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Review

A critical review on the translational journey of cardioprotective therapies!

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ABSTRACT

The failure to translate novel cardioprotective therapies tested in pre-clinical studies into the clinical setting for patient benefit can be attributed to a number of factors at different stages of the research process. This review focuses on the evidences and the gaps with regard to the translational journey of cardioprotective interventions. Gaps are classified into 3 main groups: 1) those related to pre-clinical studies, 2) those associated with the validation of infarct size as a good surrogate and 3) those based on design and interpretation of randomized clinical trials on cardioprotection. Addressing these gaps might increase the chances to successfully translate cardioprotective therapies into improving both post-STEMI heart failure and cardiovascular death rates.

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"Success consists of going from failure to failure without the loss of enthusiasm"
Winston Churchill

1. Introduction

Acute myocardial infarction presenting as ST-segment elevation (STEMI) is the result of abrupt occlusion of an epicardial coronary artery, usually due to a sudden rupture of an atherosclerotic plaque. Early reperfusion by primary percutaneous coronary intervention (PPCI) limits myocardial infarct size (IS) and changes the fate of the myocardium at risk [1]. However, the process of restoring blood flow to the ischemic myocardium induces additional myocardial damage, known as "myocardial ischemia–reperfusion injury (IRI)" [2], that negatively impacts on IS and on mortality rates.

In 1971, Braunwald et al. proposed that the extent and severity of tissue damage after coronary occlusion could be modified by therapeutic manipulations applied during ischemia [3]. This work was the starting signal for several studies testing therapies designed to limit myocardial IS, also known as cardioprotective therapies. Although cardiovascular research in the 1970s was dominated by interventions aimed at limiting IS by pharmacotherapy in the absence of reperfusion (pre-thrombolytic era), the concept of cardioprotection eventually evolved to include therapies designed to limit myocardial injury during ischemia and reperfusion [4].

Cardioprotective therapies might be applied in a wide spectrum of patients [2]. Nevertheless, this review focuses on those presenting with a STEMI treated by PPCI. Many interventions limiting myocardial IRI and reducing IS in experimental animal studies have been tested in this setting. Promising results in a number of "proof of concept" studies have been obtained with regard to their myocardial infarct-sparing effect, however a few disappointing results have also been raised in terms of clinical outcome benefit (Table 1).

The failure to translate novel cardioprotective therapies discovered in pre-clinical studies into the clinical setting for patient benefit can be attributed to a number of factors at different stages of the research process. This review summarizes the evidences and the gaps with regard to the translational journey on cardioprotection. The aim is to note deficiencies and encourage improvements in the translation of cardioprotective therapies, classifying the gaps into 3 main groups: 1) those related to pre-clinical studies, 2) those associated with the validation of IS as a good surrogate, and 3) those based on design and interpretation of randomized clinical trials (RCTs) on cardioprotection, including all the uncontrolled factors in the clinical setting.

2. The pre-clinical gap

Most of our knowledge about acute myocardial infarction (AMI) is derived from pre-clinical studies, although experimental animal models are used as approximations of human pathophysiology and it is fair to acknowledge that they present many limitations.

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[1] Both authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Table 1
The translational journey of some specific cardioprotective therapies in STEMI patients.

Therapeutic intervention	Pre-clinical knowledge	Surrogate outcome studies	Clinical outcome results	Potential reasons for neutral results in the clinical setting
Nicorandil	Nicorandil given just before IRI reduced IS in a dog model [85] *Main mechanism*: *combination of ATP-sensitive potassium channel opener and nitrate preparation*	J-WIND-KTP trial [86] tested the administration of nicorandil started after reperfusion, demonstrating no difference in myocardial IS measured using biomarkers or 6 month LVEF	No data	– Not only anterior STEMI – Treatment started after reperfusion
Glucose–insulin–potassium	GIK slows the progression of IRI in many experimental settings [87] *Main mechanism*: *promotion of glucose metabolism*	IMMEDIATE trial [34] demonstrated a reduction in myocardial IS with no difference in progression to myocardial infarction	CREATE-ECLA [88] showed no differences in mortality at 30 days	– IV GIK infusion for 24 h started after reperfusion in the majority of cases – Not only anterior STEMI – Prior TIMI flow grade not used as selection criteria
Atrial natriuretic peptide	ANP given just prior to reperfusion reduced IS in rabbit hearts [89] *Main mechanism*: *ANP targets prosurvival kinase pathways such as the cGMP and RISK pathways*	J-WIND-ANP: Intravenous carperitide (an ANP analogue) starting prior PPCI reduced IS measured by biomarker release and showed a slight increase in LVEF [86]	No data	– Further studies are needed to determine whether carperitide has an impact in clinical outcomes
Adenosine	Prior to index ischemia, adenosine reduces IS in animal models of acute IRI [90]. Whether it can also be effective when administered at the time of reperfusion is less clear. *Main mechanism*: *nitric oxide and protein kinase G*	AMISTAD study reported reductions in IS with high-dose intravenous administration [91], whilst PROMISE study [92] failed to show reproduce the results using lower doses of intracoronary adenosine	No data	– Doses and route of administration (intravenous vs. intracoronary)
IPOST	IPOST has demonstrated to be capable of reduce both myocardial IS and coronary microvascular obstruction [93] *Main mechanism*: *delayed reversal of acidosis and activation of pro-survival cascades*	Significant reduction in biomarkers release, increase in LVEF and reduction in myocardial IS by SPECT [94,95]	DANAMI 3-iPOST has failed to demonstrate clinical benefit using a composite endpoint of all-cause mortality and hospitalization for congestive heart failure[a]	– Risk of coronary microembolization – Potential influence of concomitant co-morbidities and co-treatment on the ischemic conditioning response
RIC	Consistent evidence among diverse models and species that RIC confers cytoprotection against IRI [96] *Main mechanism*: *neural and/or humoral signalling*	Increase in the myocardial salvage index at 30 days when applied in the ambulance [33]	CONDI2/ERIC-PPCI study [97] is expected to recruit 4300 patients (NCT01857414)	
Cyclosporin	Cyclosporin has demonstrated to reduce IS in many studies, with some contentious results [19] *Main mechanism*: *inhibition of MPTP opening*	Significant reduction in 72 h AUC, increase in LVEF and reduction in myocardial IS by CMR [98], although very recently the CYCLE study [99] failed to demonstrate enzymatic IS reduction and ST-segment resolution	CIRCUS trial [40] failed to improved clinical outcomes at 1 year in anterior STEMI patients	– Total ischemic times were relatively prolonged (4.5 h) – Dose and route of administration
Exenatide	Exenatide has resulted cardioprotective in both small and large animal models [100,101] *Main mechanism*: *GLP-1 analogy, NO/cGMP signalling pathway*	Increase in the myocardial salvage index at 90 days by CMR [102]	No data	– Further studies are needed to determine whether exenatide has an impact in clinical outcomes
Metoprolol	Metoprolol reduced myocardial IS and preserve LV systolic function in a swine model [103] *Main mechanism*: *unknown, although it seems to extend beyond their effect on hemodynamics and oxygen consumption*	METOCARD-CNIC trial [31] administered in the ambulance reduced IS and preserved LV systolic function EARLY BAMI trial [32] has recently reported that early intravenous metoprolol before PPCI was not associated with a reduction in infarct size in a non-restricted STEMI population	Move On! Trial [104] plans to investigate the effect of metoprolol on mortality and heart failure hospitalization	– The largest trial has been performed in all AMI locations, whilst the positive effects had been shown in anterior infarcts – The timing of drug administration might be of major importance, as a substudy reveals that the sooner metoprolol is administered in the course of infarction, the smaller is the infarct and the higher the LVEF [36]
Hypothermia	Hypothermia can reduce IS either starting before ischemia, during ischemia or immediately at reperfusion [105] *Main mechanism*: *energy preservation* (*reduction of metabolic demands*)	CHILL-MI trial [106] failed to demonstrated an overall IS reduction using hypothermia, although patients with an anterior STEMI presenting within 4 h benefited from the therapy	No data	– The main limitation to translate the therapy is the technology: further devices capable of inducing hypothermia at a faster rate are needed
TRO40303	Reduction of myocardial IS when administered at time of reperfusion in small-animal model [107], although failing in a large-animal model [108] *Main mechanism*: *inhibition of MPTP opening by attenuating ROS production*	MITOCARE study [109] failed to show IS reduction and increased myocardial salvage, using biomarkers and CMR respectively	No data	– Not enough pre-clinical evidence – Formulation and dosage of TRO40303 used in the clinical setting differed from pre-clinical studies – Difference between groups in TIMI-flow of culprit artery after PCI (12.1% in the TRO40303-group vs 6.3% in the placebo-group)

Acronyms: AMISTAD (The Acute Myocardial Infarction STudy of ADenosine); CHILL-MI (AMI: Rapid Endovascular Catheter Core Cooling Combined With Cold Saline as an Adjunct to Percutaneous Coronary Intervention for the Treatment of Acute Myocardial Infarction); CIRCUS (Cyclosporine to ImpRove Clinical oUtcome in ST-elevation myocardial infarction patients); CREATE-ECLA (Clinical Trial of MEtabolic Modulation in Acute Myocardial Infarction Treatment Evaluation-Estudios Cardiologicos Latinoamerica); CYCLE (CYCLosporinE A in Reperfused Acute Myocardial Infarction); DANAMI 3-iPOST (Third DANish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction: Ischemic Postconditioning During Primary PCI); EARLY-BAMI (Early-Beta-blocker Administration before primary PCI in patients with ST-elevation Myocardial Infarction); IMMEDIATE (Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency Care); K-WIND-ANP (Japan-Working groups of acute myocardial infarction for the reduction of Necrotic Damage by ANP); K-WIND-KTP (Japan-Working groups of acute myocardial infarction for the reduction of NecroticDamage by a K-ATP channel opener); METOCARD-CNIC (Effect of METOprolol in CARDioproteCtioN During an Acute Myocardial InfarCtion); MITOCARE (Multicenter, randomized, double-blind, placebo controlled study to assess safety and efficacy of TRO40303 for reduction of reperfusion injury in STEMI patients undergoing primary PCI); MOVE ON! (Impact of Pre-Reperfusion Metoprolol on Clinical Events After Myocardial Infarction); PROMISE (protection with adenosine during primary PCI in patients with STEMI).
Abbreviations: ANP, atrial natriuretic peptide; GIK, glucose–insulin–potassium; IS, infarct size; IPOST, ischemic postconditioning; IRI, ischemia/reperfusion injury; LVEF, left ventricular ejection fraction; MPTP, mitochondrial permeability transition pore; PPCI, primary percutaneous coronary intervention; RIC, remote ischemic conditioning; ROS, reactive oxygen species; SPECT, single photon emission computed tomography; STEMI, ST-segment elevation myocardial infarction.
[a] Presented by Dr. Thomas Engstrøm at the American College of Cardiology Annual Scientific Session, Chicago, IL, April 3, 2016.

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