Atrial fibrillation and mortality

See page 1592 for the article to which this Editorial refers

It is well recognised that the presence of atrial fibrillation confers a significant mortality and morbidity, with an increased risk of stroke and thromboembolism, in addition to important haemodynamic effects, resulting in heart failure and decreased exercise tolerance. The increasing prevalence of atrial fibrillation with age, has important implications for both primary and hospital healthcare in an increasingly elderly population. If these patients are admitted to hospital, there is often an associated high mortality, morbidity and long stay in hospital, resulting in significant costs to health services.

Is the prognosis of atrial fibrillation improving? The most recent analysis from the Framingham study examined the mortality of subjects 55–94 years of age who developed atrial fibrillation during 40 years of follow-up of the original Framingham Heart Study cohort[1]. Of the original 5209 subjects, 296 men and 325 women developed atrial fibrillation and those who did so were more likely to have hypertension, left ventricular hypertrophy on ECG, myocardial infarction, congestive heart failure, valvular heart disease, cerebrovascular disease at baseline, and be a smoker. Importantly, however, atrial fibrillation was associated with an odds ratio for death of 1·5 for men and 1·9 for women, which did not vary by age, and most of the excess mortality attributed to atrial fibrillation occurred soon after diagnosis of atrial fibrillation[1]. Nevertheless, whilst many patients with atrial fibrillation in the Framingham analysis had significant co-morbidity, up to one third of patients with atrial fibrillation may have had idiopathic or ‘lone’ atrial fibrillation, where no precipitating cause could be identified, and there was no overt evidence of organic heart disease[2].

A recent analysis of 23 years follow-up of 7746 middle aged men from the Paris Prospective Study suggests that even idiopathic atrial fibrillation was an independent risk factor for cardiovascular mortality and total death[3]. There appears to be some difference between paroxysmal and chronic lone atrial fibrillation, with the latter being associated with increased risk of thromboembolism and higher mortality after 10 years follow-up[4].

In the current issue, a report based on the Danish National Hospital Discharge Register from 1980–93 found a decrease in the relative risk of total mortality of 8–13% over this period, but no decrease in risk of cardiovascular death, after adjustment for the decreasing cardiovascular mortality rate in the general population[5]. Does this mean we are getting better at managing atrial fibrillation? Are new drugs and novel electrophysiological techniques making an impact? The report from Frost et al.[5] is dependant upon the Danish National Hospital Discharge Register statistics, where only a 50% random sample was studied. Their end-point of death was also dependent upon how the death certificates were completed and thus the accuracy of form filling by a great many busy, overworked hospital doctors. Indeed, we also do not know the time trends of drug regimens used (including antiarrhythmic agents), the impact of antithrombotic therapy as thromboprophylaxis in these patients and the presence of associated co-morbidity (such as heart failure, hypertension, etc).

The effect of antiarrhythmic drugs on mortality in patients with atrial fibrillation is not inconsequential. For example, a report from the Stroke Prevention in Atrial Fibrillation (SPAF) trial found an increase in mortality in patients with atrial fibrillation who were treated with antiarrhythmic drugs (primarily quinidine) if concomitant congestive heart failure was present, with a relative risk for cardiac death of 3·3 and arrhythmic death of 5·8[6]. The impact of antithrombotic therapy is also important. For example, non-valvular atrial fibrillation has been associated with a fivefold increase in the risk of ischaemic stroke compared to that of sinus rhythm, and with a 5–7% yearly risk, which increases with age[7]. Indeed atrial fibrillation is usually present in about 15–20% of patients with acute stroke, and these patients have a 1·5 to 3·0 fold higher mortality than stroke patients who are in sinus rhythm[8,9]. Patients with atrial fibrillation who develop a stroke have more disability and severe strokes, with a longer duration of in-hospital stay and lower rate of discharge to their own homes[8,9]. However, the benefits of anticoagulation (target INR 2–3) in ‘high risk’ patients with atrial fibrillation are now well-established, with an overall stroke risk reduction of 68% (95% confidence intervals 50% to 79%) with warfarin, which should be prescribed to high risk patients with atrial fibrillation[10].

Associated co-morbidity, such as hypertension or heart failure, in patients with atrial fibrillation, has significant implications for mortality. Such patients also appear to be at high risk of stroke and thromboembolism, whether hypertension or congestive cardiac failure is present clinically, or left ventricular...
systolic dysfunction on echocardiography. In a recent analysis from the Studies of Left Ventricular Dysfunction (SOLVD) investigators, the presence of left ventricular systolic impairment appears to be associated with an increased risk for all-cause mortality (relative risk 1.34, 95% CI 1.12–1.62), especially from progressive pump failure death. Although the presence of atrial fibrillation significantly increases mortality in patients with heart failure, the overall prognosis does seem to be improving in these patients, perhaps reflecting improvements in therapy for heart failure and the avoidance of class I antiarrhythmic agents.

Frost et al. also noted a substantial increase in atrial fibrillation hospital discharges over the same period, from 8/1000 person-years in 1980 to 13/1000 person-years in 1993. Nevertheless, this reported incidence is lower than that noted in population-based data, for example, from the Framingham study. Interestingly, nearly half of the Danish hospital admissions with atrial fibrillation had ischaemic heart disease, with hypertension being seen in under 20%, which is in keeping with hospital admission data from Glasgow and Birmingham. By contrast, population-based studies have suggested that hypertension was the commonest underlying medical problem in patients with atrial fibrillation. However, many patients with atrial fibrillation remain undiagnosed in the community, and only a third of known patients with atrial fibrillation in general practice have actually been admitted to hospital, suggesting that hospital-based datasets may not represent a true reflection of the clinical epidemiology of atrial fibrillation. Perhaps patients with atrial fibrillation and ischaemic heart disease develop more complications necessitating hospital admission. Indeed, uncomplicated coronary artery disease is a relatively uncommon cause of atrial fibrillation unless there are associated complications, such as heart failure or hypertension. For example, the Coronary Artery Surgical Study (CASS), reported that the prevalence of chronic atrial fibrillation was 0.6% and was usually associated with an older age (>60 years), male sex, mitral regurgitation, and congestive heart failure. Another reason for the disparity between hospital and population data may be the fact that many patients have asymptomatic atrial fibrillation; one study has estimated that only one in 12 episodes of atrial fibrillation in patients with paroxysmal atrial fibrillation are actually symptomatic. Recent suggestions that the prognosis in atrial fibrillation may be improving is encouraging news. Nevertheless these reports are based on hospital-defined populations. We need more contemporary data from large population-based surveys of atrial fibrillation, adjusting for associated co-morbidity and recent advances in managing atrial fibrillation, including increased antiarrhythmic therapy usage, newer (but perhaps not necessarily safer) antiarrhythmic drugs and new technology, such as electrophysiological techniques and devices such as the atrioverter. Only time will tell.

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References

Plant lipids that lower serum cholesterol

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Most cardiologists are familiar with cholesterol and its Jekyll and Hyde characteristics of being both an essential constituent of cell membranes and a prerequisite for the development of atherosclerosis. However, they probably know little or nothing about sitosterol and campesterol, which are plant-derived analogues of cholesterol. These plant (phyto-) sterols occur naturally in corn, soybean, rape and sunflower seed oils and are also present in human plasma but in much lower concentrations than cholesterol, except in homozygous carriers of the very rare, recessively inherited disorder, phytosterolaemia. Recently, plant sterols and stanols (which lack the delta-5 double bond of sterols) have come into the public eye in the guise of so-called functional foods, aimed at lowering serum cholesterol. Supplement S, which accompanies this issue of the European Heart Journal contains the Proceedings of a meeting held earlier this year to discuss the efficacy and safety of plant stanols in that context.

Mechanism of action and efficacy

Beta-sitosterol, a plant sterol, was first used to lower serum cholesterol in man 45 years ago[1], but it was not until 1986 that sitostanol, its saturated counterpart, was used for that purpose[2]. The effects of plant sterols and stanols on cholesterol and bile acid metabolism and their efficacy and safety as a means of lowering serum cholesterol have been reviewed recently[3–5].

Short-term administration of Tall Oil (derived from tall trees such as pines), containing a mixture of phytosterols and -stanols, to normo- or hyperlipidaemic subjects resulted in a 10% decrease in serum cholesterol[6]. In children with familial hypercholesterolaemia treatment with sitosterol 6 g·day⁻¹ decreased LDL cholesterol by 20%, whereas sitostanol 1·5 g·day⁻¹ resulted in a 33% decrease, suggesting that the latter was more effective[7]. Surprisingly, however, administration of sitostanol 3 g daily in capsules to hypercholesterolaemic men was ineffectual[8]. This anomalous result raised the possibility that the insolubility of plant sterols and stanols might limit their effectiveness under certain circumstances. This problem has been overcome by esterifying these compounds with mono- or polyunsaturated fatty acids derived from rape or sunflower seed oil, which greatly increases their lipid solubility and ease of incorporation into food products. After passage through the stomach the esters undergo hydrolysis within the intestinal lumen, releasing free sitosterol and sitostanol.

Despite their molecular similarity, plant sterols and stanols are absorbed much less efficiently than cholesterol, indicative of a high degree of specificity of the intestinal transport mechanism involved. Thus in one study absorption of cholesterol averaged 33% vs 9·6% for campesterol and 4·2% for sitosterol, whereas sitostanol was virtually unabsorbed[9]. In addition there was an inverse correlation between the mass of sitosterol administered and the amount of cholesterol absorbed. Sitostanol inhibits cholesterol absorption to an even greater extent than does sitosterol and it has been shown that these compounds compete with cholesterol for solubilization within mixed micelles, an essential prelude to intestinal uptake. However, this is probably not the sole mechanism involved and they may also block uptake or transport of cholesterol at the level of the enterocyte[10].

Clinical and comparative studies

Published studies of the efficacy of sitostanol ester outnumber those on sitosterol ester. Best known