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CLINICAL

The role of statins in the management of aortic stenosis

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TITLE Intensive lipid lowering with simvastatin and ezetimide in aortic stenosis

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SUMMARY

Rossebo et al. randomised 1,873 patients (mean age 67.5 years) with mild to moderate asymptomatic aortic stenosis (AS) for treatment with simvastatin 40 mg/day and ezetimide (the latter so as to improve the lipid-lowering effect while decreasing the risk of myopathy) or placebo. Eligible patients were those with echo-cardiographically evaluated peak aortic-jet velocity of 2.5–4 m per second, and patients were excluded if they had received a diagnosis or had symptoms of coronary artery disease (CAD), peripheral arterial disease, cerebrovascular disease or diabetes mellitus. The primary outcome was a composite of coronary artery bypass grafting (CABG), percutaneous coronary intervention, hospitalisation for unstable angina, non-fatal myocardial infarction, aortic valve replacement, non-haemorrhagic stroke and death from cardiovascular causes.

During a median follow-up of 52.2 months, significantly fewer patients had ischaemic cardiovascular events in the simvastatin-ezetimide group (148 vs. 187, hazard ratio 0.78; 95% CI, 0.63–0.97; p=0.02) 'mainly because of the smaller number of patients who underwent coronary-artery bypass grafting'. No significant effect was documented on the rate of aortic valve replacement, which occurred in 28.3% of the simvastatin-ezetimide group vs. 29.9% of the placebo group.

There also appeared to be an increase in cancer risk among patients receiving combined ezetimide and simvastatin therapy (105 vs. 70, p=0.01), but there was no significant difference between the study groups in overall mortality.

In the opinion of the authors, the risk of cancer was unlikely to be attributable to simvastatin, given that 'analysis of data from 14 statin trials involving approximately 90,000 patients showed no evidence of an increased incidence or death from cancer'. Ezetimide, however, had been less extensively studied in this regard.

OPINION

Degenerative AS is an age-related disorder with a prevalence of 2–7% in those over 65 years of age.[1] In that age group, CAD is one of the most important co-morbidities associated with AS.[2] Given the histological similarities between CAD and early AS,[3] it was hypothesised that 'statins may be useful agents in preventing the progression of AS'.[4]

The most recent, and largest, retrospective study testing this hypothesis is an analysis of 1,046 patients with a mean age of 70 years, 309 of whom had been treated with statins. In a multivariate analysis, statin therapy proved to be one of the three parameters that independently slowed down progression of aortic valve disease during an average follow-up of 5.6 years (range 2–19). The beneficial effect was, however, only evident in patients with aortic sclerosis and in those with mild AS.[5] Two prospective trials on smaller numbers of patients have given conflicting results, with one study showing no effect of atorvastatin on the progression of aortic stenosis,[6] and the other showing a beneficial effect of rosuvastatin.[7]

This study by Rossebo et al. is currently the most decisive report on the role of statins in AS management. It was a valid comparison between lipid-lowering therapy using statins and placebo in two subgroups of AS patients receiving comparable background treatment, including angiotensin-converting enzyme blockade, angiotensin receptor blockade, beta adrenergic blockade, aspirin and oral anticoagulants respectively. Two of the issues addressed by the study, the rate of AS progression to aortic valve replacement (AVR) and the rate of progression of associated coronary artery disease to CABG, were of high relevance to practising clinicians.

Statins did not reduce the subsequent need for AVR, but the fact that progression of coronary artery disease was retarded holds out the promise of a reduction in the rate of CABG in the event of AVR when patients

commence statin therapy sufficiently early in the evolution of AS. This is an important consideration, given that AVR-related mortality risk is higher when this procedure is combined with CABG,[8] especially in octogenarians.[9] In that age group, the rate of hospital deaths can be as low as 8.5% after isolated AVR and as high as 26.5% after combined AVR and CABG.[9]

Accordingly, this study may be the fulfilment of the hope and prediction made 11 years ago that the adjunctive use of statins in AS patients with CAD might reduce the requirement for adjunctive use of CABG in the management of AS.[10] These hopes should, however, be tempered with the recognition that all trials with composite outcomes should be interpreted with certain caveats in mind, including the risk of overstating the results of the individual outcomes.[11] The apparent benefit on CABG therefore needs to be tested in a separate trial.

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