

doi:10.1093/eurheartj/ehn444

Online publish-ahead-of-print 2 October 2008

Aortic valve stenosis management: old strategies and future directions: reply

We would like to thank Dr Bottio *et al.* for their interest in our manuscript. In the letter, they pointed out that epidural anaesthesia could be used for cardiovascular surgery in high-risk patients. We agree with this statement, and, although we chose to intervene with general anaesthesia in this series, some centres usually perform transcatheter aortic valve implantations under locoregional anaesthesia, and others have already performed transapical aortic valve implantation under epidural anaesthesia. However, the main problem raised by these particular patients was not anaesthesia *per se*, but the fact that conventional aortic valve replacement was judged at very high risk or not technically feasible by the surgical team. Thus, we cannot agree with Dr Bottio *et al.* on the statement that 'the main reason why percutaneous interventions are more acceptable by the patients is simplicity', or that 'interventional cardiologists and cardiac surgeons (team approach) are going to re-think the high-risk AS management without a well-founded clinical programme and forgetting the patients' and economic-community interests'. In fact, in our centre as in others, the team is not restricted to cardiologists and surgeons, but it also includes anaesthesiologists and geriatricians, who all participate in the final decision of whether or not to perform transcatheter aortic valve implantation. From a more general point of view, the clinical programmes concerning transcatheter aortic valve implantation for the treatment of patients with aortic stenosis have been clearly defined and detailed in the position statement from the European Association of Cardio-Thoracic Surgery and the European Society of Cardiology, in collaboration with the European Association of Percutaneous Cardiovascular Interventions, recently published in the journal.¹ They will include prospective registries and controlled trials, the earliest of which have already been presented and discussed during many scientific meetings and congresses. Finally, the economic aspects of transcatheter aortic valve implantation have obviously not been forgotten. They raise difficult questions, joining the more general problem of medical care in the elderly. These questions will take on an increasing importance due to the ageing of

the population, and solutions will have to be found at country level. However, it is now clear that, besides conventional open chest surgery, transcatheter interventions will play an increasingly important role in the treatment of valvular heart diseases in the future. In the same way, 'old' anaesthetic methods will certainly have to extend themselves to newer techniques, such as epidural anaesthesia.

The right future direction will be determined by ongoing dialogue between all the actors of the team, to define by consensus the best strategy for each individual patient.

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doi:10.1093/eurheartj/ehn445

Online publish-ahead-of-print 2 October 2008

N-acetylcysteine for the prevention of atrial fibrillation: beyond its antioxidant effect

We read with interest the manuscript of Ozaydin *et al.*¹ about the effect of N-acetylcysteine (NAC) for the prevention of postoperative atrial fibrillation. In this prospective, randomized, double-blind, placebo-controlled study, a total of 115 patients

undergoing coronary artery bypass and/or valve surgery were included. Patients were randomized to receive NAC or placebo. During follow-up period, 15 patients had atrial fibrillation. The rate of atrial fibrillation was lower in the NAC group compared with the placebo group (three patients vs. 12, odds ratio 0.20, $P=0.019$). Notably, in the multivariable logistic regression analysis, the use of NAC was an independent predictor of postoperative atrial fibrillation.

Authors considered that oxidative stress play a main role in the development of atrial fibrillation. Since NAC is a free radical scavenger antioxidant agent that reduces cellular oxidative damage, it is possible that the results of this study may in part be explained through this mechanism. However, there are other probable mechanisms of NAC that might explain these data.

Hypertension and coronary heart disease are much related with the presence of atrial fibrillation.² In fact, in the work of Ozaydin *et al.*, ~54–61% of the patients had hypertension, ~35–45% stable angina pectoris, ~31–35% non-ST-elevation myocardial infarction, and ~21–26% had ST-elevation myocardial infarction. On the other hand, several studies have suggested that angiotensin-system inhibition appears to protect against atrial fibrillation in patients with hypertension or post-myocardial infarction. The majority of patients included in the present study were taking angiotensin-converting enzyme inhibitors (ACEi) (~66%). It is well known that the antihypertensive effect of ACEi is caused not only by the decrease in angiotensin II production, but also by the decrease in degradation of the kinins. Kinins are vasodilator peptides that stimulate the synthesis of vasoactive substances, such as nitric oxide (NO). In fact, the presence of an NO synthesis inhibitor reduces the antihypertensive effect of ACEi. Therefore, NO could contribute to the activity of ACEi, probably through NO synthesis activation mediated by endogenous kinins. The addition of an SH group donor, such as NAC, may then potentiate the antihypertensive activity of the ACEi through an NO-dependent mechanism.³ Since hypertension and ischaemia are risk factors for postoperative atrial fibrillation and the inhibition of renin-angiotensin system is important in the treatment of these patients, the increase of this inhibition with the addition of NAC may potentiate the preventive effect of ACEi against atrial fibrillation.

As a result, the beneficial effects of NAC may be explained not only by its direct antioxidant effect but also by a potentiative

synergistic effect on renin–angiotensin system blockade.

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doi:10.1093/eurheartj/ehn446

Online publish-ahead-of-print 2 October 2008

N-acetylcysteine for the prevention of atrial fibrillation: beyond its antioxidant effect: reply

We would like to thank Barrios *et al.* for their kind interest on our manuscript.¹ As they addressed in their letter, we considered that oxidative stress plays a main role in the development of postoperative atrial fibrillation (AF).

As the authors stated, recent trials have suggested that rennin–angiotensin system (RAS) may play a role in the pathophysiology of AF and that inhibition of this system may

protect against AF. Meta-analyses not involving cardiac surgery patients have shown that chronic therapy with RAS blockers is associated with a reduction of new-onset AF. With respect to the postoperative AF, conflicting results have been obtained: although Mathew *et al.*² have found that RAS blockers are associated with low incidence of postoperative AF, however, other two studies were unable to confirm this association.^{3,4}

The authors stated that N-acetylcysteine (NAC) may have a potentiative synergistic effect on RAS blockade. We totally agree with them. This mechanism is shortly discussed on page 630. We appreciate their detailed contribution.

It can be speculated that addition of a sulphhydryl donor such as NAC to the RAS blockers routinely in the future trials may potentiate their effects on postoperative AF.

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doi:10.1093/eurheartj/ehn447

Online publish-ahead-of-print 1 October 2008

High resting heart rate: a cardiovascular risk factor or a marker of risk?

We read with interest the work of Kolloch *et al.*¹ about the relationship between resting heart rate (RHR) and adverse events in patients with hypertension and coronary artery disease from the population of the INternational Verapamil-SR/trandolapril STudy (INVEST study). This study reported that higher baseline and follow-up RHR were associated with increased adverse outcome risks. Taking into account that this study showed that, despite the atenolol-based strategy reduced the RHR more than verapamil-based strategy, adverse events were similar in both groups; the key question is whether this worse prognosis is because the higher RHR is associated with poorer outcomes by itself or because it is related with other cardiovascular risk factors and organ damage and this is what really increases the risk of presenting adverse events. In other words, is high RHR a cardiovascular risk factor or a marker of risk?

Although this study highlighted that some baseline characteristics such as diabetes and heart failure added more risk than RHR, there is still lack of information about this matter. It has been reported that the hypertensive population with coronary heart disease and