Peer reviewed article

Incidence of arrhythmic events in patients with implantable cardioverter-defibrillator for primary and secondary prevention of sudden cardiac death

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Summary

Background: Implantable cardioverter-defibrillators (ICD) are increasingly used for prevention of sudden cardiac death (SCD). Although mortality risk reduction is about the same in primary and secondary prevention trials (~30%), we hypothesised that the incidence and the nature of ventricular arrhythmias is different in high risk ICD recipients without prior arrhythmias compared to patients who presented with life threatening arrhythmias.

Methods: A hundred consecutive ICD recipients were allocated to 2 groups: 1) secondary prevention: an ICD was implanted for secondary prevention of episodes of ventricular tachycardia (VT) or ventricular fibrillation (VF). 2) primary prevention: patients at high risk of SCD without prior arrhythmias. They were prospectively followed and the incidence of appropriate ICD therapies was determined by reviewing stored electrograms.

Results: During a mean follow-up of 20 (10) months, the overall mortality was 5% and 5% of the patients underwent heart transplantation. Of the 67 secondary prevention patients, 40% (n = 27) had VT/VF triggering ICD therapy, whereas only 15% (n = 5) of the 33 primary prevention patients had VT/VF triggering ICD therapy ($p < 0.05$). The adjusted hazard ratio for arrhythmias triggering ICD interventions in the primary prevention group was 0.345 (95% confidence interval 0.132 to 0.902, p = 0.03).

Conclusions: The risk of developing arrhythmias triggering appropriate ICD intervention was 65% lower among the primary prevention patients than in secondary prevention patients. Importantly, ICD therapies are not correlated with lives saved, and efficacy of ICD therapy in primary and secondary prevention cannot be drawn from these data. However, the low incidence of ICD use in primary prevention patients emphasises that efforts should be made to develop better instruments for stratification.

Key words: implantable defibrillator; sudden cardiac death

Introduction

Large prospective trials have recently demonstrated that the implantation of an internal cardioverter defibrillator (ICD) improves survival in high risk patients without prior ventricular arrhythmias as well as in survivors of cardiac arrest, or in patients with sustained ventricular arrhythmias and structural heart disease [1–5]. The numbers of patients unwilling to participate, or those unsuitable for inclusion in prospective ICD trials might indeed be considerable and larger even than the numbers of patients actually enrolled in these trials. Consequently, those patients enrolled may not be representative of ICD recipients as a whole. There is however a need to characterise a population of patients undergoing ICD implantation according to guidelines derived from the results of prospective trials [6]. Therefore, we decided to conduct a prospective observational study after elective ICD implantation to examine the survival of non-selected defibrillator recipients and to assess the incidence of arrhythmias triggering ICD activity. We hypothesised that the nature and incidence of arrhythmias might be different in those patients who initially presented with life-threatening arrhythmias and received an ICD as a secondary preventive intervention, compared to patients who had never developed arrhythmias but who were assumed to be at risk of arrhythmias according to current risk stratification and received an ICD for primary prevention of sudden cardiac death (SCD).

No financial support declared.

Materials and Methods

Consecutive patients undergoing defibrillator implantation were enrolled in the study. The decision to implant a defibrillator was made in accordance to the current guidelines based on results of randomised trials and expert consensus [6]. The incidence and the type of arrhythmias, and the incidence of appropriate and inappropriate defibrillator therapies were determined by reviewing stored electrograms. Ventricular arrhythmias were classified as 1) monomorphic ventricular tachycardia, and 2) polymorphic ventricular tachycardia (varying RR intervals), ventricular flutter or ventricular fibrillation. Anti-tachycardia pacing or shocks were deemed appropriate when they occurred in response to ventricular arrhythmias and were classified as inappropriate when they were triggered by supraventricular tachycardias, self-terminating ventricular tachycardia, T wave over-sensing or when they were secondary to electrode dysfunction.

Patients were allocated to two groups according to the reason for defibrillator implantation: 1) Defibrillator implantation was categorised as a secondary prevention intervention in survivors of cardiac arrest or of sustained ventricular tachyarrhythmias, as well as in patients with structural heart disease who had suffered syncope and were found to have inducible ventricular tachyarrhythmia at electro-physiological testing (secondary prevention group); 2) Defibrillator implantation was considered a primary preventive intervention in patients at high risk of SCD but without prior spontaneous sustained ventricular arrhythmias (primary prevention group).

Statistical analysis

Results are expressed as mean (SD). The cumulative risk of ventricular arrhythmia triggering appropriate ICD intervention was estimated by the Kaplan and Meier method. Data were censored if the patient died, underwent cardiac transplantation or reached the end of the follow-up period (June 2003) without arrhythmia triggering ICD intervention. The Cox proportional-hazards model was used to calculate relative risk in primary and secondary prevention groups and to investigate potential differences in the effects of covariates including age, ejection fraction, proportion of patients under beta-blocker therapy, and the proportion of patients under anti-arrhythmic therapy. The hazard ratio for each group (primary or secondary prevention) was adjusted for other covariates. A P value <0.05 was considered significant.

Results

Survival and appropriate ICD therapies

One hundred patients were enrolled in the study. Follow-up was available in all patients and averaged 20 (10) months. The overall mortality was 5% and there was no sudden death. 5% of the patients underwent heart transplantation during the follow-up period.

Patient characteristics according to the reason for defibrillator implantation are shown in Table 1. Of the ICDs implanted in patients of the primary prevention group, 66% were implanted in patients with coronary heart disease and severely decreased left ventricular function, 21% in patients with dilatative cardiomyopathy with a history of sudden cardiac death in first-degree relatives, 12% in patients with hypertrophic cardiomyopathy and risk factors for sudden cardiac death, 3% in patients with arrhythmogenic ventricular dysplasia with a history of sudden cardiac death in first-degree relatives. Patients in the secondary prevention group were older than the patients in the primary prevention group. Length of

Table 1

Characteristics of the patients according to the indication for defibrillator implantation.

	secondary prevention group (n = 67)	primary prevention group (n = 33)
Age, years	55 (13)	49 (15)
Patients with coronary heart disease, %	70	67
Ejection fraction, %	35 (13)	36 (13)
Follow-up, months	20 (11)	20 (10)
Drug therapy		
Antiarrhythmic drugs*, %	50	30
Beta-blocker, %	87	79
ACE-inhibitor, %	76	82
Patients with appropriate defibrillator therapy, %	40	15
Triggered by monomorphic VT %	85	60
Cycle length of VT, ms	311 (39)	309 (14)
Triggered by polymorphic VT or VF, %	15	40
Number of patients with therapy including a shock, %	81	100
Time to first appropriate therapy, months	7 (7)	7 (6)
Patients with inappropriate defibrillator therapy, %	21	15

* Amiodarone (n = 37), sotalol (n = 4), or flecainide (n = 2); VT, ventricular tachycardia; VF, ventricular fibrillation

follow up, left ventricular ejection fraction, the proportion of patients with ischaemic heart disease as well as the proportion of patients under beta-blocker therapy were similar in both groups. The cumulative incidence of ventricular arrhythmias triggering appropriate defibrillator therapy was more than 2.5 times higher in secondary prevention patients than in primary prevention patients at any time in the follow-up, although use of anti-arrhythmic drug was significantly more frequent in secondary prevention patients (table 1). Kaplan Meier estimates of freedom from appropriate ICD intervention at 5 years was 80% in the primary prevention group versus 48% in the secondary prevention group. The adjusted hazard ratio for arrhythmias triggering ICD interventions in the primary prevention group was 0.345 (95% confidence interval 0.132 to 0.902, p = 0.03). The hazard ratio of 0.345 indicates a 65% reduction in the risk of developing arrhythmias among patients who received an ICD prophylactically as compared with patients in the secondary prevention group. The hazard ratios for arrhythmias triggering ICD interventions for covariates are given in Table 2. Age, ejection fraction, beta-blocker therapy, and anti-arrhythmic therapy had no significant influence on relative risk. The mean time to the first appropriate defibrillator therapy was similar in both groups. In the secondary prevention group, the arrhythmias triggering defibrillator therapy were monomorphic ventricular tachycardia in 23 patients (85%), and polymorphic ventricular tachycardia or ventricular fibrillation in 4 patients. Average heart rate of ventricular tachycardia was 195 ± 30 beats per minute. In the primary prevention group, the arrhythmia triggering defibrillator activity was ventricular tachycardia in 3 patients and polymorphic ventricular tachycardia or ventricular fibrillation in 2 patients.

When patients with non-ischaemic cardiomyopathy were compared to patients with ischaemic cardiomyopathy, Kaplan-Meier estimates of arrhythmic events were similar.

Although a ventricular tachycardia detection zone with anti-tachycardia pacing therapy was programmed in most of the patients, 87% of all defibrillator therapies included at least one shock (table 1). The proportion of defibrillator therapies including a shock was not different in the primary prevention group compared to the secondary prevention group.

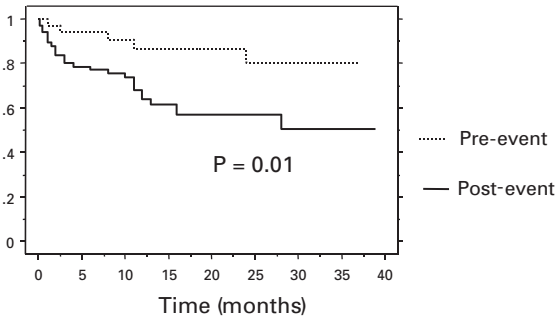
Table 2

Risk of ICD intervention according to reason for ICD implantation and relevant covariates.

	Hazard ratio	95% confidence interval
ICD for primary prevention	0.345	(0.132–0.902)
Age	1.009	(0.972–1.046)
Ejection fraction	1.004	(0.973–1.036)
Beta-blocker therapy	1.035	(0.374–2.861)
Anti-arrhythmic drug	1.418	(0.650–3.094)

Figure 1

Kaplan-Meier estimate curves of freedom from appropriate defibrillator interventions in the primary prevention and the secondary prevention groups.



Inappropriate ICD therapies

Nineteen patients (19%) experienced an inappropriate ICD therapy including an electrical shock in 12 patients. The other 7 patients had overdrive pacing attempts without shock. The trigger of the inappropriate therapy was atrial tachyarrhythmia in 8 patients, sinus tachycardia in 9 patients, and T wave over-sensing in 2 patients. The proportion of patients with inappropriate defibrillator intervention was not significantly different in the primary and in the secondary prevention groups (15% versus 21%, respectively). After a first episode of inappropriate therapy the parameter-settings of the ICD were changed or anti-arrhythmic therapy was started, so there was no recurrence of inappropriate therapy during the follow-up.

Discussion

In consecutive patients who were selected to undergo ICD implantation according to the current guidelines, there was a 65% lower risk of developing arrhythmias triggering appropriate ICD intervention among patients who received an ICD as primary prevention of SCD as compared with patients in the secondary prevention group. Clearly, the number of defibrillator interventions are not correlated with the number of lives saved. Indeed, several of the secondary prevention patients may have recurrent ventricular tachycardia that would not be fatal even without an ICD. However, ICD use in primary prevention patients is low, suggesting that the stratification tests available do not permit a high specificity in the selection of patients at high risk of life-threatening arrhythmias. Patients without prior arrhythmias have a much lower risk of developing arrhythmias than patients who have suffered sustained VT or VF. A relatively large proportion of the patients who receive a defibrillator as a primary preventive measure for SCD may not have a substrate for arrhythmias, and may not benefit from ICD therapy. Lack of specificity of selection criteria may be partly related to the relatively crude form of stratification, for example in MADIT-II study, which

enrolled patients with known coronary heart disease on the basis of a low ejection fraction only [5]. Indeed no single test may be highly predictive, and it may require a combination of predictive tests to identify a high-risk subset. The magnitude of absolute survival benefit and the cost-effectiveness of the ICD, as well as its acceptance in the medical community will depend on the efficiency by which patients who are at high risk of arrhythmic death can be identified in the population. The importance of other diagnostic strategies that delineate and/or modify the risk of life-threatening complications requires further evaluation [8]. For example, some investigators have demonstrated that adding the prerequisite of a bundle-branch block to the MADIT-II criteria and/or limiting the inclusion by selecting only patients with very low ejection fraction (<25%) allows selection of patients who are at higher risk for SCD [5, 9].

Clinical characteristics were not all similar in both study groups. Indeed, secondary prevention patients were on average 6 years older and were more often on anti-arrhythmic drug therapy (50% versus 30%) than primary prevention patients. In ICD recipients, anti-arrhythmic drug therapy may be used to slow rapid ventricular tachycardia and make it amenable to overdrive pacing (to avoid an electrical shock), to decrease the incidence of arrhythmias triggering ICD therapies, or to decrease the risk of inappropriate therapies in patients with paroxysmal supraventricular arrhythmias. Anti-arrhythmic drugs can also have pro-arrhythmic effects and may theoretically be responsible for an increased incidence of arrhythmias. However, multivariate statistical analysis showed that several covariates including age, ejection fraction, beta-blocker therapy, and anti-arrhythmic therapy had no effect on the outcome.

The nature of ventricular arrhythmias was not different in either study group. In secondary prevention patients, 85% of the arrhythmic events were regular VTs with a rate below 240 beats/min (on average 195 beats/min), whereas polymorphic VT or VF were uncommon. In primary prevention patients, the proportion of VT reached 60%. Although anti-tachycardia pacing was programmed in most of the patients in the secondary prevention group, it allowed avoidance of shock therapy in only 20% of the patients. The proportion of ICD therapies including at least one shock was not different in primary prevention and secondary prevention patients.

The overall mortality of 5% over a mean follow-up of 20 months is less than the half the mortality reported in the ICD groups of the main prospective trials for a comparable follow-up period. This is due to the fact that younger patients were included, mainly patients with non-ischaemic heart disease and that the mean age of our study group was lower than in most ICD trials. It may also partly be due to the improvement in overall prognosis conferred by the relatively high proportion of heart transplantation (5%) in our group of patients. Finally, left ventricular dysfunction may have been less severe that in other trials including only patients with coronary heart disease and low ejection fraction. Thus, there may have been fewer deaths due to pump failure in the follow-up period.

During the 20 months follow-up, 19 patients (19%) experienced an inappropriate ICD therapy including an electrical shock in 12 patients. Inappropriate ICD therapy was due to spurious detection of supraventricular tachyarrhythmia or sinus tachycardia in most of the patients. In the primary prevention group, the incidence of appropriate therapy was the same than the incidence of inappropriate therapy during the observation. In other words, the risk that a defibrillator intervention is not appropriate was about 50% in this group of patients, whereas 66% of the defibrillator interventions were appropriate in the secondary prevention group. After a first episode of inappropriate therapy the detection settings of the ICD were changed or an anti-arrhythmic therapy was introduced, so that most of the patients did not have any recurrence of inappropriate therapy.

Potential study limitations: this study presents short to intermediate-term follow-up results. Continued longitudinal observation is needed to assess long-term incidence of arrhythmias triggering ICD therapy. Factors potentially triggering arrhythmias such as ischaemia, low potassium, or hyperthyroidism were not systematically analysed at the time of arrhythmias. However, most of the ICD recipients are under tight medical control and are unlikely to have developed important exogenous arrhythmogenic factors during the follow-up. Systematic analysis of VT detection criteria was not performed. Possible differences in criteria for VT detection between groups may influence the incidence of ICD interventions.

In conclusion, the incidence of ventricular arrhythmias triggering appropriate ICD therapy was more than 2.5 times higher in secondary prevention patients than in primary prevention patients, suggesting that only a small proportion of patients determined as being at high risk according to current stratification methods really have a substrate for arrhythmias. Importantly, ICD therapies are not correlated with lives saved, and efficacy of ICD therapy in primary and secondary prevention can not be drawn from these data. However, the data suggest that the specificity of the selection criteria is relatively low and efforts should be made to increase the specificity of the selection of patients who will really benefit from ICD therapy.

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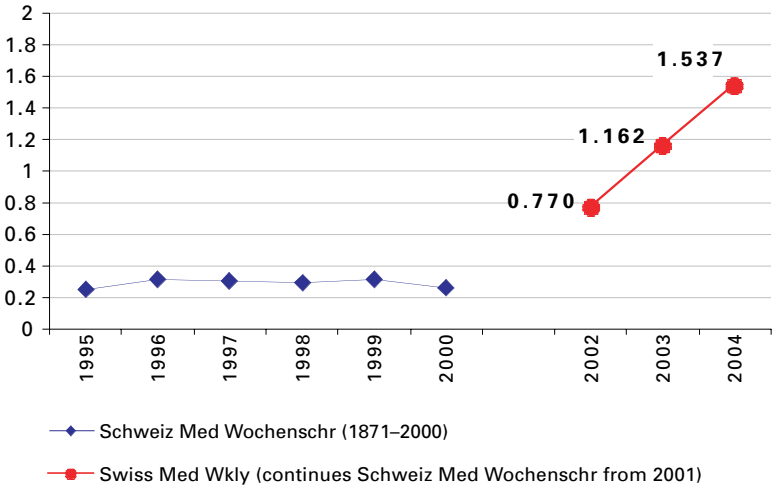

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