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Status of $P2Y_{12}$ treatment must be considered in evaluation of myocardial ischaemia/reperfusion injury

We noted with interest the recent publication by the ESC Working Group on pre-clinical assessment of novel cardioprotective therapies.[1] Because of the nearly three decades of experimental work which has not yet yielded a single intervention that has been demonstrated to diminish the amount of infarcting myocardium following ischaemia/reperfusion in patients, it is necessary to critically examine the available data to determine where there might be roadblocks. Lecour *et al.* have analysed many possible confounders that might be responsible for the failure to extrapolate observations in the animal laboratory to the cardiac catheterization suite. They are to be congratulated for this succinct summary. However, we are disappointed that they have overlooked a particularly compelling explanation for the failures. Patients with acute myocardial infarction are treated with numerous pharmacological agents before the actual percutaneous coronary intervention that will open the coronary artery. One of these agents is clopidogrel, a platelet $P2Y_{12}$ receptor antagonist, which for the past decade has been administered to all patients according to published guidelines. We have shown that it and other $P2Y_{12}$ antagonists have cardioprotective properties which are independent of their anti-thrombotic actions.[2–6] We suspect that this anti-infarct effect may well be responsible for their resounding clinical success. We suggest that any other intervention applied in such patients which uses a similar mechanism of protection as the administered $P2Y_{12}$ antagonist will not provide additional protection. Indeed, neither ischaemic pre-[2] nor post-conditioning[6] caused any additional protection in our animal models treated with a maximally protective dose of a $P2Y_{12}$ inhibitor. Only an intervention that uses a different mechanism of protection can be expected to provide incremental protection. We all agree that additional protection is needed for these patients and that the search for cardioprotective interventions must continue. However, we submit $P2Y_{12}$ inhibitors constitute an important confounder in the clinical studies, and strongly suggest that testing of future candidates for cardioprotection be examined in animal models also treated with a $P2Y_{12}$ agent[6] before submitting the new intervention to costly clinical trials.

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Platelet inhibitors influence cardioprotection: importance in preclinical study design: reply

We would like to thank Professors Cohen and Downey for highlighting platelet inhibitors, in particular platelet P2Y12 receptor antagonists, as an important confounder to take into consideration in pre-clinical studies designed to study novel cardioprotective strategies against ischaemia/reperfusion injury. As already mentioned in our recent publication from the ESC working group, both clinical and animal studies give evidence that platelet inhibitors reduce myocardial infarct size by mechanisms that may involve nitric oxide or adenosine.[1–3] Over the past few years, Cohen and Downey have published strong and convincing evidence suggesting that additional protection cannot be afforded with pharmacological and/or mechanical protective strategies sharing the same pro-survival signalling pathways as the P2Y12 antagonist (see review[3]). Therefore, we fully share their point of view that the effect of co-medication with P2Y12 antagonists or with any other medications frequently given to ischaemic heart disease patients (e.g. aspirin, statins, ACE inhibitors, beta-blockers, etc.)[1] on cardioprotective therapies needs to be tested in preclinical settings prior to translation to clinical cardioprotection as also recently reviewed in detail by Ferdinandy *et al.*[4]

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