End of story? Studies on prevention of reperfusion injury encounter perpetual defeats

Dan Atar and Stefan Agewall

Department of Cardiology, Oslo University Hospital Ullevål, and Faculty of Medicine, University of Oslo, Norway

In the current issue of the journal, Karlsson et al. present a feasibility study in patients with ST-elevation myocardial infarction (STEMI) examining the catalytic antioxidant mangafodipir as a potentially cardioprotective pharmacological adjunct therapy to primary PCI.1 Admittedly, this is a very small study with inherent problems, such as a significant imbalance between the two study arms in important baseline characteristics. One of them is pain-to-balloon time, a factor that has a decisive impact on infarct size. Although not powered for a robust primary endpoint difference, all outcome measures including biomarkers, ST-resolution on the ECG, and contrast-enhanced cardiac MRI parameters turned out negative.

Is this a surprising finding to the cardiovascular community? Not at all. In fact, this study goes in line with many failed phase II and III trials in this area—to an extend that one of the prominent researchers in the field has coined the term ‘the graveyard of myocardial protection trials’ (C. Granger, personal communication).

With a track record of so many disappointments, how can one explain the persistent drive for therapeutic testing in human beings as reflected by, for example the EU-FP7 call of 2010,2 and publications in highly reputable journals on this theme3,4

First, there may be an inherent publication bias when it comes to the reporting of studies in animal models of prevention of reperfusion injury. It is highly unlikely that negative animal studies have had the same chance for publication as their positive counterparts in the recent years.

On the other hand, cardiology journal editors have adopted a laudable policy of intentionally reporting negative studies in humans, viewing these negative results as important contributions to the understanding of the field. This may very well include high-ranked journals such as the JACC or the EHJ.5,6 The discrepancy between the conceivable under-reporting of negative animal model research and at the same time the reporting of negative human studies may in part be a stimulus for yet new clinical research attempts.

An important aspect to consider is the fact that animal models never entirely reflect the patho-physiology of the human situation. Indeed, to put a silastic snare around a coronary artery in situ in an open-chest rat model does not lead to the same mechanistic alterations that are encountered in the ruptured plaque in STEMI patients.

Some researchers may argue that these animal models are good enough, since the focus of prevention of reperfusion injury resides at the level of the myocardium, not the coronary arteries, and within the myocardium, the effects of an occluded coronary artery are universal, irrespective of the mode of occlusion.

This view, however, should now be challenged. We have accumulated much knowledge about the inflammatory and immunological aspects of coronary atherosclerosis, culminating in the mentioned plaque rupture, and the myocardium located immediately downstream these intracoronary events can hardly be unaffected of these alterations. Indeed, we know that inflammatory cellular and molecular mechanisms also play a pivotal role in the cardiomyocytes and their surrounding milieu.

Hence, a part of the explanation for the recurrent disappointments that nevertheless lead to new attempts of human testing may lie in the fact that, in this particular research area, the results from animal studies simply cannot be translated into humans.

Finally, given the incredible achievements of modern STEMI logistics, with ambulance transfer systems that take the patients seamlessly right into the cardiac catheter laboratory in many contemporary healthcare systems, we must realize that there is not much left to save. Left ventricular ejection fraction in first-time STEMI patients is often no longer seriously compromised, in fact it may be close to normal whenever successful recanalization is achieved in an expedite manner.

Taken together, research into prevention of reperfusion injury should take a time-out for a moment and let clinical scientists take a deep breath. Perhaps we have reached a point of ‘end of story’, i.e. it may be time to question the entire concept of reperfusion injury in humans, since what we predominantly see in today’s clinical practice is reperfusion benefit, not injury.

References

