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Example:

- Cardiovascular aging is a biological phenomenon caused by the accumulation over time of damage at the cellular, tissue, and organismal level leading to a progressive decline in function and structure.
- Calorie restriction, intermittent fasting, and adjusted diurnal rhythm of feeding are powerful interventions for the prevention of cardiovascular dysfunction and cardiovascular disease.
- Lowered intake of protein, specific amino acids, and saturated fatty acids and nutritional modulation of the gut microbiome can have additional cardioprotective roles.
- Regular endurance and resistance exercise, mindfulness-based stress reduction programs, and some calorie-restriction mimetic medications can potentiate the beneficial effects of a healthy diet.

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- a) Comprehensively illustrate a typical spectrum of important classic features or significantly novel findings;

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Include the title, authors’ names (including full first and last names and middle initial and degrees), total word count, and a brief title of no more than
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Provide a condensed abstract of 100 words, stressing clinical implications, for the expanded table of contents.

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The text should be structured as Introduction, Methods, Results, and Discussion. Use headings and subheadings in the Methods, Results, and Discussion sections. Every reference, figure, and table should be cited in the text according to order of mention.

ABBREVIATIONS

The abbreviations of common terms (e.g., ECG, PTCA, CABG) or acronyms (GUSTO, SOLVD, TIMI) may be used in the manuscript. On a separate page following the condensed abstract, list the selected abbreviations and their definitions (e.g., TEE = transesophageal echocardiography). The Editors may determine which lesser known terms should not be abbreviated. Please consult “Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations),” available at www.icmje.org/recommendations and most recently updated in December 2016, for appropriate use of units of measure.

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The authors should delineate clinical competencies and translational outlook recommendations for their manuscripts. These should be listed in the manuscript after the Text and before the Acknowledgments and References. Please review the examples provided below. The competencies describe the implications of the study for current practice. The translational outlook places the work in a futuristic context, emphasizing directions for additional research.

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Competency-based learning in cardiovascular medicine addresses the 6 domains promulgated by the Accreditation Council on Graduate Medical Education (ACGME) and endorsed by the American Board of Internal Medicine (Medical Knowledge, Patient Care and Procedural Skills, Interpersonal and Communication Skills, Systems-Based Practice, Practice-Based Learning, and Professionalism) (www.acgme.org/acgmeweb). The ACCF has adopted this format for its competency and training statements, career milestones, lifelong learning, and educational programs. The ACCF also has developed tools to assist physicians in assessing, enhancing, and documenting these competencies (http://www.acc.org/education-and-meetings/maintenance-of-certification-information-hub?w_nav=MN).

Authors are asked to consider the clinical implications of their report and identify applications in one or more of these competency domains that could be used by clinician readers to enhance their competency as professional caregivers.

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TRANSLATIONAL OUTLOOK

Translating biomedical research from the laboratory bench, clinical trials or global observations to the care of individual patients can expedite discovery of new diagnostic tools and treatments through multidisciplinary collaboration. Effective translational medicine facilitates implementation of evolving strategies for prevention and treatment of disease in the community. The Institute of Medicine identified 2 areas needing improvement: testing basic research findings in properly designed clinical trials and, once the safety and efficacy of an intervention has been confirmed, more efficiently promulgating its adoption into standard practice (Sung NS, Crowley WF, Genel M. The meaning of translational research and why it matters. JAMA 2008;299:3140–3148).

The National Institutes of Health (NIH) has recognized the importance of translational biomedical research, emphasizing multifunctional collaborations between researchers and clinicians to leverage new technology and accelerate the delivery of new therapies to patients (www.ncats.nih.gov/about/about.html).

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5. Glantz SA. It is all in the numbers. J Am Coll Cardiol 1993; 21:835-7.

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16. Winchester DE, Wen X, Xie L, Bavry AA. Evidence of pre-procedural statin therapy: a meta-analysis of randomized trials. J Am Coll Cardiol 2010 Aug 31 [E-pub ahead of print], https://doi.org/10.1016/j.jacc.2010.04.023.

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27. Meidell RS, Gerard RD, Sambrook JF. Molecular biology of thrombolytic agents. In: Roberts R, editor. Molecular Basis of Cardiology. Cambridge, MA: Blackwell Scientific Publications, 1993:295-324.

**Book (personal author or authors)**

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23. Cohn PF. Silent Myocardial Ischemia and Infarction. 3rd edition. New York, NY: Marcel Dekker, 1993:33.

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10. Henkel J. Testicular Cancer: Survival High With Early Treatment. FDA Consumer magazine [serial online]. January-February 1996. Available at: http://www.fda.gov/fdac/features/196_test.html. Accessed August 31, 1998.

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OBJECTIVES The aim of this study was to compare echocardiographic methods of determining tricuspid regurgitation (TR) severity against TR regurgitant volume (TRRV) by cardiovascular magnetic resonance (CMR).

BACKGROUND TR is usually assessed using echocardiography, but it is not known how this compares with quantitative measurements of TR severity by CMR.

METHODS Echocardiographic and CMR methods were compared in 337 patients. Echocardiographic methods included jet size, hepatic vein flow, inferior vena cava diameter, percentage change in inferior vena cava diameter with inspiration, right atrial end-systolic area and volume, right ventricular end-diastolic and end-systolic areas and fractional area change, vena contracta diameter, effective regurgitant orifice area, and TRRV using the proximal isovelocity surface area method. TRRV by CMR was calculated as the difference between right ventricular end-diastolic and end-systolic volumes and systolic flow through the pulmonic valve.

RESULTS Echocardiographic parameters of TR severity had variable accuracy against TRRV by CMR (area under the curve range 0.58 for jet area/right atrial end-systolic area to 0.79 for hepatic vein flow). A multiparametric approach to assessing TR severity according to the 2017 American Society of Echocardiography criteria had 65% agreement with TR severity by CMR. A hierarchal approach based on signals with higher feasibility and accuracy against CMR had 68% agreement, without missing cases of severe TR by CMR. Agreement with CMR by the hierarchal approach was higher than that by the 2017 American Society of Echocardiography guidelines (p = 0.016).

CONCLUSIONS Several individual echocardiographic parameters of TR severity have satisfactory accuracy against TRRV by CMR. A multiparametric hierarchal approach resulted in 68% agreement with CMR and 100% agreement when a 1-grade difference in TR severity is considered acceptable. (J Am Coll Cardiol Img 2020;13:1461-71) © 2020 by the American College of Cardiology Foundation.
Recommendations were based on consensus opinion of experts, but without validation. Unlike mitral regurgitation, few studies have reported on the clinical application of echocardiographic measurements without comparison against cardiac magnetic resonance (CMR).

CMR provides accurate measurements of flow and has been validated in vitro and in vivo (4,5). CMR methodology is not affected by regurgitant orifice shape and quantifies TR regurgitant volume (TRRV). Furthermore, blood flow velocities can be measured from the entire region of interest without assuming a flat flow profile. For example, CMR measurements of mitral regurgitation volume successfully identified patients with severe MR and adverse outcomes (6). Likewise, CMR is the gold standard for right ventricular (RV) size and ejection fraction (EF) (7). TRRV is obtained on CMR as the difference between the stroke volume (SV) ejected by the right ventricle with each cardiac cycle and systolic blood flow through the pulmonic valve (3). Therefore, we sought to compare echocardiographic indexes of TR severity against CMR TRRV and derive an algorithm to grade TR severity on the basis of the performance of echocardiographic measurements against CMR. The partition values for severity recommended in the ASE guidelines were applied: mild, TRRV <30 ml; moderate, TRRV 30 to 44 ml; and severe, TRRV ≥45 ml (3).

METHODS

PATIENT POPULATION. Between 2008 and 2017, all patients with TR who underwent CMR and echocardiographic imaging within 60 days, without apparent differences in hemodynamic status, were included. Imaging was obtained for clinical indications. None had greater than mild pulmonic regurgitation, congenital heart disease, or left-to-right shunts. Patients with pacemakers or implantable cardioverter-defibrillators were excluded because leads interfere with CMR measurements of RV volumes through metallic void and shadowing artifacts. Patients with atrial fibrillation were excluded because of beat-to-beat variation in RV volumes and flow measurements by CMR.

ECHOCARDIOGRAPHIC IMAGE ACQUISITION. Image acquisition was performed in standard views. Color/pulsed-wave and continuous-wave (CW) Doppler was used. TR was evaluated in RV inflow, parasternal short-axis at the aortic valve level, and apical 4-chamber views. Efforts were made to capture the complete jet, including the proximal flow convergence zone, vena contracta (VC), and jet area. The TR jet was interrogated using CW Doppler in multiple views. Hepatic venous flow was sampled using pulsed-wave Doppler. Inferior vena cava maximal diameter was acquired at 2 cm from the junction with the right atrium during spontaneous respiration and sniffing (if there was no spontaneous collapse). Sonographers obtained additional images as needed, to optimize TR jet visualization.

ECHOCARDIOGRAPHIC ANALYSIS. RV end-diastolic area (EDA), end-systolic area (ESA), and right atrial (RA) ESA were measured in the apical 4-chamber view and indexed to body surface area following chamber quantification guidelines (8). RV fractional area change (FAC) was calculated as (RV EDA – RV ESA)/RV ED A, with normal FAC ≥35% (8). Jet area, VC, and proximal flow convergence were measured in all views with satisfactory imaging. The TR jet was classified as central or eccentric, and the ratio of jet area to RA ESA was obtained. TR effective regurgitant orifice area (EROA) and TRRV were computed offline after proximal isovelocity surface area (PISA) radius and aliasing velocity (Va) were tabulated. EROA was derived with the correction factor as $2 \times \Pi \times \text{radius}^2 \times \frac{Va}{Vp - Va}$, where Vp is peak TR velocity by CW Doppler (9). The correction factor $[V_p/(V_p - V_a)]$ was used to minimize PISA flow rate underestimation. TRRV was the product of EROA and the time-velocity integral (TVI) of the TR jet by CW Doppler. Feasibility of satisfactory measurements was highest in the apical 4-chamber view and lowest in the parasternal short-axis view.

The CW signal of the TR jet was graded according to whether it was incomplete (grade 1), complete but less dense than tricuspid inflow (grade 2), or of equal brightness to tricuspid inflow (grade 3). Jet contour by CW Doppler was parabolic (grade 1) or early peaking triangular contour (grade 2). Hepatic venous flow was graded on the basis of systolic and diastolic flow signals with the average of 5 cardiac cycles into 1 of 4 categories: systolic dominance (grade 1), systolic TVI = diastolic TVI (grade 2), diastolic dominance (grade 3), and systolic flow reversal (grade 4). RV enlargement was present if RV EDA index was ≥12.6 cm$^2$/m$^2$ in men and >11.5 cm$^2$/m$^2$ in women (8). RA enlargement was present if RA volume index was ≥39 ml/m$^2$ in males and ≥33 ml/m$^2$ in women (8). Echocardiographic analyses were performed without knowledge of CMR measurements.
IMPACT OF \( V_p/(V_p - V_a) \) on EROA AND TRRV

ASE cutoff values for TR severity using PISA were based on a study that applied the correction factor (10). In several patients, underestimation of EROA and regurgitant volume occurs. Therefore, the previously validated correction factor is needed (9,10).

To assess whether different aliasing velocities affect corrected EROA and TRRV, we measured in 20 patients with varying degrees of TR proximal flow convergence radius in the apical 4-chamber view at aliasing velocities of 35, 45, 55, and 65 cm/s. \( V_p \) and TVI were measured to calculate instantaneous flow rate, EROA, and TRRV at each of the 4 velocities. The correction factor \( V_p/(V_p - V_a) \) was then applied, and “corrected” values were computed.

ECHOCARDIOGRAPHIC CRITERIA USED FOR TR SEVERITY BY 2017 GUIDELINES. TR severity was graded first by looking for specific criteria of mild and severe TR (Figures 1 and 2). The following were considered consistent with mild TR: 1) VC < 0.3 cm; 2) incomplete TR jet by CW Doppler; 3) systolic flow dominance in the hepatic veins; 4) normal RA volume index and normal RV EDA index (3); and, although not included in the algorithm of the 2017 update; and 5) jet area < 5 cm², which was considered consistent with mild TR on the basis of 2003 guidelines (11). TR was severe if the following criteria were met: 1) VC ≥ 0.7 cm; 2) central jet area/RA ESA ratio ≥ 50%; 3) dense TR jet by CW Doppler with triangular or sine wave pattern; 4) systolic flow reversal in the hepatic veins; and 5) enlarged RV with FAC ≥ 35%. TR was mild or severe if > 50% of available mild or severe parameters were met (all parameters having equal weight). If ≤ 50% of signs of mild or severe TR were present, VC diameter, EROA, and TRRV were considered, and TR severity was determined by the majority of the 3 measurements (3).

HIERARCHICAL MODEL FOR GRADING TR SEVERITY ON THE BASIS OF THE RECOMMENDED VARIABLES IN THE 2017 ASE GUIDELINES. The 2017 guidelines do not specify an order in which measurements may be applied. We devised a hierarchical approach based on starting with variables with high feasibility and accuracy against CMR. VC, EROA, and TRRV were used in later steps, if needed, to arrive at a final conclusion (Central Illustration). The model was derived from the first 237 patients and validated in the last 100 patients, using CMR measurements of TRRV as the reference method.

The first parameter evaluated was CW Doppler of the TR jet. In the presence of a dense and triangular jet, the next step is to examine hepatic vein flow. With systolic reversal, severe TR was present. In the absence of hepatic vein flow signal or absence of systolic flow reversal, and if RV size was enlarged with normal FAC, severe TR was present. If RV size was normal or the right ventricle was enlarged but with reduced FAC, quantitation with VC, EROA, and TRRV was sought to determine TR severity.

If the CW Doppler jet was faint and incomplete or dense but rounded, the next step was evaluation of RV size. With normal RV size, hepatic vein flow was examined. In the presence of predominant systolic flow, mild TR was concluded. If other findings were present in hepatic vein flow (systolic TVI = diastolic TVI or predominant diastolic flow), quantitation with
VC, EROA, and TRRV was sought. However, an enlarged right ventricle with systolic flow reversal in hepatic vein flow, severe TR was present. If the right ventricle was enlarged and there was no systolic reversal in hepatic vein flow, VC, EROA, and TRRV were considered. In the absence of the latter signals and for central jets, jet area and the ratio of jet area to RA ESA were used to draw conclusions about TR severity. For eccentric jets in the absence of quantitative signals, jet area findings were used to support severe TR if, despite being eccentric, jet area was >10 cm² or the ratio of jet area to RA end-systolic area was at least 50%.

CMR IMAGING AND ANALYSIS. CMR images were acquired using 1.5- or 3.0-T clinical scanners (Siemens Avanto, Aera, and Skyra, Siemens Healthineers, Erlangen, Germany) with phased-array coil systems. RV imaging was acquired via short-axis stacks with colocalization using 4-chamber and RV inflow-outflow views using steady-state free precession sequences with a typical flip angle of 65° to 85°, 3-ms repetition time, 1.3-ms echo time, 1.7 to 2.0 mm × 1.4 to 1.6 mm in-plane spatial resolution, 6-mm slice thickness, 4-mm interslice gap, and temporal resolution of 35 to 40 ms. Slices were prescribed from basal RV slice to apex. Flow across the pulmonic valve was assessed using phase-contrast imaging with a flip angle of 25° to 30°, repetition time of about 5 ms, 2.4-ms echo time, reconstructed in-plane spatial resolution of about 2.0 × 2.4 mm, 6-mm slice thickness, and temporal resolution of about 40 to 50 ms.

Left ventricular (LV) and RV volumes, mass, and EF were measured per CMR guidelines (12). LV
replacement fibrosis was assessed. Left atrial and RA volumes were measured using biplane area-length and single plane area-length methods, respectively. Tricuspid annular diameter was measured in the 4-chamber view in early diastole.

RV SV was determined by subtracting RV end-systolic volume from end-diastolic volume. RV EF was calculated as SV/end-diastolic volume. Pulmonary artery forward flow was computed by tracing pulmonary artery borders on phase-contrast imaging.

Echocardiographic variables and their sequence on the basis of signals with highest feasibility and accuracy against TR regurgitant volume by CMR. Quantitative measurements are used later, if qualitative indicators are absent, equivocal, or discrepant with one another. Abbreviations as in Figure 1.
TABLE 1: Baseline Characteristics of Patient Population Stratified by TR Regurgitant Volume Measured by CMR

|                | All (N = 337) | Mild (n = 209) | Moderate (n = 67) | Severe (n = 61) | p Value |
|----------------|---------------|----------------|------------------|-----------------|---------|
| Age (yrs)      | 58 ± 15       | 59 ± 15        | 59 ± 15          | 57 ± 16         | 0.734   |
| Male           | 178 (53)      | 110 (53)       | 37 (55)          | 31 (50)         | 0.85    |
| Body mass index (kg/m²) | 27.6 ± 6.3 | 27 ± 6         | 28.5 ± 6.6       | 28 ± 6.8        | 0.239   |
| Systolic BP (mm Hg) | 123 ± 19   | 124 ± 20       | 124 ± 19         | 120 ± 16        | 0.396   |
| Diastolic BP (mm Hg) | 72 ± 14      | 72 ± 14        | 72 ± 13          | 71 ± 12         | 0.834   |
| Heart rate (beats/min) | 78 ± 16     | 79 ± 17        | 75 ± 14          | 75 ± 17         | 0.07    |
| GFR (ml/min/1.73 m²) | 75 ± 34       | 79 ± 31*       | 68 ± 35          | 69 ± 39         | 0.027   |
| History of atrial fibrillation | 72 (23) | 35 (18)* | 18 (32) | 19 (35) | 0.009 |
| Hypertension   | 206 (61)      | 128 (62)       | 40 (60)          | 38 (61)         | 0.974   |
| Hyperlipidemia | 144 (43)      | 102 (49)*      | 21 (31)          | 21 (34)         | 0.011   |
| Family history of CAD | 158 (47) | 103 (50) | 27 (40) | 28 (45) | 0.405 |
| Diabetes mellitus | 76 (23)     | 48 (23)        | 15 (23)          | 13 (21)         | 0.965   |

| History of smoking | 0.161 |
|---------------------|-------|

| Current             | 123 (37) | 82 (39) | 18 (27) | 23 (38) |
|former (<1 yr)       | 27 (10)  | 7 (10)  | 6 (10)  |         |
|Never                | 191 (57) | 117 (56) | 42 (63) | 32 (52) |
|CAD                  | 76 (23)  | 43 (21) | 19 (30) | 14 (23) | 0.337   |
|Myocardial infarction| 46 (14)  | 27 (13) | 11 (16) | 8 (13)  | 0.748   |
|Dyspnea             | 181 (58) | 112 (57)* | 28 (49) | 41 (73) | 0.025   |
|Heart failure        | 147 (44) | 87 (42) | 25 (37) | 35 (57) | 0.069   |
|ACE inhibitor or ARB | 123 (37) | 81 (39) | 22 (33) | 20 (32) | 0.489   |
|Aspirin              | 137 (41) | 92 (44) | 23 (34) | 22 (35) | 0.231   |
|Diuretic agents      | 172 (51) | 99 (47) | 28 (42) | 45 (74) | <0.001  |
|Beta-blockers        | 175 (52) | 108 (52) | 34 (52) | 33 (54) | 0.975   |
|Spiroloneactone      | 59 (18)  | 33 (16) | 9 (13)  | 17 (27) | 0.084   |
|Statin               | 123 (37) | 83 (46) | 19 (28) | 18 (29) | 0.064   |

Values are mean ± SD or n (%). Diagnosis of heart failure was based on symptoms and signs of pulmonary or systemic congestion along with chest radiographic findings, serum natriuretic peptide levels, and echocardiographic findings. *p < 0.05 vs. patients with moderate or severe TR. ⊂p < 0.05 vs. patients with severe TR. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; CAD = coronary artery disease; CMR = cardiovascular magnetic resonance; GFR = glomerular filtration rate; TR = tricuspid regurgitation.

RESULTS

There were 355 patients in this cohort, with a mean time difference of 10 ± 14 days between the 2 examinations. Suboptimal echocardiographic images led to the exclusion of 18 patients. Baseline characteristics of the remaining 337 patients are listed in Table 1. There were 16 patients with primary TR, and the remainder had secondary TR. There were 2 patients with tricuspid valve prolapse. The other patients with primary TR had infective endocarditis, carcinoid heart disease, and TR after heart transplantation. Patients with secondary TR had group I, II, or III pulmonary hypertension.

On the basis of CMR, there were 209 patients with TRRV <30 ml, 67 with TRRV 30 to 44 ml, and 61 with TRRV ≥45 ml. There were no significant differences in blood pressure and heart rate at the time of the 2 examinations (p > 0.10).

CMR FINDINGS. A small proportion of patients had LV replacement fibrosis. Although left atrial maximum volume index, LV mass index, and RV EF were not significantly different among the 3 groups (Table 2), RV volumes, RA maximum volume index, and tricuspid annular diameter increased significantly with TR progression.

ECHOCARDIOGRAPHIC FINDINGS. RA volumes and RV EDA and ESA increased with progression of TR severity (Table 2), but similar to RV EF by CMR, there was no difference in RV FAC among the 3 groups. Jet area, jet area/RA ESA ratio, VC, EROA, and TRRV increased with increasing TR severity. TR jet area/RA ESA for eccentric jets was not statistically different among the 3 groups, highlighting the limitations of jet size in patients with eccentric jets.

PISA CALCULATION AND FLOW CORRECTION. After correction, instantaneous flow rate, EROA, and TRRV were not significantly different at the 4 aliasing velocities (Table 3). There were no statistically

in every frame to determine flow and then summing flows during systole. TRRV was calculated by subtracting pulmonary artery forward flow from RV SV. CMR analysis was performed without knowledge of echocardiographic findings. CMR post-processing was conducted using WEBPACS (HeartIT, Durham, North Carolina).

STATISTICAL ANALYSIS. Continuous variables are presented as mean ± SD and categorical variables as number (percentage). Differences among patients with mild, moderate, and severe TR were compared using one-way analysis of variance for continuous variables, followed by pairwise comparison using Bonferroni correction. The Shapiro-Wilk test was applied to test for normal distribution. Chi-square or Fisher exact tests were used for categorical variables. Pairwise Student’s t-tests were used to compare blood pressure and heart rate at the time of CMR and echocardiographic examinations. Receiver-operating characteristic curve analysis was applied to assess the area under the receiver-operating characteristic curve (AUC) and accuracy analysis for the individual echocardiographic variables for severe TR. Repeated-measures analysis of variance followed by Wilcoxon matched-pairs signed rank test were applied to compare flow rate, EROA, and TRRV at the 4 aliasing velocities. The McNemar test was used to compare agreement between echocardiographic algorithms and CMR for TR severity. All analyses were performed using Stata version 15 (StataCorp, College Station, Texas). Statistical significance was defined as p < 0.05.
significant differences between color Doppler measurements when compared in patients with satisfactory data available from all 3 views or when 2 of 3 views were available. Conclusions about TR severity were the same when the mean or largest value was considered in the analysis, as all sets (2 or 3 sets) were largely concordant after excluding suboptimal images.

**ACCURACY OF INDIVIDUAL MEASUREMENTS IN IDENTIFYING TR SEVERITY.** Table 4 shows sensitivity, specificity, and AUC of the individual echocardiographic measurements with cutoff values recommended in the 2017 ASE guidelines on the basis of TRRV by CMR (cutoff values for corrected EROA and TRRV) in Table 4 had the largest AUCs). Significant but modest correlations were present between quantitative echocardiographic measurements (VC, corrected and uncorrected EROA and TRRV) by CMR, ranging from 0.36 to 0.49 (p < 0.05 for all).

**ACCURACY OF THE 2017 GUIDELINES IN CLASSIFYING TR SEVERITY.** Using the 2017 ASE guidelines, 36 patients (11%) had >50% of the signals with findings meeting criteria for severe TR, while 136 patients (40%) had >50% of the signals with findings of mild TR. TR severity was determined in 165 patients (49%) on the basis of quantitation. Among these 165 patients, final conclusions could not be reached in 34 (10% of the cohort), because of equal numbers of discordant criteria, where VC, EROA, and TRRV corresponded to different degrees of TR severity.

Therefore, in 303 of 337 patients (90%), conclusions about TR severity could be reached. In 197 patients (65%), echocardiography and CMR were concordant in assigning the same grade of TR severity. Considering a 1-grade difference acceptable, echocardiography agreed with CMR in 287 (95%). In the remaining cases, 2 patients had severe TR by CMR but mild TR by echocardiography, and 14 patients with mild TR by CMR had severe TR by echocardiography (Table 5). The conclusions pertaining to TR severity in the 14 patients misclassified by echocardiography were based on color Doppler in the absence of satisfactory hepatic vein recordings.

**HIERARCHICAL APPROACH TO GRADE TR SEVERITY.**

In the derivation cohort of 237 patients, there were 142 cases of mild, 51 of moderate, and 44 of severe TR
by CMR. Echocardiography was concordant with CMR in assigning the same grade in 163 patients (69%). When a 1-grade difference in severity was considered acceptable, the concordance rate was 98% (233 patients). There were only 4 patients with mild TR by CMR (TRRV 19, 23, 25, and 26 ml) who were classified with severe TR by echocardiography (Table 5). Echocardiography correctly identified 36 of the 44 patients with severe TR by CMR, but 8 were thought to have moderate TR. Of the 8 patients deemed to have moderate TR by echocardiography but severe TR by CMR, TRRV by CMR was 40 ml in 2 patients, 41 ml in 1 patient, 42 ml in 2 patients, 44 ml in 2 other patients, and 31 to 38 ml in the remaining patients. Of the 15 patients deemed to have severe TR by echocardiography but moderate TR by CMR, TRRV by CMR was 47 ml in 1 patient and 52 to 65 ml in the remaining patients.

In the validation cohort of 100 patients, there were 67 cases of mild TR, 16 cases of moderate TR, and 17 cases of severe TR by CMR. Echocardiography correctly graded TR severity, compared with CMR, in 72 patients (72%). When a 1-grade difference in severity was considered acceptable, the concordance rate increased to 100%. Importantly, there were no patients with severe TR by CMR who were considered to have mild TR by echocardiography, and there were no patients deemed to have severe TR by echocardiography but only mild TR by CMR (Table 5). Of the 5 patients with moderate TR by echocardiography and severe TR by CMR, TRRV by CMR was 47 ml in 1 patient and 52 to 65 ml in the remaining patients.

Next, all patients included in the analysis of hierarchical approach accuracy (n = 337) and the 303 patients (in whom conclusions about TR severity could be reached) included in the analysis of the 2017 ASE guidelines were evaluated for agreement with CMR. The hierarchical approach had significantly higher agreement with CMR (p = 0.016). Table 6 presents the agreement between echocardiography and CMR with patients classified into 2 groups: severe and non-severe TR.

The agreement between echocardiography (hierarchical approach) and CMR was evaluated in the subgroup of 33 patients with eccentric TR jets. There were 11 patients with severe TR by CMR. TR was deemed severe in 9 of the 11 patients by echocardiography, and in the other 2, TR was graded as moderate. There were 7 patients with moderate TR by CMR, and 5 of the 7 were deemed to have moderate

### Table 3: Correction of Flow Rate Using $V_p/(V_p - V_a)$ in 20 Patients With Varying TR Severity

| Alising Velocity (cm/s) | 35  | 45  | 55  | 65  | p Value |
|-------------------------|-----|-----|-----|-----|---------|
| PISA radius             | 0.47 ± 0.4 | 0.41 ± 0.4 | 0.37 ± 0.3 | 0.33 ± 0.3 | <0.001 |
| Instantaneous flow rate (ml/s) | 91 ± 222 | 85 ± 193 | 77 ± 167 | 75 ± 170 | 0.005 |
| Corrected               | 110 ± 276 | 109 ± 257 | 104 ± 241 | 110 ± 266 | 0.502 |
| EROA (cm²)              | 0.44 ± 1.2 | 0.40 ± 1.08 | 0.36 ± 0.94 | 0.36 ± 0.94 | 0.006 |
| Corrected               | 0.53 ± 1.6 | 0.52 ± 1.4 | 0.49 ± 1.4 | 0.53 ± 1.5 | 0.455 |
| TRRV (ml)               | 27 ± 61 | 25 ± 53 | 23 ± 46 | 22 ± 47 | 0.004 |
| Corrected               | 32 ± 76 | 32 ± 71 | 30 ± 66 | 32 ± 73 | 0.601 |

Values are mean ± SD. PISA = proximal isovelocity surface area; TRRV = tricuspid regurgitation regurgitant volume; $V_a$ = alising velocity; $V_p$ = peak TR velocity by continuous-wave Doppler; other abbreviations as in Tables 1 and 2.

### Table 4: Accuracy of Echocardiographic Parameters for Severe TR (Defined as TRRV ≥45 ml)

| n | Guideline Threshold | AUROC (95% CI) | Sensitivity (%) | Specificity (%) |
|---|---------------------|----------------|----------------|----------------|
| VC diameter | 236 | ≥7 mm | 0.65 (0.59-0.72) | 39 | 91 |
| EROA | 216 | ≥0.4 cm² | 0.75 (0.68-0.81) | 80 | 70 |
| TRRV | 216 | ≥45 m | 0.72 (0.64-0.79) | 61 | 82 |
| Jet area/RA area | 294 | >50% (for central jets) | 0.58 (0.52-0.64) | 27 | 92 |
| Jet contour | 335 | Triangular | 0.69 (0.62-0.75) | 40 | 97 |
| Jet density | 335 | Dense | 0.67 (0.61-0.73) | 39 | 96 |
| Jet contour and density | 335 | Triangular and dense | 0.63 (0.57-0.68) | 26 | 99 |
| Hepatic vein | 265 | Systolic reversal | 0.79 (0.73-0.86) | 72 | 87 |
| Dilated right ventricle with normal FAC | 183 | RV EDA index >12.6 for men and >11.5 for women with FAC ≥35% | 0.74 (0.66-0.82) | 76 | 73 |
| Jet area (both central and eccentric jets) | 300 | >10 cm² | 0.70 (0.63-0.76) | 48 | 92 |
| IVC maximal dimension | 301 | >2.5 cm | 0.66 (0.59-0.73) | 45 | 87 |

AUROC = area under the receiver-operating characteristic curve; CI = confidence interval; FAC = fractional area change; IVC = inferior vena cava; n = number of patients in whom satisfactory measurements were feasible in the apical 4-chamber view; VC = vena contracta; other abbreviations as in Tables 2 and 3.
TR by echocardiography, while 1 patient was graded mild and the second patient was graded severe (TRv by CMR was 40 ml in the latter patient, graded as severe by echocardiography). There were 15 patients with mild TR by CMR. Of these, 13 were graded as having mild lesions, and 2 were graded as having moderate lesions by echocardiography. Thus, echocardiography correctly graded the severity of TR, compared with CMR, in 27 of 33 patients (82%). When a 1-grade difference in severity was considered acceptable, the concordance rate increased to 100%. There were 16 patients with primary TR, of whom 11 had severe TR and 5 had moderate TR. Good agreement was present between the 2 imaging modalities at 81%.

**DISCUSSION**

Several individual echocardiographic parameters of TR severity have satisfactory accuracy when compared against TRv by CMR. Using a hierarchal approach, conclusions about TR severity could be reached in all patients. Using the hierarchal approach, there were no patients with severe TR by CMR who were classified with mild TR by echocardiography.

**CW DOPPLER OF THE TR JET.** The brightness and contour of the TR jet by CW Doppler were highly specific for severe TR. Nevertheless, improper alignment with the direction of the TR jet can lead to underestimation of severity, which can be difficult to avoid in eccentric jets. Likewise, proper alignment with a central jet can result in a bright signal in mild TR. Finally, the contour of the TR jet, while influenced by TR severity, is also affected by the systolic RV-RA pressure gradient and therefore RV systolic function and loading conditions as well as RA stiffness, which can be abnormally elevated in the absence of severe TR. Thus, it is advantageous to consider both aspects of the TR jet by CW Doppler. In particular, when both findings were present, specificity was excellent at 99% for severe TR.

**PULSED-WAVE Doppler OF HEPATIC VENOUS FLOW.** Systolic flow reversal is seen with severe TR. One must pay attention not to confuse systolic flow reversal due to TR with the small mid-systolic reversal signal or late diastolic reversal seen with RA contraction. Systolic reversal had good accuracy, though specificity was not 100% (87% specificity for severe TR), as systolic reversal can occur because of markedly increased RA stiffness and thus highly elevated RA “V”-wave pressure despite a TR lesion that is not severe. Likewise, patients with RV pacing and atrioventricular dysynchrony can have some cardiac cycles with systolic reversal when the right atrium contracts against the closed tricuspid valve because of RV contraction at the same time. Thus, cardiac rhythm should be considered in the exercise to grade TR severity using hepatic venous flow. Although blunting of forward systolic flow may be seen with moderate TR and at times severe TR, a similar flow pattern occurs with elevated RA pressure with only trivial or mild TR (16), thus the limited specificity of diastolic flow dominance for severe TR in patients with systemic congestion and elevated mean RA pressure.

### Table 5: Comparison of CMR and Echocardiography

|                       | CMR Mild | CMR Moderate | CMR Severe | Total |
|-----------------------|----------|--------------|------------|-------|
| Using ASE 2017 guidelines |          |              |            |       |
| Echocardiography mild | 147 (49) | 30 (10)      | 2 (-1)    | 179 (59) |
| Echocardiography moderate | 28 (9) | 8 (3)        | 10 (3)    | 46 (15) |
| Echocardiography severe | 14 (5) | 22 (7)       | 42 (14)   | 78 (26) |
| Total                 | 189 (62) | 60 (20)      | 54 (18)   | 303 (100) |

In 237 patients of the derivation cohort using the hierarchal approach

|                       |       |              |            |       |
|-----------------------|-------|--------------|------------|-------|
| Echocardiography mild | 112 (47) | 21 (9)      | 0 (0)     | 133 (56) |
| Echocardiography moderate | 26 (11) | 15 (6)   | 8 (3)     | 49 (21) |
| Echocardiography severe | 4 (2) | 15 (6)       | 36 (15)   | 55 (23) |
| Total                 | 142 (60) | 51 (22)      | 44 (19)   | 237 (100) |

In 100 patients of the validation cohort using the hierarchal approach

|                       |       |              |            |       |
|-----------------------|-------|--------------|------------|-------|
| Echocardiography mild | 54 (54) | 8 (8)      | 0 (0)     | 62 (62) |
| Echocardiography moderate | 13 (13) | 6 (6)     | 5 (5)     | 24 (24) |
| Echocardiography severe | 0 (0) | 2 (2)       | 12 (12)   | 14 (14) |
| Total                 | 67 (67) | 16 (16)      | 17 (17)   | 100 (100) |

Values are n (%).

ASE = American Society of Echocardiography; CMR = cardiovascular magnetic resonance.

### Table 6: Comparison of CMR and Echocardiography

|                       | CMR Nonsevere | CMR Severe | Total |
|-----------------------|--------------|------------|-------|
| Using ASE 2017 guidelines with patients classified as severe or nonsevere TR |          |            |       |
| Echocardiography nonsevere | 213 (70) | 12 (4)     | 225 (74) |
| Echocardiography severe | 36 (12)      | 42 (14)    | 78 (26) |
| Total                 | 249 (82)     | 54 (18)    | 303 (100) |

In 237 patients of the derivation cohort using the hierarchal approach with patients classified as severe or nonsevere TR

|                       |            |            |       |
|-----------------------|------------|------------|-------|
| Echocardiography nonsevere | 174 (73) | 0 (0)     | 174 (73) |
| Echocardiography severe | 19 (8)     | 44 (19)    | 63 (27) |
| Total                 | 193 (81)   | 44 (19)    | 237 (100) |

In 100 patients of the validation cohort using the hierarchal approach with patients classified as severe or nonsevere TR

|                       |            |            |       |
|-----------------------|------------|------------|-------|
| Echocardiography nonsevere | 81 (81) | 5 (5)     | 86 (86) |
| Echocardiography severe | 2 (2)      | 12 (12)    | 14 (14) |
| Total                 | 83 (83)    | 17 (17)    | 100 (100) |

Values are n (%).

Abbreviations as in Tables 1 and 5.
**RA SIZE AND RV SIZE.** RA and RV size can be used to draw inferences about TR severity in patients with chronic but not acute TR, as there is no time for compensatory changes in acute lesions. Patients with mild TR usually have normal RA and RV volumes, whereas severe chronic TR is accompanied by enlarged chambers. We noted several patients in our study with mild TR but with enlarged right atria and right ventricles. This finding occurs in patients with secondary TR due to RV enlargement with or without RV systolic dysfunction. Therefore, the mere presence of chamber enlargement with reduced FAC should be carefully considered along with other indexes of TR severity as well as the clinical setting. Notwithstanding, as recommended in guidelines (3), the presence of an enlarged right ventricle with normal FAC has acceptable accuracy, with an AUC of 0.74 in our study for severe TR, and should trigger more careful evaluation of other signals to confirm the presence of severe TR.

**VC- AND PISA-BASED MEASUREMENTS OF TR SEVERITY.** VC measurements had good specificity in identifying patients with mild and severe TR. However, many patients with severe TR had VC <7 mm, and additional variables were needed to identify these patients.

Overall, corrected EROA and TRRV had reasonable accuracy in identifying patients with severe TR (AUCs of 0.75 and 0.72, respectively). The accuracy of TRRV is particularly acceptable given the variability of the method and the small difference in TRRV between mild and severe TR advocated in the 2017 ASE guidelines (16-ml difference between mild and severe TR). Given the additional time needed to perform these calculations along with their variability, we considered PISA-based measurements as a later step, if needed, in the hierarchal approach, as opposed to relying on both measurements in the first set of criteria. This is in line with the 2017 guidelines, which recommend VC, TRRV, and EROA as a second step for determining the presence of moderate TR (3).

**COMPARING THE 2017 GUIDELINES WITH A HIERARCHAL APPROACH FOR TR ASSESSMENT.** TR assessment by the 2017 ASE guidelines and by the hierarchal approach were concordant with CMR in 65% to 68% of cases, with 95% to 100% agreement when accepting a difference of 1 grade. The hierarchal approach classified TR severity in all patients, while the 2017 guidelines classified TR in 90% of patients because of suboptimal signals or an equal number of discordant variables. In addition, there were no patients in the hierarchal approach, in both the derivation and validation groups, in whom severe TR by CMR was graded mild by echocardiography. However, severe TR by CMR TRRV was graded mild by echocardiography in 2 patients (0.7%) using the 2017 guidelines. Overall, the hierarchal approach had significantly higher agreement with CMR classification of TR severity, albeit with small overall difference with 2017 guidelines.

**STUDY LIMITATIONS.** To reliably assess TR using CMR, factors that affect the accuracy of RV volumes measurement and pulmonary blood flow were excluded (pacemakers or implantable cardioverter-defibrillators and atrial fibrillation). With respect to echocardiography, 18 patients (5.1%) had technically challenging studies that precluded echocardiographic evaluation of TR severity. In addition, we could not assess all echocardiographic variables in all patients, with somewhat lower feasibility for PISA-based measurements. Lower feasibility of PISA-derived EROA and TRRV was seen in patients with mild but not moderate or severe TR, for which quantitative measurements have greater importance to judge response to treatment. In patients with mild TR, one can usually grade TR severity without the need to proceed to quantitative measurements. Importantly, it was possible to classify TR severity in all patients using the hierarchal approach with acceptable accuracy.

The time interval between echocardiography and CMR was 10 ± 14 days. Although we noted that heart rate and systemic blood pressure were similar between the 2 examinations, pre-load and afterload conditions might have been different. The hierarchal approach was prospectively validated in 100 patients, and additional studies are needed. Clinical outcomes could be of value in understanding discrepant findings between CMR and echocardiographic assessment of TR severity, the objective of future studies. Characterization of RV structure using late gadolinium enhancement could shed additional light on RV pathology in patients with TR.

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**PERSPECTIVES**

**COMPETENCY IN MEDICAL KNOWLEDGE:** Assessment of TR severity by echocardiography is feasible and has acceptable accuracy compared with TRV measured by CMR. Higher feasibility and accuracy can be achieved by starting with qualitative signals that place a given patient into either the mild or severe group and then using quantitative parameters as a second step when the qualitative signals are either absent or equivocal.

**TRANSLATIONAL OUTLOOK:** TR assessment using a hierarchal approach based on routinely acquired signals is an appealing method to grade TR. Its performance in prospective patient groups with a wide range of TR severity should be evaluated against that of CMR. Its utility to judge response to treatment is of interest.

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**KEY WORDS** cardiovascular magnetic resonance, echocardiography, tricuspid regurgitation, tricuspid valve
The Quest to Better Quantitate Tricuspid Regurgitation*

Roberto M. Lang, MD, Karima Addetia, MD

“Today, our very survival depends on our ability to stay awake, to adjust to new ideas, to remain vigilant and to face the challenge of change.”
—Martin Luther King Jr. (1)

Recent developments in the field of structural heart disease have made it possible to treat a growing assortment of valve diseases with percutaneous procedures (2). The advent of percutaneous techniques for the treatment of tricuspid regurgitation (TR) has sparked renewed interest among cardiac imagers to re-evaluate not only how we image the tricuspid valve but also how accurate is our assessment of tricuspid regurgitation. Historically, the preferred method for assessment of TR involved color Doppler techniques using echocardiography (3). However, the methodology currently used for TR quantitation largely parallels that of mitral regurgitation even though these 2 valves are not similar, operating under different loading conditions, with different annular sizes and distinct anatomic orifice areas (4), just to name a few. In fact, the multiparametric approach for TR assessment proposed by the American Society of Echocardiography (ASE) 2017 guidelines largely mirrors the quantitative approach suggested for mitral regurgitation (3). In this issue of iJACC, Zhan et al. (5) have taken a step forward in an attempt to change the currently accepted paradigm for TR quantification by comparing the accuracy of the echo-Doppler method to that of cardiac magnetic resonance (CMR)-determined regurgitant TR volumes. By performing this comparison, the authors were able to propose a novel and elegant, multiparametric echocardiographic alternative approach for TR assessment which provide results that are more in line with CMR.

To date, despite being the gold standard for assessment of right ventricular (RV) size and function (6), CMR has not been used clinically for the quantification of TR. The results of this study would be even more impactful if this was the case. CMR calculation of TR severity involves the subtraction of the stroke volume across the pulmonary valve from the RV stroke volume to calculate regurgitant volume (RVol). This parameter was used in this study as the “gold standard” for TR assessment. Advantages of this method include that CMR flow measurements using phase-contrast velocity mapping have been shown to be accurate measures of stroke volume (7) and furthermore, CMR quantitation of TR avoids the confounding effects of orifice shape or jet eccentricity. Accordingly, it is fitting that the authors chose this methodology as their reference standard for TR assessment. Nonetheless, caution should be exercised because there is a paucity of studies using CMR to assess TR severity with next to no studies correlating CMR assessment of TR with patient outcomes. In contrast, there is a large body of published reports linking echocardiography-determined TR severity with clinical outcomes (8–10). The use of CMR to assess tricuspid valve regurgitation also requires expertise to accurately measure RV volumes and acquire pulmonary valve flow parameters. Finally, in the study of Zhan et al., (5) an RVol of ≥45 ml was defined as severe TR. This value has not been validated either for CMR or for echocardiography, and recent studies and editorials have proposed larger values for torrential and massive TR (11). In spite of these limitations, Zhan et al. (5) took a very unique approach in their study. With the premise that CMR is a reasonable gold standard for the assessment of TR, they determined which of the

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Cardiovascular Imaging author instructions page.
conventional echocardiographic parameters used to categorize TR correlated better with CMR TR RVol and subsequently proposed a simplified novel multi-parametric approach to assess TR severity using echocardiography.

In this study, the authors show that the echocardiographic parameters that most closely correlate with severe TR include: hepatic vein flow reversal, dense and triangular contour of the TR continuous wave (CW) jet and a dilated right ventricle with preserved fractional area change. In fact, the authors demonstrate that these 3 parameters alone can be used to diagnose severe TR without the need for additional color Doppler parameters if all 3 or 2 of the 3 are present. When viewed from a different perspective, these results also suggest that in addition to the quantitation of TR, the impact of the latter on the right heart is also important in determining TR severity. When hepatic vein Doppler signals or TR CW jet density are underestimated or confounded, as may occur in RV dysfunction, Doppler parameters (vena contracta, effective regurgitant orifice, regurgitant volume) may be useful to assess TR severity. The idea of incorporating RV size early in the assessment of TR severity is a clever one, although RV dilatation may be secondary to many causes, TR being only 1 of them. However, one wonders whether the proposed approach by Zhan et al. could have been further improved if tricuspid annular (TA) diameter (12) would have also been incorporated into the diagnostic algorithm. Ostensibly, TA dimension not only reflects tricuspid valve dysfunction, but also the interaction between the right atrial and RV geometry and performance. Presumably, TR cannot be severe unless the TA is dilated. Several studies have suggested that tricuspid valve repair should be performed in patients with a dilated TA if surgery is being planned for the mitral valve irrespective of traditional color Doppler TR interpretation (13-15). Indeed, the

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**FIGURE 1** Echocardiographic Images in a Patient Who Presented With Acute Decompensated Biventricular Failure

### Severe TR. Dilated tricuspid annulus

Images taken at the time of acute decompensated heart failure

- Tricuspid annulus = 58 mm
- RV diameter (base) = 56 mm
- RV diameter (mid) = 37 mm

Images taken when patient returned dehydrated, hypotensive with hypokalemia

- Tricuspid annulus = 50 mm
- RV diameter (base) = 46 mm
- RV diameter (mid) = 33 mm

### Trace TR. Dilated tricuspid annulus

The right ventricle **(top)** is dilated and dysfunctional with severe tricuspid regurgitation. The tricuspid annulus is severely dilated (normal tricuspid annular dimension is 40 mm). The right ventricular basal and mid-dimensions are also dilated (normal right ventricular basal and mid-dimensions are <41 mm [basal] and <35 mm [mid], respectively). The patient was diuresed excessively **(bottom)**. The repeat echocardiogram depicted a considerably smaller right ventricle with only trace tricuspid regurgitation. Despite these changes, the tricuspid annulus remained dilated.
2014 American College of Cardiology/American Hospital Association guidelines on valvular heart disease maintain that this should be the case even if the patient has only mild TR (16). These findings are based on the premise that TR is highly load dependent and may also change significantly with inspiration and expiration, blood pressure, and fluid status. We all have seen patients with acute decompensated heart failure or fluid overload who present with severe functional TR, but once adequately diuresed or dialyzed, the TR decreases dramatically but the annulus remains dilated (Figure 1). The question is whether TA diameter could be used as an additional marker of tricuspid valve dysfunction rather than TR alone. Armed with the new approach for TR severity introduced by Zhan et al., it may be possible to further study this and other unanswered questions in the quest to better understand and quantify TR.

Zhan et al. (5) found that when applying the ASE 2017 guidelines for the assessment of TR severity to their study subjects, CMR and echocardiography were concordant in 65% of cases. If 1 grade difference between modalities was deemed acceptable, CMR and echocardiography were concordant in 95% of cases. Interestingly, in the 14 patients in whom TR was incorrectly classified by echocardiography an inadequate hepatic vein Doppler signal was considered responsible. When the hierarchical approach was compared with the ASE 2017 guidelines to assess valvular regurgitation the author’s new approach had a higher agreement with CMR even when including eccentric jets. With the advent of 3-dimensional (3D) chamber quantification (17) and 3D color Doppler imaging techniques (18), it may soon become possible to measure RV volumes and 3D proximal isovolumetric surface area and vena contracta areas in the clinical space. These advancements may improve the accuracy of echocardiography in the assessment of TR.

For the time being, however, the authors are advising us that all patients with TR should have hepatic vein Doppler assessment, TR CW Doppler jet acquisition, and RV fractional area change measurements performed to more accurately assess TR on echocardiography. We concur and further suggest that measurement of the TA could be incorporated into TR assessment.

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KEY WORDS cardiovascular magnetic resonance, echocardiography, tricuspid regurgitation
ABSTRACT

OBJECTIVES The purpose of this study was to investigate how LBBB and CRT modify RV free wall function by direct ventricular interaction.

BACKGROUND Right ventricular (RV) function influences prognosis in patients with left bundle branch block (LBBB) and cardiac resynchronization therapy (CRT). There is, however, limited insight into how LBBB and CRT affect RV function.

METHODS In 24 patients with LBBB with nonischemic cardiomyopathy, RV and left ventricular (LV) strain by speckle-tracking echocardiography was measured before and after CRT. Underlying mechanisms were studied in 16 anesthetized dogs with ultrasonic dimension crystals and micromanometers.

RESULTS Patients with LBBB demonstrated distinct early systolic shortening in the RV free wall, which coincided with the typical abnormal early systolic septal shortening. In animals, this RV free wall contraction pattern resulted in reduced myocardial work as a large portion of the shortening occurred against low pressure during early systole, coinciding with abnormal leftward septal motion. RV systolic function was maintained by vigorous contraction in the late-activated LV lateral wall, which pushed the septum toward the RV. CRT reduced abnormal septal motion and increased RV free wall work because there was less inefficient shortening against low pressure.

CONCLUSIONS LBBB reduces workload on the RV free wall because of abnormal septal motion and delayed activation of the LV lateral wall. Restoring septal and LV function by CRT increases workload in RV free wall and may explain why patients with RV failure respond poorly to CRT. (Contractile Reserve in Dyssynchrony: A Novel Principle to Identify Candidates for Cardiac Resynchronization Therapy [CRID-CRT]; NCT02525185) (J Am Coll Cardiol Img 2020;13:1475-84) © 2020 by the American College of Cardiology Foundation.
Left bundle branch block (LBBB) is a common finding in heart failure patients with left ventricular (LV) dysfunction and is associated with increased morbidity and mortality (1). The bundle branch block has a direct negative effect on LV contractile function, which contributes to heart failure (2). The influence of LBBB on right ventricular (RV) function, however, is not well known and there are conflicting data whether cardiac resynchronization therapy (CRT) improves RV function (3–7). RV function is shown to be an independent predictor of nonresponse to CRT, suggesting there may be important interaction between CRT and RV function (8).

LV function can modify RV function by either indirectly via pulmonary circulation or through direct ventricular interaction (9,10). In patients with LBBB, there is typically abnormal contraction of the interventricular septum with marked early systolic shortening and leftward motion (11–13). This is followed by lengthening and rightward septal motion when the late-activated LV lateral wall starts contracting (14,15). Because the septum is an important contributor to RV function (16), this inefficient septal motion may also affect the right ventricle. Theoretically, rightward septal systolic motion assists RV ejection, which may be of particular importance in a failing right ventricle. Mathematical simulations have shown how work performed by the left ventricle may support RV function during LBBB (17,18).

We have investigated how LBBB and CRT modify RV free wall function by direct ventricular interaction. In a clinical study, patients with LBBB were examined before and after CRT. To extend the findings in the patients and to further explore mechanisms of the interaction, we used an experimental animal model. In this model, we used sonomicrometry and invasive pressures as gold standard for evaluation of ventricular function.

METHODS

CLINICAL STUDY. Study population. Fifty consecutive patients with LBBB with nonischemic cardiomyopathy referred for CRT were evaluated for inclusion. Patients with RV failure were excluded (n = 5), defined as tricuspid annular plane systolic excursion <17 mm (19), or if strain analysis of the right ventricle was not possible because of poor or inadequate echocardiographic image quality (n = 21). Data from 24 patients were finally included (age 67 ± 11 years, 11 females), with 1 in functional class I, 15 in functional class II, and 8 in functional class III according to the New York Heart Association. They were on optimal medical treatment, in sinus rhythm, and tricuspid annular plane systolic excursion was 21 ± 3 mm. LBBB was defined according to Strauss et al. (20), and QRS duration was 162 ± 12 ms. Patients were included at the cardiology departments of Oslo University Hospital and University Hospitals Leuven from the study: CRID-CRT (Contractile Reserve in Dyssynchrony: A Novel Principle to Identify Candidates for Cardiac Resynchronization Therapy; NCT02525185).

Echocardiography and strain analysis. Two-dimensional echocardiographic apical 4- and 2-chamber views were recorded (Vivid E9 or E95, GE Vingmed Ultrasound, Horten, Norway) at 79 ± 20 frames/s. LV ejection fraction was calculated by the biplane Simpson’s method. Contraction pattern in the right ventricle was studied by strain analysis by speckle tracking echocardiography (Echopac 202, GE Vingmed Ultrasound) from an apical 4-chamber view focused on the right ventricle. Both RV free wall global longitudinal strain (RV GLS) and septal longitudinal strain was measured as peak systolic strain and given as the mean value of 3 wall segments. Early systolic strain in the RV free wall was measured at the plateau in the descending strain curve. If no plateau could be identified the value was set to zero. Recordings were performed before and within 3 ± 3 days after CRT implantation.

ANIMAL STUDY. Animal preparation. Sixteen mongrel dogs of both sexes (37 ± 3 kg) were anesthetized by either barbiturates and opioids (n = 8) (thiopentone 25 mg/kg and morphine 100 mg intravenously, followed by infusion of morphine 50 to 100 mg/h and pentobarbital 50 mg intravenously every hour) or propofol and opioids (n = 8) (single-dose methadone 0.2 mg/kg, followed by propofol 3–4 mg/kg and a bolus of fentanyl 2–3 μg/kg; thereafter, continuous infusion of propofol 0.2–4 mg/kg/min and fentanyl 5–40 μg/kg/h). All animals were ventilated, surgically prepared. In 10 animals, LBBB was induced by radiofrequency ablation, as previously described (21,22). The National Animal Experimentation Board approved the study. The animals were supplied by the Center for Comparative Medicine (Oslo University Hospital, Oslo, Norway).

Micromanometer catheters (MPC 500, Millar Instruments Inc., Houston, Texas) were introduced through the RV lateral wall into the RV cavity and via the carotid artery into the LV cavity. The micromanometers were adjusted by fluid-filled catheters in the right and left atria serving as pressure reference. Sonomicrometric crystals (Sonometrics, London, Ontario, Canada) were implanted in the myocardium...
in the RV free wall, septum, and LV lateral wall (Figure 1). Data were sampled at 200 Hz.

**Measurements and calculations.** Peak systolic and end-diastolic pressures were measured from the 2 ventricles. End-diastole was defined at onset of the QRS complex. The maximum time derivative of RV and LV pressure were calculated. Regional deformation was measured as longitudinal shortening from the intramyocardial crystals in the RV free wall, septum, and LV lateral wall. These crystals were used to assess regional longitudinal deformation (vertical arrows) and short-axis diameters (horizontal arrows). In combination with invasive RV or LV pressure, regional and short axis work was calculated. LV = left ventricle; RV = right ventricle.

**Experimental protocol.** In 10 animals, recordings were performed during baseline, LBBB, and CRT. Atrioventricular and interventricular delay was set at default, 80 and 4 ms, respectively. In 2 of these dogs, additional recordings were also performed during CRT with increasing interventricular delay where the LV lateral wall was gradually activated later than the septum (4-16-32 ms and finally no resynchronization). Furthermore, from 6 previously performed experiments in our laboratory (22), we included additional analyses from isolated pacing of the LV lateral wall (atrioventricular delay 50 ms) in dogs without LBBB. The ventilator was temporarily switched off during all recordings.

**Statistical analysis.** Values are presented as mean ± SD unless stated otherwise. In the animal study, 1-way repeated measures analysis of variance was used to compare baseline, LBBB, and CRT. Mauchly's test of sphericity was done, and if the sphericity assumption was violated, Greenhouse-Geisser correction was performed. Post hoc tests with Bonferroni adjustment were done when analysis of variance showed significance. Pearson r was used for correlation. Paired Student’s t-tests were used to compare LV lateral wall pacing versus baseline in dogs and also in the clinical study. The p < 0.05 was considered significant. IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY) was used.

**RESULTS**

Both the clinical and experimental study demonstrated that, during LBBB, there was an abnormal RV free wall contraction pattern in early systole, which was reduced by CRT (Central Illustration, Figure 2). These results are presented in detail in the following section.

**CLINICAL STUDY.** Longitudinal strain analysis demonstrated an abnormal contraction pattern with a distinctive early systolic shortening (Figure 2) in the RV free wall, followed by a “plateau” before it continued to shorten. This abnormal RV contraction pattern coincided with septal early systolic shortening as observed in 22 of 24 patients with LBBB. CRT removed (n = 13) or reduced (n = 8) this early systolic shortening. RV GLS was not significantly increased by CRT (−24 ± 4% vs. −23 ± 4% in LBBB, not significant [NS]). Septal early systolic shortening was −6 ± 2% and RV early systolic shortening was −7 ± 4% during LBBB, which correlated significantly (r² = 0.57; p < 0.01).

CRT increased LV ejection fraction from 32 ± 7% to 39 ± 9% (p < 0.01). Heart rate (70 ± 12 beats/min vs. 67 ± 10 beats/min, p = NS) and blood pressure...
(135 ± 25/70 ± 14 mm Hg vs. 133 ± 18/73 ± 13 mm Hg, p = NS) were unchanged during LBBB and CRT, respectively.

**ANIMAL STUDY. Effects of LBBB.** The animal study demonstrated identical abnormal RV contraction pattern, as seen in patients (Central Illustration, Figure 2). This appeared immediately when LBBB was induced. LBBB slowed RV pressure rise (Table 1). The increase in early systolic shortening in the RV free wall occurred during low RV pressure (Central Illustration) with a corresponding decrease in regional work (Figure 3, Table 1). Similarly, reductions in regional septal (Figure 3) and LV short-axis work were seen, coinciding with increased early systolic septal shortening and leftward septal motion, respectively. This was opposite to the LV lateral wall where regional work was increased (Table 1). CRT restored septal and LV lateral wall function to baseline levels, demonstrated as increased septal work and decreased LV lateral wall work (Table 1, Figure 3). Finally, CRT reduced septal flash with a corresponding decrease in RV short axis work and increase in LV short-axis work (Figure 4, Table 1).

**Hemodynamic changes during LBBB and CRT.** LBBB and CRT did not alter LV and RV end-diastolic pressures, RV peak systolic pressures, and heart rate compared with baseline (Table 1). LV peak systolic pressure was reduced by LBBB; however, there was no change when CRT was applied.

**Alteration in interventricular delay.** Gradually increasing interventricular activation delay resulted in increasing early systolic septal and RV free wall shortening and concomitant increasing stretch in the LV lateral wall, which demonstrated a direct relationship (Figure 5).

**Isolated pacing of the LV lateral wall.** Isolated pacing in the LV lateral wall in animals without LBBB resulted in left-to-right activation, opposite of right-to-left activation during LBBB. LV pacing induced LV lateral wall early systolic shortening and reduced regional work (−6 ± 22 mm × mm Hg vs. 47 ± 39 mm × mm Hg; p < 0.05) (Figure 6). The corresponding early systolic stretch of septum resulted in increased...
Representative findings from an animal experiment during LBBB and CRT. During LBBB, the early systolic shortening in the RV free wall and septum coincided with the abnormal septal motion (LV and RV short-axis diameter traces), and the early systolic stretch in the LV lateral wall (all in red). CRT reduced the early systolic shortening in the RV free wall. The concomitant early systolic septal shortening and the LV lateral wall early systolic stretch were also reduced. Furthermore, septal flash and rebound stretch were minimized as seen in both RV and LV diameter traces. In the electrocardiogram, aortic valve opening (AVO) and closing (AVC) as were seen in the aortic pressure curves (not given). CRT = cardiac resynchronization therapy; LBBB = left bundle branch block; LV = left ventricular; RV = right ventricular; RVP = right ventricular pressure; SL = segment length.
Animal Data From Baseline, LBBB, and CRT (N = 10)

|                          | Baseline | LBBB    | CRT     | p Value |
|--------------------------|----------|---------|---------|---------|
| RV peak systolic pressure (mm Hg) | 23 ± 2   | 27 ± 4  | 26 ± 3  | 0.09    |
| LV peak systolic pressure (mm Hg) | 99 ± 10  | 86 ± 15 | 88 ± 17 | 0.006   |
| RV end-diastolic pressure (mm Hg) | 6 ± 3    | 8 ± 4   | 7 ± 4   | 0.071   |
| LV end-diastolic pressure (mm Hg) | 8 ± 4    | 8 ± 4   | 8 ± 4   | 0.220   |
| QRS duration (ms)        | 50 ± 3   | 108 ± 9 | 75 ± 14 | 0.000   |
| Heart rate (beats/min)   | 103 ± 21 | 115 ± 13| 113 ± 14| 0.173   |
| RV dP/dt max (mm Hg/s)   | 283 ± 69 | 301 ± 62| 326 ± 71| 0.078   |
| LV dP/dt max (mm Hg/s)   | 1,301 ± 230 | 985 ± 154 | 1,136 ± 204 | 0.001 |
| RV free wall work (mm x mm Hg) | 36 ± 15  | 23 ± 14 | 36 ± 15 | 0.001   |
| Septum work (mm x mm Hg) | 96 ± 52  | 16 ± 61 | 92 ± 48 | 0.001   |
| LV lateral wall work (mm x mm Hg) | 118 ± 89 | 194 ± 111 | 82 ± 68 | 0.003   |
| LV short-axis work (mm Hg x mm) | 306 ± 140 | 114 ± 109 | 180 ± 97 | 0.000   |
| RV short-axis work (mm Hg x mm) | 41 ± 19  | 65 ± 25 | 32 ± 29 | 0.001   |
| RV free wall total strain (%)  | –2 ± 1  | –4 ± 1  | –2 ± 2  | 0.000   |
| RV free wall total strain (%)  | –10 ± 4 | –8 ± 3  | –8 ± 3  | 0.057   |
| Time from end-diastole to P50 (ms) | 57 ± 13 | 70 ± 11 | 54 ± 17 | 0.000   |

Values are mean ± SD. One-way repeated measures ANOVA was used to compare baseline, LBBB, and CRT. Post hoc tests with Bonferroni adjustment were done when ANOVA showed significance.

ANOVA = analysis of variance; CRT = cardiac resynchronization therapy; dP/dt max = maximal rate of pressure rise; LBBB = left bundle branch block; LV = left ventricular; P50 = 50% of RV pressure rise from end-diastolic pressure to peak systolic pressure; RV = right ventricular.

DISCUSSION

This study demonstrates that LBBB and subsequent application of CRT have instantaneous mechanical effects on RV function (Central Illustration, Figure 2). In patients with LBBB, there was an abnormal early systolic shortening in the RV free wall, which coincided and correlated with early systolic septal shortening. In the animal study, identical findings were seen and allowed us to study the underlying mechanisms in detail. It demonstrated how the abnormal septal work compared to normal electric conduction (141 ± 41 mm x mm Hg vs. 72 ± 32 mm x mm Hg; p < 0.01). Similarly, RV free wall work was also increased (36 ± 18 mm x mm Hg vs. 27 ± 18 mm x mm Hg; p < 0.01). LV short-axis work was higher during LV pacing compared with normal electric conduction (316 ± 177 mm x mm Hg vs. 232 ± 150 mm x mm Hg; p < 0.01), indicating increased septal contribution to the LV. RV short-axis work, however, decreased (18 ± 22 mm x mm Hg vs. 45 ± 12 mm x mm Hg; p < 0.05).

Individual data from 10 animals demonstrating regional longitudinal work from RV free wall, septum and LV lateral wall at baseline and the interventions. (Left) During LBBB, the regional work in RV free wall was reduced and then increased by CRT. (Middle) Regional work in septum changed similarly as in RV free wall (except in 1 animal). (Right) The work in the LV lateral wall increased during LBBB and was reduced during CRT, opposite to RV free wall and septum. See Table 1 for mean data and p values. CRT = cardiac resynchronization therapy; LBBB = left bundle branch block. LV = left ventricular; RV = right ventricular.
septal motion in LBBB reduced RV free wall workload. Furthermore, CRT was shown to improve LV and RV contractions, resulting in increased work in the RV free wall.

**RV FUNCTION DURING LBBB.** LBBB is an electric conduction disturbance in the LV, whereas conduction in the right ventricle remains unaffected. We have, however, demonstrated that LBBB causes significant changes in the contraction pattern in the right ventricle. This is in accordance with previous computer simulations \(^{(8,17)}\). Hence, changes in contraction pattern must have other reasons than the electric activation delay per se. During normal electric conduction, experimental studies have demonstrated that septal contraction facilitates RV ejection \(^{(23)}\), and that LV contraction accounts for up to 40% of RV systolic pressure \(^{(16)}\). Septal shortening in LBBB, however, is abnormal and septal contractile function is reduced as shown by lower myocardial work \(^{(24)}\).

Thus, septal contraction during LBBB is not optimal for supporting RV function. This is demonstrated by the present experimental study, in which leftward septal motion during early systole caused prolonged RV pressure rise. The delayed pressure rise in early systole led to RV free wall contraction against lower pressure and thereby reduced regional work, even though total shortening was unchanged (Table 1).

Despite reduced septal contraction during LBBB, the left ventricle still supports the right ventricle by pushing the septum rightwards driven by the late, but enhanced, contraction in the LV lateral wall. The early systolic septal shortening causes a systolic pre-excitation stretch of the late-activated LV lateral wall (Central Illustration), which increases regional preload on this wall \(^{(14,25)}\). Subsequent vigorous contraction of the LV lateral wall causes a systolic rightward shift of septum. This is evident as increased RV short-axis work (Table 1, Figure 4).

The rightward shift of the septum is dependent of the function in the LV lateral wall as demonstrated by a recently published experimental study from our group \(^{(26)}\). When regional ischemia was induced in the LV lateral wall, the delayed contraction in this wall was reduced, followed by a concomitant reduction in the rightward septal motion.

**DIRECT MECHANICAL CONNECTION BETWEEN RV FREE WALL AND LV LATERAL WALL.** The RV free wall shortening in early systole during LBBB may contribute directly to the stretching of the LV lateral wall because of the continuum of the epicardial fibers between the 2 ventricles \(^{(27)}\). This contraction in the right ventricle would have resulted in a considerable increase in RV pressure; if not, the septum moves leftwards. Our results demonstrated that the RV pressure rise in fact was slowed, in accordance to a leftward motion of the septum, as also seen in the traces in Central Illustration. Previously, we have demonstrated that the early systolic septal leftward motion is an active contraction \(^{(14)}\). Therefore, the direct mechanical connection between RV free wall and the LV lateral seems to be of less importance than the early septal shortening during LBBB for slowing the RV pressure rise and reduces the RV free wall work.

**RV FUNCTION DURING CRT.** CRT counteracts the delayed activation of the LV lateral wall, attenuates abnormal septal motion, and improves RV pressure rise. Hence, the opportunity to contract against low pressure in the RV free wall and septum is reduced, and thereby reducing both septal and RV free wall early systolic shortening (Central Illustration). In patients, this effect was seen shortly after CRT implantation. In animals, it was shown to be a beat-to-beat response, demonstrated by pacing with increasing interventricular delay (Figure 5). By this approach, we confirmed the direct mechanical interaction between the LV and the RV, as LV end-diastolic pressure was unchanged (Table 1). The demand on the RV free wall increased (Figure 4), which was demonstrated by
increased workload because of a rightward and upward shift of the early systolic part of the pressure-dimension relation. As also seen in Figure 4, CRT reduced short-axis work because of the support of the LV lateral wall on the RV free wall mediated by the septum.

**EARLY VERSUS LATE ACTIVATION OF THE VENTRICULAR WALLS.** We analyzed additional experiments to further explore the concept that the earliest activated ventricular wall decreases its work with a corresponding increase of work in the latest activated wall. With LV-only pacing in ventricles with normal electric activation, the pacing induced left-to-right activation as opposed to right-to-left activations as in LBBB. A corresponding opposite effect on distribution of regional work was also demonstrated. During early activation of the LV lateral wall, it became less effective and performed less work because more of its contraction occurred against lower pressure (Figure 6). The relatively later activated septum and RV free wall increased their work. Taken together, our 2 sets of experimental studies show that septal motion contributes to the earliest activated ventricle and that the latest activated region supports the early activated regions mediated through septum. These results are in line with previous studies (17,18,25,28).

**STUDY LIMITATIONS.** The experimental study was designed to demonstrate hemodynamic mechanisms. Anesthesia and surgery may modify pressure levels and ventricular function. Insertion of catheters through the RV free wall could potentially alter its contraction; however, a similar contraction pattern was found in patients. Furthermore, the anesthetic protocol was changed to propofol/fentanyl to improve rate of successful experiments. Because each animal serves as its own control during the interventions and this paper focuses on the relative changes, the change in anesthetic protocol is less important. This study accounted for immediate hemodynamic changes when CRT was applied and was not designed to analyze long-term responses to LBBB or CRT. In addition, the animal experiments were performed in nonfailing ventricles that may not always reflect the clinical setting in which CRT is applied. Thus, there may be differences in the hemodynamic response depending on the type and design of study. In the clinical study, we investigated patients with a relatively preserved RV function and further studies should be performed in patients with LBBB in RV failure.

Valvular events in the RV are not accounted for; therefore, it is not possible to determine how much of the shortening in early systole was before or after ejection. However, in the animal model, shortening was measured at 50% of pressure rise. This allowed us to measure shortening during early systole regardless of valvular events. Furthermore, this is during low pressure, and shortening in this period contributes...
less to the total work than shortening during higher pressure.

LBBB and pacing influences the atrioventricular coupling, which also may affect ventricular filling and hence preload. We used the longest possible atrioventricular delay, but with still-adequate capture, to minimize this effect. No changes were observed in the ventricular end-diastolic pressures, indicating no major effects on preload.

There is a risk of type II error in the clinical study because it was a pilot study without pro forma power calculation. However, the minor changes in RV GLS, which can achieve statistically significance with a larger number of patients, do not have any clinical significance. In patients with RV failure, this may be more important.

CONCLUSIONS

LBBB reduces RV free wall work and, instead, RV systolic function is supported by abnormal rightward septal motion during early systole because of exaggerated contraction in the late-activated LV free wall. CRT reduces the abnormal septal motion, which increases workload on the RV free wall. Future studies should evaluate if CRT may be harmful in patients with LBBB and RV failure.

ADDRESS FOR CORRESPONDENCE: Dr. Helge Skulstad, Department of Cardiology, Rikshospitalet, Oslo University Hospital, P.O. Box 4950 Nydalen, N-0424 Oslo, Norway. E-mail: helsku@ous-hf.no.
COMPETENCY IN MEDICAL KNOWLEDGE: LBBB and CRT influences RV systolic function by altering contraction pattern in the RV free wall.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The increased demand on the RV free wall during CRT could be of importance to clinicians, especially in patients with borderline RV function or in RV failure. These patients may not be able to increase their RV work.

TRANSLATIONAL OUTLOOK: Future studies should investigate if RV free wall work determines response and prognosis in CRT recipients, and whether contraction pattern in the RV free wall adds further value in prediction of CRT response in heart failure patients with LBBB.

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KEY WORDS cardiac resynchronization therapy, heart failure, left bundle branch block, myocardial work, right ventricle, septal flash
EDITORIAL COMMENT

Does the Right Go Wrong During Cardiac Resynchronization Therapy?*

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About 1 in 3 patients with chronic heart failure (HF) has left bundle branch block (LBBB) (1), a ventricular conduction disorder causing a distinct pattern of electromechanical polarization in the left ventricular (LV) wall, characterized by a decrease of work load in the early activated septum and an increase of work load in the late activated LV lateral wall (2–4). Many clinical studies have shown that LBBB is associated with increased morbidity and mortality (5,6). The introduction of cardiac resynchronization therapy (CRT) has significantly improved the prognosis of patients with HF with reduced LV ejection fraction and hallmarks of LBBB on 12-lead electrocardiogram (i.e., widening and LBBB configuration of the QRS complex) (7). The most popular working mechanism attributed to CRT is its instantaneous recoordinating effect on LV electromechanical function. Through biventricular pacing, CRT can (partially) repair the LV mechanical imbalance by inter- and intraventricular resynchronization of the electric activation (8).

AC A L LF O RF O C U SO NR I G H TV E N T R I C U L A R MECHANICAL FUNCTION

It is important to realize that the vast majority of the studies investigating LBBB and its treatment with CRT has focused on LV mechanics and pump function. The right ventricle, however, is often disregarded in these studies, although it has been known for a long time that a change in the loading condition of either ventricle directly influences the pump function of the other ventricle. Also, several studies have identified right ventricular (RV) systolic dysfunction as an independent predictor of nonresponse to CRT (9). For this reason, the publication of Storsten et al. (10) in this issue of JACC is important, as it provides mechanistic insight into the effects of both LBBB and CRT on RV mechanical function. The work is composed of an elegant combination of animal experimental and human measurements. Echocardiographic longitudinal strain analysis in a group of patients with LBBB with nonischemic cardiomyopathy and normal RV function revealed an abnormal contraction pattern in the RV free wall, characterized by premature systolic shortening before RV ejection. In most patients, this early-systolic RV free wall shortening was significantly reduced or entirely abolished by CRT.

Storsten et al. (10) observed the same premature RV systolic shortening in an animal model as soon as LBBB was induced by radiofrequency ablation of the left bundle branch. Because the intrinsic His-Purkinje conduction of the right ventricle was maintained in this acute model of LBBB, it was concluded that the RV contraction abnormality was a result of a change in direct LV-RV interaction. Interestingly, they also investigated what this change of ventricular interaction means for the distribution of work load over the ventricular walls.

MYOCARDIAL UNLOADING AND RELOADING DURING LBBB AND CRT

By combining LV and RV pressure measurements with myocardial deformation analysis using

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Sonomicrometric crystals, the distribution of myocardial work across the ventricular walls was determined during LBBB and CRT. These experimental data corroborate previous experimental and clinical studies (3,12) by showing that LBBB increases myocardial work load in the late activated LV lateral wall and decreases work load in the early activated septum and that CRT (partially) restores the distribution of myocardial work load. Furthermore, the animal experimental data validate previous computer simulation work showing that LBBB reduces work load in the RV free wall and that CRT reverts this unloading effect (3). In other words, CRT instantly increases the work load of the RV myocardium in a patient with HF with LBBB. Therefore, as Storsten et al. (10) suggest, their study raises the important question whether this pacing-induced change in RV work load can explain the association between baseline RV dysfunction and worse outcome after CRT.

**IS RV WORK LOAD THE LINK BETWEEN RV FAILURE AND NONRESPONSE TO CRT?**

For this editorial, we have performed computer simulations to test this hypothesis. We have used the well-established CircAdapt model of the human heart.
RV contractile failure signifies in terms of acute change of cardiac output relative to effect of RV failure on hemodynamic response to CRT, workload. The bottom panel of Figure 1 illustrates the effect of RV failure on hemodynamic response to CRT, in terms of acute change of cardiac output relative to baseline LVBBB conductance. The simulations predict that RV contractile failure significantly reduces the potential for acute CRT response.

**RV DEFORMATION PATTERN AS A PREDICTIVE BIOMARKER**

In an earlier study, Van Everdingen et al. (14) showed that conventional LV mechanical dyssynchrony indexes (i.e., time to peak strain between the septum and LV lateral wall, interventricular mechanical delay, and septal systolic rebound stretch) do not reflect the negative impact of RV contractile dysfunction on CRT response. The data published by Storsten et al. (10) and the simulations presented in this editorial suggest that the early systolic RV shortening can be of prognostic value, given its sensitivity to the electromechanical LBDBB substrate that is amenable to CRT and to the contractile function of the RV free wall, which seems to be a strong determinant of CRT response.

**GOING THE RIGHT WAY WITH CRT**

Taking all these data together, we strongly support the notion by Storsten et al. (10) that the diagnostic work-up of patients with HF who are candidates for CRT should include the assessment of baseline RV function. Their combination of patient and animal experimental data as well as the aforementioned computer simulations indicate that the RV free wall, which is mechanically spared in the aforementioned computer simulations, should be strong enough to bear the sudden increase in work load imposed by CRT. Future studies are needed to determine how much of the current problem of nonresponse to CRT is due to a lack of RV contractile reserve.

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KEY WORDS dyssynchrony, heart failure, right ventricle, strain, ventricular interaction
ABSTRACT

OBJECTIVES This study sought to evaluate the role of cardiac magnetic resonance (CMR) for the quantification of ischemic mitral regurgitation (IMR) and myocardial infarct size (MIS) in patients with ischemic cardiomyopathy (ICM). This study also sought to explore the interaction between IMR severity and MIS and its association with outcomes in patients with ICM.

BACKGROUND IMR occurs secondary to a disease of the left ventricle and is associated with poor outcomes. The role of CMR for the evaluation and risk stratification of patients with ICM and IMR remains uncertain.

METHODS Consecutive patients with ICM who underwent baseline CMR were included. MIS was quantified on late gadolinium enhancement imaging as the proportion of left ventricular mass. IMR was quantified with CMR by calculating the mitral regurgitant fraction (MRFraction). Cox proportional hazards models were built to assess the association of IMR and MIS quantification with the combined endpoint of all-cause death or heart transplant.

RESULTS We evaluated 578 patients (mean age: 62 ± 11 years, 76% males). The mean left ventricular ejection fraction was 25 ± 11%, with an MIS of 24 ± 16% and MRFraction of 18 ± 17%. Over a median follow-up time of 4.9 years, 198 (34%) patients experienced death or cardiac transplant. On multivariable analysis, after comprehensive medical risk score, subsequent revascularization, implantable cardioverter-defibrillator insertion, and surgical mitral valve intervention were controlled for, the interaction of IMR severity and MIS emerged as a powerful predictor of adverse outcomes (p = 0.008). For patients with significant IMR (MRFraction: ≥35%), the hazard ratio comparing moderate MIS (15% to 29%) versus small MIS (<15%) was 1.51 (0.57 to 3.98), and the hazard ratio comparing large MIS (≥30%) versus small MIS was 5.41 (2.34 to 12.7).

CONCLUSIONS Risk associated with IMR is more comprehensively described as an interaction between IMR severity and MIS. Further studies in patients IMR using comprehensive CMR evaluation are needed to verify whether this approach can improve patient selection and procedural outcomes to address IMR. (J Am Coll Cardiol Img 2020;13:1489–501) © 2020 Published by Elsevier on behalf of the American College of Cardiology Foundation.
The left ventricle (LV) remodeling that ensues after myocardial infarction produces important structural changes to the LV, which can subsequently affect the geometry of the mitral valve (MV) apparatus. Ischemic mitral regurgitation (IMR) is a common sequela of ischemic cardiomyopathy (ICM) due to underlying regional LV dysfunction, LV remodeling, and mitral annular dilation, all of which lead to impaired leaflet coaptation. The severity of IMR assessed by Doppler echocardiography has been shown to be associated with outcomes (1–4). However, despite the association between IMR severity and mortality, there is currently no evidence that surgical correction of IMR is superior to medical therapy (4,5). Furthermore, recent conflicting results from percutaneous therapy trials (6,7) addressing secondary mitral regurgitation (MR) (which includes IMR) have raised questions about the differences in the criteria used for patient selection and for MR severity (8,9).

In IMR, the accepted theory is that the problem resides within the LV. Therefore, the complex interplay between LV remodeling, myocardial infarct size (MIS), and volume overload from IMR requires a comprehensive understanding of each of these components and how they combine to result in the associated outcomes. Our group has previously shown that evaluation of LV remodeling (10) and MIS (11) by cardiovascular magnetic resonance (CMR) added incremental prognostic value to conventional clinical and echocardiographic variables in a cohort of patients with ICM and in patients undergoing surgical mitral intervention (12). Importantly, these parameters were also associated with the progression of IMR (13), a commonly reported problem after surgical repair from a large contemporary series (14).

Recent valvular regurgitation guidelines (15) have integrated CMR as an important diagnostic imaging modality for the evaluation of patients with MR. Although the CMR cutoffs for primary/organic MR associated with unfavorable outcomes are available (16), the specific CMR thresholds for secondary IMR severity are unknown. Gaasch and Meyer (17) emphasized need for comprehensive assessment provided by CMR in patients with IMR and proposed that MR fraction (MRFraction) was the single most appropriate index of MR severity as it accounts for LV stroke volume. Whether CMR quantification of IMR and MIS can be used for further risk stratification of patients with advanced ICM beyond clinical and other imaging parameters associated with adverse prognosis remains unknown.

Our study hypothesis was that CMR quantification of IMR severity and MIS in patients with advanced ICM can stratify patients with increased likelihood of the combined endpoint of all-cause mortality and/or heart transplant. Our study objectives were as follows: 1) to quantify the prognostic role of CMR for the assessment of IMR; 2) to identify clinically useful IMR quantification cutoffs with CMR by assessing the association of these cutoffs with all-cause mortality and cardiac transplant; and 3) to assess how MIS might modify the prognostic value of CMR quantification of IMR severity.

**METHODS**

**STUDY POPULATION.** This was an observational, retrospective cohort study of consecutive patients with the diagnosis of ICM (≥70% stenosis in ≥1 epicardial coronary vessel on angiography or history of myocardial infarction or coronary revascularization) with LV systolic dysfunction (LV ejection fraction of ≤40% by CMR) who were referred for clinically indicated myocardial viability assessment with CMR between January 2002 and January 2013. Exclusion criteria included prior mitral valve (MV) surgery, intrinsic MV pathology (prolapse/fail), other valvular stenosis, and patients with frequent atrial and/or ventricular arrhythmias. Given the complexity and high-risk nature of our patient population, we built a medical risk score that captured baseline demographic data, risk factors, and treatments. This score has been shown to be independently associated with outcomes in this population of patients with advanced ICM (18). More details can be found in the Supplemental Appendix.

**CLINICAL OUTCOMES.** The primary clinical outcome was the combined endpoint of all-cause mortality or heart transplant. Death notification was confirmed by observation of death certificate or verified with a family member. This study was approved by the institutional review board, with a waiver of individual consent.

**ECHOCARDIOGRAPHIC ASSESSMENT.** All patients underwent a comprehensive baseline echocardiogram with evaluation of standard parameters with commercially available instruments (Philips Medical Systems, Bothell, Washington; General Electric Medical Systems, Milwaukee, Wisconsin; and Siemens Medical Solutions USA, Inc., Malvern, Pennsylvania). Measurements and recordings were obtained according to the American Society of Echocardiography recommendations (15).
Severity of IMR was assessed by 2-dimensional (2D) transthoracic echocardiography by using the effective regurgitant orifice area (EROA), which was calculated from the proximal isovelocity surface area.

CMR ASSESSMENT. CMR examinations were performed on 1.5-T magnetic resonance scanners (Sonata and Avanto, Siemens Medical Solutions, Erlangen, Germany, or Achieva XR, Philips Medical Systems, Best, the Netherlands), as previously described (10). Additional details for CMR assessment can be found in the Supplemental Appendix.

MR volume (MRVolume) was calculated as the difference between the LV stroke volume (as determined by endocardial segmentation of cine images) and forward aortic flow volume by using breath-held phase-contrast imaging. The MRFraction was calculated as (MRVolume/LV stroke volume) × 100%. This indirect method has been shown by several prior publications to have excellent reproducibility (lower variability) (19).

Late gadolinium-enhancement images were obtained in long- and short-axis orientations approximately 15 to 20 min after injection of 0.2 mmol/kg of gadolinium dimeglumine, with segmented inversion-recovery spoiled gradient echo sequences for studies performed in 2002 and 2003 and phase-sensitive inversion-recovery spoiled gradient echo sequences for studies performed after 2003. MIS was determined as the proportion of total myocardium (infarct mass divided by total LV mass). Viable vascular territories were defined as areas with ≤50% transmural scarring based on late gadolinium enhancement assessment, according to the standard American Heart Association 16-segment model, with corresponding major epicardial coronary artery stenosis of ≥70% stenosis. Vascular territories with >50% transmural scarring were considered nonviable. CMR analysis was completely blinded to the clinical outcomes.

STATISTICAL ANALYSIS. The sensitivity and specificity of various cutpoints for echocardiography-based EROA and CMR-based MRFraction and MRVolume were estimated for patients who experienced an adverse event within the first year. The 95% confidence intervals (CIs) were constructed using the Wilson scoring method. More details can be found in the Supplemental Appendix.

The Spearman rank correlation coefficient between MRFraction-measured CMR versus EROA by 2D echocardiography was estimated by using the proximal isovelocity surface area.

Several multivariate Cox proportional hazards regression models were fit to test whether IMR

| TABLE 1 Baseline Clinical Characteristics |
|------------------------------------------|
|                                          |
| Clinical characteristics                  |
|                                          |
| Total Population (N = 578)                |
| Medically Treated (n = 273)               |
| MVR or MVR and Revascularization (n = 112) |
| Revascularization Only (n = 193)          |
| Age, yrs                                  |
| 62.4 ± 11.0                               |
| 60.5 ± 11                                 |
| 64.8 ± 10                                 |
| 63.8 ± 10                                 |
| Female                                    |
| 140 (24.2)                                |
| 60 (25.0)                                 |
| 32 (29.0)                                 |
| 39 (20.0)                                 |
| Body mass index, kg/m²                    |
| 28.7 ± 5.5                                |
| 28.6 ± 5.9                                |
| 28.4 ± 5.5                                |
| 28.8 ± 5.0                                |
| Hypertension                              |
| 306 (52.9)                                |
| 145 (53.0)                                |
| 59 (53.0)                                 |
| 102 (53.0)                                |
| Diabetes mellitus                         |
| 118 (20.4)                                |
| 56 (21.0)                                 |
| 20 (18.0)                                 |
| 42 (22.0)                                 |
| Dyslipidemia                              |
| 302 (52.3)                                |
| 153 (56.0)                                |
| 61 (54.0)                                 |
| 88 (46.0)                                 |
| >2 vessels CAD                            |
| 230 (40.6)                                |
| 80 (29.0)                                 |
| 50 (45.0)                                 |
| 100 (52.0)                                |
| Revascularization pre-CMR (CABG/PCI)      |
| 250 (43.3)                                |
| 127 (47.0)                                |
| 51 (46.0)                                 |
| 72 (37.0)                                 |
| Revascularization post-CMR (CABG/PCI)     |
| 291 (52.0)                                |
| 0 (0.0)                                   |
| 98 (88)                                   |
| 193 (100)                                 |
| CRT                                       |
| 53 (9.2)                                  |
| 23 (8.4)                                  |
| 19 (17.0)                                 |
| 11 (5.7)                                  |
| ICD                                       |
| 171 (29.6)                                |
| 72 (26.4)                                 |
| 48 (24.9)                                 |
| 51 (26.4)                                 |
| GFR, ml/min/1.73m²                        |
| 85.0 ± 36.5                               |
| 84.0 ± 37.0                               |
| 83.0 ± 36.0                               |
| 87.0 ± 36.0                               |
| Medications                               |
| ACE inhibitor                             |
| 458 (79.4)                                |
| 210 (77.0)                                |
| 86 (77.0)                                 |
| 162 (84.0)                                |
| Aldosterone blocker                      |
| 138 (24.0)                                |
| 76 (28.0)                                 |
| 26 (23.0)                                 |
| 36 (19.0)                                 |
| Aspirin                                   |
| 386 (66.8)                                |
| 206 (75.0)                                |
| 64 (57.0)                                 |
| 116 (60.0)                                |
| Beta-blocker                             |
| 475 (82.2)                                |
| 214 (78.0)                                |
| 92 (82.0)                                 |
| 169 (88.0)                                |
| Diuretic                                  |
| 211 (36.5)                                |
| 112 (41.0)                                |
| 41 (37.0)                                 |
| 58 (30.0)                                 |
| Statin                                    |
| 449 (79.1)                                |
| 218 (80.0)                                |
| 83 (75.0)                                 |
| 148 (78.0)                                |

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; CRT = cardiac resynchronization therapy; CABG = coronary artery bypass graft; CAD = coronary artery disease, defined as >70% luminal obstruction on invasive coronary angiogram; CMR = cardiac magnetic resonance; GFR = glomerular filtration rate; ICD = implantable cardiac device; MVR = mitral valve repair or replacement; PCI = percutaneous coronary intervention.
TABLE 2 Baseline CMR Imaging Characteristics

| Measure                      | Population (N = 578) | Medically Treated (n = 273) | MVrR or MVrR and Revascularization (n = 112) | Revascularization Only (n = 193) |
|------------------------------|-----------------------|-----------------------------|---------------------------------------------|---------------------------------|
| LAVI, ml/m²                  | 53 ± 47               | 54 ± 23                     | 65 ± 92                                     | 45 ± 17                         |
| LV EDVindex, ml/m²           | 140 ± 46              | 140 ± 53                    | 148 ± 35                                    | 136 ± 42                        |
| LV ESVindex, ml/m²           | 108 ± 47              | 106 ± 53                    | 116 ± 34                                    | 105 ± 43                        |
| LVEF, %                      | 25 ± 11               | 27 ± 12                     | 23 ± 8                                      | 25 ± 9                          |
| LVMI, g/m²                   | 103 ± 44              | 118 ± 51                    | 86 ± 29                                     | 92 ± 33                         |
| Mean MRFraction, %           | 18 ± 17               | 15 ± 16                     | 32 ± 17                                     | 13 ± 14                         |
| Mean MRVolume, ml            | 12 ± 13               | 11 ± 13                     | 23 ± 14                                     | 8 ± 10                          |
| MIS, % of total LV mass      | 24 ± 16               | 25 ± 15                     | 22 ± 16                                     | 22 ± 16                         |
| RVEF, %                      | 42 ± 14               | 42 ± 15                     | 40 ± 14                                     | 43 ± 14                         |

Values are mean ± SD.

LAVI = left atrial volume index; LV = left ventricular; LV EDVindex = left ventricular end-diastolic volume index; LV ESVindex = left ventricular end-systolic volume index; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; MRFraction = mitral regurgitant fraction; MRVolume = mitral regurgitant volume; MIS = myocardial infarct size; RVEF = right ventricular ejection fraction; other abbreviations as in Table 1.

RESULTS

A total of 578 patients with advanced ICM were included in the analysis, of whom 291 were subsequently revascularized (112 of 291 [38%] had concomitant MV surgical intervention: 13 underwent MV replacement, and 99 underwent MV repair), and 287 were medically treated. There were 198 adverse events (191 deaths and 7 cardiac transplants). Baseline clinical variables and medications are listed in Table 1.

This cohort had a mean age of 62 ± 11 years and was predominantly male (76%), with a high burden of comorbidities. At the time of the baseline CMR study, the prevalence of optimal medical therapy for heart failure with reduced left ejection fraction was as follows: beta-blockers: 82%; angiotensin-converting enzyme inhibitor/angiotensin receptor blocker: 79%; and aldosterone blocker: 24%. These proportions are similar those from the Get With the Guidelines-Heart Failure registry (20). The mean time between CMR and echocardiography was 3.8 ± 1.0 days, with 67% of subjects having <5 days between the 2 imaging modalities. Of note, none of the patients had an implantable permanent pacemaker, defibrillator, or resynchronization device in situ at the time of the CMR study. ICD insertion after the CMR study was treated as a time-dependent covariate.

CMR IMAGING CHARACTERISTICS. Table 2 describes the CMR imaging characteristics of this study cohort. As anticipated, in general, patients had advanced LV remodeling with severely reduced LV systolic function (LV ejection fraction: 25 ± 11%) and large MIS, encompassing on average 24% of the entire LV mass. On average, there was mild right ventricular dysfunction (right ventricular ejection fraction: 42 ± 14%). Mean MRVolume was 12 ± 13 ml, and mean MRFraction was 18 ± 17%.

IMR SEVERITY THRESHOLDS BY CMR AND OUTCOMES. Over a median follow-up time of 4.9 years (range 0 to 11.2 years), there were 198 events of the combined endpoint of death/heart transplant. At 1 year, there were 54 events: 4 transplants and 49 deaths. The
estimated area under the curve for EROA by echocardiography, MRFraction by CMR, and MRVolume by CMR were 0.64 (95% CI: 0.59 to 0.68), 0.63 (95% CI: 0.58 to 0.68), and 0.61 (95% CI: 0.57 to 0.66), respectively. Although EROA measured by echocardiography and MRFraction by CMR were highly correlated (r = 0.794; p < 0.001) (Figure 1), EROA seems to underestimate at lower levels of IMR (i.e., EROA <0.2 cm²).

Estimated sensitivities and specificities for the various cutpoints based on the methodology for IMR quantification at the 1-year follow-up are listed in Table 3. The MRFraction cutoff of ≥35% showed a high degree of specificity compared with cutpoints of 20% and even 30%. Table 4 illustrates the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) at 5 years. The specificity was excellent at ≥35%, and the estimate of PPV, although biased because patients censored before 5 years were excluded, was also very high. Based on the best combination of PPV and NPV, the cutoff of MRFraction ≥35% was chosen as the optimal cutpoint because of the optimal combination of sensitivity, specificity, PPV, and NPV. Furthermore, MRFraction adjusts for the low cardiac output typically seen in these patients with ICM (17), and it has been shown to have prognostic value in patients with MR (16).

In a multivariate Cox proportional hazards model, after adjustment for standard risk variables, MIS, LV end systolic volume index (LVESVi), ICD insertion, and treatment received (medical vs. revascularization and/or MV surgery), MRFraction by CMR was not significant as a predictor of the combined 1-year endpoint as a continuous variable (hazard ratio [HR]: 1.02; 95% CI: 1.00 to 1.03; p = 0.069) but was a statistically significant predictor when an MRFraction cutoff of ≥35% was used (HR: 2.07; 95% CI: 1.08 to 4.00; p = 0.007). MIS was also a statistically significant predictor of the combined endpoint at 1 year (HR: 1.03; 95% CI: 1.01 to 1.05; p = 0.01) (Table 5). When patients’ long-term outcomes were included in the model, MRFraction by CMR remained a predictor as a continuous variable (HR: 1.01; 95% CI: 1.00 to 1.02; p = 0.008) or when stratified by using the cutoff of ≥35% (HR: 1.65; 95% CI: 1.15 to 2.38; p = 0.007) (Table 5). Of note, LVESVi was close to significance for the association with 1-year outcomes (HR: 1.01; 95% CI: 1.00 to 1.02; p = 0.059), but it did not emerge as an independent predictor for longer-term outcomes either as a single variable (p = 0.398) or as an interaction term with MRFraction (p = 0.775) when the follow-up time was extended to 5 years.

The interaction between IMR severity and MIS as determinants of outcomes in ICM.

To evaluate the effect of MIS on the relationship between MRFraction and patient outcomes, the

| Cutpoint for EROA, cm² | Sensitivity EROA | Specificity EROA | Cutpoint for MRFraction, % | Sensitivity MRFraction | Specificity MRFraction | Cutpoint for MRVolume, ml | Sensitivity MRVolume | Specificity MRVolume |
|------------------------|------------------|------------------|---------------------------|------------------------|------------------------|--------------------------|----------------------|----------------------|
| 0.20                   | 0.556            | 0.595            | 20                        | 0.519                  | 0.614                  | 10                       | 0.648                | 0.550                |
|                        | (0.424-0.680)    | (0.552-0.636)    |                           | (0.389-0.646)          | (0.571-0.655)          |                          | (0.515-0.762)        | (0.506-0.592)        |
| 0.25                   | 0.370            | 0.817            | 30                        | 0.370                  | 0.780                  | 20                       | 0.370                | 0.782                |
|                        | (0.254-0.504)    | (0.781-0.848)    |                           | (0.254-0.504)          | (0.742-0.813)          |                          | (0.254-0.504)        | (0.744-0.815)        |
| 0.30                   | 0.185            | 0.856            | 35                        | 0.315                  | 0.842                  | 25                       | 0.278                | 0.858                |
|                        | (0.104-0.308)    | (0.823-0.884)    |                           | (0.207-0.447)          | (0.808-0.871)          |                          | (0.176-0.409)        | (0.825-0.885)        |
| 0.40                   | 0.148            | 0.934            | 45                        | 0.111                  | 0.924                  | 30                       | 0.148                | 0.901                |
|                        | (0.077-0.266)    | (0.909-0.952)    |                           | (0.052-0.222)          | (0.898-0.944)          |                          | (0.077-0.266)        | (0.872-0.924)        |

AUC EROA² AUC MRFraction AUC MRVolume

AUC EROA = 0.636 (0.589-0.684) AUC MRFraction = 0.628 (0.581-0.675) AUC MRVolume = 0.614 (0.567-0.661)

Values are mean (95% CI) or %. *None of the differences in AUC were statistically significant: EROA vs. MRFraction (p = 0.628), EROA vs. MRVolume (p = 0.217), and MRFraction vs. MRVolume (p = 0.074).

AUC = area under the curve; CI = confidence interval; EROA = effective regurgitant orifice area; IMR = ischemic mitral regurgitation; ROC = receiver-operating characteristic; other abbreviations as in Table 2.
estimated HRs from the Cox models were plotted for an increasingly more stringent definition of positivity. For increasing values of MRFraction and MIS, the estimated HR associated with their combined effect increased significantly, suggesting a potential interaction at high MRFraction and MIS values (Figure 2). With these cutoffs, 560 patients had complete data for Cox proportional hazard model analysis. A total of 98 of 560 patients had MRFraction $\geq$ 35%, and of these 98 patients, 38% had minimal myocardial scarring ($<$15%), 22% had moderate scarring (15% to 29%), and 40% had severe scarring ($\geq$30% of LV mass). Therefore, our data suggest that there is not a direct relationship between the extent of myocardial scarring and severity of IMR for this subgroup of patients with severe IMR or for the entire study group ($r = 0.04$), as one might predict.

Table 6 summarizes the Cox proportional hazards model results when the interaction of IMR quantification and MIS was added to the models. After medical risk, LVESVi, subsequent coronary revascularization, incomplete revascularization, ICD insertion, and surgical MVi were controlled for, the 2-way interaction between MRFraction and MIS emerged as a novel and powerful predictor of long-term mortality or cardiac transplant. The HR of patients with significant IMR (MRFraction $\geq$ 35%) and small MIS was $1.51$ (95% CI: 0.57 to 3.98), the HR for patients with MRFraction $\geq$ 35% and moderate MIS was 3.60 (95% CI: 1.72 to 7.52), and the HR for patients with MRFraction $\geq$ 35% and large MIS was 5.41 (95% CI: 2.34 to 12.70). Furthermore, the risk associated with large MIS of $\geq$ 30% was significantly increased in all patients with ICM across the spectrum of IMR severity. LVESVi was independently associated with 1-year outcomes (HR: 1.01; 95% CI: 1.00 to 1.01; $p = 0.033$); however, MIS and MRFraction (as an interaction term) was more strongly associated with longer-term 5-year outcomes than LVESVi (Table 6). A similar Cox proportional hazards model was built by substituting LV end-diastolic volume index.
for LVESVi and showed nearly identical findings (Supplemental Appendix).

**Figures 3 and 4** illustrate the adjusted fitted survival curves and important interaction effect between MRFraction and MIS. By using as the reference group, the patients with MRFraction of <35% and MIS of <15%. The patients were divided into 6 groups based on varying degrees of MRFraction and MIS. **Figure 3** illustrates the fitted survival curves for the 6 risk groups. Compared with subjects at the lowest risk, subjects with moderate or high MIS, but with less significant MRFraction, are at slightly increased risk (HR: 1.58 and HR: 1.81, respectively), but subjects with high MIS and greater MRFraction are at the highest risk (HR: 5.16). The risk of death or heart transplant for these subjects is significantly greater than for subjects in any other risk group (p < 0.001). **Figure 4** also displays the estimated HRs, adjusted for the standard risks listed, relative to the lowest risk group (MRFraction <35% and MIS <15%).

Exploratory subgroup analysis for the patients who underwent surgical MVi (n = 112) was carried out to evaluate whether interaction between MRFraction and MIS would have similar prognostic value as seen in the entire cohort. A total of 107 patients (96%) had complete data for the comprehensive multivariate Cox proportional model hazards model shown in **Table 7**. In this subgroup of patients, there was again a strong interaction between MRFraction and MIS such that those patients with significant IMR and high MIS had

### Table 6 Final Multivariable Cox Models With the Interaction of IMR and Infarct Size

|                | 1-Year Outcomes |         | All Outcomes |         |
|----------------|----------------|---------|--------------|---------|
|                | Estimated HR (95% CI) | p Value | Estimated HR (95% CI) | p Value |
| Medical risk score| 2.49 (1.54–4.02) | <0.001 | 2.61 (2.06–3.31) | <0.001 |
| Coronary revascularization | 0.98 (0.46–2.05) | 0.949 | 1.37 (0.97–1.95) | 0.077 |
| Surgical MV repair | 1.64 (0.69–3.94) | 0.264 | 1.28 (0.86–1.89) | 0.224 |
| ICD (time dependent) | 0.32 (0.13–0.80) | 0.014 | 0.99 (0.69–1.43) | 0.974 |
| Incomplete revascularization | 2.48 (1.22–5.03) | 0.012 | 1.95 (1.41–2.70) | <0.001 |
| LVESVi (per 1 ml/m²) | 1.01 (1.00–1.01) | 0.033 | 1.01 (0.99–1.01) | 0.323 |

2-way interactions†

|                |                |         |                |         |
|----------------|----------------|---------|----------------|---------|
| MRFraction ≥35% vs. <35% at MIS <15% | 1.20 (0.24–5.95) | 0.95 (0.41–2.21) |
| MRFraction ≥35% vs. <35% at MIS 15%–29% | 0.98 (0.21–4.59) | 0.91 (0.45–1.83) |
| MRFraction ≥35% vs. <35% at MIS ≥30% | 3.23 (1.40–7.41) | 2.86 (1.78–4.57) |
| MIS 15%–29% vs. MIS <15% at MRFraction <35% | 1.36 (0.50–3.70) | 1.58 (0.99–2.53) |
| MIS 30% vs. MIS <15% at MRFraction <35% | 1.77 (0.69–4.52) | 1.81 (1.16–2.81) |
| MIS ≥30% vs. MIS 15%–29% at MRFraction <35% | 1.30 (0.54–3.12) | 1.14 (0.77–1.71) |
| MIS 15%–29% vs. MIS <15% at MRFraction 35% | 1.10 (0.15–7.93) | 1.51 (0.57–3.98) |
| MIS ≥30% vs. MIS 15%–29% at MRFraction ≥35% | 4.27 (0.93–19.6) | 3.60 (1.72–7.52) |
| MRFraction ≥35% vs. MIS ≥30% at MRFraction ≥35% | 4.74 (1.03–21.7) | 5.41 (2.34–12.7) |

*Medical risk score includes the following variables: age, body mass index, sex, diabetes, glomerular filtration rate, hypertension, dyslipidemia, medications (beta-blocker, angiotensin-converting enzyme inhibitor/receptor blocker), left or right bundle branch block, QRS duration, and an interaction term for sex and diabetes. †The 2-way interaction of MIS (3 levels) and MRFraction (2 levels) represents a 3 × 2 categorical variable. The main effects of MIS and MRFraction are included in the model but are not shown here because they cannot be interpreted when the interaction term is in the model. Abbreviations as in Tables 2, 3, and 5.

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**Figure 3** Survival Curves Based on Severity of MRFraction and MIS

Fitted survival curves for the entire study group, categorized into the 6 risk groups based on severity of MRFraction and MIS. Compared with subjects at the lowest risk, subjects with moderate or high MIS, but less significant MRFraction, are at slightly increased risk (HR: 1.58 and HR: 1.81, respectively), but subjects with high MIS and greater MRFraction are at the highest risk (HR: 5.16). The risk of death or heart transplant for these subjects is significantly greater than for subjects in any other risk group (p < 0.001).
worse outcomes despite surgical MVi. On the other hand, patients with significant IMR (MRFraction ≥35%) but small scar burden (MIS <15%) had the best survival after MV surgery (Figure 5). Patients with significant MR and low myocardial scar burden (MSB), who received CABG and mitral valve surgery, had survival benefit over those with significant MR and high MSB (Central Illustration). Although not significant, patients receiving medical treatment had higher MIS (Supplemental Table 2). The vast majority of patients had excellent durability of their surgical MVi, with 15% (16 of 112 patients) experiencing recurrent MR during the follow-up period. Finally, in this subgroup analysis, the vast majority of patients underwent concomitant coronary artery bypass grafting. Revascularization and incomplete revascularization were associated with adverse outcomes. Increased risk associated with revascularization finding may reflect selection bias of lower-risk patients referred for surgical MVi in isolation.

Subgroup analysis for the medically treated patients and analyses substituting MIS (proportion of total scar burden) for the presence of nonviable (>50% transmural) myocardial scar is available in the Supplemental Appendix.

**DISCUSSION**

Patients with advanced ICM and IMR represent a challenging group, with high rates of morbidity and mortality events. In this large, single-center cohort of patients with advanced ICM, evaluation by CMR provided 3 main findings. First, quantification of IMR by CMR by using MRFraction (which accounts for the LV stroke volume) stratifies risk, which is proportional to the IMR severity. Second, a novel and clinically important interaction between MRFraction and MIS provides further risk stratification beyond LV volumes and clinical parameters. Our survival analysis shows that risk associated with significant IMR should not be determined in isolation but more comprehensively and completely assessed when it is described in the context of MIS. Third, presence of both significant IMR (MRFraction ≥35%) and large MIS (>30% of LV mass) carries a very high risk for all-cause mortality and/or heart transplant, despite surgical MVi. On the other hand, patients with significant IMR (MRFraction ≥35%) and low MIS (<15% of LV mass) had survival benefit after surgical MVi. Taken together, these results shows that CMR is an important noninvasive imaging modality, not only for risk stratification but also for the individualization of treatment decisions for these complex patients.

A large recent meta-analysis has shown that even mild IMR correlates with adverse outcomes in this population (5). Because the disease process lies within the LV we believe that an integrated CMR approach encompassing quantification of IMR severity, LV remodeling, and MIS extent is critically necessary, not only for risk stratification but also for guiding the timing and selection of future therapies for these patients.

CMR is an established imaging tool of great importance in the evaluation of and decision management for ICM patients. It is currently
considered the gold standard imaging method for the quantification of biventricular function, remodeling, myocardial ischemia, viability, and quantification of MIS (21). Furthermore, our previous work (12) showed the ability for myocardial scar quantification to provide powerful prognostic risk stratification in patients with ICM who underwent subsequent surgical MVi for significant IMR, quantified by echocardiography. Patients with MIS of <25% experienced improved survival if complete revascularization was achieved concurrently with MVi. However, the mortality rate was higher in patients with MIS ≥25%, despite complete revascularization at the time of MVi. Furthermore, patients with more severe IMR and increased MIS appeared to have the highest risk of mortality, despite MVi. Similarly, the prospective CTSN trial has shown that presence of basal inferior aneurysm, a strong surrogate of focal transmural scar, is associated with higher likelihood of IMR recurrence in patients with ICM who have undergone surgical MV repair (27).

Our current study expands these findings in a broader population of patients with IMR, with the approach of assessment of myocardial viability and IMR severity by CMR alone (12). Our current study shows the impact of the complex interplay and interaction between LV remodeling, IMR severity, and MIS on long-term outcomes, assessed by a comprehensive CMR examination.

Recently, high-risk patients with secondary MR treated with MitraClip (Abbott Vascular, Menlo Park, California) showed significantly improved survival compared with conservative medical therapy, and previous studies have also suggested that MitraClip therapy may provide improved survival benefit compared with surgical intervention (22–24). On the other hand, recent results of the randomized MITRA.FR trial, which included patients with at least moderate secondary MR (EROA >20 mm² or MRVolume >30 ml/beat), have shown no significant New York Heart Association functional class and/or mortality improvement of these patients treated with MitraClip versus medical therapy. Although the differences in outcomes of these studies may be related to the presence of advanced LV remodeling and the presence of disproportionate versus proportionate MR (9), an interaction between LV size and IMR did not emerge as an independent predictor in our overall study population of patients with ICM, nor in the patients undergoing surgical MVi. However, there was a significant interaction between MV MIS and IMR, suggesting that MIS is a more powerful mediator of prognosis than LV volumes in our patient population.

Updated societal guidelines for valvular regurgitation have now included CMR evaluation in patients with MR and: 1) suboptimal echocardiography images; 2) discordance between 2D echocardiographic features and Doppler findings; and 3) discordance between clinical assessment and severity of MR by echocardiography. In addition, the guidelines also acknowledge the lack of CMR-specific thresholds of MRVolume or MRFraction that would define severe MR, particularly for secondary MR (15), where there is lack of evidence based on outcomes.

Most of the current CMR published data regarding MR has evaluated patients with primary/organic pathology. Myerson and colleagues (16) showed that in primary MR, MRFraction of >40% and/or MRVolume of >55 ml/beat was associated with progression to symptoms and need for MV surgery. Penicka and colleagues (25) recently showed that MRVolume quantification by CMR, also in primary MR, had better predictive power to predict mortality or need for MV surgery than quantification by echocardiography including EROA. Uretsky et al. (26) showed that CMR-based quantification of primary MR can more reliably predict postsurgical LV reverse remodeling than echocardiography.
The top row illustrates the cardiac magnetic resonance methodology for obtaining mitral regurgitation volume, integrating left ventricular stroke volume derived from the cine short axis stack and forward flow through the ascending aorta flow velocity mapping. The middle row illustrates the methodology for quantification of myocardial infarct size. The bottom panel illustrates the prognostic impact of and significant interaction between cardiac magnetic resonance–derived mitral regurgitation fraction and myocardial infarct size in the entire study group, as well as in the subgroup of patients who underwent surgical mitral valve intervention.
Our study fills that knowledge gap by demonstrating the important role of CMR for the quantification of IMR, LV remodeling, and MIS, all of which are strongly associated with outcomes in these patients with ICM. The risk of adverse outcomes in patients with ICM and significant IMR is greatly modified by the extent of myocardial scarring. Comprehensive assessment integrating coronary/bypass graft angiography, along with CMR-derived quantification of IMR severity, LV remodeling, and MIS provide powerful incremental risk stratification that may help guide management strategies. We believe these findings highlight the importance of CMR imaging for the accurate assessment of IMR severity and LV health, both of which are important to risk stratification and to guide therapeutic decision strategies. The potential survival benefit that could be seen from IMR correction should be considered in the context of the extent of LV remodeling, IMR severity, and MIS, all of which can be evaluated by a comprehensive CMR examination.

**STUDY LIMITATIONS.** Although, to our knowledge, this is the largest to date cohort of patients with ICM with IMR and MIS quantification by CMR, it remains a retrospective, nonrandomized, single-center observation that included a selected patient population with severe ICM, and advanced LV remodeling, glomerular filtration rate of >30 ml/min/1.73 m² and without ICDs at baseline. As such, it is possible that baseline CMR data were used in the treatment decision process for the care of these complex patients and that a potential referral bias included those suitable for CMR scanning and/or facing a clinical dilemma regarding revascularization. One example is the small group of patients with significant IMR (MRFraction ≥35%) and large scar burden (MIS ≥30%) who received MVi (11 of 39 patients [28%]), contrasting with those with significant IMR (MRFraction ≥35%) but lower scar burden (<30%) (32 of 59 patients [54%]). Second, data regarding time from the index myocardial infarction, quantification of myocardial ischemia, or other clinical outcomes such as cardiac-specific mortality or heart failure hospitalizations were not available but should be evaluated in future studies. Third, evaluation of other important parameters, such as LV sphericity and LV strain, might provide important prognostic value in this population of patients with IMR, but they were not available in this current analysis. Fourth, the sensitivities for all of the regurgitation metrics were suboptimal, whereas specificities were good. This led to areas under the curve in the 0.6 range, which are modest. The modest ability for severity of functional MR, in isolation, to predict adverse outcomes is likely due to the fact that risk is also significantly affected by the presence of LV dysfunction, remodeling, and myocardial scarring. Furthermore, the severity of IMR is not directly proportional to the severity of LV dysfunction and extent of myocardial scarring. Given the high-risk nature of this patient population, it is difficult to define the best balance of optimal sensitivity and specificity. Further validation of these cutoffs is necessary, and different quantification methods may lead to different optimal MIS thresholds. Finally, we recognize the treatment heterogeneity and have attempted, to the best of our abilities, to minimize potential confounders by performing comprehensive multivariable adjustments. Our findings, although hypothesis generating, can be formally validated only by an adequately designed prospective randomized trial integrating CMR findings into the decision-making process, which is very much needed for this group of patients.

**CONCLUSIONS**

Quantification of IMR severity and MIS by CMR allows for risk stratification of patients with advanced ICM. The risk associated with significant IMR should not be determined in isolation but instead evaluated in the context of MIS. The presence of both significant IMR (MRFraction ≥35%) and significant MIS (≥30% of LV mass) carries a very high risk for all-cause mortality and/or heart transplant, despite surgical MVi. Whether CMR can improve risk stratification and patient selection by identifying individuals who could derive a survival benefit from IMR correction (either surgical or transcatheter) will require further prospective investigation.

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COMPETENCY IN PRACTICE-BASED LEARNING:
Secondary IMR is a disease of the LV that is incompletely characterized by current echocardiographic approach. In this analysis, a comprehensive assessment used CMR to quantify IMR severity, LV remodeling, and MIS. The presence of both significant IMR (MRFracion ≥35%) and significant MIS (≥30% of LV mass) was associated with a very high risk for all-cause mortality and/or heart transplant, despite surgical MVI. On the other hand, patients with significant IMR but small MIS (<15% LV mass) had a survival benefit with surgical MVI. CMR assessment may better discern which patients might benefit from correction of IMR.

TRANSLATIONAL OUTLOOK 1: Outcomes associated with IMR are driven by the comorbidities, LV remodeling, and complex interaction between IMR severity and MIS. This last aspect cannot be assessed solely by echocardiography. As such, CMR evaluation may provide a better understanding of the pathophysiology of IMR. Our group has previously shown that CMR identification of large MIS and adverse LV remodeling favor both the progression of IMR and adverse outcomes after MVI. Similarly, the prospective CTSN trial has shown that presence of basal inferior aneurysm, a strong surrogate of focal transmural scar, is associated with higher likelihood of IMR recurrence in patients with ICM who have undergone surgical MV repair.

TRANSLATIONAL OUTLOOK 2: The ongoing debate about the differences, similarities, and complementary information of the MITRA-FR and COAPT studies has generated many questions among the medical community regarding the optimal imaging characteristics that define the ideal patient. We believe that our findings are not only timely but also of critical relevance because they add a third dimension: that is, the pathophysiology construct in IMR needs to be expanded not only to include LV remodeling and IMR severity (as currently proposed) but, importantly, to quantify the severity and extent of MIS. Only then will we be able to fully understand who has proportionate and disproportionate IMR. The CMR community at large is ready to provide that comprehensive assessment, which we believe is necessary to improve decision making for our patients and better individualize the available therapies.

TRANSLATIONAL OUTLOOK 3: The potential of transcatheter therapies to address secondary IMR has created significant interest in this field, with important findings from recent randomized controlled trials using transcatheter MV repair with the MitraClip device (Abbott Vascular) including COAPT and the MITRA-FR trials. Our study shows the potential for CMR assessment to further inform risk stratification and the selection of patients who will derive the most benefit. It is possible that a less invasive transcatheter MV repair technique, such as with the use of the MitraClip device, might allow patients with significant IMR and even a larger MIS threshold to favorably benefit from intervention. However, this is hypothesis generating and will demand an important trial. Future randomized controlled studies, particular in the growing field of transcatheter MV replacement, are needed to further assess the impact of CMR assessment, before and after intervention, on predicting differential outcomes in patients with significant IMR.

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KEY WORDS cardiac magnetic resonance, ischemic mitral regurgitation, myocardial infarct size, outcomes

APPENDIX For supplemental methods and tables, please see the online version of this paper.
Mitr al regurgitation (MR) is classified as primary or secondary. Although this classification is an oversimplification, severe primary MR is a disease of the valve causing it to leak, placing a volume overload on the left ventricle that, if left untreated, leads to heart failure and death. In secondary MR, the valve itself is usually normal, but left ventricular (LV) myocardial disease leads to annular dilatation, papillary muscle displacement, wall motion abnormalities, and reduced closing force, acting in concert to cause coaptation failure. Although repair of primary MR markedly improves outcomes, returning life span to normal in many cases (1), the benefits of correcting secondary MR have remained elusive. Several surgical studies of ischemic secondary MR, comparing mitral surgery plus coronary revascularization with coronary revascularization alone or with medical therapy, showed no mortality benefit to adding mitral surgery (2–6). A large meta-analysis revealed no benefit to mitral surgery in either providing symptomatic relief or reducing mortality in secondary MR (6). A recent randomized trial (not powered for mortality) that compared mitral repair with mitral valve replacement found equally poor results with both: 10% per year mortality (7), not very different from rates seen in many studies over the past several decades. In the mitral repair limb of the ACORN trial in nonischemic secondary MR, repair led to striking reverse remodeling but still a high 5-year mortality rate, with one-third of patients dead at 5 years (8). The standard explanation for the failure of surgery to affect mortality is that the myocardium is the culprit in secondary MR, not the MR itself. As such restoring mitral competence does not fix the problem.

THE MITRA-FR, COAPT CONUNDRUM

The MitraClip is a percutaneously inserted device (percutaneous mitral valve repair [PMVRe]) that clips the edges of the 2 mitral leaflets together, reducing MR while avoiding the need for and the potentially deleterious effects of extracorporeal circulation. Two well-performed randomized trials of the clip in secondary MR reported in the same issue of the New England Journal of Medicine produced virtually opposite conclusions (9,10). The MITRA-FR (Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) trial found no mortality or rehospitalization benefit from the clip (9), while COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) showed a striking benefit of the clip in both categories (10). As such, COAPT was the first randomized trial to find a mortality benefit of mechanical intervention in secondary MR.

Much has been written in efforts to reconcile the different results of these 2 excellent trials (11–13). In MITRA-FR, there was somewhat less severe MR than in COAPT, and the patients’ LV volumes were larger in MITRA-FR. These data suggest that something other than the MR (presumably the severity of the cardiomyopathy) was driving the LV enlargement in MITRA-FR, indicating that the MR was more of a bystander than a culprit (11), whereas in COAPT, the

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*Black et al. (14) have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Cardiovascular Imaging author instructions page.
MR was likely severe enough to cause damage by itself (tertiary MR) (12).

**ENTER THE PRESENT STUDY**

The study by Cavalcante et al. (14) in this issue of JACC may well shed light on the MITRA-FR, COAPT conundrum (14). The investigators used cardiac magnetic resonance to examine the relationship between secondary MR severity and LV scar in patients with ischemic cardiomyopathy. They used regurgitant fraction to assess MR severity as opposed to effective regurgitant orifice area alone. Because MR is driven by a variety of factors in addition to effective regurgitant orifice area, the former should be the more reliable indicator of MR severity, noting that both were well correlated in the present study. The investigators found that although one might suppose that increasing scar burden would also lead to worsening MR, the 2 were not well correlated. However, prognosis did worsen with both increasing MR and increasing scar.

Most important, the combination of scar and MR severity worked in tandem to dramatically affect prognosis, with 4-year survival of only 50% in patients with large scar burden and the most severe MR (regurgitant fraction  $>$35%).

How might these data be applied to MITRA-FR and COAPT? The majority of patients in both studies had ischemic rather than nonischemic MR, thus making the Cavalcante et al. (14) report applicable to the 2 studies. Ischemia by itself rarely causes MR. Rather, it is the myocardial infarction and wall motion abnormalities caused by ischemia that cause secondary ischemic MR. Scar burden was not measured in the patients with ischemic MR in MITRA-FR or COAPT, but it is certainly reasonable to guess that it might have had an impact. It could be that patients with the largest scar burden have hearts that are so sick that they cannot benefit from PMVRe. It may be that only muscle rather than scar is able to participate in the beneficial effects of correcting MR. The notion is supported in the present study by examining the subgroup of patients who underwent mitral surgery; the patients with the highest scar burden had the worst outcomes. Perhaps the ischemic patients in MITRA-FR had larger scar burden, accounting for larger ventricles and the lack of benefit from PMVRe.

Of note, in COAPT, patients with both ischemic and nonischemic MR benefited from PMVRe, although in subgroup analysis, the ischemic group seemed to benefit more. Nonetheless those data suggest that scar burden alone cannot explain the different outcomes of the 2 studies but might be an important factor.

**SUMMARY**

From the 3 studies, 3 tenets seem likely. First, in patients with sick and enlarged left ventricles and only moderate MR, it seems unlikely that the MR is contributing much to the natural history of the disease, and therapy directed solely at the MR is unlikely to be successful. Second, in patients with diseased left ventricles and severe MR despite medical therapy, the severe MR is contributing to the disease process (tertiary MR), and mechanical therapy may be beneficial. And third, scar burden is itself a risk factor in secondary MR and might modulate the interaction between MR severity and recovery post-PMVRe.

We are still in the process of defining patients with secondary MR who will benefit from PMVRe. The totality of the data from MITRA-FR and COAPT suggest that those who benefit have severe MR recalcitrant to aggressive medical therapy and have modest but not severe LV dilatation. Going forward, it is possible that large scar burden in patients with ischemic MR will also help direct PMVRe therapy. Future studies of secondary ischemic MR should, if possible, assess scar burden prospectively to test it as an important factor in the decision of when and how to provide PMVRe for patients with secondary ischemic MR. Currently in the United States, the percentage of patients with secondary MR referred for surgical or transcatheter repair appears to be at an all-time low. Twenty years ago, secondary MR constituted approximately 50% of mitral valve repairs, but in current surgical series, it is only 5%. It is probable that the American experience will follow that of Europe, with increasing use of transcatheter repair of secondary MR in medium- to high-risk patients. It is also likely that subsets of patients will be identified who will derive at least symptomatic benefit from surgical mitral repair or replacement. It also seems likely that other patients will be identified who are best managed by addressing the LV dysfunction, with transplantation, ventricular assist devices, or other means such as regenerative matrix or stem cell therapies.

Just as we now know that primary and secondary MR are different diseases, it is almost certain that in the near future we will recognize that patients with secondary MR are themselves heterogeneous and may require more individualized therapy rather than lumping them all into 1 group.

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KEY WORDS left ventricular scar, mitral regurgitation, valvular heart disease
Original Research

Cost-Effectiveness Analysis of Stress Cardiovascular Magnetic Resonance Imaging for Stable Chest Pain Syndromes

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ABSTRACT

OBJECTIVES The aim of this study was to compare, using results from the multicenter SPINS (Stress CMR Perfusion Imaging in the United States) study, the incremental cost-effectiveness of a stress cardiovascular magnetic resonance (CMR)-first strategy against 4 other clinical strategies for patients with stable symptoms suspicious for myocardial ischemia: 1) immediate x-ray coronary angiography (XCA) with selective fractional flow reserve for all patients; 2) single-photon emission computed tomography; 3) coronary computed tomographic angiography with selective computed tomographic fractional flow reserve; and 4) no imaging.

BACKGROUND Stress CMR perfusion imaging has established excellent diagnostic utility and prognostic value in coronary artery disease (CAD), but its cost-effectiveness in current clinical practice has not been well studied in the United States.

METHODS A decision analytic model was developed to project health care costs and lifetime quality-adjusted life years (QALYs) for symptomatic patients at presentation with a 32.4% prevalence of obstructive CAD. Rates of clinical events, costs, and quality-of-life values were estimated from SPINS and other published research. The analysis was conducted from a U.S. health care system perspective, with health and cost outcomes discounted annually at 3%.

RESULTS Using hard cardiovascular events (cardiovascular death or acute myocardial infarction) as the endpoint, total costs per person were lowest for the no-imaging strategy ($16,936) and highest for the immediate XCA strategy ($20,929). Lifetime QALYs were lowest for the no-imaging strategy (12.72050) and highest for the immediate XCA strategy (12.76535). The incremental cost-effectiveness ratio for the CMR-based strategy compared with the no-imaging strategy was $52,000/QALY, whereas the incremental cost-effectiveness ratio for the immediate XCA strategy was $12 million/QALY compared with CMR. Results were sensitive to variations in model inputs for prevalence of disease, hazard rate ratio for treatment of CAD, and annual discount rate.

CONCLUSIONS Prior to invasive XCA, stress CMR can be a cost-effective gatekeeping tool in patients at risk for obstructive CAD in the United States. (Stress CMR Perfusion Imaging in the United States [SPINS] Study; NCT03192891 (J Am Coll Cardiol Img 2020;13:1505-17) © 2020 by the American College of Cardiology Foundation.)
**ABBREVIATIONS AND ACRONYMS**

- APC = ambulatory payment classification
- CAD = coronary artery disease
- CCTA = coronary computed tomographic angiography
- CMR = cardiovascular magnetic resonance
- CPT = Current Procedural Terminology
- CT = computed tomographic
- FFR = fractional flow reserve
- ICER = incremental cost-effectiveness ratio
- MACE = major adverse cardiovascular event(s)
- MI = myocardial infarction
- PSA = probabilistic sensitivity analysis
- QALY = quality-adjusted life year
- SPECT = single-photon emission computed tomography
- XCA = x-ray coronary angiography

**Coronary artery disease (CAD) remains a major cause of patient mortality and morbidity and accounts for more than $200 billion in health care expenditures in the United States annually (1). Although more than 1 million diagnostic coronary angiographic studies are performed annually in the United States (1), it has been estimated that as many as two-thirds of elective studies do not show any obstructive disease and may be unnecessary (2,3), suggesting that better noninvasive strategies are needed to triage patients according to their risk and to curb health care expenses. Stress cardiovascular magnetic resonance (CMR) perfusion imaging is a robust clinical tool with excellent diagnostic accuracy (4–7) and prognostic value (8,9). Cost-effectiveness analyses have suggested that stress CMR as an initial assessment for patients with stable chest pain syndrome is cost effective compared with other stress modalities in practice or with direct x-ray coronary angiography (XCA) (10–13), but data on comparative cost-effectiveness from the U.S. health care system are limited.**

**The SPINS (Stress CMR Perfusion Imaging in the United States) study was recently performed using a registry developed by the Society for Cardiovascular Magnetic Resonance to assess the diagnostic and prognostic values of stress CMR and the downstream costs of care in patients presenting with chest pain syndromes in a multicenter cohort in the United States (9). In the present study, using a base-case decision tree model, we compared the lifetime health benefits, health care costs, and incremental cost-effectiveness of 5 competing diagnostic strategies for stable, symptomatic patients at intermediate pre-test likelihood of obstructive coronary disease using data from the SPINS registry and contemporary published research: 1) immediate XCA for all patients, with a select number undergoing measurement of fractional flow reserve (FFR); 2) CMR-based management, in which those with abnormal test results undergo XCA; 3) single-photon emission computed tomography (SPECT)-based management; 4) coronary computed tomographic angiography (CCTA) with performance of computed tomographic (CT) FFR for a select number of patients; and 5) no initial imaging, with subsequent testing only for patients with persistent symptoms (Central Illustration).**

**METHODS**

**THE SPINS STUDY.** The methods and results of the SPINS study were recently published (9). In brief, SPINS retrospectively included consecutive patients with chest pain syndromes suspicious for obstructive CAD who underwent stress CMR between January 1, 2008, and December 31, 2013, from 13 U.S. sites (9). Stress CMR perfusion protocols were based on product pulse sequences available at the sites, and study interpretations were based on sites’ reporting of ischemia and infarction according to the 16-segment American Heart Association nomenclature for perfusion and 17-segment model for late gadolinium...
Inducible ischemia was defined as the presence of at least 1 segment with a stress perfusion defect in the absence of matching myocardial infarction (MI) by late gadolinium enhancement in a typical endocardial pattern within 1 of the coronary artery territories. Follow-up for clinical cardiovascular events occurred for a target of at least 4 years after the index stress CMR study. Major adverse cardiovascular events (MACE) included cardiovascular death, acute nonfatal MI, hospitalization for unstable angina or congestive heart failure, and late coronary artery bypass grafting >6 months following index CMR. Before the study began, definitions of all clinical variables were standardized across the sites by training webinars, instructional documents, and online postings. We obtained local Institutional Review Board approval at each participating site, with a waiver of the requirement to obtain written informed consent.

**Central Illustration**

![Conceptual Diagram of the Cost-Effectiveness Analysis](image)

Patients enter the simulation model and are assigned to 1 of 5 diagnostic strategies. The model estimates the impact of strategy choice on mortality, morbidity, and coronary disease-related cost outcomes. The trade-offs between quality-adjusted life years (QALYs) and costs are evaluated using incremental cost-effectiveness analysis methods.

**Model Overview.** We performed a computer-simulated state-transition model that projected MACE, life expectancy, quality-adjusted life years (QALYs), and lifetime health care costs for a symptomatic patient cohort at risk for obstructive coronary disease at initial clinical presentation (Figure 1). The annual risk for clinical events depended on CAD status, initiation of therapy (medical and revascularization), and risk for XCA and revascularization procedures. Death could occur as result of cardiovascular events, noncardiovascular events, or complications arising from invasive diagnostic or therapeutic options. Depending on the clinical management strategy, patients in the model received optimal therapy (including medical and revascularization procedures) immediately, later in life on the basis of disease progression, or never. Base-case model inputs and sensitivity analysis ranges are reported in Table 1. For each management strategy, health care costs and QALYs were projected to derive incremental cost-effectiveness ratios (ICERs). We used $100,000/QALY as a threshold for willingness to pay for health (14). The analyses were conducted from a health system perspective over a lifetime horizon, with all costs projected to 2017 dollars, and future health care costs and QALYs discounted at 3% annually (15). The model was programmed in TreeAge Pro 2012 (TreeAge Software, Williamstown, Massachusetts).

**Clinical Strategies Evaluated.** In the immediate XCA strategy, all patients underwent invasive angiographic procedures at the time of clinical presentation. Given that most recent guidelines recommend performance of FFR in vessel stenosis from 50% to 90% (16,17), we extrapolated that 41% of patients would undergo this procedure, on the basis of historic data on the prevalence of lesions angiographically >50% (2). We conducted a sensitivity analysis, varying the rates of FFR use between 0% and 100%. Invasive XCA carried a 0.07% chance of fatal complications in the base-case analysis (18). Patients identified to have obstructive CAD were assumed to undergo optimal medical therapy and revascularizations procedures, of which 69.2% were attributed to percutaneous coronary intervention.
and 30.8% to coronary artery bypass grafting according to the ratio in the SPINS study. Complication rates for revascularization procedures are summarized in Table 1. In the computed tomography–based strategy, all patients underwent CCTA, and 41% underwent CT FFR to additionally characterize intermediate lesions. We conducted a sensitivity analysis, varying the rates of CT FFR use between 0% and 100%. In the CMR and SPECT strategies, patients underwent XCA only if noninvasive imaging demonstrated abnormal findings. Those with true positives were assumed to undergo both medical and revascularization therapies, and this combination led to overall improved outcomes. Patients with normal findings were presumed to be free of obstructive CAD and were managed accordingly. In the no-imaging strategy, patients were initially managed without any investigations. However, we included a provision that because of escalating symptoms, 58% of patients with obstructive CAD would return within the first year, and each year thereafter, for investigations and undergo XCA directly, and we varied this proportion in sensitivity analyses (11). Similarly, in patients who initially underwent any of the imaging strategies, we assumed that each year, 58% of those with false-negative results would present with escalating symptoms and undergo XCA directly.
The demographics of the SPINS cohort were used to simulate the patient population; specifically, the model population was 53% male, with an average age of 63 years and a 32.4% probability of obstructive CAD (9). Sensitivity and specificity for the detection of angiographic significant CAD for stress CMR, SPECT, and CCTA with CT FFR were 89% and 87%, 73% and 83%, and 90% and 71%, respectively, per prior publications (19,20). As the diagnostic gold standard of angiographically significant CAD, XCA with FFR was assumed to have sensitivity and specificity of 100%.

We conducted 2 cost-effectiveness analyses, using hard MACE (cardiovascular death and acute MI) in one analysis and all composite MACE (cardiovascular death, acute MI, cardiovascular hospitalizations for unstable angina and congestive heart failure, and late coronary artery bypass grafting) in the other analysis. For patients with obstructive CAD who remained untreated (false-negative results) because of...
underdetection, we applied a hazard rate ratio of 1.43 to adjust event rates (21). For patients who experienced 1 or more cardiovascular events, we used subsequent mortality multipliers of 1.6 and 3.4 for men and 2.1 and 2.5 for women, respectively (22).

**COSTS AND HEALTH-RELATED QUALITY OF LIFE.** Costs associated with fatal and nonfatal cardiovascular events and revascularization procedures were estimated from a recent analysis of a large managed care population in the United States and from the Agency for Healthcare Research and Quality (21,23). Costs of medical therapy were not explicitly calculated but were presumed to form the cost of a chronic CAD state. All patients diagnosed with CAD were assumed to receive the same drug regimens. Costs of SPECT, stress CMR, XCA, and CCTA were derived from publicly available 2017 Medicare rates, combining Current Procedural Terminology (CPT) codes to reflect professional costs, as well as ambulatory payment classification (APC) codes to reflect average technical fee. We used estimated costs as follows: SPECT (CPT code 70452 + APC code 5593) cost $1,219, stress CMR (CPT code 75563 + APC code 5573) cost $807, XCA (CPT code 93454 + APC code 5191) cost $3,084, XCA with FFR (CPT code 93454 + CPT code 93571 + APC code 5192) cost $5,175, CCTA (CPT code 75574 + APC code 5571) cost $386, and CT FFR (CPT code 0503T) cost $1,450. Health-related quality of life was assigned to all health states in the model and was represented by utility values between 0 (death) and 1 (perfect health). Baseline state was assigned a utility value of 0.851 for men and 0.824 for women (24), which dropped to 0.778 after a nonfatal cardiovascular event. In addition, we applied a disutility of –0.041 for the first year following a nonfatal event (25).

**SENSITIVITY ANALYSES.** One-way sensitivity analyses were performed to evaluate the sensitivity of results to plausible variations in parameters for model inputs (Table 1). A 2-way sensitivity analysis was performed for the prevalence of obstructive CAD and probability that a patient with a false-negative result would return for investigation each year because of escalating symptoms. Other 2-way sensitivity analyses were performed for sensitivity and specificity of stress CMR, SPECT, and CCTA with selective CT FFR. We also performed sensitivity analyses for rate of use of both FFR and CT FFR. Overall model uncertainty was evaluated in a probabilistic sensitivity analysis (PSA) by simultaneously conducting 10,000 random draws from probability distributions (Supplemental Table 1) for selected key variables and recalculating the cost-effectiveness of each strategy.

**RESULTS**

In the base-case analysis, obstructive CAD was detected in the first year in 18.7% of patients with the no-imaging strategy, 30.9% with the stress CMR strategy, 28.7% with the SPECT strategy, 31% with the CCTA strategy, and 32.4% with the immediate XCA strategy. The no-imaging strategy resulted in the lowest total lifetime discounted costs but also the lowest QALYs. The immediate XCA strategy had the highest lifetime discounted costs among the 5 strategies but also the highest lifetime discounted QALYs (Table 2).

Table 2 shows the cost-effectiveness results for populations with a prevalence of obstructive CAD of 32.4%. When considering hard MACE, the stress CMR-based decision-making strategy had an ICER of 32.4%.
$52,000/QALY compared with the no-imaging strategy. The CMR strategy strongly dominated (i.e., had more QALYs and lower costs) the SPECT and CCTA strategies, whereas the immediate XCA strategy had an ICER of $12 million/QALY compared with the CMR-based strategy. Table 2 also shows results for the scenario analysis when considering all MACE rather than hard events alone. In this scenario, at a threshold of $100,000/QALY, the CMR-based strategy remained the preferred strategy in the base case, with an ICER of $58,000/QALY compared with the no-imaging strategy, whereas the immediate XCA strategy had an ICER of $430,000/QALY compared with the CMR-based strategy.

Under an alternative scenario in which a positive result on stress CMR was defined as the presence of at least 2 abnormal myocardial segments, the stress CMR-based decision making strategy had an ICER of $60,000/QALY compared with the no-imaging strategy, when considering hard MACE. The CMR strategy strongly dominated the SPECT, CCTA, and immediate XCA strategies.

Figure 2 shows ICER results for the CMR-based decision-making strategy compared with the no-imaging strategy for the 15 most influential variables evaluated in 1-way sensitivity analyses. Using a cost-effectiveness threshold of $100,000/QALY in the United States, the ICER for the CMR-based decision-making strategy compared with the no-imaging strategy was below this threshold in most 1-way sensitivity analyses. The cost-effectiveness results were most sensitive to uncertainty in the hazard rate ratio for treatment of CAD, prevalence of obstructive CAD, and annual discount rate. At hazard rate ratios >0.809, an initial strategy of no imaging was optimal using a cost-effectiveness threshold of $100,000/QALY; the immediate XCA strategy was optimal with hazard rate ratios <0.372. Model results were not sensitive to the proportion of patients undergoing CT FFR assessment with the CCTA strategy (Supplemental Figure 1); despite lower CCTA imaging costs, the CMR strategy strongly dominated the CCTA strategy even when this proportion was set to zero, driven by the CMR strategy resulting in fewer coronary angiographic examinations (41.1%) compared with the CCTA strategy (51.5%). Similarly, model results were not sensitive to the proportion of patients undergoing FFR assessment with the immediate XCA strategy (Supplemental Figure 1).

Figure 3 shows the 2-way sensitivity analysis results, varying the prevalence of obstructive CAD and the probability that a patient with a false negative result would return for investigation within 1 year because of escalating symptoms. Combinations of low
disease prevalence and high likelihood of return favored the no-imaging strategy; high disease prevalence and low likelihood of return favored the immediate XCA strategy. For example, a prevalence of 10% for obstructive CAD and a 90% likelihood of return would result in the no-imaging strategy being optimal, whereas values of 70% and 10%, respectively, would result in the immediate XCA strategy being optimal.

Figure 4 shows the 2-way sensitivity analysis results, varying test sensitivity and specificity of CMR (Figure 4A), SPECT (Figure 4B), and CCTA (Figure 4C). Either SPECT or CCTA is favored over CMR when performance goes beyond the 95% confidence interval from the input data sources (e.g., when both sensitivity and specificity are >90%). Figure 5 shows the cost-effectiveness acceptability curve results for the PSA. The CMR-based decision-making strategy was most likely to be optimal in the PSA using a cost-effectiveness threshold of $100,000/QALY. The CMR-based strategy was optimal in 84% of PSA iterations; no imaging was optimal in 16%; and SPECT, CCTA, and immediate XCA were optimal in 0%. Using a cost-effectiveness threshold of $50,000/QALY, no imaging was optimal in 79% of PSA iterations, while CMR was optimal in 21%. Using a cost-effectiveness threshold of $150,000/QALY, CMR was optimal in 95% of PSA iterations, and no imaging was optimal in 4% of PSA iterations.
**DISCUSSION**

Stress CMR has been shown in multiple large-scale studies over recent years to be a robust modality for diagnosis and risk stratification of patients suspected of having CAD (6,9) and determining the physiological significance of coronary stenosis (26). Compared with clinical standard of care, stress CMR has also been shown to reduce the rate of unnecessary angiographic examinations (27). Despite the robust body of published research and society recommendations supporting its use (28), contemporary data on its cost-effectiveness compared with other state-of-the-art noninvasive modalities remain limited.

In the present study, we used data from the SPINS registry, a contemporary stress CMR multicenter U.S. cohort of patients with stable chest pain syndromes, to develop a decision analytic model to evaluate
clinical management strategies. We used updated meta-analyses for noninvasive test sensitivity and specificity, with XCA with selective FFR as the gold standard to diagnose significant CAD (19,20). This was chosen given studies showing that anatomic assessment alone of lesion severity has significant limitations (29,30). In this model cohort, we found that CMR-based assessment was optimal on the basis of a $100,000/QALY cost-effectiveness threshold for the United States. The no-imaging strategy resulted in the lowest lifetime costs and lowest rate of diagnosis of obstructive CAD but also the lowest life expectancy and lifetime QALYs. The SPECT, CCTA, and immediate XCA strategies all had higher costs (driven by imaging costs, the cost of follow-up diagnostics and procedures, and downstream CAD events); SPECT and CCTA had fewer QALYs compared with the CMR strategy.

Our findings were robust to plausible variation in the diagnostic performance and cost of stress CMR. Our cost-effectiveness results were also robust to plausible variations in cohort age, rates of cardiac events, and costs of diagnostic and revascularization procedures. Our cost-effectiveness results were most sensitive to hazard rate ratio for treatment of CAD, prevalence of CAD, and discount rate. Using base-case model inputs, the CMR-based strategy was optimal for combinations of intermediate disease prevalence and lower likelihood that a patient with a false-negative result would return for angiography within 1 year. These scenario results are clinically intuitive; a high prevalence of disease favors immediate XCA, whereas a high likelihood of return after false-negative findings favors no imaging (i.e., minimizes the consequence of a false negative).

Most (10–13) but not all (21) previous studies that have examined stress CMR compared with direct XCA with and without FFR and other stress modalities have found it to be a cost-effective alternative. Boldt et al. (10) performed a cost analysis from the German
health care system and determined that stress CMR was more cost effective than SPECT in patients with low to intermediate probability of obstructive CAD. Similar to our results, XCA became the preferred approach when disease prevalence exceeded 60% (10). Moschetti et al. compared a stress CMR-guided strategy with direct XCA with FFR and concluded that the former is more cost effective with disease prevalence <82% (12). The investigators subsequently used data from the EuroCMR registry and extrapolated a cost saving of 24% in a U.S. system, when comparing stress CMR to angiography plus FFR (13). In a United Kingdom model of health care, Walker et al. (11) examined various combinations of 4 diagnostic modalities, namely, exercise treadmill testing, SPECT, stress CMR, and XCA (11). Using a base-case analysis with disease prevalence of 40%, the 2 most cost-effective strategies involved the use of stress CMR, either alone or following abnormal results on exercise treadmill testing, with a cost of £20,000 to £30,000 per QALY. Our results expand on those of previous studies in important ways. We extrapolated the cost-effectiveness of stress CMR using baseline data from the SPINS registry, which represents a large, multicenter cohort of U.S. patients. In these patients, we found that stress CMR is a cost-effective alternative compared with other imaging modalities, including SPECT, which remains the most widely used gatekeeper for invasive angiography in the United States, and CCTA with CT FFR, which is an emerging noninvasive technique for imaging of coronary anatomy and physiology. Furthermore, our results indicate that direct XCA is cost effective in the U.S. health care system only when disease prevalence exceeds 60%, which is an unlikely scenario given that most national registries report a disease rate of only approximately 50% in patients who undergo elective diagnostic angiography (2,3,31).

STUDY LIMITATIONS. First, our reliance on simulation required the combination of inputs from various sources to perform the cost-effectiveness analyses. Despite this inevitable limitation, our sensitivity analyses showed that our cost-effectiveness results were robust across plausible changes in model inputs.

Second, our decision model did not include stress echocardiography or exercise treadmill testing, given the limited number of patients and studies available to reliably derive respective sensitivities and specificities with XCA with FFR as the gold standard.

Third, XCA with selective FFR is considered the gold standard for epicardial coronary stenosis, but not microvascular disease, which can be detected on stress testing and is associated with worse long-term prognosis (32).

Fourth, SPINS included experienced CMR centers and enrolled patients at intermediate risk for obstructive CAD. Therefore, uncertainty exists as to whether the present results can generalize to lower risk patients, such as those represented in the CE-MARC trial. By design, we collected information on downstream but not upstream cardiac testing.

Finally, the clinical benefit assigned to diagnosis of obstructive CAD in our model was based on a combination of medical and revascularization therapy. The value of the latter, particularly in stable coronary disease, is controversial (33) and is currently under investigation in an ongoing large randomized trial (34).

CONCLUSIONS

Stress CMR is an emerging noninvasive technique capable of detecting obstructive CAD with excellent diagnostic accuracy. Our model-based analyses showed that a stress CMR-based strategy to diagnose patients at intermediate risk met conventional standards of cost-effectiveness in the U.S. health care system. Future randomized studies of stress CMR against comparative strategies are required to address both clinical outcomes and cost from a societal perspective.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients presenting with stable chest pain syndromes and at intermediate risk for having obstructive CAD, a decision analytic model projects stress CMR to be a cost-effective modality in the United States, compared with other common noninvasive imaging strategies or invasive XCA as the first-line investigation.

TRANSLATIONAL OUTLOOK: Stress CMR met conventional standards of cost-effectiveness for the evaluation of stable chest pain syndromes in the United States and should be considered for future clinical trials.
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KEY WORDS cost-effectiveness, noninvasive test, stress cardiac MRI

APPENDIX For a supplemental table and figure, please see the online version of this paper.
Over the past decade, in many developed health care systems, there has been dramatic increase in the use of stress cardiac magnetic resonance (CMR) imaging to aid both diagnosis and further management decisions in patients with stable chest pain syndromes. This has been driven by a strong evidence base and contemporary high-quality randomized trials that have led to a Class I recommendation by the European Society of Cardiology for the use of stress CMR as a first-line investigation (1).

CMR has a high diagnostic accuracy for the identification of significant obstructive coronary artery disease (CAD) (2,3) compared with invasive coronary angiography (ICA). More importantly, it is highly concordant with the reference standard invasive fractional flow reserve (FFR) for detection of myocardial ischemia (4), which has been shown in clinical trials to deliver better patient outcomes compared with revascularization decisions made by visual angiographic interpretation (5). A first-line strategy of stress CMR in patients with chest pain and suspected or known CAD has recently been evaluated in 2 large multicenter clinical trials. These showed that stress CMR is a highly effective gatekeeper for the catheter laboratory, significantly reducing the rates of unnecessary ICA compared with management according to the UK national Institute for Health Care Excellence (NICE) 2010 chest pain guideline (6), and noninferior to a strategy of direct to ICA ± FFR as needed, in terms of clinical outcomes at 12 months (7). Furthermore, in terms of prognostication, when adjusted for multiple cardiovascular risk factors and revascularization, CMR was more closely associated with 5-year major adverse cardiac events (MACE) than myocardial perfusion single-photon emission computed tomography (MPS-SPECT) (8).

So why is CMR not used more frequently in some health care systems? Perhaps it is related to the index procedural costs. Certainly, in some countries, the index cost of stress CMR is higher than other functional tests, but in the United States, this is not strictly the case, with CMR being less costly than MPS-SPECT ($807 vs. $1,219; based on Medicare reimbursement) and positron-emission tomography (PET). However, this is not the complete picture. To understand the true cost—and hence value—of a test, one needs to consider the false positive and false negative rates and their impact on downstream investigations and use of resources, including impact on health resulting from delayed and incorrect treatments. Only by conducting a rigorous health-economic analysis of the investigation and treatment pathway can one get a clear idea of a tests cost effectiveness in a particular health care system and start to understand the value of that test in terms of willingness to pay thresholds. Typically, the standard unit of measurement is the quality-adjusted life-year (QALY), a generic measure of health, capturing both quality and quantity of life lived, where 1 QALY equates to 1 year in perfect health. On this basis, stress CMR has been shown to be cost effective as an investigation for stable chest pain in health care systems.
systems across Europe, the United Kingdom, and the United States (9–11).

In this issue of JACC, Ge et al. (12) describe their cost-effectiveness analysis of stress CMR for stable chest pain syndromes, using data derived from the multicenter SPINS (Stress CMR Perfusion Imaging in the United States) study. SPINS was a registry conducted between 2008 and 2013, of patients with known or suspected obstructive CAD, aged between 35 and 85 years, referred for clinical stress CMR at 13 U.S. centers (13). Using a decision analytic model to estimate lifetime health care costs and QALYs, they assessed the cost effectiveness of a stress CMR first-line strategy against 4 other first-line strategies: immediate ICA with selective FFR, MPS-SPECT, CT coronary angiogram (CTCA) with selective CT-FFR, and no imaging. The analyses were conducted from a U.S. health system perspective over a lifetime horizon, with all costs in 2017 dollars, and a threshold for willingness to pay for health of $100,000/QALY. SPIN’s follow-up was for at least 4 years, for MACE (cardiovascular death, nonfatal acute myocardial infarction [AMI], hospitalization for unstable angina [UA] or congestive heart failure [CHF], and late coronary artery bypass grafting [CABG] [MACEall]), with “hard” endpoints, defined as cardiovascular death and AMI (MACEHard).

Predictably, doing no-imaging investigations was the cheapest of the 5 strategies but produced the lowest lifetime QALYs. However, in terms of MACEHard, compared with a no-imaging strategy, CMR strongly dominated (i.e., was associated with lower costs and more QALYs) both MPS-SPECT and CTCA, with an incremental cost-effectiveness ratio (ICER) of $52,000/QALY. When MACEall was considered, the CMR-based strategy remained the preferred strategy in the base case, with ICER of $58,000/QALY compared with the no-imaging strategy, and again dominated both MPS-SPECT and CTCA. As these model-based analysis techniques rely on multiple assumptions, the authors performed multiple sensitivity analyses and showed that the results remained consistent for CMR. Finally, using probabilistic sensitivity analysis (PSA) and a cost-effectiveness threshold of $100,000/QALY, the CMR-based strategy was optimal in 84% of draws and a no-imaging strategy in 16%; MPS-SPECT, CTCA, and immediate ICA were optimal strategies in 0%.

How do we interpret these findings? First, the authors should be congratulated for their efforts in developing a coherent decision analytic model, synthesizing contemporary U.S. data from the SPINS study with other published evidence. Importantly, their conclusions appear robust, and we commend the use of PSA to address the joint uncertainty across all parameters, which demonstrates a high probability of CMR being cost effective at $100,000/QALY. Nonetheless, there are potential weaknesses that could be addressed in future analyses; for example, a failure to reflect higher MACE risk in the year following a previous MACE is not in line with previous analyses, and—assuming a constant long-term MACE risk—does not reflect increasing risk with age (14,15). Similarly, the model does not reflect increasing costs of patients with increasing age (16). The use of common utility values for those with and without obstructive CAD, and the failure to consider disutility arising from nonfatal adverse events associated with ICA—or from recovery from revascularization—is questionable, the impact of which has not been considered in the uncertainty analysis. Finally, the divergence between the results based on “hard” and “all” MACE outcomes needs further consideration, as does the use of common mortality multipliers across these 2 different MACE outcomes.

The lack of accepted cost-effectiveness thresholds in the United States makes conclusions on cost effectiveness of interventions challenging; however, the ICERS suggested here for CMR fall well below most accepted values although exceed the historic and widely used—if also much maligned—$50,000 per QALY (17). The authors recommend the use of future randomized controlled trials to further evaluate these modalities; however, there are challenges in conducting such trials, given the size required to demonstrate impact on final endpoints, and the potential that the evidence already demonstrates a lack of clinical equipoise. The use of PSA in the model could be extended to consider the importance of the uncertainty of different parameters to help focus on where the most valuable future research could be conducted (18).

In summary, from a U.S. perspective, the study by Ge et al. adds the final piece to the jigsaw. CMR has high diagnostic accuracy for detection of obstructive CAD, is closely concordant with the invasive reference standard of FFR for detection of ischemia, is a strong prognosticator, and—in the United States—the index reimbursement cost of stress CMR is lower than MPS-SPECT, with CMR...
being a cost effective first-line investigation for suspected CAD in multiple scenarios (12). For these reasons, and the fact that a comprehensive ischemia/left ventricle function/viability CMR scan can be performed in as little as 20 min (19), there really is no logic as to why CMR should be under-used or undervalued anymore.

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KEY WORDS coronary artery disease, cost-effectiveness, CMR, stable chest pain, stable ischemic heart disease

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Prognostic Value of Myocardial Extracellular Volume Fraction and T2-mapping in Heart Transplant Patients

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ABSTRACT

OBJECTIVES The purpose of this study was to examine prognostic value of T1- and T2-mapping techniques in heart transplant patients.

BACKGROUND Myocardial characterization using T2 mapping (evaluation of edema/inflammation) and pre- and post-gadolinium contrast T1 mapping (calculation of extracellular volume fraction [ECV] for assessment of interstitial expansion/fibrosis) are emerging modalities that have been investigated in various cardiomyopathies.

METHODS A total of 99 heart transplant patients underwent the magnetic resonance imaging (MRI) scans including T1- (n = 90) and T2-mapping (n = 79) techniques. Relevant clinical characteristics, MRI parameters including late gadolinium enhancement (LGE), and invasive hemodynamics were collected. Median clinical follow-up duration after the baseline scan was 2.4 to 3.5 years. Clinical outcomes include cardiac events (cardiac death, myocardial infarction, coronary revascularization, and heart failure hospitalization), noncardiac death and noncardiac hospitalization.

RESULTS Overall, the global native T1, postcontrast T1, ECV, and T2 were 1,030 ± 56 ms, 458 ± 84 ms, 27 ± 4% and 50 ± 4 ms, respectively. Top-tercile-range ECV (ECV > 29%) independently predicted adverse clinical outcomes compared with bottom-tercile-range ECV (ECV <25%) (hazard ratio [HR]: 2.87; 95% confidence interval [CI]: 1.07 to 7.68; p = 0.04) in a multivariable model with left ventricular end-systolic volume and LGE. Higher T2 (T2 ≥50.2 ms) independently predicted adverse clinical outcomes (HR: 3.01; 95% CI: 1.39 to 6.54; p = 0.005) after adjustment for left ventricular ejection fraction, left ventricular end-systolic volume, and LGE. Additionally, higher T2 (T2 ≥50.2 ms) also independently predicted cardiac events (HR: 4.92; CI: 1.60 to 15.14; p = 0.005) in a multivariable model with left ventricular ejection fraction.

CONCLUSIONS MRI-derived myocardial ECV and T2 mapping in heart transplant patients were independently associated with cardiac and noncardiac outcomes. Our findings highlight the need for larger prospective studies.

Cardiovascular magnetic resonance imaging (CMR) with myocardial characterization by late gadolinium enhancement (LGE) has become an established prognostic imaging modality in various cardiovascular diseases (1–5). LGE has been shown to have a strong correlation with focal or regional myocardial fibrosis (6,7) in pathological specimens and portends worse prognosis in various...
patient populations (1-5). However, myocardial characterization by LGE imaging relies on contrast agent uptake in scar tissue relative to normal or “remote” myocardium. This approach is limited in patients with diffuse myocardial changes without discernable normal myocardium, a situation commonly encountered in myocardial diseases. Advances in cardiac magnetic resonance imaging (MRI) have enabled further myocardial characterization by parametric T1 and T2 mapping including the calculation of extracellular volume fraction (ECV) from pre- and post-gadolinium contrast T1 mapping. These methods quantify myocardial changes without the need of normal myocardium and are thus suitable for assessing diffuse changes of the myocardium in patients with various cardiovascular conditions. Factors affecting native T1 and T2 can be in either intracellular or extracellular spaces. Increased water (edema and/or inflammatory changes) and fat content (e.g., cardiac lipoma, sphingolipid in Fabry disease) lengthens both native T1 and T2. Native T1 is also affected by protein (e.g., amyloid proteins), fibrosis, and paramagnetic substances (e.g., gadolinium, iron). On the other hand, ECV is a surrogate for extracellular space that can be affected by myocyte hypertrophy (e.g., athlete’s heart), fibrosis, water (edema), and protein deposition (8).

T1 and T2 mapping have been shown to have prognostic value in a spectrum of cardiomyopathies (9-15). Recently, T1 and T2 mapping have been studied in relatively small cohorts of orthotopic heart transplant (OHT) recipients primarily for diagnostic accuracy for acute cardiac allograft rejection (ACR) (16-23). Nevertheless, prognostic evaluation of these techniques in patients with OHT is lacking. The objective of this study was to examine prognostic value of T1- and T2-mapping markers in OHT patients.

METHODS

STUDY DESIGN AND PATIENT SELECTION. This is a single-center observational prospective cohort study in OHT patients from August 2014 to March 2019. The study was approved by the institutional review board and written informed consent was obtained from all patients. Inclusion criteria were all adult patients with OHT 18 to 89 years of age at our hospital. The study patients had a baseline CMR and follow-up scans. Patients were excluded if they had contraindications to CMR (i.e., pacemakers, aneurysm clips, or shrapnel fragments) or if they were unwilling/unable to give written informed consent.

There were 114 patients enrolled in the study. After excluding 15 patients because of consent withdraw (n = 5) and incomplete T1-mapping data (n = 10 with only native T1 mapping), the patients were categorized into 2 cohorts. The objective of the first cohort (n = 90) was to evaluate the prognostic value of T1 mapping and therefore included patients who had native and postcontrast T1-mapping data. The objective of the second cohort (n = 79) was to evaluate the prognostic value of T2 mapping beyond prediction of ACR (any antibody-mediated rejection or grade >2R acute cellular rejection). To avoid potential confounding effect of ACR on prognosis, patients within their first year of OHT (n = 20) or patients who had proven ACR episode 1 month before/after the CMR scan (n = 2) were not included in this cohort.

CMR PROTOCOL. All studies were carried out on a 1.5-T MRI scanner (Magnetom, Espree, and Avanto, Siemens Healthcare, Erlangen, Germany). The CMR protocol consisted of cine steady-state free-precession (SSFP) and LGE sequences performed in matching short- and long-axis planes. Short-axis images were acquired every 1 cm (gap, 4 mm) throughout the entire heart. Breath-held segmented cine SSFP was carried out with the following typical parameters: repetition time repetition time (TR) = 3.0 ms; echo time (TE) = 1.5 ms; flip angle 70°, field of view 250 × 350, matrix 150 × 192, slice thickness 6 mm, and temporal resolution 35 to 40 ms. LGE images were obtained during breath hold using a segmented inversion-recovery sequence (in-plane spatial resolution 1.8 × 1.3 mm, slice thickness 6 mm; temporal resolution 160 to 200 ms) 10 to 15 min after intravenous contrast administration (gadobutrol, 0.2 mmol/kg). Inversion times were adjusted to null viable myocardium.

T1 mapping was performed using a modified Look-Locker inversion recovery technique as described previously (24). Short-axis slices were acquired during breath-hold before and 15 to 25 min following the intravenous administration of the contrast agent bolus. Imaging reconstruction included motion correction of the modified Look-Locker inversion images with different inversion times, and the calculation of parametric left ventricular (LV) T1 maps. T1-mapping acquisition parameters were as follows: spatial resolution (pixel size) 1 to 1.4 × 1 to
1.4 mm², slice thickness 8 mm, TE/TR 1.0 to 1.3 ms/2.0 to 2.2 ms; flip angle 35°. Patient hematocrit was collected immediately before the CMR exam.

T2-mapping was based on the successive acquisition of three T2-prepared SSFP images with varying T2-prep times (0, 24, 55 ms). Further imaging parameters were as follows: TE = 1.1 to 1.4 ms, TR = 2.2 to 2.6 ms, spatial resolution = 1.5 to 2.1 mm × 2.0 to 2.5 mm, slice thickness = 8 mm, diastolic acquisition window = 270 ms, flip angle = 70°.

**CMR DATA ANALYSIS.** Cine SSFP data were used to quantify global cardiac function parameters. LV and right ventricular (RV) volumes were measured by planimetry of the endocardial borders on a stack of short-axis images. Papillary muscles and trabeculae were included as part of the blood pool on the contours. LV end-diastolic volume, LV end-systolic volume, RV end-diastolic volume, and RV end-systolic volume were calculated by summation of these images. LV ejection fraction and RV ejection fraction were determined by subtracting the end-systolic volumes from the end-diastolic volumes and dividing the result by end-diastolic volumes. Presence of LGE was assessed qualitatively.

Native T1, T2, and postcontrast T1 values were calculated based on the American Heart Association 16-segment model using manual contouring of the LV epicardium/endocardium. Additionally, native and postcontrast regions of interest were drawn in the LV blood pool cavity. All the analysis was performed with CVI42 (Circle Cardiovascular Imaging, Calgary, Ontario, Canada). ECV was calculated with the following formula: 

\[
ECV = \frac{\Delta T1_{myocardium}}{\Delta [1/T1_{blood pool}]} \times (1 - \text{hematocrit})
\]

Δ represents the difference between the postcontrast and native T1 values. Global native, postcontrast T1 mapping, and ECV were calculated as the average of all available segmental T1-mapping values (25) from the basal and mid slices because we have noted systematically lower native T1 and higher ECV values in the apical segments compared with the basal and mid segments possibly because of partial volume effects.

**CLINICAL EVENTS DATA COLLECTION.** Baseline and follow-up characteristics were retrieved on the day of the baseline and follow-up CMR scans by dedicated research study personnel and they include patient demographics, comorbidities, history of ACR (26), current medications, and cardiac catheterization data.

Clinical events in this study were a composite of all death, nonfatal myocardial infarction (NFMI), coronary revascularization, and all unplanned hospitalization. Cardiac events were defined as a composite of cardiac death, NFMI, coronary revascularization, and heart failure hospitalization. The diagnosis of NFMI was defined as chest pain associated with a troponin I ≥0.10 ng/dl. Follow-up clinical events were collected by review of medical records. All OHT patients in our hospital were cared and communicated closely by the OHT team including visit, electronic message, and telephone communications.

**STATISTICAL ANALYSIS.** Descriptive statistics for studied variables are presented as mean ± SD for normally distributed continuous variables, median (interquartile range[IQR]) for non-normally distributed continuous variables and frequency with percentage for categorical variables. Continuous variables were compared between 2 groups with independent-samples Student’s t-test (normally distributed), Mann-Whitney U test (non-normally distributed), among 3 groups with analysis of variance and chi-square test for categorical data. T1- and T2-mapping data were analyzed as continuous and categorical variables. T1-mapping data in the same patient over time were compared using paired-samples Student’s t-test.

Cumulative clinical events as a function of time was investigated using Kaplan-Meier curve analysis. To assess influence of T1- and T2-mapping data on clinical outcomes, univariable and multivariable Cox regression analysis was used. All independent variables with p < 0.10 in univariable analysis were considered to be included into a multivariable Cox regression model. Variables with the lowest p value had higher priority to be included first. The number of independent variables included in the multivariable model was constrained to yield roughly 10 events per variable to avoid invalidity of the model (27). For independent variables with significant multicollinearity (defined as a variance inflation factor of >3), only 1 independent variable with the lowest p value was included in multivariable analysis. The risk of overfitting the model was investigated with the Akaike information criterion. The regression analysis results are presented as hazard ratios (HRs) and 95% confidence intervals (CIs). All statistical analysis was performed with IBM SPSS/ PASW Statistics 23 (SPSS Inc., Chicago, Illinois). All tests were 2-tailed with p < 0.05 considered statistically significant.

**RESULTS**

**PATIENT AND CMR CHARACTERISTICS.** The final T1-mapping cohort comprised 90 patients with the OHT-
| TABLE 1 Patient Characteristics Categorized by ECV and T2 |
|--------------------------------------------------------|
| **Global ECV**                                          |
| **ECV -25%** (1st Tercile (n = 29)                     |
| 50 ± 17 51 ± 17 48 ± 14 0.69 52.8 ± 15.3 48.9 ± 15.6 0.12 |
| **ECV 25%-29%** (2nd Tercile (n = 32)                  |
| 9 (31) 13 (41) 11 (38) 0.73 15 (39) 17 (43) 0.72 |
| **ECV 29%** (3rd Tercile (n = 29)                      |
| Any CAV                                                |
| 6.0 (3.5-8.3) 5.5 (3.0-8.0) 3.7 (0.5-7.6) 0.20 6.3 (3.9-9.1) 6.1 (4.0-8.6) 0.12 |
| Hypertension                                           |
| 25 (86) 27 (84) 24 (83) 0.94 32 (82) 38 (95) 0.07 |
| Dyslipidemia                                           |
| 20 (69) 17 (53) 10 (35) 0.03 24 (62) 21 (53) 0.42 |
| Diabetes mellitus                                      |
| 11 (38) 10 (31) 9 (31) 0.82 15 (39) 10 (25) 0.20 |
| History of rejection                                   |
| 4 (14) 10 (31) 6 (21) 0.25 8 (21) 12 (30) 0.33 |
| Antimetabolite                                         |
| 26 (90) 28 (88) 27 (93) 0.77 37 (95) 35 (88) 0.25 |
| Antiproliferative                                      |
| 28 (97) 31 (97) 29 (100) 0.61 37 (95) 40 (100) 0.10 |
| Steroid                                               |
| 11 (38) 9 (28) 16 (55) 0.10 12 (31) 10 (25) 0.75 |
| Beta-blocker                                           |
| 7 (24) 11 (34) 6 (21) 0.45 6 (15) 16 (40) 0.02 |
| CCB                                                   |
| 6 (21) 3 (9) 6 (21) 0.39 7 (18) 7 (18) 0.96 |
| ARB                                                   |
| 3 (10) 3 (9) 0 (0) 0.21 4 (10) 3 (8) 0.67 |
| ACEI                                                  |
| 13 (45) 12 (38) 14 (48) 0.68 22 (56) 20 (50) 0.57 |
| Statin                                                |
| 27 (93) 29 (91) 27 (93) 0.92 36 (92) 35 (89) 0.48 |
| Antiplatelet                                          |
| 27 (93) 26 (81) 26 (90) 0.34 31 (80) 37 (93) 0.10 |
| Aldosterone antagonist                                 |
| 4 (14) 3 (9) 3 (10) 0.85 2 (5) 7 (18) 0.08 |
| Diuretic                                              |
| 8 (28) 9 (29) 12 (41) 0.47 9 (23) 13 (33) 0.31 |
| Presence of LGE                                       |
| 11 (38) 11 (34) 10 (35) 0.95 12 (34) 16 (46) 0.33 |
| LGE extent,%                                           |
| 1.5 ± 2.5 1.4 ± 2.2 1.9 ± 4.6 0.81 1.3 ± 2.2 2.6 ± 4.4 0.14 |
| **Global native T1**                                   |
| 1.005 ms                                              |
| 12 (41) 10 (31) 8 (28) 0.67 11 (31) 15 (43) |
| 1.005-1.056 ms                                        |
| 11 (38) 12 (38) 7 (24) 15 (43) 11 (31) |
| 1.056 ms                                              |
| 6 (21) 10 (31) 14 (48) 9 (26) 9 (26) |
| **LVEF, %**                                            |
| 58 ± 10 56 ± 9 57 ± 7 0.67 56.6 ± 7.8 56.9 ± 8.8 0.86 |
| **LVEDVI, ml/m²**                                     |
| 58 ± 13 63 ± 19 66 ± 16 0.18 59.8 ± 14.4 61.7 ± 16.1 0.60 |
| **LVESVI, ml/m²**                                     |
| 25 ± 9 26 ± 12 28 ± 9 0.46 26.1 ± 8.8 25.1 ± 8.2 0.58 |
| **LVSV, ml**                                          |
| 64 ± 14 67 ± 21 73 ± 20 0.21 66.6 ± 19.1 66.9 ± 19.4 0.94 |
| **LVCO, ml**                                          |
| 5.8 ± 1.2 5.8 ± 1.6 6.3 ± 1.9 0.33 5.6 ± 1.3 6.0 ± 1.8 0.27 |
| **LVMi, g/m²**                                        |
| 58 ± 18 56 ± 14 59 ± 17 0.81 56.1 ± 18.1 52.3 ± 13.3 0.31 |
| **RVEF, %**                                           |
| 51 ± 8 50 ± 9 50 ± 8 0.88 50.2 ± 7.6 50.0 ± 9.1 0.93 |
| **RVEDVI, ml/m²**                                     |
| 65 ± 12 69 ± 15 24 ± 5 0.28 66.8 ± 15.5 70.6 ± 16.0 0.30 |
| **RVESVI, ml/m²**                                     |
| 33 ± 8 35 ± 10 16 ± 3 0.36 33.1 ± 9.1 36.0 ± 11.9 0.24 |
| **RHC-RAP, mm Hg**                                    |
| 6 ± 4 10 ± 7 10 ± 7 0.03 7.6 ± 5.4 8.9 ± 6.1 0.33 |
| **RHC-RVSP, mm Hg**                                   |
| 28 ± 8 34 ± 9 34 ± 10 0.02 30.1 ± 8.2 31.2 ± 9.1 0.38 |
| **RHC-RVDP, mm Hg**                                   |
| 4 ± 3 7 ± 6 7 ± 5 0.02 5.5 ± 5.1 6.1 ± 4.9 0.63 |
| **RHC-PASP, mm Hg**                                   |
| 27 ± 8 32 ± 11 33 ± 11 0.05 28.6 ± 8.2 30.0 ± 10.5 0.52 |
| **RHC-PADP, mm Hg**                                   |
| 12 ± 6 16 ± 9 17 ± 8 0.06 13.3 ± 5.8 14.3 ± 8.2 0.54 |
| **RHC-mPAP, mm Hg**                                   |
| 19 ± 6 23 ± 9 24 ± 9 0.04 20.3 ± 7.1 21.4 ± 8.1 0.54 |
| **RHC-PCWP, mm Hg**                                   |
| 11 ± 5 14 ± 8 16 ± 8 0.01 11.8 ± 5.3 13.6 ± 8.0 0.23 |
| **RHC-Ci, ml/m²**                                     |
| 3.2 ± 0.8 3.0 ± 0.8 2.9 ± 0.9 0.50 3.1 ± 1.0 3.0 ± 1.0 0.73 |

Values are mean ± SD, n (%), or median (interquartile range). *Statistically significant with p < 0.05.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CAV = cardiac allograft vasculopathy; CCB = calcium channel blocker; CI = cardiac index; ECV = extracellular volume; LVCO = left ventricular cardiac output; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; LVEDVI = left ventricular end-diastolic volume index; LVESVI = left ventricular end-systolic volume index; LVMi = left ventricular mass index; LVSV = left ventricular systolic volume; mPAP = mean pulmonary artery pressure; OHT-CMR = orthotopic heart transplant cardiovascular magnetic resonance imaging; PADP = pulmonary artery diastolic pressure; PASP = pulmonary artery systolic pressure; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; RHC = right heart catherization; RVDP = right ventricular diastolic pressure; RVEDVI = right ventricular end-diastolic index; RVEF = right ventricular ejection fraction; RVSP = right ventricular systolic pressure; SD = standard deviation.

The baseline CMR interval of 5.1 years (IQR: 2.0 to 8.0 years). The median interval between invasive hemodynamics and the baseline CMR was 0.5 month (IQR: 1 to 12 months). The final T2-mapping cohort comprised 79 patients with the OHT-baseline CMR interval of 6.3 years (IQR: 3.9 to 8.7 years). The median interval between invasive hemodynamics and CMR was 5 weeks (IQR: 1 to 13 weeks). Baseline clinical and CMR characteristics categorized by ECV tercile and T2 values are shown in...
Table 1. Overall, the global native T1, postcontrast T1, and ECV were 1,030 ± 56 ms, 458 ± 84 ms, and 27 ± 4%, respectively. Global T2 was 50 ± 4 ms.

Natural History of T1 and ECV. There were 44 (49%) patients who had 1 follow-up CMR after the baseline CMR. The interval between the baseline CMR and the follow-up CMR was 13 months (IQR: 10 to 23 months). In this subgroup of patients who had follow-up CMR, the global native T1, postcontrast T1 and ECV were 1,022 ± 52 ms, 483 ± 93 ms, and 27 ± 4%, respectively. At follow-up, only postcontrast T1 significantly decreased from the baseline CMR as shown in Figure 1. There was no significant change in native T1 or ECV noted at follow-up scans.

Prognostic Implication of T1 and ECV. Median follow-up duration for clinical events after the baseline scans was 2.4 years (IQR: 1.6 to 3.5 years). Clinical events occurred in 32 patients (36%), including 3 deaths (1 cardiogenic shock, 1 septic shock, 1 saddle pulmonary embolism), 6 heart failure hospitalizations, 3 percutaneous coronary interventions, and 20 non-cardiac hospitalization (17 infection-related hospitalization including pneumonia, urinary tract infection, abdominal infection, cellulitis, bacteremia, and 3 non-infection-related hospitalization including venous thromboembolism, bowel perforation, and spinal cord compression). Clinical events occurred 2.1 years (IQR: 1.4 to 2.8 years) after the baseline CMR. Patients who had clinical events had significantly higher prevalence of baseline LGE (53% vs. 26%; p = 0.01) with higher pulmonary capillary wedge pressure (PCWP) (16 ± 7 mm Hg vs. 12 ± 7 mm Hg; p = 0.03), RV (36 ± 10 mm Hg vs. 30 ± 8 mm Hg; p = 0.009) and right atrial (RA) pressures (12 ± 7 mm Hg vs. 8 ± 5 mm Hg; p = 0.008). Accuracy of ECV >29% for prediction of clinical outcomes is shown in Table 2.

Univariable Cox analysis showed significant association between clinical events and higher ECV compared with the bottom-range group, presence of LGE, larger LV end-systolic volume index (LVESVI), higher RA pressure, higher RV pressures, and higher pulmonary pressures. Multivariable analysis adjusted for presence of LGE and LVESVI demonstrates independent association of higher clinical event incidence with the top-range ECV compared with the bottom-range ECV (HR: 2.87; 95% CI: 1.07 to 7.68; p = 0.04) and presence of LGE (HR: 2.40; 95% CI: 1.19 to 4.85; p = 0.02) (Table 3). Adding ECV to LGE extent in the
Accuracy of Myocardial ECV and T2 Mapping for Clinical Outcomes

|                          | Sensitivity | Specificity | Positive Predictive Value | Negative Predictive Value |
|--------------------------|-------------|-------------|---------------------------|---------------------------|
| ECV >29% for all events   | 38          | 71          | 41                        | 67                        |
| ECV >29% for cardiac events | 40         | 69          | 14                        | 90                        |
| T2 >50.2 ms for all events | 78        | 57          | 35                        | 90                        |
| T2 >50.2 ms for cardiac events | 68       | 66          | 65                        | 69                        |

Values are %. Abbreviation as in Table 1.

Multivariable model improved predictivity of the model with borderline significance (global chi-square improved from 7 to 13 with \( p = 0.05 \)). Adjusted survival curve categorized by myocardial ECV is shown in the Central Illustration. Multivariable analysis adjusted for significant invasive hemodynamics demonstrates independent association of higher clinical event incidence with higher PCWP but not with ECV (Table 3).

There was no significant difference in incidence of cardiac events among the ECV groups (10% vs. 9% vs. 14% in the bottom-range, mid-range, and top-range groups, respectively; \( p = 0.685 \)). Univariable analysis did not reveal significant association between higher ECV groups and cardiac events (top-range group HR: 1.95; 95% CI: 0.44 to 8.74; \( p = 0.38 \) compared with the bottom-range group).

**PROGNOSTIC IMPLICATION OF T2 MAPPING.** Median follow-up duration was 3.5 years (IQR: 2.0 to 4.0 years) from the CMR scan. Clinical events occurred in 38 patients (48%), which include 18 cardiac events (3 deaths from cardiogenic shock, 12 heart failure hospitalizations, 3 percutaneous coronary interventions) and 20 noncardiac hospitalization. In those who had cardiac events, the median interval between the CMR and the cardiac event was 1.9 years (IQR: 0.9 to 2.8 years). Patients who developed events had significantly higher mean global T2 (53 \( \pm \) 4 ms vs. 50 \( \pm \) 4 ms; \( p = 0.004 \)), higher PCWP (18 \( \pm \) 9 mm Hg vs. 12 \( \pm \) 6 mm Hg; \( p = 0.01 \)), mean RA pressure (13 \( \pm \) 7 mm Hg vs. 8 \( \pm \) 5 mm Hg; \( p = 0.04 \)), PA diastolic pressure (17 \( \pm \) 9 mm Hg vs. 13 \( \pm \) 6 mm Hg; \( p = 0.05 \)), larger LVESVI (31 \( \pm \) 6 ml/m² vs. 24 \( \pm \) 7 ml/m²; \( p = 0.01 \)), and lower LVEF (52 \( \pm \) 10% vs. 58 \( \pm \) 7%; \( p = 0.004 \)). Accuracy of T2 >50.2 ms for prediction of clinical outcomes are shown in Table 2.

Univariable Cox regression analysis showed significant association of cardiac events with higher native T1, higher T2, larger LVESVI, lower LVEF, higher RA pressure, and pulmonary pressures. Multivariable analysis adjusted for significant CMR finding demonstrates independent association of higher clinical event with both higher T2 and lower LVEF as shown in Table 4. Multivariable analysis adjusted for significant invasive hemodynamic demonstrates independent association of higher cardiac event incidence with both higher T2 and higher PCWP. Adding T2 to LVEF or PCWP in the multivariable models significantly improved predictivity of the models (global chi-square improved from 11 to 21 with \( p = 0.02 \) and from 13 to 20 with \( p = 0.01 \), respectively). Adjusted survival curve categorized by T2 is shown in the Central Illustration.

Higher T2 was also significantly associated with higher all clinical event rate in the univariable analysis (HR: 2.5; 95% CI: 1.3 to 5.0; \( p = 0.009 \)). Other variables associated with all clinical events were lower LVEF, larger LVESVI, presence of LGE, higher PCWP, and higher RA, RV, and PA pressures. Multivariable analysis adjusted for significant CMR finding demonstrates independent association of higher clinical event with only higher T2 (Table 4). Multivariable analysis adjusted for significant invasive hemodynamic demonstrates independent association of higher cardiac event incidence with both higher T2 and higher PCWP (Table 4). Adding T2 to other significant CMR findings or invasive hemodynamics in the multivariable models significantly improved

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**TABLE 3** Multivariable Cox Regression Models of ECV for Clinical Events

|                          | Adjusted With CMR |       | Adjusted for Invasive Hemodynamics |       |
|--------------------------|--------------------|-------|-----------------------------------|-------|
|                          | Adjusted HR (95% CI) | p Value | Adjusted HR (95% CI) | p Value |
| Global ECV               |                     |        | Global ECV                        |        |
| 1st tercile (<25%)       | 1.00                | Ref.   | 1st tercile (<25%)                | 1.00   | Ref. |
| 2nd tercile (25%-29%)    | 2.15 (0.82-5.59)    | 0.12   | 2nd tercile (25%-29%)             | 1.64 (0.61-4.42) | 0.33 |
| 3rd tercile (>29%)       | 2.87 (1.07-7.68)    | 0.04   | 3rd tercile (>29%)                | 2.67 (0.93-7.64) | 0.07 |
| LVESVI                   | 1.03 (1.00-1.06)    | 0.11   | RHC-PCWP                          | 1.06 (1.01-1.11) | 0.03 |
| Any LGE                  | 2.40 (1.19-4.85)    | 0.02   | RHC-CI                            | 0.69 (0.43-1.12) | 0.13 |

CI = confidence interval; HR = hazard ratio; RHC-CI = cardiac index by right heart catheterization; RHC-PCWP = pulmonary capillary wedge pressure by right heart catheterization; other abbreviations as in Table 1.
predictivity of the models (global chi-square improved from 9 to 17 with $p = 0.003$ and from 7 to 16 with $p = 0.007$, respectively).

**PROGNOSTIC IMPLICATION OF BOTH ECV AND T2 MAPPING.** In the subset of 70 patients who had both ECV and T2-mapping data, multivariable analysis of ECV and T2 showed significant association of cardiac events with higher T2 (HR: 3.75; 95% CI: 1.01 to 13.91; $p = 0.049$) but not ECV (HR for ECV 25% to 29%: 1.54; 95% CI: 0.60 to 3.95; $p = 0.37$, HR for ECV >29%: 2.52; 95% CI: 0.95 to 6.71; $p = 0.07$). Similarly, multivariable analysis of ECV, T2, LVEF, and LVESVI showed significant association of all clinical events with higher T2 (HR: 2.38; 95% CI: 1.03 to 5.50; $p = 0.042$) but not ECV (HR for ECV 25% to 29%: 1.53; 95% CI: 0.58 to 4.01; $p = 0.39$, HR for ECV >29%: 2.15; 95% CI: 0.77 to 5.99; $p = 0.14$).

**DISCUSSION**
Detection of myocardial changes with CMR-derived T1- and T2-mapping techniques has been demonstrated in patients with ischemic and nonischemic
cardiomyopathies including cardiac amyloidosis, hypertrophic cardiomypathy, acute myocarditis, and Anderson-Fabry disease (9,10,12,28-32). Both techniques have also been shown to have prognostic values in these populations (9-15). Major CMR societies recommend the use of T1- and T2-mapping markers in certain clinical scenarios (33). In OHT populations, application of CMR has been described for structures and function assessment as well as myocardial characterization. Previous literature has demonstrated myocardial characterization with LGE imaging and its prognosis in this population (34-37). However, because of an innate limitation of LGE techniques, diffuse myocardial changes may be missed. Recently, contemporary T1- and T2-mapping techniques have been examined in OHT population (16-22). Both ECV and T2 have been shown to be higher in OHT patients compared with healthy controls (16) and correlate well with myocardial edema marker (17,21). ECV was also shown to correlate with histological fibrosis (18). Clinically, previous research has demonstrated possible association of higher ECV and T2 with ACR episodes (23). Nevertheless, the prognostic value of T1- and T2-mapping markers has not been established in OHT population.

Our study demonstrates that higher ECV during the baseline CMR assessment predicts overall adverse clinical events. We did not find significant association specifically between T1-mapping markers and adverse cardiac events. This association may suggest potential multifactorial causes of higher ECV in OHT patients. Higher baseline ECV in OHT patients possibly represents all cumulative myocardial insults before the baseline CMR scan including harvesting/transplantation surgery and prior infections, hemodynamic disturbance, and medications. We also found that both ECV and presence of LGE remain independently associated with adverse events after adjustment with other significant clinical characteristics and CMR findings. However, ECV became insignificant after adjustment with invasive hemodynamics. This finding supports ECV, in addition to LGE, as a promising noninvasive prognosticator in OHT patients.

Higher myocardial T2 was associated with adverse overall clinical and cardiac events in our cohort. These associations highlight the clinical importance and implications of myocardial edema. Prolonged myocardial edema and inflammation can cause decreased ventricular compliance and increased stiffness (38,39), eventually resulting in irreversible cardiac structural alterations, ventricular dysfunction, and fibrosis (40). We may speculate that increased T2 values in OHT beyond the first year after OHT is related to repetitive inflammatory events including subling biopsy negative ACR episodes (41), diffuse low-grade vasculitis component secondary to undetected CAV, which has been previously suggested by histological studies (42), or myocardial edema from congestion of the cardiac allograft as suggested by associations between increased T2 and several right heart/pulmonary invasive hemodynamic data in our study and as shown in prior literature (43).

Furthermore, our work indicates that native T1 and ECV did not change during the 13-month follow-up CMR interval, which is consistent with the lack of association between the CMR-OHT time interval and the baseline T1-mapping markers. The findings may suggest that the myocardial changes (possibly interstitial fibrosis) detected by T1-mapping markers occurred earlier after OHT and did not change significantly afterward.

**STUDY LIMITATIONS.** There are some limitations to our study. Our data were from a single-center prospective study. Multicenter larger studies with standardized diagnostic protocols are needed to confirm these findings. Our follow-up interval of T1-mapping cohort was 13 months; therefore, changes or plateau in T1-mapping markers after the follow-up period is possible. Most patients in our studies did not have longer term CMR follow-up scans to evaluate long-term change of T1-mapping markers. Last, some relevant clinical information (e.g., prior significant infections and other cardiac biomarkers such as troponins and invasive hemodynamic parameters at closer dates to the baseline and follow-up CMR) and CMR findings (e.g., CMR-derived myocardial strain and myocardial perfusion reserve) were not available for analysis. Reduced myocardial perfusion reserve index and early diastolic strain rate as potential better surrogate

### TABLE 4 Multivariable Cox Regression Models of T2 Mapping for Clinical Events

| Cardiac events | Adjusted With CMR | Adjusted for Invasive Hemodynamics |
|---------------|-------------------|-----------------------------------|
| Adjusted HR (95% CI) p Value | Adjusted HR (95% CI) p Value |
| T2 ≥50.2 ms | 4.92 (1.60-15.14) 0.005 | T2 ≥50.2 ms | 4.47 (1.25-15.99) 0.02 |
| LVEF | 0.94 (0.90-0.97) 0.001 | RHC-PCWP | 1.1 (1.00-1.10) 0.006 |
| All clinical events | | |
| T2 ≥50.2 ms | 3.01 (1.39-6.54) 0.005 | T2 ≥50.2 ms | 2.69 (1.27-5.67) 0.01 |
| LVEF | 0.99 (0.94-1.04) 0.67 | RHC-PCWP | 1.05 (1.01-1.09) 0.03 |
| Any LGE | 1.94 (0.97-3.87) 0.06 | |
| LVESVI | 1.02 (1.00-1.04) 0.05 | |

Abbreviations as in Tables 1 and 3.

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markers of cardiac allograft function were found to be associated with cardiac allograft vasculopathy and adverse clinical outcomes (44,45).

CONCLUSIONS

We demonstrate independent association of higher baseline myocardial ECV and T2 with adverse clinical and cardiac events after adjustment in multivariable models. Our findings serve as a pilot study for larger research to evaluate the role of ECV and T2 as noninvasive prognostic markers in OHT population.

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**KEY WORDS** extracellular volume fraction, heart transplantation, magnetic resonance imaging, natural history, prognosis, T1 mapping, T2 mapping
The optimal protocol for monitoring the health of the transplanted heart is uncertain, with a lack of specific guidance regarding which tests and at what frequency they should be performed as part of a comprehensive surveillance strategy. Traditional practice has included serial echocardiography, right heart catheterization, coronary angiography, and endomyocardial biopsy, although current institutional protocols depend on local expertise and experience as well available resources. Although outcomes following heart transplantation (HT) have improved compared with those from prior decades (1), the rate of improvement appears to be plateauing, and the supply of donor hearts remains finite and inadequate to meet demand. Augmenting the noninvasive armamentarium to identify and treat causes of graft dysfunction remains clinically relevant.

Allograft surveillance has focused on the early and accurate detection of acute rejection (cellular and antibody-mediated) as well as coronary allograft vasculopathy (CAV) given that they represent the most common etiologies causing graft dysfunction after the initial perioperative period (1). Available modalities for surveillance (2) lie across the spectrum from noninvasive to invasive: gene expression profiling detects acute rejection in low-risk patients, endomyocardial biopsy is performed for those with higher suspicion for rejection, and stress testing with cardiac imaging identifies CAV, although coronary angiography with or without intravascular ultrasound is still routinely used. Emerging modalities include the use of cell-free deoxyribonucleic acid (3), echocardiographic strain imaging (4), and cardiac magnetic resonance (CMR) parametric techniques to detect rejection (5), as well as coronary computed tomographic angiography (6) and perfusion (nuclear [7] and CMR [8]) imaging for CAV assessment.

Are there imaging biomarkers beyond rejection and CAV worthy of acquisition? In this issue of JACC, Chaikriangkrai et al. (9) report the association between clinical outcomes and CMR-derived metrics of myocardial health in a post-HT cohort specifically excluding those with recent rejection (and in whom CAV was equally prevalent across the range of the imaging biomarkers of interest.) Extracellular volume fraction (ECV) (10), a marker of diffuse myocardial fibrosis that has been histologically validated in the pediatric HT population (11,12), was quantified using pre- and post-contrast T1 mapping and hematocrit measurement. In addition, T2 mapping (13), a marker of myocardial edema (higher T2 time correlates with higher water content), was also quantified. Similar pulse sequences are available commercially from most major cardiac magnetic resonance vendors.

The main findings were as follows: 1) ECV predicted a composite endpoint of cardiac and noncardiac events after moderate risk adjustment for
imaging variables, although it was not significant when invasively determined pulmonary capillary wedge pressure was included in multivariable models; 2) T2 predicted outcomes in multivariable models including adjustment for imaging parameters including ECV, as well as pulmonary capillary wedge pressure; and 3) ECV and pre-contrast T1 appear stable over a median time of 13 months for follow-up measurement.

These data suggest that in the scenario in which CMR is used as part of a surveillance strategy following HT (and rejection and CAV are not detected), parametric mapping data characterizing diffuse fibrosis and myocardial edema status may provide incremental prognostic information. Of interest is the stability of ECV and pre-contrast T1 in a subset of 44 patients in whom follow-up CMR was performed, suggesting that events leading to extracellular compartment expansion may occur early in the post-HT period (or even prior to transplantation), and subsequent change may occur slowly. Although such prognostic data in isolation may not lead to changes in clinical management, they may complement the increasingly robust diagnostic ability of other CMR techniques for rejection and CAV detection. Of note, of the 32 patients in whom clinical events occurred, just over one-half of the events appear to be noncardiac in etiology (primarily hospitalization for infection). These data, and the lack of etiologic specificity in understanding the cause of ECV and T2 elevation, raise the question of whether multifactorial and noncardiac causes of graft dysfunction are at play. Of the 2 biomarkers, T2 appears more robustly associated with outcomes in multivariate modeling, and further study into potential mechanisms of T2 elevation in the post-HT population are warranted. Should potential mechanisms such as cumulative insults from injury, side effects from immunosuppressive medication, biopsy-negative rejection, and subclinical chronic inflammation and CAV leading to higher T2 be confirmed, these data support a role for CMR in guiding therapy by identifying those who may benefit from novel therapies (14) under development for allograft protection.

In 2010, the only mention of CMR in the International Society for Heart and Lung Transplantation guidelines for HT care was a Class III recommendation stating, “The routine clinical use of MRI for acute allograft rejection monitoring is not recommended” (2). Since then, an increasing body of evidence suggests that cardiac imaging, including CMR, may be able to play a more prominent role in identifying heart transplant recipients at highest risk for rejection and/or CAV. Indeed, some institutions have designed HT follow-up protocols focusing on fewer endomyocardial biopsy and more reliance on noninvasive assessment of complications (15). Potential obstacles from a CMR perspective include heterogeneity across CMR systems (with a need to create local reference ranges for T1 and T2 measurement referenced above varying CMR access and availability across institutions who routinely perform HT, contraindications to CMR such as retained defibrillator leads, and a lack of multicenter studies demonstrating robust reproducibility of the diagnostic and prognostic information derived from CMR. The dissemination of advanced CMR techniques for the noninvasive diagnosis of rejection and CAV as well as prognosis determination and patient selection for novel therapy will require increasing cross-talk between heart failure specialists and cardiovascular imagers. Such collaborations at the institutional level, and mirrored at the subspecialty society level, will advance the field closer toward the goal of robust, noninvasive surveillance of with patients HT.

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KEY WORDS cardiac MRI, heart transplantation outcomes, T1 mapping, T2 mapping
Prognostic Value of Coronary CTA in Stable Chest Pain

CAD-RADS, CAC, and Cardiovascular Events in PROMISE

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ABSTRACT

OBJECTIVES The purpose of this study was to compare Coronary Artery Disease Reporting and Data System (CAD-RADS) to traditional stenosis categories and the coronary artery calcium score (CACS) for predicting cardiovascular events in patients with stable chest pain and suspected coronary artery disease (CAD).

BACKGROUND The 2016 CAD-RADS has been established to standardize the reporting of CAD on coronary CT angiography (CTA).

METHODS PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial participants’ CTAs were assessed by a central CT core laboratory for CACS, traditional stenosis-based categories, and modified CAD-RADS grade including high-risk coronary plaque (HRP) features. Traditional stenosis categories and CAD-RADS grade were compared for the prediction of the composite endpoint of death, myocardial infarction, or hospitalization for unstable angina over a median follow-up of 25 months. Incremental prognostic value over traditional risk factors and CACS was assessed.

RESULTS In 3,840 eligible patients (mean age: 60.4 ± 8.2 years; 49% men), 3.0% (115) experienced events. CAD-RADS (concordance statistic [C-statistic] 0.747) had significantly higher discriminatory value than traditional stenosis-based assessments (C-statistic 0.698 to 0.717; all p for comparison ≤0.001). With no plaque (CAD-RADS 0) as the baseline, the hazard ratio (HR) for an event increased from 2.43 (95% confidence interval [CI]: 1.16 to 5.08) for CAD-RADS 1 to 21.84 (95% CI: 8.63 to 55.26) for CAD-RADS 4b and 5. In stepwise nested models, CAD-RADS added incremental prognostic value beyond ASCVD risk score and CACS (C-statistic 0.776 vs. 0.682; p < 0.001), and added incremental value persisted in all CACS strata.

CONCLUSIONS These data from a large representative contemporary cohort of patients undergoing coronary CTA for stable chest pain support the prognostic value of CAD-RADS as a standard reporting system for coronary CTA.
Established the Coronary Artery Disease Reporting and Data System (CAD-RADS) (17). Compared with the prevailing traditional cut points for per-lesion stenosis on CTA (0%, 1% to 49%, 50% to 69%, 70% to 100%), CAD-RADS adds additional categories intended for risk stratification: 1) explicitly differentiating between minimal (1% to 25%) and mild (30% to 49%) stenosis; 2) adding categories for left main and multivessel stenosis; and 3) including HRP features. However, the prognostic value of CAD-RADS including HRP and whether there is incremental value beyond existing traditional stenosis categories, ASCVD risk score, or CACS is not known.

Thus, the aim of this study was to determine the prognostic value of CAD-RADS and compare with established predictors of MACE in a large contemporary population with stable chest pain.

METHODS

STUDY DESIGN AND POPULATION. The PROMISE trial was a randomized comparative effectiveness trial in stable outpatients with chest pain who required noninvasive cardiac testing to determine the presence of obstructive CAD or myocardial ischemia. The study population and inclusion and exclusion criteria are detailed elsewhere (2,18). In brief, 10,003 patients from 193 sites across North America with expertise in the fields of cardiology, primary care, radiology, and anesthesia were included in PROMISE between July 2010, and September 2013. Patients were randomly assigned to either anatomic coronary CTA or functional testing (exercise electrocardiography, stress echocardiography, or nuclear stress testing), with interpretation of testing and subsequent decision making by the local physicians. Local institutional review boards approved the study, and all patients provided written informed consent.

Our analysis included PROMISE patients who were randomized to the coronary CTA arm and received diagnostic noncontrast CT for calcium scoring and atherosclerotic cardiovascular disease.

CACS = coronary artery calcium score
CAD = coronary artery disease
CAD-RADS = Coronary Artery Disease Reporting and Data System
CTA = computed tomography angiography
HRP = high-risk plaque
LM = left main coronary artery
MACE = major adverse cardiovascular event
UA = unstable angina

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Cardiovascular Imaging author instructions page.
Coronary CTA datasets were analyzed by 1 of 6 expert readers in coronary CTA who were also blinded to clinical information and outcome (19). Upfront interobserver reliability was assessed using 50 randomly selected coronary CTAs among all readers (≥70% stenosis or left main ≥50% stenosis: kappa = 0.69; HRP: kappa = 0.56). Evaluable coronary artery segments were assessed for the presence of stenosis using 5 predefined categories: 0%, 1% to 29%, 30% to 49%, 50% to 69%, or ≥70% stenosis. Stenosis was categorized in 3 ways.

First, stenosis were categorized using CAD-RADS (17). CAD-RADS was introduced after the start of the core laboratory measurements; to translate our stenosis categories to those in CAD-RADS, we made a minor modification to CAD-RADS category 1 (stenosis 1% to 29% instead of 1% to 24%) and category 2 (stenosis 30% to 49% instead of 25% to 49%). Thus, this analysis evaluates a slightly modified CAD-RADS; the term CAD-RADS is used throughout for readability.

Second, we defined traditional stenosis in 2 ways. Traditional definition 1 corresponds to the pre-existing standard for coronary CTA including stenosis categories of no CAD (0%), mild CAD (1% to 49% stenosis), moderate CAD (50% to 69% stenosis in any major vessels/branch), severe CAD (≥50% stenosis of left main [LM] or ≥70% in any major vessel/branch).

Traditional definition 2 was defined according to the obstructive CAD definition used in the PROMISE trial (14): normal (absence of coronary atherosclerosis), mildly abnormal (nonobstructive CAD: 1% to 69% stenosis in any major vessels/branch, or <50% LM stenosis), moderately abnormal (obstructive CAD: ≥70% stenosis in 1 major vessel/branch), and severely abnormal (high-risk CAD: ≥2 or more vessel disease (≥70%), or ≥50% LM stenosis, or ≥70% proximal left anterior descending [LAD] stenosis).

Beyond stenosis, all coronary segments were assessed for HRP features (positive remodeling, spotty calcification, low CT attenuation <30 HU and napkin-ring sign) as previously defined (12). As per the CAD-RADS definition, the “V” modifier for “vulnerable plaque” was defined as 2 or more HRP features in at least 1 coronary plaque/segment (17).

**STUDY ENDPOINT.** The endpoint was a composite of death from any cause, myocardial infarction (MI), or hospitalization for unstable angina (UAP). An independent clinical events committee adjudicated all endpoints in a blinded fashion on the basis of standard prospectively determined definitions (2,18).

**STATISTICAL ANALYSIS.** Continuous variables are presented as mean ± SD. Categorical and ordinal variables are presented as frequencies and proportions. Comparisons among groups were performed...
using an independent sample Student’s t-test for continuous variables, the Fisher’s exact test for categorical variables, and the Wilcoxon rank-sum test for ordinal variables.

Cox proportional hazards regression models were used to calculate hazard ratios unadjusted and adjusted for atherosclerotic cardiovascular disease (ASCVD) risk score with 95% confidence intervals and assess the relationship of test results to the time to the first clinical event (or censoring) (20). Cumulative event rates based on test results were computed for each testing strategy (CACS, stenosis, or CAD-RADS) using the Kaplan-Meier method (21).

The discriminatory value of traditional and CAD-RADS grading schemes for the composite outcome was assessed using the C-statistic (22,23). Because of low individual prevalence, CAD-RADS categories 4b and 5 were combined as 1 composite category. A stepwise C-statistic comparison between nested models assessed the incremental prognostic value of ASCVD, CACS, and CAD-RADS over ASCVD risk score. C-statistics were compared using “somersd” and “lincom” packages in Stata (SE 14.2, StataCorp LP, College Station, Texas). The Stata routines used to compare the C-statistics account for the nested-model structure.

A 2-sided p value of <0.05 was considered to indicate statistical significance. All analyses were performed using Stata.

RESULTS

Of 4,996 PROMISE patients randomized to an anatomic testing strategy (CTA), 3,840 patients (77%) were included in the analysis. The reasons for exclusion are provided in Figure 1. Excluded patients were older, differed in risk profile and presenting symptoms, and had a higher prevalence of statin therapy compared with included patients (Supplemental Table 1).

Of those patients included in the study, the mean age was 60.4 ± 8.2 years, and 49% (1,868 of 3,840) were men (Table 1). Over median follow-up of 25 months (interquartile range 18 to 34 months), 115 patients (3.0%) experienced the composite outcome, including 53 (1.4%) all-cause deaths, 29 (0.8%) cardiovascular deaths, 18 (0.5%) MIs, and 46 (1.2%) admissions for UAP.

PREVALENCE OF CAD. On coronary CTA, 1,303 (34%) of patients had no visible CAD, whereas 186 (4.8%) showed 70% to 99% stenosis (CAD-RADS 4a), and 54 (1.4%) showed ≥50% LM or ≥70% stenosis in 3 vessels (CAD-RADS 4b and 5). Using the traditional definition

| TABLE 1 Baseline Characteristics of PROMISE Patients Included in This Analysis (N = 3,840) |
|---|
| **Demographics** |
| Age (yrs) | 60.4 ± 8.2 |
| Male | 1,868/3,840 (48.7) |
| Racial or ethnic minority | 861/3,814 (22.6) |
| **Cardiac risk factors** |
| BMI (kg/m²) | 30.3 ± 5.8 |
| Hypertension | 2,461/3,840 (64.1) |
| Diabetes | 778/3,840 (20.3) |
| Dyslipidemia | 2,588/3,840 (67.4) |
| Family history of premature CAD | 1,272/3,829 (33.2) |
| Peripheral or cerebrovascular disease | 192/3,839 (5.0) |
| CAD equivalent | 920/3,840 (24.0) |
| History of heart failure | 150/3840 (3.9) |
| Metabolic syndrome | 1,393/3,840 (36.3) |
| Current or past tobacco use | 1,977/3,839 (51.5) |
| Sedentary lifestyle | 1,844/3,832 (48.1) |
| History of depression | 732/3,840 (19.1) |
| Risk factor burden and risk score |
| No risk factors | 973/3,840 (25.2) |
| Risk factor burden | 2.4 ± 1.1 |
| Combined Diamond-Forrester and Coronary Artery surgery risk score | 53.0 ± 21.1 |
| **Framingham risk score** |
| Low risk (<5%) | 253/3,834 (6.6) |
| Intermediate risk (6%-20%) | 2,006/3,834 (52.3) |
| High risk (>20%) | 1,575/3,834 (41.1) |
| **ASCVD pooled cohort risk prediction (2013)** |
| Low risk (<7.5%) | 1,249/3,795 (32.9) |
| Elevated risk (≥7.5%) | 2,546/3,795 (67.1) |
| **Relevant medications** |
| Beta-blocker | 911/3,675 (24.8) |
| ACE or ARB | 1,586/3,675 (43.2) |
| Statin | 1,670/3,675 (45.4) |
| Aspirin | 1,648/3,675 (44.8) |
| Clopidogrel | 483/3,675 (1.3) |
| Prasugrel | 1/3,675 (0.03) |
| Warfarin | 53/3,675 (1.4) |
| **Primary presenting symptom and anginal type** |
| Chest pain | 2,810/3,837 (73.2) |
| Dyspnea on exertion | 547/3,837 (14.3) |
| **Anginal type, site-reported** |
| Typical | 408/3,840 (10.6) |
| Atypical | 3,021/3,840 (78.7) |
| Nonanginal | 411/3,840 (10.7) |

Values are mean ± SD or n/N (%). Body-mass index is the weight in kilograms divided by the square of the height in meters. *A family history of premature CAD was defined as diagnosis of the disease in a male first-degree relative before 55 yrs of age or in a female first-degree relative before 65 years of age. †CAD risk equivalent was defined as diabetes, peripheral vascular disease, or cerebrovascular disease. ‡The metabolic syndrome was defined according to consensus criteria of the American Heart Association and the National Heart, Lung, and Blood Institute. §Sedentary lifestyle was defined by the patient as not participating in regular physical activities at least 1 time per week over the previous month. ‖Racial or ethnic minority group was self-reported, with the status of “minority” being defined by the patient. ¶Risk factors included hypertension, diabetes, dyslipidemia, family history of premature CAD, and tobacco use. #Combined Diamond and Forrester and Coronary Artery Surgery Study risk scores range from 0 to 100, with higher scores indicating a greater likelihood of obstructive CAD. **The type of angina was reported by the patient as typical or atypical.
1, 294 (7.7%) and 240 (6.3%) patients had moderate (50% to 69% stenosis) and severe stenosis (≥50% stenosis of LM or ≥70% in any major vessel), respectively. Using the traditional definition 2, moderately abnormal (≥70% stenosis in 1 major vessel) and severely abnormal (≥2 vessel disease [≥70%] or ≥50% left main stenosis or ≥70% proximal LAD stenosis) were detected in 145 (3.8%) and 95 (2.5%) patients, respectively.

Any HRP feature was present in 1,938 (50.5%) patients, of whom 416 (21.5%) had at least 1 coronary plaque/segment. The number of patients with presence of 2 or more HRP features per segment gradually increased across CAD-RADS categories from 9.1% (112 of 1,236) for CAD-RADS 1% to 37.0% (20 of 54) for CAD-RADS 4b and 5 (p < 0.001).

**Downstream Invasive Angiography and Revascularization.** Overall, 437 (11.4%) patients underwent invasive coronary angiography (ICA), of whom 217 (49.7%) were revascularized. As displayed in Supplemental Table 2, the rate of ICA as well as the percent leading to revascularization increased across CAD-RADS categories (both p < 0.001), with CAD-RADS 4a and 4b and 5 showing the highest rates of ICA (61.8% [115 of 186] and 64.8% [35 of 54]) and revascularization (50.5% [94 of 186] and 46.3% [25 of 54]), respectively. The proportion of ICA leading to revascularization increased from 10% (6 of 56) for CAD-RADS 1% to 82% (94 of 115) for CAD-RADS 4a and 71% (25 of 35) for CAD-RADS 4b and 5.

**Prognostic Value of Presence and Extent of CAD.** Higher CAD stenosis category by CTA was significantly associated with the composite endpoint in univariate and multivariate analysis (adjusted for ASCVD risk score) for all definitions used to categorize degree of stenosis (traditional definition 1, traditional definition 2, and CAD-RADS categories) as displayed in Table 2. The risk for the composite endpoint increased from HR 2.43 (95% CI: 1.16 to 5.08) for CAD-RADS 1 to HR 21.84 (95% CI: 8.63 to 55.26) for CAD-RADS 4b and 5. The presence of HRP features showed significant associations to the time to event (Supplemental Figure 1) and was significantly associated with a higher hazard for the composite
FIGURE 2  Kaplan-Meier Estimates

A

[Diagrams showing Kaplan-Meier Estimates for different groups: No CAD, Mild CAD, Moderate CAD, Severe CAD.]

Number at risk
- No CAD: 1,303, 1,258, 1,176, 735, 735, 475, 256
- Mild CAD: 2,033, 1,923, 1,808, 1,106, 709, 452
- Moderate CAD: 294, 277, 263, 156, 98, 50
- Severe CAD: 240, 216, 202, 118, 70, 28

B

[Diagrams showing Kaplan-Meier Estimates for different groups: Normal, Mildly Abnormal, Moderately Abnormal, Severely Abnormal.]

Number at risk
- Normal: 1,303, 1,258, 1,176, 971, 735, 475, 256
- Mildly Abnormal: 2,297, 2,200, 2,071, 1,664, 1,262, 807, 411
- Moderately Abnormal: 145, 129, 123, 97, 75, 39, 16
- Severely Abnormal: 95, 87, 79, 65, 43, 31, 12

C

[Diagrams showing Kaplan-Meier Estimates for different groups: CAD-RADS 0, CAD-RADS 1, CAD-RADS 2, CAD-RADS 3, CAD-RADS 4a, CAD-RADS 4b&5.]

Number at risk
- CAD-RADS 0: 1,303, 1,258, 1,176, 971, 735, 475, 256
- CAD-RADS 1: 1,236, 1,191, 1,123, 899, 683, 436, 229
- CAD-RADS 2: 767, 732, 685, 559, 423, 273, 132
- CAD-RADS 3: 294, 277, 263, 206, 156, 98, 50
- CAD-RADS 4a: 186, 170, 161, 134, 98, 58, 23
- CAD-RADS 4b&5: 54, 46, 41, 28, 20, 12, 5

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DISCRIMINATORY CAPACITY OF STRATIFICATION OF CAD TO PREDICT EVENTS. The capacity to discriminate future events (all-cause death, MI, UAP) for the traditional definition 1, traditional definition 2, and CAD-RADS categories were c-statistic 0.717 (95% CI: 0.673 to 0.760), c-statistic 0.698 (95% CI: 0.658 to 0.739), and c-statistic 0.747 (95% CI: 0.703 to 0.792) respectively. CAD-RADS had significantly higher discriminatory value compared with both traditional definitions (p ≤ 0.001).

As determined by log-rank test in Kaplan-Meier estimates, CAD-RADS categories also showed significant associations to the time to event, with an increase in risk for the composite endpoint with the next higher category (p < 0.001) (Table 2).

INCREMENTAL VALUE OF CTA USING CAD-RADS CATEGORIES BEYOND CACS TO PREDICT EVENTS. Information about the burden of CAC (strata) significantly improved the discriminatory capacity of the ASCVD pooled cohort risk calculator to predict the composite endpoint of all-cause death, MI, and UAP (c-statistic 0.629 [95% CI: 0.572 to 0.687] vs. 0.682 [95% CI: 0.629 to 0.735]; p = 0.008), as displayed in Tables 5 and 6. Data from CTA using CAD-RADS categories (including HRP features) further incrementally increased the prognostic value to predict the composite endpoint (C-statistic 0.776; 95% CI: 0.734 to 0.818; p < 0.001) (Central Illustration). Stratified by CAC categories, the significant incremental value of coronary CTA over ASCVD risk stratification persisted as listed in Table 6.

DISCUSSION
In a large contemporary trial of patients with stable chest pain randomized to coronary CTA, we found that the CAD-RADS reporting system had greater prognostic value and discriminatory ability for future MACE than previous traditional stenosis-based categories. This can be explained by CAD-RADS’s more granular grading of nonobstructive and obstructive CAD, inclusion of both stenosis and plaque burden components, and the inclusion of HRP features. Our second major finding is that CAD-RADS adds substantial prognostic value over the ASCVD risk score and CACS across all CACS strata. Together, these results support the prognostic value of CAD-RADS for standardized reporting of coronary CTA.

Strengths of this study include that it was conducted within a large multicenter randomized controlled trial at 193 sites, with prospective enrollment of patients, collection of CTA, and independent endpoint in univariate (HR 3.08; 95% CI: 2.04 to 4.65; p < 0.001) and multivariate analysis (HR 2.61; 95% CI: 1.71 to 3.98); p < 0.001 (Table 2).

INCREMENTAL VALUE OF CAD-RADS STENOYSIS CATEGORIES BEYOND CACS. Prevalence of CAC and the association to clinical events. Of 3,840 patients, 1,498 (39%) had CACS of 0. The CACS was 1 to 100 in 506 (13%) patients. Across CACS categories, the prevalence of CAD significantly increased (p < 0.001) (Table 3). In patients with CACS of 0, 87% were free of CAD (CAD-RADS 0), whereas 12.3% (184 of 1,498) had nonobstructive disease (CAD-RADS 1 to 3), and 0.7% (11 of 1,498) had obstructive disease (CAD-RADS 4 and 5). In 9.2% (17 of 184) of those patients with CACS of zero and nonobstructive disease (CAD-RADS 1 to 3), 2 or more HRP features were present, whereas HRP were present in 54.5% (6 of 11) of patients with a CAC of zero and obstructive disease (CAD-RADS 4 and 5).

Overall, the incidence of the composite endpoint increased across CACS categories (p < 0.001) as well as CAD-RADS stenosis categories within each CAC group (p < 0.001), as displayed in Table 4. Among patients with CAC scores of zero, 1.5% (22 of 1,498) experienced events. Ten of these patients had no visible CAD on CT (CAD-RADS 0). Nevertheless, the incidence of the primary endpoint increased with severity of CAD, reflected by increasing hazard ratios from 5.7 (95% CI: 2.3 to 14.5) for nonobstructive CAD (CAD-RADS 1 to 3) to 58.0 (95% CI: 18.1 to 185.3) for obstructive CAD (CAD-RADS 4 and 5), with a p < 0.001 for comparison with patients without plaque.

FIGURE 2 Continued
Composite outcome estimates (death, MI, and UAP) by severity of stenosis using the (A) traditional definition 1,* (B) traditional definition 2, and (C) CAD-RADS. *No CAD (0%); mild CAD (1% to 49% stenosis); moderate CAD (50% to 69% stenosis in any major vessel/branch); severe CAD (≥50% stenosis of left main [LM] or ≥70% in any major vessel/branch); Normal (absence of coronary atherosclerosis), mildly abnormal (nonobstructive CAD: 1% to 69% stenosis in any major vessels/branch or <50% LM stenosis), moderately abnormal (obstructive CAD: ≥70% stenosis in 1 major vessel/branch), and severely abnormal (high-risk CAD: 2 or more vessel disease (≥70%) or ≥70% LM stenosis or ≥70% proximal LAD stenosis) CAD-RADS—coronary artery disease reporting and data system; CAD-RADS 0—no plaque/stenosis; CAD-RADS 1—1% to 29% stenosis; CAD-RADS 2—30% to 49% stenosis; CAD-RADS 3—50% to 69% stenosis; CAD-RADS 4a—70% to 99% stenosis; CAD-RADS 4b and 5: ≥50% LM stenosis or ≥70% stenosis in 3 vessels or total occlusion.
adjudication of adverse events. In this analysis, coronary CT was interpreted for CAC, coronary artery stenosis, and high-risk coronary plaque features by a central core laboratory with expert CT readers blinded to clinical information and outcomes. These factors may explain why our results differ from that in a recent analysis of the CONFIRM registry, which found CAD-RADS did not have greater discriminatory value for MI or death (C-statistic CAD-RADS $0.705 \text{ vs. } 0.78 \text{ (24).} In the CONFIRM analysis, CTA stenosis was graded by local site physicians, who tend to call severe stenosis more often than blinded expert core laboratory readers (19). Furthermore, the CONFIRM analysis did not include HRP features, which are a part of CAD-RADS, because of their known prognostic value (12,25–28).

Our results should be interpreted in the context of previous PROMISE publications that assessed the prognostic value of CTA. First, Hoffmann et al. (14) compared the prognostic value of CTA with functional testing, finding that CTA had greater prognostic value. In contrast to the current study, this analysis used the local site interpretations of CTA and functional testing as well as disease categories tailored to allow comparison between CTA and functional testing, which may not reflect how coronary CTA is currently interpreted. A subsequent paper by Lu et al. found that blinded expert central core laboratory interpretation of coronary CTA found 41% fewer patients with stenosis $\geq 50\%$ than the site readers, yet with better accuracy using quantitative invasive coronary angiography as the reference standard (19). Ferencik et al. (12) found that HRP features on coronary CTA were associated with MACE after adjustment for stenosis and ASCVD risk score; in this study, HRP was defined differently (any plaque with at least 1 high-risk feature, not including spotty calcification) than in CAD-RADS (2 HRP features in a single segment, including spotty calcification). Finally, Budoff et al. (15) compared the coronary artery calcium score to functional testing for estimating prognosis, finding that most patients having events had calcium scores $> 0$ compared with fewer than one-half with an abnormality on functional testing. However, whether coronary CTA adds prognostic value beyond coronary calcium was not assessed.

A second major finding of our study was that CAD-RADS had greater prognostic value than the

| TABLE 4 Composite Outcome (All-Cause Death, Myocardial Infarction, Unstable Angina) by CAD-RADS Category Across CAC Strata |
|----------------------------------------------------------------------------------------------------------------------|
| CAVRADS Stenosis Categories | All Patients (N = 3,840) | CAC $0$ (n = 1,498) | CAC $1$–$100$ (n = 1,160) | CAC $>100$–$400$ (n = 676) | CAC $>400$ (n = 506) |
| No plaque/stenosis: CAD-RADS 0 | 10/1,303 (0.8) | 10/1,303 (0.8) | 0/0 (–) | 0/0 (–) | 0/0 (–) |
| 1%–29%: CAD-RADS 1 | 25/1,236 (2.0) | 6/142 (4.2) | 12/774 (1.6) | 5/254 (2.0) | 2/66 (3.0) |
| 30%–49%: CAD-RADS 2 | 33/767 (4.3) | 2/35 (5.7) | 9/273 (3.3) | 14/256 (5.4) | 8/198 (4.0) |
| 50%–69%: CAD-RADS 3 | 18/294 (6.1) | 0/7 (0.0) | 2/68 (2.9) | 8/93 (8.6) | 8/126 (6.4) |
| 70%–99%: CAD-RADS 4a | 19/186 (10.2) | 3/10 (30.0) | 2/36 (5.6) | 7/54 (13.0) | 7/86 (8.1) |
| $\geq 50\%$ LM or $\geq 70\%$ in 3 vessels or total occlusion CAD-RADS 4b–5 | 10/54 (18.5) | 1/1 (100.0) | 2/9 (22.2) | 3/14 (21.4) | 4/30 (13.3) |
| **Total** | 115/3,840 (3.0) | 22/1,498 (1.5) | 27/1,160 (2.3) | 37/676 (5.5) | 29/506 (5.7) |

Values are n/N (%).
Abbreviations as in Tables 2 and 3.
CACS. Although the CACS is one of the best-studied prognostic imaging biomarkers in asymptomatic populations (29–31), how it relates to stenosis, HRP, and events in symptomatic chest pain populations is not as well established. Indeed, CACS had limited value for diagnosing stenosis, with only one-half of patients with CACS >400 having stenoses ≥50% (Table 3). For those with a CACS between 101 and 400, only a quarter had a stenosis ≥50%. On the other hand, 13% (195 of 1,498) of patients with CACS of zero had detectable coronary plaque, and 6% (12 of 195) of patients with CACS of zero but detectable plaque on CTA experienced events in our analysis, an event rate twice as high as the overall population. It should be noted that of the 1,498 studies with CACS of zero, only 21 had events (15), yet a majority of these (12 of 21) occurred in the group with CACS of zero and nonobstructive CAD on CTA. This finding is complementary to CONFIRM observational data, finding that a minority of symptomatic patients with CACS of zero have coronary plaque on CTA and that this noncalcified plaque is associated with increased cardiac events (32). CAD-RADS had substantial incremental prognostic value over CACS, and this was true in all CACS strata (Table 5). One mechanistic explanation could be the fact that the prevalence of HRP in patients with severe stenosis was the highest in patients without CAC (55%; 6 of 11) and decreased with increasing CACS (45%; 52 of 116), reflecting the potentially higher vulnerability of plaque in patients with less CAC. The CRESCENT (Computed Tomography versus Exercise Testing in Suspected Coronary Artery Disease) randomized controlled trial, which used a tiered CT approach in patients with stable angina, suggested no need for CTA in patients without CAC and low pre-test probability (<70%) for obstructive CAD (16). In this trial, 98 of 242 patients (39%) without CAC and low pre-test probability did not undergo downstream testing, and no adverse events occurred after a follow-up of 1 year. The shorter follow-up in CRESCENT in comparison with PROMISE (median follow-up: 25 months) might partially explain the demonstrated value of CTA in patients without calcification in our analysis, as cardiovascular events in low-risk groups might not be apparent for years. Also, it is possible that events in PROMISE patients would have been even higher without the use of CTA, as CTA was shown to be associated with a higher proportion of patients newly initiated on aspirin and statins compared with standard of care (4). This demonstrates the need for longer follow-up, especially in cohorts with stable chest pain and expected low incidence of events.

A recent 1,769-patient analysis of the SCOT-HEART trial (33) found that both obstructive (≥70% stenosis) CAD and adverse plaque were associated with cardiac events; however, these associations were not independent of the CACS. This contrasts with our result that CAD-RADS had significant incremental prognostic value beyond both the ASCVD risk score and CAC.

| TABLE 5 Incremental Value of CT-Based Assessment of CAD Using CAD-RADS Categories Beyond Risk Factors and CACS in the Overall Population |
|---|
| **Univariable Model** | **C-Statistic** | **Multivariable Models** | **C-Statistic** | **p Value (Difference Between Models)** |
| ASCVD | 0.629 (0.572–0.687) | | | |
| CACS | 0.657 (0.606–0.708) | ASCVD + CACS | 0.682 (0.629–0.735) | 0.008 |
| CAD-RADS (−HRP) | 0.747 (0.703–0.792) | ASCVD + CACS + CAD-RADS (−HRP) | 0.776 (0.734–0.818) | <0.001 |

ASCVD as continuous variable; CAC as categorical variable (0, 1 to 100, 101 to 400, >400 CACS); CTA per CAD-RADS definition including HRP (vulnerable plaque). *p value shows difference of the stepwise C-statistic comparison between the specific model and the consecutive model. Abbreviations as in Tables 1 and 2.

| TABLE 6 Incremental Value of CT-Based Assessment of CAD Using CAD-RADS Categories Beyond Risk Factors and CACS Across CAC Strata |
|---|
| **CACS Strata** | **C-Stat** | **p Value** | **C-Stat** | **p Value** | **C-Stat** | **p Value** | **C-Stat** | **p Value** |
| **Model 1: ASCVD** | | | | | | | | |
| CACS 0 | 0.539 | | CACS >100 | 0.607 | | CACS >100–400 | 0.551 | | CACS >400 | 0.572 | |
| **Model 2: ASCVD + CAD-RADS (−HRP)** | | | | | | | | |
| CACS 0 | 0.751 | 0.005 | CACS >100 | 0.775 | 0.023 | CACS >100–400 | 0.673 | 0.031 | CACS >400 | 0.697 | 0.041 |

*p value calculations: Model 2 vs. 1. Abbreviations as in Tables 1 and 2.
Besides the differences in demographics and outcomes between the 2 trials, differences in how stenosis and HRP were defined may explain the discrepancy. In SCOT-HEART, stenosis was categorized as normal (0%), nonobstructive (1% to 69%), or obstructive (≤70%). This approach provides less granular information about the degree of nonobstructive stenosis and presence of multivessel disease than CAD-RADS. Furthermore, SCOT-HEART defined adverse plaque as the presence of at least 1 plaque with positive remodeling or low attenuation, in contrast to the CAD-RADS “V” modifier that requires at least 2 HRP features in a single coronary plaque segment. Nevertheless, the unadjusted hazard ratio for adverse/high-risk plaque was similar between the 2 trials (SCOT-HEART HR 3.01 [1.61 to 5.63]; p < 0.001, PROMISE HR 3.08 [2.04 to 4.65]; p < 0.001). In the end, CAD-RADS is currently the preferred reporting system for coronary CTA by the Society of Cardiovascular Computed Tomography (SCCT), American College of Radiology (ACR), North American Society for Cardiovascular Imaging (NASCI), and American College of Cardiology (ACC); therefore, we believe it has the greatest clinical relevance.

**STUDY LIMITATIONS.** First, PROMISE was a pragmatic trial in which the results of CTA were shared with patients and influenced management (34). A slightly modified CAD-RADS was evaluated, with a threshold of 30% instead of 25% between CAD-RADS 1 and 2. Overall, the prevalence of obstructive CAD was rather low, and CAD-RADS categories 4b and 5 were conflated because of small numbers. These data from a contemporary cohort of patients with stable chest pain reflect real-world practice. Patients with known CAD or previous interventions were excluded from PROMISE, and thus we could not investigate the
prognostic value of the CAD-RADS S (stent) or G (graft) category modifiers.

CONCLUSIONS

In PROMISE, a large prospective trial of coronary CTA in patients with stable chest pain and suspected CAD, the CAD-RADS reporting system had greater prognostic value than ASCVD score, CACS, and traditional stenosis-based grading schemes.

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KEY WORDS coronary CT angiography, coronary artery disease, coronary stenosis, coronary artery calcium, CAD-RADS, prognosis, high-risk plaque

APPENDIX For a supplemental figure and tables, please see the online version of this paper.
Coronary CTA-Based CAD-RADS Reporting System and the PROMISE to Predict Cardiac Events*

Ronen Rubinshtein, MD,a Ashraf Hamdan, MDb

Coronary computed tomography angiography (CCTA), which provides high-quality noninvasive images of the heart, great vessels, and coronary vasculature, has been shown to be useful and reliable in the triage of patients with chest pain of possible ischemic origin and specifically in the diagnosis of acute coronary syndrome. Current generation CT scanners (64-slice and higher) require minimal patient cooperation (short breath hold), have improved image quality (better spatial and temporal resolution), and high diagnostic accuracy. CCTA can visualize coronary plaques (including high-risk plaques) and is also gaining a role in the evaluation of coronary stents and bypass grafts.

In 2015, 2 large randomized controlled trials PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) and SCOT-HEART (Scottish Computed Tomography of the Heart Trial) proved its usefulness in patients with chest pain and demonstrated similar or superior health outcomes with CCTA-based strategy compared with traditional functional testing (1–2). Those trials, and many others, which included careful cost-effectiveness analysis, convinced the UK National Institute for Health and Clinical Excellence (NICE) to recommend a CCTA-first strategy in 2016 for patients presenting with nonacute chest pain (3). CCTA-based strategy superiority was demonstrated again later at the 5-year follow-up analysis of the SCOT-HEART trial published in 2018 (4). The number of data and amount of research gathered in the last decade have recently led the European Society of Cardiology (ESC) (2019 ESC guidelines on chronic coronary syndromes) to incorporate CCTA-based diagnostic strategy as a first-line modality (Class I indication) for evaluation of “stable” patients with chest pain and low to intermediate likelihood of having obstructive coronary artery disease (CAD) (5).

Although several anatomic severity scores and combined anatomic and clinical scoring systems have been previously evaluated with CCTA including the Lehman score, the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) score, or others (6), a need to standardization of reporting was raised by many health professionals.

To standardize and facilitate the reporting of CAD on CCTA, in 2016, the Society of Cardiovascular Computed Tomography (SCCT), the American College of Radiology (ACR), and the North American Society for Cardiovascular Imaging (NASCI) established the Coronary Artery Disease-Reporting and Data System (CAD-RADS) (7). CAD-RADS designates CAD severity category (0 to 5) for each CT study based on the severity of coronary stenosis (in which category zero means no stenosis and category 5 is assigned for total vessel occlusion), and it includes several simple modifiers incorporating the presence of left main or triple-vessel CAD, the presence of bypass graft or coronary stent, and even the presence of high-risk plaque characteristics, implying plaque vulnerability and higher event rate. Nondiagnostic studies are also addressed by the scoring system. The CAD-RADS scoring system allocate different interpretation to CCTA findings in patients with stable or acute chest pain and suggest further investigation and/or

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management according to CCTA findings and CAD-RADS category. CAD-RADS was recently shown to be clinically useful and to be associated with 5-year outcome when applied to more than 5,000 patients in the international CONFIRM registry (8).

In this issue of JACC, Bittner et al. (9) report their analysis of the CAD-RADS reporting system among 3,840 eligible patients included in the PROMISE trial and its prognostic value in this group. The authors found that the CAD-RADS scoring system had significantly higher discriminatory value than traditional stenosis-based assessment for prediction of 2-year cardiac outcome events (defined as a composite endpoint of death, myocardial infarction, or hospitalization for unstable angina). Moreover, when compared with no-plaque, a stepwise increase in CAD-RADS category was associated with a stepwise increase in event rate (a “dose-response phenomenon”) and that CAD-RADS itself provided incremental prognostic value beyond traditional CAD risk factors or even beyond the coronary calcium score. Moreover, the added incremental value of CAD-RADS over calcium score persisted in all calcium score strata (9). The authors of the current PROMISE substudy should be commended for this well-conducted prospective study and the meticulous use of a central core laboratory to analyze CCTA results. Despite the high prevalence of patients in the current study with no visible disease (34%) or zero calcium score (39%), the current study was still able to demonstrate CAD-RADS usefulness to predict “hard” events such as death or myocardial infarction. This may have been the contribution of a “core lab” standardized reporting that may have avoided over-diagnosis of coronary stenosis by local site readers and possibly, at least partly, may explain the difference between the CONFIRM and PROMISE-based reports (8,9) in this regard and the somewhat lower predictive value of the CAD-RADS scoring system for hard events in the CONFIRM registry.

Another important finding of the current analysis is in demonstrating the strong relationship between high-risk plaque features and CAD-RADS category and their relation to cardiac adverse events during the follow-up period. High-risk plaque features were indeed more prevalent with higher CAD-RADS category but were actually present in all calcium score categories. The presence of high-risk plaque features (positive remodeling, spotty calcification, low CT attenuation <30 Hounsfield unit [HU], and napkin-ring sign) may have been related to occurrence of adverse cardiac events even in patients with zero or low calcium score in the current study.

The current analysis also shows the additive prognostic value of CAD-RADS scoring system beyond and above the traditional calcium score. This is a powerful finding that demonstrates its usefulness beyond one of the most established imaging risk markers available today for clinicians. The presence of noncalcified plaque among patients with zero calcium score (13% of these patients) and even the presence of high-risk plaque features in those patients is an example of the incremental diagnostic value that CCTA may have over calcium scoring alone. More importantly, in the current analysis, 1.5% of patients with zero calcium scores experienced outcome events during the relatively short follow-up period in this study and therefore should remind us that the “power of zero” (zero calcium score) in symptomatic patients may be slightly weaker than in asymptomatic individuals.

Taken all together, the current study (9) and the previous report from the CONFIRM registry (8) strongly support the use of the CAD-RADS scoring system as the preferred reporting method for CCTA, as suggested by the professional cardiac imaging societies involved in its development. Given the predicted increase in the use of CCTA in patients with chest pain and the recent incorporation of this modality into newer clinical guidelines (5), we should probably PROMISE our patients a comprehensive and clinically useful reporting system that may have a positive effect on their diagnosis and management, and the CAD-RADS scoring and reporting system seems to be a suitable candidate.

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**KEY WORDS** CAD-RADS reporting system, chest pain, coronary artery disease, coronary CT angiography
OBJECTIVES The goal of this study was to determine whether ticagrelor reduces high-sensitivity troponin I concentrations in patients with established coronary artery disease and high-risk coronary plaque.

BACKGROUND High-risk coronary atherosclerotic plaque is associated with higher plasma troponin concentrations suggesting ongoing myocardial injury that may be a target for dual antiplatelet therapy.

METHODS In a randomized, double-blind, placebo-controlled trial, patients with multivessel coronary artery disease underwent coronary 18F-fluoride positron emission tomography/coronary computed tomography scanning and measurement of high-sensitivity cardiac troponin I. Patients were randomized (1:1) to receive ticagrelor 90 mg twice daily or matched placebo. The primary endpoint was troponin I concentration at 30 days in patients with increased coronary 18F-fluoride uptake.

RESULTS In total, 202 patients were randomized to treatment, and 191 met the pre-specified criteria for inclusion in the primary analysis. In patients with increased coronary 18F-fluoride uptake (120 of 191), there was no evidence that ticagrelor had an effect on plasma troponin concentrations at 30 days (ratio of geometric means for ticagrelor vs. placebo: 1.11; 95% confidence interval: 0.90 to 1.36; p = 0.32). Over 1 year, ticagrelor had no effect on troponin concentrations in patients with increased coronary 18F-fluoride uptake (ratio of geometric means: 0.86; 95% confidence interval: 0.63 to 1.17; p = 0.33).

CONCLUSIONS Dual antiplatelet therapy with ticagrelor did not reduce plasma troponin concentrations in patients with high-risk coronary plaque, suggesting that subclinical plaque thrombosis does not contribute to ongoing myocardial injury in this setting. (Dual Antiplatelet Therapy to Reduce Myocardial Injury [DIAMOND]; NCT02110303) (J Am Coll Cardiol Img 2020;13:1549–60) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
Coronary plaque rupture is the most common cause of acute coronary thrombosis and myocardial infarction (1). Patients who have an increased risk of recurrent plaque rupture events may benefit from intensification of secondary prevention therapy (2). In this regard, the addition of a P2Y12 receptor antagonist to low-dose aspirin reduces the risk of cardiovascular death, myocardial infarction, and stroke in patients with recent (3) or previous (4) myocardial infarction. Ticagrelor is an oral, reversible antagonist of the platelet adenosine diphosphate P2Y12 receptor. It provides faster, more potent, and more consistent P2Y12 inhibition than clopidogrel (5). In the PLATO (Platelet Inhibition and Patients Outcomes) trial of 18,624 patients presenting with acute coronary syndrome, ticagrelor was superior to clopidogrel for the prevention of cardiovascular events and death (3). Moreover, the prolonged use of dual antiplatelet therapy after myocardial infarction continues to reduce cardiovascular events, albeit at the expense of increased rates of major bleeding (4). Thus, there is a clinical need to improve the risk stratification of patients to enable physicians to better select “vulnerable” patients who may benefit from extended duration of dual antiplatelet therapy.

A novel approach for assessing patients at high risk of coronary plaque rupture is using positron emission tomography (PET) and coronary computed tomography angiography (CTA). This technique uses the radiotracer 18F-fluoride to identify regions of increased disease activity in coronary artery plaques. Previous studies have shown that coronary 18F-fluoride uptake correlates with a high-risk cardiovascular profile and identifies ruptured coronary plaques in patients with recent myocardial infarction (6,7). Importantly, we have previously reported an association between increased coronary 18F-fluoride uptake and higher plasma high-sensitivity cardiac troponin I concentrations in patients with stable coronary artery disease (7). Silent plaque rupture is common, and subclinical plaque thrombus formation is a frequent incidental post-mortem finding in patients with multivessel coronary artery disease who have died of noncardiovascular causes (8). This result suggests that coronary 18F-fluoride uptake may identify high-risk plaque that is associated with thrombus formation and subclinical myocardial injury from microemboli. If correct, this would potentially be modifiable with intensive dual antiplatelet therapy.

The current study assessed whether coronary 18F-fluoride activity identifies patients with stable multivessel coronary artery disease who respond favorably to ticagrelor as assessed by a reduction in high-sensitivity cardiac troponin I concentrations.

**METHODS**

**STUDY DESIGN.** This investigator-initiated, double-blind, randomized, parallel-group, placebo-controlled trial was conducted at a single center in Edinburgh, United Kingdom. The study was approved by the local institutional review board, the Scottish Research Ethics Committee (REC reference: 14/SS/0089), the Medicines and Healthcare products Regulatory Agency, and the United Kingdom Administration of Radiation Substances Advisory Committee. It was performed in accordance with the Declaration of Helsinki. All patients provided written informed consent before any study procedures were initiated.

**STUDY POPULATION.** Patients were recruited between March 2015 and March 2017. Patients were included if they were ≥40 years of age and already receiving aspirin therapy with angiographically proven multivessel coronary artery disease, defined as at least 2 major epicardial vessels with any combination of either: 1) >50% luminal stenosis; or 2) previous revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery). Patients were excluded if they had any of the following criteria:

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**ABBREVIATIONS AND ACRONYMS**

ADP = adenosine diphosphate

CI = confidence interval

CTA = computed tomography angiography

ECG = electrocardiogram

PE = phycoerythrin

PET = positron emission tomography

TBR = tissue to background ratio

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**AUTHOR INSTRUCTIONS PAGE.**
an acute coronary syndrome within the last 12 months, any ongoing indication for dual antiplatelet therapy, concurrent thienopyridine (clopidogrel or prasugrel) or oral anticoagulant therapy, or percutaneous coronary intervention or coronary artery bypass graft surgery within the last 3 months. Full eligibility criteria are provided in Supplemental Table 1.

**TRIAL INTERVENTION AND RANDOMIZATION.** Patients were randomly assigned 1:1 to receive either ticagrelor 90 mg twice daily or matched placebo tablets (AstraZeneca, Cambridge, United Kingdom). Randomization was performed by using a Web-based system that ensured allocation concealment, with treatment allocation incorporating minimization based on age (<65 and ≥65 years of age), sex, baseline plasma high-sensitivity troponin I concentration (<5.1 and >5.1 ng/l), and the presence or absence of coronary 18F-fluoride uptake. A random element was included with a 1 in 10 chance of the determined treatment allocation being switched to the other treatment arm.

**STUDY PROCEDURES.** All patients underwent a baseline assessment to confirm eligibility and measurement of plasma high-sensitivity cardiac troponin I concentration and platelet-monocyte aggregates. An electrocardiogram (ECG)-gated 18F-fluoride PET/coronary CTA was performed after patients had received 50 to 100 mg of oral metoprolol if their resting heart rate was >65 beats/min before the intravenous administration of 250 MBq of 18F-fluoride. After 60 min, patients were imaged with a hybrid PET/CT scanner (64-multidetector Biograph mCT, Siemens Medical Systems, Erlangen, Germany). Attenuation correction CT scans were performed before the acquisition of ECG-gated list-mode PET data using a single 30-min bed position centered on the heart. Finally, an ECG-gated coronary CTA was performed in mid-diastole during held expiration after administration of sublingual glyceryl trinitrate.

**IMAGE ANALYSIS.** PET images were reconstructed in diastole (50% to 75% of the R-R interval, 2 iterations, 21 subsets; Siemens Ultra-HD algorithm) and fused with contrast-enhanced coronary CTA. Analysis of the CT images was performed by using dedicated software (Vitrea Advanced, Toshiba Medical Systems, Otawara, Tochigi Prefecture, Japan) with multiplanar reformatting for plaque analysis as required. Coronary arteries with a diameter ≥2 mm were assessed according to the 18-segment Society of Cardiovascular Computed Tomography model. Qualitative and semiquantitative analysis of the PET images was performed by trained observers using an OsiriX workstation (OsiriX version 3.5.1, 64-bit, OsiriX Imaging Software, Geneva, Switzerland).

The analysis of coronary 18F-fluoride activity has been previously described (6,7). In brief, visual assessment for increased coronary 18F-fluoride activity was performed on both a per-patient level and a per-segment basis. For a signal to be co-localized to the coronary artery, an atherosclerotic plaque had to be present on the coronary CTA image, and the increased pattern of radiotracer had to arise from the coronary artery and follow its course over >5 mm in 3 dimensions on orthogonal views. Semi-quantitative PET analysis was undertaken for all proximal coronary segments in addition to any atherosclerotic segment with focal 18F-fluoride activity as described earlier. Maximum standardized uptake values were measured within regions of interest. Correction was made for uptake in a referent proximal coronary plaque with no evidence of increased 18F-fluoride activity. To calculate coronary target to background ratios (TBRs), coronary maximum standardized uptake values were divided by these background measures, providing TBR\text{MAX}. Coronary 18F-fluoride activity with TBR\text{MAX} >1.25 was classified a high-risk plaque.

**HIGH-SENSITIVITY CARDIAC TROPONIN I.** Plasma high-sensitivity cardiac troponin I concentrations were measured by using the ARCHITECT STAT assay (Abbott Laboratories, Abbott Park, Illinois). The limit of detection is 1.0 ng/l with an interassay coefficient of variation <10% at 4.7 ng/l (9). The upper reference limit (99th centile) based on 4,590 samples from healthy men and women is 34 ng/l for men and 16 ng/l for women (10). Samples were collected at baseline, 30 days, and 3, 6, 9, and 12 months. A value of 0.5 ng/l was imputed for troponin values below the limit of detection.

**PLATELET FUNCTION ANALYSIS.** Platelet and monocyte activation in response to adenosine diphosphate (ADP) was determined according to flow cytometry, as previously described (11). These analyses were performed by a single technician blinded to study allocation with the results of these investigations withheld from the study team until after trial database lock. Briefly, peripheral venous blood was obtained from all participants at the baseline and 1-month visits. Blood was drawn by clean venipuncture of a large antecubital vein using a 19-gauge needle, and care was taken to ensure a smooth blood draw without venous stasis. Blood was collected into tubes containing a direct thrombin inhibitor, D-phenylalanine-L-prolyl-L-arginine chloromethyl ketone (Cambridge Biosciences, Cambridge, United Kingdom). Tubes were gently inverted to ensure mixing of whole blood with anticoagulant.
Immunolabeling and flow cytometry were performed in whole blood to avoid centrifugation and washing steps, which can lead to artifactual platelet activation. All chemicals were obtained from BD Biosciences (Oxford, United Kingdom). Aliquots of whole blood (50 μl) were incubated with anti-CD14-Allophycocyanin, anti-CD42a-fluorescein isothiocyanate, anti-CD11b-PE-Cyanine7, anti-CD62p-phycocerythrin (PE), and isotype-matched controls for 20 min at room temperature in Eppendorf tubes (Eppendorf, Hamburg, Germany) with and without ADP (at a final concentration of 20 μmol/l). Thereafter, samples were fixed with 1% paraformaldehyde (P-selectin) or FACS Lysing (Becton Dickinson) (platelet-monocyte aggregates). All samples were analyzed within 24 h by using a FACSCalibur flow cytometer (Becton Dickinson, Franklin Lakes, New Jersey). Data analysis was performed by using FlowJo v10 (Treestar, Woodburn, Oregon). A medium flow setting was used to minimize leukocyte-platelet coincident events. Monocytes were identified based on their forward and side scatter characteristics and then by triggering on FL-4 to identify CD14-PE-positive monocytes and exclude large granular lymphocytes. For each measurement, a minimum of 2,500 monocytes were collected. Platelet-monocyte aggregates were defined as monocytes positive for CD42a. All results are expressed as geometric mean of fluorescence. P-selectin expression was defined as CD42a-fluorescein isothiocyanate–positive platelets that were also positive for CD62p-PE.

**STUDY ENDPOINTS.** The pre-specified primary endpoint was high-sensitivity cardiac troponin I concentrations at 30 days in patients with increased coronary \(^{18}\text{F}\)-fluoride activity. Secondary endpoints were plasma high-sensitivity cardiac troponin I concentration at 30 days in patients without coronary \(^{18}\text{F}\)-fluoride activity, and plasma high-sensitivity troponin I concentration over 1 year. Adverse events were recorded in all patients who received a single dose of study medication and included bleeding events categorized according to PLATO criteria as major life-threatening, other major, minor, or minimal bleeding (3).

**SAMPLE SIZE.** In patients with increased coronary \(^{18}\text{F}\)-fluoride uptake, we previously reported that mean ± SD troponin concentrations were more than double those in patients without increased coronary \(^{18}\text{F}\)-fluoride uptake (7.9 ± 9.3 ng/l vs. 3.1 ± 1.9 ng/l; p = 0.047) (7). It was estimated that ticagrelor would reduce the troponin concentration by one-half. Forty-eight patients per treatment arm were required to achieve 80% power at 2-sided p < 0.05. After allowing for 15% dropout, we estimated that 55 patients will be required per treatment arm. Previous studies had found that 45% of patients with advanced but stable coronary artery disease exhibited increased coronary \(^{18}\text{F}\)-fluoride uptake; thus, a total sample size of 250 patients was estimated to be required to identify 110 patients with increased coronary \(^{18}\text{F}\)-fluoride activity. Termination of further recruitment could be authorized by the trial steering committee once a per-protocol population of 110 patients with increased coronary \(^{18}\text{F}\)-fluoride activity had been randomized to treatment and completed the primary endpoint at 30 days.

**STATISTICAL ANALYSIS.** Categorical data are presented by using counts and proportions, and continuous variables are presented by using mean ± SD, median (interquartile range), minimum, maximum, and number of patients. Participants were removed from formal statistical analysis where data were missing for that outcome variable. All analyses (except safety) were performed on a per-protocol population that excluded participants without a blood sample, or whose compliance was <80% for the study medication, at the 30-day visit. For the primary analysis, the change in troponin I concentration from baseline to 30 days was compared between the 2 treatment groups (ticagrelor and placebo) by using linear regression, adjusting for the minimization variables in patients with increased coronary \(^{18}\text{F}\)-fluoride uptake. Before analysis, tests for normality were undertaken and, where data were skewed, logarithmic transformation was performed. Central estimates and 95% confidence intervals (CIs) were calculated. Similar analyses were performed for secondary outcomes.

In post hoc testing, we compared baseline troponin concentrations between patients with and without evidence of coronary \(^{18}\text{F}\)-fluoride activity and also confirmed treatment efficacy by comparison of ADP-stimulated platelet activation between the 2 trial intervention groups (ticagrelor vs. placebo). For 1-year evaluation of changes in cardiac troponin I concentrations, an adjusted linear regression model (adjusted for the minimization variables) was generated and descriptive statistics were presented for the AUC. For missing values, the value was imputed linearly from adjacent measurements. Adjustment for age was performed as a linear term. To determine whether there was efficacy of ticagrelor using a baseline troponin I concentration ≥5 ng/l, a post hoc comparison was made between groups using the method described in the primary analysis. For all analyses, a 2-sided p value <0.05 was taken as statistically significant. Statistical analysis was performed by using SAS version 9.4 (SAS Institute, Inc., Cary, North
Carolina) with the primary analysis validated by a second statistician in the Edinburgh Clinical Trials Unit. Post hoc analyses were performed separately from the primary statistical analysis plan using R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria) by 1 of the authors (P.D.A.).

**RESULTS**

**STUDY POPULATION.** A total of 361 patients were screened and 202 patients were randomized to treatment after baseline coronary ¹⁸F-fluoride PET/coronary CTA imaging (Figure 1). Eleven patients discontinued the study early due to withdrawal of consent (n = 1), new diagnosis of malignancy on baseline PET/coronary CTA (n = 1), <80% compliance with study medication at 30 days (n = 8), and sudden unexpected death before receiving study medication (n = 1). The randomized groups were well matched for the presence of cardiovascular risk factors and represented a high-risk cohort, with 70% having a history of acute coronary syndrome (median 2.25 years before study enrollment) (Table 1). A per-protocol population of 191 patients (mean age: 65.9 ± 8.3 years; 80% male) had both blood sampling at 30 days and ≥80% compliance with the study medication, comprising 94 patients in the ticagrelor group and 97 patients in the placebo group. A total of 120 (62.8%) patients had evidence of coronary ¹⁸F-fluoride activity in at least 1 epicardial vessel (Table 2, Figure 2).

The geometric mean troponin I concentration at baseline was 3.8 (geometric SD: 2.9) ng/l in patients...
with increased coronary $^{18}$F-fluoride activity compared with 2.5 (geometric SD: 2.6) ng/l in those without uptake ($p = 0.004$) (Table 2) from a post hoc analysis.

**TABLE 2 Plasma High-Sensitivity Cardiac Troponin I Concentration in the Per-Protocol Population**

| Overall (N = 191) | Ticagrelor (n = 94) | Placebo (n = 97) | p Value* |
|-------------------|---------------------|------------------|----------|
| Coronary $^{18}$F-fluoride uptake, ng/l | | | |
| N | 120 | 59 | 61 |
| Baseline | 3.8 ± 2.9 | 4.2 ± 2.9 | 3.5 ± 3.0 | 0.197 |
| 30 days | 3.6 ± 2.7 | 4.1 ± 2.5 | 3.2 ± 2.9 | 0.072 |
| Ratio of 30 days to baseline | 0.95 ± 1.87 | 0.97 ± 2.13 | 0.93 ± 1.59 | 0.907 |
| No coronary $^{18}$F-fluoride uptake, ng/l | | | |
| N | 71 | 35 | 36 |
| Baseline | 2.5 ± 2.6 | 2.5 ± 2.8 | 2.4 ± 2.4 | 0.872 |
| 30 days | 2.4 ± 2.7 | 2.4 ± 2.8 | 2.3 ± 2.6 | 0.877 |
| Ratio of 30 days to baseline | 0.97 ± 1.68 | 0.97 ± 1.77 | 0.96 ± 1.59 | 0.907 |

Values are geometric mean ± geometric SD, back-transformed from log-transformed values, unless otherwise indicated. *Post-hoc analysis.
We explored whether a reduction in cardiac troponin I could be shown over 12 months. Twelve-month troponin I concentrations were measured in 183 (95.8%) patients, comprising 91 (96.8%) patients in the ticagrelor group and 92 (94.8%) patients in the placebo group. There was no difference in area under the concentration curve of troponin I over 12 months between the ticagrelor and placebo groups (ratio of geometric means: 0.92; 95% CI: 0.74 to 1.13; p = 0.42) (Figure 4, Table 4). Post hoc analysis of the subset of patients with a baseline troponin I concentration $\geq 5$ ng/l (ticagrelor: n = 34, baseline geometric mean = 10.3 ng/l; placebo: n = 33, baseline geometric mean = 8.7 ng/l) found no change in troponin I concentration at 30 days (p = 0.89) or 12 months (p = 0.86) (Supplemental Figure 1, Supplemental Table 2).

SAFETY OUTCOMES. There were no suspected unexpected serious adverse reactions over the course of the study. Serious adverse events occurred in 7 (7%) of 100 patients who received at least 1 single dose of ticagrelor and 15 (11.9%) of 101 patients who were administered placebo (Supplemental Table 3). There were no reported major life-threatening or other major bleeding events over the course of the study. Minimal bleeding events (bruising) were reported in 64 (64.0%) patients in the ticagrelor group and 12 (11.9%) patients in the placebo group (Supplemental Table 4). Dyspnea episodes occurred in 24 (24%) patients in the ticagrelor group compared with 8 (7.9%) patients in the placebo group at 1 year.

DISCUSSION

In this randomized, placebo-controlled trial, we found no evidence that ticagrelor 90 mg twice daily reduces plasma high-sensitivity cardiac troponin I concentrations in patients with high-risk plaque and established multivessel coronary artery disease (Central Illustration). This outcome suggests that, in patients with high-risk coronary plaque, plasma cardiac troponin I concentrations are not attributable to subclinical myocardial injury from thrombotic microembolic injury.

The current study has several important strengths. This trial is the first to use PET/coronary CTA imaging with $^{18}$F-fluoride to identify patients with high-risk coronary plaque who may be at heightened risk of future coronary events and thereby have the most to gain from potent dual antiplatelet therapies. It is also the largest trial to date using coronary plaque PET imaging. Although previous PET studies have used $^{18}$F-fluorodeoxyglucose to visualize inflammation within the carotid arteries as a surrogate to guide intensification of atherosclerotic therapy (12,13), the coronary and cerebral vascular beds differ both with respect to their underlying molecular pathophysiology and also in response to the treatment
effect using ticagrelor (3,14). Second, our unique study design enabled high-risk patients with multi-vessel coronary disease and in vivo evidence of disease activity to be precisely phenotyped before randomization in a manner that can seldom be achieved in larger clinical outcome trials (3,15). Finally, this study is the first prospective randomized controlled trial to use high-sensitivity cardiac troponin I concentrations as a surrogate outcome measure for assessing future cardiovascular risk.

In trying to understand why P2Y12 inhibition did not reduce cardiac troponin in this study, it is worth addressing some of the underlying assumptions in the trial design. Does coronary 18F-fluoride activity identify patients with high-risk plaque? Studies have found that 18F-fluoride holds potential in identifying culprit plaques in the coronary circulation by classifying patients who have a high-risk cardiovascular phenotype and culprit plaque rupture after type 1 myocardial infarction (6,7). Histological validation indicates that 18F-fluoride preferentially binds to

### TABLE 3 Plasma High-Sensitivity Cardiac Troponin I Concentration at 30 Days for the Per-Protocol Population

|                | Adjusted Geometric Mean (GSE) | Ratio of Geometric Means (95% CI) | p Value |
|----------------|-------------------------------|-----------------------------------|---------|
|                | Ticagrelor Placebo             |                                   |         |
| Cardiac troponin I, ng/l (18F-fluoride activity) | 3.8 (1.1) 3.4 (1.1) | 1.11 (0.90 to 1.36) | 0.32    |
| Cardiac troponin I, ng/l (no 18F-fluoride activity) | 2.4 (1.1) 2.3 (1.1) | 1.02 (0.80 to 1.31) | 0.87    |

Estimates are back-transformed estimates from analysis of log-transformed values at 30 days adjusting for age, sex, and log-transformed baseline troponin. Ratio of geometric means is ticagrelor divided by placebo. CI = confidence interval; GSE = geometric standard error.
microcalcification in regions of plaque mineralization, a key component of high-risk plaque (16). Hydroxyapatite, the most common form of atherosclerotic microcalcification, is extruded from apoptotic macrophages and accumulates within necrotic cores, where it may destabilize the structural integrity of the fibrous cap (17,18). The identification of abnormal material composition of the arterial wall has clinical relevance, as these regions may lead to atherosclerotic plaque rupture manifesting as myocardial infarction, stroke, or aneurysm rupture (7,19,20). In our cohort, the frequency of 18F-fluoride activity (>60%) in stable coronary artery disease is similar to previous estimates in patients with a high burden of coronary artery disease and previous myocardial infarction (6). This research confirms the high prevalence of coronary 18F-fluoride activity in stable patients with multivessel coronary artery disease who had intensification of antiplatelet therapy may be considered.

A key question is whether troponin measurements below the 99th centile reflect subclinical plaque rupture with accompanying distal microvascular embolization, as has previously been posited (21). In this regard, some therapies directed at reducing the risk of atherosclerotic plaque rupture, such as pravastatin, both modify troponin concentrations and reduce the risk of myocardial infarction (22,23). In contrast, strategies that have failed to show a reduction in cardiovascular events in the context of stable coronary artery disease, such as coronary revascularization, attenuation of plaque inflammation, and

### TABLE 4 Plasma High-Sensitivity Cardiac Troponin I Concentration Over 1 Year for the Per-Protocol Population

|                      | Adjusted Geometric Mean (GSE) | Ratio of Geometric Means (95% CI) | p Value |
|----------------------|-------------------------------|----------------------------------|---------|
|                      | Ticagrelor                    | Placebo                          |         |
| AUC from 30 days to 1 yr (18F-fluoride activity) | 3.7 (1.1) | 4.4 (1.1) | 0.86 (0.63 to 1.17) | 0.33 |
| AUC from 30 days to 1 yr (no 18F-fluoride activity) | 2.4 (1.1) | 2.3 (1.1) | 1.04 (0.84 to 1.28) | 0.70 |

Estimates are back-transformed estimates from analysis of log-transformed values area under curve (AUC) from 30 days to 1 year adjusting for age, sex, and log-transformed baseline troponin. Ratio of geometric means is ticagrelor divided by placebo.

Abbreviations as in Table 3.
inhaled therapies for respiratory disease, have not correlated with a reduction in serial troponin concentration (24–26). If subclinical plaque thrombosis is the dominant mechanism underlying detectable troponin I concentrations in patients with stable coronary artery disease, a reduction in troponin I concentration would be expected after administration of potent antiplatelet therapy. The lack of response to ticagrelor in this study would suggest that other contributing mechanisms to myocardial injury should be considered. The emergence of newer therapies (e.g., sodium-glucose cotransporter 2 inhibition) that lower blood pressure may reduce troponin concentrations through an improvement in myocardial remodeling, further raising doubts over the subclinical plaque rupture hypothesis (27,28). In this study, high-sensitivity cardiac troponin I concentrations were higher in patients with 18F-fluoride activity, although the differences were small and below the established risk stratification threshold of 5 ng/l (9,22,29). It therefore seems unlikely that troponin at these concentrations reflects subclinical plaque rupture, and it is perhaps unsurprising that ticagrelor treatment did not result in an early or late reduction in troponin concentration.
Previous reports have suggested that there is a high incidence of subclinical intracoronary thrombus in patients with apparently stable coronary artery disease. Indeed, some have suggested that this outcome occurs in as many as 1 in 7 patients (8). If this is the case, it would seem that intracoronary thrombus does not track with troponin. This suggests that better noninvasive markers of coronary thrombosis, such as novel PET tracers (30) or noninvasive imaging (31), are needed to use as biomarkers of cardiovascular risk and antithrombotic therapeutic efficacy.

STUDY LIMITATIONS. The current study had a modest sample size to assess clinical outcomes of ticagrelor use in patients with stable coronary artery disease and coronary 18F-fluoride activity. The low baseline troponin I concentrations observed in this study may have limited power to show the benefit of ticagrelor in this population. Enrichment of the population by selecting patients with higher troponin I concentrations before study entry may need to be considered for future trials. It should also be acknowledged that this study was conducted in a single center with expertise in coronary 18F-fluoride imaging, and the methods for analyzing coronary 18F-fluoride activity are subject to a number of operator- and scan-dependent variables. Although recent reports have suggested that coronary 18F-fluoride activity may hold prognostic value in stratifying high-risk populations (32), larger prospective studies evaluating the prognostic utility of coronary 18F-fluoride activity in patients with cardiovascular disease are ongoing (NCT02278211).

CONCLUSIONS

In patients with multivessel coronary artery disease and in vivo coronary 18F-fluoride activity, we found no evidence that intensification of antiplatelet therapy using ticagrelor 90 mg twice daily reduces plasma high-sensitivity cardiac troponin I concentration at 30 days or 1 year. These findings suggest that in this group of patients, plasma high-sensitivity cardiac troponin I concentrations may not be a suitable marker for predicting efficacy of P2Y12 inhibition.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: High-risk coronary artery plaque and plasma high-sensitivity cardiac troponin I concentrations are associated with increased rates of cardiovascular events.

COMPETENCY IN PATIENT CARE: Patients with stable coronary artery disease and an increased risk of cardiovascular events may benefit from extended therapy with P2Y12 inhibition.

TRANSLATIONAL OUTLOOK 1: Although this study used an early biomarker (30-day plasma high-sensitivity cardiac troponin I concentration) to evaluate drug efficacy, coronary 18F-fluoride activity did not seem to be useful in identifying patients who may benefit from extended P2Y12 inhibition.

TRANSLATIONAL OUTLOOK 2: A detailed phenotype of coronary plaque disease activity using PET is both feasible and practical in the setting of a randomized, placebo-controlled trial.

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KEY WORDS 18F-fluoride, myocardial infarction, troponin

APPENDIX For supplemental tables and a figure, please see the online version of this paper.
With improvements in systems of care for acute myocardial infarction (MI), preventative therapies, and lifestyle modifications, overall mortality rates among patients with coronary artery disease (CAD) have declined (1). However, patients with CAD are a diverse cohort, and their risk of major adverse cardiovascular events can vary substantially (2). Accordingly, ongoing efforts to identify at-risk patients and personalize treatment approaches for patients with CAD are needed.

Two decades ago, the concept of therapeutic “plaque passivation” was developed; in theory, medical therapies might be applied to those with coronary plaques prone to disruption, such that risk for progression to MI might be prevented. With tools to detect such “vulnerable” high-risk plaques, application of therapies to stabilize or “passivate” the coronary artery might be expected to improve outcomes in affected patients (3). Options for this approach included aggressive lipid lowering, anti-inflammatory therapies, and antiplatelet therapies, along with the concept of “plaque sealing” by using percutaneous coronary intervention to cover plaques likely to progress to disruption. None of these approaches gained traction, however, as the ability to accurately, easily, and reproducibly detect plaques prone to rupture in a cost-effective manner was limited. Most efforts focused on invasive imaging techniques. Although concentrations of cardiac troponin informed benefit from antiplatelet therapy in those with acute coronary syndrome (4), use of biomarkers to inform therapies in more stable patients remained limited due to the inability of conventional assays to sensitively measure troponin in more stable situations. This has changed, however.

Recent refinement in troponin assays has facilitated the ability to measure troponin concentrations in ≥50% of normal individuals (5). In this regard, the prevalence of myocardial injury (defined as an elevated troponin concentration >99th percentile) among patients with stable CAD varies depending on the clinical setting in which the troponin concentration was measured; however, it may be as high as 54% in patients with obstructive CAD (6). Among patients with obstructive CAD, myocardial injury is an independent predictor of all-cause mortality, cardiovascular mortality, and incident MI (6). Curiously, this risk seems to be within months of index high-sensitivity cardiac troponin (hscTn) measurement (but not longer), implying that the biomarker reflects an active coronary lesion (7). This theory has been borne out by studies reporting modest associations between higher concentrations of hscTn with more diffuse CAD and similar associations with high-risk plaque (8-9). This creates a hypothetical construct linking plaque instability to processes leading to myocardial injury, notably including microembolism and “downstream” myocardial necrosis, reflected in increased hscTn concentrations. Importantly, a reduction in hscTn concentration is independently associated with lower risk of subsequent MI and death related to coronary heart disease (10), suggesting that strategies to contain myocardial injury through plaque-stabilizing therapies might be a rational approach.

In this issue of iJACC, Moss et al. (11) sought to evaluate the utility of ticagrelor among patients with clinically stable multivessel CAD and high-risk...
coronary plaque as determined by coronary 
^{18}F\text{-fluoride positron emission tomography/coronary computed tomography angiography imaging. Given links between high-risk plaque, antiplatelet therapy, and cardiac troponin concentrations, this approach is a logical one for “treating” myocardial injury (12). The investigators randomized 202 patients ≥40 years of age with stable multivessel CAD, who were already receiving aspirin, to receive either ticagrelor or placebo. The primary endpoint of the trial was hscTnI concentrations at 30 days among patients with increased coronary 
^{18}F\text{-fluoride activity (11). Notably, patients were enrolled regardless of their baseline hscTnI concentration. The trial was powered based on an estimated 50% reduction in hscTnI concentrations among those receiving ticagrelor at 30 days. The investigators found evidence of elevated coronary 
^{18}F\text{-fluoride activity in at least 1 vessel in 62.8% of patients. The mean baseline hscTnI concentrations were low: 3.8 ng/l among those with increased coronary 
^{18}F\text{-fluoride activity and 2.5 ng/l in those without. There was no statistically significant reduction in 30-day hscTnI concentrations among patients who received ticagrelor with/without increased coronary 
^{18}F\text{-fluoride activity. In post hoc analyses, there was no difference in troponin concentrations at 12 months’ follow-up or among those with a baseline hscTnI concentration ≥5 ng/l. These results suggest ticagrelor might not reduce myocardial injury associated with high-risk plaques.}

Strengths of the trial (11) include the novel use of positron emission tomography/coronary computed tomography angiography imaging with 
^{18}F\text{-fluoride to identify patients with high-risk coronary plaque and the exploration of strategies to mitigate hscTnI in such patients. Limitations include underpowering the trial with an overestimation of the potential impact of ticagrelor on hscTnI at 30 days, enrollment of patients regardless of their baseline troponin concentration, and a lower than expected hscTnI concentration at baseline, putting many patients in a range of higher imprecision of the assay used. Perhaps the largest limitation of the study (11) is the assumption that concentrations of hscTnI associated with high-risk plaque are linked to a biologic process that may be treated with antiplatelet therapy; of course, this is why a study such as this is performed—to explore plausible means by which to contain myocardial injury. Selection of intensive antiplatelet therapy is logical, and although the results were disappointing, it is not to say this approach cannot work; that said, it is necessary to concede that associations between concentrations of hscTn and high-risk plaque are modest, and myocardial injury is often seen in the absence of acute ischemia (13,14). Although ticagrelor did not reduce hscTn concentrations even in those with higher concentrations of the biomarker, relatively few subjects fell into this category, potentially increasing the risk for a type II error. Indeed, it is tempting to speculate that the specificity for an ischemic mechanism for myocardial injury would be enriched at higher troponin concentrations.

Moss et al. (11) are to be congratulated for taking this quest on: 20 years after the initial concepts of plaque “passivation,” we are still actively trying to find ways to mitigate the higher risk plaque vulnerable to disruption. With more refinements in ability to assess and understand such coronary lesions, the hope would be for a precision-based approach to further reduce risk for acute MI.

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KEY WORDS antiplatelet therapy, coronary angiography, coronary artery disease, troponin
Myocardial Efficiency
A Fundamental Physiological Concept on the Verge of Clinical Impact

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ABSTRACT

Myocardial external efficiency is the relation of mechanical energy generated by the left (or right) ventricle to the consumed chemical energy from aerobic metabolism. Efficiency can be calculated invasively, and, more importantly, noninvasively by using positron emission tomography, providing a single parameter by which to judge the adequacy of myocardial metabolism to generated mechanical output. This parameter has been found to be impaired in heart failure of myocardial or valvular etiology, and it changes in a characteristic manner with medical or interventional cardiac therapy. The authors discuss the concept, strengths, and limitations, known applications, and future perspectives of the use of myocardial efficiency. (J Am Coll Cardiol Img 2020;13:1564–76) © 2020 by the American College of Cardiology Foundation.

How do we know if cardiac function is normal or abnormal? We continue to lack an accurate noninvasive marker of the adequacy of cardiac function at a time when heart failure is becoming the dominant cardiovascular syndrome. The difficulties in succinctly defining heart failure speak to this. Often, left ventricular (LV) ejection fraction, stroke volume or stroke work (stroke work = stroke volume × mean arterial pressure), or global longitudinal strain are used as substitutes for cardiac function. These parameters can be measured relatively easily noninvasively, although with considerable margin of error. However, they are all strongly load dependent (1). The long quest for a load-independent reliable measure of contractility that can be obtained noninvasively has not identified a practical candidate. Furthermore, symptoms of heart failure or exercise capacity do not correlate well with common indices of cardiac function, especially in the gray zone around their lower limits (2). Specifically, the lower limit of normal cardiac function and the beginning of heart failure are difficult to identify. It is thus appealing to revisit an entirely different approach that was originally proposed 70 years ago (3), namely,
cardiac "mechanical efficiency which built on early observations that an increase in cardiac work was accompanied by an increase in oxygen uptake (4).

THE CONCEPT OF CARDIAC EFFICIENCY

Mechanical efficiency is a physics and engineering concept describing the ratio of mechanical work performed by a device (in the numerator) and the necessary energy input (in the denominator) within a given time interval, for example a heart beat. The ideal, and unobtainable, value is 1. Combustion engines of cars for example reach a mechanical efficiency of approximately 40% under ideal conditions. For the aerobically operating LV, this concept can be applied by comparing mechanical (pump) work performed to oxidative energy metabolism of the ventricle. Calculating the mechanical work of the ventricle ideally would require continuously measuring the force and wall curvature of the LV, which is extremely difficult even under experimental conditions. Instead, pressure is usually substituted for force, and mechanical work of the LV is classically described as the area of the pressure-volume relationship, encompassing external work (the area of the proper pressure-volume loop) and potential work or energy (Figure 1). However, this simplification does not account for the influence of chamber size on wall stress and therefore may be flawed when comparing LVs of substantially different sizes. Noninvasively, external mechanical work is approximated as the product of stroke volume and mean arterial pressure. Furthermore, the chemical energy generated by oxidative metabolism in the myocardium can be estimated invasively or noninvasively. Myocardium generates energy by the oxidative metabolism of fatty acids and glucose. Assuming aerobic conditions (no ischemia), the oxidative metabolism of acetate (from the glycolysis of glucose or beta oxidation of fatty acids) is the only energy supply of the myocardium; for instructive details see (4). Thus, oxygen and acetate uptake of the heart are linearly related to the energy available to the myocardium from metabolism. This energy input is normalized for myocardial mass to provide an oxygen uptake per time and mass unit (MVO2). Oxygen uptake can be measured invasively by obtaining the arteriovenous difference in oxygen content between aortic or coronary arterial blood and sinus venous blood. This difference is multiplied by the coronary sinus blood flow rate from thermodilution measurements in the coronary sinus to yield the myocardial oxygen uptake over time. Alternatively, oxygen uptake is measured noninvasively, either by measuring radioactive isotope kinetics for inhaled 15O-labeled oxygen gas (O2) or by measuring injected 11C-carbon isotope kinetics for acetate uptake by positron emission tomography (PET) (Figure 2). Use of 15O-O2, however, because of interference from lung oxygen and other problems, is technically complex and rarely used (5); therefore, acetate clearance is generally used to estimate oxygen uptake (6). Work and metabolism of cardiac chambers other than the LV are neglected. These noninvasive approaches have been validated invasively in animal experiments (6,7) and in humans, although only in small cohorts (8). Hence, the resulting entirely noninvasive formula for mechanical external efficiency (MEE) of the heart incorporating unit conversion factors is as follows:

\[
MEE = \frac{MAP \times SV \times HR \times 1.33 \times 10^{-4}}{MVO2 \times LVM \times 20}
\] (Equation 1)

with MAP indicating mean arterial pressure (mm Hg), SV indicating stroke volume (ml/beat), HR indicating heart rate (beats/min), MVO2 indicating myocardial oxygen uptake (ml/g/min), and LVM indicating LV myocardial mass (g). However, several simplifications and assumptions are necessary for this approach, as follows:

- The work and metabolism of the right ventricle and atria are not included;
- The estimation of stroke volume and mass is within the limits of accuracy of the underlying methods (e.g., echocardiography, cardiovascular magnetic resonance [CMR], cardiac computed tomography [CT], or PET);
- The substitution of stroke work by the product of stroke volume and mean arterial pressure is an approximation, because central aortic pressures are not equal to peripheral arterial pressures as measured by cuff manometry. Also, the stroke volume generated by the LV may be larger than the effective (forward) stroke volume in the case of mitral or aortic regurgitation. In this case, the work generated by the ventricle is partially lost by the valvular regurgitation, rendering overall cardiac performance less efficient even if myocardial efficiency is preserved;
- In the past, stroke volume and mass (by echocardiography, CMR, or CT), blood pressure, and myocardial oxygen uptake (by PET) could not be measured strictly simultaneously. However, stroke volume and mass can now be directly calculated from PET tracer kinetics (9,10), thus obviating the need for another imaging modality (Central Illustration);
• The so-called internal cardiac work is neglected. This is mechanical work done by the myocardium, not generating stroke volume or blood pressure but, instead, stretching elastic elements in the myocardium (therefore, sometimes also called potential energy) (Figure 1). Internal cardiac work implies the transferal of energy from systole to diastole by storage of potential energy in the elastic elements in the ventricular wall during systole, which is released in diastole when the ventricle relaxes, analogous to the compression of an elastic spring that recoils back to its resting length when compression is released. This recoil partially accounts for diastolic LV suction;

• The theoretical models used for converting 11C-acetate kinetics derived from PET into estimates of MVO$_2$ are substantially simplified and neglect the intermediate metabolism. This bird’s eye view of metabolism, which considers only the overall chemical energy used for the denominator of Equation 1, does not account for the differences in metabolic pathways that are known to exist between healthy and diseased myocardium (11);

• Furthermore, some investigators favor an approach where the myocardial 11C-acetate kinetics are modeled by a simple monoexponential curve fit (often presented as $k_{\text{mono}}$), whereas others use biexponential fitting and some a more complex concept with pharmacokinetic modeling to calculate both the wash-in rate and the wash-out rate from the same curve (12,13). A commonly used and simplified approach applicable to serial investigations in the same subjects is the work-metabolic index (WMI):

$$WMI = \frac{SBP \times SV_i \times HR}{k_{\text{mono}}}$$

(Equation 2)

with the units mm Hg × ml × m$^{-2}$, where SBP is systolic blood pressure, $SV_i$ is stroke volume index, HR is heart rate, and $k_{\text{mono}}$ the monoexponential time constant of decay for 11C-acetate (4). The WMI, unlike MEE, does not correct for LV mass and, therefore, is better for serial intraindividual comparisons than for comparing efficiency between individuals. Also, the WMI is different from MVO$_2$ in units and numeric value.

In this paper, for simplicity, we use the term myocardial efficiency synonymously with MEE. It is important to understand that myocardial efficiency, by incorporating a parameter of afterload (stroke volume times mean arterial pressure) in the numerator, is not afterload dependent, unlike ejection fraction or global longitudinal strain of the LV. The relations of myocardial efficiency with preload and contractility have not been clearly established, but in conditions of reduced myocardial contractility, for example, in dilated cardiomyopathy, MEE has always been found to be also reduced. As discussed later in the section on heart failure, some studies have shown MEE to have superior and independent prognostic value over ejection fraction.

NORMAL VALUES OF MYOCARDIAL EFFICIENCY AND THE INFLUENCE OF DEMOGRAPHIC BASELINE CHARACTERISTICS

The normal value of myocardial efficiency depends on which technique is used. The invasive approach originally resulted in a normal value of 25%, whereas noninvasive approaches have reported a wide range depending on how cardiac work, MVO$_2$, and LV
mass were measured (see Table 1). Studies have reported normal values ranging from 16 ± 6% (14) to 42 ± 6% (15). A recent study calculating stroke volumes and myocardial mass from CMR yielded normal values of 25 ± 4% (16). Efficiency values based on volumes or forward stroke volume were significantly lower with echocardiography, mainly related to underestimation of LV volumes and also overestimation of LV mass compared with CMR (16). Therefore, values of approximately 25% represent the best estimate of normal myocardial efficiency.

Two systematic evaluations of test-retest reliability for myocardial efficiency were recently reported. Hansson et al. (16), in healthy individuals, reported a coefficient of variation of 6.3% using CMR for determination of forward stroke volume and 12.9% using echocardiography instead. Wu et al. (17), in patients with reduced ejection fraction, found a coefficient of repeatability (roughly corresponding to double the coefficient of variance) in examinations repeated after 6 to 8 weeks of 22.4%, using echocardiography for forward stroke volume determination.

Several studies have investigated the relation of myocardial efficiency to sex, obesity, and diabetes. Myocardial efficiency was lower, and MVO₂ higher, in female, obese, and diabetic individuals (18). In a study of 30 obese patients before and after weight reduction by diet or gastric bypass, MVO₂ decreased, but myocardial efficiency remained largely unchanged (19). The influence of age on myocardial efficiency is unclear. Surprisingly, physical fitness seems not to play a major role for mechanical efficiency. In a study comparing 13 highly trained endurance athletes versus 13 age-matched nonathletic control individuals, similar myocardial efficiency at rest and during exercise was found (20,21). MVO₂
TABLE 1 Effect of Baseline Characteristics, Disease, and Therapeutic Interventions on MEE and MVO₂

| Characteristic                  | MEE | MVO₂ | Ref. # |
|--------------------------------|-----|------|--------|
| Age                            | ?   | ?    | –      |
| Female                         | ↓   | ↑    | (18)   |
| Obesity                        | ↓   | ↑    | (18,19)|
| Diabetes                       | ↓   | ↑    | (18,19)|
| Exercise endurance             | ↔   | (1)  | (21)   |
| Hypertension                   | ↓   | ↑    | (49,50,51,52)|
| Heart failure                  | ↓   | ↔    | (22,25)|
| Beta-blocker therapy in heart failure | ↑    | ↓    | (27,29,58)|
| Spironolactone therapy in heart failure | ↑    | ?    | (31)   |
| Dobutamine therapy in heart failure | ↓ or ↑ | ↑↑   | (32,34) |
| Cardiac resynchronization therapy | ↑    | ↓    | (43)   |
| Aortic stenosis                | ↔   | with preserved EF, | ↔   | (57,58) |
| Mitral regurgitation           | ↓   | ↔    | (59,60,61)|
| Hypertrophic cardiomyopathy    | ↓   | ↔    | (15,53,54,55,56)|

↓ = decrease; (↑) = small or no decrease; ↑ = increase; ↔ = no change; ? = unknown; EF = left ventricular ejection fraction; MEE = mechanical external efficiency; MVO₂ = myocardial oxygen uptake.

was somewhat lower in athletes (both at rest and with exercise). However, training does play a role for efficiency in patients with heart failure (see following section).

ROLE OF MYOCARDIAL EFFICIENCY IN DIFFERENT CARDIAC DISEASES

HEART FAILURE AND THERAPEUTIC INTERVENTIONS IN HEART FAILURE. In heart failure with reduced ejection fraction, global myocardial efficiency is decreased (Table 1) (22). Early on, researchers using invasive measurement of hemodynamics and oxygen uptake found preserved oxygen uptake, reduced LV work, and, thus, reduced myocardial efficiency in patients after myocardial infarction, modestly correlating with ejection fraction (23). In contrast, presence of coronary artery disease without infarction did not affect myocardial efficiency. In myocardial scar, regional MVO₂ and regional efficiency are decreased (24). Under conditions of preserved myocardial viability but decreased contraction, such as stunning or hibernation, regional efficiency is reduced due to largely preserved MVO₂ despite contractile dysfunction.

Myocardial efficiency clearly affects prognosis in patients with dilated, nonischemic cardiomyopathy. Kim et al. (25) followed 47 patients for nearly 6 years and found that invasively derived myocardial efficiency was the strongest predictor of survival compared with ejection fraction and end-diastolic LV pressure, with a best cutoff for myocardial efficiency of 11% (Figure 3).

DRUG THERAPY OF HEART FAILURE

BETA-BLOCKERS. Systemic sympathetic activation is a common finding in heart failure associated with lowered cardiac output. Catecholamines act on the myocyte level to increase contractility and, at the same time, increase LV afterload, strongly stimulating hypertrophy; they are probably responsible to a large extent for the hypertrophy commonly seen in chronic heart failure. The WMI was closely correlated with serum norepinephrine levels in 10 cardiomyopathic patients (26).

In a double-blind placebo-controlled trial by Beanlands et al. (27), metoprolol increased WMI compared with placebo, mainly by decreasing MVO₂ at unchanged cardiac work in a randomized controlled trial of metoprolol versus placebo in 40 patients with moderate/severe improved global afterload, MVO₂ use, and myocardial efficiency. In another double-blind placebo-controlled trial, acetate-PET, CMR, and echocardiography were applied serially in 40 patients with moderate/severe asymptomatic aortic stenosis. Metoprolol reduced LV afterload and MVO₂ at unchanged stroke volume, without significant change in myocardial efficiency (28).

In an entirely catheterization-based study (one of the very few not using PET for measuring oxygen uptake), Eichhorn et al. (29) demonstrated remarkable effects of metoprolol on the failing LV: in 24 patients with severe nonischemic dilated cardiomyopathy,
myocardial efficiency doubled after 3 months of 100 mg metoprolol daily. This increase was due to a near doubling of the stroke work index (partially related to the expected reduction in heart rate) and a decrease of oxygen uptake by approximately one-third. The ejection fraction increased from a mean of 22% to 33%. Both ejection fraction and cardiac output (which increased minimally from a mean of 4.7 to 4.8 l/min) failed to show the underlying profound improvement of LV performance. Furthermore, again in patients with dilated cardiomyopathy, treatment with carvedilol over 3 months was shown to improve myocardial efficiency by reducing free fatty acid metabolism by 57% (30), concomitant with an increase in ejection fraction from 26% to 37%.

**SPIRONOLACTONE.** The addition of spironolactone to heart failure therapy with angiotensin inhibitors/sartans and beta-blockers improved myocardial efficiency in a small (n = 12) uncontrolled observational study of patients with dilated cardiomyopathy (31). Myocardial efficiency, measured as WMI in 11 of 12 patients, increased by 58%, mainly due to an increase in stroke volume. The surprisingly strong recorded beneficial effects on myocardial efficiency, LV ejection fraction, and other cardiac parameters, however, may not have been due to spironolactone alone but possibly also due to previously begun beta-blocker and/or angiotensin inhibitor/sartan therapy.

**CATECHOLAMINES.** During dobutamine infusion (mean dose, 8.0 ± 2.5 μg/kg/min) in healthy volunteers, Vanoverschelde et al. (32) noted a more than doubled oxygen uptake per unit mass and time, and the parameters of cardiac output and work also increased. Myocardial efficiency, however, decreased, and this finding has been invoked to explain the adverse effects of extended sympathomimetic drug therapy in heart failure. Similar results were found with dobutamine and norepinephrine in an animal model of LV dysfunction (33). Contrary to these findings, in a small study of the effects of dobutamine infusion at higher doses (mean dose, 13.2 ± 9.2 μg/kg/min) in patients with heart failure with dilated cardiomyopathy, a small increase in mechanical efficiency was observed, and cardiac output was augmented (34). These effects seemed to be mediated by a decrease in systemic vascular resistance and a reduction in functional mitral regurgitation during dobutamine infusion.

**DRUGS FOR METABOLIC MODULATION OF HEART FAILURE**

Insights from PET metabolic imaging have led to the concept of metabolic modulation as a treatment option in heart failure. Specifically, a shift from free fatty acid metabolism to glucose use, which involves less oxygen demand, has been proposed as a therapeutic goal (35).

However, in a small study, Tuunanen et al. (36) found that a drug reducing free fatty acids by blocking lipolysis reduced stroke volume, but not oxidative metabolism, in patients with dilated cardiomyopathy, thus leading to decreased myocardial efficiency. In contrast, in healthy control individuals, stroke volume also decreased, but efficiency was preserved by a commensurate reduction in oxidative metabolism. Thus, the validity of the concept of metabolic modulation remains unproven.

Several agents, such as ranolazine, perhexiline, and trimetazidine, have been proposed and tested in small patient cohorts, mostly to alleviate angina. Ranolazine has been shown in a canine model of chronic heart failure to improve myocardial efficiency by raising cardiac output at unchanged oxygen uptake, in contrast to dobutamine, which increased cardiac output at the expense of a parallel increase in oxygen uptake (37).

Another theoretically attractive approach to metabolic modulation in heart failure is to supply specific beneficial energy substrates to the heart. Ketone bodies, which theoretically may provide a better balance of energy generation to consumed oxygen than glucose or fatty acids, might therefore be a therapeutic option in heart failure. Very recently, the short-term infusion of the ketone 3-hydroxybutyrate in patients with heart failure with reduced ejection fraction was found to promptly increase ejection fraction and cardiac output, as well as proportionally increased myocardial oxygen uptake, without compromising myocardial efficiency measured by PET, thereby possibly avoiding deleterious long-time effects, although this was not tested (38). Another candidate drug for the optimization of cardiac metabolism in heart failure is empagliflozin, which is used for the treatment of type 2 diabetes. Empagliflozin has been shown to increase invasively measured myocardial efficiency in postinfarction heart failure in an experimental, nondiabetic pig model (39). This study showed a metabolic switch to more free fatty acid and ketone body and less glucose metabolism in animals treated with empagliflozin for 2 months after infarction compared with those receiving placebo.

**EXERCISE IN HEART FAILURE**

The effect of exercise on the failing heart was assessed in a study of patients with dilated
cardiomyopathy (average ejection fraction, 34%) who underwent a 5-month physical training regime (40). Compared with nonexercising control individuals, heart rate decreased (from 69 beats/min to 60 beats/min), ejection fraction increased (from 33% to 39%), peak oxygen uptake increased (from 19 to 25 ml/min·kg), and stroke volume increased (from 94 to 104 ml), all significant, whereas no changes were seen in the nonexercising group. Myocardial efficiency, due to a mild reduction in oxidative metabolism and mild increase in stroke work, rose significantly in the exercise group (29% to 34%; p < 0.05 vs. 33% to 34%; p = NS in the nonexercising group).

CARDIAC TRANSPLANTATION

Cardiac transplantation normalizes myocardial efficiency. A study of 27 post-transplant patients free of acute rejection showed near-normal myocardial efficiency compared with a healthy control group, whereas patients with severe dilated cardiomyopathy (mean ejection fraction, 22%)

(A) Bull’s eye plot showing relative glucose metabolism by 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) in a representative patient with left bundle branch block. The point in the left ventricular (LV) myocardium with the highest FDG uptake was used as a reference (100%), and segmental values were reported as proportions of this value. The FDG-PET does not directly reflect myocardial oxygen uptake like an 13C-acetate PET but, rather, myocardial glucose metabolism. (B) Bull’s eye plot with similar anatomic distribution as in A, showing relative loop area by estimated LV pressure and longitudinal strain by speckle-tracking echocardiography. The segment with the largest loop area was used as a reference (100%), and segmental values were reported as proportions of this value. (C) Representative pictures showing regional distribution of glucose metabolism by FDG-PET for short-axis (left panel) and 4-chamber (right panel) views. (D) Correlation between regional metabolism by FDG-PET and loop area by estimated LV pressure and longitudinal strain. (E) Estimated LV pressure and longitudinal strain loops from the septum and lateral wall. Upper panel: clockwise rotation of the operating point on the septal loop implies negative work (“wasted work”). Lower panel: counterclockwise rotation from the lateral wall denotes positive (“constructive”) work. See also text. Reproduced with permission from Russell et al. (43).
had clearly and significantly decreased efficiency values (41).

CARDIAC RESYNCHRONIZATION THERAPY AND ROLE OF REGIONAL MYOCARDIAL EFFICIENCY

Myocardial efficiency by PET improves after cardiac resynchronization therapy, whereas oxidative metabolism remains unchanged (42). This has been interpreted as a favorable finding supporting the sustainability and lack of adverse effects known from inotropic stimulation in this type of heart failure therapy. The research group of Smiseth et al. (43) recently introduced a clinical method for estimation of regional LV myocardial work by echocardiography. Similar to calculation of LV stroke work by pressure-volume loops, myocardial segmental work is calculated as the area of the pressure-strain loop. Pressure is assessed noninvasively based on brachial systolic pressure and valvular event timing, whereas strain is measured by speckle-tracking echocardiography (44). The validity of this approach for assessing myocardial work is supported by good correlation between segmental work and regional myocardial metabolic rate of glucose use measured by 18F-fluorodeoxyglucose (FDG) PET. In patients with left bundle branch block, septal segments typically shorten during early systole when pressure is low and, thus, perform just a small amount of positive work (constructive work). This is often followed by systolic lengthening of the septal myocardium, which implies negative work (wasted work), and, later in systole, there is a variable degree of septal shortening and a component of positive work (constructive work). The net result is a marked reduction in septal work, and in some patients, septal segments may show net negative work. This is illustrated in Figure 4, which is from a patient with heart failure and left bundle branch block. There is markedly reduced septal work, which is likely to improve with cardiac resynchronization therapy. The wasted septal work is the result of contractions in the LV lateral wall and implies that the septum absorbs energy from the LV free wall. The increased work load on the free wall is a stimulus for remodeling, which contributes to the development or progression of global LV dysfunction and, ultimately, congestive heart failure. In patients with myocardial scar, these contraction patterns can be different from the typical left bundle branch block pattern referred to earlier (45–47). and this approach is currently being tested in a prospective study. However, strictly speaking, regional myocardial external efficiency was not evaluated, because this would necessitate assessment of regional MVO2. However, another group has compared myocardial efficiency calculated from MVO2 by 13C-acetate PET to myocardial work calculated by strain-pressure loops in patients with amyloidosis, finding a fair relationship (48). In this context, MEE is not equivalent to myocardial work efficiency, a recently introduced parameter based on LV pressure-longitudinal strain loops that does not involve any measurement of oxidative metabolism and, therefore, uses "efficiency" in a different sense.

MYOCARDIAL EFFICIENCY IN HYPERTENSION AND HYPERTENSIVE LV HYPERTROPHY

Hypertension increases stroke work and thus increases myocardial oxygen uptake; because both increase, myocardial efficiency is largely unchanged. However, once the LV hypertrophies due to hypertension, the oxygen uptake per gram of myocardium becomes normal again (49,50). The effects of LV hypertrophy on myocardial efficiency depend on the pattern of remodeling. In concentric remodeling with low stroke volume, myocardial efficiency is decreased, whereas it is preserved in eccentric remodeling with normal stroke volume. The impaired myocardial efficiency, together with a lower coronary perfusion reserve, may explain the vulnerability of the concentrically hypertrophied LV to ischemia. This loss of myocardial efficiency due to hypertensive hypertrophy has also been shown ex vivo in spontaneously hypertensive rat myocardium (51,52). Decreased fatty acid metabolism may contribute to the loss of efficiency. For LV hypertrophy due to valvular heart disease, please see the section on valvular heart disease.

HYPERTROPHIC CARDIOMYOPATHY

In patients with hypertrophic cardiomyopathy, a decrease in myocardial efficiency has been observed compared with age-matched control individuals (53). This significant decrease (mean, 21% vs. 35% in controls) occurred mostly due to the much higher mass in the denominator for patients with cardiomyopathy, and there were nonsignificant changes in oxygen uptake per gram and stroke work. Although stroke volume was considerably lower in hypertrophic cardiomyopathy, stroke work, because of the added outflow tract gradients, was actually slightly higher than in control individuals. Ex vivo experiments with
muscle strips from myectomies in patients with hypertrophic cardiomyopathies have confirmed higher energy expenditure for myocardial work, explaining the finding of decreased myocardial efficiency in this disease. Higher energy expenditure for contraction was found to a similar degree in myocardium from carriers of several different genes leading to hypertrophic cardiomyopathy (54,55). In persons who were mutation carriers without phenotypic expression of hypertrophic cardiomyopathy (i.e., without LV hypertrophy), myocardial efficiency was significantly lower than in control individuals but higher than in patients with manifestly hypertrophic cardiomyopathy (15). These findings confirm earlier work (56) showing a “mechano-energetic uncoupling” in hypertrophic cardiomyopathy that is also observed in other types of myocardial hypertrophy, such as aortic stenosis or hypertension.
CARDIAC AMYLOIDOSIS

The relation of myocardial efficiency to hemodynamic abnormalities in cardiac amyloidosis was recently explored (48). Myocardial efficiency, measured with 11C-acetate PET, was severely reduced compared with healthy volunteers. With use of right heart catheterization and Doppler echocardiography during exercise, strong correlations were found between resting myocardial efficiency and peak exercise oxygen uptake, cardiac output, and global longitudinal strain. Interestingly, the association of myocardial efficiency with measures of diastolic function was relatively poor. The investigators also found a fair relationship between myocardial work efficiency estimates by the pressure-strain loop methodology proposed by Russell et al. (43) and 11C-acetate PET.

VALVULAR HEART DISEASE

Left-sided valvular heart disease introduces changes in stroke work (for example, higher afterload in aortic stenosis and higher total stroke volumes in mitral and aortic regurgitation). Thus, myocardial efficiency can be calculated either as a net efficiency by using peripheral arterial blood pressure and effective stroke volume in the equation, but neglecting the additional work performed due to abnormal pressure, or volume load. Alternatively, and more physiologically, it can incorporate into the calculation of Equation 1 the aortic gradients in aortic stenosis or total LV stroke volume (end-diastolic minus end-systolic LV volume) in mitral and aortic regurgitation. Recently, a study compared myocardial efficiency in moderate or severe aortic stenosis (area ≤1.2 cm²) with and without preserved ejection fraction and found that MVO₂ was similar to healthy control individuals in all groups, whereas mechanical efficiency was lower in aortic stenosis with impaired ejection fraction (28). Interestingly, the subgroup with severe paradoxical aortic stenosis (low gradient and low flow, with preserved ejection fraction and aortic valve area ≥0.6 cm²/m²) also showed impaired myocardial efficiency, different from high-flow, high-gradient severe aortic stenosis. Thus, a mechano-energetic uncoupling was postulated in the patients with low-flow, low-gradient severe aortic stenosis with preserved ejection fraction. This is one of the few studies reporting both MEE and global longitudinal strain, and strain was impaired in the 2 groups of patients who also had impaired MEE. A small study showed improvement in efficiency after aortic valve replacement, which correlated with improved exercise capacity and maximal oxygen uptake, in parallel with decreased LV mass and myocardial oxygen uptake (57). Furthermore, a randomized study of 40 patients with asymptomatic aortic stenosis (aortic valve area ≤1.2 cm²) treated with metoprolol versus placebo indicated higher myocardial efficiency due to lower MVO₂ (together with lower heart rate and lower gradients) in the metoprolol group (58). There are very few data on valvular regurgitation. A recent study investigated myocardial efficiency in primary mitral insufficiency (59). Because cardiac work was based on measurement of forward stroke volume, myocardial efficiency values in patients with mitral regurgitation were lower than in control individuals. In the same study, myocardial efficiency was also calculated in patients with moderate or severe aortic stenosis. In these patients, myocardial efficiency was reduced and correlated well with symptoms of heart failure (Central Illustration). Another study evaluated 14 patients with severe primary mitral insufficiency before and after surgery. The WMI using the forward stroke volume (i.e., the effective stroke volume) was significantly improved by surgery, whereas the WMI using the total LV stroke volume incorporating the regurgitant volume was unchanged (60). The WMI also improved after surgery in secondary mitral insufficiency in

HIGHLIGHTS

- Myocardial external efficiency is a performance measure of the myocardium linking metabolism to mechanical work that can be measured by PET.
- The diagnostic and prognostic potential of myocardial efficiency in heart disease, especially heart failure, is only beginning to be explored. Decreasing costs and automation of PET will make this information increasingly available and may in the future guide the selection of drugs and therapeutic interventions in heart disease.
- Because of prohibitive costs and low availability due to the need for a cyclotron, evaluation of myocardial efficiency has in the past been a research tool. Both restrictions will decrease dramatically in the near future, enabling myocardial efficiency as a fundamental cardiac performance parameter to be tested in larger studies and making translation to clinical practice possible.
dilated cardiomyopathy of both ischemic and idiopathic origin (61).

**UNRESOLVED ISSUES AND GAPS IN KNOWLEDGE**

Current knowledge of myocardial efficiency in cardiac diseases remains limited, and even fundamental issues such as whether this parameter changes with age are essentially unknown. The shifts in oxidative metabolism occurring with heart failure are incompletely understood and may offer the chance of therapeutic intervention by optimized fuels for the failing heart. Changes in myocardial efficiency may be useful for evaluation of such therapies and might also inform other therapeutic interventions in heart failure. Regional myocardial efficiency data might predict the response to resynchronization therapy in patients with left bundle branch block. Prognostic implications of myocardial efficiency are even more sparsely explored and await broader use of PET data.

**FUTURE DIRECTIONS**

Access to PET/CT scanners for imaging and cyclotron facilities for production of radiopharmaceuticals is growing exponentially around the world due to documented clinical utility, mainly in patients with cancer (60). Cyclotrons using superconducting technology may further reduce the size of necessary infrastructure and the price of radioisotopes. This creates an opportunity for cardiology departments in hospitals with PET facilities to use myocardial efficiency as a clinical tool, which is becoming less complex than in the past. For example, it recently has become possible to derive stroke volume, both total and forward, and mass along with MVO₂ directly from PET examinations in an automated fashion, thus obviating the need for an additional imaging method to calculate myocardial efficiency (10,16) and avoiding observer bias. Broader acquisition of myocardial efficiency data will show whether they can travel from the bench to the bedside and aid in therapy optimization and prognostic stratification. Although intuitively appealing as an almost ideal index of overall cardiac function, added value for therapeutic decisions and assessment of prognosis remains to be shown in controlled trials.

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STATE-OF-THE-ART REVIEW

Cardiovascular Imaging Techniques to Assess Microvascular Dysfunction

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ABSTRACT

The understanding of microvascular dysfunction without evidence of epicardial coronary artery disease pales in comparison with that of obstructive epicardial coronary artery disease. A primary limitation in the past had been the lack of development of noninvasive methods of detecting and quantifying microvascular dysfunction. This limitation has particularly affected the ability to study the pathophysiology, morbidity, and treatment of this disease. More recently, almost all of the noninvasive cardiac imaging modalities have been used to quantify blood flow and advance understanding of microvascular dysfunction. (J Am Coll Cardiol Img 2020;13:1577–90) © 2020 by the American College of Cardiology Foundation.

The current understanding of symptoms, prognosis, and treatment strategies in patients with ischemic heart disease resulting primarily from abnormalities of the coronary microcirculation pales in comparison with that of epicardial coronary artery stenosis. Contemporary consensus statements and guidelines direct assessment and treatment of epicardial coronary artery disease (CAD) and resultant myocardial ischemia in a variety of clinical situations (1–3). With both invasive and noninvasive testing, the identification of epicardial ischemic disease is better established than the detection of microvascular disease. Beneficial treatment strategies are available for epicardial stenoses, whose significance can be fully evaluated by direct angiographic visualization with functional assessment determined by either perfusion imaging or invasive techniques to obtain fractional flow reserve (FFR), coronary flow reserve (CFR), or index of microvascular resistance (4–6). Recognizing microvascular dysfunction (MVD) required significant advancements in technology before reliable and reproducible measurements could be made so that prognostic and therapeutic trials could be pursued (7,8). There is a growing interest in diagnosing and treating MVD as more patients are diagnosed with angina without obstructive coronary disease or ischemia without obstructive coronary disease. Furthermore, MVD may play a vital role in the pathophysiological mechanisms of certain diseases, such as heart failure with preserved ejection fraction and takotsubo cardiomyopathy (9,10). The diagnosis of MVD is often

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ABBREVIATIONS AND ACRONYMS

AIF = arterial input function
CAD = coronary artery disease
CFR = coronary flow reserve
CFVR = coronary flow velocity reserve
CMR = cardiac magnetic resonance
CT = computed tomographic
CTA = computed tomographic angiography
CTP = computed tomographic perfusion
FFR = fractional flow reserve
FFR<sub>CT</sub> = computed tomographic angiography-derived fractional flow reserve
MBF = myocardial blood flow
MPR = myocardial perfusion reserve
MVD = microvascular dysfunction
PET = positron emission tomography
SPECT = single-photon emission computed tomographic

DEFINING CORONARY MVD

Before understanding the underlying technicalities required to quantify MVD, baseline knowledge of the functional anatomy of the coronary circulation is required (Figure 1). There are 3 components of the coronary arterial vasculature that are subdivided by the size of the arterial structure, its capacitance, and its resistance to myocardial blood flow (MBF) (12). The initial component is the epicardial coronary arterial tree (5 mm to 400 μm in diameter), which has near negligible coronary resistance in the absence of stenosis and consists of essentially conductive vessels. The pre-arteriole vessels follow (100 to 400 μm in size); these are still largely extramyocardial and respond primarily to flow and intravascular pressure to deliver a narrow pressure range to the arterioles (12). The third and distal component is the intramural arterioles (40 to 100 μm), which have the primary responsibility of matching blood supply to myocardial oxygen consumption. The distal capillary and venule systems are low-resistance capacitance vessels, holding up to 90% of the total intramyocardial blood volume (13). The pressure gradient between the aortic root and the right atrium is the primary driving force of flow across the myocardium (14). MBF is defined as the amount of flow through the coronary vessels over time and is typically expressed as blood flow per gram of myocardium (12).

Under normal conditions, there are elegant mechanisms of autoregulation in the pre-arteriolar and arteriolar microcirculation that allow stable coronary blood flow across a large range of perfusion pressures (12,15). For example, in the setting of hypotension, the driving pressure would decrease, and autoregulatory mechanisms would subsequently decrease microvascular resistance to attempt to maintain adequate blood flow (14). There are multiple autoregulatory mechanisms aimed at manipulating arterial tone. There is myogenic constriction of the distal pre-arterioles in response to increased pressure. Arterioles can decrease or increase their diameter in response to flow changes, leading to shear stress, which induces dilation of larger conductive vessels. In addition, arterioles can regulate blood flow in response to metabolites formed when myocardial oxygen demand increases (16).

In the setting of coronary MVD, there can be a disruption of these adaptive mechanisms, which can be assessed via various noninvasive provocative tests. One such test is sympathetic stimulation using cold pressor testing. The sympathetic response from a cold stimulus will increase myocardial work and thus a proportionate increase in MBF by metabolically initiated endothelium-related vasodilator forces in the microvasculature (14,17). Inotropic stimulation with dobutamine can increase MBF via increased myocardial oxygen demand (14). However, these methods are not commonly used, and therefore the Coronary Vaso-motion Disorders International Study Group created a consensus statement summarizing recommended invasive and noninvasive methods for detecting endothelial-dependent and endothelial-independent MVD (18). Many of these noninvasive methods are discussed within this review. The most common noninvasive method to assess MVD is to administer a vasodilating compound such as intravenous adenosine to cause maximal hyperemia. It should be noted that this is not a specific test of endothelial function, as adenosine is not an endothelial-mediated vasodilating compound. However, there may be some indirect endothelial activation via shear stress from an increase in the rate-pressure product by the systemic effects of intravenous adenosine compared with intracoronary administration of adenosine (19). “MVD” is a broad term; in the absence of obstructive coronary disease, it includes any pathology that may disrupt the microvasculature, including endothelial dysfunction, coronary spasm, inflammation, and atherosclerosis (20). Changes in arteriolar diameter or microvascular rarefaction with diffuse fibrosis, such as in heart failure with preserved ejection fraction, have been associated with MVD (21,22). A reduction in the ratio between maximal hyperemic coronary flow and baseline coronary flow indicates reduced CFR. CFR can vary by sex, age, and the modality used for measurement (23,24). Importantly, CFR is a composite measure of epicardial stenosis severity and MVD; however, in the setting of normal epicardial coronaries, abnormal CFR represents MVD (12,25). The value that represents abnormal CFR has differed among studies, and values ranging from 1.5 to 2.5 have been used in prognostic studies (20,26,27).

Traditionally, the term “CFR” has referred to the invasive measurement of flow reserve, while noninvasive measuring methods, as discussed in this
review, refer to CFR as myocardial perfusion reserve (MPR). This distinction occurs because the measurement is made through changes in myocardial perfusion rather than direct measurement at the level of the coronary arteries. Other potentially important imaging parameters are also being studied, such as microcirculatory blood volume or microvascular blood volume and intramyocardial blood volume (28–30). It has been shown that changes in these parameters or reduction in these parameters can be associated with coronary MVD (31).

**QUANTIFYING MBF: ARTERIAL INPUT FUNCTION AND COMPARTMENTAL KINETICS**

Quantifying MPR using techniques such as positron emission tomography (PET), first-pass perfusion cardiac magnetic resonance (CMR), and computed tomographic (CT) perfusion require models that describe the kinetics of the contrast agent as a function of time. The concentration-time curves at rest and with vasodilation can vary because of variables such as contrast bolus timing, contrast injection speed, and cardiac output. These parameters must be accounted for to avoid significant variability in the absolute quantification of MBF. The arterial input function (AIF) is a time-dependent radiotracer or contrast concentration input into the tissue of interest that accounts for variables related to the injection of the contrast or radiotracer that can affect MBF quantification (32). For absolute quantification of MBF, the AIF can be measured in the left ventricular cavity or in the left atrium (Figure 2). With kinetic modeling, the concentration of tracer or contrast in

| Modality                     | Technique                                                                 | Advantages                                                                 | Disadvantages                                                                 |
|------------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Contrast echocardiography    | Constant infusion of echocardiographic contrast microbubbles until the cavity is filled, followed by ultrasound destruction of microbubbles | • Bedside procedure<br>• Minimal risk<br>• No radiation<br>• Relatively inexpensive | • Microbubble use not FDA approved for perfusion (no reimbursement)<br>• Operator dependent<br>• Poor images related to obesity or the presence of lung disease<br>• Very few validation studies for MVD |
| Transthoracic Doppler echocardiography | Pulsed-wave Doppler performed on the proximal left anterior descending artery | • Bedside procedure<br>• Minimal risk<br>• No radiation<br>• Relatively inexpensive<br>• Correlated well with intracoronary Doppler wire | • Operator dependent<br>• Difficult imaging because of obesity or the presence of lung disease<br>• Poor correlation with PET<br>• Very limited data with use in nonobstructive CAD |
| CT                            | Dynamic first-pass vasodilator stress and then rest perfusion imaging     | • Anatomic coronary data and perfusion data with the same study           | • Perfusion quantification only allowed in high-radiation dynamic perfusion imaging<br>• Radiation exposure<br>• Risk for contrast-induced nephropathy and contrast allergic reactions<br>• Limited in renal failure<br>• Limited validation in nonobstructive CAD<br>• Limited availability<br>• Iodinated contrast can cause vasodilation leading to overestimation of MBF |
| PET                           | Dynamic first-pass vasodilator stress and then rest perfusion images     | • Most validated modality for MBF quantification in nonobstructive CAD<br>• Extensive prognostic data<br>• Segmented MBF<br>• Relatively low radiation exposure because of radiotracers with short half-lives<br>• Not affected by renal dysfunction<br>• Good reproducibility and accuracy<br>• CT can allow for some anatomic assessment of coronary arteries | • Radiation exposure<br>• Expensive<br>• Technology is not widely available |
| SPECT                         | Dynamic first-pass vasodilator stress and then rest perfusion images     | • More widely available than PET and CMR                                 | • Requires new-generation cameras<br>• Minimal validation in nonobstructive CAD<br>• Radiation exposure is high |
| CMR                           | Dynamic first-pass vasodilator stress and then rest perfusion images     | • No radiation exposure<br>• Excellent spatial resolution<br>• Allows tissue characterization with the same study<br>• Validated against invasive measurements and PET | • Expensive<br>• Technology is not widely available<br>• Very minimal prognostic data<br>• Difficult for patients because of frequent breath holds and length of time of the examination<br>• Limited in renal failure |

CAD = coronary artery disease; CMR = cardiac magnetic resonance; CT = computed tomography; FDA = U.S. Food and Drug Administration; MBF = myocardial blood flow; MVD = microvascular dysfunction; PET = positron emission tomography; SPECT = single-photon emission computed tomography.
(A) Components of the coronary circulation. Schematic of the macrocirculation (B) and microcirculation (C). CFR = coronary flow reserve; FFR = fractional flow reserve; IMR = index of microvasculatory resistance. Adapted with permission from De Bruyne B, Oldroyd KG, Pijls NHJ. Microvascular (dys)function and clinical outcome in stable coronary disease. J Am Coll Cardiol 2016;67:1170-2; and Taqueti et al. (82).
(A) Schematic of time–intensity curves for the arterial input function (AIF) and the tissue function (TF) in a normal coronary segment and an abnormal coronary segment. (B) Cardiac magnetic resonance-obtained stress AIF and TF signal intensity curves. (C) Positron emission tomographic stress/rest perfusion imaging with resulting AIF and myocardial time-intensity curves. Adapted with permission from Patel et al. (93).
the myocardium, also known as the tissue function, is obtained using the AIF and an established kinetic compartmental model to allow fitting of concentration-time curves (33,34).

Along with the AIF, compartmental modeling, which mathematically describes the kinetics of a contrast agent or radiotracer in a biological tissue of interest, is commonly used to accurately quantify MBF. With radiotracers, different tracers demonstrate different behaviors, and each tracer is associated with a particular compartmental model (35). For example, a 2-compartment model (blood and tissue compartments) is typically used for the radiotracers 201Tl and 13N-ammonia. Therefore, variability in radiotracer kinetics, along with other specified characteristics discussed later, are important to obtain an accurate MPR. Similar methods of compartmental modeling and contrast kinetics are applicable in CMR-derived MPR.

Additionally, blood flow can be derived through several methods without the use of compartmental modeling. Zierler’s (36) central volume principle has been used in CMR as a non-compartmental-based method for MBF quantification. It enables quantification of MBF using a simple deconvolution operation using assumptions made from myocardial tracer residue curves and the AIF (37). In addition, other methods that do not require compartmental modeling (discussed later) include the use of freely diffusible tracers such as water in the case of arterial spin labeling for CMR and the use of intravascular microbubbles in contrast echocardiography (38,39).

**MULTIMODALITY NONINVASIVE ASSESSMENT OF MVD**

**ECHOCARDIOGRAPHY.** In 1998, Wei et al. (38) demonstrated a novel method to quantify both MBF using contrast echocardiography with the use of a constant venous infusion of air-filled albumin microbubbles. The ability to quantify perfusion was based on 2 characteristics of the microbubble contrast agent. The “new” generation of microbubbles contained a higher molecular weight gas and thus was nondiffusible and less soluble, allowing myocardial opacification (40,41). Second, the microbubbles could be destroyed with ultrasound (42). These properties allowed the calculation of MBF by obtaining the mean velocity of myocardial microbubbles and the microvascular cross-sectional area. The mean velocity was obtained by measuring the rate of reappearance of microbubbles after destruction with ultrasound in the setting of a constant microbubble venous infusion. The cross-sectional area was obtained by measuring the microbubble concentration in the myocardium and is essentially a contrast echocardiographic measurement of the myocardial blood volume (38). This method was validated against PET, with a correlation coefficient of 0.88 when measuring MBF in healthy volunteers (43).

Potential benefits of the contrast echocardiographic approach include that it is a low-risk bedside procedure, is relatively inexpensive, and has limited adverse effects. The potential adverse effects from contrast microbubbles are minimal, and there is no radiation exposure compared with PET (44). However, a number of limitations have prevented its widespread use. Echocardiography is operator dependent and demonstrates considerable intraobserver and interobserver variability (45). Echocardiography can be hindered by artifacts, particularly in the setting of obesity and lung disease. Another technical issue is movement of the imaging frame during replenishment of microbubbles, which can lead to difficulty with post-processing. The use of microbubbles for myocardial perfusion assessment is currently not reimbursed in the United States, further hampering its clinical adoption. Finally, these modalities have had success in the evaluation of obstructive disease or post-percutaneous coronary intervention microvascular assessment, but in the setting of normal coronary arteries and anginal symptoms they have not shown widespread clinical utility (46,47).

Another echocardiographic method of MBF assessment uses transthoracic Doppler echocardiography to calculate the coronary flow velocity reserve (CFVR) (48,49). CFVR is obtained as the ratio of coronary flow velocity at stress and rest obtained by the use of pulsed-wave Doppler sampling of the proximal left anterior descending coronary artery (Figure 3a). This method correlates well with flow acquired from an intracoronary Doppler wire (48,50). In addition, abnormal CFVR is associated with adverse cardiovascular events (27,51). However, transthoracic Doppler echocardiographic CFVR measurement was poorly correlated (r = 0.30) with MPR calculated by PET in an evaluation of women with angina and no obstructive CAD (52). In the prospective multicenter international PROMIS-HFpEF study, transthoracic Doppler echocardiography identified a high prevalence of MVD in patients with heart failure with preserved ejection fraction (53).

**COMPUTED TOMOGRAPHY.** CT angiography (CTA) in combination with CT perfusion (CTP) has the potential to be a robust modality for the assessment of microvascular disease. Both coronary anatomic and myocardial perfusion information can be obtained in
The same study (54). There are 2 primary techniques used in CTP imaging: static CTP and dynamic CTP. Static CTP requires only a single image at peak myocardial contrast opacification, which is then compared with a single rest image, thus lowering the amount of radiation. However, only semiquantitative or qualitative perfusion assessment can be performed with this technique. Therefore, dynamic CTP involves

(A) Using transthoracic Doppler echocardiography to obtain mean diastolic velocities at rest and stress allows the derivation of coronary flow velocity reserve (CFVR). (B) Computational modeling allows calculation of the ratio of luminal volume to myocardial mass (V/M). (C) Example of V/M ratio and fractional flow reserve (FFR) in 2 patients with nonobstructive coronary artery disease. The patient with reduced FFR has a corresponding reduced V/M ratio. Reproduced with permission from Kakuta K, Dohi K, Yamada T, et al. Comparison of coronary flow velocity reserve measurement by transthoracic Doppler echocardiography with 320-row multidetector computed tomographic coronary angiography in the detection of in-stent restenosis in the 3 major coronary arteries. Am J Cardiol 2012;110:13–20; and Taylor, Gaur S, Leipsic J, et al. Effect of the ratio of coronary arterial lumen volume to left ventricle myocardial mass derived from coronary CT angiography on fractional flow reserve. J Cardiovasc Comput Tomogr 2017;11:429–36.
obtaining several sequential images over time from first pass to wash to allow quantitative perfusion (55). CTP imaging is performed using either retrospective or prospective electrocardiographically triggered image acquisition for approximately 30 s after contrast injection both at rest and with vasodilator stress. These images are then analyzed using post-processing software to obtain AIFs and time attenuation curves for the quantification of MBF (56). Even though this technology can potentially identify MVD, CTA does not have any significant advantages over other imaging modalities and is not currently used in regular clinical practice to assess MVD.

Further functional data regarding the hemodynamic effects of epicardial stenosis can be obtained without stress perfusion imaging through measurement of CTA-derived FFR (FFR\textsubscript{CT}). Using proprietary software, HeartFlow (Redwood City, California) derives a 3-dimensional coronary model with advanced mathematics to simulate maximal hyperemia and quantify MBF and FFR\textsubscript{CT} at a specified point in the coronary tree (57,58). FFR\textsubscript{CT} showed significantly better diagnostic sensitivity compared with single-photon emission CT (SPECT) imaging in stable CAD (59). The relationship between FFR\textsubscript{CT} and MVD is not well defined. However, with the same computational mathematical modeling, HeartFlow can derive other potentially useful parameters for the assessment of MVD. Interestingly, Nørgaard et al. (60) showed that a low ratio of CTA-derived coronary luminal volume to myocardial mass was an independent predictor of ischemia in nonobstructive coronary disease (Figures 3B and 3C).

To expand on this concept, Grover et al. (61) compared the ratio of coronary luminal volume to myocardial mass in 30 patients with European Society of Cardiology guideline-defined microvascular angina (62) with that in 32 age-matched asymptomatic control subjects. They showed that both the mean total coronary luminal volume and the mean myocardial mass were lower in the MVD cohort. The mean ratio of coronary luminal volume to myocardial mass was also significantly lower in the MVD group (25.6 ± 5.9 mm\textsuperscript{3}/g vs. 30.0 ± 6.5 mm\textsuperscript{3}/g; p = 0.007) (61).

Although CTA can provide a comprehensive cardiac examination, it has limitations. Radiation exposure is high for a stress/rest perfusion CTA protocol, with similar effective radiation dose as a SPECT rest/stress protocol of 12.7 mSv (63). In addition, the risk for contrast-induced nephropathy restricts the use of this technique in patients with chronic kidney disease. There are data suggesting that iodinated contrast may cause vasodilation, leading to the overestimation of coronary blood flow (64,65).

**NUCLEAR IMAGING.** Cardiac PET is the imaging modality most validated for the quantification of MBF and assessment of MVD (66). Several radiotracers are used in PET, each with unique characteristics. Ideally, a radiotracer would be freely diffusible, with high first-pass uptake, a rapid clearance rate, insignificant roll-off at elevated blood flows, and kinetics that are unaffected by extrinsic factors (44,67). In addition, the radiotracer should be safe and without side effects, and it should not affect flow hemodynamic status. The most commonly used PET radiotracers are \textsuperscript{15}O-water, \textsuperscript{82}Rb, and \textsuperscript{13}N-ammonia. Oxygen-15-water is an excellent agent for MBF calculation because of its exceptional first-pass uptake of nearly 100% and minimal roll-off at higher flows (68,69). However, because of its low counts and short half-life of 122 s, visual assessment of perfusion abnormalities with \textsuperscript{15}O-water is extremely limited, and it is not approved by the U.S. Food and Drug Administration for clinical use in perfusion imaging (70). Nitrogen-13-ammonia has a longer half-life of 2.8 min and is better for myocardial perfusion stress imaging. Additionally, it has high first-pass uptake, relatively low radiation exposure (2 mSv), and high myocardial retention but is limited by the roll-off that occurs at high coronary blood flow (67,71). Unfortunately, \textsuperscript{82}Rb has a lower extraction fraction, has more significant roll-off at high flows, and is associated with higher radiation, making \textsuperscript{13}N-ammonia the more preferred agent for accurate MBF quantification, particularly at high flows (71). However, \textsuperscript{82}Rb is more commonly used because it requires only an on-site generator as opposed to a cyclotron (71). It also has been validated against \textsuperscript{15}O-water (72).

The assessment of MBF by PET is primarily performed by post-processing software that performs automated segmentation and AIF measurements during dynamic first pass scanning (Central Illustration) (72). Depending on the radiotracer used, the post-processing software will perform the kinetic modeling on the dynamic data to compute the regional and global stress and rest MBF (66,73,74). The intrasoftware reproducibility of MBF measurements is reasonable, ranging from 4% to 15% (74–76).

Some prospective PET studies correlate MVD, defined as abnormal MPR, with adverse prognosis (77,78). Using \textsuperscript{82}Rb positron emission tomographic perfusion scanning, Ziadi et al. (78) found incremental prognostic value of MPR over the more routinely used summed stress score. They found that the adverse event rate more than doubled with MPR <2 and normal summed stress score compared with MPR...
In addition, a minimal increase in troponin without overt obstructive CAD has also been correlated to PET-derived abnormal flow reserves and is a poor prognostic indicator (79). These data have been replicated by other studies showing MBF and MPR to be predictive of adverse outcomes; these parameters may be used for risk stratification depending on normal and abnormal stress perfusion (80,81).

Mathew, R.C. et al. J Am Coll Cardiol Img. 2020;13(7):1577-90.

(A) Positron emission tomographic quantification of myocardial blood flow (MBF) shows reduced myocardial perfusion reserve (MPR) of 1.6 in this 48-year-old woman with nonobstructive coronary artery disease (CAD). (B) Rest and stress cardiac magnetic resonance–derived segmental quantification of MBF with a global MPR of 2.1 in a 59-year-old man with nonobstructive CAD. LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LV = left ventricle; MC = motion corrected; RCA = right coronary artery; RV = right ventricle; Str = stress; TOT = total.
derived MPR and MBF have been particularly useful in analyzing different subsets of populations (82). Abnormal flow reserve in patients without overt CAD was independently associated with diastolic dysfunction and increased risk for hospitalization for heart failure with preserved ejection fraction (83). There is evidence of abnormal PET-derived MBF in patients with metabolic syndrome and non-insulin-dependent diabetes (84,85). These findings are particularly profound in women, indicating the potential of important sex-related differences in MVD (82). Women, despite having less obstructive CAD compared with men, are burdened by increased symptoms and similar or worse outcomes (86,87).

Also, as recently described, comprehensive quantitative perfusion analysis by PET that includes regional absolute stress flow, relative stress flow, CFR, and quantitative subendocardial perfusion gradients can lead to better diagnostic certainty for MVD (88). It should be noted that clinically used PET protocols are not capable of accurately quantifying vasodilator-induced subepicardial to subendocardial perfusion gradients because of limitations in spatial resolution. Despite the vast amount of prognostic data in PET-derived blood flows, PET is not without its limitations, which include radiation exposure and cost, depending on which radiotracer is used (72).

SPECT imaging is the most common nuclear cardiovascular imaging modality but has been limited to date in quantification of MBF because of poor camera sensitivity and temporal resolution with the more common sodium-iodide cameras (44). However, new cadmium-zinc-telluride detectors have better sensitivity and resolution that will allow dynamic SPECT imaging and thus quantification of MBF. Early studies show encouraging flow estimates; however, larger multicenter trials are needed to improve the technical aspects of SPECT processing and to compare it with more traditional imaging methods for flow reserve quantification (89,90).

CMR. The utility of MBF and MPR quantification by CMR has been demonstrated in several studies with regard to both epicardial stenosis and microvascular angina (91–95). Similar to PET, CMR stress first-pass perfusion is performed typically with adenosine infusion or following regadenoson bolus injection. Because of the nonlinear signal response of CMR perfusion imaging as a function of gadolinium concentration, care must be taken to measure the AIF accurately using either a dual-contrast or a dual-bolus approach, and the signal intensity needs to be converted into gadolinium concentration units before modeling. However, development of perfusion mapping techniques may make the conversion of signal intensity curves to gadolinium concentration units unnecessary (96). A number of approaches have been used to determine MBF, including Fermi function deconvolution, compartmental modeling, and distributed parameter models (Central Illustration) (97).

Initial canine and porcine models assessing CMR-derived MBF showed excellent correlation (r > 0.90) with gold-standard microsphere analysis (98,99). Since then, a number of human studies have been performed. In stable CAD, there was good agreement in global MBF measurements between CMR and 13N-ammonia PET, with r = 0.92 (100). However, correlation worsened when comparing regional MBF (101). When comparing patients with chest pain and risk factors for MVD with normal patients, significant reductions in stress MBF and global MPR were noted in the MVD group (102). Liu et al. (102) showed reductions in stress MBF and global MPR in patients with nonobstructive CAD, specifically shown in the group with an elevated index of microvascular resistance (102). Index of microvascular resistance is an invasive thermodilution method to assess microvascular obstruction and has been shown to affect prognosis after an acute coronary occlusion, and it is being used as a measure of MVD in nonobstructive CAD (6,103). CMR-derived MPR index detected MVD defined by invasive coronary reactivity testing with sensitivity and specificity of 73% to 74% in symptomatic women without CAD (104). In a similar cohort, impaired MPR index correlated with elevation in native T1, suggesting a possible connection between microvascular disease and diffuse fibrosis (105).

Previously, one of the major limitations of CMR-derived MBF was the amount of time required for post-processing because of the lack of automated pipelines. Recently there have been a number of studies assessing automated perfusion mapping. Use of automated inline perfusion mapping showed excellent intrastudy and interstudy repeatability compared with PET quantitation of MBF (106). Kotecha et al. (107) successfully used automated pixel-wise perfusion mapping to differentiate MVD from multivessel CAD. Hsu et al. (96) recently showed that automated MBF measurements made at the time of first-pass perfusion imaging reveal similar results to other studies with regard to reductions in stress MBF and global MPR.

There are limitations to CMR-derived MVD assessment, including imaging artifacts, examination length, and lack of widespread availability of quantitative first-pass sequences (44). In addition, gadolinium has restricted use in class 4 and 5 chronic
kidney disease, and there is a reduction in the extraction of gadolinium with increasing flow rates, altering the quantification of MBF (44). However, a recent study revealed promising results with stress T1 parametric mapping as a noncontrast method to identify patients with MVD (102). In addition, arterial spin labeling is a noncontrast cardiac magnetic resonance sequence that imparts a magnetic tag on the freely diffusible water protons of arterial blood that differ from the magnetization of surrounding tissue, thus allowing measurement of the “tagged” flow (108). Currently arterial spin labeling is in the technological developmental stage as a non-contrast method for MBF quantification (39,108,109). Despite its limitations, one clear advantage with CMR is the lack of radiation exposure. In addition, ongoing advancements in technology will shorten the examination, improve patient tolerability, and likely reduce costs. More studies are needed to show the prognostic benefit and clinical utility of CMR assessment of MVD (Table 2).

**FUTURE DIRECTIONS**

The ultimate goal of identifying coronary MVD is to define prognostic differences, therapeutic interventions, and treatment approaches. Currently, studies that address treatment and interventions are limited by variability in defining MVD and small sample size. There are no studies that define any prognostic benefits from the treatment of MVD (110). As described earlier, there is a worse prognosis for symptomatic MVD, and therefore, many practitioners are using interventions similar to the treatment of nonobstructive single-vessel CAD. This includes lifestyle changes by encouraging diet, exercise, and smoking cessation (111). In addition, treatment of modifiable risk factors such as hyperlipidemia, hypertension, and diabetes is also pursued.

There is 1 clinical randomized control trial (NCT03417388) currently recruiting that will assess the prognostic and symptomatic benefit of intensive treatment with statins, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and aspirin versus usual care in women with suspected MVD. This is a proper initial step as a treatment approach, but MVD is more complex and mediated via multiple pathways. Now with noninvasive MPR quantification, accurately identifying patients with MVD should be less intensive; in addition, improvements in MPR can be correlated with symptoms to determine success of a particular treatment. Further studies are needed assessing the targeted treatment of MVD in other pathologies such as heart failure with preserved ejection fraction, which has no clear prognostically beneficial treatments.

**CONCLUSIONS**

A number of imaging methods are presently available to measure MBF in the setting of MVD. MBF assessment in obstructive CAD has demonstrated prognostic and clinical benefit (82). Recently, more studies have been performed using MBF measures to diagnose symptomatic MVD. Many of the modalities have been validated in the quantification of MBF, an important first step. Quantifiable endpoints will help with future clinical studies. Recent studies have shown success in correlating abnormal MPR to symptoms in nonobstructive CAD. PET has the most clinical and prognostic data compared with the other modalities, but CMR-derived MBF measures are being increasingly used to assess clinical utility and response to treatment. A few algorithms have been proposed in the clinical evaluation of microvascular angina and diagnosis of MVD, with the use of PET as the diagnostic imaging modality for the evaluation of MVD.

**HIGHLIGHTS**

- The authors discuss the nuances of MBF and MPR quantification in imaging modalities.
- Each modality, with advantages and disadvantages, has played a role in detecting MVD.
- PET-derived MBF offers the most prognostic data to date on the impact of MVD.
- Research on MBF quantification by CMR is growing as CMR becomes more accessible.
perfusion abnormalities and MBF quantification \cite{70,112}. CMR measures of MBF remain in the research realm and are not yet fully vetted for clinical use. Clinically, the type of imaging modality used is dependent on local availability of the technology, as well as risk/benefit analysis and cost to the patient. Additional studies are currently examining integrative imaging approaches and regional versus global MPR assessments; this approach shows promise for improving measurement precision \cite{88}. Even though our understanding of mechanisms and therapy for MVD is significantly less than that for obstructive epicardial disease, advances in cardiac imaging will soon allow improved identification of this disease, ultimately leading to improved therapeutic approaches.

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**KEY WORDS** cardiac magnetic resonance, computed tomography, microvascular dysfunction, echocardiography, positron emission tomography, quantitative perfusion
4-Dimensional Intracardiac Echocardiography in Transcatheter Tricuspid Valve Repair With the MitraClip System

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TRANSCATHETER TRICUSPID VALVE REPAIR (TTVR) USING THE MITRACLIP SYSTEM (ABBOTT STRUCTURAL Heart, Santa Clara, California) has demonstrated safety and efficacy (1). Procedural success, which consists of optimal leaflet insertion and reduction in tricuspid regurgitation (TR), is predictive of favorable outcomes (1). Transesophageal echocardiography (TEE) has been the pillar of intraprocedural imaging in TTVr, particularly with the tricuspid clip procedure. However, acoustic shadowing of the clip delivery system can limit confirmation of sufficient leaflet insertion during grasping and clip closure.

FIGURE 1 4-Dimensional ICE Catheter Position in the RA on Fluoroscopy

The 4-dimensional (4D) intracardiac echocardiography (ICE) catheter (Siemens Healthineers, Erlangen, Germany) (white arrow) is 12.5-F in diameter and is inserted and positioned at the right atrium (RA) via the left femoral vein. Compared with the 2D ICE catheter, the longer and wider ultrasound array on the 4D ICE catheter provides additional stability in image acquisition. The MitraClip (asterisk) is positioned in the right ventricle.
**FIGURE 2 2-Dimensional ICE View Showing Severe Tricuspid Regurgitation**

(A) The 2D ICE view (Video 1) showing all 3 tricuspid leaflets, which demonstrate (B) severe tricuspid regurgitation (Video 2). Abbreviations as in Figure 1.

**FIGURE 3 Biplane Dual View Showing Severe Tricuspid Regurgitation**

Biplane dual views with 4D color Doppler overlay (Video 3) showing severe tricuspid regurgitation in orthogonal views (top) and RA and right ventricular (RV) views (bottom). Abbreviation as in Figure 1.
Once the RV inflow view (upper left) is acquired, the multiplane feature simultaneously identifies the orthogonal view (upper right), with an en face reconstructed 2D view (bottom left) and 3D en face atrial view (bottom right) in real-time. The green circular cursor can be placed to identify the (A) septal (S) (Video 4), (B) anterior (A) (Video 5), and (C) posterior (P) (Video 6) leaflet on multiple views. Abbreviations as in Figures 1 and 3.
FIGURE 5  Steerable Guide Catheter Visualized in the RA With Real-Time 3D View

The steerable guide catheter (white arrow) can be seen in the RA. This is the view to visualize the exit of the MitraClip catheter delivery system (Video 7). Abbreviations as in Figures 1 and 3.

FIGURE 6  Clip Delivery System Exiting the SGC

The MitraClip clip delivery system (CDS) (orange arrow) is seen exiting the steerable guide catheter (SGC) (Video 8). TV = tricuspid valve.
FIGURE 7  MitraClip Steering Towards the TV

The MitraClip (orange arrow) being steered from the (A, Video 9) septal side toward the (B, Video 10) TV. The steerable guide catheter (white arrow) is visualized.

FIGURE 8  Biplane Dual View: MitraClip at the Location of Tricuspid Regurgitation

Tricuspid valve biplane views (A) without and (B) with color Doppler overlay. The MitraClip (orange arrow) is positioned at the TV where the tricuspid regurgitation jet is located (Video 11). Orthogonal views (top) and real-time 3D atrial and ventricular views (bottom) can be simultaneously displayed. Abbreviations as in Figures 1, 3, and 6.
FIGURE 9 The MitraClip Crossing the TV

(A) The MitraClip XTR (orange arrow) with arms opened positioned above the TV where the regurgitant jet is located (Video 12). (B) The MitraClip is positioned in the RV just below the A and S leaflets (Video 13). Abbreviation as in Figure 6.

FIGURE 10 Biplane Dual Views Showing the MitraClip XTR in RV With Clip Arms Open

The grasping view (top right) showing the A and S leaflets on top of the MitraClip arms (Video 14). The green circle confirms the anterior leaflet on real-time 3D RA and ventricular views (bottom). There is no acoustic interference of the clip delivery system against the tricuspid leaflets, potentially compromising image quality and confirmation of leaflet grasping. Other abbreviations as in Figures 1, 3, and 4.
The upper right shows a crosshairs image properly aligned to the TV leaflets with confirmation of insertion of both A and S leaflets (Video 15). Abbreviations as in Figures 4 and 6.
FIGURE 12 Multiplane Reconstruction View Showing Second MitraClip XTR Grasping P and S Leaflets

The top show the crosshairs image properly aligned to the TV leaflets and second MitraClip XTR (orange arrows) and the delivery system to avoid acoustic interference of the first clip delivered (Video 16). Proper alignment of the crosshairs in relation to the TV leaflets and clip arms during the second or third clip deployment is important to avoid compromise of image quality and confirmation of leaflet grasping. Abbreviations as in Figures 4 and 6.
Two MitraClip XTRs (orange arrows) are in place showing improvement in tricuspid regurgitation to mild, with corresponding 3D en face view at the lower right (Video 17). Abbreviation as Figure 1.
Intracardiac echocardiography (ICE) is a potential adjunctive intraprocedural imaging tool in TTVr with the MitraClip (2), but technology has been limited to 2-dimensional (2D) views; catheter stability can compromise image acquisition and quality. Four-dimensional (4D) ICE may overcome the limitations of TEE and 2D ICE during the tricuspid clip procedure by providing improved tricuspid valve imaging during leaflet grasping. Our paper aims to demonstrate the feasibility of using 4D ICE during TTVr with the MitraClip system in 5 cases at 2 institutions (Figures 1-14).

CONCLUSIONS

Our case series demonstrated the usefulness of 4D ICE in guiding transcatheter tricuspid edge-to-edge repair with the MitraClip system. We believe that this complementary approach of using TEE and 4D ICE can help guide other TTVr (e.g., edge-to-edge, annuloplasty) and even transcatheter tricuspid replacement procedures.

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KEY WORDS intracardiac echocardiography, MitraClip, tricuspid regurgitation

APPENDIX For supplemental videos, please see the online version of this paper.
IMAGING VIGNETTE

4-Dimensional Transesophageal Echocardiographic Guidance During TAVR With BASILICA

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BASILICA (BIOPROSTHETIC OR NATIVE AORTIC SCALLOP INTENTIONAL LACERATION TO PREVENT Iatrogenic Coronary Artery Obstruction) is an emerging technique to avoid coronary obstruction during transcatheter aortic valve replacement (TAVR) (1). Although fluoroscopic visualization during BASILICA is critical (2), the latest 4-dimensional (4D) echocardiographic technology (3D real-time), with Multivue and transillumination (TrueVue) rendering capabilities (Philips Healthcare, Amsterdam, the Netherlands), can be complementary to fluoroscopy for procedural guidance and in pinpointing the location of leaflet laceration. Our paper aims to demonstrate the feasibility of using 4D transesophageal echocardiographic (TEE) guidance to perform BASILICA during TAVR.

Our patient was an 84-year-old woman who presented with symptomatic severe native aortic valve stenosis and was deemed high risk for surgery due to her chronic kidney disease and frailty. Multidetector computed tomography revealed a tall left aortic valve cusp with low left main coronary ostium and sinus heights (Figures 1 and 2). Our team decided to perform BASILICA to avoid left main coronary obstruction during TAVR.

Four-dimensional TEE is a valuable complement to fluoroscopy in guiding the BASILICA procedure to prevent coronary obstruction in TAVR (Figures 3 to 24) (3). However, in BASILICA, in valve-in-valve TAVR with stented bioprosthetic valves that have failed, 4D TEE may be limited in its usefulness due to acoustic shadowing of the bioprosthetic valve stent frame against the catheters and the bioprosthetic valve leaflet.

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**FIGURE 1** Aortic Root Anatomy on Multidetector Computed Tomography

Using 3Mensio Valves Software version 9.0 (Pie Medical Imaging, Maastricht, the Netherlands), (A) annular dimensions measured a mean diameter of 22.0 mm, area of 377 mm² and a perimeter of 69.6 mm, suitable for a 26-mm Evolut PRO (Medtronic Inc, Minneapolis, Minnesota) transcatheter valve. (B) Left aortic sinus measured 27.4 mm, just slightly larger than the minimum threshold to implant a 26-mm Evolut PRO valve. Note the calcified and bulky non-coronary cusp (asterisk) would have potentially pushed the transcatheter valve more towards the left sinus and increased the risk of left main coronary obstruction.

**FIGURE 2** Multidetector Computed Tomographic Analysis of Left Main Coronary Obstruction Risk in TAVR

(A) Left main height (4.3 mm) and left sinus height (16.4 mm) were relatively low compared to the tall left aortic valve cusp (asterisk). (B) The left cusp length measured 15.1 mm, suggesting extremely high risk of left main coronary obstruction due to left cusp closing off the left sinus. SoV — Sinus of Valsalva.
FIGURE 3  Four-Dimensional TEE (3D Real-Time) TrueVue Showing En Face View of the Aortic Valve

The left aortic valve cusp is positioned at the top (arrow) (Video 1). 3D = 3-dimensional; TEE = transesophageal echocardiography.

FIGURE 4  Biplane TEE Showing a Pachyderm Catheter on Top of the Left Aortic Valve Cusp

A pachyderm catheter (orange arrows) housing the stiff guidewire for leaflet piercing can be seen near the center of the left aortic valve cusp (orange asterisk) (Video 2).
Position of the pachyderm catheter (asterisk) relative to the left aortic cusp (arrows) (Video 3). The long cusp length relative to the low-lying left main coronary ostium and low left sinus height is shown, as evaluated by pre-procedural multidetector computed tomography (Figure 2). A gooseneck snare is also seen in the left ventricular outflow tract (LVOT), which has been placed to snare the stiff guidewire after it pierces the left aortic valve leaflet.

(A and B) En face and (C) side views showing advancement of the Astato XS 20 stiff guidewire (Asahi-Intecc USA Medical, Tustin, California) (asterisk) (Video 4) piercing the left aortic valve leaflet and advancing into the LVOT and through the gooseneck snare. Because the true left-cusp en face view was not achievable by fluoroscopy (A and B), TEE guidance to align the catheter to the center of the leaflet and optimize the location for leaflet piercing was crucial. Abbreviations as in Figures 3 and 5.
**FIGURE 7** Biplane TEE View Showing Piercing of the Stiff Guidewire Via the Pachyderm Catheter Through the Left Aortic Valve Leaflet on the Long Axis

The TEE long-axis view shows piercing of the stiff guidewire via the pachyderm catheter (asterisk) through the left aortic valve leaflet (arrow) on the long-axis (Video 5). TEE = transesophageal echocardiography.

**FIGURE 8** 3-Dimensional Real-Time TEE of the Aortic Valve Long Axis

Multivue enhances the visualization of the pachyderm catheter (red asterisk) and the stiff guidewire (black arrows) in the LVOT after piercing through the left aortic valve leaflet (black asterisk), encased by the gooseneck snare (white arrow) (Video 6). Abbreviations as in Figures 3 and 5.
**FIGURE 9** 3-Dimensional Real-Time TEE of the Aortic Valve Short Axis

Multivue enhances the visualization of the pachyderm catheter (arrows) positioned on top of the left aortic valve cusp (asterisk) after leafllet piercing (Video 7).

**FIGURE 10** Fluoroscopy on 2 Views Confirming Successful Loop Formation Following Wire Snaring

Fluoroscopy on (A) en face and (B) side views showing successful snaring of the Astato wire and formation of the loop through the left leafllet of the aortic valve for leafllet laceration.
FIGURE 11  Fluoroscopy on En Face and Side Views Showing the 2 Looped Catheters

(A) En face and (B) side views showing the looped catheters. The 2 catheters looped through the aortic valve leaflet are in close proximity, but not in contact (arrow) before electrosurgical laceration of the left aortic valve leaflet.

FIGURE 12  4-Dimensional TEE of the Aortic Valve Short Axis

TrueVue highlights visualization of the pachyderm catheter (black asterisk) on top of the left aortic valve cusp (red asterisk) after leaflet piercing (Video 8). TEE – transesophageal echocardiography.
Transluminal rending using TrueVue with the Virtual Lightsource feature further enhances the localization of the pachyderm catheter (asterisk) on top of the left aortic valve cusp (arrows) after leaflet piercing (Video 9). Compared with Videos 1 and 2, one can be confident that the piercing occurred almost at the center of the left cusp facing the left main coronary ostium. TEE = transesophageal echocardiography.

The left aortic valve cusp was lacerated with pachyderm (orange asterisk) and right Judkins (black asterisk) catheters and the kinked “Flying V” of the stiff guidewire (arrow) pulled as 1 unit (Video 10).
FIGURE 15 4-Dimensional TEE of the Aortic Valve Short Axis on TrueVue After Successful BASILICA

TrueVue confirmed successful leaflet laceration with a mobile split segment (black arrow) facing the left main coronary ostium (Video 1). BASILICA = Bioprosthetic or Native Aortic Scallop Intentional Laceration to Prevent Iatrogenic Coronary Artery Obstruction; TEE = transesophageal echocardiography.

FIGURE 16 3-Dimensional Real-Time TEE of the Aortic Valve Short Axis After BASILICA

Multivue showed a small regurgitant jet (black arrow) at the location of leaflet laceration (Video 12). TEE = transesophageal echocardiography.
Both TEE long- and short-axis X-plane views showed the lacerated left aortic valve cusp (yellow arrow) with a gap (orange arrow) facing the left main coronary ostium (asterisk) (Video 13). Abbreviations as in Figures 3 and 15.

TEE long- and short-axis views showing a regurgitant jet at the lacerated left aortic valve cusp (Video 14). Abbreviations as in Figures 3 and 15.
FIGURE 19  4-Dimensional TEE of the Aortic Valve Short Axis With Evolut Valve Delivery Catheter

TrueVue showing the Evolut PRO (Medtronic Inc, Minneapolis, Minnesota) transcatheter valve delivery catheter (asterisk) across the aortic valve (Video 15). TEE = transesophageal echocardiography.

FIGURE 20  Fluoroscopy Showing Evolut PRO Transcatheter Valve Implantation

The Evolut PRO transcatheter was placed at the (A) initial position and (B) at 80% deployed with implant depth visualized by angiography (Videos 16 and 17).
FIGURE 21 Long- and Short-Axis Views on TEE With Color Doppler After Evolut PRO Transcatheter Aortic Valve Implantation

(A) Long- and (B) short-axis views. TEE showed mild paravalvular aortic regurgitation (arrow) after balloon post-dilatation of the Evolut PRO, with no evidence of left main coronary flow compromise (asterisk) (Videos 18 and 19). TEE = transesophageal echocardiography.

FIGURE 22 Short-Axis Aortic Valve View on TEE With Color Doppler After Evolut PRO Transcatheter Aortic Valve Implantation

Color Doppler showed laminar flow of the left main (arrow), left anterior descending (hatch symbol), and circumflex (asterisk) arteries after transcatheter valve deployment (Video 20). TEE = transesophageal echocardiography.
Final C-tab (asterisk) position was at the inner curve of the aortic root, suggesting good commissural alignment as reported by Tang et al. (3).

The final C-tab position on the fluoroscopic 3-cusp coplanar view was co-registered on pre-procedural computed tomographic (CT) image derived from 3Mensio Valves software. (A) The blue eye icon represents the position of the 3-cusp coplanar fluoroscopic view. An orange circle with 15 spokes (depicting an Evolut PRO valve with 15 crowns) is overlaid onto the annular plane and (B) the Fluoro-CT co-registration (from Figure 23) was used to evaluate commissural alignment at the sinus level between the Evolut PRO neo-commissures (orange circles) and native aortic valve commissures (white arrows) (3). In this case, good commissural alignment was achieved. LM = left main; RCA = right coronary artery.
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KEY WORDS BASILICA, TAVR, transesophageal echocardiography

APPENDIX For supplemental videos, please see the online version of this paper.
Multimodality Cardiovascular Imaging in the Midst of the COVID-19 Pandemic
Ramping Up Safely to a New Normal
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The coronavirus disease 2019 (COVID-19) pandemic created an unprecedented disruption to routine patient care (1). Health care professionals scrambled within weeks to attend to the surge of affected individuals amid concerns of hospital capacity and scarcity of personal protective equipment (PPE). Elective procedures, including cardiovascular imaging studies, in stable patients were deferred. Indeed, use of cardiovascular imaging decreased by 50% to 90%, with a shift in the use of certain modalities to conserve much needed PPE or lessen exposure risk to health care professionals.

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Several professional cardiovascular societies have put forth recommendations on appropriate use of imaging and needed precautions in the early phase of the pandemic (2–7). Currently, the COVID-19 pandemic has peaked in some parts of the world, but incident infection is still ongoing at different rates in other regions. Communities, health care professionals, and medical professional societies are considering how to “reopen” medical practices and imaging laboratories in this challenging milieu, while safeguarding the health of both the public and health care professionals (8–11). This document, initiated by the Editors of JACC: Cardiovascular Imaging and developed in collaboration with the Cardiovascular Imaging Council of the American College of Cardiology, addresses strategies and considerations on how to ramp up multimodality cardiovascular imaging laboratories to serve patients with suspected or known cardiovascular disease and their clinicians, and achieve it safely in an environment of an abating but continued pandemic. Recognizing that practice patterns and policies vary depending on institution and locale, these recommendations are not meant to be restrictive, but rather are meant to serve as a general framework during the COVID-19 pandemic and its recovery phase. Once the pandemic abates and the disease is controlled, the use and prioritization of various modalities would revert to usual and customary practice.

BALANCING SAFETY AND PATIENT CARE

The initial response to the COVID-19 pandemic resulted in a significant reduction of nonurgent medical and imaging activity. As we move on from this phase of “lockdown,” we need to balance the risks of infection with the risk posed by inadequate management of chronic medical conditions. Where we stand with this balance depends on community prevalence of active disease. The notion of “ramping up” assumes that transmission rate is falling, or low and stable, and will vary by region and country. There will likely continue to be regional flares of COVID-19 infection and possibly times that laboratories need to revert to an emergency posture, similar to earlier phases of the pandemic.

Re-establishing a more normal clinical operation depends on integrated communication among patients, referring physicians, the imaging teams, and administrative staff. There are few aspects to the resumption of “routine” activity that encompass patient and societal health, safety of health care professionals, choice of imaging test, and considerations for scheduling. These are summarized in Table 1.

PATIENT AND SOCIETAL HEALTH. Hospitals and medical centers are a potential source of viral transmission, and we hold a duty of care not only to our patients, but also to our staff and the wider community. Hand hygiene, sanitizing measures, masks, and social distancing will be part of our lives for the foreseeable future. This necessitates a redesign of patient experience and clinic facilities. Both clinical referral offices and imaging laboratories should ensure patients are educated with regard to COVID-19 safety protocols and screened for any COVID-19 symptoms prior to the date of examination. Some institutions might opt for COVID-19 testing prior to procedures—they should ensure that these are done expeditiously and minimize multiple trips to the health care facility. However, a negative COVID-19 test is not sufficiently foolproof and should not detract from usual precautions while performing the test. Patients with any COVID-19 symptoms or known exposure prior to their appointment should be instructed to reschedule examinations that could be safely deferred.

Upon arrival to the facility, health screening should be performed for both patients and health care professionals including checks for temperature and symptoms suggestive of COVID-19. The number of accompanying visitors should be kept to a bare minimum (0 to 1). The number of seats and a change in the seating arrangement should be instituted to accommodate physical distancing. For the safety of patients and health professionals, the number of needed personnel and contact time to perform the test should be kept at a minimum, but this should not be attained at the expense of test quality and acquiring the needed information. Equipment should be appropriately cleaned and disinfected based on patients’ COVID-19 status and local infection control policies.

SAFETY OF HEALTH CARE PROFESSIONALS. The SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) virus is transmitted by droplets and contact routes. In COVID-19, a significant number of patients may be asymptomatic and may transmit the virus (1). The recommended PPE for health care professionals in cardiovascular imaging laboratories are shown in Table 2. Appropriate PPE should be mandatory, as per institutional guidelines and routine training of PPE use provided. For patients without symptoms or low risk for COVID-19, standard precautions include a surgical mask, gloves, hand

ABBREVIATIONS AND ACRONYMS

CAC = coronary artery calcium
CAD = coronary artery disease
CMR = cardiac magnetic resonance
COVID-19 = coronavirus disease 2019
CT = computed tomography
CTA = computed tomography angiography
PET = positron emission tomography
POCUS = point-of-care ultrasound
PPE = personal protective equipment
SPECT = single-photon emission tomography
TEE = transesophageal echocardiography
TTE = transthoracic echocardiography
TABLE 1 Balancing Safety and Patient Care in the COVID-19 Era

| Patient and societal health |  |
|-----------------------------|---|
| Practice hand hygiene and social distancing in public and in waiting rooms, limit accompanying visitors (0–1), wear masks. |  |
| Keep needed personnel and equipment in the testing room at a minimum. |  |
| Institute antiviral sanitation of rooms and equipment between studies and at the end of the day. |  |

| Safety of health care professionals |  |
|------------------------------------|---|
| Administer health screening of patients and professionals (symptoms, temperature check). |  |
| Practice hand hygiene and social distancing, wear masks. |  |
| Use appropriate PPE for the imaging lab and for tests being performed. |  |
| Strongly consider testing for COVID-19 before TEE and possibly before exercise stress, as available. |  |
| Perform aerosol-generating procedures preferably in a dedicated, negative-pressure room with good air circulation. |  |

| Choice of cardiovascular testing |  |
|---------------------------------|---|
| Use appropriate testing that emphasizes impact on health and clinical management. |  |
| Choose the best test that provides essential information for the clinical condition. |  |
| Avoid layering of multiple tests. |  |
| Balance test safety, exposure to health care providers, and PPE resource use. |  |
| Choose alternate tests with similar accuracy and less COVID-19 related safety concerns, if possible. |  |
| Relate COVID-19 safety concerns of testing, PPE need, and resource use to the phase of the pandemic regionally and to institutional policies locally. |  |

| Scheduling considerations |  |
|---------------------------|---|
| Allow adequate time in between studies for sanitation. |  |
| Adjust to slow throughput and workflow of laboratories due to COVID-19 precautions. |  |
| Consider extended hours and opening laboratories on weekends to accommodate patient volumes and backlogs. |  |
| Prioritize backlogs of patients according to clinical need and impact of test. |  |

COVID-19 = coronavirus disease 2019; PPE = personal protective equipment; TEE = transesophageal echocardiography.

TABLE 2 Exposure Risk and Needed PPE During Cardiovascular Imaging in the COVID-19 Era

| CV Imaging Procedure | Exposure Type | Personal Protective Equipment |
|----------------------|---------------|-------------------------------|
| Cardiovascular CT/CMR | Droplet/contact | Surgical mask + gloves |
|                      |                | Surgical mask + face shield + gown + gloves* |
| Pharmacological stress (SPECT/PET/CMR) | Droplet/contact | Surgical mask + gloves |
|                      |                | Surgical mask + face shield + gown + gloves* |
| TEE/pharmacological stress echocardiography | Droplet with close contact (face-to-face) | Surgical mask + gloves |
| Exercise test (SPECT/echocardiography/ treadmill/MVO2)* | Possible aerosol generating | N95 or N99 mask + face shield + appropriate surgical gown + gloves OR Reusable PAPR + surgical gown + gloves |
| TEE* | Aerosol generating | N95 or N99 mask + face shield + appropriate surgical gown + gloves OR Reusable PAPR + surgical gown + gloves |

*For safety, test is best performed in a negative-pressure room with a good air exchange. COVID-19 testing is currently at most 80% to 85% sensitive; an N95 or N99 mask or reusable PAPR is currently still advised for optimal protection.

CMR = cardiac magnetic resonance; CT = computed tomography; CV = cardiovascular; MVO2 = myocardial oxygen consumption during exercise; PAPR = powered air-purifying respirator; PET = positron emission tomography; SPECT = single-photon emission tomography; TEE = transthoracic echocardiography; other abbreviations as in Table 1.
active disease may modify both testing choices and PPE requirements in the future.

Any staff member that develops COVID-19 symptoms or comes into contact with a known COVID-19 case without proper PPE should be immediately quarantined and only return to work after satisfying institutional criteria. Trainees should maintain physical distancing with each other and attending physicians. Minimizing exposure of trainees and nonessential staff was vital in the acute phase of the pandemic for their own safety and for conservation of PPE. However, as the community prevalence falls and more PPEs are available, these policies should be revisited in order to provide effective training.

Reading rooms should also follow sanitary requirements and physical distancing. Communication with referring physicians using digital media can be performed where applicable. Last, rostering of medical and allied health staff needs to be planned so that an infection within 1 team will not necessarily compromise another.

**CHOICE OF CARDIOVASCULAR TEST.** During the initial phase of the pandemic, the emphasis was on triage and performance of essential studies only. In the long term, this is of course potentially detrimental. In an environment of lower infective risk, the emphasis is changing to appropriate use (Central Illustration). The appropriate use criteria are widely accepted (15-19). Although there will always be exceptions to “rarely appropriate” indications, based on the patient’s clinical setting, particular attention should be paid to routine studies in asymptomatic patients. In the post-COVID-19 era, the known financial implications of redundant testing are compounded by other safety aspects outlined above. It remains difficult to provide uniform guidelines about test selection because this is often dependent on local availability, quality, and expertise. Nonetheless, now more than ever, there is the need to develop a consensus approach to, for example, noninvasive testing for coronary artery disease (CAD) or quantification of valvular heart disease at a local level.

During the acute phase of the pandemic, there was a massive reduction in the performance of TEE. However, as TEE remains the most reliable imaging approach for the detection and assessment of bacterial endocarditis, its increased use with appropriate precautions is warranted (20). Carefully selected, elective studies may be safely performed in the coming months by the use of COVID-19 testing (if available) and needed PPE for practitioners. Appropriate emphasis has been made on reducing the encounters of any potential interaction between a patient and a person collecting images. Often, this has led to a targeted examination, particularly...
echocardiography. This also is unattractive in the long term, as one of the benefits of echocardiography is the detection of significant unsuspected findings, which are likely to be missed with focused exams. It would be preferable to put in place an examination protocol that covers the full breadth of imaging and Doppler but achieve it with the minimum possible contact with the patient (e.g., using simultaneous multiplanar acquisitions). From a research standpoint, the new era should produce a new emphasis on high-quality 3-dimensional acquisitions with off-line processing, as well as robotic image acquisitions, controlled by sonographers removed from the patient, or eventually by automated algorithms based on image recognition. Such devices are already available, but further advances in haptics will enhance safety and effectiveness.

**SCHEDULING CONSIDERATIONS.** Laboratories are likely to face significant rush for cardiac imaging services due to pent-up demand over the last couple of months. It will be important to reopen these services thoughtfully, keeping in mind both safety and quality. The focused statements from cardiovascular societies are foundational documents that can help with planning and executing the return to normal level of clinical services in cardiac imaging.

Operations in laboratories are slower and disrupted by the pandemic and will require a redesign within institutions. Patients are concerned about contracting COVID-19 in medical institutions, partly accounting for fewer clinic visits and test deferral. Reaching out to patients, addressing their concerns, and stressing the safety measures undertaken are paramount. Allowing adequate time in between studies for sanitation of equipment, beds, and chairs will cause unavoidable time delays and may necessitate expanded hours of operations, possibly including weekends to accommodate testing requests. For those needing to use public transport, avoidance of rush-hour travel is prudent, providing another reason for labs to change opening and closing times. Owing to the acute phase of the pandemic and to slowing operations, backlogs of patients are likely present and need to be managed. In this scenario, patients will need to be prioritized through coordination between laboratory staff and referring physicians depending on the relative urgency of the clinical setting and impact of the test on patient management.

**CONSIDERATIONS FOR ECHOCARDIOGRAPHY**

Among imaging modalities, transthoracic echocardiography (TTE) is frequently the first line imaging test in evaluating patients with suspected or known cardiovascular disease (15,17-19,21). TTE has the advantage of a bedside examination to evaluate patients in the emergency department or those hospitalized, in isolation, or in the intensive care units, which proved particularly helpful in the care of COVID-19 patients. However, compared with other modalities, TTE acquisition necessitates the closest, face-to-face contact with the patient. TTE performance thus requires at a minimum a face shield in addition to a surgical mask and gloves; this PPE increases in the setting of a positive or suspected COVID-19 patient for all modalities (Table 2). TEE, on the other hand, is a potentially aerosolizing procedure that necessitates full PPE (Table 2). The American Society of Echocardiography has provided a comprehensive statement regarding protection of patients and providers during the outbreak and more recently during the recovery phase (2,9). These statements are foundational. We will address briefly echocardiography in the COVID-19 era and during the reopening phase of laboratories.

**TRANSTHORACIC ECHOCARDIOGRAPHY.** Because TTE is the most common imaging test performed on patients with COVID-19, attention to appropriate indications and PPE use is crucial. Recent data suggest that COVID-19 infection is frequently associated with myocardial injury, myocardial dysfunction, or clinical heart failure as seen in >50% of fatalities and >10% of survivors (22). Moreover, recent data from Wuhan and New York have suggested that an assessment of cardiac function, particularly right ventricular size and function, using limited TTE during the first week of hospital stay may be extremely insightful for early risk stratification of patients (23). With the ongoing COVID-19 pandemic, point-of-care ultrasound (POCUS) or limited TTE continue to play critical roles for driving decisions for patient care, especially for COVID-19-positive patients (24). POCUS can be particularly helpful in the hands of physicians experienced with echocardiography who are actively taking care of COVID-19 patients in the hospital. The benefits of POCUS include reduced time to diagnosis, easier disinfection, reduced costs, and help in triaging appropriate patients for limited or comprehensive echocardiograms. In intensive care units or hospital areas dedicated to COVID-19 patients, it is advisable to have a dedicated scanner, if possible. Although POCUS and limited examinations can be performed, it is imperative to emphasize the importance of comprehensiveness and quality of a study to assess and act on the information that is gleaned. The appropriate use of contrast enhancing agents for
TABLE 3 Role of Cardiovascular Imaging Specific to the COVID-19 Era: Minimize Risk, Reduce Resource Utilization, and Maximize Clinical Benefit

| Condition | Indication | TTE | TEE | CTA | CMR | Nuclear Cardiology |
|-----------|------------|-----|-----|-----|-----|-------------------|
| CAD/myocardial injury | After STEMI intervention in selected COVID-19(+) | ++++ | x | x | + | x |
| Stable NSTE/ACS | | ++++ | x | +† | + | +† |
| COVID-19(+) or suspected COVID-19 | | ++++ | x | ++++ | ++++ | ++++ |
| Low risk for COVID-19 | | ++++ | x | ++++ | ++++ | ++++ |
| Chest pain with clinical suspicion of CAD | | x | ++++ | ++++ | ++++ | + |
| Known CAD | | x | ++++ | ++++ | ++++ | + |
| Cardiomyopathy/arrhythmias | New onset heart failure/cardiomyopathy | ++++ | + | ++++ | ++++ | ++++ |
| | Myocardial viability imaging | + | x | ++++ | ++++ | ++++ |
| | LAA evaluation prior to restoration of sinus rhythm | x | +† | ++++ | + | x |
| Valvular/structural | Endocarditis (native or prosthetic valve) | +++ | ++++ | + | + | + |
| | Endocarditis, invasive complications (e.g., abscess, pseudoaneurysm) | + | ++++ | ++++ | + | + |
| | Prosthetic valve dysfunction (pannus, thrombus, calcification) | ++++ | +† | ++++ | + | x |
| | Structural intervention planning | ++++ | +† | ++++ | + | x |
| | TAVR, LAA occlusion | +++ | +† | ++++ | + | x |
| | Mitral and tricuspid valve repair | ++++ | +† | ++++ | + | x |
| Masses/other | Cardiac mass evaluation | ++++ | +† | ++++ | ++++ | + |
| | Pericardial diseases | ++++ | +† | ++++ | ++++ | x |

All clinical scenarios in the table assume no active or asymptomatic COVID-19 disease, unless otherwise specified. 1+ to 4+ denote a measure of suitability for use during the peri-COVID-19 pandemic period and not necessarily a determination of any inherent diagnostic superiority of one modality over another or comparative efficacy. Strength of the indication and use of a test (1+ to 4+; X = rarely, if at all) and its traditional appropriateness for the clinical condition may be modified by the COVID-19 pandemic as noted. The table summarizes most common clinical indications relevant during the pandemic and cannot capture all nuances in clinical presentations which may affect appropriate test use. *Stress echocardiography has similar scoring to stress nuclear for the CAD and cardiomyopathy indications on this table. The stress type for all imaging modalities, where applicable, is pharmacological stress. Exercise stress has specific considerations during the active pandemic. †Reduced test use or priority compared with other tests because of COVID-19 risk exposure or need for more PPE. This reduction in use will undoubtedly lessen and be back to usual practices once the active infection rate of COVID-19 in the community is low and the pandemic is controlled. ‡Enhanced medical therapy and conservative approach when possible in view of COVID-19 status.

As patient referral to the echocardiography laboratory increases in the inpatient and outpatient settings with gradual resumption of operations, the emphasis on safety of patients and health care professionals is still paramount. TTE examinations should provide a comprehensive evaluation of cardiac structure and function for optimal interpretation and decision making. The appropriate indications for TTE are extensive (17,18,21) and are prioritized according to the seriousness of the clinical condition, scheduling backlog, and available PPE (9). Table 3 lists the use of TTE and other modalities in selected clinical scenarios and how the pandemic has affected their use. With the measures taken for safety and scheduling, TTE activity should be able to resume to a near normal state, with the expected slowing of daily operations afforded by the added safety precautions.

Good imaging practices can make the procedure safe and efficient in the peripandemic milieu:

- In COVID-19-positive or suspected patients, the clinical relevance of the indication for TTE is paramount.
- POCUS or limited TTE can help assist bedside evaluation of cardiac structure and function and is particularly helpful in COVID-19-positive patients to help expedite care and further triage patients who need a comprehensive TTE.
- The use of ultrasound-enhancing agents is essential in technically difficult studies to enhance assessment of regional and global function and attain a diagnostic study.
- As the pandemic is abating, comprehensive TTE should be aimed for with appropriate PPE and efficiency to address the myriad of clinical questions of cardiac and valvular function, pericardial diseases, and hemodynamics.

TRANSSESOPHAGEAL ECHOCARDIOGRAPHY. TEE is a powerful modality for the evaluation of cardiac structure and function in cases in which TTE may be limited or technically difficult, and for planning or guidance during interventional procedures. Because of the safety concerns regarding potential for aerosol generation during the procedure and need for scarce PPE, the use of TEE during the acute phase of the pandemic significantly decreased, almost to a halt. A shift also was seen in certain traditional TEE indications toward alternative imaging modalities, which may offer similar diagnostic accuracy with less safety risk to staff and resource use. This scenario was commonly seen in patients undergoing cardioversion...
in which computed tomography angiography (CTA) was used to exclude left atrial thrombus. Less common clinical scenarios were those with prosthetic valve dysfunction, evaluation of cardiac masses, or pericardial effusion in critically ill patients with technically difficult TTE. Of concern is that during the acute phase of the pandemic, a significant decrease in TEE was also seen in patients with suspected endocarditis of native or prosthetic valves or complications of endocarditis such as abscess or pseudoaneurysm. Table 3 shows the current indications and strength of TEE in common clinical scenarios and where its use decreased due to the COVID-19 pandemic.

As the rate of COVID-19 infections decreases, laboratories have gradually seen an increase in TEE procedures using appropriate safety measures. As more PPE is available and most centers have access to COVID-19 testing prior to the procedure, a return to appropriate use of TEEs in the clinical scenarios in which it performs best should be aimed for (Table 3). The following are few considerations for TEE in the waning of the pandemic, aiming for maximal safety and clinical impact:

- TEEs in the era of COVID-19 ideally should be performed in a negative-pressure room with good air circulation.
- Testing for COVID-19 prior to TEE is strongly encouraged, if available, to get interim results between 0 and 3 days before the procedure, with quarantine instituted from the time of the test to the procedure.
- A negative COVID-19 polymerase chain reaction test puts the asymptomatic patient in a low-risk category but does not exclude the disease completely. Although it may alleviate some of the apprehension around the test, maintaining appropriate PPE level is still advised, for the safety of all health care staff involved.
- TEE is uniquely helpful in clinical conditions such as native or prosthetic valve endocarditis and evaluation of associated complications.
- TEE is essential in planning edge-to-edge repair of mitral or tricuspid valves.
- Although TEE is particularly helpful in the assessment of left atrium and appendage prior to cardioversion, occluder device, or atrial fibrillation ablation, alternative testing was used during the early phase COVID-19 for safety concerns and PPE availability.
- As the disease wanes and with more PPE availability, there is a gradual increase in TEE use for its classic and appropriate indications, guided by local conditions and practices.
- The PPE needed for TEE may be re-evaluated in the future by health care professionals if the prevalence of the disease and immunity in the population permit.

CONSIDERATIONS FOR STRESS TESTING MODALITIES (SINGLE-PHOTON EMISSION TOMOGRAPHY/POSITRON EMISSION TOMOGRAPHY/ECHOCARDIOGRAPHY/CARDIAC MAGNETIC RESONANCE)

Stress testing is an essential approach in the evaluation and care of patients with suspected or known cardiovascular disease (15). This includes exercise or pharmacologic testing with any of the imaging modalities of nuclear imaging (single-photon emission tomography [SPECT]/positron emission tomography [PET]), echocardiography, or cardiac magnetic resonance (CMR). In the acute phase of the COVID-19 pandemic, exercise testing was avoided, mainly due to infectious risk. Medical therapy for cardiovascular disease in COVID-19 patients needs to be maximized and testing deferred whenever possible, particularly if clinically stable (Table 3). An exercise or stress test is an elective procedure. For indications of suspected CAD in this scenario, coronary CTA is preferred over exercise, but a pharmacological study may also be appropriate. If patients have typical crescendo angina despite optimal medical therapy, coronary angiography with possible percutaneous coronary intervention may be an optimal approach.

A subgroup of COVID-19 patients experience chest pain following the acute phase of infection. As the long-term cardiovascular sequelae of COVID-19 infection remain unknown, it is likely that physicians may want to consider using a diagnostic imaging procedure for assessment of CAD risk. As the pandemic is tapering, the use of stress testing is increasing gradually, with its required safety precautions. The American Society of Nuclear Cardiology, Society for Cardiovascular Magnetic Resonance, and American Society of Echocardiography have recently published guidance on re-establishment of care in laboratories (9-11). We hereby propose some considerations for the safe reinstitution of stress testing that pertain to all imaging modalities.

GENERAL SAFETY CONSIDERATIONS FOR STRESS TESTING. The following are safety considerations specific to stress testing, in addition to the general safety detailed previously.
• Know laboratory air circulation patterns—consult engineering on optimized equipment or staff positioning. Given the uncertainty regarding the aerosol generating capacity of exercise stress testing, it may be prudent to use a dedicated room for exercise testing, with negative pressure if possible.
• Allow time for air changes (outpatient facilities usually have a lower exchange than inpatient facilities) before cleaning surfaces and putting a new patient in the room.
• Avoid manual blood pressure measurement if possible. Automated blood pressure is commonly used and reasonably accurate in stationary patients undergoing pharmacological stress testing. For patients undergoing treadmill or bicycle exercise stress testing, accuracy of blood pressure readings may depend on equipment available.
• Personnel overseeing the test should maintain distance (6 feet or 2 m) to the patient whenever possible, with brief closer encounters as needed.
• Personnel involved should wear appropriate PPE, including mask, face shield (particularly during stress echocardiography), and gloves. When possible, the patient should be encouraged to exercise while wearing a surgical mask. If this is not possible, consider the use of face shields.

**CHOOSING EXERCISE VERSUS PHARMACOLOGIC STRESS.** The following are considerations for exercise versus pharmacological stress testing:

• In settings of moderate to high prevalence of active COVID-19 in the community, pharmacological stress is preferred over exercise, when clinically appropriate, because of added safety concerns and needed PPE during exercise.
• If pharmacological stress is used, careful history can provide information on functional capacity.
• If exercise is thought to be necessary, consider COVID-19 testing before the exercise test.
• If exercising, choose exercise protocols carefully to improve time efficiency. Match the appropriate protocol to the patient—slower protocols lengthen interaction time. A bicycle protocol is associated with lower peak ventilations per minute.
• When a very low prevalence of active COVID-19 is reached in the community, exercise may reclaim first choice when indicated, driven by its provision of much additional information and higher workloads than pharmacological stress.

**CONSIDERATIONS FOR TREADMILL TESTING AND CARDIOPULMONARY EXERCISE TESTING.** Cardiopulmonary exercise testing is an elective procedure and should be deferred during the acute pandemic phase because collection of exhaled air may enhance concentration of viral particles in the room. However, in the deceleration or indolent phase with low community prevalence of active infections, the use of exercise testing without imaging to assess exercise tolerance, assess arrhythmias during exercise, and determine myocardial oxygen consumption in evaluating patients for heart transplantation are all essential tests, the neglect of which may compromise patient care. The following are some considerations for stress testing in the COVID-19 era:

• Avoid cardiopulmonary exercise testing in patients with prior COVID-19 diagnosis unless clinical recovery is confirmed along with 2 negative COVID-19 tests.
• Assess whether pharmacological stress in association with imaging is an appropriate alternative test. Converting an exercise treadmill test to a pharmacological test is costlier. The precautions noted against exercise need to be weighed.
• Consider available questionnaires alternatively to estimate physical work capacity (e.g., Duke Activity Status Index).
• In heart failure patients being evaluated for transplantation or ventricular assist therapy, consider COVID-19 testing prior to determination of myocardial oxygen consumption during exercise. Also, consider alternatives such as a 6-min walk test that allow for safe distancing between the staff and patients.

**GENERAL CONSIDERATIONS FOR NUCLEAR CARDIOLOGY**

Nuclear imaging has a robust knowledge base of clinical experience, diagnostic value, and outcomes, and the increasing availability of PET significantly enhances its utility. It was one of the most widely used modalities in cardiac imaging before the COVID-19 pandemic and is likely to regain those usage levels as this pandemic gradually recedes. All commonly used cardiac nuclear imaging procedures are non-aerosolizing and have other advantages of relatively short contact time with the patient, largely automated and time-efficient protocols, and machines that do not need personnel to be in close proximity to the patient for operation. This can reduce spread of infection as well as conserve precious resources. Although cardiac nuclear imaging has minimal utility in managing the acute stages in COVID-19-positive patients, it becomes increasingly valuable as we reopen services to the general population.
Good imaging practices can make the procedure safe and efficient in the peripandemic milieu (3,10,26,27):

- Following best practices for the COVID-19 era, as recommended by various nuclear imaging societies.
- Using protocols that minimize study time without affecting test accuracy, e.g., stress only imaging where feasible and safe.
- Incorporating use of PET instead of SPECT where feasible.
- Avoiding protocols that can aerosolize (e.g., using pharmacological stress instead of exercise stress).

Nuclear cardiology studies are generally not needed in managing acute cardiac illness in COVID-19-positive patients. However, nuclear cardiology has an advantageous role in the peripandemic milieu in patients without known COVID-19 or its risk factors in the following (10,27-31):

- Evaluating ischemia in patients with known CAD.
- Evaluating patients with chest pain syndromes. It is particularly useful in patients that are not good candidates for anatomic noninvasive imaging (e.g., patients with stents, significant coronary calcification, dye allergy, risk of worsening renal function).
- Evaluating for myocardial viability.
- Screening for amyloidosis.
- Identifying inflammatory stages of sarcoidosis.
- Identifying infections in implanted devices.

**GENERAL CONSIDERATIONS FOR COMPUTED TOMOGRAPHY**

Computed tomography (CT) can be used to rapidly evaluate multiple forms of cardiac disease throughout all phases of the COVID-19 pandemic, with efficiency and safety (4). The selective use of CT has been shown to be valuable in the acute phase of COVID-19 and will likely serve an important role for new symptomatic or asymptomatic patients during the convalescent or chronic phase of their illness (15,16). As institutions begin to reintroduce full cardiovascular imaging services, CT will continue to allow for safe and rapid diagnosis of conditions ranging from CAD to valvular heart disease (8,15,18,19,21) (Table 3).

**CT IN ACUTE CORONARY SYNDROMES WITH KNOWN OR SUSPECTED COVID-19.** Patients with definitive ST-segment elevation myocardial infarction should proceed directly to expedited therapy (percutaneous coronary intervention or thrombolysis) as per local institutional protocol. In COVID-19-positive patients with elevated cardiac biomarkers, the differential diagnosis may include acute coronary syndrome, myocarditis, or myocardial injury (32). In this setting, the value of coronary CTA to help stratify risk and guide the need for and timing of intracoronary angiography is becoming increasingly established (33,34). Multiphase coronary CTA imaging can allow for an evaluation of left ventricular ejection fraction and regional wall motion abnormalities. Coronary CTA may enable the evaluation of myocarditis through a dedicated delayed iodine enhancement protocol at highly specialized centers (35). Overall, coronary CTA in this setting should only be considered if it is expected to result in a meaningful change to patient management or outcomes, as well as reduce resource use (i.e., avoid invasive angiography) (Table 3) (4).

- Coronary CTA may be useful in selected patients who have elevated cardiac enzymes, inconclusive electrocardiogram, and symptoms of possible acute coronary syndrome in order to exclude obstructive CAD.
- Coronary CTA may enable the evaluation of pulmonary embolism and incidental pulmonary findings such as pneumonia. If typical or atypical pulmonary findings are encountered, consultation with a radiologist with thoracic expertise is encouraged.

**CT IN THE DECELERATION OR INDOLENT PHASE OF COVID-19.** Coronary CTA may have distinct advantages in the deceleration and indolent phases of the coronavirus pandemic with regard to efficiency, safety, and resource use (4,7). The ability of coronary CTA to decisively exclude CAD or high-risk anatomy may prevent the need for inpatient admissions from the emergency department, resource use, and exposure to health care workers. On the one hand, in suspected or known cases of COVID-19 disease, coronary CTA is generally preferred over stress testing modalities that increase aerosolization risk (e.g., exercise stress testing) or pharmacological stress tests with long acquisition times and exposure time to patients. In these cases, it is advisable to postpone testing till after recovery from the viral infection. On the other hand, stress testing is preferred over coronary CTA in patients with known CAD, heavy coronary calcifications, and previous stents, and in patients with contraindications to iodinated contrast agents (Table 3). Other clinical scenarios in which coronary CTA may be preferred or a reasonable alternative cardiac imaging modality in the COVID-19 era are the following (4,7,36,37) (Table 3):
• Evaluation of patients with no known CAD presenting with symptoms of possible angina.
• Identifying patients with CAD who can be treated conservatively (e.g., by excluding high-risk anatomy or through the use of CT-fractional flow reserve to exclude functionally significant lesions).
• Cardiac CTA may be preferred in the planning of structural heart procedures such as transcatheter aortic valve replacement and left atrial appendage closure. TEE is still the preferred modality for planning mitral and tricuspid valve edge-to-edge repair.
• Cardiac CTA may be preferred or a reasonable alternative to TEE in the COVID-19 era in excluding left atrial or appendage thrombus prior to cardioversion.
• Cardiac CTA may be a reasonable alternative to TEE in the evaluation of prosthetic and mechanical heart valve dysfunction, perivalvular extension of endocarditis, or possible myocardial abscesses.

The scenarios of preference to or alternate to TEE again depend on the status of the pandemic, continued safety concerns and availability of needed PPE.

CORONARY ARTERY CALCIUM SCORING. Coronary artery calcium (CAC) imaging is the test with the least urgent indication during the pandemic. Dedicated CAC imaging may be considered to decide on the decision to withhold, postpone, or initiate statin therapy as per current American College of Cardiology/American Heart Association guidelines for primary prevention in patients at intermediate or borderline risk. This can be performed at a later phase during the pandemic when the incidence of active infection has tapered, and institutions have determined they may fully resume routine imaging services with appropriate safety considerations. However, CAC may be detected on all noncontrast chest CTs and may be helpful in identifying patients with COVID-19 who have atherosclerotic plaque and cardiac risk.

GENERAL CONSIDERATIONS FOR CMR IMAGING DURING COVID-19

CMR is well positioned to address the cardiac complications from COVID-19, particularly myocarditis, in addition to the myriad of other clinical indications (15,18,19,21). CMR also provides comprehensive answers, by multicomponent imaging in one setting, and thus may reduce PPE use and the need for patient transportation to multiple testing laboratories, and limits infectious exposure during the COVID-19 pandemic. CMR examination, including pharmacological stress, is not an aerosolizing procedure, and its PPE requirement is similar to that of CT. In a single imaging session, CMR can assess cardiac function, ischemia, viability, and valvular function (15,18,19,21). The advent of rapid protocols as well as real-time and single-heartbeat data acquisition ameliorates this situation and decreases the staff and room exposure time (38–40). In concert with global hospital planning to cope with local surges of COVID-19, CMR programs have deferred many nonurgent studies to reduce risk of infection spread, reduce usage of PPE, and conserve hospital resources. However, we are now positioned to advance appropriate use of CMR to meet the needs for cardiac examination in concordance with society recommendations (11). Several general recommendations on use of CMR during the pandemic can be made (Table 3):

• Shortened, focused CMR protocols (maximum of ~30 min) should be used across all clinical indications.
• CMR is a preferred method in diagnosing the etiology of left ventricular dysfunction by assessing the pattern of cardiac dysfunction and myocardial tissue characteristics using myocardial perfusion, late gadolinium enhancement, and tissue mapping.
• In patients with chest pain and recent/previous myocardial injury, CMR can assess the underlying etiology (ischemia vs. myocarditis) and residual ischemic burden. The test should be performed if it alters planned medical management and should be avoided or postponed during an active COVID-19 infection.
• In patients with suspected ischemia, pharmacological stress CMR can be safely added to a study session to diagnose and risk-stratify CAD to guide the use of invasive angiography.

With multicomponent imaging, CMR may obviate the need to perform some TEEs during COVID-19. CMR can determine pulmonary vein anatomy and detect left atrial or appendage thrombus (41,42) and may lessen the need for TEE in patients with atrial fibrillation before urgent electrophysiological procedures. The most common approach of CMR imaging in this setting employs a combination of cine imaging, contrast-enhanced magnetic resonance angiography, and late gadolinium enhancement with long inversion time (42). Other technical strengths of late gadolinium enhancement with long inversion time include high feasibility in presence of irregular cardiac rhythm, high tissue contrast between thrombus and
CONCLUSIONS

The COVID-19 pandemic has affected human life, stressed health care capacity, and delayed usual delivery of care. As we enter a deceleration or indolent phase of the disease and a return to a “new normal” for the foreseeable future, cardiovascular imaging laboratories will adjust to a different workflow and safety precautions for patients and staff alike. The focus ultimately is the ability to offer the necessary cardiovascular tests and information for the clinical team to provide the best care for patients. To be successful in this new safety-driven modus operandi, innovation, coordination, and adaptation among clinicians, staff, and patients is necessary until herd immunity or control of COVID-19 is achieved.

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**KEY WORDS**

- cardiac computer tomography
- cardiac magnetic resonance
- cardiovascular imaging
- COVID-19
- echocardiography
- nuclear cardiology
Colocalization of Intracoronary Lipid-Rich Plaques and Calcifications
An Integrated NIRS-IVUS Analysis

Atherosclerotic plaques consist of various components, including lipids and calcium. Although high lipid content has been associated with increased plaque vulnerability (1), calcifications, depending on their size, have been related to both plaque stabilization and vulnerability (2). Both plaque components can be detected simultaneously using near infrared spectroscopy–intravascular ultrasound (NIRS-IVUS) (3). Our aim was to investigate the incidence of the colocalization of lipids and calcium in coronary arteries.

In this single-center retrospective study, we included all patients from the prospective IBIS-3 (Integrated Biomarker and Imaging Study-3) trial for whom a combined NIRS-IVUS (TVC system, Burlington, Massachusetts) pullback of the proximal segment of a nonculprit coronary artery was available (4). The study was approved by the local institutional review board (METC Erasmus Medical Center, Rotterdam, the Netherlands), conducted according to the Declaration of Helsinki, and registered in the Netherlands trial register (no. NTR2872). All patients provided written informed consent.

One frame per millimeter of each pullback was analyzed. Calcium on IVUS was defined as a high-intensity signal (bright on the image) with a low-intensity region (dark shadow) behind it. Calcium angles were manually indicated using QCU-CMS software version 4.69 (LKEB, Leiden, the Netherlands). No distinction between deep and superficial calcium was made. Combining the NIRS data with the calcium angles, we assessed the colocalization of NIRS signal and calcium. The lipid core burden index (LCBI) was calculated for all frames and 4-mm segments. LCBI scores were subdivided into 3 different groups: lipid-free (LCBI: 0); low-lipid (LCBI: 1 to 250), and high-lipid (LCBI >250). A similar methodology was used to calculate the IVUS-based calcium score, resulting in a calcium score per frame and a 4-mm segment. Large calcifications were defined as a calcium score >250.

For continuous variables, mean ± SD or median (interquartile range [IQR]) were calculated. Categorical variables were reported as frequencies (%) and compared with the chi-square test. Statistical analysis of the colocalization of the different calcium score groups and lipids groups was performed using generalized linear mixed models, with LCBI groups as a fixed factor. To correct for a potential clustering effect of multiple frames per vessel, the individual vessel was added as random factor in this statistical model. All tests were 2-tailed and a p value <0.05 was considered significant. SPSS statistics version 25 for Windows (IBM Corp, Armonk, New York) was used for statistical analysis.

A total of 154 vessels from 139 patients (9,811 frames) were analyzed, with a mean pullback length of 63 ± 19 mm. Mean age was 61 ± 10 years, and 81% of the patients were men.

Calcifications and a NIRS positive signal were present in 25.2% and 21.7% of the frames respectively, and 9.3% of the frames showed both lipids and calcium. Lipid-rich segments had a greater likelihood for the presence of any calcification compared with segments with no lipids (LCBI >250 vs. LCBI 0: odds ratio [OR]: 6; 95% confidence interval [CI]: 4 to 10; p < 0.001) and LCBI 1 to 250 vs. LCBI 0: OR: 4; 95% CI: 3 to 5; p < 0.001). Segments with a high LCBI score (>250) had a greater likelihood for large calcification (>250) compared with segments with no lipids (OR: 54; 95% CI: 23 to 128; p < 0.001). For segments with LCBI 1 to 250, the likelihood for large calcification remained higher than that in segments with no lipids (OR: 10; 95% CI: 6 to 19; p < 0.001) (Figure 1).

Although both calcifications and lipid-rich plaques proved to be associated with inferior clinical outcome, little is known about the colocalization of both components and their individual contribution to plaque vulnerability and future adverse clinical events. Because calcification is known to originate from inflammation, the colocalization of calcium and a positive NIRS signal could confirm more advanced plaques phenotypes. Histological studies showed that calcifications are often present around inflamed lipid-rich necrotic cores (5). Conversely, NIRS-positive segments without calcification might indicate unstable vulnerable plaques and segments with extensive calcifications, but no positive NIRS signal might indicate more stable disease because...
Calcifications might have replaced lipid-rich content in necrotic cores (2).

To the best of our knowledge, the present study was the first to demonstrate a significant correlation between calcium and LCBI scores, with significantly higher calcium scores in segments, with a higher LCBI score. This suggests that both plaque characteristics should not be seen as separate entities that might independently predict future adverse events. Combining calcium burden with LCBI score has the potential to improve the detection of vulnerable plaques and improve individual risk assessment.

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**Prognostic Value of Coronary Computed Tomographic Angiography in Patients With Nonalcoholic Fatty Liver Disease**

Nonalcoholic fatty liver disease (NAFLD) is a strong predictor of the incidence of cardiovascular (CV) disease independent of established CV risk factors (1). Some studies have reported a significant association between NAFLD and the prevalence of
computed tomographic angiography (CTA)-verified high-risk plaques (HRPs) (2,3). However, the association of NAFLD with HRPs and CV events remains unknown. This study was performed to determine if HRPs are more frequent in patients with incidental evidence of NAFLD by computed tomography for suspected coronary artery disease and to assess whether HRPs predict CV events in patients with NAFLD.

This prospective study was based on 862 consenting Japanese outpatients who underwent coronary CTA for suspected coronary artery disease at Okayama University Hospital. After excluding patients with heavy alcohol intake, known liver disease, use of oral corticosteroids and/or amiodarone, and poor image quality, 721 patients were included in the cross-sectional analysis. All patients underwent abdominal noncontrast computed tomographic scans at the umbilical level before cardiac imaging. The median radiation exposure of the abdominal scan was 3.4 mSV. A liver-to-spleen ratio $<1.0$ was taken as the cutoff for a positive diagnosis of NAFLD (3). Coronary computed tomographic images were assessed for the presence of $>50\%$ stenosis and HRPs, which were defined as the presence of 2 or more plaque characteristics including positive remodeling, low-density plaque, and spotty calcification. The study was approved by the Institutional Review Board of Okayama University Hospital.

Among the 721 patients, 572 underwent clinical follow-up. After excluding patients who died of non-CV causes and were scheduled for coronary revascularization within 30 days on the basis of findings on CTA, 493 patients were included in the follow-up cohort and analyzed. CV events were defined as CV death, acute coronary syndrome (ACS), coronary revascularization, and admission for heart failure.

Of 721 patients in the cross-sectional study (51% men, mean age 63±15 years), NAFLD was identified in 173 patients (24%). Patients with NAFLD had a higher prevalence of conventional CV risk factors than did patients without NAFLD. Regarding coronary computed tomographic angiographic characteristics, HRPs were more frequent in patients with NAFLD (39% vs. 26%; $p = 0.002$). The presence of $>50\%$ stenosis was not different between the groups (24% vs. 20%; $p = 0.282$). In the multivariate logistic analysis, NAFLD was an independent factor associated with HRPs (odds ratio: 2.039; 95% confidence interval [CI]: 1.243 to 3.345; $p = 0.005$) after adjusting for traditional CV risk factors.

In total, 493 patients (122 with NAFLD, 371 without NAFLD) were available for the follow-up analysis, in which baseline clinical characteristics and findings on coronary CTA were similar to those in the cross-sectional study. During the follow-up period (median of 5.4 years), 19 CV events occurred in patients with NAFLD (revascularization, $n = 9$; ACS, $n = 5$; CV death, $n = 2$; heart failure, $n = 3$), and 22 occurred in
patients without NAFLD (revascularization, n = 13; ACS, n = 3; CV death, n = 2; heart failure, n = 4). Kaplan-Meier analysis showed that patients with NAFLD experienced more CV events than those without NAFLD during follow-up (Figure 1A). Stepwise multivariate Cox regression analysis using traditional CV risk factors, NAFLD, HRPs, and >50% stenosis demonstrated that NAFLD (hazard ratio [HR]: 2.302; 95% CI: 1.236 to 4.289; p = 0.009), HRPs (HR: 5.061; 95% CI: 2.092 to 12.244; p < 0.001), and >50% stenosis (HR: 3.689; 95% CI: 1.790 to 7.601; p < 0.001) were independent predictors of CV events. Figure 1B shows the occurrence of acute coronary events including ACS and CV death in patients with NAFLD according to the presence of HRPs. In patients with NAFLD, the incidence of ACS and CV death was markedly higher in patients with than without HRPs. Cox univariate regression analysis showed that HRPs in patients with NAFLD were significantly associated with ACS and CV death (crude HR: 8.816; 95% CI: 1.058 to 73.440; p = 0.044).

In conclusion, NAFLD was significantly associated with CV events. CV events were predicted by the presence of NAFLD and HRPs independently. Furthermore, HRPs in patients with NAFLD were a predictor of ACS and CV death. The prognostic significance of these data should be confirmed in larger studies.

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T2 Mapping Identifies Early Anthracycline-Induced Cardiotoxicity in Elderly Patients With Cancer

Current measures of anthracycline-induced cardiotoxicity, defined by decreases in left ventricular ejection fraction (LVEF), may become apparent only at a late stage when the myocardium has been significantly damaged, exceeding its ability to compensate (1). Our group has recently shown in a large animal model that T2 relaxation time (T2) cardiac magnetic resonance (CMR) identifies intracardiomyocyte edema as the earliest marker of anthracycline-induced cardiotoxicity. T2 prolongation preceded LVEF decrease and occurred at a reversible stage of cardiotoxicity (2). Here, we present T2 mapping trajectories during treatment in a population of elderly patients with cancer undergoing anthracycline chemotherapy.

Current measures of anthracycline-induced cardiotoxicity, defined by decreases in left ventricular ejection fraction (LVEF), may become apparent only at a late stage when the myocardium has been significantly damaged, exceeding its ability to compensate (1). Our group has recently shown in a large animal model that T2 relaxation time (T2) cardiac magnetic resonance (CMR) identifies intracardiomyocyte edema as the earliest marker of anthracycline-induced cardiotoxicity. T2 prolongation preceded LVEF decrease and occurred at a reversible stage of cardiotoxicity (2). Here, we present T2 mapping trajectories during treatment in a population of elderly patients with cancer undergoing anthracycline chemotherapy.

CARTIER (Cardiotoxicity in the Elderly; NCT03981588) is a prospective study of elderly patients (>65 years of age) with cancer undergoing serial CMR before, during, and after chemotherapy. The study protocol was approved by the ethics committee, and participants provided written informed consent. All patients underwent CMR imaging before the first (baseline assessment), third, and fifth cycles of a regular chemotherapy course and 3, 6, 9, and 12 months after the completion of treatment. At all time points, the CMR protocol included LVEF and T2 mapping (3). Cardiotoxicity was defined as any follow-up LVEF <53%, in which case heart failure therapy was initiated (4). Here, we present initial CMR data for CARTIER patients receiving anthracyclines.

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Categorical variables are described as percentages and continuous variables as median (interquartile range [IQR]). Nonparametric tests at the ordinal level were used for dependent (Wilcoxon test) or independent (Mann-Whitney U test) samples. Area under the receiver-operating characteristic curve (AUC) was used to assess the predictive capacity of T2 mapping.

A total of 110 consecutive patients were enrolled in CARTIER, of whom 34 (31%) received anthracyclines; 20 patients had lymphoma, 8 breast cancer, 2 leukemia, 2 gastric cancer, 1 myxoid chondrosarcoma, and 1 Kaposi sarcoma. One patient with claustrophobia and 5 patients undergoing only baseline CMR (unable to follow the protocol because of poor clinical

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conditions) were excluded from this analysis. Thus, a final cohort of 28 patients, 169 of the 196 per protocol planned CMR examinations, constituted this study evaluation. The median age was 73 years (IQR: 68 to 79 years), 57% of patients were women, 93% had cardiovascular risk factors, 36% had cardiovascular histories, and 79% had concomitant cardiovascular medications. The majority of patients received 6 cycles of chemotherapy. Compared with 10 sex- and age-matched population-based (NCT03429452) healthy volunteers (median LVEF 69% [IQR: 66% to 73%]; median T2 53 ms [IQR: 48 to 57 ms]), patients in our cohort had similar baseline LVEFs (median 64%; IQR: 59% to 71%; p = 0.189) but slightly higher baseline T2 (median 56 ms [IQR: 53 to 62 ms]; p = 0.052). T2 was not different between patients with cardiotoxicity and those without (median 56 ms [IQR: 53 to 61 ms] vs. 56 ms [IQR: 53 to 62 ms], respectively; p = 0.939). In patients with cardiotoxicity, compared with baseline, T2 was prolonged after 2 (median 61 ms; IQR: 59 to 65 ms; p = 0.089) and 4 (median 63 ms; IQR: 59 to 74 ms; p = 0.027) cycles of chemotherapy. Conversely, in the group of patients without cardiotoxicity, T2 remained unchanged during chemotherapy (Figure 1). T2 (median 53 ms; IQR: 51 to 55 ms) decreased 12 months after chemotherapy for all patients with cancer compared with baseline, to similar measurements to those previously reported among healthy volunteers (p = 0.921).

T2 after 2 cycles of chemotherapy was revealed to be a good predictor of cardiotoxicity development, with an AUC of 0.86 (95% confidence interval [CI]: 0.70 to 1.00; p = 0.012). A T2 cutoff of 59 ms after 2 cycles had sensitivity of 100% and specificity of 71% for the prediction of cardiotoxicity. Neither baseline T2 (AUC = 0.62; 95% CI: 0.36 to 0.88; p = 0.386) nor post-treatment T2 later in time (i.e., before the fifth cycle) (AUC = 0.71; 95% CI: 0.45 to 0.97; p = 0.149) was a better predictor of future cardiotoxicity.

These observations are in line with those of a previous clinical study showing changes in T2 following anthracycline initiation in younger patients with breast cancer (4). Our data suggest that if T2 is to be used to best detect early cardiotoxicity, CMR should
be performed soon after anthracycline chemotherapy initiation (2 cycles in our study). The high negative predictive value of a T2 cutoff value of 59 ms after 2 cycles of chemotherapy would make it possible to rule out future cardiotoxicity development and thus limit subsequent CMR examinations.

T2 tended to normalize in the long term in patients who developed cardiotoxicity. We speculate that this is secondary to the initiation of anti-heart failure therapies according to clinical recommendations (1), but it could also be related to the intersection between cancer and cardiovascular disease (5), as it is observed even in patients who do not develop cardiotoxicity. This normalization in T2 after intervention is in line with our experimental data, in which changing the chemotherapeutic protocol in which changing the chemotherapeutic protocol intervention is in line with our experimental data, in which changing the chemotherapeutic protocol in which changing the chemotherapeutic protocol with suspected/known ischemic heart disease (IHD) (1). CMR is advocated in international clinical practice guidelines and recent multicenter trials like CE-MARC-2 (Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease-2) (2) and MR-INFORM (MR Perfusion Imaging to Guide Management of Patients With Stable Coronary Artery Disease) (3) have shown that CMR as a first-line test is highly effective as a gatekeeper for diagnostic invasive coronary angiography and also to guide coronary revascularization. However, a perceived limitation of CMR is that it is difficult and time consuming to perform. The aim of this feasibility study was to show that using a standard MR scanner, assessment of left ventricular function, ischemia and myocardial viability could be reliably performed in ~20 min while maintaining image quality.

Consecutive stable patients in sinus rhythm, referred for routine comprehensive assessment of suspected/known IHD, were investigated on a 1.5T Philips Ingenia system equipped with a 24-channel digital receiver coil and patient-adaptive radio-frequency shimming. The Rapid-IHD protocol consisted of the following.

1) Free breathing low-resolution survey of the chest and standard cine imaging to define long and short axis (balanced steady-state free precession, single-slice/breath-hold, typical parameters: echotime 1.3 ms, repetition time 2.6 ms, flip angle 40°, field of view 320 to 420 mm, sensitivity encoding (SENSE, undersampling factor 2), slice thickness

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10 mm, spatial resolution 1.1 × 1.1 mm, 30 phases/cardiac cycle).

2) Stress perfusion: adenosine 140 μg/kg/min (option to increase to 170 and/or 210 μg/kg/min in the absence of symptoms or adequate hemodynamic response). Sequence: 2-dimensional (2D), T1-weighted saturation recovery-prepared gradient echo pulse sequence in 3 short-axis slices, using SENSE (factor 2) after IV bolus of 0.075 mmol/kg dimeglumine gadopentetate gadobutrol (Gadavist, Bayer Inc., Hanover, New Jersey) followed by a 15-ml saline flush (5 ml/s).

3) A further intravenous bolus of 0.075 mmol/kg Gadavist, followed immediately by early gadolinium enhancement imaging (2D inversion recovery sequence, field of view 350 mm repetition time/echo time 5.5/2.7 ms inversion time 440 ms, flip angle 15°), 2D inversion recovery sequence, field of view 300 × 300 × 120mm, matrix 169/384, acquired in-plane resolution 1.83 × 2.00 mm² reconstructed to 1.17 × 1.17 × 5 mm² (4).

Scan duration was recorded as time of initiation of table movement for patient positioning in the scanner isocenter to end of table movement after removal from the scanner bore. Written informed consent was provided. Image quality for each component (function, perfusion, LGE) was graded. Ethical approval was given by the Yorkshire & The Humber, Leeds West Research Ethics Committee (reference 12/YH/0551).

Eighteen patients (15 males) were investigated (14 with de novo chest pain and 4 with known IHD); all completed the full protocol without complication. All components of the multi-parametric scan were of diagnostic quality with high image quality scores (Table 1). Mean time taken to perform the Rapid IHD Protocol was 17.2 ± 0.5 min. Representative images are in Figure 1.

### Table 1: Patient Demographics and IQS

| Age/Year | Height/cm | Weight/cm | LVEDVi ml/m² | LVEF/% | IQS function | IQS perfusion | IQS LGE |
|----------|-----------|-----------|--------------|--------|--------------|--------------|---------|
| 61.6 ± 10.9 | 171.2 ± 7.3 | 84.4 ± 16.9 | 87.6 ± 28.4 | 49.9 ± 10.9 | 1.3 ± 0.6 | 1.4 ± 0.5 | 1.6 ± 0.6 |

Values are mean ± SD. Score: 4 = nondiagnostic; 3 = acceptable diagnostic quality; 2 = good quality; 1 = excellent quality

IQS = image quality score; LGE = late gadolinium enhancement; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction.

### Figure 1: Representative Images From RAPID-IHD Protocol

(A) Short axis cine of the left ventricle. (B) Mid-ventricular slice of the left ventricle during stress perfusion showing an anterolateral perfusion defect. (C) Mid-ventricular slice showing late gadolinium enhancement imaging showing a subendocardial inferior scar (Videos 1 and 2).
Rapid comprehensive assessment of IHD by CMR is feasible to perform in <20 min, whereas the excellent image quality that is an inherent strength of CMR was maintained. In general, CMR protocols can be shortened by several methods: 1) speeding up the acquisition such as by using compressed sensing (not used here) or using 3D sequences such as the mDIXON LGE sequence (used here), which allowed full coverage of the left ventricle in a single breath-hold as opposed to a 2D LGE stack that requires a breathhold for each slice (4); 2) eliminating unnecessary components of the protocol, for example rest perfusion imaging, which is increasingly recognized to add little to diagnostic accuracy by visual or quantitative techniques (5). Ultimately, one of the major rate-limiting steps to faster scanning is the time taken for gadolinium to reach steady state before performing LGE (scar) assessment. Potential methods to reduce this period include using a phase-sensitive inversion recovery dark blood sequence with the inversion time set to null the blood pool, allowing earlier LGE images to be acquired or perhaps using noncontrast-based techniques such as T1 mapping for scar detection.

In summary, comprehensive CMR assessment of IHD is feasible in approximately 20 min, with shorter scan times being potentially more tolerable for patients and allowing improved workflow efficiency.

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APPENDIX
For supplemental videos, please see the online version of this paper.

Diabetes and Hypertension Associate Differently With the Risk of Ascending Thoracic Aortic Aneurysm

A CT Study of 21,295 Patients

Atherosclerotic comorbidities are risk factors for descending aortic aneurysm, but this relationship is unknown for ascending aneurysm in the context of unstandardized size criteria and imaging modalities used in prior studies (1). Known risk factors for abdominal aortic aneurysms may not apply to ascending aneurysms, because the mechanism of aneurysm formation, vascular wall structures (2), and atherosclerotic profiles (3) differ between the two. We used a large dataset of protocolized aortic measurements based on computed tomographic images to evaluate associations between atherosclerotic risk factors and ascending thoracic aortic aneurysm (ATAA).

We conducted a cross-sectional review of all computed tomographic scans (contrast or noncontrast with or without cardiac gating) done at a tertiary center between 2013 and 2016 in patients ≥50 to 85 years of age. Scans were performed during inpatient, outpatient, and emergency department encounters for any indication, excluding those from outside facilities to minimize referral bias. Scans with the finding of a dissection (n = 30) were excluded. Age limits were applied because ATAA is extremely rare at ≤50 years (4), and the benefit of detection decreases in older patients. We excluded all subsequent scans done on the same patient during the study period, yielding 21,295 unique patients with scans. The Yale Institutional Review Board approved this study.
We used double-oblique measurement between the outer walls of the mid ascending aorta above the aortic root, and defined ATAA as diameter $\geq 4.5$ cm. The technique measures the plane perpendicular to the long axis of the aorta by taking the average of 3 diameter measurements taken 60° apart from one another on the cross-sectional plane. The threshold of 4.5 cm was chosen to increase the sensitivity of detecting an enlarged aorta in the screening context while acknowledging that existing studies defined aneurysm variably (5). One author (S.Y.) trained by a senior radiologist specialized in cardiac imaging (H.M.) obtained measurements.

Patient demographics, comorbidities, and smoking history were extracted from electronic medical records. Multivariate logistic regression model related covariates in Table 1 to the risk for ATAA. Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina).

Of the 21,295 CT scans, ATAAAs $\geq 4.0$ cm, $\geq 4.5$ cm, and $\geq 5.0$ cm were present in 551 (2.6%), 178 (0.8%), and 38 (0.2%) patients, respectively. Patients with ATAAAs were older and more likely to be male with larger body habitus. A multivariate model demonstrated that in addition to older age, male sex, and higher body surface area, hypertension was significantly associated with increased risk for ATAA $\geq 4.5$ cm (odds ratio: 2.08; 95% confidence interval: 1.44 to 3.03; $p < 0.001$). Diabetes was associated with lower risk for ATAA (odds ratio: 0.60; 95% CI: 0.40 to 0.87; $p = 0.008$) (Table 1). Similar risk factors, including diabetes and hypertension, were identified using a $> 4.0$-cm threshold.

This study offers unique insights through computed tomography-based definition of ATAAAs, which lacked in prior claims-based studies that suggested associations between atherosclerotic comorbidities and aortic aneurysm (1). Diabetes may render the aorta resistant to enlargement via the tensile strength conferred by glycation of extracellular matrix. Hypertension may increase the risk for ATAA via chronic exertion of mechanical force against the aortic wall. Interestingly, higher pack-year smoking history was associated with lower risk for ATAA, although the effect size was small. These findings may aid in targeted screening of patients with ATAA to facilitate timely surgical intervention.

The tertiary care setting may limit the generalizability of our findings, although we excluded external scans to minimize the bias related to referrals. Because the scans were obtained for various indications, related selection bias must be considered. However, the scans encompassed all encounter settings, and the large cohort and sample heterogeneity may allow generalization of the predictors of ATAA.

### Table 1: Predictors of Ascending Aortic Aneurysm

| Demographic                  | Aorta $\geq 4.5$ cm (n = 21,117) | Aorta $\geq 4.5$ cm (n = 178) | OR* | 95% CI | p Value |
|------------------------------|----------------------------------|-----------------------------|-----|--------|---------|
| Age (yrs)                    | 66.4 (59.0–73.9)                 | 69.4 (63.1–78.2)            | 1.04| 1.03–1.06| $<0.001$|
| Female (reference male)      | 9,221 (44)                       | 33 (19)                     | 0.38| 0.25–0.56| $<0.001$|
| Race                         |                                  |                             |     |        |         |
| White                        | 16,915 (80)                      | 150 (84)                    | Ref.|        |         |
| Black                        | 2,252 (11)                       | 12 (7)                      | 0.61| 0.33–1.11| 0.16    |
| Asian                        | 311 (1)                          | 3 (2)                       | 1.50| 0.47–4.81| 0.56    |
| Other                        | 1,639 (8)                        | 13 (7)                      | 1.09| 0.61–1.95| 0.88    |
| BSA (m²)                     | 1.9 (1.7–2.1)                    | 2.0 (1.8–2.2)               | 3.55| 2.07–6.09| $<0.0001$|

Comorbidities

| Diabetes                      | 4,772 (23)                       | 35 (20)                     | 0.60| 0.40–0.87| 0.008   |
| Hypertension                  | 12,338 (58)                      | 136 (76)                    | 2.08| 1.44–3.03| $<0.001$|
| Dyslipidemia                  | 9,100 (43)                       | 80 (45)                     | 0.78| 0.57–1.07| 0.12    |
| Congestive heart failure      | 1,771 (8)                        | 28 (16)                     | 1.77| 1.15–2.73| 0.0099  |
| Chronic kidney disease        | 1,519 (7)                        | 18 (10)                     | 1.13| 0.67–1.88| 0.65    |
| Myocardial infarction         | 1,297 (6)                        | 8 (4)                       | 0.53| 0.26–1.10| 0.089   |
| Smoking (pack-yrs)            | 0.0 (0–20)                       | 0 (0–15)                    | 0.99| 0.98–0.99| 0.022   |

Values are median (interquartile range) or n (%). Bold signifies statistical significance ($p < 0.05$). *OR, 95% CI, and p value were derived from a multivariate logistic regression model using all variables in the table as covariates.

BSA = body surface area by Mosteller equation; CI = confidence interval; OR = odds ratio.

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underdetection related to coding practice. Our age criteria likely under-represented those with type 1 diabetes.

In conclusion, using protocolized computed tomography–based definition of ATAA, we demonstrated that diabetes was associated with reduced risk for ATAA, while hypertension was associated with increased risk for ATAA. Other atherosclerotic risk factors (chronic kidney disease, myocardial infarction) were not predictive, suggesting that atherosclerotic process may not be a primary driver of ascending aortic aneurysm formation.

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Outcomes of Patients With Discordant High-Gradient Aortic Valve Stenosis

Severe aortic stenosis (AS) is defined by a peak velocity (PV) of ≥4 m/s, a mean pressure gradient (MPG) of ≥40 mm Hg, and an aortic valve area (AVA) of <1.0 cm² (1). However, these parameters are often discordant (AVA <1.0 cm² and MPG <40 mm Hg or AVA ≥1.0 cm² and MPG ≥40 mm Hg) despite a normal left ventricular ejection fraction (LVEF) (2,3). Patients with discordant low-gradient AS have received the most attention; little is known about the outcome of patients with high-gradient discordant AS (HGDIS-AS).

Among participants of the COFRASA (Aortic Stenosis in Elderly: Determinant of Progression)/GENERAC (Genetic of Aortic Valve Stenosis - Clinical and Therapeutic Implications) prospective cohort of asymptomatic patients with at least mild, pure, isolated, degenerative AS (NCT00338676 and NCT00647088), we selected patients with preserved LVEF and moderate AS (MOD-AS), high-gradient discordant (HGCON-AS), and HGDIS-AS severe AS. At study entry, all patients underwent comprehensive transthoracic echocardiography and noncontrast computed tomography (CT) for the measurement of the degree of aortic valve calcification (AVC). The occurrence of AS-related events (sudden death, congestive heart failure, or new onset of symptoms [dyspnea, angina, or syncope]) were recorded prospectively. Event-free survival was assessed using Kaplan-Meier analysis. Comparison of event-free survival according to AS subgroups was performed by log-rank test. Cox proportional-hazard analyses evaluated the predictive value of hemodynamic parameters for event-free survival in univariate and multivariate analyses. Analysis were repeated after matching patients with HGDIS-AS and HGCON-AS for body surface area and MPG. The study was approved by our regional ethics committee. All patients provided written informed consent.

We prospectively enrolled 234 patients: 155 patients with MOD-AS; 56 with HGCON-AS; and 23 patients with HGDIS-AS. By design, patients with HGDIS-AS had larger AVAs than those with HGCON-AS (1.16 ± 0.15 cm² vs. 0.77 ± 0.11 cm²; p < 0.0001), but there was only a small difference compared with those with MOD-AS (1.23 cm² ± 0.13 cm²; p = 0.02). Patients with HGDIS-AS had similar N-terminal pro–natriuretic peptide levels and AVC scores compared with the patients with the HGCON-AS subset (261 pg/ml [range 134 to 423 pg/ml] vs. 337 pg/ml [range 121 to 789 pg/ml]; p = 0.43 and 2,927 AU [range 1,237 to 3,658 AU] vs. 3,066 AU [range 2,075 to 4,684 AU]; p = 0.28, respectively), but both were significantly larger compared with patients with MOD-AS (46 pg/ml [range 66 to 357 pg/ml] and 1,018 AU [range 682 to 1,610 AU]; both p < 0.05). AS-related events occurred in 106 patients (46%) over a median...
follow-up of 2.9 years. Patients with MOD-AS displayed the best outcome, whereas the event-free survival of patients with HGCON-AS and HGDIS-AS were similar (p < 0.0001 overall; p = 0.45 between the 2 high-gradient groups) (Figure 1). After adjustment for age, sex, and valve anatomy (bicuspid or tricuspid aortic valve), both MPG and AVA were independent predictors of outcome (p = 0.02 and p < 0.0001, respectively). When the analysis was restricted to the 79 patients with high-gradient AS, MPG was predictive of outcome (p = 0.02), whereas AVA was not (p = 0.32). MPG was significantly higher in patients with HGCON-AS compared with patients with HGDIS-AS (59 ± 16 mm Hg vs. 46 ± 6 mm Hg; p < 0.05), but similar outcomes were also observed after matching the 2 groups for body surface area and MPG (21 patients in each group) (p = 0.81).

The American Society of Echocardiography/European Association of Cardiovascular Imaging guidelines indicate that any of the 3 parameters (PV ≥4 m/s, MPG ≥40 mm Hg, or AVA <1.0 cm²) suggest severe AS and recommend, despite the absence of definitive outcome data, that patients with PV ≥4 m/s (or MPG ≥40 mm Hg) should be considered as having severe AS independently of AVA after the exclusion of the causes of increased flow. In the present study, we observed that the prognosis of these patients was largely driven by the transvalvular gradient. Both the multivariate analysis and the matched analysis showed that AVA provided no prognostic information and that the prognoses of patients with HGDIS-AS and HGCON-AS were similar. Furthermore, the AVC score was similar in both groups, which further attested to the similarity of AS severity.

The anatomic determinants of the patients with the HGDIS-AS subset deserve specific comments. Patients with HGDIS-AS exhibited larger body surface areas than patients with HGCON-AS but AVA index (AVA/body surface area) continued to be larger in patients with HGDIS-AS. Left ventricular outflow tract (LVOT) diameter was also larger (2.45 ± 0.17 cm vs. 2.32 ± 0.19 cm; p < 0.05). The LVOT is an elliptically shaped structure, and it is possible that LVOT measurements in patients with HGDIS-AS trended more toward the major axis than in those with HGCON-AS. However, the dimensionless index was also larger in patients with HGDIS-AS (0.24 ± 0.03 vs. 0.18 ± 0.03; p < 0.05). Of note, the rate of BAV was higher in patients with HGDIS-AS than in patients with HGCON-AS but did not reach statistical significance (52% and 32%, respectively; p = 0.11).

This was a single-center study with a relatively small sample size, especially for the matched population, and we could not exclude that we might have missed power to demonstrate the additional weak prognostic value of AVA in patients with HG AS, or a lower AVC score/higher incidence rate of bicuspid aortic valve in patients with HGDIS-AS. Contrast CT was not performed, and the cross-sectional area and eccentricity index of the LVOT could not be evaluated.

In patients with HG AS, MPG (and not AVA) provides important prognostic information and should be used to guide decision-making. Our study provides important data to support current American Society of Echocardiography and European Association of Cardiovascular Imaging recommendations and management strategy.

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The Current State of Cardiovascular Imaging Training

Results of the Cardiovascular Imaging Program Directors’ Survey

The field of cardiovascular (CV) imaging as a distinct subspecialty has matured, and there is a growing need for formalized training pathways and standardized competencies (1). Many trainees now pursue dedicated training in an advanced cardiovascular imaging (ACVI) training program, which provides expertise in multiple modalities that build on imaging skills obtained in a general CV fellowship. As ACVI is not accredited by the Accreditation Council for Graduate Medical Education, there is no uniformity of training requirements and variable funding sources. The heterogeneity of ACVI training programs and employment opportunity trends have been previously described (2,3). We sought to expand upon prior work to comprehensively characterize the current state of ACVI training programs.

The American College of Cardiology Cardiovascular Training and Cardiovascular Imaging councils launched a survey of all known U.S. and Canada program directors (PDs) of ACVI training programs (Table 1). A program-specific link was sent by e-mail with subsequent reminders. The survey was open from March 2019 to April 2019, and data was collected in a deidentified manner. The study was approved by the institutional review board.

The survey was sent to 66 programs (64 U.S., 2 Canadian). A total of 50 (76%) programs (49 U.S., 1 Canadian) completed the survey, representing a total of 151 total ACVI trainees. Median program size was 1 trainee (interquartile range: 1 to 4 trainees) and most (70%) programs were 1 year in length. There were 91 (60%) men and 60 (40%) women. In the prior 2 years, 89 and 90 fellows had graduated, respectively. The majority of programs (92%) had adult CV disease trainees, 16% had trainees board-eligible in internal medicine only, and 12% had radiology trainees. Most programs had cardiology faculty (98%), 58% had radiology faculty, 10% had nuclear medicine physicians, and 4% had anesthesiologists. The median time programs had been active was 9 years (interquartile range: 4 to 13 years). In total, 17 (35%) training programs had been active for 5 years or fewer. Funding sources were variable, and included direct institutional/departmental (74%), research grant (22%), trainee self-support with clinical work (14%), industry funding (14%), and philanthropy (4%). Almost all PDs (96%) were cardiologists. The majority of PDs had multimodality expertise and actively participated in multiple imaging modalities (echocardiography 66%, cardiac computed tomography [CCT] 60%, cardiac magnetic resonance [CMR] 60%, nuclear 38%). The primary imaging focus for PDs was identified as MR (42%), echocardiography (34%), and nuclear or computed tomography (12% each). A total of 46% of PDs received no protected time for their role, and 40% had <10% protected time.

Almost all programs (94%) offered training in more than 1 modality (CMR 94%, CCT 84%, echocardiography 74%, and nuclear cardiology 48%). This is consistent with previous data (3) and may represent the fact that level II or III echocardiography training is achievable in CV fellowships, creating less demand for this in ACVI fellowships. A majority of programs mandated training in CMR, CCT, or echocardiography, whereas only 20% mandated nuclear cardiology training. In programs with nuclear training, 71% offered PET training. Most (78%) echocardiography programs offered advanced structural/interventional training. Almost one-half of PDs (46%) felt that ACVI training should be focused on 1 to 2 modalities, whereas 22% believed that it should be broad with significant training in 3 to 4 modalities.
PDs were mixed on the importance of imaging certification examinations. Almost one-half (48%) found them important, 34% were neutral, and 16% did not think they were important. Regarding examination content, 14% favored a single integrated multimodality examination, 48% favored a modular examination allowing for modality specific modules, 28% favored each modality having its own examination, and 6% favored having no certification examinations.

In the past 2 years, 62% of programs had graduates take imaging focused jobs in academic centers, and 36% of programs had graduates accept imaging focused positions in community-based practices. For positions in which imaging was a secondary focus, 44% of programs had graduates take positions at academic centers, and 30% of programs had graduates accept positions in community-based practices.

Several important observations arise from this survey. First, ACVI training programs are non-standardized and heterogeneous, at least in part due to the number of modalities available. Second, despite lack of Accreditation Council for Graduate Medical Education recognition, ACVI trainees (n = 151) represent a large pool of trainees, comparable to other cardiac subspecialties (interventional cardiology [n = 339], clinical cardiac electrophysiology [n = 259], and advanced heart failure and transplantation [n = 105]) (4). Third, most ACVI PDs (72%) do not favor the current state of imaging certification where each modality has its own certification examination. Fourth, funding and time protection remains a significant challenge. The majority of programs rely on institutional or departmental funding, and most PDs have minimal protected time for their roles. In summary, ACVI programs and their trainees are a large but heterogeneous cohort of CV subspecialists with unique challenges in both training and subsequent clinical practice. It is time for the ACVI community to work together and identify collaborative solutions for this unique CV subspecialty.

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| TABLE 1 | Issues Identified by PDs in CV Imaging Training |
|---|---|
| Funding | Number and cost of multiple imaging board examinations |
| | Lack of ACGME accreditation |
| | Lack of cohesive curriculum rules and uniformity |
| | Not enough training opportunities in specific modalities (e.g., CMR or CCT) |
| | Challenges to curriculum design to adequately teach learners multiple modalities |
| | Length of training |
| | CV imaging not recognized as a distinct specialty |

ACGME = Accreditation Council for Graduate Medical Education; CCT = cardiac computed tomography; CMR = cardiac magnetic resonance imaging; CV = cardiovascular; PD = program director.

Effect of PCSK-9 Inhibitors on Lipid-Rich Vulnerable Coronary Plaque Assessed by Near-Infrared Spectroscopy

Patients with acute coronary syndrome (ACS) face a substantial risk of future adverse cardiovascular events, including recurrent ACS (1,2). Because this risk is partly attributable to lipid-rich vulnerable plaque, high-intensity statin therapy is recommended as a secondary prevention therapy, regardless of baseline low-density lipoprotein cholesterol (LDL-C) levels. In addition, several
randomized controlled trials have reported that proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors reduced the remaining risk of cardiovascular events in high-risk cardiovascular patients with optimized lipid-lowering therapy by further reducing LDL-C levels (1,2). However, the clinical effect of PCSK9 inhibitors on vulnerable coronary plaque remains undetermined. This study aimed to evaluate the serial change in vulnerable coronary plaque in patients with ACS before and approximately 8 months after administration of PCSK9 inhibitors using the lipid core burden index (LCBI) as assessed by near-infrared spectroscopy (NIRS) combined with intravascular ultrasound (IVUS) (3).

This single-center retrospective observational study included 5 patients with ACS who were administered PCSK9 inhibitors because they had LDL-C levels $\geq 70$ mg/dl, despite receiving an optimized, consistent dose of statin therapy during the study period. This therapy was covered by insurance in Japan. NIRS-IVUS was performed before and approximately 8 months after the administration of PCSK9 inhibitors at our institution between May 2017 and May 2019. The study protocol complied with the Declaration of Helsinki and was approved by the institutional ethics committee.

Nine vessels from 5 patients with $\geq 50\%$ stenosis were analyzed in both lesion- and patient-wise manners. The NIRS-IVUS (TVC Imaging System MC8 and Makoto Intravascular Imaging System MCIQ [NIRS-IVUS]) and (B and D) chemograms at baseline and 8 months. (E) A significant decrease in maximum lipid core burden index for any 4-mm segment (maxLCBI$_{4mm}$) was observed.
used to assess regression of vulnerable plaque (3). The secondary endpoints were set as the serial change in the LDL-C level and plaque burden (PB) at the center of the maxLCBl4mm site in each vessel. The PB was calculated with the following formula: 100 × (external elastic membrane [EEM] cross-sectional area [CSA] minus lumen CSA)/EEM CSA (%). Continuous variables were expressed as medians and interquartile ranges (IQRs), and the serial change was assessed using the Wilcoxon signed-rank test, considering parity with a statistical significance of < 0.05. Hypothetical testing was performed as 2-sided for a lesion-wise analysis, and as 1-sided for a patient-wise analysis, in which an alternative hypothesis was set as the true location shift as >0, respectively. All statistical analysis was performed using Microsoft R Open version 3.3.2 (Microsoft, Redmond, Washington).

The median age of the study population was 52 years (IQR: 50 to 80 years), and 3 (60.0%) patients were men. Two (40.0%) patients received alirocumab subcutaneously (75 mg every 2 weeks), and 3 (60.0%) patients received evolocumab (either 140 mg every 2 weeks or 420 mg every month, according to patient preference). PCSK9 inhibitors were administered for 246 days (IQR: 224 to 286 days). The median maxLCBl4mm showed a significant decrease from 442 to 191 (IQR: 230 to 450 and IQR: 14 to 219, respectively; p = 0.008) in a lesion-wise analysis, and from 388 to 120 (IQR: 289 to 445 and IQR: 68 to 328, respectively; p = 0.031) in a patient-wise analysis (Figure 1). The median LDL-C level also decreased significantly from 115 to 44 mg/dl (IQR: 104 to 133 mg/dl and IQR: 38 to 55 mg/dl, respectively; p = 0.009). In contrast, the median PB showed no significant changes from 54.0% to 49.3% (IQR: 45.0 to 56.0 and IQR: 45.0 to 53.0, respectively; p = 0.20).

This preliminary single-center retrospective observational study demonstrated a significant decrease in maxLCBl4mm and LDL-C but no statistical change in PB, approximately 8 months after administration of PCSK9 inhibitors. A previous randomized controlled trial that involved 87 patients reported that intensive statin therapy showed a significant decrease in maxLCBl4mm from 490.6 to 336.1 (IQR: 363.8 to 689.7 and IQR: 252.3 to 479.9, respectively) 7 weeks after the introduction of the intensive statin therapy, which suggested that intensive statin therapy contributed to the stabilization of the vulnerable plaque (3). Considering that PCSK9 inhibitors are more effective than intensive statin therapy in lowering LDL-C levels and decreasing the rate of major adverse cardiovascular events, our data suggested that the stronger stabilization of vulnerable plaque could be one of the main mechanisms for clinical benefits from use of PCSK9 inhibitors compared with intensive statin therapy (1,2).

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