SCREENING FOR SUDDEN DEATH IN ADULTS

KEY POINTS:

1. Sudden cardiac death is a major public health hazard in the UK, with up to 75,000 to 100,000 such deaths each year. Most of these are due to the effects of coronary heart disease. It is common for people to assume that most of these deaths are in the setting of a sudden myocardial infarction, but in about 80% of those due to a heart attack, the heart attack often happened long before the sudden cardiac death. This means that the risk of sudden death after a heart attack can be assessed and many deaths could be prevented with the right treatment. Most such sudden cardiac deaths come with no warning symptoms, so a skilled assessment of risk, based on the published evidence, needs to be available in a timely fashion.
2. Preventing the commoner causes of sudden cardiac death requires measures to reduce the risk of heart attacks, such as smoking-cessation and lipid-lowering measures.
3. Screening for patients with high risk of arrhythmias should be confined mainly to two groups, those with poor left ventricular function and those with a family history of sudden death or inherited heart disease.
4. Patients with poor left ventricular function are at high-risk of sudden cardiac death.
5. There is good evidence that all these patients with poor left ventricular function could benefit from an ICD, reducing their risk of dying by between 30 and 50%.
6. A screening programme should be set up to identify these high risk patients and offer them treatment, usually an ICD.
7. Workfore constraints make it unfeasible for all eligible patients at risk after a previous myocardial infarction to receive an ICD. Up to 800/patients/million may be affected. Even vast sums of money would leave some patients waiting years for treatment. Care needs to be focussed on the sickest patients, and a 10-year plan should aim for increase the numbers implanted towards the total of those at risk.
8. Patients with inherited heart defects are at increased risk of sudden death. These include patients with generalised electrical faults, as in Long QT syndrome and Brugada Syndrome, patients where heart muscle is infiltrated with abnormal tissue, as in right ventricular dysplasia, and patients with overgrowth of heart muscle, as in hypertrophic cardiomyopathy. These patients should be seen with their relatives in specialist clinics with genetic support and genetic testing available.
9. Young patients who die suddenly should have a specialist pathologist examine their heart, and their relatives should be seen in a specialist clinic, with either an interest in the disease identified or inherited sudden death syndromes if no cause is found.

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INTRODUCTION

Sudden cardiac death is a major cause of mortality in England, with 75,000-100,000 such deaths a year, with around two thirds being due to coronary heart disease.[1] The majority of these patients have no warning. The only proven effective therapy to prevent sudden death is the ICD, which is inappropriate to treat very large numbers of patients at very low risk. More general measures to reduce the incidence and progression of heart disease in the general population are a more reasonable approach, which is largely the purpose of the first 12 chapters of the NSF for CHD. There is probably no role for total population general screening for risk of sudden death in adults with a view to ICD implantation.

However there are two general groups of patients in whom the individual risks are sufficiently high and well characterised to consider primary prevention of sudden death with an ICD. The biggest group are those known to have poor left ventricular function (LVEF $\geq$35%) due to coronary heart disease or other causes. This population have a very high risk of sudden death with a large decrease in this death rate with ICDs implanted. The second group are inherited cardiac conditions with a high-risk of life-threatening arrhythmias, which range from fairly common to rare. In the inherited group it is important to identify relatives at high risk to offer them treatment.

The two groups to be screened.

a) Patients with arrhythmia risk from known structural heart disease.

1. Ischaemic heart disease.
2. Dilated cardiomyopathy.
3. Hypertrophic cardiomyopathy.
4. Congenital heart disease.

b) Relatives of patients with sudden death or genetic arrhythmia diagnosis.

1. Hypertrophic cardiomyopathy.
2. Long QT syndrome.
3. Arrhythmogenic Right Ventricular Dysplasia.
4. Brugada Syndrome.

And very rarely:

5. Progressive cardiac conduction defect (Lenegre disease).
6. Catecholaminergic Polymorphic Ventricular Tachycardia syndrome.
7. Andersen Syndrome.

THE SIZE OF THE PROBLEM – Patients with a Previous Heart Attack and Poor Left Ventricular Function.

In patients with ischaemic heart disease and poor LVEF there are two groups where the evidence is available for ICD implantation. The first group, accepted by the NICE guidelines on ICDs, are patients with:

- LVEF<=35%
- Non sustained VT on ambulatory ECG recording
- Inducible VT on EP study.

This population was studied by the MADIT [2,3] and MUSTT study, and showed a 47% reduction in mortality. The number of these patients is variously calculated around 100/million of such patients if appropriate screening was performed [4]

Further Evidence

A much bigger population of patients would be included if only left ventricular function was used to select patients. MADIT II[5] the second Multicenter Automatic Defibrillator Implantation Trial, enrolled 1232 patients with coronary artery disease, a history of myocardial infarction (>1 month), and an LVEF of 30 percent or less. Documentation of spontaneous or inducible arrhythmias was not required. Patients were randomly assigned to either ICD therapy or conventional medical therapy. Antiarrhythmic therapy was used in less than 20 percent of patients in both groups. During an average of 20 months of follow-up, mortality from all causes was 19.8 percent in the control group and 14.2 percent in the defibrillator group. Thus mortality was reduced by 31%. Subgroups of MADIT II patients with QRS duration >0.12 seconds or LVEF </=25% appear to derive the greatest benefit from ICD therapy.

Estimates of this population size are around 1,000/million, and of course include the patients in the first MADIT group. These results were supported by the SCD-HeFT[6] and COMPANION[7] studies, and both these studies also included non ischaemic patients.

Much earlier implantation of ICDs in patients following an acute MI, i.e. within a few days, with a poor LVEF have not shown a benefit (DINAMIT, [8]).

The data on non-ischaemic cardiomyopathy and non sustained VT is less clear. AMIOVERT (9) trialled amiodarone versus ICDs and showed no difference in survival at one and three years. The CAT[10] trial showed no reduction in deaths at 4 years. DEFINITE (11)(ICD versus no ICD) showed a significant decrease in arrhythmic deaths, but the overall death reduction did not reach significance. However all these trials were small (100-200 patients) and trended to a 35% reduction in mortality.

SCD-HeFT[6] included about 50% non-ischaemic patients and randomly assigned 2521 patients with NYHA Class II or III heart failure with an EF<=35% to one of three treatment arms: placebo, amiodarone, or ICD. Patients reported taking high levels of background therapy, including other cardiac drugs, angiotensin converting enzyme (ACE) inhibitors (85%), ACE inhibitors or angiotensin receptor blockers (ARB's) (96%), beta blockers (69%), spironolactone (19%), loop diuretics (82%), aspirin (56%), and statin therapy (38%).

After a median 45.5 months of follow-up, overall mortality in the placebo group was 36.1%, representing an annual mortality rate of 7.2% a year. Compared to placebo, amiodarone had no effect on mortality (HR, 1.06; p=0.529), and ICD therapy reduced mortality by 23% (HR, 0.77; p=0.007). Significant benefit was identical in the ischaemic and non-ischaemic groups.

The larger trials have confirmed the trends in the smaller studies for significant reduction in mortality in patients with poor left ventricular function, whatever the aetiology. The challenge to treat these patients will initially be to set up the structure to screen for these patients. This is already in part addressed by the heart failure and CHD NSFs push towards echocardiograms in all patients with

heart failure or structural heart disease. The second part of the challenge will be safely implant large numbers of ICDs and follow them up.

If the indication for ICD expanded to all patients with LVEF <=30%, then 800 to 1,500/million patients could be eligible for implantation [4]

THE SIZE OF THE PROBLEM – Non Heart Failure patients

The non heart failure patients at high risk for sudden cardiac death are a much smaller number. Estimates of prevalence are difficult. Hypertrophic cardiomyopathy (HCM) may be seen in 1/500 of the population, ARVD and Long QT rare (1/10,000) and the others very rare in the UK population. However their rareness makes them an easier population to screen and not all at risk patients necessarily need an ICD. There is good evidence of b-blockers showing benefit in patients with Long QT and perhaps HCM, and some of the others can be risk stratified as low risk.

Sudden Death – No Cause Found

An important group are 'patients' who have had a relative die suddenly with an apparently normal heart at autopsy, with a range of 4-20% of sudden deaths. There are estimated to be approximately 400 sudden unexplained deaths per annum in previously young healthy people in the UK. Another major group with a high risk of sudden cardiac death are patients with epilepsy. The risk of SUDEP is estimated to be 3 times normal, and is probably up to 15x higher in younger patients, and appears to be seizure-related, with poorly-controlled seizures conferring a 23-fold increase in the risk of sudden death, (see chapter 10)

These circumstances require:

- A skilled, comprehensive, systematic provision of cardiac pathology services so that cardiac post-mortem examinations achieve sustained high standards throughout the UK [12]
- Screening of the families of the deceased, this will unearth a cause in about 25%.[13]
- A network of support services, building on the excellent work of many patient groups, often started by bereaved relatives of young people with sudden unexplained death.
- Publically-funded, multi-centre systematic research into causes and mechanisms, focussing on areas such as SUDEP. The NHS should excel at such research, having a single management hierarchy and being a monopoly provider.

The family members clearly need screening to reassure or treat the risk they run. About a quarter will have an inherited disease diagnosed. Familial syndromes are individually very rare, so such clinics need to be run by specialists, and supported by geneticists and genotyping where available.

SCREENING IN Heart Failure Patients

Patients from the ischaemic and non ischaemic populations benefit from ICDs. To identify MADIT^2 patients the following recommendations should be issued;

1. All patients with heart failure and a diagnosis of CHD should have an echocardiogram.
2. All patients with LVEF ≤35% should have an ambulatory ECG.
3. All patients with non sustained VT (3or more beats at >120 bpm) should have EPS.
4. Patients with VT/VF induced at EPS should have an ICD.

Patients fulfilling MADIT II[5] criteria are much more numerous, and are more easily screened by the finding of an LVEF ≤30%. Currently, the UK cannot achieve the modest rates of ICD implantation recommended in the 2000 NICE Guidelines, and achieving implantation rates of 100/million to meet MADIT I criteria will be a major challenge.

Strategies to be considered include:

- Selecting subgroups of MADIT II patients who appear to have the highest risk and the most to gain from treatment with an ICD, i.e. those with a QRS duration ≥0.12 seconds or LVEF ≤25%.
- Concentrating on MADIT I patients, but acknowledging that the resources to study those with poor LVEF and non-sustained VT are also in short supply.
- Putting in place a comprehensive plan to grow the medical and non-medical workforce over time in order to meet these challenges, whilst accepting that the resources are not currently in place to achieve these high rates of implantation, support and follow-up. Even vast financial resources would still leave many patients waiting years for treatment with current staffing levels.

Recommendations:

1. At minimum all patients with known structural heart disease should have an echo. All patients with LVEF <= 35% should be considered for ICD implantation and screened for high risk of sudden death, on the basis of the current literature.

2. IF MADIT/NICE was used as the guideline, all patients with a previous MI should have an echo at least 6 weeks after the MI. All with EF < 35% should have a 24 hour tape and EPS if non sustained VT seen. All with VT/VF induced should have ICD+/- RCT.

3. Over a 10-year planned increase in staffing and other necessary resources, the numbers of patients being implanted for a high risk of sudden cardiac death will increase towards the levels required in line with current published evidence.

INHERITED DISEASE/ CHANCE FINDING IN ASYMPTOMATIC PATIENTS

A clinic setting for these diseases requires;

1. Cardiac Electrophysiologist
2. Geneticist

The clinic should see and screen most of these patients. Patients with HCM may have very significant haemodynamic problems, and need to spend a lot of time in the care of a non electrical cardiologist, who should specialise in HCM.

Hypertrophic Cariomyopathy [14]

All relatives (1st degree) should have an ECG and echocardiogram, with further family screening as directed by family members with HCM. Genetic diagnosis should be sought.

All patients with HCM should undergo an echocardiogram, treadmill exercise test and ambulatory ECG recording.

Patients with two or more of the following criteria should be considered for ICD therapy:

- Interventicular septal thickness on echocardiogram of >3cm
- Non-sustained VT on ambulatory ECG recording.
- Family history of young (<40 years) sudden cardiac death.
- Blood pressure drop on exercise.
- History of syncope.

Long QT [16-18]

Prevalence is unknown (0.01%) but the prevalence of QTc>=440 msecs is 9%. Need a family with clear disease for screening to be helpful. Genetics is well described (A-dominant) and 90%+ patients have family members affected.

Recommendations are:

- All potentially affected family members screened with ECG and ambulatory ECG recording.
- Genetic diagnosis should be available.
- ECG help with diagnosis and risk assessment.
- ambulatory ECG recording may shows dynamic changes and VT.
- ETT not helpful.
- Treat effected individuals with b-blocker up to age 40.

Arrhythmogenic Right Ventricular Dysplasia[19-20]

This has a general prevalence of approximately 1 in 10,000 but in Northern Italy the prevalence is higher (6 in 10,0000). There are nine abnormal genes known. Diagnosis is difficult.

Major criteria for diagnosis:

- Family history at necropsy/surgery/biopsy.
- Epsilon waves in V1-3.
- Severe RV dysfunction/dilation or severe localised abnormality.
- Tissue diagnosis (fatty deposits).

Minor criteria for diagnosis:

- Family history of premature sudden death (<35 years)/clinical criteria.
- Late potentials on ECG.
- T wave inversion V1-3.
- Sustained or non-sustained LBBB VT.
- >1000/24 hr VPBs.
- Mild RV abnormality.

Ntwo major, 1 major and 2 minor or 4 minor risk factors are required to make a diagnosis.

Screen asymptomatic relatives with Echo and ECG.
MRI and angio if doubt.
Treatment for asymptomatic relatives unknown.

Brugada Syndrome [21-23]

The prevalence is 0.14% of Japanese adults, but is much lower in Caucasians. A family history is present in 30-50% (autosomal dominant). It is only worth screening if there is a family history of young sudden death.

Recommendations:-

- ECG and ECG with IV flecainide to confirm diagnosis.
- Risk stratify with EPS and VT stimulation studies.
- Genetics not useful clinical tool.
- ICD only treatment available.

Sudden unexplained death in young patient (under 45 yrs old) with no clues

This is an important if small group of relatives of a sudden death patient. Estimated to be around 200 cases a year[12] they never the less represent an enormous stress to the relatives. It is very important that the post mortem is done by a skilled cardiac pathologist[12]. It is also important that the relatives are seen in a specialist clinic, as there are many rare diagnoses.

Recommendations:

- Specialist pathologist examines heart, either locally or via a network of outreach services.
- Specialist clinic for relatives.

At that clinic

- Screen 1st degree relatives.
- Assess Family history.
- ECG.
- Echo.
- Ambulatory ECG recording.
- Flecainide test.
- ETT if exercise related.

Recommendation:

1. All patients with a first degree relative with a known inheritable arrhythmic heart disease should be referred to specialist cardiac clinic for such conditions with access to genotyping and invasive testing as necessary.
2. These clinics should be supported by a geneticist and genetic counsellors, and appropriate genotyping should be available.
3. All patients who die without a diagnosed cause should have their heart examined by a specialist cardiac pathologist. Tissue genotyping should be considered.
4. A small tissue sample should be retained for genotyping.

CONCLUSIONS

Screening for high risk for fatal arrhythmias should be performed in two populations.

1. Patients with structural heart disease, especially those with poor left ventricular function. This group are already identified, in part due to the CHD NSF and heart failure chapter. They have a considerable mortality annually which is significantly reduced by therapy, principally the ICD. This group represents the area where the most deaths can be prevented. The NSF must provide a strategy to identify and treat these patients, based on the excellent evidence base.
2. Relatives or asymptomatic patients with potentially high risk cardiac conditions should be referred to a specialist clinic for risk assessment and appropriate treatment. Genetic and pathological support should be available, with genotyping available nationally.

LAY SUMMARY

Sudden cardiac death is a major public health hazard in the UK, with up to 75,000 to 90,000 such deaths each year. Most of these are due to the effects of heart attacks, where a coronary artery suddenly becomes blocked, an area of heart muscle dies, and scar tissue replaces muscle if the patient survives the initial attack. 25% of patients die from an acute heart attack before getting medical help. Many more patients survive but are later at high risk of sudden cardiac death, especially if the heart muscle damage has been severe. Subsequently, in about 80% of cases of cardiac arrest due to a heart attack, the heart attack often happened long before the sudden cardiac death. This means that the risk of sudden death after a heart attack can be assessed and many deaths could be prevented with the right treatment. Most such sudden cardiac deaths come out-of-the-blue, with no warning symptoms. General measures can help reduce risk. These measures include stopping smoking, lowering cholesterol and taking aspirin and regular exercise.

The search for patients at high risk of a cardiac arrest means approaching patients who have had no warning that they are at risk, and this must be done with great care so as not to cause alarm. There is always uncertainty that a given patient will suffer a future cardiac arrest, so the aim must be to find the most deserving patients, and these are of two types. Firstly, those with the most badly damaged hearts after a heart attack should be assessed, and published research shows that their risk can be reduced by 30 and 50% if they receive an ICD. Secondly, patients with inherited heart defects are at increased risk of sudden death. These include patients with generalised electrical faults, as in Long QT syndrome and Brugada Syndrome, patients where heart muscle is infiltrated with abnormal tissue, as in right ventricular dysplasia, and patients with overgrowth of heart muscle, as in hypertrophic cardiomyopathy. These patients should be seen with their relatives in specialist clinics with genetic support and DNA testing available. We believe that a screening programme should be set up to identify these high risk patients and offer them treatment, usually an ICD.

However, the number of patients who might benefit from an ICD is 20-30 times the number that are currently treated. Even if the NHS had unlimited funds, lack of qualified staff would mean that many patients could currently wait years for treatment. They would be at risk while they waited, and they would have to cope with the stress of awareness of this risk, because it would be explained before they went onto a waiting list. We therefore advocate a gradual, steady expansion in staff, facilities and numbers of patients treated, over a 10-year period.

In young patients who die suddenly a specialist pathologist must examine their heart. If this cannot be done at a special centre distant from the place of death, then systems need to be put in place to bring specialists in to local hospitals to undertake the examinations. Relatives of the deceased should be seen in a specialist clinic for these diseases, and screened to identify any abnormality. Currently such screening is far from perfect, and often a condition cannot be completely ruled out. However, techniques are improving all the time. For some conditions, blood tests have had to be sent to Holland for analysis, and resources must now be provided to allow this work within the NHS.

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