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SUDDEN CARDIAC DEATH - A PREDICTABLE, AVOIDABLE AND TREATABLE EVENT?*

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The risk of sudden cardiac death in an unselected adult population is only two per thousand persons per year.[1] Thus, screening of the general population is impractical and not cost-efficient, and risk-stratification focuses efforts on patients who have survived sudden death (secondary prevention), and those with heart disease known to predispose to sudden death (primary prevention). Such patients include those recovering from a myocardial infarction (MI) and those with dilated cardiomyopathy, hypertrophic cardiomyopathy (HCM), and the long QT syndrome. Other groups at risk include competitive athletes and those abusing solvents.

Patients predisposed to sudden death:
- Those who have previously experienced a sudden collapse.
- Post-myocardial infarction.
- Dilated cardiomyopathy.
- Hypertrophic cardiomyopathy.
- Long QT syndrome.
- Competitive athletes.
- Solvent abusers.

POST-MYOCARDIAL INFARCTION

The largest group for risk stratification is post-MI patients, for whom mortality is highest in the first six months.[2] The main predictors of this late mortality are left ventricular dysfunction, ventricular arrhythmias, residual ischaemia and age. When the left ventricular ejection fraction is > 40%, cardiac mortality at one year is < 4%, compared with almost 50%, when the ejection fraction is < 20%.[1] Although ischaemia can trigger ventricular fibrillation (VF), it is a non-specific predictor considering the relative frequency of ischaemic episodes compared with the less frequent incidence of VF following an MI.[3]

Various investigations have been utilised to identify high-risk patients for sudden death following a MI.[1] These include assessment of left ventricular function, 24-hour ambulatory ECG monitoring, signal averaged ECG, heart rate variability (HRV), reflex baroreceptor sensitivity (BRS) and electrophysiological (EP) studies. When EP studies are used in risk-stratification in patients with uncomplicated MIs, a negative study is associated with an excellent prognosis but a positive study is poorly predictive of sudden death.[1] Likewise it has been demonstrated that various combinations of two or more non-invasive investigations have high negative predictive values (90-100%) but low

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positive predictive values.[4] Thus non-invasive and invasive investigations used separately or together identify low-risk patients, most patients in the high-risk group after risk stratification never have an arrhythmic event. Therefore more specific means are required to identify patients at highest risk.

Arrhythmic events occur in response to certain triggers. Both the autonomic nervous system and electrolyte imbalances have been strongly linked to arrhythmic death in MI survivors.[5,6] The autonomic nervous system can be assessed using heart rate variability (HRV) which reflects resting vagal tone and baroreceptor sensitivity (BRS), the latter reflecting reflex vagal activity during stress. The ATRAMI (autonomic tone and reflexes post MI) study examined the usefulness of these measurements in predicting mortality following a MI.[7] It was a prospective multicentre trial involving 1,284 patients who had a MI within 28 days prior to enrollment. HRV was measured as the standard deviation of all normal R-R intervals on a 24-hour ambulatory ECG. BRS was assessed as the heart rate slowing following increase in blood pressure induced by i.v. boluses of phenylephrine. A low BRS (<3ms/mmHg) was associated with an increased two-year cardiac mortality (9% versus 2%). Likewise a low HRV (<70ms) was associated with increased cardiac mortality (10% vs 2%). In multivariate analysis, which included left ventricular ejection fraction and ventricular premature complexes (VPC), low BRS and low HRV were still associated with increased mortality.[7]

Predictors of sudden mortality in post-MI patients:
- Left ventricular dysfunction.
- Ventricular arrhythmias (autonomic stimulation; electrolyte imbalance).
- Residual myocardial ischaemia.
- Age.

PRIMARY PREVENTION OF SUDDEN DEATH

Drug therapy

Drugs used in primary prevention include beta-blockers (Class II agents) with anti-arrhythmic and anti-ischaemic properties, ACE inhibitors and anti-arrhythmic agents. Both the Norwegian multicentre trial (with timolol) and the β-blocker 'heart attack' trial (with propranolol) demonstrated a reduction in sudden death.[8,9] In the Trandolapril TRACE study treatment with the ACE inhibitor, trandolopril reduced sudden deaths.[10] The CAST I and II trials demonstrated that Holter-guided suppression of ventricular arrhythmias using the Class I agents flecainide, encainide or moricizine increased sudden death.[11,12] The Class III agent, amiodarone, was investigated in the CAMIAT and EMIAT trials.[13,14] In CAMIAT, patients were recruited following a MI if on Holter they had $\geq$10 VPC/hr or $\geq$1 run of ventricular tachycardia (VT). In EMIAT, post-MI patients were enrolled if they had an ejection fraction of $\leq$40%. In both studies there was a reduction in sudden death (48.5%, 35%) respectively but with an increase in non-arrhythmic cardiac deaths. The pure potassium channel blocker D-Sotalol was investigated in post-MI patients with heart failure and an ejection fraction $\leq$40% in the SWORD study.[15] This study was terminated prematurely because of an increased mortality in the treatment arm (4.6% vs 2.7%). The Class IV agents, i.e. calcium antagonists, generally lack benefit.[16]

Revascularisation and/or reperfusion

In the coronary artery surgery study (CASS), myocardial revascularisation prevented

sudden cardiac death in high-risk patients.[17] Patients with three-vessel disease and history of congestive heart failure treated surgically had a 9% incidence of sudden death during a five-year follow-up compared with 31% in similar patients managed medically. Acute intervention following a MI results in patent infarct-related arteries, with lower incidence of inducible arrhythmias at EP studies and probably a reduction in sudden death.[1]

Implantable cardioverter defibrillators (ICD)

In the MADIT trial, 196 asymptomatic patients with a prior MI, ejection fraction $\leq$35%, spontaneous non-sustained VT and induced sustained non-suppressible (with IV procainamide) VT were randomised to ICD or anti-arrhythmic drugs.[18] At a mean follow-up of 27 months there was a significant reduction in mortality in the ICD group compared with the anti-arrhythmic group, mainly amiodarone (16% vs 39%, $p<0.01$). The 60% mortality reduction was mainly due to a reduction in arrhythmic deaths. In the CABG-patch trial, patients were randomised to ICD (446) or control (454) if they had coronary artery disease, ejection fraction <36%, an abnormal SAECG (signal averaged ECG) and were undergoing CABG.[19] At a mean follow-up of 32 months there was no significant difference in mortality (ICD 101 pts, Control 95).

SUMMARY

In the primary prevention of sudden death post-MI, in asymptomatic patients the need for coronary revascularisation requires assessment prior to arrhythmic risk stratification. All patients should receive aspirin and β-blockade unless there is a significant contraindication. ACE inhibitors should be given to those with left ventricular EF<40%. It has been proposed that two non-invasive investigations should be performed in all patients.[4] When both tests are negative no further risk assessment is required. If both are positive, the patient should proceed to EP studies. In the case of discordant results a BRS test should be performed, and if BRS is <3 the patient should also have EP studies. If no VT is inducible at EP studies, no further treatment is required. If VT is induced and is not suppressed by drugs, the optimal management is probably with an ICD.

SECONDARY PREVENTION SUDDEN DEATH

There are 300,000-500,000 sudden cardiac deaths per year in the United States and similarly in Europe.[5,6] Approximately 1% of victims of cardiac arrest are resuscitated and survive to leave hospital.[5] In this population there is a high risk of sudden death, up to 40% at two years.[20]

Anti-arrhythmic drugs

The ESVEM trial investigated whether EP or Holter-guided suppression of arrhythmias was superior in predicting long-term anti-arrhythmic drug efficacy in VF/VT patients (n=486).[21] It also assessed the relative efficacy of various anti-arrhythmic agents. It found that arrhythmia recurrence was not significantly different in the EP or Holter-guided therapy, and that recurrence of arrhythmia and mortality were lower (50% at one year) in those treated with DL sotalol than with Class I drugs. In the CASCADE trial, empiric amiodarone was compared with guided (Holter or EP) with standard (Class I) antiarrhythmic therapy in survivors of out-of-hospital cardiac arrest due to VF.[22] The combined end-point of cardiac death, resuscitated VF or syncopal shock (in ICD patients) was reduced in the amiodarone-treated patients (9% vs 23% at one year). In the CASH trial, an interim report suggested that in 230 survivors of cardiac arrest,

propafenone provided less effective prophylaxis against sudden death compared with randomly assigned amiodarone, metoprolol or ICD. It was therefore excluded from further study.[20]

Implantable defibrillators

The interim results of the CASH trial also suggested that ICDs were superior to metoprolol or amiodarone in preventing sudden death; the incidence of sudden death with a mean follow-up of 11 months was 0%, 11.4% and 8.8% respectively.[20] In the AVID trial empirical amiodarone was compared with EP or Holter-guided sotalol therapy and ICD therapy.[23] After recruiting 1,013 patients the study was terminated early because of a statistically significant benefit in favor of ICD compared with drug therapy. We await the results of the Canadian Internal Defibrillator study (amiodarone vs ICD).[24]

DILATED CARDIOMYOPATHY (PRIMARY PREVENTION SUDDEN DEATH)

In the Gesica trial, 516 patients with predominantly non-ischaemic dilated cardiomyopathy (ejection fraction 20%) were randomised to amiodarone or placebo.[25] It was stopped after a mean follow-up of 13 months because of improved survival in the amiodarone arm. The reduction in sudden death was observed early (within 30 days) and was not influenced by the presence or absence of non-sustained VT. In the CHF-stat trial, 674 patients with symptoms of congestive heart failure with impaired left ventricular function (EF$\leq$40%) and $\geq$10 VPCs per hour were randomised to placebo or amiodarone.[26] There was no difference in mortality at two years but among those with non-ischaemic cardiomyopathy there was a trend toward reduced mortality. We await the results of the SCD-HeFT trial in which 2,500 patients with dilated ischaemic or non-ischaemic cardiomyopathy will be randomised to placebo, low-dose amiodarone or ICD and followed for 2.5 years.[27]

SECONDARY PREVENTION SUDDEN DEATH

In those with a history of sustained VT/VF or syncope, ACE inhibitors, carvedilol, β-blockers, amiodarone and ICDs have been used.

HYPERTROPHIC CARDIOMYOPATHY

The estimated prevalence of HCM in the general population is 0.2%. However, it accounts for 50% of all sudden cardiac deaths in those aged less than 35 years.[28] Risk-stratification can include clinical and genetic markers. The non-invasive investigations of QT dispersion, HRV and late potentials are poor predictors for sudden death. Clinical features which predict sudden death include - a family history of premature (age<25) sudden death, recurrent syncope, non-sustained VT and an abnormal BP response on exercise stress testing.[28] Genetic defects associated with a poor prognosis include those involving the troponin T gene, and a substitution of arginine to glutamine at position 403 of the β myosin heavy chain. In contrast a substitution of valine to methionine at position 606 of this gene is associated with a near-normal prognosis.[28]

Primary prevention of sudden death is indicated where two or more of the adverse clinical features are present. Treatment is also indicated for those with sustained VT or non-sustained VT. This is usually with amiodarone and/or an ICD.[28]

LONG QT

Gene mutations which encode for cardiac ion channels have been identified in the

congenital long QT syndromes.[29] Adrenergic stresses such as emotional excitement may trigger arrhythmias. Since 40% of long QT-sudden deaths occur at first presentation, screening of family members should be performed to facilitate primary prevention of pre-symptomatic individuals. All affected individuals should be treated. Initially treatment is with β-blocking agents and with the specific gene defect identified, targeted channel blocker medication is a possibility.[29]

ATHLETES

The competitive athlete has been described as one who participates in an organised team or individual sport requiring systematic training and regular competition against others, while placing a high premium on athletic excellence and achievement.[30] Sudden death in athletes is uncommon, with an incidence of two per 100,000 subject years.[30] It has been estimated that congenital malformations relevant to athletic screening account for a combined prevalence of 0.2% in athletic populations.[30] The cost-effectiveness of screening all young people is controversial. Rather, efforts have been made to target young people with a family history of sudden death or premature coronary disease. In athletes under the age of 30 years, the most common cause is HCM or coronary artery anomalies. In those over 30 years, the most common finding is coronary artery disease (defined as at least 75% narrowing in at least one coronary artery).[30]

A rarer but recognised cause of sudden death is non-penetrating trauma to the anterior chest wall in contact sports which can result in damage to the left anterior descending coronary artery or, if the blunt trauma results in a premature beat interrupting the peak of the T wave, VF may result.[31] At present the only recommended pre-participation screening of competitive athletes involves personal and family history and physical examination.

SOLVENT ABUSE

Solvent abuse is defined as the deliberate inhalation of vapour in order to become intoxicated. Solvents that are commonly encountered in abuse-related deaths include (1) fuel gases (30%) such as cigarette lighter refills (butane), propane and gasoline/petrol; (2) solvents (30%) including typewriter correction fluids, dry-cleaning fluids (trichloroethane) and fire extinguishers (bromochlorodifluoroethane); (3) adhesives (20%) e.g. toluene; and (4) aerosol propellants (20%) (halons and/or butane).[32]

Volatile substance abuse sensitises the heart to circulating catecholamines such that sudden alarm or exercise (e.g. fright or running) may precipitate sudden death. The mechanisms of cardiac arrest include cardiac arrhythmias (major risk), anoxia, respiratory depression and vagal stimulation, aspiration of vomit or trauma.[33]

Resuscitation is rarely successful in those with sudden death associated with volatile substance abuse since the majority of the deaths are unwitnessed. In the attempted correction of the sudden collapse, the traditional treatment of cardiac arrhythmias should be followed. However, sympathomimetic drugs should be avoided and β-blockers should be administered to protect the catecholamine-sensitised heart. Early intubation should be avoided if the inhalational agent was associated with laryngospasm. In the case of respiratory failure, supportive therapy with correction of hypoxia is required.[32] Hypokalaemia and metabolic acidosis should be corrected early.

RECOMMENDATIONS FOR RISK STRATIFICATION IN SUDDEN DEATH PREVENTION

Ischaemic heart disease remains the major cause of sudden death. The arrhythmic risk can be assessed by two non-invasive tests, followed by EP studies where appropriate.

Available data do not support the use of anti-arrhythmic drugs in the prevention of sudden death in high-risk patients. Evolving evidence suggests that ICD implantation is of value for improving survival in selected high-risk groups. Identification by non-invasive means of a heart failure population at risk for sudden death in comparison with pump failure is essential .

REFERENCES

[1] Gilman JK, Jalal S, Naccarelli GV. Predicting and preventing sudden death from cardiac causes. *Circulation* 1994; 90:1083-92.

[2] Buxton AE, Fisher JD, Josephson ME *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.

[3] Cohn PF. Predictive value of measures of myocardial ischemia in patients who have had a myocardial infarction. *Cardiac Electrophysiology Review* 1997; 1/2:205-6.

[4] Viskin S, Barron HV. Prediction of sudden death after myocardial infarction: value of electrophysiologic parameters. *Cardiac Electrophysiology Review* 1997; 1/2:193-7.

[5] Bigger JT. The predictive value of RR variability and baroreflex sensitivity in coronary heart disease. *Cardiac Electrophysiology Review* 1997; 1/2:198-204.

[6] Domanski MJ, Zipes DP, Schron E. Treatment of sudden cardiac death. Current understandings from randomized trials and future research directions. *Circulation* 1997; 95:2694-9.

[7] La Rovere MT, Bigger JT, Marcus FI *et al*. Baroreflex sensitivity and heart rate variability in prediction of total cardiac mortality after myocardial infarction. *Lancet* 1998; 351:478-84.

[8] The Norwegian Multicentre Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med* 1981; 304:801-7.

[9] β-blocker heart attack trial. A randomized trial of propranolol in patients with acute myocardial infarction. I Mortality results. *JAMA* 1982; 247:1707-14.

[10] Kober L, Torp-Pedersen C, Carlsen JE *et a*l. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. *N Engl J Med* 1995; 333:1670-6.

[11] 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.

[12] The Cardiac Arrhythmia Suppression Trial II investigators. Effect of the anti-arrhythmic agent moricizine on survival after myocardial infarction. *N Engl J Med* 1992; 327:227-33.

[13] Cairns JA, Connolly SJ, Roberts R, Gent M. Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations: CAMIAT. Canadian Amiodarone Myocardial Infarction Arrhythmia Trial Investigators. *Lancet* 1997; 349:675-82.

[14] Julian DG, Camm AJ, Frangin G *et al*. Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. European Myocardial Infarct Amiodarone Trial Investigators. *Lancet* 1997; 349:667-74.

[15] Waldo AL, Camm AJ, deRuyter H *et al*. Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. The SWORD Investigators. Survival With Oral d-Sotalol. *Lancet* 1996; 348:7-12.

[16] Teo KK, Yusuf S, Furberg CD. Effects of prophylactic anti-arrhythmic drug therapy in acute myocardial infarction. An overview of results from randomized controlled trials. *JAMA* 1993; 270:1589-95.
[17] Holmes DR, Davis KB, Mock MB *et al*. Participants in the coronary artery surgery study. The effect of medical and surgical treatment on subsequent sudden cardiac death in patients with coronary artery disease: a report from the coronary artery surgery study. *Circulation* 1986; 73:1254-63.
[18] Moss AJ, Hall WJ, Cannom DS *et al*. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med* 1996; 335:1933-40.
[19] Bigger JT. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. *N Engl J Med* 1997; 337:1569-75.
[20] Siebels J, Kuck K-H. Implantable cardioverter defibrillator compared with anti-arrhythmic drug treatment in cardiac arrest survivors (the Cardiac Arrest Study Hamburg). *Am Heart J* 1994; 127:1139-44.
[21] The ESVEM Investigators. Determinants of predicted efficacy of antiarrhythmic drugs in the electrophysiologic study versus electrocardiographic monitoring trial. *Circulation* 1993; 87:323-9.
[22] The CASCADE Investigators. Randomized anti-arrhythmic drug therapy in survivors of cardiac arrest (the CASCADE Study). *Am J Cardiol* 1993; 72:280-7.
[23] The anti-arrhythmics versus implantable defibrillators (AVID) investigators. A comparison of anti arrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near fatal ventricular arrhythmias. *N Engl J Med* 1997; 337:1576-83.
[24] Connolly SJ, Gent M, Roberts RS *et al*. Canadian Implantable Defibrillator Study (CIDS): study design and organization. CIDS Co-Investigators. *Am J Cardiol* 1993; 72:103F-108F.
[25] Doval HC, Nul DR, Grancelli HO *et al*. Randomised trial of low-dose amiodarone in severe congestive heart failure. Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA). *Lancet* 1994; 344:493-8.
[26] Singh SN, Fletcher RD, Fisher SG, Singh BN *et al*. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. *N Engl J Med* 1995; 333:77-82.
[27] Bardy GH, *et al*. Sudden Cardiac Death - Heart Failure Trial (SCD-HeFT). University of Washington (Oral communication).
[28] McKenna WJ, Sharma S. Arrhythmias and sudden death in hypertrophic cardiomyopathy. Epidemiology, pathophysiology, primary prevention, immediate evaluation and management, long-term management, experimental and theoretical developments. *Cardiac Electrophysiology Review* 1997; 1/2:229-32.
[29] Vincent GM, Timothy K, Zhang L. Congenital long QT syndrome. *Cardiac Electrophysiology Review* 1997; 1/2:258-61.
[30] Maron BJ, Thompson PD, Puffer JC *et al*. Cardiovascular preparticipation screening of competitive athletes. A statement for health professionals from the sudden death committee (clinical cardiology) and congenital cardiac defects committee (cardiovascular disease in the young), American Heart Association. *Circulat*ion 1996;94:850-6.
[31] Maron BJ. The young competitive athlete: causes of sudden death, detection, preparticipation screening, and standards for disqualification with cardiovascular abnormalities. *Cardiac Electrophysiology Review* 1997; 1/2:274-7.
[32] Adgey AAJ, Johnston PW, McMechan S. Sudden cardiac death and substance abuse. *Resuscitation* 1995; 29:219-21.
[33] Boon NA. Solvent abuse and the heart. *BMJ* 1987; 294:722.