ORIGINAL ARTICLE

The clinical management of relatives of young sudden unexplained death victims; implantable defibrillators are rarely indicated

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ABSTRACT
Objective Following national guidance on management of sudden unexplained death (SUD) in the young, inherited cardiac conditions (ICC) clinics were established to identify and treat relatives thought to be at increased risk. Studies have examined diagnostic yield of these clinics but outcome of clinical management has not been reported.

Setting Regional ICC clinic.

Patients 193 individuals (188 families) referred to a regional ICC clinic following SUD/aborted cardiac arrest of a young relative (mean follow-up 16.5 months, range 0.1–61).

Interventions All individuals underwent assessment by history, examination, ECG and echocardiography. Exercise electrocardiography, ajmaline provocation, further imaging techniques and genetic testing were performed in selected individuals. Implantable cardioverter-defibrillator (ICD) insertion based on national guidelines.

Main outcome measures and results Forty-five patients (23%) from 38 families (38%) were diagnosed with an inheritable cause of sudden death. Eighteen had potentially prognostically important medication commenced and 4 had an ICD inserted on clinic recommendation (2 hypertrophic cardiomyopathy, 1 dilated cardiomyopathy, 1 arrhythmogenic right ventricular cardiomyopathy). Two other individuals had ICDs removed after negative testing for familial RyR2 mutations. No deaths have occurred during follow-up to date.

Conclusion A diagnosis of an inheritable cause of sudden death was obtained in a significant minority of those with a family history of SUD/aborted cardiac arrest. The number of ICDs inserted as a result of specialist assessment was very small (2%). A major function of the clinic is reassurance of the clinically normal and cessation of treatment after exclusion of familial disease by genetic testing.

plained death (SUD) of young individuals have revealed evidence of potentially inherited structural cardiac disease in a high proportion of cases. In a significant minority pathological findings are normal and toxicological results are negative; this latter group is said to have sudden arrhythmic death syndrome (SADS).1 In March 2005, the management of SUD in the young within the UK was addressed by the National Service Framework, with an aim to identify people who are at increased risk, and assessing them and their families, to reduce their chances of dying from an arrhythmic condition.2 One of the key recommendations of this framework was the establishment of specialist inherited cardiac conditions (ICC) clinics in order to identify and support family members considered at risk.3 Several studies have examined the diagnostic yield of such clinics4–6,7 the aim of the current study was to examine the outcome of the clinical management of these individuals.

METHODS
We present data on 193 consecutive individuals from 188 families referred to a regional ICC clinic because of SUD or aborted cardiac arrest of a young relative. The mean age on referral was 38±17 years and the mean duration of follow-up was 16.5 months (range 1 day–61 months). None of the 191 individuals had a personal history of aborted sudden death.

The mean age of the SUD victims was 32±16 years (range 1–66 years) and the mean number of SUD/aborted deaths in the affected family was 1.5±1.4 (147 SUDs (129 men), 9 aborted deaths (2 men)). Twenty victims died during or immediately after exercise (1 aborted death after exercise) and 14 died apparently during sleep.

All individuals underwent clinical assessment by history, examination, ECG and echocardiogram (Figure 1). Treadmill exercise testing was performed if not undertaken in the previous 6 months. Further
imaging by cardiac MRI or contrast echocardiography was performed in those with structurally abnormal hearts or with T wave inversion in V1-V4 (11 individuals). Ajmaline provocative testing using standard electrocardiographic lead positions was performed in those with a history and/or ECG suggestive of Brugada syndrome (20 individuals). In 60 patients, underwent ambulatory electrocardiography because of symptoms suggestive of arrhythmias or suspected Long QT syndrome. Two patients underwent implantation of subcutaneous loop recorders.

Genetic testing was offered to clinic attendees as per the HRUK guidelines.6 This resulted in genetic testing being carried out in 44 attendees and offered to a further 8 who declined.

RESULTS

Diagnoses and drug treatment

Of the 193 individuals studied, 45 (23%) from 38 families (30%) were diagnosed with an inheritable cause of sudden death. One hundred and forty-six of the 198 individuals were relatives of a presumed SADS victim (Group 1, figure 2) and 47 were relatives of a sudden death victim found to have structural heart disease at post-mortem (Group 2). In terms of the SADS families, an inheritable cause of sudden death was diagnosed in 31 individuals (21%) and in 25-84 families (39%). Evaluation of the relatives of sudden death victims with post mortem evidence of structural heart disease revealed an inheritable cause of sudden death in 14 individuals (30%) and in 10-24 families (42%). One hundred and forty-four patients were clinically normal. Four patients were found to have other conditions; atrioventricular nodal re-entrant tachycardia, skeletal myopathy associated with an RYR1 mutation, mild aortic stenosis and congenital sub-aortic membrane. Of the 45 patients diagnosed with an inheritable cause of sudden death, 12 had medication commenced by the clinic and 13 others were continued on cardioactive medication (figure 3). Beta-blockers constituted at least part of the medication in 28 of these 31 patients, 10 patients with LQT (all 10 commenced on propranolol), 3 with ARVC (2 commenced on bisoprolol and 1 on propranolol), 4 with catecholaminergic polymorphic ventricular tachycardia (CPVT) (all 4 on propranolol), 6 with dilated cardiomyopathy (DCM) (all bisoprolol) and five patients with hypertrophic cardiomyopathy (HCM) (2 on atenolol, 3 on bisoprolol).

In the 12 patients diagnosed with Long QT Syndrome (LQTS), 6 were initially asymptomatic with syncopal/presyncope events. The QTc interval was prolonged in 11/12 patients (mean QTc 489±18 ms, range 470-522 ms). The single patient with normal QTc was found to have a mutation in KCNQ1 shared by another family member with overt QT prolongation. Genetic testing was performed on 11 patients (in 8 families); one individual was not tested as she was an obligatory carrier of a known pathogenic mutation. Pathogenic mutations were identified in 6 patients, 4 in KCNQ1 (2 families), 2 in KCNH2. Of the 6 LQTS patients that were initially asymptomatic, one experienced transient symptoms after commencing propranolol, associated with brief discontinuation of the drug. No patients had unequivocal evidence of the Brugada-type ECG pattern at rest, but diagnostic changes were evident in two asymptomatic individuals during intravenous ajmaline. Genetic testing was performed in one patient and revealed no mutation in SCN5A.

Of the five patients diagnosed with CPVT, three were diagnosed on the basis of exercise electrocardiographic evidence; one had bidirectional ventricular tachycardia, one had bidirectional ventricular extraaystoles and one had exercise-induced runs of unidirectional ventricular extraaystoles. This latter patient was a sister to a fourth individual who had bidirectional VT on a catecholamine provocation test. A fifth patient, whose daughter had died suddenly during exertion, was identified after a pathogenic RYR2 mutation was discovered despite absence of exercise-induced arrhythmias. Genetic testing was performed on all five patients with CPVT; three had pathogenic mutations in RYR2. Symptoms/ventricular arrhythmias were suppressed by β-blockade in all patients.

The 10 patients with a clinical diagnosis of HCM were all diagnosed on the basis of myocardial thickening on echocardiography (mean interventricular septal thickness 1.8±0.3 cm, range 1.4–2.4 cm). Only one patient was symptomatic with progressive breathlessness and a single syncopal event. Nine HCM patients underwent genetic testing. Of those 5 were found to have pathogenic mutations; 4 in MYBPC3 and 1 in TNNI3. A further individual with no evidence of hypertrophy was found to have a pathogenic mutation in MHC. This patient’s father and uncle were found to have HCM at post-mortem examination.

All seven patients with DCM were diagnosed on the basis of echocardiography; mean LVED 41±0.5 cm, mean EF 40±17%. Only one of these patients was symptomatic. Genetic testing was performed in one patient and no mutations were found in the Lamin A/C gene. ACE inhibitors were commenced/continued in all seven patients with DCM and two were commenced/continued on spironolactone.

The diagnosis of ARVC was made in accordance with recent Task Force guidance,7–8 on the basis of a proven diagnosis at post-mortem combined with preclinical ECG changes and/or RV abnormalities on echocardiography/CMR. None were symptomatic. Genetic testing was performed in five patients; three were found to have pathogenic mutations in PKP2 and one had a mutation of uncertain significance in DSP. One asymptomatic patient was diagnosed with LV non-compaction on echocardiography.11,12

Device implantation

Six patients already had implantable cardioverter-debrilllators (ICDs) at the time of referral to the ICC clinic. Two of these patients had poor left ventricular function and normal coronary arteries (ejection fraction <35%), both with a broad complex ECG in sinus rhythm (one had undergone device reimplantation after developing septicaemia). One patient with LQTS, with a mother who had died suddenly and a son who had suffered aborted sudden death, was asymptomatic but with a QTc >500 ms. One had a family history of sudden death and a skeletal myopathy of undetermined type; subsequent investigation revealed evidence of a RYR1 mutation. Two further individuals, a mother and son, were asymptomatic and clinically normal but had a very extensive and dramatic history of sudden death in close relatives (see below).
ICDs were implanted following evaluation in the clinic in a total of only four patients. Assessment in regard to the decision to implant an ICD was based on criteria detailed in the HRUK position statement. Devices were inserted in two patients with HCM and with two or more risk factors for sudden death, both had non-sustained ventricular tachycardia on ambulatory monitoring and one also had a personal history of unexplained syncope. One ICD was implanted in a young woman with ARVC despite the presence of only mild disease and no evidence of sustained arrhythmias. In her particular case, the knowledge that she was considered to be at low risk was insufficient to prevent disease-related anxiety of such a magnitude that it significantly impaired her quality of life. One ICD was implanted in a patient with DCM and an ejection fraction <20%. No appropriate therapies (ATP or shocks) were delivered in the follow-up period (mean 27 months, range 19–40 months) in any of these patients. Two patients have had inappropriate shocks; one from a lead fracture and the other from sinus tachycardia.

Treatments withdrawn
Four individuals had treatment withdrawn after negative genetic testing for an established familial mutation. Three belonged to the one family, a mother and her two sons, with a very strong family history of sudden unexpected death (figure 4). Diagnosis in this family was elusive with normal clinical findings and investigations in all three family members evaluated. At the time of original evaluation the mother and her two sons were commenced on β-blockade. The mother elected to have an ICD implanted at this time, and subsequently one of her sons did also. Neither had any appropriate shocks, but the son had inappropriate shocks due to lead fracture. In 2009 an RYR2 mutation was discovered in the asymptomatic maternal grandfather of the two boys and in tissue from one of the deceased aunts. Subsequent genetic testing showed the mother to be negative for this mutation. Beta-blockers were withdrawn from the sons (not the mother as she had hypertension) and both ICDs were inactivated/removed.

The final therapy withdrawal was in a young girl with a strong family history of LQTS, a personal history of syncope and a borderline prolonged QTc who had been commenced on β-blockade. She was subsequently shown to be negative for the familial LQT1 mutation. Of the 45 patients with an identified cause of sudden death, all are alive (follow-up mean 25 months, range 6–37 months). Of the 144 patients felt to be clinically normal, 81 were reassured and discharged, 54 are undergoing annual review in view of a family history of inherited cardiac disease. Nine patients with normal investigations failed to re-attend for further testing despite numerous invitations back to clinic.

DISCUSSION
The main findings of this study are (a) evaluation at a specialist ICC clinic revealed a familial cardiac condition associated with sudden death in a significant minority of relatives of young sudden death victims, in keeping with previous studies, (b) identification of these conditions resulted in potentially prognostically important changes in medication (in particular addition of β-blockade) to the majority of individuals identified as having a familial condition, (c) implantation of ICDs was relatively rarely indicated and (d) a major benefit of the assessment is reassurance of the clinically normal and cessation of treatment after exclusion of familial disease by genetic testing.

The population under evaluation in the current study consisted both of relatives of sudden death victims who had undergone post-mortem examination with normal findings (Group 1) and relatives of those with evidence of structural heart disease at post-mortem (Group 2). Previously reported studies have described findings either of relatives of SUD victims with or without post-mortem examination. The diagnostic sensitivity for familial cardiac disease in these studies is in keeping with the current findings. Of the total group of 193 individuals in the current study, 45 (23%) from 20 families (59%) were diagnosed with an inheritable cause of sudden death. The equivalent figures for Group 1 were 21% and 30% respectively, and for Group 2 were 30% and 42% respectively. Behr et al identified familial cardiac disease in 29% of first-degree relatives of SUD victims. In our Group 1 patients the most commonly identified condition was congenital LQTS (in 6% of Group 1 patients). The LQTS was also the most common diagnosis in the group studied by Behr et al, with corresponding rates of 9% (for definite LQTS) and 4% (for possible/probable LQTS). The percentage of relatives identified as having cardiomyopathy was 9% in the current study (predominantly HCM) compared with 7% (predominantly ARVC) in the group described by Behr et al. Van der Weel et al have recently presented data from investigation of 140 families of young SUD victims. A potentially inherited cause of sudden cardiac death was identified in approximately one third of families evaluated, very similar to the findings of the current study. Although the diagnostic yield of both the current and previous studies are likely to be affected by referral bias, the similarity of the findings suggests that they are likely to be representative of ICC clinics in general.

The key rationale for the screening of relatives in this setting is the evidence that appropriate treatment can prolong the lives of these individuals. In the case of the LQTS there is good evidence that treatment with β-blockade can improve prognosis, even if the first clinical presentation is with aborted cardiac arrest. In terms of the particular agent used, European experience is principally with propranolol and nadolol. In patients with LQT1, mortality on β-blockade is almost zero, non-compliance and the use of QT-prolonging drugs being responsible for almost all life-threatening, β-blocker failures. In LQT2, the Italian experience would again suggest an excellent impact on prognosis. The published experience with LQT3 patients is relatively small but recent reports suggest that although infants who suffer cardiac events during their first year of life suffer from a highly malignant form of the disease, most LQT3 patients do well on current therapies.

In Brugada syndrome the mainstay of prevention of sudden death is ICD implantation. Both Brugada patients identified in this study were considered low risk and no ICDs were implanted. High lethality is said to be a particular feature of CPVT and that the protection afforded by β-blockade less than that in the LQTS. This is difficult to measure in any objective way given that CPVT is a much more recently discovered condition with initial series likely to be biased.
towards the most severely affected individuals. In the largest study of CPVT patients reported to date, the incidence of fatal/near-fatal events in those patients prescribed β-blockade was significantly lower than those without β-blockade (1.2% vs 3.1%) per year respectively. The β-blocker failures that did occur could be attributed in part to non-compliance or low dosage of medication.

Historically, patients with HCM have been placed on various cardioactive drugs in an attempt to reduce sudden death risk. However, registry data suggests that any protection provided by medication is at best partial with continued appropriate shocks occurring in 9%–17% of those on β-blockers and 20%–27% of those on amiodarone.23 24 In the current series no new medications were commenced in any HCM patients. While only one patient with DCM was commenced on the heart failure triad of β-blocker, ACE inhibitor and spironolactone all other DCM patients were already established on these medications prior to clinic attendance. Outside β-blockers, no other antiarrhythmic medication has been shown to prevent sudden death.21 No antiarrhythmic drug has been demonstrated to improve prognosis in ARVC although β-blockade is widely prescribed in view of the fact that a proportion of arrhythmic events in ARVC occur during exercise or presynaptic infarction.26

The clinical-decision making process with regard to selection of patients for ICDs is complex particularly in the case of an individual who has yet to experience a life-threatening arrhythmic event. The 2006 AHA/ACC/ESC guidelines on sudden death give very broad criteria for ICD implantation, in keeping with the current range of clinical opinion in this area.27 Decision-making with regard to ICD implantation in the current study was broadly in line with the HRU UK position statement,28 with an emphasis on estimated absolute risk of sudden death within specified clinical subgroups. This resulted in a relatively small number of ICDs being implanted (2%), although a further 3% already had ICDs implanted prior to specialist assessment. The results of follow-up of the whole cohort to date (mean follow-up 16.5 months, range 0–46) provides support for this management strategy, with no individual without an ICD suffering spontaneous malignant arrhythmias. Indeed, even in the small group of patients selected for ICD implantation there have been no appropriate device discharges, confirming the low risk nature of this group overall. In the group of patients with ICDs a number of complications have occurred, confirming previous studies showing a relatively high complication rate in this group.26 29 30 These findings, although based on relatively short follow-up, argue against the use of a lower threshold for ICD implantation.

While the establishment of a diagnosis is a crucial step in the prevention of sudden death in relatives of a sudden death victim, there are some disadvantages for the relatives in this process. Individuals who are identified as having cardiac disease are likely to suffer disease-related anxiety that can be long-lasting.26 Young individuals in particular can have the quality of their lives impaired by limitations on competitive sporting activity. It is not unusual for schools and colleges to impose restrictions beyond those advised for these conditions. There is some evidence that disease-related anxiety can be reduced by attendance at ICD clinics adopting an integrated approach to care such as that described in the current study, including the close involvement of a genetic counsellor.30

Perhaps the most clear-cut benefit of specialist evaluation in this low-risk group is the ability to exclude familial disease in some individuals, thereby removing the anxiety associated with the condition.25 31 The results of the present study confirm the efficacy of this approach, supporting recommendations for continued follow-up and treatment. This is particularly true when a pathogenic mutation can be identified in the family that can then be used to definitively exclude the disease in some individuals. Somewhat less clear-cut is the benefit or reassurance provided by the presence of normal findings after clinical testing in the absence of a defined familial disease-causing mutation. Under these circumstances complete reassurance cannot be given but the lack of evidence of significant disease argues strongly for an extremely low risk subgroup in terms of sudden death. The psychological and emotional benefits of such reassurance have been previously documented, both for the attendee and their wider family.20 32

Contributors Professor LG designed the study and was heavily involved in the writing of the manuscript. Dr JC was heavily involved in writing the manuscript. MR, MM, MN, MK, ML, UK, SH, KM and Professor WH were all involved in managing the patients and in reviewing the manuscript.

Competing interests None.

Patient consent Obtained.

Future approval Report of clinical outcomes, not a formal trial.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES


**Key messages**

The study is essentially one of clinical outcomes of a 'representative' Inherited Cardiac Conditions clinic, the principal findings being the overall good prognosis and low ICD implantation rate. The study identifies the main roles of these clinics as being the reassurance of the clinically normal and cessation of treatment after exclusion of known familial disease by genetic testing.
Figure 2  Detailed breakdown of results of diagnostic assessment in individuals with family history of sudden unexplained death. The individuals are divided into 2 groups: Group 1 in whom no cause of sudden death was identified at post-mortem examination/toxicology screening, and Group 2 in whom a structural cause was established at post-mortem (ARVC 5, HCM 7, DCM 8, evidence of coronary disease 4). No patients had evidence of non-atherosclerotic coronary artery disease. None of the 9 probands with aborted sudden death had evidence of structural heart disease (after investigation according to the algorithm in figure 1) and the relatives of these patients are included in Group 1. In only one of the cases was a ‘molecular autopsy’ performed successfully (see figure 4), due to either non-retention of tissue prior to clinic referral (the great majority of cases) or poor quality of DNA obtained from retained material.

Figure 3  Treatment of individuals diagnosed with inheritable cause of sudden unexplained death.
Figure 4 Pedigree of a family with multiple young sudden deaths. The mother (consulted) is indicated by the arrow, clinically affected members are identified by filled symbols. One of the mother’s sisters had a history of ‘seizures provoked by arguments’ and was presumed to have died of epilepsy aged 22. Another sister had a history of collapses and died suddenly aged 18 while on a fairground ride. One brother died aged 20 having raced a friend into the water at a swimming pool. A second brother died suddenly aged 18 after jumping over a fence. No abnormalities were found at post mortem in any of the siblings.