CHAPTER 2

Risk stratification for ventricular arrhythmias in ischaemic cardiomyopathy: the value of non-invasive imaging

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ABSTRACT
The introduction of the implantable cardioverter defibrillator (ICD) has had a major impact on survival and treatment of patients with ischaemic cardiomyopathy. However, only a third of patients receive appropriate ICD discharges during the first 3 years of follow-up, hence creating opportunities for improvement in patient care as well as for health care costs containment. Therefore, refinement of ICD implantation criteria is needed. Evaluation of pathophysiological substrates related to electrical instability with imaging modalities such as nuclear imaging, cardiac magnetic resonance imaging, and echocardiography might yield important prognostic information. This review discusses the currently available literature regarding the value of these imaging modalities for prediction of ventricular arrhythmias in patients with ischaemic cardiomyopathy.

INTRODUCTION
The number of patients suffering from ischaemic cardiomyopathy (CMP) is steadily increasing in Western civilized countries, among other reasons due to advances in pharmacological and revascularization therapies in coronary artery disease, which have improved outcome. Despite these advances, this patient population remains at increased risk of sudden cardiac death (SCD). The introduction of the implantable cardioverter defibrillator (ICD) has had a major impact on survival and, as a consequence, on treatment of patients with ischaemic CMP. The Multicenter Automatic Defibrillator Implantation Trial (MADIT) II has shown that in patients with an ischaemic CMP and a left ventricular ejection fraction (LVEF) <30%, prophylactic implantation of an ICD resulted in a relative risk reduction in all-cause mortality of 31% during a follow-up of 3 years. After confirmation of a mortality reduction in the SCD-HeFT trial, primary prevention of SCD by means of an ICD has been implemented as at least a IIa classification in the ACC/AHA/ESC guidelines. Consequently, an exponential growth in ICD implantations and concomitant costs has occurred. However, only 35% of implanted patients receive ICD therapy for a life-threatening ventricular arrhythmia during the first 3 years of follow-up. As the majority of patients remains free from ICD therapy, a further refinement of criteria is needed to select those patients who are most likely to benefit from this treatment modality.

Currently, effort is put into the development of enhanced risk stratification methods which assess myocardial electrical instability such as microvolt T-wave alternans and signal-averaged electrocardiogram. Although assessment of electrical instability is a valid approach to determine the risk of ventricular arrhythmias, evaluation of pathophysiological substrates related to electrical instability like scar burden, ischaemia, altered mechanical function, and innervation defects might yield complementary prognostic information. The latter can be performed using imaging modalities including nuclear imaging, cardiac magnetic resonance imaging (CMR), and echocardiography. This review discusses the currently available literature regarding the value of these imaging modalities for prediction of SCD, ventricular arrhythmias, and ICD therapy in patients with ischaemic CMP.

PATHOPHYSIOLOGICAL SUBSTRATES OF VENTRICULAR ARRHYTHMIAS
Traditionally, ventricular arrhythmias are divided into those based on abnormalities in impulse formation (abnormal automaticity and triggered activity) in which abnormal ionic currents play a major role and abnormalities in impulse conduction (re-entry) in which abnormal depolarization pathways play an important role. In ischaemic heart...
disease, either mechanism may occur, but typically a complex interplay between both mechanisms is responsible for the occurrence of ventricular arrhythmias.

Scar tissue as a result of myocardial infarction may constitute an area of conduction block which is a prerequisite for re-entry. The re-entry circuit includes residual viable myocytes located within scar tissue, which are characterized by slow propagation of electrical impulses.7 The presence of a re-entry circuit seems to be related to the extent of scarring as patients with a larger myocardial scar tend to be at augmented risk for ventricular arrhythmias.8 Extensive scarring of the left ventricle additionally leads to loss of contractile function, which in turn may lead to geometrical alterations and heart failure. This remodelling process results in an inhomogeneous distribution of regional wall stress and an increase in adrenergic drive. As a consequence, myocyte hibernation is affected, which leads among others to increased intracellular calcium levels and changes in the expression of connexins.9 These changes at the molecular level are known to have arrhythmogenic effects. Considering a decreased LVEF a surrogate marker of heart failure and remodelling, it has proved to be a predictor of SCD.10

In addition, impairment of perfusion may induce ischaemia, stunning, or hibernation. These conditions modulate myocyte automaticity, excitability, and refractoriness, resulting in dispersion of repolarization and enhanced susceptibility for ventricular arrhythmias.11 The relation between perfusion abnormalities and vulnerability for arrhythmias has been well documented.12,13 The border zone of scar is also an important factor in the susceptibility for ventricular arrhythmias, as it is frequently composed of both fibrosis and preserved myocytes characterized by inherent conduction abnormalities. Furthermore, these areas may suffer from insufficient perfusion resulting in ischaemia. The border zone seems to function as a substrate for ventricular arrhythmias, as the extent predicts inducibility of ventricular arrhythmias.14 Moreover, innervation may be absent in the border zone. As nerve endings are more vulnerable to ischaemia than myocytes, the area of denervation is generally larger than the area of the scar after infarction.15 Areas of viable myocardium in the border zone that lack innervation seem to have a significantly longer refractory period and are probably prone to ventricular arrhythmias.16 Animal experiments have shown that the occurrence of perfusion/innervation mismatch areas is related to inducible ventricular tachycardias which seem to originate from these mismatch areas.15

Various imaging modalities have the capacity to visualize one or more of these pathophysiological processes and hence facilitate risk stratification for ventricular arrhythmias (Table 1). The strengths and weaknesses of each of these imaging modalities are discussed below.

<table>
<thead>
<tr>
<th></th>
<th>Echocardiography</th>
<th>CMR</th>
<th>Nuclear imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricle geometry</td>
<td>++</td>
<td>+++</td>
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</tr>
<tr>
<td>Scar</td>
<td>+</td>
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<tr>
<td>Heterogenic scar zone</td>
<td>-</td>
<td>+</td>
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<td>Perfusion</td>
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<td>Innervation</td>
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</table>

NUCLEAR IMAGING

Nuclear imaging non-invasively tracks various biochemical pathways depending on the biological behaviour of the tracer used. The ability to visualize multiple pathophysiological processes provides the opportunity to reveal different substrates that may induce ventricular arrhythmias. The predictive value of resting perfusion defects, compatible with either scar tissue or hibernating myocardium, was evaluated by Morishima et al.17 using technetium 99m-tetrofosmin single photon emission computed tomography (SPECT) imaging in ischaemic CMP patients who met the MADIT II criteria. Receiver operating characteristics analysis revealed that a SPECT defect volume >47.5 mL, a left ventricular end-diastolic volume index >145 mL/m², and an end-systolic volume index >97.1 mL/m² were all associated with spontaneous ventricular arrhythmic events [RR 6.34 (95% CI: 1.76–22.8); P = 0.005, RR 3.96 (95% CI: 1.37–11.4); P = 0.011, and RR 3.44 (95% CI: 1.07–11.1); P = 0.039, respectively]. Interestingly, the degree of left ventricular dysfunction in this patient group with LVEF <30% provided no incremental prognostic information. Multivariate analysis was not conducted in this study. In contrast, Paganelli et al.18 could not detect a clear link between resting perfusion defects, using thallium-201 SPECT, and the occurrence of inducible ventricular arrhythmias in patients with a first acute myocardial infarction. The extent of stress-induced defects, however, was significantly associated with inducible arrhythmias. However, no correction was made for potential confounders. To examine in more detail the contribution of hibernating myocardium, Krause et al.19 identified viable myocardium by assessment of the 99mTc-tetrofosmin SPECT and 18F-FDG positron emission tomography (PET) mismatch area in 33 patients with a prior myocardial infarction and various degrees of left ventricular dysfunction and documented spontaneous ventricular arrhythmias. In comparison with
a representative control group free from arrhythmias, viability was considerably more common. Furthermore, multivariate analysis, including LVEF, indicated that the presence of hibernating myocardium was a superior predictor of arrhythmias in comparison to the amount of scar tissue. These results suggest that arrhythmogenic effects of ischaemia and viability may be of more importance than the extent of scar tissue.

Recently, a renewed interest has emerged to explore the role of cardiac innervation impairment and its contribution to the development of cardiac arrhythmias. As already discussed, it is well documented that myocardial denervation adjacent to an infarct area results in prolonged refractory periods and may therefore precipitate potential lethal arrhythmias. Although a number of tracers are available to visualize myocardial innervation, most experience has been gained with $^{123}$I-mIBG SPECT and $^{11}$C-hydroxyephedrine PET. In conjunction with routine perfusion imaging, mismatch patterns indicate denervated viable myocardium (Figure 1). In a proof-of-principle study, Sasano et al.15 inflicted a myocardial infarction upon pigs and subsequently quantified the mismatch area with the aid of $^{11}$C-epinephrine and $^{13}$N-ammonia PET. The extent of denervated myocardium was directly related to the occurrence of inducible ventricular tachycardias (VTs) that originated from the mismatch area. In an effort to translate this concept into clinical practice, Bax et al.20 performed electrophysiological testing in 50 patients with ischaemic CMP and LVEF ≤49% in whom the innervation/perfusion mismatch area was assessed using $^{123}$I-mIBG and $^{99}$mTc-tetrofosmin SPECT. In contrast to Sasano et al., however, the presence of mismatch areas could not be linked to inducible VTs. Surprisingly and in contradiction with previous studies, perfusion defect size did not correlate with arrhythmias either. These negative results may be related to methodological issues, such as the use of relatively low-resolution SPECT in comparison with PET. In the ADMIRE-HF trial, presented at the 2009 American Heart meeting, $^{123}$I-mIBG SPECT was investigated to demonstrate its prognostic usefulness in a large population (964 patients) of heart failure patients with both ischaemic and non-ischaemic CMP.21 Global cardiac innervation was clearly related to adverse cardiac events. Moreover, abnormal cardiac innervation proved to be an independent predictor of potentially life-threatening arrhythmic events [HR: 2.72 (95% CI: 1.17–6.30); P = 0.020]. However, regional innervation defects were not assessed in this study, and there was no subgroup analysis of ischaemic CMP patients. Clearly, more studies are warranted to elucidate the effect of denervation on the occurrence of arrhythmias in patients with ischaemic CMP.

**CARDIAC MAGNETIC RESONANCE IMAGING**

Late gadolinium enhancement (LGE) CMR can accurately assess the location and extent of a non-viable scar after myocardial infarction, because of its high spatial resolution, and hence can be applied for risk assessment. The predictive values for inducibility of ventricular arrhythmias of infarct size measured by LGE were determined in a study of 48 patients with coronary artery disease and a mean LVEF of ~35% who were referred for electrophysiological testing. Logistic regression analysis revealed that scar burden was a significant predictor of inducibility of VTs, whereas LVEF was not. In LGE CMR studies, assessment of LVEF is a welcome side product which can additionally be used for risk stratification, as CMR is a reliable tool to assess left ventricular volume and function.22 However, CMR studies that focused solely on LVEF for SCD risk stratification are lacking. Myocardial function can be assessed in more detail by tissue tagging, which has the ability to assess regional mechanical contractile behaviour with a high spatial resolution. In a study of 46 patients with a history of a myocardial infarction referred for ICD implantation, for primary prevention regional mechanical function was measured by means of tissue tagging in combination with scar assessment by LGE and was correlated to inducibility of VTs.23 In inducible patients, time to peak circumferential shortening was significantly reduced and peak circumferential shortening was significantly increased in the areas adjacent to the scar (P < 0.001 and P < 0.05, respectively). Those patients also displayed significantly more extensive scar burden.

**Figure 1:** Positron emission tomography polar maps show regional distribution of myocardial innervation assessed by $^{11}$C-HED (left) and myocardial rest perfusion assessed by $^{15}$O-H$_2$O (right). Clearly, innervation defect exceeds perfusion defect, indicating denervated viable myocardium. $^{11}$C-HED: $^{11}$C-hydroxyephedrine.
In addition, myocardial perfusion and viability can be examined qualitatively by CMR. First-pass perfusion is currently utilized to determine myocardial perfusion semi-quantitatively, and effort is put into absolute quantification. Viability of the myocardium has already been proved to be assessed accurately by CMR with LGE. Assessment of both impaired perfusion and viability by CMR could be useful in risk stratification for ventricular arrhythmias, as the presence of myocardial perfusion defects and viability assessed by nuclear imaging have already been associated with the occurrence of ventricular arrhythmias. Nevertheless, currently, no studies have been conducted to assess the risk stratification potential of perfusion and viability assessment by CMR for ventricular arrhythmias.

The border zone of scar is another characteristic which can be assessed by LGE. Owing to the presence of both fibrosis and viable myocytes in the border zone, it has an enhancement intensity higher than normal myocardium, but lower than the infarct core. This composite mixture of tissue makes it possible to measure the extent of the border zone (Figure 2). Border zone as a predictor of cardiac mortality and all-cause mortality was investigated by Yan et al. in 144 patients with a prior myocardial infarction and a mean LVEF of 44%. After a follow-up of 2.4 years, patients with an above-median percentage of border zone area were at a significantly higher mortality risk compared with those with a lower percentage (28 vs. 13%, respectively). The percentage of border zone area was shown to be an independent risk factor for all-cause mortality [HR: 1.45 (95% CI: 1.15–1.84) per 10% border zone; P = 0.002] and cardiovascular mortality [HR: 1.51 (95% CI: 1.11–2.06) per 10% border zone; P = 0.009]. Schmidt et al.14 evaluated the predictive value of the border zone for inducibility of monomorphic VTs in patients with a history of myocardial infarction and LVEF <35%. Baseline characteristics, including infarct size and LVEF, were comparable between inducible and non-inducible patients. However, inducible patients showed a larger extent of border zone (19±8 vs. 13±9 g, respectively; P = 0.015). In logistic regression analysis, the extent of the border zone was the only significant predictor of inducibility. In a recently published study of Roes et al., the predictive value of LGE for appropriate ICD therapy was evaluated in patients with ischaemic CMP. Both primary and secondary prevention patients were included. Multivariable analysis revealed that the extent of border zone was the strongest predictor of the occurrence of spontaneous ventricular arrhythmias with subsequent ICD therapy [HR: 1.49 (95% CI: 1.01–2.20) per 10 g; P = 0.04]. Total infarct size and LVEF were not demonstrated to be significant predictors in the multivariable analysis, although they were in the univariate analysis. Aforementioned studies are promising for the utilization of CMR for SCD risk stratification in patients with ischaemic CMP. However, a major issue is the absence of standardized criteria for the assessment of the border zone, which makes it difficult to compare studies. Nevertheless, owing to the high reproducibility of data and the non-invasiveness of CMR, it is a potential tool for risk stratification, and future studies should define its role.

![Figure 2: (A) Cardiac magnetic resonance imaging short-axis image of the left ventricle with late gadolinium enhancement indicating scar. (B) Cardiac magnetic resonance imaging short-axis image of the left ventricle with the core of late gadolinium enhancement (red) and the heterogenic border zone of late gadolinium enhancement (yellow). CMR: cardiac magnetic resonance imaging.](image)

**ECHOCARDIOGRAPHY**

Echocardiography is an imaging modality readily available in daily clinical practice and therefore easily applicable for risk stratification for ventricular arrhythmias. Left ventricular ejection fraction assessed by echocardiography was used in the majority of the large ICD trials, and based on the results of these trials, LVEF is presently incorporated in the guidelines as a risk stratifier. However, several additional echocardiographic parameters have been evaluated as risk stratifiers for SCD.

Presence of echocardiographic wall motion abnormalities often indicates scar in combination with partial ischaemia and/or hibernating myocardium. The predictive value of the extent of wall motion abnormalities assessed by the global wall motion score index (WMSI) for the composite endpoint of appropriate ICD therapy and all-cause mortality was evaluated in a study of 140 patients with ischaemic CMP and a mean LVEF of 32%. In a multivariate model including LVEF, it was shown that for every 1-point increase in the global WMSI, the risk of any event after ICD therapy increased two-fold [HR: 2.18 (95% CI 1.03–4.65); P = 0.04].

Furthermore, diastolic functional parameters can be assessed excellently by echocardiography. The relationship between diastolic functional parameters and ventricular arrhythmias has been investigated by Bruch et al. In their study of 86 CMP patients with an LVEF <45%, the presence of a restrictive filling pattern and E/E’ ratio were significant predictors of appropriate ICD discharge and death caused by pump failure. In multivariate analysis, the only independent predictor of an event was the presence of a
restrictive filling pattern [HR: 3.65 (95% CI 1.54–8.64); P = 0.011]. In contrast, Dini et al.30 did not observe a relation between a restrictive filling pattern and cardiac death. In this study, multivariate analysis showed that the indexed area of the left atrium >18 cm²/m² and LVEF ≤25% were independent predictors of cardiac death [HR: 2.0 (95% CI 1.1–3.7); P = 0.024 and HR: 1.8 (95% CI 1.0–3.6); P = 0.066, respectively].

Myocardial ischaemia can be detected by echocardiographic evaluation of exercise or dobutamine-induced wall motion abnormalities. Its risk stratification potential was assessed in a study of 90 patients with a history of coronary artery disease who received an ICD because of primary or secondary prevention.31 In multivariate analysis, induction of wall motion abnormalities was shown to be an independent predictor of appropriate ICD therapy or all-cause mortality [HR: 2.1 (95% CI 1.2–3.5); P < 0.01]. Baseline wall motion abnormalities were not mentioned as having a predictive value, which might suggest that the arrhythmogenic effect of ischaemia is more important than scar and hibernating myocardium. The echocardiographic parameters mentioned in these studies seem potential additives to LVEF for risk stratification for ventricular arrhythmias, and the wide availability of echocardiography makes it easily applicable. However, substantial intra- and interobserver variability hamper decision-making in individual cases.

LIMITATIONS

Although the above-mentioned studies show promising results, there are several limitations hampering clinical applicability. The major limitation concerns the different endpoints used. A substantial number of studies employed all-cause mortality as an endpoint or a composite endpoint of ventricular arrhythmias and cardiac death or all-cause mortality. Sudden cardiac death is a rather small subset of cardiac death and all-cause mortality, and therefore predictors of cardiac death or all-cause mortality are not necessarily predictors of SCD. Furthermore, surrogate endpoints like inducibility of VTs on electrophysiological testing and appropriate ICD therapy were used. Although there is a significant correlation between inducibility of monomorphic VTs on electrophysiological testing and SCD, the positive predictive value is quite low, which limits this type of testing to identify patients at risk of SCD.21 In addition, appropriate ICD therapy is not necessarily a predictor of ICD benefit, as not all treated ventricular arrhythmias will result in SCD.21 These different endpoints complicate the interpretation of the predictive values of these studied parameters for SCD.

Intra- and interobserver variability and test–retest variability are potential limitations for the implementation of imaging parameters for risk stratification, since large variabilities hamper decisionmaking in individual cases. Assessment of left ventricular volumes by CMR has excellent intra- and interobserver variability and test–retest variability ranging from 2.4 to 8.5%, whereas 2D echocardiographic test–retest variability for left ventricular volumes ranges from 5.5 to 24%.34,35 A myocardial scar can be assessed accurately by LGE CMR (test–retest variability of 2.4%), and assessment of the heterogenic scar zone by LGE has an interobserver variability of ~3% and a test–retest variability of ~5%.14 Perfusion imaging parameters have slightly higher variability values. Technetium 99m-tetrofosmin perfusion imaging defect score has an intra- and interobserver variability of 4.1 and 5.4%, respectively, and a test–retest variability of 9.1%.37 Positron emission tomography perfusion imaging has a test–retest variability of ~10%.38 Myocardial scar size and perfusion can also be assessed semi-quantitatively with the echocardiographic WMSI in rest and stress, which have an interobserver variability of <6%.39 Diastolic filling parameters assessed by echocardiography have considerable test–retest variabilities of above 10%.40 Myocardial innervation imaging has not been evaluated with respect to variabilities so far. The values reported above are comparable to many other diagnostic tests, with CMR showing the highest reproducibility, thus rendering them useful for risk stratification purposes.

Additionally, several studies had a retrospective design or used the investigated imaging modality as an inclusion criterium, which may have introduced a bias. The deficiency of a multivariate analysis in some studies makes it difficult to interpret the actual value of the possible risk stratification parameters.

SUMMARY

Scar burden, ischaemia, altered mechanical function, and innervation defects are important substrates for electrical instability and can be assessed using nuclear imaging, CMR, and echocardiography. The potential for risk stratification for ventricular arrhythmias and SCD of these imaging modalities has been demonstrated and studies have shown that several investigated parameters might have additive predictive value on top of LVEF (Table 2). The utilization of the different imaging modalities to assess these substrates might be a step forward in risk stratification, but interpretation of study results is presently hampered by important study limitations, as described above. In addition, based on the presently available study results, it seems unlikely that a single risk stratifier will emerge to improve risk stratification significantly. Combining results of different imaging modalities with established electrophysiological risk stratifiers, however, might improve the risk stratification process, since these parameters provide information on different (morphological, mechanical, electrophysiological, and hormonal) properties of the heart.
<table>
<thead>
<tr>
<th>Study</th>
<th>Imaging modality</th>
<th>Study population</th>
<th>Mean LVEF</th>
<th>Predictive parameter(s)</th>
<th>End-point</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morishima et al.</td>
<td>SPECT</td>
<td>106 patients meeting MADIT II criteria (LVEF &lt; 30%, ischemic CMP)</td>
<td>25%</td>
<td>Rest perfusion defect volume &gt; 47.5 mL</td>
<td>Potential lethal arrhythmic events</td>
<td>Univariate analysis: HR: 6.34 [95% CI: 1.76-22.8]; p=0.005</td>
</tr>
<tr>
<td>Paganelli et al.</td>
<td>SPECT</td>
<td>90 patients with first myocardial infarction</td>
<td>40%</td>
<td>Presence of myocardial ischemia</td>
<td>Inducibility on EPS</td>
<td>Univariate analysis: HR: N/A; p&lt;0.05</td>
</tr>
<tr>
<td>Krause et al.</td>
<td>SPECT and PET</td>
<td>47 patients with ischemic CMP</td>
<td>30-40%</td>
<td>Presence of 99mTc-tetrofosmin SPECT/18F-FDG PET mismatch</td>
<td>Spontaneous ventricular arrhythmias</td>
<td>Multivariate analysis: OR: 21.21 [95% CI: 1.64-274.1]; p=0.02</td>
</tr>
<tr>
<td>Sasano et al.</td>
<td>PET</td>
<td>11 pigs with a myocardial infarction</td>
<td>33%</td>
<td>13N-ammonia/11C-epinephrine mismatch</td>
<td>Inducibility on EPS</td>
<td>Univariate analysis: HR: N/A; p=0.019</td>
</tr>
<tr>
<td>Bax et al.</td>
<td>SPECT</td>
<td>50 patients with ischemic CMP and LVEF &lt; 50%</td>
<td>32%</td>
<td>4-hour 123I-mIBG SPECT defect score, 123I-mIBG/99mTc-tetrofosmin SPECT mismatch score</td>
<td>Inducibility on EPS</td>
<td>Multivariate analysis: HR: N/A; p=0.005 and p=NS, respectively</td>
</tr>
<tr>
<td>ADMIRE-HF</td>
<td>SPECT</td>
<td>961 patients with NYHA II or III and LVEF &lt; 35%</td>
<td>27%</td>
<td>Heart/leftventricleratio &lt; 1.6 on 123I-mIBG SPECT</td>
<td>Spontaneous ventricular arrhythmias</td>
<td>Univariate analysis: HR: 2.72 [95% CI: 1.17-6.30]; p=0.020</td>
</tr>
<tr>
<td>Bello et al.</td>
<td>CMR</td>
<td>48 patients with ischemic CMP</td>
<td>32%</td>
<td>Scar size with LGE</td>
<td>Inducibility on EPS</td>
<td>Multivariate analysis: $\chi^2 = 6.6$; p&lt;0.02</td>
</tr>
<tr>
<td>Fernandes et al.</td>
<td>CMR</td>
<td>46 patients with ischemic CMP</td>
<td>29%</td>
<td>Peak circumferential shortening strain and time to peak circumferential shortening strain in areas adjacent to scar measured with tissue tagging</td>
<td>Inducibility on EPS</td>
<td>Univariate analysis: HR: N/A; p=0.001</td>
</tr>
<tr>
<td>Yan et al.</td>
<td>CMR</td>
<td>144 patients with ischemic CMP</td>
<td>44%</td>
<td>Extent of border zone of scar measured with LGE</td>
<td>All-cause mortality and cardiovascular mortality</td>
<td>Multivariate analysis: HR: 1.45 [95% CI: 1.15-1.84]; p=0.002 and 1.50 [95% CI: 1.11-2.06]; p=0.009 per 10% border zone, respectively</td>
</tr>
<tr>
<td>Schmidt et al.</td>
<td>CMR</td>
<td>47 patients with ischemic CMP and LVEF &lt; 35%</td>
<td>30%</td>
<td>Extent of border zone of scar measured with LGE</td>
<td>Inducibility on EPS</td>
<td>Multivariate analysis: HR: N/A; p=0.03</td>
</tr>
<tr>
<td>Roes et al.</td>
<td>CMR</td>
<td>91 patients with ischemic CMP and scheduled for ICD implantation</td>
<td>28%</td>
<td>Extent of border zone of scar measured with LGE</td>
<td>Appropriate ICD therapy</td>
<td>Multivariate analysis: HR: 1.49 [95% CI: 1.01-2.20] per 10g; p=0.04</td>
</tr>
<tr>
<td>Mahenthiran et al.</td>
<td>Echocardiography</td>
<td>140 ICD patients</td>
<td>32%</td>
<td>WMSI</td>
<td>Appropriate ICD therapy or all-cause mortality</td>
<td>Multivariate analysis: HR: 2.18 [95% CI: 1.03-4.65] per 1 point WMSI; p=0.04</td>
</tr>
<tr>
<td>Bruch et al.</td>
<td>Echocardiography</td>
<td>84 ICD patients with LVEF &lt; 45%</td>
<td>29%</td>
<td>Restrictive filling pattern, defined by E/A ratio &gt; 2, deceleration time of &lt; 150 ms, and mitral annular E' velocity of &lt; 8 cm/s</td>
<td>Appropriate ICD therapy or death due to pump failure</td>
<td>Multivariate analysis: HR: 3.65 [95% CI: 1.54-8.64]; p=0.011</td>
</tr>
<tr>
<td>Dini et al.</td>
<td>Echocardiography</td>
<td>207 patients with LVEF &lt; 45%</td>
<td>32%</td>
<td>Indexed LA size &gt; 16 mm², LVEF &lt; 25%</td>
<td>Cardiac death</td>
<td>Multivariate analysis: HR: 2.0 [95% CI: 1.1-3.7]; p=0.024 and HR: 1.8 [95% CI: 1.0-3.6]; p=0.066, respectively</td>
</tr>
<tr>
<td>Elhendy et al.</td>
<td>Echocardiography</td>
<td>90 ICD patients with ischemic CMP</td>
<td>34%</td>
<td>Presence of wall motion abnormalities during stress</td>
<td>Appropriate ICD therapy and all-cause mortality</td>
<td>Multivariate analysis: HR: 2.1 [95% CI: 1.2-3.5]; p&lt;0.01</td>
</tr>
</tbody>
</table>

Overview of risk stratification studies and the outcomes. (CMR: cardiac magnetic resonance imaging; SPECT: single photon emission computed tomography; PET: positron emission tomography; LGE: late gadolinium enhancement; WMSI: wall motion score index; LA: left atrial; LVEF: left ventricular ejection fraction; EPS: electrophysiological study; ICD: implantable cardioverter defibrillator; N/A: not available; HR: hazard ratio; CI: confidence interval; OR: odds ratio).

Table 2: Overview of risk stratification studies and the outcomes.
In conclusion, the imaging modality-based risk stratification parameters are promising but currently insufficiently developed to be implemented in daily clinical practice. Future studies should be conducted with (i) appropriate endpoints and inclusion criteria to establish the actual predictive value in daily clinical practice of the different parameters studied and (ii) focus on combination of different risk-stratifying modalities, including non-imaging risk stratification tools, to elaborate complementary potential.

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CHAPTER 2 Risk stratification for ventricular arrhythmias in ischaemic CMP


