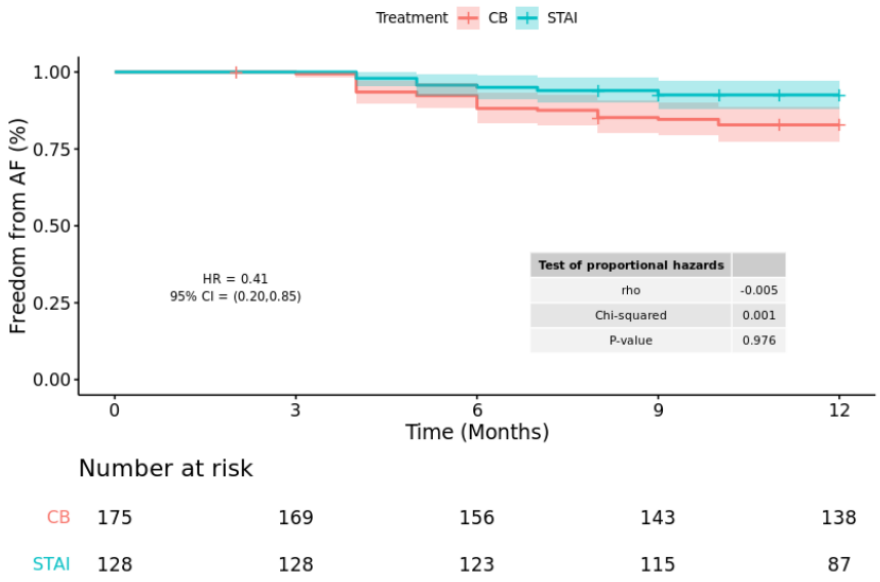
Abbreviations: CB = second-generation cryoballoon; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Figure 3: Hazard ratio for AF recurrence (Solimene IPD vs. pooled CB cohorts)



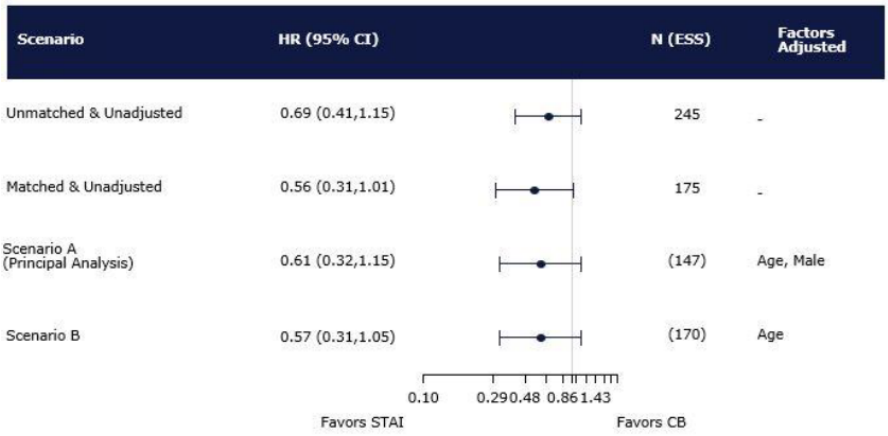
Forest plot for Solimene IPD vs. pooled CB cohorts showing the HR (95% CI) for arrhythmia recurrence with STAI compared to CB at 12-months follow-up. Hazard Ratio < 1 represents lower recurrence with STAI than CB, whereas HR > 1 represents greater recurrence with STAI than with CB.
Abbreviations: AF = atrial fibrillation; CB = second-generation cryoballoon, ESS = effective sample size; IPD = individual patient data; ITC = indirect-treatment comparison; HR = hazard ratio; STAI = THERMOCOOL SMARTOUCH™ with Ablation Index.

Figure 4: Kaplan-Meier curve of freedom from AF comparing Solimene IPD to pooled CB trials



Abbreviations: AF = atrial fibrillation; CB = second-generation cryoballoon; CI = confidence interval; HR = hazard ratio; KM = Kaplan-Meier; STAI = THERMOCOOL SMARTTOUCH™ with Ablation Index.

Figure 5: Hazard ratio for AF recurrence (Solimene + Hussein IPD vs. pooled CB cohorts)



Forest plot for Solimene + Hussein IPD vs. pooled CB cohorts showing the HR (95% CI) for arrhythmia recurrence with STAI compared to CB at 12-months follow-up. Hazard Ratio < 1 represents lower recurrence with STAI than CB, whereas HR > 1 represents greater recurrence with STAI than with CB.
Abbreviations: AF = atrial fibrillation; CB = second-generation cryoballoon; ESS = effective sample size; IPD = individual patient data; ITC = indirect-treatment comparison; HR = hazard ratio; STAI = THERMOCOOL SMARTTOUCH™ with Ablation Index.

TABLES

Table 1: Summary of study design, patient selection, and reported efficacy outcome in STAI and CB studies

	Individual Patient Data (STAI) All Patients			Individual Patient Data (STAI) PAF Patients			Summary-Level Data (CB)			
	Solimene	Hussein	Pooled	Solimene	Hussein	Pooled	Giovanni	Jourda	Zhao	Pooled
Sample Size	156	89	245	132	43	175	50	75	50	175
Age (years)	58.3 (10.0)	62.2 (9.1)	59.7 (9.9)	57.9 (10.2)	61.6 (10.4)	59.8 (10.4)	54.8 (12.7)	59.9 (9.8)	60.4 (11.2)	58.4 (11.5)
Male, N (%)	76 (48.7)	67 (75.3)	143 (58.4)	63 (47.7)	29 (67.4)	92 (52.6)	32 (65.0)	55 (73.3)	40 (80.0%)	113 (72.8)
PAF, N (%)	132 (84.6)	43 (48.3)	175 (71.4)	-	-	-	50 (100.0)	75 (100.0)	50 (100.0)	175 (100.0)
Body Mass Index	-	29.0 (4.8)	-	-	29.0 (4.8)	-	-	28.2 (4.6)	-	-
CHADS	-	0.7 (0.8)	-	-	0.5 (0.6)	-	1.1 (1.0)[a]	0.7 (0.9)	0.8 (0.4)	-
Diabetes, N (%)	6 (3.8)	13 (14.8)	19 (7.8)	5 (3.8)	3 (7.1)	8 (4.6)	-	6 (8.0)	7 (14.0)	-
Heart disease, N (%)	69 (44.2)	-	-	61 (46.2)	-	-	-	8 (10.7)	9 (18.0)[b]	-
Heart failure, N (%)	-	2 (2.3)	-	-	0 (0.0)	-	2 (4)	5 (6.7)	-	-
Hypertension, N (%)	-	30 (34.1)	-	-	12 (28.6)	-	11 (22.0)	26 (34.7)	18 (36.0)	55 (31.4)
Left atrium diameter (mm)	45.4 (8.5)	42.2 (6.0)	44.2 (7.8)	45.2 (8.3)	39.2 (5.7)	43.8 (8.2)	41.2 (6.4)	-	-	-
Left atrium volume (ml)	84.3 (31.4)	-	-	84.6 (32.5)	-	-	-	-	-	-
Left ventricular ejection fraction (%)	57.1 (5.8)	-	-	57.3 (6.0)	-	-	60.0 (5.8)	64.4 (7.4)	61.0 (7.9)	61.9 (7.1)
Stroke/TIA, N (%)	2 (1.3)	3 (3.4)	5 (2.0)	1 (0.8)	1 (2.4)	2 (1.1)	-	3 (4.0)	-	-

Values presented as N (%) or mean (SD).
Abbreviations: CB = second-generation cryoballoon; PAF = paroxysmal atrial fibrillation; ml = milliliters; mm = millimeters; N = number; STAI = THERMOCOOL SMARTOUCH™ with Ablation Index; TIA = transient ischemic attack.
[a] CHA_2DS_2-Vasc; [b] Cardiopathy (any).

Table 2: Summary statistics for CB trials, pre-matched IPD, post-matched IPD, and matched and adjusted IPD in the primary analysis of recurrence of atrial arrhythmias after a single procedure

Variables	Pooled Summary-Level Data (CB)	Solimene Individual Patient Data (STAI)		
		Unmatched	Matched	Matched and Adjusted
Age (years)	58.4 (11.5)	58.3 (10.0)	57.9 (10.2)	58.4 (11.6)
N (ESS)	155	156	132	(125)
MAIC Diagnostics	Proportion of matched IPD set with MAIC weights = 0			0% [a]
	Distance of MAIC weights from unity, median (Q1, Q3)			-0.69 (-0.81, -0.36)

Values presented as N (%) or mean (SD).
Abbreviations: CB = second-generation cryoballoon; ESS = effective sample size; IPD = individual patient data; MAIC = matched adjusted indirect comparison; N = number; Q1 = first quartile; Q3 = third quartile; STAI = THERMOCOOL SMARTOUCH™ with Ablation Index.
[a] See **Appendix S7**. MAIC weight histograms.

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ORIGINAL ARTICLE

WILEY

Prospective use of Ablation Index targets improves clinical outcomes following ablation for atrial fibrillation

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Abstract

Aims: Late recovery of ablated tissue leading to reconnection of pulmonary veins remains common following radiofrequency catheter ablation for AF. Ablation Index (AI), a novel ablation quality marker, incorporates contact force (CF), time, and power in a weighted formula. We hypothesized that prospective use of our previously published derived AI targets would result in better outcomes when compared to CF-guided ablation.

Methods: Eighty-nine consecutive drug-refractory AF patients (49% paroxysmal) underwent AI-guided ablation (AI-group). AI targets were 550 for anterior/roof and 400 for posterior/inferior left atrial segments. Procedural and clinical outcomes of these patients were compared to 89 propensity-matched controls who underwent CF-guided ablation (CF-group). All 178 procedures were otherwise similar, and both groups were followed-up for 12 months. The last 25 patients from each group underwent analysis of all VisiTags™ for ablation duration, CF, Force-Time Integral, and impedance drop.

Results: First-pass pulmonary vein isolation (PVI) was more frequent in AI-group than in CF-group (173 [97%] vs. 149 [84%] circles, $P < 0.001$), and acute PV reconnection was lower (11 [6%] vs. 24 [13%] circles, $P = 0.02$). Mean PVI ablation time was similar (AI-group: 42 ± 9 vs. CF-group: 45 ± 14 minutes, $P = 0.14$). Median impedance drop for AI-group was significantly higher than in CF-group (13.7 [9-19] Ω vs. 8.8 [5.2-13] Ω, $P < 0.001$). Two major complications occurred in CF-group and none in AI-group. Atrial tachyarrhythmia recurrence was significantly lower in AI-group (15 of 89 [17%]) than in CF-group (33 of 89 [37%], $P = 0.002$).

Conclusion: AI-guided ablation is associated with significant improvements in the incidence of acute PV reconnection and atrial tachyarrhythmia recurrence rate compared to CF-guided ablation, potentially due to creation of better quality lesions as suggested by greater impedance drop.

KEYWORDS
ablation index, atrial fibrillation, contact force, impedance drop, pulmonary vein isolation

1 | INTRODUCTION

Complete pulmonary vein isolation (PVI) is the primary target for catheter ablation of both paroxysmal and persistent atrial fibrillation (AF).[1] However, even when complete PVI has been achieved with radiofrequency (RF) ablation, high rates of late PV reconnection are seen, leading to AF recurrence.[2] Therefore, several strategies have been suggested to maximize the durability of RF ablation lesions, including the prospective use of real-time monitoring of contact force (CF) or minimum Force-Time Integral (FTI) targets during each ablation application.[3,4] Although the use of CF and FTI targets has resulted in improved AF ablation outcomes, up to two-thirds of patients were still found to have at least one reconnected PV at repeat procedures performed 2–3 months after the initial ablation.[3–5]

There therefore remains a need for a more effective lesion delivery strategy in order to achieve enduring PV isolation with a

single ablation procedure. A novel marker of ablation lesion quality that incorporates power in addition to CF and time in a weighted formula was found to accurately estimate ablation lesion depth in preclinical studies.[6] This formula, termed Ablation Index (AI), has been integrated as an ablation lesion quality monitoring module into the automated lesion tagging software (VisiTag™) in the CARTO 3 V4 3-D electroanatomic mapping system (Biosense Webster, Inc., Diamond Bar, CA, USA). A multicenter retrospective study and a prospective study involving protocol-mandated repeat procedures used VisiTag™ analysis to determine minimum regional AI target values that would be required to prevent PV reconnection (acute reconnection in the former study and late reconnection at protocol-mandated repeat study after 2 months in the latter) in the various left atrial (LA) regions.[7,8]

We hypothesized that the prospective use of AI-guided ablation using the derived target values from these studies would result in an improvement in acute PV reconnection and clinical outcomes when compared to previously used CF-guided ablation. We also hypothesized that AI-guided lesions would result in a greater impedance drop compared to CF-guided lesions, suggestive of more effective lesion creation.

2 | METHODS

2.1 | Study patients

The study included consecutive patients who underwent first-time RF PVI for symptomatic drug-refractory AF by two electrophysiologists at our institution between January 2013 and December 2015. Both operators (DG/RS) had prior experience of over 500 RF PVI procedures, including >200 procedures with CF-sensing catheters since 2011. Procedures performed between January 2013 and October 2014 were CF-guided, whereas those between November 2014 and December 2015 were AI-guided. Each patient provided written informed consent before the procedure. Outcome data were extracted from an institutional review board-approved registry. The first 10 patients treated with AI-guided ablation (AI learning curve) were excluded, as were patients who had been involved in any other research study. After exclusions, the final AI-guided ablation cohort (AI group) was propensity-matched with the CF-guided cohort so that a final CF-guided cohort was derived (CF group).

2.2 | AF ablation technique

The procedures were performed under either conscious sedation or general anesthesia, under uninterrupted oral anticoagulation and with the use of vascular ultrasound to guide venous access.[9] Our standard ablation technique has been published previously.[5] Intravenous heparin was administered at the time of transseptal puncture and as needed, targeting an activated clotting time of ≥300 seconds. In all cases, a 3-D navigation system (CARTO 3, Biosense Webster, Inc.) was used to create an electroanatomical map of the left atrium (LA) with possible integration with a computed tomography or magnetic resonance imaging reconstruction of the LA (CartoMerge, Biosense Webster, Inc.).

A baseline fast anatomical map of the left atrium was created using a 20-pole spiral catheter (Lasso NAV, Biosense Webster, Inc.), and between 8–10 "location-only" points were acquired with the ablation catheter (Thermocool SmartTouch, Biosense Webster, Inc.) around each vein pair. Care was taken that these points were ≥10 mm outside the PV ostia, and that the local electrograms did not show near-field PV signals. RF was then delivered in a point-by-point fashion joining these location-only points. Wide area circumferential ablation (WACA) was performed around each PV pair using the Thermocool SmartTouch CF-sensing RF ablation catheter, advanced via a nonsteerable sheath (Mullins, Cook *Inc.*, Bloomington, IN, USA). Point-by-point lesions were created at least 10 mm outside the PV ostia, except on the anterior ridge of the lateral PVs, where lesions were delivered just inside the ridge. Automated lesion tagging (VisiTag™, Biosense Webster, Inc.) was used to mark the location of each lesion, with the lesion tag display size of 2 mm. The VisiTag™ settings were as follows: minimum time 8 seconds, maximum range 3 mm, minimum CF 5 g and force-over-time 30%. These VisiTag™ settings were identical to the ones used in earlier published work from which AI targets were derived.[8] The RF lesions were contiguous (center-to-center distance <5 mm) as confirmed by the overlap of adjacent VisiTag™ lesions. The power settings were 25–40 W depending upon the region of the LA being targeted. Esophageal temperature was monitored continuously for cases performed under general anesthesia, and RF delivery was terminated when esophageal temperature reached >39 °C.

During Phase 1 of the study (CF group: January 2013 to October 2014), lesion creation was guided by CF targets of 5–40 g, aiming for local signal attenuation of ≥80% at each point. These parameters were agreed on by the UK Multicentre Trials Group for a randomized trial running concurrently assessing the efficacy of CF-guided AF ablation.[10] Procedures performed in Phase 2 (AI group: November 2014 to December 2015) were guided by AI target values for each lesion as follows: 550 for anterior/roof segments and 400 for posterior/inferior segments of the LA. These target values were rounded up from the values of 540 and 380 that had been found to have 100% positive predictive value for absence of acute reconnection in the anterior/roof and posterior/inferior segments respectively in a previous multicenter study.[7] In case of catheter displacement before an AI target could be reached, RF was recommenced at the same spot until a lesion reaching the target value was placed. If RF delivery had to be terminated because of a rise in esophageal temperature, a subtherapeutic AI lesion was accepted. As AI is the composite of CF, power and time, operators were at liberty to alter its individual components as long as the pre-specified target AI value was achieved as the end point of ablation. The broad range of CF aimed for in Phase 2 was the same as that used during Phase 1 at 5–40 g, but by midway during Phase 2 of the study, the operators felt comfortable to increase delivered powers from 30 W to 35–40 W, so as to allow the AI targets to be reached with shorter RF applications.

Impedance drop and FTI values were not monitored prospectively nor targeted during ablation in either group.

The Lasso NAV catheter was positioned inside the WACA circle during ablation, and first pass isolation was defined as isolation of both ipsilateral pulmonary veins that occurred either before or at completion of the WACA lesion set, without the need for ablation on the intervenous carina or for additional segmental ablation. The WACA circle was completed even in cases where first pass isolation occurred before the completion of the circle.[2] A waiting period of at least 20 minutes after the last circle was mandated.[11] Note that 15 mg of intravenous adenosine was administered for each WACA circle to unmask dormant PV reconnection if no spontaneous reconnection was seen.[12] Any spontaneous or adenosine-induced reconnection was addressed with further RF application.

In patients with paroxysmal AF, the lesion set in the LA was restricted to PVI only. Patients underwent cavotricuspid isthmus (CTI) ablation in addition if they had documented atrial flutter. In some patients with nonparoxysmal AF, the LA posterior wall was targeted with a box lesion set as per the standard practice of one of the operators.[13] No additional linear lesions and no ablation of CFAEs were performed in any patient.

2.3 | Clinical follow-up

All patients were followed up at three monthly intervals with mandatory 12-lead ECG recordings, supplemented with symptom-determined 24-hour Holter ECG monitoring as needed. All antiarrhythmic drugs were stopped by 3 months. Atrial tachyarrhythmia (AT) recurrence was defined as >30 seconds of any atrial arrhythmia (AF, atrial flutter, or atrial tachycardia) documented on ECG after a 3-month blanking period without antiarrhythmic drugs. To allow for the different time periods of procedures in the two groups, follow-up duration was capped at 12 months for all patients.

2.4 | Ablation lesion data analysis

The last 25 patients from each group underwent detailed offline retrospective analyses of each of their WACA circle ablation lesions. The data for each VisiTag™ included: ablation duration, CF, impedance drop, FTI, and AI. CF was defined as the mean CF during ablation, and impedance drop as the difference between the preablation and the lowest recorded impedance values during ablation. Impedance drop, which is the only tissue-related ablation parameter in the VisiTag™ module, was used as a surrogate to evaluate ablation lesion effectiveness. An impedance drop cutoff of ≥10 Ω was chosen as a predictor of adequate lesion formation based on observations from previous *in vitro*[14] and human studies.[15,16]

The CARTO 3 system automatically calculates FTI and AI values for each lesion. FTI is calculated by multiplication of the mean CF during energy application by the duration of the application and is measured in gram seconds (gs). AI is calculated using a complex weighted exponential formula allocating different weights to CF, time, and power.[6]

To analyze the effect of using different AI target values for the various LA regions, each WACA circle was divided into six segments (roof, two anterior, inferior, and two posterior). We then categorized the segments into two categories according to the regional AI targets used for the AI group (anterior/roof segments and posterior/inferior segments; Fig. 1).

2.5 | Statistical analysis

Propensity matching was used to adjust for patient age, sex, LA size, and type of AF when comparing study groups. Continuous variables were expressed as mean and standard deviation if they were normally distributed, or median and quartiles (25th–75th percentiles) if they were not normally distributed. For continuous variables, Student's *t*-test, Mann–Whitney *U* test, or Kruskal–Wallis test was used for unpaired group comparison. Categorical variables were presented as frequency or percentage and were compared by the x^2 test. Spearman's rank correlation coefficient was used to assess the correlation between various variables. Multiple linear regression analysis was used to assess the relationship between ablation group, ablation lesion parameters and impedance drop. Univariable and multivariable logistic regression analysis were used to assess the predictive value of ablation group and ablation lesion parameters for ablation clinical outcome success defined as freedom from AT at 12 months. The multivariable model included predictors with a univariable significance level of $P < 0.1$. Receiver operating characteristic curve (ROC) analysis was performed to determine the optimum AI values that would result in a clinically relevant impedance drop in the various LA regions. All tests were two-sided and a P value <0.05 was considered statistically significant. All statistical analysis was performed using SPSS (version 24, IBM Corp., Armonk, NY, USA).

3 | RESULTS

Ninety-nine patients underwent AI-guided PVI in Phase 2 of the study period. The first 10 cases in this cohort were excluded as their procedures were considered to have been performed during the AI-guided ablation learning curve, leaving 89 patients for analysis (AI group). One hundred and sixty-eight patients underwent CF-guided AF ablation during Phase 1 of the study period, and propensity matching with the AI-group left 89 patients for analysis (CF group).

3.1 | Patient characteristics of AI and CF groups

As the groups were propensity matched, the baseline characteristics in terms of age, sex, type of AF, LA diameter, and BMI were similar. Demographic information for both AI and CF groups is provided in Table 1.

3.2 | Procedural results of AI and CF groups

A comparison between the procedural data of the two groups is provided in Table 2. First pass WACA circle isolation was significantly higher in the AI group (173 of 178 [97%] circles compared to 149 of 178 [84%] circles in the CF group, $P < 0.001$). Of the five (3%) WACA circles in which first pass isolation failed to occur, four (80%) related to

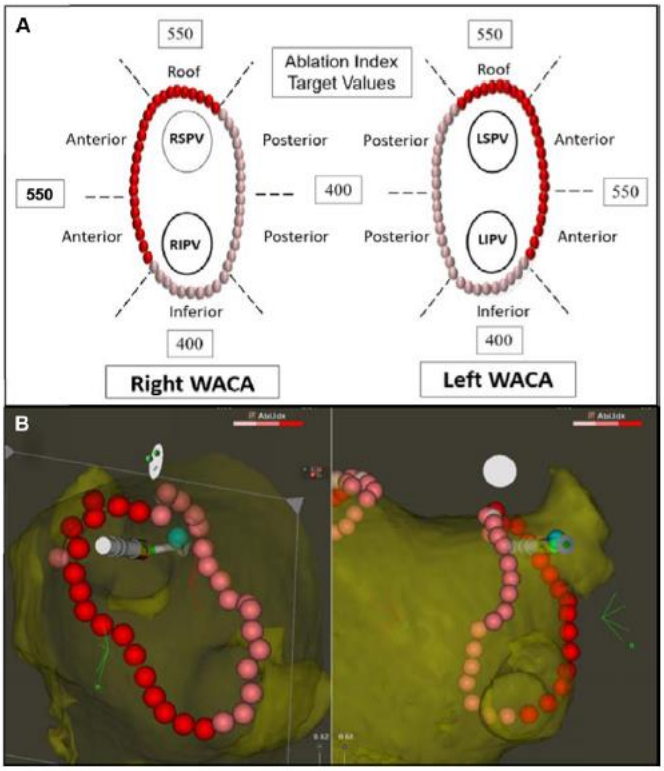

FIGURE 1 A: Diagram showing the 12 WACA segments and the AI target values used for each segment in the AI group. The red dots represent ablation lesions with AI target values ≥550 while the pink dots represent AI target values ≥400 but <550. B: Screenshots showing right WACA with VisiTags™ color-coded by AI value. The red VisiTags™ seen in the anterior/roof region have AI target values ≥550 while the pink VisiTags™ seen in the posterior/inferior region have AI target values ≥400

the right ipsilateral PVs and required further RF delivery on the right intervenous carina to achieve isolation.

After a minimum 20-minute waiting period, spontaneous PV reconnection was seen in eight (4%) circles in the AI group, compared to 19 (20%) circles in the CF group (P = 0.02). Either spontaneous or adenosine-induced PV reconnection was identified in 11 (6%) circles in the AI group (three on the left and eight on the right) compared to 24 (11%) circles in the CF group (12 on the left and 12 on the right; P = 0.02). All acute reconnections were successfully eradicated with further RF applications.

The mean PVI ablation time was similar for the two groups (AI group: 42 ± 9 vs. CF group: 45 ± 14 minutes, P = 0.14). Neither the mean procedure time (AI group: 175 ± 31 vs. CF group: 163 ± 47 minutes, P = 0.08) nor the mean fluoroscopy time (AI group: 11.9 ± 7.7 vs. CF group: 11.8 ± 5.6 minutes, P = 0.94) was significantly different between groups.

Two major complications (2%) occurred in the CF group (phrenic nerve palsy and retroperitoneal hematoma), while none occurred in the AI group (P = 0.15).

3.3 | Follow-up and clinical outcome results

The median follow-up of the CF and AI groups was identical at 12 months for each.

Recurrence of AT, defined as AT recurrence after a 3-month postablation blanking period following a single procedure off antiarrhythmic drugs, was significantly lower in the AI group than in the CF group (15 [17%] patients vs. 33 [37%] patients, P = 0.002). Kaplan–Meier survival analysis showed significantly improved freedom from AT at 12 months in the AI-group as compared to the CF-group (log rank P = 0.004, Fig. 2). Subgroup analysis showed recurrence rates were significantly lower in both the non-paroxysmal AF subgroup: (8 of 46 [17%] AI-group patients vs. 17 of 44 [39%] CF-group patients, P = 0.02), as well as in the paroxysmal AF subgroup (7 of 43 [16%] AI-group patients vs. 16 of 45 [36%] CF-group patients, P = 0.04).

3.4 | Ablation lesion data analysis

The mean number of analyzed WACA ablation lesions (VisiTags™) for each patient was 78 ± 17, and this was not significantly different

TABLE 1 Demographic information for AI and CF groups

	AI Group (N = 89)	CF Group (N = 89)	P Value
Age, years	62 ± 9.1	62 ± 9.1	0.88
Male gender, n (%)	67 (75%)	65 (73%)	0.73
LA diameter, cm	4.2 ± 0.6	4.1 ± 0.6	0.46
BMI, kg/m^2	29 ± 4.8	29 ± 5.0	0.96
Hypertension, n (%)	30 (34%)	27 (30%)	0.22
Diabetes mellitus, n (%)	13 (15%)	8 (9%)	0.24
Congestive heart failure, n (%)	2 (2%)	3 (3%)	0.65
Stroke or transient ischemic attack, n (%)	3 (3%)	8 (9%)	0.30
Mean CHADS2 Score	0.65 ± 0.77	0.65 ± 0.93	> 0.99
Mean number of failed AADs	1.4 ± 1.1	1.4 ± 1.0	> 0.99
Type of AF			0.98
PAF	43 (48%)	45 (50%)	
PeAF	31 (35%)	29 (33%)	
LSPeAF	15 (17%)	15 (17%)	
Duration of persistent AF (months)			
PeAF	7 (5–10)	9 (5–12)	0.40
LSPeAF	22 (12–28)	24 (18–33)	0.80

BMI = body mass index; PAF = paroxysmal atrial fibrillation, PeAF = persistent atrial fibrillation; LSPeAF = longstanding persistent AF; AAD = antiarrhythmic drug.

TABLE 2 Procedural data of AI and CF groups

	AI Group (n = 89)	CF Group (n = 89)	P Value
Mean fluoroscopy time, minutes	11.9 ± 7.7	11.8 ± 5.6	0.94
Mean DAP, cGY.cm^2	1,656 ± 1,425	1,613 ± 1,345	0.85
Mean PVI ablation time, minutes	42 ± 9	45 ± 14	0.14
LA posterior wall ablation, n (%)	25 (28%)	36 (40%)	0.08
CTI line, n (%)	16 (18%)	27 (30%)	0.05
Mean total ablation time, minutes	48 ± 10	53 ± 13	0.03
Mean total procedure duration, minutes	175 ± 31	163 ± 47	0.08
Complications, n (%)	0 (0%)	2 (2%)	0.15

DAP = dose area product.

between the two groups (73 ± 17 for the AI group vs. 82 ± 18 for the CF group, P = 0.09). In total, 4,018 VisiTags™ across both groups were analyzed, of which 146 VisiTags™ were excluded because of incomplete data.

3.5 | Relationship between ablation strategy, lesion parameters, and impedance drop

The median impedance drop per VisiTag™ lesion was significantly higher in the AI group than in the CF group (15.2 [11.7–18.5]Ω vs. 9.5 [7.2–12]Ω, P < 0.001, Figure 3A). In addition, the number of ablation lesions that were associated with impedance drop of ≥10 Ω was significantly higher in the AI group 1,356 (74%), compared to 899 (44%) in the CF group, P < 0.001.

The median CF was also significantly higher in the AI group than in the CF group (12.2 [9.3–17.2]g vs. 10.2 [8.0–14.0]g, P < 0.001, Figure 3B). The results of univariable logistic regression analysis for prediction of freedom from AT at 12 months are shown in Table 3. In a multivariable model including both AI-group membership and CF as covariates, AI-group membership remained independently predictive of freedom of AT at 12 months (OR = 1.94, 95% CI = 1.29–2.91, P = 0.001), whereas CF was not (OR = 1.03, 95% CI = 0.99–1.07, P = 0.18).

3.6 | Correlations between ablation index, CF, force–time integral, and impedance drop

Scatterplots showing the relationships between each of CF, FTI, and AI with impedance drop in AI group patients are shown in Figure 4. AI was found to have a highly significant but moderate correlation to impedance drop (Spearman r = 0.42, P < 0.001). Similarly, FTI correlated significantly but with moderate correlation with impedance drop (r = 0.42, P < 0.001). CF correlated significantly but weakly with impedance drop (r = 0.29, P < 0.001). A very strong correlation was seen between AI and FTI (r = 0.89, P < 0.001).

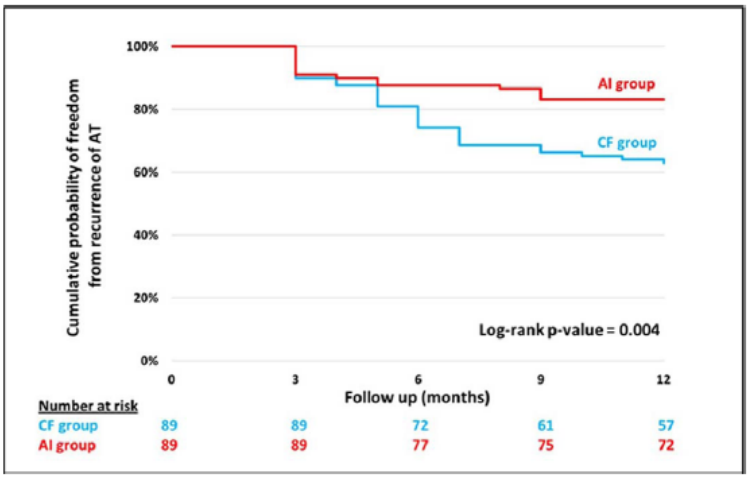

FIGURE 2 Kaplan–Meier curves of the groups' arrhythmia-free survival during the 12-month follow-up post procedure [Color figure can be viewed at wileyonlinelibrary.com]

3.7 | Regional differences in ablation lesion parameters

Table 4 depicts the regional median values of CF, FTI, AI, and impedance drop in the anterior/roof and the posterior/inferior regions in both AI and CF groups. In anterior/roof segments, the median ablation time, power, CF, FTI, AI, and impedance drop were significantly higher in the AI group as compared to the CF group. However, for posterior/inferior segments, whilst the median power, AI and impedance drop were higher in the AI group as compared to the CF group, the ablation time, CF and FTI values were similar.

3.8 | Relationship between impedance drop and regional AI target values

ROC analysis of the AI group ablation data showed that the AI cut-off (Youden Index) that predicted an impedance drop of ≥10 Ω for anterior/roof segments was 444 (sensitivity 85.1%, specificity 36.9% and positive predictive value 85.5%), and for posterior/inferior segments was 382 (sensitivity 77.8%, specificity 53.6%, and positive predictive value 75.7%).

4 | DISCUSSION

4.1 | Main findings

To our knowledge, this is the first study to investigate the prospective use of tailored AI targets to guide AF ablation, and to compare procedural and clinical outcomes to the commonly used current practice of CF-guided AF ablation.

Our findings show that, when compared to CF-guided ablation, tailored AI-guided ablation provided significantly improved outcomes in three important areas. First, better procedural outcomes were seen, with both a much higher rate of first-pass isolation and lower incidence of acute PV reconnection. Second, with regard to clinical outcomes, the AI group experienced significantly improved freedom from AT at 12 months. Third, AI-guided ablation was associated with a significantly higher impedance drop, suggesting creation of better quality lesions. Although the median CF was slightly higher in AI-guided patients who underwent detailed lesion analysis when compared to corresponding CF-guided patients, CF was found not to be independently associated with freedom from AT at 12 months. This is not surprising, as a difference of 2 g, though statistically significant in any analysis of 3,872 lesions, is unlikely to be responsible to any degree for the marked improvement in outcomes seen. In comparison, AI-group membership was independently predictive of freedom from AT at 12 months.

Furthermore, although the sample size is relatively small, there did not appear to be any signal of increased risk associated with this approach. This may well be related to the more tailored approach to LA ablation afforded by use of AI targets, with more ablation targeted to the thicker anterior portions of the chamber compared to that seen in the CF group (FTI value of 508 gs compared to 319 gs) but little change in posterior wall ablation (FTI 256 gs vs. 247 gs). Furthermore, the use of AI targets allowed delivery of higher powers, resulting in achieving greater impedance drops without the need to increase RF times or CF on the LA posterior wall.

4.2 | Advantages of AI over CF or FTI

Since the advent of CF-sensing catheters, there has been much interest in how these real-time data can be best utilized to improve AF ablation outcomes. Although some studies have suggested CF thresholds needed for durable lesion formation,[4,18] availability of CF

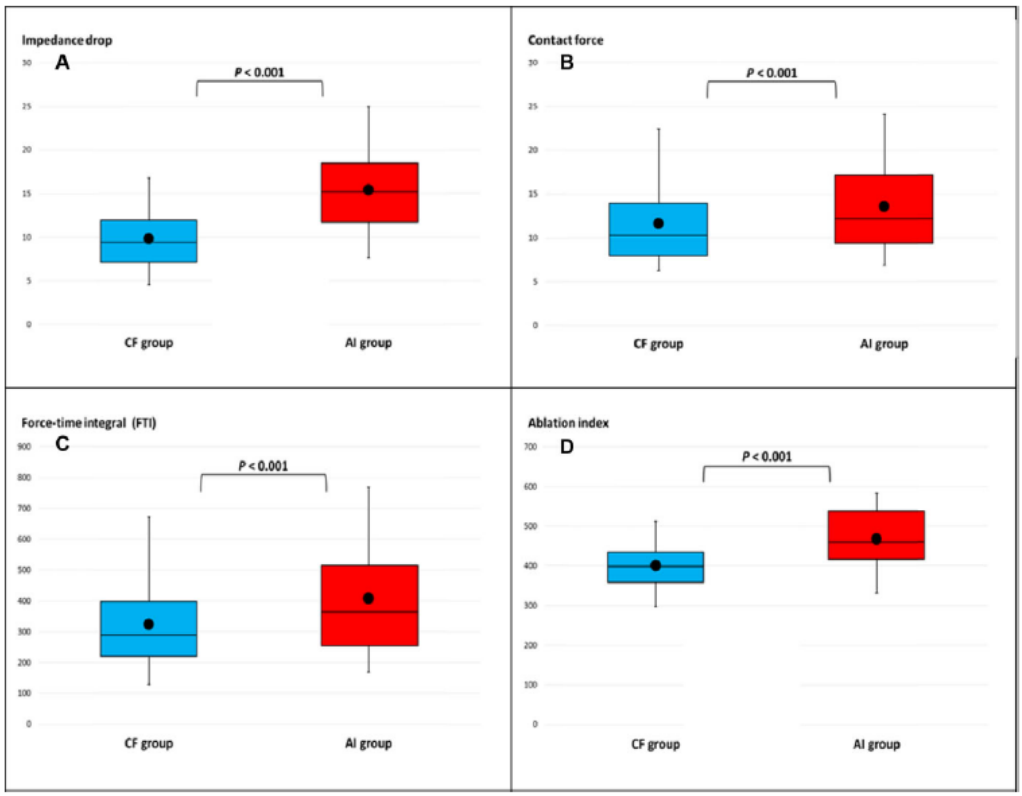

FIGURE 3 Box and whisker charts comparing A: Impedance drop in AI and CF groups, B: Contact Force in AI and CF groups, C: Force Time Integral in AI and CF groups, and D: Ablation Index in AI (prospective) and CF (calculated retrospectively) groups. Each box is bounded on the top by the third quartile and on the bottom by the first quartile. The line that divides the box is the median value and the dark dot inside the box is the mean value. The top whisker extends to the maximum value and the bottom whisker extends to the minimum value [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Logistic regression analysis for prediction of freedom from AT

	Univariable Analysis		Multivariable Analysis	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Contact force	1.03 (1.00–1.08)	0.06	1.03 (0.99–1.07)	0.18
AI group membership	2.04 (1.37–3.04)	<0.001	1.94 (1.29–2.91)	0.001

information alone has not necessarily translated into improved results.[10,19–22] This should not come as a great surprise, as lesion creation is not only dependent upon catheter–tissue contact, but also the duration of energy application and power delivery.

Recent focus has moved from CF to FTI, which combines application time with CF in a linear fashion. However, this approach still has two significant limitations. First, the interplay between CF and time in lesion creation is more complex than simple multiplication of these two factors,[23] and secondly FTI continues to omit the important role of power delivery. The latter point was clearly illustrated in an *in vitro* study by Guerra et al., in which it was shown that with a fixed FTI of 300gs, an increase from 20W to 35W resulted in an almost three-fold increase in lesion volume.[24] Accordingly, FTI target-guided ablation has been shown to improve the rate of PV reconnection at repeat study, but not to hoped-for levels, with still more than one-third of patients exhibiting one or more gaps.[4,18] AI potentially overcomes these limitations by not only incorporating power delivery, but also combining these three factors in a weighted equation which has been shown to correlate to lesion depth in an animal model.[6] The rate of late PV reconnection following AI-guided ablation is currently under evaluation (ClinicalTrials.gov NCT02628730).

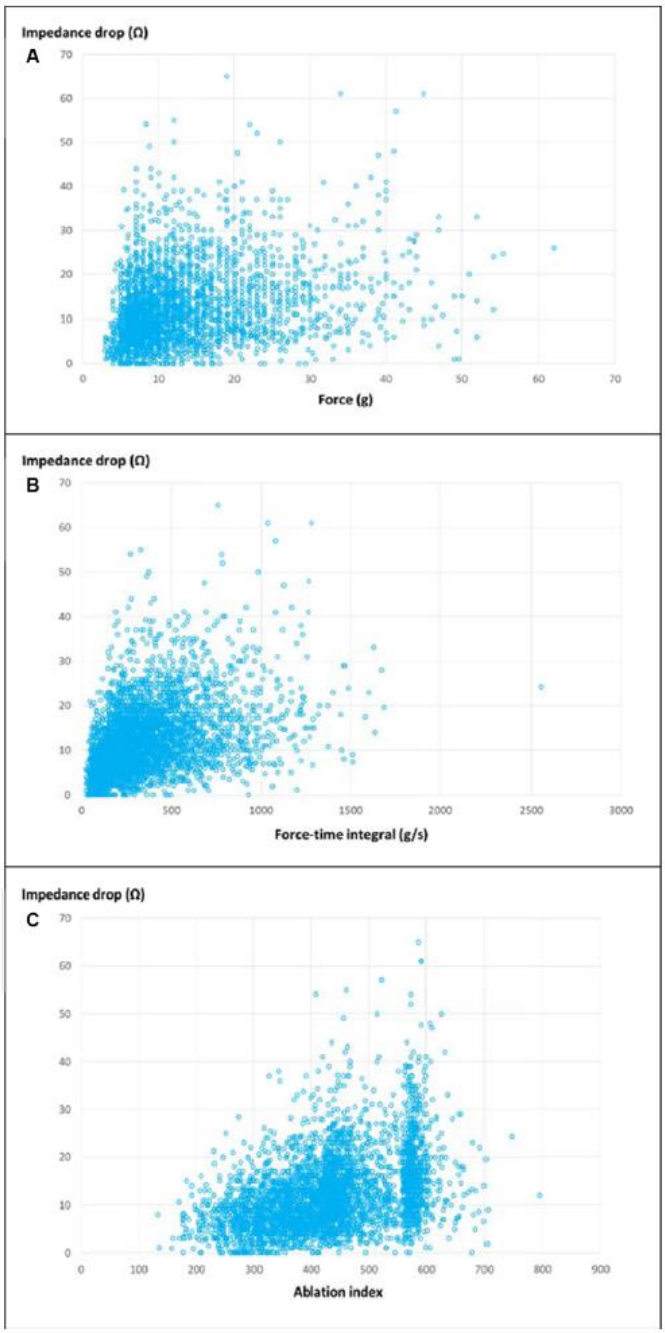

FIGURE 4 Scatter plots showing the relationships between A: CF and impedance drop, B: FTI and impedance drop, C: AI and impedance drop, and D: AI and FTI [Color figure can be viewed at wileyonlinelibrary.com]

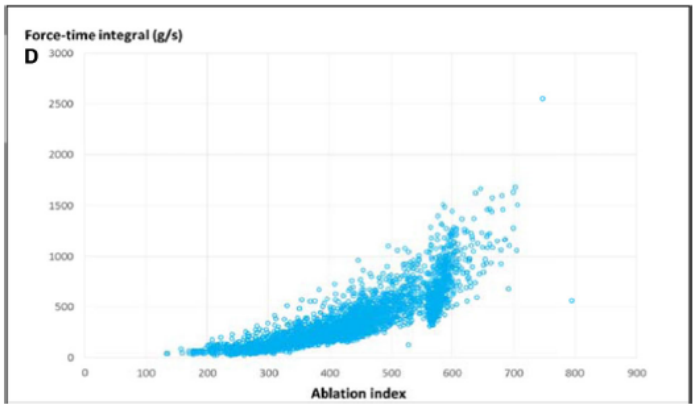

FIGURE 4 Continued

TABLE 4 Regional median values of RF times, CF, FTI, AI, and impedance drop in AI and CF groups*

		AI Group VisiTags™ (N = 1829)	CF Group VisiTags™ (N = 2043)	P Value
Time (s)				
	Anterior/Roof	36.0 (31.0–42.5)	30.0 (25.1–37.1)	<0.001
	Posterior/Inferior	25.7 (21.1–29.6)	26.3 (19.9–30.6)	0.94
Power (W)				
	Anterior/Roof	35 (34–40)	30 (30–30)	<0.001
	Posterior/Inferior	35 (30–39)	30 (29–30)	<0.001
CF (g)				
	Anterior/Roof	14.5 (11.1–19.0)	10.6 (8.5–15.8)	<0.001
	Posterior/Inferior	10.5 (8.3–13.5)	9.7 (7.8–12.6)	0.08
FTI (gs)				
	Anterior/Roof	508 (416–626)	319 (261–436)	<0.001
	Posterior/Inferior	256 (208–335)	247 (174–331)	0.16
AI				
	Anterior/Roof	537 (483–575)	416 (389–456)	<0.001
	Posterior/Inferior	420 (379–448)	376 (336–413)	<0.001
Impedance drop (Ω)				
	Anterior/Roof	16.6 (13.4–20.5)	10.3 (7.6–13.1)	<0.001
	Posterior/Inferior	13.2 (10.0–16.5)	8.8 (6.3–11.0)	<0.001

*Derived from the last 25 patients from each group.

4.3 | Regional AI target values

We have previously demonstrated that the minimum AI value required to avoid *late* PV reconnection (identified at a protocol-mandated repeat LA EP study 2 months post-PVI) in anterior and roof segments of the LA (480) was significantly higher than that required for posterior and inferior segments (370).[8] A similar difference between these segments was also observed in minimum AI values predictive of *acute* reconnection (540 vs. 380).[7] These findings are unsurprising, as it is well-recognized that wall thickness varies considerably within the LA and can be particularly thick at the anterior left PV/appendage ridge.[25]

In this study, we assessed the optimal AI values associated with an impedance drop of ≥10 Ω, a value that has been shown to predict adequate lesion formation in previous *in vitro* and human studies.[14–16] Again, a significant difference between LA regions was demonstrated (444 for the anterior/roof region compared to 382 for the posterior/inferior region), and these values were notably similar to those identified for avoidance of acute and late PV reconnection.[8]

A single FTI target value of 400–500gs has been suggested to be necessary to create adequate ablation lesions,[26,27] and, in the EFFICAS studies, to avoid late PV reconnection.[4,18] While this value may well be required in some regions of the LA, there is concern that it may be

excessive in more thin-walled areas, increasing the risk of damage to adjacent structures such as the esophagus. A recent study has demonstrated that the optimal FTI value for achieving an effective lesion is dependent on the underlying atrial wall thickness,[28] and we have previously reported that FTI values of only 230gs were associated with no reconnection of posterior/inferior segments at repeat electrophysiology study.[8]

4.4 | Clinical utility of AI-guided ablation

The primary aim of an AF ablation procedure is to deliver a lesion set that effectively and durably isolates the PVs while minimizing the risk of damage to adjacent tissue. This study demonstrates that the prospective use of AI regional target values is associated with more effective PV isolation, with less acute reconnection seen. Although all acute reconnections in both groups were eradicated by additional ablation, better clinical outcomes were noted in the AI group. This can be explained by the findings of our previous study which demonstrated that the vast majority (92%) of sites of late PV reconnection identified at repeat study did not manifest acutely in spite of a 30-minute waiting period and the use of IV Adenosine, whereas a very high proportion of acute reconnection sites (86%) remained isolated following re-ablation.[17]

Lower acute reconnection and less recurrence of AT during follow-up in the AI-guided group were both achieved without an associated increase in ablation time, as compared to CF-guided ablation alone. The use of AI targets may therefore provide a more tailored approach to LA ablation, balancing ablation efficacy with avoidance of unnecessarily excessive ablation in thin-walled, higher-risk regions. AI-guided ablation therefore has the potential to enhance PVI outcomes and merits further investigation. Future research could dwell on whether patient specific factors can be used to derive truly individualized optimal AI values for each patient.

4.5 | Limitations

Our study has several limitations. First, it is a retrospective analysis of a nonrandomized consecutive series of patients who underwent CF-guided or AI-guided AF ablation. Although the two groups underwent propensity-matching resulting in similarities in their baseline characteristics, a possible confounding effect of other unknown variables cannot be excluded. In addition, temporal bias and its associated effect via institutional and operator learning curve cannot be excluded because the two groups were recruited in a consecutive rather than parallel fashion. However, all procedures were performed by two very experienced electrophysiologists in an established high volume center, using identical equipment and an identical ablation strategy. The increase in RF power during the study period makes it difficult to exclude the possibility that some of the benefits seen in the AI group was contributed to by this change. However, in our opinion this only serves to highlight another advantage of using AI, in that it allows operators more flexibility in varying any of the component parameters of AI such as power, RF time and CF, confident in the knowledge that the total amount of delivered RF energy will be limited by the composite AI value. A further limitation is that the limited intensity of ECG monitoring on follow-up would likely fail to detect asymptomatic AF recurrences, and thereby overestimate ablation success rates. However, the monitoring protocol was identical for the two study groups, and so it is unlikely that this would have been a significant source of bias affecting one study group more than the other. Lastly, the very low rate of complications such as esophageal fistula and stroke seen in modern AF ablation practice means that our study cohort is too small to provide definitive safety assessment of the AI-guided ablation strategy. However, the same two operators have now performed AI-guided AF ablation procedures using the updated power settings in over 400 patients since November 2014, and the absence of a single case of cardiac tamponade, stroke/TIA or esophageal fistula in this cohort would appear to suggest that this strategy is likely to be at least as safe as CF-guided ablation.

4.6 | Conclusion

In this study, the first to investigate the prospective use of AI targets to guide AF ablation, AI-guided ablation was associated with significant improvements in the incidence of acute PV reconnection and in the rate of AT recurrence during follow-up, without change in the mean ablation time for PV isolation, as compared to CF-guided ablation. The use of different AI regional targets, with higher values for the anterior/roof region compared to posterior/inferior region, delivers more effective ablation to thicker-walled areas while obviating the risk of excessive ablation on thinner-walled regions.

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RAPID FIRE SESSION 4 - CATHETER ABLATION OF ATRIAL FIBRILLATION: PREDICTORS AND OUTCOME

1360

Surveillance of AF recurrence post AF ablation using implantable cardiac monitor: 3 year follow up

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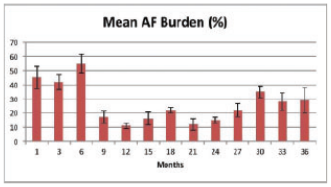
Although pulmonary vein isolation is an effective treatment for recurrent atrial fibrillation (AF), there is no consensus on the definition of success or follow up strategies. Existing data are limited to intermittent trans-telephonic monitoring with reliance on patient symptoms.
Objective: We sought to determine the outcomes of catheter AF ablation and post ablation AF surveillance with a implantable cardiac monitor (ICM)
Method: One hundred and forty-six patients with drug-refractory paroxysmal or persistent AF underwent pulmonary vein isolation. An ICM (Medtronic Reveal XT) was implanted subcutaneously post ablation to assess AF recurrence. AF recurrence was defined as >1 AF episode with a duration of >60 seconds. The device-stored data was downloaded weekly over the internet, and all transmitted events were adjudicated by two reviewers. Patients are followed every 6 months in clinic for 36 months.
Results: A total of 15860 AF automatic and patient-activated AF episodes were analyzed over a follow-up of 36 months. Of these AF episodes, 62% were asymptomatic. Furthermore, only 60% of patient-activated episodes were truly AF. AAF recurrences was highest in the first 3 months and substantially decreased 6 months post ablation. AF recurrences are common after 12 months (Fig 1). Ninety-eight patients underwent two or more AF ablations. The overall freedom from AF recurrences at the end of follow-up was 48%. Thirty-day telemetry recordings was used in 30 patients to compare the device stored episodes, the sensitivity of the device to detect AF was 98% and the specificity was 75%.
Conclusion: The ICM provides an objective measure of AF ablation success and may be useful in making clinical decision. This device could be used in future ablation studies to develop a more rigorous definition of procedural success.



Abstract 1360 Figure.

1361

Does zero atrial fibrillation burden after atrial fibrillation ablation mean that patients are free of symptoms?

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Introduction: Success of atrial fibrillation (AF) ablation is usually defined as freedom of AF, although symptomatic relief often is what the patient's desire. After ablation the proportion of 'silent' AF increases and success based on symptomatic AF recurrence may be overestimated.
Purpose: To investigate the symptomatology of patients who are truly free of AF after ablation.
Methods: In 57 patients the symptomatology after AF ablation was assessed as perceived by the patient using a validated AF-specific symptom questionnaire (AF6) and the overall treatment effect (OTE), and as classified by the physician using the EHRA score, at baseline, 6, 12 and 24 months. The cardiac rhythm was continuously monitored by an implantable loop recorder throughout the 2-year follow-up.
Results: At 6, 12 and 24 months 14 (26%), 23 (43%) and 23 (43%) patients had an AF burden 0% during the past 6 months, and 13 of them had an AF burden 0% during the entire 2 year follow-up. All patients reported 'OTE better' at all time-points. All patients were also classified into EHRA I at 6 months. Being completely free of AF for six months periods did not mean complete freedom of symptoms, but the median AF6 sum score was consistently low with a narrowing IQR over time, 0 (IQR 0-27), 0.5 (IQR 0-7) and 0 (IQR 0-11) at 6, 12 and 24 months. At 6 months 8/14 patients (57%) scored AF6=0, the others 6, 11, 26, 28, 30 and 46 points. At 12 months 13/23 patients (56%) scored AF6=0, the others 1,1,3,3,5,7,7,7,14 and 22 points. At 24 months 12/23 (52%) patients scored AF6=0, the others 1, 1, 2, 4, 9, 11, 17, 20, 24, 32 and 42 points. Among the AF6 items, 'worry/anxiety due to AF' was the most common, while 'tiredness due to AF' was the highest scoring item. In the patients with AF burden 0% during the entire 2-year follow-up all patients were improved in OTE and all patients were classified into EHRA class I at all times after ablation and the median AF6 sum score was 4 (IQR0-28), 0.5 (IQR 0-8) and 1 (0-5) at 6, 12 and 24 months after ablation.
Conclusions: Sudden elimination of AF by ablation does not automatically eliminate all symptoms that the patients associated with AF, but all patients felt better and were classified in EHRA class I at all time-points. Less than a half of the patients at any time-point scored some symptoms, but the symptoms gradually decreased over time, especially between 6 and 12 months.

1362

Prospective use of ablation index targets improves clinical outcomes following ablation for atrial fibrillation

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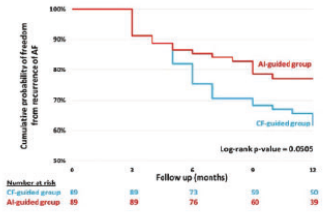
Background: Despite use of contact force (CF)-sensing catheters for PVI, atrial tachyarrhythmia (AT) recurrence due to late pulmonary vein reconnection (PVR) is still common. Ablation Index (AI) is a novel ablation quality marker that incorporates CF, time and power in a weighted formula. We hypothesised that prospective use of our previously-published derived AI ablation targets would result in better acute and late outcomes when compared to CF-guided ablation.
Methods: 89 consecutive patients (44 paroxysmal AF) underwent AI-guided PVI for symptomatic drug-refractory AF. AI targets for each lesion were 550 for anterior wall/roof and 400 for posterior/inferior walls. Procedural and clinical outcomes of these patients were compared to 89 propensity-matched controls who underwent CF-guided PVI. All 178 procedures were otherwise identical in use of Carto, VisiTag, point-by-point ablation, non-steerable sheath, and systematic Adenosine to unmask PVR. In each group, 25 patients underwent detailed analysis of all VisiTags (N=4018) for ablation duration, CF, FTI and impedance drop.
Results: Patient demographics and follow-up duration (median 12 months) were not different between groups. No major complications occurred in any patient in either group. First-pass isolation was more frequent in AI group than CF group (173 (97%) vs 149 (84%) circles, P<0.001), and acute PVR was lower (10 (11%) vs 24 (27%) patients, P=0.008). Ablation time was lower in AI group (48±10 min vs 53±13, P=0.03). The median impedance drop for AI group was significantly higher than in CF group (13.7 Ω (IQR 9-19) vs 8.8 (5.2-13), P<0.001), as was the median CF (11g (8-17) vs 9.3 (7-13.3), P<0.001). After adjustment for CF using multivariable linear regression, AI group membership was still associated with significantly higher impedance drop (P<0.001). Over the follow-up period, AT recurrence was significantly lower in AI group (19/89 (21%)) than in CF group (32/89 (36%)), P=0.03).
Conclusion: AI-guided ablation is associated with significant improvements in the incidence of acute PVR and in the rate of AT recurrence during follow-up as compared to CF-guided ablation. Impedance drop data suggest that improved results are due to creation of higher quality lesions with lower ablation times.



Abstract 1362 Figure.

1363

Incidence of major complications during electrophysiological studies and ablation procedures

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Funding Acknowledgements: Bolyai Janos Research Scholarships of the Hungarian Academy of Sciences, Hungarian Scientific Research Fund (OTKA K 105555)

Introduction: Although ablation therapy for cardiac arrhythmias has made a huge progress in terms of efficacy and safety in the past decade, major complications are still present.
Purpose: Since limited data exist regarding the burden and trends in adverse outcomes of ablation therapy, our aim was to evaluate the incidence of major complications occurring during electrophysiological studies and ablation procedures.
Methods: In our prospective study we involved all patients undergoing diagnostic and ablation procedure in our electrophysiology laboratory between January 2013 and December 2015. Occurrence of complications was evaluated within 3 months after each procedure. Only major complications – defined as an event requiring interventional treatment, causing long-term disability, death, or resulting a prolonged hospitalization – were included in our study. We evaluated data using descriptive statistics.
Results: During the three-year period 4157 procedures were performed: 1573 (38%) ablation for atrial fibrillation, 1523 (36%) for supraventricular tachycardia, 493 (12%) for ventricular arrhythmia and 568 (14%) electrophysiological studies without ablation. Major complications occurred in 50 (1.18%) cases of all events: 20 (0.48%) pericardial tamponade, 4 (0.10%) pulmonary vein stenosis, 4 (0.10%) stroke and transient ischemic attack, 9 (0.22%) vascular complications, 11 (0.26%) atrioventricular block, 2 (0.02%) death.
Conclusions: Our study provides an update on the incidence of major complications of electrophysiological studies and ablations performed at a high-volume center. Occurrence of major complications was within the previously reported range in our electrophysiology laboratory. We can assume that catheter ablation in general is associated with low risk and most complications can be treated properly by an experienced team with surgical backup.

1364

LGE-MRI atrial fibrosis predicts 5 year outcome of atrial fibrillation ablation

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Introduction: Late gadolinium enhancement magnetic resonance imaging (LGE-MRI) has been used to assess left atrial fibrosis. The degree of left atrial fibrosis has been shown to predict the 1 year success of atrial fibrillation (AF) ablation but has been studied for the long-term ablation success.
Methods: LGE-MRIs of sufficient quality to quantify atrial fibrosis were obtained in 247 consecutive patients prior their first AF ablation. Left atrial fibrosis was classified in 4 Utah stages (I: 0-10%; II: 10-20%; III: 20-30%; IV: >30%). Patients were followed up for up to 5 years and time of first arrhythmia recurrence or second ablation was recorded.
Results: Patient cohort had the following characteristics: mean age was 62.9 ±12.4 years; 39.7% were female; 45% had paroxysmal AF; mean left atrial fibrosis score was 16.3 ±10.6%. Patients with more advanced atrial fibrosis were more likely to experience recurrent AF (absolute risk of recurrence at 5 years, I: 40.0% II: 61.6%: III: 66.0% IV: 95.0%) (Figure 1). After full multivariable adjustment, patients in stage IV versus stage I had a statistically significantly higher risk of arrhythmia recurrence (HR, 4.92; 95% CI, 2.38-10.17). Patients with stage IV fibrosis were four times more likely to have a repeat ablation performed than patients in stage I.
Conclusion: The degree of left atrial fibrosis is predictive of AF ablation success at up to 5 years follow up. The long-term maintenance of sinus rhythm after AF ablation is low in patients with advanced left atrial fibrosis.

1365

Which patients develop recurrent atrial tachycardia but not atrial fibrillation after catheter ablation for atrial fibrillation?

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Background: Although it has been considered that ablation gap contributes to atrial tachycardia (AT) recurrence after radiofrequency catheter ablation (RFCA) for atrial fibrillation (AF), the underlying mechanism of AT recurrence after RFCA for atrial fibrillation AF is yet unclear.
Objective: The purpose of this study is to investigate the association of the degree of atrial remodeling and recurrence pattern after AF ablation without the effect of antiarrhythmic drugs.
Methods: Among 2047 patients who underwent AF ablation, 501 patients (351 [70.1%] men) who experienced recurrence after RFCA, excluding recurrence with the effect of antiarrhythmic drugs, were included in this study. Among these patients, 333 (66.5%) were diagnosed with paroxysmal AF. Circumferential pulmonary vein isolation (CPVI) was performed in 257 patients, while additional linear ablation after CPVI was performed in the remaining 244 patients.
Results: 1. During a mean follow-up of 43.2±24.2 months, 42.5% of the recurring atrial arrhythmias were AT, and the proportion of AT recurrence was not different between the CPVI only (44.7%) and additional linear ablation groups (40.2%, p=0.321). 2. Absence of hypertension (OR 0.529, 95% CI 0.313–0.893, p=0.017), small left atrial (LA) volume index (OR 0.979, 95% CI 0.965–0.990, p=0.002), high LA voltage (OR 1.892, 95% CI 1.171–3.058, p=0.009), and early recurrence within 3 months (OR 2.060, 95% CI 1.205–3.523, p=0.008) were independently associated with AT recurrence, whereas additional linear ablation (p=0.300) and number of ablation lines (p=0.352) were not. 3. Among 97 patients who underwent a redo-procedure, bidirectional block states of previous linear ablation (p=0.288) were not significantly different between those with AT recurrence and those with AF recurrence.
Conclusion: The degree of LA remodeling is significantly associated with AT recurrence after AF ablation, irrespective of potential ablation gaps in the linear lesion.

1366

Comparison of radiofrequency catheter ablation for paroxysmal atrial fibrillation between patients with and without sick sinus syndrome: Insights from Kansai Plus Atrial Fibrillation (KPAF) registry

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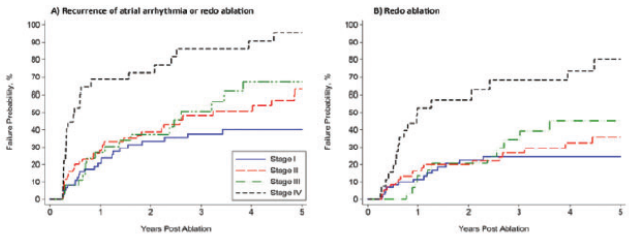

Abstract 1364 Figure.

for each vein was computed as total mm of gap divided by total vein perimeter and fibrosis percentage as fibrosis area divided by total atrial area (including ~1 cm of vein segment, excluding mitral area). Normalized fibrosis area was defined as fibrosis percentage divided by total non-gap percentage.
Results: From the cohort of 15 laser patients, one was excluded from analysis for lack of DE-CMR and two because PVI was not complete due to complications in the procedure. Gap percentage, fibrosis area and normalized fibrosis area were computed for 12 laser patients and matched RF cases. Laser patients had significantly smaller gap percentage than RF patients: 9.5%±10.3% of gap for left veins and 30.5%±25.2% of gap for right veins, compared to 34.4%±24.4% and 50.5%±30.3%, respectively. Fibrosis area was comparable for both groups (laser: 22.6%±10.9%, RF: 21.4%±12.8%), but significantly smaller in laser patients when normalized by non-gap percentage (17%±7.2% vs. 38.1%±9.3% in RF patients). Full DE-CMR isolation was achieved at 25% of laser-ablated veins and 8.3% of RF-ablated veins. Mean laser procedure time was 189.5 minutes, with 25.1 minutes of fluoroscopy time, compared to 135.6 minutes for RF procedures, with 23.6 minutes of fluoroscopy. Recurrences at 6 months presented no statistically significant difference: 25% (3 out of 12) of laser patients recurred, compared to 17% (2 out of 12) of RF patients.
Conclusion: Laser ablation requires longer procedure time but DE-CMR images show less gap and smaller fibrosis area compared to RF ablation. Procedure duration for laser may be longer due to operators being still in the learning curve.

C-PO04-99

CRYOENERGY-DOSING GUIDED BY TIME-TO-ISOLATION IN PULMONARY VEIN ISOLATION WITH THE 3RD GENERATION CRYOBALLOON: A CLINICAL 1-YEAR-FOLLOW-UP

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Background: Real time monitoring of the time-to-isolation (TTI) has emerged as a valuable parameter to estimate the quality of a lesion during cryoballoon PVI. The 3rd generation cryoballoon (Medtronic Arctic Front Advance ST, AFA-ST) facilitates real-time registration of PV isolation due to a shorter distal tip, thus enabling the implementation of TTI-based freeze protocols.
Objective: To evaluate the efficacy of an individualized freeze duration we retrospectively compared the clinical outcome of patients treated with a TTI-guided ablation protocol to the outcome of patients treated with a fixed ablation protocol.
Methods: In this monocentric, case-control trial, we compared 100 patients treated with the AFA-ST cryoballoon with a TTI-based protocol to 100 patients treated with the 2nd generation cryoballoon (Medtronic Arctic Front Advance, AFA) using a fixed freeze protocol. In the AFA-ST group freeze cycle length was 180 seconds, if TTI was between 30 and 60 s or undeterminable. Freeze duration was reduced to 120 seconds, if TTI was < 30 s. In case of a TTI > 60 s freeze cycle length was 180 seconds followed by bonus freeze of 180 seconds. In the AFA group patients were treated with a freeze cycle length of 240 seconds followed by a bonus freeze of 240 seconds after successful pulmonary vein isolation. Primary end point was recurrence of atrial fibrillation or any other atrial tachyarrhythmia.
Results: Freedom from atrial tachyarrhythmia estimated by Kaplan-Meier after one year of follow-up was not significantly different between the AFA-ST group (73%) and the AFA group (81%; p=0.134). Mean procedure duration was 87 ±27 min in the AFA-ST group compared to 115 ±28 min in the AFA group (p<0.001). Mean fluoroscopy duration was 18 ±7 min in the AFA-ST group and 22 ±10 min in the AFA group (p<0.01).
Conclusion: We suggest, that our individualized freeze protocol with a TTI-guided freeze cycle length might be as effective for pulmonary vein isolation as a protocol with a substantially longer fixed freeze duration. Procedure duration and fluoroscopy duration was significantly reduced in the AFA-ST group. Further evaluation by a randomized controlled trial are mandatory to definitely determine the efficacy of our protocol.

C-PO04-100

PROSPECTIVE USE OF ABLATION INDEX TARGETS IMPROVES CLINICAL OUTCOMES FOLLOWING ABLATION FOR ATRIAL FIBRILLATION

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Background: Despite use of contact force (CF)-sensing catheters for PVI, atrial tachyarrhythmia (AT) recurrence due to late pulmonary vein reconnection (PVR) is still common. Ablation Index (AI) is a novel ablation quality marker that incorporates CF, time and power in a weighted formula. We hypothesised that prospective use of our previously-published derived AI ablation targets would result in better acute and late outcomes when compared to CF-guided ablation.
Objective: N/A
Methods: 89 consecutive patients (44 paroxysmal AF) underwent AI-guided PVI for symptomatic drug-refractory AF. AI targets for each lesion were 550 for anterior wall/roof and 400 for posterior/inferior walls. Procedural and clinical outcomes of these patients were compared to 89 propensity-matched controls who underwent CF-guided PVI. All 178 procedures were otherwise identical in use of Carto, VisiTag, point-by-point ablation, non-steerable sheath, and systematic Adenosine to unmask PVR. In each group, 25 patients underwent detailed analysis of all VisiTags (N=4018) for ablation duration, CF, FTI and impedance drop.
Results: Patient demographics and follow-up duration (median 12 months) were not different between groups. No major complications occurred in any patient in either group. First-pass isolation was more frequent in AI group than CF group (173 (97%) vs 149 (84%) circles, *P*<0.001), and acute PVR was lower (10 (11%) vs 24 (27%) patients, *P*=0.008). Ablation time was lower in AI group (48±10 min vs 53±13, *P*=0.03). The median impedance drop for AI group was significantly higher than in CF group (13.7 Ω (IQR 9-19) vs 8.8 (5.2-13), *P*<0.001), as was the median CF (11g (8-17) vs 9.3 (7-13.3), *P*<0.001). After adjustment for CF using multivariable linear regression, AI group membership was still associated with significantly higher impedance drop (*P*<0.001). Over the follow-up period, AT recurrence was significantly lower in AI group (19/89 (21%)) than in CF group (32/89 (36%)), *P*=0.03).
Conclusion: AI-guided ablation is associated with significant improvements in the incidence of acute PVR and in the rate of AT recurrence during follow-up as compared to CF-guided ablation. Impedance drop data suggest that improved results are due to creation of higher quality lesions with lower ablation times.

ABLATION INDEX-GUIDED PULMONARY VEIN ISOLATION FOR ATRIAL FIBRILLATION MAY IMPROVE CLINICAL OUTCOMES IN COMPARISON TO CONTACT FORCE-GUIDED ABLATION

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Background: Despite use of contact force (CF)–sensing catheters for PVI, atrial tachyarrhythmia (AT) recurrence due to late pulmonary vein reconnection (PVR) is still disappointingly common. Ablation Index (AI) is a novel ablation quality marker that incorporates contact force, time and power in a weighted formula, and therefore offers potential advantages over contact force alone or Force-Time Integral. Our previously published retrospective analyses have shown that both acute and late PVR correlate highly with the minimum AI value achieved for any given PV segment. We hypothesised that prospective use of derived AI targets to guide ablation would result in lower acute PVR and improved freedom from AT during follow-up as compared to CF–guided ablation.
Methods: 64 consecutive patients underwent AI-guided PVI for symptomatic drug refractory AF. AI targets for each lesion were 550 for the anterior wall and 400 for the posterior wall. The procedural and clinical outcomes of these 64 patients were compared to 54 propensity-matched historical controls who had undergone CF-guided PVI. All 118 procedures were otherwise identical in the use of Carto, VisiTag and a point-by-point ablation strategy, as well as in the use of IVAdenosine for each WACA circle at the end to unmask latent conduction.
Results: Patient demographics, procedural characteristics, and follow up duration of the two groups are shown in the Table, and were not different between groups. No major complications occurred in any patient in either group. No spontaneous or adenosine-induced acute PVR was seen in any patient or in any WACA circle (0/64, 0/128) in the AI-guided group compared to 10 (19%) patients and 13 (12%) WACA circles in the CF-guided group (both $P < 0.001$). Over the follow-up period, AT recurrence was significantly lower in the AI-guided group (12/64 (19%)) than in the CF-guided group (19/54 (35%), $P = 0.04$).
Conclusion: The use of AI-guided ablation is associated with highly significant decreases in the incidence of acute PV reconnection and in the rate of AT recurrence during short-term follow-up compared to CF-guided ablation. This suggests the creation of more durable, higher quality lesions when AI targets are used. AI-guided ablation may therefore be beneficial in improving outcomes from PVI and merits further investigation.

Table: Patient Demographic and Clinical Characteristics of the AI-guided and CF-guided groups

	AI-guided group (n = 64)	CF-guided group (n = 54)	*P* value
Age, years	61.3 ± 10	62 ± 9.7	0.62
Sex, n (%)			
Male	45 (70%)	37 (69%)	0.83
Female	19 (30%)	17 (31%)	
Type of AF, n (%)			
PAF	35 (55%)	21 (39%)	0.08
PeAF	20 (31%)	28 (52%)	
LSPeAF	9 (14%)	5 (9%)	
BMI, kg/m^2	29.7 ± 2.3	29.4 ± 6.1	0.75
LA Size, cm	4.2 ± 0.6	4.3 ± 0.4	0.43
Total procedure duration, mins	173 ± 40	186 ± 55	0.16
Total ablation time, mins	47 ± 11	53 ± 16	0.06
Fluoroscopy time, mins	11 ± 8	12 ± 6	0.61
Mean follow-up duration, months	7 ± 3	9 ± 3	1.00

Circulation: Arrhythmia and Electrophysiology

ORIGINAL ARTICLE

Use of Ablation Index-Guided Ablation Results in High Rates of Durable Pulmonary Vein Isolation and Freedom From Arrhythmia in Persistent Atrial Fibrillation Patients

The PRAISE Study Results

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BACKGROUND: Catheter ablation for persistent atrial fibrillation (AF) is associated with less favorable outcomes than for paroxysmal AF. Substrate modification is often added to pulmonary vein isolation (PVI) to try to improve success rates. Recent studies have shown improved clinical outcomes with use of regional ablation index (AI) targets for PVI. We hypothesized that prospective use of AI-guided PVI in persistent AF patients would result in a low rate of PV reconnection at repeat electrophysiology study and that a high success rate can be achieved with durable PVI alone.

METHODS: Forty consecutive patients with persistent AF underwent AI-guided PVI with target values of 550 for anterior and 400 for posterior left atrial regions, followed by a protocol-mandated repeat procedure after 2 months. Patients were monitored for atrial tachyarrhythmia recurrence via daily plus symptom-initiated ECG recordings for 12 months. Recurrence was defined as ≥30 seconds of any atrial tachyarrhythmia after a 3-month blanking period.

RESULTS: PV reconnection was seen at repeat electrophysiology study in 22% of patients, affecting 7% of PVs. Ablation on the intervenous carina was required in 44% patients to achieve durable PVI. Atrial tachyarrhythmia recurrence was documented in 8 (20%) patients, only one of whom had PV reconnection at repeat study. At 12 months, 38/40 (95%) patients were in sinus rhythm, with 4 (10%) patients having started antiarrhythmic drugs. Higher body mass index and excess alcohol consumption were the only significant factors associated with atrial tachyarrhythmia recurrence.

CONCLUSIONS: Use of AI targets results in a high level of durable PVI. A good clinical outcome can be achieved in the great majority of persistent AF patients with AI-guided PVI alone.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT02628730.

VISUAL OVERVIEW: An online visual overview is available for this article.

Key Words: ablation index ■ atrial fibrillation ■ body mass index ■ catheter ablation ■ pulmonary veins

https://www.ahajournals.org/journal/circep

WHAT IS KNOWN?

- Ablation index is a novel marker incorporating contact force, time, and power in a weighted formula.
- Retrospective analysis found that the minimum ablation index value within a segment of the encircling pulmonary vein isolation lesion is predictive of pulmonary vein reconnection in that segment at repeat electrophysiology study and that higher values were required for durable isolation in anterior/roof segments compared with posterior/inferior segments.

WHAT THE STUDY ADDS?

- Ablation index regional targets-guided ablation results in high rate of durable pulmonary vein isolation at repeat electrophysiology study, with 93% of pulmonary veins found to remain durably isolated.
- Late reconnection is the most commonly encountered in carinal regions, and, therefore, consideration needs to be given to ablating these regions preemptively.
- An ablation index-guided pulmonary vein isolation-only strategy provides a high rate of clinical success in patients with persistent atrial fibrillation with no significant structural heart disease, potentially because of improved durability of pulmonary vein isolation.

Complete pulmonary vein isolation (PVI) has been recommended as the best-established target for ablation of paroxysmal atrial fibrillation (AF) and has been found to be noninferior to more extensive ablation in persistent atrial fibrillation (PeAF).[1–3] Late recovery of ablated tissue has been the Achilles' heel of radiofrequency ablation, with late reconnection of at least 1 PV reported in ≈70% of patients even after complete acutely successful PVI.[1] The introduction of contact force (CF)-sensing catheters and use of force-time integral (FTI)-targeted ablation has improved results, but not to the levels hoped for, with 38% to 62% of patients still showing late PV reconnection.[4,5]

Ablation index (AI) is a novel marker of ablation lesion quality that incorporates power, CF, and time in a weighted formula and was found to accurately estimate ablation lesion depth in preclinical studies.[6] The AI formula is proprietary and is shown below with the constants replaced with letters.

$$Ablation\,Index = \left(K * \int_0^t CF^a(\tau) P^b(\tau) d\tau \right)^c$$

That formula has been recently integrated as an ablation lesion quality monitoring module into the automated lesion tagging software (VisiTag) in the CARTO 3 V4 3D electroanatomic mapping system (Biosense Webster, Inc, Diamond Bar, CA). A multicenter retrospective study and a prospective study involving protocol-mandated repeat procedures after 2 months defined the minimum regional AI target values that would be required to prevent acute PV reconnection in the former study and late PV reconnection in the latter study, as 550 for anterior and roof and 400 for posterior and inferior left atrial (LA) segments.[5,7]

We hypothesized that prospective use of these AI targets would result in a low rate of PV reconnection and that durable PVI alone may be adequate to achieve a high rate of clinical success in patients with PeAF. We, therefore, designed the PRAISE study (Pulmonary Vein Reconnection Following Ablation Index-Guided Ablation: a Success Evaluation), in which 40 patients underwent a protocol-mandated repeat electrophysiology procedure following AI-guided ablation to determine the prevalence of late PV reconnection. Patients were then monitored intensively >12-month follow-up period for clinical outcomes.

METHODS

The data, analytic methods, and study materials have been made available to other researchers for purposes of reproducing the results or replicating the procedure.

The study population comprised 40 consecutive patients with PeAF, of <12 months duration, and with no significant structural heart disease who underwent AI-guided PVI at 3 sites: Liverpool Heart and Chest Hospital, Liverpool, United Kingdom; Freeman Hospital, Newcastle upon Tyne, United Kingdom; and Centro Cardiologico Monzino, Milan, Italy. The study was registered prospectively: PRAISE. The study was approved by the individual Institutional and National Ethics Committees, as well as monitored by a Data Monitoring and Safety Committee. Each patient provided written informed consent before participation.

Initial Ablation Procedure

All procedures were performed under general anesthesia or deep conscious sedation. Vitamin K antagonist treatment was uninterrupted while non-Vitamin K anticoagulants were omitted on the morning of the procedure. After ultrasound-guided right femoral venous access,[8] 2 transseptal punctures were performed using fluoroscopic guidance with additional pressure monitoring, after which intravenous unfractionated heparin boluses were administered to maintain an activated clotting time of >300 seconds. If the patient was in AF, electric cardioversion was performed to restore sinus rhythm. A 3-dimensional navigation system (CARTO 3, Biosense Webster, Inc, Diamond Bar, CA) was used to create a 3-dimensional electroanatomical voltage map of the LA, with integration with a computed tomography or magnetic resonance imaging reconstruction of the LA (CartoMerge, Biosense Webster, Inc) where available.

PVI was performed with radiofrequency energy in a point-by-point wide area circumferential ablation (WACA) pattern using a Thermocool SmartTouch irrigated tip CF-sensing

ablation catheter (Biosense Webster, Inc) introduced via a nonsteerable sheath. The WACAs were created >10 mm outside the PV ostia, where the local electrograms did not show near-field PV signals. For the left pulmonary veins, ablation was performed just inside the ridge anterior to the veins. Ablation on the intervenous carinae was not delivered as part of initial lesion set, unless it was needed to achieve PVI. None of the patients received additional ablation in the left atrium, and the only other additional ablation permitted was cavotricuspid isthmus ablation for documented typical atrial flutter.

The VisiTag settings for all 40 patients were as follows: catheter position stability: minimum time 10 seconds, maximum range 2 mm; force over time: 30%, minimum force 5 g; and lesion tag size: 2 mm. The protocol required that the operator should aim to deliver contiguous lesions (center-to-center distance ≤6 mm).[9] A CF of 5 to 40 g was targeted at each site. Power settings were at the individual operator's discretion within the range of 20 to 40 W depending on the LA segment. Each lesion was guided by AI targets: 550 at the roof and anterior walls and 400 at the posterior and inferior walls (Figure 1).[10] Impedance drop and FTI data were neither displayed nor targeted. Esophageal temperature monitoring was performed in all general anesthesia cases, and radiofrequency delivery was stopped as soon as the esophageal temperature reached 39°C, even if the target AI value of 400 had not been reached. Further radiofrequency was not delivered on the posterior wall until the esophageal temperature reached baseline level. If there was evidence of residual conduction into the PVs on the posterior wall after completion of the WACA, radiofrequency was delivered inside the WACA, that is, further away from the esophagus, as shown in Figure 2.

The acute end point of the procedure was complete PVI, as demonstrated by entrance block using a 20-pole circular mapping catheter (Lasso NAV Eco; Biosense Webster, Inc) placed sequentially in each of the PVs. After a minimum of 20 minutes from the last ablation to that WACA lesion set, ipsilateral PVs were rechecked with the Lasso catheter to determine if spontaneous PV reconnection had occurred, and these sites were tagged. If overt PV reconnection had not occurred, a bolus of intravenous adenosine (12–18 mg) was administered to unmask any sites of dormant conduction. Further ablation was performed at any sites of overt or unmasked reconnection to achieve PVI once again.

Repeat Electrophysiology Study

All patients underwent protocol-mandated repeat procedure, regardless of AF recurrence, 8 to 10 weeks after the initial procedure. Periprocedural anticoagulation management and procedural protocol were identical to the first procedure, including creation of a LA map using CARTO and integration with the original computed tomography or magnetic resonance imaging reconstruction of the LA, where available. Each PV was then assessed in turn for late reconnection with a Lasso catheter and reconnection sites were recorded. All reconnection sites were reablated using a Thermocool SmartTouch irrigated ablation catheter until PVI was successfully achieved. The same AI target values as for the initial procedure (550 for the roof and anterior wall and 400 for the posterior and inferior walls) were used, as safety data for higher AI values than these are not available.

If the patient remained in AF after achieving isolation of all PVs, electric cardioversion was performed. No additional ablation was performed.

ECG Follow-Up

All patients were provided with a validated portable ECG monitor (Omron HCG-801-E, Omron Healthcare, Kyoto, Japan).[11] After training them in its use, patients were instructed to self record a 30 seconds ECG every day and additionally whenever they experienced symptoms. ECG recordings were downloaded at each follow-up visit and were analyzed for the presence and dates of any atrial tachyarrhythmia (AT) by experienced clinicians blinded to patient symptoms.

Patient Follow-Up

Follow-up visits were arranged after 6 weeks and 3, 6, and 12 months. Any antiarrhythmic medications, including β blockers, were stopped 3 months after the initial ablation

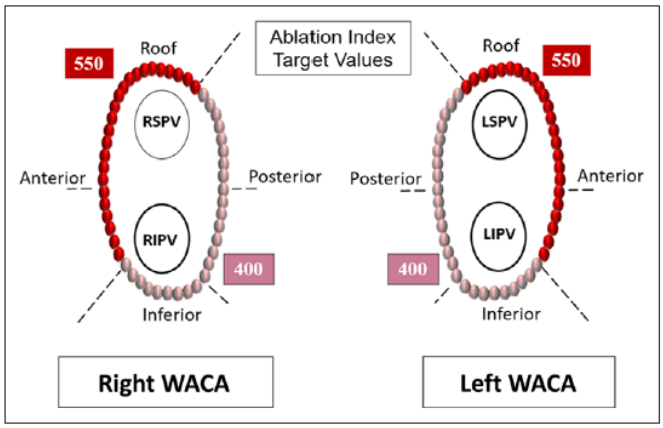

Figure 1. Diagram showing the anterior/roof and the posterior/inferior segments and the ablation index (AI) target values used for each of these segments in AI-group.
The red dots represent ablation lesions with AI target values ≥550 while the pink dots represent AI target values ≥400 but <550. LIPV indicates left inferior pulmonary vein; LSPV, left superior pulmonary vein; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; and WACA, wide area circumferential ablation.

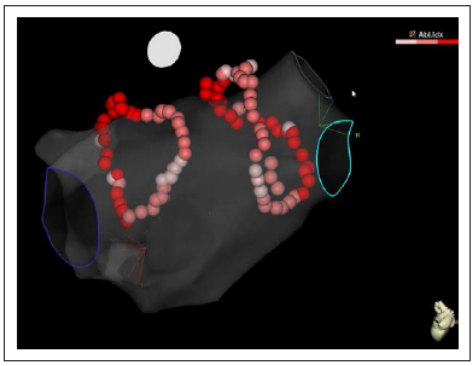

Figure 2. Carto 3 paroxysmal atrial (PA) view of one of the study patients. The VisiTags are color coded according to the following ablation index (AI) target values; red for values ≥550, pink for values 400 to 549, and light pink for values <400. Note the subtherapeutic VisiTags that were initially delivered to the posterior left atrial wall because of the associated rise in esophageal temperature (yellow arrow). Further radiofrequency delivery was needed more distally just inside the initial wide area circumferential ablation set to treat acute reconnection of the right lower pulmonary vein (white arrow).

unless substantial AT continued to occur beyond 3 months. The validated AF effect on quality of life questionnaire, which includes 20 questions across 3 domains (symptoms, daily activities, and treatment concerns) using a 7-point Likert scale, was completed at baseline and at 6 and 12 months.[12]

Study Outcomes

The primary outcome measure was freedom from AT recurrence after the 3-month blanking period after the initial ablation procedure. AT recurrence was defined as documented AF, atrial flutter, or atrial tachycardia lasting ≥30 seconds.[13] Secondary outcome measures were as follows: quality of life 6 and 12 months after initial ablation; time to first AT recurrence; AT burden during the primary outcome period; reinitiation of antiarrhythmic medication; and the occurrence of major complications.

Per-Protocol Analysis

The occurrence of any of the following was regarded as a protocol violation and the relevant WACA circle/patient was excluded from PV reconnection data analysis: any technical problem that prevented the delivery of the full ablation lesion set during the initial ablation procedure; if the initial ablation lesion set was not delivered in a WACA pattern (>1 cm outside the PV ostia); or the presence of >8 gaps (defined as an interlesion distance of >6 mm) in a WACA circle.[9]

Ablation Lesion Data Analysis

All patients underwent detailed offline retrospective analyses of each of their WACA circle ablation lesions. The data for each VisiTag included ablation duration, CF, impedance drop, FTI, and AI. CF was defined as the mean CF during ablation, and impedance drop as the difference between the preablation impedance value and the lowest recorded value during ablation. The CARTO 3 system automatically calculates FTI and AI values for each lesion. FTI is calculated by multiplication of the mean CF during energy application by the duration of the application and is measured in gram-seconds (gs). AI is calculated using a complex weighted exponential formula allocating different weights to CF, time, and power.[6] To analyze the effect of using different AI target values for the various LA regions, each WACA circle was divided into 6 potential reconnection segments (roof, 2 anterior, inferior, and 2 posterior). We then categorized these 6 segments into 2 regions per WACA circle according to the regional AI targets used for AI-group: anterior and posterior regions (Figure 1).

Statistical Analysis

Continuous variables are presented as mean and SD or median and interquartile range (25th–75th percentiles) where appropriate. Student *t* test or the Mann–Whitney *U* test was used for unpaired group comparison. Categorical variables were compared by χ^2 or Fisher exact test and are presented as frequency and percentage. All tests were 2-sided, and a $P<0.05$ was considered statistically significant.

Statistical analysis was performed using SPSS (version 24, IBM Corp, Armonk, NY).

RESULTS

The demographic and procedural data for the 40 patients are presented in Table 1. As the patient cohort comprises patients with PeAF, the mean LA size was relatively large at 43±5 mm and LV function was impaired in 8 (20%) of patients. The median duration of PeAF was 9.5 (6–12) months, and 28/40 (70%) patients had undergone at least 1 attempt of electric cardioversion before the initial PVI. All 40 patients returned for repeat study, and no major complications occurred in any of the 80 procedures.

A total of 2764 VisiTags was analyzed with a mean number of 69±12 VisiTags per patient. The mean ablation time was 36±9 minutes, and the mean CF was 13±2 g.

Four WACAs (2 left sided and 2 right sided), with the relevant 4 patients, 8 PVs, and 24 segments, were excluded from PV reconnection analysis because of protocol violation: 2 because of the presence of >8 gaps in the WACA circle, 1 because segmental ostial (rather than WACA) PVI was performed, and 1 because of equipment failure.

Acute PV Isolation and Acute Reconnection

All of the 147 PVs included for analysis were successfully isolated. A carina line to achieve PV isolation was required in 9/76 (12%) WACAs in 9/36 (25%) patients. After the 20-minute waiting period and the use of adenosine, acute reconnection was seen in 10 (28%) patients affecting 14 (10%) PVs (Table 2). Acute reconnection occurred in 15 (3%) segments, the majority of

Table 1. Demographic and Procedural Data

Age, y	61±8
Male, n (%)	30 (75%)
Left atrial AP diameter, mm	43±5
LV ejection fraction >55%, n (%)	32 (80%)
Hypertension, n (%)	12 (30%)
Diabetes mellitus, n (%)	3 (8%)
CHA_2DS_2Vasc score	1 (0–2)
Atrial fibrillation duration, mo	9.5 (6–12)
Antiarrhythmic drugs before ablation	36 (90%)
Procedure time, min	158±34
Ablation time, min	36±9
Number of VisiTags per patient	69±12
Fluoroscopy time, min	12 (8–14)
General anesthesia, n (%)	39 (98%)
Major complications, n (%)	0 (0%)
Interval between procedures, d	64±6
Mean CF, g	13±2
Mean FTI, gs	327±77
Mean AI	486±42
Ablation time per lesion for anterior segments, s	35 (27–44)
Ablation time per lesion for the posterior segments, s	23 (17–28)
Patients who received CTI ablation, n (%)	3 (8%)

AI indicates ablation index; AP, anteroposterior; CF, contact force; CTI, cavotricuspid isthmus; FTI, force-time integral; and LV, left ventricular.

which (13/15 [87%]) was spontaneous reconnections. The distribution of segments of acute reconnection is shown in Figure 3 (Upper). All 15 acutely reconnected segments were successfully reablated.

Late PV Reconnection at Repeat Electrophysiology Study

The mean interval between the initial PVI procedure and repeat electrophysiology study was 64±6 days. Late PV reconnection was identified in 13 (3%) segments in 8 (22%) patients, affecting 11 (7%) PVs (Table 2). All reconnected PVs in the 8 patients with late PV reconnection were successfully reisolated. The median ablation time required for reisolation was 5.6 (4.5–7.9) minutes. The distribution of segments with late reconnection is shown in Figure 3 (Lower).

Relationship Between Acute and Late PV Reconnection

Late reconnection occurred in only 1 segment (1/15 [7%]) that exhibited acute reconnection during the initial PVI, compared with 12 of 441 (3%) segments that did not exhibit acute reconnection during the initial PVI (P=0.37). However, the proportion of PVs with reisolated acute reconnection that exhibited late reconnection was significantly higher than that for PVs without acute reconnection (5/14 [36%] versus 6/133 [5%]; P<0.001).

Table 2. Prevalence of Acute and Late Pulmonary Vein Connections in the Study Group*

	Acute PV Reconnection at Initial Ablation	Late PV Reconnection at Repeat Procedure
By patients, n=36	10 (28%)	8 (22%)
By WACA circle, n=76	10 (13%)	8 (11%)
By WACA segment, n=456	15 (3%)	13 (3%)
By pulmonary veins, n=147	14 (10%)	11 (7%)

PV indicates pulmonary vein; and WACA, wide area circumferential ablation.

*Four WACAs with their relevant 4 patients and 24 WACA segments were excluded because of protocol violation.

Regional Variation in the Pattern of Acute and Late PV Reconnection

The commonest segments for acute reconnection were in the right posterior/inferior regions (9/15 [60%]; Figure 3; Upper). Conversely, segments with late reconnection were the most common in the left anterior/roof regions (5/13 [38%]; Figure 3; Lower).

AI Values for Reconnected Versus Nonreconnected Segments

There was no significant difference in the minimum AI values for segments with acute reconnection compared with those without, either for anterior/roof regions (566 [492–573] versus 558 [384–567]; P=0.23) or for posterior/inferior regions (425 [414–437] versus 417 [348–430]; P=0.15). This was also true for segments with and without late reconnection (anterior/roof regions: 563 [424–570] versus 557 [383–566]; P=0.72 and posterior/inferior regions: 434 [353–435] versus 415 [348–429]; P=0.27).

PV Reconnection in Relation to PV Anatomy

Intervenous Carina Ablation

A carina ablation line for reisolation was needed in 4/10 (40%) of the acute reconnected WACAs. Similarly, there was a need for a carina ablation line at repeat study to reisolate 4/8 (50%) of the late reconnected WACA circles (Figure 3). In total, 16/76 (21%) WACA circles (10 right sided and 6 left sided) in 16/36 (44%) patients required a carina line at some point during the 2 procedures.

Esophageal Proximity to PVs

During the initial PVI procedures, an esophageal temperature rise of >39°C was encountered in 12 patients

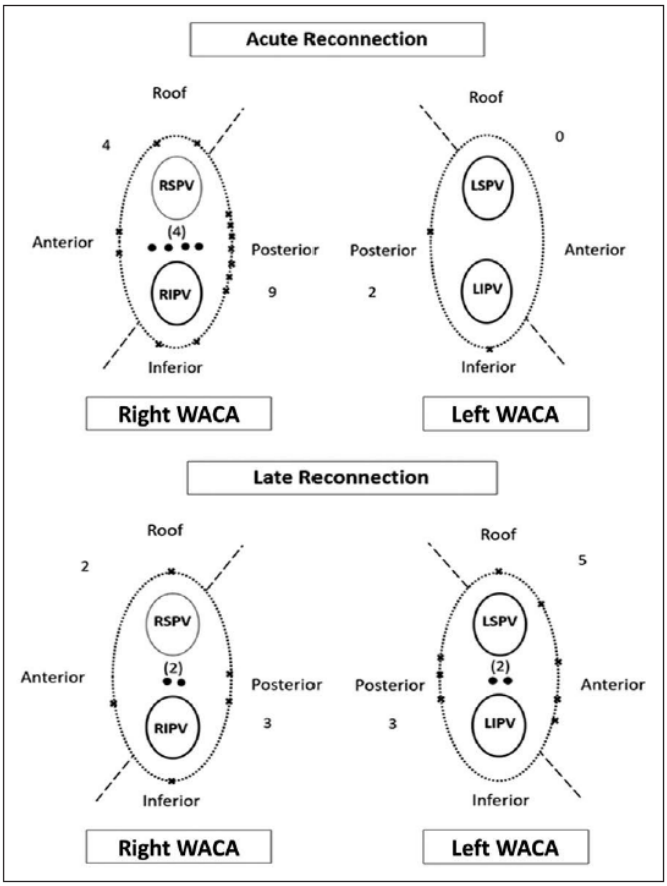

Figure 3. Diagram showing the number of segments with reconnection identified within each region acutely (upper) and at repeat electrophysiology study (lower). Asterisks represent sites of reconnection in segments of the wide area circumferential ablation (WACA) circle, while black dots indicate carina involvement in ipsilateral WACA reconnection requiring additional carina line ablation. LIPV indicates left inferior pulmonary vein; LSPV, left superior pulmonary vein; RIPV, right inferior pulmonary vein; and RSPV, right superior pulmonary vein.

affecting 14 posterior segments (7 right and 7 left), necessitating premature termination of radiofrequency energy application before the AI target of 400 was reached (Figure 2). The highest recorded peak esophageal temperature during ablation on the LA posterior wall was 40.4°C. The incidence of acute reconnection was significantly higher in the posterior segments where esophageal temperature rise was detected (4/14 [29%]), compared with the posterior segments where there was no such rise (4/62 [6%]; *P*=0.015).

After successful reisolation of these acutely reconnected segments, there was no significant difference in the incidence of late reconnection between posterior segments that were or were not affected by esophageal temperature rise (1/11 [9%] versus 4/65 [6%]; *P*=0.72).

Recurrence of AT

No patient was lost to follow-up, and patient compliance with the daily handheld ECG recording was excellent. A total of 14424 ECG recordings were obtained and analyzed. The median number of ECGs recorded during the 12-month follow-up period was 372 (342–405) recording per patient, with 100 (89–107) recorded during the blanking period, and 270 (240–302) recorded during the primary outcome period.

In the period between the end of blanking period and the end of 12-month follow-up, AT recurrence was documented in 8/40 (20%) patients (Figure 4), only 1 of whom had late reconnection at repeat study. AT recurrence was in a paroxysmal pattern in 5 (62.5%) patients (of whom 3 patients had AT documented on a single day only) and in a persistent pattern requiring electric cardioversion in 3 (37.5%) patients. The median time to first AT recurrence 184 (133–191) days, and the AT burden during the primary outcome period was 11 (1–48) days. By the end of the 12-month follow-up period, 38 (95%) patients were in sinus rhythm, with only 4 (10%) patients taking antiarrhythmic drugs or β-blockers.

Freedom from AT recurrence was not significantly different between patients who needed redo ablation for PV reconnection, and those who had no reconnection (75% versus 81%; *P*=0.69).

Patient Characteristics in Relation to AT Recurrence

Table 3 presents patient demographics and clinical characteristics of patients with and without AT recurrence. Higher body mass index and excess alcohol intake, defined as >30 g/wk, were the only 2 factors significantly associated with AT recurrence during the outcome period.

Early Recurrence of AT

During the blanking period, early recurrence of AT occurred in 12 (30%) of patients. Only 2 patients with early recurrence of AT required redo ablation for PV reconnection at repeat study and neither had further AT recurrence during the study follow-up period. Of the 10 remaining patients with early recurrence of AT but no PV reconnection, 4 went on to have postblanking period AT, indicating a non-PV driver for their recurrent AT. The absence of early recurrence of AT during the blanking period was significantly associated with freedom from late recurrence of atrial tachyarrhythmia at 12 months (85.7% versus 66.7%; *P*<0.01).

AF Effect on Quality of Life Scores

For all patients at 6 months after the initial PVI procedure, AF effect on quality of life scores showed a highly significant improvement in patient quality of life compared with baseline (63.9 [39.1–69.9] versus 91.7 [84.3–97.2]; *P*<0.001). This became even more evident at 12 months (98.2 [81.5–99.5]; *P*<0.001).

DISCUSSION

Main Findings

This study is the first to investigate the durability of PVI after AI-guided ablation, as assessed at protocol-mandated repeat electrophysiology study, and clinical outcomes at 12 months after a PVI only strategy in patients with PeAF. The main findings of this study are (1) AI-guided ablation was associated with high rate of durable PVI of 93% PVs in a PeAF population; (2) around one-third of posterior segments where therapeutic AI values could not be reached because of a rise in esophageal temperature exhibited acute PV reconnection after the 20-minute waiting period; (3) almost half of patients in the AI-group required ablation on the intervenous carina to achieve permanent PVI; (4) an AI-guided PVI only ablation strategy was associated with a successful outcome in the vast majority of patients >12 months, most probably because of more durable PVI; and (5) higher body mass index and excess alcohol consumption were significantly associated with AT recurrence.

Reduction of Acute and Late Reconnection

Experiments in an animal model have suggested that AI accurately predicts the depth of ablation lesions,[6] and AI has, therefore, been proposed as a novel marker of ablation lesion quality. Previous retrospective analysis of Visi-Tag data in a multicenter retrospective study identified minimum AI values of 540 and 380 that were predictive of freedom from acute reconnection in the anterior/roof and posterior/inferior regions, respectively.[7] In our previously-published CF-guided paroxysmal AF ablation trial, the PRESSURE trial (Pulmonary Vein Re-Isolation as a Routine Strategy: a Success Rate Evaluation), similar AI values were also found to predict freedom from late

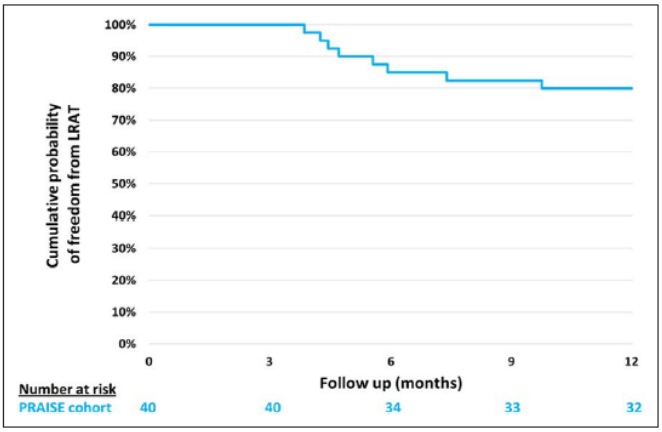

Figure 4. Kaplan-Meier curve of freedom from atrial tachyarrhythmia recurrence for all PRAISE (Pulmonary Vein Reconnection Following Ablation Index-Guided Ablation: a Success Evaluation) patients.
LRAT indicates late recurrence of atrial tachyarrhythmia.

Table 3. Demographic and Clinical Characteristics in Relation to AT Recurrence

	No AT Recurrence (n=32)	AT Recurrence (n=8)	*P* Value
Age, y	61 (56–69)	55 (49–68)	0.15
Male sex, n (%)	24 (75)	6 (75)	1.00
BMI, kg/m^2	27.3 (25.5–32.1)	31.1 (29.1–34.0)	0.02
Duration of AF before PVI, mo	10 (6–12)	8 (5–11)	0.44
CHA_2DS_2VASc score	1 (0–2)	1 (0–2)	0.96
Hypertension, n (%)	11 (34.4)	1 (12.5)	0.40
Diabetes mellitus, n (%)	1 (3.1)	2 (25)	0.10
Excess alcohol of >30 g/wk, n (%)	0 (0)	3 (37.5)	0.006
LVEF <40%, n (%)	6 (18.8)	2 (25)	0.65
LA AP diameter, cm	4.3 (4.1–4.6)	4.0 (4.1–4.9)	1.00

AF indicates atrial fibrillation; AP, anteroposterior; BMI, body mass index; LA, left atrial; LVEF, left ventricular ejection fraction; and PVI, pulmonary vein isolation.

reconnection at protocol-mandated repeat procedure after 2 months.[5] Although the ablation protocol used in both studies was virtually identical with the exception of the use of AI targets in this study, the study populations are different which limits direct comparisons, though enrollment of PeAF patients with larger LA size in the present study would be expected to confer a disadvantage. Nevertheless, the prospective use of AI target values in the current study resulted in a substantial reduction in the proportion of acutely reconnected WACA circles (13% versus 26%), late reconnected WACA circles (11% versus 35%), and patients with late reconnection (22% versus 62%) compared with CF-guided ablation in the PRESSURE trial.[14] These findings indicate that AI-guided ablation results in more durable PVI.

These results are consistent with our previous findings that the use of this strategy is associated with a significant reduction in AT recurrence compared with CF-guided ablation, possibly because of creation of better quality lesions as suggested by a greater impedance drop.[10] Recently, Taghji et al[15] have also demonstrated excellent clinical results with the use of AI-guided PVI in a cohort of patients with paroxysmal AF. The wider reproducibility of this strategy is now being tested in a multicenter study of paroxysmal AF patients (URL: https://www.clinicaltrials.gov. Unique identifier: NCT03062046).

Despite the reduction in acute reconnection with AI-guided ablation, a predilection for this phenomenon was still seen in the right posterior regions. This finding may be related in part to the inability to deliver therapeutic lesions (AI target of 400) on the posterior LA wall whenever a significant rise in the esophageal temperature was encountered during the initial radiofrequency ablation.

Carinal Ablation

There was a greater need for carinal ablation, especially on the right side, to achieve initial PVI, and the intervenous carinae were also common sites for both acute and late reconnection. This is likely to be related to the relatively large LA size in the study group, and may also be explained by a recent study using computed tomography that demonstrated that the carinae are the thickest segments of the PV-LA junction.[16]

Because around half of WACA circles required carina ablation overall, routine ablation of the carinal regions, especially on the right side, could be considered a necessary part of the WACA lesion set in patients with PeAF. This may be of particular importance in cases where attempts at delivering therapeutic lesions are thwarted by esophageal temperature rise, or where the right WACA circle is particularly wide because of anatomic reasons such as presence of a dilated left atrium. We think that the overall improvement in the acute and late reconnection rates with AI-guided ablation along the circumferential WACA lesion sets allowed identification of unablated carinae as the weak links in achieving permanent PVI. It is notable that each carinal region is obligatorily ablated twice during cryoballoon PVI, and this may partly account for the high durable PVI rates described with this technology.[17]

Overall Relationship Between Acute and Late PV Reconnection With AI-Guided Ablation

In keeping with previous findings,[14] the proportion of segments with acute reconnection that exhibited late reconnection at repeat study was not different from the proportion of segments that did not exhibit acute reconnection at the initial procedure, indicating effective reablation at these segments. However, the proportion of PVs with acute reconnection that exhibited late reconnection was significantly higher than the proportion of PVs without acute reconnection. These findings suggest that even with the use of AI-guided ablation, there may be an additional impediment to delivering effective ablation

in some PeAF patients, such as the presence of thicker or more fibrotic tissue. This merits further investigation.

High Incidence of Durable PVI With a Single Procedure

A few previous studies have studied patients with a protocol-mandated repeat electrophysiology study 2 to 3 months after PVI to investigate the prevalence of late PV reconnection (Table 4). The percentage of patients with late reconnection of at least 1 PV was 60% to 70% in studies where CF information was not available,[1,18] or where CF-sensing catheters were used without FTI target values.[20] In the EFFICAS II study, where a minimum FTI target of 400 gs globally was used to guide ablation, this was reduced to 38%, but the increased efficacy came at the expense of serious complications (tamponade) in 8.3%.[4]

Our durable PVI rate of 93% with the use of regional AI targets is the highest reported, and this was achieved without any complications. The durability of PVI in our study is comparable to the small single-center SUPIR study (Sustained PV Isolation With Arctic Front Advance) in which at least two 4-minute freezes were delivered to each PV with the second-generation cryoballoon.[17] However, patients included in that study had paroxysmal AF, with presumably smaller left atria, there was a 3/21 (14.3%) complication rate and 2/21 (9%) drop-out rate, and assessment for late reconnection was solely with a circular catheter. A subsequent study of the second-generation cryoballoon, in which a single 3-minute freeze was delivered to each PV, showed considerably higher rates of late reconnection affecting 27% of PVs in 66% of patients when assessed by both a circular mapping catheter and electroanatomical mapping, as in our study.[19]

Considering the fact that a strategy of a routine repeat procedure at 2 months is not feasible in routine clinical practice, the 12-month arrhythmia-free success rate of 81% in patients who did not require ablation at the repeat procedure (n=28) was equivalent to those who required repeat ablation (n=12). This single-ablation procedure outcome is superior to the 66.7% arrhythmia-free single-procedure success rate at 12 months using PVI only in PeAF patients seen in a recently published systematic review,[21] and likely represents an estimate of what is achievable with a durable WACA-based PVI. Moreover, these results are also consistent with our previously reported results from a wider clinical cohort, albeit in whom the intensity of ECG monitoring during follow-up was not as intensive as in this study.[9]

Factors Associated With Late AT Recurrence

Patients in our study with late AT recurrence after catheter ablation were found to have a higher body mass index and a greater proportion consumed excess alcohol (>30 g/wk), findings which are consistent with previous work.[22,23] Our study findings, therefore, support recommendations to pursue healthy lifestyle modifications, such as weight reduction and avoidance of excess alcohol, to facilitate rhythm control after AF ablation.[24]

Limitations

The study is not a randomized controlled study and, therefore, direct comparisons with CF-guided ablation cannot be made. Second, despite the absence of complications in this study across the 3 centers, the study size is too small to provide definitive safety assessment of AI-guided ablation strategy. However, between January 2015 and April 2018, we at Liverpool Heart and Chest Hospital have performed 542 AF ablation procedures guided by AI targets for 385 de novo and 157 redo cases.

Table 4. Studies That Examined Late Pulmonary Vein Reconnection at Mandated Repeat Electrophysiology Study After PVI

	EFFICAS I[18]	EFFICAS II[4]	SUPIR[17]	Miyazaki et al[19]	PRESSURE[20]	PRAISE
Patients, n	46	26	21	32	40	40
Repeat EPS, n (%)	40 (86.9)	24 (92.3)	19 (91)	32 (100)	40 (100)	40 (100)
Population	PAF	PAF	PAF	PAF	PAF	PeAF
Ablation tools	Contact force/3D mapping	Contact force/3D mapping	Second-generation cryoballoon	Second-generation cryoballoon	Contact force/3D mapping	Contact force/3D mapping
Technique	Blinded to CF	CF and FTI targets	2×4-min freezes	Single 3-min freeze	CF and EGM targets	AI targets
Complications, n (%)	0	2 (7.7)	3 (14.3)	1 (3.1)	1 (2.5)	0
Late PV reconnection						
By patients, n (%)	26/40 (65%)	9/24 (38%)	4/19 (21%)	21 (66%)	25/40 (62%)	8/36 (22%)
By PVs, n (%)	44/160 (28%)	14/91 (15%)	7/75 (9%)	34 (27%)	41/160 (26%)	11/147 (7%)

3D indicates 3-dimensional; AI, ablation index; CF, contact force; EFFICAS I, Electrical Reconnection After Pulmonary Vein Isolation Is Contingent on Contact Force During Initial Treatment; EFFICAS II, Optimization of Catheter Contact Force Improves Outcome of Pulmonary Vein Isolation for Paroxysmal Atrial Fibrillation; EGM, intracardiac electrograms; EPS, electrophysiology study; FTI, force-time integral; PAF, paroxysmal atrial fibrillation; PeAF, persistent atrial fibrillation; PRAISE, Pulmonary Vein Reconnection Following Ablation Index-Guided Ablation: a Success Evaluation; PRESSURE, Pulmonary Vein Re-Isolation as a Routine Strategy: a Success Rate Evaluation; PVI, pulmonary vein isolation; and SUPIR, Sustained PV Isolation With Arctic Front Advance.

In these cases, the following major complications were observed: 2 cardiac tamponades (both caused by LA perforation with the mapping catheter before application of RF energy), 2 hematomas delaying hospital discharge, and 1 transient ischemic attack with full neurological recovery. There were no cases of phrenic nerve palsy, atrioesophageal fistula, or stroke. These findings are also consistent with our recently published early experience with AF ablation guided by these same AI targets.[10]

Four WACAs, and the corresponding 4 patients, had to be excluded from detailed CARTO analysis because of protocol violation; however, we have presented clinical results data for the whole cohort of 40 patients. Finally, in the absence of continuous ECG monitoring, it is possible that brief asymptomatic episodes were missed, thereby overestimating clinical success rates.

Conclusions

AI regional target-guided ablation results in a low rate of PV reconnection at repeat electrophysiology study, with 93% of PVs found to remain durably isolated. Late reconnection was most commonly encountered in carinal regions, and, therefore, consideration needs to be given to ablating these regions preemptively. An AI-guided PVI only strategy in patients with persistent AF of <12 months duration, and with no significant structural heart disease provides a high rate of clinical success, potentially because of improved durability of PVI.

ARTICLE INFORMATION

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RELATIONSHIP BETWEEN LEFT ATRIAL BIPOLAR VOLTAGES AND PULMONARY VEIN RECONNECTION FOLLOWING ABLATION INDEX-GUIDED ABLATION IN PATIENTS WITH PERSISTENT ATRIAL FIBRILLATION

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Background: Use of regional Ablation Index (AI) targets has been shown to greatly reduce, but not completely eradicate pulmonary vein reconnection (PVR) following Pulmonary Vein Isolation (PVI).
Objective: We aimed to study the potential effect of left atrial (LA) voltages on PVR following AI-guided PVI.
Methods: 33 patients with persistent AF (27 male, 61±7 yrs, LAd 43±4mm) underwent CARTO bipolar voltage LA mapping with a Lasso catheter during fixed rate atrial pacing after cardioversion. They then received PVI by contiguous point-by-point wide antral circumferential ablation (WACA) ablation using AI-targets (550 anterior, 400 posterior regions). All patients underwent mandatory repeat CARTO EP study at 2 months to identify late PVR with a Lasso catheter. Detailed analysis of LA body voltage points (n=7223) was performed offline to identify potential associations between these and PVR in various WACA regions.
Results: Acute PVR was seen in 10/66 (15%) WACAs (2 left and 8 right), and late PVR in 7/66 (11 %) WACAs (3 left and 4 right). The mean LA voltage in patients with WACA showing PVR was greater, though insignificantly, than in patients with WACA not showing PVR (1.68±1.11 vs 1.55±0.87mV, P=0.29). The mean LA voltage in patients with PVR seen in left WACA was 1.82±1.08 mV, and in patients with PVR of right WACA was 1.55±1.14 mV. There was a significant positive correlation between mean LA voltage and reconnection of the left WACA (Pearson r=0.35, P= 0.048), but not with reconnection of the right WACA (Pearson r=-0.23, P= 0.59).
Conclusion: The incidence of acute and late PVR is low with an AI-guided PVI strategy, and suggests that the current AI targets are valid across a range of atrial voltages. PVR around the left WACA is related to higher LA bipolar voltages at baseline, possibly related to a thicker left lateral ridge. Therefore, this area may require higher target AIs, especially in the presence of high LA voltages.

S-PO03-143

LONG-TERM OUTCOMES AFTER LOW POWER, SLOW MOVEMENT VERSUS HIGH POWER, FAST MOVEMENT FORCE SENSING IRRIGITATED-TIP CATHETER ABLATION FOR ATRIAL FIBRILLATION

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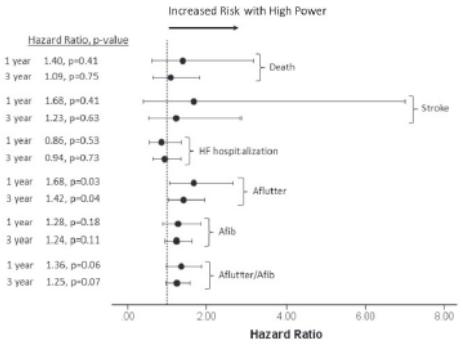
Background: High power approaches (50 W) with continuous catheter movement have been advocated to increase efficacy and minimize deep tissue thermal injury during atrial fibrillation (AF) ablation. Lower power, slow movement ablation allows for more catheter stability which may minimize injury outside of target regions and the extent of edema and inflammation.
Objective: Evaluate the long-term outcomes of AF ablation guided by either high versus low power.
Methods: Of a total of 2,337 first time AF ablation with >3 years of follow up, propensity-matched populations for baseline risk factors were created comprising of 402 patients treated with low power (30 W), slow movement ablation and 402 patients treated with high power (50 W), fast or continuous movement ablation. All operators had performed >500 AF ablations. Death, stroke, heart failure, and AF/AFL outcomes after a 90-day blacking period were assessed and compared.
Results: The average age of the populations were 66 vs 67 years (p=0.44), 65% vs 63% (p=0.51) were male, 87% vs 89% (p=0.28) had hypertension, 47% vs 47% (p=0.89) had heart failure, and 50% vs 53% (p=0.40) had persistent AF. In the high power group additional left atrial linear ablation was performed in 150 vs 118 in the lower power group (p=0.02). Over a follow-up of 1,589±880 (median: 1,616) days, multivariate adjusted risk, including for additional ablation, of AFL was higher with high power ablation (Figure). Patients with a low power ablation had lower rates of need for a repeat ablation (24 vs 35%, p=0.0002).
Conclusion: High power ablation increased risk of AFL and need for repeat ablation compared to low power ablation. Both approaches had similar long-term risk of recurrent AF.



S-PO03-144

DO SCARS FROM EXTENSIVE ABLATION INCREASE THE RISK OF STROKE?

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Background: LGE-MRI studies have reported a direct association between pre-ablation left atrial scar and thromboembolic (TE) events in AF patients.
Objective: We evaluated the association of the post-ablation scar with stroke-risk in patients undergoing extensive ablation

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Reverse electrical and structural remodeling of the left atrium occurs early after pulmonary vein isolation for persistent atrial fibrillation

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Abstract

Purpose Adverse left atrial (LA) remodeling is known to be associated with persistent atrial fibrillation (PeAF). The time course and pattern of reversal of LA remodeling following catheter ablation is poorly understood. We aimed to evaluate LA chamber volumes and dimensions, LA conduction velocities, and LA bipolar voltages at baseline and at 2 months after catheter ablation for PeAF.

Methods Twenty-three patients with PeAF underwent detailed LA mapping during fixed rate atrial pacing using the CARTO3 navigation system prior to undergoing pulmonary vein isolation. All patients returned for protocol-mandated repeat electrophysiology study at 2 months, irrespective of symptoms or arrhythmia recurrence, during which all measurements were repeated using an identical mapping protocol. Patients then underwent daily ECG monitoring for 12 months.

Results Nineteen out of twenty-three (83.6%) patients had durable PVI of all veins at repeat electrophysiology study, while 4 (17.4%) patients had late reconnection of a single vein each. In the blinded offline analysis, LA volume at follow-up was significantly lower as compared with baseline (55 ± 14 mL/m^2 vs. 65 ± 15 mL/m^2, $P < 0.001$). LA conduction velocities were significantly greater at 2 months (0.90 ± 0.13 m/s vs. 0.78 ± 0.13 m/s, $P = 0.01$). There was non-uniform regional LA voltage evolution, with a significant increase in bipolar voltages observed on the LA posterior wall (2.18 ± 0.85 mV vs. 1.83 ± 0.49 mV, $P = 0.04$), but not elsewhere. Individual variables of remodeling were not associated with AF recurrence.

Conclusion Significant structural and electrical reverse remodeling of the LA can be seen as early as 2 months following successful catheter ablation for PeAF.

Keywords Left atrium reverse remodeling · Atrial fibrillation · Ablation · Mapping · Atrial fibrosis · Low-voltage points · Conduction velocities

1 Introduction

One in four middle-aged adults in Europe and the USA will develop atrial fibrillation (AF). While AF is a frequent arrhythmia, its electrophysiological mechanisms are still debated. Animal models consistently point to an important role of atrial fibrosis in the development and maintenance of atrial fibrillation [1]. LA remodeling, resulting in LA fibrosis, is particularly known to be associated with persistent AF (PeAF) [2], and an increasing risk of thromboembolic events [3]. Fibrosis is associated with LA enlargement, increased conduction times, and decreased LA voltages [2].

Pulmonary vein isolation (PVI) by catheter ablation has become an effective therapy for AF. Reverse LA remodeling is associated with improved success rates following ablation for PeAF [4], but the time course and pattern of this remodeling is poorly understood. We therefore designed this study to evaluate chamber volumes, linear dimensions, conduction velocities, and bipolar voltages in the LA through invasive studies at baseline and at 2 months after catheter ablation for PeAF.

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2 Methods

2.1 Study population

Twenty-three consecutive patients with PeAF, enrolled in a trial evaluating Ablation Index (AI) (CARTO3 V4, Biosense

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Webster, Inc., Diamond Bar, CA) target-guided PVI, [5] were included in this study. PeAF was defined as an AF episode that either lasted longer than 7 days or required termination by cardioversion, either with drugs or by direct current cardioversion. In order to study patients with a current pattern of PeAF, we only included patients who were in continuous AF at the time of enrolment, or who had undergone electrical cardioversion less than 6 months preceding their procedure. All patients gave written informed consent before study enrolment and the study was approved by the United Kingdom National Research Ethics Service and the institutional research committee.

2.2 Electrophysiological and anatomic mapping

All ablation procedures were performed under general anesthesia by two experienced operators (DG/RS). Details of our peri-procedural protocol and standard ablation technique have been published previously [5]. Following left atrial access, patients in AF were cardioverted by direct current cardioversion to restore sinus rhythm. Electro-anatomical mapping of the LA was performed during constant pacing from the proximal coronary sinus at a cycle length of 600 ms, using a circular multi-electrode mapping catheter (Lasso NAV Eco, Biosense Webster, Inc.) combined with a SmartTouch (Biosense Webster, Inc.) contact force-sensing catheter. Points were acquired using the CARTO ConfiDENSE module in the auto-freeze mode if the stability criteria in space (< 6 mm) and local activation time (< 5 ms) were met. Point visualization on both map views was enabled, and the nominal fill-threshold setting of 15 mm was used. Attempts were made to cover all areas of the LA, including the mitral valve annulus and the left atrial appendage. In 16 patients, the electro-anatomical map was integrated with a contrast computed tomography or magnetic resonance imaging scan obtained less than 4 weeks prior to the procedure (CartoMerge, Biosense Webster, Inc.). Data on chamber volumes, conduction times, or bipolar voltages were not displayed to the operator in real time. All 23 patients underwent repeat invasive electrophysiological study at 2 months, irrespective of arrhythmia, or symptom recurrence. LA maps were created using an identical protocol to be used at the initial procedure. Operators were blinded to the electrophysiological and anatomic mapping data from the initial procedure.

2.3 Catheter ablation

After LA mapping, point-by-point radiofrequency energy was delivered in a wide area circumferential ablation (WACA) pattern around each pulmonary vein pair guided by Ablation Index (Biosense Webster, Inc.) targets of 550 for the roof and anterior wall, and 400 for the posterior and inferior walls [6]. Ablation Index is a lesion quality marker that utilizes contact force, time, and power in a weighted formula. No additional LA ablation was performed in any patient. In patients with documented typical cavotricuspid isthmus (CTI)-dependent flutter ($n = 2$), CTI ablation was performed. During the second procedure, any sites of PV reconnection identified were ablated, but again, no extra-PV ablation in the LA was performed.

2.4 Follow-up

All anti-arrhythmic drugs, including beta-blockers, were stopped 4 weeks after the initial ablation procedure. For 12 months following ablation, patients used a validated hand-held recording device (Omron HCG-801) to record at least one ECG daily, as well as during any symptoms. Follow-up appointments were organized at 6 weeks, 3 months, 6 months, and 1 year after the first procedure, where symptoms, ECG, and use of the anti-arrhythmic drug were recorded. Early AF recurrence was defined as recurrence occurring less than 3 months after the first procedure, with atrial arrhythmia occurring more than 3 months after the first procedure defined as long-term recurrence.

2.5 Blinded offline analysis

Detailed offline analysis of the 46 LA maps was performed by one experienced observer (BM) who was blinded to the clinical outcomes of the ablation procedures. The ECGs ($n = 8372$) recorded during follow-up were analyzed by two experienced electrophysiologists (AH, VC) who were blinded to the CARTO data.

The following characteristics were determined (Fig. 1):

2.5.1 LA volume and dimensions

The CARTO system provides an automated assessment of the volume for each collected map. To allow for standardization across maps, respiratory data were excluded. The distal parts of the left atrial appendage (LAA) and the PVs were also excluded, retaining only the proximal 1 cm of each structure. LA dimensions were measured manually in three orthogonal planes using the distance-measuring tool in CARTO V3. The lateral LA dimension was assessed at the LA roof as the distance between the top of the ostia of the two superior PVs, and at the LA floor as the distance between the bottom of the ostia of the two inferior PVs. The coronal dimension was the straight distance between the anterior and posterior wall midway between the left- and right-sided PVs. The LA height dimension was the straight distance between the LA roof and the lowest inferior wall point midway between the left- and right-sided PVs. WACA perimeters corresponded to elliptical perimeters drawn around the right- and left-sided PVs through the PV/LA junction of each vein. The observer was

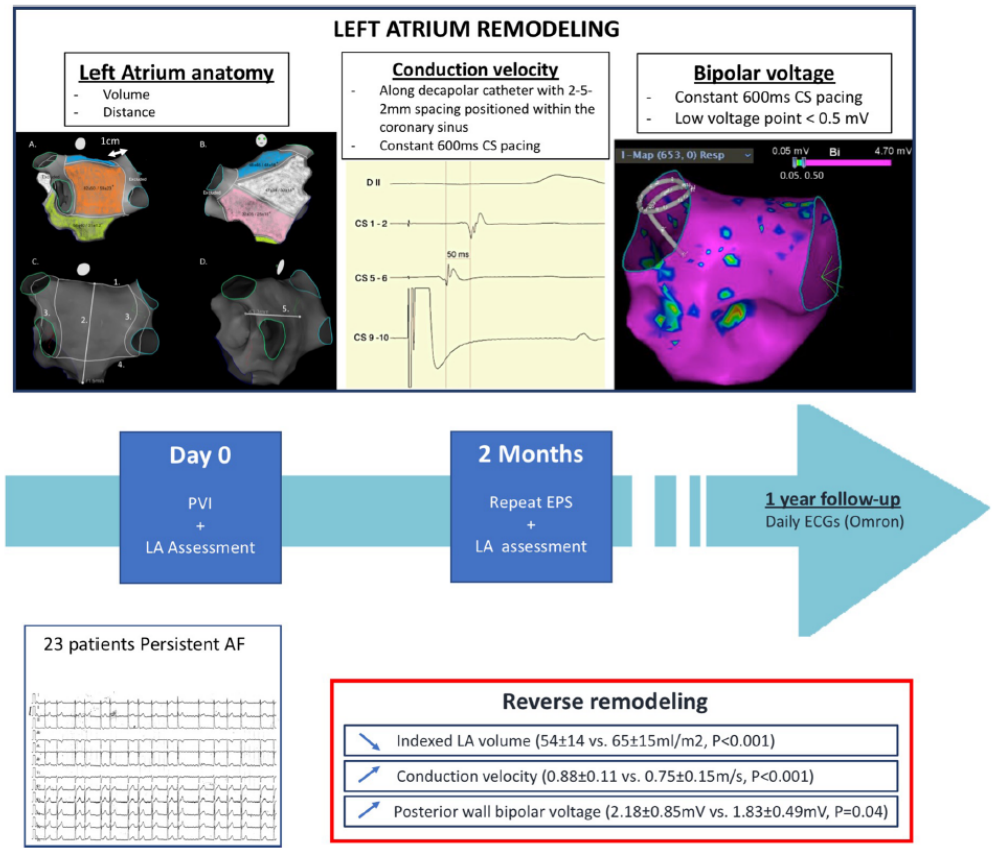

Fig. 1 CS, coronary sinus; WACA, wide area circumferential ablation; PVI, pulmonary vein isolation; LA, left atrium; EPS, electrophysiological study; AF, atrial fibrillation **Left atrium remodeling: Left atrium anatomy** Postero-anterior view (A and C). Right antero-oblique view (B). Left lateral view (D). Values shown for each region are the number of points collected at the first procedure/second procedure (mean ± standard deviation); $^{+}p > 0.05$, $^{*}p < 0.05$ **LA segmentation (A and B):** ***LA body***: Orange, posterior wall; blue, roof; green, inferolateral wall; pink, septal wall; white, anterior wall ***Pulmonary vein antrum*** (gray) **Distance measurement (C and D):** 1, roof; 2, LA height; 3, WACA perimeter; 4, floor; 5, antero-posterior diameter **Conduction Velocity:** On-screen digital calipers at a sweep speed of 200 mm/s Local activation time was manually annotated to the peak of the first deflection on bipolar electrograms, between two alternate bipoles **Bipolar voltage:** Left atrium bipolar voltage map after exclusion of all points located distal to the WACA perimeter ellipse

blinded to the results of the measurement from the first procedure.

2.5.2 LA voltage

In order to get comparable LA voltage data, all points located distal to the WACA perimeter ellipse were excluded in order to only retain points considered part of the LA body. The tissue proximity indicator filter was systematically applied offline and points collected by the circular catheter that was found not to be in contact with the shell were excluded. Each individual electrogram collected by the Lasso and contact force catheters in the 46 maps ($n = 58{,}326$ points) was then manually assessed by an experienced observer (BM) for point quality, as previously published [7]. Briefly, after first excluding ventricular far-field points and noise, the observer confirmed that the atrial signal was recorded during constant coronary sinus pacing with atrial capture at a cycle length of 600 ms. The observer then analyzed the shape of the signal to categorize it as a far-field or near-field point, based on the presence and number of sharp peaks, the aspect of adjacent signals, the stability of the signal, and the anatomical location

of the point. Points that were considered far-field points or remained uncertain were excluded. Bipolar voltage was measured from the peak-to-peak bipolar signal, filtered at 30 to 250 MHz. An index of LA voltage heterogeneity was determined by calculating the covariance.

Consistent with previous studies involving atrial mapping using the CARTO system, [8, 9] low-voltage points (LVP) were defined as a bipolar voltage amplitude < 0.5 mV. As shown in Fig. 1, for the purposes of evaluating regional voltage differences, each LA body good quality point was assigned to one of the following 5 LA regions: roof, anterior wall, posterior wall, septum, inferolateral wall.

2.5.3 Atrial conduction velocity

Atrial conduction time was assessed along a decapolar catheter with 2–5–2-mm spacing positioned within the coronary sinus [10]. Offline analyses were performed with on-screen digital calipers at a sweep speed of 200 mm/s. The local activation time (LAT) was manually annotated to the peak of the first deflection on bipolar electrograms. During constant pacing from the coronary sinus ostium at a cycle length of 600 ms, the conduction times between two alternate bipoles (between 5–6 and 1–2 or between 7–8 and 3–4) were measured. Conduction time was averaged over 5 beats during stable capture. Conduction velocity was calculated by dividing the distance between alternate bipoles (18 mm) by the conduction time. The analysis was performed for all patients and then repeated after excluding those with a change of antiarrhythmic drugs therapy between ablation procedures.

2.6 Reverse LA remodeling

Each of these LA remodeling criteria (LA volume and dimensions, LA voltage, and LA conduction velocity) was then compared between the first and the second procedure for each patient. "Super responder" patients with regard to reverse LA remodeling were defined as patients who exhibited an improvement in all LA remodeling criteria, defined as a ≥ 15% decrease in volume [11], ≥ 5% increase in bipolar voltage and a ≥ 5% higher conduction velocity.

2.7 Statistical analysis

All continuous variables with a normal distribution are expressed as mean ± standard deviation. Variables with a skewed distribution are expressed as median (Q1-Q3). Categorical variables are expressed as number of subjects (%). Comparisons of normally distributed continuous variables were made using analysis of variance, Student's *t* test or paired *t* test as appropriate. Non-parametric variables were compared using a Wilcoxon's test or Fisher's exact test as appropriate. A *P* value of less than 0.05 was considered statistically significant.

3 Results

3.1 Patient demographics and ablation results

Patient demographic information is shown in Table 1. The mean duration of continuous PeAF was 8.6 ± 3.7 months. Twenty-one of twenty-three (91.3%) patients had undergone previous attempts at electrical cardioversion. Sixteen (69.6%) patients were in AF at the start of the initial ablation procedure and were cardioverted after the trans-septal punctures. In the other 7 patients, the interval between the last cardioversion and the ablation procedure was 59 (14–136) days.

LA mapping at the first procedure yielded 1302 ± 306 points per map. Isolation of all PVs was successfully achieved in all patients. Two (8.7%) patients had additional CTI ablation for previously documented typical atrial flutter. The mean ablation time was 33.6 ± 5.5 min. Eight (34.8%) patients experienced early recurrence of AF. Among them, 5 (21.7%) patients had a recurrence of AF between the two procedures, of whom 4 underwent cardioversion and one reverted to sinus rhythm spontaneously. At repeat electrophysiology study, performed 62 ± 4 days after the index procedure, LA mapping (1233 ± 443 points per map, $P = 0.53$) revealed that 4 (17.4%) patients had evidence of late reconnection of a single PV in each. This was successfully ablated after the mapping

Table 1 Demographic data and ablation results

Clinical characteristics at the first procedure	
Age (years)	60.5 ± 6.4
Male gender, *n* (%)	17(74%)
BMI (kg/m^2)	29.2 ± 4.3
CHA_2DS_2-VASc	1(0–2)
Mild heart dysfunction, *n* (%)	6(26%)
Diabetes mellitus, *n* (%)	1(4%)
Hypertension, *n* (%)	7(30%)
AF duration (months)	8.6 ± 3.7
Duration of SR prior to 1st ablation (days)	0(0–22)
Additional CTI ablation, *n* (%)	2(8.7%)
Use of anti-arrhythmic drugs	12(52.1%)
Amiodarone, *n* (%)	9(39.1%)
Dronedarone, *n* (%)	1(4.3%)
Flecainide, *n* (%)	2(8.7%)
Catheter ablation results	
Recurrence of AF, *n* (%)	8(34.8%)
Late PV reconnection, *n* (%)	4(17.4%)
Radiofrequency Duration (min)	33.6 ± 5.6

BMI, body mass index; *CTI*, cavotricuspid isthmus ablation

data had been collected. Of these 4 patients, only 1 had experienced AF recurrence between the 2 procedures. The remaining 4 patients with early AF recurrence between the 2 procedures were all found to have persistent isolation of all 4 PVs. As per the study protocol, these patients solely underwent a diagnostic EP study, with no empirical ablation delivered and no attempt made to identify extra-PV triggers.

3.2 Electrophysiological and anatomic mapping

Electrophysiological and anatomic mapping data at baseline and the repeat procedure are shown in Table 2.

3.2.1 LA volume and dimensions

A decrease in LA volume between the two procedures was seen in 22/23 (95.6%) patients, with 10 (43.5%) meeting the criteria of a ≥ 15% reduction. Both the absolute and indexed LA volumes were significantly lower at repeat procedure compared with the initial procedure (absolute LA volume 115 ± 36 vs. 139 ± 35 ml, $P < 0.001$; indexed LA volume 54 ± 14 vs. 65 ± 15 ml/m^2, $P < 0.001$). All spatial dimensions showed a trend towards reduction at repeat study, although the threshold for statistical significance was only reached for the inferior wall (roof 34.6 ± 6.0 vs. 35.9 ± 5.3 mm, $P = 0.14$; inferior 51.2 ± 5.6 vs. 53.8 ± 6.4 mm, $P = 0.008$; coronal diameter 38.3 ± 7.5 vs. 40.5 ± 5.3 mm, $P = 0.06$; LA height 61.7 ± 7 vs. 63.9 ± 7 mm, $P = 0.19$). In addition, the diameter of the PV antra showed marked contraction (left and right antrum perimeter 121.4 ± 10.9 vs. 130.9 ± 15.3 mm, $P = 0.02$ and 121.4 ± 13.7 vs. 131.5 ± 15.2 mm, $P = 0.03$, respectively).

As illustrated in Table 3, patients with LA volume reverse remodeling had a shorter length of AF history (13.5 (8.7–19.9) vs. 21.5 (18.4–59.4) months, $P = 0.047$) and longer duration of sinus rhythm pre-ablation (18 (0–59) vs. 0 (0–0) days, $P = 0.02$). These patients were also less likely to experience early AF recurrence (0 (0%) vs. 8 (61.5%) patients, $P = 0.002$), with a strong trend towards a lower body mass index (BMI) also seen (27.9 (25.7–29.1) vs. 32.7 (26.4–34.7) kg/m^2, $P = 0.05$).

3.2.2 Conduction velocity

LA conduction velocities were significantly greater at 2 months (0.88 ± 0.11 vs. 0.75 ± 0.15 m/s, $P < 0.001$). After excluding the 11 patients who discontinued anti-arrhythmic drug therapy between the two procedures, LA conduction velocity remained significantly greater at 2 months (0.90 ± 0.10 vs. 0.78 ± 0.18 m/s, $P = 0.03$) in the remaining 12 patients (of whom 11 did not take an anti-arrhythmic agent at any point and 1 continued to take dronedarone until after their second procedure).

Patients with LA conduction reverse remodeling were found to have a shorter length of AF history (18.4 (9.7–21.5) vs. 53.4 (24.3–72.9) month, $P = 0.049$) and were less likely to have PV reconnection (1 (5.9%) vs. 3 (50%) patients, $P = 0.01$) (Table 4).

3.2.3 LA voltage

After selecting only points considered as part of the LA body and following manual assessment of each individual electrogram [7], the number of points meeting the quality criteria was 264 ± 149 and 198 ± 76 points for the first and the second procedure, respectively ($P = 0.11$).

The overall mean LA voltage was not different in the second procedure (2.00 ± 0.59 vs. 2.07 ± 0.53 mV, $P = 0.43$). However, regional LA analysis demonstrated non-uniform reverse remodeling, with a significant decrease in voltage at the second procedure in the septal wall (1.51 ± 0.51 vs. 2.28 ± 1.85 mV, $P = 0.04$) and the inferolateral wall (1.83 ± 0.65 vs. 2.04 ± 0.56 mV, $P = 0.01$). Relative voltage stability was seen in the roof (2.08 ± 0.88 vs. 2.08 ± 0.59 mV, $P = 0.97$) and anterior walls (1.89 ± 0.76 vs. 2.09 ± 0.80 mV, $P = 0.21$), with a significant voltage increase in the posterior wall (2.18 ± 0.85 mV vs. 1.83 ± 0.49 mV, $P = 0.04$).

When considering low-voltage points (< 0.5 mV) as a percentage of total points, there was a trend towards this being lower at the second procedure (6.5 ± 6.2% vs. 8.5 ± 6.7%, $P = 0.06$). It is notable that there was a low prevalence of low-voltage points in our study population at baseline, with only 7 (30.4%) patients exhibiting a low-voltage point proportion of more than 10%. There was also a trend towards lower voltage heterogeneity at the second procedure (64.8 ± 11.2% vs. 71.6 ± 12.4%, $P = 0.07$). Regional heterogeneity voltage analyses did not show any regional modification between the two procedures.

As shown in Table 5, patients with LA voltage reverse remodeling were found to have had a longer period of sustained sinus rhythm prior to ablation (36 (0–93) vs. 0 (0–0) days, $P = 0.02$).

3.3 Clinical follow-up

During 12-month follow-up with daily ECG monitoring, 5 (21.7%) patients experienced AF recurrence after a 3-month blanking period. Three of these experienced a single paroxysmal AF episode each, occurring at 129, 180, and 297 days after the first procedure. One patient restarted anti-arrhythmic drug therapy, while the other two spontaneously maintained sinus rhythm. Two patients experienced a return of persistent AF at 135 and 169 days respectively after the first procedure, and a rate-control strategy was agreed upon. In all, 21 (91.3%) patients were in sinus rhythm at 12 months, and 20 (87.0%) patients were in sinus rhythm and free of anti-arrhythmic drugs.

Table 2 Electrophysiological and anatomic mapping data at baseline and repeat procedure

	Baseline ($N = 23$)	Repeat procedure ($N = 23$)	*P value*
LA volume (ml)	139 ± 35	115 ± 36	< 0.001
Indexed LA volume (ml/m^2)	65 ± 15	55 ± 14	< 0.001
LA dimension (mm)			
Roof line	35.9 ± 5.3	34.6 ± 6	0.14
Inferior line	53.8 ± 6.4	51.2 ± 5.6	0.008
Antero-posterior line	40.5 ± 5.3	38.3 ± 7.5	0.06
Height	63.9 ± 5.6	61.7 ± 7	0.19
Left antrum perimeter	130.9 ± 15.3	121.4 ± 10.9	0.02
Right antrum perimeter	131.5 ± 15.2	121.4 ± 13.7	0.03
LA mean voltage (mV)	2.07 ± 0.53	2.00 ± 0.59	0.43
LVP (%)	8.5 ± 6.7	6.5 ± 6.2	0.06
Count (*n*)	264 ± 149	198 ± 76	0.11
Roof mean voltage (mV)	2.08 ± 0.59	2.08 ± 0.88	0.97
LVP (%)	6.2 ± 6.5	6.9 ± 8.8	0.71
Count (*n*)	46 ± 46	48 ± 58	0.88
Posterior mean voltage (mV)	1.83 ± 0.49	2.18 ± 0.85	0.04
LVP (%)	9.2 ± 7.9	6.4 ± 7.7	0.18
Count (*n*)	82 ± 50	59 ± 23	0.06
Anterior mean voltage (mV)	2.09 ± 0.80	1.89 ± 0.76	0.21
LVP (%)	9.0 ± 14.5	9.9 ± 14.6	0.77
Count (*n*)	47 ± 34	33 ± 18	0.10
Septum mean voltage (mV)	2.28 ± 1.85	1.51 ± 0.51	0.04
LVP (%)	5.7 ± 10.6	11.5 ± 15.0	0.02
Count (*n*)	32 ± 35	25 ± 15	0.43
Inferolateral mean voltage (mV)	2.04 ± 0.56	1.83 ± 0.65	0.01
LVP (%)	7.5 ± 8.6	8.5 ± 9.9	0.62
Count (*n*)	56 ± 40	31 ± 12	0.02
LA conduction velocity (m/s)	0.75 ± 0.15	0.88 ± 0.11	< 0.001

LA, left atrium; LVP, low-voltage point

Table 3 Demographic and procedural parameters by volume reverse remodeling outcome

	Volume reverse remodeling: no ($n = 13$)	Volume reverse remodeling: yes ($n = 10$)	*P* value
Male, *n* (%)	8 (61.5%)	9 (90.0%)	0.12
Age (years)	60 (55–66)	61 (58–65)	0.4
BMI (kg/m^2)	32.7 (26.4–34.7)	27.2 (25.7–29.1)	0.050
CHA_2DS_2-VASc score	1 (0–2)	1 (1–1)	1
Length of AF history (months)	21.5 (18.4–59.4)	13.5 (8.7–19.9)	0.047
Duration of SR prior to 1st ablation (days)	0 (0–0)	18 (0–59)	0.02
Early recurrence of AF, *n* (%)	8 (61.5%)	0 (0%)	0.002
Indexed LA volume (1st procedure) (ml/m^2)	57.6 (48.6–73.4)	65.5 (59.8–78.7)	0.15
RF duration (min)	33.5 (31.1–34.4)	31.5 (30.5–36.3)	0.95
PV reconnection, *n* (%)	2 (15.4%)	2 (20%)	0.77

LA, left atrium; *BMI*, body mass index; *SR*, sinus rhythm

Volume reverse remodeling was defined as ≥15% decrease in volume. PV reconnection: pulmonary vein reconnection documented at repeat electrophysiological study at 2 months

Table 4 Demographic and procedural parameters by conduction reverse remodeling outcome

	Conduction reverse remodeling: no ($n=6$)	Conduction reverse remodeling: yes ($n=17$)	P value
Male, n (%)	5 (83.3%)	12 (70.6%)	0.5
Age (years)	60.5 (53–62)	61 (57–67)	0.44
BMI (kg/m^2)	30.8 (27.9, 32.6)	27.4 (25.8–33.1)	0.36
CHA_2DS_2-VASc score	1 (1–1)	1 (0–2)	0.91
Length of AF history (months)	53.4 (24.3–72.9)	18.4 (9.7–21.5)	0.049
Duration of SR prior to 1st ablation (days)	45 (0–98)	0 (0–0)	0.13
Early recurrence of AF, n (%)	3 (50%)	5 (29.4%)	0.36
Indexed LA volume (1st procedure) (ml/m^2)	65.9 (57.3–85.7)	61.3 (51.6–68.9)	0.32
RF duration (min)	34.4 (32.4–39.1)	31.9 (29.1–33.5)	0.11
Change AAD after 1st procedure, n (%)	2 (33.3%)	9 (52.9%)	0.40
PV reconnection, n (%)	3 (50%)	1 (5.9%)	0.01

LA, left Atrium; *AAD*, anti-arrhythmic drugs; *BMI*, body mass index; *SR*, sinus rhythm. Conduction reverse remodeling was defined as ≥ 5% higher conduction velocity. PV reconnection: pulmonary vein reconnection documented at repeat electrophysiological study at 2 months

Table 6 shows demographic and procedural parameters for patients with and without long-term recurrence of AF. Patients with long-term AF recurrence had a higher body mass index (BMI) (33.1 (32.7–34.9) vs. 27.2 (25.7–30.1), $P=0.02$) and were more likely to have experienced early AF recurrence (4 (80%) vs. 4 (22%) patients, $P=0.03$).

Five patients were identified as "Super responders" but the proportion of patients with and without long-term AF recurrence who were "Super responders "was not different (1 (20%) vs. 4 (22.2%), $P=1.00$). This was also true for each of the individual reverse remodeling factors.

3.4 Presentation for the initial procedure in sinus rhythm or AF

Table 7 shows demographic and procedural parameters for patients in sinus rhythm or AF at the time of the first procedure. There were no differences in patient characteristics between the two groups at baseline other than greater use of anti-arrhythmic drugs in the sinus rhythm group. A significantly higher proportion of patients who were in sinus rhythm at the time of their initial procedure showed LA volume and voltage reverse remodeling as compared to those who were in AF (85.7% vs. 25%, $P=0.007$ and 71.4% vs. 18.7, $P=0.01$, respectively). However, there was no difference in freedom from AF between these 2 groups ($P=0.60$).

4 Discussion

Our study is the first study to evaluate structural and electrical reverse remodeling in the left atrium after catheter ablation for persistent AF through systematic, protocol-driven repeat invasive electrophysiological studies. Our findings suggest that (1)

Table 5 Demographic and procedural parameters by voltage reverse remodeling outcome

	Voltage reverse remodeling: no ($n=15$)	Voltage reverse remodeling: yes ($n=8$)	P value
Male, n (%)	12 (80%)	4 (50%)	0.93
Age (years)	60 (54.5–61)	64 (60–67.5)	0.43
BMI (kg/m^2)	29.2 (26.0–33.8)	28.1 (26.6–29.6)	0.73
CHA_2DS_2-VASc score	1 (0–2)	1 (0–3)	0.52
Length of AF history (months)	21.3 (12.7–59.4)	17.3 (7.5–44.4)	0.43
Duration of SR prior to 1st ablation (days)	0 (0–0)	36 (0–93)	0.02
Early recurrence of AF, n (%)	7 (47%)	1 (12.5%)	0.47
Indexed LA volume (1st procedure) (ml/m^2)	67.2 (50.1–78.4)	60.3 (57.1–64.6)	0.94
Proportion of low-voltage points (%)	4.5 (2.0–6.6)	3.5 (2.1–16.3)	0.56
RF duration (min)	33.4 (28.7–34.4)	31.6 (30.1–40.9)	0.50
PV reconnection, n (%)	3 (20%)	1 (12.5%)	0.65

LA, left atrium; *BMI*, body mass index; *SR*, sinus rhythm. Voltage reverse remodeling was defined as ≥ 5% increase in mean bipolar voltage at 2 months. PV reconnection: pulmonary vein reconnection documented at repeat electrophysiological study at 2 months

Table 6 Demographic and procedural parameters by long-term recurrence outcome

	Long-term recurrence: no ($n = 18$)	Long-term recurrence: yes ($n = 5$)	P value
Age (years)	61 (58.5–65)	57 (50–67.5)	1.00
Male, n (%)	13 (72.2%)	4 (80.0%)	0.5
BMI (kg/m^2)	27.2 (25.7–30.1)	33.1 (32.7, 34.9)	0.02
CHA_2DS_2-VASc score	1 (0–2)	1 (0–1)	1.00
Length of AF history (months)	15.6 (9.9–53.4)	21.0 (21.0–24.6)	0.33
Indexed LA volume (1st procedure) (ml/m^2)	60.3 (56.2–76.7)	67.1 (49.8–82.9)	1.00
Early recurrence of AF, n (%)	4 (22.2%)	4 (80%)	0.03
Late PV reconnection, n (%)	4 (22.2%)	0 (0%)	0.25
Volume remodeling, n (%)	9 (50%)	1 (20%)	0.34
Conduction remodeling, n (%)	13 (72.2%)	4 (80%)	1.00
Voltage remodeling, n (%)	6 (33.3%)	2 (40%)	1.00
"Super responder" patient, n (%)	4 (22.2%)	1 (20%)	1.00

LA, left atrium; *BMI*, body mass index. PV reconnection: pulmonary vein reconnection documented at repeat electrophysiological study at 2 months. Volume reverse remodeling was defined as ≥ 15% decrease in volume; conduction reverse remodeling was defined as ≥ 5% higher conduction velocity; voltage reverse remodeling was defined as ≥ 5% increase in bipolar voltage. "Super responder" patients were defined as patients who exhibited improvement on all LA reverse remodeling criteria

significant structural remodeling is seen almost universally following PVI, (2) structural and electrical remodeling is clearly manifest within 2 months following ablation, and (3) factors associated with remodeling include the length of AF history, duration of sinus rhythm pre-ablation, early AF recurrence, and PV reconnection. However, none of the individual reverse remodeling parameters nor meeting criteria for reverse remodeling for all 3 parameters ("Super responder") were associated with long-term freedom from AF. Patients with long-term AF recurrence had a significantly higher BMI and were more likely to have experienced early AF recurrence.

4.1 Atrial structural reverse remodeling

Previous non-invasive studies have shown reverse structural LA remodeling after catheter ablation and even after electrical

Table 7 Demographic and procedural parameters according to atrial rhythm at the time of the first procedure

	In AF at the first procedure $n = 16$	In SR at the first procedure $n = 7$	P value
Age (years)	61 (57–66)	61 (55–64)	NS
Men, n (%)	11 (68.7%)	6 (85.7%)	NS
BMI (kg/m^2)	27.4 (25.5–34.5)	29.3 (27.8–29.8)	NS
CHA_2DS_2-VASc score	1 (0–4)	1 (0–3)	NS
Anti-arrhythmic drug use, n (%)	6 (37.5%)	6 (85.7%)	0.03
PV reconnection, n (%)	3 (18.7%)	1 (14.3%)	NS
Initial indexed LA volume (ml/m^2)	59.8 (50.8–74.5)	63.8 (57.6–78.5)	NS
Volume reverse remodeling, n (%)	4 (25%)	6 (85.7%)	0.007
Initial LA voltage (mV)	2.01 (1.74–2.27)	2.11 (1.94–2.63)	NS
Voltage reverse remodeling, n (%)	3 (18.7%)	5 (71.4%)	0.01
Initial LA velocity (m/s)	0.78 (0.68–0.85)	0.77 (0.71–0.79)	NS
Velocity reverse remodeling, n (%)	13 (81.2%)	4 (57.1%)	0.2
Early recurrence of AF, n (%)	7 (43.7%)	1 (14.3%)	0.17
Late recurrence of AF, n (%)	3 (18.7%)	2 (28.6%)	0.6

DCCV, Direct Current Cardioversion; *LA*, left atrium; *BMI*, body mass index. PV reconnection: pulmonary vein reconnection documented at repeat electrophysiological study at 2 months. Volume reverse remodeling was defined as ≥ 15% decrease in volume; conduction reverse remodeling was defined as ≥ 5% higher conduction velocity; voltage reverse remodeling was defined as ≥ 5% increase in bipolar voltage

Early recurrence of AF is defined as AF recurrence less than 3 months after the first procedure

Late recurrence of AF is defined as AF recurrence more than 3 months after the first procedure

cardioversion [11, 12], indicating a relationship between the restoration of sinus rhythm and atrial structural remodeling. We have also demonstrated early structural reverse remodeling, with a significant decrease in LA volume. The role of restoration of sinus rhythm in this process is indicated by the finding that patients with significant (≥ 15%) volume reduction were markedly less likely to have experienced AF recurrence between procedures and had a longer duration of sinus rhythm pre-ablation. This may be because patients who can sustain sinus rhythm for longer after electrical cardioversion have a less permanent structural change, allowing greater remodeling after restoration and maintenance of sinus rhythm. This hypothesis is supported by the finding that volume remodeling patients had a shorter length of total AF history, which suggests that structural changes become irreversible after protracted periods of continuous AF. Of note, volume reduction does not appear to be related to a contractile effect from transmurally ablated tissue, as radiofrequency ablation duration was not different between patients with and without volume remodeling.

4.2 Atrial electrical reverse remodeling

Through increases in LA conduction velocity and regional LA bipolar voltage amplitude, this study has demonstrated evidence of electrical reverse remodeling within the first 2 months after catheter ablation. Logan et al. previously demonstrated that the *a*-wave in the atrial pressure curve remained absent after cardioversion of AF [13], and later studies using echocardiographic techniques revealed that it could take months before atrial transport function fully recovered [14]. This atrial contractile dysfunction was also found to correlate with the duration of AF and, just as for volume remodeling, our study appears to show a link between the length of the AF history and conduction velocity remodeling. This may again indicate irreversible electrical changes with prolonged AF. As was also seen with volume remodeling, duration of sinus rhythm pre-ablation was longer in patients with voltage remodeling, suggestive of less established substrate.

Patients with conduction velocity remodeling were also found to be significantly less likely to have PV reconnection at repeat study, though notably, the proportion of patients with early AF recurrence was not statistically different between groups. As patients with PV reconnection had only 1 reconnected PV each, it is possible that recurrent PV firing occurred in these patients, insufficient to initiate AF but influencing conduction velocity changes.

To our knowledge, this study is the first invasive human study to demonstrate an improvement in LA voltage. This may well be explained by the study design, with patients systematically re-studied after 2 months regardless of early clinical outcome. Two previous studies of patients undergoing a redo procedure for clinical AF recurrence 6 months after PVI showed lower mean voltages in the right atrium [15] and LA [16], as might be expected in patients with ongoing arrhythmia. Although there was no change seen in the overall LA body voltage between procedures, the regional analysis demonstrated localized changes. The decreased voltage seen in the septal wall can likely be explained by the two trans-septal punctures performed at the initial procedure. However, the increase in posterior wall voltage following PVI-only ablation is of substantial interest given the predilection of this area for non-PV driver regions [17] and the development of apparent fibrosis earlier in the disease course. It is possible that if the posterior wall has a propensity for reduced voltage following sustained AF, maintenance of sinus rhythm may preferentially induce electrical remodeling in this region. This in turn raises the question of whether low-voltage-guided posterior wall ablation is a necessary strategy beyond sole PVI.

4.3 Long-term recurrence of AF

Previous echocardiographic and MRI studies have shown structural reverse remodeling with a significant reduction in LA volume after catheter ablation for AF to be a predictive factor for freedom from AF recurrence [18].

In our study, no association was seen between long-term recurrence of AF and any individual reverse remodeling parameter, nor the composite factor of "Super response." However, this finding is limited by the relatively small study population, and particularly, the small proportion of patients who experienced recurrence of AF. It is notable that elevated BMI was associated with the long-term AF recurrence, as has been in other studies. Obesity is known to result in structural and electrical negative remodeling [19], and a trend towards the absence of volume reverse remodeling was seen in this study.

4.4 Effect of maintenance of sinus rhythm prior to ablation

A significantly higher proportion of patients who were in sinus rhythm at the time of their initial procedure showed LA reverse remodeling as compared to those who were in AF. A greater proportion of patients in sinus rhythm were taking anti-arrhythmic drugs at the time of the initial procedure and therefore, one potential explanation for this seemingly paradoxical finding could be that maintenance of sinus rhythm with anti-arrhythmic drugs following prior DC cardioversion may confer a benefit with regard to LA remodeling. However, it should be noted that 14 of the 16 patients in AF at the start of the initial ablation procedure had previously undergone DC cardioversion, and it is likely that several of these patients were taking anti-arrhythmic drugs at the time. It is possible that, at least in some cases, AF returned despite anti-arrhythmic drugs (which were subsequently stopped), and

therefore, it could be postulated that patients in the sinus rhythm group may have been at a less advanced and more reversible stage of the disease process, allowing them to maintain sinus rhythm for longer after prior DC cardioversion.

However, the greater LA remodeling in the sinus rhythm group was not associated with better clinical outcomes in terms of freedom from AF recurrence, although the study was not powered to assess this fully. The potential influences of the timing of cardioversion, use of anti-arrhythmic drugs to maintain sinus rhythm, and changes in other parameters such as changes in left atrial pressure are difficult to determine from this study and require further investigation.

4.5 Limitations

The invasive nature of this study resulted in a small sample size, and the study findings need to be interpreted in this context. Also, we observed a very high incidence of durable PVI in our cohort with Ablation Index-guided ablation, and our study findings may not be applicable to techniques where there is a higher incidence of late PV reconnection. Our PeAF cohort was largely healthy, as indicated by a median CHA_2DS_2-VASc score of 1, and our findings of positive remodeling may not be replicable in the presence of extensive comorbidities. Furthermore, 2 months may not have been sufficient for full remodeling to occur and scheduling the second procedure for 6–12 months following the first one may have yielded more marked changes. However, a long-time lag between procedures would have increased the probability of clinical variables like BMI and age affecting measurements, rather than the AF ablation itself [20]. Finally, the focus of the present investigation was to study those parameters that could only be evaluated at repeat left atrial electrophysiology study. Additional measures potentially relevant to LA remodeling, such as P wave duration or LA pressure measurement, were not collected but may have yielded relevant findings.

5 Conclusion

This is the first invasive study to demonstrate early structural and electrical LA reverse remodeling in the initial months after PVI-only catheter ablation for PeAF. Factors thought to be linked with less LA fibrosis, such as shorter total duration of AF history and ability to maintain sinus rhythm after electrical cardioversion, were associated with volume and electrical reverse remodeling. However, reverse remodeling was not found to be associated with long-term clinical outcomes, with a significant association seen only with higher BMI and the presence of early AF recurrence.

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Compliance with ethical standards

All patients gave written informed consent before study enrolment and the study was approved by the United Kingdom National Research Ethics Service and the institutional research committee.

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ORIGINAL ARTICLE

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Accuracy of left atrial bipolar voltages obtained by ConfiDENSE multielectrode mapping in patients with persistent atrial fibrillation

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Abstract

Introduction: The ConfiDENSE™ module (Carto3 v4) allows rapid annotation of endocardial electrograms acquired by multielectrode (ME) mapping. However, its accuracy in assessing atrial voltages is unknown.

Methods and results: Two ConfiDENSE™ left atrial voltage maps were created during continuous pacing in 20 patients undergoing catheter ablation for persistent AF using a ME lasso catheter and a contact force (CF) sensing ablation catheter. The automated tissue proximity indicator (TPI) filter was then applied to the ME map to yield a TPI map. Reference maps (RM) were created offline by a blinded observer by manually assessing all points against fidelity criteria. Bipolar voltages and proportion of low voltage points (< 0.5 mV) derived from the ME, CF, and TPI maps were compared with those derived from the RM.

Note that 853 ± 365 points, 252 ± 184 points, and 144 ± 73 were collected for ME, TPI, and CF maps, respectively, and 429 ± 153 points were included in the RM. Voltages with CF and TPI maps were similar to those with RM (1.57 ± 0.47 mV vs. 1.63 ± 0.31 mV, P = 0.57 and 1.50 ± 0.38 mV vs. 1.63 ± 0.31 mV, P = 0.07, respectively), whereas ME maps showed a significantly lower mean voltage (1.00 ± 0.22 mV, P < 0.001). As compared to RM maps (17 ± 8%), low voltage points were significantly overestimated by the ME maps (50 ± 9% (P < 0.001) and TPI maps (28 ± 13% (P < 0.001), but not by the CF maps (22 ± 14%, P = 0.17).

Conclusion: Application of the TPI filter to ConfiDENSE maps significantly increases the quality of the voltage data, conserving a reasonable point density, but still overestimates low voltage points as compared to CF-sensing maps or maps reviewed manually.

KEYWORDS
atrial fibrillation, catheter ablation, far-field, mapping, tissue proximity indicator, voltage

1 | INTRODUCTION

Although atrial fibrillation (AF) is a very common arrhythmia, its electrophysiological mechanisms are still debated. Animal models consistently point to the important role of atrial fibrosis in its development and maintenance, particularly in persistent AF.[1,2] Bipolar voltage mapping of the left atrium (LA) has been suggested as a way to assess substrate for AF, with low voltage areas being considered surrogates for atrial fibrosis and potential targets for catheter ablation.[3,4]

Previous studies reporting LA voltage data in patients with persistent AF have shown a very wide range of proportions of low voltage area of between 2% and 77%.[5–7] Some studies have suggested that this wide variation may partly be related to the LA mapping protocol.[8] A major complexity of LA mapping is assessment of the proximity between catheter and tissue, in order to omit recording of far-field points that can falsely indicate low voltage areas. The ConfiDENSE™ module in Carto 3® V4 (Biosense Webster, Inc., Diamond Bar, CA, USA) allows rapid annotation of endocardial points acquired by

multielectrode (ME) mapping. The tissue proximity indicator (TPI) filter is an impedance-based automated algorithm designed to exclude map points deemed not in contact with the shell.[9] However, the accuracy of voltage data obtained by ConfiDENSE™ mapping using the TPI filter has not been studied. The aim of our study was therefore to evaluate the accuracy of a LA mapping protocol to assess LA voltage obtained by ConfiDENSE™ mapping using the TPI filter in a persistent AF population, as compared to standard ME mapping without the TPI filter or point-by-point mapping.

2 | METHODS

2.1 | Study population

Twenty patients undergoing catheter ablation for persistent AF, with a continuous AF duration of at least 6 months were studied. Exclusion criteria included: age less than 18 years, underlying structural heart disease such as greater than mild left ventricular dysfunction or hypertrophic cardiomyopathy, and moderate or greater valvular stenosis or regurgitation. All patients provided written, informed consent for this study, which was approved by both institutional and national ethics committees.

2.2 | Electrophysiological and anatomic mapping

All patients underwent ablation for AF using a pulmonary vein isolation-only approach. All procedures were performed under general anesthesia by two experienced operators (DG/RS). Details of our periprocedural protocol and standard ablation technique have been published previously.[10] After femoral venous access guided by ultrasound,[11] a deflectable decapolar diagnostic catheter with a 2-5-2 mm electrode configuration was placed in the coronary sinus. Two transseptal punctures were then performed, with intravenous heparin given to achieve a target ACT of >300 seconds. A deflectable 20-pole circular mapping catheter (Lasso NAV Eco, Biosense Webster, Inc.) and a 3.5-mm irrigated tip contact force (CF)-sensing ablation catheter (SmartTouch, Biosense Webster, Inc.) were then advanced into the LA via nonsteerable sheaths. Patients in AF were cardioverted by direct current cardioversion at this point to restore sinus rhythm. Respiratory gating was performed and CF-sensing was calibrated.

Electroanatomical mapping of the LA was performed during constant pacing from the proximal coronary sinus electrodes at a cycle length of 600 milliseconds, first using the Lasso ME catheter and then using the SmartTouch CF-sensing catheter. All the points collected by the CF catheter were at stable but light contact between 2 and 10 g, in order to prevent atrial ectopy induced by CF above this level.[12] For both the ME and CF maps, points were acquired using the CARTO ConfiDENSE module in the auto-freeze mode if the stability criteria in space (<6 mm) and local activation time (≤5 milliseconds) were met. The TPI filter was not applied during ME or CF mapping. Point visualization on both map views was enabled, and the nominal fill-threshold setting of 15 mm was used, consistent with other recent studies.[5] Attempts were made to cover all areas of the LA, including the mitral valve annulus and the left atrial appendage, to allow satisfactory fusion with a LA image segmented from a contrast computed tomography or magnetic resonance imaging scan obtained less than 4 weeks prior to the procedure (CartoMerge, Biosense Webster, Inc.). Point collection was gated according to respiratory cycle.

2.3 | Catheter ablation

After creation of both maps, point-by-point radiofrequency energy was delivered in a wide area circumferential ablation pattern around each pulmonary vein pair guided by Ablation Index (Biosense Webster, Inc.) targets of 550 for the roof and anterior wall, and 400 for the posterior and inferior walls. Ablation Index is a lesion quality marker that utilizes CF, time, and power in a weighted formula.[13] No additional LA ablation was performed in any patient.

2.4 | Offline LA voltage analysis

TPI is an impedance-based automated algorithm designed to exclude map points deemed not in contact with the LA shell. To generate the TPI map for each patient, the TPI filter was applied offline to the ME map collected with the Lasso catheter. For CF maps, any points acquired with the CF catheter with a CF of <2 g were excluded. For all three maps, all points located more than 1 cm distal to the pulmonary vein ostia were excluded.

A reference map (RM) was then generated for each patient. Each individual electrogram in the 20 ME maps was manually assessed by an experienced observer (BM). As shown in Figure 1, points were analyzed at 200 mm/s as time scale and 1 mV/cm as voltage scale. The observer first confirmed that the atrial signal (ventricular far-field points and noise were excluded) was recorded during constant coronary sinus pacing with atrial capture at a cycle length of 600 milliseconds. The observer then analyzed the shape of the signal to categorize it as a far-field or near-field point, based on the presence and number of sharp peaks, the aspect of adjacent signals, the stability of the signal and the anatomical location of the point[2,14–16] (Figure 1). In keeping with a previous study,[17] near-field signals were defined as high frequency signals, with a minimum of two sharp peaks required to consider the signal as near-field. Next, the width of the signal was visually analyzed to confirm the point as high frequency. After that, consistency with adjacent signals (temporally and geographically) in terms of the morphology of the electrogram was assessed. Points that did not fit these criteria of sharp peaks and stability were considered to be far-field signals or uncertain, and these were excluded to yield the RM. Bipolar voltage was measured from the peak-to-peak bipolar signal, filtered at 30 to 250 MHz. An index of LA voltage heterogeneity was determined by calculating the covariance. To assess interobserver reproducibility of RM points, 100 randomly chosen electrograms were evaluated independently by a second experienced observer (AH).

Consistent with previous studies involving atrial mapping using the CARTO system, very low-voltage points (VLVP) were defined as those with a bipolar voltage amplitude <0.5 mV.[3,6] Because recent studies have suggested a higher voltage threshold for low voltage points,[4,18] we considered two additional thresholds: points with

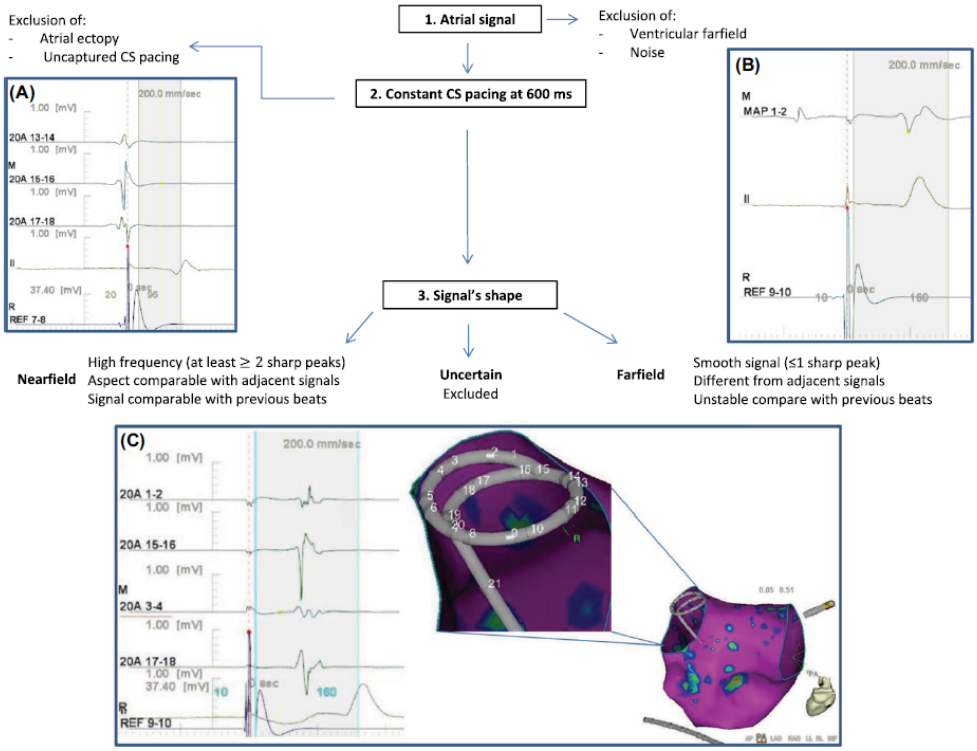

FIGURE 1 Signal interpretation algorithm to yield reference map Screen display at 200 mm/s. Bipolar voltage scale is 1 mV/cm. Note that "20A" signals correspond to multipolar electrode catheter signals. "*MAP*" correspond to ablation catheter signals. "*II*" represents lead II of the surface ECG. "*REF*" corresponds to CS catheter signals. The red dotted line is marked as a time reference. The highlighted grey area corresponds to the interval of automatic signal recording by the ConfiDENSE™ mapping module. A, Example of atrial ectopy: Atrial depolarization (20A 17–18) appears before REF 7–8, because of an atrial ectopic. It is incorrectly interpreted by the software as a low voltage point. B, Example of ventricular far-field records: MAP 1–2 signal in the grey area corresponds to a ventricular far-field signal (as assessed by lead II). C, Constant REF 9–10 pacing at 600 milliseconds. According to the endocardial mapping and catheter position shown on the right, the ME catheter is placed at the antrum of the left upper pulmonary vein (LUPV). 20A 3–4 and 20A 17–18 are close together, as are 20A 15–16 and 20A 1–2. 20A 3–4 and 20A 1–2 are slightly deeper in the LUPV. Interpretation of signals reveals a first component of atrial depolarization followed by antrum depolarization. 20A 15–16 and 20A 17–18 mainly record the atrial potential followed by a small fractionated potential that corresponds to the antrum potential. 20A 1–2 mainly records the antrum depolarization. 20A 1–2, 15–16, and 17–18 are near-field potentials, whereas 20A 3–4 is only a far-field potential and was excluded

voltages between 0.5 and 0.75 mV were considered as representing moderate low voltage points (MoLVP), and those between 0.75 and 1.0 mV as mild low voltage points (MiLVP).

Bipolar voltages and proportions of low voltage points derived from the baseline ME maps, CF maps, and TPI maps were then compared with those derived from the RM.

2.5 | Statistical analysis

All continuous variables with a normal distribution are expressed as mean ± standard deviation. Bipolar voltage repartition has been defined as Gaussian repartition. Variables with a skewed distribution are expressed as median (Q1–Q3). Categorical variables are expressed as number of subjects (%). Comparisons of normally distributed continuous variables were made using analysis of variance, Student's *t*-test or paired *t*-test as appropriate. Linear correlation between continuous variable were analyzed using Spearman correlation coefficient (rho). A P value <0.05 was considered statistically significant.

3 | RESULTS

3.1 | Demographic data

Patient demographics and procedural data are listed in Table 1. Mean age was 62 ± 5 years, mean BMI was 29.6 ± 4.5 kg/m^2, and median CHA_2DS_2-VASc score was 1 (0–5). Mean LA diameter assessed by

TABLE 1 Demographic data

Age, years	62 ± 5
Male gender, n (%)	15 (75%)
Left atrial diameter on echo, mm	42 ± 3
No enlargement, n (%)	3 (15%)
Mild to moderate enlargement, n (%)	13 (65%)
Severe enlargement, n (%)	4 (20%)
Body mass index, kg/m^2	29.6 ± 4.5
CHA_2DS_2-VASc score	1 (0–5)
Mild left ventricular dysfunction, n (%)	4 (20%)
Diabetes mellitus, n (%)	1 (5%)
Hypertension, n (%)	4 (20%)
Atrial fibrillation duration, months	8.5 ± 4.9
Previous cardioversion, n (%)	19 (95%)
Use of antiarrhythmic drugs, n (%)	10 (50%)
Amiodarone, n (%)	7 (40%)
Flecainide, n (%)	3 (10%)

echocardiogram was 42 ± 3 mm and 4 (20%) patients were reported as having a severely dilated LA. The mean duration of continuous AF was 8.5 ± 4.9 months. Eight (40%) patients were in sinus rhythm at the time of the procedure, having been cardioverted recently (<3 months).

3.2 | Point collection using different mapping techniques

Included in the analyses were 989 ± 353 points per map (range 422—1,954 points). The mean LA surface on the Carto maps, after excluding respiratory data, was 178 ± 31cm^2. Note that 853 ± 365 points were collected with the Lasso catheter and were included in ME maps. Of these, 252 ± 184 points per map were considered in close proximity according to the TPI filter. Also, 144 ± 73 points per map were collected with the CF catheter, with a mean CF of 3.3 ± 1.2 g, of which 113 ± 52 reached the CF threshold of ≥2 g and were included in CF maps. Accordingly, ME maps provided the highest density of points (4.88 ± 2.16 points/cm^2). The point density obtained with TPI maps was significantly lower (1.44 ± 1.07 points/cm^2, P < 0.001) and was lower still with CF maps (0.60 ± 0.26 points/cm^2, P < 0.001).

3.3 | Offline creation of RM

After offline analyses, 429 ± 153 points per map met the criteria for fidelity and were included in the RM, giving a point density of 2.47 ± 0.97 points/cm^2 (P < 0.001 compared to ME maps).

3.4 | Interobserver reproducibility of RM points

Individual bipolar voltage analyses for 100 randomly chosen points showed 98% agreement between the two observers for far-field and near-field points.

3.5 | LA voltage values between mapping techniques

As illustrated in Figure 2, RM provided the highest mean LA voltage value (1.63 ± 0.31 mV). Voltages were similar with CF maps and TPI maps (1.57 ± 0.47 mV, P = 0.57 and 1.50 ± 0.38 mV, P = 0.07, respectively), whereas ME maps showed a significantly lower mean LA voltage (1.00 ± 0.22 mV, P < 0.001). However, only ME and TPI map bipolar voltage mean values showed a correlation with RM values (R = 0.86; P < 0.001 and R = 0.61; P = 0.004, respectively), whereas CF map bipolar mean values did not show any correlation (R = 0.008; P = 0.73; Figure 3).

3.6 | Sample heterogeneity

CF maps showed the lowest sample heterogeneity (72 ± 14%). This was significantly higher for RM (83 ± 12%, P = 0.01). In turn, TPI map sample heterogeneity was significantly higher compared with RM (92 ± 20%, P = 0.01), while ME maps showed the greatest sample heterogeneity (125 ± 17%, P < 0.001 compared with RM).

3.7 | Comparison of low voltage points between mapping techniques

The proportion of points within each of the three low voltage categories for the four map types is shown in Figure 4. The RM showed the

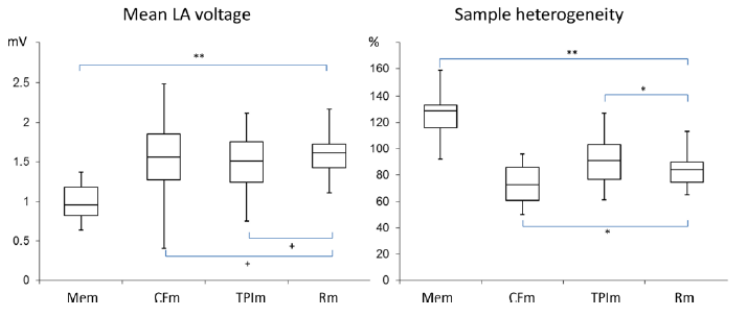

FIGURE 2 Mean bipolar and heterogeneity of LA voltages according to different left atrial mapping strategies. **P < 0.001, *P < 0.05, +P = NS. CFm = contact force-sensing mapping; MEm = multielectrode mapping; Rm = reference mapping; TPIm = tissue proximity indicator mapping [Color figure can be viewed at wileyonlinelibrary.com]

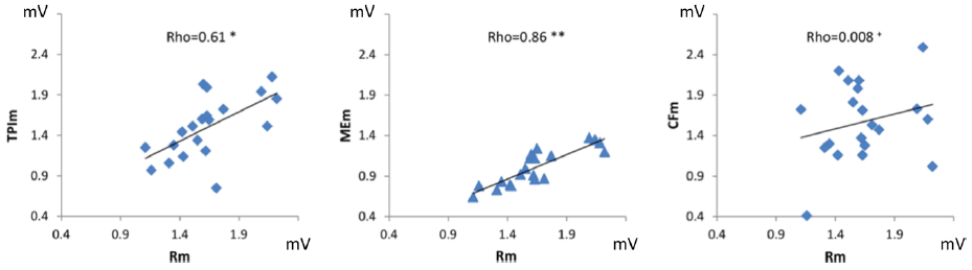

FIGURE 3 Bipolar voltage mean value correlation according to mapping techniques. R = Spearman correlation coefficient. **P < 0.001, *P < 0.05, +P = NS. CFm = contact force-sensing mapping; MEm = multielectrode mapping; Rm = reference mapping; TPIm = tissue proximity indicator mapping [Color figure can be viewed at wileyonlinelibrary.com]

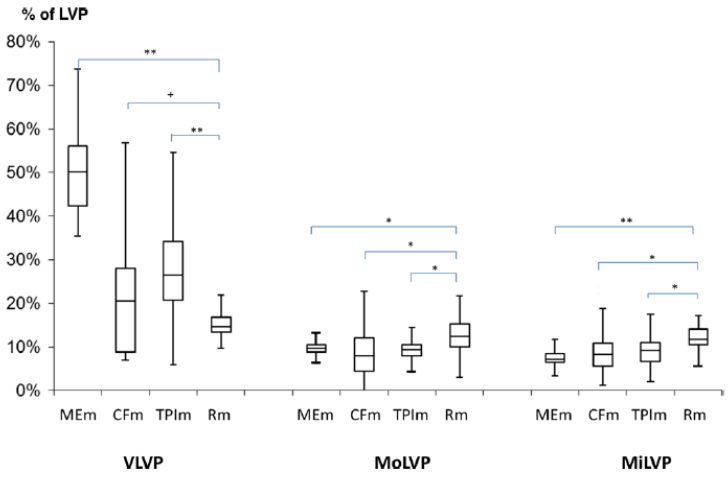

FIGURE 4 Proportion of low voltage points between mapping techniques. **P < 0.001, *P < 0.05, +P = NS. CFm = contact force-sensing mapping; MEm = multielectrode mapping; Rm = reference mapping; TPIm = tissue proximity indicator mapping MiLVP = mild low voltage points (between 0.75 mV and 1 mV);MoLVP = moderate low voltage points (between 0.5 mV and 0.75 mV);VLVP = very low voltage points (< 0.5 mV) [Color figure can be viewed at wileyonlinelibrary.com]

following proportions of low voltage points: VLVP 17 ± 8%, MoLVP 13 ± 4%, and MiLVP 12 ± 3%.

Proportions of low voltage points were significantly different according to the different mapping techniques, driven mainly by an overestimated proportion of VLVP. ME maps and TPI maps showed VLVP proportions of 50 ± 9% and 28 ± 13%, respectively (both P < 0.001 as compared to RM maps). However, there was a statistically significant correlation between the VLVP proportion in both ME maps and TPI maps compared with RM in individual patients (R = 0.58, P = 0.007 and R = 0.51, P = 0.02, respectively), indicating systematic over-representation of these points. As suggested by Figure 4, it is likely that the inclusion of far-field points recorded as VLVP in the TPI and particularly the ME maps is responsible for this overestimation of low voltage area. On the other hand, there was no significant difference in the proportion of VLVP between CF maps (22 ± 14%) and RM (P = 0.17). Once again, a correlation was seen in individual patients (R = 0.46, P = 0.04). In a comparison of proportions of MoLVP and MiLVP, these proportions were lower for all three mapping techniques when compared to the RM. These differences were less marked but remained significant.

4 | DISCUSSION

4.1 | Main findings

In this study, we have demonstrated that using the TPI filter while creating ME maps with the ConfiDENSE™ module increases the quality of sampling by decreasing point heterogeneity and by representing LA voltage values more accurately compared to standard ME mapping. While both TPI and ME mapping overestimate the proportion of low

voltage points compared to RM, the difference is markedly less after applying the TPI filter. ConfiDENSE™ mapping with a CF catheter further improves point heterogeneity and more accurately identifies the proportion of low voltage points but is limited by point density and a lack of correlation with RM mean voltage. ME mapping with the TPI filter may therefore provide the best balance between point heterogeneity and point density, resulting in accurate estimation of low voltage points.

4.2 | Relevance of proximity mapping

During repeat ablation procedures for AF, a recent study[5] aimed to compare LA voltage and accuracy of scar identification (defined as voltage amplitude lower than 0.2 mV) of two mapping techniques using CF and a Lasso catheter. Using a similar mapping protocol, they assessed the catheter contact with the LA surface using intracardiac echocardiography, orthogonal fluoroscopy, and electrogram characteristics, while we used the TPI filter. The authors showed a lower LA scar percentage for ME maps, though this may have been influenced by the markedly higher point density for these maps. The study also confirmed that improved mapping quality depends on proximity with the LA surface. Our findings suggest that by decreasing the proportion of far-field points, use of the TPI filter could be a simple, noninvasive, non-time-consuming, and less expensive option to assess proximity with the LA surface.

4.3 | Relevance of low-voltage areas

Fibrosis is considered as a substrate for AF maintenance, particularly in persistent AF, and a strategy of substrate-guided ablation has been used in many recent studies.[3,4] Because cardiac MRI assessment of LA scar is not yet reproducible across centers, LA voltage mapping has become increasingly important and identified low voltage areas are frequently considered as ablation targets. However, point-by-point mapping is time consuming, and automated ME mapping such as with the ConfiDENSE™ module is therefore attractive. CARTO is the most widely used electroanatomical mapping system, but the accuracy of voltage data assessed by ConfiDENSE™ mapping had not previously been assessed.

Our RM was based on offline signal analyses, and different parameters are known to influence recording signals. Zipes et al. reported that when using a bipolar catheter in contact with tissue, the risk of a far-field potential is very low.[16] Therefore, collection of near-field potentials requires contact with tissue, whereas far-field potentials are recorded when there is insufficient contact with tissue or no local signal (dense scar). More recent studies have described morphological signal criteria to identify near-field potentials. Although the amplitude of the signal is not sufficient criteria for classification as a near-field potential,[2,14] the amplitude of far-field potentials was usually smaller than that of near-field potentials. A lower slope (characterized by a lower dv/dt) is also usually associated with far-field potentials, whereas signal fractionation and shorter signal duration are usually associated with near-field potentials.

The influence of mapping techniques on voltage amplitude has also been described. One study described significant systematic voltage amplitude variation using different catheters and differently spaced electrode bipoles,[19] hence the reason only points collected with the ME catheter were included in our RM. A recent study has shown that atrial voltages may also vary with different pacing rates.[20] This potential confounding factor was averted in our study as all our maps were collected during constant pacing at a fixed rate of 600 milliseconds. Differences in local conduction time may have uncovered areas of fixed and dynamic substrate. However, because the objective of this study was to investigate the role of different mapping approaches to quantify voltages, we didn't evaluate conduction times.

Although identification of low voltage areas has taken on greater importance, the specific cut-off value to identify low voltage points is still debated. Indeed, there is no agreement among studies on the definition of low voltage points, with a wide range between 0.05 mV and 1.0 mV being described in previous studies.[5,17,18] Moreover, assessment of those low voltage points may be influenced by the underlying rhythm (AF, sinus rhythm, or atrial pacing).[20] We chose to use 0.5 mV as the cut-off value for VLVP because this threshold has been most commonly been used in other studies.[3,6]

4.4 | Clinical implications

Standard ME mapping can result in an overestimation of low voltage areas, which has the potential to lead to errors in mapping interpretation. This could lead to unnecessary ablation where substrate-based ablation is employed, masked PV reconnection, or even missed slow conduction areas in the case of an organized atrial arrhythmia.

Offline generation of a RM to accurately determine low voltage areas is obviously not practical to guide decision making in real time. CF mapping with point acquisition when a CF of $\geq$2 g is achieved appears to result in accurate assessment of low voltage points but suffers from low point density. However, ME mapping with application of the TPI filter reduces overestimation of low voltage points without being impractically time-consuming, or requiring additional resources such as intracardiac echocardiography. This therefore could be considered the optimal approach for LA mapping using ConfiDENSE mapping.

4.5 | Limitations

We included 20 patients in our study, which is a small sample size. However, these maps yielded over 20,000 individual voltage points, each of which was subjected to manual analysis. In this study, the TPI filter was only applied offline after mapping and this resulted in a relatively low point density for TPI and RM. Conversely, the TPI filter could have been applied during mapping and removed offline to create the ME maps. While we would expect that this would have increased the point density of the TPI, ME, and RM, we would not expect this to have any significant effect on the proportions of low voltage points. Additionally, circular mapping catheters (Lasso ECO Nav) were used in this study as this is the standard practice for AF ablation due to their utility in confirming PV isolation.[22] Use of a differently designed high-density

mapping catheter such as the PentaRay catheter (Biosense Webster, Inc.) may have yielded different results.

The sample population comprised patients with persistent AF, some of whom were in sinus rhythm at the outset of the procedure due to successful prior electrical cardioversion, and some of whom required cardioversion after achieving LA access. While this potentially results in a heterogeneous population, comparisons were made between mapping techniques within individuals rather than between patients. As electrical remodeling with consequent increases in voltage amplitude starts immediately after cardioversion, this may have affected sequential maps in patients cardioverted at the start of the procedure, but this is likely to have been only to a very minor degree as the CF map was created immediately after the ME map.

We did not specifically categorize extremely low bipolar voltages (<0.05 mV) in our analyses, and where these were adjudicated to be near-field points, they were recorded as very low voltage points. Equally, it is possible that the proportion of very low voltage points may have been underestimated in the RM because some such dense scar points may have been annotated as far-field points due to the difficulty in differentiating between these. However, given the very low CHADSVASC score of our population and the fact that no patient had undergone prior ablation, it is unlikely that the proportion of extremely low bipolar voltages in our cohort would be significant. We used a fill threshold setting of 15 mm while collecting the maps, and it is probable that using lower settings may have unmasked very localized areas of scar. However, the 15 mm threshold is the nominal setting on the CARTO system, and is the one used most frequently in clinical practice and in similar research studies.[5] Furthermore, the clinical relevance of, and the benefit of ablation of tiny circumscribed scar areas that may only be identifiable with tight fill thresholds is debatable. Finally, the orientation of the catheter electrode against the atrial wall (parallel or perpendicular) was not prespecified for the CF maps and was unknown in the other maps.[25]

5 | CONCLUSION

The LA voltages derived from ConfiDENSE maps created with a ME non-CF catheter are significantly lower than those assessed by manual inspection. The resulting misrepresentation of low voltage areas can result in erroneous overestimation of the target ablation area. Application of the TPI filter to ConfiDENSE maps significantly increases quality of the voltage data, conserving a reasonable point density. However, it still overestimates low voltage points as compared to CF-sensing maps or maps reviewed manually.

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33

ACCURACY OF LEFT ATRIAL BIPOLAR VOLTAGES OBTAINED BY CONFIDENSE MULTIELECTRODE MAPPING IN PATIENTS WITH PERSISTENT ATRIAL FIBRILLATION

B Maille (Presenting Author)[1], M Das[2], A Hussein[1], M Shaw[1], V Chaturvedi[1], M Morgan[1], C Ronayne[1], and R Snowdon[1]

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Background: Endocardial bipolar voltage mapping of the left atrium (LA) has been suggested as a way to assess substrate for atrial fibrillation (AF), with low voltage areas being considered surrogates for atrial fibrosis and targets for catheter ablation (CA). The ConfiDENSE module in Carto V4 allows rapid annotation of endocardial points acquired by multi-electrode (ME) mapping, but the accuracy of voltage data obtained by ConfiDENSE mapping has not been studied.
Methods: 20 patients undergoing CA for continuous persistent AF (PeAF) (60±5 years old, duration of PeAF 9±5months, mean LA size 42±3mm) were included in the study. All patients underwent electrical cardioversion after LA access, and maps of the LA were first created with the Lasso catheter using ConfiDENSE (ME) and then with a contact force-sensing catheter (CF) during constant atrial pacing at 600 msec cycle length. Bipolar voltages were assessed for the ME maps before and after application of the Tissue Proximity Indicator (TPI) filter, which is an impedance based automated algorithm designed to exclude map points deemed not in contact with the shell. Each individual electrogram in all 20 maps was then manually assessed by a single observer. Points that failed to meet established criteria for fidelity (far-field points and pulmonary vein points) as well as those not obtained during pacing were excluded to yield the reference map (RM). >2g was considered the threshold value for tissue contact in CF maps. Bipolar voltages and the proportion of low voltage points (LVP) (<0.5mV), derived from the baseline ME, TPI and CF maps, were compared with those derived from the RM.
Results: An average of 989±353 points (range 422-1954 points) were collected per ME map. For the RM, an average of 527±158 points met the criteria for fidelity. Mean LA voltage was 1.67±0.25 mV, sample heterogeneity 80±9% and the proportion of LVP was 15±5%. As compared to the RM, baseline ME maps had a much lower mean LA voltage (1.01±0.19 mV, $P<0.001$), significantly higher proportion of LVP (46±8%, $P<0.001$) and higher sample heterogeneity (117±13%, $P<0.001$). Application of the TPI filter in the TPI map reduced the number of collected points (252±184 points), but significantly improved sample heterogeneity (92±19%, $P=0.002$), and increased mean LA voltage closer to the RM value (1.50±0.38 mV, $P=0.04$). However, the proportion of LVP was still higher as compared to RM (28±13 %, $P<0.001$). The mean LA voltage in the CF map (114±52 points) was similar to the RM (1.62±0.38 mV, $P=0.4$), as was the proportion of LVP (19±10%, $P=0.05$).
Conclusion: The LA voltages derived from ConfiDENSE maps created with a multi-electrode non-contact force catheter are significantly lower than those assessed by manual inspection. The resulting misrepresentation of low voltage areas can result in erroneous overestimation of the target ablation area. Application of the TPI filter to ConfiDENSE maps significantly increases quality of the voltage data, but still overestimates LVP as compared to maps created with a CF-sensing catheter.

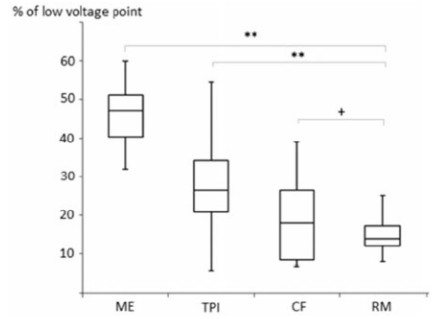

Figure 1. Box and whiskers plots of percentage of map points with low voltage (<0.5mV) between different left atrial maps ** $P<0.001$ + $P=0.05$ **ME, TPI, CF, RM:** Abbreviations in text

34

THE IMPACT OF THE PRESENCE OF LEFT ATRIAL LOW VOLTAGE AREAS ON OUTCOMES FROM PULMONARY VEIN ISOLATION

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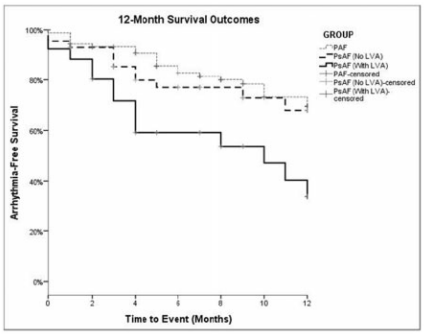
King's College Hospital NHS Foundation Trust, London, UK

Introduction: AF ablation (AFA) with pulmonary vein isolation (PVI) is a highly successful treatment for patients with paroxysmal atrial fibrillation (PAF). However, success rates for AFA with PVI alone in persistent AF (PsAF) are significantly lower and the optimal ablation strategy for PsAF remains unclear.
The presence of left atrial low voltage areas (LVA), assessed invasively by electro-anatomic mapping, appear to predict success from AFA in small series. In this single-centre study we evaluate whether the presence of LVA predict success from AFA, and whether the absence of LVA can identify a group of patients with PsAF that benefit from a PVI-based ablation strategy.
Methods: We included consecutive patients undergoing first-time AFA using point-by-point radiofrequency (RF) ablation. PVI was performed in all patients followed by electrical cardioversion (DCC) if AF persisted. After PVI voltage mapping using a multipolar catheter was performed in sinus rhythm (SR). A voltage cut-off of 0.5mV was used to define LVA. Patients were categorised as having LVA based on the presence of LVA in more than 10% of the LA, assessed visually by the operator.
Empiric adjunctive LA ablation was not performed. However further tailored adjunctive LA ablation was performed in 3 situations: (1) to treat spontaneous intra-procedural arrhythmias (atrial flutter/tachycardia), (2) DCC failed to restore SR after PVI, (3) to isolate/homogenise LVA. The exact adjunctive LA ablation strategy was at the operators' discretion.
Following ablation patients were routinely followed for 12 months with periodic Holter monitoring. The study end-point was the recurrence of any sustained atrial arrhythmia (AF/AT/flutter). No blanking period was employed.
Results: During the 2-year study period 190 patients had a first-time RF AFA, of which 160 had LA scar maps performed (84%) and were included in the analysis (mean age 60±10 years; n = 108, 68% male; n = 91, 57% PAF).
LVA were present in 31% (n = 49) of patients and were more common in PsAF (n = 26/69, 38%) than PAF (n = 23/91, 25%) (p < 0.001). Adjunctive LA ablation was performed in 14% (n = 22) of patients – 5/111 (5%) patients without LVA and 17/49 (35%) with LVA. This comprised linear lesions (n = 14), LVA homogenisation/isolation (n = 11) and CFAE ablation (n = 2).
12-month arrhythmia-free survival was higher for PAF than PsAF (70% vs. 56%; p = 0.04). In multivariable cox-regression analysis including 13 clinical, laboratory, echo and scar variables the presence of LVA (p = 0.03), LA size (p = 0.02) and hypertension (p = 0.01) were independent predictors of arrhythmia recurrence, whereas the type of AF (PsAF vs. PAF) was not (p = 0.07).
Patients with LVA compared to those without had significantly lower 12-month arrhythmia-free survival in both PAF (55% vs. 75%; p = 0.04) and PsAF (34% vs 68%; p = 0.02). PsAF patients without LVA (68%) had similar arrhythmia-free survival to patients with PAF (70%).
Furthermore, compared to patients without LVA, recurrence in patients with LVA was more likely to be due to an organised atrial arrhythmia (atrial flutter/tachycardia) rather than AF - 15/33 recurrences due to AT/Flutter in LVA patients versus 2/33 recurrences due to AT/flutter in patients without LVA (p < 0.001).
Conclusions: The presence of LVA predicts success as well as the type of arrhythmia recurrence following AFA. The absence of LVA identifies a group of PsAF patients that respond well to a PVI-based ablation strategy, with similar arrhythmia-free survival to patients with PAF.



conjunction with a 3D mapping system. Data was obtained using a 64-electrode FIRM-map catheter in all patients. Initially, FIRM analysis for guidance of ablation therapy was performed in all patients. The same datasets (epochs) used for FIRM mapping before and after rotor ablation or PVI, subsequently underwent EGF analysis.
Results: AF drivers identified with EGF, were correlated with rotors identified on the FIRM map. EGF allowed for differentiation between active and passive rotors, as well as non-rotational AF drivers. Some of the rotors identified by FIRM mapping might be only passive according to EGF. Furthermore, EGF allowed monitoring of stability of AF drivers over several minutes.
Conclusion: Valuable additional information is obtained with EGF during endocardial AF driver analysis. Discrimination between active and passive rotors and non-rotational drivers by EGF might help to optimize guidance of AF ablation therapy in the future. Long-term stability of rotors may help to identify critical AF targets.

P330

Reverse remodelling of the left atrium occurs early after catheter ablation for persistent atrial fibrillation

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Funding Acknowledgements: B. Maille received a grant from the "Rhythmology group of the French Society of Cardiology" for a fellowship at Liverpool Heart and Chest Hospital

Background: Adverse Left atrium (LA) remodelling is known to be associated with persistent atrial fibrillation (PeAF), and to impact success rates following catheter ablation (CA). The time course and pattern of reversal of LA remodelling following CA is poorly understood.
Objective: We evaluated LA volumes, linear dimensions, conduction velocity and bipolar voltages during invasive studies at baseline and at two months after catheter ablation for PeAF.
Methods: Twenty patients with PeAF underwent detailed mapping using a 3D navigation system for LA chamber volume and dimensions. After cardioversion and at constant pacing from coronary sinus, LA bipolar voltage maps were created using a contact force sensing mapping catheter and LA conduction times were assessed. Patients then underwent Pulmonary vein isolation (PVI) using minimum Ablation Index targets guided point-by-point RF ablation. No additional ablation in the LA was performed in any patient. All patients returned for protocol mandated repeat electrophysiology study at 2 months, regardless of arrhythmia recurrence, during which all measurements were repeated using an identical protocol to that of the baseline study.
Results: 2(10%) patients had evidence of late reconnection of a single vein each at repeat EPS performed 62+/-4 days after the index procedure. There was a significant LA volume reduction at follow-up when compared with baseline (55±15 ml/m2 vs 65±15 ml/m2, P< 0.0001). This difference appeared to be driven largely though a significant decrease in the transverse dimension (roof 32±6 mm vs 36±7mm, P< 0.0001 and inferior 47±9mm vs 51±8mm, P= 0.005), while the antero-posterior diameter (41±8mm vs 43±5 mm, P= 0.20) and LA height (63±7mm vs 63±6mm, P= 0.32) were not significantly different. All patients but one experienced an absolute decrease in LA volumes. LA conduction velocities were significantly greater at 2 months (0.90±0.13m/s vs 0.78±0.13m/s, P= 0.01). The overall mean LA voltage and voltage heterogeneity were not different between the two procedures (respectively 1.89±0.47mV vs. 1.73±0.51mV, P= 0.12 and 61.2±18.6 % vs. 59.4±15.2%, P= 0.79).
Conclusion: Significant structural and electrical reverse remodelling of the LA can be seen as early as two months following successful ablation for PeAF. However, bipolar voltages do not change over this time period, and whether this reflects a slower process, or merely the limitations of using intracardiac bipolar voltage mapping to ascertain substrate, is unclear.

P331

Low Voltage Area and Fractionated Potentials after Cryo-Balloon Ablation as Index Procedure; Analysis of Re-Do Procedures

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Kerckhoff Heart and Thorax Center, Bad Nauheim, Germany

Background: Although pulmonary vein isolation (PVI) with cryo-balloon (CBA) the 2nd and 3rd generation has been shown to be highly effective approximately 20% of the patients have recurrence of AF. Low voltage area (LVA), fractionated atrial potentials (FAP) within sinus rhythmus or complex fractionated atrial electrograms (CFAEs) by AF, were supposed to be responsible for recurrence of AF.
Objective: Aim of this study was to investigate the possible reasons of recurrence and incidence of possible non-PV AF triggers.
Methods: Since May 2012 a total of 832 pts were ablated in our institution using CBA, a total of 152 (18 %) of them experienced recurrence of AF. In 67 pts with recurrence repeat ablation was performed.using a double trans-septal approach with a SL1 and Agilis sheath. The Carto 3 or NavX System was used for electro-anatomical mapping. Mapping of the PV signals was performed with a Lasso catheter. Once localized, RF applications were applied on the conduction gaps until PV re-isolation was achieved. LVA, FAP or CFAEs were mapped and ablated.
Results: The median age of included pts was 65 years, history of AF 53 months, CHA2DS2-VASc-Score 2.16±1.39. LA area was 22.4 cm2. During repeat ablation using Carto 3D or NavX System we found in 31 pts reconnected PVs only. In 20 pts all PVs remained isolated. Out of pts with isolated PVs in 7 LVA, in 9 CFAEs, in 2 FAP and in 2 perimitral flutter were identified. In 16 pts reconnected PVs were found to be accompanied by 5 LVA, 5 CFAEs, and 6 FAP. Age and left atrial area were revealed to be predictive for presence of LVA or CFAEs. Within median follow up of 6 months after the re-do procedure, recurrences were observed in 25 pts. The recurrence rate in pts with identified LVA or CFAES (11/25 (44%)) was higher as in remained pts (14/42 (33%)), however the difference was not significant (p=.077).
Conclusions: In our study presence of possible non-PV AF triggers was found in 54% of the pts. The probability of these potential non-PV AF triggers increases with the age and left atrial size. These results suggest that re-do procedure after AF-recurrence following PVI with CBA should be performed with RF technique and electro-anatomical mapping systems, especially in elderly pts with increased left atrium. These results should be proven in larger cohort of pts.

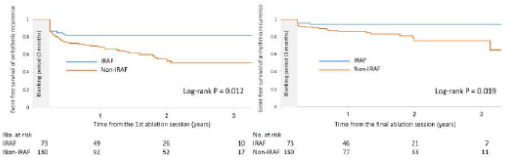
P332

Very low dose fluoroscopic imaging for electrophysiology procedures

F. Bourier; T. Reents; V. Semmler; S. Brooks; M. Kommayer; M. Kottmaier; M. Telishevska; M. Deiss; G. Hessling; I. Deisenhofer
Deutsches Herzzentrum Technische Universitat, Department of Electrophysiology, Munich, Germany

Background: This study presents and evaluates the impact of a new lowest-dose fluoroscopy protocol (Siemens AG), specially designed for electrophysiology (EP) procedures, on X-ray dose exposure.
Methods: From 10/2014 to 03/2015, n=200 patients underwent an EP procedure on an Artis zee angiography system. The conventional low dose imaging protocol ("out-of-the-box") was operated at 23 nGy (fluoroscopy, 3 fps) and at 120 nGy (cine-loop, 7.5 fps), the new lowest dose protocol was operated at 8 nGy (fluoroscopy, 3 fps) and at 36 nGy (cine-loop, 7.5 fps). In n=160 complex left atrial (atrial fibrillation, atypical flutter) and in n=40 standard EP procedures (AVNRT, PVC, typical flutter), X-ray data and procedural data were documented. For left atrial procedures, procedural times for each step (puncture, mapping, ablation) as well as cine-loop times, angulations and doses were documented separately. Procedure- and radiofrequency (RF)- times and complications were documented as further study parameters.
Results: The resulting dose-area-products are summarized in Figure 1. In the low dose and lowest dose group, procedure times were 129±33min vs. 124±33min (p=0.34, complex procedures) and 72±21min vs. 85±44min (p=0.24, standard procedures), RF-times were 52±26min vs. 49±26min (p=0.47, complex procedures) and 10±10min vs. 12±15min (p=0.60, standard procedures), X-ray times were 10±8min vs. 9±6min (p=0.37, complex procedures) and 7±5min vs. 8±6min (p=0.40, standard procedures). Two minor vascular complications occurred in each group (p=1.0). There was no difference in baseline characteristics, BMI or body surface area between groups.
Conclusions: X-ray dose exposure was reduced by 80% when fluoroscopy was operated at new lowest dose imaging settings. The reported X-ray dose values are very low when compared to previously published data. From an operator standpoint, lowest X-ray dose levels create a different, reduced image quality. However, although unfamiliar, the new image quality did not significantly affect procedure times, clinical outcome or RF-times and did not result in higher complication rates. Regarding radiological protection, operating at lowest dose settings should become standard in EP procedures.

Figure



The arrhythmia recurrence rates were significantly lower in the patients with IRAF(blue line) than in those without (orange line) both after the first session (P=0.012) and the final session (P=0.019) .

B-PO05-080

EFFICACY OF ADDITIONAL ABLATION OF THE LEFT ATRIAL POSTERIOR WALL ISOLATION AND SUPERIOR VENA CAVA ISOLATION IN PATIENTS WITH RECURRENCE OF ATRIAL FIBRILLATION AFTER CRYOBALLOON ABLATION

Hideko Toyama, MD, PhD and Koichiro Kumagai. Fukuoka Sanno Hospital, Fukuoka, Japan

Background: Pulmonary vein (PV) isolation with the second-generation cryoballoon is widely performed in the patients with paroxysmal atrial fibrillation (AF). However, the next ablation strategy is controversial during the second procedure in patients with AF recurrence.
Objective: To evaluate the outcomes after cryoablation and the efficacy of additional ablation of the left atrial (LA) posterior wall isolation and superior vena cava (SVC) isolation in patients with AF recurrence.
Methods: A total of 333 patients with paroxysmal AF underwent PV isolation using cryoballoon (Arctic Front Advance™ cryoballoon, Medtronic, Inc.). LA voltage maps were created during sinus rhythm. Low-voltage areas (defined as under 0.5 mV) were found in 20 (6%) patients. In patients with AF recurrence after the first procedure, a second procedure was recommended. During the second procedure, if PV reconnections were found, re-PV isolation was performed using an irrigated radiofrequency ablation catheter. Subsequently, roof and floor linear ablation isolating the LA posterior wall was additionally performed. SVC isolation was always performed in all patients. If other non-PV foci were identified, ablation of the triggers was performed.
Results: During 26±3 months of follow-up, 56 (17%) patients had AF recurrence. Low-voltage areas were observed in 7 (13%) of 56 patients with AF recurrence and 15 (5%) of 277 patients without AF recurrence (P=NS). Among patients with AF recurrence, 33 patients underwent a second procedure. PV reconnections were observed in 38/132 (29%) PVs (left superior: 11, left inferior: 10, right superior: 5, right inferior PV: 12). New non-PV foci were occurred from SVC in two and the posterior LA in one, however, these triggers were eliminated after the posterior LA isolation and SVC isolation. The LA posterior wall and SVC were successfully isolated in all patients. Other non-PV focus from LA appendage was identified and ablated in one patient. After a second procedure, 29 of 33 patients had no recurrence of AF, and AF-free rate increased to 92%.
Conclusion: Low-voltage areas may not be related to AF recurrence. In patients with AF recurrence after cryoablation, additional ablation of the LA posterior wall isolation and SVC isolation may be effective.

B-PO05-081

INCIDENCE AND PREDICTORS OF LATE PULMONARY VEIN RECONNECTION AFTER ABLATION INDEX-GUIDED ABLATION IN PATIENTS WITH PERSISTENT ATRIAL FIBRILLATION

Ahmed A. Hussein, Moloy Das, MBBS, Graeme J. Kirkwood, Baptiste Maille, Stefania I. Riva, Maureen Morgan, Christina Ronyane, Akanksha Gupta, Matthew Shaw, Andrea Natale, MD, FHRS, Antonio Dello Russo, MD, Richard L. Snowdon, MBCHB and Dhiraj Gupta, MBBS, MD. Research Dept., Liverpool Heart and Chest Hospital, Liverpool, United Kingdom, Freeman Hospital, Newcastle upon Tyne, United Kingdom, Texas Cardiac Arrhythmia Institute at St. David's Medical Center, Austin, TX, Centro Cardiologico Monzino, Milan, Italy, Cardiothoracic Centre, Liverpool, United Kingdom, Liverpool Heart and Chest Hospital, Liverpool, United Kingdom

Background: Recent studies showed that use of regional Ablation Index (AI) targets results in improved clinical outcome following AF ablation. We hypothesized that this is due to a high rate of durable PVI.
Objective: To study predictors of late reconnection (LRC) after AI-guided ablation.

Methods: 40 patients (30 male, 61±8 yrs, LAd 43±5mm) underwent uncomplicated PVI with AI-guided contiguous point-by-point wide antral circumferential ablation (WACA) for drug-refractory persistent AF at 3 centers. A SmartTouch catheter was used with RF power 30-40W, irrigation 17-30ml/min, and AI targets 550 for anterior and 400 for posterior segments. All patients underwent mandatory repeat LA study after 2 months to identify LRC. All VisiTags (n=5993) were analysed offline for predictors of reconnection in a 12-segment model.
Results: 4/80 WACA circles were excluded for protocol violation. LRC was seen in 11 (7%) PVs affecting 13/456 (3%) segments in 8 (22%) patients. There was no difference in minimum Contact Force, FTI, AI or Impedance Drop values between segments with or without LRC (Table). Segments with LRC had a significantly lower mean catheter tip temperature. Mean transverse diameter was significantly greater in WACA circles with LRC compared to those without LRC (27.1±8.6 vs. 20.4±5.3mm, P=0.025) but there was no difference in the number of inter-lesion gaps of >6 mm (both 1 (0-3), P=0.83).
Conclusion: AI-guided ablation is associated with a high incidence of durable PVI in patients with persistent AF. Larger WACA circle size is associated with a higher incidence of late PV reconnection. The significantly lower tip temperature seen in LRC segments suggests excessive irrigation with current settings.

B-PO05-082

FRAILTY AND MORTALITY IN ATRIAL FIBRILLATION

Peter Hanlon, MBChB, Bhautesh Jani, PhD, Derek Thomas Connelly, MD, Barbara Nicholl, PhD, Ross McQueenie, PhD, Duncan Lee, PhD and Frances Mair, MD. University of Glasgow, Glasgow, United Kingdom, Golden Jubilee National Hospital, Glasgow, United Kingdom

Background: Multimorbidity (≥2 long-term conditions (LTCs)) is associated with increased mortality in people with atrial fibrillation (AF). Frailty is associated with multimorbidity and AF may be a marker of frailty in elderly patients. The prevalence and impact of frailty in middle-older aged individuals with AF is unknown.
Objective: (1) To assess the prevalence of frailty/pre-frailty in middle-older aged participants with AF. (2)To assess the impact

Appendix B Letter Regarding the Retrospective Analysis study

Liverpool Heart and Chest Hospital NHS
NHS Foundation Trust

Department of Research & Innovation

Date: 01/03/2019

☎ 0151 600 1467

Dear Ahmed,

I am writing this letter in regard to the 'The Retrospective Analysis Study' that took place whilst conducting the PRAISE (Pulmonary vein Reconnection following Ablation Index-guided ablation: a Success Evaluation Study) at Liverpool Heart & Chest Hospital NHS Foundation Trust.

This was a retrospective analysis of 89 patients who underwent Ablation Index-guided ablation Procedures performed between November 2014 and December 2015, and compared their data to patients who underwent Contact Force -guided ablation between January 2013 and October 2014.

No formal Ethics Review Board approval was required for this study because the study was a retrospective analysis of anonymised data from patients that had attended their routine clinical EP procedures.

Please let us know if you need any more assistance in this matter.

Yours sincerely,

B. Matata

Dr. Bashir Matata

(Head of Research & Innovation)

Appendix C Ablation Index (VISITAG SURPOINT ™) FDA Approval

June 1, 2018

Biosense Webster, Inc.
Phuong Chau
Senior Regulatory Affairs Program Lead
33 Technology Drive
Irvine, CA 92618

Re: K180238
Trade/Device Name: CARTO 3 EP Navigation System Version 6.0 and Accessories
Regulation Number: 21 CFR 870.1425
Regulation Name: Programmable Diagnostic Computer
Regulatory Class: Class II
Product Code: DQK
Dated: May 24, 2018
Received: May 25, 2018

Dear Phuong Chau:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820);

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
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and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/) and CDRH Learn (http://www.fda.gov/Training/CDRHLearn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (http://www.fda.gov/DICE) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

for

Bram D. Zuckerman, M.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*
K180238

Device Name
CARTO 3 EP Navigation System Version 6.0 and Accessories

Indications for Use *(Describe)*
The intended use of the CARTO® 3 System is catheter-based cardiac electrophysiological (EP) procedures. The CARTO 3 System provides information about the electrical activity of the heart and about catheter location during the procedure. The system can be used on patients who are eligible for a conventional electrophysiological procedure. The system has no special contraindications.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

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510(k) Summary

Applicant:	Biosense Webster, Inc. 33 Technology Drive Irvine, CA 92618, USA Tel.: (800) 729-9010 Fax: (909) 839-8500
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Authored by:	Anna Gantman Quality and Regulatory Program Manager Biosense Webster (Israel), Ltd. And Phuong Chau Senior Regulatory Affairs Program Lead Biosense Webster, Inc.
Date:	April 10, 2018
Device Trade Name:	CARTO® 3 EP Navigation System Version 6.0 and Accessories
Device Common Name:	Cardiac Mapping System
Manufacturing Number:	FG-5400-00
Device Classification:	Programmable diagnostic computer Class II, 21 CFR 870.1425
Product Code	DQK
Predicate Device:	CARTO® 3 EP Navigation System Version 6.0 and Accessories 510(k)#: K170600
Manufacturing Facilities:	Biosense Webster (Israel), Ltd. a Johnson & Johnson Company 4 Hatnufa Street Yokneam, ISRAEL 2066717 Biosense Webster, Inc. 15715 Arrow Hwy Irwindale, CA 91706

Device Description:

The CARTO® 3 EP Navigation System, Version 6.0 is a catheter-based atrial and ventricular mapping system designed to acquire and analyze data points, and use this information to display 3D anatomical and electroanatomical maps of the human heart. The location information needed to create the cardiac maps and the local electrograms are acquired using a specialized mapping catheters and reference devices. The system allows electrograms and cardiac maps display based on the received intracardiac signals from the catheters. The CARTO® 3 System V6.0 uses two distinct types of location technology – magnetic sensor technology and Advanced Catheter Location (ACL) technology.

The CARTO® 3 System V6.0 consists of the following components:

- Patient Interface Unit (PIU)
- Graphic User Interface (GUI)
- Wide-Screen monitors, keyboard, and mouse
- Intracardiac In Port
- Intracardiac Out Port
- Power Supply
- Patches Connection Box and Cables
- Pedals
- Location Pad

All hardware components of the CARTO® 3 System V6.0with the VISITAG SURPOINT™ Module are identical to those described for the predicate device.

Indications for Use:

The intended use of the CARTO® 3 System is catheter-based cardiac electrophysiological (EP) procedures. The CARTO® 3 System provides information about the electrical activity of the heart and about catheter location during the procedure. The system can be used on patients who are eligible for a conventional electrophysiological procedure. The system has no special contraindications.

Technological Characteristics:

The modified CARTO® 3 EP Navigation System, Version 6.0 with VISITAG SURPOINT™ Module, has the same technological characteristics (i. e., design, material, chemical composition, energy source) as the predicate CARTO® 3 EP Navigation System, Version 6.0. A summary of the technological characteristics of the new device compared to the predicate device is as follows:

- Have identical intended use.
- Use the same fundamental scientific technology.

- Have the same hardware platform.
- Have identical magnetic location mapping technology.
- Have identical magnetic location sensor accuracy.

The main difference between the predicate device and the modified device is the enhancement of the VISITAG Module to add the VISITAG SURPOINT™ Module. The module is used to display Tag Index calculations performed by the VISITAG SURPOINT™ EPU device. Additionally, an HD Coloring feature was implemented to provide high definition coloring of electroanatomical maps. The HD coloring feature includes the following GUI enhancements: Cleaner map visualization, Enhanced wave propagation display, Enhanced visualization of projected points and Enhancements for the Early Meets Late mechanism.

Performance Data: The CARTO® 3 EP Navigation System, Version 6.0 with the VISITAG SURPOINT™ Module underwent extensive bench testing to verify the new and modified features and to demonstrate with regression testing that these modifications did not negatively affect existing features. All testing passed in accordance with appropriate test criteria and standards, and the modified device did not raise new questions of safety or effectiveness.

Conclusions: The CARTO® 3 EP Navigation System, Version 6.0 and Accessories with the VISITAG SURPOINT™ Module is substantially equivalent to the currently cleared CARTO® 3 EP Navigation System, Version 6.0 based on the completion of non-clinical bench testing and pre-clinical testing as well as similar principles of design, operation and indications for use.

Appendix D PRAISE Study Protocol

Pulmonary vein **R**econnection following **A**blation **I**ndex-guided ablation: a **S**uccess **E**valuation (**PRAISE**)

1 Lay Summary

1.1 Atrial fibrillation (AF) is the commonest condition affecting the rhythm of the heart. Tablets to try to normalise the heart rhythm rarely work well. As a result, doctors have devised a treatment called catheter ablation in which special wires are used to deliver heat energy (called ablation lesions) on the inside surface of the heart. Unfortunately, in many patients (almost 1 in 2), some of these ablation lesions recover, and this leads to AF recurrence. Many of these patients then need a second procedure to deliver further ablation at these recovered areas.

1.2 Recent research has shown that monitoring of heat delivery with a factor called Ablation Index may be useful in predicting which ablation lesions are less likely to recover. Therefore, we aim to carry out AF ablation guided with Ablation Index and observe whether this will be associated with better durability of ablation lesions, and thereby better freedom from AF.

1.3 This study will include patients with persistent AF, those whose AF episode(s) last for longer than seven days. All patients participating in the study will undergo an initial ablation treatment guided by ablation Index (AI). All patients will undergo a repeat procedure 8-10 weeks after their initial treatment. Any gaps found during the second procedure will be closed again by delivery of ablation.

1.4 All participants will be issued with a simple to use handheld heart rhythm monitor, and asked to make a 30-second recording of their heart rhythm each day and also whenever they have symptoms. The monitor stores these recordings and they will be downloaded at review appointments arranged 6 weeks, 3 months, 6 months and 12 months after the initial ablation procedure.

2 Background

2.1 Creation of durable ablation lesions during pulmonary vein isolation (PVI) for atrial fibrillation (AF) is of critical importance to prevent late PV reconnection, which is responsible for the great majority of arrhythmia recurrence in patients with paroxysmal AF.[1] Despite improvements in technology, the proportion of PVs remaining chronically isolated following radiofrequency ablation has remained disappointingly low.[2,3] This has led to much interest in the delivery of effective ablation lesions.

2.2 In the absence of real-time assessment of lesion development and transmurality, surrogate measures of lesion quality are commonly utilized. The fall in local impedance during ablation, which has been shown to relate to lesion size,[4,5] is commonly used as a marker of the direct effect of ablation on cardiac tissue.[6-9] More recently, the minimum Force-Time Integral (FTI), which multiplies contact force by radiofrequency application duration has been shown to be predictive of PVI segment reconnection at repeat electrophysiology study.[2] Prospective use of a minimum FTI-target during each ablation application improved rates of persistent PV isolation but nevertheless, over one-third of patients were still found to have at least 1 reconnected PV.[10] This may be because FTI does not take into account the important role of power delivery, and is derived from a simple multiplication of contact force by time, whereas it is likely that these factors along with power provide differing contributions to lesion formation.[11,12] Furthermore, using a single target FTI value for all segments of the circumferential PVI circle, as has previously been suggested,[2] assumes that tissue thickness, and therefore the ablation depth required, is the same for all areas of the left atrium. However, it is known from anatomical studies that tissue thickness varies considerably between different left atrial regions.[13]

2.3 Ablation Index (AI) (CARTO 3 V4, Biosense Webster, Inc., Diamond Bar, CA) is a novel marker of lesion quality that incorporates contact force, time and power in a weighted formula, and has been shown to accurately estimate lesion depth in canine studies.[14,15]

3 Hypothesis

3.1 Primary Hypothesis:

Pulmonary vein isolation (PVI) achieved with Point by point catheter Radiofrequency Wide Area Circumferential ablation (WACA), and guided by Ablation Index (AI) targets results in durable PVI, as confirmed at repeat electrophysiology (EP) study.

3.2 Secondary hypotheses:

3.2.1 Durable WACA PVI, without additional left atrial ablation, results in good clinical success rates in patients with Persistent Atrial Fibrillation (AF)

3.2.2 There is a significant difference between the rate and pattern of PV reconnection in patients with and those without documented early AF recurrence.

3.2.3 Sites of acute PV reconnection (including those unmasked by adenosine) and late PV reconnection correlate with Ablation Index data from the initial PVI procedure.

3.2.4 Patients with Persistent AF who have AF recurrence following their repeat PVI procedure are those who have areas of low voltages (scar) in the atria.

4 Design

4.1 Prospective cohort study in 40 patients with Persistent AF.

4.2 Active Group (AI guided ablation): An initial PVI procedure will be performed guided by AI targets of 550 for the roof and anterior wall, and 400 for the posterior and inferior walls. All patients (regardless of AF recurrence) will undergo a repeat EP study at 8-10 weeks to identify and re-ablate PV reconnection

4.3 Historical control group (Contact Force Guided Ablation): will be formed by the 40 patients enrolled to the repeat study arm of the PRESSURE study (ClinicalTrials.gov Identifier: NCT01942408). All 40 patients underwent contact force-guided PVI followed by a repeat EP study after 8-10 weeks.

5 End-points

5.1 Primary outcome measure:

The proportion of patients with PV reconnection seen at repeat EP study

5.2 Secondary outcome measures:

5.2.1 The proportion of reconnected PVs seen at repeat EP study

5.2.2 The proportion of patients maintaining freedom from atrial tachyarrhythmia for 12 months (after an initial 12 week blanking period)

5.2.3 QOL 6 and 12 months after initial ablation, as quantified by the validated AFEQT questionnaire.

5.2.4 Major complication rates (occurring within 60 days after a PVI procedure), to include cardiac tamponade, stroke/TIA, myocardial infarction, phrenic nerve paralysis, oesophageal perforation/atrio-oesophageal fistula, major vascular complications and death.

6 Patients

Patients will be recruited from the heart rhythm clinics at Liverpool Heart and Chest Hospital, Liverpool, UK, Freeman Hospital, Newcastle, UK and Centro Cardiologico Monzino, IRCCS, Milan, Italy. Patients listed for RF ablation of persistent AF and felt to be suitable for inclusion by their responsible Consultant will be approached and offered information regarding the study. Patients interested in taking part will be provided with the Participant Information Sheet (PIS) by a member of the research team and offered the opportunity to take this literature home to discuss it with relevant relatives and friends. The PIS contains a contact phone number and email address for the research team should they wish to get in contact with any queries. A follow-up phone call may be arranged to provide a further opportunity for discussion. If the patient wishes to enrol, they will be invited to return the signed consent form by post (in which case, consent will then be re-confirmed in person at the time of a subsequent hospital visit) or to sign the consent form at the time of their next hospital visit.

6.1 Inclusion criteria:

- Aged over 18 years
- Persistent AF (defined, according to the ESC/EHRA Guidelines for the Management of Atrial Fibrillation 2010, as AF episode that either lasts longer than 7 days or requires termination by cardioversion, either with drugs or by direct current cardioversion (DCC)).
- Symptomatic in spite of drug treatment
- Due to undergo pulmonary vein isolation by RF ablation

6.2 Exclusion criteria:

- Inability or unwillingness to receive oral anticoagulation with a Vitamin K antagonist (VKA) or non-VKA (NOAC) agent
- Previous catheter or surgical ablation procedure for AF
- Unwillingness or inability to complete the required follow-up arrangements

- Current pattern of paroxysmal AF
- Long standing persistent AF (continuous AF longer than 12 months before ablation)
- Prior prosthetic mitral valve replacement or severe structural cardiac abnormality [17]
- Known infiltrative cardiomyopathy
- Known severe left ventricular systolic function (ejection fraction <35%)
- Pregnancy

7 Outline Protocol

7.1 Pre-procedure management:

- Echocardiographic data will be collected as part of routine care, including: left ventricular (LV) ejection fraction, LV end-systolic and end-diastolic dimensions, and left atrial diameter.
- Patients may undergo MRI scan prior to the ablation procedure to produce a detailed 3D reconstruction of the left atrial anatomy at the operator's discretion.
- Patients on VKA agents will continue these in the peri-procedural period, and a pre-procedure INR of between 2 and 4 would be considered acceptable. All NOAC agents will be continued peri-procedurally or withheld on the morning of the procedure as per the operators' preference.
- Trans-oesophageal echocardiography (TOE) may be undertaken at the discretion of the operator prior to the procedure to exclude left atrial thrombus as per standard care (indications may include sub-therapeutic INR readings in the 4 weeks prior to the ablation procedure for those taking warfarin, or missed doses for those taking alternative oral anti-coagulants).

7.2 Initial ablation procedure:

7.2.1 PVI will be performed under general anaesthesia in a standard fashion. One or two transseptal punctures will be made using fluoroscopic guidance with additional pressure monitoring, following which intravenous unfractionated heparin boluses will be administered to maintain an Activated Clotting Time (ACT) of approximately 250-300s. The use of echocardiographic monitoring to guide transseptal punctures will be allowed.

7.2.2 If the patient is in AF, elecrical cardioversion will be performed to restore sinus rhythm. Voltage map of the left atrium will be created during atrial pacing using ConfiDense mapping (Carto 3, Biosense Webster, Inc.), and where appropriate, the left atrial map will be integrated with the MRI of the left atrium (CartoMerge, Biosense Webster, Diamond Bar, California, USA).

7.2.3 Patients will then undergo PVI using point-by-point RF application in a wide area circumferential ablation (WACA) pattern using a Thermocool® SmartTouch™ irrigated RF ablation catheter. Drag lesions will NOT be utilised. Standardised VisiTag™ settings will be used for all cases (Catheter Position Stability: Minimum time 8 sec, Maximum range 3 mm; Force over Time: Time 30%, Minimum force 3 g; Lesion tag size: 3 mm). These VisiTag settings are the mean of the values used for cases performed at the 4 sites that contributed to the retrospective evaluation of Ablation Index.[1] Attempts will be made to create contiguous VisiTag lesions along the WACA at least 2 cm outside the ostia of the PVs, except on the anterior wall of the left PVs where ablation will be delivered on the appendage ridge. Each RF lesion will be guided by AI targets: 550 at the roof and anterior walls, and 400 at the posterior and inferior walls. Power setting will be at the operator's discretion within the range of 20-40W. PVI (entry and exit block) will be confirmed with a circular mapping catheter (Lasso® NAV Eco, Biosense Webster, Diamond Bar, California, USA) placed sequentially in each of the PVs. Intervenous carina ablation will not be performed routinely unless required to achieve PV isolation. No additional left atrial linear lesions or ablation of complex fractionated atrial electrograms will be performed, unless the patient develops sustained regular atrial tachycardia or flutter amenable to mapping and ablation. Patients with documented atrial flutter in the past will receive linear ablation on the Cavotricuspid isthmus until bidirectional block is achieved.

7.2.4 If the patient is still in AF after achieving isolation of all PVs, electrical cardioversion will be performed. Left and right atrial voltage maps will then be created during atrial pacing using ConfiDense mapping (Carto 3, Biosense Webster, Inc. After a minimum of 20 minutes since the last ablation to that WACA lesion set, ipsilateral PVs will be rechecked with the circular catheter to determine if spontaneous PV reconnection has occurred. If overt PV reconnection has not occurred, a bolus of intravenous adenosine (12-18mg) will be given to unmask any sites of dormant conduction. Further ablation will be performed at any sites of overt or unmasked reconnection to achieve PVI once again. Intravenous protamine may, at the discretion of the operator, be given to reverse the effects of heparin at the end of the procedure.

7.2.5 Oesophageal temperature monitoring will be performed in all cases with an audible temperature alarm set at 38.9 degrees Celsius. RF delivery will be stopped promptly as soon as the oesophageal temperature crosses this value, or earlier at the operator's discretion. Oesophageal temperature will be allowed to drop below 37.5 degrees before further RF energy is delivered in the vicinity.

7.2.6 Acute complete procedural success will be defined as electrical isolation of all PVs. Partial procedural success will be defined as electrical isolation of 3 or more, but not all, PVs. Procedural failure will be defined as electrical isolation of less than 3 PVs.

7.3 Post-procedure management

7.3.1 All current antiarrhythmic drug therapy will be continued for at least 1 month. It can then be discontinued as per physician preference.

7.3.2 All patients will be prescribed a Proton Pump Inhibitor (e.g., Lansoprazole 30 mg OD) for at least 1 month.

7.4 Post-PVI monitoring for AF recurrence:

All patients will be provided with a validated handheld ECG monitoring device, to be kept for the duration of the study of 12 months. Patients will be asked to self-record a 30s ECG recording once a day for the duration of the study, as well as each time they experience symptoms of palpitations.

7.5 Repeat EP study:

7.5.1 The repeat procedure will be performed in the same way as outlined above for the initial procedure. Peri-procedural and intra-procedural anti-coagulation management will be identical. While performing transseptal puncture, use may be made of any residual foramen ovale defect related to the initial procedure as appropriate. As before, voltage map of the left atrium will be created during atrial pacing using ConfiDense mapping and integrated with the original MRI reconstruction of the left atrium (CartoMerge, Biosense Webster, Diamond Bar, California, USA) where available.

7.5.2 Each PV will be assessed in turn for late reconnection with a circular mapping catheter and reconnection site(s) will be recorded for subsequent analysis. All identified sites of reconnection will be re-ablated using a Thermocool® SmartTouch™ irrigated RF ablation catheter, with a target Ablation Index of 550 or 400 depending on location and RF power set at the operator's discretion until PV re-isolation has been successfully achieved. If the patient is in AF after achieving isolation of all PVs, electrical cardioversion will be performed. No additional left atrial linear lesions or ablation of complex fractionated atrial electrograms will be performed, unless the patient develops sustained regular atrial tachycardia or flutter amenable to mapping and ablation. Patients with documented atrial flutter will receive linear ablation on the Cavotricuspid isthmus until bidirectional block is achieved, and those patients who had cavo-tricuspid isthmus (CTI) ablation on the previous procedure will have bidirectional block confirmed.

7.5.3 Heparin-reversal and post-procedural anti-coagulation will be as per the initial procedure.

7.6 Follow-up:

- Continued daily (plus symptom episode) ECG recordings as described above for 12 months from the initial procedure.

- A clinical review appointment at 6 weeks, and then at 3, 6 and 12 months. Data from the handheld ECG monitors will be downloaded at these visits.
- Participants will be asked to complete AFEQT and EQ5D questionnaires at the time of the 6 and 12 month clinic visits.
- As far as possible, anticoagulation with warfarin or another oral anticoagulant agent will be continued for at least 3 months following the index ablation procedure. At that point the decision whether or not to continue will be made individually, based on the patient's CHA2DS2/CHA2DS2-VASc score and patient preference.
- Any episodes of atrial tachyarrhythmia ≥30s in duration documented after the 12 week blanking period will be defined as a recurrence. This will signify that that the patient has reached the primary end-point of the study and further management (including re-initiation of anti-arrhythmic medications, electrical cardioversion or listing for repeat PVI) will be at the discretion of the patient's responsible Consultant.

7.7 Study visit diagram

Procedure	Week							
	Recruit	Pre-adm	Procedure Day 0	6	8	12	26	52
Clinical review	✓			✓	✓	✓	✓	✓
ECG Review	✓			✓	✓	✓	✓	✓
Handheld monitor provision		✓						
QOL forms	✓						✓	✓
PVI procedure			✓		✓			

8 Safety

8.1 Major complications:

Definitions for major complications are derived from the HRS/EHRA/ECAS Expert Consensus Statement published in 2012.[1] A major complication is defined as: a complication that results in permanent injury or death, requires intervention for treatment, or prolongs or requires hospitalization for more than 48 hours. Definitions of individual complications are 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

8.2 Expected major complication rates

- A local audit of 150 first-time AF ablation procedures revealed the following complications and rates: significant (delaying discharge) groin haematoma (1.3%), stroke (0.7%), pericardial effusion requiring drainage (0.7%). The combined incidence of significant complications was 2.7%, in keeping with other high volume centres. [16]
- Local data for repeat procedures have demonstrated a lower combined complication rate of around 1%.

8.3 Serious adverse event reporting

- Any suspected major complication (as defined above) occurring in the course of the study, either whilst in hospital or during the period of follow up, will be reported as per the standard local adverse Event Reporting procedure.

8.4 Data monitoring committee

- A data monitoring committee will be convened to review interim safety data from the trial.

8.5 Insurance/indemnity

- Indemnity will be provided through the NHS indemnity scheme or professional indemnity.

9 Sample size calculation

9.1 Of the patients randomised to the Repeat Study arm of the PRESSURE study, 62.5% had reconnection of 1 or more PVs. We expect this rate to be at least halved when ablation is guided by AI targets. A formal sample size calculation was therefore performed assuming a proportion of patients with PV reconnection of 31% in the AI-guided group and 62.5% in the CF-guided group.

9.2 With these values, an alpha error set at 0.05 and power set at 80%, the number of patients required for a two-sided test would be 36 per group. Allowing for 10% of patients who may be lost to follow-up gives an intended sample size of 40 per group. This sample size has already been met for the CF-guided group.

10 Statistical analysis

10.1 All end points will be examined by means of an intention-to-treat analysis.

10.2 All categorical variables will be compared with χ^2 or Fisher's exact test as appropriate. The dependent variables will be checked for normal distribution by the Shapiro-Wilk statistic and appropriate descriptive statistics generated. Continuous variables that are normally distributed will be expressed as means (±SD) and will be compared using Student's t-test. Variables that are not normally distributed will be expressed as a median (interquartile range) and will be compared with Wilcoxon rank-sum and signed-rank tests.

10.3 The primary hypothesis (3.1, that Pulmonary vein isolation (PVI) achieved with Point by point catheter Radiofrequency Wide Area Circumferential ablation (WACA), and guided by Ablation Index (AI) targets results in durable PVI) will be examined using a one-sided Z-test as we are looking for a reduction in the proportion of patients with a reconnection. Secondary outcomes 3.2.1 and 3.2.4 will also be examined using a one-sided Z-test. Secondary outcome 3.2.2 will be examined using a two-sided test as we are unsure of the direction of effect; a t-test will be used to assess continuous measures and Chi-squared (or Fisher's exact) test will be used to assess categorical measures. Spearman's Rank Correlation Coefficient will be used to assess secondary outcome 3.2.3.

10.4 All data will be analysed using SPSS for Windows version 18 and alpha will be set at the 0.05 level.

11 Sponsor

The study is sponsored by the Liverpool Heart and Chest Hospital NHS Foundation Trust.

12 Funding

This research will be conducted with support from the Investigator-Initiated Study Program of Biosense Webster, Inc. (BWI-IIS-386).

13 Trial registration

13.1 The study will be prospectively registered on the ClinicalTrials.gov database before recruiting commences

13.2 An application will also be submitted for the study to be included in the NIHR Clinical Research Network (CRN) Portfolio.

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Appendix E PRAISE Study Participant Information Sheet

Liverpool Heart and Chest Hospital NHS
NHS Foundation Trust

Participant Information Sheet

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

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

Thank you for reading this.

Part 1
Study title

Pulmonary vein **R**econnection following **A**blation **I**ndex guided ablation: a **S**uccess **E**valuation (**PRAISE**)

Why have I been invited to participate?
You have been invited because you have been offered ablation treatment for the type of atrial fibrillation (AF) you have (persistent AF).

What is the purpose of the study?
The success rate for catheter ablation for persistent AF is around 50-60% at 1 year after 1 procedure. This means that up to 40-50% of patients will experience recurrence of AF, and most of these go on to undergo a second procedure. This study attempts to improve that success rate through two strategies. The first one involves performing the initial ablation procedure using guidance by a factor that can monitor the effectiveness of ablation. This factor is known as Ablation Index (AI). The second strategy involves performing a diagnostic procedure at 8-10 weeks after the first one, with repeat ablation performed as needed to "touch up" any areas that have recovered by then. This repeat procedure will take place regardless of whether an AF recurrence has occurred by that point, as it is assumed that these recovered areas may well result in AF recurrence down the line.

As such, the study is designed to find out whether the routine use of AI monitoring during ablation will mean that lesions are more likely to be durable, and whether this results in better freedom from AF.

Do I have to take part?

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

What will happen to me if I take part?

Before your ablation procedure, you may have a magnetic resonance imaging (MRI) scan of the heart performed. This is standard practice and the information is used to help with your ablation. If an MRI is not possible for any reason, then it is not mandatory. You will be given a handheld ECG monitor to keep for the duration of the study (1 year). You will be asked to take a 30-second recording of your heart rhythm each day, and whenever you have any symptoms suggestive of AF. The monitor will save these recordings and we will download them when you attend for routine appointments – no extra visits to the hospital are needed for this. This monitoring is additional to usual care – a monitor is not normally provided and monitoring is usually only arranged for short periods if you have symptoms.

The initial ablation procedure will be carried out in a similar manner to what would happen if you were not taking part in the trial.

You will be asked to return for a follow-up appointment 6 weeks after your ablation – this is an extra hospital visit to usual care. As mentioned above, you will be given a date 8-10 weeks after your first ablation for your second procedure. This will be carried out in the same way as the first procedure, but will usually be much shorter.

You will be asked to return for follow-up appointments at 3, 6 and 12 months after the ablation – this is the same as usual practice. You will be asked to complete quality of life (QOL) questionnaires when you enrol and at the 6 and 12 month visits. These take just a few minutes to complete and are part of routine practice. If you are found to have a recurrence of atrial fibrillation, your options will be discussed with you. These may include electrical cardioversion (putting your heart rhythm back to normal with electricity), medication or a further ablation procedure.
A flow chart is attached to the end of this sheet to help summarise what will happen.

What are the possible disadvantages and risks of taking part?

There are no significant issues relating to the initial ablation procedure, as you will have a standard clinical indication for undergoing the procedure.

Both the initial and any subsequent procedures will be carried out by, or under the direct supervision, of fully qualified Consultants in Cardiac Electrophysiology with considerable experience in performing AF ablation. The procedures will be carried out in a fully equipped electrophysiology laboratory. The safety of trial participants would not be expected to significantly differ from that of patients deciding not to enrol.

The procedure performed for study participants will be exactly the same as that for non-participants, apart from the fact that additional data regarding the health of the underlying heart tissue will be collected during the procedure. This may increase the procedure duration by around 5-10 minutes.

Subsequently, all study participants will undergo a repeat procedure 8-10 weeks after their initial ablation procedure. It would be expected that a significant proportion of these participants will have a symptomatic recurrence at some point in time and therefore the repeat study could be considered as simply "bringing forward" the procedure that would have been warranted on clinical grounds.

For those who would never have gone on to have a recurrence, the risks from the repeat procedure are entirely additional (as they would not be expected to ever need a repeat procedure on clinical grounds). However, it is not possible to identify these patients prospectively.

If pulmonary vein reconnection is found at repeat study, it may be expected that further ablation to achieve pulmonary vein isolation will result in a lower long-term risk of AF recurrence (it is the purpose of this study to determine this), which would be of benefit to the participant.

Both the initial and repeat ablation procedures have a small risk of a serious complication happening. The serious complications include; stroke, significant bleeding around the heart, major bleeding in the groin, narrowing of the pulmonary veins, paralysis of the diaphragm, perforation of the gullet and death. However, it is expected that the level of risk for repeat procedures would be considerably lower than that for the initial procedure as: a) access to the left atrium is often easier due to the previous procedure, and b) considerably less extensive ablation is usually required compared to the original procedure, and no ablation will be performed if there is no pulmonary vein reconnection.

Radiation and the Ionising Radiation (Medical Exposure) Regulations – (IRMER)

X-rays are a form of ionising radiation. In order to perform an ablation, we need to use X-rays. The X-ray exposure related to the initial ablation procedure is part of usual clinical care. If you undergo an MRI scan, please note that this is not associated with any radiation exposure.

There will be an additional exposure to X-rays with the second procedure. However, as mentioned above, many of these patients would have needed this repeat procedure at a later time anyway, so the X-ray exposure will, in effect, be the same for these patients. For those patients who would not have needed a second procedure though, the X-ray exposure related to the repeat study will be additional.

Radiation exposure "adds up" over your lifetime. Therefore, if you have had significant exposure to X-rays previously (for example, received radiotherapy, had several CT scans or undergone other invasive procedures that use X-rays), you may wish to take this into account when considering taking part in this study.

For patients under the age of 70, the lifetime additional risk of cancer from 2 ablation procedures is estimated to be 1 in 1500. This is calculated using the maximum expected radiation exposure. The added risk from the second ablation procedure is around 1 in 2000. For patients over 70 years old, these risks are approximately 5 times less.
For comparison, the overall lifetime risk of cancer in the general population is 1 in 3.

What are the possible benefits of taking part?

All participants will benefit from close monitoring of their heart rhythm that is more in frequency than usual; therefore, they will be offered the appropriate treatment as soon as significant heart rhythm abnormality is detected.

Also, all participants will have a repeat procedure performed and these will identify whether they have any sites of electrical reconnection. The presence of such sites is likely to increase the likelihood of future recurrence of AF. As these sites will then be ablated again to achieve PV isolation, it would be expected that these participants will have a lower AF recurrence rate in the future. This has never been studied in patients with this type of AF, hence the need for this study. If no benefit is proven, the effect would be expected to be neutral rather than negative.

Additionally, as some data have already emerged regarding the ablation lesion characteristics needed to create lasting lesions, we will be applying these data at participants' repeat procedures, which may improve their long-term likelihood of procedural success.

What happens when the research study stops?

Depending on each individual's ongoing clinical requirement, some people will continue to be followed up by the Heart Rhythm team at Liverpool Heart and Chest Hospital whilst others will be discharged back to the care of their GP or local Cardiologist.

What if something goes wrong?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. Detailed information on this is given in Part 2.

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

This completes Part 1 of the information sheet.
If you are interested in taking part, please read Part 2, which provides further information that you may find useful.

PART 2

What if relevant new information becomes available?

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

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

You can withdraw from treatment but keep in contact with us to let us know your progress. Information collected may still be used.

What if there's a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. Contact details can be found at the end of this information sheet. You can also contact the Liverpool Heart and Chest Hospital Customer Care Team on 0151 600 1517 or 0151 600 1257 or email lisa.gurrell@lhch.nhs.uk
In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Liverpool Heart and Chest Hospital NHS Foundation Trust but you may have to pay your legal costs. If appropriate, the normal National Health Service complaints mechanisms will still be available to you.

What will happen to the results of the research study?

The results of the study will be available after it finishes and will usually be published in medical journals and presented at scientific conferences. Results may also be made available online. They will also form part of a thesis for the degree of Doctor of Medicine (MD) at University of Liverpool, Liverpool. The data will be anonymous and none of the patients involved in the trial will be identified in any report or publication.
Should you wish to see the results, or the publication, please ask your study doctor.

Will my taking part in the study be kept confidential?

If you consent to take part in this study, the records obtained while you are in this study, as well as related health records, will remain strictly confidential at all times. The

information will be held securely on paper and electronically at Liverpool Heart and Chest Hospital under the provisions of the 1998 Data Protection Act. Your name will not be passed to anyone who is not involved in the trial or who is not part the research team or the research sponsor. You will be allocated a trial number, which will be used as a code to identify you on all trial forms.
Your records will be available to people authorised to work on the trial but may also need to be made available to people authorised by the research sponsor, which is the organisation responsible for ensuring that the study is carried out correctly. A copy of your consent form may be sent to the research sponsor during the course of the study. By signing the consent form, you agree to this access for the current study and any further research that may be conducted in relation to it, even if you withdraw from the current study.
The information collected about you may also be shown to authorised people from the UK Regulatory Authority and Independent Ethics Committee; this is to ensure that the study is carried out to the highest possible scientific standards. All will have a duty of confidentiality to you as a research participant.
If you withdraw consent from further study treatment, unless you object, your data and samples will remain on file and will be included in the final study analysis. In line with Good Clinical Practice guidelines, at the end of the study, your data will be securely archived for a minimum of 10 years. Arrangements for confidential destruction will then be made.

Informing your General Practitioner (GP) and other relevant doctors

If you agree to take part in this study, we will notify your GP and other doctors who are treating you that you are taking part in this study. A letter will be sent to your GP and any other relevant doctors explaining the details of the trial and informing him/her that you are participating.

What should I do if I want to take part?

A member of the research team is on hand to discuss this study further and to answer your questions. They will provide you with a consent form, a QOL questionnaire and a stamped, addressed envelope for you to take away while you consider taking part in the study. They will also arrange to contact you by phone in 1 week's time for a further discussion. If you wish to take part, the signed consent form and QOL questionnaire can be returned to us by post and we will re-confirm that you wish to take part at one of your next visits to hospital.

Who is organising and funding the research?

The study is being carried out by members of staff at the Liverpool Heart and Chest Hospital, which is acting as research sponsor for the study. Funding for part of the study

has been provided by Biosense Webster Inc., a medical devices company that makes equipment used in AF ablation procedures.

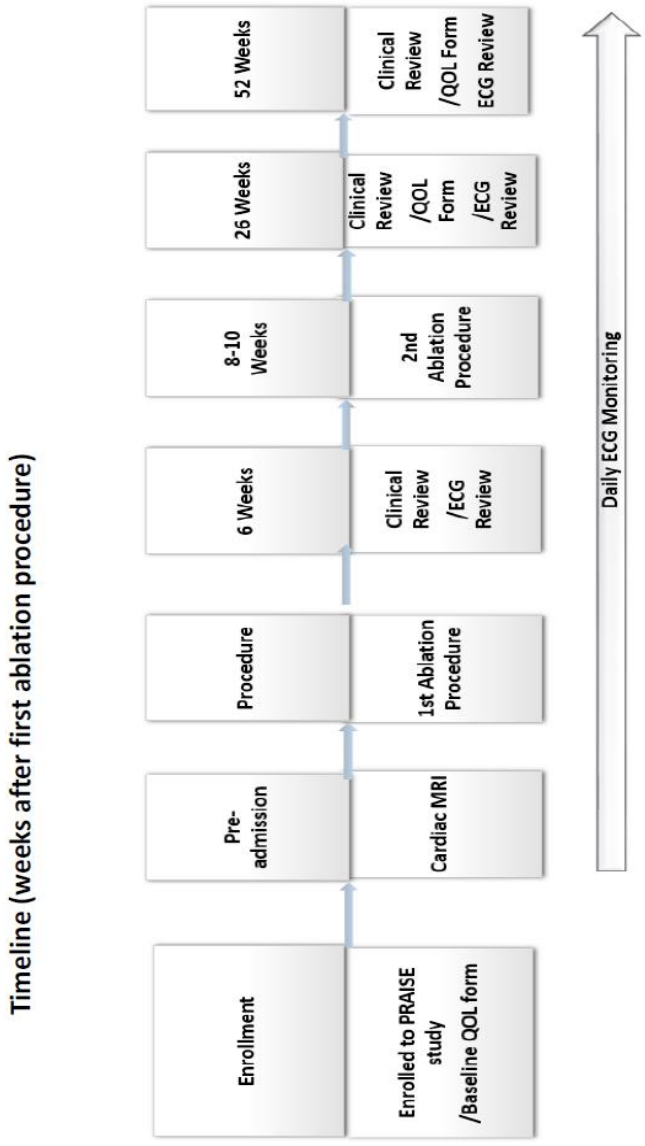
Who has reviewed the study?

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

Contact for Further Information
If you have any further questions, you can get additional information from Dr Ahmed Hussein, Electrophysiology Research Fellow, via his email address **AhmedAbdellatif.Hussein@lhch.nhs.uk** or by contacting the Liverpool Heart and Chest Hospital switchboard on **0151 600 1616**.

This completes Part 2 of the information sheet.
Thank you for taking the time to read this information.

Liverpool Heart and Chest Hospital NHS
NHS Foundation Trust



Appendix F PRAISE Study Consent Form

Liverpool Heart and Chest Hospital NHS
NHS Foundation Trust

CONSENT FORM

Patient Identification Number for this trial:

Title of Project: **P**ulmonary vein **R**econnection following **A**blation **I**ndex guided ablation: a **S**uccess **E**valuation (**PRAISE**)

Name of Researcher: **Dr Ahmed Hussein**

Please initial box

1. I confirm that I have read and understand the information sheet dated 9 November 2015 (Version 4) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected ☐

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from regulatory authorities or from this or another hospital, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to my GP being informed of my participation in the study. ☐

5. I agree to take part in the above study. ☐

Name of Patient	**Date**	**Signature**
---	---	---
Name of Person taking consent	**Date**	**Signature**
---	---	---

When completed 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes.

Pulmonary vein Reconnection following AI guided ablation – V5 (18 November 2015)

Excellent, Compassionate and Safe care for every patient, every day

Appendix G The Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT) Questionnaire

Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) Questionnaire

Section 1. Occurrence of atrial fibrillation **Name or ID:**_____

Are you currently in atrial fibrillation? ☐ Yes ☐ No

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

__earlier today
__within the past week
__within the past month
__1 month to 1 year ago
__more than 1 year ago
__I was never aware of having atrial fibrillation

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

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

	Not at all bothered Or I did not have this symptom	Hardly bothered	A little bothered	Moderately bothered	Quite a bit bothered	Very bothered	Extremely bothered
1. Palpitations: Heart fluttering, skipping or racing	1	2	3	4	5	6	7
2. Irregular heart beat	1	2	3	4	5	6	7
3. A pause in heart activity	1	2	3	4	5	6	7
4. Lightheadedness or dizziness	1	2	3	4	5	6	7

On a scale of 1 to 7, over the past 4 weeks, have you been limited by your atrial fibrillation in your:
(Please circle one number which best describes your situation)

	Not at all limited	Hardly limited	A little limited	Moderately limited	Quite a bit limited	Very limited	Extremely limited
5. Ability to have recreational pastimes, sports, and hobbies	1	2	3	4	5	6	7
6. Ability to have a relationship and do things with friends and family	1	2	3	4	5	6	7

On a scale of 1 to 7, over the past 4 weeks, as a result of your atrial fibrillation, how much difficulty have you had in:
(Please circle one number which best describes your situation)

	No difficulty at all	Hardly any difficulty	A little difficulty	Moderate difficulty	Quite a bit of difficulty	A lot of difficulty	Extreme difficulty
7. Doing any activity because you felt tired, fatigued, or low on energy	1	2	3	4	5	6	7
8. Doing physical activity because of shortness of breath	1	2	3	4	5	6	7
9. Exercising	1	2	3	4	5	6	7
10. Walking briskly	1	2	3	4	5	6	7
11. Walking briskly uphill or carrying groceries or other items, up a flight of stairs without stopping	1	2	3	4	5	6	7
12. Doing vigorous activities such as lifting or moving heavy furniture, running, or participating in strenuous sports like tennis or racquetball	1	2	3	4	5	6	7

Developed by AFEQT Core Team-John Spertus, MD, Mid America Heart Institute, Kansas City, MO; Paul Dorian, MD, St. Michaels Hospital, Toronto, ON; Rosemary Bubien, RN, University of Alabama, Birmingham, AL; Caroline Burk, Pharm D. M.S; Steven Lewis, PhD; Donna Godejohn, BSN, St. Jude Medical, St. Paul, MN.

Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) Questionnaire

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

	Not at all Bothered	Hardly bothered	A little bothered	Moderately bothered	Quite a bit bothered	Very bothered	Extremely bothered
13. Feeling worried or anxious that your atrial fibrillation can start anytime	1	2	3	4	5	6	7
14. Feeling worried that atrial fibrillation may worsen other medical conditions in the long run	1	2	3	4	5	6	7

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

	Not at all bothered	Hardly bothered	A little bothered	Moderately bothered	Quite a bit bothered	Very bothered	Extremely bothered
15. Worrying about the treatment side effects from medications	1	2	3	4	5	6	7
16. Worrying about complications or side effects from procedures like catheter ablation, surgery, or pacemakers therapy	1	2	3	4	5	6	7
17. Worrying about side effects of blood thinners such as nosebleeds, bleeding gums when brushing teeth, heavy bleeding from cuts, or bruising.	1	2	3	4	5	6	7
18. Worrying or feeling anxious that your treatment interferes with your daily activities	1	2	3	4	5	6	7

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

	Extremely satisfied	Very satisfied	Somewhat satisfied	Mixed with satisfied and dissatisfied	Somewhat dissatisfied	Very dissatisfied	Extremely dissatisfied
19. How well your current treatment controls your atrial fibrillation?	1	2	3	4	5	6	7
20. The extent to which treatment has relieved your symptoms of atrial fibrillation?	1	2	3	4	5	6	7

Name or ID:_____

Developed by AFEQT Core Team-John Spertus, MD, Mid America Heart Institute, Kansas City, MO; Paul Dorian, MD, St. Michaels Hospital, Toronto, ON; Rosemary Bubien, RN, University of Alabama, Birmingham, AL; Caroline Burk, Pharm D. M.S; Steven Lewis, PhD; Donna Godejohn, BSN, St. Jude Medical, St. Paul, MN.

Appendix H PRAISE Study Approvals

NHS
Health Research Authority
National Research Ethics Service

North West - Greater Manchester West Research Ethics Committee
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

04 January 2016

Dr Dhiraj Gupta
Cardiology Department
Liverpool Heart & Chest Hospital
Thomas Drive, Liverpool
L14 3PE

Dear Dr Gupta

Study title:	**Pulmonary vein Reconnection following Ablation Index-guided ablation: a Success Evaluation (PRAISE)**
REC reference:	**15/NW/0930**
IRAS project ID:	**193216**

Thank you for your submission, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Anna Bannister, nrescommittee.northwest-gmwest@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

The Chair noted the independent reviewer commented that although a randomised control trial would be a better way to show improved outcomes, the use of historical controls will provide evidence to support future trials. Also noted was the reviewer's identification of risks to

participants and that the researchers are well placed to manage those risks.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has

been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering letter on headed paper [PRAISE Cover letter V1 16 Nov 2015]	Version 1	16 November 2015
GP/consultant information sheets or letters [PRAISE GP Letter V4 16 Nov 2015]	Version 4	16 November 2015
IRAS Checklist XML [Checklist_18112015]		18 November 2015
Letter from funder	Version 1	03 March 2014
Other [PRESSURE study paper]	Version 1	24 June 2015
Other [AFEQT_Questionnaire version 1 anonymised]		
Other [PRAISE Study consent form V5 18 December 2015]	Version 5	18 December 2015
Other [PRAISE trial review Prof Lambiese]		21 December 2015
Other [Letter to REC dated 29 Dec 2015]		29 December 2015
Other [PRAISE PIS V5 18 December 2015 with tracked changes]	Version 5	18 December 2015
REC Application Form [REC_Form_04012016]		04 January 2016
Research protocol or project proposal [PRAISE study Protocol V5 16 Nov 2015]	5.0	16 November 2015
Summary CV for Chief Investigator (CI) [Dhiraj Gupta CV for IRAS 2015]	Version 1	14 November 2015
Summary CV for student [Ahmed Hussein CV for IRAS November 2015]	Version 1	16 November 2015
Summary CV for supervisor (student research) [Dhiraj Gupta CV for IRAS 2015]	Version 1	14 November 2015
Validated questionnaire [EQ-5D-5L Questionnaire]	Version 1.0	

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

15/NW/0930	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely

PP K. Southgate

On behalf of Dr Lorraine Lighton (Chair)
Chair

Email: nrescommittee.northwest-gmwest@nhs.net

Enclosures: After ethical review – guidance for researchers

Copy to: *Dr Margarita Perez-Casal, RLBUH Trust*

Liverpool Heart and Chest Hospital NHS
NHS Foundation Trust

Thomas Drive
L14 3PE
Department of Clinical Quality
☎ 0151 600 1370

03/02/2016

Dear Dr Hussein

SURE Group Approval
R&D 1091 PRAISE
Pulmonary vein **R**econnection following **A**blation **I**ndex-guided ablation: a **S**uccess **E**valuation

The above project was discussed at the SURE group meeting on 1ST February 2016. I am pleased to inform you that the group gave their full approval to your study.

The following documents have been reviewed and approved:

- ICF– V6
- Lay Summary
- PIS V.6

I wish you all the best with your research.

Yours sincerely,

Dr Margarita Pérez-Casal
Head of Clinical Quality

CC. Dr Jay Wright, Chair of the Research Committee
R&D files

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Tuesday 9th February 2016

Dear Dr Gupta

R&D 1091 –
Pulmonary vein Reconnection following Ablation Index guided ablation: a Success Evaluation (PRAISE)

The above project has now been granted full R&D Permission.

The following documents have been reviewed and approved:

Document	*Version*	*Date*
Covering letter on headed paper [PRAISE Cover letter V1 16 Nov 2015]	Version 1	16 November 2015
GP/consultant information sheets or letters [PRAISE GP Letter V4 16 Nov 2015]	Version 4	16 November 2015
IRAS Checklist XML [Checklist_18112015]		18 November 2015
Letter from funder	Version 1	03 March 2014
Other [PRESSURE study paper]	Version 1	24 June 2015
Other [AFEQT_Questionnaire version 1 anonymised]		
Other [PRAISE Study consent form V5 18 December 2015]	Version 5	18 December 2015
Other [PRAISE trial review Prof Lambiese]		21 December 2015
Other [Letter to REC dated 29 Dec 2015]		29 December 2015
Other [PRAISE PIS V5 18 December 2015 with tracked changes]	Version 5	18 December 2015
REC Application Form [REC_Form_04012016]		04 January 2016
Research protocol or project proposal [PRAISE study Protocol V5 16 Nov 2015]	5.0	16 November 2015
Summary CV for Chief Investigator (CI) [Dhiraj Gupta CV for IRAS 2015]	Version 1	14 November 2015
Summary CV for student [Ahmed Hussein CV for IRAS November 2015]	Version 1	16 November 2015
Summary CV for supervisor (student research) [Dhiraj Gupta CV for IRAS 2015]	Version 1	14 November 2015
Validated questionnaire [EQ-5D-5L Questionnaire]	Version 1.0	

Please note you have from 9th February 2016 until 10th March 2016 to recruit your first patient.

If you have any issues or problems with the conduct of your research please notify me immediately and I will endeavour to help.

I wish you all the best with your research.

Yours sincerely,

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Appendix I PRESSURE Study Protocol

Pulmonary vein **RE**connection and clinical **S**uccess rates with ablation using the **S**martTo**U**ch catheter: a **R**epeat **E**valuation and ablation study (**PRESSURE**)

1. Lay summary

1.1 Atrial fibrillation (AF) is the commonest condition affecting the rhythm of the heart, and causes an irregular and often rapid heartbeat. Developing this condition may cause significant health problems, such as symptoms that affect normal day-to-day activities. Patients with AF also have a shorter life expectancy on average. Tablets to try to normalise the heart rhythm rarely work well. As a result, doctors have devised a treatment to try to cure this condition. Special wires (called catheters) are used to deliver heat energy (called ablation) on the inside surface of the heart. This technique has been used more and more in recent years for patients with troublesome symptoms due to AF.

1.2 The aim of the treatment is to draw lines of ablation in specific places in the heart. Unfortunately, a lot of patients (almost 1 in 2) get AF again after this treatment and most of these patients have a second treatment performed. We usually find at this second treatment that gaps have developed in the lines of ablation that were drawn the first time around. We think that automatically doing a second treatment to close these gaps a couple of months after the first treatment may mean that fewer of these patients will get AF again in the future. We also want to find out what factors make a line of ablation less likely to develop gaps.

1.3 In our study, participants will be assigned to one of two groups:

1. a “standard care” group, who will have a single treatment initially
2. a “repeat study” group, who will have the initial treatment followed by a second treatment 8-10 weeks later.

1.4 For patients in the “repeat study group”, we will see how many have developed gaps since their first treatment. We will look at where these gaps are and will compare this with information collected during the first treatment to try to work out why the gap has developed. Any gaps found at the second treatment will be closed again. We will then monitor participants carefully over 12 months to see how many patients from each group get AF again.

2. Background

2.1 Atrial fibrillation (AF) is the most commonly-occurring cardiac arrhythmia, affecting 1-2% of the general population,[1-3] and is associated with increased stroke-risk and mortality. Pulmonary vein isolation (PVI) using radiofrequency (RF) ablation has been used increasingly as a treatment strategy, and current guidelines list PVI as a first line management strategy for AF in certain circumstances,[5] particularly for those with paroxysmal AF.

2.2 Despite improvements in the safety and efficacy of this procedure, success rates following PVI for paroxysmal AF remain significantly lower than those for most other ablation procedures.[6,7] Recurrence of AF, either symptomatic or asymptomatic, occurs in up to 1 in 2 patients after PVI.[8,9] Commonly this is due to electrical reconnection of one or more of the pulmonary veins. Further ablation is often then performed to re-isolate the PVs, with a resulting improvement in freedom from AF.[10] Many patients experience a recurrence of AF early after a first PVI procedure, but commonly these recurrences are deemed "non-clinical" as they fall within a 3-month post-PVI "blanking period", as per HRS/EHRA/ECAS recommendations. However, data have shown that these individuals have lower long-term success rates than those without early recurrence, suggesting that this may be of clinical relevance.[11-13] One study has demonstrated improved freedom from AF at 12 months in patients with a very early recurrence who underwent repeat PVI 4 weeks after the initial procedure. Many other patients who do not have an early recurrence still go on to have AF at a later point in time and undergo repeat PVI at that stage, but commonly suffer significant symptoms during the period between AF recurrence and the redo procedure.

2.3 Recent data have demonstrated that 65% of patients undergoing a repeat electrophysiology study 3 months post-PVI have reconnection of 1 or more PVs.[14] However, it is not currently known whether there is a difference in the proportion of patients who have developed PV reconnection early after an initial PVI procedure between those with and without an early recurrence. Additionally, the effect of re-isolation of reconnected PVs in these patients, who would not currently be offered a repeat ablation, on freedom from AF during the first year of follow-up is also unknown.

2.4 The process of electrical reconnection can be considered as occurring acutely or late after the procedure. Acute reconnection is identified during the initial PVI procedure by the spontaneous return of conduction into or out of the PVs, or using adenosine to unmask dormant conduction.[15] Late reconnection can only be identified at a repeat study subsequent to the initial PVI procedure. It is believed that PV reconnection relates, at least in part, to RF ablation lesion quality. This is thought to be associated with a combination of the contact force between the catheter tip and the atrial wall, the duration of ablation in a single location, and the RF power delivered. The ThermoCool® SmartTouch™ (Biosense Webster, Diamond Bar, California, USA) is a CE Mark-approved RF ablation catheter which features a contact force sensor at its tip. While this provides real-time monitoring of the pressure being applied to the atrial wall, it is not possible to determine whether any individual RF ablation lesion is of "high" or "low" quality. A new software update to the CARTO 3 electroanatomical mapping system (Biosense Webster, Diamond Bar, California, USA), termed Visitag™, is able to record and display composite data on contact force, duration of ablation in a single location and power application for each individual RF ablation lesion that is performed. A previous study using a different contact force-sensing

catheter showed that the Force-Time Integral (total contact force integrated over the time of ablation delivery) was significantly lower in areas where electrical gaps occurred as opposed to areas that remained isolated.[14] However, the relationship between lesion quality (assessed by Visitag™) and subsequent acute or late electrical reconnection has not been defined.

3. Original hypotheses/research questions

3.1 Primary hypothesis

A routine two-stage strategy of performing a repeat EP study to assess and re-isolate PV reconnection in all patients at 8-10 weeks following initial PVI reduces the risk of AF recurrence up to one year after the initial procedure.

3.2 Secondary hypotheses

1. Patients who routinely undergo a repeat study and PV re-isolation at 8-10 weeks will have improved quality of life (QOL) measures at 12 months compared with patients receiving standard treatment.
2. In patients undergoing a repeat electrophysological study 8-10 weeks after their initial ablation there is a significant difference between the rate of PV reconnection in patients with and those without documented early AF recurrence.
3. In patients undergoing a repeat electrophysical study 8-10 weeks after their initial ablation the pattern of sites of PV reconnection is affected by the presence or absence of early AF recurrence
4. Sites of acute PV reconnection (including those unmasked by adenosine) and late PV reconnection correlate with Visitag™ Force-Time-Power Integral data from the initial PVI procedure.
5. Patients with persisting PV isolation seen at a repeat EP study remain free of AF during follow up.

Time to first AF recurrence (after the initial blanking period) is longer in patients undergoing routine redo ablation than with standard care.

4. Design

4.1 Prospective randomised, controlled, non-blinded trial. Eligible consenting patients will be randomised, via a computerised randomisation process, in a 1:1 ratio to one of two groups:

- Repeat study group: Following an initial PVI procedure, all patients (regardless of early AF recurrence) will undergo a repeat EP study at 8-10 weeks post-initial PVI, with re-isolation of any PV reconnection(s) identified
- Standard care group: Patients will undergo an initial PVI procedure. Further management will be determined by AF recurrences at the responsible Consultant's discretion as per standard care

5. End-points

5.1 Primary outcome measure:

1. The proportion of patients maintaining freedom from atrial tachyarrhythmias for 12 months post-initial PVI (after an initial 3 month blanking period)

5.2 Secondary outcome measures:

1. QoL 12 months after initial ablation, as quantified by the validated AFEQT questionnaire.
2. Comparison of major complication rates (occurring within 30 days after a PVI procedure), to include cardiac tamponade, stroke/TIA, myocardial infarction, pulmonary vein stenosis, phrenic nerve paralysis, oesophageal perforation/atrio-oesophageal fistula, major vascular complications and death

5.3 Sub-analyses:

1. Correlation between initial Force-Time-Power Integral (as assessed using Visitag™) and a) sites of acute PV reconnection (including those unmasked by adenosine), and b) late PV reconnection (8-10 weeks after their initial PVI)
2. The proportion of patients without early recurrence maintaining freedom from atrial tachyarrhythmias for 12 months post-initial PVI
3. The proportion of patients with early recurrence maintaining freedom from atrial tachyarrhythmias for 12 months post-initial PVI
4. Comparison of prevalence, distribution and location of sites of late PV reconnection (8-10 weeks after their initial PVI) between patients with and without early AF recurrence in the "repeat study" group.

6. Patients

6.1 Patients will be recruited from the heart rhythm clinics at the Institute of Cardiovascular Medicine and Science. Patients listed for RF ablation of paroxysmal AF and felt to be suitable for inclusion by their responsible Consultant will be approached and offered information regarding the study. Patients interested in taking part will be provided with the Participant Information Sheet (PIS) by a member of the research team and offered the opportunity to take this literature home to discuss it with relevant relatives and friends. The PIS contains a contact phone number, address and email address for the research team should they wish to get in contact with any queries. A follow-up phone call will be arranged for 1 week later to provide a further opportunity for discussion. If the patient wishes to enrol, they will be invited to return the signed consent form by post. Consent will then be reconfirmed in person at the time of a subsequent hospital visit.

6.2 Inclusion criteria:

- Aged over 18 years

- Paroxysmal atrial fibrillation (defined as ECG proven episodes of atrial fibrillation which are self-limiting and last less than 7 days on each occasion, or which were cardioverted electrically or pharmacologically less than 48 hours from onset)
- Due to undergo pulmonary vein isolation by RF ablation

6.3 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
- Persistent (episodes of atrial fibrillation which last longer than 7 days or which last longer than 48 hours but require electrical or pharmacological cardioversion) or permanent atrial fibrillation
- Prior prosthetic mitral valve replacement or severe structural cardiac abnormality[25]
- Reversible cause for atrial fibrillation
- Known infiltrative cardiomyopathy
- Known severe left ventricular systolic function (ejection fraction <35%)
- Pregnancy

7. Outline Protocol

7.1 Baseline Data (to be collected at time of recruitment/initial clinic visit)

Patients will have quality of life recorded at recruitment using the validated AFEQT questionnaire. Their functional status will also be assessed according to the EHRA and CCS classification.

7.2 Pre-procedure management

- Those patients who are on Amiodarone will have this drug stopped a minimum of 2 months prior to their PVI procedure. Where possible, it will be replaced with another anti-arrhythmic drug. All anti-arrhythmic drugs will be stopped 5 days prior to the procedure.
- Echocardiographic data will be collected as part of routine care, including: left ventricular (LV) ejection fraction, LV end-systolic and end-diastolic dimensions, and left atrial diameter.
- Unless contraindicated, all patients will undergo a cardiac MRI scan prior to the ablation procedure to produce a detailed 3D reconstruction of the left atrial anatomy as part of routine care.
    - Patients unable to undergo cardiac MRI may undergo an ungated cardiac CT scan to produce a detailed 3D reconstruction of the left atrial anatomy at the operator's discretion.
- Trans-oesophageal echocardiography (TOE) will not be performed routinely, but may be undertaken at the discretion of the operator prior to the procedure to exclude left atrial thrombus as per

standard care (indications may include sub-therapeutic INR readings in the 4 weeks prior to the ablation procedure for those taking warfarin, or missed doses for those taking alternative oral anti-coagulants).

7.3 Initial ablation procedure:

7.3.1 All patients anticoagulated pre-preprocedurally will continue oral anticoagulation in the peri-procedure period. An INR level between 2.0 and 3.5 will be considered acceptable for those taking warfarin[30,31]. Peri-procedural use of novel oral anti-coagulants (direct thrombin or Factor Xa inhibitors) will be according to local guidelines for patients taking these agents.

7.3.2 PVI will be performed under conscious sedation or general anaesthesia in a standard fashion, as previously described.[32] One or two transseptal punctures will be made using fluoroscopic guidance with additional pressure monitoring, following which intravenous unfractionated heparin boluses will be administered to maintain an Activated Clotting Time (ACT) of approximately 300s.

7.3.3 An electroanatomical map of the left atrium will be created using a 3D navigation system (Carto 3, Biosense Webster, Diamond Bar, California, USA) and, whenever possible, integrated with the MRI or CT reconstruction of the left atrium (CartoMerge, Biosense Webster, Diamond Bar, California, USA)[33,34].

7.3.4 Patients will undergo PVI using point-by-point RF application in a wide area circumferential ablation (WACA) pattern using a Thermocool® SmartTouch™ irrigated RF ablation catheter. A contact force of >12 g and <40g will be aimed for at each site. RF power will be set at the operator's discretion but a maximum of 35W within the left atrium. Visitag™ software (Biosense Webster, Diamond Bar, California, USA) will be used to record RF data at each individual point along the WACA set but this will not be visible to the operator to avoid biasing the lesions applied. PVI will be confirmed with a circular mapping catheter(Lasso Nav) placed sequentially in each of the PVs. No additional linear lesions or ablation of complex fractionated atrial electrograms will be performed, unless the patient develops a regular atrial tachycardia or flutter amenable to mapping and ablation.

7.3.5 If the patient is in AF after achieving isolation of all PVs, electrical cardioversion will be used to restore sinus rhythm. With the patient in sinus rhythm, and after a minimum of 20 minutes since the last ablation to that PV, the PVs will be rechecked with the circular catheter to determine if spontaneous PV reconnection has occurred. If overt PV reconnection has not occurred, a bolus of intravenous adenosine (12-18mg) will be given to unmask any sites of dormant conduction. Further ablation will be performed at any sites of overt or unmasked reconnection to achieve PVI once again, following which the procedure will be ended. Intravenous protamine may, at the discretion of the operator, be given to reverse the effects of heparin at the end of the procedure.

7.3.6 Oral anti-coagulation will be continued post-procedure as per hospital protocol. Anti-arrhythmic medications will not be restarted. A blood sample for high-sensitivity Troponin T analysis will be drawn 12-24 hours following the procedure.

7.3.7 Acute procedural success:

Acute complete procedural success will be defined as electrical isolation of all PVs. Partial procedural success will be defined as electrical isolation of 3 or more, but not all, PVs. Procedural failure will be defined as electrical isolation of less than 3 PVs.

7.4 Post-PVI monitoring for AF recurrence:

All patients will be provided with a handheld ECG monitoring device, to be kept for the duration of the study (12 months) (Reference). Patients will be asked to self-record a 30s ECG recording once a day for the duration of the study, as well as each time they experience symptoms of palpitations.

7.5 Repeat study group:

7.5.1 Definition of early recurrence:

A repeat PVI procedure will be arranged for 8-10 weeks after the initial procedure. Following the initial procedure, a 4-week absolute blanking period will be applied, during which episodes of atrial tachyarrhythmia will not be considered as true recurrence. Any episodes of atrial tachyarrhythmia 30s (or longer) in duration documented between 4 weeks post-initial PVI and the second PVI procedure will be termed early recurrence – these will not contribute to the primary outcome measure. Patients with documented early recurrence who are suffering significant symptoms may have an anti-arrhythmic medication (other than amiodarone) restarted or undergo electrical cardioversion at the discretion of their responsible Consultant.

Repeat ablation procedure:

7.5.2 The repeat procedure will be performed in the same way as outlined above for the initial procedure Peri-procedural and intra-procedural anti-coagulation management will be identical. While performing transseptal puncture, use may be made of any residual foramen ovale defect related to the initial procedure as appropriate. As before, an electroanatomical map of the left atrium will be created using the Carto 3 3D navigation system (Biosense Webster, Diamond Bar, California, USA) and integrated where possible with the original MRI or CT reconstruction of the left atrium (CartoMerge, Biosense Webster, Diamond Bar, California, USA).

7.5.3 Each PV will be assessed in turn for late reconnection with a circular mapping catheter and sites will be recorded for subsequent analysis. All identified sites of reconnection will be re-ablated using a Thermocool® SmartTouch™ irrigated RF ablation catheter, with a target contact force of 12 – 40g and RF power set at the operator's discretion. Once PV re-isolation has been successfully achieved, the procedure will be ended. Heparin-reversal and post-procedural anti-coagulation will be as per the initial procedure. Anti-arrhythmic medications again will not be restarted.

7.5.4 Following the repeat procedure, a further blanking period will be applied until 12 weeks have elapsed since the initial PVI procedure (ie. 2-4 weeks following the repeat procedure). As for the initial 4 week blanking period, patients with documented recurrence during this second blanking period who are suffering significant symptoms may have an anti-arrhythmic medication (other than amiodarone) restarted or undergo electrical cardioversion at the discretion of their responsible Consultant. Any

reinitiated anti-arrhythmic drugs will be stopped again at the end of the second blanking period (12 weeks after the initial PVI procedure).

7.6 Standard care group:

A 12 week *clinical blanking period* (with regard to consideration of repeat PVI) will be applied as per current HRS/EHRA/ECAS recommendations. For the purposes of the study, an initial 4 week *absolute blanking period* will be applied, during which episodes of atrial tachyarrhythmia will not be considered as true recurrence. Any episodes of atrial tachyarrhythmia ≥30s in duration recorded between 4 weeks and 12 weeks post-PVI will be documented as early recurrence, but will not contribute to the primary outcome measure. Patients with documented "early recurrence" who are suffering significant symptoms may 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 will not be performed, in keeping with HRS/EHRA/ECAS guidelines. Any reinitiated anti-arrhythmic drugs will be stopped again at the end of the 12 week blanking period.

7.7 Follow-up:

- Continued daily (plus symptom episode) ECG recordings as described above for 12 months from the initial procedure. ECG analysis will be blinded.
- A clinical review appointment at 6 weeks, followed by (as per standard care) clinical reviews at 3, 6 and 12 months. Data from the handheld ECG monitors will be downloaded at these visits.
- Participants will be asked to complete an AFEQT questionnaire at the time of the 6 and 12 month clinic visits.
- Anti-coagulation with warfarin or another oral anticoagulant agent will be continued for at least 3 months following the last ablation procedure. At that point the decision whether or not to continue will be made individually, based on the patient's CHA_2DS_2/CHA_2DS_2-VASc score and patient preference.
- Any episodes of atrial tachyarrhythmia ≥30s in duration documented after the 12 week blanking period will be defined as a recurrence. This will signify that that the patient has reached the primary end-point of the study and further management (including re-initiation of anti-arrhythmic medications, electrical cardioversion or listing for repeat PVI) will be at the discretion of the patient's responsible Consultant.

7.8 Study visit diagram

Procedure	Week							
	Recruit	Pre-adm	Procedure (Week 0)	6	8	12	26	52
Clinical review	✓			✓		✓	✓	✓
ECG Review				✓	✓*	✓	✓	✓

QOL form	✓						✓	✓
Cardiac MRI		✓						
PVI procedure			✓		✓*			

* "Repeat study" patients only

8. Safety

8.1 Major complications:

Definitions for major complications are derived from the HRS/EHRA/ECAS Expert Consensus Statement published in 2012. A major complication is defined as: a complication that results in permanent injury or death, requires intervention for treatment, or prolongs or requires hospitalization for more than 48 hours. Definitions of individual complications are as follows:

- Cardiac tamponade – the development of a significant pericardial effusion, resulting in hemodynamic compromise, requiring elective or urgent pericardiocentesis,
- 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

8.2 Expected major complication rates

A recent local audit of 150 first-time AF ablation procedures revealed the following complications and rates: significant (delaying discharge) groin haematoma (1.3%), stroke (0.7%), pericardial effusion

requiring drainage (0.7%). The combined incidence of significant complications was 2.7%, in keeping with other high volume centres[9].

Local data for *repeat* procedures have demonstrated a lower combined complication rate of around 1%.

8.3 Serious adverse event reporting

Any suspected major complication (as defined above) occurring in the course of the study, either whilst in hospital or during the period of follow up, will be reported as per the standard local adverse Event Reporting procedure.

8.4 Data monitoring committee

A data monitoring committee will be convened to review interim safety data from the trial.

8.5 Insurance/indemnity

Indemnity will be provided through the NHS indemnity scheme or professional indemnity.

9. Sample size calculation

9.1 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.

9.2 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%.[ThermAF] 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.

9.3 The projected success rate for the "repeat study" group is 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.[JAIS] As we feel that success rates will be further improved by treating PV reconnection in patients who have not had an early recurrence (but are at risk of having a subsequent one), a conservative success rate of 90% was estimated.

9.4 With these estimates, an alpha error set at 0.05 and a beta of 20% (80% power), the number of patients required would be 76 (38 in each group). Allowing for 5% of patients who may be lost to follow-up gives an intended sample size of 80 (40 per group).

9.5 The study is therefore underpowered to detect a smaller difference between group outcomes. This has been done intentionally, as the additional expected complications and healthcare costs

associated with a routine repeat procedure strategy can only be justified by a major improvement in success rate at 12 months. The study has therefore only been powered to detect a benefit of 26% or more.

10. Statistical analysis

10.1 All end points will be examined by means of an intention-to-treat analysis.

10.2 All reported *P* values will be two-sided. All categorical variables will be compared with χ^2 or Fisher's exact test as approporiate. The dependent variables will be checked for normal distribution by the Shapiro-Wilk statistic and appropriate descriptive statistics generated. Continuous variables that are normally distributed will be expressed as means (±SD) and will be compared using Student's t-test. Variables that are not normally distributed will be expressed as a median (interquartile range) and will be compared with Wilcoxon rank-sum and signed-rank tests. Time to first ECG recurrence will be assessed using Kaplan-Meier analysis and a comparison made between groups using the log-rank test.

11. Sponsor

The study is sponsored by the Liverpool Heart and Chest Hospital NHS Foundation Trust.

12. Funding

The study is funded by an educational grant from Biosense Webster, Inc (BWI-IIS-0239).

13. Trial registration

13.1 The study will be prospectively registered on the ClinicalTrials.gov database before recruiting commences

13.2An application will also be submitted for the study to be included in the NIHR Clinical Research Network (CRN) Portfolio.