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Themed Issue: Risk factors, comorbidities, and comedications in cardioprotection

EDITORIAL

Risk factors, co-morbidities, and co-medications in cardioprotection: Importance for translation

On behalf of the EU-CARDIOPROTECTION COST Action (CA16225 – www.cardioprotection.eu), in this Themed Issue "Risk factors, co-morbidities, and co-medications in cardioprotection," we provide an up-to-date account on the influence of cardiovascular risk factors on cardioprotection. In particular, the Themed Issue focusses on co-morbidities and their co-medications on acute myocardial ischemia/reperfusion injury, cardioprotection, and their importance in the development of new cardioprotective therapies from preclinical to clinical studies.

Since the original observations in the mid-nineties showing that hypercholesterolaemia attenuated the effect of preconditioning in rabbits (Szilvassy et al., 1995) and rats (Ferdinandy et al., 1997), it has become evident that the cardioprotective signalling is markedly affected by risk factors such as aging, sex and environmental factors, as well as by co-morbidities and their medications (Ferdinandy, Schulz, & Baxter, 2007; Ferdinandy, Hausenloy, Heusch, Baxter, & Schulz, 2014; Ruiz-Meana et al., 2020; Perrino et al., 2020; Figure 1) and that there are large numbers of non-responders to cardioprotective stimuli (Schreckenberg et al., 2020). Moreover, in spite of a number of preclinical studies showing robust cardioprotection by a variety of cardioprotective interventions, their clinical translation is still lacking, as shown by the number of large clinical trials with neutral outcome for efficacy of these cardioprotective interventions (Davidson et al., 2019; Ferdinandy et al., 2014; Hausenloy et al., 2017).

Accordingly, in this Themed Issue, Kleinbongard, Bøtker, Ovize, Hausenloy, and Heusch (2020) critically reviewed the fact that translation of cardioprotection from robust experimental evidence to beneficial clinical outcome for patients has been largely disappointing. They analysed the evidence for confounders of cardioprotection in patients with acute myocardial infarction and in patients undergoing cardiovascular surgery. They showed that there is solid experimental evidence for such confounding of cardioprotection by single co-morbidities and co-medications, but that the clinical evidence from retrospective analyses of the limited number of clinical data is less robust.

Papers in this Themed Issue provide updates on well-known risk factors and co-morbidities interfering with cardioprotection. Ruiz-

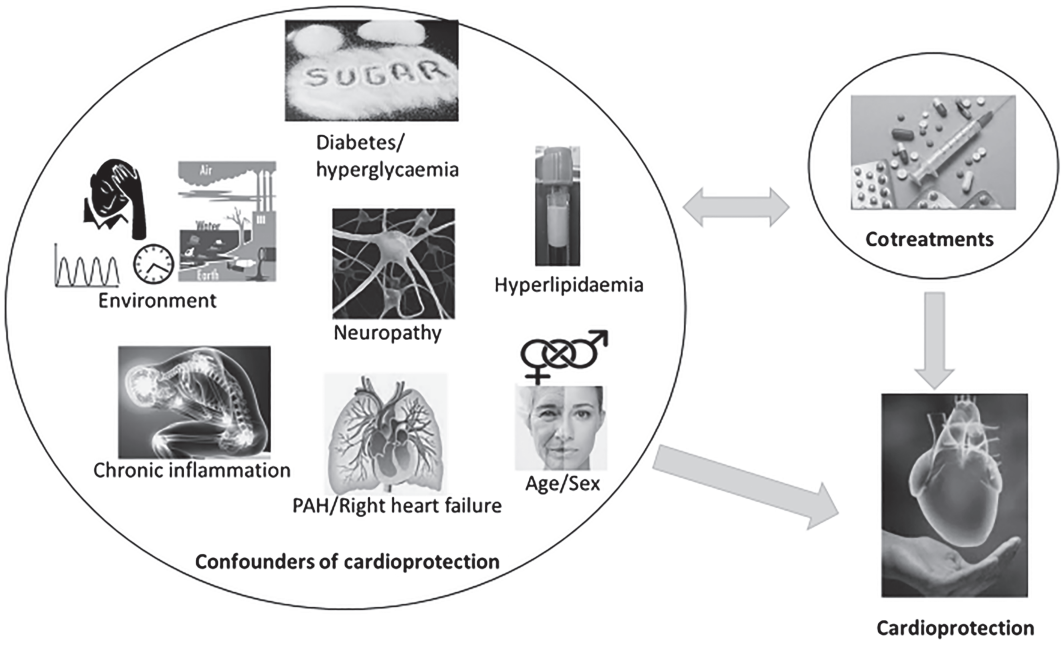

FIGURE 1 Summary of confounding factors for cardioprotection

Meana et al. (2020) review the effects of age and sex on the susceptibility and outcome of ischaemic heart disease. Andreadou et al. (2020) summarize the existing data on animal models of hypercholesterolaemia (total, low density, and HDL abnormalities) and hypertriglyceridaemia used in ischaemia/reperfusion injury and cardioprotection and provide recommendations on animal models of translational value. Penna et al. (2020) review the effect of diabetes and hyperglycaemia on cardioprotection. They overview the available animal models of diabetes and hyperglycaemia investigating acute myocardial ischaemia/reperfusion injury and cardioprotection. Moreover, they highlight the effects of anti-hyperglycaemic agents on acute myocardial ischaemia/reperfusion injury and cardioprotection.

Other papers in this Themed Issue give overviews of less studied confounding factors of cardioprotection. Bencsik et al. (2020) review the effect of sensory neuropathy of diverse aetiology (including diabetes and hyperglycaemia) on cardioprotection and the mechanisms by which neuropathies may interfere with ischaemic heart disease and cardioprotective signalling. They also suggest future therapeutic options targeting both ischaemic heart and sensory neuropathy. Lazou et al. (2020) review the effect of major chronic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, psoriasis and inflammatory bowel disease on cardioprotection. They give recommendations to evaluate common molecular targets of inflammatory and cardiovascular disease to design therapies to alleviate inflammatory disease-related cardiovascular diseases. In line with this, Chen et al. (2020) showed that a novel chalcone derivative exhibits atheroprotective effects by reducing inflammation-induced endothelial dysfunction.

According to epidemiological data, environmental risk factors (air pollution and noise) are associated with higher risk for cardiovascular, metabolic, and mental diseases, including hypertension, heart failure, myocardial infarction, diabetes, arrhythmia, stroke, depression, and anxiety disorders. Li et al. (2020) provide an overview on the effects of the external exposome comprising risk factors/exposures on cardiovascular health with a focus on dysregulation of stress hormones, mitochondrial function, redox balance and inflammation, with special emphasis on the circadian clock. They assess the effects of circadian clock dysregulation on cardiovascular health and the potential of environment-specific preventive strategies including “chrono” therapy for cardioprotection.

Boengler, Schlüter, Schermuly, and Schulz (2020) highlight an interesting issue of cardioprotection, that is, protection of the right heart. Whereas the molecular mechanisms of conditioning in the left ventricle are well characterized, cardioprotection of the right ventricle is much less studied. Similar to what is known for the left ventricle, a dysregulation in signalling pathways seems to play a role in ischaemia/reperfusion injury of the healthy and failing right ventricle and in the ability/inability of the right ventricle to respond to a conditioning stimulus. They highlight that, although similar molecular mechanisms mediate ischaemic and pharmacological preconditioning in the left and right ventricles, the two ventricles seem to respond differently, for example, to exercise-induced preconditioning.

In conclusion, papers in this Themed Issue underline the importance of careful preclinical assessment of novel cardioprotective therapies is necessary in clinically relevant animal models of different risk factors and co-morbidities and their medications to gather more knowledge on individual responses to cardioprotective therapies, thereby allowing better planning of clinical studies for cardioprotection in different patient populations.

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CONFLICT OF INTEREST

P.F. is the founder and CEO of Pharmahungary Group, a group of R&D companies. The rest of the authors declare no conflict of interest.

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