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COMMENTARY

New Drug Avenues for Cardioprotection in Patients with Acute Myocardial Infarction

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Acute myocardial infarction (AMI) is a leading cause of heart failure and premature death worldwide [1]. Both immediate medical treatment and rapid reperfusion to limit myocardial damage are 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 cardiac cell death [4]. New therapeutic strategies that directly target the reperfusion-mediated damage have been proved to reduce infarct size (IS) in experimental animal models. These approaches include (1) ischemic postconditioning [5, 6] and even remote postconditioning [7]; (2) pharmacological postconditioning including cyclosporine A [8] or normalization of intracellular calcium homeostasis [9, 10]; and (3) genetic perturbation in animal models of critical proapoptotic pathways involved in reperfusion injury [11, 12]. These new approaches have been shown to improve ventricular remodeling and clinical outcomes after AMI [13–17].

IR lesions are partly mediated and worsened by oxidative stress [18]. One of the most known anti-oxidative agents is *N*-acetylcysteine (NAC), but results in clinical translation have been most often disappointing as regards cardiovascular disease [19] as well as nephrology [20]. Nevertheless, NAC is currently under study in various fields of medical research, as briefly presented in the Table 1, noticeably in psychiatry disorders. This venerable drug had been already proposed as an interesting candidate for cardioprotection for decades [21–24], but controversial results have been obtained.

In this issue of the Journal, Talasaz et al. [25] once again address the efficacy of NAC to control post-MI remodeling. They suggest that NAC could improve the myocardial remodeling following AMI in a proof-of-concept clinical trial. In this prospective, double-blinded, randomized clinical trial, 98 patients were allocated to placebo or NAC at the dose of 600 mg orally twice daily during three days upon hospital arrival. The authors showed that serum levels of metalloproteinase (MMP)-9 and MMP-2 after 72 h and major adverse cardiac events including re-infarction during the 1-year follow-up were significantly lower in the treated group than in the placebo group. However, several limitations have to be underlined, and this proof-of-concept trial has to be confirmed in larger trials. Among the limitations, mainly biochemical and baseline echographic parameters have been considered, so it is difficult to conclude on echocardiographic evolution, IS (whether this was accurately measured) or specific clinical outcomes. Reperfusion is not always obtained (only 40 % of the patients received primary coronary intervention), collateral flow or area at risk are not taken into consideration, and, importantly, the sample is small. Whether the design of the study, especially the timing (as soon as possible to treat the IR lesions), the route (would intravenous/intracoronary route, if safe, be more efficient?), and the very drug under study, including

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Table 1 Incomplete trials evaluating *N*-acetylcysteine that are currently registered on the clinicaltrials.gov registry

Field	Pathology	Country	Number of patients; detail on the design	Number in clinicaltrials.gov
Nephrology	Angiographic procedures in high-risk patients	USA	8,680	NCT01467466
	Contrast nephropathy	Iran	549	NCT01820195
		Israel	80	NCT01564303
	Diabetic nephropathy	USA	110	NCT01265563
	Sickle cell nephropathy	Jamaica	30	NCT01891292
Airways	COPD	USA	65	NCT01599884
			65	NCT01639963
	Bronchiolitis obliterans after allergenic hematopoietic cell transplantation	Korea	20	NCT01327625
	Sarcoidosis	USA	20	NCT01587001
Blood diseases	Thrombotic thrombocytopenic purpura	USA	3	NCT01808521
	Sickle cell disease	The Netherlands	140	NCT01849016
		USA	5	NCT01800526
Cancer	Breast cancer	USA	35	NCT01878695
Cardiovascular	Hypertrophic cardiomyopathy	USA	75; NAC 600-mg capsule or matching placebo, 1 twice daily for 90 days, then increase to NAC 1,200 mg or matching placebo, 2 capsules twice daily for 270 days	NCT01537926
	Patients undergoing PCI	Turkey	400; 30 mg/kg/15 min IV bolus preprocedural and 50 mg/kg/8 h IV infusion during and after the procedure	NCT01878669
	Acute STEMI	Turkey	300; 30 mg/kg/15 min IV bolus preprocedural and 50 mg/kg/8 h IV infusion during and after the procedure	NCT01878344
Brain	Cannabis withdrawal	France	150	NCT01439828
		USA	300	NCT01675661
	Alcoholism	USA	150	NCT01214083
	Cocaine abusers	USA	15	NCT01392092
	Schizophrenia	USA	24	NCT01885338
		USA	60	NCT01339858
		Switzerland	33	NCT01354132
	Treatment-resistant obsessive-compulsive disorder; obsessive compulsive disorders in children	Brazil	40	NCT01555970
		USA	40	NCT01172275
	Bipolar disorder	USA	160	NCT01797575
	Tourette syndrome	USA	40	NCT01172288
	Self-arm in adolescents	USA	20	NCT01111734
	Post-traumatic stress disorder	South Korea	96	NCT01664260
	Parkinson disease	USA	60	NCT01470027
Others	Chronic pain	USA	40	NCT01840345
	Bacterial infection due to *H. pylori*	Taiwan	120	NCT01572597

COPD chronic obstructive pulmonary disease, *IV* intravenous, *NAC* *N*-acetylcysteine, *PCI* percutaneous coronary intervention, *STEMI* ST-segment elevation myocardial infarction

the dose (dose-effect? high dosage?), the formulation, or even the chemical modifications [26] could be improved remains to be explored.

Beyond oxidative stress, several drugs have been recently evaluated in the clinic (recent reviews are available, see, for instance, [27–30]) or are presently under

Table 2 Ongoing clinical trials evaluating pharmacological conditioning

Drug group/class	Drug	Country	Number of patients	Trial details	ClinicalTrials.gov identifier
RAAS	Canrenoate	UK	150	1st dose (day 0) given IV (potassium-canrenoate), before primary PCI; day 1–12 weeks: oral spironolactone 25 mg/day, uptitrated to 50 mg/day after 2 weeks, if possible	NCT01882179
	Spironolactone	France	1,600	Canrenoate 200 mg IV followed by oral spironolactone 25 mg/day for 6 months	NCT01059136
β-Blockers	Metoprolol	Spain	221	IV	NCT01311700
Growth factor	Erythropoietin			See a recent review on the topic [31]	
Vasodilators	Sodium nitrite, NO				NCT01388504
					NCT01584453
					NCT01398384
Metabolism	Exenatide (GLP-1 agonist)	Czech Republic	38	CABG	NCT01373216
	Metformin	The Netherlands	380	Improvement of LVEF and IS	NCT01217307
	Rosuvastatin	South Korea	180		NCT01153334
	Mecasermin (recombinant IGF-1)	Ireland	45	Intracoronary administration of IGF-1	NCT01438086
Antioxidant	Melatonin	Denmark	40		NCT01172171
		Spain	272		NCT00640094
	Vitamin C	Italy	80		NCT01090895
Immunomodulation	Tocilizumab (IL-6 antagonist)	Norway	120	NSTEMI, primary outcome is inflammation	NCT01491074
	POL6326 (CXCR4 antagonist)	Europe	140		NCT01905475
	Everolimus	Switzerland	150		NCT01529554
	Ciclosporine A	Italy	444	Primary outcome: ST-segment resolution	NCT01650662
		France	100	STEMI + cardiogenic shock	NCT01901471
		France	972	Clinical composite outcomes	NCT01502774
	Methotrexate	Brazil	80		NCT01741558
Other	Ranolazine	USA	200		NCT01767987
	MTP-131 (Bendavia™, a mitochondria-targeting peptide)	International	200	Primary outcome: IS (enzymatic method)	NCT01572909
	Sevoflurane	Canada	50		NCT00971607
	RGN-352 (thymosin β4, an actin sequestering protein)	USA	75	Currently suspended	NCT01311518

CABG coronary artery bypass graft surgery, *GLP* glucagon-like peptide, *IGF* insulin-like growth factor, *IL* interleukin, *IS* infarct size, *IV* intravenous, *LVEF* left ventricular ejection fraction, *NSTEMI* Non-STEMI, *PCI* percutaneous coronary intervention, *STEMI* ST-segment elevation myocardial infarction

study in the cardioprotection field, as briefly presented in the Table 2. Detailed descriptions of included trials can be accessed from the clinicaltrials.gov site. The focus of the trials included in Table 2 is on reduction of IS. Despite our efforts to present an exhaustive list, trials that could not be identified by the keywords used here (e.g., cardioprotection, myocardial infarction) would have been missed.

The largest trials currently underway are evaluating the interest of cyclosporine A (a well-known immunomodulator) (see Table 2). All the drugs presented in Table 2 aim at

one or several specific targets involved in IR lesions. Antiplatelet effect or correction of microcirculation, cooling, controlled reperfusion, and blood pressure control represent other powerful cardioprotective strategies described elsewhere. Some distinct families are schematically depicted in Table 2: inflammation, metabolism, immunomodulation, vasodilators, etc. Obviously, there are numerous cross-talk and redundant pathways. For instance, although cyclosporine A is mainly used as an immunomodulator, its putative interest as regards cardioprotection is its impact on the mitochondrial permeability transition pore (mPTP). Research is particularly intense on molecules targeting metabolism and immune response, as well as on anti-inflammatory agents, as depicted in Table 2. Some of these studies precisely target the IR lesions, whereas others target cardiac remodeling more specifically (e.g., spironolactone) or other phenomena, depending on the design of the study.

Whether NAC or other pharmacological agents can deliver on their promise is currently being investigated in clinical trials. This is a highly active field, both in basic research and in clinical translation. A combination of various strategies could also be considered in the future: optimal medical treatment including ACE inhibitors, high-dose statins, mineralocorticoid receptor antagonists, antiplatelet agents, pharmacological/remote/post-conditioning, but also cooling or other physical stimuli. Furthermore, the ideal timing is difficult to determine, as are the ideal patients. Treatments and/or comorbidities could affect the efficiency of treatment modalities. Combining inexpensive and relatively nontoxic drugs such as NAC could then be an interesting option in the future.

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