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Reduced ejection fraction after myocardial infarction: is it sufficient to justify implantation of a defibrillator?

THESE

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La diminution de la fraction d'éjection après infarctus du myocarde est-elle suffisante pour justifier l'implantation prophylactique de défibrillateur ?

Introduction: La diminution de la fraction d'éjection (FE) est un facteur prédictif majeur de mortalité cardiaque chez les patients avec ancien infarctus du myocarde (IM). Les plus récentes études, pour la plupart conduites à la fin des années 90, montrent une diminution de la mortalité post-hospitalière à 10 à 20% par année. Une amélioration de la survie par implantation prophylactique de défibrillateurs a été démontrée chez les patients avec dysfonction myocardique avancée après ancien IM dans la cadre de l'étude MADIT II (Multicenter Automatic Defibrillator Implantation Trial) et est depuis lors, considérée comme une thérapie recommandée.
Le bénéfice de l'implantation prophylactique de défibrillateurs en terme de nombre nécessaire de patients à traiter pour prévenir un évènement est d'un intérêt primordial en raison des complications potentielles liées à la procédure et l'appareillage, des implications psychologiques ainsi qu'en raison de l'analyse coût-efficacité. Le nombre de patients à traiter est corrélé au risque actuel de mortalité rythmique, probablement influencé par les récentes avancées thérapeutiques dans la prise en charge aigue de l'IM (notamment par angioplastie primaire) et de l'insuffisance cardiaque. Or, dans l'étude MADIT II, le recrutement des patients était effectué entre 1997 et 2001 et l'intervalle moyen entre l'IM et le recrutement était de plus de 6 ans. Le but de l'étude était donc d'évaluer, dans la pratique générale, la mortalité actuelle de patients ayant survécu à un IM avec diminution consécutive significative de la FE. La stratification du risque sur la base des variables hospitalières a de même été explorée.
Méthode: Une analyse de cohorte de patients avec infarctus aigu du myocarde admis de 1999 à 2000 a été effectuée dans 2 centres hospitaliers (un universitaire et un cantonal). Tous les dossiers cliniques des patients sortis d'hôpital avec FE documentée $\leq 0{\cdot}40$ ont été inclus. Les caractéristiques des patients, les procédures diagnostiques et thérapeutiques ainsi que la médication étaient reportées. La période de suivi débutait à la sortie d'hôpital. Les end-points primaires étaient la mortalité globale, la mortalité cardiaque et les morts subites. Une analyse bivariée et multivariée a été effectuée.
Résultats: 165 patients ont été inclus. Durant un suivi médian de 30 mois (interquartile range 22-36), 18 patients sont décédés (5 morts classifiées comme cardiaques, 8 comme subites, 5 de causes non cardiaques). Les taux de mortalité à un et deux ans selon analyse de Kaplan-Meier étaient de 6.7 et 8.6%, respectivement. Les variables reflétant l'atteinte coronarienne et sa prise en charge (antécédent d'IM, reperfusion aigue, revascularisation complète) étaient plus significativement associées à la mortalité comparées aux variables reflétant la dysfonction myocardique (FE, classe Killip à l'admission).
Conclusion : La mortalité des patients ayant survécu à un IM avec dysfonction myocardique avancée a diminué de façon substantielle depuis la fin des années 90. La diminution de la mortalité rythmique implique une augmentation proportionnelle du nombre de patients à traiter par implantation de défibrillateur pour prévenir un évènement. Par ailleurs, une stratification du risque après IM basée uniquement sur la FE semble être inappropriée au vu de son impact mineur sur la mortalité comparé aux autres facteurs de risque identifiés dans notre étude. Les patients sans antécédents d'infarctus et ceux ayant bénéficié d'une revascularisation aigue ou complète avait une mortalité cumulée à 2 ans de, respectivement, 2.5%, 3.9% et 2.3%. Pour ce type de patients à bas risque le bénéfice de l'implantation prophylactique de défibrillateur doit être remis en question. Au vu de cette étude, une stratification additionnelle du risque avant implantation de défibrillateur est à considérer.

Reduced Ejection Fraction After Myocardial Infarction*

Is It Sufficient To Justify Implantation of a Defibrillator?

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Background: Improved survival after prophylactic implantation of a defibrillator in patients with reduced left ventricular ejection fraction (EF) after myocardial infarction (MI) has been demonstrated in patients who experienced remote MIs in the 1990s. The absolute survival benefit conferred by this recommended strategy must be related to the current risk of arrhythmic death, which is evolving. This study evaluates the mortality rate in survivors of MI with impaired left ventricular function and its relation to pre-hospital discharge baseline characteristics.
Methods: The clinical records of patients who had sustained an acute MI between 1999 and 2000 and had been discharged from the hospital with an EF of ≤ 40% were included. Baseline characteristics, drug prescriptions, and invasive procedures were recorded. Bivariate and multivariate analyses were performed using a primary end point of total mortality.
Results: One hundred sixty-five patients were included. During a median follow-up period of 30 months (interquartile range, 22 to 36 months) 18 patients died. The 1-year and 2-year mortality rates were 6.7% and 8.6%, respectively. Variables reflecting coronary artery disease and its management (*ie*, prior MI, acute reperfusion, and complete revascularization) had a greater impact on mortality than variables reflecting mechanical dysfunction (*ie*, EF and Killip class).
Conclusions: The mortality rate among survivors of MIs with reduced EF was substantially lower than that reported in the 1990s. The strong decrease in the arrhythmic risk implies a proportional increase in the number of patients needed to treat with a prophylactic defibrillator to prevent one adverse event. The risk of an event may even be sufficiently low to limit the detectable benefit of defibrillators in patients with the prognostic features identified in our study. This argues for additional risk stratification prior to the prophylactic implantation of a defibrillator.
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Key words: arrhythmia therapy; artery disease; cardiology; coronary artery; epidemiology; myocardial infarction

Abbreviations: CABG = coronary artery bypass graft; EF = ejection fraction; ICD = implantation of a cardioverter defibrillator; IQR = interquartile range; MADIT = Multicenter Automatic Defibrillator Implantation Trial; MI = myocardial infarction; NNT = number of patients needed to treat; PCI = percutaneous coronary intervention

Reduced ejection fraction (EF) is considered one of the major independent determinants of cardiac mortality among survivors of acute myocardial infarction (MI).[1–3] However, EF does not discriminate between modes of death or identify patients for whom death is more likely to be the result of arrhythmia.[4,5] The EF-mortality curve exhibits a hyperbolic trend with an upturn in mortality occurring at EF values of < 40%.[1,2] More recent studies[3,6–10] evaluating post-hospital discharge mortality among patients with cardiac dysfunction, most of them conducted in the late 1990s, documented a trend toward a decrease in mortality but still reported rates of 10 to > 20% at 1 year. More recent data are not available.

The Multicenter Automatic Defibrillator Implantation Trial (MADIT) II showed that prophylactic implantation of a cardioverter defibrillator (ICD) in patients with advanced left ventricular dysfunction

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and remote MI sustained in the 1990s improves survival and should be considered as a recommended therapy.[11] Eligible patients were not required to undergo any prior risk stratification, such as Holter recording or electrophysiologic testing.

The magnitude of the effect of prophylactic ICD, expressed as the number of patients needed to treat (NNT) to prevent one adverse event is of particular interest due to procedure-related and device-related complications, the psychosocial impact of ICD therapy, and for cost-effectiveness considerations. The NNT has to be related to the risk of arrhythmic death, which is evolving. Sudden cardiac death risk is likely to have been reduced by the cumulative effects of recent advances in the management of acute MI (*ie*, the timely restoration of blood flow in the infarct-related artery) and left ventricular dysfunction. Furthermore, the cumulative benefit resulting from recent therapeutic advances is likely to have modified risk stratification among survivors of acute MI.

Therefore, the purpose of our study was to evaluate, in general practice, the current mortality and sudden death rates in survivors of acute MI who had a significant reduction in EF. We also explored the relationship between pre-hospital discharge baseline characteristics and subsequent outcomes.

Materials and Methods

Patient Selection

A cohort analysis of patients with acute MI who were admitted to the hospital between January 1999 and December 2000 was conducted at two hospital centers (one university-based and one community-based). The university hospital provided facilities for cardiac catheterization and cardiac surgery. The community hospital had neither. Patients who were discharged from the hospital alive with a pre-hospital discharge EF of $\leq 40\%$ were included for further follow-up. Patients with a diagnosis of MI were identified using the *International Classification of Diseases*, tenth revision, database. EF was obtained before hospital discharge from the following sources (in preferred order): a left ventriculogram; a radionuclide ventriculogram; or an echocardiogram. The diagnosis of acute MI was based on the report of the American College of Cardiology Task Force on Clinical Data Standards,[12] including a typical rise and fall of biochemical markers of myocardial necrosis (troponin and creatine kinase-MB) with at least one of the following: ischemic symptoms; development of pathologic Q waves on the ECG; ECG changes indicative of ischemia (*ie*, ST-segment elevation or depression); or coronary artery intervention. We validated eligibility by specifically reviewing the clinical records.

Follow-up and End Points

The follow-up period started at the time of hospital discharge. At the end of the follow-up, data were obtained from the primary care physicians through a questionnaire. For patients whose general practitioner was unknown, a telephone interview with the patient was conducted by a staff physician. Supplementary data were then obtained from the patient's physician. All patients gave verbal informed consent.

The primary end point was death from any cause. Secondary end points were death from a cardiac cause and sudden death. Sudden death was defined either as occurring within 1 h of onset of new symptoms (or in a patient with no symptoms or stable symptoms) or as not witnessed within 24 h of the patient being known not to have new symptoms. Other end points assessed were as follows: New York Heart Association functional class at last contact; nonfatal clinically documented MI; revascularization procedures; and ICD.

Statistical Analysis

Quantitative parameters were given as the median and interquartile range (IQR) for continuous variables and percentages for categoric variables. The bivariate relationship between categoric variables and mortality was explored by plotting the actuarial survival curves using the Kaplan-Meier method, and significance was estimated by the log-rank test. Comparisons between continuous variables were carried out using the Cox regression analysis. Multivariate analysis was performed using the Cox proportional hazards model to assess independent associations between prognostic variables and mortality. Possible interactions were assessed, and proportionality assumptions were tested. For continuous covariables, the appropriate mathematical transformation was assessed using fractional polynomials. Statistical significance was assumed for p values of < 0.05. Statistical analysis was performed using a statistical software package (STATA, version 8; Stata Corp; College Station, TX).

Ethics

Procedures were all conducted in accordance with the ethical standard of the Hospital Ethics Committee.

Results

Patients' Characteristics and Procedures

Eight hundred twenty-eight patients were identified, of whom 169 patients (20%) had no assessment of left ventricular EF during their hospital stay and 446 (54%) had an EF of $> 40\%$. Of the 213 patients (26%) with an EF of $\leq 40\%$, 37 died in the hospital and 176 were discharged from the hospital alive. Of these, 170 patients were eligible as 6 did not fulfill the definition criteria of acute MI based on the American College of Cardiology clinical data standards.[12] Five patients were subsequently excluded from the study because they were not resident in the country. Follow-up data were obtained for 164 patients. One patient was lost to follow-up. The baseline characteristics, clinical presentation, and ECG findings for the 164 patients are presented in Table 1. Men accounted for 75% of the population, and the median age was 68 years (IQR, 60 to 75 years). The proportion of patients who sustained at least one previous documented MI was 29%. There was ST-

Table 1—*Baseline Characteristics of the 164 Patients

Characteristics	Values
Baseline	
Median age,† yr	68 (60–75)
Male sex, %	75
Previous MI, %	27
Previous PCI, %	15
Previous CABG surgery, %	7
Diabetes, %	19
Hypertension, %	48
Clinical presentation	
Killip class ≥ 2, %	38
Not available	12
ECG findings, %	
ECG changes	
ST-segment elevation	79
Non-ST-segment elevation	13
Left BBB/paced rhythm/not available	7
Location of ECG changes	
Anterior	64
Lateral	4
Inferior	21
Posterior	2
Left BBB/paced rhythm/not available	11
QRS duration	
< 0.12 s	86
≥ 0.12 s	11
Paced rhythm	3
Q waves on follow-up ECG (new or preexistent),‡ %	92
Rhythm at hospital discharge	
Sinus rhythm	94
Atrial fibrillation	4
Paced rhythm	2

*BBB = bundle branch block.
†Values in parentheses are the IQR.
‡Any Q wave in leads V1 through V3 ≥ 30 ms in leads I, II, aVL, aVF, V4, V5, and V6 (with two contiguous leads and ≥ 1 mm in depth).[12]

Table 2—*Cardiac Procedures During Index Hospitalization and Medications at Last Contact

Cardiac Procedures	Values
Admissions to hospitals without PCI facilities, %	52
Acute reperfusion, %	
Thrombolysis (no PCI facilities vs PCI facilities)	34 (47 vs 20)
Primary angioplasty (no PCI facilities vs PCI facilities)	15 (6 vs 23)
Median EF,† %	35 (30–40)
Cardiac catheterization, %	81
Vessels with stenosis of ≥ 50%, %	
None	3
One	38
Two	29
Three	29
PCI, %	55
LAD	71
LCx	1
RCA	17
Two vessels	12
CABG surgery, %	15
Automatic defibrillator implantation, %	1
Medications at last contact, %	
Antiplatelet therapy	68
Anticoagulation	37
Antiplatelet therapy or anticoagulation	95
ACE inhibitor or AT_1 receptor blocker	84
β-blocker	61
Diuretic	39
Cholesterol-lowering drugs	68
Digitalis	9

*LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery; ACE = angiotensin-converting enzyme; AT = angiotensin.
†Values cited are the last ones obtained before hospital discharge. Values in parentheses are the IQR.

segment elevation (*ie*, ≥ 1 mm in two or more contiguous leads) in 79% of patients. The location of ECG change was anterior in 64% of patients.

The cardiac procedures and medications administered at last contact are presented in Table 2. Acute reperfusion therapy was performed in 49% of patients. Thrombolysis and primary angioplasty were carried out in 34% and 15% of patients, respectively. These two procedures were used equally in the hospital with percutaneous coronary intervention (PCI) facilities (20% vs 23%, respectively). The median EF was 35% (IQR, 30 to 40%), with 62% of patients having an EF of ≤ 35%. Coronary angiography during the hospital stay was performed in 81% of cases. PCI was performed in 55% of the patients, and coronary artery bypass graft (CABG) surgery in 15% of patients.

Follow-up End Points

During a median follow-up of 30 months (IQR, 22 to 36 months), 18 patients died (all-cause mortality rate, 11.0%). Five deaths were classified as cardiac (progressive heart failure, four patients; MI, one patient), eight deaths were classified as sudden, and five were classified as noncardiac. By Kaplan-Meier analysis, the overall 1-year and 2-year mortality rates were 6.7% and 8.6%, respectively. Kaplan-Meier estimates of all-cause mortality are shown in Figure 1.

Progression to marked symptomatic heart failure, classified as a New York Heart Association functional class of ≥ 3 occurred in 20% of patients. Six percent of patients had experienced at least one clinically documented nonfatal MI during the follow-up period. Revascularization procedures were performed in 16% of patients (PCI, 12%; CABG surgery, 4%). Automatic defibrillator implantation was performed in one patient with asymptomatic, unsustained ventricular tachycardia.

Bivariate Analysis

An analysis of the associations between the characteristics of selected patients and outcome during

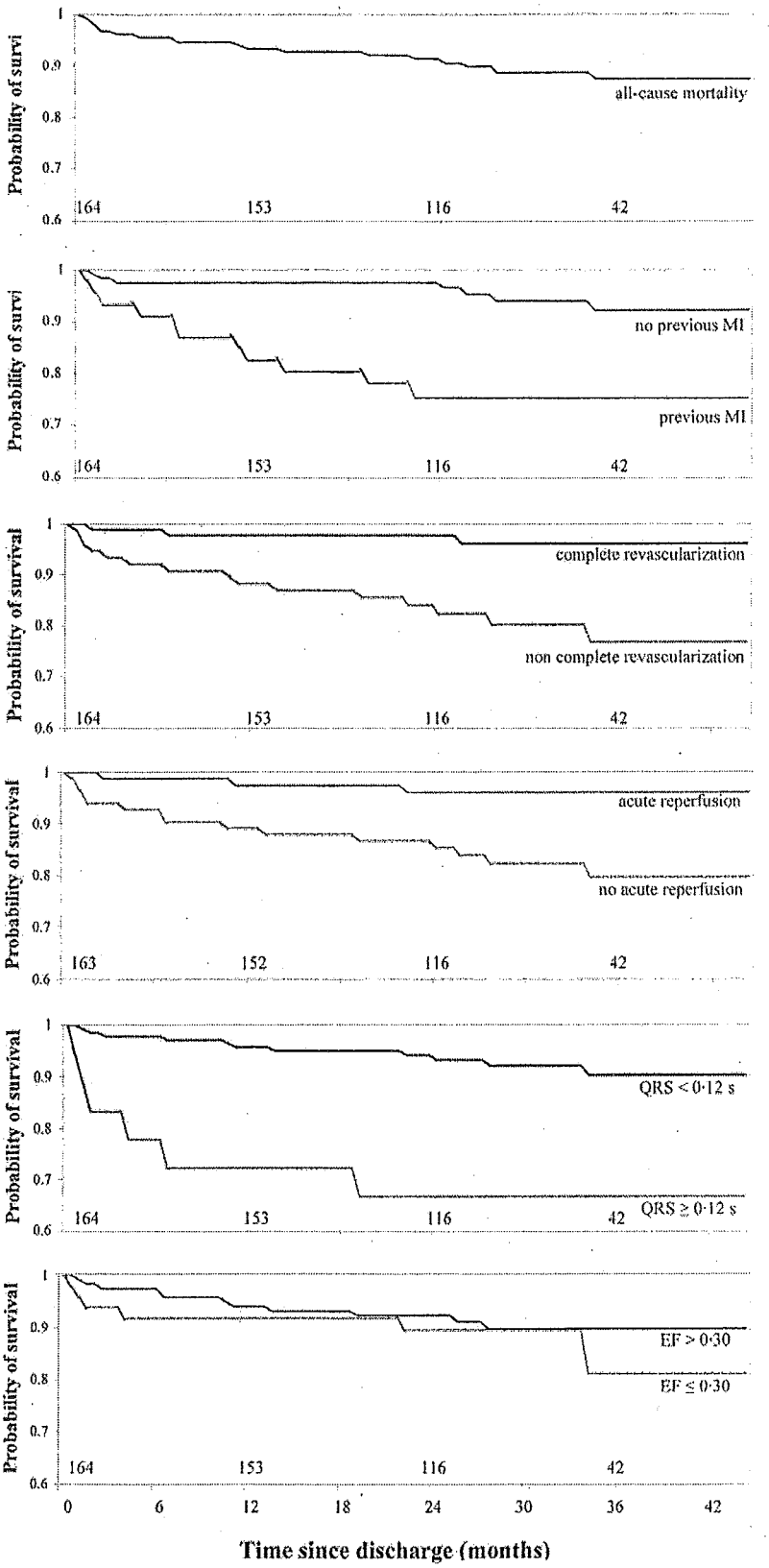

FIGURE 1. Kaplan-Meier estimates of all-cause mortality, and survival curves for death occurring in patients with and without a previous MI, complete revascularization, acute reperfusion, a QRS duration of < 0.12 s, and an EF of $\leq 30\%$. Numbers above the abscissa indicate the number of patients who are at risk.

the follow-up period is shown in Table 3. The factors that showed the most significant associations with all-cause mortality were as follows: age; duration of QRS of ≥ 0.12 s; and the variables that reflected coronary artery disease and its management (*ie*, presence of a previous documented MI, timely restoration of blood flow in the infarct-related coronary artery [thrombolysis or primary angioplasty]; and documented complete revascularization) [Fig 1]. In contrast, the variables reflecting mechanical cardiac dysfunction (*ie*, Killip class and left ventricular EF) did not significantly discriminate between those patients who survived and those who died.

Multivariate Analysis

Multivariate analysis demonstrated an independent relation to all-cause death for the clinical variable previous MI. With regard to coronary artery disease and its management, acute reperfusion and, to a lesser extent, documented complete revascularization were of independent predictive value (Table 4).

Discussion

Our study shows that the 1-year and 2-year mortality rates among patients discharged from the hospital after experiencing an acute MI with an EF of ≤ 40% have decreased markedly compared to the rates cited in more recent studies evaluating post-hospital discharge mortality among patients with cardiac dysfunction, with reported rates of 10 to > 20% at 1 year.[3,6–10] This is all the more significant because most prior studies were interventional trials enrolling patients with numerous exclusion criteria,

Table 3—*Bivariate Analysis of the Associations Among Selected Variables and All-Cause Mortality

All-Cause Death	No (n = 146)	Yes (n = 18)	p Value
Age, yr	66.5 (58–73)	76.5 (67–80)	0.0001
Male sex	75	78	0.7042
Diabetes	18	33	0.0964
Left ventricular EF	35 (30–40)	33.75 (28.125–37.5)	0.1864
Left ventricular EF ≤ 30%	28	39	0.3305
Killip class ≥ 2	41	61	0.1132
QRS ≥ 0.12 s	8	35	0.0004
Previous MI	24	61	0.0003
Acute reperfusion (thrombolysis or primary angioplasty)	53	17	0.0048
Documented complete revascularization (acute or not)	57	17	0.0007

*Values are given as median (IQR) or %, unless otherwise indicated.

Table 4—*Multivariate Analysis of the Associations Among Selected Variables and All-Cause Mortality

All-Cause Death	HR (95% CI)	p Value
Age	1.067 (0.997–1.142)	0.059
Male sex	2.076 (0.652–6.610)	0.216
Left ventricular EF	1.020 (0.939–1.108)	0.634
Previous MI	3.632 (1.356–9.728)	0.010
Acute reperfusion	0.267 (0.072–0.992)	0.049
Documented complete revascularization (acute or not)	0.279 (0.074–1.050)	0.059

*HR = hazard ratio; CI = confidence interval.

including age, and with participating physicians more prone to apply new therapies.[13] In contrast, in our study patients were retrospectively identified, thereby avoiding interference with the usual practice.

Our study shows that today's patients are at a lower risk than patients treated for acute MI in the 1990s, such as those in the MADIT II study.[11] In that trial, recruitment was performed between 1997 and 2001, and the mean interval between the most recent MI was > 6 years (≥ 15 years in 10%).[14]

Our analysis suggests that, in a population with reduced EF after experiencing an MI, a QRS duration of ≥ 0.12 s, and factors reflecting coronary artery disease and its management have more impact on mortality than EF. Namely, for a given EF, the subsequent risk of an arrhythmic event will differ greatly between patients whether acute reperfusion has been performed or not, in the presence of a prior MI, and, probably to a lesser extent, if complete revascularization has been performed.

Our data are concordant with the reported observations that arrhythmic mortality (and all-cause mortality) can be affected independently of myocardial salvage (or left ventricular function preservation). This is illustrated by the results of several randomized trials of acute reperfusion therapy in patients who experienced acute MI showing enhanced survival despite similar pre-hospital discharge EFs.[15–17] One of the mechanisms involved may be increased electrical stability. Clinical evidence suggests that thrombolysis and patency of the infarct-related artery significantly reduce the incidence of late potentials[18–21] and the inducibility of ventricular tachycardia, and improve arrhythmic outcome[22,23] independently of left ventricular function.

Documented complete revascularization before hospital discharge was associated with a better prognosis. In our study, reperfusion, when not performed acutely, was performed mostly in the early post-MI period. There is clinical evidence that late reperfusion (*ie*, > 24 h after MI) after substantial myocar-

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