Prediction of Arrhythmic Events in Ischemic and Dilated Cardiomyopathy Patients Referred for Implantable Cardiac Defibrillator

Evaluation of Multiple Scar Quantification Measures for Late Gadolinium Enhancement Magnetic Resonance Imaging

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Background—Scar signal quantification using late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) identifies patients at higher risk of future events, both in ischemic cardiomyopathy (ICM) and nonischemic dilated cardiomyopathy (DCM). However, the ability of scar signal burden to predict events in such patient groups at the time of referral for implantable cardioverter-defibrillator (ICD) has not been well explored. This study evaluates the predictive use of multiple scar quantification measures in ICM and DCM patients being referred for ICD.

Methods and Results—One hundred twenty-four consecutive patients referred for ICD therapy (59 with ICM and 65 with DCM) underwent a standardized LGE-CMR protocol with blinded, multithreshold scar signal quantification and, for those with ICM, peri-infarct signal quantification. Patients were followed prospectively for the primary combined outcome of appropriate ICD therapy, survived cardiac arrest, or sudden cardiac death. At a mean follow-up of 632±262 days, 18 patients (15%) had suffered the primary outcome. Total scar was significantly higher among those suffering a primary outcome, a relationship maintained within each cardiomyopathy cohort (P<0.01 for all comparisons). Total scar was the strongest independent predictor of the primary outcome and demonstrated a negative predictive value of 86%. In the ICM subcohort, peri-infarct signal showed only a nonsignificant trend toward elevation among those having a primary end point.

Conclusions—Myocardial scar quantification by LGE-CMR predicts arrhythmic events in patients being evaluated for ICD eligibility irrespective of cardiomyopathy etiology. (Circ Cardiovasc Imaging. 2012;5:448-456.)

Key Words: ventricular arrhythmia □ MRI □ implantable cardioverter-defibrillator (ICD) □ sudden cardiac death

Approximately two thirds of fatal cardiovascular events in patients with a left ventricular ejection fraction (LVEF) ≤35% are caused by sudden cardiac death (SCD). Implantable cardiac-defibrillators (ICD) offer significant reductions in SCD in patients with both ischemic cardiomyopathy (ICM) and nonischemic dilated cardiomyopathy (DCM). These devices currently are recommended for patients with symptomatic heart failure and an LVEF ≤35%, and for asymptomatic ICM patients with an LVEF ≤30%. However, post hoc analysis of the MADIT II study identified that only 35% of patients receiving ICDs subsequently received appropriate therapy at 3 years. Furthermore, many patients with resuscitated SCD are found to have an LVEF above current ICD implantation guidelines thresholds. Therefore, current selection criteria for primary prevention ICD are suboptimal and emphasize a need for supplementary or alternate risk stratification tools.

Clinical Perspective on p 456

Myocardial scar is a recognized substrate for the development of malignant arrhythmias in patients with systolic dysfunction. While the mechanisms contributing to arrhythmia generation in this population remain complex, relatively simple markers of scar burden from late gadolinium...
enhancement-cardiovascular magnetic resonance (LGE-CMR) imaging appear to hold prognostic value. In patients with DCM, the presence of myocardial hyper-enhancement (HE) on LGE-CMR has been associated with future arrhythmic events. Similarly, HE extent has been associated with future cardiac death and appropriate ICD therapy in patients with ischemic cardiomyopathy. Collectively, these studies suggest HE signal quantification to be potentially useful as a risk stratification tool in both ICM and DCM patients being referred for ICD. The aim of this study was to assess the predictive use of HE signal quantification for the prediction of appropriate ICD therapy, survived cardiac arrest (SCA), or SCD in patients with ICM or DCM being referred for ICD therapy.

**Methods**

**Study Population**

This prospective cohort study was conducted at a large, tertiary care referral center (London Health Sciences Centre, London, Ontario, Canada). The study population consisted of 124 consecutive patients referred to the electrophysiology service for consideration of ICD. Patients were eligible for the study if they had a LVEF \( \leq 35\% \) estimated by echocardiography and were on maximal tolerated heart failure therapy for \( \geq 3 \) months. Prior to enrollment all patients underwent coronary angiography or computed tomography angiography (CTA) to determine cardiomyopathy etiology. ICM was defined as those with obstructive coronary artery disease in \( \geq 1 \) major epicardial vessel (stenosis \( \geq 70\% \)), all other patients being classified as DCM. CMR imaging was performed in all consenting patients, with the LGE provided to assist in clinical decision making. Patients were excluded if standard contraindications to LGE-CMR existed, inclusive of a glo-merular filtration rate of \( \leq 60 \) mL/min/1.73 m\(^2\).

All patients agreed to participation by giving both verbal and written informed consent. The study was approved by the Health Sciences Research Ethics Board at the University of Western Ontario.

**Cardiovascular Magnetic Resonance Imaging Protocol**

Cardiovascular magnetic resonance imaging was performed using a 3T magnetic resonance imaging (MRI) scanner (TIM Trio or Verio, Siemens) equipped with a 32-channel cardiac coil. Cardiac function was assessed in sequential short axis views at 10 mm intervals from the atrioventricular annulus to apex using a standard steady state free precession (SSFP)-based “cine” pulse sequence. Typical imaging parameters were slice thickness 6 mm, gap 4 mm, TE 1.3 ms, flip angle 10 degrees, matrix 256×205, iPAT 2, and temporal resolution 28 to 38 ms. Ten to 15 minutes following intravenous administration of Gadolinium contrast (0.15–0.2 mmol/kg, Gadovist, Bayer Inc; Toronto, Canada) LGE imaging was performed using a standard, segmented inversion recovery gradient echo pulse sequence in identical imaging planes. Typical imaging parameters were slice thickness 6 mm, gap 4 mm, TR 800 ms, TE 3.9 ms, flip angle 20 degrees, matrix 256×205, segments 13 to 21, and iPAT 2. The inversion time was optimized to null normal myocardium, as previously described.

**Cardiovascular Magnetic Resonance Image Analysis**

Quantitative image analysis was performed using commercially available software (CMR42; Circle Cardiovascular Imaging Inc, Calgary, Canada). Cine images were examined to determine the LV end systolic volume, LV end diastolic volume, and LV mass by semiautomated endocardial and epicardial contour tracing. An experienced CMR interpreter (J.A.W.), blinded to all baseline and clinical outcome variables, performed HE signal quantification on de-identified and randomly ordered short axis LGE datasets.

The presence or absence of any myocardial HE was visually determined and the most dominant pattern scored, as follows: (1) subendocardial based, (2) midwall, or (3) subepicardial. HE signal quantification then was performed using manual endocardial and epicardial contour tracing, with the manual exclusion of any visible artifacts. Employing the signal threshold versus reference myocardium (STRM) technique, as previously described, 3 different signal thresholds for the definition of total HE were evaluated: \( \geq 2SD \), \( \geq 3SD \), and \( \geq 5SD \) above the mean signal of reference myocardium. This was performed to identify the optimal threshold for the prediction of clinical events using this signal analysis technique. The reference myocardium was identified manually as the largest contiguous region of homogeneously nullified myocardium, as shown in Figure 1. In those with ICM, peri-infarct signal also was calculated as described by Yan et al as the difference between total HE measured by \( \geq 2SD \) and \( \geq 3SD \) thresholds. In this cohort HE signal analysis also was performed using the full width half max (FWHM) technique, as previously validated and described, similarly used to quantify both the total HE and peri-infarct zone signal. All HE measures were expressed in grams by multiplying HE area by slice thickness, and then converting to mass by multiplying by a specific gravity of 1.05.

**Interobserver and Intraobserver Variability**

Inter- and intraobserver variability was evaluated for HE signal quantification. Two experienced and blinded interpreters independently performed and described signal analysis on 2 separate occasions. This was performed for 10 randomly selected ICM cases and 10 randomly selected DCM cases.

**Device Implantation and Programming**

Implantable cardiac-defibrillator implantations were performed in a standard fashion at a median of 27 days (interquartile range 8–45) following CMR. ICD devices were programmed to detect ventricular fibrillation (VF) if 18 of 24 R-R intervals were \( \leq 240 \) ms. “Fast ventricular tachyarrhythmias (VT)” was defined as 18 of 24 consecutive R-R intervals \( \leq 320 \) ms and “slow VT” as 16 consecutive R-R intervals \( \leq 400 \) ms. For primary prevention patients’ devices routinely were programmed to deliver antitachycardia pacing (ATP) or shock therapy for VF or fast VT, and to monitor (ie, not deliver therapy) for slow VT. In patients receiving secondary prevention ICD this programming was altered to treat slow VT using both ATP and shock therapies.

**Follow-Up and Clinical Events**

Clinical follow-up was initiated from the time of CMR imaging. The primary composite clinical outcome was defined as the occurrence of appropriate ICD therapy, SCA, or SCD. Occurrence of the primary outcome or nonsudden cardiac death served as a secondary composite clinical outcome. In patients having \( \geq 2 \) clinical events registered during follow-up, the time to first clinical event was used for analysis of event-free survival.

All patients receiving ICDs underwent interrogations at 1, 3, and 6 months, and every 6 months thereafter. At study closure all interrogations were de-identified and adjudicated by 2 electrophysiologists blinded to CMR analysis. Appropriate ICD therapy was defined as ATP or shock for fast VT (R-R \( <320 \) ms) or VF. ICD therapy was classified as inappropriate when delivered for non-target arrhythmias, such as sinus or supraventricular tachycardia, T-wave oversensing, or for any device system malfunction, such as lead conductor wire fracture. All study patients, irrespective of ICD implantation status, were evaluated for the clinical occurrence of SCA or SCD. SCD was defined as death occurring within 1 hour of symptom onset. This was performed at 12 month intervals and at study closure by telephone interview and a review of all medical records.

**Statistical Analysis**

Continuous data are expressed as mean±SD and categorical data in frequencies and percentages. Respective baseline differences between
patients with and without the primary outcome were compared by
the independent sample t test, and Chi-square ($\chi^2$) test. ANOVA was
used for comparison of means from multiple groups. Survival curves
were estimated by the Kaplan-Meier method and compared by the
log-rank test. Univariable and multivariable analyses of event free
survival were performed according to the Cox regression model.
We constructed a multivariable model to assess the incremental as-
sociation of total HE and all baseline clinical variables (Table 1) to
the primary outcome using backward stepwise selection ($P<0.10$ for
entry and $P>0.05$ for removal). Only a single variable ("primary pre-
vention ICD") was found to be eligible and therefore was used to
provide an adjusted hazards ratio (HR) for total HE. Due to the lim-
ited number of events ($N=18$), no other covariates were forced into
the model to comply with the general rule that 10 events should be
available for each variable tested. $^{19,20}$ Unadjusted and adjusted HRs
with corresponding 95% CIs then were described. Receiver operating
curve analysis with logistic regression and discriminant predicted prob-
babilities was performed to test associations between
HE measure and the primary outcome.

Interobserver and intraobserver variability was assessed using
Bland-Altman analysis and interclass correlation coefficient (ICC)
with 95% CI. ICC was used rather than the correlation coefficient as
it incrementally provides assessment of systematic error between ob-
servers. $^{21}$ All tests were 2-sided with a level of statistical significance
set at $P<0.05$. All analyses were performed using the SPSS software
package 19.0 (SPSS, Inc.).

Results

Baseline Patient Characteristics
A total of 124 patients were enrolled, 59 with ICM and 65
with DCM. Of the latter group, a definite etiology was estab-
lished in 18 patients by combined consideration of patient his-
tory, clinical records, and CMR imaging findings. These were
viral cardiomyopathy (N=8, defined by a clear history of viral
illness plus midwall or subepicardial HE), cardiac sarcoi
(N=6), chemotherapy-induced cardiomyopathy (N=3),
and arrhythmogenic right ventricular cardiomyopathy (ARVC)
with LV involvement (N=1). All other baseline clinical char-
acteristics are presented in Table 1.

Of all patients enrolled, 79 (64%) underwent ICD implan-
tation, 41 with ICM, and 38 with DCM. Of these, 69 devices
(87%) were inserted for the primary prevention of SCD, while
10 patients (13%) had a prior history of sustained VT (N=8)
or VF (N=2). No differences were observed in ICD insertion
rates between those with ICM or DCM ($P=0.37$). Forty-five
patients (57%) received cardiac resynchronization therapy (19
with ICM and 26 with DCM). Of patients that did not receive
an ICD, 21 failed to verify LVEF criterion by CMR imaging,
all having an LVEF between 36% and 40%. All other patients
met LVEF criteria but either refused to proceed with device
implantation (N=14) or were declined on the basis of comor-
bidity (N=10). Of the latter group 5 had severe heart failure, 3
had severe pulmonary disease, and 2 had a cancer detected by
screening investigations.

Clinical Follow-Up: Primary and Secondary Events
All patients prospectively were followed for the occurrence
of survived SCA, SCD, or, in those receiving devices,
appropriate ICD therapy. During a mean follow-up of
632±262 days, 18 patients (15%) suffered a primary out-
come, 10 patients with ICM and 8 patients with DCM. Of
these patients 15 had an appropriate ICD therapy (ATP in
13, shock in 11), 2 had SCD, and 1 patient had SCA. In
addition, 6 patients suffered a non-sudden cardiac death
due to progressive heart failure (4 with ICM and 2 with DCM), contributing to a total of 24 secondary outcomes.

Non–Hyper-Enhancement Cardiovascular Magnetic Resonance Measures
Baseline CMR imaging findings are presented in Table 2 for the total population, ICM subcohort, and DCM subcohort. The mean LVEF of the population was 26±7%. No significant differences were observed among any non-HE variables between those with and without a primary outcome, irrespective of cardiomyopathy etiology (Table 2).

Prevalence and Pattern of Hyper-Enhancement by Visual Interpretation
Overall, 105 patients (85%) had any HE scored by visual assessment, 59/59 ICM patients (100%) and 46/65 DCM patients (71%; Table 2). Eleven patients with ICM (19%) demonstrated a secondary pattern of nonischemic HE, and 8 DCM patients demonstrated incidental subendocardial ischemic injury. Of the 46 DCM patients showing nonischemic HE, 31 patients (67%) had a predominantly midwall pattern, while 17 patients (37%) had a predominantly subepicardial pattern. Neither the presence of HE nor any of these patterns of HE showed significant

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**Table 1. Non-Magnetic Resonance Imaging Baseline Patient Characteristics, Presented for the Total Population and for Those With and Without the Primary Outcome**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Population (N=124)</th>
<th>Without Primary Outcome (N=106)</th>
<th>With Primary Outcome (N=18)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61±11</td>
<td>61±11</td>
<td>60±11</td>
<td>0.518</td>
</tr>
<tr>
<td>Male sex</td>
<td>100 (81%)</td>
<td>85 (80%)</td>
<td>15 (83%)</td>
<td>0.522</td>
</tr>
<tr>
<td>Race (Caucasian)</td>
<td>103 (83%)</td>
<td>89 (84%)</td>
<td>14 (79%)</td>
<td>0.522</td>
</tr>
<tr>
<td>Cardiomyopathy etiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICM (ICM)</td>
<td>59 (48%)</td>
<td>49 (46%)</td>
<td>10 (55%)</td>
<td>0.468</td>
</tr>
<tr>
<td>DCM (DCM)</td>
<td>65 (52%)</td>
<td>57 (53%)</td>
<td>8 (44%)</td>
<td>0.468</td>
</tr>
<tr>
<td>Hypertension</td>
<td>64 (52%)</td>
<td>54 (51%)</td>
<td>10 (56%)</td>
<td>0.720</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>30 (24%)</td>
<td>26 (24%)</td>
<td>4 (22%)</td>
<td>0.834</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>72 (58%)</td>
<td>61 (58%)</td>
<td>11 (61%)</td>
<td>0.779</td>
</tr>
<tr>
<td>Smoking</td>
<td>53 (43%)</td>
<td>44 (42%)</td>
<td>9 (50%)</td>
<td>0.505</td>
</tr>
<tr>
<td>Any prior revascularization</td>
<td>42 (34%)</td>
<td>36 (34%)</td>
<td>6 (33%)</td>
<td>0.959</td>
</tr>
<tr>
<td>History of MI</td>
<td>57 (46%)</td>
<td>46 (43%)</td>
<td>11 (61%)</td>
<td>0.166</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>119±18</td>
<td>118±18</td>
<td>116±21</td>
<td>0.515</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>72±9</td>
<td>72±9</td>
<td>69±8</td>
<td>0.186</td>
</tr>
<tr>
<td>GFR (mL/min/1.73 m²)</td>
<td>76±19</td>
<td>75±19</td>
<td>72±19</td>
<td>0.478</td>
</tr>
<tr>
<td>LBBB</td>
<td>55 (44%)</td>
<td>46 (43%)</td>
<td>9 (50%)</td>
<td>0.606</td>
</tr>
<tr>
<td>QRS duration (msec)</td>
<td>136±29.8</td>
<td>136±30</td>
<td>136±22</td>
<td>0.963</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>2.5±0.9</td>
<td>2.5±0.9</td>
<td>2.2±1.0</td>
<td>0.196</td>
</tr>
<tr>
<td>ICD implantation</td>
<td>79 (64%)</td>
<td>64 (60%)</td>
<td>15 (83%)</td>
<td>0.062</td>
</tr>
<tr>
<td>Primary prevention</td>
<td>69 (56%)</td>
<td>58 (55%)</td>
<td>11 (61%)</td>
<td>0.023*</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>10 (8%)</td>
<td>6 (6%)</td>
<td>4 (22%)</td>
<td>0.093*</td>
</tr>
<tr>
<td>CRT Implantation</td>
<td>45 (36%)</td>
<td>39 (37%)</td>
<td>6 (33%)</td>
<td>0.780</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>88 (71%)</td>
<td>75 (71%)</td>
<td>13 (72%)</td>
<td>0.946</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>9 (7%)</td>
<td>8 (8%)</td>
<td>1 (6%)</td>
<td>0.758</td>
</tr>
<tr>
<td>ARB</td>
<td>31 (25%)</td>
<td>29 (27%)</td>
<td>3 (17%)</td>
<td>0.332</td>
</tr>
<tr>
<td>ASA</td>
<td>84 (68%)</td>
<td>72 (68%)</td>
<td>12 (67%)</td>
<td>0.874</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>99 (80%)</td>
<td>86 (81%)</td>
<td>13 (72%)</td>
<td>0.342</td>
</tr>
<tr>
<td>Digoxin</td>
<td>29 (23%)</td>
<td>25 (24%)</td>
<td>4 (22%)</td>
<td>0.885</td>
</tr>
<tr>
<td>Diuretic</td>
<td>73 (59%)</td>
<td>62 (58%)</td>
<td>11 (61%)</td>
<td>0.871</td>
</tr>
<tr>
<td>Plavix</td>
<td>14 (11%)</td>
<td>13 (12%)</td>
<td>1 (6%)</td>
<td>0.404</td>
</tr>
<tr>
<td>Statin</td>
<td>66 (53%)</td>
<td>55 (52%)</td>
<td>11 (61%)</td>
<td>0.497</td>
</tr>
</tbody>
</table>

*Considered eligible for multivariable analysis.
Continuous data are expressed as mean±SD, categorical data as n (%). ICM indicates ischemic cardiomyopathy; DCM, dilated cardiomyopathy; MI, myocardial infarction; BP, blood pressure; GFR, glomerular filtration rate; LBBB, left bundle-branch block; NYHA, New York Heart Association; CRT, cardiac resynchronization therapy; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid.
association with the primary outcome (Table 3). The number of HE patterns (ie, combined patterns) similarly was not predictive.

**Total Hyper-Enhancement by Quantitative Analysis**

Table 2 summarizes the results of quantitative HE signal analysis. STRM-based analysis, previously validated for use in both cohorts, showed total HE to be significantly higher in those with ICM versus those with DCM ($P<0.001$). Within each subcohort the burden of total HE did not differ between those receiving versus not receiving an ICD ($P=0.4$ for both comparisons).

**Total Hyper-Enhancement Versus the Primary Outcome**

Among the entire population, STRM-based analysis showed total HE to be significantly higher among those suffering a primary outcome, irrespective of the signal threshold used (Table 2). Using a ≥2SD threshold, the mean total HE mass among those with versus without a primary outcome was 59±30g versus 32±19g ($P=0.001$). This difference was maintained when analysis was constrained to those receiving an ICD ($P<0.001$). In the group not receiving an ICD, clinical events occurred in 3 patients (2 SCD and 1 survived SCA). Total HE mass ≥2SD still was significantly higher among those suffering events (41±19 versus 22±16g, $P=0.05$).

**Total Hyper-Enhancement Versus the Secondary Outcome**

Among the total population total HE was higher among those with versus those without a secondary outcome. However, in contrast to the primary outcome, this only reached statistical significance for the ≥2SD STRM-based signal threshold (47±26 versus 33±24g, $P=0.04$).

**All Baseline and Magnetic Resonance Imaging Variables Versus the Primary Outcome**

Univariable analysis of all baseline clinical and MRI variables revealed only “primary prevention ICD” and total HE mass (all signal thresholds) to be associated with the primary outcome. The HR obtained for total HE mass ≥2SD was 1.40/10g (95% CI, 1.21–1.62, $P=0.001$), with similar hazards identified for ≥3SD and ≥5SD thresholds (HR 1.40 and 1.43, respectively). Multivariable analysis, performed separately for each total HE threshold definition, reliably revealed total HE to be the strongest independent predictor of the primary outcome. Following adjustment for “primary prevention ICD”, the adjusted HR for total HE ≥2SD was 1.38/10g (95% CI, 1.18–1.62, $P<0.001$).
Sub-Cohort Analysis: Ischemic Cardiomyopathy and Dilated Cardiomyopathy

Within each of the ICM and DCM subcohorts, total HE mass was significantly higher among those with a primary outcome versus those without, irrespective of the signal threshold used. The mean total HE mass ≥2SD in those with and without a primary outcome was 69±17 versus 42±19g (P=0.001) for those with ICM, and 46±38 versus 23±15g (P=0.003) for those with DCM (Figure 2). Univariable analysis revealed that, while all signal thresholds were predictive, a ≥2SD threshold produced the highest HR in the ICM subcohort, while a ≥5SD threshold produced the highest HR in the DCM cohort (Table 3). A nonsignificant trend toward elevation in total HE mass was seen among those having a secondary outcome in each subcohort.

Event-Free Survival

Kaplan-Meier analyses were performed individually for the ICM and DCM subcohorts using their respective median values for total HE mass (signal threshold versus reference myocardium [STRM] ≥2SD threshold) in those with and without a primary outcome. Values are shown for the total population, ischemic cardiomyopathy (ICM) subcohort, and dilated cardiomyopathy (DCM) subcohort.

![Figure 2](http://circimaging.ahajournals.org/)
based techniques. Within the ICM cohort, the FWHM approach showed
suffering from appropriate ICD therapy, SCA, or SCD. Irrespective of cardiomyopathy etiology. Total HE mass was
demonstrated excellent agreement for all HE measures. The
Interobserver and Intraobserver observer variability testing obtained using these techniques. For example, area under
the curve (AUC) values for the STRM-based thresholds of
≥2SD, ≥3SD, and ≥5SD were 0.78, 0.76, and 0.76, while the
FWHM-based total HE achieved an AUC of 0.75.
Peri-infarct signal was calculated using the previously
published STRM-based method (2SD minus 3SD)\textsuperscript{13} and
the FWHM-based method.\textsuperscript{14} These measures, summarized
in Table 2, showed only nonsignificant trends toward being
higher in those with a primary outcome.

Ischemic Cardiomyopathy Subcohort: Full Width
Half Max-Based Analysis and Quantification of the
Peri-Infarct Zone
To compare the use of STRM-based versus FWHM-based HE
measures in those with ICM, individual receiver operating
characteristic analyses were performed. This revealed only
minor differences in predictive accuracy for total HE mass
obtained using these techniques. For example, area under
the curve (AUC) values for the STRM-based thresholds of
≥2SD, ≥3SD, and ≥5SD were 0.78, 0.76, and 0.76, while the
FWHM-based total HE achieved an AUC of 0.75.
Peri-infarct signal was calculated using the previously
published STRM-based method (2SD minus 3SD)\textsuperscript{13} and
the FWHM-based method.\textsuperscript{14} These measures, summarized
in Table 2, showed only nonsignificant trends toward being
higher in those with a primary outcome.

Interobserver and Intraobserver Reproducibility
Interobserver and intraobserver observer variability testing demonstrated excellent agreement for all HE measures. The
ICC for intraobserver reliability for total HE measure was
0.96 (95% CI, 0.89–0.98), with ICC for interobserver reliability being 0.90 (95% CI, 0.78–0.96). Bland-Altman analyses of all HE measures are shown in Figure 4. Overall, the
STRM-based ≥2SD measure demonstrated the best reproducibility. Within the ICM cohort, the FWHM approach showed
marginally better reproducibility compared with STRM-based techniques.

Discussion
This study identifies predictive utility for the quantification of
HE by LGE-CMR in patients being referred for ICD therapy, irrespective of cardiomyopathy etiology. Total HE mass was
found to be significantly higher among ICM and DCM patients suffering from appropriate ICD therapy, SCA, or SCD.

The extent of irreversible myocardial injury has been rec-
ognized as a marker of arrhythmia risk in ICM for some time. Bolick et al\textsuperscript{22} demonstrated in 1986 that the extent of myo-
cardial scar on autopsy correlated with a prior history of VT in patients with ICM. Supporting this, Van der Burg et al\textsuperscript{23}
subsequently demonstrated that the extent of fixed perfusion
defects on single photon emission computed tomography imaging predicted future arrhythmic events and death in
patients with a history of survived SCA. Following these observations, Bello et al\textsuperscript{24} performed a sentinel study demonstrating the direct measurement of myocardial scar extent by
LGE-CMR and its correlation with the rate of VT inducibility at electrophysiological testing.

While clinical outcome-based studies evaluating the prog-
nostic utility of LGE imaging have emerged,\textsuperscript{13,25,26} only 3 have evaluated arrhythmic events in an ICD referral population, each being limited to ICM.\textsuperscript{14,15,27} In the first study, published by Roes et al,\textsuperscript{14} 91 patients with ICM referred for primary or secondary prevention ICD were followed for the occurrence of appropriate ICD therapy (20%) over a median of 8.5 months. Using FWHM-based HE analysis, total mass and the peri-infarct gray zone were found to be significantly higher in those with a primary outcome. In a second study, published by Scott et al,\textsuperscript{15} the FWHM technique was used again to measure total percent scar in 64 patients with ICM referred for ICD, and showed a strong association with the occurrence of appropriate ICD therapy (HR 1.75/10%). Finally, a recent study by de Haan et al\textsuperscript{27} evaluated 55 patients with ICM referred for ICD, measuring total scar, core scar, and the peri-infarct zone. In this study total scar was predictive of arrhythmic events but, as seen in the current study, no incremental predictive value was provided by the measurement of the peri-infarct zone. This latter study also compared STRM-based and FWHM-based approaches for HE quantification, and found them to be similar for the estimation of total scar size, similar to the current study.

Our study provides further support for the predictive utility of HE quantification in patients with ICM referred for ICD, but incrementally suggests that HE quantification may be of
value in those referred with DCM. Similar to their ICM counterparts, patients with DCM suffering from arrhythmic events demonstrated a significantly higher burden of total HE.

Study Limitations
Similar to published studies to date, ours was performed
within a single center, was limited by a small sample size, and accrued a modest number of events. This underscores the
need for larger, multicenter clinical studies aimed at evaluating the use of LGE imaging for the prediction of arrhythmic
events in patients referred for ICD. Accordingly, our findings require confirmation within such a setting prior to their clinical
application.

The study population consisted of patients being referred for ICD therapy with their MRI findings (LVEF) being accessible for clinical decision making. Accordingly, a number of patients were declined for ICD therapy due to a failure to confirm guideline-based LVEF criteria, all such patients having an LVEF between 36% and 40%. In addition, several patients were declined for ICD therapy due to comorbidity or to patient refusal to proceed. All enrolled patients were included in the final
analysis as it was the intent of this study to evaluate the role of LGE-CMR to predict future events when performed at time of ICD referral. In those patients not receiving ICD, a more robust clinical outcome (SCD or SCA) was mandated. All analyses were repeated with adjustment for ICD implantation status and demonstrated no significant differences.

The composite primary end point included appropriate ICD therapy, an outcome inherently dependent on programmed device settings. Ventricular tachyarrhythmias with cycle lengths slower than 320 ms (ie, “slow VT”) were monitored only by the device and not included within the composite primary end point. Progression of any such rhythm to life-threatening events (ICD therapy, SCD, or SCA) was captured routinely.

The FWHM-based HE quantification approach was employed only in the ICM cohort as it has not been validated for use in patients with DCM. From our center’s experience, the FWHM approach is not well-suited to HE quantification in DCM, as the peak HE signal is frequently modest and inherently leads to regions of normally nulled myocardium being labeled as “enhanced” relative to the modest HE reference signal. We do not consider this to be a limitation of the study, rather an inherent limitation of the described quantification technique for this patient cohort.

Conclusions
Total HE mass, measured by LGE-CMR imaging, is a strong predictor of appropriate ICD therapy, resuscitated SCA, or SCD among patients with ICM or DCM referred for ICD.

Acknowledgments
All authors have read and agree to the manuscript as written. Drs White, Gao, Pallaveshi, and Drangova have had full access to the study data and take responsibility for its integrity. The authors would like to thank Linda Marziali, Kris Carter (RN), Kim Krueger (RMT), and John Butler (RMT) for their important contributions to this research.

Sources of Funding
Dr White is supported by a Clinician Scientist award with the Heart and Stroke Foundation of Ontario, Canada. Dr Drangova is supported by a Career Scientist award from the Heart and Stroke Foundation of Ontario. Dr Krahn is a Career Investigator of the Heart and Stroke Foundation of Ontario. This research was supported in part by Heart and Stroke Foundation grant # NA6488 (PI: J.A.W.), the Canada Foundation of Innovation Leaders Opportunity Fund, the Ontario Research Fund, Imaging in Cardiovascular Therapeutics grant, and the Program of Experimental Medicine (POEM).

Disclosures
Dr White receives in-kind research support from Bayer, Inc., Canada, and has received consultative fees from Medtronic, Inc. Dr
Gao was supported by a fellowship-training grant from Medtronic, Inc., China.

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Circ Cardiovasc Imaging. 2012;5:448-456; originally published online May 9, 2012; doi: 10.1161/CIRCIMAGING.111.971549

Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-9651. Online ISSN: 1942-0080

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