



Universiteit  
Leiden  
The Netherlands

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

Borleffs, C.J.W.

### **Citation**

Borleffs, C. J. W. (2010, September 30). *Implantable cardioverter defibrillator treatment : benefits and pitfalls in the currently indicated population*. Retrieved from <https://hdl.handle.net/1887/16004>

Version: Corrected Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/16004>

**Note:** To cite this publication please use the final published version (if applicable).



## Part I

Long-term follow-up and  
baseline risk stratification of  
ICD patients

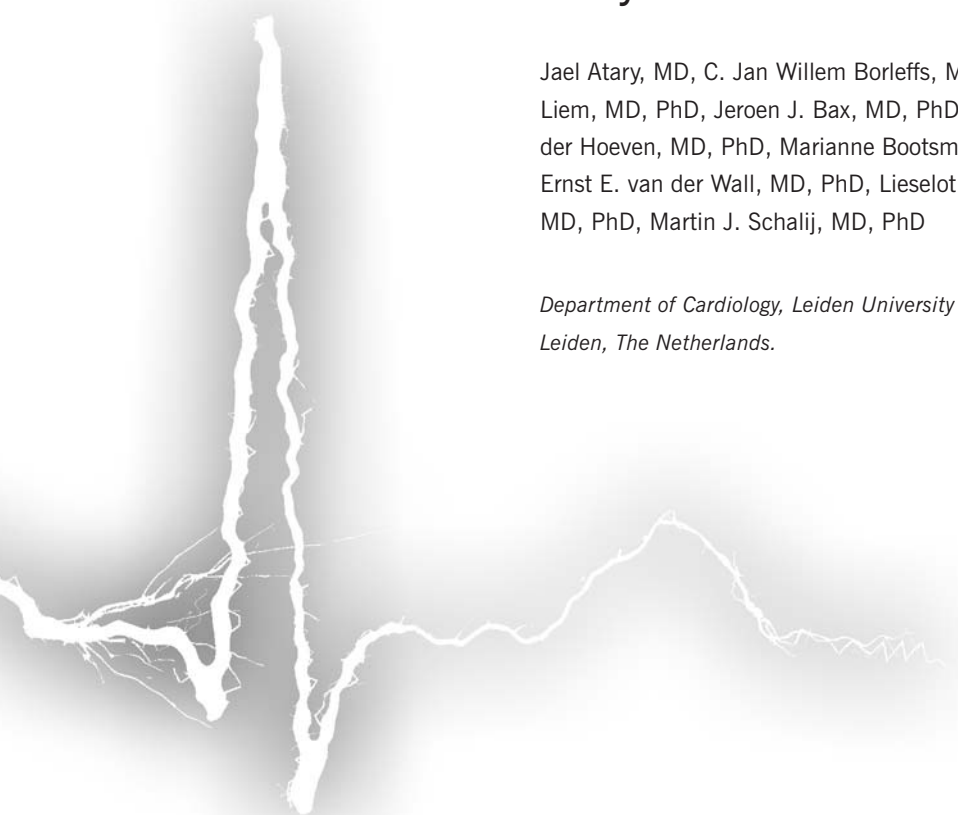


## Chapter 2

### Structured Care for Patients after Acute Myocardial Infarction: Sudden Cardiac Death Prevention. Data from the Leiden MISSION! AMI study.

Jael Atary, MD, C. Jan Willem Borleffs, MD, Su San Liem, MD, PhD, Jeroen J. Bax, MD, PhD, Bas L. van der Hoeven, MD, PhD, Marianne Bootsma, MD, PhD, Ernst E. van der Wall, MD, PhD, Lieselot van Erven, MD, PhD, Martin J. Schalij, MD, PhD

*Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands.*



## Abstract

**Aim:** To assess the percentage of patients in daily clinical practice that meets criteria for implantation of an Implantable Cardioverter Defibrillator (ICD) following Acute Myocardial Infarction (AMI).

**Methods:** The MISSION! protocol contains pre-hospital, in-hospital and out-patient clinical framework for decision making and treatment of AMI patients and prevention of Sudden Cardiac Death (SCD) and is based on international guidelines.

**Results:** A total of 676 consecutive AMI patients (78% male, mean age  $59 \pm 12$  years) treated according to the MISSION! protocol were included in this analysis. LVEF at 3 months was  $54 \pm 10\%$ . Only 39 (6%) patients met criteria for implantation of an ICD <1 year post-MI. These patients suffered more extensive infarctions as indicated by higher peak troponin T values (mean  $14.5 \pm 8.3 \mu\text{g/l}$  vs.  $6.5 \pm 14.7 \mu\text{g/l}$ ;  $p < 0.001$ ) and had more LAD related infarctions (79% vs. 46%;  $p < 0.001$ ). Cumulative first appropriate therapy rate was 15% at 3 years follow-up. No sudden cardiac death was observed in the study population.

**Conclusions:** After implementation of an aggressive optimized treatment protocol for AMI patients, prophylactic ICD implantation was warranted in only 6% of patients. Accordingly, an easy-to-use, guideline-based protocol tailored to fit within routine practice is able to reduce the rate of severe deterioration of LV function and SCD to a minimum and helps maintain ICD implantation rates within manageable proportions.

## Introduction

Patients after acute myocardial infarction (AMI) are at risk of sudden death due to life threatening ventricular arrhythmias.<sup>1</sup> Large randomized trials demonstrated that both arrhythmic death and total mortality can be lowered by implantation of an Implantable Cardioverter Defibrillator (ICD) in post-MI patients with a low left ventricular ejection fraction (LVEF) with or without ventricular arrhythmias.<sup>2-4</sup> These findings resulted in a Class I indication for all patients with an ischemic cardiomyopathy and a low LVEF, even in the absence of ventricular arrhythmias.<sup>5,6</sup> Most of these trials however included patients years after the index event (more than 75% of patients in the two Multicenter Automated Defibrillator Trials (MADIT) were enrolled >6 months after MI and 89% in the Multicenter Unsustained Tachycardia Trial (MUSTT) were enrolled >1 year post MI). Furthermore with the current practice of aggressive reperfusion strategies to limit the extent of the damage caused by the infarction it is not known how many patients will become candidate for ICD implantation in the year following the index event.

A regional AMI guideline implementation program (MISSION!) was developed to optimize the use of evidence-based medicine in practice.<sup>7</sup> MISSION! contains a pre-hospital, in-hospital and out-patient clinical framework for decision making and treatment of AMI patients. This prospective and well-defined cohort offers a unique opportunity to evaluate and follow patients after AMI and to assess the need for ICD treatment.

## Methods

### Patients and protocol

Since 2004, all patients presenting with AMI at Leiden University Medical Center were treated according to the MISSION! protocol, as previously described in detail.<sup>7</sup> The protocol is based on the ACC/AHA/ESC guidelines for AMI and focuses on the reduction of onset of symptoms-to-balloon time, optimization of pharmacological treatment, and the structured prevention of SCD during follow-up.<sup>7-9</sup> The global in-hospital and out-patient clinical framework for the decision-making process and treatment up to one year following the index event is outlined in Figure 1.

AMI diagnosis was confirmed by the presence of an unstable coronary lesion on angiography and/or the elevation of cardiac biomarker(s) above normal levels.<sup>10</sup> Patients without typical ST-elevation in-hospital, but with ischemic symptoms and elevated cardiac enzymes (CKMB and troponin T) were also diagnosed and included as AMI patients in the program. In the absence of complications, the hospital admission was limited to three days. Patients on mechanical ventilation at the time of the index event were excluded from the pre-hospital and in-hospital MISSION! protocol. These patients did, however, receive the same

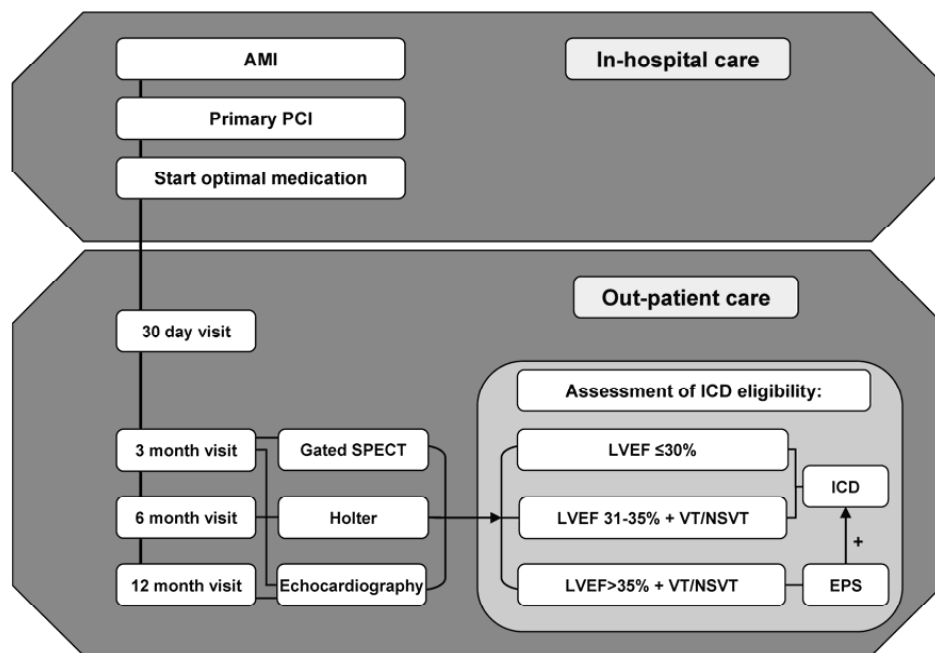


Figure 1. MISSION! protocol flowchart.

out-patient treatment after discharge. Patients were excluded from the study population in case of death prior to the acquisition of the gated single photon emission computed tomography (SPECT) three months after the index event, or if the assessment of LV function on gated SPECT was not possible due to poor image quality.

Data of each MISSION! patient was collected prospectively in an electronic patient file and data management system (EPD-VISION 6.01, Leiden University Medical Center).

### Follow-up

In the outpatient phase all patients were scheduled for regular clinical visits 30 days after the index event and after that every 3 months in the course of a year.

Gated SPECT (<sup>99m</sup> tetrofosmin gated myocardial perfusion SPECT) was used as the preferred method for the assessment of LVEF and was conducted at 3 months follow-up.<sup>11,12</sup>

### ICD eligibility

The ICD screening protocol was loosely based on large primary prevention ICD trials that contributed to the development of the guidelines.<sup>2-4,6</sup>

Patients were subsequently divided into the following groups, according to the LVEF: (1) LVEF ≤30%; (2) LVEF 31-35%; and (3) LVEF >35%. Patients with LVEF ≤30% as determined from gated SPECT were directly assigned to ICD therapy as in MADIT II.<sup>4</sup>

Patients with LVEF 30-35% were considered eligible for ICD therapy when non sustained ventricular tachycardias (nsVT) were observed on 24-hour Holter monitoring similar to protocols of trials like MADIT I or MUSTT.<sup>2,3</sup> Patients with a LVEF  $\geq 35\%$  and abnormal 24-hour Holter monitoring revealing nsVT were also referred for an electrophysiological test to evaluate indication for antiarrhythmic therapy.

## Endpoints

The primary endpoint was ICD eligibility, as determined by the described protocol. Secondary endpoints were all-cause death, further subdivided into death from cardiac causes, sudden death (unwitnessed), or non-cardiac death.

Furthermore, in patients receiving an ICD, secondary endpoints were appropriate and inappropriate defibrillator discharge (antitachycardia pacing [ATP] or shock).

## ICD evaluation

Device interrogation was scheduled every 3 months. All printouts were checked for appropriate and inappropriate ICD therapy (ATP or shocks). Therapies were classified as appropriate when they occurred in response to VT or ventricular fibrillation (VF) and as inappropriate when triggered by sinus or supraventricular tachycardia, T-wave oversensing, or electrode dysfunction. Cutoff rate of the monitor or first therapy zone was noted.

## Statistical Analysis

Continuous data are expressed as mean  $\pm$  SD; dichotomous data are presented as numbers and percentages. Differences at baseline were assessed using a Chi-square test using Yate's correction or student t-test for independent samples where appropriate. Event rates over time were analyzed by method of Kaplan-Meier.

Univariable and multivariable cox regression analyses were performed as appropriate to determine a relation between potential risk factors at baseline and the incidence of all cause death. All variables with a p value of  $<0.25$  entered the multivariable regression analysis. Only adjusted Hazard Ratio (HR) is reported with the corresponding 95% confidence interval (CI). All tests were two-sided, a p-value of  $< 0.05$  was considered significant.

# Results

## Patient population

From February 2004 until December 2006 799 patients were admitted with AMI at the Leiden University Medical Center and were treated according to the MISSION! protocol. Forty-seven (6%) patients died  $< 3$  months after the index event (before the gated SPECT



test). Causes of death included progressive heart failure (41/47, 87%), sudden cardiac death (4/47, 9%), and non cardiac death (2/47, 4%). Additional patients were excluded from the analysis due to incomplete gated SPECT data (n=76, 10%).

Accordingly, a total of 123 (15%) patients were excluded from the analysis. The remaining 676 were included and were followed for a median 32 months with an interquartile range (IQR) of 25 months (25<sup>th</sup> percentile) and 40 months (75<sup>th</sup> percentile).

### Study population

Baseline characteristics of the study population are reported in Table 1. Patients were mostly male (78%) and had a mean age of  $59 \pm 12$  years (range 22-88). Frequent risk factors for cardiovascular disease included current smoking (50%), a family history of cardiovascular disease (43%), and hypertension (31%). Nearly all patients underwent a primary PCI procedure (97%); the remaining patients received thrombolytic therapy. The left anterior descending coronary artery (LAD) was the culprit vessel in 48%. Mean symptom-onset to balloon time was  $288 \pm 1282$  minutes and the mean duration of hospitalization was  $3 \pm 2$  days. Medication at discharge was optimal and included aspirin in 95%, statin in 99%, ACE-inhibitor in 96%, clopidogrel in 99%, and  $\beta$ -blocker in 93%. When aspirin was not prescribed at discharge it was because anticoagulant treatment was prescribed instead (alongside clopidogrel treatment) in order to avoid increased risk of bleeding complications. Anticoagulants were prescribed for patients with atrial fibrillation, severely impaired LV function or LV aneurysm.

### Evaluating ICD eligibility

The mean LVEF, 3 months after the index event, was  $54 \pm 10\%$ , as derived from gated SPECT. Twenty-five (4%) patients had a LVEF  $\leq 30\%$ , warranting ICD treatment. LVEF between 30% and 35% was observed in 27 (4%) patients, of whom 7 demonstrated nsVT on 24-hour Holter monitoring, indicating them for defibrillator implantation. Of the remaining 624 (92%) patients with LVEF  $\geq 35\%$ , another 7 patients were candidates for ICD based on inducible VT/VF during electrophysiological (EP) testing. Additionally, one patient received an ICD due to late ( $>48$  hr) sustained VTs following the AMI and another 3 patients were treated with an ICD as a result of deterioration of LV function during the year following the index event.

Accordingly, 39 (6%) patients underwent ICD implantation, which was successful in all, without major complications.

### ICD group characteristics

As is shown in Table 1, patients indicated for ICD therapy had more extensive AMI, evidenced by a higher maximum troponin T (no ICD  $6.5 \pm 14.7 \mu\text{g/l}$ , ICD  $14.5 \pm 8.3 \mu\text{g/l}$ ,  $p < 0.001$ ) and creatine kinase (no ICD  $2185 \pm 1820 \mu\text{g/l}$ , ICD  $4403 \pm 2730 \mu\text{g/l}$ ,  $p < 0.001$ ).

**Table 1.** Patient characteristics.

	Total n=676	No ICD indication n=637	ICD indication n=39	p-value
<b>Demographics</b>				
Male	529 (78)	499 (78)	30 (77)	0.8
Age (years)	59 ± 12	59 ± 12	57 ± 13	0.2
<b>Medical History</b>				
Diabetes	69 (10)	66 (10)	3 (7)	0.8
Hyperlipidemia	149 (22)	144 (23)	5 (13)	0.2
Hypertension	212 (31)	199 (31)	13 (33)	0.7
Current smokers	336 (50)	314 (49)	22 (56)	0.4
Family History	291 (43)	273 (43)	18 (46)	0.7
Previous myocardial infarction	42 (6)	39 (6)	3 (7)	1.0
Previous PCI	29 (4)	26 (4)	3 (7)	0.5
Previous CABG	7 (1)	7 (1)	0 (0)	1.0
<b>Clinical characteristics</b>				
Culprit vessel LAD	325 (48)	294 (46)	31 (79)	<0.001
Killip class at admission				
I	632 (93)	595 (93)	37 (95)	1.0
II	23 (3)	22 (3)	1 (3)	1.0
III/IV	21 (3)	20 (3)	1 (3)	1.0
Troponine T max (μg/l)	6.9 ± 14.5	6.5 ± 14.7	14.5 ± 8.3	<0.001
CK (μg/l)	2309 ± 1947	2185 ± 1820	4403 ± 2730	<0.001
Body mass index (kg/m <sup>2</sup> )	26.4 ± 4.0	26.4 ± 4.0	25.3 ± 3.9	0.1
Symptom-onset-balloon (minutes)	288 ± 1282	287 ± 1317	303 ± 321	0.1
Primary PCI	655 (97)	620 (97)	35 (90)	0.2
Duration of hospitalization (days)	3 ± 2	3 ± 2	6 ± 5	<0.001
LVEF	54 ± 12	55 ± 11	31 ± 9	<0.001
<b>Medication at discharge</b>				
Aspirin	642 (95)	604 (95)	38 (97)	0.7
Statin	670 (99)	631 (99)	39 (100)	1.0
ACE-inhibitor	651 (96)	612 (96)	39 (100)	0.7
Beta-blocker	627 (93)	589 (93)	38 (97)	0.4
Clopidogrel	671 (99)	632 (99)	39 (100)	1.0
Anticoagulant	33 (5)	32 (5)	1 (3)	0.7

Furthermore, the LAD was more often the culprit vessel in the implanted group (no ICD 46%, ICD 79%,  $p<0.001$ ) and the duration of hospitalization was longer (no ICD  $3 \pm 2$  days, ICD  $6 \pm 5$  days,  $p<0.001$ ). No significant differences were observed in the occurrence of risk factors for cardiovascular disease, Killip class at admission, or medication at discharge. By definition, LV function was less in the ICD indicated group.

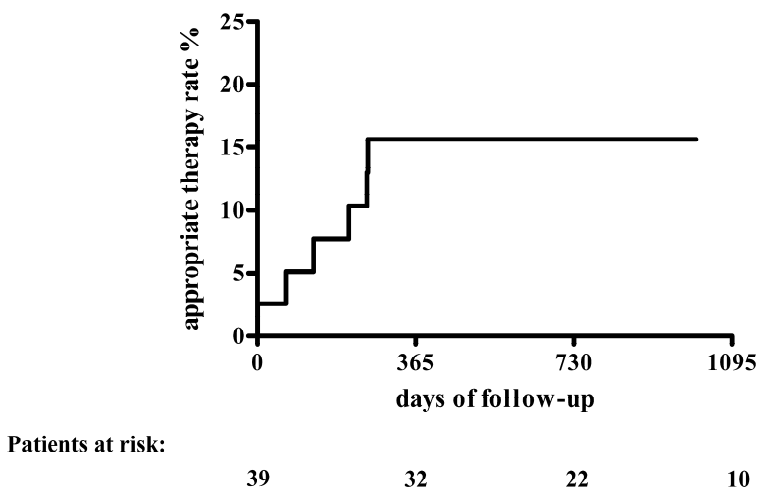
### Device therapy

During a median follow-up of the ICD treated population of 31 months (IQR 19 months and 42 months), 6 patients (15%) received appropriate device therapy for ventricular arrhythmias. Cumulative event rate was 8% (95% CI 0-16%) after 6 months, 15% (95% CI 4-27%) after one year, and 15% (95% CI 4-27%) after 3 years (Figure 2). No appropriate ICD discharge was observed in the implanted group with LVEF  $\geq 35\%$ . The group with LVEF  $\leq 30\%$  and those with LVEF between 30 and 35% did not demonstrate differences in the occurrence of appropriate ICD therapy (appropriate therapy in LVEF  $\leq 30\%$ : 19% vs. LVEF 30-35%: 29%,  $p=0.8$ ). Inappropriate therapy occurred in 3 of 39 (8%) ICD recipients.

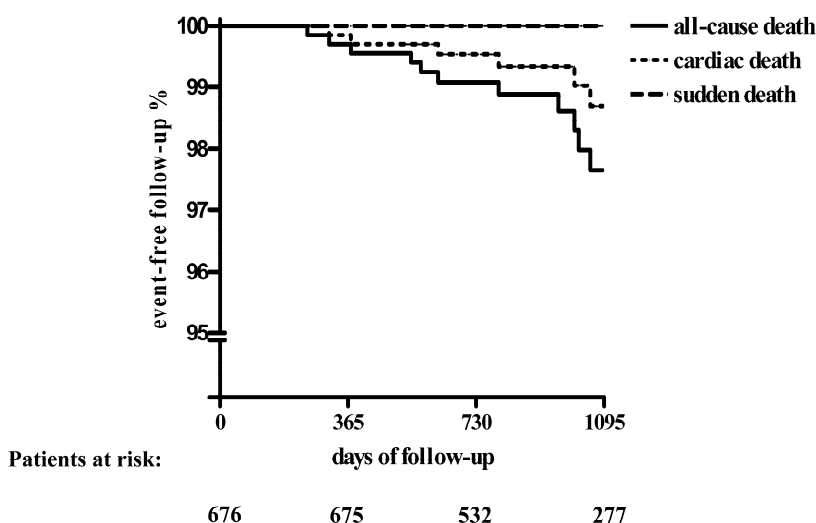
### Mortality

In the population, 12 patients (2%) died during follow-up. The 2 deaths occurring in the ICD treated group were related to progressive heart failure. Causes of death in the group without a defibrillator were progressive heart failure in 5 (50%), and non-cardiac in the other 5 (50%) patients. Of note, no cases of sudden death were observed. The 4 sudden deaths that occurred  $<3$  months after the acute MI happened due to uncertain, but likely cardiac etiology and took place after hospital discharge. They are best described as sudden unexplained death and took place at day 13, 16, 25 and 51 post-MI respectively. All four patients had a left ventricular ejection fraction calculated with biplane echocardiography as  $>35\%$ .

As is shown in Figure 3, the cumulative event-free follow-up after 3 years is 98% (95% CI 96-99%) for all-cause mortality, 99% (95% CI 98-100%) for cardiac mortality, and 100% for sudden death.



**Figure 2.** Kaplan-Meier curve for the cumulative rate of first appropriate ICD-therapy.



**Figure 3.** Kaplan-Meier curve for the event-free follow-up for mortality.

Multivariate cox regression analysis for mortality > 3 months after the index event revealed hyperlipidemia (HR 5.9, 95%CI 1.3-26.1), no aspirin use at hospital discharge (HR 8.4, 95%CI 1.5-46.0) and no ACE-inhibitor use at discharge (HR 7.9, 95%CI 1.2-50.4) as independent predictors of death. Age, gender, peak troponine T, ICD treatment, culprit target vessel, other risk factors for CAD (including hypertension, smoking, diabetes, history of MI, family history of coronary artery disease) and LVEF could not be identified as independent predictors of death.

## Discussion

In the assessment of an easy-to-use, structured protocol for the treatment of AMI patients and prevention of SCD, the findings can be summarized as follows: (1) Defibrillator implantation was warranted in only 6% of AMI patients; (2) No SCD occurred in the study population; (3) Compliance to evidence based medicine was excellent; (4) In ICD recipients, the cumulative event rate for appropriate ICD therapy was 15% at 3 years follow-up.

### Structured care for AMI patients

In past decades important insights have been gained into the management of patients with AMI. Measures such as rapid triage and quick access to reperfusion therapy can reduce treatment delay, prevent unnecessary infarct extension, and save lives.<sup>13,14</sup> Furthermore, the efficacy of early optimal pharmacological therapy has been recognized.<sup>15</sup> International guidelines on the optimal treatment of patients with AMI advocate early and aggressive

reperfusion strategies and recommend use of a combination of evidence-based medicine and support programs to stimulate a healthier lifestyle.<sup>7,9</sup> The degree of compliance to these guidelines has proven to be independently correlated to 1-year mortality after AMI.<sup>16</sup> We maximized the use of evidence-based medicine in daily clinical practice by developing and implementing a structured pre-hospital, in-hospital and out-patient AMI care program: MISSION!.<sup>7</sup> By implementing this protocol in daily clinical practice a high compliance to evidence based medicine was achieved which was reflected by the consistent prescription of optimal medication at discharge and follow-up

### Prevention of SCD

AMI survivors are at increased risk for sudden death from cardiac causes, in most patients due to a ventricular arrhythmia.<sup>1,17</sup> Thus far, LV function has proven to be a strong indicator for an increased risk of SCD.<sup>18-20</sup> Therefore, an important goal in reducing the risk of SCD in AMI patients is preserving LV function and the identification of patients with a low LVEF during follow-up. Prevention of severe LV dysfunction post-MI was addressed by focusing on minimal treatment delays, aggressive reperfusion therapy and the use of early and consistent optimal pharmacological therapy. Screening for SCD prevention commenced 3 months after the acute event in contrast to guidelines recommending a period of 40 days post MI. However, of all deaths occurring in the first 3 months after MI, the vast majority (46/47, 98%) occurred <40 days after AMI and therefore could not have been prevented by commencing screening after 40 days.

Nuclear imaging (gated SPECT) functioned as gatekeeper for risk stratification at 3 months post-MI. It facilitated the first step toward the detection of patients at increased risk for SCD. A previous study highlighted the importance of scintigraphic evaluation of patients with coronary artery disease.<sup>12</sup> Gated SPECT was able to detect patients with extensive scar tissue and LVEF  $\leq 30\%$ , which were at high risk for recurrence of ventricular arrhythmias. Patients that were excluded from the study population due to inconclusive gated SPECT results ( $n = 76$ , 10%) had either poor quality gated SPECT result (due to irregular heartbeat or attenuation artifacts) or did not undergo gated SPECT because they either refused protocol or were involved in other treatment protocols related to comorbidities. These patients did, however, all undergo echocardiography around the same time ( $\pm 3$  months after the acute event) and had estimated biplane ejection fractions above 35% which excluded them as likely candidates for ICD implantation. Had they been included in the final study population, the ratio of patients with an ICD indication versus patients without an ICD indication, would have probably been even smaller.

With implementation of the MISSION! protocol only 6% of patients had severe LV dysfunction warranting prophylactic ICD implantation and, more importantly, no SCD was observed in the study population.

## ICD indication

Large randomized trials have proven the beneficial effect of primary prevention ICD treatment in post-MI patients with a severely depressed LVEF.<sup>3,4,21</sup> Implementation of these findings in the current international guidelines significantly and rapidly expanded the indications for ICD implantation.<sup>5</sup> Correspondingly, while patients with LVEF 30-35% included in the present study were only considered eligible for ICD implantation when nsVT was observed on 24-hour Holter, the most current guidelines elevated ICD therapy for patients with LVEF <35% to a Class I indication regardless of nsVT.<sup>5</sup> Due to these rapid changes, clinicians have expressed concern that the population, eligible for primary prevention ICD treatment, is of such magnitude that provision of ICD therapy will strain financial resources and the pool of trained personnel.<sup>22</sup> Despite the in some ways more lenient ICD eligibility criteria as compared to current guidelines, the present study showed successfully that the proportion of post-MI patients potentially eligible for an ICD, when treated optimally and aggressively for AMI, is smaller than anticipated.<sup>23-25</sup> By using the pre-specified protocol merely 6% of AMI patients were identified as candidates for ICD implantation and no sudden deaths occurred in the study population.

## Device therapy

In the ICD treated population, the cumulative event rate for first appropriate ICD therapy at 3 years follow-up was 15% (95% CI 4-27%), which is lower than the event rates reported from trials like MADIT II (35%).<sup>26</sup> Possible reasons for this difference may be the smaller ICD patient group in the current study and the more preserved LV function in the current study's ICD treated population (LVEF  $31 \pm 9\%$ ), when compared to the MADIT II population (LVEF  $23 \pm 5\%$ ). Furthermore, in MADIT II 42% of patients who underwent coronary revascularization, had the procedure >60 months before enrollment in the study (median 107 months) whereas patients in the current study were risk stratified for ICD implantation <1 year post-MI. The low arrhythmic event rate in the population selected with the MISSION! protocol suggests a low rate of potential SCD in these patients.

As expected, appropriate ICD therapy was more common among patients with the lowest LVEF. In the group with most preserved LVEF ( $\geq 35\%$ ) none of the patients benefited from "life-saving therapy". Interestingly, all incidents of first appropriate therapy took place within the first year after ICD implantation, although the small number of ICD patients warrants caution in the interpretation of the data. An increased tendency for arrhythmic events in the first year after implant is consistent with prior reported data on ICD patients.<sup>27,28</sup> Nevertheless, results from the eight year follow-up of the MADIT II trial<sup>29</sup> provides substantial evidence for long term mortality benefit of ICDs and suggests that more long-term randomized trial data is needed to evaluate long-term benefit of ICD treatment. While ICD therapy was shown to result in significant survival benefits in the first four years of follow-

up in MADIT II, long-term analysis proved that ICD therapy was associated with additional life-saving benefits during the extended four to eight years of follow-up.

### Clinical implications

Using a standardized clinical protocol like the MISSION! algorithm can not replace personal judgment and individualized risk assessment, but can aid in applying evidence-based medicine in clinical practice and can help in achieving optimal results at the lowest possible cost, in terms of health, quality of life and finance. Interestingly, results of the multivariable analysis suggested that by applying ICD therapy to all patients with low LVEF, low LVEF in itself was no longer an independent predictor of death in the studied population. Of note, when removing the variable ICD treatment from the multivariable cox regression analysis LVEF did become significantly associated with death. This seems to confirm that ICD treatment is probably the reason why low LVEF was no longer associated with (all-cause) death in the study population after ICD screening. It remains possible that follow-up and relatively small patient numbers in the low LVEF group were not sufficient to see a significantly different distribution of (particularly heart failure related) deaths between the low LVEF and the high LVEF group.

The findings of the current study show that implementation of a guideline-based protocol for the treatment of AMI and structured prevention of SCD during follow-up reduces the rate of severe deterioration of LV function, and SCD during follow-up to a minimum. This suggests that such an easy-to-use, guideline-based protocol should be tailored to fit within daily clinical practice in the care for patients with AMI and during follow-up.

### Limitations

This is a single-center study based on the data of real clinical practice without the strict controlled conditions of a trial. Only patients with conclusive gated SPECT LVEF results were included in the study population.

Three-year event rates should be interpreted with caution due to relatively short follow-up and the small number of patients that received an ICD.

## Conclusion

After implementation of an aggressive optimized treatment protocol for AMI patients, prophylactic ICD implantation was warranted in only 6% of patients. Accordingly, an easy-to-use, guideline-based protocol tailored to fit within routine practice is able to reduce the rate of severe deterioration of LV function and SCD to a minimum and helps maintain ICD implantation rates within manageable proportions.

## References

1. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death. Structure, function, and time-dependence of risk. *Circulation* 1992; 85: 12-10.
2. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. *N.Engl.J.Med.* 1999; 341: 1882-90.
3. Moss AJ, Hall WJ, Cannom DS *et al.* Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N.Engl.J.Med.* 1996; 335: 1933-40.
4. Moss AJ, Zareba W, Hall WJ *et al.* Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N.Engl.J.Med.* 2002; 346: 877-83.
5. Epstein AE, Dimarco JP, Ellenbogen KA *et al.* ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices): Developed in Collaboration With the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *Circulation* 2008; 117: 2820-40.
6. Zipes DP, Camm AJ, Borggrefe M *et al.* ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death--executive summary: A report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death) Developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Eur.Heart J.* 2006; 27: 2099-140.
7. Antman EM, Anbe DT, Armstrong PW *et al.* ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation* 2004; 110: e82-292.
8. De BG, Ambrosioni E, Borch-Johnsen K *et al.* European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur.Heart J.* 2003; 24: 1601-10.
9. Van de WF, Ardissino D, Betriu A *et al.* Management of acute myocardial infarction in patients presenting with ST-segment elevation. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. *Eur.Heart J.* 2003; 24: 28-66.
10. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J.Am.Coll.Cardiol.* 2000; 36: 959-69.
11. Ioannidis JP, Trikalinos TA, Dianas PG. Electrocardiogram-gated single-photon emission computed tomography versus cardiac magnetic resonance imaging for the assessment of left ventricular volumes and ejection fraction: a meta-analysis. *J.Am.Coll.Cardiol.* 2002; 39: 2059-68.



12. van der Burg AE, Bax JJ, Boersma E, Pauwels EK, van der Wall EE, Schalij MJ. Impact of viability, ischemia, scar tissue, and revascularization on outcome after aborted sudden death. *Circulation* 2003; 108: 1954-9.
13. Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet* 1996; 348: 771-5.
14. De LG, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. *Circulation* 2004; 109: 1223-5.
15. Mukherjee D, Fang J, Chetcuti S, Moscucci M, Kline-Rogers E, Eagle KA. Impact of combination evidence-based medical therapy on mortality in patients with acute coronary syndromes. *Circulation* 2004; 109: 745-9.
16. Schiele F, Meneveau N, Seronde MF *et al.* Compliance with guidelines and 1-year mortality in patients with acute myocardial infarction: a prospective study. *Eur.Heart J.* 2005; 26: 873-80.
17. Myerburg RJ. Implantable cardioverter-defibrillators after myocardial infarction. *N.Engl.J.Med.* 2008; 359: 2245-53.
18. Risk stratification and survival after myocardial infarction. *N.Engl.J.Med.* 1983; 309: 331-6.
19. Rouleau JL, Talajic M, Sussex B *et al.* Myocardial infarction patients in the 1990s--their risk factors, stratification and survival in Canada: the Canadian Assessment of Myocardial Infarction (CAMI) Study. *J.Am.Coll.Cardiol.* 1996; 27: 1119-27.
20. Morishima I, Sone T, Tsuboi H *et al.* Risk stratification of patients with prior myocardial infarction and advanced left ventricular dysfunction by gated myocardial perfusion SPECT imaging. *J.Nucl.Cardiol.* 2008; 15: 631-7.
21. Olshansky B, Wood F, Hellkamp AS *et al.* Where patients with mild to moderate heart failure die: results from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). *Am.Heart J.* 2007; 153: 1089-94.
22. Hlatky MA, Mark DB. The high cost of implantable defibrillators. *Eur.Heart J.* 2007; 28: 388-91.
23. Al-Khatib SM, Anstrom KJ, Eisenstein EL *et al.* Clinical and economic implications of the Multicenter Automatic Defibrillator Implantation Trial-II. *Ann.Intern.Med.* 2005; 142: 593-600.
24. Barold HS. Using the MADIT II criteria for implantable cardioverter defibrillators-what is the role of the Food and Drug Administration approval? *Card Electrophysiol.Rev.* 2003; 7: 443-6.
25. Essebag V, Eisenberg MJ. Expanding indications for defibrillators after myocardial infarction: risk stratification and cost effectiveness. *Card Electrophysiol.Rev.* 2003; 7: 43-8.
26. Moss AJ, Greenberg H, Case RB *et al.* Long-term clinical course of patients after termination of ventricular tachyarrhythmia by an implanted defibrillator. *Circulation* 2004; 110: 3760-5.
27. Koller MT, Schaer B, Wolbers M, Sticherling C, Bucher HC, Osswald S. Death without prior appropriate implantable cardioverter-defibrillator therapy: a competing risk study. *Circulation* 2008; 117: 1918-26.
28. sheikh-Ali AA, Homer M, Maddukuri PV, Kalsmith B, Estes NA, III, Link MS. Time-dependence of appropriate implantable defibrillator therapy in patients with ischemic cardiomyopathy. *J.Cardiovasc.Electrophysiol.* 2008; 19: 784-9.
29. Goldenberg, I. Long-Term Outcome after Implantation of Cardioverter Defibrillator: An Eight Year Follow-Up Study of the Multicenter Automatic Defibrillator Trial II. Abstract Presented at Heart Rhythm 2009 Scientific Sessions May 14, 2009; Boston Massachusetts, United States.