Evolution of Left Ventricular Ejection Fraction After Acute Myocardial Infarction

Implications for Implantable Cardioverter-Defibrillator Eligibility

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Background—Implantable cardioverter-defibrillator therapy improves survival in patients with reduced left ventricular ejection fraction (LVEF) after acute myocardial infarction (AMI). Although the risk of sudden cardiac death is highest in the first month after AMI, there is no survival benefit of early implantable cardioverter-defibrillator implantation, and the optimal time frame has yet to be established. Thus, the aim of this study was to investigate what proportion of post-AMI patients had improved LV function to such an extent that the indication for implantable cardioverter-defibrillator was no longer present.

Methods and Results—Patients admitted for AMI with reduced LVEF (≤40%) were eligible for inclusion. Repeat echocardiographic examinations were performed 5 days, 1 month, and 3 months after the AMI. We prospectively included 100 patients with LVEF of 31±5.8% after AMI. At the 1-month follow-up, 55% had an LVEF >35%. The main improvement in LVEF had occurred by 1 month. The mean difference in LVEF over the next 2 months was small, 1.9 percentage units. During the first 9 weeks, 10% of the patients suffered from life-threatening arrhythmias.

Conclusions—Most patients have improved LVEF after AMI, and in the majority, the improvement can be confirmed after 1 month, implying that further delay of implantable cardioverter-defibrillator implantation may not be warranted. Life-threatening arrhythmias occurred in 10% of the patients, illustrating the high risk for sudden cardiac death in this population. **(*Circulation*. 2014;130:743-748.)**

Key Words: defibrillators, implantable ■ echocardiography ■ heart failure ■ myocardial infarction ■ risk assessment

A significant proportion of deaths in patients with chronic ischemic cardiomyopathy are due to heart failure or sudden cardiac death (SCD).[1] Numerous clinical trials have confirmed the benefit of implantable cardioverter-defibrillator (ICD) treatment in patients with reduced left ventricular (LV) function after an acute myocardial infarction (AMI).[2–4] Despite the risk of SCD being highest during the first month after AMI,[5–7] there is no benefit of ICD treatment early after myocardial infarction.[5,8] The Defibrillation in Acute Myocardial Infarction Trial (DINAMIT) and the Immediate Risk Stratification Improves Survival (IRIS) study showed that although ICD implantation early after AMI reduced the number of SCDs, the rates of nonarrhythmic deaths were increased.[5,8] It has been speculated that the factors associated with arrhythmias also implicate a high risk of nonsudden death, abolishing the benefit of ICD treatment.[9] Another explanation could be that the impaired LV function seen immediately after AMI is due to some extent to myocardial stunning. In previous studies, improvement of the LV ejection fraction (LVEF) has been observed in 30% to 50% of post-AMI patients.[10–12]

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Guidelines advocate primary preventive ICDs for patients with LVEF ≤35% after >40 days after AMI, but a delay of at least 3 months is recommended after revascularization. Implantation of primary preventive ICDs is also recommended for patients with LVEF ≤40%, nonsustained ventricular arrhythmias (ventricular tachyarrhythmias) caused by prior AMI, and inducible ventricular tachyarrhythmias during electrophysiological studies.[13] The optimal timing for ICD implantation has not been evaluated in prospective studies.[14] A substudy of Multicenter Automatic Defibrillator Implantation Trial (MADIT) II showed more benefit with ICD in patients with more remote AMI,[15] but post hoc analysis of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) study implicates that the duration after AMI does not modify

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Received March 9, 2014; accepted June 16, 2014.

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Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.114.009924**

the effect of ICD on all-cause mortality.[16] However, a delayed decision about ICD after AMI is associated with a lower likelihood of implantation of a potentially life-saving device.[17,18]

The aim of this study was to investigate what proportion of patients with reduced LV function after an AMI reached an LVEF >35%, thereby no longer qualifying for ICD treatment. We also investigated the time to improvement to allow earlier identification of possible ICD candidates.

Methods

Patients admitted with AMI at Danderyd University Hospital or Södersjukhuset in Stockholm between November 2010 and December 2013 were eligible for participation in the study if a clinical echocardiography showed an LVEF of ≤40%. An AMI was defined according to the second and third universal definitions of myocardial infarction.[19,20] All clinical echocardiographies of potentially eligible patients were reviewed by a participating research cardiologist with echocardiographic expertise who confirmed that the LVEF was indeed ≤40% according to the modified Simpson biplane method at inclusion.[21] Patients were excluded if they had short life expectancy (<1 year), if informed consent was not acquired, or if >8 days had passed since the AMI.

The echocardiography was performed with commercially available equipment (Vivid 7, GE Vingmed, Horton, Norway) with a standard phased-array 2.5-MHz multifrequency transducer. Standard echocardiographic recordings and calculations were performed according to the recommendations of the European Society of Echocardiography.[21] Apical scans of the LV in the 4-chamber, 2-chamber, and apical long-axis views were performed. Recordings were saved on a digital medium and postprocessed on a workstation (EchoPAC, GE, Horton, Norway). LVEF was calculated according to the modified Simpson biplane method. If <80% of the endocardial border was adequately visualized, a contrast agent (SonoVue, Bracco Imaging) was used. A certified biomedical analyst with vast echocardiographic experience performed the echocardiographies before discharge (3–8 days after the AMI) and again after 1 and 3 months. The clinical echocardiography that determined the inclusion was called echocardiography 1; the first study echocardiography before discharge was called echocardiography 2; the echocardiography performed after 1 month was called echocardiography 3; and the echocardiography performed 3 months after the AMI was called echocardiography 4.

Data on background demographic factors, ECG, results from coronary interventions, and medication were collected.

Two independent investigators performed all LVEF estimations. If there was a discrepancy of >5 percentage units, a third investigator proceeded with the analysis, and a consensus decision was reached. Assessment of the intraobserver and interobserver variability was performed by an additional reviewing and estimation of the LVEF in 20 random examinations by 3 investigators blinded to the results of the others. One of the investigators also analyzed the same examinations on 2 different occasions without information about the previous results.

Statistics

To calculate the sample size, we assumed a mean LVEF at baseline of 30% and a variance of 10%. The null hypothesis to be tested was that there is no difference in LVEF after 3 months, and the alternative hypothesis was that there is a difference of >10 percentage units in LVEF after 3 months. With the assumption that we have a dropout rate of 20%, we calculated that enrollment of 100 patients would provide 80% power to detect a difference of at least 10 percentage units in LVEF. Sample size calculating was performed with IBM SPSS Sample Power version 2.0. Continuous data were presented as mean±SD or median (range) when appropriate. Nominal data are presented as number of cases (percent). The Fisher exact test was used for comparison between categorical variables, and the Student paired *t* test was used for comparison of continuous variables over time, when normal distribution was assumed. Normal distribution was tested with the Shapiro-Wilk test and plots. If the parameters were normally distributed, confidence intervals were calculated. When we did not assume normal distribution, the Wilcoxon signed-rank test was used. ANOVA was used to compare >2 groups. A 2-sided value of $P<0.05$ was considered statistically significant. Both the intraobserver and interobserver variabilities were calculated as the mean percent error, which was expressed as the absolute difference between 2 sets of observations divided by the mean of observations.[22] A multiple logistic regression model was used to examine the value of different baseline characteristics as predictors of LVEF recovery and arrhythmic events. All statistical analyses were performed with IBM SPSS Statistics version 21.

The study was performed in accordance with the Declaration of Helsinki and was approved by the Regional Ethical Review Board in Stockholm, Sweden (2010/882-31/2). All participants gave their written informed consent.

Results

There were 121 potential patients, but 21 were not included in the study as a result of disagreement about the LVEF estimation between the clinical echocardiography and the echocardiography core laboratory. Of the 100 included patients with an LVEF ≤40% after AMI, 9 patients dropped out before echocardiography 2: 8 because of complications after the AMI (cardiac embolism, pulmonary embolism, and 6 cases of severe heart failure) and 1 because of poor imaging quality despite the use of echocardiography contrast. The baseline characteristics are based on the remaining 91 patients. Five patients did not perform echocardiography 3 and 3 patients did not perform echocardiography 4 because of fatigue or coronary artery bypass graft surgery.

The intraobserver and interobserver variabilities were 5±3% and 8±5%, respectively.

Baseline Characteristics

Clinical baseline characteristics are presented in Table 1. The majority of the study population were men. The most common comorbidities were hypertension and diabetes mellitus. There was no previously known heart disease in 66 patients (71%). Both mean and median LVEFs at inclusion were 31% (range, 17.5%–40%). ST-segment–elevation myocardial infarction was more common than non–ST-segment–elevation

Table 1. Baseline Characteristics (n=91)

Characteristic	
Male sex, n (%)	71 (78)
Age, mean±SD, y	68±10
LVEF at inclusion mean±SD, %	31±5.8
Smoking, n (%)	25 (28)
Hypertension, n (%)	43 (47)
Previous heart failure, n (%)	14 (15)
Previous AMI, n (%)	11 (12)
Previous revascularization, n (%)	9 (10)
Atrial fibrillation, n (%)	13 (14)
Kidney disease, n (%)	6 (6.5)
Diabetes mellitus, n (%)	18 (20)
Previous stroke, n (%)	6 (6.5)
STEMI, n (%)	54 (59)

AMI indicates acute myocardial infarction; LVEF, left ventricular ejection fraction; and STEMI, ST-segment–elevation myocardial infarction.

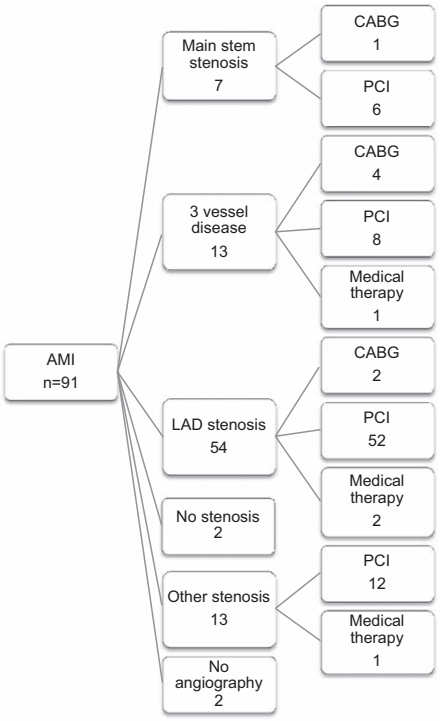

Figure 1. Type of acute myocardial infarction (AMI) and revascularization. Two patients had both percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery (CABG). LAD indicates left anterior descending coronary artery.

myocardial infarction, and most patients had a stenosis in the left anterior descending artery and were treated with percutaneous coronary intervention (Figure 1). A total of 78 patients (86%) were treated with percutaneous coronary intervention and 7 (7.7%) with coronary artery bypass graft surgery. Of these, 2 patients (2.2%) were treated with both percutaneous coronary intervention and coronary artery bypass graft surgery. Even if all patients in the study were considered for revascularization, percutaneous coronary intervention was not possible in 2 patients, medical therapy was thought to be the best therapy in 2 patients, 2 patients had no stenosis, and 2 patients refused coronary angiography.

Echocardiography 1 Versus 2

The results of both the LV dimensions and LVEF measurements are shown in Table 2. There was on average 3 days between echocardiographies 1 and 2, but there still was a small improvement in LVEF of a mean 1.3 percentage units after this short time (P=0.05 Wilcoxon signed-rank test). There was a statistically significant difference in LV end-diastolic diameter between echocardiographies 1 and 2 (5.2±0.8 versus 5.4±0.8 cm; P<0.001), which was not considered to be of clinical importance.

Echocardiographies 1 Through 4

There was a general improvement in LVEF at 1 month that continued, albeit to a lesser extent, to the 3-month echocardiography (Table 2). After 3 months, the echocardiography results were widely divergent between patients, and the mean and median LVEFs were 40±11% (range, 10%–60%). The mean improvement in LVEF between echocardiographies 1 and 4 was 8.4 percentage units (95% confidence interval, 6.4–10; P<0.001; Figure 2). Improvement in LVEF by ≥10 units was observed in 40 patients (47%). However, we also found a deterioration of >5 units in 9 patients and ≥10 units in 2 patients.

After 1 month, 38 patients (45%) had LVEF ≤35% and thus an indication for primary preventive ICD. After 3 months of follow-up, 6 of these patients had improved further and no longer met the ICD criterion (mean LVEF, 41%). The difference in LVEF between echocardiographies 3 and 4 was small but significant (1.9 percentage units; P=0.01). Among the patients with LVEF > 35% at inclusion (n=17), 2 patients had a lower LVEF at 3 months and met the criteria for ICD. If the patients with LVEF of 36% to 40% at inclusion were excluded, it did not affect the main result, and 50% (n=34) of the patients with LVEF ≤35% at inclusion had improvement in their LVEF at 1 month to such a degree that an ICD was no longer indicated. Among these patients, the mean improvement in LVEF between echocardiographies 1 and 4 was 7.9 percentage units.

Among the 8 patients who were not successfully revascularized, 2 patients improved and had LVEF ≥35% at both 1 and 3 months of follow up (LVEF, 47% and 60% after 1 month). There were no clinically important differences in LV end-diastolic diameters between echocardiographies 1 and 4.

Patients With LVEF >35% Compared With Those With LVEF ≤35% at the 3-Month Follow-Up

The baseline characteristics of the patients with LVEF ≤35% at the 3-month follow-up are compared with the others in Table 3. Multiple regression with the cofactors, for example, previously known heart failure, previous AMI, LVEF at inclusion, and 3-vessel disease, showed that LVEF at inclusion was the only variable that differed significantly between the groups (odds ratio, 0.82; 95% confidence interval, 0.73–0.93; P=0.002). Among the 19 patients with an LVEF ≤25% at inclusion, only 2 patients improved and no longer met the ICD criterion after 3 months (LVEF, 38% and 40%).

Table 2. Echocardiographic Parameters

Echocardiographic Examination	Definition	Time After AMI	LVEF (mean±SD), %	LV End-Diastolic Diameter, cm	P Value for Differences in LVEF vs Echocardiography 1
1	Clinical echocardiography, determining inclusion	2.1±1.3 d	31±5.8	5.2±0.7	
2	First study echocardiography, before discharge	5.0±2.3 d	32±7.0	5.4±0.8	0.05
3	Second study echocardiography	1 mo	38±11	5.4±0.8	<0.001
4	Third study echocardiography	3 mo	40±11	5.3±0.6	<0.001

AMI indicates acute myocardial infarction; LV, left ventricular; and LVEF, left ventricular ejection fraction.

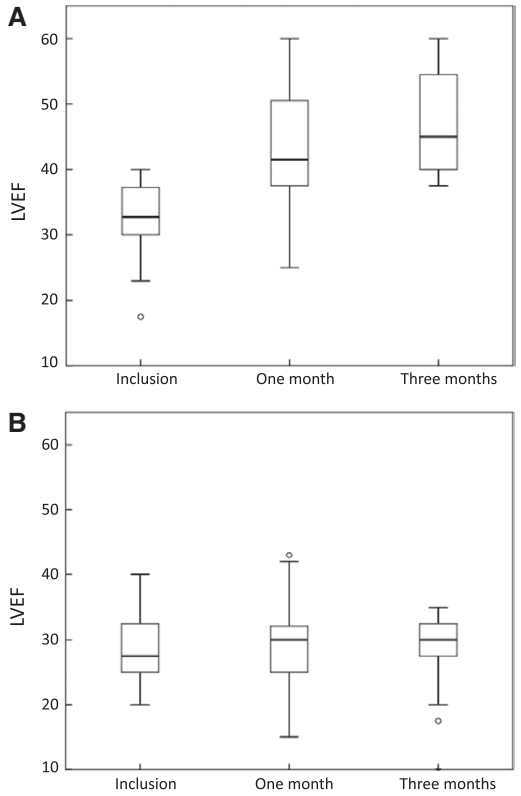

Figure 2. A, Left ventricular ejection fraction (LVEF) at inclusion, 1 month, and 3 months after acute myocardial infarction (AMI) among the patients who did not meet the criteria for implantable cardioverter-defibrillator (ICD) after 3 months (n=51). **B**, LVEF at inclusion, 1 month, and 3 months after AMI among the patients who did meet the criteria for ICD after 3 months (n=35).

Early Malignant Ventricular Arrhythmia or Death

Within 3 months after the AMI, 2 patients died. The causes of death were severe infection in both cases. In addition 1 of the patients suffered a stroke, and the other had severe heart failure after coronary artery bypass graft surgery.

During the first 9 weeks, 9 patients (10%) had life-threatening arrhythmias. Of these, 7 patients required resuscitation from ventricular fibrillation or torsade de points. The other 2 patients had sustained ventricular tachycardia: 1 underwent direct current cardioversion and the other terminated spontaneously. All 9 patients survived. The mean time from the AMI to the ventricular arrhythmia was 10 days (range, 4–60 days), and 4 patients had already been discharged from the cardiology ward. The clinical characteristics of these patients were not particularly different from those of the patients without ventricular arrhythmias, apart from the fact that the patients with arrhythmias more often had previous AMI and all patients were male (Table 4). Multiple regression analysis with the cofactors of previous AMI and sex showed that previous AMI was the best predictor of ventricular tachyarrhythmias, but it was not significant (odds ratio, 4.3; 95% confidence interval, 0.83–22.2; P=0.08). Three of the patients with ventricular arrhythmias had an LVEF of >35% at the 3-month follow-up (LVEF, 43%–58%).

Discussion

The main finding from this study is that among patients with an LVEF ≤40% after an AMI, the majority (55%) show rapid improvement to such extent after 1 month that there was no longer a clear indication for ICD treatment. This can be an explanation for the lack of benefit in mortality rates that has been seen with ICD implantations early after AMI.

Table 3. Comparison Between Patients With and Without an Indication for ICD at the 3-Month Follow-Up

	LVEF ≤35% at 3 mo After AMI (n=35), n (%)	LVEF >35% at 3 mo After AMI (n=51), n (%)	*P* Value for Differences
LVEF at inclusion (mean±SD), %	28±5.6	34±4.5	0.001
Age (mean±SD), y	69±9.8	67±11	0.55
Male sex, n (%)	29 (83)	39 (76)	0.59
Previous heart failure, n (%)	9 (26)	4 (8)	0.03
Previous AMI, n (%)	7 (20)	4 (8)	0.11
STEMI, n (%)	18 (51)	32 (64)	0.49
Main stem stenosis, n (%)	4 (11)	3 (6)	0.43
3-Vessel disease, n (%)	7 (20)	4 (8)	0.11
Stenosis in the left anterior descending artery, n (%)	18 (51)	34 (67)	1.0
Revascularization CABG /PCI, n (%)	30 (86)	49 (96)	0.11
Diabetes mellitus, n (%)	7 (20)	8 (16)	0.77
Atrial fibrillation, n (%)	6 (18)	6 (12)	0.54
Smoking, n (%)	12 (33)	12 (24)	0.47
Hypertension, n (%)	19 (54)	22 (43)	0.38
β-Blocker therapy, n (%)	34 (97)	51 (100)	0.48
ACE inhibitor or angiotensin receptor blocker therapy, n (%)	34 (97)	51 (100)	0.48
Spironolacton therapy, n (%)	9 (26)	9 (18)	0.26

ACE indicates angiotensin-converting enzyme; AMI, acute myocardial infarction; CABG, coronary artery bypass graft surgery; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

Differences in LVEF Between Echocardiographies 1 Through 4

Despite the fact that there were only 3 days between echocardiographies 1 and 2, there was a small but significant improvement in LVEF, indicating that recovery of the LVEF is a rapid process starting early after the AMI.

This is further supported by the fact that the main improvement in LVEF occurred within 1 month and the difference in LVEF between 1 and 3 months was small (1.9 percentage units). Only 6 of the 38 patients with LVEF ≤35% after 1 month improved to such an extent that an ICD was no longer indicated after 3 months. This results suggests that ICD implantation may be considered as early as after 1 month in patients with moderately impaired LVEF regardless of revascularization. Because earlier studies have demonstrated that a delayed decision about ICD after AMI is associated with a lower likelihood of implantation,[17,18] it would be beneficial to offer ICD treatment at the 1-month follow-up.

Mildly Impaired LVEF at Inclusion

Although current international guidelines state that ICD therapy is warranted in patients with LVEF≤35% after prior AMI, we included patients with LVEF ≤40% in this study. Our rationale

Table 4. Comparison Between Patients With and Without Ventricular Arrhythmias

	Patients With No Ventricular Arrhythmia (n=82), n (%)	Patients With Ventricular Arrhythmia (n=9), n (%)	*P* Value
LVEF at inclusion (mean±SD), %	32±10	31±5	0.69
Age (mean±SD), y	68±11	71±5	0.19
Male sex, n (%)	62 (76)	9 (100)	0.19
Previous heart failure, n (%)	13 (16)	1 (11)	0.70
Previous AMI, n (%)	8 (10)	3 (33)	0.08
Main stem stenosis, n (%)	7 (8)	0	0.35
3-Vessel disease, n (%)	12 (15)	1 (11)	0.73
Stenosis in the left anterior descending artery, n (%)	62 (76)	8 (89)	0.31
Diabetes mellitus, n (%)	16 (20)	2 (22)	0.94
Atrial fibrillation, n (%)	12 (15)	1 (11)	0.76
Smoking, n (%)	23 (28)	2 (22)	0.89
Hypertension, n (%)	37 (45)	6 (67)	0.29
β-Blocker therapy, n (%)	81 (99)	9 (100)	
ACE inhibitor or angiotensin receptor blocker therapy, n (%)	82 (100)	8 (89)	
Spironolacton therapy, n (%)	13 (16)	2 (22)	0.44

ACE indicates angiotensin-converting enzyme; AMI, acute myocardial infarction; and LVEF, left ventricular ejection fraction.

was that estimation of LVEF is challenging and the Simpson rule requires accurate tracing of endocardial borders, which sometimes can be difficult.[23] Interestingly, 10 patients experienced deterioration in LVEF of ≥5 percentage units after discharge, but only 2 of the patients with LVEF of 36% to 40% at inclusion met the indication for ICD after 3 months. However, even patients with a mildly reduced LVEF at discharge should receive optimized medical therapy for congestive heart failure and should be followed up with repeat echocardiography.

Early Ventricular Arrhythmia After AMI

Although the treatment for AMI has improved with early revascularization and modern drug therapies, some patients develop a deteriorated heart function that may increase the risk for SCD. In our study, 9 patients had life-threatening arrhythmias shortly after the AMI. In 5 patients, the arrhythmias occurred before discharge, and in the remaining 4 patients, cardiopulmonary resuscitation was begun by bystanders. All 9 patients survived. The patients in our study who developed ventricular arrhythmias had an LVEF at discharge (32%) similar to that of patients without arrhythmias. The high incidence of malignant arrhythmias illustrates the need for early identification of patients suitable for ICD treatment. Perhaps ICD should be consider before discharge among patients with severely impaired LV function because only 2 patients with LVEF ≤25% improved to such an extent that ICD was not indicated after 3 months. Another possible solution would be to offer life vest defibrillators or subcutaneous ICDs to patients with heart failure during the first month after AMI. The high occurrence of life-threatening arrhythmias in this study illustrates the need for early identification of patients suitable for ICD treatment.

Characteristics Among Patients With Arrhythmias and Low LVEF at Follow-Up

In our study, there were no significant differences between the 9 patients who had life-threatening arrhythmias and those who did not. This means that it is difficult to prevent SCD that appears shortly after AMI. Neither were there any special features among patients who did not improve their LV function other than very impaired LV function.

It would be beneficial to determine a method to predict which patients with reduced LVEF after AMI are not likely to improve so that ICD treatment can be offered earlier at a time when the risk of SCD is strikingly increased.

Limitations

One limitation is that LVEF estimation can sometimes be difficult because of a lack of proper visualization of the endocardium. In that case, we used contrast agents and harmonics to increase the accuracy of the method. Another issue is the intraobserver and interobserver variability among observers. The intraobserver and interobserver variations for calculating LVEF can be high because of the inappropriate quality of echocardiography recordings. In our study, we had relatively low intraobserver and interobserver variabilities for calculating LVEF.

Sources of Funding

This study was supported by the Swedish Heart and Lung Foundation and by nonrestricted grants from Medtronic Inc and Boston Scientific Inc.

Disclosures

All authors have completed the Unified Competing Interest form, which is available on request from Dr Sjöblom. Dr J. Sjöblom has received research grants from Medtronic and Boston Scientific. Dr Frykman has conducted studies in collaboration with Medtronic and St. Jude Medical. Dr Witt has received lecture fees from St Jude Medical. Drs Muhrbeck and Alam report no conflicts.

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CLINICAL PERSPECTIVE

Despite modern treatment, many patients with reduced systolic left ventricular function after acute myocardial infarction are at high risk of sudden cardiac death, especially during the first weeks after the infarction. This study shows that with current treatment, including early revascularization, most patients will improve their ejection fraction within 1 month to such an extent that a primary prophylactic implantable cardioverter-defibrillator is no longer indicated. Further improvement after 1 month is limited, implying the benefit of early implantable cardioverter-defibrillator implantation in patients who do not improve during the first month. Patients with a severely reduced ejection fraction were unlikely to recover beyond the limits of implantable cardioverter-defibrillator therapy. This study also illustrates the substantial risk for malignant ventricular arrhythmias early after an acute myocardial infarction and the difficulty in predicting which individuals will be affected.

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Evolution of Left Ventricular Ejection Fraction After Acute Myocardial Infarction: Implications for Implantable Cardioverter-Defibrillator Eligibility

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Circulation. 2014;130:743-748; originally published online July 29, 2014;
doi: 10.1161/CIRCULATIONAHA.114.009924
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539