JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2017 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

VOL. 70, NO. 16, 2017
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2017.08.041

ORIGINAL INVESTIGATIONS

Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction

The CAMERA-MRI Study

Sandeep Prabhu, MBBS,[a,b,c,d] Andrew J. Taylor, MBBS, PhD,[a,b,e] Ben T. Costello, MBBS,[a,b] David M. Kaye, MBBS, PhD,[a,b,e] Alex J.A. McLellan, MBBS, PhD,[a,b,c,d] Aleksandr Voskoboinik, MBBS,[a,b,c,d] Hariharan Sugumar, MBBS,[a,b,c,d] Siobhan M. Lockwood, MBBS,[f] Michael B. Stokes, MBBS,[f] Bhupesh Pathik, MBBS,[c,d] Chrishan J. Nalliah, MBBS,[c,d] Geoff R. Wong, MBBS,[c,d] Sonia M. Azzopardi, RN,[a,b] Sarah J. Gutman, MBBS,[a,b] Geoffrey Lee, MBBS, PhD,[c] Jamie Layland, MBCHB, PhD,[e] Justin A. Mariani, MBBS, PhD,[a,b,d] Liang-han Ling, MBBS, PhD,[a,b,d] Jonathan M. Kalman, MBBS, PhD,[c,d] Peter M. Kistler, MBBS, PhD[a,b,d]

JACC JOURNAL CME/MOC

This article has been selected as the month's *JACC* Journal CME/MOC activity, available online at http://www.acc.org/jacc-journals-cme by selecting the *JACC* Journals CME/MOC tab.

Accreditation and Designation Statement

The American College of Cardiology Foundation (ACCF) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The ACCF designates this Journal-based CME/MOC activity for a maximum of 1 *AMA PRA Category 1 Credit(s)*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Method of Participation and Receipt of CME/MOC Certificate

To obtain credit for *JACC* CME/MOC, you must:

1. Be an ACC member or *JACC* subscriber.
2. Carefully read the CME/MOC-designated article available online and in this issue of the journal.
3. Answer the post-test questions. At least 2 out of the 3 questions provided must be answered correctly to obtain CME/MOC credit.
4. Complete a brief evaluation.
5. Claim your CME/MOC credit and receive your certificate electronically by following the instructions given at the conclusion of the activity.

CME/MOC Objective for This Article: After reading this article, the reader should be able to: 1) discuss the immediate, short-, and long-term treatment options for patients presenting with concurrent atrial fibrillation and systolic dysfunction; 2) compare the effectiveness of rate control compared to rhythm control strategies for the long-term management of persistent atrial fibrillation and otherwise unexplained systolic dysfunction; and 3) identify the physiological mechanism of improvement in ejection fraction and clinical benefits of the restoration of sinus rhythm in patients with unexplained systolic dysfunction and rate controlled atrial fibrillation.

CME/MOC Editor Disclosure: *JACC* CME/MOC Editor Ragavendra R. Baliga, MD, FACC, has reported that he has no financial relationships or interests to disclose.

Author Disclosures: St. Jude Medical provided 14% of the implantable loop recorders used in this study ex gratia; however, St. Jude provided no funding and had no role in the study design, data collection, data analysis, data interpretation, or writing. This research is supported in part by the Victorian Government's Operational Infrastructure Funding. This research was in part supported by fellowship stipends provided by the Baker Heart and Diabetes Institute, the National Health and Medical Research Council of Australia, and the National Heart Foundation of Australia. Dr. Kistler has received funding from St. Jude for consultancy and speaking engagements. Dr. Kalman has research and fellowship support from St. Jude, Medtronic, Biosense Webster, Boston Scientific, and Abbott; and has received payment for advice to Biosense Webster. Dr. Mariani has received consultancy and speaking fees from St. Jude, Medtronic, Biotronik, and Boehringer Ingelheim; and funding from St. Jude, Boston Scientific, and Medtronic for fellowship support for a clinical assistant. Dr. Ling has received fellowship support from Medtronic, Biotronik, and St. Jude. Dr. McLellan has received fellowship support from St. Jude. Dr. Wong has received consultancy fees from St. Jude. Dr. Sugamar has received fellowship support from St. Jude and Medtronic. Drs. Prabhu, Ling, McLellan, Voskoboinik, Nalliah, and Pathik have received funding from the Australian National Health and Medical Research Council and/or the National Heart Foundation of Australia. Drs. Prabhu and McLellan have received funding from the Baker Heart and Diabetes Research Institute. Drs. Kalman, Lee and Kistler are in part supported by the National Health and Medical Research Council. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Medium of Participation: Print (article only); online (article and quiz).

CME/MOC Term of Approval

Issue Date: October 17, 207
Expiration Date: October 16, 2018

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

JACC VOL. 70, NO. 16, 2017
OCTOBER 17, 2017:1949–61

Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction

The CAMERA-MRI Study

Sandeep Prabhu, MBBS,[a,b,c,d] Andrew J. Taylor, MBBS, PhD,[a,b,e] Ben T. Costello, MBBS,[a,b] David M. Kaye, MBBS, PhD,[a,b,e] Alex J.A. McLellan, MBBS, PhD,[a,b,c,d] Aleksandr Voskoboinik, MBBS,[a,b,c,d] Hariharan Sugumar, MBBS,[a,b,c,d] Siobhan M. Lockwood, MBBS,[f] Michael B. Stokes, MBBS,[f] Bhupesh Pathik, MBBS,[c,d] Chrishan J. Nalliah, MBBS,[c,d] Geoff R. Wong, MBBS,[c,d] Sonia M. Azzopardi, RN,[a,b] Sarah J. Gutman, MBBS,[a,b] Geoffrey Lee, MBBS, PhD,[c] Jamie Layland, MBCHB, PhD,[e] Justin A. Mariani, MBBS, PhD,[a,b,d] Liang-han Ling, MBBS, PhD,[a,b,d] Jonathan M. Kalman, MBBS, PhD,[c,d] Peter M. Kistler, MBBS, PhD[a,b,d]

ABSTRACT

BACKGROUND Atrial fibrillation (AF) and left ventricular systolic dysfunction (LVSD) frequently co-exist despite adequate rate control. Existing randomized studies of AF and LVSD of varying etiologies have reported modest benefits with a rhythm control strategy.

OBJECTIVES The goal of this study was to determine whether catheter ablation (CA) for AF could improve LVSD compared with medical rate control (MRC) where the etiology of the LVSD was unexplained, apart from the presence of AF.

METHODS This multicenter, randomized clinical trial enrolled patients with persistent AF and idiopathic cardiomyopathy (left ventricular ejection fraction [LVEF] ≤45%). After optimization of rate control, patients underwent cardiac magnetic resonance (CMR) to assess LVEF and late gadolinium enhancement, indicative of ventricular fibrosis, before randomization to either CA or ongoing MRC. CA included pulmonary vein isolation and posterior wall isolation. AF burden post-CA was assessed by using an implanted loop recorder, and adequacy of MRC was assessed by using serial Holter monitoring. The primary endpoint was change in LVEF on repeat CMR at 6 months.

RESULTS A total of 301 patients were screened; 68 patients were enrolled between November 2013 and October 2016 and randomized with 33 in each arm (accounting for 2 dropouts). The average AF burden post-CA was 1.6 ± 5.0% at 6 months. In the intention-to-treat analysis, absolute LVEF improved by 18 ± 13% in the CA group compared with 4.4 ± 13% in the MRC group ($p < 0.0001$) and normalized (LVEF ≥50%) in 58% versus 9% ($p = 0.0002$). In those undergoing CA, the absence of late gadolinium enhancement predicted greater improvements in absolute LVEF (10.7%; $p = 0.0069$) and normalization at 6 months (73% vs. 29%; $p = 0.0093$).

CONCLUSIONS AF is an underappreciated reversible cause of LVSD in this population despite adequate rate control. The restoration of sinus rhythm with CA results in significant improvements in ventricular function, particularly in the absence of ventricular fibrosis on CMR. This outcome challenges the current treatment paradigm that rate control is the appropriate strategy in patients with AF and LVSD. (Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction [CAMERA-MRI]; ACTRN12613000880741) (J Am Coll Cardiol 2017;70:1949–61)

From the [a]The Baker Heart & Diabetes Institute, Clinical Electrophysiology Research, Melbourne, Australia; [b]The Heart Centre, The Alfred Hospital, Melbourne, Australia; [c]Department of Cardiology, Royal Melbourne Hospital, Melbourne, Australia; [d]Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Melbourne, Australia; [e]Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, Australia; and [f]MonashHeart, Monash Medical Centre, Melbourne, Australia. St. Jude Medical provided 14% of the implantable loop recorders used in this study ex gratia; however, St. Jude provided no funding and had no role in the study design, data collection, data analysis, data interpretation, or writing. This research is supported in part by the Victorian Government's Operational Infrastructure Funding. This research was in part supported by fellowship stipends provided by the Baker Heart and Diabetes Institute, the National Health and Medical Research Council of Australia, and

Atrial fibrillation (AF) and heart failure are burgeoning cardiovascular epidemics (1,2) and frequently co-exist (3). AF in patients with left ventricular systolic dysfunction (LVSD) is associated with worsening heart failure, stroke, and mortality (4). It is a common clinical conundrum for cardiologists and general physicians alike to determine the "chicken-and-egg" relationship between AF and heart failure, as each can lead to the other. Given the morbidity and mortality associated with AF in heart failure, it might be expected that the restoration of sinus rhythm may be beneficial. However, a large multicenter trial did not show superiority of a pharmacological rhythm versus rate control strategy (5).

SEE PAGE 1962

Recently, catheter ablation (CA) for AF has emerged as a superior alternative strategy to pharmacological rhythm control (6). However, randomized trials of CA in LVSD have shown mixed results, with no or only modest improvements in left ventricular ejection fraction (LVEF) (6–10). Consequently, current guidelines have no specific recommendations for CA in patients with LVSD, with medical rate control (MRC) the accepted standard treatment (11). A recent meta-analysis suggested that improvements in LVEF may be greater in those with idiopathic cardiomyopathy (12), where prevalence of AF is up to 20% (13,14). A critical drawback of previous randomized trials has been the heterogeneous nature of the study cohorts, with etiologies such as ischemic and valvular heart disease largely responsible for LVSD. AF in this instance is more likely a secondary phenomenon than a primary cause limiting the effect of CA. Therefore, the goal of the present randomized study was to determine whether the restoration of sinus rhythm with CA could improve LVSD compared with MRC in which the etiology of the underlying cardiomyopathy was otherwise unexplained, apart from the presence of AF.

METHODS

STUDY DESIGN. This study involved a prospective, parallel-group, open-label, multicenter randomized clinical trial. Recruitment took place over 3 tertiary hospitals in Australia (The Alfred Hospital, The Royal Melbourne Hospital, and Monash Medical Centre), with ablations performed at the Alfred and Royal Melbourne hospitals. Ethics committee approval was obtained at each participating center. The study protocol is available online via the Australian New Zealand Clinical Trials Registry website.

STUDY POPULATION. Patients meeting inclusion criteria were recruited. Patients were included if they were: 1) 18 to 85 years of age; 2) had New York Heart Association (NYHA) functional class ≥II; 3) had persistent AF; 4) had an LVEF ≤45% on baseline cardiac magnetic resonance (CMR); 5) had significant coronary artery disease excluded via conventional or computed tomography-guided angiography or functional imaging; and 6) had no other identifiable cause explaining the left ventricular dysfunction. Patients were excluded for the following reasons: 1) if they were unable or unwilling to consent or commit to follow-up requirements; 2) if they had any contraindication to AF ablation; 3) if they had any contraindication to cardiac magnetic resonance imaging (MRI); or 4) if they had paroxysmal AF. The upper age limit was raised to 85 years during the study to facilitate recruitment. All participants provided written informed consent to partake in the study.

RANDOMIZATION AND MASKING. After CMR, provided LVEF was ≤45%, patients were block randomized 1:1 to receive either CA or ongoing MRC. Randomization was performed electronically by using commercially available software from an independent third party. Block randomization (block size, n = 8)

ABBREVIATIONS AND ACRONYMS

6MWT = 6-min walk test

AF = atrial fibrillation

BNP = brain natriuretic peptide

CA = catheter ablation

CMR = cardiac magnetic resonance

DCCV = direct current cardioversion

ILR = implantable loop recorder

LGE = late gadolinium enhancement

LVEDV = left ventricular end-diastolic volume

LVEF = left ventricular ejection fraction

LVESV = left ventricular end-systolic volume

LVSD = left ventricular systolic dysfunction

MRC = medial rate control

MRI = magnetic resonance imaging

SF-36 = 36-Item Short-Form Health Survey

the National Heart Foundation of Australia. Dr. Kistler has received funding from St. Jude for consultancy and speaking engagements. Dr. Kalman has research and fellowship support from St. Jude, Medtronic, Biosense Webster, Boston Scientific, and Abbott; and has received payment for advice to Biosense Webster. Dr. Mariani has received consultancy and speaking fees from St. Jude, Medtronic, Biotronik, and Boehringer Ingelheim; and funding from St. Jude, Boston Scientific, and Medtronic for fellowship support for a clinical assistant. Dr. Ling has received fellowship support from Medtronic, Biotronik, and St. Jude. Dr. McLellan has received fellowship support from St. Jude. Dr. Wong has received consultancy fees from St. Jude. Dr. Sugamar has received fellowship support from St. Jude and Medtronic. Drs. Prabhu, Ling, McLellan, Voskoboinik, Nalliah, and Pathik have received funding from the Australian National Health and Medical Research Council and/or the National Heart Foundation of Australia. Drs. Prabhu and McLellan have received funding from the Baker Heart and Diabetes Research Institute. Drs. Kalman, Lee and Kistler are in part supported by the National Health and Medical Research Council. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received July 27, 2017; revised manuscript received August 18, 2017, accepted August 20, 2017.

was used to ensure the equal distribution of key baseline characteristics, including the presence of ventricular late gadolinium enhancement (LGE). Randomization was performed centrally. The study investigator performing the randomization was blinded to block size to minimize potential selection bias. Patients and investigators performing ablation necessarily could not be blinded to treatment allocation. Investigators and physicians reporting CMR and echocardiography were blinded to treatment allocation but could not be blinded to cardiac rhythm or the presence of implantable loop recorders (ILRs). Investigators reporting imaging were not involved in the performance of ablation procedures or clinical management. Investigators performing CA were blinded to the LGE status, and these data were withheld or masked on CMR reports.

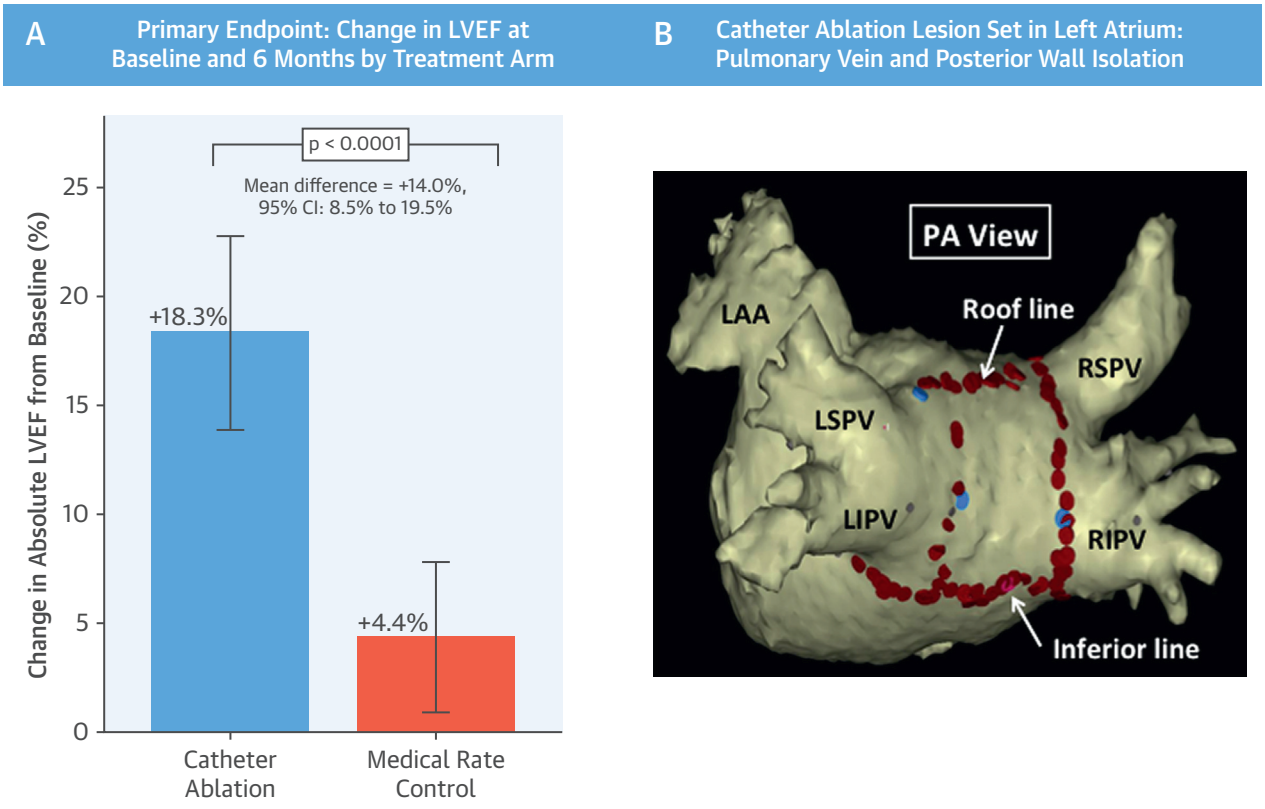
PROCEDURES. Patients meeting the inclusion criteria underwent baseline echocardiography, CMR, 24-h Holter monitoring, 6-min walk test (6MWT), 36-Item Short-Form Health Survey (SF-36), serum brain natriuretic peptide (BNP), and clinical review before randomization. Clinical review was repeated at 6 weeks and at 3 and 6 months; SF-36 and 6MWT were repeated at 3 and 6 months; and CMR, BNP, and echocardiography were repeated at 6 months. Late procedural complications were reassessed at 6 months. After completion of the study, patients in the MRC arm could undergo CA at physician discretion.

Cardiac magnetic resonance. Before performance of CMR, rate control was optimized for 4 weeks aiming for an average ventricular rate <100 beats/min on 24-h Holter monitoring. Baseline and 6-month CMR were performed on a clinical 1.5-T MRI scanner (Signa HD 1.5-T, GE Healthcare, Waukesha, Wisconsin). Sequences were acquired during breath-holds of 10 to 15 s. Initial cine CMR sequences were performed in 3 standard long-axis (4-, 3-, and 2-chamber views) and short-axis (basal, mid, and apical) slices, kept identical for each subsequent sequence throughout the CMR examination. To calculate left ventricular volume and function, a contiguous short-axis steady-state free precession stack was acquired (8-mm-thick slice, no gap), extending from the mitral valve annulus to the left ventricular apex. LGE was obtained in both long- and short-axis views 10 min after a bolus (0.2 mmol/kg body weight to a maximum of 20 mmol) of gadolinium-diethylenetriamine pentaacetic acid (Magnevist, Bayer Schering, Berlin, Germany) to identify regional fibrosis by using a T1-weighted inversion-recovery gradient echo technique. LGE was quantified by manually contouring regions of increased signal intensity consistent with scar, using commercially available software (CVI42, Circle Cardiovascular Imaging, Calgary, Alberta, Canada). For the purposes of this analysis, LGE negative was defined as <1% LGE present in the myocardium.

Medial rate control. Patients randomized to ongoing MRC underwent 24-h Holter monitoring at 3 and 6 months after randomization, with medical therapy titrated to achieve a resting rate <80 beats/min, an average 24-h ventricular rate <100 beats/min, and a post-exercise (6MWT) rate <110 beats/min in accordance with current guidelines (11). Although cross-over to CA before the 6-month CMR assessment was discouraged, it was permitted at the discretion of the treating physician.

CA procedure. Catheter ablation was performed within 1 month of randomization. Oral anticoagulation was discontinued 24 h before the procedure with the exception of vitamin K antagonists or dabigatran, which were continued. Antiarrhythmic medication was discontinued 5 half-lives pre-procedure with the exception of amiodarone. All procedures were performed under general anesthesia with the assistance of a 3-dimensional mapping system (Carto, Biosense Webster, Irvine, California). After exclusion of intracardiac thrombus, transesophogeal echocardiographic-guided double transseptal punctures were performed. Unfractionated heparin was administered to achieve an activated clotting time >350 s. Mapping of the left atrium and pulmonary veins was performed with a 20 pole circular mapping catheter and ablation with a 3.5-mm irrigated-tipped catheter (SmartTouch Thermocool, Biosense Webster) following direct current cardioversion (DCCV) to restore sinus rhythm (power range: 25 W [posteriorly] to 30 W; contact force range: 10 to 40 g anteriorly and 10 to 25 g posteriorly). Pulmonary vein isolation was achieved with wide antral circumferential ablation with additional roof and inferior lines performed to achieve posterior wall isolation (**Central Illustration**). In general, antiarrhythmic medications were continued if present or commenced after early recurrence. Repeat procedure was permitted for symptomatic recurrence occurring beyond 3 months' post-index procedure. AF recurrence was monitored via ILR (Confirm [St. Jude Medical, St. Paul, Minnesota] or Reveal LINQ [Medtronic, Dublin, Ireland]) implanted at the time of the procedure. Recurrence was defined as documented AF or atrial tachycardia >30 s occurring beyond a 4-week blanking period. Recorded traces were manually verified by study investigators. AF burden was expressed as the percentage of total time in AF from time of implant beyond blanking period.

CENTRAL ILLUSTRATION **Change in Absolute LVEF From Baseline According to Treatment Arm**



Prabhu, S. et al. J Am Coll Cardiol. 2017;70(16):1949–61.

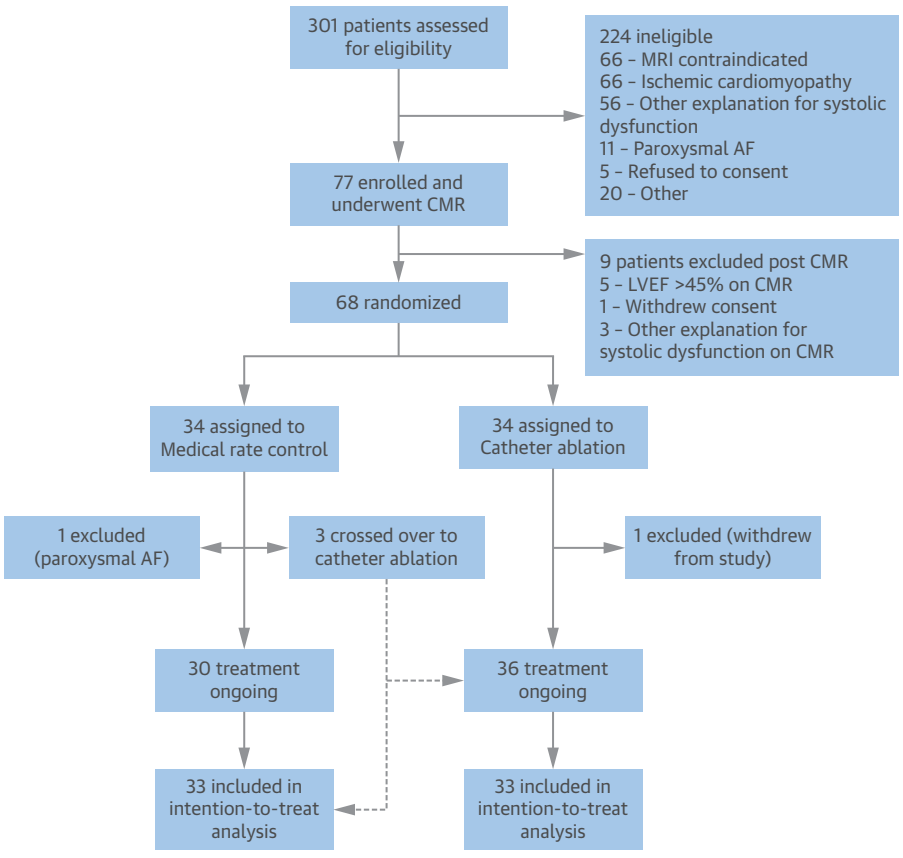
(A) Graph illustrating the primary endpoint: left ventricular ejection fraction (LVEF) change from baseline in catheter ablation versus the medical rate control group on an intention-to-treat analysis. **Bars** represent 95% confidence intervals (CI). **(B)** An integrated computed tomography image depicting a typical ablation strategy used in this study. Posterior wall or "box isolation" involves the addition of a roof line and inferior line between the superior and inferior aspects of the wide encirclement ring to achieve electrical isolation of the posterior wall. LAA = left atrial appendage; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; PA = posterior/anterior; RIPV = right superior pulmonary vein; RSPV = right superior pulmonary vein.

PRIMARY AND SECONDARY ENDPOINTS. The primary endpoint was the change in LVEF from baseline at 6 months on CMR. All CMRs were performed and assessed centrally. The effect of LGE status on LVEF improvement was a pre-specified secondary endpoint. Other secondary endpoints included: 1) change in CMR chamber dimensions; 2) NYHA functional class; 3) BNP level; 4) 6MWT distance; 5) physical composite scores (SF-36); 6) mental composite scores (SF-36); 7) AF recurrence; 8) AF burden; and 9) procedural complications.

STATISTICAL ANALYSIS. The sample size calculation for the primary endpoint of LVEF assumed an average expected SD of baseline LVEF of 10% based on preliminary data (15). For the primary endpoint, we aimed to detect a minimum absolute change in LVEF of 10% between the CA and MRC groups, requiring a minimum of 16 patients in each group to provide a power of 0.8 at an alpha value of 0.05 (15). Estimating the short-term success of restoring sinus rhythm by CA of 80%, 20 patients in each comparative group would be required. In addition, a secondary endpoint was to assess the effect of CA versus MRC in patients with or without LGE (n = 20 for each of 4 groups). However, due to the lower-than-anticipated incidence of LGE in the study population, this secondary endpoint recruitment target was abandoned, and the study was terminated after 68 patients were randomized to treatment.

Data are expressed as mean ± SD unless otherwise indicated. Cardiac chamber dimensions are indexed to body surface area. Two-group comparisons were

FIGURE 1 Trial Profile



CONSORT diagram illustrating the recruitment for this study. AF = atrial fibrillation; CMR = cardiac magnetic resonance; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging.

made by using the Student *t* test for continuous variables or the chi-square test or Fisher exact test for categorical variables. The independent sample Mann-Whitney *U* test was used for non-normally distributed variables. Confidence intervals for the difference of 2 independent proportions were calculated by using the Newcombe-Wilson score method (uncorrected) (16). McNemar's test was used for comparisons of proportions of paired samples. Primary outcome analysis was performed on an intention-to-treat basis. Other outcome analyses have been specified in the text. Procedural outcomes are reported for all patients undergoing CA, regardless of treatment assignment unless otherwise specified. Analyses were conducted by using SPSS version 24 (IBM SPSS Statistics, IBM Corporation, Armonk, New York). The trial was registered with the Australia New Zealand Clinical Trials Registry (ACTRN12613000880741).

RESULTS

STUDY POPULATION. Patient recruitment was from September 3, 2013, through December 23, 2016. The first patient was enrolled on November 27, 2013, and the last on October 6, 2016. Of 301 patients screened, most (n = 132) were excluded due to ischemic cardiomyopathy or MRI-incompatible implanted cardiac devices. Sixty-eight patients were randomized to receive CA (n = 34) or MRC (n = 34). Two patients were excluded post-randomization. One patient in the CA arm withdrew from the study and did not complete follow-up. One patient in the MRC arm was excluded due to screening failure (paroxysmal AF). Overall, 66 patients were analyzed (33 in each arm). Three patients in the MRC arm crossed over to CA before follow-up CMR due to symptoms of uncontrolled heart failure (**Figure 1**).

BASELINE CHARACTERISTICS. Study participants had an average baseline LVEF of 33 ± 8.6%, an average CHA_2DS_2VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category) score of 2.4 ± 0.9, moderately enlarged left atria (left atrial volume: 54 ± 17 ml/m^2), and had previously failed DCCV in 95%. They were well established on anti-heart failure medical therapy (renin angiotensin aldosterone system inhibition: 94%; beta-blockade: 97%) and had well-controlled ventricular rate (resting heart rate: 78 ± 18 beats/min; 24-h mean heart rate: 86 ± 15 beats/min; post-6MWT heart rate: 94 ± 21 beats/min). All patients had persistent AF, with the majority (74%) having long-standing persistent AF. There were 2.1 ± 0.76 DCCV attempts per person (median: 2: interquartile range: 1) with 76% having ≥2 attempts and 23% having ≥3 attempts. A single attempt may include up to 3 DCCVs to establish sinus rhythm. In addition, 86% had failed or been intolerant of amiodarone. Baseline characteristics following randomization are shown in Table 1.

TABLE 1 Baseline Characteristics (N = 66)

	Catheter Ablation (n = 33)	Medical Rate Control (n = 33)
Demographics		
Age, yrs	59 ± 11	62 ± 9.4
Male	94 (31)	88 (29)
CHA_2DS_2VASc score	2.42 ± 0.87	2.36 ± 0.96
Hypertension	39 (13)	36 (12)
Diabetes	12 (4)	15 (5)
Hyperlipidemia	27 (9)	27 (9)
Body mass index, kg/m^2	30 ± 7.5	31 ± 4.1
Obstructive sleep apnea	36 (12)	21 (7)
Stroke/transient ischemic attack	6.1 (2)	0 (0)
Medications		
ACE inhibitor or ARB	94 (31)	94 (31)
Cardioselective beta-blocker	88 (29)	85 (28)
Any beta-blocker	97 (32)	97 (32)
Spironolactone	33 (11)	48 (16)
Antiarrhythmic therapy	24 (8)	24 (8)
Anticoagulation	100 (33)	100 (33)
AF history		
Mean duration of continuous AF, months	23 ± 18	21 ± 15
Longstanding persistent AF	72 (24)	76 (25)
Previous DCCV	97 (32)	94 (31)
Average no. of DCCV attempts per patient	2.1 ± 0.8	2.0 ± 0.7
Amiodarone therapy ineffective or intolerant	91 (30)	82 (27)
Resting HR, beats/min	79 ± 17	77 ± 19
24-h average HR, beats/min	86 ± 14	85 ± 17
Post-6MWT HR, beats/min	93 ± 23	95 ± 20
LV systolic dysfunction history		
Co-diagnosis of AF and LV systolic dysfunction	70 (23)	67 (22)
AF preceded LV systolic dysfunction	24 (8)	27 (9)
LV systolic dysfunction preceded AF	6.1 (2)	6.1 (2)
Cardiac MRI findings		
LVEF, %	32 ± 9.4	34 ± 7.8
LVEF <35%	52 (17)	45 (15)
Late gadolinium enhancement present	36 (12)	36 (12)
Echocardiography findings		
LVEF, %	35 ± 9.8	35 ± 9.3
Fractional shortening, %	20 ± 8.4	18 ± 8.8
LV end-diastolic diameter, mm	59 ± 7.7	59 ± 6.4
LV end-systolic diameter, mm	45 ± 10	47 ± 9.2
LA diameter, mm	48 ± 5.5	47 ± 8.2

Values are mean ± SD or % (n).

6MWT = 6-minute walk test; ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin II receptor blocker; CHA_2DS_2VASc = congestive heart failure, hypertension, age ≥75 yrs, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category; DCCV = direct current cardioversion; HR = heart rate; LA = left atrial; LV = left ventricular; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging.

CA OUTCOME. In those undergoing CA (n = 36), pulmonary vein isolation was achieved in 100% and posterior left atrial wall isolation attempted in 94% and achieved in 85%. The average procedure time was 200 ± 47 min; radiation dose was 46 ± 53 mGy; dose area product was 22,407 ± 11,552 mGy·cm^2; fluoroscopy time was 15.4 ± 5.4 min; and ablation time was 43 ± 12 min. The single procedure freedom from AT/AF (>30 s) after 1 month blanking period off antiarrhythmic drugs was 56% and on antiarrhythmic drugs was 75%. The average AF burden at 6 months was 1.6 ± 5.0% with an AF burden >10% in 2 patients. Antiarrhythmic therapy was continued post-ablation in 33% (n = 12 of 36) (amiodarone: 72%, sotalol: 28%), and 14% (n = 5 of 36) required DCCV beyond the blanking period. All patients in the MRC arm remained in AF for the duration of the study period. All patients in the CA group were in sinus rhythm at time of repeat CMR assessment.

MRC OUTCOME. In the MRC group, the average ventricular rate was well controlled from baseline (85 ± 18 beats/min) to 6 months (80 ± 10 beats/min; p = 0.10). The post-6MWT heart rate significantly improved at 3 months (95 ± 19 vs. 85 ± 15 beats/min; p = 0.0325) and was maintained at 6 months (86 ± 17 beats/min; p = 0.0434). In the CA group, the restoration of sinus rhythm with CA significantly improved resting heart rate (62 ± 10 vs. 79 ± 16 beats/min; p < 0.0001), mean heart rate (67 ± 9.1 vs. 86 ± 14 beats/min; p < 0.0001), and post-6MWT heart rate (92 ± 24 vs. 73 ± 12 beats/min; p = 0.0001) at 6 months compared with baseline, with improvement evident at 3 months. All measures were significantly lower in the CA group at 6 months (post-6MWT: p = 0.0009; resting and mean heart rate: p < 0.0001).

PRIMARY ENDPOINT. In the intention-to-treat analysis (Central Illustration), the CA group reported a significant improvement in LVEF (18.3%; p < 0.0001) at 6 months. The MRC group also had significantly

TABLE 2 Primary and Secondary Endpoints

	Catheter Ablation (n = 33)		Medical Rate Control (n = 33)		Comparison Between Treatment Arms	
	Baseline	6 Months	Baseline	6 Months	Mean Difference	p Value*
Primary endpoint						
LVEF (MRI), %	31.8 ± 9.4	50.1 ± 11†	34.1 ± 7.8	38.5 ± 8.7‡	14.0 (8.5 to 19.5)	<0.0001
Secondary endpoints						
LVEF (echocardiography), %	35.0 ± 9.8	52.7 ± 11.9†	34.8 ± 43.7	43.7 ± 12.7‡	7.5 (1.6 to 13.5)	0.0137
LV end-systolic volume, ml/m^2	79.5 ± 33.3	55.3 ± 30.5†	76.3 ± 27.2	68.2 ± 26.3§	−16.1 (−27.7 to −4.5)	0.0075
LV end-diastolic volume, ml/m^2	114 ± 40	106 ± 33§	113 ± 32	109 ± 39	−2.1 (−14.5 to 10.4)	0.74
LA volume, ml/m^2	54.4 ± 16.1	43.4 ± 13.3†	53.9 ± 18.9	55.6 ± 14.6	−13.4 (−20.4 to −6.5)	0.0003
LV stroke volume, ml/m^2	34.9 ± 12.7	50.5 ± 10.1†	38.6 ± 12.5	40.5 ± 14.8	−16.1 (−27.7 to −4.45)	<0.0001
Average NYHA functional class	2.55 ± 0.62	1.33 ± 0.48†	2.45 ± 0.56	2.06 ± 0.50‡	−0.82 (−1.13 to −0.51)	<0.0001
BNP, log[ng/l]	2.34 ± 0.38	1.84 ± 0.37†	2.27 ± 0.43	2.14 ± 0.56	−0.38 (−0.65 to −0.11)	0.0063
BNP, ng/l‖	266 ± 210	98 ± 77	256 ± 208	247 ± 197	-	0.0131
6MWT distance, m	491 ± 147	546 ± 82§	489 ± 132	518 ± 119†	27 (−28 to 79)	0.34
SF-36 physical component scores	41.6 ± 11.6	48.5 ± 8.2†	38.8 ± 10.4	44.6 ± 11.2‡	1.3 (−3.9 to 6.5)	0.62
SF-36 mental component scores	49.1 ± 10.6	53.3 ± 7.7‡	50.3 ± 11.2	52.9 ± 8.9	1.6 (−3.1 to 6.3)	0.49

Values are mean ± SD and 95% CI. *p value for comparison of mean difference from baseline to 6 months between the catheter ablation and medical rate control treatment arms. †p < 0.0001 for comparison between baseline and 6 months. ‡p < 0.01 for comparison between baseline and 6 months. §p < 0.05 for comparison between baseline and 6 months. ‖Non-normally distributed; therefore, confidence intervals are not displayed. The p value determined by using the Mann-Whitney *U* test.

BNP = brain natriuretic peptide; NYHA = New York Heart Association; SF-36 = 36-item Short-Form Health Survey; other abbreviations as in Table 1.

improved LVEF (4.4%; p = 0.0145) at 6 months. The improvement in LVEF was significantly greater in the CA group (p < 0.0001) (Table 2). At 6 months, 58% of patients undergoing CA had normalized systolic function (LVEF ≥50%) compared with 9% in the MRC group (p = 0.0002). In the CA group, the proportion of patients with severe systolic dysfunction (LVEF <35%) was significantly reduced from 52% to 9% (p = 0.0001) at 6 months but not in the MRC group (45% to 36%; p = 0.61).

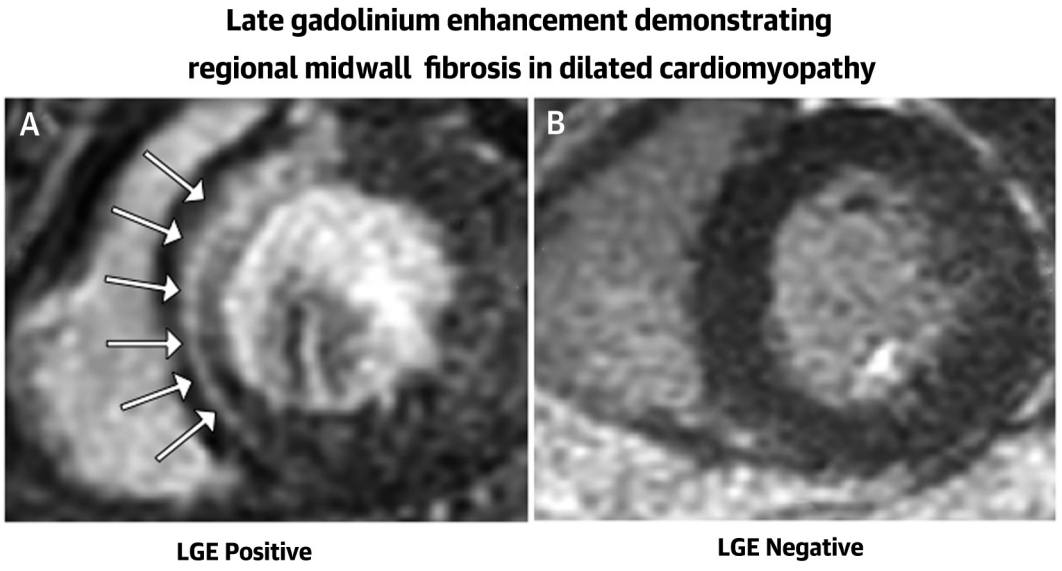
SECONDARY ENDPOINTS. Cardiac chamber dimensions. Left ventricular end-systolic volume (LVESV) was significantly decreased in the CA group (-24 ± 24 ml/m^2) compared with the MRC group (-8.0 ± 20 ml/m^2; p = 0.007) with more also reducing by ≥15% (73% vs. 27%; p = 0.0011). Left ventricular end-diastolic volume (LVEDV) decreased from baseline in the CA group but not the MRC group, with no difference between the groups. Left atrial volume significantly decreased in the CA group with no change in the MRC group (change in left atrial volume: -12 ± 13 ml/m^2 vs. 1.7 ± 14 ml/m^2; p < 0.0001).

Other secondary endpoints. Serum BNP levels significantly decreased in the CA group compared with the MRC group. In addition, NYHA functional class reduced significantly in the CA group compared with the MRC group (p < 0.0001). The 6MWT distance and physical component summary scores significantly improved from baseline in both groups, and the mental component summary scores improved in the CA group only, but with no significant difference between the groups.

LGE and LVEF improvement post-ablation. Ventricular LGE was present on baseline CMR in 36% (n = 24) of patients (36% in the CA group and 36% in the MRC group). A midwall fibrosis pattern (Figure 2) was seen in the majority of patients (83% [20 of 24]), with the remainder displaying either a subendocardial or diffuse patchy enhancement pattern. There was no significant difference in LVEF between LGE-positive (31 ± 9%) and LGE-negative (34 ± 8.5%; p = 0.13) patients; however, LVESV and LVEDV were significantly larger in LGE-positive patients (p = 0.0114 and p = 0.0138, respectively).

In those undergoing CA (n = 36), the LGE-negative group (n = 22) had a significantly greater improvement in absolute LVEF at 6 months compared with LGE-positive patients (n = 14) (11.6% vs. 22.3%; p = 0.0069) (Figure 3A). LGE-negative patients were more likely to normalize left ventricular function (73% vs. 21%; p = 0.0093 (Table 3); PPV (positive predictive value) = 73% [95% CI: 58% to 84%], NPV (negative predictive value) = 71% [95% CI: 49% to 87%]) and reduce indexed LVESV by ≥15% (86% vs. 43%; p = 0.0057; PPV = 86% [95% CI: 70% to 95%], NPV = 57% [95% CI: 38% to 75%]) at 6 months compared with LGE-positive patients. The proportion of patients with LVEF <35% decreased from 50% to 0% (p < 0.0001) in the LGE-negative group compared with 64% to 21% (p = 0.022) in the LGE-positive group

FIGURE 2 MRI-Detected Midwall Ventricular Fibrosis in Idiopathic Cardiomyopathy



An example of midwall fibrosis as detected by the presence of late gadolinium enhancement (LGE) on CMR. **Panel A** shows a short-axis view demonstrating midwall fibrosis highlighted in **white** along the inter-ventricular septum **(arrows)**. **Panel B** shows a patient with no detectable LGE. Abbreviations as in Figure 1.

(between-group difference: p = 0.051). We performed a univariable and multivariable analysis of significant predictors of LVEF normalization (including baseline LVEF, baseline mean heart rate, age, longstanding persistent AF, body mass index, AF duration, LGE status, and indexed LVEDV and LVESV) at 6 months in patients undergoing CA. The presence of LGE (p = 0.0296), indexed LVESV (p = 0.0203), and indexed LVEDV (p = 0.0195) were significant univariable predictors of LVEF normalization. On multivariable analysis, only the absence of LGE predicted LVEF normalization (p = 0.0342).

In those undergoing CA, the percentage of ventricular myocardium LGE was determined (range 0.98% to 22%; mean: 8.6 ± 7.3%). Two patients were excluded from analysis due to artifacts from ILR precluding accurate quantification. LGE percentage inversely correlated with the absolute improvement in LVEF as determined by CMR (R = -0.67; p = 0.0094) (Figure 3B).

COMPLICATIONS. There were 4 unplanned admissions in the MRC group compared with none in the CA group (excluding admission for elective DCCV for early AF recurrence). Two patients required treatment for decompensated heart failure and 2 patients required an implantable cardiac defibrillator (p = 0.11).

There were 2 procedural complications in the CA group. One patient had groin and ILR implantation site bleeding requiring blood transfusion. The other had post-procedural pneumonia. There were no deaths or thromboembolic complications.

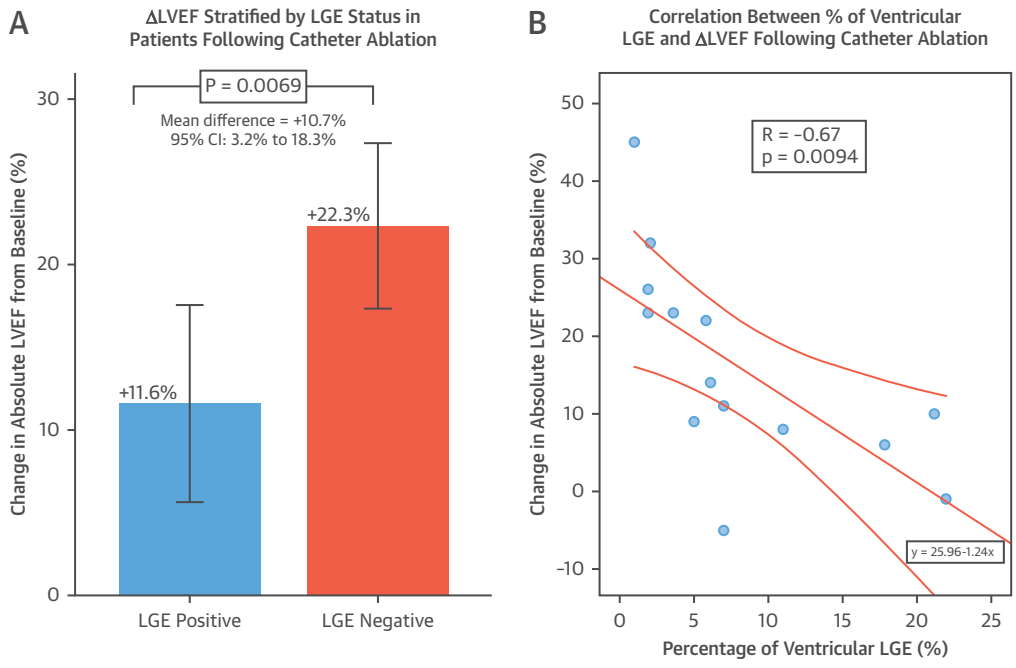
DISCUSSION

This trial is the first randomized clinical study to compare LVEF improvement after the restoration of sinus rhythm with CA versus ongoing AF with adequate MRC in patients with persistent AF and idiopathic cardiomyopathy. The key findings were as follows:

1. In the intention-to-treat analysis, CA was associated with a significant improvement in LVEF. This finding was accompanied by reductions in atrial and ventricular chamber dimensions, BNP level, and NYHA functional class.
2. The absence of ventricular LGE on cardiac MRI imaging was associated with a greater improvement in LVEF, and a higher likelihood of normalization of left ventricular function.

These findings indicate that in these patients, AF may either significantly contribute to, or indeed be entirely responsible for, LVSD. Importantly, the benefits of sinus rhythm with CA as confirmed on ILRs were present in spite of adequate rate control supporting the concept that AF-mediated

FIGURE 3 LGE and Change in Absolute LVEF



(A) Graph illustrating the LVEF change from baseline in those patients undergoing catheter ablation stratified according to the presence or absence of LGE on CMR. **Bars** represent 95% confidence intervals (CI). **(B)** Correlation between the percentage of ventricular LGE and percent change in LVEF from baseline as determined by CMR. Abbreviations as in Figures 1 and 2.

cardiomyopathy may occur independently of rapid ventricular rates. Furthermore, those patients without LGE on CMR exhibited significantly greater improvement in systolic function with the restoration of sinus rhythm suggestive of an underlying arrhythmia-mediated cardiomyopathy.

Importantly, this study population had largely failed pharmacological rhythm control, principally with amiodarone (86%), with 96% of patients having had an average of 2 separate DCCV attempts. In this study, CA offered an effective rhythm control strategy for these patients, with previously ineffective antiarrhythmic medications used in concert in one-third of patients. This outcome is consistent with the findings of a recent large, multicenter randomized trial, which found that CA was superior to amiodarone in maintaining sinus rhythm in patients with systolic dysfunction (6).

PRIOR STUDIES. Five randomized clinical trials have evaluated the role of CA in patients with AF and LVSD. Khan et al. (8) randomized 81 patients with either paroxysmal (46%) or persistent AF (51%) and predominantly ischemic cardiomyopathy (71%) to receive either CA (n = 41) or biventricular pacing and AV node ablation (n = 40); they found a significant, albeit modest improvement in LVEF (8 ± 8%). MacDonald et al. (9) randomized 41 patients with more severe LVSD (LVEF: 20.0 ± 5.5%; 48% ischemic) to receive CA (n = 22) or MRC (n = 19) and found no significant improvement in LVEF; the reduced procedural success (50%) in this advanced heart failure population, however, may have explained these findings. Jones et al. (7) randomized 52 patients with LVSD (LVEF: 23.5 ± 7.5%; 23% ischemic) to CA or MRC. Despite a significant improvement in maximal oxygen uptake, quality of life, and BNP, there was no significant improvement in LVEF. Hunter et al. (10) randomized 50 patients to receive either CA (n = 26) or MRC (n = 24; 26% ischemic). Ablation was associated with a modest but significant improvement in LVEF (8.1 ± 5.1% vs. -3.6 ± 4.1%; $p < 0.001$), quality of life, functional capacity (maximal oxygen uptake), and BNP at 6 months. Recently, the AATAC-AF (Ablation versus Amiodarone for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure and an Implanted ICD/CRTD) trial (6) randomized 203 patients with AF and LVSD (LVEF: 30 ± 6%; 46%

TABLE 3 Improvement in LVEF Stratified According to LGE Status: Actual Treatment Analysis

	Comparison within each group (LGE positive vs. LGE negative)			
	LGE Positive (n = 14)	**LGE Negative (n = 22)**	**Mean Difference**	**p Value**
Patients undergoing catheter ablation (n = 36)				
Baseline LVEF, %	32.1 ± 8.7	31.7 ± 9.4	0.4 (−5.9 to 6.8)	0.89
6 month LVEF, %	43.7 ± 11.2	54.0 ± 8.5	10.3 (3.3 to 17.0)	0.0036
Change in LVEF from baseline, %	11.6 ± 10.3	22.3 ± 11.3	10.7 (3.2 to 18.3)	0.0069
LVEF ≥50% at 6 months	29 (4)	73 (16)	44.2 (10.7 to 66.1)	0.0093
Improvement in LVEF by ≥15%	29 (4)	82 (18)	53.2 (20.2 to 73.3)	0.0014
Patients undergoing medical rate control (n = 30)	LGE Positive (n = 10)	LGE Negative (n = 20)	Mean Difference	p Value
Baseline LVEF, %	29.0 ± 7.8	36.8 ± 7.0	7.7 (2.1 to 13.3)	0.0089
6-month LVEF, %	33.8 ± 7.3	39.3 ± 9.8	5.5 (−1.0 to 12.0)	0.09
Change in LVEF from baseline, %	4.8 ± 8.5	2.9 ± 9.8	2.3 (−5.1 to 9.7)	0.54
LVEF ≥50% at 6 months	0 (0)	10 (2)	10 (−25 to 33)	0.30
Improvement in LVEF by ≥15%	0 (0)	10 (2)	10 (−25 to 33)	0.30
Comparison between treatment arms (catheter ablation and medical rate control)	**Mean Difference**		**95% CI**	**p Value**
LGE positive				
Change in LVEF from baseline	6.8		−1.5 to 15.0	0.10
LVEF ≥50% at 6 months	29		−3.9 to 54.7	0.06
LGE negative				
Change in LVEF from baseline	19.8		13.1 to 26.4	<0.0001
LVEF ≥50% at 6 months	63		30.0 to 80.4	<0.0001

Values are mean ± SD, % (n), or %, unless otherwise indicated.
Abbreviations as in Tables 1 and 2.

nonischemic) to receive either rhythm control with CA or amiodarone. In addition to demonstrating the superiority of CA as a rhythm control strategy, those patients in either arm that maintained sinus rhythm demonstrated improvements in median LVEF (9.6% vs. 4.2%; $p < 0.001$), 6MWT distance, and heart failure symptoms.

Other nonrandomized studies have also shown variable improvements in LVEF after CA (12,17,18), likely explained by the contribution of ischemic injury or ventricular fibrosis to LVSD. A meta-analysis of 1,838 patients found that although overall CA modestly improved LVEF, the greatest improvements were in the idiopathic or dilated cardiomyopathy group (12). Prabhu et al. (19) retrospectively evaluated the outcomes of 101 patients with reduced LVEF undergoing CA stratified according to etiology. Patients with an idiopathic cardiomyopathy reported significant improvements in LVEF compared with those with a known cause of LVSD, such as myocardial infarction or valvular disease.

To the best of our knowledge, the present study is the first to specifically evaluate patients with persistent AF and an idiopathic cardiomyopathy in a prospective randomized fashion with ILRs to confirm the presence of sinus rhythm with CA. Based on the present findings, we report that the restoration of sinus rhythm with CA resulted in substantial improvements in systolic function and that AF was an underestimated cause of LVSD in this patient population.

LGE AND LVEF IMPROVEMENT. Within this patient population, further stratification may identify those patients who benefit most from the restoration of sinus rhythm. In the present study, more than two-thirds of patients were co-diagnosed with AF and LVSD on first presentation. Frequently, the clinical history cannot determine the temporal relationship of both conditions. A noninvasive tool such as CMR may provide further insights. In the present study, the absence of ventricular fibrosis (as determined by LGE) on CMR was associated with a significantly greater improvement, including normalization, of LVEF in the CA group. There is an 8-fold increase in risk of heart failure hospitalization, appropriate implantable cardiac defibrillator therapy or cardiac-related death in nonischemic LGE-positive cardiomyopathy (20). In a retrospective analysis of patients undergoing CA for AF, the presence of ventricular LGE was associated with a lack of recovery of LVEF (21). Normalization of LVEF in this population was associated with a reduction in heart failure hospitalization and mortality. Furthermore, the reduction in LVESV ≥15%

reported in the CA group has been previously correlated with improved survival in LVSD (22). Ling et al. (15) prospectively evaluated improvement in LVEF after CA in 16 patients with LVSD (LVEF <50%) and the absence of LGE on baseline CMR imaging demonstrating an absolute improvement in LVEF of 20 ± 10% at repeat CMR in 6 months. This outcome is consistent with the findings of this study with a similar magnitude of improvement in LVEF in the LGE-negative patients. A lesser improvement in left ventricular function was seen in LGE-positive patients (**Figure 3A**). Some improvement may be expected because ventricular fibrosis is not a binary phenomenon supported by a significant inverse correlation demonstrated between the extent of ventricular LGE and the magnitude of left ventricular recovery (**Figure 3B**). As such, these findings should not necessarily be used to proscribe CA in LGE-positive cardiomyopathy because significant improvements in LVEF may still occur; rather, it should be a consideration in clinical decision making.

IMPACT ON PRIMARY PREVENTION IMPLANTABLE CARDIAC DEFIBRILLATOR THERAPY. The potential to prospectively identify those patients likely to respond to CA may have important implications for primary prevention device therapy in this patient population. CA reduced the number of patients meeting current guideline criteria for primary prevention implantable cardiac defibrillator (LVEF <35%) by almost one-third compared with MRC ($p = 0.0082$). In addition, no patients in the LGE-negative group undergoing CA met guideline criteria at 6 months compared with 21% in the LGE-positive group.

"ARRHYTHMIA" VERSUS "TACHYCARDIA"-MEDIATED CARDIOMYOPATHY. Reduced systolic function in the setting of AF has been termed "tachycardia-mediated cardiomyopathy"; however, although the rate of improvement with the restoration of sinus rhythm was notable, the present study clearly supports the role of several other mechanisms by which AF may lead to systolic impairment (23). Irregular ventricular activity (24,25) and the loss of atrial contraction (26) also contribute to reduced cardiac output, whereas shared mechanisms, such as activation of neurohormonal (27) and pro-fibrotic (28,29) pathways, also play a significant role. Despite the presence of adequate rate control at baseline, which improved over the course of the study in the rate control group, there was only a modest improvement in LVEF compared with the substantial recovery of LVEF after CA with accompanying improvements in NYHA functional class, reductions in BNP level, and cardiac dimensions. The term "arrhythmia-mediated cardiomyopathy" may be more appropriate to describe LVSD attributable to AF.

STUDY LIMITATIONS. The exclusion of patients with non-MRI-compatible cardiac devices (predominantly defibrillators) may have added selection bias to the study population. CA was associated with an AF burden of 1.5% at 6 months, which is unlikely to represent the long-term single procedure success of CA because AF recurrence continues to occur over time. Further improvements in reverse remodeling may have been seen if patients were followed up for >6 months. Patients with paroxysmal AF were excluded because significant variation in AF burden may affect the likelihood of AF contributing to the underlying systolic dysfunction. Although this study is the largest randomized study to date comparing CA and pharmacological rate control in AF and LVSD, the endpoints are surrogates for clinical outcomes. The study was underpowered to detect outcomes such as heart failure hospitalization and mortality, which should become the focus of larger, longer-term randomized studies in this specific population.

CONCLUSIONS

A significant proportion of patients with persistent AF and otherwise unexplained LVSD have an under-recognized arrhythmia-mediated cardiomyopathy present despite adequate ventricular rate control. The restoration of sinus rhythm with CA is associated with considerable improvements in LVEF, cardiac remodeling, and functional capacity.

The absence of CMR-detected ventricular fibrosis identifies "super responders" to CA. CA in conjunction with CMR should be considered in patients with persistent AF and otherwise unexplained systolic dysfunction. These findings challenge the current treatment paradigm that rate control is adequate in AF and heart failure.

ACKNOWLEDGMENTS The authors acknowledge the support of the cardiology departments of the Alfred, Royal Melbourne Hospital and Monash Medical Centre in running this clinical trial. Statistical analyses were reviewed by the Statistical Consulting Centre, University of Melbourne, Australia (Ian Gordon).

ADDRESS FOR CORRESPONDENCE: Dr. Peter M. Kistler, Baker Heart and Diabetes Institute, 75 Commercial Road, Melbourne, Victoria, Australia 3004. E-mail: peter.kistler@baker.edu.au.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Rate control with AV-nodal blocking drugs is the standard treatment for patients with persistent AF and LV systolic dysfunction, but restoration of sinus rhythm through catheter ablation results in a greater degree of improvement in LV ejection fraction, particularly in patients without ventricular fibrosis detected by CMR.

TRANSLATIONAL OUTLOOK: Larger, longer-term studies are needed to assess the impact of catheter ablation on clinical outcomes in patients with AF and LV dysfunction.

REFERENCES

1. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation 2014;129:837–47.

2. Roger VL. Epidemiology of heart failure. Circulation Res 2013;113:646–59.

3. Sanders P, Morton JB, Davidson NC, et al. Electrical remodeling of the atria in congestive heart failure: electrophysiological and electroanatomic mapping in humans. Circulation 2003;108:1461–8.

4. Miyasaka Y, Barnes ME, Gersh BJ, et al. Incidence and mortality risk of congestive heart failure in atrial fibrillation patients: a community-based study over two decades. Eur Heart J 2006;27:936–41.

5. Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med 2008;358:2667–77.

6. Di Biase L, Mohanty P, Mohanty S, et al. Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: results from the AATAC multicenter randomized trial. Circulation 2016;133:1637–44.

7. Jones DG, Haldar SK, Hussain W, et al. A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. J Am Coll Cardiol 2013;61:1894–903.

8. Khan MN, Jais P, Cummings J, et al. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. N Engl J Med 2008;359:1778–85.

9. MacDonald MR, Connelly DT, Hawkins NM, et al. Radiofrequency ablation for persistent atrial fibrillation in patients with advanced heart failure and severe left ventricular systolic dysfunction: a randomised controlled trial. Heart 2011;97:740–7.

10. Hunter RJ, Berriman TJ, Diab I, et al. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). Circ Arrhythm Electrophysiol 2014;7:31–8.

11. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893–962.

12. Anselmino M, Matta M, D'Ascenzo F, et al. Catheter ablation of atrial fibrillation in patients with left ventricular systolic dysfunction: a systematic review and meta-analysis. Circ Arrhythm Electrophysiol 2014;7:1011–8.

13. Aleksova A, Merlo M, Zecchin M, et al. Impact of atrial fibrillation on outcome of patients with idiopathic dilated cardiomyopathy: data from the Heart Muscle Disease Registry of Trieste. Clin Med Res 2010;8:142–9.

14. Tuomainen PO, Magga J, Fedacko J, et al. Idiopathic dilated cardiomyopathy and chronic atrial fibrillation. Clin Physiol Funct Imaging 2014;34:133–7.

15. Ling LH, Taylor AJ, Ellims AH, et al. Sinus rhythm restores ventricular function in patients with cardiomyopathy and no late gadolinium enhancement on cardiac magnetic resonance imaging who undergo catheter ablation for atrial fibrillation. Heart Rhythm 2013;10:1334–9.

16. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med 1998;17:873–90.

17. Hsu LF, Jaïs P, Sanders P, et al. Catheter ablation for atrial fibrillation in congestive heart failure. N Engl J Med 2004;351:2373–83.

18. Chen MS, Marrouche NF, Khaykin Y, et al. Pulmonary vein isolation for the treatment of atrial fibrillation in patients with impaired systolic function. J Am Coll Cardiol 2004;43:1004–9.

19. Prabhu S, Ling LH, Ullah W, et al. The impact of known heart disease on long-term outcomes of catheter ablation in patients with atrial fibrillation and left ventricular systolic dysfunction: a multicenter international study. J Cardiovasc Electrophysiol 2016;27:281–9.

20. Wu KC, Weiss RG, Thiemann DR, et al. Late gadolinium enhancement by cardiovascular magnetic resonance heralds an adverse prognosis in nonischemic cardiomyopathy. J Am Coll Cardiol 2008;51:2414–21.

21. Addison D, Farhad H, Shah RV, et al. Effect of late gadolinium enhancement on the recovery of left ventricular systolic function after pulmonary vein isolation. J Am Heart Assoc 2016;5.

22. Bertini M, Hoke U, van Bommel RJ, et al. Impact of clinical and echocardiographic response to cardiac resynchronization therapy on long-term survival. Eur Heart J Cardiovasc Imaging 2013;14:774–81.

23. Medi C, Kalman JM, Haqqani H, et al. Tachycardia-mediated cardiomyopathy secondary to focal atrial tachycardia: long-term outcome after catheter ablation. J Am Coll Cardiol 2009;53:1791–7.

24. Clark DM, Plumb VJ, Epstein AE, Kay GN. Hemodynamic effects of an irregular sequence of ventricular cycle lengths during atrial fibrillation. J Am Coll Cardiol 1997;30:1039–45.

25. Ling LH, Khammy O, Byrne M, et al. Irregular rhythm adversely influences calcium handling in ventricular myocardium: implications for the interaction between heart failure and atrial fibrillation. Circulation Heart Failure 2012;5:786–93.

26. Benchimol A, Duenas A, Liggett MS, Dimond EG. Contribution of atrial systole to the cardiac function at a fixed and at a variable ventricular rate. Am J Cardiol 1965;16:11–21.

27. Schneider MP, Hua TA, Bohm M, Wachtell K, Kjeldsen SE, Schmieder RE. Prevention of atrial fibrillation by renin-angiotensin system inhibition a meta-analysis. J Am Coll Cardiol 2010;55:2299–307.

28. Iles L, Pfluger H, Phrommintikul A, et al. Evaluation of diffuse myocardial fibrosis in heart failure with cardiac magnetic resonance contrast-enhanced T1 mapping. J Am Coll Cardiol 2008;52:1574–80.

29. Ling LH, Kistler PM, Ellims AH, et al. Diffuse ventricular fibrosis in atrial fibrillation: noninvasive evaluation and relationships with aging and systolic dysfunction. J Am Coll Cardiol 2012;60:2402–8.

KEY WORDS catheter ablation, idiopathic cardiomyopathy, late gadolinium enhancement, medical rate control, persistent AF

Go to http://www.acc.org/jacc-journals-cme to take the CME/MOC quiz for this article.