Prevention of Sudden Cardiac Death

— Lessons From Recent Controlled Trials —

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Sudden cardiac death (SCD), presumably because of ventricular tachyarrhythmias, remains one of the major challenges of contemporary cardiology. Major randomized controlled trials conducted in patients with coronary artery disease (CAD) with the aim of primary prevention of SCD are providing insights. Several large-scale studies have demonstrated that treatment with β -blockers, angiotensin-converting enzyme inhibitors, aldosterone antagonists, and statins results not only in a reduction in all-cause mortality but specifically also in SCD. On top of this optimized pharmacological therapy, implantable cardioverter-defibrillators (ICD) further decrease the risk of overall and SCD mortality in carefully selected patient groups. The sum of these trials indicates, however, that the benefit associated with ICD therapy is most prominent in patients with chronic stable CAD. In contrast, patients early after myocardial infarction derive less benefit from ICD treatment, presumably because of a high competing risk of non-arrhythmic cardiovascular death. Optimized pharmacological therapy, together with the ICD, can substantially improve the prognosis of high-risk CAD patients. (*Circ J* 2005; 69: 625–629)

Key Words: Coronary artery disease; Implantable cardioverter-defibrillator; Randomized controlled trials; Sudden cardiac death

Sudden cardiac death (SCD) remains one of the leading killers in the industrialized world, responsible for an estimated 300,000–400,000 deaths every year in the USA. Episodes of ventricular tachycardia (VT) or ventricular fibrillation (VF) are the underlying cause in the majority of cases of SCD; at the time of emergency intervention, VF is found in approximately 40% of SCD victims, with asystole and electromechanical dissociation becoming more frequent the longer the intervention is delayed! In patients in whom the time interval between the clinical event and the first ECG is less than 4 min, the incidence of VF has been documented to be as high as 95%. Most victims of SCD suffer from structural heart disease that may not have been known prior to the event. In the best of all worlds, approximately 5–15% of all victims of cardiac arrest can be resuscitated and leave the hospital without major neurological deficits. Given these numbers, recent years have seen major research efforts around the world aimed at primary prevention of SCD by both pharmacological and non-pharmacological means. We review the most important randomized controlled trials (RCT) of prevention of SCD in patients with coronary artery disease (CAD) that have been published over the past 2–3 years.

Pharmacological Therapy

Many trials have evaluated the potential of various membrane-active antiarrhythmic drugs to prevent SCD^{2–6}. In general, none has demonstrated a benefit associated with prophylactic treatment with a class I or III antiarrhythmic compound in patients deemed to be at high risk for SCD.

At best, the antiarrhythmic drug proved to be not inferior to placebo without any clear benefit^{4–6} and many other trials confirmed that there is harm associated with prophylactic administration of specific antiarrhythmic drugs^{2,3}.

The RCT evaluating the effects of various groups of non-antiarrhythmic drugs for prevention of cardiovascular death and SCD in particular have yielded more promising results. These drugs are listed in Table 1, together with the key RCT that have studied them. Beta-blockers, angiotensin-converting enzyme inhibitors (ACEI), angiotensin-receptor blockers, and aldosterone antagonists have been demonstrated to reduce all-cause mortality as well as SCD in high-risk patients.

Beta-Blockers

The antifibrillatory efficacy of β -blockers has been established for a long time. RCT have established the beneficial effects of these compounds beyond any doubt in patients after myocardial infarction (MI)⁷ and those with congestive heart failure^{8,9}. For instance, the carvedilol post-infarct survival control in left ventricular dysfunction trial¹⁰ randomized patients 3–21 days after MI who had an left ventricular ejection fraction (LVEF) ≤ 0.40 to receive carvedilol or matching placebo. There was a highly significant reduction in overall mortality in patients on anti-adrenergic therapy compared with the controls. More importantly, sustained ventricular tachyarrhythmic events were reduced by more than 70% over the follow-up period (hazard ratio (HR) 0.24, 95% confidence interval (CI) 0.11–0.49)¹¹. Accordingly, that RCT convincingly demonstrated that, even in the era of reperfusion therapy, during the acute phase of MI β -blocker therapy improves survival.

ACEI

The ACEI are one of the mainstay therapeutic modalities in patients with congestive heart failure that has been shown

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Table 1 Recent Key Randomized Control Trials of Nonantiarrhythmic Drugs and the Effect on SCD

Drug	Reference	Study characteristics	n	Hazard ratio for SCD (95%CI)
β -blocker	11	CAPRICORN: acute MI (3–21 days), LVEF ≤ 0.40	1,959	0.24 (0.11–0.49)*
ACEI	13	Meta-analysis of 15 RCT (patients with CHF)	15,104	0.80 (0.70–0.92)
ACEI	14	HOPE population (patients without CHF or LV dysfunction)	9,297	0.79 (0.64–0.98)
Spironolactone	15	CHF, LVEF ≤ 0.35	1,663	0.70 (0.54–0.95)
Eplerenone	16	Acute MI (3–14 days), LVEF ≤ 0.40	6,632	0.79 (0.64–0.97)

*Hazard ratio for ventricular tachycardia/fibrillation.

SCD, sudden cardiac death; CI, confidence interval; CAPRICORN, carvedilol post-infarct survival control in left ventricular dysfunction trial; MI, myocardial infarction; LVEF, left ventricular ejection fraction; ACEI, angiotensin-converting enzyme inhibitors; RCT, randomized controlled trial; CHF, chronic heart failure; HOPE, heart outcomes prevention evaluation trial.

Table 2 Prophylactic Implantable Cardioverter Defibrillator Trials in Coronary Artery Disease Patients

Trial (reference)	Year	n	Key enrollment criteria
MADIT I ¹⁸	1996	196	LVEF ≤ 0.35 , nonsustained VT on Holter, EP-inducibility, no suppression of induced VT by procainamide
CABG-Patch ¹⁹	1998	900	Elective CABG, positive SAECD
MUSTT ²⁰	1999	704	LVEF ≤ 0.40 , nonsustained VT on Holter, EP-inducibility, no response to antiarrhythmic drug therapy
MADIT 2 ²¹	2002	1,232	LVEF ≤ 0.30
DINAMIT ²²	2004	674	Recent infarct (6–40 days), LVEF ≤ 0.35 , evidence of autonomic imbalance
COMPANION ²³	2004	1,520	Advanced heart failure, QRS duration > 120 ms
SCD-HeFT ²⁴	2005	2,521	LVEF ≤ 0.35 , congestive heart failure

MADIT, multicenter automatic defibrillator implantation trial; LVEF, left ventricular ejection fraction; VT, ventricular tachycardia; CABG-Patch, coronary artery bypass graft patch trial; SAECD, signal-averaged ECG; MUSTT, multicenter unsustained tachycardia trial; DINAMIT, defibrillators in acute myocardial infarction trial; COMPANION, comparison of medical therapy, pacing and defibrillation in heart failure; SCD-HeFT, sudden cardiac death in heart failure trial.

to improve survival. Even in high-risk cardiovascular patients without signs of heart failure or LV dysfunction, these medications yield significant survival benefits.¹² In 1999 Domanski et al¹³ conducted a meta-analysis of all published ACEI trials (15 studies including 15,104 patients) and found a 20% relative risk reduction for the endpoint of SCD (HR 0.80, 95%CI 0.70–0.92). More recently, the heart outcomes prevention evaluation trial database was examined to see whether in this large population of 9,297 high-risk cardiovascular patients without clinical heart failure or overt LV dysfunction the composite endpoint of unexpected death, documented arrhythmic death and resuscitated cardiac arrest was reduced by the ACEI, ramipril.¹⁴ Compared with the placebo group, the endpoint was reduced by 21% (HR 0.79, 95%CI 0.64–0.98; $p=0.028$) in patients treated with the ACEI. According to these findings, therefore, there can be no doubt that ACEI have preventive potential against SCD in high-risk CAD patients.

Aldosterone Antagonists

Recently, 2 well-designed RCT have evaluated the effects of spironolactone¹⁵ and eplerenone¹⁶ on mortality in patients with congestive heart failure and in MI survivors with LV dysfunction who were enrolled 3–14 days after the index event. In both of these trials, not only was all-cause mortality in patients on aldosterone antagonists signifi-

cantly reduced but also SCD mortality. In the EPHEsus trial, for instance, the risk for SCD was reduced by 21% (HR 0.79; 95%CI 0.64–0.97; $p=0.03$).¹⁶ The mechanisms underlying these beneficial effects are not entirely clear. Besides the beneficial effects of aldosterone antagonists on electrolytes and plasma volume, these drugs have been shown to reduce coronary vascular inflammation and the risk of subsequent interstitial fibrosis, to improve endothelial dysfunction, and to decrease sympathetic drive.

Statins

To date, there is not a published RCT on the effects of statins on SCD in a high-risk population. However, there are at least 2 retrospective studies in implantable cardioverter-defibrillators (ICD) populations that point to a potential beneficial effect of these compounds on ventricular tachyarrhythmic events.^{17,18} Both studies suggest that appropriate ICD therapy occurs less frequently in patients treated with statins as compared with those who have not taken these lipid-lowering drugs. Again, the pathophysiological mechanisms responsible for a decrease in ventricular tachyarrhythmic events remain speculative. However, there is experimental evidence that statins may reduce myocardial ischemia, improve angiogenesis, and decrease ventricular dilatation and fibrosis. Currently, a randomized placebo-controlled trial in ICD recipients is being conducted to prospectively evaluate the effects of statins on ventricular

tachyarrhythmias.

Primary Prevention of SCD in CAD: Impact of the ICD

The multicenter automatic defibrillator implantation trial (MADIT) 1 trial was the first RCT to demonstrate that CAD patients who were carefully selected on the basis of spontaneous nonsustained VT on Holter monitoring and inducibility of sustained arrhythmias in the electrophysiology laboratory benefited from prophylactic ICD therapy.¹⁹ Shortly thereafter, however, the coronary artery bypass graft patch (CABG-Patch) trial in patients undergoing coronary artery bypass surgery who had a positive signal-averaged ECG showed no improved survival when they were randomly allocated to receive an ICD.²⁰ These seemingly discrepant results caused some confusion but demonstrated that careful selection of the patients most likely to benefit from ICD therapy is mandatory. The multicenter unsustained tachycardia trial study, which was not a randomized ICD trial, showed that in patients with inducible VT electrophysiologically guided antiarrhythmic drug therapy was of no value, but that mortality was reduced when nonresponders to drug therapy received a device.²¹ The MADIT 2 study proved that coronary patients who had reduced left ventricular function ($LVEF \leq 0.30$) had a better outcome not only in terms of arrhythmogenicity, but in fact also in all-cause mortality, when they received a defibrillator.²² Importantly, the MADIT 2 investigators did not use any additional risk stratification to select the patients. The key enrollment features of all of these ICD studies are summarized in Table 2. These trials have led to a substantial increase in the use of ICD worldwide, which in turn has led to considerable debate about the cost-effectiveness of prophylactic ICD therapy. In particular, the question of whether all coronary patients with clinically significant ventricular dysfunction after MI should receive an ICD.

Recent ICD Trials in CAD Patients

During the past 12 months, 3 important multicenter RCT of ICD therapy in CAD patients have been published^{23–25} and their results can help to refine the selection of appropriate patients for ICD therapy.

The international defibrillators in acute myocardial infarction trial (DINAMIT) study asked the important question whether ICD therapy shortly after an acute MI that has resulted in significant impairment of LV function in a patient who already has evidence for impaired cardiac autonomic tone will benefit from ICD therapy.²³ A total of 674 MI survivors were randomized to ICD therapy or control during the first 6–40 days after their heart attack. After a mean follow-up of 30 months, all-cause mortality was not substantially different between the 2 groups despite a highly significant reduction in arrhythmogenic mortality (HR 0.42, 95%CI 0.22–0.83; $p=0.009$). This reduction, however, was completely offset by an increase in cardiovascular nonarrhythmic mortality in the group of ICD recipients (HR 1.75, 95%CI 1.11–2.76; $p=0.02$). Accordingly, this trial identified a group of CAD patients with risk factors for SCD from cardiac causes in whom device therapy may not provide a survival benefit, which was in contrast to previous ICD studies in MI survivors.^{19,21,22} However, the characteristics of the DINAMIT patients differed in important ways from those of the prior studies, most importantly in the short time interval after the index infarct and the presence of autonomic imbalance. All prior primary prevention studies have enrolled patients after much longer time

periods; for instance, in the MADIT 2 study the mean time interval between the most recent MI and study enrollment was 6.5 years.²² Of note, a recent substudy of MADIT 2 demonstrated that in this patient population no survival benefit existed for patients in whom this time interval was less than 18 months,²⁶ which confirms therefore the findings of DINAMIT. Preliminary data from the DINAMIT study indicate that recurrent ischemic events may have played an important role in causing the increase in nonarrhythmic mortality.^{27,28} In addition, there is the possibility that the presence of markers of autonomic dysfunction identified a patient cohort at high risk for death from progressive heart failure. As pointed out in a recent editorial²⁹ recurrent sustained ventricular tachyarrhythmias may be a harbinger of advancing heart failure, which would imply that although sustained ventricular tachyarrhythmias occurred and were successfully treated by the device, the patients died of subsequent heart failure. It is important to emphasize the similarities between DINAMIT and the CABG-Patch trial. The latter also reported that the ICD reduced arrhythmic mortality by 45%, but did not reduce all-cause mortality because the majority of deaths (71%) were nonarrhythmic in nature.²⁰ Accordingly, these 2 studies support the concept that successful termination of VT or VF occurring as a consequence of progressive heart failure or recurrent myocardial ischemia may simply convert what would have been a sudden death to death from other cardiovascular causes, without an effect on survival.

In summary, therefore, DINAMIT indicates that the benefits from ICD implantation accrue after a considerable time following an acute MI. On this basis, the Centers for Medicare and Medicaid Services have recently decided that ICD therapy should be deferred at least for 1 month after an infarct.

The second most recently reported trial is the SCD-in heart failure trial (SCD-HeFT) study, which enrolled patients with left ventricular dysfunction of any etiology and used the presence of heart failure despite medical therapy and a $LVEF \leq 0.35$ as an entry criterion.²⁵ In the context of the present review it is important to note that 52% of the enrolled patients ($n=1,310$ patients) suffered from ischemic cardiomyopathy. Patients were randomly assigned to placebo or amiodarone therapy or to receive an ICD and were followed for a median of 45 months. The trial convincingly demonstrated that amiodarone therapy did not reduce mortality among heart failure patients, and also showed that ICD therapy was associated with a significant 23% reduction in the risk for all-cause mortality compared with placebo. The absolute risk reduction was approximately 1.2% per year of follow-up. This risk reduction was smaller than reported in earlier studies,^{19,21,22} which may be a reflection of better medical background therapy. Two features of this study deserve particular emphasis. SCD-HeFT again enrolled patients a long time after their MI, with the average duration of heart failure amounting to 24 months. Second, patients with New York Heart Association class II had a significant benefit from device therapy whereas patients in functional class III did not. Although the latter may have been a chance finding, it does emphasize the importance of the timing of ICD therapy. In summary, this largest of all primary prevention ICD trials emphasizes that ICD therapy in patients with CAD (and nonischemic cardiomyopathy as well) and left ventricular dysfunction should be considered a long-term rather than a short-term intervention.

The third important ICD study that was reported in the past 12 months is the comparison of medical therapy, pacing and defibrillation in heart failure trial,²⁴ which tested the hypothesis that prophylactic cardiac resynchronization by means of biventricular stimulation with or without an ICD would reduce the risk of death and hospitalization (primary study endpoint) in patients with advanced chronic heart failure and intraventricular conduction delays. The investigators enrolled 1,520 patients of whom 837 (55%) suffered from ischemic cardiomyopathy. Patients were randomly assigned to a control group, a biventricular pacing device alone or such a device including an ICD. As compared with medical therapy alone, cardiac resynchronization therapy with the pacemaker reduced the risk of the primary endpoint by 19%, as did the combined resynchronization ICD treatment (20% risk reduction). The secondary endpoint of death from any cause was only significantly reduced by the combined resynchronization ICD therapy (36% relative risk reduction, $p=0.003$). Importantly, however, when mortality was analyzed according to the presence of ischemic vs nonischemic cardiomyopathy, the reduction in the risk of death from any cause was no longer statistically significant for patients with CAD (HR 0.73; 95%CI 0.52–1.04; $p=0.082$). As pointed out recently, these results indicate that patients with advanced heart failure and intraventricular conduction delays who are candidates for prophylactic ICD therapy may have additional benefit from a device capable of biventricular pacing.³⁰

Conclusions

Over the last few years, several large-scale well-conducted RCT have tremendously increased our knowledge on potential treatment strategies to prevent SCD in patients with CAD. As the main lesson from the trials of various drug treatments, optimal pharmacological therapy should include β -blockers, ACEI, aldosterone antagonists, and statins. With the background of this optimized pharmacological therapy, the ICD has been demonstrated to significantly reduce all-cause mortality, and arrhythmic mortality in particular. However, not all patient groups appear to benefit from device therapy. Obviously, patients with chronic stable CAD and/or congestive heart failure are the best candidates for prophylactic ICD therapy whereas those who have recently had an acute MI or coronary artery bypass surgery derive no benefit because the competing risk for nonarrhythmic cardiovascular death is too large in those patient groups. Finally, we need better ways to predict which patient populations will benefit most from prophylactic device therapy. Accordingly, research in the field of noninvasive risk stratification needs to be intensified in order to further improve the cost–benefit ratio of device therapy.

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