aggressive cholesterol lowering might be expected to slow progression and thus reduce events in the angioplasty group.

Sir Ronald Fisher chose 0.05 as the boundary for statistical significance based on nothing more than mathematical convenience. This boundary was adjusted downward to 0.045 in AVER T because of interim analyses that were done for safety purposes. Although the $P$ value of 0.048 is slightly above this, the odds that a real difference exists between the two treatment groups are still approximately 19 of 20. The time to event analysis yielded a $P=0.03$. More importantly, the absolute difference in event rates between the two groups, 8%, is large for a cardiovascular trial with only 18 months of follow-up, and yields a ‘number needed to treat’ of 12.5.

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About EMIP-FR and reperfusion damage in AMI: a comment to the comment

Trimetazidine has been in use as an antianginal drug for many years, but its mechanism of action has been elucidated only recently. Trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain-3-ketoacyl coenzyme A thiolase. The cardioprotective action of trimetazidine has been attributed to this metabolic shift. The distinctive characteristics of trimetazidine, when prescribed to angina patients, are the absence of haemodynamic effects, its minimal toxicity, and its cardioprotective action.

Even before the mechanism of action of trimetazidine was fully understood, a possible benefit from the addition of this drug to the therapeutic regimen of AMI has been hypothesised, because TMZ has been shown to reduce oxidative stress in vivo and in vitro and to reduce reperfusion injury in man during PTCA and CABG.

The EMIP-FR project

Based on these observations and on the assumption that a burst of free radicals lowers the effectiveness of thrombolytic therapy in reducing mortality following acute myocardial infarction, a randomized, multicentre trial (EMIP-FR) was undertaken to test the hypothesis that trimetazidine might reduce mortality due to reperfusion injury in patients with acute myocardial infarction. Nineteen thousand, seven hundred and twenty-five patients, treated within 24 h of symptom onset, were randomized to trimetazidine or placebo.

The results of this trial were published in a September issue of the European Heart Journal. Overall, there was no significant reduction in mortality as a consequence of trimetazidine administration. So EMIP-FR has to be added to the long list of studies where agents that prevent reperfusion damage in animal models, fail to confirm their efficacy when tested in humans.

Methodological limitations and pitfalls of the EMIP-FR project

In the discussion section of the paper, the Investigators propose various hypotheses to explain the negative results of the trial, including inappropriate dosing of trimetazidine, wrong site of delivery, and/or bad timing of administration of the agent. Actually, in animal models several agents have been shown to prevent reperfusion damage if delivered intracoronarily and/or administered before reperfusion. The same agents become ineffective when given intravenously at or after reperfusion. The explanation for this apparent inconsistency may be simple. The very presence of the coronary occlusion prevents agents administered intravenously from reaching the area at risk. As the burst of oxygen free radicals occurs within 2–3 min after vessel reopening, agents intended to prevent their deleterious effects must be present in the area in advance. When an agent is injected intravenously in adjunct to a thrombolysis, there are two possibilities: either the infarct-related vessel is still occluded, in which case the agent goes everywhere except where it is needed, or the infarct-related vessel is already reopened, in which case the agent reaches its target too late to prevent reperfusion damage.

In addition to these points, there are other factors that may have contributed to the negative results of the EMIP-FR project. Reperfusion damage, to be clinically relevant and to contribute to mortality, must be additive to ischaemic damage. For this to be the case, the infarct-related vessel must be recanalized before the necrotic process is completed and the wave of necrosis has reached the epicardial surface of the heart. It is self-evident that only myocardium still viable at the end of the ischaemic period can lose viability as a consequence of reperfusion. If the entire myocardium at risk has already been irreversibly damaged, no additional damage can be caused by reperfusion, hence no benefit can be expected by its prevention.

In experimental animals the time course of cell necrosis following coronary artery ligation has been described in detail. In man, these time intervals are less defined and could be longer than in animal models due to pre-existing collaterals, to preconditioning or to intermittent occlusions. However, the few clinical trials that have specifically looked at the effect of time delays on myocardial salvage, have concluded that time to reperfusion up to 2 h is important for survival and recovery of left ventricular function. After 2 h, recovery of function is modest and survival is relatively independent of reperfusion.

In EMIP-FR, patients where admitted up to 24 h after symptom onset, as a consequence, the majority of them were treated too late for any sizable amount of myocardium to be still viable.

EMIP-FR was a pioneer study, designed more than ten years ago, when time course and pathogenetic mechanisms of ischaemia-reperfusion injury were incompletely understood. So, we have to admit that site of drug delivery and time of administration rendered the study negative, regardless of the agent chosen.

Clinical relevance of reperfusion damage

Surprisingly enough, in the Editorial comment to this study, only two hypotheses were considered: (1) inactivity of the drug and (2) absence of clinical relevance of the reperfusion injury. Only to conclude that reperfusion injury has no clinical relevance and to proclaim the official closure of this chapter.

Unfortunately, unbiased observation of acute coronary syndrome patients has rendered clinical and interventional cardiologists too familiar with reperfusion injury to prematurely close the discussion of this complex topic.

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with the no-reflow phenomenon, with myocardial stunning, with hibernating myocardium, in a word with the classical markers of ischaemia–reperfusion injury [11]. We have learnt, much to our disappointment, that vessel recanalization by pharmacological and/or mechanical interventions does not necessarily result in effective myocardial reperfusion or left ventricular functional recovery. We have also learnt that impaired myocardial perfusion, despite successful coronary artery recanalization, is consistently associated with a negative prognosis [12,13].

The need to protect cells and tissue from ischaemia–reperfusion injury in order to maximize the beneficial effects of early coronary recanalization was emphasized by Braunwald and Kloner more than 15 years ago, and has been the subject of numerous research since then [14].

In this time span, clinical and experimental evidence has accumulated, further emphasizing the clinical relevance of reperfusion damage as well as the need for effective therapeutic interventions. Flow restoration is clearly perceived today as a necessary but insufficient step in the prevention of left ventricular dysfunction in patients suffering an acute myocardial infarction [15].

The multiplicity of mechanisms involved in ischaemia–reperfusion injury encourages a multifactorial approach to management. Targets for treatment include, among others, the mismatch between glucose oxidation and anaerobic glycolysis, oxygen free radicals, the inflammation process, microvascular integrity, and purinergic receptors. Large clinical trials on cell protection are ongoing with inhibitors of the sodium-potassium exchange (NHE), with antiselectins and antiintegrins, with the antiIC5 component of the complement system, and with adenosine receptors agonists. Contemporary to the report on the EMIP-FR project, other papers with more encouraging results have been published. Marzilli et al. addressed the problem of prevention of no-reflow and reperfusion damage in acute myocardial infarction and demonstrated that the addition of adenosine to primary PTCA improves myocardial perfusion; obviates left ventricular remodelling and reduces major adverse cardiac events [17]. Mahaffey et al., adding adenosine to thrombolytic therapy obtained a significant reduction in infarct size [18]. Karila-Cohen et al. have confirmed the protective effect of pre-infarction angina in acute myocardial infarction and have demonstrated a convincing relationship between preservation of microvascular integrity and recovery of left ventricular function [19]. Ruppel et al., administered cariporide, a NHE inhibitor, before reperfusion and observed improved left ventricular function [20].

Conclusions

Left ventricular function remains the major determinant of prognosis in coronary artery disease. Restoration of flow has attracted most research and clinical efforts in the last decade. Cell protection by metabolic preservation is now perceived as the new challenge for acute patient management in several settings including coronary care units, the catheterization laboratory, and the operating room. Negative results of pioneer projects should not discourage pursuit of these objectives. Conversely, unbiased evaluation of the study protocols can be useful in identifying methodological errors to be avoided in future attempts.

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Trimetazidine and reperfusion injury

We have read with interest the editorial comment[1] on the final report of the study EMIP-FR[2]. We completely agree with Dr Tognoni on the importance of publishing the results of negative clinical studies. We also agree on the need to be extremely cautious in deriving wishful conclusions on the potential positive effects based on ’a posteriori’ subset analysis, although we think that the possibility of performing such new studies cannot be rejected ’a priori’.

Considerable investigations provide a sound mechanistic explanation for the selective beneficial effect of trimetazidine in patients with acute myocardial infarction not receiving thrombolytic therapy the feasibility and potential benefits of new clinical studies to test this hypothesis should be considered and weighed against the risk and costs. However, we disagree with Tognoni’s extrapolations and statements regarding the clinical relevance of reperfusion injury. While the clinical importance of reperfusion injury may be debated, it is simply a matter of logic that the negative results of a particular intervention against a particular hypothetical mechanism of reperfusion injury do not exclude the existence of the phenomenon, its clinical relevance, or the possibility of its prevention by other therapeutic interventions. This is more so because ischaemia–reperfusion leads to extremely complex and imperfectly understood biochemical derangements that can eventually lead to cell death by necrosis or apoptosis[3–5]. Among them oxygen free radicals, the mechanism hypothetically targeted by trimetazidine in the EMIP Project, could be of lesser importance[3]. The evidence that antiradical treatments may limit necrosis after transient coronary occlusion is weak and highly controversial. On the contrary, there is increasingly solid evidence that interventions set up to interfere with other pathomechanisms of cell death, like alterations of cellular cation homeostasis leading to excessive contractile activation and hypercontracture, can effectively limit myocardial cell death when applied at the time of reperfusion[3,6]. The main contribution of the EMIP Project to the issue of the clinical relevance of reperfusion injury could remind us that the era during which reperfusion injury was synonymous with oxygen free radical injury is well over.

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The EMIP-FR Study: the evolution of scientific background as a non-controlled parameter

The results of the large scale collaborative study EMIP-FR were published in issue 18, vol. 21 of the European Heart Journal[1] together with an Editorial discussing the results in the light of the rationale of the study[2]. However, as viewed by a basic scientist not involved in clinical concerns, an important angle of this debate remained unexplored in these two papers. The clinical trial included nearly 20 000 patients in the acute phase of myocardial infarction to investigate the effect of trimetazidine with and without interventional thrombolysis. The rationale for this study was based on numerous pharmacological data suggesting the efficiency of trimetazidine in reducing the effects of oxidative stress, both in vivo and in vitro, which would confer to the molecule a beneficial effect in reperfusion injury. On this basis, the study was clearly built to demonstrate a positive effect of short-term trimetazidine treatment (48 h) in the thrombolysed stratum, considered as a prompt to reperfusion injury, and no effect of the drug in the non-thrombolysed stratum. The results of the study pointed out, as outlined in the editorial, that trimetazidine ‘does not provide any clinical advantage over placebo in patients exposed to the risk of reperfusion injury’[2]. Conversely, the authors of the EMIP-FR study reported a significant beneficial effect of the drug in the non-thrombolysed stratum. The editorial points out that the results contradict the trial hypothesis, and suggests that the claim for the use of trimetazidine (or any molecule with the same pharmacological rationale) in non-thrombolysed patients cannot be justified from this trial[2]. The editorial concludes that the EMIP-FR trial addresses the question of the clinical relevance of reperfusion injury.

Large scale trials like EMIP-FR involving 20 000 patients, 393 centres in 15 countries, hundreds of investigators, and a huge amount of money need several years from the conception of the rationale to the publication of the results. During this time, the research continues and, from a pharmacological point of view, it appears necessary to revisit the EMIP-FR story to follow the progress of this concept during the 1993–2000 period, running from decision to publication of the EMIP-FR project.

The data that served as a basis for the EMIP-FR study, reported a positive effect of trimetazidine in oxidative stress in vitro. Since no free-radical scavenger property could be demonstrated, the mechanism was considered either able to correct the situation promptly to generate free radicals, or as a protective effect against the free radicals’ deleterious effects.