## Late gadolinium enhancement

**Table 3b-i.1: Validation studies with LGE.** Agreement expressed as Pearson r-coefficient. ICM- ischemic cardiomyopathy, NICM –non-ischemic cardiomyopathy, LGE - late gadolinium enhancement, SD – standard deviation, FWHM - full-width half-maximum

| Author | N | Disease model | Histological Staining | Time-points | Correlation | | |
|---|---|---|---|---|---|---|---|
| **Histological validation** | | | | | | | |
| **Animal studies** | | | | | **LGE method** | **R** | **P value** |
| **Kim[1]** | 9 | ICM (Dogs) | Hematoxylin and eosin and/or Masson's trichrome | 1, 3 days and 8 weeks after the intervention | LGE >2SD | Day 1 (r= 0.99)<br>Day 3 (r= 0.99)<br>Week 8 (r= 0.97) | p< 0.001 |
| **Fieno[2]** | 24 | ICM (Dogs) | Triphenyltetrazolim chloride-stained | 4 h, 1 day, 3 days, 10 days, 4 weeks and 8 weeks after the intervention. | LGE >3SD | r=0.99 | p< 0.001 |
| **Wagner[3]** | 15 | ICM (Dogs) | Triphenyltetrazolim chloride-stained | 2 days after the coronary artery occlusion/reperfusion | LGE >2 SD | r=0.98 | p≤0.05 |
| **Human studies** | | | | | | | |
| **Gulati[4]** | 16 | NICM | Picrosirius red/ Qualitative assessment | median of 5.3 years | FWHM | Excellent correlation | NA |
| **Iles[5]** | 11 | NICM/ICM | Masson trichrome, Picrosirius red/ 2-10 SD | / | LGE > 6 SD | r=0.91 | p< 0.001 |

**Table 3b-i.2: Reproducibility of measurements for LGE.** Values are expressed as MD±SD and CoV in brackets when available. AMI - acute myocardial infarction, CMI - chronic myocardial infarction, HCM - hypertrophic cardiomyopathy, NICM - non-ischaemic cardiomyopathy, SD - standard deviation, FWHM: full-width half-maximum.

| Author | Type of patients | N of patients | LGE definition | Interobserver | Intraobserver | Interstudy |
|---|---|---|---|---|---|---|
| **Thiele[6]** | AMI, CMI | 21 | Manual quantification | -0.7% ±2.2 (1.6%) | 0.3% ±1.7 (2.8%) | -0.5% ±2.4 (2.4%) |
| **Desch[7]** | AMI | 20 | Manual quantification | (2.4%) | (2.4%) | 0.1 ± 2.2 (11%) |
| **Flett [8]** | AMI, CMI and HCM | 60 (20+20+20) | Manual quantification, 2,3,4,5,6 SD and FWHM | For inter- and intraobserver FWHM was the most reproducible in all 3 conditions (interstudy reproducibility was not performed) | | |
| **McAlindon [9]** | AMI | 40 | Manual quantification, 2-,3-,5- SD, Otsu and FWHM | Manual was the most reproducible followed by FWHM for myocardial scar and Otsu for myocardial oedema | | |
| **Khan[10]** | AMI | 20 | Manual quantification, 5-8 SD, FWHM and Otsu | FWHM had lowest observer variability at 1.5T | | |
| **Neilan[11]** | NICM | 15 | 2SD and FWHM | **2SD:** 0.8 | **2SD:** 1.1 | |
| | | | | **FWHM**: 0.5 | **FWHM**: 0.5 | |
| **Chan[12]** | HCM | 24 | 6SD | (6.3) | (5.9) | |

**Table 3b-i.3. Comparative studies with other imaging techniques in ischaemic heart disease.** CAD – coronary artery disease, AMI – acute myocardial infarction, CMI – chronic myocardial infarction, SPECT - single photon emission computed tomography, PET – positron emission tomography.

<table>
<tr><th colspan="7">Validation against established imaging techniques</th></tr>
<tr><th>Author</th><th>Disease model</th><th>N</th><th>Assessment</th><th>Study design</th><th colspan="2">Outcome</th></tr>
<tr><td>Wagner[13]</td><td>Suspected/known CAD</td><td>91</td><td>Visual</td><td>Prospective</td><td>Associations</td><td>SPECT is systematically less sensitive for subendocardial scar compared to CMR and histology.<br>Rate of SPECT-detected infarcts as defined by CMR increases with transmurality:
<table>
<tr><td>CMR transmurality</td><td>SPECT sensitivity</td></tr>
<tr><td>1-25%</td><td>50%</td></tr>
<tr><td>26-50%</td><td>57%</td></tr>
<tr><td>51-75%</td><td>77%</td></tr>
<tr><td>76-100%</td><td>100%</td></tr>
</table></td></tr>
<tr><td>Ibrahim[14]</td><td>AMI</td><td>78</td><td>Visual</td><td>Prospective</td><td>Comparisons</td><td>CMR is more sensitive than SPECT in detecting small MI, non-Q MI and non-anterior MI</td></tr>
<tr><td rowspan="2">Wu[15]</td><td rowspan="2">CMI</td><td rowspan="2">116 (CMR vs SPECT)<br>46 (CMR vs PET)</td><td rowspan="2">Visual</td><td rowspan="2">Retrospective</td><td rowspan="2">Correlations</td><td>Overall agreement of viability criteria between SPECT and CMR: 96.8 % (κ = 0.62). Agreement in dysfunctional segments: 86 % (κ = 0.52).</td></tr>
<tr><td>Overall agreement of viability criteria between PET and CMR: 92.7% (κ = 0.51)</td></tr>
</table>

**Table 3b-i.4. Outcome studies with LGE.** Follow-up is expressed in months. HR and AUC are provided followed by 95% CI limits in brackets. Studies with n> 100 patients and hard CV endpoints qualified for inclusion. Absolute values are expressed as mean followed by SD. All analyses are multivariable/adjusted unless otherwise stated (†). § - Given the few events statistical comparisons were not performed.
STEMI – ST elevation MI, FWHM - full-width half-maximum, MACE – major adverse cardiovascular events, HR – hazard ratio, AUC – area under the curve, LGE – late gadolinium enhancement, LVEF – LV ejection fraction, MVO – microvascular obstruction, SPECT - Single Photon Emission Computed Tomography, MSI - myocardial salvage index, HF - heart failure, CAD - coronary artery disease, UA - unstable angina, VT – ventricular tachycardia, ICD - implantable cardioverter defibrillator, ICM - ischemic cardiomyopathy, NICM - non-ischemic cardiomyopathy, SCD - sudden cardiac death, AF – atrial fibrillation, CT - cardiac transplantation, HCM - hypertrophic cardiomyopathy, NSVT - non-sustained ventricular tachycardia, PM - pacemaker.

| Author | N | Population | LGE Assessment method | Follow-up | Endpoints | CMR-outcomes | | |
|---|---|---|---|---|---|---|---|---|
| **Acute myocardial infarction** | | | | | | | | |
| **Larose[16]** | 103 | STEMI | FWHM | 33 | MACE | LGE present | HR 1.36(1.11-1.66) | 0.03 |
| | | | | | | LGE extent | AUC 0.92 (0.84-0.98) | <0.001 |
| | | | | | | | HR 1.72 (1.43-2.01) for MACE | 0.007 |
| **Wu[17]** | 122 | STEMI | Manual | 18 | MACE | LGE extent was the strongest predictor for MACE | | |
| | | | | | | LGE extent | HR 1.06 (1-1.12) | 0.04 |
| | | | | | | LVEF | HR 0.96 (0.88-1.05) | 0.39 |
| | | | | | | LGE≥18.5% → sensitivity 88%, NPV 96% for MACE. Predictor of MACE (p=0.007) and LV adverse remodeling (p=0.004). | | |
| **Hadamitzky[18]** | 281 | STEMI | FWHM 2-, 3-, 4-, 5- and 6-SD | 36 | MACE | MVO was the strongest predictor for MACE | | |
| | | | | | | MVO | HR 1.17 (1.1-1.25) | <0.001 |
| | | | | | | LGE extent (CMR- 6SD) | HR 1.85 (1.21-2.81) | 0.0043 † |
| | | | | | | LGE extent (SPECT) | HR 2.02 (1.33-3.06) | <0.001 † |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Eitel[19]** | 738 | STEMI | 5SD | 12 | MACE | CMR parameters were predictive of 1-y MACE | | |
| | | | | | | LVEF≤47% | AUC 0.69 (0.66-0.73) | <0.001 |
| | | | | | | | HR 4.38 (2.49-7.71) | <0.001 † |
| | | | | | | LGE extent ≥19% | AUC 0.72 (0.69-0.76) | <0.001 |
| | | | | | | | HR 5.41 (2.78-10.5) | <0.001 † |
| | | | | | | MSI ≤35 | AUC 0.7 (0.66-0.74) | <0.001 |
| | | | | | | MVO ≥1.4% | AUC 0.73 (0.69-0.76) | <0.001 |
| | | | | | | | HR 5.62 (3-12-10.1) | <0.01 † |
| | | | | | | | HR 3.63 (1.35-7.9) | 0.004 |
| **Eitel[20]** | 208 | STEMI | 5- SD | 6 | MACE | CMR parameters were predictive of 6-m MACE | | |
| | | | | | | MVO | HR 1.1 (1.03-1.17) | 0.004 † |
| | | | | | | LGE extent | HR 1.08 (1.05-1.12) | <0.001 † |
| | | | | | | MSI | HR 0.95 (0.93-0.97) | <0.001 † |
| | | | | | | | HR 0.93 (0.91-0.96) | <0.001 |
| | | | | | | HF hospitalization | HR 1.20 (1.19-1.21) | <0.0001 |
| **Stone**[21] | 1889 | STEMI | Metanalysis | 12 | Survival | All-cause mortality | HR 1.19 (1.18-1.20) | <0.0001 |
| **De Waha**[22] | 1688 | STEMI | Metanalysis | 6 | MACE | All-cause mortality | HR 1.14 (1.09–1.19) | |
| | | | | | | HF hospitalization | HR 1.08 (1.05–1.12) | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Stable coronary artery disease** | | | | | | HF hospitalization | HR 1.20 (1.19-1.21) | <0.0001 |
| Steel[23] | 254 | Suspected CAD | 2-SD | 17 | MACE | LGE absent → 98.1% event-free survival | | |
| | | | | | | LGE present | | |
| | | | | | | CV death/MI | HR 5.31 (2.35-12) | <0.0001 |
| | | | | | | CV death/ MI/UA | HR 8.09 (3.9-16.8) | <0.0001 |
| Kwong[24] | 195 | Suspected CAD with no prior MI | 2-SD | 16 | MACE | LGE present >7-fold risk of events | | |
| | | | | | | CV death | HR 9.43 (3.15-28.3) | <0.0001 |
| | | | | | | MACE and VT and HF | HR 5.98 (2.68-13.3) | <0.0001 |
| **Mixed patient groups (heart failure, indication for ICD, etc)** | | | | | | | | |
| Iles[25] | 103 | ICD for primary prevention (NICM/ICM) | 2-SD | 19 | ICD shock | LGE+ | 21 (+) vs 0% (-) | 0.01 |
| | | | | | | No differences per aetiology (29% NICM vs 14% ICM, P=NS).<br>Similar LVEF in LGE+/- and ICD shock +/-. | | |
| Gao[26] | 124 | ICD for primary prevention (NICM/ ICM) | FWHM 2-, 3-, 5-SD, | 21 | ICD shock/ SCD | LGE mass predicts arrhythmic events. (events vs no events) | | |
| | | | | | | Total | 59±30 vs 32±19 g | 0.001 |
| | | | | | | NICM | 46±38 vs 23±15g | 0.003 |
| | | | | | | ICM | 69±17 vs 42±19g | 0.001 |
| Klem[27] | 137 | ICD for primary prevention (NICM/ ICM) | 3-SD | 24 | Death, ICD shock | Scar size (>5% LV mass) predicted adverse outcomes and improved risk stratification beyond LVEF. | | |
| | | | | | | Death | HR 8.75 (1.89-41) | 0.006 |
| | | | | | | ICD shock | HR 4.76 (1.65-13.7) | 0.004 |
| | | | | | | Death/ICD shock | HR 4.59 (1.79-11.8) | 0.002 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Wu[28] | 234 | ICD for primary prevention (NICM/ ICM) | 2-SD (infarct core FWHM) | 43 | CV death/ ICD shock | Gray zone was associated with clinical endpoint. | | |
| | | | | | | 2nd tertile | HR 3.9 (1.2-12.4) | 0.02 |
| | | | | | | 3rd tertile | HR 4.6 (1.4-15.4) | 0.01 |
| Mordi[29] | 157 | ICD for primary prevention (NICM/ ICM) | 5-SD | 30 | Death/ICD shock | LGE (per 1% increase) | HR 1.04 (1-01-1.07) | 0.001 |
| Almehmadi[30] | 318 | NICM/ICM | 5-SD | 15 | SCD/ ICD shock | 78% had LGE, 24% more than 1 pattern. Midwall striae involved the worst prognosis. | | |
| | | | | | | LGE + | HR 3.8 (1.4-10.8) | 0.01 † |
| | | | | | | LGE (per 1%) | HR 1.02 (1.01-1.03) | 0.008 † |
| | | | | | | Midwall stria | HR 2.4 (1.2-4.6) | 0.01 |
| Neilan[31] | 664 | AF | FWHM | 42 | Death | LGE extent (per 1%) | HR 1.16 (1.1-1.22) | <0.0001 |
| **Non-ischaemic cardiomyopathies** | | | | | | | | |
| Müller[32] | 185 | NICM | Manual | 21 | Death/CT/SCD/VT/HF | LGE + | 67.4 (+)vs 27%(-) | 0.021 |
| | | | | | | | HR 1.1 (0.6-2.1) | 0.676 |
| | | | | | | LVEF≤40% | HR 3.9 (1.9-8.1) | <0.0001 |
| Neilan[11] | 162 | NICM | FWHM 2-SD | 29 | CV death/ ventricular arrhythmia | The presence of LGE predicted clinical endpoint → sensitivity 92%, specificity 69% | | |
| | | | | | | LGE + | HR 6.21 (1.73-22.2) | 0.0004 |
| | | | | | | | HR 1.16 per 1% (1.07-1.21) | <0.0001 |
| | | | | | | LGE >6.1% | AUC 0.92 | |
| Gulati[4] | 472 | NICM | FWHM | 64 | Death, CV death, SCD, HF, CT | LGE extent | | |
| | | | | | | Death | HR 2.43 (1.5-3.9) | <0.001 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | HR 1.11 per 1% (1.06-1.16 ) | <0.001 |
| | | | | | | CV death / CT | HR 3.22 (1.9-5.3) | <0.001 |
| | | | | | | | HR 1.15 per 1% (1.1-1.2) | <0.001 |
| | | | | | | SCD | 4.61 (2.75-7.74) | <0.001 |
| | | | | | | | HR 1.1 per 1% (1.05-1.16) | <0.001 |
| | | | | | | HF/ CT | HR 1.62 (1-2.61) | 0.049 |
| | | | | | | | HR 1.08 per 1% (1-04-1.13) | <0.001 |
| Masci[33] | 228 | NICM | Manual | 23 | CV death/ HF/SCD | LGE present | HR4.02 (2.08-7.8) | <0.001 |
| | | | | | | LGE extent | HR 1.24 (1.11-1.38) | <0.001 |
| Assomull[34] | 101 | NICM | 2-SD | 22 | Death/CV hospitalization, SCD/VT | Midwall fibrosis is a predictor of poor outcomes | | |
| | | | | | | Death/CV hospital | HR 5.9 (1.1-32.2) | 0.04 |
| | | | | | | SCD/VT | HR 5.2 (1-26.9) | 0.03 |
| Lehrke[35] | 184 | NICM | 2-SD | 22 | CV death/ HF/ ICD shock | LGE present | 20.1(+) vs5.3%(-) | 0.002 |
| | | | | | | | HR 3.37 (1.26-9) | 0.015 |
| | | | | | | LGE >4.4% | HR 5.28(1.8-15.5) | 0.01 |
| Perazzolo-Marra[36] | 137 | NICM | 2-SD | 36 | SCD/VT /ICD | LGE present | HR 3.8 (1.3-10.4) | 0.01 |
| Leyva[37] | 97 | NICM | Manual | 104 | Death, CV death, hospitalization for HF or MACE, | Midwall fibrosis associated with mortality/morbidity | | |
| | | | | | | CV death | HR 18.1 (3.5-98.5) | <0.0001 |
| | | | | | | Death/MACE hospitalization | HR 7.57 (2.71-21-2) | <0.0001 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | CV death/HF hospitalization | HR 9.9 (2.72-33.6) | 0.0004 |
| Wu[38] | 65 | NICM | 2-SD | 17 | CV death/ HF/ICD shock | LGE present | 44 (+) vs 8% (-) | <0.001 |
| | | | | | | | HR 8.2 (2.2-30.9) | 0.002 |
| Bruder[39] | 243 | HCM | 2-SD | 36 | Death, CV death | Death | HR 5.47 (1.24-24.1) | 0.01 † |
| | | | | | | CV death | HR 4.81 (1-04-61.9) | 0.035 |
| Maron[40] | 202 | HCM | 6-SD | 22 | Death/ SCD/HF | LGE was associated with LVEF (r=-0.4, p<0.001), but not with clinical events (5.5% LGE+ vs 3.3% LGE-, p=0.5) | | |
| O´Hanlon[41] | 217 | HCM | FWHM | 7 | CV death/ VT/ ICD shock | LGE presence and extent were predictors of adverse outcomes | | |
| | | | | | | Clinical endpoint | 25 (+) vs 7.4% (-) | 0.046 |
| | | | | | | | HR 2.7 (1.01-7.1) | |
| | | | | | | | HR 1.15 per 5% (1.01-1.3) | 0.03 |
| | | | | | | HF | HR 2.6 (1.08-6.5) | 0.033 |
| | | | | | | | HR 1.21 per 5% (1.06-1.37) | 0.004 |
| Rubinshtein[42] | 424 | HCM | Manual | 43 | VT, SCD, ICD shock | LGE was more common among those with events | | |
| | | | | | | Genotype + | 75% vs. 53% | <0.001 |
| | | | | | | NSVT | 27 vs. 8.5% | <0.001 |
| | | | | | | SCD/ICD shock | 3.3 vs. 0% | 0.01 |
| Chan[12] | 1293 | HCM | 6-SD | 40 | SCD | Presence and extension of LGE predicts SCD | | |
| | | | | | | LGE absence | HR 0.39 (0.18-0.84) | 0.002 |
| | | | | | | LGE extent | HR 1.46 per 10% (1.12-1.91) | 0.002 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | HR 1.77 per 15% (1.22-2.43) | 0.008 |
| | | | | | | | HR 2.14 per 20% (1.3-3.26) | 0.008 |
| Greulich[43] | 155 | Sarcoidosis | Manual | 31 | Death/ SCD/ICD shock | LGE+ | HR 31.6 | 0.0014 |
| Nadel[44] | 106 | Sarcoidosis | Manual | 37 | SCD, VT | LGE+ was associated with higher arrhythmic risk | | |
| | | | | | | SCD/VT | 38(+) vs 1.4%(-) | <0.001 |
| | | | | | | | HR 12.52 (1.35-116.2) | 0.03 |
| | | | | | | SCD | 15.6(+) vs1.4%(-) | 0.005 |
| Patel[45] | 81 | Sarcoidosis | Manual | 22 | Death/ICD shock/PM | LGE+ | 17.2 (+) vs 1.9% (-) | § |
| Grün[46] | 203 | Myocarditis | 2-SD | 56 | Death, CV death | LGE is the best predictor of mortality | | |
| | | | | | | Death | HR 8.4 | 0.004 |
| | | | | | | CV death | HR 12.8 | <0.01 |
| Schumm[47] | 405 | Myocarditis | 2-SD | 36 | CV death/ SCD/ ICD shock | LGE + | HR 3.98 | 0.11 |
| | | | | | | | HR 10.83 (2.26-51.82) | <0.001 † |
| | | | | | | Normal CMR | HR 0.14 (0.01-0.34) | <0.0001 |
| Fontana[48] | 250 | Amyloidosis | Transmural LGE | 24 | Death | Transmural LGE | HR: 5.4 (2.1-13.7) | <0.0001 |
| Neilan[49] | 137 | Aborted SCD (no MI) | FWHM | 29 | Death/ICD shock | LGE + | HR 6.7 (2.38-18.85) | <0.001 |
| | | | | | | LGE (per 1%) | HR 1.15 (1.11-1.19) | <0.001 |

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