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REVIEWS

Calcific aortic stenosis: same old story?

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Abstract

Calcific aortic stenosis is the commonest adult valvular heart condition seen in the western world. Its prevalence is continuing to rise, with predominance in older patients who are frequently undergoing successful aortic valve replacement. This review discusses the natural history of calcific aortic stenosis, highlights recent insights into its pathogenesis, and outlines current medical and surgical management. The potential role of novel therapeutic interventional strategies is discussed.

Keywords: *aortic stenosis, aetiology, pathogenesis, management, medical therapy, elderly*

Introduction

Aortic stenosis is the commonest adult heart valve condition seen in the western world. Over the last 30–50 years, its diagnosis and management have been revolutionised by the development of invasive (cardiac catheterisation) and non-invasive (echocardiography) haemodynamic assessments as well as potentially curative cardiac surgery. Recent insights have been made into the pathogenesis of calcific aortic stenosis, resulting in speculation that the disease mimics atherosclerosis and progression could be delayed or prevented by the use of lipid lowering therapy. This exciting concept is currently under investigation in a number of centres and, if successful, may potentially reduce the need for aortic valve surgery.

Epidemiology

Calcific aortic stenosis was first documented in 1904 [1] and at that time was regarded as uncommon. In the 19th century, calcific aortic stenosis was not recognised as a clinical entity since pathological studies revealed only cusp thickening and sclerosis [2]. As a result, aortic valve sclerosis (thickening without stenosis) and aortic valve stenosis were regarded as different pathological conditions for many decades. Recent evidence, however, suggests that they represent different stages of the same disease process [**3**–5]: sclerosis arising from the development of valvular calcific lesions that progress slowly over several decades before ultimately causing aortic stenosis [6]. The current prominence of calcific aortic valve disease is likely to represent increased human longevity associated with the declining prevalence of rheumatic fever.

Aortic valve sclerosis is present in 20–30% of individuals over 65 years and 48% over 85 years [7], and aortic stenosis in 2% and 4%, respectively [**3**, **7**, **8**]. Calcific sclerosis and valvular stenosis occur in patients with both a normal tricuspid aortic valve as well as in those with a bicuspid valve. The prevalence of bicuspid aortic valves is difficult to determine but is estimated to affect 1–2% of the general population [9]. Up to 70% of patients with a bicuspid aortic valve develop valvular stenosis [9] and will require aortic valve replacement 1–2 decades earlier in life (5th–6th decade) than in those with a tricuspid aortic valve.

Natural history

Prior to the introduction of haemodynamic assessment and cardiac surgery, the natural history of aortic stenosis was described by its clinical presentation. Calcific aortic stenosis is a gradually progressive disease, characterised by a long asymptomatic phase lasting several decades, followed by a shorter symptomatic phase usually associated with severe narrowing of the aortic valve orifice.

The outlook for patients with asymptomatic aortic stenosis is generally good and closely matches that of life table estimates for age- and sex-matched controls [10]. A striking feature of aortic stenosis is that the prognosis changes dramatically with the onset of symptoms in association with severe outflow obstruction: a 2-year survival rate of 50%. Although few studies specifically assessed the influence of age, patients over the age of 70 have a worse prognosis with 2- and 3-year survival rates of 37% and 25%, respectively [11]. The prognosis also depends upon the clinical presentation with a mean survival of 3 years for those presenting with angina

and syncope, 2 years with the onset of breathlessness, and as little as 1 year in those who develop overt left ventricular failure [12, 13].

Other cardiovascular events

Despite the favourable outlook in those patients with mild asymptomatic disease, there is an increased risk of cardiovascular events unrelated to the aortic valve disease. Otto and colleagues demonstrated that, in patients with aortic sclerosis, there is a 50% increased risk of myocardial infarction and cardiovascular death even in the absence of significant outflow tract obstruction [7]. The Helsinki Aging Study also suggested that patients with moderate to severe aortic stenosis had higher all cause and cardiovascular mortality irrespective of associated symptoms. In particular, a higher rate of stroke related death was noted although the majority of these patients had atrial fibrillation [**14**].

Pathology of calcific aortic stenosis

For many decades, calcific aortic stenosis has been attributed to prolonged 'wear and tear' and age-associated valvular degeneration. Contrary to this supposition, however, is the absence of aortic valve calcification or stenosis on echocardiography in a third of individuals over the age of 80 [**8**]. Recent evidence suggests that calcific aortic stenosis may result from an active inflammatory process involving biochemical, humoral and genetic factors.

Histology

Normal aortic valve leaflets are macroscopically smooth, thin and opalescent, with clearly defined tissue layers at a microscopic level and very few cells [15]. Increasing age gives rise to non-specific thickening of the tips of the valve leaflets, with an increase in the number of adipose cells and thinning of tissue layers [**16**]. In calcific aortic stenosis, there is characteristic leaflet thickening, with irregular nodular masses on the aortic aspect of the valve. Microscopic assessment of both mild and severely affected valves reveals endothelial and basement membrane disruption, with underlying subendothelial thickening. The lesion itself contains disorganised collagen fibres, chronic inflammatory cells, lipoproteins, lipid, extracellular bone matrix proteins and bone mineral [15, **16**].

Pathogenesis

The histological features described closely resemble those seen in atherosclerosis and are strongly suggestive of chronic inflammation. In calcific aortic stenosis, the factors initiating the inflammatory process have not been identified but mechanical injury to the endothelium is thought to pave the way for subsequent inflammation. This concept is supported by the pattern of aortic valve cusp involvement that corresponds to areas of low shear and high tensile stress: namely the aortic surface of the leaflets and predilection for the non-coronary cusp [17–20]. Congenitally bicuspid aortic valves are less efficient than tricuspid valves at distributing mechanical stress and this may account for the more rapid development of stenosis [21].

Role of lipids

Endothelial injury or disruption may allow circulating lipids to enter the valvular interstitial tissue [**22**] and accumulate in areas of calcification and inflammation [**22**, **23**]. The lipoproteins implicated in atherogenesis, including low-density lipoprotein (LDL) and lipoprotein (a), are present in early aortic valve lesions [**22**] and undergo oxidative modification [**23**]. These oxidised lipoproteins are highly cytotoxic [24] and capable of stimulating inflammatory activity [25, 26] and mineralisation [27–**29**].

Inflammation

Both macrophages and activated T lymphocytes are present in the early and advanced lesions of congenitally bicuspid [30] and tricuspid aortic valves [15, **16**]. Migration of these effector inflammatory cells appears to be mediated through increased endothelial expression of cellular adhesion molecules such as E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) [31, 32]. Once recruited into the subendothelium, the inflammatory cells release enzymes, such as matrix metalloproteinases, that cause degradation of collagen, elastin and proteoglycans within the aortic valve cusps [33].

Calcification

Mineralisation is a characteristic of both atherosclerotic and aortic valve lesions, and arises in close proximity to areas of inflammation. It is a prominent feature in calcific aortic stenosis and has been demonstrated in early [**16**] as well as advanced lesions [**34**]. Surgically excised valves have even revealed areas of mature lamellar bone, haemopoietic marrow and bone remodelling [**34**]. Several features suggest the presence of an active highly regulated process closely resembling developmental bone formation [35, **36**].

The initiation of mineralisation (nucleation) may be stimulated by the presence of cellular degradation products following apoptosis [37] or by the presence of oxidised lipids [**23**, 34]. *In vitro* studies of cultured explants of stenotic valves have identified cells with osteoblastic characteristics capable of phenotypic differentiation and spontaneous calcification [38]. Their origin is unknown but they may be derived from a pool of circulating immature pluripotent mesenchymal cells [39]. These osteogenic cells or 'calcifying valvular cells' express and produce a variety of regulatory bone matrix proteins including osteopontin [40, 41] and bone morphogenetic protein [**34**].

Similarities and differences with atherosclerosis

Although the similarities with atherosclerosis were recognised as long ago as 1917 [42], they were largely disregarded until recently [43–**45**]. The histological studies described above have highlighted the common features but also confirmed differences in the cellular and mineral components of the two lesions.

Smooth muscle proliferation and lipid-laden macrophages (or foam cells) are prominent features of vascular atheroma but are virtually absent in stenotic aortic valves. In

addition, mineralisation is an earlier and more extensive feature of aortic valve lesions compared with atherosclerosis [**16**]. These differences may, in part, explain why only 40% of patients with severe aortic stenosis have significant coronary artery disease [46–**50**] and why the majority of patients with coronary artery disease do not have aortic stenosis. As the underlying pathology for the two conditions appears to be similar, it is likely that other unknown factors influence the development of valvular as opposed to vascular lesions [**51**].

Clinical presentation

Patients present with either an incidentally noted asymptomatic systolic murmur or with symptoms of severe disease including angina, exertional syncope, breathlessness, and reduced exercise tolerance or lethargy. In simple terms, progressive obstruction to outflow results in a gradual rise in left ventricular pressures, left ventricular hypertrophy, and diastolic dysfunction. Once the degree of stenosis is severe, further small decreases in aortic valve area result in large changes in the pressure gradient across the valve. Symptoms and decompensation arise due to the development of inadequate cardiac reserve, myocardial oxygen demand mismatch or pressure overload of the left ventricle. Symptoms rarely occur unless the degree of stenosis is of at least moderate severity (with an aortic valve area of less than 1.0 cm^2) but patients may remain asymptomatic for long periods with even very severe stenosis [46].

Clinical risk factors

In keeping with the apparent parallels with atherosclerosis, calcific aortic stenosis is associated with coronary artery disease [48, **50**] and many of its risk factors (Table 1) [**3**]. Calcific aortic stenosis is also seen in association with severe homozygous familial hypercholesterolaemia, and its development appears to be influenced by the length of exposure to elevated serum cholesterol concentrations [52]. Interestingly, aggressive lipid lowering therapy with plasmapheresis has been reported to regress aortic stenosis in such patients [53]. Milder forms of hypercholesterolaemia have also been associated with calcific aortic stenosis [**54**, 55, 56], particularly in patients with non-rheumatic tricuspid valves [**54**].

Conditions affecting calcium metabolism, such as chronic renal impairment with secondary hyperparathyroidsim [57–59] and advanced Paget's disease [60], predispose individuals to aortic valve calcification and accelerated stenosis. Such patients also tend to have diffuse cardiac calcification affecting the mitral valve, myocardium and conducting system.

A number of twin studies and case reports suggest that hereditary factors may influence the development of calcific aortic valve stenosis [61, 62]. There has been a single report of a genetic association between aortic stenosis and a vitamin D receptor polymorphism [63] but this finding has yet to be confirmed.

Table 1. Risk factors for calcific aortic stenosis

Clinical	Biochemical
Age	Hyperlipidaemia (LDL and Lp (a))
Male sex	Hypercalcaemia
Smoking	Elevated serum creatinine
Hypertension	
Diabetes mellitus	
Coronary artery disease	
Chronic renal failure	
Paget's disease	
Hyperparathyroidism	

LDL = Low-density lipoprotein; Lp (a) = Lipoprotein a.

Investigations

The assessment of valvular stenosis and monitoring of disease progression has only been possible over the last five decades using cardiac catheterisation, echocardiography and more recently magnetic resonance (MR) imaging and computed tomography (CT). Magnetic resonance may have some advantages over echocardiography in assessment of stenosis severity [64], but its availability is limited and measurements are time consuming to perform. Although currently limited to clinical research, CT has recently been validated as an accurate means of quantifying aortic valve calcification, a measure that correlates well with the severity of stenosis estimated by echocardiography [**65**]. Echocardiography remains the current gold standard for monitoring of disease progression and left ventricular function in patients with aortic stenosis.

The severity of aortic valve stenosis is assessed using both two-dimensional and Doppler echocardiography (Table 2). Narrowing of the aortic valve orifice results in acceleration of blood flow across the valve. Using spectral Doppler, the velocity of blood passing through the left ventricular outflow tract (pre-valve) and aortic valve orifice (post-valve) can be measured and is usually expressed in metres per second. The peak instantaneous pressure gradient across the aortic valve has a simple relationship with the peak post-valve velocity and is described as four times the square of the velocity (modified Bernoulli equation). For example, a peak post-valve velocity of 4 m/s gives an instantaneous pressure gradient of $4 \times 4^2 = 64$ mmHg. Where there are concerns that impaired left ventricular function limits the ability to generate an adequate pressure gradient across the valve, measurement of the aortic valve area may

Table 2. Echocardiographic measures of severity of aortic stenosis (AS)

	Normal	Mild AS	Moderate AS	Severe AS
Peak post-valve velocity (m/s)	0.9–1.8	2.5–3.0	3.0–4.0	>4.0
Peak gradient (mmHg)	<25	25–36	36–64	>64
Aortic valve area (cm^2)	2.0–3.5	1.0–2.0	0.5–1.0	<0.5

need to be made using direct planimetry or indirectly using the continuity equation. On occasions, dobutamine stress echocardiography may be used as method of distinguishing true aortic stenosis causing left ventricular dysfunction from aortic pseudostenosis where the impairment of the left ventricle causes poor excursion of the aortic valve cusps giving the impression of stenotic valvular restriction.

Disease progression

Echocardiography provides the most accurate evaluation of disease progression, which can be unpredictable and extremely variable. Some individuals show little or no evidence of deterioration over time, yet others progress rapidly from mild to severe stenosis within a few years.

In patients with aortic valve sclerosis, progression to stenosis (arbitrarily defined as a peak post-valve velocity ≥2.5 m/s, or peak gradient ≥25 mmHg) is a relatively slow process with mean increases in peak post-valve velocity and peak gradient of 0.07 m/s and 1.4 mmHg per year, respectively [**66**]. However, once the valve is classified as stenotic, disease progression is more rapid with average increases of 0.3 m/s and 7–8 mmHg per year, corresponding to a decrease in aortic valve area of 0.1 cm^2 per year [67–**71**].

Predictors of progression and clinical outcome

Disease progression and clinical outcome have been linked to many of the risk factors for calcific aortic stenosis, including age, male sex, hyperlipidaemia, hypertension, diabetes mellitus, smoking, hypercalcaemia and chronic renal impairment [69, 72, **73**–75]. However, much of the evidence is conflicting and limited by the retrospective nature of the studies. The most consistent and strongest predictors of disease progression are severity of stenosis at baseline [**71**] and degree of valvular calcification [72, 76, **77**]. The more severe the stenosis at baseline and the more heavily calcified the valve, the faster the rate of progression. Clinical outcome is also influenced by the degree of valvular calcification, with nearly 80% of patients with moderate to severe calcification who progress rapidly (>0.3 m/s/yr) either dying or undergoing aortic valve replacement within 2 years [**77**].

Management of calcific aortic stenosis

At the present time, there is no known therapy that can slow or reverse disease progression in patients with calcific aortic stenosis. Current management includes monitoring disease progression, and ensuring patient awareness of the need for antibiotic prophylaxis against infective endocarditis. For those patients with severe symptomatic disease, the therapeutic options include conventional medical therapy for symptom control and aortic valve replacement.

General advice

All patients should be advised of the need for antibiotic prophylaxis against endocarditis for dental and other invasive procedures. Patients with moderate or severe disease should be advised to avoid strenuous physical exercise and competitive sport, and to report promptly the onset of symptoms.

Monitoring of disease progression

Since disease progression is so unpredictable, the majority of patients should be reviewed regularly to monitor changes in stenosis severity and watch for the onset of symptoms. As a rule of thumb, asymptomatic patients with mild to moderate stenosis require review and echocardiography every 1–2 years, and those with moderate to severe stenosis every 6–12 months. Patients developing symptoms between appointments should be reviewed immediately.

Asymptomatic severe aortic stenosis

One contentious area of management is determining the optimal timing for aortic valve replacement. It is universally accepted that surgery is indicated as soon as symptoms appear in patients with severe stenosis. Although many cardiologists are loath to refer patients without symptoms for valve surgery, there are some who feel uncomfortable managing patients with severe asymptomatic valvular stenosis because of the potential risk for sudden cardiac death. However, this is rare and occurs in less than 1% of asymptomatic patients per year [**78**]. The combined risk of aortic valve replacement (2–10% mortality) and prosthesis-related complications (2–3%/year) is thus greater than the risk of sudden cardiac death. 'Watchful waiting' is therefore recommended.

The onset of symptoms in patients with severe stenosis may be subtle and insidious, particularly in the elderly where co-morbidity may mislead or obscure the presentation. For this reason careful history taking for changes in exercise tolerance as well as the classical symptoms of breathlessness, chest pain and syncope is required. In cases where patients may be underplaying symptoms, attributing them to 'old age', or unknowingly avoiding activity that induces symptoms, physician supervised exercise testing may be helpful in both revealing symptoms as well as determining the haemodynamic response to exercise. Patients who develop symptoms during exercise, become hypotensive, manifest marked ST segment changes or develop ventricular arrhythmias are at high risk and should be referred for valve replacement [79–**81**].

Symptomatic severe aortic stenosis

As soon as patients with severe aortic stenosis develop symptoms the treatment of choice is aortic valve replacement because this substantially improves quality of life and prognosis. In those patients declining valve surgery, or the frail elderly in whom major cardiac surgery would be inappropriate, palliation with conventional medical therapy, or in exceptional circumstances, balloon valvotomy are the only alternatives. Percutaneous aortic valve replacement is a promising new technique that is currently under development in highly selected patient populations [82, 83].

Medical therapy

Breathlessness

Patients with evidence of pulmonary congestion may benefit from the judicious use of diuretics, vasodilators and positive inotropic agents such as digoxin. Excessive use of diuretics should be avoided since patients with severe aortic

stenosis often have diastolic dysfunction and depend on an adequate pre-load in order to maintain their cardiac output.

Despite the widespread belief that ACE inhibitors can cause dangerous hypotension in severe aortic stenosis, and are therefore contraindicated, there are little data to support this. From the limited literature available, two small studies demonstrated that first dose hypotension did not occur in patients with severe aortic stenosis, and that cardiac output and symptoms improved substantially [84, 85]. Although further study is required, some patients with heart failure and severe aortic stenosis could benefit from ACE inhibitors provided that they are carefully introduced in a hospital setting. Certainly those patients already established on therapy need not have it withdrawn since this may precipitate the onset of heart failure.

Digoxin can be helpful in the management of heart failure but should only be used in the presence of atrial fibrillation or where there is documented evidence of left ventricular systolic dysfunction. Atrial fibrillation is not well tolerated in the presence of severe stenosis and restoration to sinus rhythm (through DC cardioversion or pharmacological cardioversion using amiodarone) should be attempted wherever possible.

Angina

In those individuals where angina is the predominant symptom, cautious use of beta blockers and nitrates may be of benefit.

Syncope

Patients with syncope or pre-syncope should be further evaluated with a 24-hour cardiac monitor since aortic stenosis is commonly associated with atrioventricular block. There is no specific therapy for syncope unless it is caused by a bradyarrhythmia or tachyarrhythmia, where pacemaker insertion or antiarrhythmic therapy, respectively, should be considered.

Balloon valvotomy

Although balloon valvotomy plays an important role in the management of adolescents and young adults with aortic stenosis, it has largely been abandoned in older patients. The functional improvement obtained is limited, the restenosis and complication rates are high, and the long-term outlook poor (<80% survival at 1 year) [**78**, 86]. On rare occasions, balloon valvotomy may play a role in patients with a limited life expectancy for other reasons, or as a bridge to aortic valve replacement in critically ill patients with cardiogenic shock.

Aortic valve replacement

Aortic valve replacement incurs the virtual abolition of symptoms associated with improvements in physical functioning and quality of life, and a dramatic improvement in survival. Operative mortality in middle-aged adults is in the region of 5–8% [**87**, **88**, 89] with 5- and 10-year survival rates of approximately 80% [**87**, 90] and 65%, respectively [**87**], which approaches actuarial survival rates for the general population [**87**].

Factors associated with a higher operative mortality include increasing age [91], the presence of renal impairment, cerebrovascular and peripheral vascular disease [92], the presence of impaired left ventricular function [91], and the need for simultaneous coronary artery bypass grafting [**88**]. Despite the increased operative risk associated with the presence of left ventricular failure, this is not an absolute contra-indication to surgery. Indeed these patients may have the most to gain from valve surgery in terms of improvements in prognosis.

Aortic valve replacement in octogenarians

Successful aortic valve replacement is becoming increasingly common in patients over the age of 80. Despite evidence suggesting that it should be offered to all suitable patients regardless of age, several studies have demonstrated a reluctance to refer older patients for valve surgery [8, 93, 94]. This probably reflects both patient and physician misconceptions of the risks and benefits of operative intervention.

Although operative mortality is higher in octogenarians (nearer 5–15%), these individuals have almost as much to gain as their younger counterparts in terms of improved prognosis (5-year survival being 55–70%). Of perhaps greater importance is that the majority of survivors achieve a significant reduction in symptoms [92, 95, 96, **97**, **98**] associated with a marked improvement in physical functioning and quality of life [**88**, 95, 96, **98**]. Although intensive care [92, **98**] and overall hospital stay [95, **97**, **98**] may be longer, the majority return to their own homes and retain their independence on discharge [92, 95]. However, post-operative complications are more common with a higher incidence particularly of stroke (4%) and acute renal failure (7–10%) [**98**]. In contrast to younger patients, octogenarians are usually offered a bioprosthetic (as opposed to a mechanical) valve, thus reducing the risk of valve thrombosis and anticoagulant associated haemorrhage.

Potential role for HMG CoA reductase inhibitors

Hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitors or statins are now well established in the primary and secondary prevention of coronary artery disease [99, 100]. Several studies have also shown that these drugs can cause regression of coronary artery disease [101] as well as reduce the calcific volume of coronary plaques [102]. Given the clinical association of calcific aortic stenosis with hyperlipidaemia and coronary artery disease, and the striking histological similarities with atheroma, the speculation that statins may have the potential to influence disease progression in aortic stenosis is an intriguing hypothesis [**103**, **104**].

Recent retrospective studies [105–**109**] have demonstrated that statins may delay disease progression in aortic stenosis through their lipid-lowering and anti-inflammatory actions [**109**]. These observational data should be interpreted with caution since none of these studies was randomised, and the statin doses were small. This preliminary evidence has been the rationale for establishing several ongoing randomised controlled trials of statin therapy in patients with aortic stenosis, such as the Scottish Aortic stenosis and

Lipid lowering Therapy, Impact on REgression (SALTIRE) and Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trials.

Conclusion

The need for an alternative to aortic valve surgery is highlighted by the increasing longevity of the population and rising prevalence of aortic stenosis. New therapeutic strategies to limit disease progression are needed in order to delay, and potentially avoid, the need for valve surgery. The outcomes of several ongoing randomised controlled trials investigating the role of lipid-lowering therapy in aortic stenosis are awaited with interest.

Key points

- Aortic stenosis is increasingly common.
- Severe aortic stenosis in the presence of symptoms carries a very poor prognosis.
- Aortic valve replacement dramatically improves survival and quality of life, even in octogenarians.
- Too few older patients are offered aortic valve replacement.
- Lipid-lowering therapy may have a potential role in the prevention of disease progression.

Conflicts of interest declaration

The authors are currently involved in the SALTIRE trial funded by the British Heart Foundation with an additional educational grant award from Pfizer (UK) Limited, as well as the SEAS study which is sponsored by Merck Sharp and Dohme Limited.

Please note

The very long list of references supporting this review has meant that only the most important are listed here and are represented by bold type throughout the text. The full list of references is available on the journal website (http://www.ageing.oupjournals.org).

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Between the Devil and the Deep Blue Sea—balancing the risks and potential benefits of warfarin for older people with atrial fibrillation

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Keywords: *atrial fibrillation, stroke, warfarin, older people.*

Introduction

Atrial fibrillation (AF) is a common arrhythmia and a potent independent risk factor for embolic stroke [1]. Data taken from the Framingham study [2], a prospective epidemiological study, indicate that 15% of all strokes are associated with AF and this association becomes more prevalent with age, from 6.7% of all strokes for patients aged 50–59 years to 36.2% of all strokes for patients aged 80–89 years. The initial stroke occurring with AF is often severe, for example in one study 71% of patients died or had severe permanent neurological deficits [3].

The prevalence of AF increases with age and increases sharply in older people. A UK based community study indicated a prevalence of 4.7%, rising to 10% in men aged over 75 [4].

Antithrombotic trials

Six of the seven major randomised trials evaluating antithrombotic therapy in AF were primary stroke prevention trials [5–10]. The seventh, the European Atrial Fibrillation Trial (EAFT), was a secondary prevention trial that compared anticoagulation, aspirin and placebo in patients with prior stroke or transient ischaemic attack (TIA) [11].

A meta-analysis of the pooled primary prevention data from five of the six major study groups attempted to identify patient features predictive of high or low risk of stroke, to assess the efficacy of anti-thrombotic therapy in major patient subgroups and to estimate the efficacy and risks associated with anticoagulation in AF [12]. Warfarin reduced the risk of stroke by 68% from ~4.5% to 1.4% per year, with little increase in the frequency of major bleeding episodes (warfarin 1.2%, control 1.0%) or intracranial haemorrhage (warfarin 0.3%, control 0.1%).

The age-associated variation in prevalence of AF is not truly reflected in the population base of these trials. Around 50% of patients with AF are over 75 years of age [13] whereas only 20% of the trial patients were in this age bracket, 32% of patients are over 80 years and were not included in the trials. Exclusion criteria included old age