1 **ECG-I Phenotyping of Persistent AF Based on Driver Burden and Distribution**

2 **to Predict Response to Pulmonary Vein Isolation (PHENOTYPE-AF).**

3 Word Count 5997

4 Short title: Phenotype AF

5 Dhillon GS MRCP BSc, Honarbakhsh S MRCP BSc, Graham A MRCP BSc, Abbass H MSc, Welch

6 S PhD, Daw H MSc, Sporton S MD FRCP, Providencia R PhD, Chow A FRCP MD, Earley MJ MD

7 FRCP, Lowe M MD FRCP, Lambiase PD PhD FHRS, Schilling RJ MD FRCP, Hunter RJ PhD FESC

8 FEHRA.

9

10 Barts Heart Centre, St Bartholomew's Hospital, Barts Health NHS Trust, London, United

11 Kingdom.

12

13 Corresponding Author:

14 Professor Ross J Hunter FESC PhD

15 Director of Electrophysiology Research

16 Barts Heart Centre

17 Barts Heart NHS Trust

18 EC1A 7BE

19 Email: ross.hunter3@nhs.net

20

23

32 **DATA AVAILABLITY STATEMENT**

33 The data that support the findings of this study are available from the corresponding author

34 upon reasonable request.

35

ABSTRACT

Background:

This prospective trial sought to phenotype persistent AF based on AF mechanisms using ECGI mapping to determine whether this would predict long term freedom from arrhythmia after pulmonary vein isolation (PVI).

Methods:

Patients with persistent AF of < 2 years duration underwent cryoballoon PVI. ECGI mapping was performed prior to PVI to determine potential drivers (PDs) defined as rotational activations completing ≥ 1.5 revolutions or focal activations. The co-primary end point was the association between (1) PD burden (defined as the number of PD occurrences) and (2) PD distribution (defined as the number of segments on an 18 segment model of the atria harbouring PDs) with freedom from arrhythmia at 1 year follow up.

Results:

Of 100 patients, 97 completed follow up and 52 (53.6%) remained in sinus rhythm off antiarrhythmic drugs. Neither PD burden nor PD distribution predicted freedom from arrhythmia (HR 1.01, 95% CI 0.99 – 1.03, p = 0.164; and HR 1.04, 95% CI 0.91 – 1.17, p = 0.591 respectively). Otherwise, the burden of rotational PDs, rotational stability, and the burden of PDs occurring at the pulmonary veins and posterior wall all failed to predict arrhythmia recurrence (all p > 0.10).

58   Conclusions:

59   AF mechanisms as determined using ECGI mapping do not predict outcome after PVI for

60   persistent AF. Further studies using different methodologies to characterise AF mechanisms

61   are warranted. (NCT03394404)

INTRODUCTION

Although pulmonary vein isolation (PVI) is effective for paroxysmal atrial fibrillation (AF), it is only moderately effective for persistent AF. Registry data have reported 12-month freedom from atrial arrhythmia in the region of 50-60 % in persistent AF patients following catheter ablation[1,2]. PVI has been shown to be at least as effective as other ablation strategies that incorporate PVI with additional substrate ablation such as targeting of fractionated electrograms or linear ablation[3,4].

Studies have suggested that time spent in persistent AF, increasing left atrial dimensions, and atrial scarring all impact on success rates after persistent AF, but it remains unclear why some patients with persistent AF respond to PVI and others do not. Recent studies investigating the mechanisms of persistent AF utilising non-invasive mapping and contact electrograms have suggested persistent AF is maintained by localised sources termed drivers[5–7]. These 'drivers' have been described as either focal or rotational activation patterns that can seemingly originate in either atria, the pulmonary veins or vena cava[6,8]. It is possible that the burden and distribution of these drivers might determine the success with a PVI strategy and that it might therefore be possible to phenotype AF in this way that would usefully determine the response to ablation therapy.

The Electrocardiographic Imaging (ECGI) system (CardioInsight, Medtronic, USA) is a non-invasive mapping technology that panoramically analyses both atria to identify focal and rotational activation patterns that are potential drivers (PDs) of persistent AF[8–10]. We recently

85   published a trial utilising the ECGI system to target ablation of potential drivers in persistent

86   AF patients[11]. However, this study utilized the ECGI system to evaluate PD burden and

87   distribution in patients with persistent AF prior to PVI to determine whether these factors

88   predicted response to therapy in a prospective clinical trial. It was hypothesized that patients

89   with a lower burden of PDs that were less widely distributed would be more likely to remain

90   free from atrial arrhythmia at long term follow up.

METHODS

Patient Population

Consecutive patients undergoing first time catheter ablation for persistent AF of less than two years duration were prospectively enrolled as this was perceived by our group to be the most common cohort of patients undergoing catheter ablation for persistent AF and would allow comparison to similar other AF outcome studies[10,12–14]. All participants provided written informed consent. The study was approved by the national ethics committee and was prospectively registered on clinicaltrials.gov (NCT03394404). Exclusion criteria are detailed within Supplementary Methods 1.

Catheter Ablation

Patients underwent cryoablation PVI as detailed within Supplementary Methods 2. A small number of patients underwent additional cavotricuspid isthmus (CTI) ablation where sustained typical atrial flutter had been documented previously or where AF terminated to sustained typical atrial flutter with PVI, but no other structures were targeted with ablation.

Contact Mapping

Cycle lengths (CLs) were recorded from each PV, the left atrial appendage (LAA), right atrial appendage (RAA) and proximal coronary sinus (CS) over 30 consecutive cycles. With the exception of the PVs, CLs were recorded at these sites again following PVI unless the patients were in sinus rhythm.

112

Non-invasive ECGI Mapping

ECGI mapping methods have described previously and is detailed in supplementary methods 3[8].

116

Potential Driver Analysis

PD burden was defined as the total number of PD occurrences. This was assessed in the atria overall, but also divided into those occurring at the PVs and posterior wall, and those occurring elsewhere. To assess the distribution of PDs we utilised an 18 segment biatrial model that has been described previously[8]. The PD distribution was then defined as the number of segments on the 18 segment model harbouring PDs. We discarded rotational wavefronts with an unstable wandering core. Where a PD occupied an area that straddled more than one segment on the 18-segment model, it was counted as a single driver occurrence but ascribed to more than one segment for the purposes of assessing distribution. We evaluated the temporal stability of rotational activation patterns defined as the mean number of rotations per PD occurrence, and the proportion of PDs that were rotational or focal.

129

Follow up and definitions of clinical success

Patients were evaluated clinically at three, six, nine and at twelve months. Clinical evaluation included 12 lead ECG and assessment of patient symptoms. In addition, patients underwent 24-hour ECG holter monitoring at six and twelve months. Clinical success was determined at

134 1 year and was defined as freedom from documented atrial arrhythmia lasting ≥ 30 seconds

135 following a 3 month blanking period after a single procedure off antiarrhythmic drugs as per

136 guidelines[15]. During the blanking period antiarrhythmic drugs were permitted.

137

138 **Study End Points**

139 The co-primary end points were the association between PD burden (defined as the number

140 of PD occurrences) and distribution (defined as the number of segments harbouring PDs on

141 the 18-segment model) on baseline ECGI maps, and clinical success at 12-months. Secondary

142 end points were exploratory and included an assessment of whether other PD features were

143 associated with clinical success at 1 year.

144

145 **Statistical Analysis**

146 Normally-distributed data were expressed as mean ± standard deviation or, if not normally-

147 distributed, as median with interquartile range. Student's t test was performed for normally-

148 distributed variables and Mann-Whitney U test was performed for non-parametric variables.

149

150 The burden and distribution of PDs as defined above were continuous variables. Cox

151 regression analysis was performed on a univariate basis to analyse association between

152 factors including PD burden and distribution and clinical outcomes. As a secondary alternate

153 analysis, receiver operating characteristics (ROC) analysis was used to test the association

154 between PD burden and distribution with clinical success at 1 year. Optimal cut offs were

155 determined manually from ROC curves aiming for balanced sensitivity and specificity. All

156   Statistical analysis were performed using SPSS (IBM SPSS Statistics, Version 25 IBM Corp,

157   Armonk, NY, USA). A P-value of <0.05 was taken to indicate statistical significance.

RESULTS

100 patients were enrolled between January and December 2018. Patient demographics are displayed in Table 1. Mean age was 61.3 ± 12.1 with 74 being male. Median duration of continuous AF was 8 (5 – 15) months. 93 patients were managed on a direct oral anticoagulant. Three patients died during the follow up period for non-procedure or AF related illness and were excluded from the follow up analysis (acute myocardial infarction at 7 months post procedure, complications post elective coronary bypass operation at 7 months, and metastatic pancreatic cancer at 9 months) and therefore 97 patients completed 1 year of follow up. ECGI mapping was unsuccessful in one patient due to inability to reduce the ventricular rate sufficiently and the occurrence of frequent ventricular ectopy with intravenous adenosine. Therefore, 96 patients had 1 year follow up data and baseline ECGI mapping data for inclusion in the ECGI outcome analysis.

Pulmonary Vein Isolation

Procedural data for this cohort has been published previously[8]. In brief, all 4 PVs were successfully isolated in all patients using the cryoballoon. In ten patients an additional cavotricuspid isthmus line was ablated using an irrigated radiofrequency ablation catheter. Procedure time was 57 (48 – 68) minutes. The median number of applications per vein was 1.5 (1.25 – 1.75) including applications that were abandoned. The median total freeze time was 15.7 (13.0 – 20.3) minutes per patient. Median fluoroscopy time was 4.1 (3.0 – 6.0) minutes. Following cryoablation, 85 patients were not in sinus rhythm and required cardioversion.

180   Two major complications occurred: a tamponade detected at the end of the procedure

181   (thought to be due to a difficult transseptal puncture) requiring percutaneous drainage and

182   one phrenic nerve palsy in a patient with a right common PV (occurred at -36°C, 56 seconds)

183   which persisted at the end of the procedure but had recovered by 3 months.

184

185   **Clinical Outcomes**

186   Clinical outcomes of this study are summarised in Figure 2. Of the 97 patients that completed

187   follow up 52/97 (53.6%) remained free from atrial arrhythmia at 12-months and off

188   antiarrhythmic drugs after a single procedure (although none of the 3 subjects who died

189   during follow up had AF documented in the follow up period prior to death, these patients

190   were excluded as they did not reach 1 year of follow up). This measure was used for the below

191   analysis of factors predicting clinical success at one year. Freedom from AF was 62/97 (63.9%)

192   at 1 year and this was used for a secondary analysis of factors predicting recurrent AF in

193   particular.

194

195   45/97 (46.4%) patients had documented recurrence of atrial arrhythmia. Of these 35/45

196   (77.7%) had recurrent AF, 5/45 (11.1%) had atrial tachycardia and 5/45 (11.1%) had typical

197   right atrial flutter.

198

199   **ECGI Baseline Maps**

200   Pre-PVI baseline maps were obtained in 96 of the 97 patients with 1 year follow up data. The

201   mean duration of cumulated intervals per map was 15352.0 (15112.0 – 15599.5) ms

202   comprised of 15 (13 – 16) intervals. An example of a focal and rotational PD are shown in

203   Figures 3.1 and 3.2. The number of patients with PDs at the PV ostia and therefore the number

204   of patients in whom PDs were targeted with ablation was 95.

205

206   **Primary end-point: Prediction of Long-term Outcomes from Baseline Arrhythmia**

207   **Mechanisms**

208   For analysis of the primary end point, Cox regression analysis (Table 2) showed no significant

209   relationship between either the burden of PDs or their distribution and the recurrence of

210   arrhythmia at 1 year. An alternative analysis using ROC analysis also showed no relationship

211   between these parameters and outcome (Supplemental Table 1).

212

213   Examining the association between PD burden and PD distribution and recurrent AF in

214   particular showed no significant association on either Cox regression or ROC analysis

215   (Supplemental Tables 2 & 3 respectively).

216

217   *Burden of PDs and arrhythmia recurrence*

218   The total number of PD occurrences (HR 1.014, 95 % CI 0.994 – 1.034, p = 0.164) did not

219   predict arrhythmia recurrence. Examining the constituents of this, an increasing number of

220   focal activations predicting arrhythmia recurrence failed to reach significance (HR 1.041, 95

221   % CI 0.996 – 1.089, p = 0.076), and there was no impact of the burden of rotational activations

222 (HR 1.004, 95 % CI 0.995 – 1.014, p = 0.368). On a regional analysis, neither the burden of PD

223 occurrences at the PVs and posterior wall (HR 1.038, 95 % CI 0.978 – 1.101, p = 0.216) nor the

224 burden of PD occurrences excluding the PVs and Posterior wall (HR 1.014, 95 % CI, 0.991 –

225 1.037, p = 0.234) were significant predictors of arrhythmia recurrence. Furthermore, the

226 proportion of PD occurrences at the PVs and PW relative to elsewhere did not predict

227 arrhythmia recurrence (HR 0.889, 95 % CI 0.192 – 4.112, p = 0.881).

228

229 *Distribution of PDs and arrhythmia recurrence*

230 The total number of segments harbouring drivers did not predict arrhythmia recurrence (HR

231 1.035, 95 % CI, 0.912 – 1.174, p = 0.591). On a regional analysis, neither the number of

232 segments at the PVs and posterior wall (HR 1.020, 95 % CI 0.777 – 1.340, p = 0.885), nor the

233 number of segments elsewhere excluding the PVs and posterior wall (HR 1.053, 95% CI, 0.893

234 – 1.241, p = 0.538) were significant predictors of arrhythmia recurrence. Furthermore, the

235 proportion of segments harbouring PDs at the PVs and PW relative to elsewhere did not

236 predict arrhythmia recurrence (HR 7.139, 95 % CI 0.115 – 444.259, p = 0.351).

237

238 **Comparison of AF Mechanisms in patients with and without arrhythmia recurrence**

239 Comparison of the burden and distribution of PDs at baseline in those with and without

240 arrhythmia recurrence at 12 months showed no significant differences between groups (Table

241 3). Comparison of patients with AF recurrence in particular to those who remained in sinus

242 rhythm showed no significant differences either (Supplemental Table 4).

243

244   **The response to PVI and long-term outcome**

245   *Termination of AF and outcome*

246   Fifteen patients acutely terminated to sinus rhythm following PVI. There was no significant

247   difference in arrhythmia recurrence between patients that terminated acutely compared to

248   those who did not (p = 0.781), nor was there a significant difference in AF recurrence between

249   patients who acutely terminated following PVI compared to those who did not (p = 0.780).

250

251   *Cycle length slowing and outcome*

252   Baseline CL measurements were performed at the left atrial appendage, the right atrial

253   appendage, the coronary sinus, and the pulmonary veins. Although none of these predicted

254   arrhythmia recurrences at 1 year with Cox regression analysis (Table 2), ROC analysis

255   performed revealed shorter LAA (AUC, 0.632, 95% CI, 0.514 – 0.750, p = 0.031) and mean PV

256   CL (AUC, 0.627, 95% CI, 0.512 – 0.742, p = 0.037) were weakly predictive of AF recurrence at

257   1 year.

258

259   Comparison of CL change following PVI (in those who remained in AF post PVI prior to

260   cardioversion) in patients with and without atrial arrhythmia recurrence at 12 months

261   (Supplemental Table 5) did not reveal a significant difference. Similarly, Cox regression and

262   ROC analysis showed no association between CL slowing following PVI and freedom from

263   either atrial arrhythmia or AF in particular (Table 2 and Supplemental Tables 1-3).

264

265   *Acute impact of PVI on PDs and outcome*

266   Excluding the 15 patients in whom PVI acutely terminated AF, 81 patients had ECGI maps

267   recorded post PVI. Of these 81 patients, atrial arrhythmia recurred in 38 (46.9%). ROC analysis

268   did not reveal a significant relationship between PD burden and distribution post PVI and

269   arrhythmia recurrence or AF recurrence at 1 year (Supplementary Tables 6). Comparing

270   patients with and without arrhythmia recurrence at 1 year there was no difference in the PD

271   burden or the PD distribution recorded post PVI (Supplemental Table 7).

272

273   **Patient factors and arrhythmia recurrence**

274   Of the patient factors analysed, increasing LA dimensions showed an association with

275   recurrence of arrhythmia (Table 2). The duration of persistent AF prior to ablation was not

276   found to be predictive (within the range of patients recruited into the study, since only

277   patients with a duration of AF < 2 years were included).

DISCUSSION

Main Findings

This is the first study to evaluate whether the mechanisms sustaining persistent AF, as determined non-invasively using the ECGI mapping system, predict the outcome after PVI for persistent and long-standing persistent AF of up to 2 years duration. In a prospective trial of 100 patients, neither of the co-primary end points of PD burden or PD distribution impacted on freedom from atrial arrhythmia or freedom from AF at 1 year. No other factor assessed including the proportion of PDs that were focal or rotational, the stability of rotational PDs, or their concentration at the PVs significantly affected outcome. The burden of rotational PDs did not affect outcome, but a weak influence of the burden of focal PDs on outcome cannot be excluded. Similarly, no features on mapping post PVI predicted outcomes at 1 year, nor did the acute impact of PVI on PD characteristics.

1. Outcomes of Pulmonary Vein Isolation for persistent AF

This study reports on the largest cohort of patients with persistent and longstanding persistent AF undergoing catheter ablation with the cryoballoon with formal clinical trial follow up with systematic monitoring of asymptomatic patients. Freedom from atrial arrhythmia off antiarrhythmic drugs was achieved in 53.6 % of patients at 12 months follow up, with freedom from AF achieved in 63.9%. This is in keeping with large registry data of clinical outcomes[1,2]. Recent registry data has suggested similar outcomes for patients with mostly early persistent AF when using the cryoballoon to achieve pulmonary vein isolation[16,17].

300 There are several factors which have been shown to predict recurrence of arrhythmia

301 following catheter ablation for persistent AF, most noticeably female gender, time in

302 persistent AF, left atrial dimensions and obesity[16–18]. Scoring systems have been devised

303 combining these factors and others in attempts to predict outcomes for AF ablation[19–21], but

304 there remains scope for improvement in patient selection and possibly for strategy selection

305 in terms of PVI alone or with additional ablation. MRI data has attempted to evaluate the left

306 atrial substrate for evidence of disease progression beyond left atrial dimensions in terms of

307 scarring[22]. However, the predictive value of these techniques remains limited and it is often

308 unclear why some patients respond to ablation whereas others do not. This study aimed to

309 phenotype patients on a mechanistic level, to examine the burden, distribution and other

310 properties of drivers in persistent AF with the aim of determining a mechanistic phenotype

311 likely to respond to PVI.

312

313 **2. Mechanisms of AF**

314 Studies utilising contact mapping systems such as basket catheters or other multipolar

315 mapping catheters suggest that AF is driven by localised sources, which are spatially stable

316 but with temporal periodicity. Such drivers display focal and rotational activation patterns

317 with significant variation in the burden and distribution of these drivers[6,12,23]. This is in keeping

318 with the picture painted of the mechanisms sustaining persistent AF observed in other studies

319 using the ECGI system such as the multicentre AFACART study,[8,10,24] and is compatible with

320 the observations regarding AF mechanisms in this study.

321

322   Although PVI appears to be a fairly effective treatment for persistent AF, it is unclear why this

323   is the case. It is unclear whether PVI simply removes PV triggers, whether it eliminates antral

324   drivers, or whether it eliminates sites of ganglionated plexi innervation. Given the anatomical

325   variation and patient specific locations of drivers, the differing burdens between patients, the

326   difference in how distributed drivers are throughout the atria or how concentrated they are

327   at the PV ostia, and the differences in the mix of focal versus rotational drivers, it is unclear

328   which factors might be relevant to the outcome of PVI for persistent AF.

329

330   **3. Mechanisms of AF predicting outcome after ablation**

331   PVI in AF impacts significantly on the burden of fractionated electrograms and dominant

332   frequency in the atria[25,26]. We have previously published on the acute impact of PVI in this

333   cohort, using the ECGI mapping system to study AF mechanisms before and after PVI[8]. In fact,

334   although PVI reduced the total burden of PDs through its effect at the PVs and posterior wall,

335   it had no acute impact upon the total number of PD occurrences outside of these areas, the

336   overall distribution of PDs outside of this area, the proportion of PDs that were focal versus

337   rotational, or any other factor studied. This is compatible with previous work using different

338   contact mapping modalities, suggesting that drivers outside the pulmonary veins seem

339   relatively unaffected by PVI[6,7,12]. However fewer focal PDs were found to be predictive of acute

340   termination of AF with PVI[8]. Other work using contact mapping has observed AF termination

341   exclusively with targeting of focal drivers[27]. Furthermore, in patients undergoing targeting of

342   focal and rotational activations based on contact mapping, ablation at sites of focal

343   activations may better predict AF termination[28].

344

345 This study found that persistent AF mechanisms as determined using the ECGI mapping

346 system did not determine clinical outcome at 1 year following a PVI procedure. Ablation

347 procedures involved only PVI since this was believed to be current practice. No other ablation

348 was allowed and PDs were deliberately not targeted since this might have obscured the result.

349 Neither the burden of PDs (in terms of the number of PD occurrences) nor distribution of PDs

350 (in terms of how many segments on an 18 segment model of the atria harboured PDs) had

351 any impact on subsequent freedom from arrhythmia, or freedom from AF in particular. On

352 further analysis, neither the proportion of drivers found at the PVs and posterior wall, the

353 proportion of drivers that were focal verses rotational, nor the temporal stability of rotational

354 PDs were significant predictors of outcome. There was a trend in favour of more focal drivers

355 predicting recurrent arrhythmia (p = 0.076) which may have reached significance in a larger

356 study, but given that 96 patients were included in this analysis it is unlikely that this would

357 emerge as a strong predictor of arrhythmia recurrence that would go on to be clinically useful

358 for patient selection if it did not reach significance in this cohort. Notably, PD characteristics

359 post PVI did not predict 1 year outcome either.

360

361 It might have been expected that patients with a high proportion of PDs at the PVs and

362 posterior would benefit from PVI. However, this was not evident in this cohort. The examples

363 shown in Figure 4 illustrate that patients with a lower burden of drivers concentrated at this

364 location did not necessarily benefit from PVI. This could be taken as evidence that targeting

365 of driver regions may not impact outcomes.

366

367   Of the other factors studied only left atrial dimensions predicted outcome at 1 year. Time in

368   persistent AF did not reach significance in this cohort, but then there was a fairly narrow range

369   of persistent AF duration which is always difficult to estimate accurately, and the time with

370   progressive paroxysmal AF prior to AF becoming persistent is difficult to account for. Similarly,

371   factors such as baseline AF cycle length, cycle length slowing post PVI, or acute termination

372   of AF with PVI were not significant predictors of freedom from atrial arrhythmia or AF at 1

373   year. Novel mapping strategies are needed to examine AF mechanisms, both to determine

374   who is likely to benefit from PVI, who might benefit from some sort of additional ablation,

375   and who does not stand to benefit from ablation at all.

376

377   **Validation of ECGI**

378   ECGI has been used in several studies to record PD data and has been validated in terms of

379   mapping focal and re-entrant tachycardias[29]. To date there have been limited studies

380   published using ECGI in AF. The AFACART study was a multicentre study in which patients

381   underwent ablation guided by ECGI. Acute termination was high with 64% of patients acutely

382   terminating and 76.8% were free from AF at 12 months, but 49% of these experienced at least

383   one episode of AT[10]. Haissaguerre et al, reported 75% acute AF termination following ECGI

384   guided driver ablation[24]. We reported similar results in the recent TARGET AF trial[11]. Further

385   validation of the ECGI system in terms of its ability to map AF drivers is desirable, although

386   this remains difficult as there is no accepted gold standard method to map AF drivers for the

387   purposes of validation – indeed there is not yet a firm consensus on the mechanisms

388   maintaining AF. Clarification of which PDs reported by the system are mechanistically

389   important and refinement of this detection process may improve PD characterisation.

390   Ultimately this study has shown that AF mechanisms as determined by the ECGI system did

391   not predict clinical outcome with PVI, but this may reflects limitations of the technology, and

392   further studies using different approaches to studying AF mechanisms remain desirable.

393

394   **Limitations**

395   This study has relied on the ECGI mapping system for mapping of PDs. Although there are

396   several published studies using this technology it is accepted that not all PDs visualised using

397   the system are necessarily real or mechanistically relevant. Further validation of the ECGI

398   system is required. It is recognised that ECGI assessment of AF mechanisms is only one 'view'

399   of this disease process, and the lack of any demonstrable relationship between AF

400   mechanisms and clinical outcome with PVI may be clouded by limitations of the technology.

401   Further investigations using different technologies remains desirable.

402

403   **Conclusion**

404   AF mechanisms as determined by the ECGI mapping system did not predict clinical outcome

405   at 1 year with PVI. AF cycle length at baseline, cycle length slowing with PVI, and AF

406   termination with PVI also showed no association with clinical outcome. This arguably suggests

407   that the efficacy of PVI in persistent AF relates more to removal of initiating PV ectopy or

408   autonomic modification than to any impact on the mechanisms sustaining persistent AF once

409   initiated. Further assessment of AF mechanisms in relation to treatment modalities and

410   clinical outcomes using different technologies for different 'views' of AF mechanisms remains

411   desirable.

412

REFERENCES:

1.   Cappato R, Calkins H, Chen S-AA, et al.: Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circ Arrhythm Electrophysiol 2010; 3:32–38.

2.   Clarnette JA, Brooks AG, Mahajan R, et al.: Outcomes of persistent and long-standing persistent atrial fibrillation ablation: a systematic review and meta-analysis. Europace 2018; 20:f366–f376.

3.   Verma A, Jiang C, Betts TR, et al.: Approaches to Catheter Ablation for Persistent Atrial Fibrillation. New England Journal of Medicine 2015; 372:1812–1822.

4.   Vogler J, Willems S, Sultan A, et al.: Pulmonary Vein Isolation Versus Defragmentation the CHASE-AF Clinical Trial. J Am Coll Cardiol Elsevier, 2015; 66:2743–2752.

5.   Lim HS, Zellerhoff S, Derval N, et al.: Noninvasive Mapping to Guide Atrial Fibrillation Ablation. Cardiac Electrophysiology Clinics Elsevier Inc, 2015; 7:89–98.

6.   Honarbakhsh S, Hunter RJ, Ullah W, Keating E, Finlay M, Schilling RJ: Ablation in Persistent Atrial Fibrillation Using Stochastic Trajectory Analysis of Ranked Signals (STAR) Mapping Method. JACC: Clinical Electrophysiology 2019; 5:817–829.

7.   Honarbakhsh S, Schilling RJ, Dhillon G, et al.: A Novel Mapping System for Panoramic Mapping of the Left Atrium: Application to Detect and Characterize Localized Sources Maintaining Atrial Fibrillation. JACC: Clinical Electrophysiology 2018; 4:124–134.

8.   Dhillon GS, Schilling RJ, Honarbakhsh S, et al.: Impact of pulmonary vein isolation on mechanisms sustaining persistent atrial fibrillation: Predicting the acute response. J Cardiovasc Electrophysiol 2020; .

9.   Lim HS, Hocini M, Dubois R, et al.: Complexity and Distribution of Drivers in Relation to Duration of Persistent Atrial Fibrillation. J Am Coll Cardiol 2017; 69:1257–1269.

10. Knecht S, Sohal M, Deisenhofer I, et al.: Multicentre evaluation of non-invasive biatrial mapping for persistent atrial fibrillation ablation: the AFACART study. EP Europace [Internet] 2017; :1302–1309. Available from: https://academic.oup.com/europace/article/2996769/Multicentre

11. Honarbakhsh S, Dhillon G, Abbas H, et al.: Non-invasive Electrocardiographic Imaging guided targeting of drivers of persistent atrial fibrillation: the TARGET-AF1 trial. Heart Rhythm 2022; .

12. Honarbakhsh S, Schilling RJ, Finlay M, Keating E, Hunter RJ: Prospective STAR Guided Ablation in Persistent AF using Sequential Mapping with Multipolar Catheters. Circulation: Arrhythmia and Electrophysiology 2020; .

13. Verma A, Jiang C, Betts TR, et al.: Approaches to Catheter Ablation for Persistent Atrial Fibrillation. New England Journal of Medicine [Internet] 2015; 372:1812–1822. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1408288

14. Honarbakhsh S, Hunter RJ, Dhillon G, et al.: Validation of a novel mapping system and utility for mapping complex atrial tachycardias. Journal of Cardiovascular Electrophysiology [Internet] 2018; 29:395–403. Available from: http://doi.wiley.com/10.1111/jce.13437

452 15. Calkins H, Hindricks G, Cappato R, et al.: 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert
453   consensus statement on catheter and surgical ablation of atrial fibrillation: Executive
454   summary. Europace Elsevier Inc., 2018; 20:157–208.

455 16. Sawhney V, Schilling RJ, Providencia R, et al.: Cryoablation for persistent and longstanding
456   persistent atrial fibrillation: Results from a multicentre European registry. Europace 2020; .

457 17. Tondo C, Iacopino S, Pieragnoli P, et al.: Pulmonary vein isolation cryoablation for patients
458   with persistent and long-standing persistent atrial fibrillation: Clinical outcomes from the
459   real-world multicenter observational project. Heart Rhythm 2018; .

460 18. du Fay de Lavallaz J, Badertscher P, Kobori A, et al.: Sex-specific efficacy and safety of
461   cryoballoon versus radiofrequency ablation for atrial fibrillation: An individual patient data
462   meta-analysis. Heart Rhythm 2020; .

463 19. Akkaya E, Berkowitsch A, Greiss H, et al.: PLAAF score as a novel predictor of long-term
464   outcome after second-generation cryoballoon pulmonary vein isolation. Europace 2018; .

465 20. Kornej J, Hindricks G, Shoemaker MB, et al.: The APPLE score: a novel and simple score for
466   the prediction of rhythm outcomes after catheter ablation of atrial fibrillation. Clinical
467   Research in Cardiology 2015; .

468 21. Winkle RA, Jarman JWE, Mead RH, et al.: Predicting atrial fibrillation ablation outcome: The
469   CAAP-AF score. Heart Rhythm 2016; .

470 22. Marrouche NF, Wilber D, Hindricks G, et al.: Association of atrial tissue fibrosis identified by
471   delayed enhancement MRI and atrial fibrillation catheter ablation: The DECAAF study. JAMA -
472   Journal of the American Medical Association 2014; .

473 23. Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel W-J, Miller JM: Treatment of
474   Atrial Fibrillation by the Ablation of Localized Sources. J Am Coll Cardiol 2012; 60:628–636.

475 24. Haissaguerre M, Hocini M, Denis A, et al.: Driver Domains in Persistent Atrial Fibrillation.
476   Circulation 2014; 130:530–538.

477 25. Hunter RJ, Diab I, Tayebjee M, et al.: Characterization of fractionated atrial electrograms
478   critical for maintenance of atrial fibrillation a randomized, controlled trial of ablation
479   strategies (the CFAE AF trial). Circulation: Arrhythmia and Electrophysiology 2011; 4:622–629.

480 26. Roux JF, Gojraty S, Bala R, et al.: Effect of pulmonary vein isolation on the distribution of
481   complex fractionated electrograms in humans. Heart Rhythm 2009; 6:156–160.

482 27. Honarbakhsh S, Schilling RJ, Providencia R, et al.: Automated detection of repetitive focal
483   activations in persistent atrial fibrillation: Validation of a novel detection algorithm and
484   application through panoramic and sequential mapping. Journal of Cardiovascular
485   Electrophysiology 2018; .

486 28. Article O, Verma A, Sarkozy A, et al.: Characterization and significance of localized sources
487   identified by a novel automated algorithm during mapping of human persistent atrial
488   fibrillation. Journal of Cardiovascular Electrophysiology 2018; 29:1480–1488.

489 29. Shah A, Hocini M, Haissaguerre M, Jaïs P: Non-invasive Mapping of Cardiac Arrhythmias.
490   Current Cardiology Reports 2015; 17.

491

492

FIGURES

Figure 1. Image of the portable ECGI workstation.

The ECGI workstation comprises of two components. A computer running the ECGI software and secondly an amplifier that connects to the ECGI Vest Array.

Figure 2. Phenotype AF Procedural Outcomes Flow Chart.

The diagram summarises the PHENOTYPE AF procedural outcomes. AF – Atrial Fibrillation, AT – Atrial Tachycardia, RAF – Typical Right Atrial Flutter. [+]3 patients died, all between 6 and 12 months follow up: acute myocardial infarction, post elective coronary bypass operation and metastatic pancreatic cancer.

Figure 3.1. Focal Potential Driver originating from Left Inferior Pulmonary Vein as shown on the ECGI Workstation

Left: Posterior-Anterior (PA) view of a bi-atrial activation map of the focal potential driver breaking out from the left pulmonary vein. Right: Same focal potential driver shown on an ECGI Composite atrial map.

Figure 3.2: Superior view of a Rotational Potential Driver Originating from the Left Superior Pulmonary Vein as shown on the ECGI Workstation

513   A: Sequential views of a rotational driver rotating superior to the Left Superior Pulmonary

514   Vein.

515   B: ECGI composite map showing the same rotational potential driver with the number of

516   rotations shown on map (1.8 in this example). The green line highlights the wondering core

517   of the rota.

518   C: Activation map with 6 coloured points selected by the ECGI workstation with the

519   corresponding computed electrograms shown to the right. During processing the

520   electrograms are checked for each potential driver to ensure that it the potential driver is

521   plausible.

522

523   **Figure 4.0. ECGI composite maps from patient 22 in whom AF recurred compared to**

524   **patient 32 who remained in sinus rhythm post PVI.**

525   Posterior-Anterior and Left Anterior Oblique views of patient 32 and patient 22. Patient 32

526   ECGI maps revealed a high burden of PDs which were widely distributed but remained in

527   sinus rhythm at 1 year post PVI, compared to patient 22 who had a low burden of PDs

528   primarily at the PVs and posterior wall yet had recurrent AF post PVI.

529

530

531 **Table 1. Demographics of enrolled participants**

532

Baseline Characteristics	
Number of Patients	100
Age (years) Mean ± SD	61.3 ± 12.1
Male n (%)	74 (74.0)
Hypertension n (%)	47 (47.0)
Diabetes Mellitus n (%)	14 (14.0)
Ischaemic Heart Disease n (%)	10 (10.0)
Cerebrovascular Accident n (%)	9 (9.0)
CHA2DS2VASC Score mean ± SD	1 (0 – 3)
LA Diameter (mm)	39 (33 – 43)
LA Volume (ml)	62 (49 – 83)
Median duration of AF: diagnosis to procedure (months)	24 (16 – 48)
Duration of Persistent AF (months)	8 (5 -15)
Persistent AF (< twelve months)	67 (67.0)
Longstanding AF (> twelve months)	33 (33.0)
Number of Anti-arrhythmic Drugs failed	1 (1 - 1)
Anticoagulation with direct oral anticoagulant n (%)	93 (93.0)

533

534 Values are given as no. (%), mean ± standard deviation or median (Interquartile Range).

535

Table 2. Cox Regression analysis of factors in predicting atrial arrhythmia recurrence at 12 Months

Factor	Hazard Ratio	95% Confidence Interval	P Value
Burden of PDs			
Total PD Occurrences	1.014	0.994 – 1.034	0.164
Total Number of Foci	1.041	0.996 – 1.089	0.076
Total Rotations	1.004	0.995 – 1.014	0.368
No of PD Occurrences at PV and PW	1.038	0.978 – 1.101	0.216
No of PD occurrences exc. PVs and PW	1.014	0.991 – 1.037	0.234
Proportion of PDs at PVs and PW (%)	0.889	0.192 – 4.112	0.881
Rotational Stability	1.400	0.742 – 2.640	0.299
Distribution of PDs			
Total Segments with PDs	1.035	0.912 – 1.174	0.591
No of Segments with PDs at PVs and PW	1.020	0.777 – 1.340	0.885
No of Segments excluding the PVs and PW	1.053	0.893 – 1.241	0.538
Proportion of Segments with PDs at PVs and PW (%)	7.139	0.115 – 444.259	0.351
Demographic Factors			
LA Diameter (mm)	1.035	1.000 – 1.070	0.048
LA Area (cm2)	1.037	0.984 – 1.094	0.179
LA Volume (ml)	1.009	0.999 – 1.020	0.089
Time from diagnosis AF to PVI (Months)	1.002	0.996 – 1008	0.462
Duration of continuous Persistent AF (Months)	1.002	0.959 – 1.047	0.941
Cycle Length Measurements			
LAA CL	0.996	0.986 – 1.005	0.357
RAA CL	0.995	0.987 – 1.003	0.207
Prox CS CL	0.997	0.989 – 1.004	0.373
Average of LAA, RAA and Prox CS	0.994	0.985 – 1.004	0.225
Average of PVs	0.994	0.982 – 1.005	0.263
Ratio CL of PVs to LAA	1.245	0.119 – 12.999	0.855
LAA Difference post PVI	1.006	0.991 - 1.021	0.439
LAA percent change	0.996	0.976 – 1.017	0.733
RAA Difference post PVI	1.000	0.997 – 1.004	0.853
RAA percent change	1.000	0.992 – 1.007	0.936
Average of LAA, RAA and Prox CS difference Pre and Post	1.001	0.995 – 1.007	0.800
Average Percent change of LAA, RAA and Prox CS difference Pre and Post	1.000	0.987 – 1.013	0.992

536
537
538
539
540

541   **Table 3. Comparison of baseline ECGI maps in patients with and without arrhythmia**

542   **recurrence at 12 Months.**

Factor	No Arrythmia Recurrence	Arrhythmia Recurrence	P Value
No of PDs at PVPW	8.38 ± 4.78	9.39 ± 4.64	0.302
No of PDs elsewhere	30.90 ± 11.47	34.11 ± 14.00	0.220
Total Number of PDs	39.29 ± 13.57	43.50 ±16.58	0.174
Rotational Stability	2.31 ± 0.46	2.40 ± 0.41	0.324
Proportion of PDs at PVs and PW	0.26 ± 0.28	0.25 ± 0.17	0.850
Total Number of Segments with PDs	12.42 ± 2.25	12.80 ± 2.78	0.471
No of Segments with PDs at the PVs and Posterior Wall	3.52 ± 1.08	3.55 ± 1.21	0.911
No of Segments with PDs excluding the PVs and Posterior Wall	8.90 ± 1.66	9.25 ± 2.18	0.380

543

544   Values are given as no. (%), mean ± standard deviation. P value of > 0.05 taken to be
545   significant.

546

547 **Figure 1. Image of the portable ECGI workstation.**

548

549 The ECGI workstation comprises of two components. A computer running the ECGI software

550 and secondly an amplifier that connects to the ECGI Vest Array.
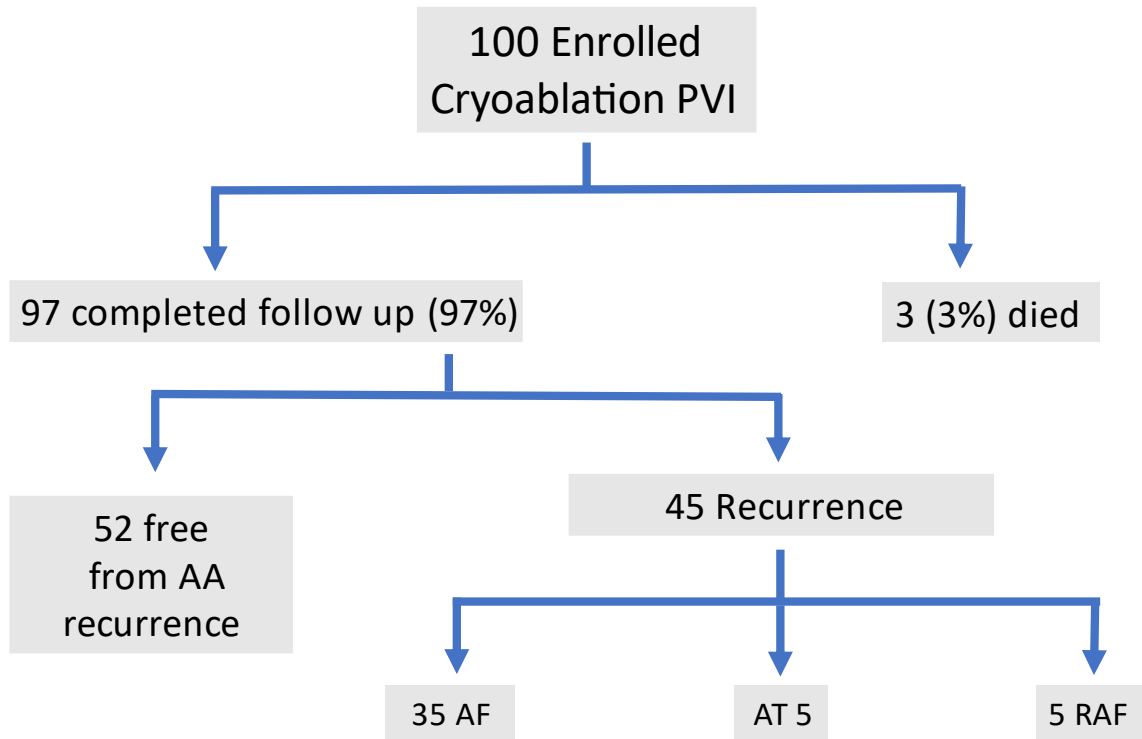
551

552

553

554 **Figure 2. Phenotype AF Procedural Outcomes Flow Chart.**

555

556

557 The diagram summarises the PHENOTYPE AF procedural outcomes. AF – Atrial Fibrillation,

558 AT – Atrial Tachycardia, RAF – Typical Right Atrial Flutter. [+]3 patients died, all between 6 and

559 12 months follow up: acute myocardial infarction, post elective coronary bypass operation
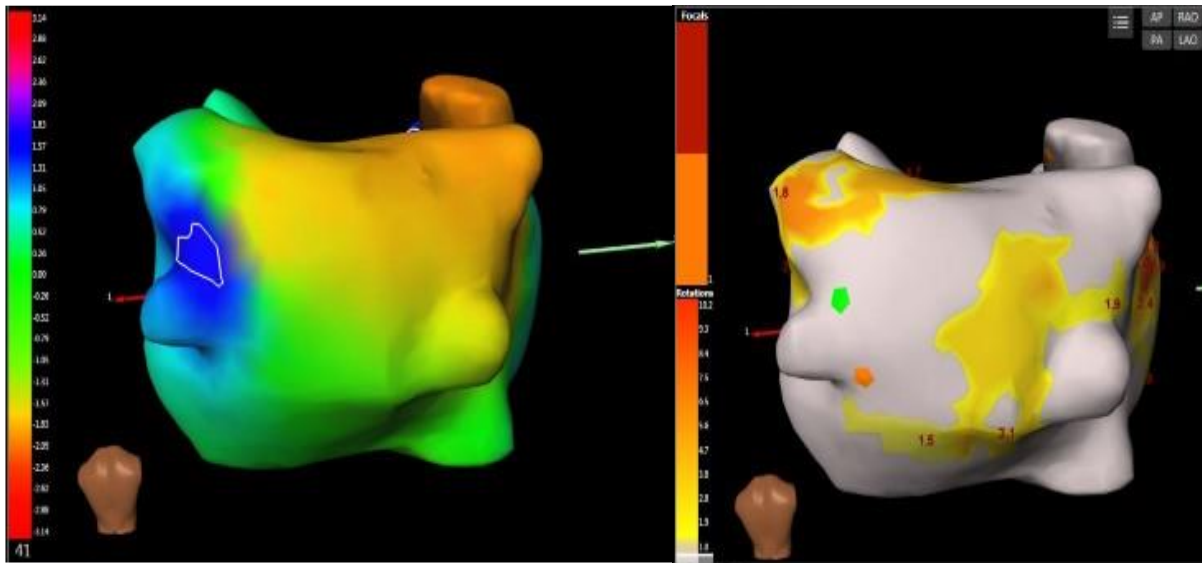
560 and metastatic pancreatic cancer.

561

562

563

564

565 **Figure 3.1. Focal Potential Driver originating from Left Inferior Pulmonary Vein as shown**

566 **on the ECGI Workstation**

567

568 Left: Posterior-Anterior (PA) view of a bi-atrial activation map of the focal potential driver

569 breaking out from the left pulmonary vein. Right: Same focal potential driver shown on an
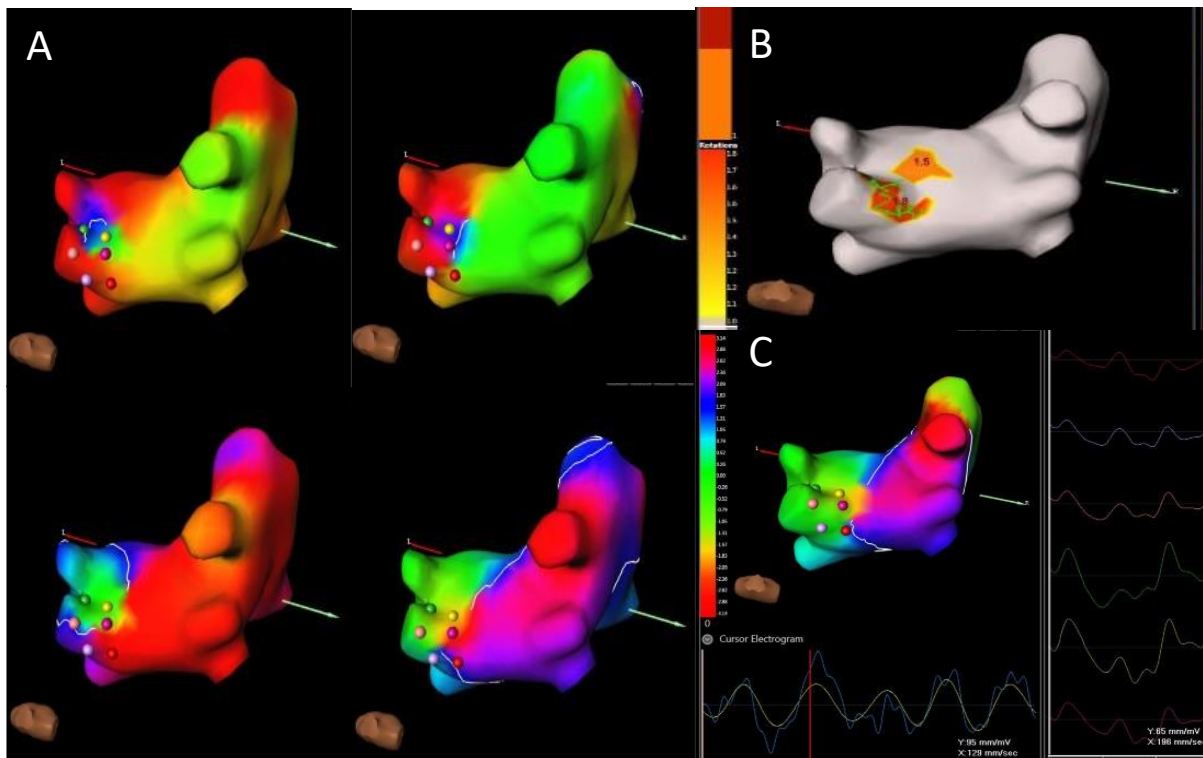
570 ECGI Composite atrial map.

571

572

573

574

575

576 **Figure 3.2: Superior view of a Rotational Potential Driver Originating from the Left**

577 **Superior Pulmonary Vein as shown on the ECGI Workstation**

578

579 A: Sequential views of a rotational driver rotating superior to the Left Superior Pulmonary

580 Vein.

581 B: ECGI composite map showing the same rotational potential driver with the number of

582 rotations shown on map (1.8 in this example). The green line highlights the wondering core

583 of the rota.

584 C: Activation map with 6 coloured points selected by the ECGI workstation with the

585 corresponding computed electrograms shown to the right. During processing the

586 electrograms are checked for each potential driver to ensure that it the potential driver is

587 plausible.

588 **Figure 4.0. ECGI composite maps from patient 22 in whom AF recurred compared to**

589 **patient 32 who remained in sinus rhythm post PVI.**
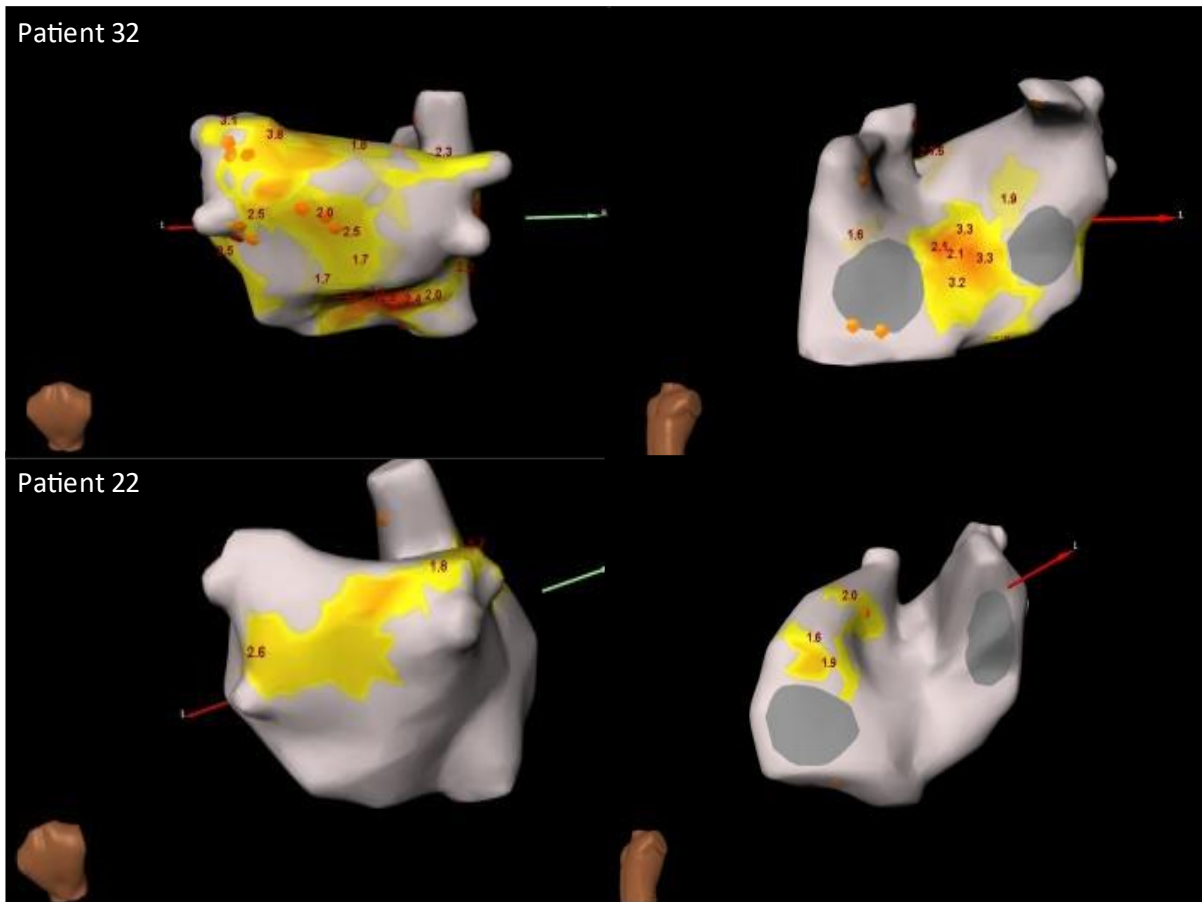
590

591

592 Posterior-Anterior and Left Anterior Oblique views of patient 32 and patient 22. Patient 32

593 ECGI maps revealed a high burden of PDs which were widely distributed but remained in

594 sinus rhythm at 1 year post PVI, compared to patient 22 who had a low burden of PDs

595 primarily at the PVs and posterior wall yet had recurrent AF post PVI.