## Aspirin bias in SPORTIF III trial

Sir—The results of the open-label SPORTIF III trial (Nov 22, p 1691)[1] could have been biased by the uneven distribution of recipients of aspirin treatment after randomisation. The authors claim that aspirin was given to patients enrolled in the trial, as per present guidelines for treatment of concomitant coronary atherosclerotic disease, which is acceptable.[2] However, the randomisation clearly indicates that the proportion of patients with coronary atherosclerotic disease is equal in both treatment groups—ie, 40% each.[3] Significantly more people received post-randomisation aspirin treatment in the ximelagatran group than in the warfarin group. A reason for this difference has not been provided to the extent that it would not invalidate the results. Was the observed non-inferiority due to bias by concurrent aspirin treatment, which was more common in the ximelagatran treatment group? Was this bias introduced by treating physicians, since it was an open-label trial?

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1 Olsson SB. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. *Lancet* 2003; **362:** 1691–98.
2 Olsson SB. Ximelagatran or warfarin in atrial fibrillation? *Lancet* 2004; **363:** 736.
3 Halperin JL. Ximelagatran compared with warfarin for prevention of thromboembolism in patients with nonvalvular atrial fibrillation: rationale, objectives, and design of a pair of clinical studies and baseline patient characteristics (SPORTIF III and V). *Am Heart J* 2003; **146:** 431–38.

### *Author's reply*

Sir—Murali Karthick Vadivelu raises an important question regarding differences in the use of aspirin by patients in the two treatment groups of the SPORTIF III trial, and suggests that this could potentially have been owing to bias resulting from the open-label design of the trial. Concurrent aspirin use of up to 100 mg per day was allowed for patients with associated coronary atherosclerotic disease, at the discretion of treating physicians, in both the SPORTIF III and SPORTIF V trials, as recommended by current practice guidelines. Concomitant aspirin was given more frequently to ximelagatran-treated patients (337; 20%), than warfarin-treated patients (290; 17%) in the SPORTIF III trial (p=0·042).

By way of reassurance as to the validity and robustness of the conclusion of non-inferiority between the groups, however, the results between treatment groups are consistent, irrespective of aspirin use. The estimated difference, with 95% CIs, between treatment for non-users of aspirin was similar to the overall results. Overall, 40 events occurred in the ximelagatran group during 2446 patient-years, a yearly rate of 1·64%, compared with 56 in the warfarin group during 2440 patient-years, a yearly rate of 2·29%, yielding a difference of –0·66% (95% CI –1·45 to 0·13). For patients receiving concomitant aspirin during the trial, 14 events occurred during 477 patient-years (2·94%) in the ximelagatran group versus 16 events during 399 patient-years (4·01%) for the warfarin group, a difference of –1·08% (–3·57 to 1·42). The corresponding results for patients not receiving concomitant aspirin during the trial were 26 events during 1969 patient-years (1·32% per year) for the ximelagatran group versus 40 events during 2042 patient-years (1·96% per year) in the warfarin group, a difference of –0·64% (–1·43 to 0·15). The test for an interaction between the study drug and concomitant aspirin use resulted in a p value of 0.85.

The SPORTIF Executive Steering Committee acknowledge the potential implication of these data, which are being considered fully in association with the results from the sister trial, SPORTIF V (which was identical in design except for being double-blind), as is the full preplanned pooled analysis of the results from both trials. These data could provide additional insights into any potential imbalance of aspirin use between the groups. However, we cannot divulge these data before their full peer review and subsequent publication. In addition, a secondary manuscript focusing specifically on the topic of aspirin use in the SPORTIF trials is being considered by an authoring group for publication after both SPORTIF studies have been published in full.

I have served as a consultant and received payment from AstraZeneca to attend meetings related to the trial, and for travel expenses, speaking engagements, or research.

*S Bertil Olsson, on behalf of the SPORTIF III and V Executive Steering Committee*

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## Convergence of atherosclerosis and Alzheimer's disease

Sir—In their Review on dementias, Ivan Casserly and Eric Topol (Apr 3, p 1139)[1] include many details (some of them factual, other ones mainly speculative) on the pathogenetic links between vascular and degenerative dementias. In that regard we were rather surprised that they missed a reference to the prestigious Medical Research Council Cognitive Function and Aging Study.[2]

Even more surprising was the finding that the authors managed to avoid the term "hypertension" throughout their text, thereby letting go of a vast body of literature on hypertension as a key factor in both vascular dementia and Alzheimer's disease.[3,4] They mention the word just once, hidden in a panel and referring to a single study,[5] which, although covering hypertension, did not carry the word in its title.

We cannot help wondering why the authors, who otherwise present so many tiny details in their text, saw fit to lump such a distinctive disorder as hypertension together with other vascular conditions under the vague cover of "vascular" risk factors. In our view such a camouflage totally undermines their attempt to develop a fresh and distinctive paradigm. From a pragmatic point of view they also bear the responsibility of having done a disservice to one of the few proven prophylactic angles[4] in the uphill battle against the rising incidence of dementias.

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2 Neuropathology Group of the Medical Research Council Cognitive Function and Aging Study (MRC CFAS). Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. *Lancet* 2001; **357:** 169–75.
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