Combination therapy to target reperfusion injury following ST-segment elevation myocardial infarction: A more effective approach to cardioprotection

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Timely reperfusion therapy by primary percutaneous coronary intervention (PPCI) combined with effective secondary preventative therapy, have contributed to a decline in mortality rates following ST-segment elevation myocardial infarction (STEMI) over the last few years. However, the incidence and severity of heart failure following STEMI is rising. As such, novel cardioprotective therapies are required to reduce myocardial infarct (MI) size and preserve left ventricular (LV) systolic function, in order to prevent heart failure and improve clinical outcomes following PPCI[1,2].

Over recent years, a large number of cardioprotective therapies, which have been demonstrated to be effective at reducing MI size in the laboratory setting, have been unable to either reduce MI size or improve clinical outcomes following STEMI. The reasons for this are manifold, and have been discussed extensively in the recent literature[1-3]. In summary, the failure to translate cardioprotection for patient benefit has been attributed to several key factors: the inadequacy of the animal models used for testing novel cardioprotective therapies in the laboratory setting; a failure to demonstrate consistent and robust cardioprotection in experimental studies before proceeding to clinical studies; and poorly designed clinical cardioprotection studies[1-3].

Another major reason for the failure to translate cardioprotection, may have been due to the adoption of a single-targeted mono-therapy approach, a strategy which may be inadequate to address the multi-faceted components of myocardial reperfusion injury – these include endothelial dysfunction, microvascular obstruction, oxidative stress, calcium overload, mitochondrial dysfunction, and inflammation[2,4]. In order to address this issue, an emerging concept in the cardioprotection field has been to adopt a multi-targeted strategy

using two or more therapies in combination to reduce MI size following STEMI[1,2,5-7]. The adoption of combination therapy as a multi-targeted cardioprotective strategy may be mediated as follows: (1) using two or more therapies to target different cardioprotective intracellular signaling pathways within the cardiomyocyte[5,7]; (2) using two or more therapies to target cardioprotection in different cell components within the heart such as endothelial cells, platelets, cardiomyocytes, and inflammatory cells; and (3) using one therapy with capabilities of reducing MI size through two or more cardioprotective targets such as inflammatory cells and cardiomyocytes.

In this regard, the NACIAM study by Pasupathy et al[8], in this issue of *Circulation,* investigated the MI-limiting effects of combining 2 'old' cardioprotective therapies, N-acetylcysteine (NAC, anti-oxidant) and Nitroglycerin (NTG, a nitric oxide donor)[9], in STEMI patients treated by PPCI. In a multi-center study of 112 STEMI patients, they found that the administration of a 48-hour intravenous (IV) infusion of NAC, initiated prior to PPCI, on a background of a low dose 48-hour IV NTG infusion, reduced acute MI size by over 30% in a subset of 75 patients (quantified by late gadolinium enhancement cardiovascular magnetic resonance, CMR). Importantly, the MI-limiting effect of NAC was still present at 3 months post-PPCI, with a 50% reduction in chronic MI size when compared to placebo, suggesting a long-term cardioprotective effect with this therapeutic approach.

Interestingly the concept of combining NTG and NAC was first tested nearly 30 years ago in unstable angina patients, and was shown to reduce the incidence of acute myocardial infarction and was based on the premise that NAC may augment the anti-platelet and vasodilatory effects of NTG, although

significant hypotension resulted from this combination[10]. However, the combination had not been tested on MI size in STEMI patients, and importantly, the combination of NAC and NTG did not cause symptomatic hypotension in the NACIAM trial[8].

Previous experience with anti-oxidant therapies to target myocardial reperfusion injury have been largely disappointing with NAC failing to reduce MI size in experimental studies[11] and trimetazidine having no beneficial effects following STEMI[12]. The failure of anti-oxidant therapy as a cardioprotective strategy has been attributed to the inability to effectively scavenge reactive oxygen species, especially at the level of mitochondria. As such, the use of a relatively high dose of NAC (29g over 48 hours) in the NACIAM trial, may, in part, have overcome this limitation of anti-oxidant therapy.

The authors are to be congratulated for demonstrating a cardioprotective effect with the anti-oxidant, NAC, in STEMI patients on a background of low-dose NTG. However, there are several issues to be discussed concerning the trial design of the NACIAM trial. First, is the lack of factorial design for testing the cardioprotective effects of NAC and NTG, separately, and in combination – this would have allowed the authors to ascertain whether the combination of NAC and NTG is more effective at reducing MI size in STEMI patients, when compared to either agent given alone. Given that it is not routine clinical practice to give low-dose IV NTG for 48 hours to reperfused STEMI patients, it is not clear why this was adopted as background therapy for the NACIAM trial. The factorial design would have also provided additional information on whether IV NTG *per se* can limit MI size in the STEMI setting. Nitric oxide (NO) is a well-known mediator of cardioprotection, and NO donors have been shown to limit

MI size in experimental animal models. However, the use of intracoronary nitrite[13] and inhaled nitric oxide (NOMI trial NCT01398384) as adjuvants to PPCI, have all failed to reduce MI size following STEMI, although this may relate to patient selection (post-hoc subgroup analysis showed benefit in STEMI patients presenting with an occluded coronary artery)[13], and prior administration of sublingual nitrates (NOMI trial NCT01398384).

Secondly, the wide range of timing of the initial CMR scan in the NACIAM trial of 3 to 7 days post-PPCI, may have impacted on detection of the edema-based area-at-risk (AAR), microvascular obstruction, and MI size, given that recent data have suggested that these CMR variables are dynamic in nature over the first week following PPCI[14]. Under ideal circumstances the acute CMR scan should be performed between 3 to 5 days following STEMI, when these variables are at their peak[15], However, it is appreciated that timing the initial CMR scan to particular days can be logistically challenging in the first few days following STEMI. Moreover, the use of different CMR vendors (Philip and Siemens) within the NACIAM trial, may also have impacted on the quantification of the AAR by T2-weighted CMR and MI size by CMR.

Finally, the authors demonstrated impressive reductions in MI size (30-50%) with NAC treatment on the initial and follow-up CMR scans, and yet, there were no beneficial effects on post-MI left ventricular (LV) remodeling with no change in either LV dimensions or ejection fraction at 3 months. The reason for the discrepancy, is unclear, and further studies are required to investigate the impact of NAC treatment on parameters of post-MI LV remodeling, and whether it can improve clinical outcomes following STEMI.

In summary, the NACIAM study by Pasupathy et al[8], marks a step in the right direction for the field of cardioprotection, as it highlights the therapeutic potential of combining two different cardioprotective therapies to reduce MI size following STEMI. However, further studies are required to elucidate the individual contributions of NAC and NTG to the cardioprotective effects observed in the NACIAM study, and to also investigate the effects of NAC on post-MI LV remodeling and clinical outcomes following PPCI.

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