Acute myocardial infarction treatment : from prehospital care to secondary prevention

Atary, J.Z.

Chapter 9

Structured care for patients after acute myocardial infarction: Sudden cardiac death prevention. Data from the Leiden MISSION! AMI study.

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

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

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ABSTRACT

Aim

To assess the number of patients in daily clinical practice that meets criteria for implantation of an implantable cardioverter defibrillator (ICD) following acute myocardial infarction (AMI) when treated according to an aggressive treatment protocol.

Methods

Patients were treated according to the MISSION! protocol. The protocol encompasses pre-hospital, in-hospital and out-patient clinical framework for the acute and chronic treatment of AMI patients and the decision making regarding primary prevention of Sudden Cardiac Death (SCD).

Results

A total of 676 consecutive AMI patients (78% male, mean age 59±12 years) treated according to the MISSION! protocol were included in this analysis. LVEF at 3 months was 54±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±8.3µg/l vs. 6.5±14.7µg/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

Aggressive treatment of AMI patients and close monitoring after the index event according to a standardized protocol, results in only a small number of patients becoming candidate for prophylactic ICD implantation. An easy-to-use protocol combining aggressive reperfusion, optimal medication and a risk stratification algorithm tailored to fit within routine practice may help to 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.[1] 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.[2-4] 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.[5;6] 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 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.[7] 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.[7] 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.[8-10] 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. 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.[11] 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

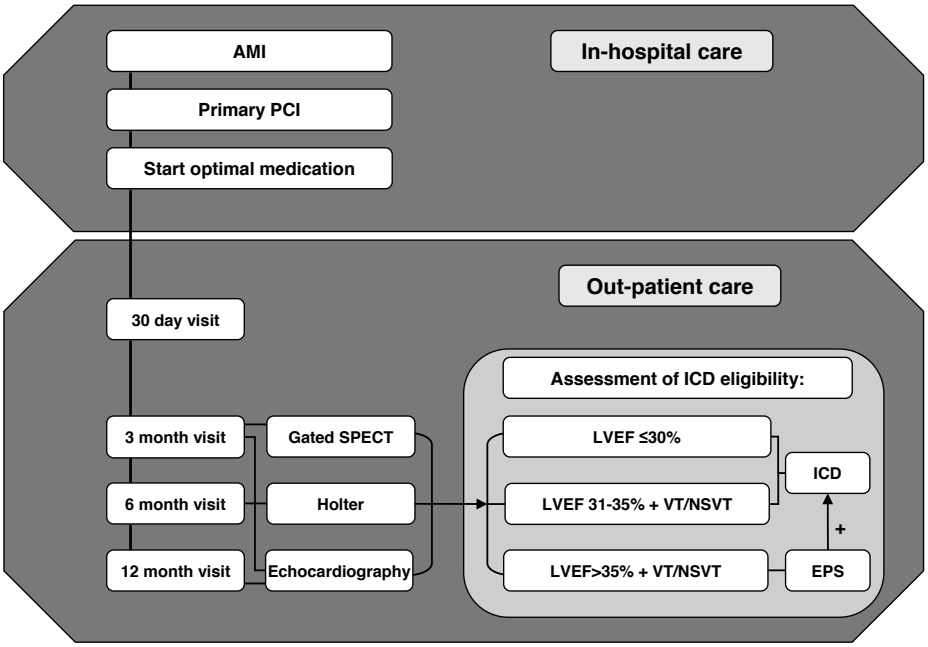

Figure 1. MISSION! protocol flowchart.

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 (^{99m} tetrofosmin gated myocardial perfusion SPECT) was used as the preferred method for the assessment of LVEF and was conducted at 3 months follow-up.[12;13]

ICD eligibility

The ICD screening part of the protocol was designed at a time when the guidelines for primary prevention of SCD were still evolving and was therefore based primarily on the large primary prevention ICD trials at the time.[2-4;6]

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.[4] 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.[2;3] Patients with a LVEF ≥35% and abnormal 24-hour Holter monitoring revealing nsVT were also referred for an electrophysiological test to evaluate indication for antiarrhythmic therapy. It should be noted that this protocol differs from the most current guidelines that elevated ICD therapy for patients with LVEF <35% to a Class I indication regardless of the presence of nsVT.

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, a secondary endpoint was appropriate defibrillator therapy (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 ± 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.

Table 1. Patient characteristics.

	Total n=676	No ICD indication n=637	ICD indication n=39	p-value
Demographics				
Male	529 (78)	499 (78)	30 (77)	0.8
Age (years)	59 ± 12	59 ± 12	57 ± 13	0.2
Medical History				
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
Clinical characteristics				
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/m²)	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
Medication at discharge				
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

Values are expressed as n (%) or mean ± standard deviation.
Hyperlipidemia= Total cholesterol ≥190 mg/dl or previous pharmacological treatment.
Hypertension = Blood pressure ≥140/90 mm Hg or previous pharmacological treatment.

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 of 32 months with an interquartile range (IQR) of 25 months (25th percentile) and 40 months (75th 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 ± 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. Medication at discharge was optimal. When aspirin was not prescribed at discharge anticoagulant treatment was prescribed instead (alongside clopidogrel treatment) in order to avoid increased risk of bleeding complications. Anticoagulants were prescribed in case of atrial fibrillation, severely impaired LV function or LV aneurysm.

Evaluating ICD eligibility

The mean LVEF, 3 months after the index event, was 54 ± 10%, as derived from gated SPECT. Twenty-five (4%) patients had a LVEF ≤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 ≥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, the statistically most significant differences between patients with an indication for ICD therapy and patients without an indication for ICD therapy were more extensive infarctions in the implanted group, evidenced by a higher maximum troponin T and creatine kinase, longer duration of hospitalization, and more anterior infarctions. 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

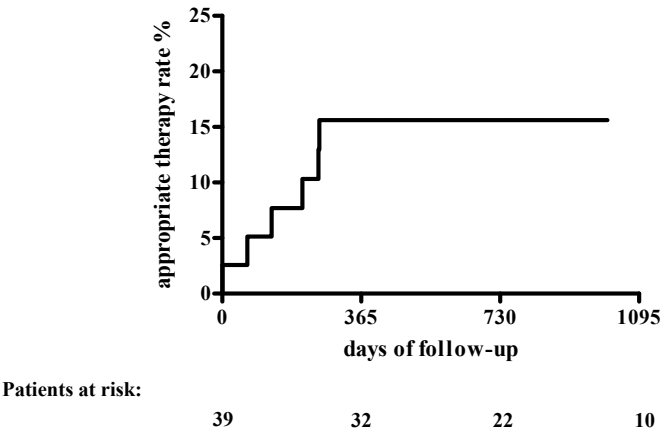

Figure 2. Kaplan-Meier curve for the cumulative rate of first appropriate ICD-therapy.

was observed in the implanted group with LVEF ≥35%. The group with LVEF ≤30% and those with LVEF between 30 and 35% did not demonstrate differences in the occurrence of appropriate ICD therapy (appropriate therapy in LVEF ≤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 of >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.

Multivariate cox regression analysis for mortality > 3 months after the index event revealed hyperlidemia (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.

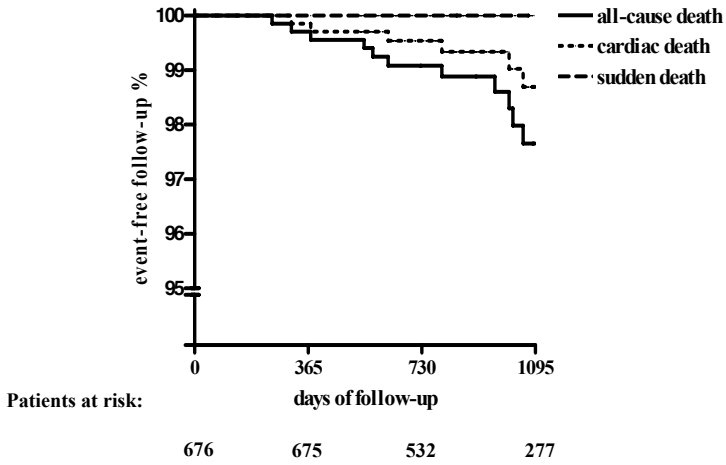

Figure 3. Kaplan-Meier curve for the event-free follow-up for mortality.

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.[14;15] Furthermore, the efficacy of early optimal pharmacological therapy has been recognized.[16] 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.[8;10] The degree of compliance to these guidelines has proven to be independently correlated to 1-year mortality after AMI.[17] The pre-hospital, in-hospital and out-patient AMI treatment protocol called MISSION! was therefore designed to increase use of evidence-based medicine in daily clinical practice.[7]

Prevention of SCD

AMI survivors are at increased risk for sudden death from cardiac causes, in most patients due to a ventricular arrhythmia.[1;18] Thus far, LV function has proven to be a strong indicator for an increased risk of SCD.[19-21] 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.

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.[13]

ICD indication

Large randomized trials have proven the beneficial effect of primary prevention ICD treatment in post-MI patients with a severely depressed LVEF.[3;4;22] Implementation of these findings in the current international guidelines significantly and rapidly expanded the indications for ICD implantation.[5] 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 the presence of nsVT.[5] 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.[23] 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.[24-26] 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%).[27] A possible explanation for this difference is 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 ± 9%), when compared to the MADIT II population (LVEF 23 ± 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 frequent in patients with lowest LVEF. In the group with a more preserved LVEF (≥35%) none of the patients had appropriate ICD 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.[28;29] The low percentage of patients benefiting from appropriate ICD therapy demonstrates that despite use of a structured protocol, accurate SCD risk stratification is difficult. Nevertheless, results from the eight year follow-up of the MADIT II trial [30] provides substantial evidence for long term mortality benefit of ICD therapy.

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 ICD implantation in all patients with low LVEF, reduced the value of low LVEF as independent predictor of death. When ICD treatment was removed from the multivariable cox regression analysis low LVEF did regain its significant association with increased death rate. This seems to confirm that ICD treatment is probably the reason why low LVEF was not associated with (all-cause) death in the study population after the 3-month screening period. It remains possible that relatively short follow-up and 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.

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 in order to avoid confusion about the protocol. Excluded patients (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. They did however undergo echocardiography at 3 months follow-up and had estimated biplane ejection fractions above 35% which excluded them as likely candidates for ICD implantation. Their inclusion would therefore not have changed the main outcome of the study.

Of note, screening for SCD prevention commenced 3 months after the acute event in contrast to current 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. Finally, 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

Aggressive treatment of AMI patients and close monitoring after the index event according to a standardized protocol, results in only a small number of patients becoming candidate for prophylactic ICD implantation. An easy-to-use protocol combining aggressive reperfusion, optimal medication and a risk stratification algorithm tailored to fit within routine practice may help to maintain ICD implantation rates within manageable proportions.

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