Singapore Med J 1999; Vol 40(11):707-710

Treatment and Prevention of Sudden Cardiac Death – What Have We Learnt from Randomised Clinical Trials?

R M L Kam, W S Teo, T H Koh, Y L Lim

ABSTRACT

Sudden cardiac death is most commonly caused by ventricular tachycardia or fibrillation. Three groups of patients at highest risk for sudden cardiac death are survivors of previous sudden cardiac death, those with recurrent documented episodes of sustained ventricular tachycardia and patients with recurrent syncope of unknown origin. The experience with antiarrhythmic drugs has been discouraging. Only beta-blockers have been shown to unequivocally reduce both arrhythmic and total mortality in randomised trials. Class I antiarrhythmic drugs increase mortality, especially in an ischemic substrate. Class III drugs such as sotalol and amiodarone have had variable success. Racemic sotalol has both beta-blocker as well as Class III actions and some of the benefits may be due to the former effect. D-sotalol which has only pure Class III action, increases mortality in the post myocardial infarction patient. Amiodarone is superior to Class I antiarrhythmic drugs for patients with previous cardiac arrest. In the high-risk myocardial infarction patient, it seems to reduce sudden death but not total mortality. In the cardiac failure patient, the effect of amiodarone on total mortality is controversial. Several randomised trials of implantable cardioverter-defibrillator (ICD) therapy versus drugs have however concluded that the ICD is superior to drugs in reducing total mortality. In comparison with many other high volume therapies used in medicine today, ICD is still a cost-effective therapy.

Keywords: sudden death, implantable cardioverter-defibrillator, antiarrhythmic drugs, survival, cost effectiveness

National Heart Centre
Mistri Wing
Third Hospital Ave
Singapore 169608

R M L Kam, MBBS, MRCP (UK), MMed (Int Med)
Consultant

W S Teo, MBBS, FRCP (UK), MMed (Int Med)
Senior Consultant

T H Koh, MBBS, MMed (Int Med)
Senior Consultant and Head
Department of Cardiology

Y L Lim, MBBS, PhD, FRACP
Director

Correspondence to:
Dr R M L Kam

INTRODUCTION

Sudden cardiac death occurs in a variety of clinical substrates including ischemic heart disease, hypertrophic or dilated cardiomyopathy, right ventricular dysplasia, aortic stenosis, long QT syndrome and primary electrical instability of the heart. In approximately 85% of cases, the cause is a lethal ventricular tachyarrhythmia, namely ventricular tachycardia (VT) or fibrillation (VF)[1]. In such circumstances, the probability of reaching the hospital alive is 2% – 15%, depending on the availability of trained paramedical staff and ambulances equipped with defibrillators[2]. Of those who reach the hospital, only half are discharged to the community alive. Contrary to popular belief, only a minority (20%) of sudden cardiac deaths occur in the setting of an acute myocardial infarction[2]. It has been shown that VF that is not associated with, or occurs more than 72 hours from a myocardial infarction, has a high recurrence rate of about 30% per year[2]. Other high-risk groups that are at risk for sudden death and therefore warrant further evaluation are those patients who present with recurrent episodes of sustained ventricular tachycardia or recurrent syncope of unknown origin. There are only 3 treatment strategies at present for the prevention of sudden cardiac death – drug therapy, the implantable defibrillator (ICD) and surgical or catheter ablation.

Pharmacological therapy

Pharmacological therapy is non-invasive, appears to be more inexpensive in the short term, has no surgical morbidity and mortality and may be appropriate for some patients, such as those who refuse any invasive procedures, those with multisystem disorders and limited life expectancy anyway because of other co-morbidities. On the other hand, drug therapy is often associated with intolerable side effects, organ toxicity and non-compliance. More importantly, antiarrhythmic drug therapy may increase mortality due to pro-arrhythmic effects and depression of myocardial function. In recent years, many antiarrhythmic drug trials have been conducted in several patient populations deemed to be at high risk for sudden death, namely those who have been resuscitated from sudden cardiac death, those with congestive cardiac failure, and the post-myocardial infarction population.

Trials of antiarrhythmic drugs versus placebo

In the history of antiarrhythmic drug trials for the post-myocardial infarction population, only beta-blockers have been shown unequivocally to reduce both sudden and non-sudden cardiac death. In the Beta Blocker Heart Attack Trial (BHAT)[3,4] involving 3,837 patients, the use of propranolol compared to

placebo, reduced total mortality by 27% and 25% and sudden death by 47% and 13% in those with and without congestive heart failure respectively. The risk reduction is greatest in those with impaired ventricular function and, paradoxically, it is in this group of patients that beta-blocker therapy is often withheld because of the fear of precipitating heart failure.

Increased ventricular ectopy is recognised as a risk marker of sudden cardiac death. Yet, the hypothesis that suppressing the marker, ie. the frequency of ventricular ectopics, would prevent sudden death, was ignominously debunked by the Cardiac Arrhythmia Suppression Trial (CAST) study. The CAST study[5] randomised 1,498 patients with a previous myocardial infarction and more than 6 ventricular ectopics per hour, suppressible with encainide, flecainide or moricizine, to placebo or one of the above drugs. The study was terminated prematurely after 14 months because of excess mortality in the encainide and flecainide arm. The moricizine arm[6] was continued and later found to confer no significant benefit over placebo. The SWORD study[7] (Survival With Oral D-sotalol post-infarction) randomised over 3,000 patients with ejection fraction less than 41% to d-sotalol, an antiarrhythmic agent with pure Vaughn-Williams Class III activity (no beta blocker activity), or placebo. This study was also terminated prematurely because of excess mortality in the d-sotalol treated group.

In the EMIAT study[8] (European Myocardial Infarct Amiodarone Trial), 1,486 patients post-myocardial infarction, with ejection fraction less than 41% were randomised to amiodarone therapy or placebo, irrespective of the presence of ventricular ectopy. The study showed a reduction in arrhythmic deaths but not total mortality in the amiodarone treated group. The CAMIAT study[9](Canadian Amiodarone Myocardial Infarction Arrhythmia Trial) randomised 1,202 patients who were post-myocardial infarction and had more than 10 ventricular ectopics on Holter recording, to amiodarone and placebo, and similarly found a 48.5% risk reduction in arrhythmic deaths but no statistically significant reduction in non-arrhythmic or all-cause mortality.

In the congestive cardiac failure population, two large randomised trials comparing amiodarone versus placebo have shown conflicting results. In the CHF-STAT[10] study (Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy), 674 patients with New York Heart Association Class II to IV and ejection fraction less than 41%, with more than 10 ventricular ectopics per hour, were randomised to amiodarone or placebo. Amiodarone was found to suppress ventricular ectopy and improve ventricular fraction more than placebo, but did not improve survival compared to placebo. A comparable study (GESICA study[11]) in South America, randomised 516 patients to amiodarone and placebo and found that the two-year mortality was reduced from 41% (placebo) to 34%. However this population had a greater proportion of non-ischemic cardiomyopathy patients that may account for the discordance in results with the CHF-STAT study.

Trials of conventional antiarrhythmic drugs versus sotalol or amiodarone

The preceding trials have suggested that drugs like amiodarone which possess Class III antiarrhythmic activity may be fundamentally different from the Class I drugs such as those tested in the CAST study. While the Class I drugs have consistently demonstrated increased mortality, amiodarone has at least, not been shown to be harmful, and in some studies, to be protective against sudden death. Trials directly comparing amiodarone against conventional Class I drugs such as the CASCADE study[12] (Cardiac Arrest in Seattle – Conventional versus Amiodarone Drug Evaluation) in a population of patients who had been resuscitated from sudden death showed that amiodarone conferred a better survival benefit. However the mortality was still significant for the amiodarone group (18% at 2 years, 34% at 4 years and 46% at 6 years).

In the ESVEM study[13] (Electrophysiologic Study versus Electrocardiographic Monitoring) which was actually a trial comparing two methods of predicting efficacy of drug therapy, patients who had been resuscitated from sudden death, VT or recurrent syncope were randomised to Holter monitoring (HM) or electrophysiological study (EPS) for guiding antiarrhythmic drug therapy. The drugs used included six Class I drugs (quinidine, procainamide, propafenone, mexilitine, imipramine and pirmenol) and sotalol. There was no difference in arrhythmia recurrence between the two methods. However what also emerged from the trial was that those who had an efficacy prediction for sotalol had significantly less arrhythmia recurrence than those who had efficacy predictions by other drugs. But even with sotalol, the one-year mortality for this group of patients was 10%, with 20% one-year recurrence of arrhythmia. Extrapolating the results from ESVEM to clinical practice, it would appear that HM is a cheaper and non-invasive means of managing such patients pharmacologically, except that the ESVEM data is only applicable to only 15% of patients who must have both non-sustained VT on Holter and inducible VT at EPS. In addition, because this was not a trial of randomised drug therapy, drawing conclusions about the comparative efficacy of the antiarrhythmic drugs is problematic. Tolerance to sotalol may have pre-selected a "less sick" patient population who were able to tolerate a beta blocker.

Trials comparing antiarrhythmic drugs with the ICD

When the ICD was approved by the Food and Drug Administration (FDA) in the United States for the treatment of life-threatening ventricular arrhythmias in 1985, an explosive increase in the use of this therapy occurred, especially in the United States. It soon became apparent that randomised controlled trials were needed to demonstrate an overall survival benefit for this new and expensive therapy. MADIT[14] (Multicenter Automatic Defibrillator Implantation Trial) was the first randomised controlled trial to show an overall survival benefit with the ICD over

conventional antiarrhythmic drugs.

MADIT included post-infarction patients with ejection fraction less than 36% and non-sustained VT on Holter and inducible VT during EPS that was not suppressible by procainamide, to conventional antiarrhythmic drug therapy or ICD. Conventional antiarrhythmic drug therapy was left at the discretion of the physician, but the majority (80%) were given empiric amiodarone therapy. One hundred and ninety-six patients were randomised and the ICD group had a 54% reduction in total mortality. The results led the FDA to approve a new indication for ICD in this particular group of patients. While MADIT was a landmark study for the ICD, its inclusion criteria make it applicable to only 5% of the overall post infarction population.

The AVID (Antiarrhythmics versus Implantable Defibrillator) study[15] was the second landmark trial for the ICD. Patients who had previous VF, or hemodynamically unstable VT were randomised to 3 treatment arms, namely ICD, empiric amiodarone or EPS or Holter-guided sotalol treatment. One thousand and sixteen patients were randomised and the study was terminated prematurely 16 months early because of the convincing 38% reduction in total mortality at one year and 26% and 30% reduction in years two and three for the ICD group.

After AVID, other studies such as CIDS[16] (Canadian Implantable Defibrillator Study) and CASH[17] (Cardiac Arrest Study Hamburg) have confirmed the superiority of the ICD over conventional antiarrhythmic drugs and amiodarone or sotalol in the cardiac arrest population. In CASH, ICD reduced mortality by 37% in the first year and in CIDS the mortality reduction was 20%. Another high risk group, the post infarction patient, already scheduled for coronary artery bypass surgery, with ejection fraction of less than 36%, and an abnormal signal averaged electrocardiogram (SAECG) were randomised to ICD versus no therapy (CABG Patch Study)[18]. The mortality at two years was no different between the ICD and no ICD group (25%). This may have been because the SAECG may not be as good a risk predictor as EPS and hence the selection criteria may have biased the outcome in favor of the "placebo" group.

The MUSTT study[19] (Multicenter Unsustained Tachycardia Trial) is an ongoing trial randomising post-infarction patients with ejection fraction less than 41% and non-sustained VT on Holter and inducible VT on EPS to no treatment or EP-guided drug therapy. Those non-drug responders will be given an ICD. SCD-HEFT[20] (Sudden Cardiac Death in Heart Failure Trial) will randomise Class II or III heart failure patients with ejection fraction less than 36% to amiodarone, ICD or placebo. The primary end-point will be total mortality and secondary end-points will include arrhythmic deaths, cardiac mortality, quality of life and cost effectiveness.

Are ICDs cost-effective?

With the positive results of MADIT, AVID, CIDS and CASH, the ICD is fast becoming the therapy of choice in the groups of patients represented by these studies. Aware of the economic burden to an already besieged health care system, many studies on cost-effectiveness have been done on ICD versus drug therapy. The basic premise is that a therapy or intervention must be measured in terms of clinical outcomes as well as costs. Clinical outcome is often defined as the average number of years lived after the therapy. It also takes into account the quality of life after the therapy. The cost of a therapy not only includes the initial cost of the therapy, but also the ongoing costs of maintenance and the costs of treating side effects and complications. Researchers may use charges or reimbursement figures to calculate costs.

Two methods typically used in cost-effectiveness analyses are average cost-effectiveness and incremental cost-effectiveness. Average cost-effectiveness is the cost of therapy divided by the average number of years lived after the therapy (cost per life year). When two competing therapies (A and B) are compared, incremental cost-effectiveness is computed by taking the total cost of A minus the total cost of B, divided by the number of years lived after A minus number of years lived after B. This gives us the differential cost of each additional life-year saved by therapy A. In these types of analyses, if this figure is negative, then the therapy is cost-saving. If this value is $20,000 or less, the therapy is highly cost-effective; cost-effective if between $20,000 and $40,000, borderline cost-effective if between $40,000 and $60,000, expensive if between $60,000 and $100,000, and unattractive if more than $100,000[21]. Several incremental cost-effectiveness studies concluded that ICD therapy is cost-effective ($7,400 to $27,000 per life year saved)[22-26].

Another method of assessing cost-effectiveness looks at hospitalisation costs pre- and post-therapy and compares an initial strategy of ICD implantation versus drug therapy. Valenti[27] et al found that there was a dramatic reduction in hospitalisation costs one-year after ICD implantation compared to drug therapy. The "break-even" point or the point at which the cost of drug therapy overtook ICD therapy and henceforth became more expensive was found to be 19 months. Since ICD patients are estimated to have an average life expectancy of 6.1 years, compared with 3.9 years for amiodarone and 2.5 years for other antiarrhythmic drugs[24], it is clear that ICD therapy will emerge the winner. With increasing longevity of the new generation ICDS, some projecting to as many as 10 years, and smaller devices, making implantation easier, moving implants from the operating theatre to the electrophysiology laboratory and hospital stay shorter, it is envisaged that ICD therapy will become even more cost-effective in the future.

CONCLUSION

Sudden death continues to be a vexing problem in a heterogenous patient population comprising ischemic heart disease, dilated cardiomyopathy, hypertrophic cardiomyopathy, right ventricular dysplasia, congestive heart failure, long QT syndrome and idiopathic

ventricular fibrillation. Through randomised clinical trials, we have learnt that only beta-blockers reduce both sudden and non-sudden deaths. Amiodarone has been shown to reduce sudden deaths although not total mortality in a number of studies. Other antiarrhythmic drugs conversely have increased mortality, partly due to proarrhythmic effects, and partly due to myocardial depression and other organ toxicities. The ICD has emerged as a powerful weapon against sudden death but also seems to reduce non-sudden deaths as well. It is also a cost-effective therapy compared to many other high volume therapies used in medicine, such as coronary angioplasty for single vessel disease and peritoneal dialysis for end-stage renal failure.

The cost-effectiveness will increase further as ICDs increase in longevity and the implant procedure is made simpler. The greatest challenge for the future lies in finding more effective preventive strategies for coronary heart disease and perhaps better understanding for the molecular basis for some forms of sudden death such as those due to dilated and hypertrophic cardiomyopathy and long QT syndrome with their consequent implications for gene therapy.

REFERENCES

1. Bayes de Luna, Coumel P, Leclerq JF. Ambulatory sudden cardiac death: mechanisms of production of fatal arrhythmias on the basis of data from 157 cases. Am Heart J 1989; 117:151-9.
2. Cobb LA, Baum RS, Alvarez H, Schaffer WA. Resuscitation from out-of-hospital ventricular fibrillation; 4 years follow-up. Circulation 1975; 52: III 223-35.
3. Beta-Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction, I: mortality results. JAMA 1982; 247:1707-14.
4. Chadda K, Goldstein S, Byington R, Curb JD. Effect of propranolol after acute myocardial infarction in patients with congestive heart failure. Circulation 1986; 73:503-10.
5. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med 1989; 321:406-12.
6. The Cardiac Arrhythmia Suppression Trial II Investigators. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. N Engl J Med 1992; 327:227-33.
7. Waldo A, Camm JA, de Ruyter H, Friedman PL, MacNeil DJ, Pitt B. Survival with oral d-sotalol in patients with left ventricular dysfunction after myocardial infarction: rationale, design and methods (the SWORD Trial). J Am Coll Cardiol 1995; 75:1023-7.
8. Julian D, Camm A, Frangin G, Janse M, Schwartz P, Simon P, for the European Myocardial Infarct Amiodarone Trial Investigators. Randomized trial of effect of amiodarone on mortality in patients with left ventricular dysfunction after recent myocardial infarction: EMIAT. Lancet 1997; 349:667-74.
9. Cairns JA, Connolly SJ, Roberts R, Gent M, for the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial Investigators. Randomized trial of outcome after myocardial infarction in patients with frequent or repetitive premature depolarizations: CAMIAT. Lancet 1997; 349:675-82.
10. Singh S, Fletcher R, Fisher S, Singh B. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia: Survival Trial of Amiodarone in Patients with Congestive Heart Failure. N Engl J Med 1995; 333:77-82.
11. Doval HC, Nul DL, Grancelli HO, Perrone SV, Bortman GR, Curiel R. Randomized trial of low dose amiodarone in severe congestive heart failure. Lancet 1994; 344:493-8.
12. The CASCADE Investigators. Randomized antiarrhythmic drug therapy in survivors of cardiac arrest (the CASCADE Study). Am J Cardiol 1993; 72:280-7.
13. Mason JW for the Electrophysiologic Study Versus Electrocardiographic Monitoring Investigators. A comparison of electrophysiologic testing with Holter monitoring to predict antiarrhythmic drug efficacy for ventricular tachyarrhythmias. N Engl J Med 1993; 329:445-51.
14. Moss A, Hall J, Cannom D, Daubert J, Higgins S, Klein H, et al for the Multicenter Automatic Defibrillator Implantation Trial. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. N Engl J Med 1996; 335: 1933-40.
15. The Antiarrhythmics Versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997; 337:1576-83.
16. Connolly S, Gent M, Roberts R, Dorian P, Green MS, Klein GJ, et al. Canadian Implantable Defibrillator Study (CIDS): study design and organization. Am J Cardiol 1993; 72:103F-8F.
17. Siebels J, Cappato R, Ruppel R, Schneider MA, Kuck K and the CASH Investigators. Preliminary results of the Cardiac Arrest Study Hamburg (CASH). Am J Cardiol 1993; 72:109F-13F.
18. The CABG Patch Trial Investigators and Coordinators. The Coronary Artery Bypass Graft (CABG) Patch Trial. Prog Cardiovasc Dis 1993; 36:97-114.
19. Buxton AE, Fisher JD, Josephson M, Lee K, Pryor DB, Prystowsky EN, et al. Prevention of sudden death in patients with coronary artery disease: the Multicenter Unsustained Tachycardia Trial (MUSTT). Prog Cardiovasc Dis 1993; 36:215-26.
20. The Prevention of Sudden Cardiac Death in Heart Failure Trial. Washington, DC: NIH Physician Pamphlet; 1997. National Institutes of Health.
21. Goldman L, Gordon DJ, Rifkind BM. Cost and health implications of cholesterol lowering. Circulation 1992; 85:1960-8.
22. Kuppermann M, Luce BR, McGovern B, Podrid PJ, Bigger JT, Ruskin JN. An analysis of the cost effectiveness of the implantable defibrillator. Circulation 1990; 81:91-100.
23. Wever EFD, Hauer RNW, Schrijvers G, Van Capelle FJL, Tijssen JGP, Crijns HJGM, et al. Cost-effectiveness of implantable defibrillator as first choice therapy versus electrophysiologically guided tiered strategy in post-infarct sudden death survivors. Circulation 1996; 93:489-96.
24. Larsen GC, Manolis AC, Sonnenberg FA, Beshansky JR, Estes NAM, Pauker SG. Cost effectiveness of the implantable defibrillator: effect of improved battery life and comparison with amiodarone therapy. J Am Coll Cardiol 1992; 19:1323-34.
25. Kuppersmith J, Hogan A, Guerrero P, Gardiner J, Mellits ED, Baumgardner R, et al. Evaluating and improving the cost effectiveness of the implantable cardioverter-defibrillator. Am Heart J 1995; 130:507-15.
26. Owens DK, Sanders GD, Harris RA, McDonald KM, Heidenreich PA, Dembitzer AD, et al. Cost-effectiveness of implantable cardioverter-defibrillator relative to amiodarone for the prevention of sudden cardiac death. Ann Intern Med 1997; 126:1-12.
27. Valenti R, Schlapfer J, Fromer M, Fischer A, Kappenberger L. Impact of the implantable cardioverter-defibrillator on rehospitalizations. Eur Heart J 1996; 17: 1565-71.