

THE UNIVERSITY of EDINBURGH

# Edinburgh Research Explorer

## Atrial CARdiac Magnetic resonance imaging in patients with embolic stroke of unknown source without documented Atrial Fibrillation (CARM-AF): Study design and clinical protocol

### Citation for published version:

Kotadia, ID, O'dowling, R, Aboagye, A, Sim, I, O'hare, D, Lemus-solis, J, Roney, CH, Dweck, M, Chiribiri, A, Plein, S, Sztriha, L, Scott, P, Harrison, J, Ramsay, D, Birns, J, Somerville, P, Bhalla, A, Niederer, S, O'neill, M & Williams, SE 2022, 'Atrial CARdiac Magnetic resonance imaging in patients with embolic stroke of unknown source without documented Atrial Fibrillation (CARM-AF): Study design and clinical protocol', Heart Rhythm O2. https://doi.org/10.1016/j.hroo.2022.01.005

#### **Digital Object Identifier (DOI):**

10.1016/j.hroo.2022.01.005

#### Link:

Link to publication record in Edinburgh Research Explorer

#### **Document Version:**

Version created as part of publication process; publisher's layout; not normally made publicly available

**Published In:** Heart Rhythm O2

#### **General rights**

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

#### Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.



#### Atrial CARdiac Magnetic resonance imaging in patients with embolic stroke of unknown source without documented Atrial Fibrillation (CARM-AF): Study design and clinical protocol Irum D. Kotadia, MBBS, BSc, \*† Robert O'Dowling, MB, BCh, BAO, † 11 Q10 Akosua Aboaqye, BSc, PqDip, MSc,<sup>†</sup> Iain Sim, MBBS, BSc,\* Daniel O'Hare, BMBS, BEng, \* José-Alonso Lemus-Solis, PhD, \* Caroline H. Roney, PhD, \* Marc Dweck, MD, PhD,<sup>‡</sup> Amedeo Chiribiri, MBBS, PhD,<sup>\*</sup> Sven Plein, MD, PhD,<sup>\*</sup> Laszlo Sztriha, MD, PhD,<sup>§</sup> Paul Scott, MBChB, DM, BMedSci,<sup>§</sup> James Harrison, MA, PhD,<sup>||</sup> Deborah Ramsay, MRCP,<sup>||</sup> Jonathan Birns, BSc, MBBS, PhD,<sup>†</sup> Peter Somerville, MBBS, MA,<sup>†</sup> Ajay Bhalla, MBBS, MD,<sup>†</sup> Steven Niederer, PhD,<sup>\*</sup> Mark O'Neill, MBBCh, DPhil, \*<sup>†</sup> Steven E. Williams, BSc, MBChB, PhD\*<sup>‡</sup> **Q2** From the \*King's College London, London, United Kingdom, <sup>†</sup>Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom, <sup>‡</sup>Centre for Cardiovascular Science, The University of Edinburgh, Edinburgh, United Kingdom, <sup>8</sup>King's College Hospital, London, United Kingdom, and <sup>¶</sup>Princess Royal **Q3** University Hospital. **RESULTS** Baseline data collection, noninvasive electrocardio-**BACKGROUND** Initiation of anticoagulation therapy in ischemic stroke patients is contingent on a clinical diagnosis of atrial fibrilgraphic data analysis, and imaging postprocessing will be perlation (AF). Results from previous studies suggest thromboembolic formed at the time of enrollment. Primary analysis will be risk may predate clinical manifestations of AF. Early identification of performed following 12 months of continuous ILR monitoring, this cohort of patients may allow early initiation of anticoagulation with interim and delayed analyses performed at 6 months and 2 and reduce the risk of secondary stroke. and 3 years, respectively. **OBJECTIVE** This study aims to produce a substrate-based predic-CONCLUSION The CARM-AF Study will use atrial structural and tive model using cardiac magnetic resonance imaging (CMR) and electrocardiographic metrics to identify patients with AF, or at baseline noninvasive electrocardiographic investigations to high risk of developing AF, who may benefit from early initiation improve the identification of patients at risk of future thromboemof anticoaqulation. bolism. METHODS CARM-AF is a prospective, multicenter, observational KEYWORDS Ischemic stroke; Embolic stroke of unknown source; cohort study. Ninety-two patients will be recruited following an Atrial fibrillation; Atrial cardiomyopathy; Cardiac magnetic resoembolic stroke of unknown source (ESUS) and undergo an atrial nance imaging; Electrocardiogram CMR followed by insertion of an implantable loop recorder (ILR) as per routine clinical care within 3 months of index stroke. Remote (Heart Rhythm 0<sup>2</sup> 2022; ■:1–8) © 2022 Heart Rhythm Society. Pub-ILR follow-up will be used to allocate patients to a study or control group determined by the presence or absence of AF as defined by ILR lished by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/). monitoring. Introduction Atrial fibrillation (AF) is a major risk factor for ischemic

stroke resulting in significant morbidity and mortality, but may not be identified by routine clinical monitoring during poststroke care.<sup>1</sup> It is estimated that 25% of embolic strokes

3

9

of unknown source (ESUS) can be attributed to undiagnosed AF, with the risk of stroke recurrence in this cohort being high following the primary stroke event.<sup>2,3</sup> Secondary stroke risk reduction in AF patients can be achieved by timely initiation of anticoagulation therapy.

Address reprint requests and correspondence: Dr I. D. Kotadia, Division of Imaging Sciences and Biomedical Engineering, King's College London, 4th Floor North Wing, St. Thomas' Hospital, 249 Westminster Bridge Rd, London, SE1 7EH United Kingdom. E-mail address: irum.kotadia@kcl.ac.uk.

2666-5018/© 2022 Heart Rhythm Society. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

https://doi.org/10.1016/j.hroo.2022.01.005

FLA 5.6.0 DTD ■ HROO199\_proof ■ 4 February 2022 ■ 7:23 pm ■ ce

### Heart Rhythm 0<sup>2</sup>, Vol ■, No ■, ■ 2022

172

173

174

175

176

177

178

179

180

181

182

183

184

185

186

187

188

189

190

191

192

193

194

195

196

197

198

199

200

201

202

203

204

205

206

207

208

209

210

211

212

213

214

### **KEY FINDINGS**

- Undiagnosed atrial fibrillation is the underlying cause of a significant proportion of strokes originally classified as embolic stroke of unknown source (ESUS).
- Atrial fibrillation is associated with marked structural abnormalities of the left atrium, including dilatation, spherical remodeling, and atrial late gadolinium enhancement, which may be quantified using atrial cardiac magnetic resonance imaging.
- This study will test the hypothesis that identification of these structural abnormalities using atrial cardiac magnetic resonance imaging can identify the subset of ESUS patients at risk of atrial fibrillation using the gold standard of implantable loop recorder monitoring as the comparator.
- A poststroke model assessing atrial substrate predictive of developing atrial fibrillation may allow for earlier detection of patients at thromboembolic risk and allow earlier initiation of anticoagulation in these patients.

Current guidelines for initiation of anticoagulation mandate electrocardiographic documentation of AF.<sup>4</sup> Two landmark trials (EMBRACE and CRYSTAL-AF) provide evidence that increased AF detection rates are possible with prolonged ambulatory monitoring or following insertion of an implantable loop recorder (ILR).<sup>5,6</sup> However, median AF detection time in real-world studies ranges from 40 days (interquartile range: 14–84 days) to 112 days (interquartile range: 35–293 days).<sup>5,7</sup> With a risk reduction from 12% to 4% per year (hazard ratio 0.34; 95% CI 0.36–0.79) following the use of anticoagulation, delays in initiation of therapy are likely to have an impact on the incidence of secondary stroke.<sup>8</sup> In addition, a requirement for prolonged monitoring is associated with an increased cost burden and need for further resources to accommodate follow-up.

A further limitation on the requirement of AF documenta-154 tion is the discordance in temporality, biological gradient, 155 and specificity between AF and ischemic stroke previously 156 reported.9-11 Both the ASSERT and IMPACT trials 157 enrolled patients with an implantable cardiac device prior to the index stroke event and demonstrated discordance in temporality, with up to 16% of patients in the ASSERT 160 study being diagnosed with AF after the index stroke event despite prior device insertion.<sup>9-11</sup> These studies suggest that elevated thromboembolic risk may exist prior to clinical detection of AF. Furthermore, while the ROCKET-164 AF Trial suggested an increase in adjusted rates of stroke 165 or systemic embolism in the persistent AF group compared 166 with the paroxysmal AF group (OR: 2.18 vs 1.73), the 167 RE-LY Trial found no statistically significant change in 168 thromboembolic risk between groups, suggesting that 169 increased duration of AF may not be associated with increased stroke risk.<sup>12,13</sup> In addition, previous 170 171

meta-analyses have suggested that restoration of sinus rhythm does not reduce the risk of stroke,<sup>14,15</sup> providing the underlying basis for continuation of anticoagulation for the purposes of stroke risk reduction regardless of treatment strategy following AF diagnosis if risk factors are present. As such, it is conceivable that patients with short paroxysms of AF who remain at high risk for secondary stroke may be undiagnosed by current standards of poststroke investigation of AF, which often include an electrocardiogram (ECG) and 24hour Holter monitor. Combined, these studies suggest that elevated thromboembolic risk may exist prior to clinical detection of AF and represent a further delay in initiation of anticoagulation therapy in a high-risk cohort.

Previous ESUS studies, including NAVIGATE-ESUS and RESPECT-ESUS, have unsuccessfully attempted to identify this cohort for early initiation of anticoagulation.<sup>16,17</sup> Recent models suggest comorbidities associated with elevated stroke risk (eg, hypertension, diabetes, vascular disease) and known to be associated with atrial disease may provide an atrial thromboembolic substrate even prior to the development of clinical arrhythmia.<sup>9,18</sup>

A poststroke model assessing atrial substrate predictive of developing AF may allow for earlier detection of patients at thromboembolic risk, allowing for earlier initiation of anticoagulation.

A novel term, "atrial cardiomyopathy," has been described that refers to atrial remodeling resulting in "clinically relevant structural and electrophysiological changes of the atrium."<sup>19</sup> Atrial fibrosis plays a central role in the AF substrate, having been identified histologically in patients with AF and in patients with risk factors for AF. Atrial geometry also plays an important role in the pathogenesis of AF, with left atrial enlargement being greater in patients with persistent vs paroxysmal AF and atrial sphericity more pronounced in those with recurrent AF.<sup>20</sup> In patients with AF, increasing atrial late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging is associated with increased risk of major adverse cardiovascular and cerebrovascular events, driven primarily by an increased risk of stroke or transient ischemic attack.<sup>21</sup> Although atrial CMR imaging has frequently been used for substrate assessment in patients with known AF, few studies have published data regarding atrial substrate assessment in ESUS patients, highlighting a key knowledge gap.<sup>22</sup> Identifying ESUS patients displaying these structural changes in the absence of AF may arguably identify patients at higher risk of developing AF and who may benefit from early anticoagulation poststroke.

Similarly, electrophysiological changes present on surface ECG have previously been highlighted in the literature as indirect surrogate markers of atrial cardiomyopathy and stroke. Analyses of p waves from the surface ECG show that p-wave terminal force in lead  $V_1$  (PTFV<sub>1</sub>) is independently associated with stroke, as well as structural atrial disease including atrial dilatation and fibrosis.<sup>23,24</sup> Both PTFV<sub>1</sub> and supraventricular ectopy have also previously been shown to be strong predictors of paroxysmal AF in ischemic stroke patients.<sup>25,26</sup>

2

#### Kotadia et al CARM-AF Study Design

Taken together, these observations suggest that left atrial structural and electrical remodeling are associated with stroke and predictive of the presence of paroxysmal AF even in the absence of documented AF at the time of the index stroke.

234 The CARM-AF study therefore seeks to detect atrial re-235 modeling in a subset of patients with prior ischemic stroke and no AF detected during routine assessment. We hypothe-236 237 size that the degree of structural and electrical remodeling 238 present at the time of the first stroke will be predictive of 239 the subsequent occurrence of AF as documented by gold-240 standard long-term ILR monitoring. The results of CARM-AF can inform future randomized controlled trials where 241 242 clinical decisions regarding anticoagulation therapy are 243 made at the time of the index stroke, potentially reducing 244 the risk of secondary stroke. 245

#### Objectives

246

247 **ODJECTIVES**248 The overall research aim is to produce a substrate-based pre249 dictive model using CMR and electrocardiographic parame250 ters that may better identify ESUS patients at risk of
251 developing AF.

The principal research question is to determine if atrial 252 CMR imaging can predict the occurrence of AF in advance 253 of the clinical arrhythmia in patients with confirmed ischemic 254 stroke. The specific hypotheses that will be tested are as fol-255 lows: (1) left atrial LGE in patients with ESUS is greater in 256 patients with AF than those without AF documented by 257 ILR; and (2) left atrial sphericity in patients with ESUS is 258 greater in those patients with AF than those without AF docu-259 mented by ILR. 260

The secondary research question is to determine whether 261 electrocardiographic parameters can predict the occurrence 262 of AF in advance of the clinical arrhythmia in patients with 263 confirmed ischemic stroke. The specific hypotheses that 264 will be tested are as follows: (3)  $PTFV_1$  in patients with 265 ESUS is greater in those patients with AF than those without 266 AF documented by ILR; and (4) supraventricular ectopy in 267 patients with ESUS is greater in those patients with AF 268 than those without AF documented by ILR. 269

As described in Data Analysis, below, further analysis will be performed to combine structural and electrical variables into a single score to improve prediction of AF status, which can be employed in future randomized controlled trials.

#### Design

270

271

272

273

274

275

276 The CARM-AF Study is a multicenter, prospective, observa-277 tional study of patients who have been diagnosed with an 278 embolic stroke of unknown source in the absence of docu-279 mented atrial fibrillation. The study conforms to the princi-280 ples outlined in the Declaration of Helsinki. Ethical 281 approval has been granted by Health Research Authorities 282 and the South London Research Ethics Committee (REC: 283 19/LO/1933). The study is funded by the British Heart Foun-284 dation (PG/19/44/34368). 285

#### 3

286

287

288

289

290

291

292

293

294

295

296

297

298

299

300

301

302

303

304

305

306

307

308

309

310

311

312

A total of 92 patients will be recruited to undergo a CMR scan for investigation of features suggestive of left atrial remodeling. This will be followed by implantation of an ILR as standard of care for detection of AF as per the 2021 NICE guidelines.<sup>27</sup> Remote ILR follow-up will occur at 6 months, 1 year, 2 years, and 3 years as part of this study. Throughout the study period routine follow-up will be conducted by daily telemetric monitoring using the Reveal CareLink system (Medtronic). Patients in whom AF has been detected will be allocated to the study group and patients in whom AF has not been detected will be allocated to the control group (Figure 1). Group allocation will be determined by 2 independent experts.

#### Sample size justification

Previous data suggest that ILR monitoring will identify AF in 25% of ESUS patients with a  $CHA_2DS_2VASc$  score of 3.<sup>2</sup> We anticipate that our study population will have a 3:1 ratio of non-AF and AF patients. This ratio has subsequently been validated in the recent LOOP study.<sup>28</sup>

Pilot data analysis was performed using CEMRGapp, using the image intensity ratio to define atrial fibrosis at image intensity ratio >0.97<sup>29</sup> This analysis suggested a population mean difference of 6% in left atrial LGE burden between AF and non-AF patients, with standard deviations of 9% and 4% in the AF and non-AF group, respectively (Figure 2). For estimating the sample size required to detect a difference in LGE burden between stroke patients with and without AF, we allow for unequal variances and assume that cases (AF on ILR monitoring) represent 25% of the study population while controls (no AF on ILR monitoring) represent 75% of the study population. Group sample sizes of 21 and 63 would achieve 80.8% power to reject the null hypothesis of equal means when the population mean difference is  $\mu 1 - \mu 2 = 47.0 - 41.0 = 6.0$ , with standard deviations of 9.0 for group 1 and 4.0 for group 2, and with a significance level (alpha) of 0.05 using a 2-sided 2sample unequal-variance t test.

For estimating the sample size required to detect a difference in sphericity between stroke patients with and without AF, we again assume cases and controls represent 25% and 75% of the study population, respectively. Group sample sizes of 14 and 42 would achieve 82.5% power to reject the null hypothesis of equal means when the population mean difference is  $\mu 1 - \mu 2 = 80.0 - 77.0 = 3.0$ , with a standard deviation for both groups of 3.3 and with a significance level (alpha) of 0.05 using a 2-sided 2-sample equal-variance t test. Taking the larger of these estimates and allowing for 10% loss to follow-up indicates that a sample size of 92 patients is required for this study. With this sample size, assuming the 3:1 ratio of non-AF to AF individuals we would be able to estimate the area under the curve of a receiver operating characteristic (ROC) curve with 95% confidence interval width (upperlower confidence limit) of between 0.21 and 0.28 for

339

340

341

### **ARTICLE IN PRESS**

Heart Rhythm 0<sup>2</sup>, Vol ■, No ■, ■ 2022



**Figure 1** Trial flowchart. AF = atrial fibrillation; CMR = cardiac magnetic resonance; GSTT = Guy's and St Thomas' Hospital; ILR = implantable loop recorder.

area-under-the-curve values between 0.85 and 0.65, respectively.

#### Eligibility

Potential research participants who meet the eligibility criteria (Table 1) are identified on the stroke unit or in the transient ischemic attack outpatient clinic. All patients undergo a minimum set of diagnostic investigations to assess eligibility, including brain imaging confirming ischemic stroke (computed tomography / magnetic resonance imaging [MRI]), vascular imaging (head and neck), and a minimum of 24 hours of heart rhythm monitoring (telemetry/24-hour Holter). Patients in whom the stroke etiology is determined after study inclusion (for example, if a cause of stroke is identified via CMR imaging) will be excluded from final analysis.

#### Consent

PO PO

396 ම්

If eligible for recruitment, patients are informed about the study, and a Patient Information Sheet and Informed Consent Form is provided. Capacity to consent is assessed by the patient's clinical team and should the patient be unable to provide written informed consent, study information is provided to a consultee (next of kin) and assent is subsequently obtained from the patient with the consultee acting as a patient advocate. Patients are recruited via both methods in order to preserve the heterogeneity of the study population.

#### **Baseline data collection**

On enrollment, patient data collected includes patient demographics, preexisting medical history, CHA<sub>2</sub>DS<sub>2</sub>VASc score, and data from relevant stroke investigations (routine blood panel, carotid Dopplers, computed tomography / MRI brain).

#### Noninvasive electrophysiological data

All patients will undergo a 12-lead surface ECG and 24 hours of heart rhythm monitoring using telemetry or 24-hour Holter prior to insertion of an ILR (LINQ; Medtronic). Electrocar- $Q_5$  diographic metrics to be assessed include mean heart rate, atrial high rate episodes, atrial ectopy burden, PTFV<sub>1</sub>, and PR interval.

#### Cardiac magnetic resonance imaging

CMR imaging is performed within 3 months of the index stroke and prior to ILR implantation. All imaging is performed on a 1.5 Tesla clinical MRI scanner. Localizer scans are acquired in the 3 standard imaging planes (sagittal, coronal, and transverse), followed by vertical long-axis, horizontal long-axis, and short-axis imaging. Cine imaging of the 4-chamber and 2-chamber views are acquired in



**Figure 2** Atrial cardiac magnetic resonance (CMR) pilot data in stroke and control patients. Illustration of atrial CMR findings in stroke (n = 8) and control patients (n = 8). **A:** Raw data and processed data appearances. **B:** Late gadolinium enhancement and sphericity quantification illustrating medians, interquartile ranges, and data ranges. IIR = image intensity ratio; LA = left atrium.

### **ARTICLE IN PRESS**

#### Kotadia et al CARM-AF Study Design

#### Table 1 Inclusion and exclusion criteria

477

Inclusion criteria	Exclusion criteria
<ul> <li>Patient consent or assent can be obtained</li> <li>Confirmed acute ischemic stroke with evidence on brain CT and/or MRI within 3 months of study enrollment</li> <li>Ischemic stroke of unknown source with brain imaging suspicious for embolic etiology</li> <li>Expected survival &gt;12 months</li> <li>At least 1 additional stroke risk factor (ie, CHA<sub>2</sub>DS<sub>2</sub>VASc ≥3)</li> <li>Sinus rhythm on 12-lead ECG, 24 hours of heart rhythm monitoring (telemetry/Holter), and a regular pulse on clinical examination</li> <li>Above 18 years of age</li> </ul>	<ul> <li>Unable to obtain patient consent or assent</li> <li>History of atrial fibrillation</li> <li>Atrial fibrillation detected on ECG and/or telemetry/Holter (AF duration of at least 30 seconds required for diagnosis), eGFR &lt;30 mL/min</li> <li>Indication for pacemaker/implantable cardioverter-defibrillator</li> <li>Contraindication to undergo cardiac MRI (eg, severe claustrophobia, unable to lie flat for prolonged period, ferromagnetic implant)</li> <li>Carotid stenosis &gt;50% on duplex ultrasound associated with anterior circulation infarction</li> <li>Vertebrobasilar stenosis &gt;50% on CT/MR angiography associated with posterior circulation infarction</li> <li>Single, isolated lacunar stroke with a corresponding lacunar infarct on brain CT/MRI</li> <li>Specific etiology for cause of stroke (eg, arteritis, dissection, drug abuse)</li> </ul>

478 end-expiration using a standard balanced steady-state free 479 presession cine technique.

Gadolinium (Gadovist; Bayer HealthCare Pharmaceuti-480cals, Berlin, Germany) is administered at 0.2 mmol/kg at a 481 482 rate of 0.3 mL/s followed by 30 mL normal saline flush. 483 Following gadolinium, an ECG-triggered, contrast-enhanced 484 magnetic resonance angiogram (CE-MRA) 3D dataset is ac-485 quired to delineate the left atrial endocardial border 90 sec-486 onds after gadolinium administration, after which a full 487 short-axis stack including the ventricles and atria is acquired.

488 For LGE imaging, the inversion time is determined from a 489 multiphase inversion time mapping sequence (TI-Scout/ 490 Look-locker) performed immediately prior to each LGE 491 scan to ensure adequate nulling of ventricular myocardium. 492 Two separate sequences are used to acquire LGE imaging: 493 a respiratory-navigated sequence and an image-navigated 494 sequence. Respiratory navigator artefacts are a limitation of 495 left atrial imaging that the image-navigated sequence seeks 496 to eliminate.

497 For image-navigated imaging, an ECG-triggered free-498 breathing image-navigated dual-echo 3D inversion recovery 499 spoiled gradient echo sequence (iNav LGE) is acquired 15-20 minutes after gadolinium administration according to 500 501 our previous sequence optimization and routine clinical practice for preablation atrial imaging at our institution.<sup>30</sup> The 2D 502 image navigators enable data collection throughout respira-503 504 tion, ensuring no data rejection and significantly reducing scan time and, subsequently, motion artefact. Dual echo 505 506 readout allows for water and fat separation, providing LGE images of both fat suppression and fat distribution.<sup>31</sup> 507 Coverage includes the left and right atrium. Typical parame-508 ters are as follows: TR 7.16 ms, TE 2.38/4.76 ms, flip angle 509 20°, centric k-space ordering,  $1.3 \times 1.3 \times 4 \text{ mm}^3$  acquired 510 voxel size with interpolation to  $1.3 \times 1.3 \times 2 \text{ mm}^3$  during 511 512 reconstruction, SPIR fat suppression, anterior-posterior 513 phase encoding direction.

For respiratory-navigated imaging, a second LGE sequence is performed 20-25 minutes after gadolinium enhancement. This comprises an ECG-triggered free-breathing diaphragmatic navigated 3D inversion recovery spoiled gradient echo sequence (dNav LGE) that conforms to current clinical standards within our institution for atrial imaging. Coverage includes the left and right atrium. Typical parameters are as follows: TR 4.2 ms, TE 1.8 ms, flip angle 20°, centric k-space ordering,  $1.3 \times 1.3 \times 4 \text{ mm}^3$  acquired voxel size with interpolation to  $1.3 \times 1.3 \times 2 \text{ mm}^3$  during image reconstruction, SPIR fat suppression, anterior-posterior phase encoding direction, navigator gating acceptance window of 5 mm in end-expiration.

For all 3 of the 3D sequences (CE-MRA, iNav LGE, dNav LGE) subject-specific trigger delay and acquisition window are identified using the 4-Chamber cine image to identify atrial diastole and reduce cardiac motion artefact. The field of view is identical in both LGEs and the CE-MRA to facilitate registration between the images during postprocessing.

Primary structural metrics collected from CMR imaging include left atrial surface area and volume, visual and guantitative LGE assessment, and sphericity. Secondary anatomical metrics collected include left atrial appendage orifice size and flow.

#### Image postprocessing

All CMR scans are postprocessed shortly after acquisition prior to completion of ILR follow-up, patient group assignment, and, where relevant, exclusion of patients owing to the identification of a secondary cause of stroke on CMR imaging (see Eligibility, above). This approach is taken in order to eliminate any potential postprocessing bias after study/ control group allocation. Postprocessing is performed using the previously validated open-source Cardiac

568

569

FPO 

veb



Work flow for postprocessing of iNav late gadolinium enhancement (LGE) imaging. MRA = magnetic resonance angiography; R = registration. Q9 Figure 3

Electro-Mechanics Research Group App (CEMRG) platform (http://www.cemrg.co.uk).<sup>32</sup> Imaging is reinterpolated to 1  $\times$  1  $\times$  1 mm<sup>3</sup>.<sup>33</sup> A total of 8–12 semiautomatic axial seg-mentations of the atrial blood pool are then performed using the CE-MRA image and interpolated to reconstruct a 3D atrial shell. Rigid body registration is then used to align the CE-MRA and dNav LGE image. This is performed by iden-tifying the rotations and translations required to optimize the normalized mutual information as the similarity measure of the 2 images giving rise to a displacement field. This is then used to transform the CE-MRA segmentation and over-lay it with the dNav LGE image for review of image align-ment. In case of malalignment, segmentation is performed using the dNav image directly.

Next, the pulmonary veins and appendage are removed from the atrial shell. The distal end of each pulmonary vein and the left atrial appendage are manually tagged. Center lines are formed from these points and converge to a central point in the body of the left atrium. Pulmonary vein/appendage clippers are then displayed perpendicular to the entry of the vein/appendage into the body of the left atrium. This is defined by the rate of increase of the cross-section area of the vein/appendage, starting from the distal end of the vein/appendage and toward the atrial body. As the cross-section approaches the atrial body, its area increases substantially; this inflection is used to iden-tify the opening of the chamber. Clippers can be manually adjusted prior to removal of the pulmonary veins/atrial appendage.

The last step prior to analysis is clipping of the mitral valve. In order to provide a clipping plane, the valve is viewed en face and 3 points around the valve are selected at 3, 7, and 10 o'clock to create a best-fit circle that is subse-quently used as the orthodrome of a spherical clipper. The clipper is then manually reviewed for accuracy of valve posi-tioning prior to valve removal.

#### Fibrosis assessment

The dNav LGE image is then interrogated and an LGE map generated using a maximum-intensity projection technique whereby a 3 mm external projection and 1 mm internal projection is used by default to adequately capture the full thickness of the atrial wall and to account for minor misalignment between the CE-MRA and LGE imaging. To quantify LGE, a blood pool segmentation is derived using a 3-voxel size erosion of the previously segmented left atrial body. Mean and standard deviation of blood pool signal intensity are automatically calculated and are used as reference values. LGE assessment is then performed using the image intensity ratio method using a range of predefined thresholds.<sup>34</sup> ROC analysis will be performed to delineate the optimal image intensity ratio for use within the predictive model for identification of study vs control group allocation.

#### Sphericity assessment

Atrial sphericity is automatically calculated using the left atrial sphericity predictor method.<sup>20</sup> A best-fit sphere of the left atrium is calculated using the center of mass determined by the average radius of all left atrial wall points. The coefficient of variation of the sphere is then used to identify the best-fit sphere. The deviation of the segmented atrial body from the best-fit sphere is then calculated to quantify sphericity.

Additional postprocessing for assessment of iNav LGE imaging An additional registration step is performed for alignment of the CE-MRA atrial segmentation and iNav LGE image. Pulmonary vein, left atrial appendage, and mitral valve clipping planes are registered and transformed from the dNav LGE image and overlaid to the iNav LGE image using the same image registration and transformation techniques described earlier. An LGE map can then be created and LGE and

sphericity quantified as performed for dNav LGE imaging forcomparison (Figure 3).

#### 688 Implantable loop recorder programming

689 All patients receive a Reveal LINQ (Medtronic) ILR device 690 as per routine clinical care for detection of AF. Nominals 691 are set to detect increased sensitivity of AF detection 692 threshold, aggressive ectopy rejection, and storage of all 693 AF/AT episodes to maximize AF detection. AF is detected 06 694 following 2 minutes of ILR monitoring as per the Medtronic 695 AF detection algorithm. Each episode will be reviewed by 2 696 independent experts prior to study/control group allocation. 697 Daily remote data collection will occur as part of routine clin-698 ical care. 699

#### Data analysis

687

700

701 Primary analysis will be performed following 12 months of 702 continuous ILR monitoring with interim and delayed ana-703 lyses performed at 6 months and 2 and 3 years, respectively. 704 Descriptive statistics will be used to characterize the study 705 population. Structural and electrocardiographic metrics will 706 be summarized. Results will be reported as a comparison be-707 tween the standard deviation and mean difference. If groups 708 show a normal distribution, t test will be performed to assess 709 for a significant difference between groups; otherwise, a 710 Mann-Whitney U test will be used. The  $\chi^2$  test will be used 711 for categorical data. Any P value <.05 will be considered 712 significant. For qualitative assessment of LGE, patients will 713 be categorized as per our routine clinical practice using com-714 bined assessment of both LGE methods as none, mild, mod-715 erate, or severe LGE. Survival analysis will be performed 716 using Kaplan-Meier curves with atrial fibrillation as the 717 outcome measure. For qualitative assessment of atrial LGE, 718 our open-source platform, CEMRGApp, will be used to 719 create LGE scores. ROC analysis will be used to determine 720 if there is a quantitative LGE cut-off with adequate specificity 721 and sensitivity to detect atrial fibrillation during follow-up. 722 To combine these variables into a single score, the use of lo-723 gistic regression, shallow classifiers, atrial computational 724 modeling, or combining variables using summated z-scores 725 will be explored to improve the predictive value for AF. 726

#### 728 **Trial significance**

727

729 At present, there is limited published data regarding 730 advanced atrial CMR imaging in either non-AF patients or 731 ESUS patients. The CARM-AF Study will provide novel in-732 formation regarding the difference in structural and electrical 733 remodeling in patients with and without AF. Several large 734 randomized controlled trials including CRYSTAL-AF and ROCKET-AF provide evidence to support prolonged heart 735 736 rhythm monitoring in ESUS patients. The most recent 2021 737 NICE guidelines advocate the use of ILR implantation as a 738 diagnostic aid to improve AF detection but continues to 739 rely on a diagnosis of AF for initiation of anticoagulation 740 in the ESUS population. We aim to produce a substrate-741 based model that can be used to predict ESUS patients at higher risk of AF, allowing for initiation of anticoagulation at the time of stroke, rather than relying on future clinical arrhythmia detection. Furthermore, this would negate the need for ILR insertion and follow-up, resulting in a significant reduction in cost burden and use of limited resources.

We anticipate that this study will form the basis of a randomized controlled trial with the potential to revolutionize poststroke care in ESUS patients, where patients are anticoagulated on the basis of atrial substrate rather than the presence or absence of an AF clinical diagnosis.

**Funding Sources**: This work was supported by the Wellcome/EPSRC Centre for Medical Engineering (WT203148/Z/16/Z) at King's College London and the British Heart Foundation (PG/19/44/34368). IK acknowledges support from the British Heart Foundation (FS/CRTF/21/24166). SW acknowledges support from the British Heart Foundation (FS/20/26/34952). SP was funded by the British Heart Foundation (BHF) under grant number CH/16/2/32089.

**Disclosures**: Professor O'Neill has received research support and honoraria from Biosense Webster and has received consultation fees from Medtronic, Biosense Webster, St. Jude/Abbott, and Siemens. Dr Williams has received research support from Biosense Webster and EPD-Philips and consultation fees from Imricor Medical Systems.

Authorship: All authors attest they meet the current ICMJE criteria for authorship.

**Patient Consent**: If eligible for recruitment, patients are informed about the study, and a Patient Information Sheet and Informed Consent Form provided.

**Ethics Statement**: The study conforms to the principles outlined in the Declaration of Helsinki. Ethical approval has been granted by Health Research Authorities and the South London Research Ethics Committee (REC: 19/LO/1933).

#### References

- Wolf PA, et al. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. Stroke 1991;22:983–988.
- Cotter PE, et al. Incidence of atrial fibrillation detected by implantable loop recorders in unexplained stroke. Neurology 2013;80:1546–1550.
- Freedman B, et al. Stroke prevention in atrial fibrillation. Lancet 2016; 388:806–817.
- Hindricks G, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2021;42:373–498.
- Gladstone DJ, et al. Atrial fibrillation in patients with cryptogenic stroke. N Engl J Med 2014;370:2467–2477.
- Sanna T, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med 2014;370:2478–2486.
- Ziegler PD, et al. Long-term detection of atrial fibrillation with insertable cardiac monitors in a real-world cryptogenic stroke population. Int J Cardiol 2017; 244:175–179.
- European Atrial Fibrillation Trial Study. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. Lancet 1993; 342:1255–1262.
- Kamel H, et al. Atrial fibrillation and mechanisms of stroke: time for a new model. Stroke 2016;47:895–900.
- 10. Brambatti M, et al. Temporal relationship between subclinical atrial fibrillation and embolic events. Circulation 2014;129:2094–2099.
- Martin DT, et al. Randomized trial of atrial arrhythmia monitoring to guide anticoagulation in patients with implanted defibrillator and cardiac resynchronization devices. Eur Heart J 2015;36:1660–1668.
- Steinberg BA, et al. Higher risk of death and stroke in patients with persistent vs. paroxysmal atrial fibrillation: results from the ROCKET-AF Trial. Eur Heart J 2015;36:288–296.
- Flaker G, et al. Efficacy and safety of dabigatran compared to warfarin in patients with paroxysmal, persistent, and permanent atrial fibrillation: results from the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study. J Am Coll Cardiol 2012;59:854–855.

## **ARTICLE IN PRESS**

FLA 5.6.0 DTD ■ HROO199 proof ■ 4 February 2022 ■ 7:23 pm ■ ce

### Heart Rhythm 0<sup>2</sup>, Vol ■, No ■, ■ 2022

 Al-Khatib SM, et al. Rate- and rhythm-control therapies in patients with atrial fibrillation. Ann Intern Med 2014;160:760.

- 800
   801
   801
   802
   15. Zheng YR, et al. Long-term stroke rates after catheter ablation or antiarrhythmic drug therapy for atrial fibrillation: a meta-analysis of randomized trials. J Geriatr Cardiol 2015;12:507–514.
- B03
   16. Diener HC, et al. Dabigatran for prevention of stroke after embolic stroke of undetermined source. N Engl J Med 2019;380:1906–1917.
- 804 17. Hart RG, et al. Rivaroxaban for stroke prevention after embolic stroke of undeter 805 mined source. N Engl J Med 2018;378:2191–2201.
- 806
   18. Okin PM. P-wave morphology and the risk of incident ischemic stroke in the Multi-Ethnic Study of Atherosclerosis. Stroke 2014;45:2786–2788.
- 807
   19. Goette A, et al. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. Europace
   809
   2016;18:1455–1490.
- 810
   811
   20. Bisbal F, et al. Left atrial sphericity: a new method to assess atrial remodeling. Impact on the outcome of atrial fibrillation ablation. J Cardiovasc Electrophysiol 2013;24:752–759.
- 812
  813
  21. King JB, et al. Left atrial fibrosis and risk of cerebrovascular and cardiovascular events in patients with atrial fibrillation. J Am Coll Cardiol 2017; 70:1311–1321.
- 814 22. Kühnlein P, et al. Atrial fibrosis in embolic stroke of undetermined source: a multicenter study. Eur J Neurol 2021;28:3634–3639.
  815 22. Kühnlein P, et al. Atrial fibrosis in embolic stroke of undetermined source: a multicenter study. Eur J Neurol 2021;28:3634–3639.
- 23. Hancock EW, et al. AHA/ACCF/HRS Recommendations for the standardization and interpretation of the electrocardiogram. Part V: electrocardiogram changes associated with cardiac chamber hypertrophy: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation;

and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol 2009;53:992–1002.

- Kamel H, et al. Electrocardiographic left atrial abnormality and risk of stroke: Northern Manhattan study. Stroke 2015;46:3208–3212.
- Goda T, et al. P-wave terminal force in lead V1 predicts paroxysmal atrial fibrillation in acute ischemic stroke. J Stroke Cerebrovasc Dis 2017;26:1912–1915.
- Dewland TE, Vittinghoff E, Mandyam MC, et al. Atrial ectopy as a predictor of incident atrial fibrillation: a cohort study. Ann Intern Med 2013;159:721–728.
- NICE Guideline. Atrial fibrillation diagnosis and management. British Columbia and Ministry of Health; 2021.
- Svendsen JH, et al. Implantable loop recorder detection of atrial fibrillation to prevent stroke (The LOOP Study): a randomised controlled trial. Lancet 2021; 6736:1–10.
- 29. Sim I, et al. Reproducibility of atrial fibrosis assessment using CMR imaging and an open source platform. JACC Cardiovasc Imaging 2019;3057.
- Chubb H, et al. Optimization of late gadolinium enhancement cardiovascular magnetic resonance imaging of post-ablation atrial scar: a cross-over study. J Cardiovasc Magn Reson 2018;20:30.
- 31. Zeilinger MG, et al. 3D Dixon water-fat LGE imaging with image navigator and compressed sensing in cardiac MRI. Eur Radiol 2021;31:3951–3961.
- 32. Sim I, et al. Left atrial voltage mapping: defining and targeting the atrial fibrillation substrate. J Interv Card Electrophysiol 2019;56:213–227.
- Cox RW, et al. A (sort of) new image data format standard: {NIfTI-1. NeuroImage 2004;22:1.
- Khurram IM, et al. Image intensity ratio, a novel magnetic resonance-based measure for quantification of left atrial fibrosis, correlates with the distribution of atrial bipolar voltage. Heart Rhythm 2012;9:1917–1918.