Radiology

Cardiovascular CT, MRI, and PET/CT in 2021: Review of Key Articles

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This review focuses on three key noninvasive cardiac imaging modalities—cardiac CT angiography (CTA), MRI, and PET/CT—and summarizes key publications in 2021 relevant to radiologists in clinical practice. Although this review focuses primarily on articles published in *Radiology*, important studies from other major journals are included to highlight "must-know" articles in the field of cardiovascular imaging. Cardiac CTA has been established as the first-line test for patients with stable chest pain and no known coronary artery disease, and its value remains central to the assessment of surgical or transcatheter aortic valve replacement. Artificial intelligence continues to evolve in a number of applications in cardiovascular disease. In cardiac MRI studies, 2021 has seen an emphasis on nonischemic cardiomyopathies, valvular heart disease, and COVID-19 disease cardiac manifestations and the authors highlight the key articles on these topics. A section featuring the increasing role of cardiac PET/CT in the assessment of cardiac sarcoidosis and prosthetic valves is also provided.

Cardiovascular imaging now plays a central role in individualizing diagnosis and management of heart disease in major clinical trials published in the highest-impact clinical journals, and many such publications are foremost in the perspectives of referring cardiologists. The current review summarizes the most relevant articles published in 2021 on advances in coronary CT angiography (CTA), MRI, and PET/CT that provide new insights for the practicing radiologist in the field of cardiovascular imaging.

Coronary Artery Disease

Severity and Extent of Coronary Artery Disease

In 2021, studies of coronary CTA for cardiovascular disease have strengthened its ability as a predictor of cardiovascular events and as a diagnostic tool in clinical decision making. The VERDICT (Very Early Versus Deferred Invasive Evaluation Using Computerized Tomography in Patients with Acute Coronary Syndromes) trial examined whether coronary artery disease (CAD) assessed with coronary CTA holds similar prognostic information to invasive coronary angiography (ICA) in patients with non-ST segment elevation acute coronary syndromes (1). In that study, coronary CTA was performed before ICA in 978 patients. The primary end point was a composite of all-cause death, nonfatal recurrent myocardial infarction (MI), hospital admission for refractory myocardial ischemia, or heart failure. Over a median follow-up duration of 4.2 years, the primary end point was 1.7-fold higher in patients with obstructive CAD than in those with nonobstructive CAD as defined with coronary CTA (hazard ratio [HR], 1.74; 95% CI: 1.22, 2.49; P = .002) or ICA (HR, 1.54; 95% CI: 1.13, 2.11; P = .007). Likewise, the rate of the primary end point in patients with high-risk CAD was 1.5-fold higher than that in patients with non–high-risk CAD as defined with coronary CTA (HR, 1.56; 95% CI: 1.18, 2.07; P = .002) or ICA (HR, 1.28; 95% CI: 0.98, 1.69; P = .07) (Fig 1). The trial highlights the similar prognostic value of coronary CTA as comparable to ICA for the assessment of long-term risk in patients with non-ST segment elevation acute coronary syndromes.

A multicenter retrospective cohort study evaluated the prognostic value of the CAD Reporting and Data system (CAD-RADS) for major adverse cardiovascular events (MACE) in patients with acute chest pain (2). Overall, 1492 patients (mean age, 58 years ± 14 [SD]; 51% men) presenting to the emergency department with acute chest pain were assessed with coronary CTA and followed up over a median duration of 2.6 years. Moderate to severe coronary artery calcium (CAC) score and CAD-RADS categories from 3 to 4 or 5 were associated with MACE (HR range, 2.3–4.4 [P < .001 to <.01] and 3.2–8.5 [P < .001], respectively). However, the CAD-RADS classification (C-index, 0.85) improved risk stratification more than clinical risk factors alone (C-index, 0.63; P < .01) or combined with CAC score (C-index, 0.76; P < .01). Thus, the trial shows the increasing utility and safety of coronary CTA above traditional scores and investigations as a prognostic tool in patients with acute chest pain.

Ischemia versus Coronary Stenosis

The ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) landmark trial assessed whether patients with moderate to severe ischemia on stress testing would have improved outcomes if managed with a conservative approach supported with medical therapy versus an upfront invasive strategy (3). There were no differences between the two groups for the primary end point (composite of time to cardiovascular death, MI, hospi-

Abbreviations

CAC = coronary artery calcium, CAD = coronary artery disease, CTA = coronary CT angiography, FDG = fluorodeoxyglucose, HR = hazard ratio, ICA = invasive coronary angiography, LGE = late gadolinium enhancement, LVEF = left ventricular ejection fraction, MACE = major adverse cardiovascular events, MI = myocardial infarction, TAVR = transcatheter aortic valve replacement

Summary

Cardiac imaging plays an increasingly central role in the diagnosis and prognostication of cardiovascular disease.

Essentials

- In 2021, cardiac CT was incorporated into high-impact cardiovascular trials, including patient selection for invasive coronary angiography, prognostication, assessment of coronary stenosis as well as structural heart disease, particularly catheter-based valve implantation.
- Cardiac MRI demonstrated its importance in risk stratification in nonischemic cardiomyopathies, malignant arrhythmias, and valve disease.
- PET/CT studies have shown it to be an important investigation in predicting treatment response in cardiac sarcoidosis, assessing cardiac-related infections, and predicting bioprosthetic valve degeneration.
- Artificial intelligence played an evolving role in quantitative analysis of coronary artery disease, dose-reducing automatic calculation of coronary artery calcium scores, and identification of specific parameters at coronary CT to aid in prognostication.
- Cardiac CT and MRI played an important role in cardiovascular statements and guidelines such as imaging evaluation and diagnosis of chest pain, aortic valve disease, cardiac amyloid, and myocardial viability.

talization for unstable angina, heart failure, or resuscitated cardiac arrest) over a median follow-up period of 3.2 years. In a secondary analysis, authors investigated whether ischemia or severity of CAD were associated with outcomes as well as their relationship with overall management strategy (4). The primary end point was all-cause mortality. Across all three degrees of ischemia severity (no or mild, moderate, severe), there was no association with increased risk of mortality (Fig 2A). However, there was an increasing association between the severity of CAD and all-cause mortality (Fig 2B). Similar results were also observed when the trial primary end point was evaluated. Although more severe ischemia was associated with increased risk for MI, this association was no longer significant when adjusted for CAD. Last, increasing CAD severity was associated with an increased risk of MI. Overall, an initial invasive strategy did not influence all-cause mortality in any CAD or ischemia subgroups, emphasizing that optimal medical therapy should be the first-line treatment for patients with stable CAD. The findings also suggest that in patients with stable CAD, coronary CTA may be superior to stress testing for risk prediction.

In a related secondary analysis of ISCHEMIA conducted by Chaitman et al (5), the impact of the various subtypes of MI on event frequency and subsequent prognosis (using the primary and secondary composite end points of the ISCHEMIA trial) was examined. A detailed description of primary and secondary MI definitions based on a hierarchy of markers and threshold values as well as a set of rules can be found in the aforementioned study. All MIs were classified based on the Universal MI classification (type 1, primary MI; type 2, secondary MI; type 3, sudden death MI; type 4a, MI related to percutaneous coronary intervention; type 4b, MI related to stent thrombosis; type 4c, MI related to stent restenosis; type 5, MI related to coronary artery bypass graft; and silent MI) with nonprocedural MI identified as types 1, 2, 4b, and 4c. Although procedural MI was higher in the invasive arm, spontaneous type 1 MI was shown to be higher in the conservative strategy and this subtype MI was the only MI type associated with an increased risk of cardiovascular death (5). These findings highlight that the debate around early revascularization is not yet over.

Sex Differences in Plaque Prevalence and Characteristics

Williams et al (6) evaluated the prognostic value of coronary plaque characteristics in men and women with symptoms suggestive of CAD. From the SCOT-HEART (Scottish CT of the Heart) trial including 1769 patients (57% were men), coronary stenosis severity, adverse plaque features, and quantitative plaque measurements were assessed (6). CAD and atherosclerotic plaque of all subtypes were more prevalent in men than in women. The incidence of MI over a median of 4.7 years was 1.4% for women and 3% for men. Men had a higher calcific burden but similar total, noncalcified, and low-attenuation plaque burdens compared with women. In a multivariate analysis adjusted for sex, cardiovascular risk score, CAC, and obstructive CAD, low-attenuation plaque was independently associated with MI (Fig 3), highlighting the fact that plaque characteristics provide incremental prognostic value above coronary stenosis severity (7). Importantly, quantitative CAD analysis of plaque volume and subtype were used in that study, and such applications to produce quantitative coronary plaque metrics are likely to increase in coronary CTA trials going forward.

Fractional Flow Reserve CT versus Conventional Management for Stable Angina

The FORECAST (Fractional Flow Reserve derived from Computed Tomography Coronary Angiography in the Assessment and Management of Stable Chest Pain) trial investigators examined whether the use of fractional flow reserve CT as compared with standard care would be cost-effective and improve clinical outcomes (8). In total, 1400 patients with symptoms suggestive of stable CAD were randomized to a standard care pathway based on National Institute for Health and Care Excellence (NICE) CG95 guidance for chest pain of recent onset (standard group) (9) or coronary CTA with selective fractional flow reserve (experimental group). The primary outcome was total cost over a period of 9 months. Secondary outcomes were quality of life, angina status, MACE, and use of ICA. The mean total cardiac cost was £1605 ($1817) in the experimental group and £1491 ($1688) in the standard group, with a 95% CI of −£112 (−8%) to +£337 (+23%) (−$127 [−9%] to +$382 [+26%]); the difference in mean costs between the two groups was not significant (P = .10). During the follow-up period, a

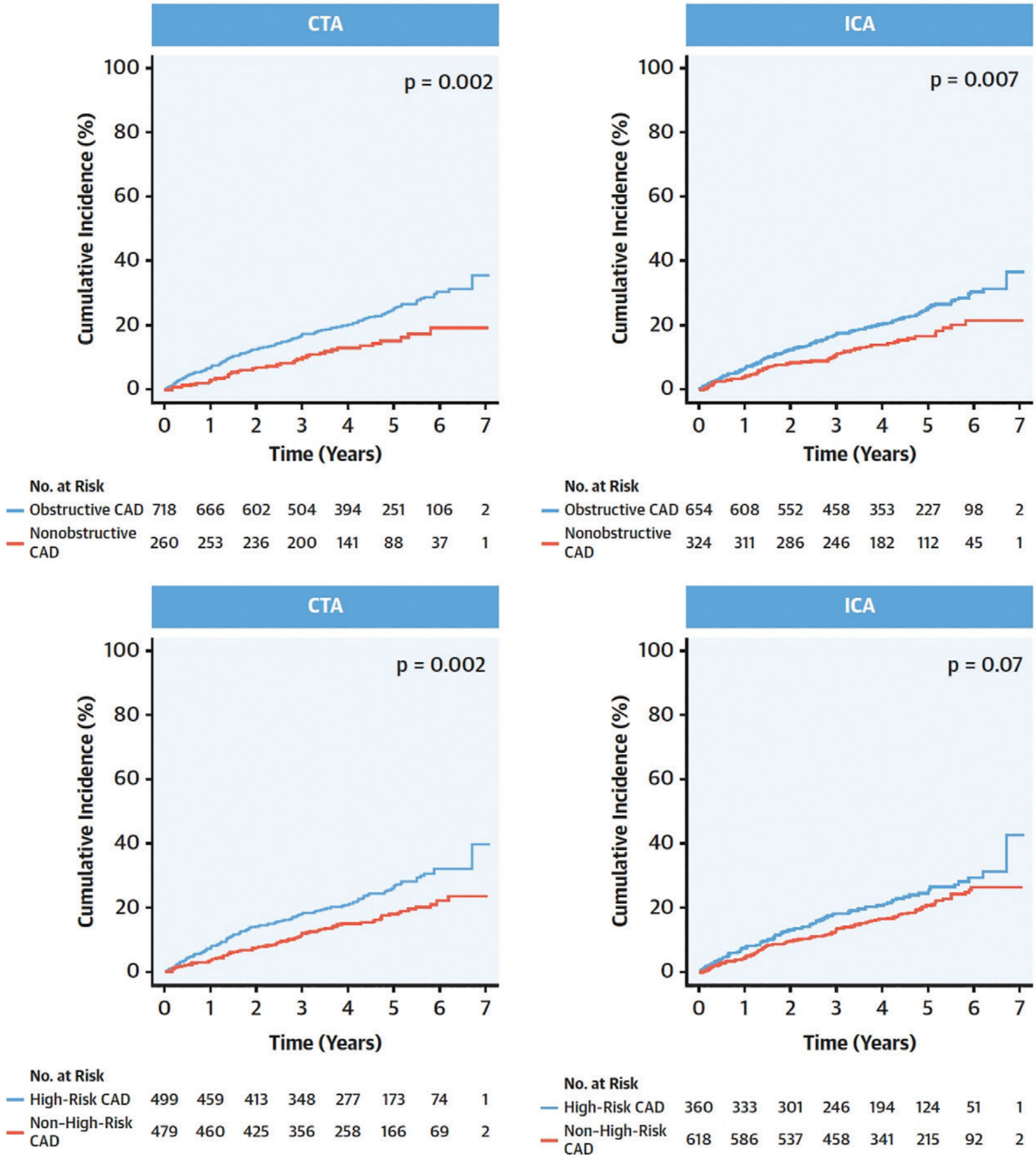

Figure 1: The VERDICT (Very Early Versus Deferred Invasive Evaluation Using Computerized Tomography in Patients with Acute Coronary Syndromes) trial evaluated whether the extent and severity of coronary artery disease (CAD) assessed with coronary CT angiography (CTA) holds similar prognostic information to invasive coronary angiography (ICA) in patients with non-ST segment elevation acute coronary syndromes. Coronary CTA and ICA were performed in 978 patients who were then followed up for a median of 4.2 years. Time-to-event curves for both CTA and ICA show the severity (top) and extent (bottom) of obstructive CAD. Similar trends were found for the primary end point of all-cause death, nonfatal recurrent myocardial infarction, hospital admission for refractory myocardial ischemia, or heart failure between modalities, indicating that coronary CTA was equivalent to ICA for the assessment of long-term risk in patients with non-ST segment elevation acute coronary syndromes. (Adapted, under a CC BY license, from reference 1.)

similar degree of improvement was observed for both groups for quality of life and angina status. The overall rate of MACE did not differ significantly between the two groups. However, the fractional flow reserve CT arm exhibited a significant reduction in the use of ICA compared with the standard group of care (19% vs 25%, $P = .01$), without affecting the overall rate of coronary revascularization between the two groups (Fig 4). Overall, the study illustrates that the use of fractional flow reserve CT as a first-line tool in a low-risk population with stable chest pain did not reduce total cardiac cost and led to similar clinical outcomes when compared with standard care practice.

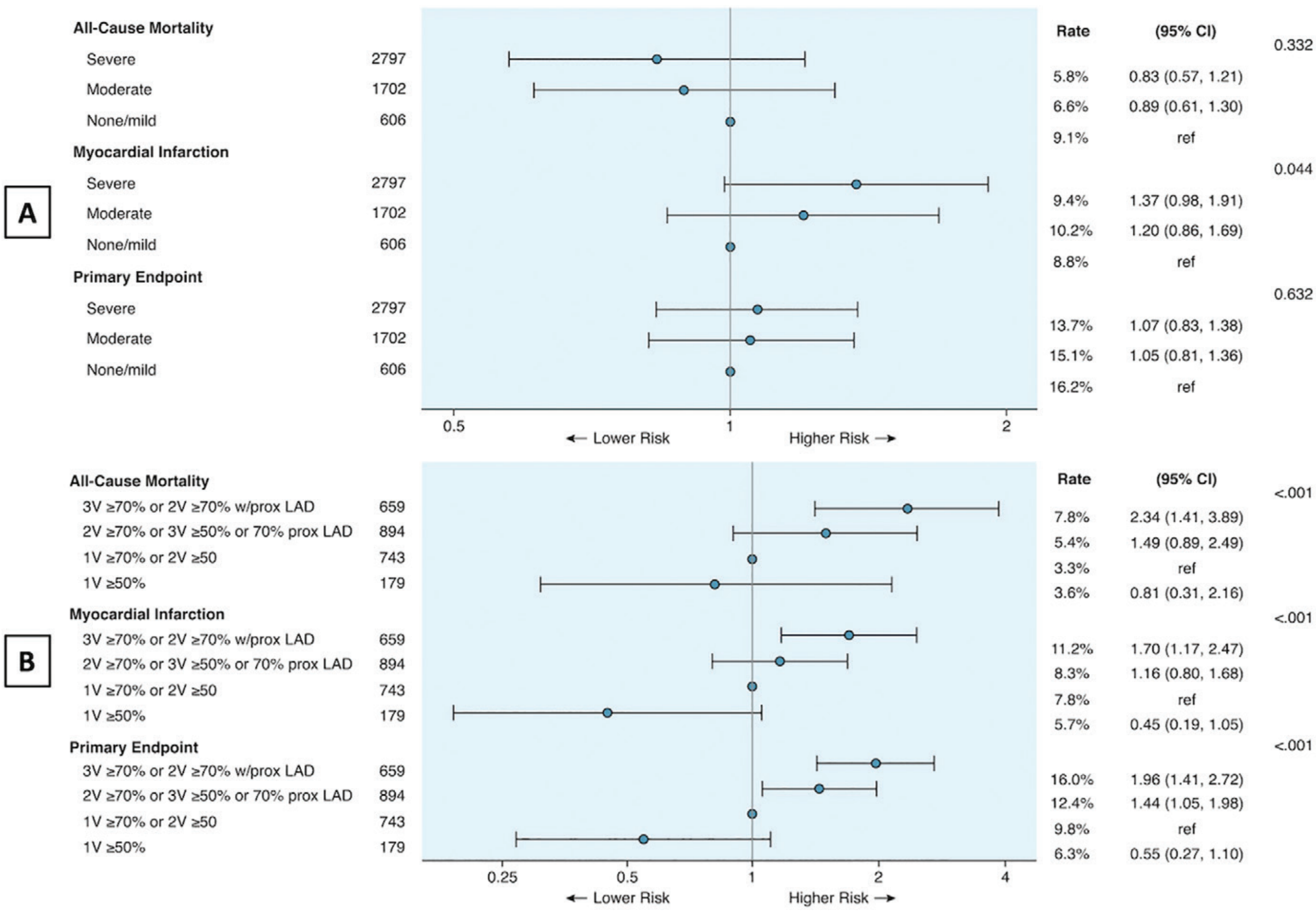

Figure 2: The ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial authors sought to investigate whether ischemia or severity of coronary artery disease (CAD) was associated with outcome as well as their relationship with overall management strategy. **(A)** Association between ischemia severity and outcomes. **(B)** Association between CAD severity and outcomes. Across all three degrees of ischemia severity (none/mild, moderate, severe), there was no association with increased risk of mortality. However, there was an increasing association between the severity of CAD and all-cause mortality. Although more severe ischemia was associated with increased risk for myocardial infarction (MI), this association was no longer significant when adjusted for CAD. Lastly, increasing CAD severity was associated with an increased risk of MI. The findings suggest that in patients with stable CAD, CT angiography may be superior to stress testing for risk prediction. LAD = left anterior descending coronary artery, 1V = one vessel, prox = proximal, ref = reference, 3V = three vessel, 2V = two vessel. (Adapted, with permission, from reference 3.)

Structural Heart Disease

Hypoattenuated Leaflet Thickening

Over the past 2 decades, transcatheter aortic valve replacement (TAVR) has evolved from a niche procedure to the dominant treatment strategy for intermediate- or high-risk patients with severe aortic stenosis and even for certain low-risk patients (10–12). The reference standard for diagnosing subclinical leaflet thrombosis remains four-dimensional cardiac CT, with curvilinear meniscoid hypoattenuating opacity at the base of valve leaflets being the main characteristic finding. The incidence of hypoattenuated leaflet thickening was evaluated by two multicenter randomized trials, the Evolut Low Risk and PARTNER 3 (Placement of Aortic Transcatheter Valves) trials, both illustrating that its incidence is similar between TAVR and surgical bioprosthetic valves (approximately 10%–30%) but also dynamic, with spontaneous resolution and new appearance over a period of time (13,14). In a study published online in 2021, the incidence of leaflet thickening was evaluated in 638 patients who underwent CT 1 month after TAVR (15). The incidence at 30 days was 12.3%. Over a median follow-up period of 2.2 years, patients with hypoattenuated leaflet thickening had increased mortality (30% vs 20%, $P = .001$). More importantly, leaflet thickening remained independently associated with long-term mortality when evaluated in a Cox regression analysis (HR, 1.83 [95% CI: 1.13, 2.97]; $P = .014$). These findings are particularly important considering that in both Evolut Low Risk and PARTNER 3 trials, the presence of leaflet thickening did not affect echocardiographic parameters.

One of the biggest challenges related to subclinical leaflet thrombosis is the lack of therapeutic strategy guidelines. A recent study of 94 patients sought to investigate the optimal treatment after TAVR (16). Patients were randomized to aspirin versus warfarin plus aspirin. Over a follow-up period of 30 days, the primary end point (a composite of leaflet thickening, reduced leaflet motion, hemodynamic dysfunction, transient ischemic attack, or stroke) was met in 7% of patients on warfarin plus aspirin compared with 26.5% on aspirin. Further clarity is needed to help answer this question and provide guidelines

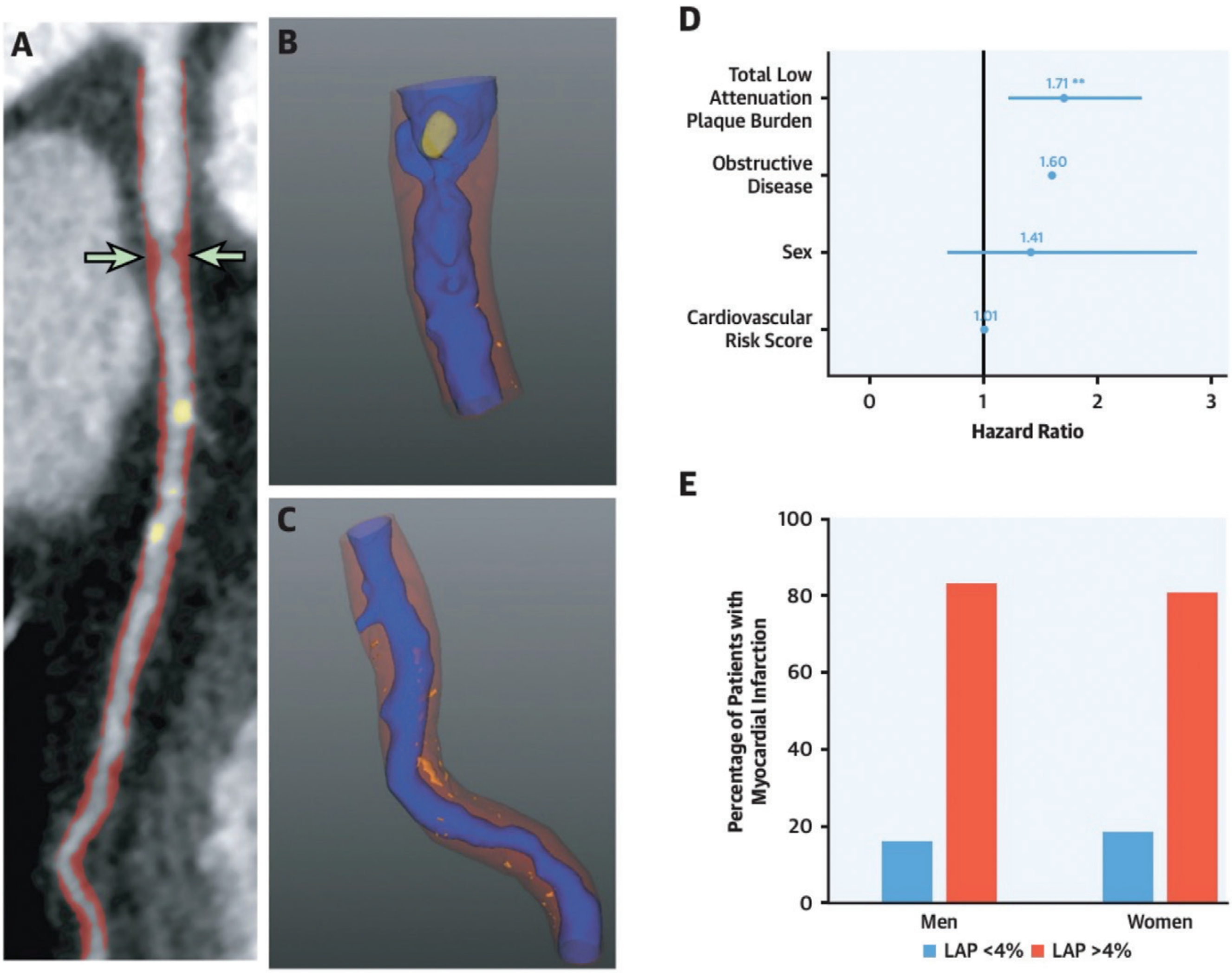

Figure 3: In the SCOT-HEART (Scottish CT of the Heart) trial including 1769 patients (57% were men), coronary stenosis severity, adverse plaque features, and quantitative plaque measurements were assessed for sex differences. Coronary artery disease (CAD) and atherosclerotic plaque of all subtypes were more prevalent in men than in women. The incidence of myocardial infarction (MI) over a median follow-up duration of 4.7 years was 1.4% for women and 3% for men. The latter had a higher calcific burden but similar total, noncalcified, and low-attenuation plaque burdens compared with women. In a multivariate analysis adjusted for sex, cardiovascular risk score, coronary calcium score, and obstructive CAD, low attenuation plaque was independently associated with MI. **(A)** Curved planar reformatted image from coronary CT angiography in a 58-year-old-woman shows obstructive disease in the left anterior descending artery (arrows) with diffuse noncalcified plaque (red) and calcified plaque (yellow). **(B, C)** Three-dimensional reformatted images of the proximal (**B**) and mid-distal (**C**) left anterior descending artery show noncalcified (red), low-attenuation (orange), and calcified (yellow) plaque and coronary lumen (blue). **(D, E)** Results calculated from a multivariate analysis (**) show low-attenuation plaque (LAP) burden as a predictor of subsequent MI (**D**) and the percentage of women or men with MI who had low-attenuation plaque above or below 4% (**E**). (Adapted, under a CC BY license, from reference 6.)

for the appropriate therapeutic management in the context of subclinical leaflet thrombosis.

Aortic Valve and CAC Score

With the CAC score being established as an essential tool in primary prevention assessment of CAD and with the rate of TAVR rising rapidly, Eberhard et al (17) investigated the prognostic value of CAC in patients scheduled for TAVR. A total of 309 patients (mean age, 81 years ± 7; 57% women) underwent CT before TAVR. A CAC score of 1000 or higher was found to be an independent predictor of 1-month (compared with a CAC score <1000; P = .007) and 1-year (compared with the reference category of a CAC score of 0–99; P = .008) mortality after TAVR (Fig 5). Addition of the CAC score in the European System for Cardiac Operative Risk Evaluation (EuroSCORE II) improved model performance, highlighting the fact that CAC score may help risk stratification in patients undergoing TAVR.

An interesting analysis from the PARADIGM registry provided further insights on the association between the progression of aortic valve calcification and coronary plaque volume and the potential underlying mechanisms related to the findings of the previous study (18). Qualitative and quantitative coronary CTA plaque characterization was performed in 594 participants who underwent serial coronary CTA at a time interval of every 2 years or longer. Aortic valve calcification was

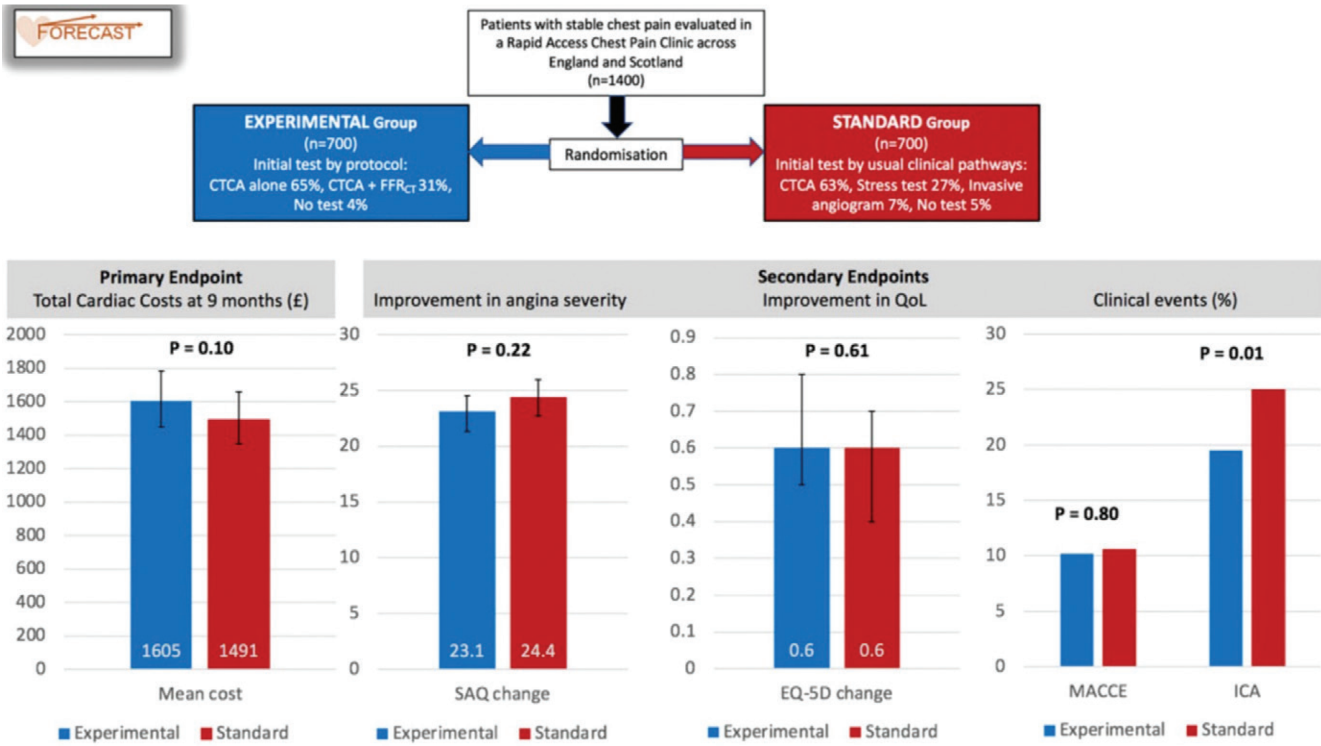

Figure 4: The FORECAST trial assessed whether fractional flow reserve CT (FFR_{CT}) as compared with standard care was cost-effective and improved clinical outcomes. The mean total cardiac cost was similar between the two groups (*P* = .10). During the follow-up period, a similar degree of improvement was observed for both groups with regard to quality of life (QoL) and angina status. The overall rate of major adverse cardiac and cerebrovascular events (MACCE) did not differ significantly between the two groups. Invasive coronary angiography (ICA) was reduced in the fractional flow reserve CT arm. CTCA = CT coronary angiography, EQ-5D = EuroQol five dimensions questionnaire, SAQ = Seattle Angina Questionnaire. (Adapted, with permission, from reference 8.)

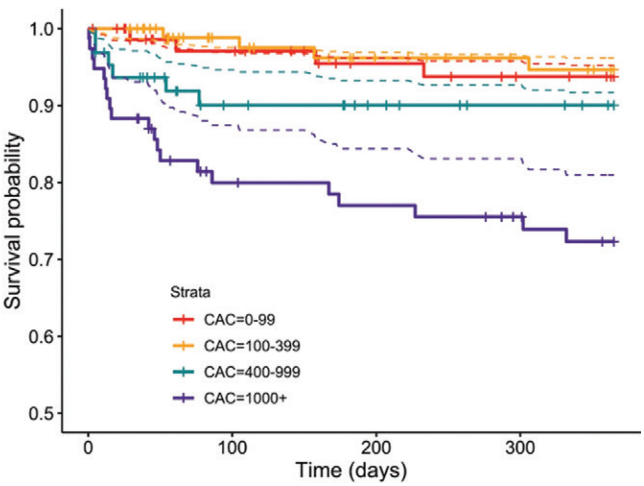

Figure 5: Coronary artery calcium (CAC) scoring and transcatheter aortic valve replacement (TAVR). The prognostic value of the CAC score was investigated in 309 patients who underwent TAVR. A CAC score of 1000 or higher was found to be an independent predictor of 1-month mortality (compared with a CAC score <1000; *P* = .007) and 1-year mortality (compared with the reference category of a CAC score of 0–99; *P* = .008) after TAVR. (Adapted, with permission, from reference 17.)

also assessed at baseline and follow-up coronary CTA. Aortic valve calcification progression was associated with progression of total coronary plaque burden, most notably the calcified coronary plaque (*P* = .001), when adjusted for clinical risk factors and medication (19). Yet, the progression of noncalcified plaque volume was not associated with aortic valve calcification progression despite this plaque component being the subtype most closely associated with cardiac events. The authors went on to suggest that different underlying pathophysiologic mechanisms may bring about a similar end result of calcification in different tissue subtypes.

Cardiomyopathies

Predicting Outcomes Using Cardiac MRI

Nonischemic dilated cardiomyopathies are well known to carry a significant ventricular arrythmia risk, and current guidelines recommend consideration for implantable defibrillator placement when the left ventricular ejection fraction (LVEF) reaches 35% or less (20). Several randomized trials have not shown LVEF to be a strong predictor of ventricular arrythmias, and experts have called for additional risk biomarkers to be increasingly used, including myocardial late gadolinium enhancement (LGE). In a study spanning a wide spectrum of LVEFs, Di Marco et al (21) examined event rates and outcomes in 1165 patients with dilated cardiomyopathy over a median follow-up of 36 months. LGE was an independent predictor of the arrhythmic end point, and this association was consistent across all strata of LVEFs. They also found LGE to be a powerful independent predictor of arrhythmic events in cardiomyopathies with LVEF greater than 35%. LGE-positive patients with LVEF greater than 35% had significantly higher ar-

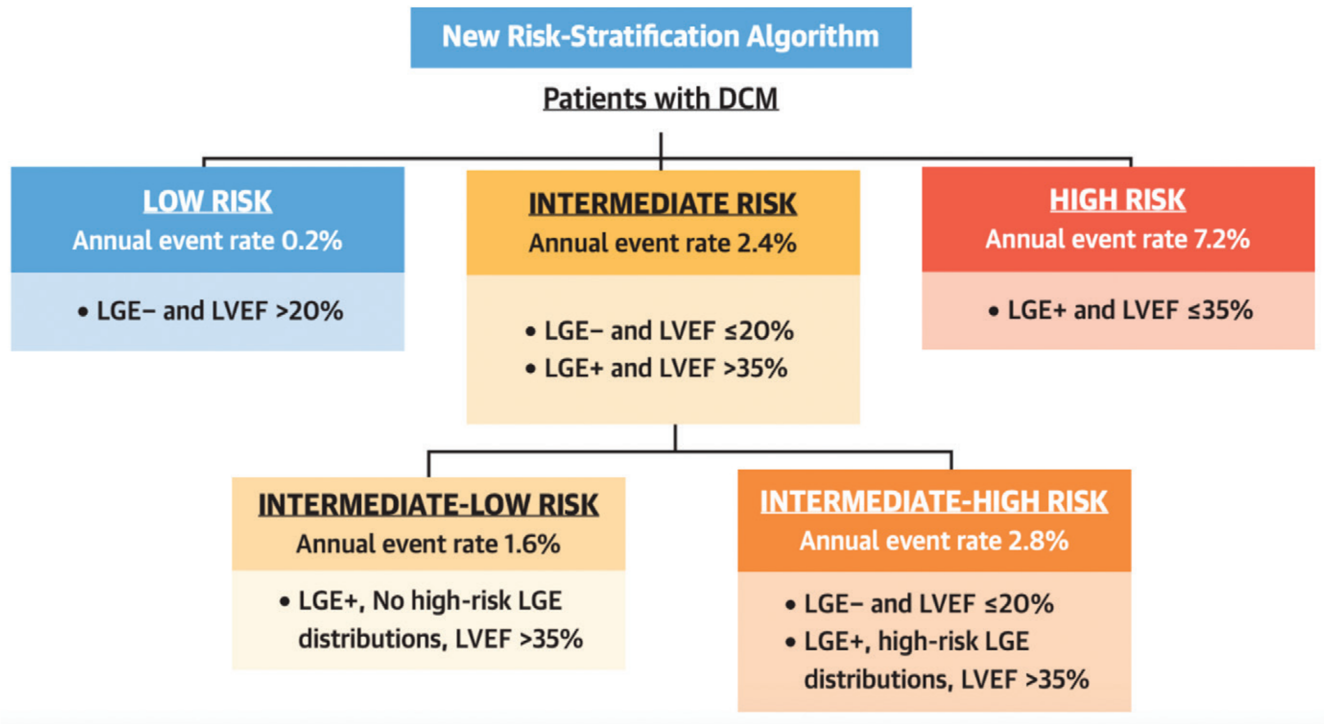

Figure 6: Dilated cardiomyopathy (DCM) risk stratification. Proposed clinical risk model for dilated cardiomyopathy combining left ventricular ejection fraction (LVEF) and late gadolinium enhancement (LGE) findings on cardiac MRI scans with associated annual event rates. (Adapted, with permission, from reference 21.)

rhythmic risk compared with LGE-negative patients with LVEF of 21%–35%. Finally, risk stratification models combining LGE and LVEF performed significantly better than LVEF dichotomized at the 35% cut-off, and the authors proposed a useful clinical risk prediction algorithm combining LVEF and LGE (Fig 6).

Another prospective, longitudinal outcomes registry reported on 1020 consecutive patients with dilated cardiomyopathy who underwent cardiac MRI for the assessment of LVEF and LGE at three centers (22). During a median follow-up of 5.2 years, 277 patients (27%) died. LVEF of 35% or less and LGE were strongly associated with all-cause and cardiac mortality. Although scar was strongly related to sudden cardiac death, there was no significant association between LVEF of 35% or less and sudden cardiac death. Multivariable regression analysis revealed the addition of LGE extent (optimal threshold, 2%) resulted in significant reclassification improvement of 25.5% for all-cause death, 27.0% for cardiac death, and 40.6% for sudden cardiac death. Thus, evidence continues to grow that the extent of LGE should be considered as a criterion for defibrillator placement.

LGE has been associated with an increased risk of life-threatening ventricular arrythmias in patients without cardiomyopathy. However, risk stratification of patients with ventricular arrythmias and normal LVEF remains challenging. A retrospective observational study from an ongoing international ventricular arrthymias cardiac MRI registry included 686 patients with both nonsustained and sustained ventricular arrthymias from seven institutions across the United States, Europe, and Japan (23). The authors describe a "ringlike" pattern of LGE (left ventricle subepicardial and/or midmyocardial LGE involving at least three contiguous segments in the same short-axis section) (Fig 7). The authors found that 4% of patients had a ringlike pattern of scar, 11% had a non-ringlike pattern, and 85% had a normal cardiac MRI scan. After a median follow-up of 61 months (range, 34–84 months), the composite outcome of all-cause death, resuscitated cardiac arrest because of ventricular fibrillation or hemodynamically unstable ventricular tachycardia, and appropriate defibrillator therapy occurred in 50.0% of patients with the ringlike LGE pattern compared with only 19.0% of patients with non-ringlike LGE and 0.3% of those with no LGE. The study highlights the significant prognostic implications of extensive LGE in predicting MACE.

Left Ventricular Noncompaction

Left ventricular noncompaction is a poorly understood heterogeneous entity characterized by prominent myocardial trabeculations in the left ventricle (24). There is clearly a spectrum of risk, from very low to high including complications such as arterial embolism, heart failure, arrythmias, and death. Casas et al (25) followed up 585 patients diagnosed with left ventricular noncompaction (diagnosed using the Jenni criteria with two-dimensional transthoracic echocardiography and, when available, both Petersen and Jacquier criteria by cardiac MRI) for a median of 5.1 years and found MACE occurred in 38% of patients. LVEF was the main predictor of MACE, although LGE was associated with heart failure and ventricular arrythmias in patients with LVEF greater than 35%. The authors emphasize that a normal LVEF and no LGE constitute a low-risk cohort for MACE and provide a useful clinical algorithm combining LVEF and LGE in a risk prediction model (Fig 8).

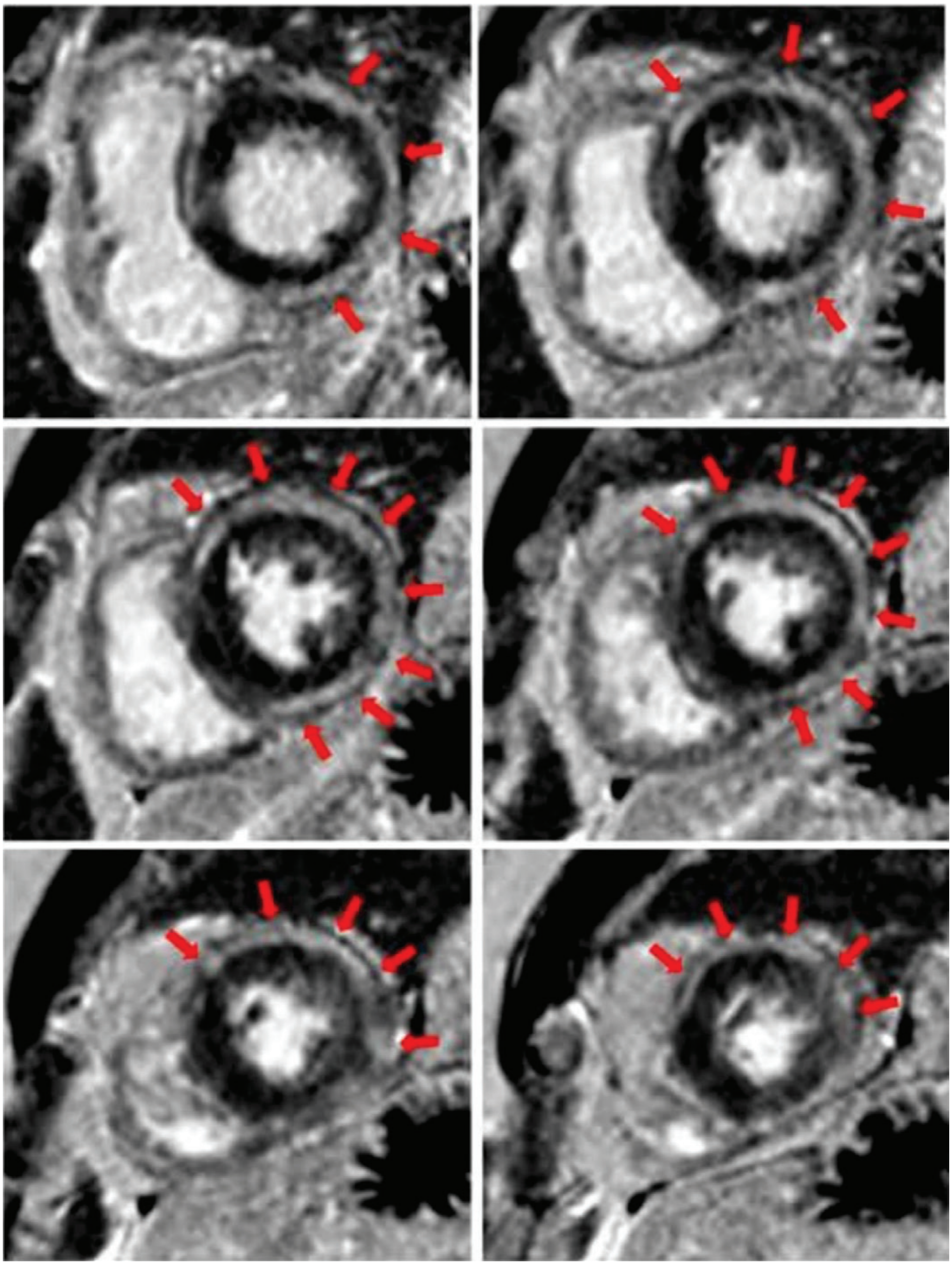

Figure 7: Ringlike late gadolinium enhancement (LGE). In a retrospective observational study from an ongoing international ventricular arrhythmia cardiac MRI registry, the presence of a specific midmyocardial and/or subepicardial ringlike LGE pattern was associated with a particularly high risk of malignant arrhythmic events, which was independent of the total LGE burden and presence of other additional risk factors. Cardiac MRI scans were obtained in a 54-year-old man who presented with palpitations related to multifocal premature ventricular contractions. Images show a "ringlike" pattern of subepicardial myocardial fibrosis (arrows) involving the left ventricular free wall. (Adapted, with permission, from reference 23.)

Valves

Mitral Valve Prolapse

Mitral valve prolapse affects 2%–3% of the population and can be associated with trace to severe mitral regurgitation but also heart failure, arterial embolism, rhythm disorders, and sudden cardiac death (26). Many patients with prolapse show LGE at cardiac MRI, but, to our knowledge, the implications have not been assessed in a large prospective cohort. In a prospective observational study of 400 patients with mitral valve prolapse (27), patients were followed up for up to 4 years. LGE was identified in 28% of patients (Fig 9), and the extent of LGE increased with severity of regurgitation. In trace to mild regurgitation, despite the absence of significant volume

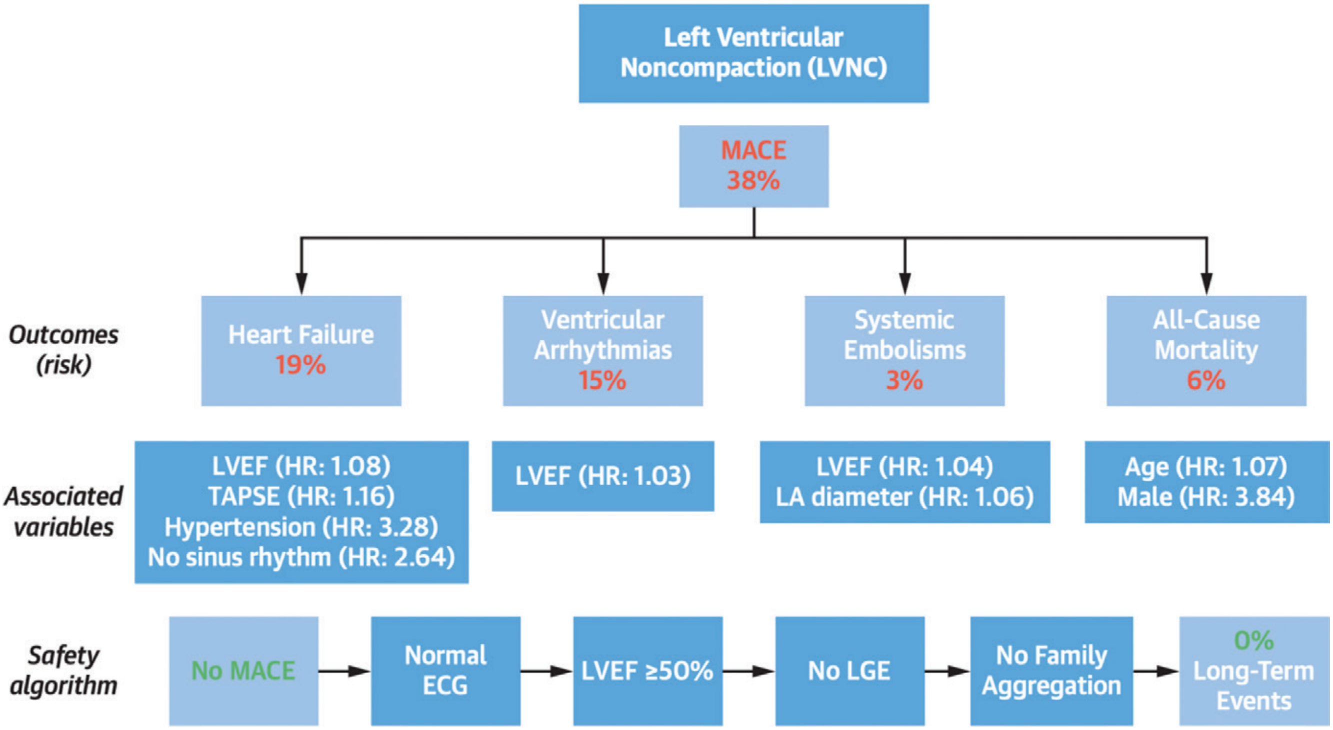

Figure 8: Left ventricular noncompaction (LVNC) safety algorithm. A total of 585 patients fulfilling electrocardiographic or cardiac MRI criteria for left ventricular noncompaction were followed up for a median of 5.1 years, and major adverse cardiovascular events (MACE) occurred in 38% of patients. Left ventricular ejection fraction (LVEF) was the main predictor of MACE, although late gadolinium enhancement (LGE) was associated with heart failure and ventricular arrhythmias in patients with LVEF greater than 35%. The figure illustrates a proposed clinical algorithm of safety for left ventricular noncompaction by Casas et al (25). ECG = electrocardiogram, HR = hazard ratio, LA = left atrium, TAPSE = tricuspid annular plane systolic excursion. (Adapted from reference 25.)

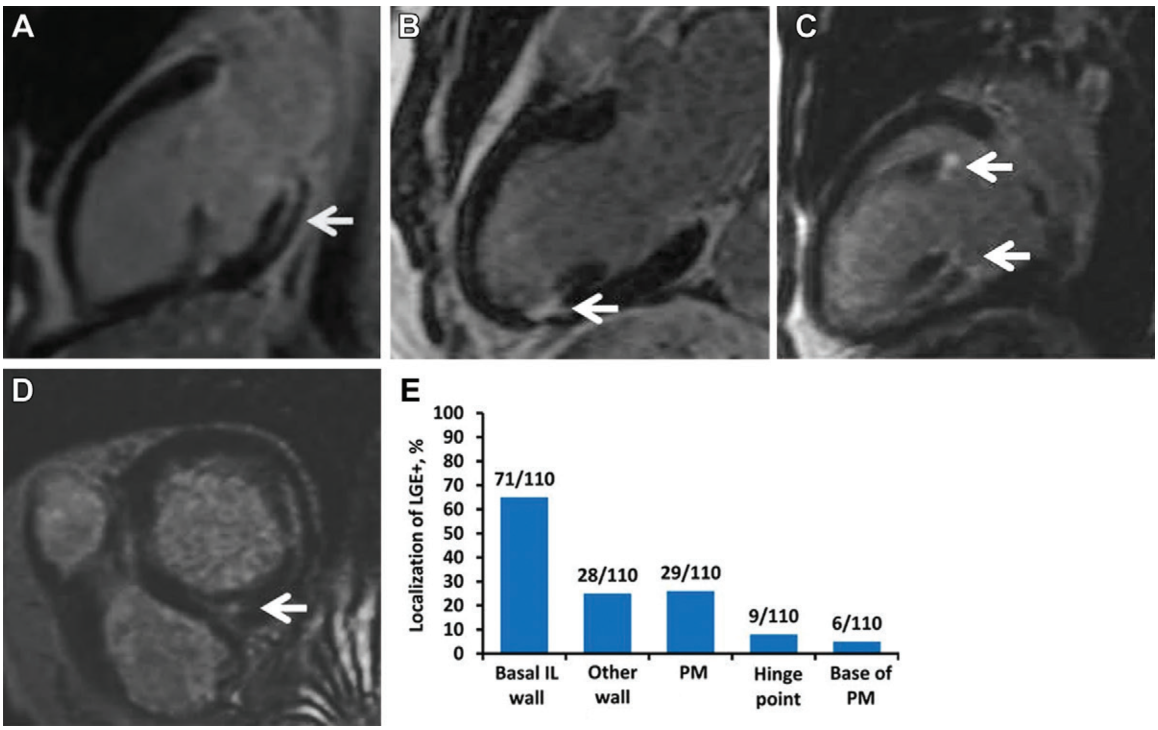

Figure 9: A prospective observational study of 400 patients with mitral valve prolapse was performed with 4-year follow-up. Late gadolinium enhancement (LGE) was found in 28% of patients. **(A–D)** MRI scans show four different types of LGE (arrows) among the 110 (28%) patients with LGE. **(A)** Linear basal inferolateral midwall LGE. **(B)** Nodular myocardial wall LGE at the base of the papillary muscle. **(C)** Tip papillary muscles LGE. **(D)** Small nodular inferior left-to-right ventricular hinge point LGE. **(E)** Chart shows distribution of the different types of LGE identified in patients with mitral valve prolapse. IL = inferolateral, LGE+ = LGE positive, PM = papillary muscle. (Adapted, with permission, from reference 27.)

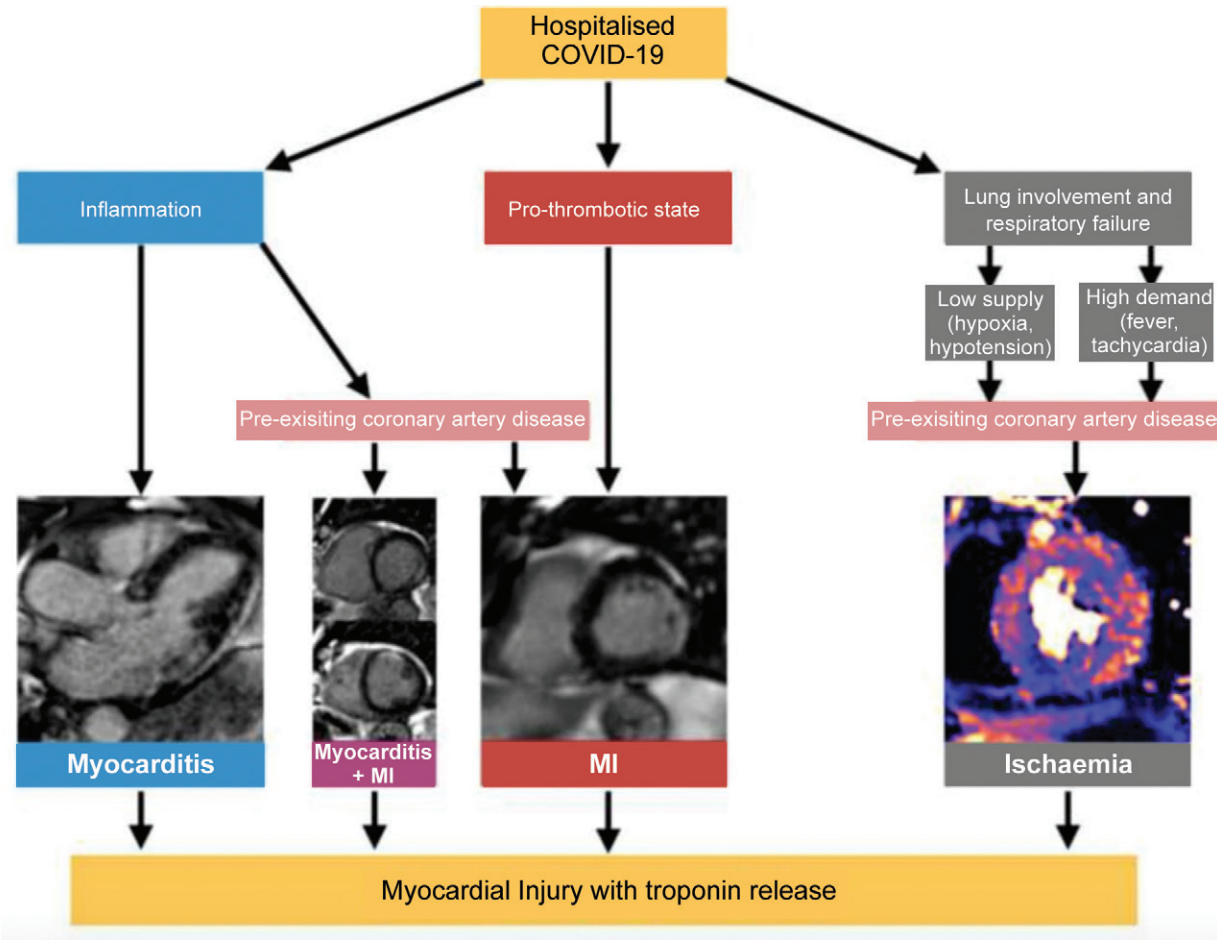

Figure 10: COVID-19 disease cardiac manifestations. Kotecha et al (31) suggest that a combination of myocardial inflammation, a prothrombotic state, and lung inflammation are all likely to contribute to myocardial injury in patients hospitalized for COVID-19 disease. MI = myocardial infarction. (Adapted, under a CC BY license, from reference 31.)

overload, abnormal left ventricular dilatation was observed in 16% of patients and ventricular arrhythmia in 25%. Correlates of LGE in multivariable analysis were left ventricular mass and moderate to severe regurgitation. LGE was also associated with worse 4-year cardiovascular event–free survival. All together, these findings show that cardiac MRI can provide prognostic information in mitral valve prolapse–associated myocardial disease.

Severe Mitral Regurgitation

Two echocardiographic findings considered to indicate possible severe mitral regurgitation are a flail leaflet and the regurgitant jet flowing along the side wall of the left atrium (Coandă effect) (28). Measuring the regurgitant volume or fraction can be difficult with such findings. A study by Uretsky et al (29) examined the utility of cardiac MRI to measure regurgitant volume and fraction by subtracting the phase contrast forward flow across the ascending aorta from the left ventricular stroke volume. With the use of cardiac MRI–derived regurgitant volume, 35%, 46%, and 59% of patients had severe regurgitation with the presence of a Coandă, flail leaflet, or both, respectively. With the use of cardiac MRI–derived regurgitant fraction, 25%, 31%, and 40% of patients had severe regurgitation with the presence of a Coandă, flail leaflet, or both, respectively. The authors suggest that severe regurgitation is depicted more frequently with cardiac MRI than with echocardiography in the presence of a flail leaflet or Coandă effect.

Systemic Disease

COVID-19 Disease

The cardiac implications of COVID-19 disease continued to evolve in 2021, with varying conclusions depending on which type of patient cohort was studied. A study of 41 troponin-negative patients with mild to moderate COVID-19 disease, most of whom did not require hospitalization (30), showed that at a median time of 103 days, no cardiac MRI evidence of active myocardial inflammation was evident compared with age- and sex-matched controls. However, another multicenter study involving six acute hospitals (31) evaluated 148 patients with severe COVID-19 disease infection (all requiring hospital admission and 48 [32%] requiring ventilatory support) and troponin elevation. Convalescent cardiac MRI was performed at a median of 68 days (31). Left ventricular function was normal in 89% and LGE and/or ischemia was found in 54%, with a pattern of myocarditis-like scar in

26%, infarction and/or ischemia in 22%, and dual pathology in 6%. Myocarditis-like injury was limited to three or fewer myocardial segments in 88% of patients with no associated left ventricle dysfunction; of these, 30% had active myocarditis. MI was found in 19% and inducible ischemia in 26% of those undergoing stress perfusion (including seven with both infarction and ischemia). Of patients with an ischemic injury pattern, 66% had no history of CAD. The authors suggest that while some patients undoubtedly had pre-existing CAD, a proportion of MIs in these patients could have been the result of a COVID-19 disease–related prothrombotic state in patients with underlying vulnerability due to cardiovascular risk factors resulting in type 1 MI occurring during the acute infection (Fig 10). They conclude that during convalescence after severe COVID-19 disease infection with troponin elevation, myocarditis-like and ischemic injury can be encountered, with limited extent and minimal functional consequence. Finally, a study evaluating 40 patients recovering from moderate to severe COVID-19 disease pneumonia used cardiac MRI feature tracking strain analysis and found left ventricular longitudinal strain was reduced in patients with COVID-19 disease at a mean of 158 days from admission compared with controls (32). Thus, certain sophisticated cardiac MRI techniques may show subclinical abnormalities in patients with more severe COVID-19 disease several months after acute infection. Whether this translates into long-term clinical sequelae for patients is currently unknown.

A related issue described in 2021 was the discovery of COVID-19 disease vaccination-related myocarditis. An "Images in *Radiology*" report showed cardiac MRI scans in a 15-year-old boy 1 day after his second vaccination dose (BNT162b2 mRNA SARS-CoV-2, BioNTech/Pfizer) (33). Images showed T2, LGE, and mapping abnormalities consistent with acute myocarditis. Adult cases with recent vaccination and similar cardiac MRI abnormalities have subsequently been described (34). In five adults (male-to-female ratio, 4:1; age range, 17–38 years), cardiac MRI showed myocarditis-like findings including a nonischemic pattern of LGE, corresponding signal intensity abnormalities on T2-weighted images, and pericardial enhancement. All patients showed reactive axillary lymphadenopathy in the vaccinated arm.

HIV Infection

It is well known that HIV infection is associated with an increased risk of MI; however, the prevalence of plaque subtypes and relationship to therapy is less clear. Plaque quantification was assessed in the prospective Canadian HIV and Aging Cohort Study in 233 participants (155 people with HIV and 78 healthy volunteers) (35). After adjusting for cardiovascular risk, CAC score and overall plaque burden were not statistically different between groups. However, the prevalence of noncalcified plaque in people with the virus was higher than that in healthy volunteers. Moreover, the overall plaque volume as well as the mixed plaque volume were higher in patients treated with protease inhibitors. Thus, the study highlights the utility of coronary CTA in asymptomatic people living with HIV without cardiovascular risk factors.

Cardiac PET/CT

Cardiac Sarcoidosis

Fluorodeoxyglucose (FDG) PET/CT is proving increasingly useful in patients known to have or suspected of having cardiac sarcoidosis and is recommended by 2017 multimodality imaging guidelines for cardiac sarcoidosis (36). Subramanian et al (37) examined the predictors of response to immunosuppressive treatment using FDG PET/CT in 96 patients with known cardiac sarcoidosis. Complete responders showed higher myocardial FDG uptake, a greater number of abnormal left ventricular segments, and increased uptake index on the baseline FDG PET/CT scans compared with partial responders and nonresponders; these results suggest that the burden of metabolically active myocardial inflammation is a useful predictor of the likelihood of treatment response to therapy.

Prognosis

The prognostic value of FDG PET/CT in cardiac sarcoidosis was retrospectively evaluated in two studies, one by Patel et al (38) and the other by Bekki et al (39). In the former study, the authors studied 197 patients who were not receiving therapy for the primary end point of time to arrythmia or death. They concluded that a drop in LVEF of 10% and an increase in summed rest score based on rest myocardial perfusion imaging using rubidium 18 of 3 or 4 points was associated with a 20% risk of the primary end point. In the latter study, the location of abnormal myocardial FDG uptake in cardiac sarcoidosis was addressed in 90 treatment-naive patients suspected of having cardiac involvement. Multivariate analysis demonstrated that increased FDG uptake in the right ventricle (HR, 2.8; $P = .047$) or left ventricular basal anterolateral segment with a corresponding perfusion abnormality (HR, 4.64; $P = .001$) was associated with adverse events after adjustment for left ventricular systolic dysfunction.

Bioprosthetic Valve Degeneration

Fluorine 18 (^{18}F) sodium fluoride (NaF) PET/CT provides molecular imaging of valvular and/or vascular calcification and can be used as a marker of disease severity in native aortic valve stenosis (40). Kwiecinski et al (41) evaluated the potential role of ^{18}F-NaF PET/CT in the assessment of disease activity within the retained native aortic valve and of bioprosthetic valve durability after TAVR. Forty-seven patients underwent baseline ^{18}F-NaF PET/CT at a single time point after TAVR (range, 1 month to 5 years). Comparisons were made with a group of 51 patients with surgical aortic valve replacement who had undergone the same imaging protocol. The TAVR group demonstrated increased ^{18}F-NaF uptake around the outside of the bioprosthetic valve consistent with ongoing metabolic activity in the retained native aortic valvular tissue (Fig 11). The prevalence of increased ^{18}F-NaF activity on the bioprosthetic valve leaflets was nearly doubled in the surgical group (29% vs 15%, $P = .09$). Baseline prosthetic valve ^{18}F-NaF uptake was associated with subsequent change in aortic peak systolic velocity in both the TAVR and surgical groups ($r = 0.7$, $P < .001$ for both) and was the only pre-

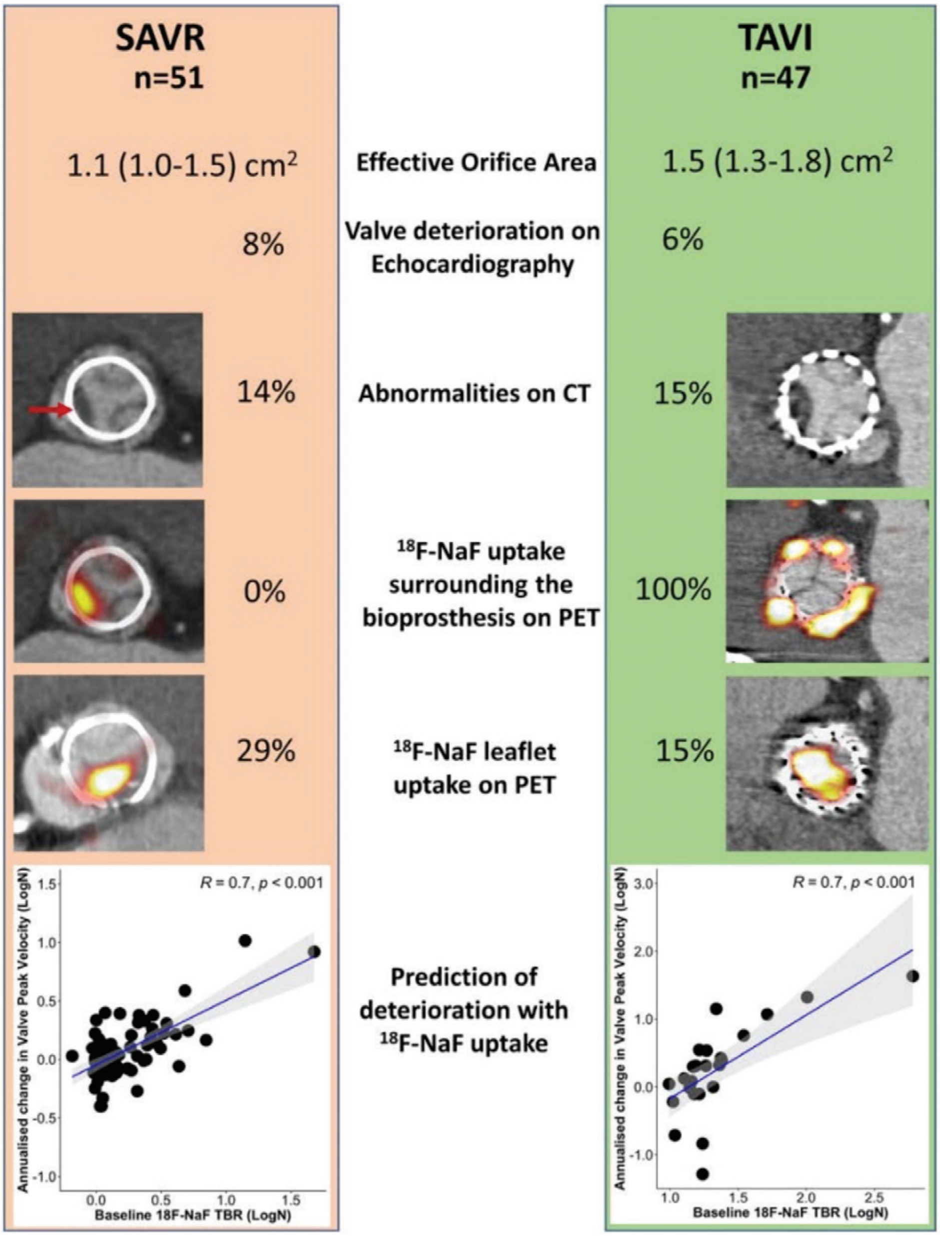

Figure 11: Fluorine 18 (^{18}F) sodium fluoride (NaF) PET/CT use with aortic valve replacement. ^{18}F-NaF PET/CT provides molecular imaging of valvular and vascular calcification and can be used as a marker of disease severity in native aortic valve stenosis. In a study of 47 patients with transcatheter aortic valve implantation (TAVI) and 51 with surgical aortic valve replacement (SAVR) who underwent ^{18}F-NaF PET/CT at baseline, transcatheter aortic valve implantation showed increased uptake in the valve consistent with ongoing disease activity in the retained native aortic valvular tissue. Baseline prosthetic valve ^{18}F-NaF uptake was associated with subsequent change in aortic peak systolic velocity in both transcatheter aortic valve implantation and SAVR groups. TBR = target-to-background ratio. (Adapted, under a CC BY license, from reference 41.)

dictor of bioprosthetic aortic peak systolic velocity progression on multivariable analysis ($P < .001$). These results suggest that ongoing disease activity in the native aortic valve after TAVR is detectable using ^{18}F-NaF PET. Furthermore, ^{18}F-NaF PET/CT appears to be a reliable predictor of bioprosthetic valve dysfunction in both TAVR and surgical valve replacements and may play a role in identifying patients at a higher risk of bioprosthetic valve degeneration in future studies.

Artificial Intelligence and Machine Learning

Separate nonenhanced CT to quantify CAC score often precedes coronary CTA, but quantifying CAC scores directly at coronary CTA would eliminate the additional radiation. Current software modules are unable to calculate CAC scores from contrast-enhanced scans. In a retrospective study, Mu et al (42) used a deep learning method to quantify CAC scores from coronary CTA. The correlation between the semiautomated

Table 1: Cardiac MRI Recommendations for Acute Chest Pain from the 2021 AHA/ACC Chest Pain Guidelines

Patient Type and Section	Recommendation	Strength of Recommendation
Patients with intermediate risk and no known CAD		
4.1.2.1	For intermediate-risk patients with acute chest pain and no known CAD who are eligible for cardiac testing, either exercise EKG, stress echocardiography, stress PET/SPECT MPI, or stress cardiac MRI is useful for the diagnosis of myocardial ischemia	Strong
4.1.2.1	For intermediate-risk patients with acute chest pain and no known CAD, with an inconclusive CTA, stress imaging with echocardiography, PET/SPECT MPI, or cardiac MRI can be useful for the diagnosis of myocardial ischemia.	Moderate
Patients with intermediate risk and known CAD		
4.1.2.2	For intermediate-risk patients with acute chest pain and known CAD who have new onset or worsening symptoms, stress imaging (PET/SPECT MPI, cardiac MRI, or stress echocardiography) is reasonable	Moderate
High-risk patients with acute chest pain		
4.1.3	For high-risk patients with acute chest pain who are troponin positive in whom obstructive CAD has been excluded with CTA or ICA, cardiac MRI or echocardiography can be effective in establishing alternative diagnosis	Moderate

Source.—Reference 44.

Note.—ACC = American College of Cardiology, AHA = American Heart Association, CAD = coronary artery disease, CTA = CT angiography, ICA = invasive coronary angiography, EKC = electrocardiography, MPI = myocardial perfusion imaging.

Table 2: Cardiac MRI Recommendations for Other Causes of Acute Chest Pain from the 2021 AHA/ACC Chest Pain Guidelines

Patient Type and Section	Recommendation	Strength of Recommendation
Patients with suspected acute aortic syndrome		
4.2.1	In patients with acute chest pain where there is clinical concern for aortic dissection, TEE or cardiac MRI should be performed to make the diagnosis if CT is contraindicated or unavailable	Strong
Patients with suspected myopericarditis		
4.2.3	In patients with acute chest pain and myocardial injury who have nonobstructive coronary arteries on anatomic testing, cardiac MRI with a gadolinium-based contrast material is effective to distinguish myopericarditis from other causes, including myocardial infarction and nonobstructive coronary arteries (MINOCA)	Strong
4.2.3	In patients with acute chest pain with suspected acute myopericarditis, cardiac MRI is useful if there is diagnostic uncertainty, or to determine the presence and extent of myocardial and pericardial inflammation and fibrosis	Strong
Patients with VHD		
4.2.4	In patients presenting with acute chest pain with known or suspected VHD, cardiac MRI is reasonable as an alternative to TTE and/or TEE is nondiagnostic	Moderate

Source.—Reference 44.

Note.—ACC = American College of Cardiology, AHA = American Heart Association, TEE = transesophageal echocardiography, TTE = transthoracic echocardiography, VHD = valvular heart disease.

nonenhanced CT CAC score and the deep learning algorithm of coronary CTA was excellent ($r^2 = 0.92$, $P < .001$). Likewise, the risk categorization agreement for both modalities was excellent, with 93% of CT scans being categorized accurately. Thus, machine learning allows CAC calculation from coronary CTA from a single scan acquisition.

Another study analyzed plaque characteristics and angiographic CT parameters to investigate their prognostic value (43). A total of 643 patients (1013 vessels) with available coronary CTA data sets and invasive fractional flow reserve measurements were evaluated. Machine learning identified relevant features associated with hemodynamically significant stenosis (fractional flow reserve <0.8)

Table 3: Cardiac MRI Recommendations for Stable Chest Pain from the 2021 AHA/ACC Chest Pain Guidelines

Patient Type and Section	Recommendation	Strength of Recommendation
Patients with intermediate to high risk and no known CAD		
5.1.3	For intermediate- to high-risk patients with stable chest pain and no known CAD, stress imaging (stress echocardiography, PET/SPECT MPI, or cardiac MRI) is effective for diagnosis of myocardial ischemia and for estimating risk of MACE	Strong
Recommendations for sequential or add-on testing if index test results are positive or inconclusive		
5.1.3	For intermediate- to high-risk patients with stable chest pain after inconclusive CTA, stress imaging is reasonable	Moderate
Patients with obstructive CAD		
5.2.1	For patients with obstructive CAD who have stable chest pain despite optimal GDMT, stress PET/SPECT MPI, cardiac MRI, or echocardiography is recommended for diagnosis of myocardial ischemia, estimating risk of MACE, and guiding therapeutic decision-making	Strong
5.2.1	For patients with obstructive CAD and stable chest pain symptoms who are undergoing stress PET MPI or stress cardiac MRI, the addition of MBFR measurement is useful to improve diagnosis accuracy and enhance risk stratification	Moderate
Patients with prior CABG surgery		
5.2.1.1	In patients who have had prior CABG surgery presenting with stable chest pain who are suspected to have myocardial ischemia, it is reasonable to perform stress imaging or CTA to evaluate for myocardial ischemia or graft stenosis or occlusion	Moderate
Patients with known nonobstructive CAD		
5.2.2	For patients with known extensive nonobstructive CAD with stable chest pain symptoms, stress imaging (PET/SPECT, cardiac MRI, or echocardiography) is reasonable for the diagnosis of myocardial ischemia	Moderate
5.2.3	For patients with persistent stable chest pain and nonobstructive CAD (INOCA), stress cardiac MRI with the addition of MBFR measurement is reasonable to improve diagnosis of coronary myocardial dysfunction and for estimating risk of MACE	Moderate

Source.—Reference 44.

Note.—ACC = American College of Cardiology, AHA = American Heart Association, CABG = coronary artery bypass graft, CAD = coronary artery disease, CTA = CT angiography, GDMT = guideline-directed medical therapy, INOCA = ischemia and no obstructive coronary artery disease, MACE = major adverse cardiovascular events, MBFR = myocardial blood flow reserve, MPI = myocardial perfusion imaging.

and 5-year MACE (cardiac death, target vessel MI, and target vessel revascularization). Six functionally relevant features (minimum lumen area, plaque and percentage atheroma volume, fibrofatty and necrotic core volume, proximal left anterior descending coronary lesion, and remodeling index) were identified for low fractional flow reserve. Interestingly, an increasing number of these individual features concurrently was associated with a greater risk of 5-year MACE (fig 9 in their online supplement). This study suggests that machine learning–derived coronary CTA parameters have the potential to provide prognostic information derived from plaque characteristics and improve clinical decision-making.

Statements and Guidelines

Guidelines for the Evaluation and Diagnosis of Chest Pain

In 2021, the American College of Cardiology and American Heart Association Joint Committee updated guidelines on the evaluation and diagnosis of chest pain (44). A major guideline change was that low-risk patients with normal high-sensitivity troponin values should be discharged without further outpatient testing with an outpatient CAC score scan considered for long-term risk stratification. Furthermore, a class IA recommendation was given to coronary CTA for intermediate- to high-risk patients with stable chest pain and no known CAD (fig 2 in their online supplement). Coronary CTA was also considered a class IA imaging modality for intermediate-risk patients with acute chest pain and no known CAD after an inconclusive or negative evaluation for acute coronary syndrome (fig 3 in their online supplement).

In patients at intermediate risk with acute chest pain, no known CAD, and evidence of previous mildly abnormal stress test results (≤1 year), coronary CTA was recommended as an alternative strategy. Coronary CTA was also

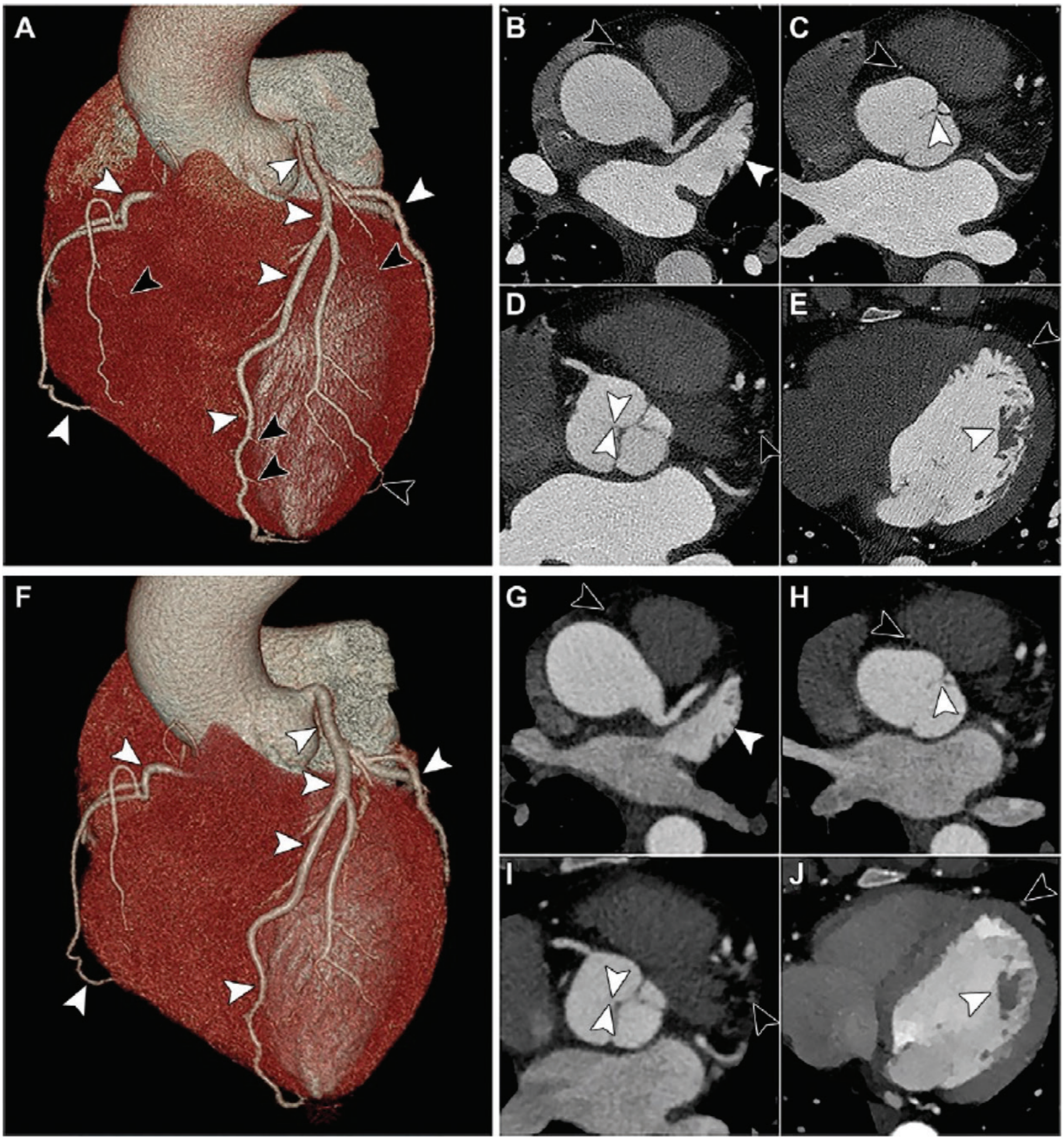

Figure 12: Examples of coronary imaging with photon-counting and dual-layer CT. **(A–E)** Coronary photon-counting CT scans and **(F–J)** dual-layer CT angiograms in a 44-year-old woman with normal coronary morphologic characteristics and cardiac anatomy. **(A, F)** Volume-rendered images from photon-counting CT (**A**) and CT (**F**) show proximal coronary arteries (white arrowheads in **A** and **F**); however, the distal segments of coronary arteries are better depicted on photon-counting CT (black arrowheads in **A**) compared with CT images. On axial images, pectinate muscle **(B, G)**, aortic cusp commissure **(C, H)**, noncoronary cusp **(D, I)**, and papillary muscle **(E, J)** were better depicted on photon-counting CT images **(B–E)** than on CT images **(G–J)** (white arrowheads). The depiction of the distal segment of coronary arteries on axial images is better on photon-counting CT images than on CT images (black arrowheads).

deemed useful to determine CAD progression of atherosclerotic plaque for intermediate-risk patients with acute chest pain and known CAD. Fractional flow reserve CT should also be considered for patients with acute symptoms suggestive of CAD and a coronary stenosis of 40%–90% in a proximal or middle coronary artery.

There were also recommendations for cardiac MRI, which we have outlined in Tables 1–3.

Updated End Points for Aortic Valve Disease

The Valve Academic Research Consortium provides standardized definitions across a large spectrum of clinical end points related to aortic valve disease (45). In an updated consensus statement, the authors described the central role of CT in the diagnosis and clinical management of leaflet and valve thrombosis. Additional technical recommendations for the evaluation of leaflet thickening are described. Furthermore, guidance for stratification assessment of the severity of hypoattenuating leaflet thickening is provided.

Cardiac Amyloidosis

A 2021 expert consensus statement published recommendations for the noninvasive cardiovascular imaging of cardiac amyloidosis (46). The writing committee provided a comprehensive review of all relevant imaging modalities in screening, diagnosis, and management of cardiac amyloidosis—in particular bone scanning and cardiac MRI.

Multimodality Imaging and Myocardial Viability

In an expert consensus document from the European Association of Cardiovascular Imaging, a comprehensive review of imaging modalities for the assessment of myocardial viability has been published (47). Beyond merely describing the presence of myocardial viability for coronary revascularization, the statement describes how viability has become important in several other myocardial diseases such as nonischemic cardiomyopathies and valvular heart disease.

Frontiers in Imaging Science

Quantification of MI

Prompt revascularization remains the cornerstone of successful management for ST-elevation MI. However, reperfusion injury and the associated inflammatory mechanisms can lead to further loss of viable myocardium (48). Targeted treatment against pathophysiologic inflammatory pathways that are activated during reperfusion could reduce the infarct size, improving clinical outcomes after ST-segment elevation MI. Cardiac MRI can quantify the extent of MI related to ischemia and necrosis. In the ASSAIL-MI (Assessing the Effect of Anti-IL-6 Treatment in Myocardial Infarction) trial (49), 195 patients with ST-segment elevation infarction were randomized to receive interleukin-6 or placebo before revascularization. The myocardial salvage index as measured with cardiac MRI was evaluated after 3–7 days. The myocardial salvage index (in percentage) was defined as (area at risk – infarct size/area at risk) × 100, where area at risk is the volume of the ischemic myocardium while the infarct size is the necrotic myocardium (50). Interleukin-6 increased the myocardial salvage index in comparison with placebo (95% CI: 0.22, 11.3; $P = .04$). Thus, anti-inflammatory therapy may play an increasing role in reducing the inflammatory response to infarct-related myocardial damage, and this effect can be quantified using cardiac MRI.

Photon-counting CT

Photon-counting CT is an emerging technology that has the potential to bring clinical CT to a new level of performance. Technical details are provided in an illuminating review in 2021 of next-generation hardware advances in CT (51). Early descriptions of its benefits in coronary CTA are emerging. Si-Mohamed et al (52) compared conventional coronary CTA with photon-counting CTA in 14 patients with CAD. Overall, quality and diagnostic confidence for CAD and stent evaluation, as assessed by three experienced cardiac radiologists, were higher with photon-counting CTA than with conventional CTA (Fig 12). This novel imaging modality will potentially create opportunities for CT images with better spatial resolution, further improving diagnostic accuracy.

Conclusion

In 2021, cardiac CT trials evaluated prognostication in coronary artery disease (CAD) and assessment of coronary stenosis and structural heart disease. Cardiac MRI trials evaluated risk stratification in nonischemic cardiomyopathies, malignant arrhythmias, and valve disease. PET/CT trials focused on predicting treatment response in cardiac sarcoidosis, assessing cardiac-related infections, and predicting bioprosthetic valve degeneration. Artificial intelligence continued to play an evolving role in quantitative analysis of CAD, dose-reducing automatic calculation of coronary artery calcium scores, and identification of specific parameters at coronary CT angiography to aid in prognostication. Cardiac CT and MRI featured prominently in multiple cardiovascular statements and guidelines.

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