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Immediate Risk-Stratification Improves Survival (IRIS): study protocol

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Abstract Background   To date, the implantable cardioverter-defibrillator (ICD) has been shown to be effective for primary prevention of sudden cardiac death only in selected groups of patients in the chronic phase after myocardial infarction.
Methods and results   The Immediate Risk-Stratification Improves Survival (IRIS) Study compares ICD therapy with no ICD therapy in selected high risk patients early after myocardial infarction. Special emphasis is placed on optimal acute and long term medical therapy in all patients including metoprolol CR/ZOK. The hypothesis is tested that use of the ICD reduces overall mortality. For that purpose, consecutive acute ST elevation or non-ST elevation myocardial infarction patients are collected in a registry. From this denominator, patients are screened, and enroled early after myocardial infarction (day 5 to day 31) if they exhibit both a reduced left ventricular ejection fraction $\leq 40\%$ and a heart rate ≥ 100 bpm on the first available electrocardiogram (criterion I), or non-sustained ventricular tachycardia at a rate ≥ 150 bpm during Holter (criterion II).
Conclusions   IRIS is a large scale prospective, randomized trial to evaluate the benefit of ICD therapy for reduction of total mortality in patients considered at high risk of sudden death early after acute myocardial infarction.
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Introduction

Despite the general improvement of outcome in survivors of acute myocardial infarction, sudden cardiac death mostly due to ventricular tachyarrhythmia, is held responsible for approximately 20−50% of all fatalities still occurring in this population [1−5]. Therefore, prevention of sudden cardiac death after myocardial infarction remains a goal of paramount importance [6]. Previous drug studies demonstrated that, by the use of class I antiarrhythmic drugs or *d*-sotalol, the outcome may be worsened instead of improved [7,8]; amiodarone, while not being associated with excess mortality, also failed to improve outcome in two large scale postmyocardial infarction trials [3,9]. Therapy with the implantable cardioverter-defibrillator (ICD), on the other hand, has in the meantime been established for secondary prevention in patients after cardiac arrest [10−12]. The question, therefore, arose whether the ICD might also be used for primary prevention of sudden death after myocardial infarction.

As a first proof of concept, the Multicenter Automatic Defibrillator Implantation Trial, indeed, showed that this is possible [13]. In essence, a highly selected group of patients with myocardial infarction in the past, left ventricular ejection fraction below 35% and non-sustained ventricular tachycardia was studied. No attempt was undertaken to assess the denominator of patients from whom the very small sample size of 196 patients was drawn.

The results of the Multicenter Automatic Defibrillator Implantation Trial were confirmed by the Multicenter Unsustained ventricular Tachycardia Trial in 1999 [14]. While several drawbacks of the former study were eliminated, the Multicenter Unsustained Tachycardia Trial also included only few patients early after myocardial infarction. Very recently, the Multicenter Automatic Defibrillator Implantation Trial II demonstrated a significant survival benefit of a prophylactically implanted defibrillator in patients with remote myocardial infarction selected exclusively on the basis of a reduced left ventricular ejection fraction of 0.30 or less [15]. As in the previous two studies, patients with acute myocardial infarction were not included.

Contrary to these three studies, the Immediate Risk-Stratification Improves Survival (IRIS) Study addresses the question of a survival benefit by ICD implantation in selected, asymptomatic survivors of acute myocardial infarction. Special emphasis is placed on determination of the denominator of

patient enrolment by a registry. In addition, infarct treatment is individually optimized for all study patients, consisting of acute recanalization of the infarct vessel either by PTCA/stent implantation or systemic lysis, and application of baseline medical therapy including aspirin, beta blockers, ACE inhibitors and statins during the acute phase as well as follow-up [16,17].

Study objectives

The primary objective of IRIS is to assess whether prophylactic implantation of an ICD will lead to a significant reduction of overall mortality in survivors of acute myocardial infarction (day 5 to day 31). Patients will be randomly assigned in a one-to-one ratio to receive an ICD or not. Secondary objectives of the study are to compare sudden cardiac death, non-sudden cardiac death, non-cardiac death, arrhythmic episodes such as ventricular fibrillation, successful resuscitation, symptomatic sustained VT (lasting longer than 30 s), serious cardiac and extracardiac events such as recurrent myocardial infarction, PTCA, coronary bypass operation, stroke, hospital readmissions of all causes, costs incurred, and quality of life. In patients receiving an ICD, the adequacy of ICD interventions (antitachycardia pacing and shocks) as well as ICD-associated complications will be determined. Cause of death will be classified by a validation committee in a blinded manner as sudden, non-sudden cardiac, and non-cardiac.

Study design

Early risk stratification

Even with earlier and improved attempts of reperfusion, approximately 15% of patients die in the first weeks after acute myocardial infarction, and an additional 10% die in the first year [18,19]. ICD implantation performed one month or later after acute MI as performed in the Multicenter Automatic Defibrillator Implantation Trials I and II may be too late for many patients. Therefore, early risk stratification within the hospital appears promising to identify more patients at risk of sudden death after myocardial infarction.

Simple risk stratification

Non-invasive methods will be used, which are routine in most hospitals where patients with acute

myocardial infarction are treated: (1) resting ECG (for determination of heart rate); (2) echocardiography (for determination of left ventricular ejection fraction); (3) 24-h-Holter (for documentation of non-sustained ventricular tachycardia).

1. Heart rate on first available ECG: In a report on 1807 infarct patients, one-year mortality in patients with a heart rate more than 110 bpm was markedly higher than in patients with normal heart rate in the admission ECG (48% versus 15% [20]). Similarly, one-year mortality in patients with acute myocardial infarction was 11.8% in those in whom heart rate in the admission ECG was more than 90 bpm, compared with only 4.3% in patients with a heart rate of less than 70 bpm [21]. In this study, the prognostic value of heart rate proved independent of other risk factors in a multivariate analysis.

2. Left ventricular ejection fraction: Several studies in patients after acute myocardial infarction have shown that left ventricular ejection fraction predicts outcome. Reduced left ventricular ejection fraction in most of these studies proved to be the most consistent independent risk factor for cardiac death in multivariate analyses [1,22,23].

3. Non-sustained ventricular tachycardia: The value of spontaneous non-sustained ventricular tachycardia for prediction of sudden cardiac death has been confirmed recently [24]. In the Munich and Berlin Infarction Study, a Holter-recording was performed in 1202 postinfarct patients before hospital discharge. Fourteen percent of patients with documented non-sustained ventricular tachycardia in that recording ($\geq$ 3 consecutive ventricular premature beats) either died suddenly or developed symptomatic sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) within the next two years, compared with only 3.5% of patients without documentation of non-sustained ventricular tachycardia [4]. The predictive value of rapid non-sustained ventricular tachycardia was even more impressive: if the rate of non-sustained ventricular tachycardia was $\geq$ 150 bpm (prevalence 3.7%), the rate of either sudden death or sustained ventricular tachyarrhythmias (VT or VF) was 22%, the relative risk being six times higher than the risk of patients without demonstration of rapid non-sustained ventricular tachycardia [25]. Interestingly, prediction of total mortality by this criterion was improved only 3.3 times in the same population, suggesting a rather specific

role for rapid non-sustained ventricular tachycardia to predict sudden death and sustained ventricular tachyarrhythmias [25]. The predictive value of rapid non-sustained ventricular tachycardia was confirmed in the post-infarction study population of the St. Georges Hospital Medical School London (M. Malik, personal communication).

Eligibility

Patients are included with first or repeated ST elevation or non-ST elevation myocardial infarction within 31 days, if they demonstrate either one or both of the following criteria:

Criterion I: Heart rate $\geq$ 100 bpm on the first available ECG (within 48 h after myocardial infarction) and ejection fraction $\leq$ 40% (day 5 to day 31).

Criterion II: Non-sustained ventricular tachycardia during Holter with a heart rate $\geq$ 150 bpm (day 5 to day 31).

Acute ST elevation myocardial infarction requires all of the following three criteria:

1. Chest pain: More than 20 min or equivalent symptoms.
2. ECG: $\geq$ 0.1 mV ST elevation in two neighbouring extremity leads, and/or $\geq$ 0.2 mV ST elevation in two neighbouring chest leads, or left bundle branch block, or new appearance of Q-waves ($\geq$ 0.03 s).
3. Enzymes: CK-elevation ($\geq$ twice the upper normal limit) and CK-MB $>$ 6%, or troponin positive.

Acute non-ST elevation myocardial infarction requires both of the following criteria:

1. Chest pain: More than 20 min or equivalent symptoms.
2. Enzymes: troponin positive.

While in a prior version of our protocol only transmural myocardial infarctions were allowed to be included, the recent ESC/ACC Consensus Document (Myocardial Infarction Redefined) [26] includes both ST elevation infarction (transmural infarction) and non-ST elevation infarcts. Accordingly, the protocol was adapted to include both types of infarction from June 1, 2002.

A flow chart of patient recruitment is depicted in Fig. 1. The study protocol has been approved by all local ethical committees of the participating centres.
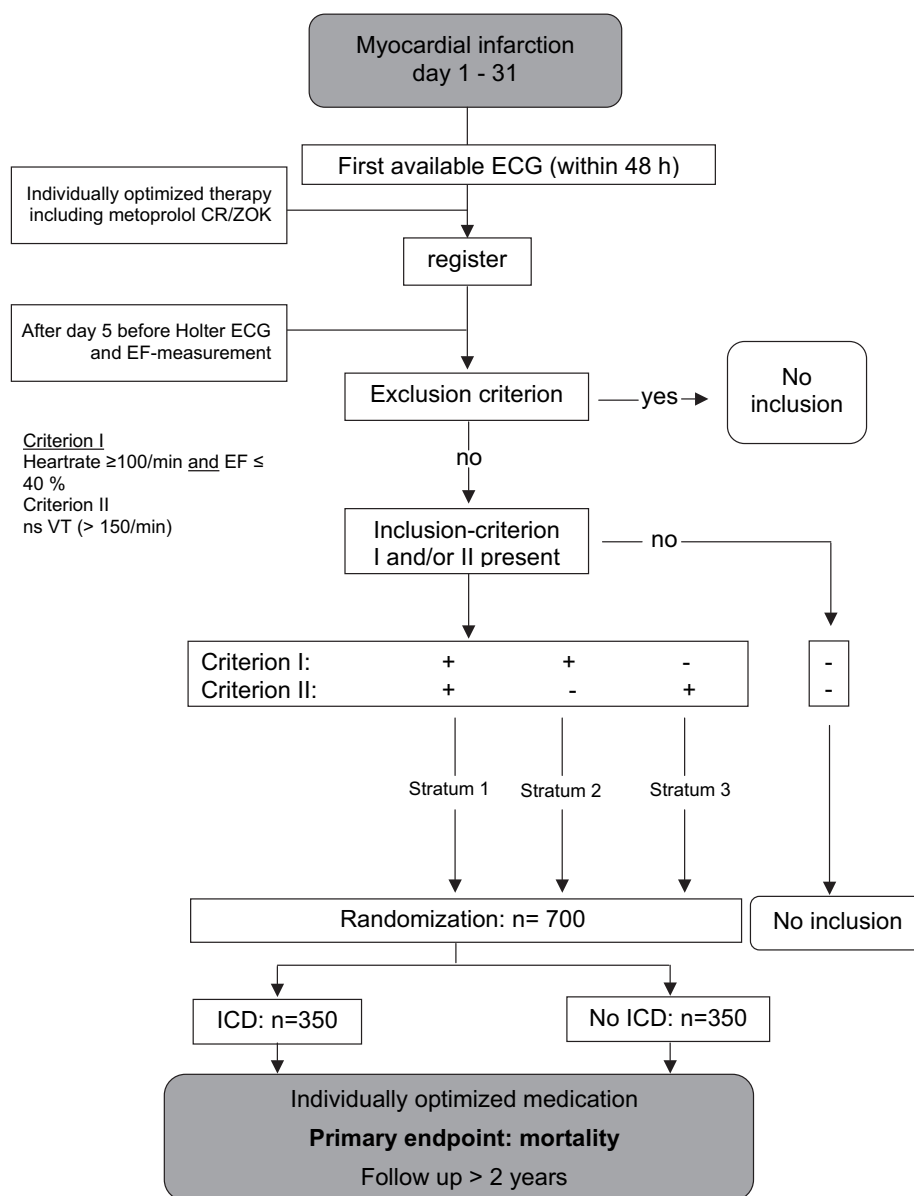
Abbreviations: EF= ejection fraction; ns VT= non-sustained ventricular tachycardia

Figure 1 Flow chart of IRIS.

Exclusion criteria are as follows:

- age younger than 18 or older than 80 years;
- haemodynamically relevant ventricular arrhythmias before index infarction or more than 48 h later, needing treatment;
- drug refractory heart failure (New York Heart Association IV);
- myocardial infarction older than 31 days;
- no ECG documentation within the first 48 h after onset of chest pain;
- indication for coronary bypass surgery before study entry;
- psychiatric disorders;
- severe concomitant disease;
- patients with right-sided artificial heart valves;
- poor compliance;
- participation in other trials;
- unstable clinical condition;
- pregnancy;
- no patient consent.

All consecutive patients with acute myocardial infarction in the participating centres are listed in a registry and checked first for exclusion criteria (see above), followed by evaluation of inclusion

criteria. If none of the exclusion criteria and at least one of the inclusion criteria are met and the patient agrees to participate, randomization is performed by the data coordinating centre (PFK, Martinsried/Munich).

The study is being conducted in 80 hospitals all over Germany and hospitals in other countries, e.g. Austria, Czech Republic, Hungary, Poland and Sweden will recruit patients.

ICD implantation and programming

ICD implantation is performed as soon as possible after randomization. Single chamber ICD models of Medtronic (GEM™II, Model 7229 or successor model) will be used. All products use active can™-technology and are suited for pectoral implantation. Defibrillation testing requires that two consecutive episodes of induced ventricular fibrillation are terminated with an energy at least 10 J less than the maximal energy of the ICD. After surgery, the device is programmed for detection and therapy of ventricular fibrillation, detection of ventricular tachycardia, and stimulation for bradycardia (VVI 40 per minute). The detection interval for ventricular fibrillation is set at 300 ms, with 18 out of 24 intervals to be detected; delivered shock energy is set at the maximal value. The detection interval for ventricular tachycardia is set at 400 ms with 32 intervals to be detected, the stability criterion is set at 30 ms, and electrogram width criterion is set ON. Antitachycardia pacing is initially not programmed.

Follow-up

All patients have follow-up at 3 and 6 months after randomization, thereafter at intervals of 6 months up to 2 years. At these visits, a clinical evaluation is performed as well as an ICD interrogation. Changes in medication, adverse events, hospital stays, etc. will be documented. All adverse events are classified according to their intensity and severity and procedures to treat these events as well as their association with the ICD. The death of a patient will be immediately reported to the data coordinating centre. The cause of death will be classified as sudden cardiac, non-sudden cardiac, non-cardiac and unknown, depending on all information available (witnesses, family members, circumstances surrounding death, hospital records, autopsy reports). Sudden cardiac death is defined as cardiac death within minutes after the onset of acute symptoms, death as a result of documented cardiac arrhythmia, and unwitnessed death, which occurs

unexpectedly and without recognizable causes (e.g. during sleep). A validation committee blinded to the randomization process will review all available data and determine the cause of death.

Statistical methods

Sample size calculation

The primary efficacy parameter is the overall survival measured by the time from randomization to death. Based on our own patient registries [25,31], the mortality rate in the control group is expected to be approximately 30%. For calculation, a mortality of 16% is assumed for the first and the second year. Half of these fatalities are caused by ventricular tachyarrhythmias, and ICD therapy is able to prevent 70% of these arrhythmia episodes. Furthermore, it is assumed that 1% of all patients receiving an ICD die before or during implantation. As a consequence, the mortality rate after two years will be 29.4% in the control group, and 20.6% in the ICD group, respectively (i.e., relative reduction of risk of 30%).

The comparison of the survival rates between the ICD group and the control group will be evaluated by a two-sided log-rank test. With a significance level of $\alpha = 0.05$, a power of 80%, an enrolment period of 2.5 years, a minimal follow-up period of 2 years, and a yearly drop-out rate of 1%, a total of 700 patients is necessary in the two treatment arms (350 patients each).

A total of 20,000 patients after acute myocardial infarction have to be screened. This is based on the assumptions that 25% of all AMI patients will have one or more exclusion criteria, 6% of all screened patients will fulfil one or both inclusion criteria, and that about 22% of them will finally not agree to participate in the study (see calculation of sample size in Fig. 2).

Randomization

Eligible patients with written informed consent are enroled into the study. The inclusion criteria I and II are used for the risk stratification (three strata: only criterion 1, only criterion II and both criteria). The randomization is performed via the data coordinating centre and considers the risk stratification ensuring a balanced number of patients with ST elevation and non-ST elevation infarction between ICD and control group within these strata.

Statistical analysis

Approximately 200 deaths are expected in the study. One administrative analysis will be performed after 20 deaths (10%), and three interim
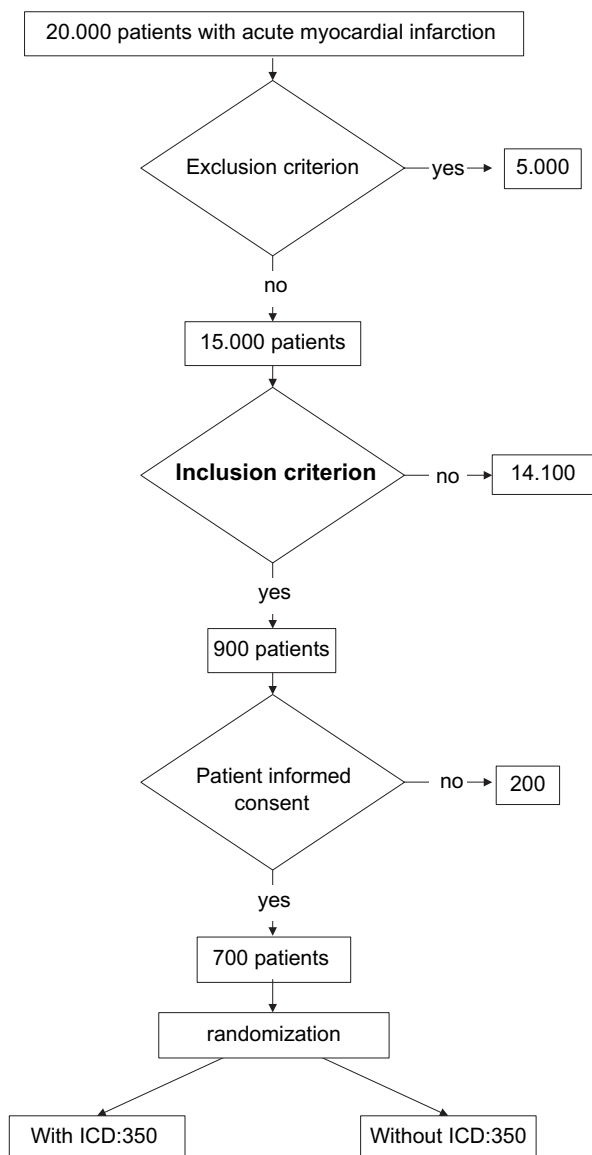
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        ┌──────────────────────────────────────────┐
        │ 20.000 patients with acute myocardial infarction │
        └──────────────────────────────────────────┘
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                  ◇ Exclusion criterion ◇ ── yes → ┌───────┐
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                  │ 15.000 patients │
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                          │                        │ 14.100 │
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          │ With ICD:350  │  │ Without ICD:350  │
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Figure 2   Calculation of sample size.

analyses will be performed during the study after occurrence of 50 (25%), 100 (50%), and 150 (75%) deaths. In order to keep the overall significance level to 0.05, the predefined interim analyses and the final analysis will be performed with individual significance levels according to the sequential plan of O'Brien-Fleming. An independent Data and Safety Monitoring Board (DSMB) will decide about the continuation of the study based on the interim results.

The primary analysis compares the mortality rates between ICD and control group. Among others, a secondary objective will be to compare the treatment groups within the risk-stratified subgroups (strata 1—3, ST elevation and non-ST elevation infarction) for the purpose of trend analysis.

Quality of life

For determination of quality of life, the SF-36 will be used. This questionnaire is answered by the patient during the first follow-up visit, and then yearly (i.e., 12, 24, etc. months after randomization). During these visits, the questionnaire is always completed before clinical examination.

Study organization

The steering committee consists of six scientists with clinical and methodological expertise as well as one (non-voting) member from the sponsors. A board for data validation and evaluation of adverse events, and an external Data and Safety and Monitoring Board report to the steering committee. The data coordinating centre (PFK, Martinsried/ Munich) is responsible for the case report forms, data base, process of randomization, monitoring and data assessment as well as reports on adverse events, interim analyses and a final statistical report to the steering committee.

Discussion

Rationale of performing a post-infarction trial

Prevention of sudden cardiac death after myocardial infarction remains a goal of paramount importance. While the Multicenter Automatic Defibrillator Trial published in 1996 showed as a first proof of concept that this is possible with an ICD, it does not really apply to acute myocardial infarction: patients with myocardial infarction within the past three weeks were excluded from enrolment, and the time interval between myocardial infarction and study entry was more than 6 months in 75—76% of the cases.

In the Multicenter UnSustained Tachycardia Trial, only 18% of the study population was included in the time frame between day 4 and 1 month after the most recent MI, 38% within 1 year, and 52% after 3 years [27].

Finally, patients with myocardial infarction within 1 month were not included in the Multicenter Automatic Defibrillator Implantation Trial II, and the interval between the most recent myocardial infarction and enrolment was more than 6 months in 87—88% of cases [15].

Assuming that the risk of dying suddenly is highest in the first weeks and months after MI, it can be conceived that many more patients could be

protected by implantation of an ICD early after myocardial infarction. On the other hand, the risk of ICD implantation might be increased early after MI. While a pilot study on 33 patients seems to indicate that this is not the case [28], the safety of the procedure must be demonstrated in a larger group of patients. All of this culminates in the urgent need for a large prospective randomized trial early after myocardial infarction.

Special features of IRIS

Three trials are presently running with the aim of determining the role of the ICD for primary prevention of sudden death early after myocardial infarction.

The Defibrillator in Acute Myocardial Infarction Trial uses for inclusion reduced left ventricular function (EF $\leq 0.35\%$) and impairment of cardiac autonomic function by depressed heart rate variability (standard deviation of normal-to-normal R—R intervals SDNN ≤ 70 ms, or elevated average 24-h heart rate measured as mean 24-h R-R interval ≤ 750 ms by Holter monitoring) [29]. The Beta Blocker Strategy plus Implantable Cardioverter Defibrillator Trial again uses reduced left ventricular function (EF $\leq 35\%$) and SDNN <70 ms, ≥ 10 premature ventricular contractions per hour or an abnormal signal-averaged ECG; tolerance of beta blocker therapy is a prerequisite for inclusion, presence of non-sustained ventricular tachycardia a criterion for exclusion [30].

As a special feature, IRIS uses two separate criteria.

Criterion I, the combination of resting heart rate on admission of ≥ 100 bpm and left ventricular ejection fraction $\leq 40\%$, was prospectively evaluated in two post-infarction registries in Germany led by two of the authors (J.S. and K.S.) [Post-Infarction Risk Stratification Study, $n = 1029$; Maximal Individual Therapy in Acute Myocardial Infarction (MITRA), $n = 5967$]. In the first, the positive value to predict 1-year mortality was 27% [31], in the second 43%, with a prevalence of these abnormal findings in 7.8% of patients studied.

Criterion II is derived from another acute post-infarction study performed by another two authors of this manuscript (G.S. and D.A.) [4]. While programmed electrical stimulation provided prognostic information in addition to Holter monitoring and determination of left ventricular ejection fraction, this invasive evaluation appeared not to be generally applicable in this population: so it was not performed in more than 50% of patients who had exhibited an abnormal finding in either Holter

monitoring or determination of ejection fraction for a number of reasons, such as clinical condition deemed unstable, CABG planned, and refusal of the patient [4]. Looking for equally good, non-invasive, cheap and simple tools for risk stratification, it was noted that the presence of rapid non-sustained ventricular tachycardia fulfils these requirements. Possibly because rapid non-sustained ventricular tachycardia contains prognostic information not only about triggers, but also about the capability of sustaining rapid ventricular arrhythmias, this criterion—independent of left ventricular ejection fraction and separate from criterion I—is a very promising predictor of arrhythmic mortality that may be prevented by an ICD.

Acknowledgements

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