Why does pre-clinical success in cardioprotection fail at the bedside?

Isabella Tritto and Giuseppe Ambrosio*

Division of Cardiology, Department of Medicine, University of Perugia, Perugia, Italy

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This editorial refers to ‘Translational failure of anti-inflammatory compounds for myocardial infarction: a meta-analysis of large animal models’ by G.P.J. van Hout et al., pp. 240–248.

Translating findings from experimental studies into effective treatments for patients is never an easy task. Hurdles are particularly high when one tries to reproduce at the bedside the positive effects of cardioprotective interventions obtained in animal models of ischaemia/reperfusion injury. Despite the wealth of successful cardioprotective interventions in animals, none of the subsequent clinical trials has yet fulfilled this goal or changed clinical practice. Some small ‘proof-of-concept’ clinical studies have shown encouraging results, only to be negated later by larger trials.1

Controversy and frustration are evident in the reviews2,3 and position papers4–6 that have been written on this topic; however, these documents have done little to allay doubts. One possible explanation for the difficulty in translating pre-clinical findings into clinically useful therapies may have to do with the design of experimental studies. Van Hout et al.7 address this matter by undertaking a meta-analysis of the experimental studies, i.e. by carrying out a systematic review of the available evidence as it is typically done in the clinical settings. By using this approach, they point out some potential weaknesses of animal studies and highlight possible limitations and biases. Their meta-analysis focuses on ‘anti-inflammatory’ interventions, based on the widely accepted theory that (at least in animal models) post-ischaemic reperfusion injury is mostly driven by a local inflammatory reaction and leucocyte activation. They report that treatment with various anti-inflammatory drugs is influenced by the size (or the species) of animals in which it has been tested, being mostly effective in large animal models of myocardial infarction (MI). Timing of outcome assessment, gender, and internal and external quality controls were also significantly associated with the outcome. These factors may explain, at least in part, the translational failure of these interventions, and indicate that due consideration to design of the study should be given when planning a pre-clinical study of cardioprotection.

Thus, the paper by Van Hout et al.7 is a welcome reminder that, before moving into the clinical arena, we should carefully assess whether the experimental data available are sufficiently convincing and solid to allow a reasonable possibility of success in patients. A pre-defined study protocol together with careful data collection and analyses (e.g. in terms of animal number, choice of experimental model, blinded evaluation of data, adequate statistical analysis) and publication of negative results would guarantee a more robust experimental framework upon which clinical trials can be based.

A second possible explanation for the failure of experimental intervention to translate into clinical benefit, which adds to the technical problems described above, is that patients with acute MI may differ from animal models of infarction in many different ways, besides obvious considerations related to species difference. In particular, while investigators painstakingly try to obtain a reproducible site of coronary occlusion (and, hence, size of ischaemic territory) in animals, this is obviously impossible to replicate in patients, in whom the site of occlusion, degree of collateral flow, and possible presence of additional coronary artery stenosis at other sites are widely variable. A similar limitation applies to duration of ischaemia, which is kept strictly constant in animal experiments, while it largely fluctuates among patients. Germane to this consideration is the possibility that short episodes of ischaemia preceding MI may already lead to ischaemic preconditioning in large subsets of patients, thereby leaving little room for further improvement. Moreover, while experiments are typically performed in healthy young animals, most patients with acute coronary syndromes are middle-age/elderly and present with a wide range of comorbidities (e.g. diabetes, hypertension, hyperlipidemia, kidney failure), which may affect the myocardial cardioprotective response.8 – 10 Such patients would already be under chronic treatment with drugs, such as statins, ACE inhibitors, beta-blockers, antiplatelets, that are endowed with putative cardioprotective effects,9,10 which in turn may mask any beneficial action of the agent under investigation.

Finally, another mechanism through which concomitant therapies may affect the ability to effectively investigate cardioprotection in patients has again to do with preconditioning. Glitazolamide, a common anti-diabetic drug, blocks the K+-ATP channel signalling pathway of preconditioning,8 while other drugs given to MI patients may pharmacologically mimic preconditioning (nitroglycerin,11 ACE inhibitors,8,12 opioids,8,12 adenosine-enhancing agents such as ticagrelor13). All these variables concur to make patients recruited in clinical trials very different from experimental models used in pre-clinical studies. A third
explanation has to do with the design and implementation of clinical trials. Timing of administration, choice of dose, appropriate patient selection, sample size are all factors that may impact on the trial outcome. The most recent case in point is LATITUDE-TIMI60, a trial evaluating Losmapimod, a p38MAP-kinase inhibitor, in 3503 patients with acute coronary syndrome, which was prematurely stopped after an interim futility analysis excluded a measurable beneficial effect of Losmapimod on the primary endpoint (cardiovascular death, reinfarction, recurrent ischaemia requiring urgent coronary artery revascularization).

Consequently, the second phase of the trial, which would have included over 20 000 patients, was cancelled ([https://www.gsk.com/en-gb/media/press-releases/2015/gsk-provides-update-on-latitude-timi-60-lomapimod-cardiovascular-study/]], 8 January 2016, date last accessed). As LATITUDE-TIMI60 showed a non-significant 30–50% reduction in the composite endpoint in the subset of STEMI patients, it is tempting to speculate that the trial might have had a different outcome if conducted in patients with STEMI who are more likely to benefit because of their greater ischemic injury), and/or if it would have enrolled a higher number of patients, as originally planned.

Where do we go next? A position paper by the ESC Working Group ‘Cellular Biology of the Heart’, aimed at improving pre-clinical assessment of cardioprotective therapies called for multicentric randomized animal studies, as it is done in the context of clinical trials, to obtain more robust data. A move towards that direction is the birth of the NIH-CAESAR (Consortium for preclinical assessment of cardioprotective therapies), a US network of laboratories with expertise in MI models that aims to improve translation of experimental results into clinical care. At the same time, it would seem wise to move away from the ‘cleanest’ possible experimental model, and start investigating new therapies under conditions that are more akin to the common clinical scenario (e.g. in animals who also have diabetes, hypertension, or are being treated with drugs that are commonly used in patients).

In summary, to increase translation of experimental data into clinical practice, we should be mindful that, just like any other treatment, cardioprotective interventions need to be administered ‘at the right dose, to the right patient, at the right time’ using an unbiased and robust experimental design. Any other approach would befit the old joke that ‘a drug is a compound that when injected in a mouse produces a publication’, but would rarely result in benefit to patients.

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References


