Translating cardioprotection for patient benefit:

The EU-CARDIOPROTECTION COST Action

[1]Derek J Hausenloy, MD, FACC and [2]Gerd Heusch, MD, FACC

[1] The Hatter Cardiovascular Institute, Institute of Cardiovascular Science, University College London, UK; Cardiovascular and Metabolic Disorders Program, Duke-National University of Singapore, Singapore
[2] Institute for Pathophysiology, West German Heart and Vascular Centre, University of Essen Medical School, Essen, Germany

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Corresponding author:

Prof. Dr.med. Dr.hc. Gerd Heusch, FACC, FESC, FRCP
Institute for Pathophysiology,
West German Heart and Vascular Center,
University of Essen Medical School,
Hufelandstrasse 55,
Essen, Germany 45122.
E-mail: Gerd.Heusch@uk-essen.de.

Acute myocardial infarction and the subsequent development of heart failure are among the leading causes of death and disability globally. The most effective treatment for limiting infarct size and preventing subsequent heart failure is timely interventional or surgical reperfusion but even then, mortality and morbidity remain significant. Accordingly, new treatments are required but the translation of adjunct cardioprotection to clinical practice has been largely disappointing so far. Reasons for such poor translation and novel strategies are addressed in the ongoing European Union (EU)-CARDIOPROTECTION Cooperation in Science and Technology (COST) Action (CA16225).

The EU COST has run since 1971 and supports trans-national cooperation across Europe. It provides 4 years' funding for the creation of research networks (COST Actions) and funds workshops, conferences, training schools, short-term scientific missions, and dissemination activities. COST Actions offer a multi-disciplinary platform for collaboration among scientists across Europe (and beyond) and facilitate advancements in research and innovation. The EU-CARDIOPROTECTION COST Action comprises a research network of 32 European Union countries, whose overall research objective is to improve the translation of cardioprotection from the experimental setting to the clinical arena (www.cost.eu/actions/CA16225). It is organized into 4 Working Groups with specific research aims (see **Fig. 1**).

Working Group 1 - NEW TARGETS

COST Action aims to identify novel signaling pathways and therapeutic targets of cardioprotection both within and outside the cardiomyocyte. There is a series of articles in a Cardiovascular Research Spotlight Issue 'Cardioprotection beyond the cardiomyocyte', which highlight non-cardiomyocyte targets, such as the coronary circulation (1), immune cells (2), innate immunity (3), circulating hematopoietic cells

and extracellular vesicles (4), and the cardiac innervation (5). A special issue in International Journal of Molecular Sciences 'Novel molecular targets for cardioprotection' will showcase novel signaling pathways and therapeutic targets for cardioprotection. Whereas many experimental studies rely on a reductionist strategy focused on a single signaling pathway or target, the working group aims to use innovative unbiased multi-omics strategies and network bioinformatics analyses to identify new signaling pathways and targets for cardioprotection.

Working Group 2 - COMBINATION THERAPY

Most experimental cardioprotection studies have been directed to one particular signaling pathway or target. However, acute myocardial infarction is a complex phenomenon which involves not only cardiomyocytes, but also coronary microvasculature, nerves, immune and circulating blood cells, and extracellular vesicles. Working group 2 aims to identify multi-target therapies directed to multiple signaling pathways and end-effectors both within and outside the cardiomyocyte that can be used in combination to achieve additive and/or synergistic cardioprotective effects. A roadmap for synergistic multi-target therapies as a more effective strategy for translating cardioprotection to patient benefit has just been published in JACC (6).

Working Group 3 – CONFOUNDERS

Experimental studies mostly use healthy and young animal models with acute coronary ligation, whereas most patients suffering myocardial infarction are middle-aged or elderly, have co-morbidities (such as diabetes, hyperlipidemia, hypertension), and are on multiple medications all of which may impact on the efficacy of cardioprotection. Working group 3 aims to identify key co-morbidities and co-medications which impact on cardioprotection and the mechanisms underlying their interference.

Working Group 4 - CONSORTIUM

Most cardioprotective therapies which have failed in the clinical setting did not provide robust cardioprotection in the experimental setting. This lack of robustness is attributed to methodological limitation such as lack of randomization, non-blinded treatment allocation and data analysis, failure to standardize acute myocardial ischemia and reperfusion protocols, and lack of rigor in statistical analysis. Working group 4 has provided a detailed cook-book of practical guidelines to improve rigor and reproducibility of experimental and clinical cardioprotection studies (7). Eventually, a European Cardioprotection Consortium (ECC) for multi-center experimental testing of novel cardioprotective therapies in a randomized controlled and blinded manner, using clinically relevant small/large animal AMI models will be set up, in part following the NIH-sponsored CAESAR network.

COST Action networking activities (see **Fig. 1**):

- **Scientific Meetings:** Bi-annual Scientific Meetings have been held in Brussels, Vienna, Santorini, and Kragujevac to provide a forum for COST members and others to disseminate and share knowledge pertinent to cardioprotection. Leading researchers from Europe and worldwide have been invited to provide their expert input.
- **Training Schools:** Training schools are organized on topics relevant to cardioprotection research, such as multi-omics strategies and choice of clinically relevant animal models with co-morbidities and co-medications. In 2019, COST Action will participate in the European Society of Cardiology Council of Basic Cardiovascular Science Summer School by organizing sessions relevant to cardioprotection.

- **Short-Term Scientific Missions:** COST Action has so far funded 20 early career investigators to learn new research techniques and gain valuable knowledge and research experience in other European partner laboratories.
- **Communication and Dissemination Activities:** COST Action communicates its activities through its website www.cardioprotection.eu. Working groups have published original articles, reviews and position papers. COST Action has sponsored joint scientific sessions relevant to cardioprotection at the International Society of Heart Research-European Section annual scientific meeting.
- **Conference Grants:** These grants enable PhD students and early career investigators from less research-intensive European partner countries to attend international conferences to present their research.

In summary, COST Action has put in place a pan-European research network of leading experts and young investigators in cardioprotection to develop new strategies for finding innovative and more effective approaches to cardioprotection, so as to improve their translation for patient benefit.

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Figure 1: Overview of the EU-CARDIOPROTECTION COST Action CA16225 organization and activities.

The COST Action Management Committee (comprising 32 EU countries) oversees the EU-CARDIOPROTECTION COST Action CA16225 Program. The COST Action utilizes the COST Action Networking and Collaborative Activities to achieve the research objectives of the four Working Groups (WGs). Figure modified from (3).