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PRIMARY PREVENTION DEFIBRILLATORS IN CLINICAL PRACTICE

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Abstract

Introduction: Guidelines for primary prevention of sudden cardiac death (SCD) advocate implantable cardioverter defibrillator (ICD) therapy in patients with reduced left ventricular ejection fraction (LVEF). Many patients are not considered for treatment and the net benefit of ICDs in real life is insufficiently studied. The aims of these studies were to investigate compliance to guidelines and to study the balance between benefits and complications of ICD therapy.

Methods and Results: *Paper I:* In a retrospective study of the medical records of 187 patients with acute myocardial infarction (AMI), with LVEF ≤35%, we evaluated the decision process behind ICD treatment. Inadequate follow-up according to guidelines was found in 32% of the patients, while 41% showed an improvement in LVEF to such a degree that an ICD was no longer indicated. *Paper II*: A prospective study of 100 patients with AMI and reduced LVEF (≤40%). The incidence and time span of improvement of LVEF were studied. At one month of follow-up, 55% of the patients had an LVEF of >35%. The mean difference in LVEF between one and three months was small (1.9 percentage units). A high risk of life-threatening arrhythmias (9%) was found in the first few weeks after AMI. *Paper III*: Using register data, 865 patients with reduced LVEF treated with ICDs for primary prevention of SCD were identified. The medical records were scrutinized. We found that annually 6% of the patients had correctly treated arrhythmias, 2.4% had inappropriate shocks and 4.4% had complications requiring reoperation. Men were twice as likely to receive correct ICD treatment compared with women. *Paper IV*: We analyzed intracardiac electrograms from 125 explanted ICDs from deceased patients. During the last 24 h of life, 31% of the patients had received shock treatment. Although 52% of the patients had a do-not-resuscitate order, 65% of them still had ICD shock therapies activated.

Conclusions: Follow-up after AMI is insufficient. Most patients show improved LVEF after AMI and in the majority the improvement can be confirmed after one month, implying that further delay of ICD implantation may not be motivated. Patients (especially men) with heart failure benefit from ICD treatment, but complications are common and it is crucial to inactivate shock treatment towards the end of life.

LIST OF SCIENTIFIC PAPERS

I. Primary prevention of defibrillator implantation after myocardial infarction: clinical practice and compliance to guides.
Sjöblom J, Ljung L, Frick M, Rosenqvist M, Frykman-Kull V.
Europace. 2012;14:490-5.

II. Early identification of ICD candidates after acute myocardial infarction.
Sjöblom J, Muhrbeck J, Witt N, Alam M, Frykman-Kull V, Submitted.

III. Efficacy of primary preventive ICD therapy in an unselected population of patients with reduced left ventricular ejection fraction. *Sjöblom J, Kalm T , Gadler F, Ljung L, Frykman-Kull V, Rosenqvist M, Platonov PG, Borgquist R. Submitted.*

IV. Implantable defibrillator therapy before death – High risk for painful shocks at end of life. *Kinch Westerdahl A, Sjöblom J, Mattiasson A-C, Rosenquist M, Frykman V. Circulation. 2014 Jan 28;129(4):422-9.*

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LIST OF ABBREVIATIONS

AF	Atrial fibrillation
AMI	Acute myocardial infarction
ATP	Anti-tachycardia pacing
CABG	Coronary artery bypass graft(ing)
CI	Confidence interval
CRT	Cardiac resynchronization therapy
CRT-D	Cardiac resynchronization therapy in combination with ICD
DDD	Dual chamber pacing, sensing and response
DDD(R)	Dual chamber pacing, sensing, response and rate adaptive
DNR	Do not resuscitate
ECHO	Echocardiography
EGM	(Intracardiac) electrogram
EOL	End of life (battery depletion)
ICD	Implantable cardioverter defibrillator
LBBB	Left bundle branch block
LV	Left ventricular
LVEF	Left ventricular ejection fraction
NYHA	New York Heart Association
PCI	Percutaneous coronary intervention
SCD	Sudden cardiac death
VF	Ventricular fibrillation
VT	Ventricular tachycardia
VVI	Ventricular pacing, sensing and inhibiting

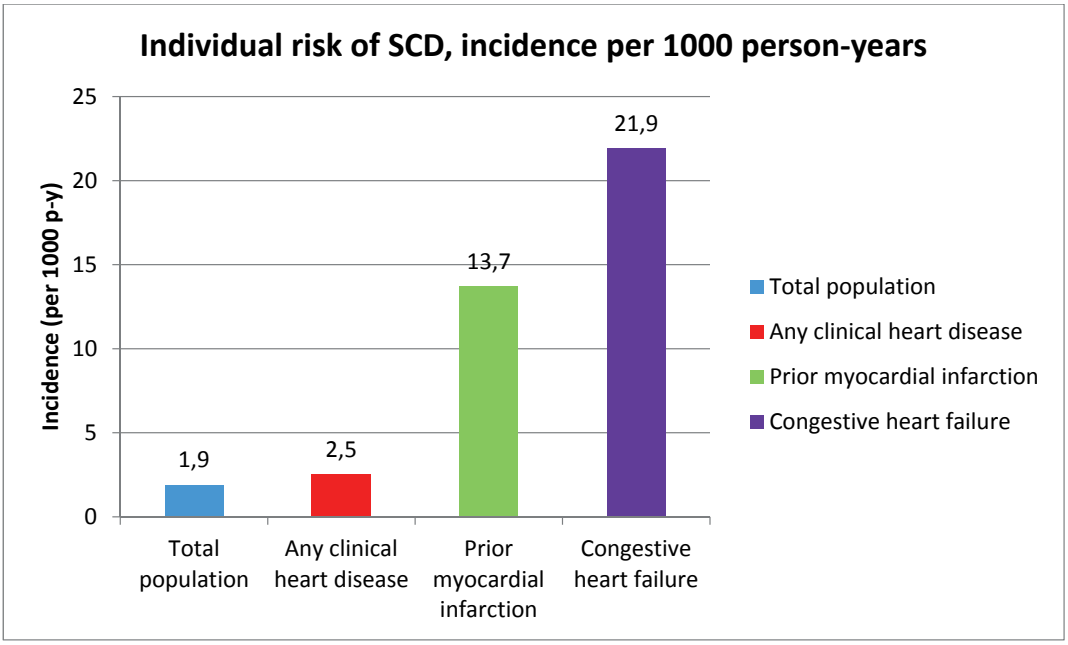
1 INTRODUCTION:

1.1 SUDDEN CARDIAC DEATH:

Cardiovascular disease is the leading cause of death in Western countries, and in Sweden it accounts for 45% of all deaths. Although the overall mortality from cardiovascular diseases has declined in recent decades, this does not apply to the same degree for sudden cardiac death (SCD). Annually, 8000–10,000 people in Sweden suffer from SCD (1).

A problem with preventing SCD is the lack of accurate and reliable methods of identifying persons at risk (2). Individuals with mild or subclinical heart disease account for the majority of sudden deaths, but the likelihood that an individual in this group will experience a cardiac arrest over the decades is very low (3). Many risk factors have been identified for SCD. One of the most common causes of SCD is coronary artery disease (CAD), and about 80% of those who develop SCD have CAD. Persons with ventricular arrhythmias are known to be at high risk of cardiac arrest, but they represent only a small fraction of all victims of SCD. Another major risk factor of SCD is heart failure defined as impaired left ventricular function/ejection fraction (LVEF) especially after acute myocardial infarction (AMI) (4, 5) (Figure 1).

Figure 1: Cardiac arrest incidence among persons 50–79 years old in a large, population-based health maintenance organization in the USA between1986 and 1994. *Rea T, Pearce RM, Raghunathan TE, Lemaitre RN, Sotoodehnia N, Jouven X, et al. Incidence of out-of-hospital cardiac arrest. Am J Cardiol. 2004;93(12):1455-60.*



Sudden cardiac death involves a malignant ventricular arrhythmia, which can start around scar tissue in the heart, often caused by myocardial infarction. This compromised tissue can allow reentry ventricular tachycardia (VT) or ventricular fibrillation (VF). Another more uncommon mechanism behind SCD involves VT caused by triggered automaticity. This is seen in rare diseases such as long QT and Brugada syndrome. Most of these diseases are genetically inherited ion-channel disorders with symptoms presenting early in life.

Electrical defibrillation of the myocardium is the only practical means of terminating ventricular fibrillation. Successful defibrillation is achieved when a critical mass of the myocardium is depolarized by establishing a voltage gradient throughout the ventricular tissue (3).

1.2 IMPLANTABLE CARDIOVERTER AND DEFIBRILLATOR, HISTORY

The implantable cardioverter and defibrillator (ICD) was invented by Dr Mieczyslaw Mirowsky, who was born in Poland, and due to his jewish origin, escaped to the US and later became director of the Coronary Care Unit at Sinai Hospital in Baltimore, Maryland. He was inspired to develop a defibrillator when one of his colleagues died suddenly. In the mid-1970s, after several years of research, the first defibrillators were implanted in animals. The first human implantation was performed in 1980 and five years later the ICD was approved for commercial sale by the Food and Drug Administration (6).

The first ICD implantations required open thoracotomy. The leads were epicardial patches and the device was very large and had to be implanted in the abdomen (Figure 2). The device only delivered defibrillation therapy and pacing support function was not added until the 1990s. Initially, the complex implantation procedure required postoperative hospitalization of approximately one week and the device only had a longevity of less than two years (7).

1.3 ICD FUNCTIONS

Modern ICDs are much smaller, the leads are transvenous and implantation is faster, safer and less complicated (Figure 3). All ICDs are now equipped with regular pacemaker functions as well as the ability to recognize and attend to life-threatening ventricular arrhythmias. If VT or VF is detected, the ICD can convert the arrhythmia to sinus rhythm by either delivering high-voltage shocks (500–700 volts) or by carefully timed pacing impulses at a rate faster than the VT, so-called antitachycardia pacing (ATP). ATP is painless and converts 90% of all VTs, but there is 1–3% risk of acceleration of the arrhythmia (3). The devices have a memory function so that information regarding the morphology and rate of the arrhythmia is stored, as well as information regarding electrocardiographic signals before, during and after therapy.

ICD systems are implanted transvenously under local anesthesia. The surgery takes approximately 60 minutes. In many places acute defibrillation testing, after

implantation, is performed by inducing VF and letting the device deliver a shock to ensure a safety margin for treatment of spontaneous arrhythmias. Since defibrillator testing involves inducing potentially fatal arrhythmias it is not without risk, and today there is a growing preference not to test the defibrillation threshold (8, 9).

Figure 2. The first ICD. "*Materials "[Image] provided courtesy of Boston Scientific. © 2014 Boston Scientific Corporation or its affiliates. All rights reserved."*

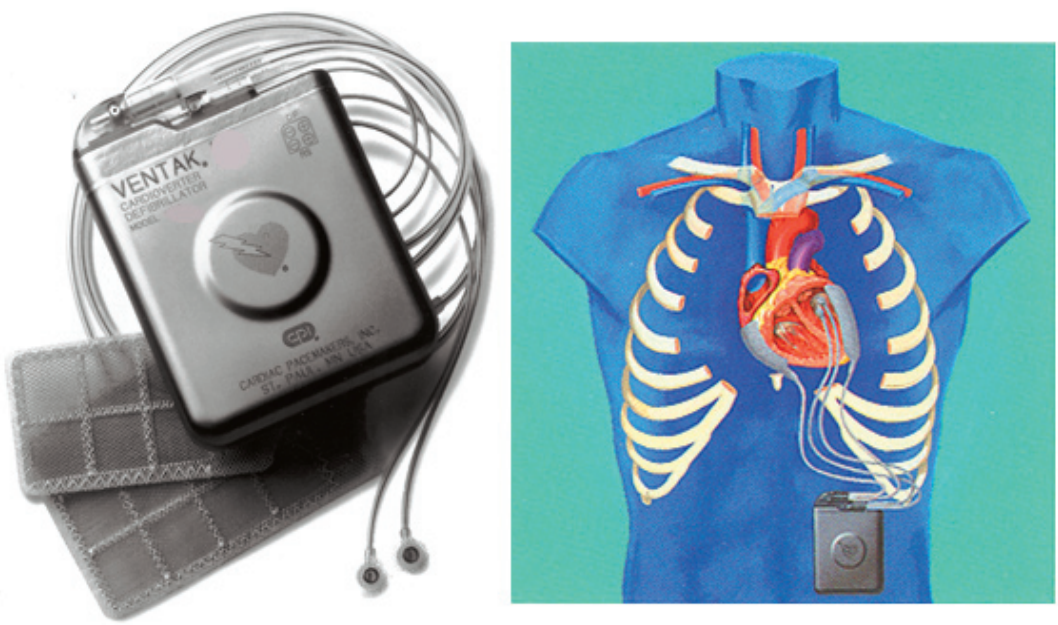


Figure 3. The first ICDs and the evolvement. "*Materials "[Image] provided courtesy of Boston Scientific. © 2014 Boston Scientific Corporation or its affiliates. All rights reserved."*

In order to deliver a high-voltage shock to the heart, a special type of lead is required which has one or two special coils of wire capable of delivering the high energy. It is important that the lead can pace and sense even small intrinsic signals. In particular, VF is often characterized by low amplitude ventricular signals that must be interpreted correctly, and at the same time it is important that the device does not oversense T-waves, noise or far-field signals (3). Modern ICDs are made of titanium and often have lithium-vanadium batteries. The devices can deliver shock therapy of 2–42 J by way of store and charge capacitors, and the longevity is 6–8 years.

There are several types of ICD system. Single-chamber ICDs have only a high-voltage lead and in addition to defibrillation can allow VVI(R) pacing. Dual-

chamber ICDs are today more common than single-chamber devices. In addition to the defibrillator lead they have an atrial lead which enables DDD(R) pacing and this may improve the discrimination between atrial and ventricular tachycardia. ICDs can also be combined with cardiac resynchronization therapy (CRT) to improve left ventricular function among patients with broad QRS and congestive heart failure (10).

1.4 CARDIAC RESYNCHRONIZATION THERAPY (CRT)

Heart failure is often associated with disordered electrical timing, which can cause heterogeneous and delayed ventricular activation. Delayed ventricular electric activation is manifest by prolonged QRS duration, usually in the form of a left bundle branch block (LBBB).

Prolonged atrioventricular delay may result in atrial contraction before venous return is completed, and early mitral valve closure which can diminish ventricular volume and cause mitral regurgitation.

Optimal inter- and intraventricular coupling is important for maximal ventricular pumping function. Interventricular delay refers to the coordination between the right and left ventricle, whereas intraventricular delay refers to the coordination between the septum and lateral wall in the left ventricle (7). By placing an electrode in a vein, outside the left lateral wall, in combination with the ordinary leads, CRT works by partially or wholly correcting the atrioventricular, interventricular and most importantly the intraventricular dyssynchronies (11). A meta-analysis of four large CRT studies covering more than 5300 patients showed that CRT was effective in reducing both mortality and hospitalization (12).

1.5 INDICATIONS FOR AN ICD

Initially, ICDs were solely recommended as secondary prevention for survivors of cardiac arrest or previously documented life-threatening arrhythmia unrelated to a transient or reversible cause.

In recent years, implantation of primary preventive ICDs among patients at high risk of SCD has become frequent.

The term “primary prevention” is used to describe the use of ICD therapy in individuals at risk of SCD but without a history of sustained ventricular arrhythmias.

For primary prevention of SCD, current guidelines in both Europe and the USA recommend ICD implantation for patients with previous AMI (≥40 days post MI) who have LVEF ≤35% and NYHA class II–III, or LVEF ≤30% and NYHA class I. An ICD is also recommended in patients with non-sustained and inducible VT and LVEF ≤40% and in non-ischemic patients with LVEF ≤35%. It is recommended to wait three months before ICD implantation after revascularization (13, 14). According to guidelines, patients have to be on optimal medical therapy and in good functional status with respect to their non-cardiac comorbid situation before implantation (14). A contraindication to ICD treatment is expected survival of less than one year.

Updated guidelines from the Swedish National Board of Health recommend implantation of primary preventive ICDs in patients with LVEF ≤35% and NYHA class II–III regardless of etiology and ≥40 days after AMI. Recently, primary preventive ICDs were recommended first three months after AMI (1).

It is also advisable to implant a primary preventive ICD in patients with familial conditions with a high risk of SCD, for example Brugada syndrome, long QT syndrome or severe hypertrophic cardiomyopathy.

According to both European and American guidelines, CRT or CRT-D can be recommended for patients with LBBB, QRS duration ≥120 ms, EF ≤35% and NYHA class II–III and can be considered in patients with non-LBBB who have QRS duration ≥150 ms (13). If NYHA class IV patients are stable, CRT without an ICD is recommended.

1.6 FREQUENCY OF ICD IMPLANTATION

ICD treatment, especially for primary prevention, is becoming more common. It is used worldwide and the number of implantations has grown exponentially in almost every surveyed country since 2005 (Figure 4). In 2007 the average implantation rate in western European countries was 155 per million inhabitants (15). The USA remains clearly the world's largest implanting country, with 133 262 ICD implants, or 434 new implants per million inhabitants in 2009 (16). In Sweden the rate of ICD implantations increased from 74 per million inhabitants in 2007 to 136 per million in 2012, but compared with other western European countries Sweden still has a low implantation rate (Figure 5) (15, 17). The reason for this is not clear, but it may be due to economic concerns, fear of adverse effects, inadequate follow-up after AMI, or lack of identification of patients that will benefit from the treatment.

Figure 4. ICD implantation rates 2005 and 2012 in Europe *(Source population data: Eurostat Units - Eucomed based on reports from major manufacturers* Europe represents total of listed countries (N/A countries excluded).*

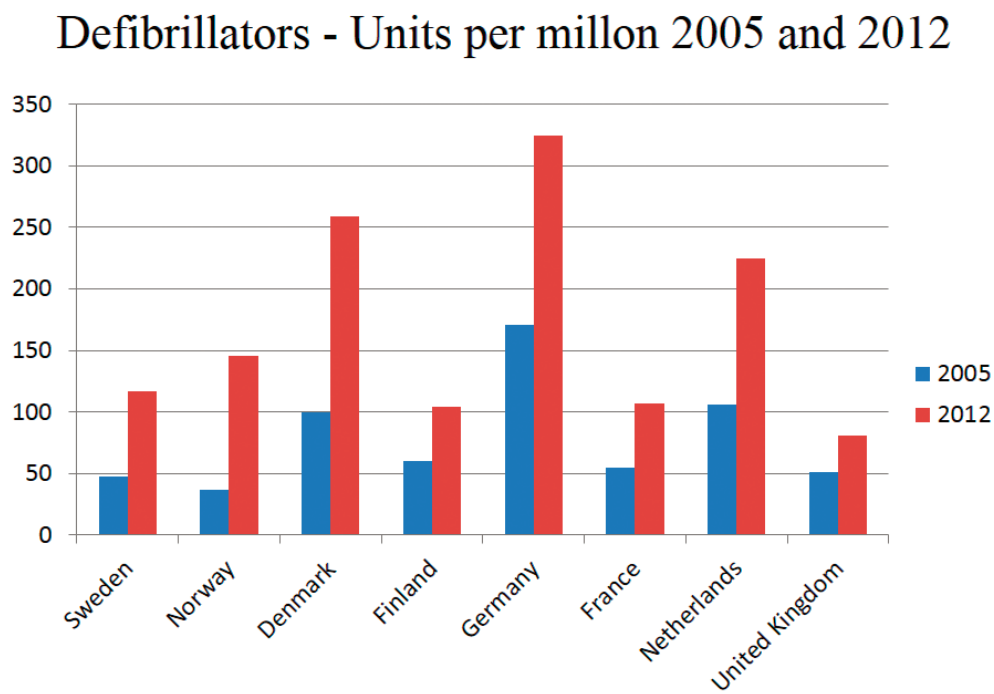
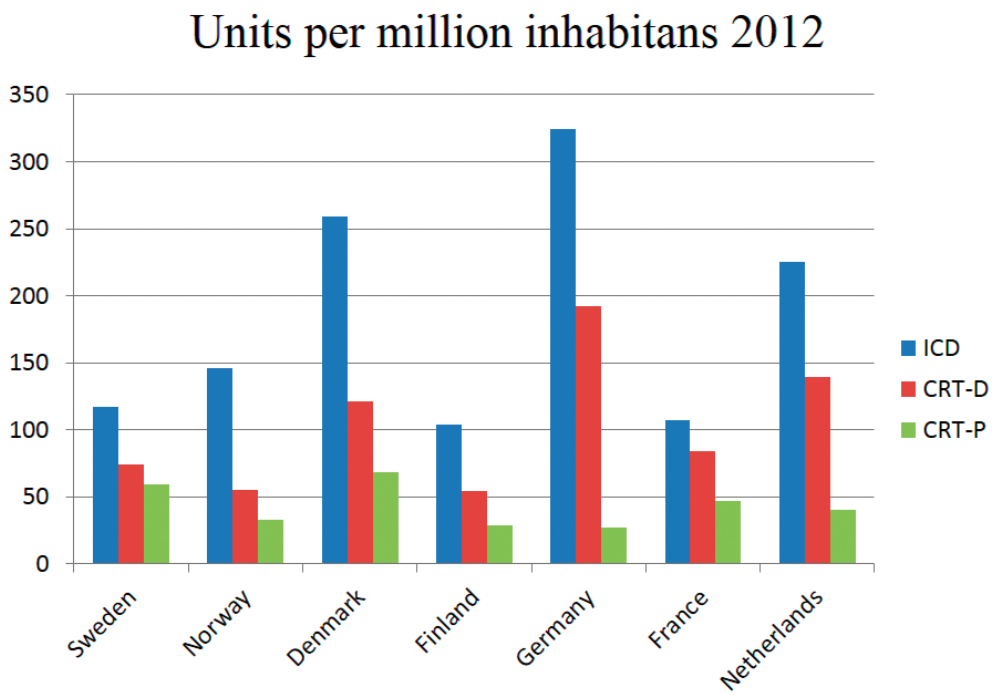


Figure 5. ICD, CRT-D and CRT-P implantation rates 2012 (*Source population data: Eurostat Units - Eucomed based on reports from major manufacturers* Europe represents total of listed countries (N/A countries excluded)*



1.7 STUDIES OF ICD EFFICACY

A large number of randomized trials illustrating the efficacy of ICD therapy have been published. The first studies were performed in high-risk patients with aborted cardiac arrest or poorly tolerated VT. ICDs were compared with best medical therapy and the results demonstrated a large survival benefit in the ICD groups (18). The MADIT and MUST studies were the first primary preventive ICD trials. They included patients with heart failure after AMI and non-sustained VT; thus patients at a high risk of SCD. The results showed a large absolute risk reduction with ICD treatment, of more than 25% (19, 20).

At the beginning of the 21st century a large number of studies performed in patients with lower risks of SCD were published. The MADIT II study included patients with LVEF ≤30% and remote AMI (21). In the SCD-HeFT study both patients with ischemic and non-ischemic etiologies of heart failure were included (22) and in the DEFINITE trial , patients with only non-ischemic etiology and reduced LVEF were randomized to ICD or best medical therapy (23). Pooled analyses of these and other primary preventive studies have provided strong evidence for the beneficial effect of ICD therapy and an approximately 8% absolute risk reduction of all-cause mortality regardless of etiology (24, 25).

There are few studies designed to compare CRT in combination with ICD (CRT-D) with CRT only. A systematic analysis performed to compare the efficacy of these devices showed no reduction in all-cause mortality in the CRT-D group compared with the CRT group during the first year after implantation. However, after one year of follow-up there was a reduction in mortality in the CRT-D group (26). The result of this analysis is uncertain, however, as apart from the Companion study (27), all other included studies in the analysis were non-randomized and heterogeneous in demographic factors.

In contrast to the few studies carried out to compare CRT with CRT-D therapy, there are several recently published studies (RAFT, REVERSE, MADIT-CRT trial) in which ICD and CRT-D treatment have been compared. In summary, it seems beneficial to use CRT-D rather than ICD treatment in patients with broader QRS (≥150 ms) who are in NYHA class II or III (28-32).

1.8 TIMING OF ICD IMPLANTATION

Although the risk of SCD is highest in the first month after AMI (33, 34), there is no benefit in having ICD treatment early after myocardial infarction. In both the DINAMIT and the IRIS study patients with moderately reduced LVEF a few days after AMI were randomized to ICD or medical therapy (33, 35). Although the risk of SCD was reduced in the ICD groups there were no differences in all-cause mortality. There are a number of reasons why these two trials failed to show improved survival. It is possible that patients shortly after AMI suffer from re-infarction, worsened heart failure or other causes of death. Another explanation could be that many patients recover their left ventricular function after AMI (36).

International guidelines advocate primary preventive ICDs for patients with reduced LVEF more than 40 days after AMI or after three months in cases of revascularization, but the optimal timing has never been evaluated in prospective studies.

Post hoc analyses of the SCD-HeFT study imply that time since AMI does not modify the effect of ICD treatment as regards all-cause mortality (37), but other studies indicate that the risk of ventricular arrhythmias increases with time elapsed from revascularization (38). A recently published meta-analysis of nine primary preventive ICD trials revealed no evidence that the efficacy of primary prevention ICD therapy depends on time to implantation from 40 days or more after AMI (39). However, delayed decisions regarding ICD therapy after AMI are associated with a lower likelihood of implantation (40).

1.9 SELECTION OF PATIENTS FOR PRIMARY PREVENTIVE ICDS

At the moment, the guidelines for implantation of primary preventive ICDs are based on LVEF and NYHA class, but there is no evidence that this is the best method to identify patients who will benefit the most from ICD therapy (41). In one study, many patients with LVEF ≤35% did not had ICD therapy during 5 years of follow-up (22), and ICD treatment is costly and may cause complications.

One problem is that factors associated with an increased risk of SCD are also associated with increased all-cause mortality. For instance, patients receiving dialysis have a high risk of SCD, but cardiovascular mortality remains high even if they receive defibrillators (42). However, the results of a recently published meta-analysis imply that although mortality is high in patients with impaired renal function, ICDs still reduce mortality (43). Another example is advanced age. The incidence of SCD increases with age, but data regarding ICD efficacy in older age groups is limited and divergent, particularly as regards patients of 75 years of age or more. However the results of a meta-analysis suggest that primary prevention ICDs in older patients may be beneficial (44).

Another question is if women benefit equally from primary preventive ICDs compared with men. A meta-analysis of five trials with a total of 934 female patients failed to show a reduction in all-cause mortality (45), raising the question of whether indications for ICD treatment should be different for women than for men. On the other hand, women seem to benefit more from CRT therapy. In the MADIT-CRT trial, women showed significant reductions in death and heart failure, and consistent echocardiographic evidence of reverse cardiac remodelling (46).

Many earlier studies have been carried out in an attempt to identify risk factors that could help pinpoint patient subgroups expected to gain the most benefit from ICD therapy. In the VALIANT trial >11 000 patients with AMI were included. In the short term the risk of SCD was increased among patients with higher heart rate and impaired renal function, but in the long term a reduced LVEF was a stronger predictor of SCD (47).

Retrospective post hoc analyses of patients enrolled in the MADIT-II study (48) showed that age >70 years, a history of atrial fibrillation (AF), renal failure, affected ventricular depolarization and advanced heart failure (NYHA class III–IV class) were significantly associated with prognosis in a J-shaped relationship. Patients without risk factors and patients at a very high risk showed no benefit from ICD therapy, while medium-score patients treated with an ICD demonstrated a large reduction in the risk of death. These findings were also

reproduced in two American registry-based studies (49, 50). A meta-analysis carried out to identify factors associated with mortality in patients with heart failure treated with ICDs was published recently. In addition to earlier-identified risk factors, patients with chronic obstructive pulmonary disease, diabetes, peripheral vascular disease and appropriate and inappropriate ICD shocks had a higher mortality rate (51). Similar results were found in a prospective study in the USA, where poor functional status, low mean arterial pressure, diabetes, low BMI and AF were strongly associated with death within a year in spite of ICD treatment (52). In summary, these studies imply that the net benefit ICDs decreases in patients with increased morbidity because death occurs as a result of causes other than lethal arrhythmia.

1.10 COMPLICATIONS

Controversy exists concerning the cost-efficacy of ICDs for primary prevention in patients with heart failure, partly because of the relatively high rates of post-implantation hospitalization and device-related complications (53, 54).

The reported complication rates associated with ICD treatment vary in different studies from 1.8 to 31% (55-57). Complication rates in real-life surveys are much higher than in randomized studies, which could be due to different selection of patients and the time-span of follow-up. There are also problems with early failure of small calibre defibrillator leads, and lead problems increase with time (58). Both primary CRT-D implantations and upgrade procedures are associated with more complications than primary ICD implantation, and an increased risk of complications is associated with device replacement (59).

Another issue is device-related infections. Multiple studies confirm increasing infection rates and the fact that the risk of infections increases with both time since primary implantation and the number of surgical procedures, and this may eventually have an impact on mortality (60-62).

There are also deaths associated with incorrect deactivation of defibrillators (63) and the true incidence of ICD malfunction is not known as a result of an absence of systematic post-mortem assessment of these devices (63, 64). Only a few

devices are sent in and interrogated after death, despite the fact that the Heart Rhythm Society emphasizes the importance of returning explanted devices to manufacturers for analysis (64). Implantable cardioverter-defibrillators are supposed to protect patients from SCD, but several studies have shown that only 60% of potentially fatal arrhythmias can be terminated (25). Data analysis of ICDs from deceased patients could help us to understand the mechanisms behind SCD in patients with ICDs and perhaps optimize the programming of the devices.

1.11 SHOCK TREATMENT

ICD shock treatment can be lifesaving but it can also cause great pain and anxiety. Patients who receive shocks experience a worse quality of life (65-67). There are also studies that imply that shock therapy, both appropriate and inappropriate, is associated with higher mortality (68), but perhaps only in patients with ischemic cardiomyopathy and during the first four years after device implantation (69). There is also a risk that an ICD is not always able to stop ventricular arrhythmias. How common arrhythmias are at the end of life and the incidence of shock therapy is unknown . There is a possibility that terminally ill patients develop conditions such as hypoxia, electrolyte disturbances, stroke and heart failure, all with an increased risk of triggering arrhythmias and thereby increasing the risk of shock and an unnecessarily painful death.

The frequency of inappropriate shocks varies in different studies (70), but there are ways to minimize the number of unnecessary shocks. More “conservative” programming (i.e. higher VT zones with longer detection intervals and more ATP therapies before shock therapy) may contribute to reducing the number of unnecessary shocks (71, 72).

2 AIMS

- To investigate compliance to guidelines regarding implantation of a primary preventive ICD.
- To examine the extent and timing of improvement in left ventricular function after AMI, in order to rapidly identify candidates appropriate for ICD therapy for primary prevention.
- To evaluate the net benefit of ICD treatment in patients with heart failure with regard to the incidence of appropriate and inappropriate ICD therapies, complications and possible gender differences.
- To investigate the occurrence of arrhythmias and shocks in ICD-treated patients at the end of life.

3 MATERIAL AND METHODS

Study I

We carried out a retrospective study of medical records from AMI patients admitted to Södersjukhuset and Danderyd University Hospital between January 2008 and December 2009. Patients with an LVEF of ≤35% and age ≤80 years at the time of admission were included. Evaluation of follow-up and echocardiographic recordings 1–3 months after AMI was performed. We reviewed indications and contraindications as regards primary prevention ICDs and whether or not the responsible physician made a decision concerning ICD treatment. We also evaluated mortality and the causes of death, based on medical records, death certificates and autopsy reports when available.

Contraindications regarding ICD treatment were assessed by two independent reviewers from different hospitals. In cases of conflicting opinions, consensus was reached by way of mutual decision. Contraindications to ICD therapy were defined as dementia, severe mental illness, current alcohol or drug abuse, NYHA Class IV or expected survival <1 year because of underlying morbidity. In patients with repeated echocardiography (ECHO), we evaluated the proportion of patients with LV function improved to such a degree that an indication for an ICD was no longer present.

Echocardiographic recordings at discharge and at follow-up were assessed with respect to LVEF. We considered the follow-up as inadequate in patients with impaired LV function and no contraindications to ICD treatment, if follow-up ECHO was not performed in 1–3 months, and/or the physician did not discuss ICD treatment.

The patients that had received inadequate follow-up according to guidelines were offered a new follow-up with ECHO and a decision on treatment with an ICD if appropriate.

Study II

A prospective study of 100 AMI patients admitted to Danderyds University Hospital or Södersjukhuset with heart failure defined as LVEF ≤40%. The main exclusion criterion was a short life expectancy. Patients that fulfilled the inclusion criteria and accepted participation in the study were included. Dobutamine stress ECHO was performed on day 3–8 after myocardial infarction and this was followed by serial ECHO examinations after 1, 3, 6 and 12 months. The patients' morbidity, medication, ECG, angiography findings and NYHA classes were recorded. Blood sample were collected and the patients underwent Holter registration.

The paper based on this study was focused on the ECHO results 3–8 days, one month and three months the AMI.

Study III

Using Swedish national ICD registry data, 865 consecutive patients receiving an ICD for primary prevention during 2006–2011 were identified at four tertiary care hospitals in Stockholm and Lund. All patients who had primary preventive ICDs implanted due to heart failure (defined as LVEF ≤35%) were included. We excluded patients with a history of previous sustained ventricular arrhythmias, cardiac arrest, Brugada and long QT syndromes, arrhythmogenic right ventricular dysplasia and hypertrophic cardiomyopathy.

The medical records of all 865 patients were scrutinized in order to assess the presence of appropriate and inappropriate therapies, complications and mortality. The data was cross-validated regarding survival status using the national Swedish Cause of Death Registry

Data was extracted regarding clinically relevant risk factors known at the time of ICD implantation. The patients were assign to one of three risk factor groups and we investigated if the groups differed as regards mortality and appropriate therapy. The risk factors used were NYHA class >II, age >70 years, kidney

diseases defined by blood urea nitrogen ≥50 mg/dl and/or serum creatinine ≥2.5 mg/dl, QRS duration ≥120 ms, atrial fibrillation and diabetes.

The paper based on this study was focused on the results of analyses of appropriate and inappropriate therapies, complications, mortality and gender differences.

Study IV

We prospectively studied 130 ICD devices explanted after death from 26 participating hospitals. The study population's demographic data, time and cause of death were obtained from patients' medical records, the Swedish ICD and Pacemaker register, the National Board of Health and Welfare and death certificates from the Swedish Tax Agency. All the ICDs were interrogated and all available intracardiac electrograms (EGMs) from the last 24 h before death were retrieved.

Three investigators, two of them blinded to the patients' medical records and arrhythmic histories performed the review and analysis of the EGMs independently. If the investigators disagreed on the origin of the arrhythmia, i.e. ventricular or supraventricular, a fourth blinded investigator proceeded with the analysis and a consensus decision was taken.

The incidence of ventricular tachyarrhythmia and shock treatment was recorded. Shocks were classified as appropriate or inappropriate. In addition to the occurrence of any shocks, we assessed the number of shocks received during the last 24 hours of life.

We also investigated the cause of death, whether the death occurred at hospital and if there was a Do-Not-Resuscitate order.

4 STATISTICAL ANALYSES

Continuous data are presented as mean ± standard deviation or median [IQ range] as appropriate and nominal data as percentage (number of cases). Fischer's exact test was used for comparison between categorical variables and Student's *t*-test for comparison of continuous variables. If the parameters were normally distributed, confidence intervals (CIs) were calculated, and in cases where we did not assume a normal distribution Wilcoxon's Signed Rank Test was used. Analysis of variance (ANOVA) was used when comparing more than two groups. A two-sided p-value < 0.05 was considered statistically significant. For survival analysis we used Kaplan–Meier curves, with log-rank testing. Cox regression analysis was used for evaluation of independent predictors of survival and event-free survival. All variables with a p-value <0.20 in univariate analysis were entered into multivariate backwards stepwise regression analysis. Assessment of intra-observer variability as regards LVEF was performed by calculating LVEF twice during the same examination on two different occasions without knowing the previous result. Similarly, assessment of inter-observer variability for LVEF estimations was performed without any knowledge of the result from the other researcher. Variability was calculated as the mean percentage error expressed as the absolute difference between two sets of observations divided by the mean of the observations. All analyses were carried out with SPSS software (IBM, Version 21). In Paper II we assumed a 20% dropout rate and we calculated that enrollment of 100 patients would provide 80% power to detect a difference of at least 10 percentage units in LVEF.

Ethics

All studies were approved by the local ethics committee and were performed in accordance with the Declaration of Helsinki.

DNR: 2010/882-31/2; 2012/771; 2008/1527–31/4

The patients in Study II gave written informed consent.

5 RESULTS

5.1 STUDY I:

Acute myocardial infarction was diagnosed in 3372 patients during the pre-defined period. Of these, 2023 (60%) patients were of age ≤80 years, and 187 (9.2%) had an EF of ≤35%.

Baseline charactersitics are presented in Table 1. Most patients with AMI and LV dysfunction received a follow-up visit after the myocardial infarction, but inadequate follow-up according to guidelines was found in 32%, mainly because of lack of an ECHO examination in time, and in some cases ICD treatment was not considered. An ICD for primary prevention was implanted in 13% of the patients and the median time to implantation was 6.6 months. Contraindications for ICD implantation were found in 28% of the patients (Figure 6). Many patients (41%) showed improvement in LV function to such a degree that ICD treatment was no longer indicated. The mortality rate was high (9%) and a few of those who died might have been saved by ICD treatment (Figure 7).

The main results of this study demonstrate that follow-up after AMI is insufficient and may increase the risk of SCD. Another finding is that the number of patients who develop low LVEF (≤35%) after AMI is small, and a significant proportion of patients experience improvements in LV function, making primary preventive ICD treatment redundant.

Table 1. Characteristics of patients with ejection fraction ≤35%, and age <80 years.

Characteristics	**Patients n=187 (%)**
Age, years (±SD)	67.5 ± 9
Male/Female	137 (73) / 50 (27)
Diabetes mellitus	62 (33)
Hypertension	91 (49)
History of congestive heart failure	55 (29)
Prior coronary artery bypass graft surgery	43 (23)
Prior myocardial infarction	71 (38)
Angina pectoris	58 (31)
Atrial fibrillation	52 (28)
Baseline EF, % (±SD)	29 ± 6

Figure 6. Patients with acute myocardial infarction in 2008–2009 discharged from Södersjukhuset or Danderyds sjukhus.

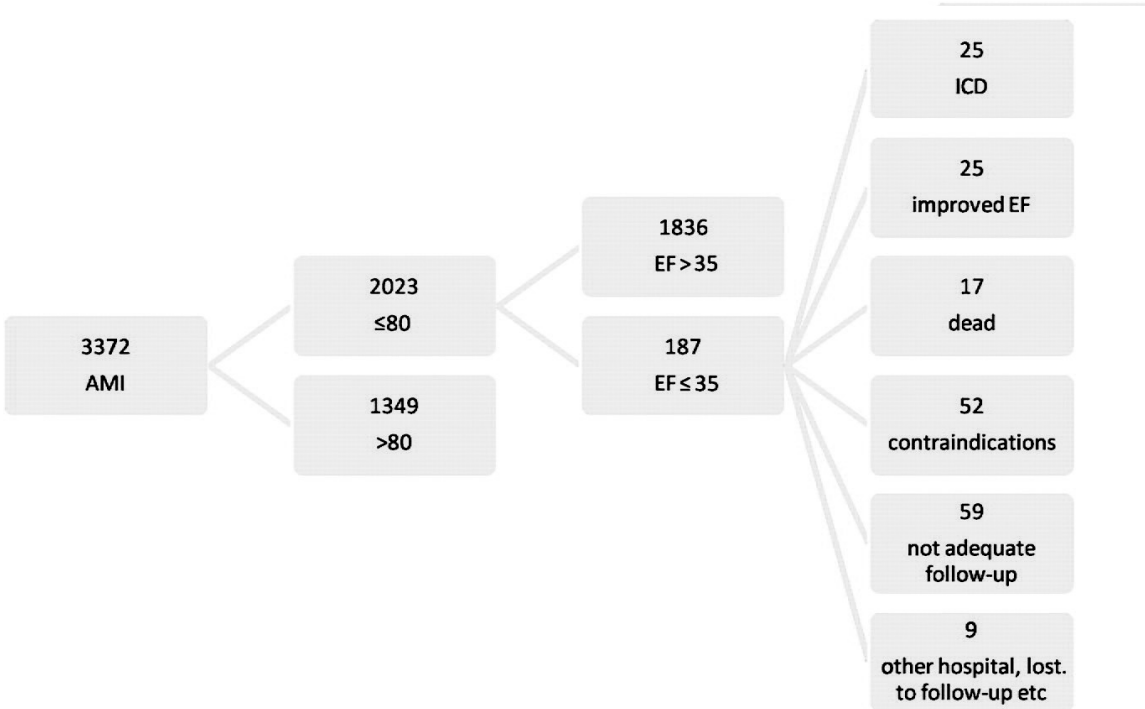
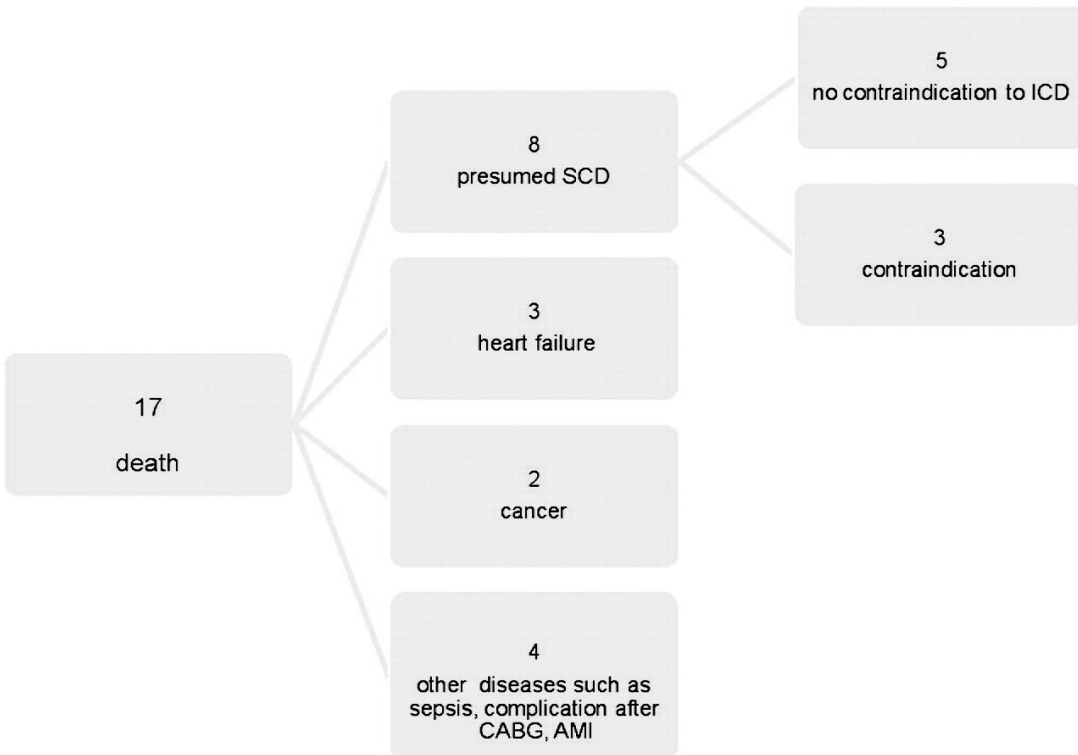


Figure 7. Cause of death.



5.2 STUDY II

Out of the 100 patients included originally, nine were excluded before the first ECHO due to complications after AMI or inadequate quality of the echcardiographic examinations. Baseline data are based on the remaining 91 patients. In addition, five patients did not undergo all the ECHOs because of fatigue or coronary artery bypass grafting (CABG).

The study population mostly consisted of men (78%), with a mean age of 68 years and 71% without previously known cardiac disease. Mean and median EF at inclusion was 31% [17.5–40] (Table 2). Most patients (59%) had stenosis in the left anterior descending artery and 86% of all patients were treated by means of percutaneous coronary intervention (PCI). All patients except one were started on beta-blockers and ACE inhibitors or angiotensin II receptor antagonists.

At one month of follow-up, more than half (55%) of the patients had improved to such an extent that there was no longer a clear indication for ICD treatment. The mean improvement in LVEF between inclusion and one month was 6.5±9 percentage units ($p<0.001$). Only four of the 38 patients with LVEF <35% at one month improved further and no longer met the ICD criterion (LVEF range 38–48%) after three months. The mean difference in LVEF between one and three months was small but significant, 1.9 percentage units (Figure 8).

During the first weeks of follow-up 9% (n=8) of the patients suffered from life-threatening arrhythmia requiring resuscitation. These patients survived and had an ICD implanted. Two other patients succumbed to non-sudden cardiac death.

The patients that developed life-threatening ventricular arrhythmias did not differ significantly from the other patients in baseline characteristics nor in LVEF at inclusion. Patients who did not show improved LVEF were more likely to have heart failure and low LVEF at inclusion.

Table 2. Left ventricular ejection fraction and end-diastolic diameter following acute myocardial infarction.

ECHO §	Definition	Time after AMI*	LVEF† (%, mean±SD)	LV ‡ end-diastolic diameter (cm)	p-value for difference in LVEF vs. ECHO 1
ECHO 1	Clinical ECHO, determining inclusion	2.1±1.3 days	31±5.8	5.2±0.7	
ECHO 2	First study ECHO, before discharge	5.0±2.3 days	32±7.0	5.4±0.8	p=0.005
ECHO 3	Second study ECHO	1 month	38±11	5.4±0.8	p<0.001
ECHO 4	Third study ECHO	3 months	40±11	5.3±0.6	p<0.001

§ ECHO = Echocardiography, * AMI = Acute Myocardial Infarction, † LVEF = Left Ventricular Ejection Fraction, ‡ LV = Left Ventricular

Figure 8a. Left ventricular ejection fraction at inclusion, one month and three months after AMI among the patients who met the criterion for ICD treatment after three months (n=35).

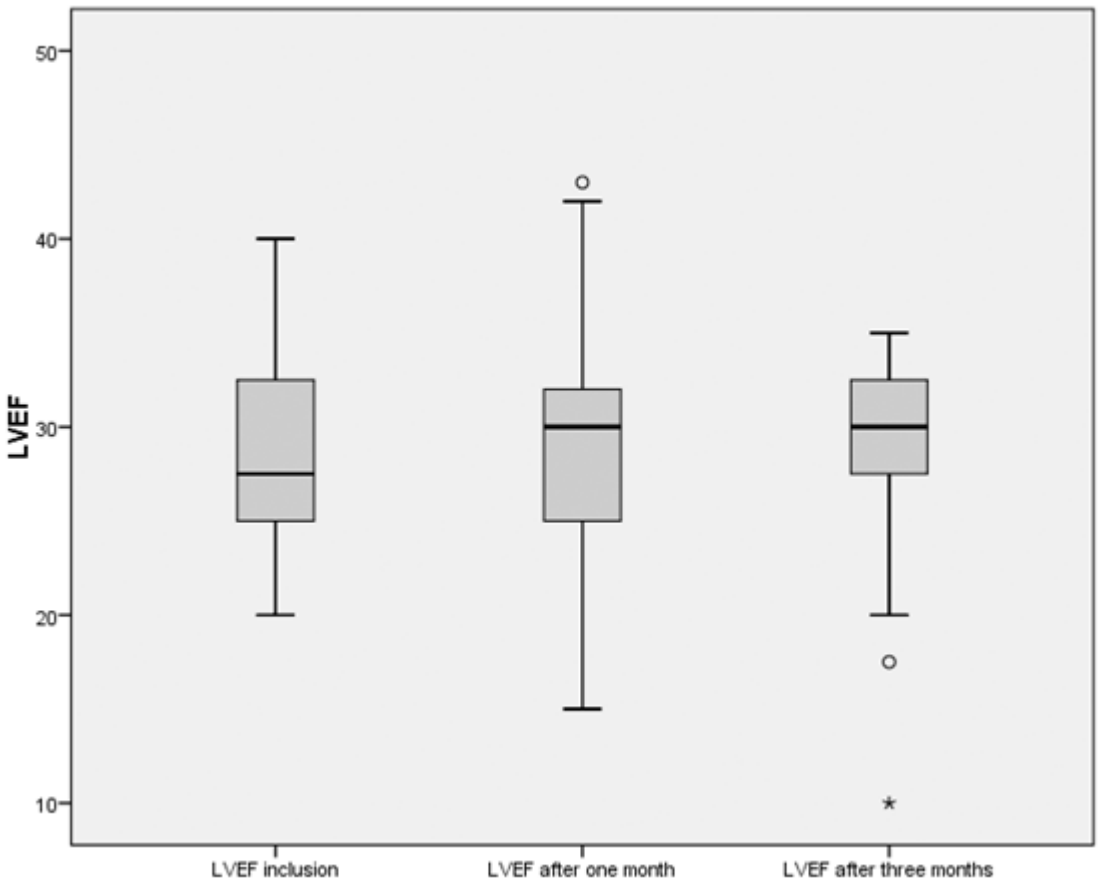
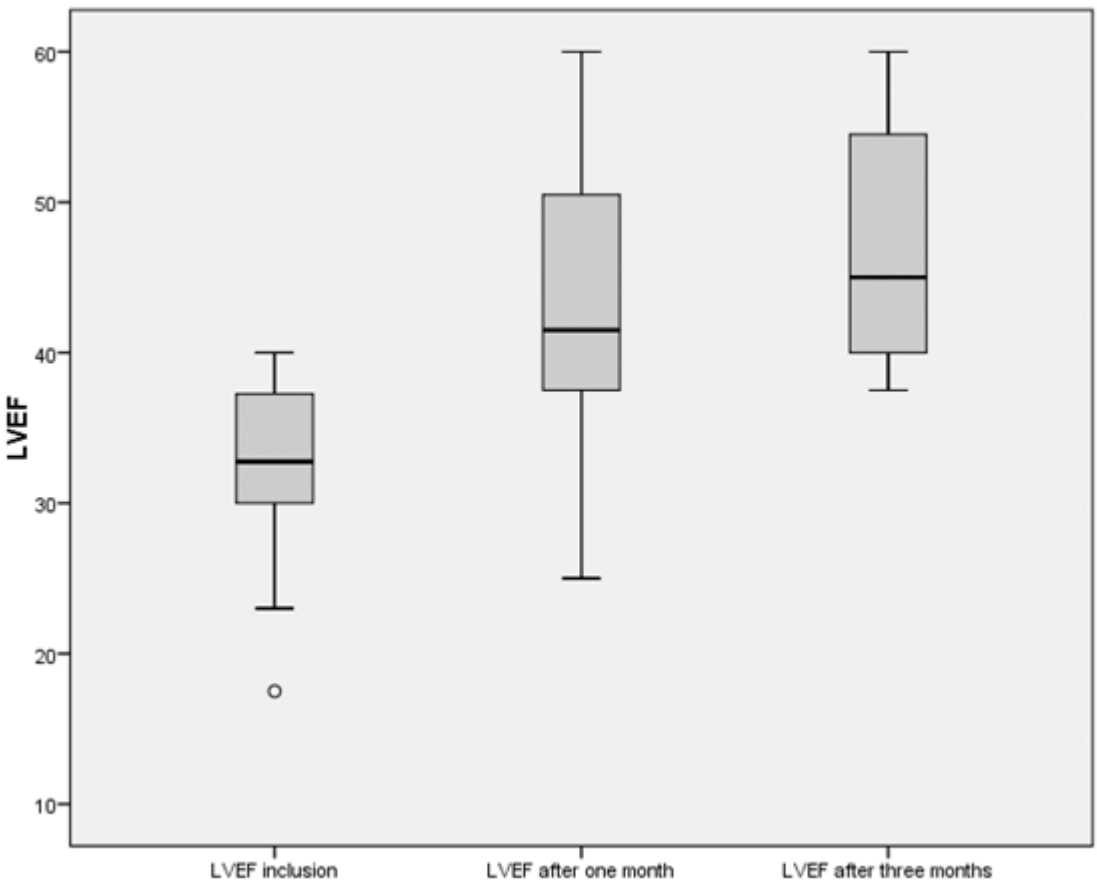


Figure 8b. Left ventricular ejection fraction at inclusion, one month and three months after AMI among the patients who did not meet the criterion for ICD treatment after three months (n=51).



5.3 STUDY III

Out of the 865 consecutively included patients with primary preventive defibrillators, 82% were male, the mean age was 64±11 years, 62% had ischemic etiology behind heart failure and mean LVEF at inclusion was 26±11%. The baseline characteristics of the patients in our cohort were compared with those in patients in three major randomized prospective clinical trials (COMPANION, DEFINITE and MADIT II studies) (27, 73, 74) and overall the only important differences were higher prevalences of atrial fibrillation and beta-blocker treatment, and longer follow-up (three years).

The annual rate of appropriate ATP and/or shock treatment because of ventricular arrhythmias was 6%. Men were more than twice as likely to receive ICD treatment compared with women (p=0.02; Figure 9). Complications were common. The annual rates of inappropriate shocks and complications requiring reoperation were 2.4% and 4.4% respectively. The most common problem requiring reoperation was dislocation or dysfunction of the ICD electrode or the LV electrode, which together accounted for 60% of all the complications. Infections accounted for 13% of the complications and all these patients had to have their entire device systems removed. Very few patients had per-operative complications such as perforation or pneumothorax (Table 3). The time between primary implantation and reoperation varied widely, the median time being 10 months [range 0–67 months]. There was no gender difference in complication rates.

The annual mortality rate was 8.4%, and among those who died, 21% had previously suffered ventricular arrhythmia correctly treated by means of ATP or shock. In patients who received appropriate treatment and later died, the median time from first correctly treated arrhythmia to time of death was 16 months [range 0.2–47 months]. The most common cause of death was heart failure (40%) and 4% died as a result of intractable ventricular arrhythmia (Figure 10).

Figure 9. Percentages of male and female patients receiving appropriate therapy, inappropriate shocks, complications requiring reoperation, or death during 35 months of follow-up.

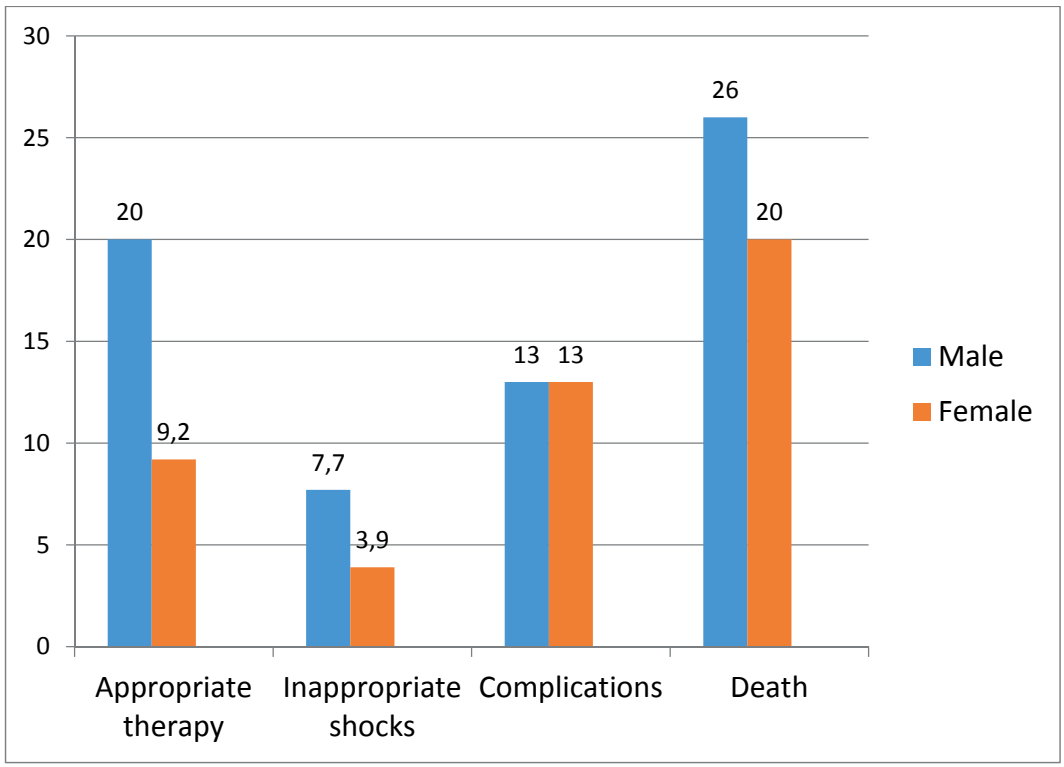
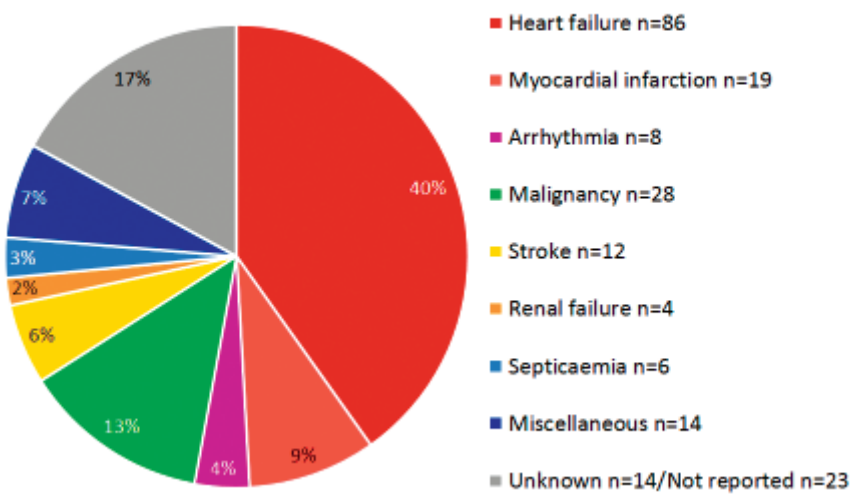


Table 3. Device-related complications

Type of complication	**Number (%)**
Perioperative complications	
Pneumothorax	3 (0.3%)
Perforation	2 (2.0%)
Other	4 (0.5%)
Postoperative complications	
ICD-electrode dysfunction	36 (4.2%)
LV-electrode dysfunction	31 (3.6%)
Atrial-electrode dysfunction	12 (1.4%)
Pocket-related problems	3 (0.3%)
Infection	15 (1.7%)
Multiple	7 (0.8%)
Inappropriate shocks	61 (7.0%)
Other	3 (0.3%)
Total	**177 (20.4%)**

Figure 10. Cause of death



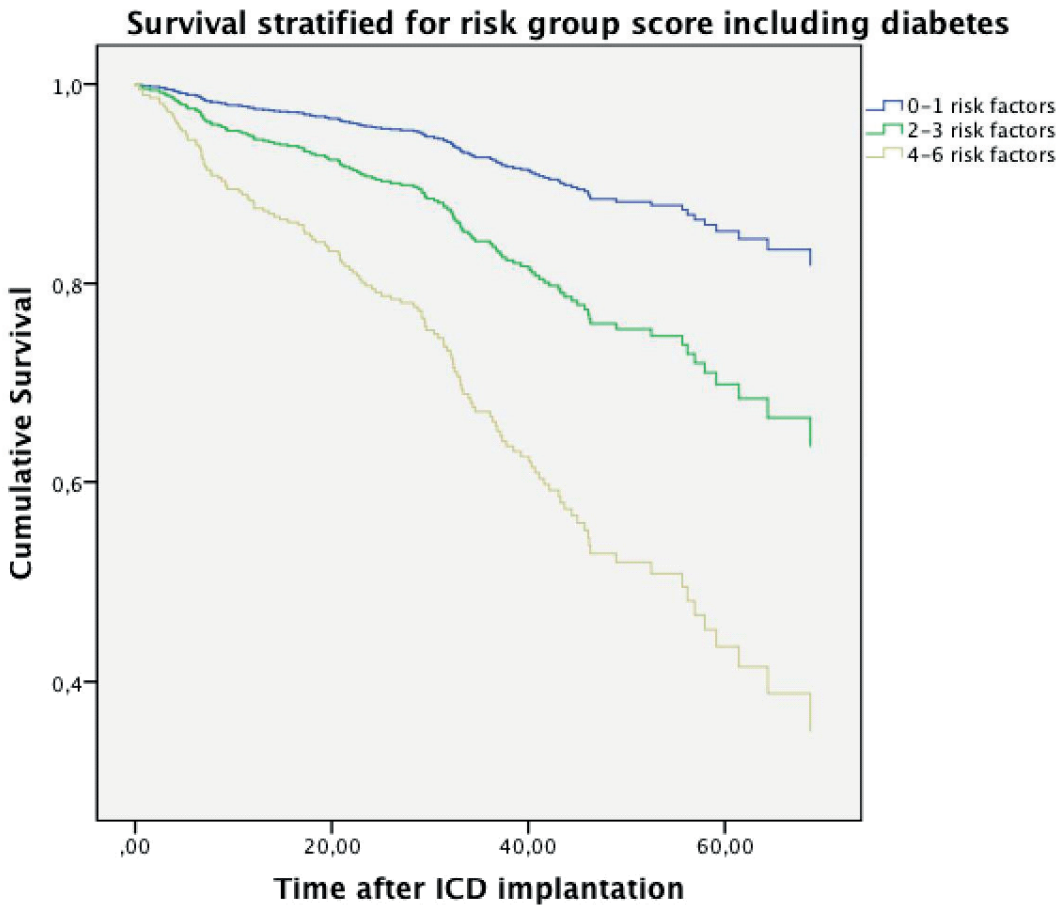
In the same cohort the 865 ICD patients were evaluated as regards morbidity before implantation. In 790 patients there was enough data, and these patients were assigned to one of three risk-factor groups. The average number of risk factors was 2.2±1.3, and in 7% no risk factors (low risk) were identified, 54% had 1–2 risk factors (medium risk) and 39% had 3–5 risk factors (high risk). The patients in the high-risk factor group generally had more co-morbidity in addition to the conditions included in the risk score, compared with those in the low- and intermediate-risk groups. There was no significant difference in survival between the low- and medium-risk groups, but a significant increase in mortality in the high-risk group. Neither appropriate nor inappropriate therapy differed significantly between groups.

Since diabetes was an independent predictor of both death and "death or appropriate ICD therapy", a new risk score was constructed, incorporating diabetes. Multivariate analysis was repeated, showing a highly significant

independent predictive value for all-cause mortality using the new risk-group variable, but no differences in appropriate therapy (Figure 11).

In conclusion, the results of this study show that ventricular arrhythmias necessitating ICD therapy are common (6% annually). Women are less likely to have correct ICD treatment, but have the same degree of treatment complications, thus reducing the net benefit of their treatment. Despite considerable mortality associated with a high-risk score, similar ICD-discharge rates across all three risk factor groups was demonstrated suggesting similar SCD prevention benefit.

Figure 11. Kaplan–Meier curves for all-cause mortality, using the proposed new risk-score system including diabetes.



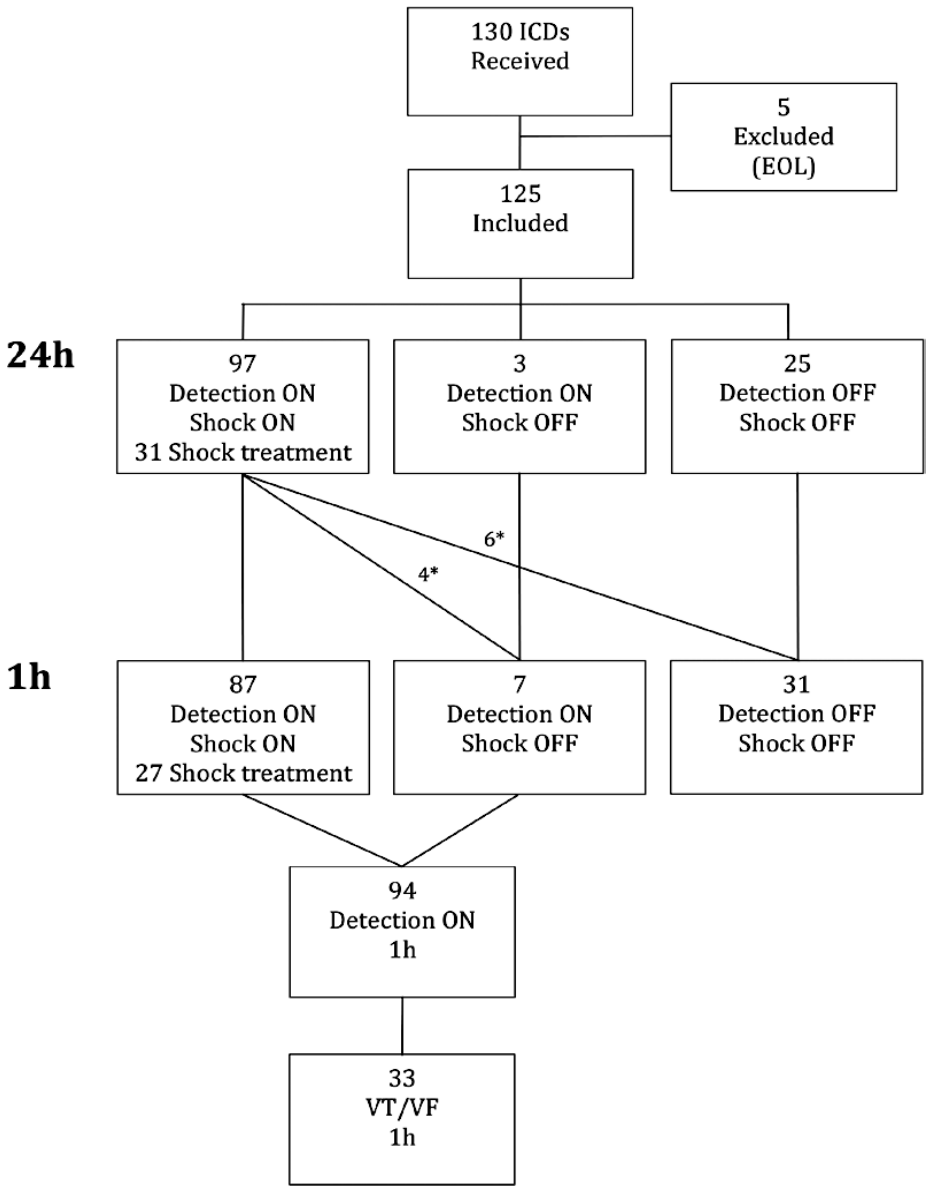
5.4 STUDY IV

Devices from 130 ICD patients who died between 2003–2010 were collected. Due to battery depletion after death, five of the devices were excluded, and descriptive data was based on the remaining 125. The most common indication for implantation was secondary prevention of SCD (82%) and 35% had CRT-D. Most of the patients (80%) were in hospital or a care facility at the time of death. More than half (52%) of the 125 patients had a Do-Not-Resuscitate (DNR) order that was active in their medical records.

Ventricular arrhythmias were common. In the last 24 hours of life 38 patients had VT or VF and in the last hour 33 patients had ventricular arrhythmias (Figure 12). Among the 97 patients with shock treatment programmed on, there were 31 who experienced shock treatment during the last 24 hours of life. Of these, 45% had 1–2 shocks, 23% had 3–10 shocks and 32% had more than 10 shocks. Inappropriate therapy was given to 4 patients as a result of supraventricular tachycardia or oversensing. In 39% of the patients receiving shock treatment in the last 24 h, there was evidence suggesting that the patient had recognized that shock therapy was given by showing signs of pain or stress.

Among the 65 patients with a DNR order, 65% of them still had ICD shock treatment on and 10 patients had shock treatment. One of them received 42 shocks during the last hour in life.

Figure 12. Inclusion, exclusion, arrhythmia detection and shock therapy given at 24 hours and 1 hour before death. *Change in programming during the last 24 hours.



The most common cause of death was heart failure (37%). Arrhythmic death was the primary cause of death in 13% and in 3% of cases the patient's death could have been system-related, caused by possible device malfunction (undersensed VF, or lead failure with death caused by bradycardia).

The main finding in this study was that ventricular tachyarrhythmias are common during the last 24 hours of life, and almost one third of the ICD patients (31%) had shock therapy. In spite of a Do-Not-Resuscitate order many patients still had shock therapy turned on.

6 DISCUSSION

Low ICD implantation rates in Sweden

Compared with other countries in the Western hemisphere, Sweden has a low ICD implantation rate. Insufficient follow-up after AMI, which was demonstrated among nearly one third of the patients in the first study, could be one explanation. In clinical practice, many patients in Sweden have revisits to a cardiologist one month after AMI and since the majority are treated by means of revascularization it has been consider too early to discuss ICD implantation. Delayed decisions regarding ICD therapy after AMI are associated with a lower likelihood of implantation (40).

Other possible explanations for low implantation rates could be insufficient routines or referral patterns regarding patients with heart failure, individual physician's preferences regarding ICD therapy and safety issues of the devices, lack of knowledge and financial restraints. Perhaps the health-system structure in Sweden also influences implantation rates. Previous studies have shown that implanting hospitals are more likely to have cardiovascular procedure capabilities, are larger and more often have an academic affiliation (75). In Sweden, there are several small hospitals in which ICD implantations are not carried out and many patients with AMI or heart failure are followed up by doctors who are not specialized in arrhythmology.

There are several ways to increase implantation rates. One way could be to boost information about the net benefit of ICD therapy among both doctors and the public. Another would be to decide about ICD therapy one month after discharge. It is also necessary, in this context, to optimize congestive heart failure treatment. However, it is most important that all patients that may benefit from ICD treatment should be informed about both the advantages and disadvantages of the treatment and thereafter make an informed decision.

Improvement in left ventricular function after AMI

Although the risk of SCD is highest during the first month after AMI, there are no benefits associated with early ICD implantation (33, 35). One explanation could be that many patients show improved LV function early after AMI, thereby diluting the positive effect. In our studies, 41–55% of patients showed improved LV function to such a degree that an ICD was not indicated. Recovery of LVEF seems to be a rapid process that starts early after AMI, and regardless of revascularization most patients showed improvement after one month. This suggests that ICD implantation may be considered after one month.

The best situation of course would be if one could determine which patients would benefit from ICD treatment as early as during hospitalization for AMI. However, in our study there were no special features among patients who did not show improved LV function other than known heart failure and very impaired LV function. Among the 20 patients with LVEF ≤25% at inclusion, only two improved (LVEF 38% and 40% after three months). This implies that an ICD could be considered before discharge in patients with pronounced impaired LV function after AMI.

In future analyses we will investigate if low-dose dobutamin stress ECHO can be used to pinpoint AMI patients who will show improved LV function before discharge.

Efficacy of ICD treatment

Ventricular arrhythmias are common among all patient categories with heart failure. In our studies both patients with and without an ICD had ventricular arrhythmias. In Study III, 6% of the patients annually had appropriate therapy. This is almost the same proportion as seen in previous well-known randomized ICD studies (22, 73, 76, 77). Earlier published studies have indicated that patients with no or many risk factors have no use of an ICD (78, 79), but we observed that both patients with low and high morbidity had similar rates of ventricular arrhythmias requiring ICD therapy, indicating that no patient should not be considered for an ICD implant solely on the basis of comorbidities.

It is of course impossible to say if the arrhythmias treated in our study by means of ATP or shocks would have been fatal without therapy. Many arrhythmias are self-terminating and modern ICD programming tries to accommodate this and avoid unnecessary treatment by using delayed detection algorithms (71, 80). We chose to report both ATPs and shocks because many clinicians program ATP even for very fast ventricular arrhythmias according to data from Pain Free and similar studies (71, 72).

Complications

We showed that many ICD patients (4.4% annually) suffer from device-related complications requiring reoperation. This is higher than in earlier randomized trials and almost as high as in a real-life survey carried out in Germany (57). One important explanation for higher complication rates in real-life surveys may be that in randomized studies the patients are highly selected and in our study all ICD patients meeting the inclusion criteria were evaluated without exception, thereby including patients with potentially high risks of complications. Another important factor is study duration. Complications increase with time. The longer you look, the more you find! The most frequent complications were lead-related. Not surprisingly, many had problems with the left-ventricular leads, but ICD-lead complications were even more common, and the problems often appeared after several months. Problems with ICD leads have also been reported in other studies, and some types of lead show an annual failure rate of 2.6% (58).

Another issue, which will probably continue to increase over time, is the occurrence of device-related infections. Multiple studies confirm increasing infection rates and the National Hospital Discharge Survey reported a 57% increase in infections but only a 12% increase in devices implanted between 2004 and 2006 (60). The reason for the increasing infection problem is unknown, but multiple leads, several surgical procedures, generator replacement, pocket hematoma and a high level of morbidity are factors that are correlated to higher infection rates (81). Perhaps more antibiotic use and increased bacterial resistance in the community also contribute to the higher infection rates seen today.

Complications are resource-demanding and even in low absolute numbers they have an impact on the net health-economic benefit of treatment, and the quality of life of affected patients. However, no complications in our study were lethal and there was no association between complications and increased mortality.

Shocks

Shocks from ICDs can have a traumatic impact on the patient, causing stress, great pain and anxiety. Repeated shocks have been shown to have a particularly negative impact on the quality of life of ICD patients, causing considerable emotional distress (82, 83).

In our study only 7% of patients (2.4% annually) had unnecessary shocks, a figure slightly lower than in many other studies, in which the occurrence of inappropriate shocks has ranged from 10% to 24% over 20 to 45 months of follow-up (84, 85). The main reason for inappropriate therapy in our study, as in several others, was atrial fibrillation. Better knowledge and more "conservative" programming (i.e. higher VT zones with longer detection intervals and more ATP therapy attempts before shock therapy) may have contributed to the reduced number of unnecessary shocks. Use of newer or improved discriminatory features such as continually updated morphology templates may also have improved correct arrhythmia classification.

Even correct shock treatment is painful and causes stress if the patients are awake. In our study we showed that 31% of the ICD patients had shocks at the end of life. Many patients had shock treatment programmed ON even if they had a DNR order. This highlights the need to address the problem of ICD shocks during the end-of-life period and to improve knowledge about ICDs among other professions in palliative care units. It is also necessary to discuss device deactivation with patients and their families when the end of life approaches.

Deaths

Patients with heart failure after AMI have a high mortality rate. We showed that mortality increased distinctly with morbidity, but there were no gender differences. We found no association between death and inappropriate shocks or complications requiring reoperation.

The most common cause of death among ICD patients was heart failure, especially among patients with a high level of morbidity. Another common cause of death was malignancy, but even patients with ICDs sometimes died of arrhythmia. Since devices seldom are explanted after death the true numbers of cases of arrhythmia and device malfunction are not known. In our study of explanted ICDs, four had signs of device malfunction and in Study IIII we showed that the devices were seldom interrogated after death.

Many patients with an ICD (21%) had previous arrhythmia appropriately treated by ATP and/or shocks before death, but neither previous shock nor ATP therapy were associated with death during follow-up. The median time from first correctly treated arrhythmia to time of death was 16 months (range 0.5–47 months) and perhaps the ICD prolonged their lives. Neither appropriate nor inappropriate therapy were correlated to death in our study. This contradicts the results of earlier published studies which have reported an association between shock therapy and death (68, 84).

Patients with a high level of morbidity have a high mortality rate in spite of ICD therapy, but ICD treatment may extend their lives. It is important to identify these patients before implantation and give them correct information regarding realistic assessment of the expected benefit of ICD therapy. It is possible that some patients will choose not to undergo ICD therapy, or prefer a CRT pacemaker instead of a CRT defibrillator.

Gender differences

In all our studies, as in many other studies regarding ICD therapy, there were significantly fewer women than men. One explanation could be that women have

a lower incidence of coronary heart diseases and are older when they become ill. Even so, the question remains – are women offered the treatment to the same extent as men? In the national Swedish registry for coronary heart disease, the incidence of AMI is consistently about 50% lower per age group in women compared with men, but this does not explain the fact that only 18% of primary prophylactic ICD recipients are women (1).

Another question is – do women have equal benefit from ICD treatment? We observed that women had a significantly lower rate of correctly treated arrhythmia episodes (9% compared with 20% in men), but the mortality rate was the same. Earlier published meta-analyses of gender differences in primary preventive ICD treatment have also shown that women have a significantly lower rate of appropriate therapies and fewer survival benefits (86). Perhaps men have a greater propensity for ventricular arrhythmia and a higher rate of sudden cardiac death (87). There is a need for prospective studies including all implanted patients ("real- world" cohorts) in order to clarify this issue.

Real-life cohort

All papers in this thesis are based on real-life data and not controlled randomized studies. The cohorts in Paper III were based on consecutive patients from four large hospitals in Sweden, representing almost 30% of the yearly ICD implants in the country, which supports the ability to generalize the study findings. Since all patients in the hospital catchment areas who actually received ICD treatment were included, the findings are more likely to represent the "true" net result of primary prophylactic ICD treatment, as compared with selected patient cohorts in prospective randomized trial populations. In most randomized studies, patients with high-level morbidity, advanced age or previous infarction are excluded.

7 CONCLUSIONS

- Compliance to guidelines regarding primary preventive defibrillators needs to be improved. Many patients are not offered treatment even if they fulfill criteria for ICD therapy.

- Many patients show significantly improved LV function after AMI to such an extent that an indication for ICD implantation is no longer present. This may be one explanation for why early ICD implantation after AMI has failed to show survival benefit.

- Improvement of LV function after AMI is a rapid process regardless of revascularization. Most patients show improved LV function after one month and further improvement up to three months is minor. This indicates that we can offer ICD treatment to patients at risk at an earlier stage.

- Many patients, 6% annually, with a primary preventive ICD because of congestive heart failure have correctly treated ventricular arrhythmias and thereby benefit from the treatment.

- Complications of ICD therapy are common during long-term follow-up. Complications requiring reoperation occurred annually in 4.4% of cases, and inappropriate shocks in 2.4%. Complications were not associated with increased mortality.

- Men were twice as likely to receive ICD therapy compared with women, but neither total mortality nor complication rates differed significantly.

- More than a third of the ICD patients studied had ventricular tachyarrhythmia within the last hour of life. Devices remained active in more than half of the patients with a do-not-resuscitate order. Increased knowledge about ICD treatment is nescessary among healthcare professionals.

8 FUTURE PERSPECTIVES

Decisions concerning ICD implantation as early as one month after AMI will probably increase implantation rates in Sweden. It is to be hoped that future analyses of the results of dobutamin stress ECHO will answer the question of whether or not it is possible to determine if LV function will improve before discharge after AMI, thereby allowing ICD implantation even earlier than one month after infarction. Further echocardiographic analyses after six and twelve months will give us information regarding what happens among patients with LVEF slightly > 35% in a longer perspective. We also hope that analyses of Holter registrations, blood samples and other parameters will help to pinpoint patients at the highest risk of SCD.

It is important to increase knowledge of ICD therapy both in society and, more particularly, among professionals in palliative care units.

There is a need of more studies to investigate the net benefit of ICD therapy among women with congestive heart failure.

9 SVENSK SAMMANFATTNING

Varje år drabbas 8 000-10000 personer i Sverige av plötslig hjärtdöd. Högst risk för plötslig död har patienter med tidigare hjärtinfarkt och hjärtsvikt. Ett flertal studier har visat att förebyggande behandling med inopererad defibrillator (ICD) markant minskar dödligheten hos patienter med nedsatt hjärtfunktion oavsett om den är orsakad av en hjärtinfarkt eller inte. Trots att risken för plötslig död är som störst första månaden efter en hjärtinfarkt har ICD behandling under denna tidsperiod inte visat ökat överlevnad. Både svenska och internationella riktlinjer förordar förebyggande behandling med inopererad defibrillator (ICD) till patienter med bestående hjärtsvikt och minst måttligt nedsatt pumpkraft tidigast 40 dagar efter en hjärtinfarkt och man bör vänta i 3 månader om patienten behandlats med en kranskärlsoperation eller ballongvidgning av hjärtat blodkärl.

I **studie 1** undersöktes hur vi följer riktlinjerna avseende ICD behandling till patienter med hjärtsvikt efter en hjärtinfarkt och hur vanligt det är att hjärtat återhämtar sig efter en hjärtinfarkt. Vi undersökte de medicinska journalerna från 187 patienter med hjärtinfarkt som vid utskrivningen från sjukhus hade minst måttligt nedsatt pumpkraft i hjärtat. Vi fann att 32 % av patienterna inte fick korrekt uppföljning där man tog ställning till ICD behandling och att 41 % förbättrade sin hjärtfunktion till en sådan grad att de inte längre hade nytta av ICD behandling.

I **studie 2**, undersökte vi dels andelen patienter som förbättrade sin hjärtfunktion efter en hjärtinfarkt och dels hur lång tid förbättringen tog. Vi inkluderade 100 patienter med akut hjärtinfarkt och hjärtsvikt i studien och utförde upprepade ultraljudsundersökningar efter fem dagar, en och tre månader efter infarkten. Vi fann att redan efter en månad hade 55 % av patienterna förbättrat sin hjärtfunktion i sådan omfattning att ICD behandling inte var aktuellt, detta trots att merparten behandlats med ballongvidgning av hjärtats kranskärl. Fortsatt förbättring av hjärtfunktionen skedde, men i liten omfattning, talande för att beslut om ICD kan tas redan 1 månad efter hjärtinfarkten. Vi fann också att 9 % drabbades av livshotande rytmrubbningar de första veckorna efter hjärtinfarkten vilket poängterar den stora risken för plötslig död kort tid efter en hjärtinfarkt.

I **studie 3** undersökte vi nyttan och komplikationsrisken med ICD behandling. Vi analyserade medicinska journalerna från 865 patienter som fått förebyggande behandling med ICD på grund av hjärtsvikt. Vi fann att 6 % av patienterna årligen fick korrekt behandling för livshotande arytmier, men kvinnorna i studien hade bara hälften så mycket arytmier som männen. Den årliga risken för komplikationer var 6.8% och av dessa var 4.4% komplikationer som krävde ny operation och 2.4% felaktiga chocker.

I **studie 4** analyserade vi vad som skedde med ICD behandlande patienter det sista dygnet i livet. Vi samlade in 125 ICD doser från avlidna patienter. Vi fann att många patienter drabbades av både rytmrubbningar (38 %) och chock behandling (31 %) det sista dygnet i livet. Trots att man i många fall tagit ställning till att återupplivning inte var aktuell hade man inte inaktiverat defibrillatorns chock-behandling.

Sammanfattningsvis visade studierna att uppföljningen efter hjärtinfarkt är bristfällig. Förbättring av hjärtfunktionen efter en hjärtinfarkt sker hos många och den har hos flertalet patienter redan inträffat efter 1 månad, talande för att vi inte behöver vänta längre med ICD behandling. Hjärtsviktspatienter, speciellt män, har nytta av ICD behandling men komplikationer är vanliga och det är viktigt att inaktivera ICD behandlingen i livets slutskede.

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