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EDITORIAL

Cardioprotection—Time to Take Into Account Clinical Complexity: The Case of Antiplatelet Agents

Editorial to "Two Classes of Anti-Platelet Drugs Reduce Anatomical Infarct Size in Monkey Hearts" by Xi-Ming Yang et al.

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Acute myocardial infarction (AMI) is a leading cause of heart failure and premature death worldwide [1]. Immediate medical treatment is required and includes antiplatelet agents such as aspirin or thienopyridines [2]. Rapid reperfusion to limit myocardial damage is also strongly recommended [2,3]. However, reperfusion has the potential to initiate additional lethal injury, known as "ischemia-reperfusion (IR) injury" and could result in increased cardiomyocyte death [4]. New therapeutic strategies that directly target the reperfusion-mediated damage have been proven to reduce infarct size in experimental animal models. These approaches include 1) ischemic postconditioning [5] (which has been shown to be effective in animals even when the postconditioning stimulus is delayed [6]); 2) pharmacological postconditioning with cyclosporine [7] or other molecules such as erythropoietin (EPO) (unpublished information); and 3) genetic perturbation in animal models of critical proapoptotic pathways involved in reperfusion injury [8,9]. Some of these new approaches have been shown to improve ventricular remodeling and clinical outcomes after AMI [10–13].

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It is difficult to dissect the molecular mechanisms mediating the beneficial effects of these promising approaches because of several confounding factors (see Fig. 1). Antiplatelet agents could be among the most powerful cardioprotective drugs. Yang *et al.* now provide one of the first basic studies shedding light on the role of anti-platelet agents in cardioprotection. Recently, the same authors described their initial findings in a rabbit model (in press) [14], providing mechanistic insights into the action of these anti-platelet agents. Based on the rabbit model, they proposed that the cardioprotective effects of these anti-platelet agents are not mediated by a reduction of microvascular obstruction.

In this issue of Cardiovascular Drugs and Therapy, they confirmed and report for the first time similar results in a primate model, providing convincing evidence of the cardioprotective benefits provided by antiplatelet agents following MI [15]. This is an important finding as most studies in clinical settings are hampered by the systematic use of these agents. The authors demonstrate, in a rarely used IR monkey model, a cardioprotective effect of two different classes of antiplatelet therapies: cangrelor, a powerful P2Y12 receptor inhibitor and a novel murine antibody against the collagen receptor glycoprotein VI (OM2). The antibody against the collagen receptor glycoprotein VI reacts only with the primate protein. Although the primate model has technical limitations (for example, it is difficult to dissect the molecular mechanisms mediating these beneficial effects) it also provides a reliable model for clinical translation. Both drugs provided efficient cardioprotective effects with a reduction of the infarct size/area at risk ratio between 23 % and 41 %. This benefit is most likely mediated through the effect of the drugs on platelets, which could limit IR injury. The drugs could prevent platelet activation [16] and release of deleterious cytokines, which otherwise could have enhanced inflammation [17] or activated other cell types including

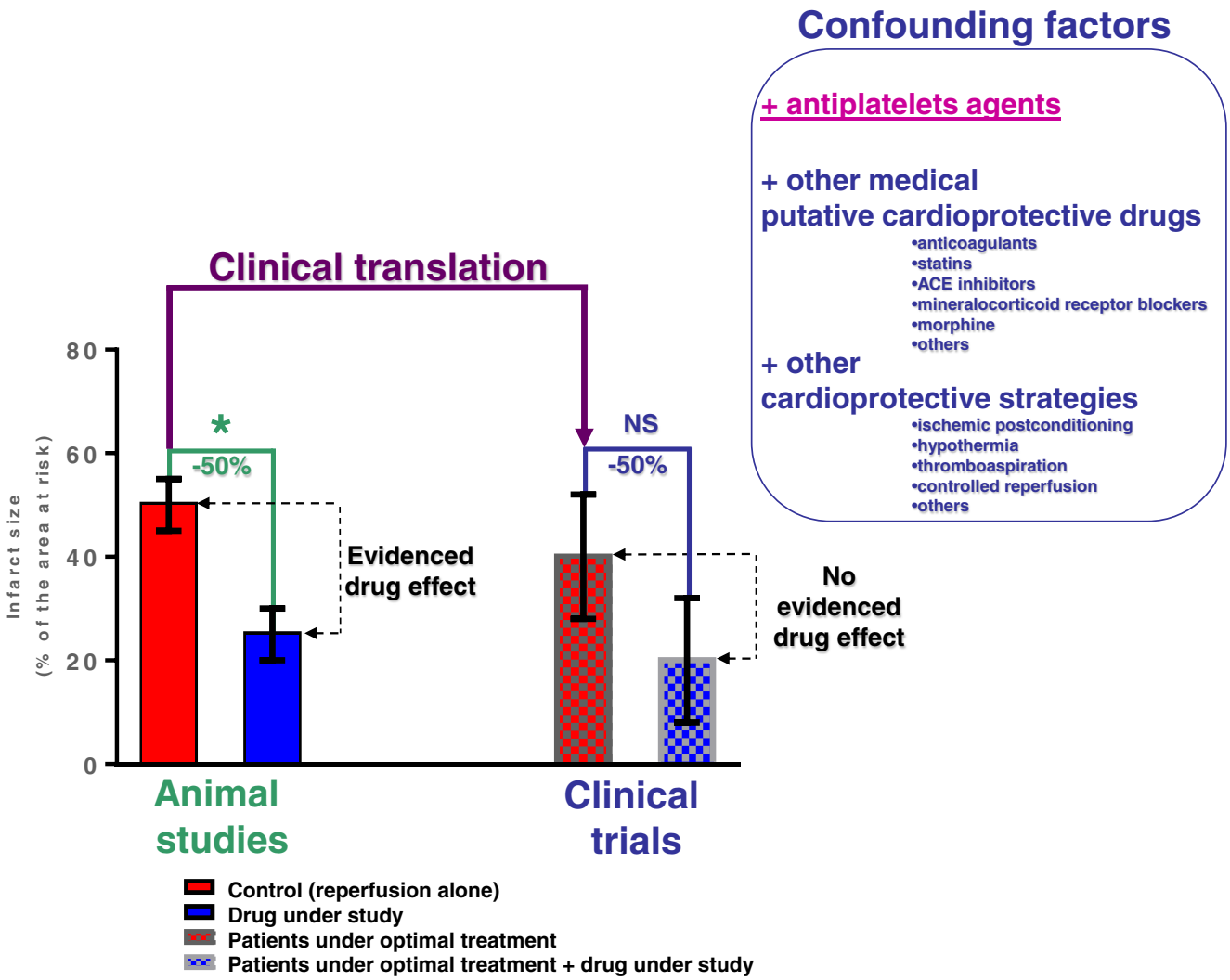

Fig. 1 Impact of cardioprotective drugs such as anti-platelet agents unheeded in the design of a clinical trial on cardioprotection, based on previous data. In animal studies on cardioprotection, infarct size (IS) after reperfusion is about 50 % of the area at risk (AAR), depending on the experimental model (*left* panel). Many efficient cardioprotective strategies such as preconditioning, ischemic postconditioning, pharmacological postconditioning with morphine, erythropoietin (EPO), cyclosporine or others result in IS decreases of up to 50 %. The small variability of the effect (S.E.M is shown) combined with the large baseline AAR, large therapeutic effect, and high reproducibility contribute to the demonstration of the drug effect. By contrast, in clinical settings (*right* panel), baseline IS is reduced because of endogenous cardioprotective phenomena, mainly collateral flow, as well as exogenous ones mainly other efficient unavoidable cardioprotective agents such as statins, some anti-hypertensive agents, and morphine. Antithrombotic and antiplatelet agents are the cornerstone of reperfusion with or without primary coronary intervention. Their impact could hamper the demonstration of a statistically significant effect on IS of a beneficial drug under study. Besides, clinical heterogeneity because of varying ages, comorbidities, concomitant treatments, and patient management can compound this problem and increase variability. *: The difference is statistically significant. NS: The difference is not statistically significant, although the relative risk reduction (50 %) is the same. ACE inhibitors: angiotensin-converting-enzyme inhibitors

leukocytes [18], endothelial cells [19] or microparticles [20]. Interestingly, the OM2 antibody offered a promising therapeutic window with an efficient anti-platelet effect and a smaller bleeding risk, when compared to cangrelor.

Despite these important findings, there are certain limitations to the model. First, a wide variability in area at risk was noted in this primate model; in contrast, this variability is not as pronounced in mouse, rat or rabbit models. This could reflect technical difficulties, such as variability of the level of artery occlusion, and/or variability among animals. Importantly, this observation could highlight the large variability, which is also observed in clinical settings, of ischemia duration (another important cause of clinical heterogeneity), received drugs and other clinical parameters. As noted above, it is difficult to study the mechanistic pathways in a primate model, a limitation which weakens the authors' conclusions. Finally, although outside the scope of the paper, it would have been of interest to compare a powerful cardioprotective strategy such as ischemic postconditioning to ischemic postconditioning complemented with antiplatelet agents to further

support the notion of protection offered by antiplatelet strategies alone.

Taken together, the important findings by Yang *et al.* and various experimental and clinical data support a cardioprotective role of anti-platelet agents following MI. Importantly, the mechanisms of such a cardioprotective effect of antiplatelet agents, if confirmed, remain to be better understood and may provide an explanation for the large beneficial effects observed in clinical trials. With regards to clinical settings, three recent controlled, randomized, proof-of-concept studies aimed at determining whether ischemic postconditioning could limit infarct size in patients with STEMI, were retrospectively analyzed and underlined the cardioprotective effect of the antiplatelet agent clopidogrel [21]. In 88 patients, ischemic postconditioning and the anti-platelet agent clopidogrel (300–600 mg before primary coronary intervention) were the only two additive therapeutic independent predictors of final infarct size determined by cardiac enzyme release. The cardioprotective effect was here explained by the reduction of IR injury.

Finally, all the putative cardioprotective drugs should be evaluated for their actual impact during myocardial infarction, particularly when several drugs of the same class are available, to guide our choices and treatment recommendations.

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