

Primary Prevention of Sudden Cardiac Death – Implications on ICD Functionality

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Summary

Sudden cardiac death is responsible for 300,000 to 400,000 deaths annually in the USA. With implantable cardioverter defibrillator (ICD) therapy for secondary prevention, only a small portion of high risk patients may be protected. The MADIT II trial has proven the benefit from prophylactic ICD therapy in a large patient population for the first time. It is expected that the number of patients eligible for ICD therapy may increase by a factor of two. Other trials are currently being undertaken to evaluate the use of ICD therapy in higher risk patients such as those with acute myocardial infarction or congestive heart failure. However, our health care systems are not prepared to accommodate the potential increase in patients, and current ICD technology is not suited to prevent the rapidly expanding indications of sudden cardiac death. The author argues that development of a specific prophylactic ICD is required for the optimal primary prevention of sudden cardiac death: A prophylactic ICD needs a capacity for very few shocks, backup VVI pacing, and tachyarrhythmia Holter memory but no antitachycardic or preventive pacing functions.

Key Words

Implantable cardioverter defibrillator, primary prevention, prophylactic, sudden cardiac death

Introduction

When implantable cardioverter defibrillators (ICD) were first introduced in the 1980's, the primary goal of treatment was the prevention of sudden cardiac death (SCD) in patients who had survived cardiac arrest due to malignant ventricular tachyarrhythmia. Given that implantation of an ICD was associated with open heart surgery and efficacy of ICD therapy was discussed controversially these days, it was certainly good clinical practice to be very restrictive with applying this new method in clinical routine and to offer ICD therapy only to those patients who already had experienced an episode of ventricular fibrillation (VF). However, the dilemma in using this specific approach was that only a limited number of patients actually survived their first episode of VF. In other words, only a few thousand out of the 300,000 to 400,000 annual victims of SCD reported in the USA have the chance to be treated with an implantable cardioverter defibrillator [1,2].

There are two ways to resolve this problem: One is to improve the chances of surviving SCD, i.e., to ensure

that a victim of SCD is treated with an external defibrillator within the first three to eight minutes; otherwise the chances of survival are extremely low. Since such fast response times do not exist within the established rescue services, it has been suggested that so-called "public access defibrillators" become available in virtually all public places. Nonetheless, this strategy will not help to reduce the risk of dying for the majority of patients who will have their episodes at home. A different approach to reduce the mortality following SCD is to identify those patients with an elevated risk already before they have their first episode of VF and to implant an ICD prophylactically.

Trials on the Use of ICD Therapy for Primary Prevention of Sudden Cardiac Death

In the early 1990's the first four controlled randomized trials to investigate the use of ICD therapy in the primary prevention of SCD were initiated. The MADIT I

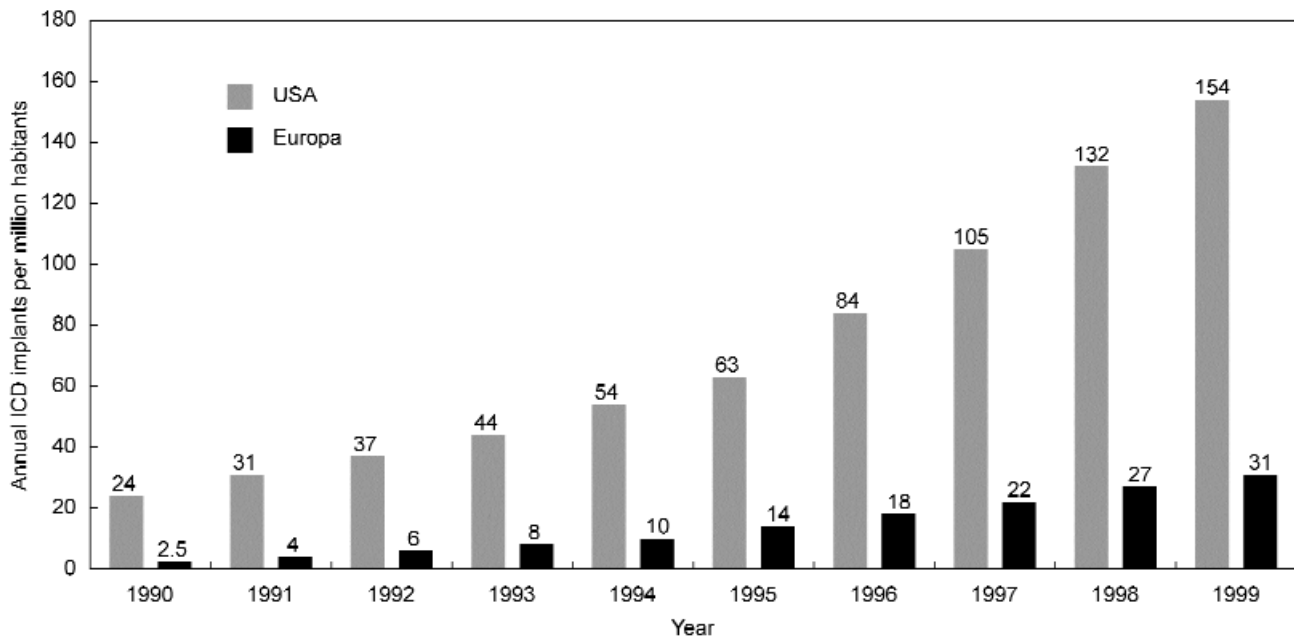


Figure 1. European and US ICD implant rates (excluding replacements) according to Camm and Nisan [7].

trial addressed patients with a myocardial infarction at least one month ago, a left ventricular ejection fraction (LVEF) of less than or equal to 0.35 and a documented episode of non-sustained ventricular tachycardia (VT) at a rate of more than 120 beats/min [3]. Patients were included if they had a sustained VT inducible during electrophysiologic testing that was not suppressed by procainamide. Although a rather small number of patients was included ($n = 196$), MADIT I was able to clearly demonstrate a relative reduction in mortality of 42% after four years of follow-up. These initial results were discussed controversially until they were eventually confirmed by the MUSTT trial three years later [4]. However, the remaining two trials in this first series on primary prevention had a negative outcome: The CABG-Patch trial failed to demonstrate the benefits of prophylactic ICD therapy in patients following coronary artery bypass graft surgery who were identified on the basis of an LVEF < 0.36 and an abnormal signal-averaged ECG [5]. The Cardiomyopathy Trial (CAT) which investigated patients with idiopathic dilated cardiomyopathy and LVEF ≤ 0.3 was terminated early because the one-year mortality rate for all causes did not reach the expected 30% in the control group [6].

The MADIT I and MUSTT trials paved the way for a whole series of primary prevention trials, which aimed

to expand the indications for ICD implantation. While MADIT II, DINAMIT and IRIS addressed the chronic and sub-acute post MI patients, SCD-HeFT and DEFINITE investigated the use of prophylactic ICD implantation in the heart failure population. However, the direct effect of MADIT I and MUSTT on ICD implantation numbers, was not overwhelming [7] (Figure 1), since these two trials addressed a highly selective patient population. Nor did the MADIT I or MUSTT trials affect the further development of ICD functionality: In 1997, Higgins et al. explicitly addressed the question whether MADIT I patients should be provided with devices with a reduced functionality [8]. After the data had been analyzed with respect to patient characteristics, therapy delivery, diagnostic functions, etc., the authors concluded that the answer was a clear no. Instead, the technological development of ICD therapy focused on dual-chamber devices for the advanced discrimination of supraventricular tachycardias (SVT) and DDD pacing, as well as on more sophisticated diagnostic and therapeutic functions. While these new functions helped to make ICD therapy more effective in selected patients, they significantly increased the general complexity of the devices. Although scientific evidence for a reduced functionality is lacking, the empirical knowledge seems to put into question whether really all patients

should receive a maximum function maximum complexity – and maximum cost device. D. P. Zipes addressed this issue for the first time in his well-known editorial in a 2001 edition of *Circulation* with the provocative title "Implantable Cardioverter-Defibrillator: A Volkswagen or a Rolls Royce: How Much Will We Pay To Save A Life?" [9].

Just a few months later, in November 2001, the MADIT II trial was terminated earlier than expected because the end-point had been reached. After 2 years of follow-up the MADIT II trial showed that prophylactic implantation of an ICD reduced mortality by 31% in patients with a previous myocardial infarction (≥ 4 weeks before ICD implantation) and an LVEF ≤ 0.3 [10]. The MADIT II trial potentially lead to an increase in the number of patients eligible for ICD therapy by as much as 100%. The positive outcome of the trial has stimulated an intensive discussion on the socio-economic impact of drastically increased patient numbers. The scientific evidence of the benefit from ICD therapy in the MADIT II population, however, is undisputed: The updated ACC/AHA/NASPE and ESC guidelines have recently classified MADIT II as a class IIa indication [11,12].

Concept of a Special Device for Prophylactic ICD Therapy

One trivial answer to the problem of increased patient numbers is the claim that the industry can reduce the cost of the devices. It is reasonable to predict that prices should decrease when the number of units sold increases. In fact, this has already happened in the past, when increased implantation figures led to a simultaneous decrease in price; therefore it seems realistic to expect further price reductions. Another trivial answer is to increase the health care budget for ICD therapy. One could argue that the safety and efficacy of ICD therapy has been proven on a high scientific level. In addition, ICD therapy has also been shown to be cost-effective in comparison to other expensive therapies such as renal dialysis, estrogen replacement or treatment of hypertension [7]. Obviously, it is very unlikely that the two trivial answers will be sufficient to solve the problem of a 100% increase in patient numbers. In fact, they have already turned out to be insufficient in the domain of secondary prevention: ICD implantation rates still lag behind the epidemiological data, even in the USA.

Therefore, it seems to be reasonable to further elaborate on Zipes' idea of a special device for prophylactic implantation. These patients never have had an episode of ventricular tachyarrhythmia, and most of them never will have one for many years. In the MADIT II trial, the cumulative probability of receiving therapy from the device within 3 years for treatment of VT/VF was 34%, and the probability of an appropriate first shock for VF was 4% at one year, increasing to 10% at four years [13]. Thus, the capacity for delivering therapy may be markedly reduced in a prophylactic ICD, whereas the service time should be as long as possible. Patients without a history of arrhythmias will not require most of the sophisticated functionality found in modern ICD's. What they do need is protection from a potentially life-threatening episode of sustained VT or VF through delivery of a cardioverting or defibrillating shock. Ideally, a prophylactic ICD would be "maintenance-free" while it is fulfilling its role as a silent life-guard and inform the physician independently, when an episode had been detected and treated. In order to achieve this goal, the device must function as simply as possible, i.e., the programmability of such an ICD has to be reduced to the minimum that is necessary to protect the patient's life. More precisely, a prophylactic ICD will certainly have to provide shock therapy, VVI back-up pacing, and a VT episode Holter memory, but e.g. antitachycardic or preventive pacing functions might not be required.

In those prophylactic ICD patients, where an episode of sustained VT/VF has occurred, the scenario changes: The implantation of an ICD for secondary rather than primary prevention is indicated. This is far more than a formal classification; it has clinically relevant implications. So, one would expect that these patients will use their devices in the same way as those who had an indication for secondary prevention right from the beginning. This means that they would need a device that offers total functions with the capability to deliver therapy. Thus, it may be argued that a prophylactic ICD should be replaced with a "standard" ICD after having successfully detected and treated the first episode in a specific patient. In other words, the capacity of such a device has to ensure the safe and effective treatment of a single episode of a life-threatening tachyarrhythmia, which means that a prophylactic ICD must deliver only one effective therapy – a "single shock" device. Obviously, the capacity of a prophylactic ICD has to be somewhat greater, since ineffective or

inappropriate therapies can not be completely excluded. Nevertheless, a high specificity is even more important for prophylactic ICD patients, since they are asymptomatic at implantation. Since most inappropriate detections occur at comparably slow ventricular cycle lengths, the problem of inadequate shock delivery could be reduced if therapy would not be delivered during slow tachycardias. Instead, during slow VT a prophylactic ICD might be restricted to a pure monitoring and holter storage function because the risk of inappropriately delivered therapies seems to be greater than the risk of inappropriately withheld therapies in patients without a history of VT.

Clinical Implications of a Prophylactic ICD

Assuming that a prophylactic ICD as defined above would exist, how would it behave in clinical practice? What is the mean episode-free survival of ICD patients? We sought to investigate whether it is possible to extrapolate this information from the data on therapy delivery that is available from the randomized ICD trials. In the field of secondary prevention, data on the incidence of tachyarrhythmic episodes is available from the AVID and CIDS trials but not from CASH. The AVID trial reports that VT/VF occurred more frequently in patients whose index arrhythmia was VT than in those with VF [14]. The respective cumulative probabilities were 68%/39% at one year of follow-up, 81%/53% at two years, and 85%/69% at three years. The Canadian Implantable Defibrillator Study revealed a cumulative risk for receiving an ICD shock of 65.4% at four years [15]. In the area of primary prevention, data on the incidence of therapy delivered is available from MADIT I and II but not from MUSTT. By analyzing the data on shock delivery from MADIT I, Higgins et al. found a cumulative probability for receiving a therapy of 40% at one year, 60% at two years, and more than 70% at three years of follow-up [8]. Since the majority of the ICD's had no electrogram storage capabilities, these figures include shocks for treatment of VT and VF, as well as inappropriate shocks. To date, the MADIT II data on therapy delivered have only been published in the framework of the US Food and Drug Administration's premarket approval application [13]. The cumulative probability for receiving a therapy due to VT/VF was 34% at three years of follow-up; with respect to VF only, the probability for receiving the first appropriate shock was 4% at one year, increasing to 10% at four years of follow-up.

Age	Mean \pm SD	65 \pm 13 years
Sex	Male	82%
Cardiac disease	Coronary artery disease	67%
	Myocardial infarction	61%
	Dilated cardiomyopathy	24%
	Idiopathic	4%
	Other	4%
Left ventricular ejection fraction	Mean \pm SD	0.35 \pm 0.14
	< 0.3	41%
	> 0.3	59%
NYHA functional class	Mean \pm SD	2.22 \pm 0.79
	I	18%
	II	47%
	III	31%
	IV	4%

Table 1. Clinical characteristics of ICD patients database (Klinikum Coburg). SD = standard deviation.

There are several implications from these figures on the incidence of therapy delivered in ICD patients. First, in all trials, a substantial portion of patients who received an ICD after surviving VF or sustained VT had no second episode at all, or only after a long period of time. Second, a history of VT is associated with a higher incidence of therapy delivered than a history of VF. This may be an additional reason for the rather high probability for receiving a shock in the MADIT I trial. Although a history of sustained VT was an exclusion criterion in MADIT I, inducibility was explicitly required, and this may explain why the patients also had a higher risk for developing spontaneous sustained VT. Third, in MADIT II, where the patients had no history of sustained VT/VF and where inducibility was not required, the probability of receiving a therapy was about 50% smaller than in the AVID, CIDS or MADIT I trials. Its absolute value of 34% at three years of follow-up is in a range where the scenario of a prophylactic ICD as described above becomes a reasonable alternative to standard devices. Since the other randomized primary prevention trials are still on-going, one may only speculate whether the respective patient groups would also benefit from the above prophylactic ICD. It is certainly less speculative to concentrate on the data that is currently available. Therefore, we retro-

Age	Mean \pm SD	65 \pm 11 years
Sex	Male	83%
Cardiac disease	Coronary artery disease	69%
	Myocardial infarction	35%
	Dilated cardiomyopathy	22%
	HOCM/RV dysplasia	4%
	Idiopathic	1%
	Other	4%
Left ventricular ejection fraction	Mean \pm SD	0.34 \pm 0.13
	\leq 0.3	51%
	$>$ 0.3	49%
NYHA functional class	Mean \pm SD	2.1 \pm 0.7
	I	20%
	II	55%
	III	24%
	IV	1%

Table 2. Clinical characteristics of ICD patients database (Biotronik). SD = standard deviation.

spectively analyzed two ICD databases – our own clinical database and the database of the regulatory studies of one of the device manufactures (Biotronik, Germany).

Our own ICD database includes 145 patients whose clinical characteristics are summarized in Table 1. We investigated 43 patients (30%) who had no history of sustained VT/VF. Two of these patients were implanted for primary prevention, the remaining 41 patients were inducible during electrophysiological testing. The mean duration of follow-up in this patient group was 18.7 ± 13.6 months (range: 0.1 to 53.2 months). During the 1.5 years of average follow-up, 37% of the patients had at least one episode of sustained VT or VF. The incidence is distinctly lower than in MADIT I, because inappropriate detections are not included. However, they were observed in five patients (12%) due to supraventricular tachycardias ($n = 3$) or ventricular oversensing. These false detections led to shock releases in all patients except for one of the SVT patients. While the cycle lengths during oversensing could not be retrieved, the mean ventricular cycle lengths in the remaining two SVT patients were 270 ms and 405 ms, respectively. This anecdotal data supports the above proposal for implanting a prophylactic ICD, which has no VT therapy zone but only an

aggressively programmed VF therapy zone.

The Biotronik database that we used included 400 patients who were implanted with the Phylax AV, Tachos DR and Deikos A+ devices (all Biotronik) during regulatory approval studies. Details of the clinical characteristics of the patients are found in Table 2. Again, the additional analysis focused on the patients without a history of sustained VT/VF ($n = 27$; 6.8%). These patients were followed-up for 10.9 ± 6.4 months (range: 0.1 to 23.5 months). Six patients (22%) had an episode of VT or VF, and inappropriate detections were observed in four patients (15%). Atrial fibrillation or flutter were responsible for VT detection in three patients and caused inappropriate delivery of therapy in two of them. In the remaining patient, temporary ventricular oversensing led to initial detection in the VF zone; however, no therapy was delivered. As in our own data, the incidence of VT/VF was lower than in MADIT I, and again sacrificing a VT therapy zone would have reduced the disadvantage of inappropriately delivered shocks.

So far, most of the data cited refers to patients with coronary heart disease. Except for the small CAT and AMIOVIRT trials, no data from randomized trials on prophylactic ICD therapy for patients with non-ischemic cardiomyopathies have been published. However, in 1995, Grimm et al. retrospectively investigated the use of ICD therapy for secondary prevention of SCD in 49 patients with no coronary artery disease or valvular heart disease [16]. At one, three, and five years of follow-up the actuarial incidence for any shock was 20%, 58%, and 77%, respectively; the incidence of appropriate shocks was 16%, 49%, and 72%. These values are distinctly smaller than the values found in patients with ischemic heart disease. Therefore, it may be reasonable to expect that the incidence for shock releases would also be low in patients without a history of sustained VF/VT.

Conclusion

Implantable cardioverter-defibrillator therapy could potentially save up to 1000 lives per million population who die each year from SCD. Initially the application of ICD therapy was limited because we did not know how to identify the patients, and today we can still only identify a small percentage of them. Nevertheless, our health care system does not provide an ICD to all those patients where there is general evidence that their lives

could be saved by the device. In order to reach the implantation rate that is justified by scientific evidence, it has been suggested that the cost of the devices must be reduced, the health care budget for ICD therapy must be increased, and a special device needs to be offered to patients who have no history of sustained VT/VF. The functionality of such a device should be limited to detecting the first episode of life-threatening tachyarrhythmia in formerly asymptomatic patients and treating them through defibrillation. Then the device should be replaced with a standard ICD. An analysis of the published literature on primary prevention trials and of two other databases provided evidence for the clinical validity of this new approach to ICD therapy. This analysis further revealed that there are two large patient groups who are expected to benefit from the proposed device for prophylactic ICD therapy: the post myocardial infarction population and the heart failure population.

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