The effectiveness and timing of elective pharmacological cardioversion for paroxysmal atrial fibrillation

Paroxysmal atrial fibrillation is undesirable from both prognostic and symptomatic points of view. The burden of symptoms in these patients is often considerable and difficult to alleviate. The optimal strategy for the management of paroxysms in these patients centres around being able to time the cardioverting intervention — be it electrical or pharmacological — so that its risks are outweighed by that of the persisting paroxysm. The thromboembolic risk–benefit equation is considered generally to depend upon the duration of fibrillation so that anticoagulation should be started after 48 to 72 h of continuing fibrillation.

Ideally the timing of the cardioverting intervention should be based upon studies of the natural duration of paroxysms. The duration of an individual paroxysm depends upon the state of the ‘substrate’ — including features such as remodelling and disease-induced pathological changes in the atria — as well as the cessation of focal initiating and maintaining sources; and of course cardioverting interventions. However, the optimal time frame for non-emergency cardioversion is not well defined, largely because of the lack of data relating to the natural history of paroxysms of atrial fibrillation.

In this issue Cotter et al. describe the results of a study in which they randomized two well matched groups of 50 patients with paroxysmal atrial fibrillation to placebo vs 3 g of amiodarone administered intravenously over 24 h. Having excluded patients with a history of atrial fibrillation lasting more than 48 h, they found that nearly 66% of patients reverted to sinus rhythm spontaneously within 24 h, while 92% of those in the amiodarone group reverted during the same time period without experiencing significant adverse effects inspite of the high doses used. A recently published survey similarly found that the longest symptomatic paroxysm lasted less than 24 h in 44% of patients and 60% of paroxysms terminated spontaneously.

Two findings emerged from the analysis of the placebo group. Firstly, 91% of spontaneous conversion to sinus rhythm occurred within 8 h of admission and secondly, that age greater than 70 years, the presence of ischaemic heart disease, hypertension or congestive heart failure and echocardiographic abnormalities of an enlarged left atrium, a reduced left ventricular ejection fraction or significant mitral regurgitation were all significantly associated with failure to convert to sinus rhythm. While we are not provided information on the incidence of spontaneous conversion with both clinical and echocardiographic abnormalities (including various combinations), this may be an additive influence.

The analysis of the amiodarone group provided an interesting comparison, in that the rate of conversion to sinus rhythm matched the placebo group until about 8 h and then diverged before plateauing at about 10 to 11 h after admission or initiation of amiodarone. This indicated that amiodarone takes about 8 h to be effective, perhaps related to both plasma and tissue levels of amiodarone and its active metabolite desethylamiodarone and/or that this is the time window of maximum sensitivity to the action of amiodarone. This window may be related to variations in driving/maintaining factors as mentioned above. Moreover, none of the clinical or echocardiographic variables associated with lower spontaneous conversion rates were found to exert a similar influence in the amiodarone group; instead a diagnosis of ischaemic heart disease and the presence of ST depression resulted in slightly but significantly lower conversion rates. The effectiveness of amiodarone was further buttressed by the achievement of high conversion rates in the cross-over group. Interestingly from a pathophysiological viewpoint, there was a rather high incidence of development of chronic atrial fibrillation in patients resistant to intravenous amiodarone who later underwent electrical cardioversion.

Based upon their findings, the authors advocate the withholding of pharmacologically cardioverting treatment (in non-emergency situations) for 8 h of observation in anticipation of spontaneous conversion, followed by the selection of patients with the clinical and/or echocardiographic variables described above for some form of elective cardioversion — presumably pharmacological. The data in this study do not allow us to conclude that this is in fact a superior strategy, but one that is certainly more effective than placebo, and is safe in the high doses used here. Amiodarone in the context of both ischaemic heart disease as well as left ventricular
dysfunction has certain advantages which weigh in its favour compared to other drugs, and mild bradycardia was the commonest finding in this study.

However, selecting patients with predictors of non-conversion at the outset for administration of intravenous amiodarone, while observing the remaining and administering amiodarone to those still in fibrillation after 8 h may be a more effective strategy. DC cardioversion could then be considered in those resistant to 24 h of intravenous amiodarone at 125 mg/h.

The natural course of paroxysms lasting more than 48 h is, however, undefined and may represent a group with a greater incidence of heart disease as well as lower response rates to pharmacological cardioversions; in such a group (historically identified) as well as those with shorter paroxysms resisting pharmacological cardioversion earlier electrical cardioversion may prevent or reduce electrical remodelling and perhaps the development of persistent atrial fibrillation.

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References

A plea for provisional stenting

See page 1783 for the article to which this Editorial refers

It has been convincingly shown in landmark randomized trials, that primary stenting may reduce the rate of restenosis and major adverse cardiac events in selected patients compared to balloon angioplasty alone[1]. On the other hand it evolved that restenosis after stenting, if it occurs, is more difficult to treat and fraught with a worse prognosis than restenosis after balloon angioplasty. An especially diffuse in-stent restenosis has been termed a 'malignant' disease due to a risk of a restenosis rate of >60% and the lack of appropriate interventional strategies to overcome this problem.

As there is clear evidence from several multivariate analyses, that the degree of residual stenosis after balloon angioplasty is the most important predictor of future restenosis, many cardiologists chose to selectively perform stent implantation in patients with suboptimal results after PTCA. This strategy of 'provisional stenting' for suboptimal PTCA results is currently the most applied indication for stent implantation. A recent assessment of the opinions of European interventional cardiologists revealed that a suboptimal angiographic result, defined as a residual stenosis after PTCA >30%, is considered an indication for stent placement by 55% of the responding interventionalists[2]. There are, however, little data, supporting such a strategy of a selective use of stents in patients with a suboptimal result following balloon angioplasty. Moreover there is no agreement on a definition of this group of patients.

The study of Knight et al.[3] in this issue is the first prospective trial that randomized patients with suboptimal PTCA results to either stent implantation or no further treatment. In only 11% of the 143 patients was an optimal result (defined as a residual stenosis <15%) obtained. In this group of patients no stent implantation was performed. In 35% of their patients stenting was required due to significant dissection (abrupt or threatened closure) or PTCA failure (residual stenosis >50%). The remaining patients with a suboptimal result (residual stenosis ≥15%, <50%) were randomized. Restenosis occurred in 53% of the patients with a suboptimal result (residual stenosis >50%). The remaining patients with a suboptimal result, randomized to PTCA alone, compared to 24% of the patients randomized to stent (P=0.023). The restenosis rate was 14% in patients with an optimal PTCA result and 14% in those who required stent implantation for abrupt or threatened closure.

Subgroup analyses from BENESTENT I and II revealed similar clinical outcomes in stented patients and...