Impact of molecular genetics on clinical cardiology

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The last decade has seen major progress towards understanding both the genetic defect and molecular pathogenesis of many monogenic disorders of the cardiovascular system including hypertrophic cardiomyopathy (HCM), long QT syndrome (LQTS) and Marfan syndrome (Table 1)[1]. Unlike the single gene disorders, however, the genetics of common diseases such as essential hypertension and coronary artery disease is proving much more difficult to unravel, although progress is being made as these diseases become the focus of intensive genetic research. We will review the impact of molecular genetics on clinical management in HCM, LQTS and Marfan syndrome, about which much information is available, to illustrate how molecular genetic knowledge is beginning to have a direct role in patient management.

These three diseases are all autosomal disorders inherited in a dominant manner. Affected individuals are heterozygous: that is, they have one normal and one mutant copy of the gene. Offspring of affected individuals will therefore have a one in two risk of inheriting the mutation; they may, however, have a somewhat smaller risk of manifesting the disease as not all gene carriers are symptomatic (incomplete penetrance). HCM, LQTS and Marfan syndrome all have the potential to devastate families by sudden deaths. Previous studies suggest that dominant mutations associated with diseases of this severity do not survive for long enough to create marked founder effects (ie, apparently unrelated families descend from an unidentified common ancestor), so these conditions are likely to be evenly distributed among different populations worldwide[2].

Hypertrophic cardiomyopathy

HCM is a clinically and genetically heterogeneous disorder characterised macroscopically by increased left ventricular mass (in the absence of a demonstrable cause) and histologically by myofibrillar and myocyte disarray. It may affect as many as one in 500 of the general population[3]. The vast majority of individuals with HCM have familial disease inherited from one or other parent; true sporadic disease (arising *de novo*) accounts for less than 10% of cases with HCM[4]. Earlier family studies suggesting that only 50% of HCM was familial did not recognise that the disease may not be completely penetrant, and that individuals may carry the causal mutation with mild or occasionally undetectable manifestations of HCM. Offspring of such non-penetrant individuals (or 'carriers') are however still at a one in two risk of inheriting the mutation and may well manifest the disease.

Genetic mapping studies in families with HCM have led to the identification of seven disease genes in which mutations can cause the condition[5]. A variety of mutations is found in each gene, such that many families have a 'private' mutation. HCM should no longer be considered an idiopathic heart muscle disorder, but rather a disease of the sarcomere[6]. Mutations are found in the genes for components of the cardiac muscle contractile apparatus, involving both the thick filament (β-cardiac myosin heavy chain, essential and regulatory myosin light chains, and cardiac myosin binding protein C) and also the

Key Points

► A complete and detailed family history is the cornerstone of management of patients with genetic disease

► Clinical screening should be offered to all first-degree relatives (parents and siblings as well as offspring) of newly diagnosed cases with hypertrophic cardiomyopathy (HCM), long QT syndrome (LQTS), and Marfan syndrome

► A much lower diagnostic threshold is appropriate when interpreting diagnostic tests in first-degree relatives of patients affected with HCM and LQTS. In particular, there should be careful examination of the ECG as well as the echocardiogram in family screening for HCM

► Genetic diagnosis can be useful in families with HCM and LQTS in settings in which clinical diagnosis is not possible, but this remains technically demanding

► Genetic diagnosis in isolated individuals is generally not practicable

► Laboratories that offer genetic testing are limited to research institutions with an interest in inherited cardiovascular disorders. (Information about the laboratories is available from the regional genetic services in the UK)

thin filament (cardiac troponins T and I, and α-tropomyosin) (Table 1). Three of these genes appear to be important numerically:

- myosin heavy chain (MHC)[7]
- troponin T (TnT)[8]
- cardiac myosin binding protein C (MyBPC)[9].

Existing data suggest that each of the three common disease genes is associated with different clinical features and prognosis of HCM. These differences are quantitative, rather than qualitative, but may be of sufficient magnitude to modify management. As with all risk factors, the genotypes are predictive of *mean* risk in a cohort and the disease will behave differently in some individuals. Thus, genetic stratification is best used in combination with, not in place of, other risk stratifiers.

Myosin heavy chain mutations

Different mutations appear to be associated with quite widely varying risk of sudden death[7]. Certain mutations have been consistently associated with a benign prognosis of HCM and a low incidence of sudden death in most affected pedigrees, while others are associated with a classically malignant phenotype. For example, the Arg403→Gln mutation in myosin is typically associated with 50% mortality by the age of 40. There is also a wide range in the degree of hypertrophy seen with MHC mutations, but available data suggest that those associated with a poor prognosis are also associated with clinically overt disease and high penetrance[10]. Subclinical carriers with MHC mutations are thus not likely to be at major risk.

Troponin T mutations

TnT mutations typically appear to be associated with the worrying combination of high incidence of sudden death and mild, often clinically borderline, hypertrophy[8,11]. In these families, mutation carriers found on clinical investigation to have only minor, non-diagnostic abnormalities may be at considerable risk. On the basis of present knowledge, screening for mutations is most indicated in families that appear to fit with the TnT phenotype.

Table 1. Genes that cause cardiovascular disease (adapted from Ref 1).

Category	Condition	Gene	Function
Cardiomyopathies	Hypertrophic cardiomyopathy	β-Myosin heavy chain Myosin essential light chain Myosin regulatory light chain Troponin T Troponin I Cardiac myosin binding protein C α-Tropomyosin	Contractile proteins involved in force generation
	Dilated cardiomyopathy	Dystrophin Actin	Cytoskeletal protein Sarcomere protein involved in force transduction
	Mitochondrial myopathies	tRNAs	Mitochondrial energy production
Arrhythmias	Long QT syndrome (Romano-Ward syndrome)	KvLQT1 (LQT1) HERG (LQT2) KCNE1 (minK) (LQT5) SCN5A (LQT3)	Potassium channel Potassium channel Potassium channel Sodium channel
	Long QT syndrome with neural deafness (Jervell & Lange-Nielsen syndrome)	Recessive KvLQT1 Recessive KCNE1 (minK)	Potassium channel Potassium channel
	Brugada syndrome	SCN5A	Sodium channel
Vascular disorders	Marfan syndrome Supravalvular aortic stenosis Hereditary haemorrhagic telangiectasia	Fibrillin Elastin Endoglin	Microfibrillar protein Microfibrillar protein TGF-β receptor complex
Congenital heart disease	Holt-Oram syndrome	TBX5	Transcription factor
	Atrial septal defect with heart block	NKX2-5	Transcription factor

TGF = transforming growth factor

Myosin binding protein C mutations

MyBPC mutations are typically associated with a late-onset form of HCM which may manifest in clinically detectable abnormalities only in mid-to-later life[9,12]. Consequently, individuals with these mutations are often not recognised as having familial disease; at the time of diagnosis, their affected parents are likely to have died, and adolescent or young adult children are not yet clinically affected. Fortunately, families with these mutations have so far presented with good prognosis overall; in particular, there appears to be a very low incidence of sudden death before the onset of hypertrophy in later life. Although screening for these mutations may be deemed less urgent in view of the good prognosis, the high percentage of apparently non-penetrant carriers (who may later develop the disease) increases the value of a genetic diagnosis.

Long QT syndrome

Hereditary LQTS is a familial disorder characterised by delayed or prolonged ventricular repolarisation on the ECG and a propensity for syncope, polymorphic ventricular tachycardia (*torsade de pointes*) and sudden death. Two forms are recognised clinically:

- an autosomal recessive form associated with congenital deafness (Jervell and Lange-Nielsen syndrome)
- an autosomal dominant form (Romano-Ward syndrome), with normal hearing.

The estimated incidence of Romano-Ward syndrome (1 per 10,000) is higher than that of the Jervell and Lange-Nielsen syndrome (3 per million), and those affected generally have milder symptoms[13].

The prolonged QT interval results from an increased duration of the cardiac action potential. On a molecular basis, the LQTS is caused by defects in ion channel genes that regulate the action potential. Disease-causing muta-

tions have been identified in four specific cardiac ion channel genes (Table 1). The genes for LQT1 (KvLQT1), LQT2 (HERG) and LQT5 (minK, co-assembled with KvLQT1) encode potassium channels involved in the repolarisation phase of the action potential. LQT3 is caused by a defective sodium-channel gene, SCN5A, which fails to become inactivated, resulting in sustained depolarisation and prolongation of the action potential.

Molecular genetic studies have clarified the relationship between the Romano-Ward syndrome and the Jervell and Lange-Nielsen syndrome. The latter has been shown to be caused by mutations in both copies of the KvLQT1 or KCNE1 (minK) genes[14,15]. Therefore, parents and offspring of patients with the Jervell and Lange-Nielsen syndrome are obligate heterozygotes for LQT-associated mutations and are at increased risk for arrhythmia. Family screening by ECG is indicated in these families.

ECG and genotype

In patients with LQTS, the ECG T wave repolarisation pattern is influenced by genotype[16]. Patients with mutations in the SCN5A sodium channel gene on chromosome 3 may have a distinctive late appearing T wave that is different from the low amplitude, moderately delayed T wave characteristically seen in affected patients who are carriers of the HERG potassium channel gene mutation on chromosome 7. Both these repolarisation patterns are different from the broad-based, prolonged T wave pattern found in patients who are carriers of the abnormal KvLQT1 gene on chromosome 11. There is, however, considerable variability in T wave morphology within and between families with the same genotype, with overlap in the T wave patterns among the three genotypes. Therefore, although there is a relationship between genotype and ECG phenotype in LQTS, the morphological pattern of the T wave cannot be used reliably to identify the disease gene in patients with suspected hereditary LQTS.

Clinical course and genotype

An association has been observed in LQT1 patients between physical or emotional stress and syncope, while LQT3 patients seem to be more at risk during rest or sleep, and LQT2 patients are between these two extremes[17]. Furthermore, heart rate increase was shown to produce marked shortening of the QT interval among LQT3 patients, an effect less evident among LQT2 patients and controls[17]. It could be inferred that LQT3 patients may be at lesser risk of cardiac events during physical exercise, when the progressive heart rate increase may allow appropriate QT shortening.

Data from the international LQTS registry indicate that the clinical course of families with LQT1, LQT2 and LQT3 also differs[18]. Subjects with mutations at the LQT1 or LQT2 locus have a significantly higher likelihood of cardiac events than those with the SCN5A mutation at the LQT3 locus. Younger age at onset and a higher likelihood of recurrent cardiac events have also been observed in the LQT1 and LQT2 families. Cumulative mortality by the age of 40 years, however, was found to be similar regardless of genotype, underlining the fact that the percentage of lethal cardiac events was significantly higher in families with mutations at the LQT3 locus.

Current therapy

Mortality in untreated symptomatic LQTS cases exceeds 60% within 15 years of diagnosis. Effective treatments are currently available, and their use has reduced mortality to approximately 3–4% within 10 years from the first episode. The mainstays of treatment are β-blockers, left cardiac sympathetic denervation and pacing whenever there is clear evidence of pause-induced or bradycardia-dependent syncope.

Prospects for gene-specific therapy

The identification of ion channel mutations in LQTS has given rise to the prospect of gene-specific therapy. Initial

studies demonstrated that short-term therapy with sodium channel blocking drugs such as mexiletine, lidocaine, and tocainide shorten the QT interval and normalise the T wave morphology in LQT3[17,19]. Together with the observation that increases in heart rate have a favourable effect on the QT interval in patients with LQT3, these studies offer a preliminary suggestion that sodium channel blocking drugs and cardiac pacing may become key therapeutic modalities in the care of patients with sodium channel-based LQT3.

In patients with HERG potassium channel mutation, potassium infusion together with oral spironolactone shortens the prolonged repolarisation in LQT2[20], but this strategy for extreme manipulation of potassium levels may not be easily translated into clinical practice. In addition, animal studies and an isolated case report suggest that potassium channel openers such as nicorandil may have a beneficial effect in LQT2 patients[21].

No information is currently available on the efficacy of these gene-specific therapies for the prevention of arrhythmic events.

These exciting potential new treatments for LQTS remain experimental at present; the small numbers of patients and individual mutations studied so far do not allow extrapolation to the entire population affected by LQTS. It is clear, however, that further development is likely to have an impact on the management of these patients by allowing novel and highly specific interventions to be tested[22].

Marfan syndrome

Marfan syndrome is an autosomal dominant disease primarily affecting the cardiovascular, ocular, and skeletal systems (Fig 1), with a very wide phenotypic range both within and between affected families. The prevalence of the disorder is one in 10,000. Although most cases are familial, approximately 25% are sporadic and result from new mutations[23].

The defect that causes this syndrome lies in fibrillin (FBN)-1, a 350 kDa protein
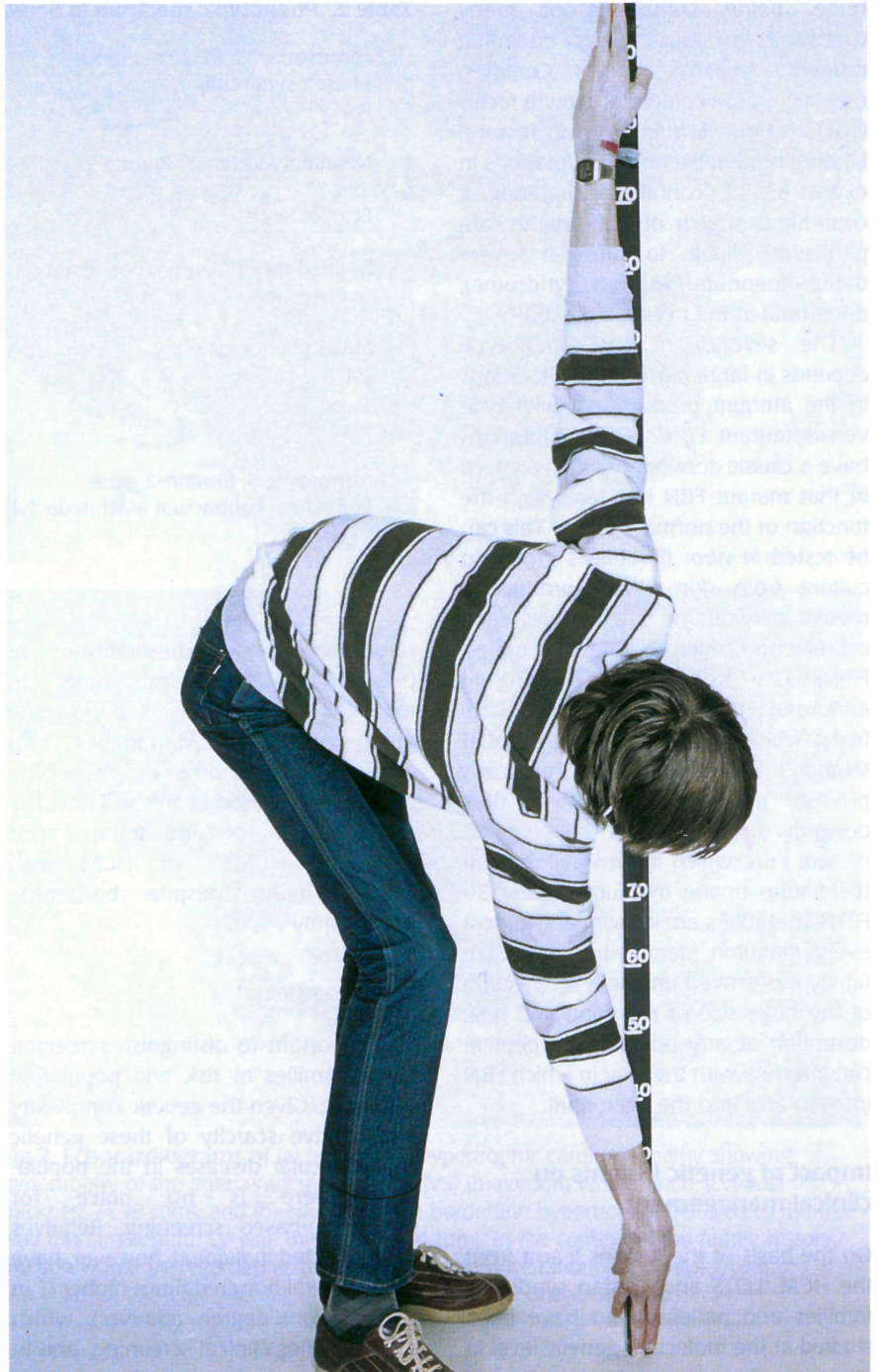

Fig 1. Long extremeties (arm span 2 m) in Marfan syndrome.

produced by connective tissue cells and secreted into the extracellular matrix where it forms a major component of microfibrils which serve in adhesion of connective tissue structures. The best characterised components of microfibrils are the FBN1 and FBN2. Marfan syndrome is caused by mutations in FBN1, while mutations in FBN2 cause the phenotypically related syndrome, congenital contractual arachnodactyly. FBN1 mutations are known to cause not only Marfan syndrome but also a wide spectrum of phenotypically related conditions (listed in Table 2).

The FBN1 gene on chromosome 15 is

huge, being comprised of many thousands of base pairs encoding numerous repetitive motifs. Common repeats include epidermal growth factor (EGF) and transforming growth factor-β binding protein-like motifs. Mutations in exons 23–32, containing the longest continuous stretch of EGF repeats, are particularly liable to cause a severe defect (neonatal Marfan syndrome), often fatal in the neonatal period[23].

The severity of the phenotype depends in large part on the alterations in the amount produced of wild type versus mutant FBN[22]. Some mutations have a classic dominant negative effect, in that mutant FBN interferes with the function of the normal protein. This can be tested *in vitro*: fibroblasts grown in culture from skin biopsy produce a regular network of microtubules seen on electron microscopy as bundles. Fibroblasts from subjects carrying abnormal FBN genes produce microfibrils which form thinner fragmented strands, while very severe cases produce none. The phenotype thus depends on the ratio of wild type to mutant FBN, which in turn depends on the nature of the mutation. Over 130 FBN1 mutations are known, and almost every mutation identified in a Marfan family has proved unique – a reflection of the huge size of the gene and how disruption at any point in the peptide can interfere with the way in which FBN incorporates into the microfibril.

Impact of genetic insights on clinical management

On the basis of the lessons learnt from the HCM, LQTS and Marfan syndrome families and patients who have been studied at the molecular genetic level in research programmes, some recommendations can be made for their management in the clinical setting.

Better use of the family history

The cornerstone of managing a patient with any of these three syndromes is a full family history of the ages at death and causes of death. The risk of sudden death in HCM must be determined by

Table 2. Phenotypic spectrum in fibrillin gene defects[22].

Chromosome 15, fibrillin-1 gene	
Marfan syndrome	Eye dominant
	Skeleton dominant
	Cardiovascular system dominant
Neonatal Marfan syndrome	
Ectopia lentis	
Isolated familial aortic root dilatation/aortic dissection	
MASS phenotype	**M**itral prolapse
	Aortic root dilatation
	Skeletal abnormality
	Skin involvement

Chromosome 5, fibrillin-2 gene
Congenital contractual arachnodactyly

reference to the denominator of presumed affected individuals; in extended families, this is a powerful guide to risk. HCM families with characteristic patterns of phenotype must be recognised as this will alter the management of individuals with late-onset HCM[9,12] or HCM with sudden death despite borderline hypertrophy[8,11].

Clinical screening

It is important to distinguish screening within families at risk and population screening. Given the genetic complexity and relative scarcity of these genetic cardiovascular diseases in the population, there is no place for population-based screening. Relatives of an affected individual, however, have a risk several hundred times higher (1 in 2 for second-degree relatives), which easily justifies clinical screening, and in some circumstances genetic screening for a mutation. Effective treatments are available for LQTS and Marfan syndrome, and to some extent for HCM. Clinical screening should therefore be offered to all first-degree relatives of newly diagnosed cases (parents and siblings as well as children). Screening should always be coupled with counselling because of the added complexities of presymptomatic diagnosis. The

wishes of family members who do not want to participate must be respected.

Clinical screening in individuals at risk of HCM is best performed every second year in childhood and annually through adolescence. In families in which individuals have presented with disease in adolescence or early adult life, screening can usually be discontinued in the early 20s. In families in which individuals have been diagnosed later in life, there is the possibility of late-onset HCM, so a normal clinical examination in the 20s does not exclude the later development of the disease and occasional further review (especially in the advent of symptoms) is appropriate.

Clinical diagnosis

With the availability of a molecular diagnosis as a 'gold standard', it has been possible to re-evaluate the sensitivity and specificity of clinical diagnostic criteria. In HCM and LQTS it has become clear that many affected individuals do not have classical features of the disease, and subtle signs must be interpreted in the context of the high prior likelihood of the disease.

Different diagnostic criteria must be used in families with HCM. A much lower threshold is appropriate for interpreting clinical tests in an indivi-

dual with an affected first-degree relative[24-26] (Fig 2). Genetic studies show that clinicians tend to underdiagnose HCM within families and that individuals with borderline features can still be at risk of sudden death and are at the same risk of having clinically affected children. It is important not to overlook the following:

- ECG abnormalities, even in the presence of a normal echocardiogram – unless these have another obvious explanation, they usually indicate underlying HCM.

- Borderline hypertrophy (eg 13 mm maximum wall thickness).

- QT prolongation, which is known to be variable under different circumstances (such that repeat measurement of QTc is necessary), and intermediate measurements must be considered suspicious in a family member.

Genetic diagnosis in families

Clinical tools will detect only a proportion of gene carriers in affected families. If there are three or more clinically affected individuals within a family with genetic disease in which the disease-causing gene is known, it is usually possible to use linkage analysis to determine which disease gene is likely to be mutated and which therefore should be screened.

Hypertrophic cardiomyopathy. Genetic diagnosis can be useful in families with HCM in situations in which clinical diagnosis is not possible:

- *Childhood and adolescence:* preclinical diagnosis is possible in families with multiple affected individuals[27]. When a mutation is identified, children at risk can be classified as:

  - *unaffected*, in which case they do not need further screening and their offspring will not develop the disease

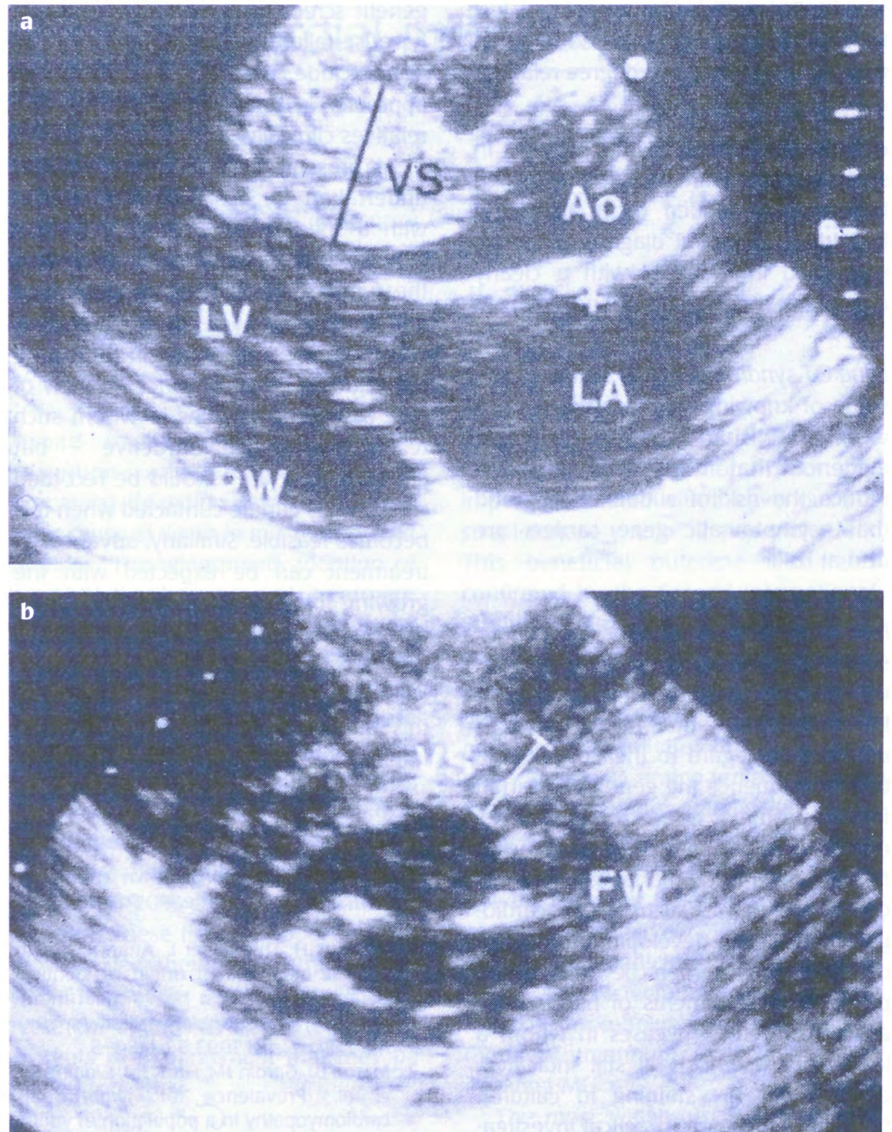 - *mutation carriers*, who will need careful follow-up and assessment for

Fig 2. Echocardiograms of (a) father with hypertrophic cardiomyopathy showing hypertrophy of the interventricular septum (VS) (maximum left ventricle (LV) wall thickness = 18 mm); and **(b)** adult son with borderline hypertrophy localised to the free wall (FW) (maximum LV wall thickness = 14 mm). In the context of the family history, the son would be regarded as affected. Both had a mutation in α tropomyosin. (Ao = aorta; LA = left atrium). (Photograph courtesy of Dr Paolo Spirito.)

treatment in the advent of any abnormal symptoms or signs. Despite the lack of hard prospective evidence, the clinical consensus is that available therapies (eg amiodarone or implantable cardioverter-defibrillator) reduce the risk of sudden death in symptomatic individuals. The early identification of affected individuals is therefore generally appropriate, provided that careful counselling is given.

- *Adults*: the clinical diagnosis of HCM is one of exclusion, so a firm diagnosis can sometimes not be reached in individuals who are hypertensive, markedly obese, highly athletic, etc. If such individuals are members of an extended family, a genetic diagnosis can be

sought. This will be important not just for their management but also to determine whether their first-degree relatives are also at risk.

• *Antenatal diagnosis*: HCM presents in some families with an extremely high incidence of sudden death in young individuals. Prenatal diagnosis may be warranted in a family with a clearly documented malignant phenotype.

Long QT syndrome. In LQTS families, the value of knowing who has the gene is well established[22]. There is clear evidence that drug treatment will reduce the risk of sudden death and that asymptomatic gene carriers are also at risk.

Marfan syndrome. A case for genetic screening cannot be made for families with Marfan syndrome. The gene for FBN is so large that every family is unique with regard to their own mutation. To sequence the gene in a Marfan family is a major research undertaking, not a routine clinical tool. Marfan families have to be managed by simple clinical techniques such as echocardiography to detect developing aortic root dilatation, and carriers be detected by physical measurements of hands, feet, aortic root, etc[22]. In cases in whom a laboratory diagnosis is still indicated, analysis of FBN staining in cultured fibroblasts is a more practical investigation than a search for a mutation at the DNA level.

Genetic diagnosis in individuals

Mutation detection in single affected individuals is technically demanding, and in most cases the work involved will not be justified by its clinical usefulness. In HCM, genetic analysis in single individuals is probably appropriate only where relatives of a surviving case died suddenly and were found to have minimal hypertrophy – a genetic diagnosis would then be of relevance to all family members. In survivors of a HCM case diagnosed at autopsy, and in the absence of living affected individuals,

genetic screening is currently not useful because failure to find a mutation does not exclude the diagnosis. A useful approach is to screen all first-degree relatives clinically.

At present, the laboratory work is undertaken by research laboratories with a specialist interest in molecular genetics of cardiovascular disorders. In the future, as advances in technology make mutation detection easier, this work may be undertaken in the UK by the regional genetic service. In view of this, cases and families in whom such testing would be attractive – but currently difficult – should be recorded so that they can be contacted when this becomes feasible. Similarly, advances in treatment can be expected with the growing biological understanding of disease mechanisms in these inherited disorders and the availability of genetically manipulated animal models. For this reason too, registries of affected families and individuals are worthwhile.

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Acute myocardial infarction

Extended Review

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Despite improvements in primary prevention and treatment, acute myocardial infarction (AMI) remains a major cause of death in most developed countries. The widespread adoption of thrombolytic therapy and treatment with agents such as aspirin, β-blockers and angiotensin-converting enzyme (ACE) inhibitors has resulted in dramatic improvements in outcome for those patients suffering AMI who reach hospital care[1]. Despite these advances, 10–15% of the estimated 180,000 patients hospitalised annually in the UK with AMI die during hospitalisation and another 15–20% die during the following year[2]. These figures support a need for improved therapeutic strategies in AMI. This article reviews the current treatment options available and newer concepts of management that may be applied to AMI.

Therapies aimed at reperfusion of occluded coronary arteries

Thrombolytic therapy

Following clarification of the central role for thrombotic coronary occlusion in AMI in the early 1980s[3], it has become recognised that the most important therapeutic goal in the management of AMI is the early, complete and sustained restoration of blood flow to the ischaemic myocardium. The first use of thrombolytic agents was four decades ago[4], but it was not until 1986 that their benefit was proven in a large randomised trial[5]. The Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI) trial showed an 18% reduction in mortality in patients treated with intravenous (IV) streptokinase within 12 hours of AMI[5]. This beneficial outcome was later confirmed by the Second International Study of Infarct Survival (ISIS-2)[6]. Subsequently, a number of large trials have compared different thrombolytic agents and different regimens combining thrombolytic drugs, aspirin, and various anticoagulants, antithrombin and other antiplatelet agents. Over 200,000 patients have been randomised to clinical trials of thrombolytic therapy, making this the most extensively investigated therapy in medicine[7]. These studies have conclusively established the role of thrombolysis as an effective mode of treatment for patients with evolving MI.

The most widely used thrombolytic agents in UK are streptokinase and tissue plasminogen activator (t-PA). The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial[8] demonstrated that an accelerated regimen of t-PA with IV heparin given within six hours of the onset of symptoms was associated with mortality as low as 6.3% at 30 days. Overall, administration of t-PA saved 10 lives per 1,000 patients treated, at a cost of two extra strokes compared with streptokinase[8]. In addition, t-PA gave better results for the combined end-point of death plus non-fatal disabling stroke (6.9% vs 7.8%, $p < 0.01$).

Angiographic studies from the GUSTO trial have demonstrated a