LETTERS TO THE EDITOR

doi:10.1093/eurheartj/ehp095
Online publish-ahead-of-print 1 April 2009

Hotline sessions of the 30th European Congress of Cardiology

I read with interest the summary of the hotline sessions of this year's ESC Congress provided by Bergman *et al.*[1] The paper discusses the results of the F.I.R.E. study, which investigated the effect of a new drug, FX06 (fibrin-derived peptide Bβ15-42), for the prevention of ischaemia/reperfusion injury in the setting of acute STEMI, which we presented at hotline III. We think that the conclusion given in the *EHJ* that FX06 failed to significantly reduce reperfusion injury parameters in this STEMI population does not provide a fair judgement to the interesting results obtained in this trial.

There is ample evidence from the literature that even small reductions in permanently damaged myocardium measured acutely after STEMI have the potential to provide sustained benefit for patients.[2] This has been specifically demonstrated for microvascular obstruction by several groups, who found this parameter to by an independent predictor of long-term patient outcome.[3,4] In this context, the reduction of the mass of unrecoverable myocardium by >50% is a very remarkable finding. It should also be noted that both the incidence and extent of microvascular obstructions trended lower in FX06-treated patients, even though the difference did not reach statistical significance. Interestingly, there were also trends in favour of FX06 in cardiac events, including cardiac death and new onset heart failure, which are encouraging and warrant further investigation in larger trials.

We would also like to put the apparent lack of difference to placebo in scar mass measured at 4 months into perspective. Patients were followed for 4 months primarily for safety reasons, looking for cardiac death and MACE. It is important to take into account that most MACE as a sequel of the index infarction occur early after PCI, so the acute size of the infarct has very strong relevance for patient outcome. For instance, in the recently published APEX-AMI trial, the combined event rate of cardiac death, CHF, and shock was 9.1% at 30 days, and increased only marginally to 10.2% at 90 days.[5] Second CMR imaging at 4 months was done in the F.I.R.E. trial to assess whether FX06 treatment had an effect on scar formation; however, it was unlikely that a significant effect would be demonstrated, since this was just a single bolus treatment and we did not control for confounding effects and medication during the follow-up period. Scar mass was indeed numerically, but not significantly, lower at the 4 month time point compared with placebo. The study design did not allow for any evaluation of infarct expansion or shrinkage with respect to necrotic core size at 5 days and scar size at 4 months. More importantly, 15% of patients (FX06 14, placebo 16) did not return for repeat CMR at 4 months. This included, of course, patients who died from cardiac cause, five in the placebo group and only two in the FX06 group; this unequal loss to follow up leads to a distortion because patients who died could be considered of having large infarctions. The follow-up data are further distorted by the likelihood that more large infarcts were followed up in the FX06-treated group. Analysis of only patients with paired CMR images (completers) showed no difference in infarct size relative to LV mass in patients treated with FX06 at Day 5 and 4 months, whereas shrinkage by approximately 50% was observed in the placebo group. However, analysis of completers only introduces another selection bias. It is possible that the infarcts of patients treated with FX06 were already so small that there was not much apparent shrinkage during remodelling (unlike under placebo). Remodelling with scar shrinkage is actually an ominous sign that may lead to wall thinning, so the lack of shrinkage in the FX06 patients may be seen as beneficial.

In summary, we would like to emphasize that the F.I.R.E. study as an exploratory trial provided a very consistent set of data suggesting a cardioprotective role of FX06 achieved by a reduction of ischaemia/reperfusion injury. The full study results have just been published.[6]

Funding

Funding to pay the Open Access publication charges for this article was provided by Prof. Dan Atar.

References

1. Bergman H, Rolink AM, Verheugt FWA. Hotline sessions of the 30th European Congress of Cardiology. *Eur Heart J* 2008;**29**:3061–3064.
2. Wu E, Ortiz JT, Tejedor P, Lee DC, Bucciarelli-Ducci C, Kansal P, Carr JC, Holly TA, Lloyd-Jones D, Klocke FJ, Bonow RO. Infarct size by contrast enhanced cardiac magnetic resonance is a stronger predictor of outcomes than left ventricular ejection fraction or end-systolic volume index: prospective cohort study. *Heart* 2008;**94**:730–736.
3. Wu KC, Zerhouni EA, Judd RM, Lugo-Olivieri CH, Barouch LA, Schulman SP, Blumenthal RS, Lima JA. Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. *Circulation* 1998;**97**:765–772.
4. Bruder O, Breuckmann F, Jensen C, Jochims M, Naber CK, Barkhausen J, Eibel R, Sabin GV. Prognostic impact of contrast enhanced CMR early after acute ST segment elevation infarction (STEMI) in a regional STEMI network. *Herz* 2008;**33**:136–142.
5. Apex AMI Investigators, Armstrong PW, Granger CB, Adams PX, Hamm C, Holmes D Jr, O'Neill WW, Todaro TG, Vahanian A, Van de Werf F. Pexelizumab for acute ST-elevation myocardial infarction in patients undergoing primary percutaneous coronary intervention: a randomized controlled trial. *J Am Med Assoc* 2007;**297**:43–51.
6. Atar D, Petzelbauer P, Schwitter J, Huber K, Rensing B, Kasprzak JD, Butter C, Grip L, Hansen PR, Süselbeck T, Clemmensen PM, Marin-Galiano M, Geudelin B, Buser PT; F.I.R.E. Investigators. Effect of intravenous FX06 as an adjunct to primary percutaneous coronary intervention for acute ST-segment elevation myocardial infarction results of the F.I.R.E. (Efficacy of FX06 in the Prevention of Myocardial Reperfusion Injury) trial. *J Am Coll Cardiol* 2009;**53**:720–729.

Dan Atar
Division of Cardiology
Aker University Hospital and Faculty of Medicine
University of Oslo
Norway
Tel: +47 23 033 125
Fax: +47 22 894 721
Email: dan.atar@online.no