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Defibrillator Implantation Early after Myocardial Infarction

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ABSTRACT

BACKGROUND

The rate of death, including sudden cardiac death, is highest early after a myocardial infarction. Yet current guidelines do not recommend the use of an implantable cardioverter–defibrillator (ICD) within 40 days after a myocardial infarction for the prevention of sudden cardiac death. We tested the hypothesis that patients at increased risk who are treated early with an ICD will live longer than those who receive optimal medical therapy alone.

METHODS

This randomized, prospective, open-label, investigator-initiated, multicenter trial registered 62,944 unselected patients with myocardial infarction. Of this total, 898 patients were enrolled 5 to 31 days after the event if they met certain clinical criteria: a reduced left ventricular ejection fraction (≤40%) and a heart rate of 90 or more beats per minute on the first available electrocardiogram (ECG) (criterion 1: 602 patients), nonsustained ventricular tachycardia (≥150 beats per minute) during Holter monitoring (criterion 2: 208 patients), or both criteria (88 patients). Of the 898 patients, 445 were randomly assigned to treatment with an ICD and 453 to medical therapy alone.

RESULTS

During a mean follow-up of 37 months, 233 patients died: 116 patients in the ICD group and 117 patients in the control group. Overall mortality was not reduced in the ICD group (hazard ratio, 1.04; 95% confidence interval [CI], 0.81 to 1.35; P=0.78). There were fewer sudden cardiac deaths in the ICD group than in the control group (27 vs. 60; hazard ratio, 0.55; 95% CI, 0.31 to 1.00; P=0.049), but the number of non-sudden cardiac deaths was higher (68 vs. 39; hazard ratio, 1.92; 95% CI, 1.29 to 2.84; P=0.001). Hazard ratios were similar among the three groups of patients categorized according to the enrollment criteria they met (criterion 1, criterion 2, or both).

CONCLUSIONS

Prophylactic ICD therapy did not reduce overall mortality among patients with acute myocardial infarction and clinical features that placed them at increased risk. (ClinicalTrials.gov number, NCT00157768.)

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Despite the general improvement in outcomes among survivors of acute myocardial infarction the rate of death, including sudden cardiac death, remains highest in the weeks after the event.[1,2] Sudden cardiac death due to ventricular tachyarrhythmias accounts for approximately 20 to 50% of all deaths in this population.[3-5] Therefore, prevention of sudden cardiac death after myocardial infarction remains an important goal. With the exception of beta-blockers, antiarrhythmic drugs do not reduce this risk. Several randomized trials have shown that an implantable cardioverter–defibrillator (ICD) can reduce mortality both among patients who have had sustained ventricular tachyarrhythmias[6] and among selected patients who have a depressed left ventricular ejection fraction (LVEF) without ventricular arrhythmias.[7,8] However, guidelines based on the results of these trials — including one that showed a neutral effect of defibrillator implantation early after myocardial infarction[9] — recommend that implantation of an ICD for the primary prevention of sudden death be withheld for at least 40 days after an acute myocardial infarction.

The Immediate Risk Stratification Improves Survival (IRIS) trial was based on the hypothesis that early implantation of an ICD, as compared with optimal medical therapy, would improve survival among patients with acute myocardial infarction and predefined markers of elevated risk. LVEF, heart rate (as determined on the admission electrocardiogram [ECG]), and the occurrence of rapid, nonsustained ventricular tachycardia were the factors used to determine each patient's level of risk.[3,10-16]

Methods

Patient Population and Randomization

Between June 9, 1999, and October 15, 2007, the records of 62,944 patients who had an acute myocardial infarction with or without ST-segment elevation were collected in a registry from which our study population would be derived. Exclusion criteria consisted of the presence of ventricular arrhythmias that occurred before the index infarction or more than 48 hours after the event and that required treatment, New York Heart Association (NYHA) class IV drug-refractory heart failure, an interval of more than 31 days between myocardial infarction and presentation, no ECG documentation within the first 48 hours after the onset of chest pain, an indication for coronary-artery bypass surgery before study entry, a psychiatric disorder, severe concomitant disease, a history of poor compliance with treatment, either the inability to participate in this trial or current participation in another trial, and an unstable clinical condition. After 26,445 patients had been excluded on the basis of these criteria, 36,499 were screened for inclusion.

Patients had to meet at least one of two criteria for inclusion. Criterion 1 was a heart rate of 90 beats per minute or more on the first available ECG (obtained within 48 hours after the myocardial infarction) and an LVEF of 40% or less (on one of days 5 to 31 after myocardial infarction). Criterion 2 was nonsustained ventricular tachycardia consisting of three or more consecutive ventricular premature beats during Holter ECG monitoring, with a heart rate of 150 beats per minute or more (on days 5 to 31).

A total of 1311 eligible patients, 18 to 80 years of age, met one or both criteria for inclusion in the study; 409 patients declined to participate, and written consent was missing for 4. The remaining 898 patients (86% of whom were still in the hospital) were randomly assigned to a study treatment — 445 to receive an ICD and 453 to receive medical therapy alone — at a mean (±SD) of 13±7 days after infarction.

Study Design

The primary objective of IRIS was to assess overall mortality in the two patient groups; secondary end points included sudden cardiac death, nonsudden cardiac death, and noncardiac death. The design of this European investigator-initiated trial has been described previously.[17] A group-sequential design according to O'Brien and Fleming,[18] with three interim analyses, after 50, 100, and 150 events, was selected initially and was described in the study protocol. However, in its first session, the data and safety monitoring board advised us to replace this strategy with the corresponding Lan–DeMets approach,[19,20] which is based on the same alpha-spending function, to allow deviations from the fixed numbers of events. On January 9, 2005, this change was made as an addendum to the protocol.

The study protocol was approved by the local

ethics committees at all 92 participating centers, and all the patients provided written informed consent. To increase recruitment, two modifications were made during the course of the study: patients with non–ST-elevation myocardial infarction were included as of June 1, 2002; and the qualifying heart rate on the first available ECG as part of criterion 1 was reduced from 100 or more to 90 or more beats per minute beginning on October 14, 2004.

Of the patients randomly assigned to the ICD group, 78% received Medtronic models of the GEM family, 11% Micro Jewel II, 8% Maximo, and 3% Marquis. Of this group, 81% received a single-chamber ICD, and a Fidelis lead was used in 21% of the patients. The protocol required two consecutive terminations of ventricular fibrillation at 10 J below the maximum ICD output and single-chamber ventricular demand (VVI) pacing at 40 beats per minute, with maximal shock energy turned on for treatment of ventricular fibrillation (threshold for treatment, ≥200 beats per minute) and treatment for ventricular tachycardia turned off initially.

After discharge, patients were followed at intervals of 3 and 6 months after randomization and at 6-month intervals thereafter.

The academic authors designed the trial, collected and analyzed the data, and wrote the report. The sponsors (Medtronic and AstraZeneca) were informed about the study outcome after the evaluation had been completed. Apart from an opportunity to review and provide comments about the predefined final-analysis plan and the manuscript, neither sponsor had a role in the study design, data analysis, or interpretation of the results.

CLASSIFICATION OF DEATHS

An adverse-event committee that was unaware of the treatment assignments classified the 233 fatal events as definitely cardiac (148 cases), unknown (46 cases), or definitely noncardiac (39 cases) and as sudden or nonsudden. For the purpose of analysis, patients whose events were classified as both definitely cardiac and unknown were combined under the category of presumably cardiac death. A death, either in the hospital or out of the hospital, was assumed to be a sudden cardiac death if a cardiac death occurred within minutes after the onset of acute symptoms, resulted from a documented cardiac arrhythmia, or was not witnessed and occurred unexpectedly and without recognizable causes (e.g., during sleep). Furthermore, a death was classified as a sudden cardiac death regardless of the underlying condition.

STATISTICAL ANALYSIS

According to the plan decided upon before unblinding, data collection and statistical analysis were executed by Oncology Services Europe, an independent data-coordinating center, which used SAS software, version 9.1.3. Statistical analysis was independently repeated by one of the authors with full access to the data. Subdistribution hazard analyses were performed using R software (cmprsk package), and baseline comparisons were carried out by means of Fisher's exact tests, chi-square tests, or Wilcoxon tests, as appropriate. The primary analysis was performed on an intention-to-treat basis and included all randomized patients from whom written informed consent had been obtained. The cumulative risks of death from any cause were estimated separately for each treatment group with the use of the Kaplan–Meier procedure[21] and were compared between groups with the use of the log-rank test.[22] Cumulative mortality by year and annual rates were calculated with the use of an inverse Kaplan–Meier analysis.

For sample-size calculation, 2-year survival rates were assumed to be 70.6% in the control group and 79.4% in the ICD group (a relative-risk reduction of approximately 30% in the latter group). To calculate the required number of patients, we assumed an alpha error of 5% (two-sided), a beta error of 20%, a 30-month recruitment period, and a minimum follow-up of 2 years. With a lost-to-follow-up rate of 1% per year and taking into account the group-sequential design, the required number of patients in each therapy group was 350. Because the percentage of screened patients who were excluded was unexpectedly high, the recruitment time was more than doubled.

On December 13, 2005, because of a lower-than-expected mortality rate, the data and safety monitoring board advised us to increase the number of patients to 900 and to extend follow-up until the last patient had been in the study for 1 year. These changes were agreed to by the steering committee, and the group-sequential pro-

Table 1. Baseline Demographic and Clinical Characteristics of the Patients, According to Study Group.*

Characteristic	ICD Group (N=445)	Control Group (N=453)
Male sex — no. (%)	345 (77.5)	344 (75.9)
Age — yr	62.8±10.5	62.4±10.6
STEMI — no. (%)	341 (76.6)	348 (76.8)
Reperfusion in STEMI — no./total no. (%)		
None	43/340 (12.6)	48/348 (13.8)
PTCA	243/340 (71.5)	253/348 (72.7)
Thrombolytic therapy, with or without PTCA	54/340 (15.9)	47/348 (13.5)
Anterior-wall MI — no./total no. (%)	282/439 (64.2)	300/449 (66.8)
Heart failure on admission — no./total no. (%)	197/444 (44.4)	209/453 (46.1)
Previous MI — no./total no. (%)	77/444 (17.3)	89/453 (19.6)
Atrial fibrillation — no./total no. (%)	60/445 (13.5)	61/453 (13.5)
Diabetes mellitus — no./total no. (%)	165/444 (37.2)	137/453 (30.2)
Left bundle-branch block — no./total no. (%)	45/445 (10.1)	29/453 (6.4)
Hypertension — no./total no. (%)	296/444 (66.7)	300/453 (66.2)
Criteria for inclusion — no. (%)		
Criterion 1 only	299 (67.2)	303 (66.9)
Criterion 2 only	99 (22.2)	109 (24.1)
Criteria 1 and 2	47 (10.6)	41 (9.1)
Left ventricular ejection fraction — %	34.6±9.3	34.5±9.4
Criterion 1 only	32.2±6.3	31.9±6.7
Criterion 2 only	45.9±10.8	44.8±11.0
Criteria 1 and 2	29.6±7.0	31.4±6.7
Medical therapy on admission — no./total no. (%)		
Antiplatelet agents	438/443 (98.9)	442/452 (97.8)
Beta-blockers	394/442 (89.1)	388/453 (85.7)
ACE inhibitors	361/443 (81.5)	373/453 (82.3)

* Plus–minus values are means ±SD. ACE denotes angiotensin-converting enzyme, ICD implantable cardioverter–defibrillator, MI myocardial infarction, PTCA percutaneous transluminal coronary angiography, and STEMI ST-elevation myocardial infarction.

cedure was adapted by replacing the fixed O'Brien and Fleming strategy by a Lan–DeMets approach.[19,20] However, the alpha-spending function was not changed. The final primary analysis was performed with the use of ADDPLAN, version 4.0.[23]

Calculation of hazard ratios and subgroup analyses with respect to the primary end point were performed on the basis of Cox proportional-hazards models. The proportional-hazards assumption was tested on the basis of Schoenfeld residuals. Subgroup analyses were performed one by one, with the use of the corresponding interaction test for comparison of the treatment effect between subgroups. Thirteen subgroup analyses were prespecified, and one post hoc subgroup analysis was added (for the effect of amiodarone). Two of these subgroup analyses (NYHA class and use or nonuse of amiodarone) involved information collected at discharge and thus were based on data from the patients who were still in the study when they left the hospital.

Since the causes of death represented competing risks, introducing bias in the Kaplan–Meier analysis, these were analyzed on the basis of proportional-subdistribution-hazard models.[24]

Hazard ratios for the subdistribution models and P values for interaction are reported in the same way as the results of the Cox proportional-hazards models.

RESULTS

The baseline demographic characteristics of the two randomized groups were well balanced, although diabetes and left bundle-branch block were slightly more frequent in the ICD group (P=0.03 and P=0.05, respectively) (Table 1).

At discharge, the NYHA class could be assessed in 885 of the surviving patients and was judged to be class I in 247 patients (28%), class II in 531 (60%), and class III in 106 (12%); the class changed to IV in 1 patient (0.1%). Discharge medications in the ICD group and the control group included beta-blockers (in 97.1% and 95.3% of patients, respectively), angiotensin-converting–enzyme (ACE) inhibitors (90.9% and 91.1%), antiplatelet agents (96.1% and 95.8%), and statins (91.6% and 91.5%), whereas use of antiarrhythmic drugs (mainly amiodarone) was slightly more frequent in the control group (17.4%, vs. 13.4% in the ICD group; P=0.11).

RISK OF DEATH AND EFFECTS OF THE ICD

Figure 1 shows the cumulative risk of death from any cause for the two patient groups. During an average follow-up of 37 months (range, 0 to 106), 117 patients in the control group died and 116 patients in the ICD group died. The cumulative death rates at 1, 2, and 3 years were 12.5%, 18.2%, and 22.9%, respectively, in the control group and 10.6%, 15.4%, and 22.4%, respectively, in the ICD group. No significant difference in survival was detected between the two treatment groups (P=0.76, and P=0.78 after adjustment for interim analyses, by the log-rank test); the hazard ratio for death in the ICD group was 1.04 (95% confidence interval [CI], 0.81 to 1.35; P=0.15 by the test of proportional-hazards assumption).

Figure 2 shows the hazard ratios for subgroups of interest. As for the overall study population, a neutral effect of the ICD on overall mortality is seen in all three prespecified subgroups (patients meeting criterion 1 only, those meeting criterion 2 only, and those meeting both criteria).

Figure 3 and Table 2 show the relationship between ICD therapy and the cause of death.

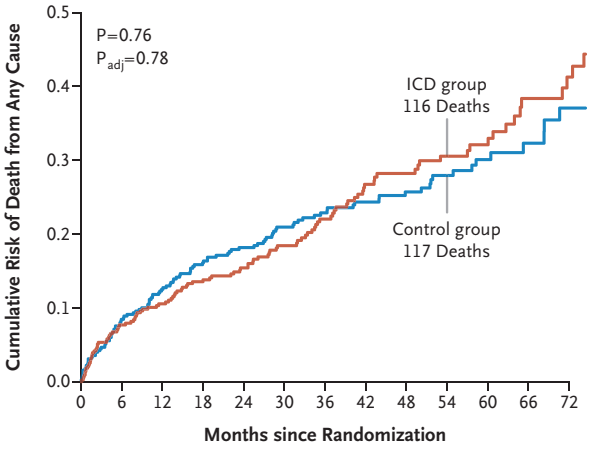

Figure 1. Cumulative Risk of Death from Any Cause According to Study Group.

At the close of the study, definitive information about vital status was available for 897 patients. One patient was lost to follow-up. For patients who withdrew their consent, data were censored at the time of withdrawal. ICD denotes implantable cardioverter–defibrillator.

There were fewer sudden cardiac deaths in the ICD group than in the control group (27 vs. 60) (hazard ratio, 0.55; 95% CI, 0.31 to 1.00; P=0.049) (Fig. 3A). However, this decrease is paralleled by an increase in nonsudden cardiac death in the ICD group as compared with the control group (68 vs. 39) (hazard ratio, 1.92; 95% CI, 1.29 to 2.84; P=0.001) (Fig. 3B). The effects were almost identical in the three predefined subgroups of patients based on the inclusion criteria (interaction, P=0.99 or P=0.71 for sudden or nonsudden cardiac death, respectively) (Table 2).

COMPLIANCE WITH THERAPY AND ADVERSE EVENTS RELATED TO ICD

Of the 445 patients in the ICD group, 415 actually received the ICD system. Thirty patients did not receive an ICD: 14 patients withdrew their consent, 11 refused ICD implantation, and 5 died before implantation could take place. In 378 patients (91.1%), implantation was performed during the hospitalization for the index infarction. In one patient, the inserted lead became entangled in the tricuspid valve and was removed surgically. In 14 patients, the ICD was explanted or permanently deactivated during follow-up, at a

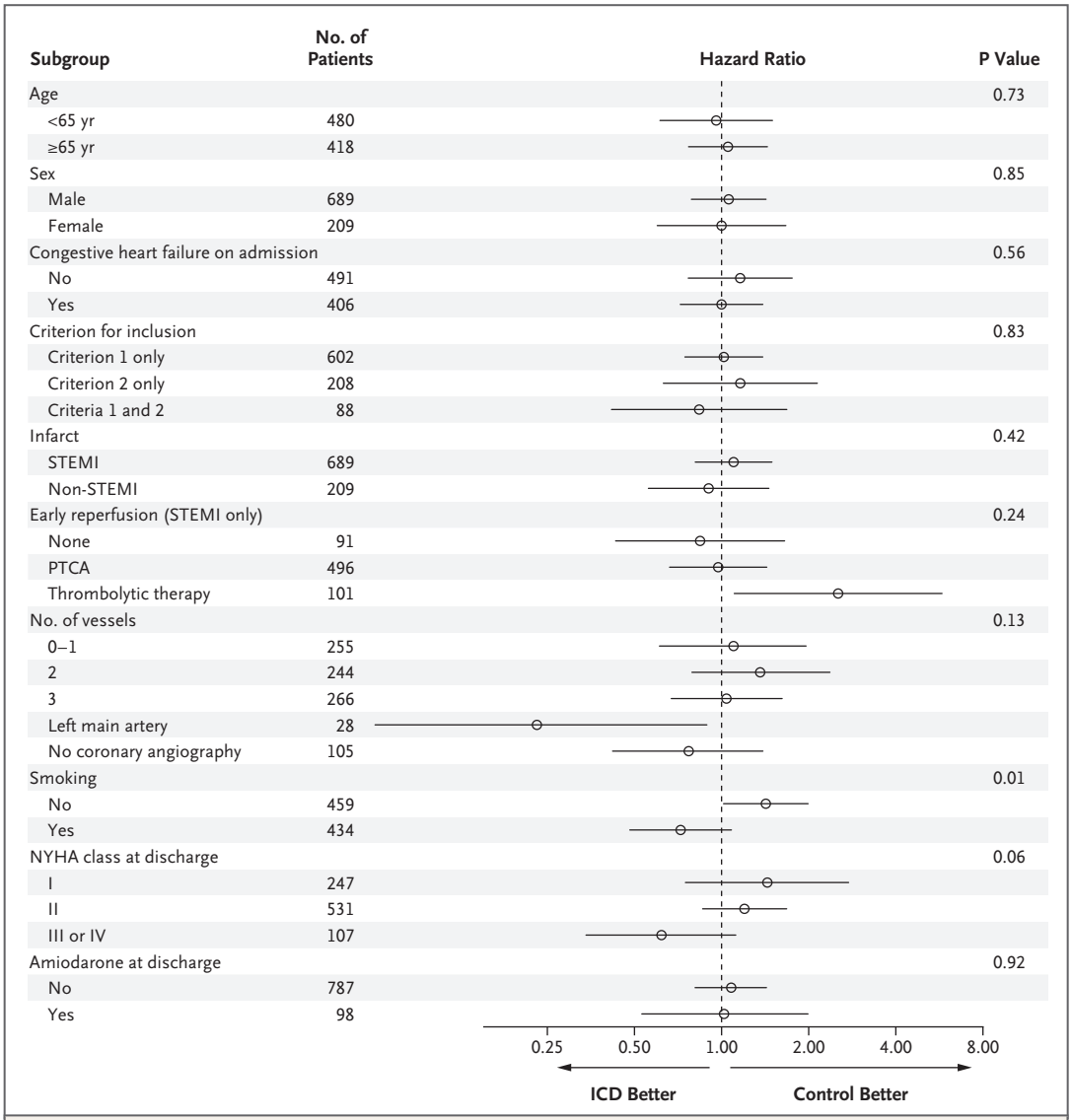

Figure 2. Hazard Ratios for Death from Any Cause in Selected Subgroups of Patients.

Not included in the figure are hazard ratios for subgroups based on the presence or absence of diabetes, hypertension, and lipid abnormalities and on the number of risk factors (0 to 2 vs. 3 or 4, for diabetes, hypertension, smoking, and lipid abnormality), which were similar in the two study groups. ICD denotes implantable cardioverter–defibrillator, NYHA New York Heart Association, PTCA percutaneous transluminal coronary angiography, and STEMI ST-elevation myocardial infarction.

median of 6.8 months after implantation. In summary, at study termination there were 45 patients without an ICD, as opposed to 39 patients in the control group who received an ICD at a median of 7.6 months after randomization.

Of the 415 patients who received an ICD as assigned during the study, a total of 65 (15.7%) had 76 clinically significant complications associated with ICD therapy that required hospitalization, surgical correction, or intravenous drug administration: in 19 patients (4.6%) during the post-implantation period (up to 30 days after implantation), and in 48 patients (11.6%) during follow-up. These complications included lead-related problems that required surgical revision in 10 patients, 4 of whom underwent replacement of Fidelis leads.

Seven patients in the ICD group died during

the post-implantation period (within 30 days after implantation) owing to myocardial reinfarction in four patients and heart failure in three. One of them died during implantation. Within 30 days after randomization, 9 patients in the ICD group died, as compared with 11 patients in the control group.

DISCUSSION

This large-scale, randomized study assessed the benefit of prophylactic ICD implantation early after myocardial infarction in a contemporary population. The majority of the patients (75%) had undergone reperfusion therapy (percutaneous transluminal coronary angiography or thrombolysis) as well as optimal long-term medical therapy with beta-blockers, ACE inhibitors, statins, and antiplatelet drugs. For risk stratification, we used the following criteria: impaired left ventricular function associated with an increased heart rate, as well as rapid unsustained ventricular tachycardia. Although average left ventricular function was better preserved in this study (ejection fraction, 35%) than in other primary-prevention trials (e.g., 23% in the Second Multicenter Automatic Defibrillator Implantation Trial [MADIT II], 25% in the Sudden Cardiac Death in Heart Failure Trial [SCD–HeFT, ClinicalTrials.gov number, NCT00000609], and 28% in the Defibrillator in Acute Myocardial Infarction Trial [DINAMIT]), actual mortality was still substantial — that is, 23% at 3 years; nevertheless, ICD implantation did not convey a prognostic advantage in our study. Thus, with different risk markers, generating a larger population at risk, and a longer follow-up period, our trial confirms the results of DINAMIT.[9] According to the calculated confidence interval for the corresponding hazard ratio, risk reductions of up to 19% in our trial (24% in DINAMIT) as well as risk increases of up to 35% (55% in DINAMIT) may have gone undetected.

With respect to the type of death, the ICD significantly reduced the rate of sudden cardiac death, which was counterbalanced by an increase in the rate of cardiac death from other causes, again confirming the findings in DINAMIT.[9] It should be kept in mind that this categorization of deaths was done by an event committee on the basis of available data about the circumstances of death, but the committee members were unaware of the study-group assignments.

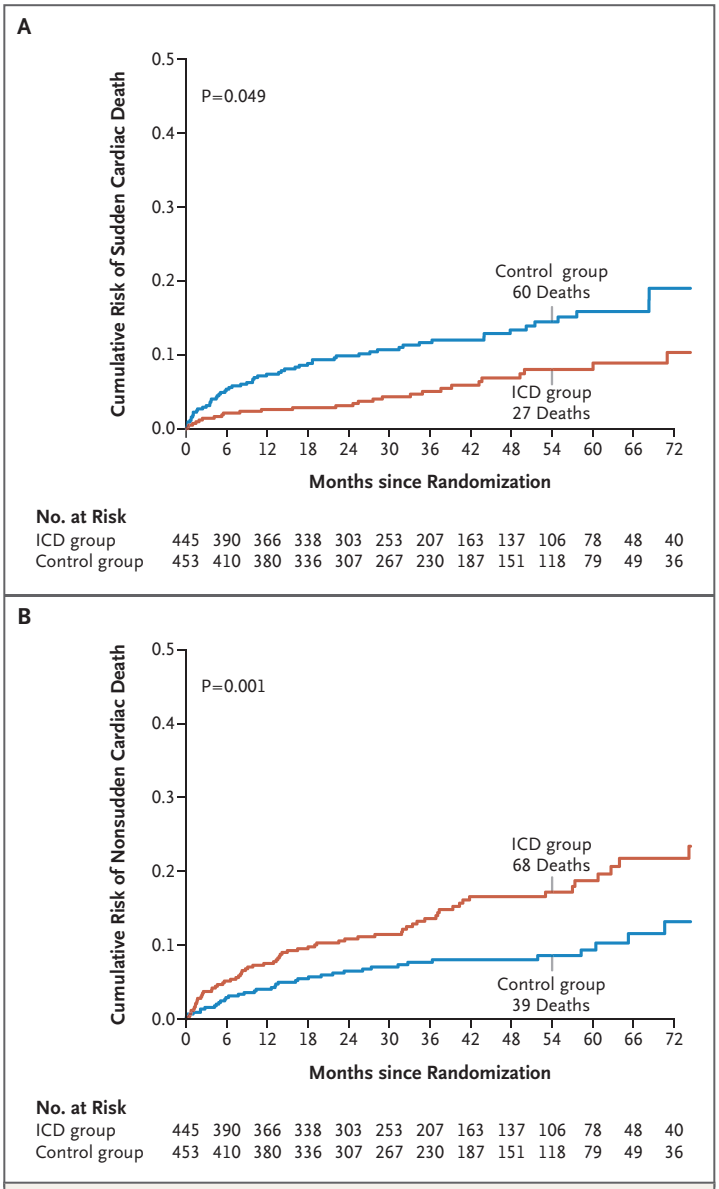

Figure 3. Cumulative Risk of Cardiac Death, According to Study Group.
The cumulative risk of sudden cardiac death is shown in Panel A, and the cumulative risk of nonsudden cardiac death is shown in Panel B. ICD denotes implantable cardioverter–defibrillator.

An increase in the rate of cardiac death other than sudden cardiac death might theoretically be caused by an imbalance in baseline characteristics between the two randomized groups; complications related to ICD implantation; the development of heart failure due to ventricular pacing of the ICD; study-group crossovers; untoward effects of defibrillator shocks and antitachycardia pacing; the substrate of acute myocardial

Table 2. Causes of Death in the Study Groups.*

Cause of Death	ICD Group	Control Group	Subdistribution Hazard Ratio	Unadjusted P Value
	no./total no. (%)			
All patients				
Any cause	116/445 (26.1)	117/453 (25.8)	1.04	0.76
Sudden cardiac death	27/445 (6.1)	60/453 (13.2)	0.55	0.049
Nonsudden cardiac death	68/445 (15.3)	39/453 (8.6)	1.92	0.001
Noncardiac death	21/445 (4.7)	18/453 (4.0)	1.23	0.51
Patients meeting criterion 1 only				
Any cause	78/299 (26.1)	82/303 (27.1)	1.02	0.91
Sudden cardiac death	20/299 (6.7)	45/303 (14.9)	0.46	0.003
Nonsudden cardiac death	44/299 (14.7)	27/303 (8.9)	1.80	0.02
Noncardiac death	14/299 (4.7)	10/303 (3.3)	1.52	0.32
Patients meeting criterion 2 only				
Any cause	21/99 (21.2)	20/109 (18.3)	1.16	0.63
Sudden cardiac death	3/99 (3.0)	7/109 (6.4)	0.46	0.25
Nonsudden cardiac death	13/99 (13.1)	6/109 (5.5)	2.58	0.06
Noncardiac death	5/99 (5.1)	7/109 (6.4)	0.74	0.60
Patients meeting criteria 1 and 2				
Any cause	17/47 (36.2)	15/41 (36.6)	0.84	0.62
Sudden cardiac death	4/47 (8.5)	8/41 (19.5)	0.36	0.08
Nonsudden cardiac death	11/47 (23.4)	6/41 (14.6)	1.53	0.39
Noncardiac death	2/47 (4.3)	1/41 (2.4)	1.50	0.72

* The data include all deaths during a follow-up period of up to 106 months (average, 37). ICD denotes implantable cardioverter–defibrillator.

infarction studied (i.e., rapid ventricular tachycardia and fibrillation due to pump failure, which led to death anyway); other, unidentified side effects of the ICD; and between-group differences in the use of concomitant therapies.

Baseline characteristics were well balanced between the two groups, mortality at 1 month was similar, and backup ventricular pacing was programmed to 40 beats per minute; thus, the first three explanations seem unlikely. The rate of crossover from the ICD group to the control group was higher in our study (10.1% [45 of 445 patients]) than in the SCD–HeFT (6.0%), whereas the rate of crossover from the control group to the ICD group was somewhat lower in our study (8.6% [39 of 453 patients]) than in the SCD–HeFT (11.1%).

A recent follow-up study of SCD–HeFT showed that although patients with heart failure have an overall benefit from prophylactic ICD implantation, those receiving shocks have a substantially increased risk of death.[25] A similar, though less pronounced, effect of the ICD had also been reported for MADIT II.[26-28]

The question of which mechanisms considered above might have contributed to the increased risk of nonsudden cardiac death in the ICD group in our study, as well as the extent of the contribution, remains unresolved.

With respect to risk stratification, in our total registry of 62,944 patients, the proportion of patients who met criterion 1 (LVEF ≤40% and heart rate on admission ≥90 beats per minute) and the proportion of patients who met criterion 2 (rapid, nonsustained ventricular tachycardia [≥150 beats per minute]) were very small (1.1% and 0.5%, respectively), accounting for the extension of the recruitment phase to 8 years.

The major reason for difficulties in conducting this study was the unanticipated and multifacto-

rial improvement in outcomes seen in contemporary unselected patient populations after myocardial infarction.[1,2,29] After hospital discharge of patients whose myocardial infarction is treated according to current guidelines, sudden cardiac death is not as great a threat as it once was.[2]

Risk stratification as applied in the IRIS trial has identified a subgroup of patients who are at increased risk for death, including sudden death, but who do not have a response to the early initiation of ICD therapy. Any further attempts to reduce the risk of sudden death with the use of more refined algorithms of identification (e.g., T-wave alternans[30] or improved assessment of heart rate variability[31]), new treatment strategies beyond current guidelines, or both these approaches will probably face similar, major difficulties with respect to study conduct and resources, as reported here for the IRIS trial.

In conclusion, we found no evidence that implantation of an ICD improved survival in patients with acute myocardial infarction who received optimal medical therapy and underwent risk stratification based on elevated heart rate on admission, low LVEF, and rapid, nonsustained ventricular tachycardia. Although the risk of sudden cardiac death was reduced by ICD therapy, this effect was offset by an increase in the risk of nonsudden cardiac death — an observation that deserves further study.

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APPENDIX

The following institutions and investigators participated in the IRIS study: **Investigators by country** (in descending order of number of enrolled patients) — **Austria:** *Landes KH Universitätskliniken Innsbruck:* F. Hintringer. **Czech Republic:** *FNKV Prague:* M. Herold; *Fakultni nemocnice Hradec Kralove:* M. Pleskot, M. Tauchmann; *IKEM Prague:* J. Kauzner. **Germany:** *Klinikum Coburg:* J. Brachmann, K. Gutleben, S. Schnupp; *Klinik am Eichert, Göppingen:* F. Hofgärtner; *Klinikum Leverkusen:* J. Aring; *St. Johannes-Hospital, Dortmund:* H. Heuer, D. Schmitz, M. Schulz; *Klinikum Friedrichstadt Dresden:* E. Altmann, E. Wunderlich; *Amper Kliniken Klinikum Dachau:* M. Weber, M. Desaga, J. Schwab; *Klinikum am Urban, Berlin:* D. Andresen, F. Gindele, N. Ewertsen; *Klinikum der Stadt Ludwigshafen:* J. Senges, K. Seidl, M. Strauss; *Klinikum St. Marien, Amberg:* H. Friedl, M. Piana, H. Frank; *Klinikum Großhadern, LMU Munich:* G. Steinbeck, M. Ulbrich; *Sana Klinikum Lichtenberg Berlin:* O. Göing, J. Rudolph, J. Heim; *Leinebergland-Kliniken Gronau/Leine:* H. Duwald, B. Behrens; *Klinik f. Innere Medizin III der FSU Jena:* G. Dannberg, K. Tittel; *Klinikum Ludwigsburg:* G. Liebau, A. Rötzer; *Schwarzwald-Baar Klinikum Villingen-Schwenningen:* W. Jung, M. Brasch; *Westpfalz-Klinikum, Rockenhausen:* W. Feth; *Ruppiner Kliniken, Neuruppin:* K. Schmailzl, S. Abdija; *Marienhospital Gelsenkirchen:* H. Blanke, I. Janda; *Philippusstift–Katholische Kliniken Essen:* B. Hailer, H. Schäfer; *Kreiskrankenhaus Kirchberg:* L. Griesbach; *Westpfalz-Klinikum Kaiserslautern:* H. Glunz, E. Helmling; *St.-Marien-Hospital Lünen:* C. Perings, R. Halfenberg; *Katholisches Klinikum Marienhof, Koblenz:* M. Manz, D. Burkhardt; *Vivantes Humboldt-Klinikum Berlin:* S. Behrens, U. Bach; *Segeberger Kliniken, Bad Segeberg:* G. Richardt, R. Schomburg; *Spital Waldshut:* H. Jenss, S. Kim; *Krankenhaus München Neuperlach:* H. Mudra, A. Schwende; *Städtisches Krankenhaus München-Bogenhausen:* E. Hoffmann, P. Landwehr, U. Dorwarth; *Privatklinik Schindlbeck, Herrsching:* B. Cabell; *Universitätsklinikum Mannheim:* C. Wolpert; *Robert-Koch-Krankenhaus Gehrden:* C. Bossaller, M. Voges; *Städtisches Krankenhaus Sindelfingen:* H. Nebelsieck, U. Pfeilsticker; *Mathias Spital, Rheine:* H. Odenthal, S. Middendorf; *Vivantes Klinikum im Friedrichshain, Berlin:* R. Fenzl, J. Retter; *Städtische Kliniken Bielefeld Mitte:* C. Stellbrink, C. Strunk-Mueller; *Universitätsklinikum Heidelberg:* R. Becker, A. Bauer; *Klinikum der Hansestadt Stralsund:* T. Ittel, M. Suter; *Klinikum Chemnitz:* G. Baumann, T. Vieth; *Klinikum der Universität Regensburg:* S. Fredersdorf; *Klinikum Fulda:* G. Strupp, B. Kalschne; *Helmut-G.-Walther-Klinikum Lichtenfels:* E. Dünninger, H. Hümmer; *Schwalm-Eder-Kliniken Schwalmstadt:* R. Zotz; *St.-Josefs-Krankenhaus Salzkotten:* C. Kirsch, S. Fromel; *St. Josef Hospital–Kliniken der Ruhr-Universität, Bochum:* A. Mügge, H. Neubauer, J. Börger; *Städtisches Klinikum München Schwabing:* W. Doering, D. Müller; *Kreisklinik Biberach:* J. Isbary, T. Brummer; *Klinikum Lippe-Detmold:* U. Tebbe, B. Boden; *Klinikum Kempten-Oberallgäu:* F. Seidel, I. Bubinger; *Katharinen-Hospital Unna:* K. Weber, C. Steffens; *Klinikum St. Georg Leipzig:* A. Hartmann, F. Mickley; *SLK Kliniken Heilbronn — Klinikum am Plattenwald Bad Friedrichshall:* J. Manthey, K. Munderloh, K. Ullrich; *Kreiskrankenhaus Wolfach:* B. Kaufmann; *Josephs-Hospital Warendorf:* T. Dorsel, N. Wistorf; *Oberschwaben-Klinik Krankenhaus St. Elisabeth Ravensburg:* M. Sigg, M. Hartl; *Sana Krankenhaus Süd Lübeck:* B. Schneider; *Klinikum Kassel:* J. Neuzner, C. Hansen; *Klinikum Herford:* R. Zotz. **Hungary:** *Zala County Hospital Zalaegerszeg:* G. Lupkovics, B. Nemeth; *Semmelweis University AOK Budapest:* B. Merkely, G. Szucs; *Debreceni Egyetem Debrecen:* I. Édes, R. Kolozsvári; *Szegedi Tudományegyetem Szeged:* T. Forster, A. Makai, L. Sághy. **Poland:** *Szpital Wolski, Warsaw:* D. Wojciechowski, M. Kowalewski, T. Gdowski, T. Roman; *Silesian Center for Heart Disease, Zabrze:* M. Zembala, Z. Kalarus, B. Sredniawa, E. Markowicz; *Pomorska Akademia Med. Szczecin:* C. Kornacewicz-Jach, J. Kazmierczak, R. Rzeuski; *SPSK Academii Medycznej Białystok:* W. Musial, J. Paruk, M. Witkowski; *Szpital Uniwersytecki im. A. Jurasza Bydgoszcz:* J. Kubica, W. Krupa, S. Sielski, T. Fabiszak; *Samodzielny Publiczny Centralny Szpital Kliniczny Warsaw:* G. Opolski, P. Stolarz, A. Oręziak; *I Klinika Kardiologii Gornoslaskie Centrum Medyczne Katowice:* M. Trusz-Gluza, W. Orszulak, A. Filipecki, W. Kwasniewski, D. Kawecka; *SP Wojewodzki Szpital Szczecin:* M. Kurowski, T. Rozpara, W. Plewik; *SPSK Nr 7 Gornoslaskie Centrum Medyczne Katowice:* W. Kargul, K. Snajder, K. Goscinska-

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