Letters to the Editor

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Is atrial fibrillation an inflammatory disorder?

I read with great interest the excellent review on the influence of inflammation in the pathogenesis of atrial fibrillation (AF) by Boos *et al*.[1] As the authors have demonstrated, there is compelling evidence supporting the role of inflammation in the pathogenesis of this arrhythmia. I was surprised, however, to find no mention of the possible efficacy of beta-blockers with anti-inflammatory properties in this respect. Carvedilol, in particular, is a slightly beta 1-selective beta-blocker, which also possesses alpha 1-blocking and antioxidant properties.[2] Indeed, part of its reported beneficial effects on ventricular remodelling effects and coronary microcirculation has been attributed to its antioxidant activities.[2] Recently, we have provided evidence that carvedilol is probably more efficient than bisoprolol in the prevention of AF recurrences in an unselected patient population.[3] In our study, 90 patients undergoing cardioversion of persistent AF were randomized to bisoprolol 5–10 mg once daily or carvedilol 12.5–25 mg twice daily. By intention-to-treat analysis, 23 (46%) patients in the bisoprolol group and 17 (32%) patients in the carvedilol group relapsed into AF, during the 1 year of total follow-up period ($P = 0.486$). Patients treated with carvedilol had a 14% (hazard ratio = 0.86) lower risk to relapse to AF when compared with patients on bisoprolol group. This issue deserves closer attention, particularly when discussing the limitations of current anti-arrhythmic drugs as far as their anti-inflammatory action is concerned.

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Is atrial fibrillation an inflammatory disorder?: reply

We thank Katritsis for his supportive comments in response to our article dealing with the concept of inflammation and atrial fibrillation (AF).[1,2] He has emphasized the anti-inflammatory effects of beta-blockers, in particular carvedilol, as an additional mechanism to explain the drugs' anti-arrhythmic effects in preventing AF.

We agree that there are some data available, which conceptually supports potential immunoregulatory properties for several beta-blockers, for example, bisoprolol and metoprolol in patients with dilated cardiomyopathy and carvedilol in patients with dilated cardiomyopathy.[3–5] However, at present, there is a lack of convincing data to show superiority of carvedilol over other beta-blockers in the prevention or treatment of AF.

In the study by Katritsis *et al*.[6] comparing carvedilol with bisoprolol for the prevention of AF after cardioversion, there was no significant difference in AF relapse rates, over the 1-year follow up, between the two groups ($P = 0.47$). In a further study, Merritt *et al*.[7] did demonstrate lower rates of AF after cardiac surgery among patients treated with carvedilol ($n = 26$) compared with those treated with metoprolol/atenolol ($n = 89$); however, this was an observational retrospective study. Neither of these two studies investigated the potential relationship between drug efficacy, AF, and/or its inflammatory substrate.

Although we do accept the need for further investigation into the potential anti-inflammatory/antioxidant effects of beta-blockers in terms of AF prevention, the superiority of carvedilol over other beta-blockers in terms of AF prevention has not been clearly demonstrated to date. Furthermore, we feel that, at present, it is simply not possible to clearly dissociate the potential anti-inflammatory effects of carvedilol and other beta-blockers from their favourable haemodynamic and anti-adrenal effects in the setting of AF.

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Diuretic usage in heart failure: a continuing conundrum in 2005

Notwithstanding the fact that the use of low-dose diuretics (overwhelmingly thiazides) in

anti-hypertensive regimes has been associated with a risk reduction of the order of 0.51 (95% confidence interval 0.42–0.62) in the incidence of congestive heart failure,[1] the absence of scrutiny of these drugs, to which the authors allude,[2] has also included the failure to address the issue of whether the anti-hypertensive efficacy of long-acting loop diuretics such as torasemide might be comparable to that of thiazides, and whether, for both classes of drugs, the anti-hypertensive efficacy might be solely attributable to sustained natriuresis. A related issue is whether the protection that thiazides confer against hypertension-related heart failure might be rivalled, if not surpassed, by diuretics such as torasemide, which potentially possess cardioprotective properties by virtue of additional anti-aldosteronergic effects.[3] The time is long overdue for these issues to be addressed, given the inescapable risk of hyponatraemia (including severe hyponatraemia) inherent in the use of thiazides,[4–6] by virtue of their physiological actions on the renal tubule and collecting ducts.[6]

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Diuretic usage in heart failure: a continuing conundrum in 2005: reply

Dr Jolobe points out further important issues in the use of diuretics. The authors agree that properly conducted clinical trials regarding these issues are long overdue.

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Beta-blockers and heart failure in older people

The role of beta-blockers in older people (>75 years) with heart failure has been prospectively studied in the SENIORS study[1] and retrospectively analysed from trials of metoprolol.[2] In the recently published editorial accompanying the SENIORS study, it was concluded that it 'is disappointing to see how infrequently elderly patients are prescribed these effective treatments'.[3]

As geriatricians, our concerns about the increased prevalence of adverse drug reactions in older people frequently impacts on our decision to prescribe medications.[4] However, in the case of beta-blockers and heart failure, we also have concerns about the efficacy data.

The SENIORS study states[1] 'As age was a particular focus of the SENIORS trial, we also analysed patient cohorts between median age (75.2 years) and 85 years ($n = 459$ for nebivolol and $n = 482$ for placebo), where the HR for the primary endpoint was 0.91 (95% CI 0.74–1.13), and for patients >85 years ($n = 69$ for nebivolol and $n = 54$ for placebo), where the HR was 1.32 (95% CI 0.73–2.37). There was no difference between the groups for hospitalization for heart failure [placebo 144 (13.7%), nebivolol 145 (13.9%), HR = 0.99 (95% CI 0.79–1.25, $P = 0.95$)]'. Thus, the data show that in the older cohort (>75.2 years) of the SENIORS study, there was no statistically significant efficacy.

In an analysis of clinical trials of metoprolol by Deedwania *et al.*,[2] the risks of the primary outcomes also were not significant over the age of 75 years. The authors state: 'There were 490 patients >75 years of age in total [mean age 77 years (1.5); mean ejection fraction 0.27 (0.07)], of whom 247 were randomized to placebo and 243 to metoprolol CR/XL. Of these, 34 patients died in the placebo group and 24 in the metoprolol CR/XL group (relative risk 0.71, 95% CI 0.42–1.19); corresponding data for sudden death were 17 vs. 8 deaths (0.47, 0.20–1.10), for death from heart failure 12 vs. 9 deaths (0.75, 0.32–1.77), and for the combined endpoint of all-cause mortality or hospitalization for worsening heart failure 67 vs. 53 patients (0.79, 95% CI 0.55–1.14)'.

How do we evaluate these results and apply them to our patients over 75 years? As epidemiologists, we could state that there is no statistical interaction between age and outcomes over a range of age cohorts. However, as geriatricians, is it not appropriate to ask the single question 'are these drugs effective over the age of 75 years?' In this case, the data fail to reach statistical significance. Furthermore, the lack of statistical benefit seen in this older age group is biologically plausible given the effects of age on beta receptors and clinically plausible given the effects of age on pharmacokinetics, comorbidity, and disease mechanisms.[4]

Until clinical trial data show unequivocal improvement in outcomes with beta-blockers in typical older heart failure patients with their comorbidities and polypharmacy, we believe that risk-to-benefit analysis should be undertaken for each individual patient, rather than simply applying blanket guidelines and then reproaching under-prescribing.

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