Noninvasive imaging modalities are changing the management of cardiovascular disease. Cardiovascular magnetic resonance (CMR) has matured as a clinical tool, having passed through validation, standardization, and clinical roll-out phases.1-5 CMR now aids the prediction of clinical outcomes with a growing prognostic evidence base, systematically reviewed here with a summary of 32 CMR outcome studies with 8855 patients (range, n=25 to 1299). Ongoing trials on the clinicaltrials.gov website are also highlighted.

Methods
The methodologies of systematic review were used with a search of electronic databases (PubMed, Medline) for studies published from 1998 to 2008 using key words in combination as both MeSH terms and text words. Major article references and the 2008 American Heart Association, American College of Cardiology, European Society of Cardiology (ESC), and Society for Cardiovascular Magnetic Resonance (SCMR) abstracts were also reviewed. In total, 32 CMR studies with outcome data (8855 patients, 22 253 patient-years) were included. In addition, more than 380 CMR trials registered on clinicaltrials.gov were reviewed for the presence of prognostic primary/secondary end points to indicate future research directions.

CMR in Ischemic Heart Disease
The assessment of ischemic heart disease (IHD) benefits from the multiplicity of techniques available within a single CMR study. Rest function is typically combined with the use of gadolinium chelate contrast agents in 3 postcontrast temporal phases: Perfusion (first pass) for microvascular obstruction (MVO, the tissue equivalent of no-reflow) and for ischemia, either at rest or during stress; early for MVO and thrombus detection; and late for focal interstitial expansion—the late gadolinium enhancement (LGE) technique for myocardial infarction (MI) and focal myocardial damage. The spatial resolution (up to 60-fold greater than single-photon emission computed tomography [SPECT]) and excellent image contrast of CMR makes it ideal for detecting these effects in a variety of clinical settings, as discussed below.6

Acute Coronary Syndromes
In acute chest pain, the ECG and biomarkers identify most high-risk patients, but there remain some with undetected coronary artery disease (CAD). In patients with troponin-negative chest pain, Ingkanisorn et al7 (Figure 1, n=135; follow-up, 467 days) performed CMR including function, adenosine stress perfusion, and LGE. The adenosine stress results (100% sensitivity, 93% specificity) were more predictive than risk factors alone for adverse events at 1 year (negative predictive value, 100%; area under the curve, 0.97 versus 0.76, P<0.002; HR, 207; CI, 28 to 26 000). Complementing this, the LGE results were highly specific (97%; sensitivity, 55%). The short follow-up period and relatively low event rates account for the large CIs quoted. Several studies are currently underway to address this further (NCT00564382 and NCT00678639).

Infarct Size
The transmural infarct resolution of CMR has redefined chronic infarct classification.8 CMR quantifies acute infarction accurately, and this correlates with known prognostic markers such as Q waves and improvement in wall motion.9 More recently, infarct characteristics have been used to further stratify patients on the basis of pathophysiological substrate. Wu et al10 (n=122; follow-up, 2 years) found that 1 week after ST-segment elevation myocardial infarction treated by primary percutaneous coronary intervention (PCI), CMR measures of infarct size, end-systolic volumes (ESV), and ejection fraction (EF) were all associated with outcome, with infarct size the only independent predictor on multivariate analysis (HR, 1.06; CI, 1.0 to 1.1; P=0.04). Furthermore, CMR can define new features of the substrate of MI including regions of MVO and the peri-infarct zone, promising greater insights into underlying pathophysiological processes.

Microvascular Obstruction
MVO is found at the core of some infarcts where myocytes and capillaries undergo necrosis. Even when epicardial vessel morphology is anatomically restored, for example, by PCI, MVO will not reperfuse. Contrast CMR detects this using first-pass perfusion or early enhancement techniques.14 CMR-measured MVO is correlated with greater myocardial damage by ECG and echocardiography and poorer left ventricular (LV) function and predicts poor functional recovery.12 An initial study by Wu et al15 (n=44; follow-up, 16 months) demonstrated that patients with MVO had more cardiovascular events (45% versus 9%, P=0.016) independent of the total infarct size. A larger study by Hombach et al16 (Figure 2, n=110; follow-up, 100 days) found that infarct size, MVO, LV end-diastolic dimension, and EF predicted major adverse cardiac events (MACE), with MVO the strongest predictor (13.2% more events). MVO was associated with more pericardial effusions, pericarditis, adverse remodeling, and larger infarcts. Cochet et al17 (n=184; follow-up, 1 year) showed that MVO and Global Registry of Acute Coronary Events (GRACE) score were significant predictors of MACE (odds ratio [OR], 8.7; CI, 3.6 to 21.1; P<0.001; OR, 2.8; CI, 1.3 to 6; P=0.01, respectively). Bruder et al16 (n=67; follow-up, 1 year) performed CMR early after ST-segment elevation myocardial infarction. Patients with MACE had larger infarcts (14±10% versus 8±6% DE), lower EF (44±17% versus 48±14%), and larger MVO (3±5% versus 2±3%). By multivariate analysis, only MVO was related to outcome (OR=3.9; CI, 1.1 to 13.9). Wu et al10 (n=122;
follow-up, 2 years) found no relationship between MVO and outcomes, although event rates in this study were low. Looking to the future, the use of CMR tissue characterization techniques in clinical trials as surrogate, mechanistic, and secondary end points may increase.17

The Peri-Infarct Zone
A potentially important pathophysiological substrate for adverse post-MI events is the peri-infarct zone. LGE produces high signal at the core of an infarct, less so in the peri-infarct zone as first described in animal models.18 It is postulated that this area contains viable myocardium, providing a substrate for dysrhythmia such as electrophysiologically inducible ventricular tachycardia (VT).19 In a study by Yan et al20 (Figure 3, n = 144; follow-up, 2.4 years), when normalized to total infarct area, the presence of a peri-infarct zone was an independent predictor (superior to ESV and EF) for mortality (28% versus 13%; HR, 1.96; CI, 1.13 to 3.41), female sex (RR, 1.83; CI, 1.06 to 3.16), and the mean transmurality score predicted events (death or transplant). These small studies form the basis for 2 currently recruiting trials: (NCT00729430). In ischemic cardiomyopathy, Yokota et al32 (n = 1217; follow-up, 2.6 years) with severe ischemic cardiomyopathy (EF of <24%). They attributed patients with a transmurality score based on LGE. Total scar score greater than a median of 2.3 (RR, 1.96; CI, 1.13 to 3.41), female sex (RR, 1.83; CI, 1.06 to 3.16), and the mean transmurality score predicted events (death or transplant).

Silent MI Detection
Population and autopsy studies have revealed that unrecognized MIs are common (between 25% and 43% of all MIs).26,27 CMR can demonstrate small infarcts missed by SPECT and occurring without wall motion abnormality (WMA).6 Kwong et al28 (Figure 4, n = 195; follow-up, 16 months) demonstrated that silent MI confers an adverse prognosis for MACE (HR, 8.3; CI, 3.92 to 17.5; P < 0.0001) and cardiac death (HR, 10.9; CI, 3.75 to 31.9; P < 0.0001) exceeding traditional risk factors and angiographic data. Even very small infarcts are detrimental; patients with the lowest tertile of LGE had a 7-fold increase of MACE. Silent infarction carried the same or possibly worse prognosis as manifest clinical infarction in diabetic patients.29 A similar trial (n = 185, 8-year follow-up) has been completed, and results are awaited. (NCT00493168).
the DETERMINE trial (Defibrillators To Reduce Risk by Magnetic Resonance Imaging Evaluation) of 1550 patients to determine whether ICD insertion in LV dysfunction and infarct size myocardium improves survival and another trial (NCT00181233, n=400) of patients with heart failure before ICD insertion to determine CMR-derived markers of sudden death risk.

**Resynchronization Therapy**

In patients considered for cardiac resynchronization therapy, Chalil et al34 (n=62; follow-up, 741 days) showed that the presence of transmural posterolateral LGE was predictive of failure to respond (response rate, 83% versus 47%) and cardiovascular death and worsening heart failure (HR, 3.06; CI, 1.63 to 7.7). They went on to show (n=77; follow-up, 764 days)35 that CMR-derived tissue synchronization index (TSI) was an independent predictor of death/MACE (HR, 2.45; CI, 1.51 to 4.34).

**Stress CMR**

Like stress echocardiography or nuclide techniques, CMR can be performed with either inotrope or vasodilator stress with similar results.36

**Dobutamine Wall Motion Assessment**

In patients with poor echo windows, Hundley et al37 (Figure 5, n=275; follow-up, 20 months), showed that inducible WMA or an EF <40% were associated with future MI and cardiac death (HR, 3.3; CI, 1.1 to 9.7; HR, 4.2; CI, 1.3 to 13.9), an effect independent of the presence of risk factors for CAD. The 1-year event rate in those with inducible ischemia was 10.6% per year. Apical segment involvement is more significant than basal/mid (HR, 6.2 versus 1.4).38 In a study by Kuijpers et al39 (n=299, follow-up 2 years), patients with inducible WMAs had a higher MACE rate (18% versus 0.56%; P=0.001). In mild LV impairment (EF, 40% to 55%), Dall’Armellina et al40 (n=200; follow-up, 5 years) demonstrated that inducible WMAs were associated with a greater risk of MI and cardiac death beyond that associated with the resting EF and/or cardiac risk factors (P<0.001), and they were the only independent predictor on multivariate analysis (HR,1.7; p 0.008). However, in this study, in severe LV impairment (EF <40%), induced defects were not additionally predictive of outcome over rest EF.

**Mixed Stress (Dobutamine and Adenosine)**

Jahnke et al41 (Figure 6, n=513; follow-up, 2.3 years) studied patients with CAD, performing adenosine and dobutamine stress CMR. Myocardial ischemia detected by either adenosine first-pass perfusion or dobutamine WMAs predicted subsequent cardiac death or nonfatal MI (HR, 12.5; CI, 3.6 to 43.0; HR, 5.42; CI, 2.2 to 13.50; P<0.001, respectively). Normal perfusion had a high negative predictive value (3-year death rate, 0.8% versus 16.5%), a result subsequently reproduced by Pilz et al42 using adenosine and LGE (n=218, 1-year follow-up; event-free rate, 99.1%).

**Vasodilator CMR Perfusion**

Bodi et al43 (n=420; follow-up, 420 days) used dipyridamole in patients with CAD. Rest and inducible WMA, perfusion defects, and LGE were associated with MACE and cardiovascular death (HR, 6.2 versus 1.4). In a study by Bingham et al44 (n=1002; follow-up, 2.6 years) in which adenosine stress CMR and LGE were performed in consecutive patients, mortality and cardiovascular mortality rates were significantly higher in patients with perfusion defects (11% versus 5.9%), and LGE added incremental prognostic information after adjusting for risk factors.

**Cardiomyopathy**

Heart failure remains a prominent health challenge worldwide. Recent CMR studies have provided prognostic data and new insights into underlying pathophysiology, particularly for dyssynchrony, nonischemic scarring, and cardiac iron overload.
Dilated Cardiomyopathy

In dilated cardiomyopathy (DCM), CMR may detect specific myocardial substrate pathologies of prognostic significance. Up to 28% of patients with DCM have midwall LGE representing fibrosis. Assomull et al46 (Figure 7, n=101; follow-up, 658 days) showed that this was associated with mortality and cardiovascular events (HR, 3.4; CI, 1.4 to 8.7) and was the best predictor of sudden cardiac death and VT (HR, 5.4; CI, 1.0 to 26.9) even after correction for EF. This result was reproduced by Wu et al47 (n=65; follow-up, 17 months) where LGE predicted adverse outcomes in patients scheduled for ICD implantation with a higher event rate (heart failure, appropriate ICD discharge, and cardiac death, 44% versus 8%; P=0.001; HR, 8.2; CI, 2.2 to 30.9; P=0.002). Sometimes the distinction between DCM and IHD is unclear by conventional tests (including angiography). Valle et al48 (n=300; follow-up, 833 days) performed CMR in consecutive patients with heart failure. Mortality and heart failure admissions were greater in patients with known IHD than DCM (63% versus 29% event rates). However, in those patients with normal coronary angiography and LGE (unrecognized IHD labeled as DCM), the risk was similar to IHD (53% versus 63%). By multivariate analysis, LGE was the strongest predictor of cardiac events (HR, 1.7; CI, 1.07 to 2.88).

Thalassemia

CMR-derived T2* measures of cardiac iron deposition in thalassemia allows targeted high-intensity chelation therapy. Modell et al49 studied survival of UK patients with thalassemia to assess any impact of T2* measurement in changing national outcomes. Between 1999 (before cardiac T2* measurement) and subsequently, all-cause mortality reduced dramatically from 12.7 to 4.3 deaths per 1000 patient-years (62%, P<0.05), mostly due to a reduction in cardiac iron overload deaths (7.9 to 2.3 deaths per 1000 patient-years, −71%, P<0.05), a result attributed to the use of T2* identification of severe myocardial iron loading and consequent intensification of iron chelation.

Hypertrophic Cardiomyopathy

CMR is increasingly used in the assessment of hypertrophic cardiomyopathy (HCM). Maron et al50 (n=1299; follow-up, 4.1 years)
identified LV apical aneurysms in 2% of patients with HCM using CMR (echo missed 43% of them). Such patients had a higher than anticipated annual event rate of 10.5%. LGE representing focal fibrosis is present in up to 80% of patients, and LGE extent correlates with risk factors for sudden death and presence of heart failure and is predictive of nonsustained VT and atrial fibrillation. Rubinshtein et al\(^5\) (n=424; follow-up, 34 months) showed the absence of LGE conferred an excellent prognosis (no events versus 4.6% in those with LGE, \(P<0.002\)). LGE affecting >5% myocardium, septal thickness >30 mm, and AF were independent predictors of death or appropriate ICD discharge.

**Arrhythmogenic Right Ventricular Cardiomyopathy**
CMR can detect in vivo myocardial fibro-fatty replacement in arrhythmogenic right ventricular cardiomyopathy, the likely substrate for adverse outcome. LGE is not uncommon\(^5\) and predicts the inducibility of sustained VT, fibrosis on endomyocardial biopsy, and right ventricular (RV) impairment, but the prognostic value of CMR has yet to be shown.

**Myocarditis**
CMR is now a gold standard investigation for myocarditis.\(^1,5,59\) Acutely, LGE extent reflecting focal myocarditis is inversely correlated with 3-year EF,\(^60\) and the patterns of LGE may reflect different effects of viral etiology on LV recovery. However, the prognostic value of CMR has yet to be established.

**Amyloidosis**
In cardiac amyloidosis, the deposition of amyloid protein in the myocardium causes a restrictive cardiomyopathy. In up to 69%, typical subendocardial LGE is found.\(^61\) Maceira et al\(^62\) (n=29; follow-up, 623 days) showed that LGE was not related to prognosis, but death was predicted by gadolinium kinetics, with postgadolinium intramyocardial T1 difference between the subepicardium and subendocardium predicting mortality with 85% accuracy (the smaller the T1 intramyocardial gradient, the worse the prognosis). This was superior at predicting survival than response to chemotherapy or diastolic function.

**Other Conditions**

**Pulmonary Arterial Hypertension**
Van Wolferen et al\(^63\) (n=64; follow-up, 1 year) showed that several CMR parameters predicted adverse outcome (low SV, RV dilation, impaired LV filling, and serial deterioration in these parameters). Substrate changes may also be important, with LGE linked to RV end-diastolic volume (EDV), RV mass, mean pulmonary artery pressure, pulmonary vascular resistance, and inversely with RVEF,\(^64\) but no studies have yet linked LGE in pulmonary arterial hypertension to outcome.

**Congenital Heart Disease**
CMR for congenital heart disease patients has reduced the use of invasive procedures\(^65\) and is cost-effective.\(^66\) CMR functional parameters predict morbidity in repaired tetralogy of Fallot (TOF),\(^67\) and substrate changes detected as LGE correlate with adverse clinical markers.\(^68\) Knauth et al\(^69\) (n=88; follow-up, 4.2 years) showed that CMR functional parameters (RV EDV, LVEF <55% or RVEF <45%) predicted MACE (OR, 4.55; CI, 1.10 to 18.8; \(P=0.037\); OR, 8.05; CI, 2.14 to 30.2; \(P=0.002\); OR, 5.60 1.47 to 21.2; 0.011, respectively).

Figure 7. Right, LGE patterns in dilated cardiomyopathy in short axis. The enhancement pattern (arrow) is distinct from that associated with CAD because of endocardial sparing and noncoronary territory distribution. Left, Kaplan-Meier curves based on the presence of LGE. Reproduced with permission from Assomull et al.\(^46\)

Figure 8. Middle, Fibrous cap rupture and hemorrhage into a carotid atherosclerotic plaque on MRI. Right, A Mallory trichrome–stained section demonstrates the presence of the hemorrhage (arrowhead). Left, Kaplan-Meier curves of patients remaining free of ipsilateral cerebrovascular events for subjects with (lower curve) and without (upper curve) intraplaque hemorrhage (IPH). Reproduced with permission from Takaya et al.\(^71\)
Table. Prognostic Evidence Base of CMR

<table>
<thead>
<tr>
<th>Disease</th>
<th>Technique</th>
<th>End Point, n, (Patient-Years)</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>ACS chest pain</td>
<td>Adenosine stress</td>
<td>MACE, 131, (168)</td>
<td>Ingkanisorn et al, 2006</td>
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<tr>
<td>Infarction</td>
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<td>Wu et al, 2007</td>
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<tr>
<td>Peri-infarct zone</td>
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<td>Mortality, 144, (346)</td>
<td>Yan et al, 2006</td>
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<td>Impaired LV</td>
<td>Dobutamine stress</td>
<td>MI/mortality, 200, (1000)</td>
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<td>Chalil et al, 2007; Chalil et al, 2007</td>
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<td>CMR TSI pre-CRT</td>
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<td>DCM</td>
<td>LGE</td>
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<td>Mortality, 29, (49)</td>
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<td>PAH</td>
<td>Volumes</td>
<td>Mortality, 64, (64)</td>
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<td>RV morphology</td>
<td>MACE, 88, (370)</td>
<td>Knauth et al, 2006</td>
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<tr>
<td>Stroke</td>
<td>Carotid plaque</td>
<td>Stroke, 154, (490)</td>
<td>Takaya et al, 2006</td>
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</table>

*Abstract.
†It is not clear how many patients were followed up with CMR in this cohort.

Plaque Characterization and Stroke Prediction
CMR can quantify carotid plaque size and composition with good accuracy and reproducibility, and these measures correlate with previous stroke/TIA. In a study by Takaya et al, (Figure 8, n=154; follow-up, 38.2 months) consecutive subjects with asymptomatic carotid stenosis were assessed by carotid CMR. Several CMR plaque characteristics predicted subsequent stroke: the presence of a thin or ruptured fibrous cap (HR, 17.0; CI, 2.2 to 132.0; P=0.001), intraplaque hemorrhage (HR, 5.2; CI, 1.6 to 17.3; P=0.005), larger mean intraplaque hemorrhage area (HR for 10 mm² increase, 2.6 CI, 1.4 to 4.6; P=0.006), larger maximum percent lipid-rich/necrotic core (HR for 10% increase, 1.6; CI, 1.20 to 2.0; P=0.004), and larger maximum wall thickness (HR for a 1-mm increase, 1.6; CI, 1.1 to 2.3; P=0.008). Further study is underway using CMR to risk stratify moderate carotid stenosis (n=200, NCT00451529).

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Disclosures
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5. CMR Update. Editor and publisher, Schwitter J. Zurich, Switzerland.


