With respect to the other comments, we respectfully disagree:

(i) Lack of risk-adjusted analyses: we believe this was not warranted as there was no imbalance in the baseline characteristics between randomly assigned groups. Another reason for adjusting is to increase the precision with which the treatment effect is estimated, but this is only relevant to normal regression models and not to the Cox model used in this study.[2]

(ii) We used a composite outcome measure including mortality as the primary endpoint, as the compared treatments were expected to impact mortality and major morbidity, resulting in an increased power when compared with mortality alone. As recommended by the ICH harmonized tripartite guideline, the outcomes that contributed to the composite outcome were associated with the primary objective of the trial, and the components of the composite outcome were defined as secondary outcomes and reported alongside the results of the primary analysis in a table. As no difference was observed for any endpoint, adjustment for multiplicity would have not modified the conclusions of the trial.

(iii) Using a secondary endpoint combining the primary endpoint and admission for heart failure has not 'created a shadow of uncertainty' but is a standard procedure in trials ascertaining the benefit of interventions in heart failure. In addition, all admissions were validated by a critical event committee.

(iv) Length of the study: although we agree that, in principle, it would be ideal to have long-term follow-up, 34 months duration as in DECOPI, it is expected to offset any initial risks related to early harm from the procedure.

(v) Absence of coronary angiography beyond 6 months: in our study, all the patients underwent a baseline angiogram and a repeat angiogram at 6 months. We believe that it would be difficult to justify a third coronary angiogram, especially if the trial is powered on clinical outcomes.

(vi) We are thankful to Dr Achrafi for reminding us of the importance of myocardial perfusion as opposed to epicardial coronary revascularization in assessing the outcome of percutaneous coronary intervention in the setting of acute myocardial infarction,[3] but we fail to understand the point of myocardial contrast echocardiography or intracoronary Doppler flow velocity mapping in a clinical outcomes trial.

(vii) Finally, Dr Achrafi recommends substituting left ventricular ejection fraction with other measures which he believes are better correlated to survival, some of which are unfamiliar to us. However, left ventricular ejection fraction remains a simple, clinically meaningful index, highly correlated to long-term outcomes in the post-myocardial infarction setting.

Although we welcome scientific discussion and open criticism, we must also disagree with the concept that DECOPI brought 'more smoke on the horizon'. On the contrary, we believe that the ultimate truth in science is often reached through progressive reduction in uncertainty brought by cumulative evidence from multiple trials.

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doi:10.1093/eurheartj/ehi324
Online publish-ahead-of-print 17 June 2005

Quinidine plus verapamil vs. quinidine alone to prevent recurrences of atrial fibrillation

The excellent PAFAC[1] and SOPAT[2] trials demonstrated that quinidine, in combination with verapamil, is at least equivalent to sotalol in the prevention of recurrences of atrial fibrillation (AF). The combination of verapamil with quinidine in this setting may be beneficial for several reasons. First, verapamil has the ability of suppressing after depolarizations underlying the onset of torsades de pointes, which justifies the low rate of pro-arrhythmic events observed with quinidine during the follow-up period of these trials.[1–3] Secondly, it has been already demonstrated that the addition of verapamil to Class IC or III antiarrhythmic drugs significantly reduces recurrences of AF,[4] an effect that may also occur with quinidine, a Class IA drug. Finally, the concomitant administration of verapamil is also desirable to avoid arrhythmia recurrences with high ventricular rates due to enhanced atrioventricular conduction promoted by the vagolytic effect of quinidine. Despite all these benefits, clinical trials routinely did not use the combination of quinidine with verapamil. Thus, we expected that the PAFAC and the SOPAT trials had explored the clinical effects of this association throughout. These trials clearly presented the efficacy and the pro-arrhythmic complications of antiarrhythmic therapy, but failed in presenting the ventricular rates during recurrences of AF.

Comparing quinidine alone vs. sotalol to prevent arrhythmia recurrences after chemical or electrical cardioversion of AF, we observed that sotalol tended to be associated with more tolerated recurrences when compared with quinidine, which was related to a decrease in ventricular rates during recurrences, from a mean of 98 ± 18 b.p.m. in the baseline recording before conversion to 82 ± 20 b.p.m. during treatment ($P = 0.02$).[5] In the quinidine group, ventricular rates tended to increase during recurrence, from a mean of 102 ± 28 b.p.m. in the initial episode to 113 ± 44 b.p.m. ($P = 0.06$). Another randomized trial comparing quinidine alone vs. sotalol also demonstrated that ventricular rate after relapsing into AF was higher in patients treated with quinidine (109 b.p.m.) when compared with patients treated with sotalol (78 b.p.m., $P < 0.001$).[6] In this study, patients treated with sotalol were also less symptomatic at the time of relapse when compared with relapsing patients in the

quinidine group. Differently from the PAFAC and the SOPAT trials, these previous studies were limited because they did not use transtelephonic electrocardiographic monitoring to detect asymptomatic or short episodes of paroxysmal arrhythmia.

In conclusion, the results of the PAFAC and the SOPAT trials strongly suggest that the combination of quinidine with verapamil is superior to quinidine alone in patients with AF. The theoretical benefits of this combination when compared with quinidine alone to reduce recurrence rate of AF, avoid pro-arrhythmic events, and control ventricular rates during arrhythmia recurrence should be investigated in a randomized trial.

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