Treatment of heart failure

Sir,

I read with interest the article on treatment paradigms in heart failure (vol 62(2), 2002, p. 80). There are a couple of errors in this otherwise excellent article. *Table 1* contains some inconsistencies: the reduction in all-cause mortality seen in the MERIT-HF (1999) study was 34%, not 49% as stated. The reduction in all-cause mortality in the MDC (metoprolol) trial (Waagstein et al, 1993) was not statistically significant, so should have had (NS) after the 34%. Furthermore, all-cause mortality was not a primary end point in the ANZ study, so the point estimate should have been given as it was for other trials.

On a more general note trials suggest that benefits on mortality may not be a class effect. Despite a large mortality trial (Beta-Blocker Evaluation of Survival Trial Investigators, 2001) bucindolol did not significantly reduce mortality, so we cannot assume that all beta-blockers would have this beneficial effect. The formulation may be important: the effect on mortality in MERIT-HF was with a controlled-release formulation, in contrast to the smaller MDC trial which used the standard formulation and did not prove a statistically significant reduction in mortality. With regard to dose, only for carvedilol, an alpha1-, beta1- and beta2-antagonist, do we have evidence for effect at low doses (as low as 6.25 mg twice daily, Bristow, 1996). The CIBIS trial (1994) that used bisoprolol 5 mg did not reach statistical significance.

Beta-blockers may differ in the extent to which they antagonize effects of sympathetic nervous system overactivity, not least because of the different effects of beta-receptor sub-type down-regulation pointed out by the authors. We await the first major head-to-head comparison of carvedilol *vs* metoprolol standard formulation (the COMET trial) as a meta-analysis by Packer (2001) has raised the possibility of a greater long-term effect of carvedilol on left ventricular ejection fraction compared to metoprolol.

Beta-blockers might differ in a clinically relevant manner in their effects on the natural history of heart failure, and dose and formulation may be important. Although the importance of ancillary properties and the degree of multireceptor blockade remain to be proven, use of beta-blockers should be restricted to those proven and approved: bisoprolol in class III/IV patients and carvedilol in all grades of severity, provided recent decompensation has been stabilized.

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Packer M (2001) Comparative effects of carvedilol and metoprolol on left ventricular ejection fraction in heart failure: results of a meta analysis. *Am Heart J* **141:** 899–907
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Sir,

We are grateful to Professor Coats for his comments on our article. He raises important issues which were only partially addressed in an article intended (perhaps ambitiously) to cover all treatments for heart failure.

We thank him for pointing out the error in *Table 1* relating to the mortality reduction in the MERIT-HF trial – we quoted a figure for deaths from worsening heart failure. The correct all-cause mortality is a 34% reduction with metoprolol compared to placebo. He is also right to highlight the lack of significance of the MDC trial, a small trial which showed a reduction in primary end points of 34% (P=0.058) (Waagstein et al, 1993). In Australia–New Zealand Heart Failure Research Collaborative Group (1995) the primary end points were changes in left ventricular ejection fraction and treadmill exercise duration, not mortality. No point estimate nor data to calculate this from is given.

If one is arguing that beta-adrenoceptor antagonism is an effective treatment for heart failure then showing efficacy in different beta-blockers supports this. However, in promoting the 'treatment paradigm' of beta-blockade in heart failure, we did not intend to imply that all beta-blockers are equal. Discussion of crosstalk between receptor subtypes and relative affinities of different antagonists was beyond the remit of the article.

We agree about the caution required in accepting all the benefits of beta-blockers as being a class effect – we discussed the lack of effect on mortality of bucindolol (Domanski, 1999) and the increase in mortality with xamoterol (Xamoterol in Severe Heart Failure Study Group, 1990). But we still feel that there are good data to support the use of carvedilol, bisoprolol and metoprolol in heart failure. We agree that the use of these drugs should be guided by available evidence.

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Correction

In the article *Neuroimaging in schizophrenia: from theory to practice* (Vol 63(6), 2002, p. 328), two authors' affiliations were given incorrectly. Dr Veena Kumari and Mr Alex Sumich work at the Section of Cognitive Psychopharmacology, Institute of Psychiatry, London. We would like to apologize for any confusion caused.