# Implantable cardioverter defibrillator treatment : benefits and pitfalls in the currently indicated population

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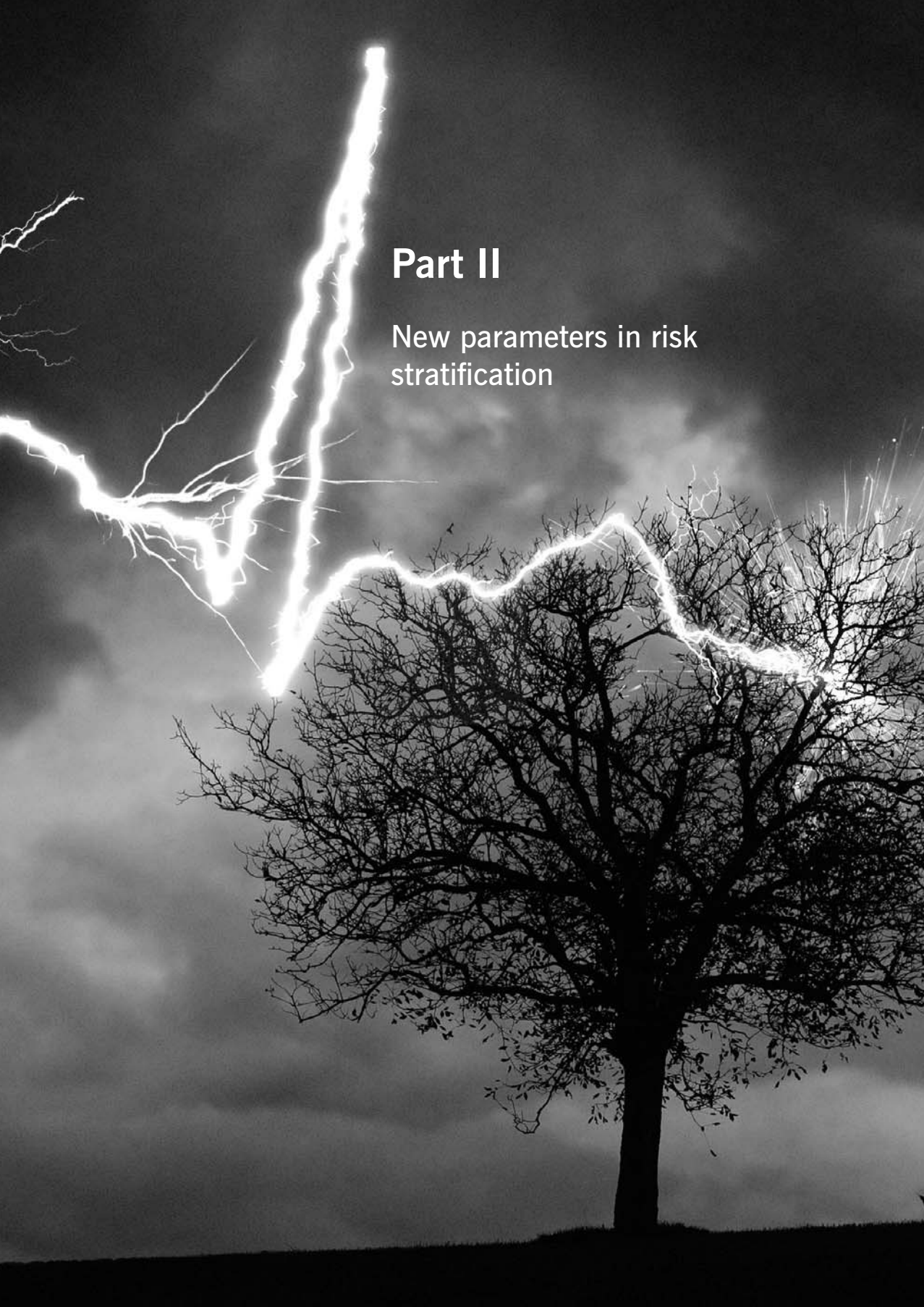

# Part II

## New parameters in risk stratification

# Chapter 8

## Infarct Tissue Heterogeneity Assessed with Contrast-Enhanced Magnetic Resonance Imaging Predicts Spontaneous Ventricular Arrhythmia in Patients with Ischemic Cardiomyopathy and Implantable Cardioverter-Defibrillator

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## Abstract

**Background:** The relation between infarct tissue heterogeneity on contrast-enhanced magnetic resonance imaging (MRI) and the occurrence of spontaneous ventricular arrhythmia (VA) (or sudden cardiac death (SCD)) is unknown. Therefore, the study purpose was to evaluate the predictive value of infarct tissue heterogeneity assessed with contrast-enhanced MRI on the occurrence of spontaneous VA with subsequent implantable cardioverter-defibrillator (ICD) therapy (as surrogate of SCD) in patients with previous myocardial infarction (MI).

**Methods and results:** Ninety-one patients (65±11 years) with previous MI scheduled for ICD implantation underwent cine-MRI to evaluate left ventricular (LV) function and volumes and contrast-enhanced MRI for characterization of scar tissue (infarct gray zone as measure of infarct tissue heterogeneity, infarct core and total infarct size). Appropriate ICD therapy was documented in 18 patients (20%) during a median follow-up of 8.5 months (interquartile range 2.1-20.3). Multivariable Cox proportional hazards analysis revealed that infarct gray zone was the strongest predictor of the occurrence of spontaneous VA with subsequent ICD therapy (hazard ratio 1.49/10g, confidence interval 1.01-2.20, chi-square 4.0, p=0.04).

**Conclusions:** Infarct tissue heterogeneity on contrast-enhanced MRI is the strongest predictor of spontaneous VA with subsequent ICD therapy (as surrogate of SCD) among other clinical and MRI variables e.g. total infarct size, LV function and volumes, in patients with previous MI.

# Introduction

Sudden cardiac death (SCD) is a common cause of death in developed countries and coronary artery disease (CAD) is the most frequent underlying disease.[1] Implantable cardioverter-defibrillator (ICD) implantation is an established therapy in patients with a history of life threatening ventricular arrhythmia (VA).[2] The effect of ICD implantation on survival in patients without a history of life threatening VA, but who are at risk for SCD, has been evaluated by several important clinical trials.[3-5] The second Multicenter Automated Defibrillator Implantation Trial (MADIT II) demonstrated that prophylactic ICD implantation was associated with improved survival in patients with previous myocardial infarction (MI) and left ventricular (LV) dysfunction (LV ejection fraction (LVEF) ≤30%) without the requirement for spontaneous or inducible VA.[4] Subsequently, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) demonstrated that ICD implantation reduced mortality in patients with evidence of CAD on coronary angiography (CAG) or previous MI, LV dysfunction (LVEF ≤35%), and New York Heart Association (NYHA) class II and III.[5] These studies resulted in a class I indication for prophylactic ICD implantation in patients with prior MI, LVEF ≤35% and NYHA class II or III and in patients with prior MI, LVEF ≤30% and NYHA class 1.[2]

However, post-hoc analysis of the MADIT II study population showed that only 35% of the patients that received an ICD developed VA requiring ICD therapy, during 3-year follow-up.[6] Accordingly, there is a need for refinement of selection criteria for ICD implantation.

Although the exact mechanism underlying lethal VA is not clear, it has been demonstrated that scar tissue may serve as a substrate for these arrhythmias.[1, 7] Contrast-enhanced magnetic resonance imaging (MRI) is a reliable non-invasive technique enabling accurate assessment of scar tissue.[8] Bello et al. reported that infarct size on contrast-enhanced MRI was superior to LVEF for identification of patients with inducible monomorphic ventricular tachycardia (VT) during programmed ventricular stimulation (PVS).[9] Yan et al. demonstrated that infarct tissue heterogeneity characterized by contrast-enhanced MRI is a powerful predictor of mortality in patients after MI.[10] Subsequently, Schmidt et al. showed that infarct tissue heterogeneity on contrast-enhanced MRI was the only significant predictor of inducibility of sustained monomorphic VT during PVS or device testing.[11] The results presented in these studies suggest that infarct tissue heterogeneity on contrast-enhanced MRI may identify patients at risk for SCD and consequently enable superior risk stratification for ICD implantation among patients with prior MI compared to conventional variables as LVEF and NYHA class.

However, inducibility of monomorphic VT during PVS does not completely predict the occurrence of spontaneous VA in physiological conditions (or SCD).

No studies have reported yet on the predictive value of infarct tissue heterogeneity on contrast-enhanced MRI on the occurrence of *spontaneous* VA in patients with ischemic cardiomyopathy. Accordingly, the purpose of this study was to evaluate patients with ischemic

cardiomyopathy who underwent contrast-enhanced MRI before ICD implantation and to assess the predictive value of infarct tissue heterogeneity on the occurrence of spontaneous VA with subsequent ICD therapy (as surrogate of SCD).

## Methods

### Study population and protocol

The study was conducted at the Leiden University Medical Center, Leiden, the Netherlands. The study population consisted of 91 consecutive patients with ischemic cardiomyopathy, who were referred for cardiac MRI to evaluate cardiac function and extent of scar tissue for clinical reasons and who were scheduled for ICD implantation. Patients received an ICD as primary or secondary preventive therapy. Survivors of life-threatening VA were evaluated according to a standardized protocol[12] and subsequent ICD implantation was considered a secondary preventive therapy. In patients with poor LV function, without a history of life threatening VA, ICD implantation was performed as primary preventive therapy.13 Patients eligible for cardiac resynchronization therapy (CRT) according to previously described criteria received a combined CRT-ICD device.[14]

Before ICD implantation, clinical characteristics were registered and patients underwent an MRI examination consisting of a cine MRI to evaluate LV function, LV volumes and LV mass and contrast-enhanced MRI for characterization of scar tissue (infarct gray zone as measure of infarct tissue heterogeneity, infarct core and total infarct size). Follow-up started at ICD implantation and the occurrence of spontaneous VA with subsequent ICD therapy (e.g. appropriate ICD therapy) and mortality were documented. Subsequently, the clinical characteristics and MRI variables were related to appropriate ICD therapy (primary endpoint) and the composite of appropriate ICD therapy or cardiac mortality (secondary endpoint).

### Magnetic Resonance Imaging: data acquisition

A 1.5-T Gyroscan ACS-NT/Intera MRI scanner (Philips Medical Systems, Best, The Netherlands) equipped with powertrack 6000 gradients and 5-element cardiac synergy coil was used. Patients were positioned in the supine position. Images were acquired during breath-holds of approximately 15 seconds using vector electrocardiographic gating.

The heart was imaged from apex to base,[15] with 10-12 imaging levels (dependent on heart size, one slice per breath-hold) in short-axis view using a balanced turbo-field echo sequence with parallel imaging (SENSE, acceleration factor 2). Typical parameters were a field of view (FOV) 400×320mm$^2$, matrix 256×206 pixels, slice thickness 10mm, no slice gap, flip angle (α) 35°, time to echo (TE) 1.67ms, and time to repeat (TR) 3.3ms. Temporal resolution was 25-39 ms.

Contrast-enhanced images were acquired approximately 15 minutes after bolus injection of gadolinium diethylenetriamine penta-acetic acid (Magnevist, Schering/Berlin, Germany;0.15 mmol/kg) with an inversion-recovery 3-dimensional turbo-field echo sequence with parallel imaging (SENSE, acceleration factor 2). Inversion time was determined with real-time plan scan in order to null normal myocardial signal. The heart was imaged in one breath-hold with 20-24 imaging levels (dependent on heart-size) in short-axis view. Signal outside the field-of-view was suppressed (using two saturation slabs) to avoid fold-over artifacts. Typical parameters were FOV 400×400mm$^2$, matrix 256×206 pixels, slice thickness 5mm, α 15°, TE 1.06ms, and TR 3.7ms.



## Magnetic Resonance Imaging: data analysis

Data analysis was performed with previously validated software (MASS, research software developed at our institution). Endocardial and epicardial borders were outlined manually on short-axis cine images. Papillary muscles were regarded as part of the ventricular cavity, and epicardial fat was excluded. LV end-systolic (ESV) and LV end-diastolic volume (EDV) and LV end-diastolic mass (LV mass) were computed. Subsequently, ESV was subtracted from EDV and LV ejection fraction (EF) was calculated.

Contrast-enhanced images were analyzed to calculate the size of the infarct core, infarct gray zone (as measure of infarct tissue heterogeneity) and total infarct size (infarct core plus infarct gray zone). First, endocardial and epicardial borders were outlined manually on the short-axis contrast-enhanced images (Figure 1A). Subsequently, the maximum signal intensity (SI) within the infarct region in the study was determined. The infarct core was defined as myocardium with SI≥50% of the maximum SI (red area Figure 1B).[11] The infarct gray zone was defined as myocardium with SI≥35% but with SI<50% of the maximum SI (yellow area Figure 1C). Summation of the infarct core and infarct gray zone yielded the

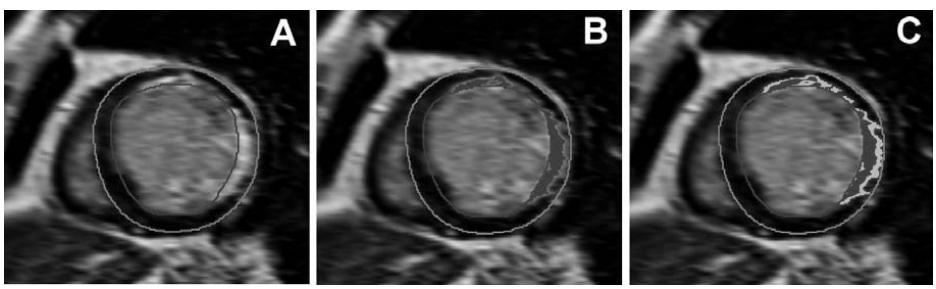


**Figure 1.** Assessment of the infarct gray zone: Short-axis contrast-enhanced MRI of a patient with a previous myocardial infarction. 1A.Endocardial (red) and epicardial (green) borders were outlined manually. Subsequently, the maximum signal intensity (SI) within the infarct region was determined. 1B.The infarct core was defined as myocardium with SI ≥ 50% of the maximum SI (red area). 1C.The infarct gray zone was defined as myocardium with SI ≥ 35% but with SI < 50% of the maximum SI (yellow area). Summation of the infarct core and infarct gray zone yielded the total infarct size (red plus yellow area).

total infarct size. In each patient, the infarct core, infarct gray zone and total infarct size were expressed in grams of myocardium.

Infarct gray zone measurements were repeated in 18 patients by the same observer and by a second observer to assess intra- and inter-observer agreement.

### ICD devices

Patients received a CRT-ICD device (Contak, Contak renewal, Cognis, Boston Scientific (Natick, United States [formerly Guidant Corp.]);Lumax, Biotronik (Berlin, Germany); In-Sync III and InSync Sentry, Medtronic Inc. (Minneapolis, United States); Epic, Atlas or Atlas II, St. Jude Medical (St. Paul, United States)), a dual chamber ICD (Lumax, Biotronik; Vitality 2, Teligen, Boston Scientific; Entrust, Marquis DR, Medtronic Inc.) or a single chamber ICD (Vitality 2, Ventak Mini,Boston Scientific).

### Follow-up and events

Follow-up was performed by device interrogation, scheduled every three-six months and chart review. The median follow-up duration was 8.5 months (interquartile range 2.1-20.3). Appropriate ICD therapy, the primary endpoint, was defined as anti-tachycardia pacing (ATP) and/or shock in response to VT or ventricular fibrillation (VF). ICD therapy was classified as inappropriate when triggered by sinus or supraventricular tachycardia, T-wave oversensing, or electrode dysfunction. Furthermore, total mortality was reported, which was further classified as cardiac and non-cardiac mortality. Cardiac mortality included death caused by end-stage heart failure, acute MI or SCD. The composite of appropriate ICD therapy or cardiac mortality was regarded as the secondary endpoint.

### Statistical analysis

Continuous variables are presented as means±standard deviation (SD) and categorical data are summarized as frequencies and percentages. Differences in baseline characteristics between patients who reached the primary endpoint and those who did not were analyzed using the independent samples *t*-test or Fisher's exact tests, as appropriate.

The a-priori aim of this study was to evaluate the association between infarct tissue heterogeneity and the primary endpoint (appropriate ICD therapy) and secondary endpoint (composite of appropriate ICD therapy or cardiac mortality) during follow-up. Univariable and multivariable Cox proportional hazards regression models were constructed to study the relation between infarct tissue heterogeneity and the primary and secondary endpoint. Adjusted hazard ratios were obtained after adjustment for potential confounders.Only variables that appeared to be associated with the primary or secondary endpoint at the $p<0.10$ level in univariable analysis were included since we had to limit the number of covariables because of the number of events (primary endpoint:LVEF, total infarct size and infarct gray zone; secondary endpoint:extent of CAD, LVEF, total infarct size and infarct gray

zone). Total infarct size and infarct gray zone could however not be included simultaneously in one multivariable Cox proportional hazards regression model, since these variables were strongly interrelated (Pearson's correlation 0.8, $p<0.001$). Therefore, infarct core instead of total infarct size was included in the multivariable models. Unadjusted and adjusted hazard ratios (HR) with their corresponding 95% confidence intervals (CI) are reported.

To check the proportional hazard assumption (i.e.,that the hazard ratio for 2 subjects with fixed predictors is constant over time) log(−log[survival probability]) for different categories was plotted against time to ensure that the curves were reasonably parallel. In general, all proportionality assumptions were appropriate.

Since infarct gray zone extent was significantly related with the primary endpoint, the study population was divided into 2 groups, based on the observed median value of the infarct gray zone, and the event-rate of both cohorts was further analyzed by the method of Kaplan-Meier. Difference in event-rate over time was evaluated by a log-rank test. Furthermore, the negative predictive value of a small extent of infarct gray zone (≤ median value of 16.7 g) was calculated.

Intra- and inter-observer agreement for infarct gray zone measurements was calculated using the intraclass correlation coefficient (ICC) for absolute agreement.

All tests were 2-sided and $p<0.05$ was considered statistically significant. The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.



## Results

### Study population

The baseline characteristics are listed in Table 1. The mean age of the study population was 65±11 years. All patients had a previous MI, of which 9 patients (18%) had a clinically unrecognized MI. Ten patients (11%) received an ICD as secondary preventive therapy; the remaining 81 patients (89%) as primary preventive therapy. A combined CRT-ICD device was implanted in 73 patients (80%). Sixteen patients (18%) received a dual chamber ICD and 2 patients (2%) a single chamber ICD.

### Follow-up and events

Appropriate ICD therapy (primary endpoint) was documented in 18 patients (20%). The first VA episode was terminated by ATP in 12 patients (67%) and 6 patients (33%) received ATP directly followed by shock or shock only. The total mortality in the study population was 16% (15 patients). Non-cardiac death was reported in 4 patients (4%). Cardiac death occurred in 11 patients (12%):10 patients (11%) died of end-stage heart failure and 1 patient (1%) died after recurrent acute MI. Three patients (3%) who died of cardiac causes

**Table 1.** Baseline clinical characteristics

| Variable | Total population (n=91) | No appropriate ICD therapy (n=73) | Appropriate ICD therapy (n=18) | p-value |
|---|---|---|---|---|
| Age,yrs | 65±11 | 64±11 | 65±11 | 0.9 |
| Male gender | 74(81) | 59(81) | 15(83) | 1.0 |
| Indication ICD implantation | | | | |
| Secondary prevention | 10(11) | 8(11) | 2(11) | 1.0 |
| Primary prevention | 81(89) | 65(89) | 16(89) | |
| Previous ventricular arrhythmia | | | | |
| Non-sustained ventricular tachycardia | 9(10) | 6(8) | 3(17) | |
| Sustained ventricular tachycardia | 9(10) | 8(11) | 1(6) | 0.3 * |
| Ventricular fibrillation | 1(1) | 0(0) | 1(6) | |
| Cardiac resynchronization therapy | 73(80) | 57(78) | 16(89) | 0.5 |
| LBBB | 31(45) | 24(33) | 7(39) | 0.8 |
| QRS duration(ms) | 130±33 | 142±38 | 127±31 | 0.08 |
| Previous PCI | 40(44) | 34(47) | 6(33) | 0.4 |
| Previous CABG | 44(48) | 36(49) | 8(44) | 0.8 |
| Extent of CAD | | | | |
| 1-vessel | 22(24) | 20(27) | 2(11) | |
| 2-vessel | 24(26) | 17(23) | 7(39) | 0.2 † |
| 3-vessel | 45(50) | 36(49) | 9(50) | |
| Diabetes | 23(25) | 19(26) | 4(22) | 1.0 |
| Hypertension | 36(40) | 29(40) | 7(39) | 1.0 |
| Hypercholesterolemia | 67(74) | 54(74) | 13(72) | 1.0 |
| Smoking | 44(48) | 33(45) | 11(61) | 0.3 |
| NYHA functional class | 2.5±0.7 | 2.5±0.7 | 2.5±0.8 | 0.9 |
| Medication | | | | |
| β-blockade (including Sotalol) | 72(79) | 57(78) | 15(83) | 0.8 |
| Amiodarone | 15(17) | 12(16) | 3(17) | 1.0 |
| Calcium channel blocker | 15(17) | 11(15) | 4(22) | 0.5 |
| ACE inhibitor/ATII antagonist | 77(85) | 60(82) | 17(94) | 0.3 |
| Oral anticoagulant | 84(43) | 67(44) | 17(39) | 1.0 |
| Statin | 74(81) | 60(82) | 14(78) | 0.7 |
| Nitrate | 27(30) | 23(32) | 4(22) | 0.6 |
| Diuretic | 69(76) | 55(75) | 14(78) | 1.0 |

Continuous data are expressed mean±standard deviation, categorical data as number of patients (%).
*p-value of Fisher's exact test based on 2x2 tables after combining non-sustained ventricular tachycardia, sustained ventricular tachycardia, ventricular fibrillation
†p-value of Fisher's exact test based on 2x2 tables after combining 2-and 3-vessel disease.
ACE:angiotensin converting enzyme, ATII:angiotensin II, CABG:coronary artery bypass grafting, CAD:coronary artery disease, ICD:implantable cardioverter-defibrillator, PCI: percutanous coronary intervention, LBBB:left bundle branch block, NYHA:New York Heart Association

received appropriate ICD therapy (>1 month) before death. Accordingly, the composite secondary endpoint of appropriate ICD therapy or cardiac mortality occurred in 26 patients (29%).

## MRI variables

MRI findings are listed in Table 2. Mean LVEF in the entire study population was 28±9%. A non-significant difference in LVEF was reported between patients who received appropriate ICD therapy compared to patients who did not receive appropriate ICD therapy (25±7 vs. 29±9%, p=0.06). No difference in LV EDV, LV ESV and LV mass was observed between the two groups.

All patients had evidence of scar tissue on contrast-enhanced MRI. The mean total infarct size in the entire study population was 46±25g. The mean infarct core was 26±17g and the mean infarct gray zone was 20±13g. The total infarct size (58±29g vs. 43±23g, p=0.02) and infarct gray zone (28±16g vs. 18±11g, p=0.002) were significantly larger in patients who received appropriate ICD therapy compared to those who did not receive appropriate ICD therapy.

The ICC for infarct gray zone measurements was 0.97 and 0.91 for respectively intra- and inter-observer agreement (p<0.001).

## Predictors of appropriate ICD therapy

As demonstrated in Table 3 and 4, the infarct gray zone was the only significant predictor of appropriate ICD therapy in univariable analysis. Univariable analysis yielded similar results when we focused on patients who received an ICD as primary preventive therapy (HR 1.59/10g, CI 1.15-2.20, chi-square 7.8, p=0.005). In the total study population, after adjustment for LVEF and infarct core (See Methods section), the infarct gray zone remained

**Table 2.** Baseline MRI variables

| Variable | Total population (n=91) | No appropriate ICD therapy (n=73) | Appropriate ICD therapy (n=18) | p-value |
|---|---|---|---|---|
| LVEF (%) | 28±9 | 29±9 | 25±7 | 0.06 |
| LV EDV (ml) | 333±112 | 331±117 | 339±95 | 0.8 |
| LV ESV (ml) | 245±107 | 241±110 | 259±94 | 0.5 |
| LV mass (g) | 148±40 | 148±41 | 149±38 | 0.9 |
| Total infarct (Infarct core+gray zone)(g) | 46±25 | 43±23 | 58±29 | 0.02 |
| Infarct core (g) | 26±17 | 25±16 | 30±17 | 0.2 |
| Infarct gray zone (g) | 20±13 | 18±11 | 28±16 | 0.002 |

Data are expressed as mean±standard deviation

LV:left ventricular, LV EDV:LV end-diastolic volume, LV ESV:LV end-systolic volume, LVEF:LV ejection fraction

**Table 3.Univariable** analysis of clinical characteristics for prediction of appropriate ICD therapy.

| | Hazard Ratio | 95%Confidence Interval | Chi-square | p-value |
|---|---|---|---|---|
| Age | 0.94/10yr | 0.61-1.46 | 0.1 | 0.8 |
| Male gender | 1.02 | 0.29-3.53 | 0.0 | 1.0 |
| Indication ICD implantation (secondary vs. primary prevention) | 0.88 | 0.20-3.86 | 0.0 | 0.9 |
| Previous ventricular arrhythmia* | 1.89 | 0.66-5.35 | 1.4 | 0.2 |
| Cardiac resynchronization therapy | 0.63 | 0.17-2.31 | 0.5 | 0.5 |
| LBBB | 0.93 | 0.36-2.41 | 0.0 | 0.9 |
| QRS duration (ms) | 1.00 | 0.99-1.02 | 0.4 | 0.5 |
| Previous PCI | 0.69 | 0.26-1.84 | 0.5 | 0.5 |
| Previous CABG | 0.91 | 0.36-2.30 | 0.0 | 0.8 |
| Extent of CAD† | | | | |
| 2-vessel | 3.07 | 0.63-14.87 | 1.9 | 0.2 |
| 3-vessel | 1.64 | 0.35-7.70 | 0.4 | 0.5 |
| Diabetes | 0.82 | 0.27-2.49 | 0.1 | 0.7 |
| Hypertension | 0.83 | 0.32-2.18 | 0.1 | 0.7 |
| Hypercholesterolemia | 1.03 | 0.37-2.89 | 0.0 | 1.0 |
| Smoking | 2.10 | 0.80-5.55 | 2.3 | 0.1 |
| NYHA functional class | 0.76 | 0.37-1.56 | 0.6 | 0.5 |
| Medication | | | | |
| β-blockade (including Sotalol) | 2.32 | 0.65-8.29 | 1.7 | 0.2 |
| Amiodarone | 0.80 | 0.23-2.79 | 0.1 | 0.7 |
| Calcium channel blocker | 1.42 | 0.46-4.31 | 0.4 | 0.5 |
| ACE inhibitor/ATII antagonist | 4.91 | 0.65-37.11 | 2.9 | 0.1 |
| Oral anticoagulant | 0.83 | 0.11-6.41 | 0.0 | 0.9 |
| Statin | 1.28 | 0.41-3.99 | 0.2 | 0.7 |
| Nitrate | 0.72 | 0.24-2.20 | 0.3 | 0.6 |
| Diuretic | 0.87 | 0.28-2.64 | 0.1 | 0.8 |

*Non-sustained ventricular tachycardia, sustained ventricular tachycardia and ventricular fibrillation combined, †Increased risk of event as compared to 1-vessel disease.
ACE:angiotensin converting enzyme, ATII:angiotensin II, CABG:coronary artery bypass grafting, CAD:coronary artery disease, ICD:implantable cardioverter-defibrillator, PCI:percutanous coronary intervention, LBBB:left bundle branch block.

the only significant predictor of appropriate ICD therapy (Table 5). Total infarct size was not a significant predictor of appropriate ICD therapy when entered simultaneously with

**Table 4.Univariable** analysis of MRI variables for prediction of appropriate ICD therapy

| | Hazard Ratio | 95%Confidence Interval | Chi-square | p-value |
|---|---|---|---|---|
| LVEF | 0.53/10% | 0.27-1.04 | 3.4 | 0.06 |
| LV EDV | 1.00/10ml | 0.95-1.04 | 0.0 | 0.9 |
| LV ESV | 1.00/10ml | 0.97-1.05 | 0.2 | 0.7 |
| LV mass | 0.97/10g | 0.86-1.11 | 0.2 | 0.7 |
| Total infarct size (Infarct core+gray zone) | 1.15/10g | 0.99-1.33 | 3.4 | 0.06 |
| Infarct core | 1.10/10g | 0.87-1.37 | 0.6 | 0.4 |
| Infarct gray zone | 1.56/10g | 1.14-2.14 | 7.6 | 0.006 |

LV:left ventricular, LV EDV:LV end-diastolic volume, LV ESV:LV end-systolic volume, LVEF:LV ejection fraction

**Table 5.** Multivariable Cox proportional hazards model for prediction of appropriate ICD therapy

| | Hazard Ratio | 95%Confidence Interval | Chi-square | p-value |
|---|---|---|---|---|
| LVEF | 0.72/10% | 0.32-1.64 | 0.6 | 0.4 |
| Infarct gray zone | 1.49/10g | 1.01-2.20 | 4.0 | 0.04 |
| Infarct core | 0.92/10g | 0.69-1.22 | 0.3 | 0.6 |

LVEF:left ventricular ejection fraction

LVEF in one multivariable model (HR 1.07/10g, CI 0.89-1.29, chi-square 0.6, p=0.4, HR 0.62/10%, CI 0.28-1.41, chi-square 1.3, p=0.3 for resp. total infarct size and LVEF).

The median value of infarct gray zone on contrast-enhanced MRI (16.7g) was used to separate patients with a large extent of infarct gray zone (infarct gray zone>16.7g, n=45) from those with a small extent of infarct gray zone (infarct gray zone≤16.7g, n=46). Fifteen patients (33%) with a large extent of infarct gray zone received appropriate ICD therapy compared to only 3 patients (7%) with a small extent of infarct gray zone (p=0.003,Figure 2).

The negative predictive value of a small extent of infarct gray zone (infarct gray zone ≤16.7g) was 93% for the entire study population and 95% if only patients who received an ICD as primary preventive therapy (n=81) were included.

## Predictors of appropriate ICD therapy or cardiac mortality

In univariable analysis, LVEF (HR 0.56/10%, CI 0.32-0.96, chi-square 4.4, p=0.04) total infarct size (HR 1.15/10g, CI 1.03-1.29, chi-square 5.7, p=0.02) and the infarct gray zone (HR 1.56/10g, CI 1.19-2.06, chi-square 10.1, p=0.001) were significant predictors of the secondary endpoint. A non-significant association was observed between the extent of CAD and the secondary endpoint (HR 3.99, CI 0.86-18.55, chi-square 3.1, p=0.08, HR 2.62, CI 0.59-11.57, chi-square 1.6, p=0.2, resp.2-and 3-vessel compared to 1-vessel

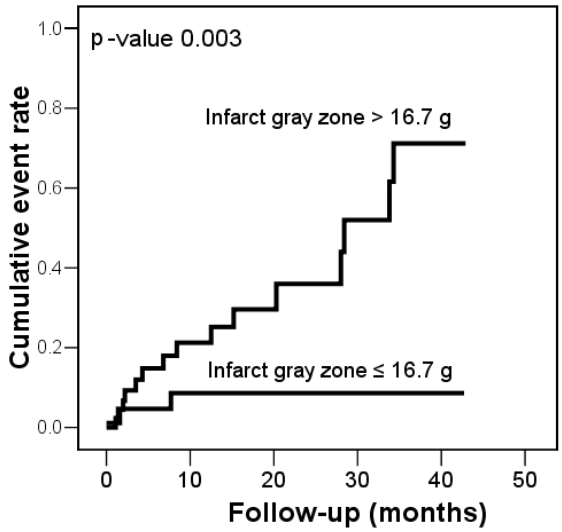


**Figure 2.Kaplan-Meier** curve analysis showing the difference in appropriate ICD therapy when patients are stratified according the median value of infarct gray zone (16.7g). Fifteen patients (33%) with a large extent of infarct gray zone (infarct gray zone>16.7 g) received appropriate therapy compared to only 3 patients (6.5%) with a small extent of infarct gray zone (infarct gray zone≤16.7 g).

disease). In multivariable analysis including the extent of CAD, LVEF, infarct gray zone and infarct core (see Methods section), the infarct gray zone was the only significant predictor of the composite secondary endpoint of appropriate ICD therapy or cardiac mortality (HR 1.47/10g, CI 1.04-2.08, chi-square 4.7, p=0.03).

Total infarct size was not a significant predictor of appropriate ICD therapy or cardiac death when entered simultaneously with extent of CAD and LVEF in one multivariable model (CAD: HR 2.91, CI 0.60-14.02, chi-square 1.8, p=0.2, HR 2.26, CI 0.51-10.11, chi-square 1.1, p=0.3, resp.2-and 3-vessel compared to 1-vessel disease, total infarct size: HR 1.08/10g, CI 0.93-1.26, chi-square 1.0, p=0.3, LVEF: HR 0.74/10%, CI 0.38-1.42, chi-square 0.8, p=0.4).

## Discussion

The main finding in this study is that infarct tissue heterogeneity assessed with contrast-enhanced MRI is the strongest predictor of spontaneous VA with subsequent ICD therapy (as surrogate of SCD) among other clinical and MRI variables e.g. total infarct size, LV function and volumes, in patients with previous MI. Furthermore, infarct tissue heterogeneity is the strongest predictor of the composite endpoint of spontaneous VA with subsequent ICD therapy (as surrogate of SCD) and cardiac mortality in these patients.

The annual incidence of sudden arrhythmic deaths has been estimated between 184,000 and 462,000 in the United States.[16] Although measures including early access to medical care, early cardiopulmonary resuscitation and early defibrillation have improved survival, overall mortality from cardiac arrest remains high. [16] During the last decades, ICD devices have been developed and ICD implantation is now an established secondary preventive therapy in patients with a history of life threatening VA.(2) In addition, the MADIT studies and SCD-HeFT demonstrated improved survival of patients with previous MI and depressed LVEF, but without a history of life threatening VA.[3-5]

However, post-hoc analysis of the MADIT II study revealed that only 35% of the patients received appropriate therapy at 3 years after implantation.[6] Furthermore, ICD therapy is costly and the incidence of inappropriate shocks associated with an adverse effect on the patient's quality of life ranges between 10% to 35%.[17-19] Accordingly, refinement of selection criteria for ICD implantation is necessary.

The vast majority of patients with cardiac arrest is diagnosed with an underlying structural heart disease; predominantly CAD[1] and VT and VF are the most common underlying arrhythmias accounting for 70% of the cases.[20] In patients with previous MI, scar tissue may serve as a substrate for VA, most likely through areas of slow conduction due to intermingling of viable myocytes and fibrous tissue, leading to reentrant tachycardia.[21-23]

Contrast-enhanced MRI is a valuable technique that allows for accurate delineation of scar tissue in patients with CAD.[8]. Bello et al. studied patients with chronic MI using contrast-enhanced MRI and demonstrated that infarct size identified patients with a substrate for inducible VT during electrophysiological examination.[9] A more recent study by Ashigaka et al. evaluated the relation between 3D scar geometry assessed with contrast-enhanced MRI and VT reentry circuits in a swine model with chronic MI. MRI revealed scar with spatially complex structures containing a mixture of viable and necrotic tissue, particularly at the isthmus, that serve as a substrate for multiple VT morphologyWhile most previous contrast-enhanced MRI studies used a binary approach for assessment of scar tissue by categorizing myocardium into scar tissue versus normal (remote) myocardium,[8, 25] two recent studies have used a more differentiated method for analysis of contrast-enhanced images.[10, 11] These studies assessed infarct tissue heterogeneity by quantifying myocardium with an intermediate SI (the peri-infarct border zone or gray zone), most likely reflecting an admixture of scar tissue and viable myocardial strands.[10, 11] Yan et al. demonstrated that infarct tissue heterogeneity characterized by contrast-enhanced MRI is a powerful predictor of mortality in patients after MI.[10] Subsequently, Schmidt et al. showed that infarct tissue heterogeneity on contrast-enhanced MRI was the only significant predictor of inducibility of sustained monomorphic VT during PVS or device testing.[11]

However, inducibility of VT during PVS or device testing does not completely predict occurrence of *spontaneous* VA.[26] Studying patients who have received an ICD though,

enables unraveling the relation between infarct tissue heterogeneity and the occurrence *spontaneous* VA (as surrogate of SCD).

Several studies evaluated the prognostic value of infarct size and/or infarct tissue heterogeneity on contrast-enhanced MRI in patients with ischemic cardiomyopathy.[9-11, 27-32] The prognostic value of scar tissue on contrast-enhanced MRI has also been recognized in patients with non-ischemic cardiomyopathy; however, these studies have not evaluated infarct tissue heterogeneity.[33-35] Accordingly, until now only 2 studies evaluated infarct tissue heterogeneity and this is the first study that evaluated the predictive value of infarct tissue heterogeneity assessed with contrast-enhanced MRI on the occurrence of spontaneous VA, which can be regarded as a substitute for SCD.

The two previous studies evaluating infarct tissue heterogeneity used different criteria to discriminate the infarct gray zone from the infarct core. Yan et al. defined the infarct core as areas with SI > mean SI plus 3 SD of remote myocardium and areas with SI between mean SI plus 2 SD and 3 SD was recognized as the infarct gray zone.[10] Schmidt et al.however, used a simplified version of the full-width half-maximum method and defined myocardium with SI >50% of maximal SI in the hyperenhanced areas as the infarct core and the infarct gray zone as myocardium with SI>peak SI of remote myocardium but <50% of maximum SI.[11] The thresholds used by Yan et al. were not applicable in our dataset, since they resulted in a large overestimation of both infarct core and infarct gray zone.[10] Accordingly, the definition for infarct core described by Schmidt et al. was applied in the current study. However, using the peak SI of remote myocardium to define infarct gray zone might be unfavorable, since this approach may be susceptible to suboptimal signal suppression of remote myocardium (T1 nulling) and image artifacts, both affecting the SI of the remote myocardium. Furthermore, the presence of (minimal) fibrosis in the area indicated as remote myocardium cannot be completely excluded. Therefore, and to minimize the variability due to user-interaction, the definitions used in the current study are based exclusively on the maximum SI in the hyper enhanced infarct area. The thresholds used to identify the infarct gray zone and infarct core in the current study (35% versus 50% of maximum SI) were selected in line with the study of Yan et al. in which the ratio of the threshold SI for infarct gray zone versus infarct core was also 2:3 (assuming good signal suppression of remote myocardium).[10] Nonetheless, as previously emphasized,[36] these novel methods for assessment of infarct tissue heterogeneity should be evaluated in additional studies and experimental studies comparing the extent of infarct gray zone assessed with contrast-enhanced MRI and the histological extent of heterogeneous myocardium containing both fibrosis and viable myocardium are highly desirable.

An important limitation of this study is the relatively small sample size and the limited follow-up duration; therefore the present conclusion requires confirmation in larger study groups with longer follow-up duration. In addition, larger studies may help to identify the best definition for characterization of the infarct gray zone.

Furthermore, in the present study an inversion recovery 3D technique was used, whereas an inversion recovery 2D technique was applied in the previous studies that measured infarct heterogeneity, which resulted in a differently defined infarct gray zone.[10, 11] Accordingly, comparative studies evaluating the relative value of the different techniques for assessment of infarct tissue heterogeneity and its predictive value for the occurrence of VA are needed.

## Conclusions

Infarct tissue heterogeneity on contrast-enhanced MRI is the strongest predictor of spontaneous VA with subsequent ICD therapy (as surrogate of SCD) among other clinical and MRI variables e.g. total infarct size, LV function and volumes, in patients with previous MI.

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