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Interaction of Cardiovascular Nonmodifiable Risk Factors, Comorbidities and Comedications With Ischemia/Reperfusion Injury and Cardioprotection by Pharmacological Treatments and Ischemic Conditioning

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ABBREVIATIONS: ACE, angiotensin II converting enzyme; Akt, protein kinase B; AMI, acute myocardial infarction; ATP, adenosine triphosphate; CABG, coronary artery bypass grafting; CsA, cyclosporine A; DPP-IV, dipeptidyl peptidase IV; ECG, electrocardiogram; ERK, extracellular signal related kinase; GSK-3β, glycogen synthase kinase-3β; HF, heart failure; IL, interleukin; I/R, ischemia/reperfusion; IRI, ischemia/reperfusion injury; IS, infarct size; KATP, ATP-dependent potassium channel; LDL-C, LDL-cholesterol; LV, left ventricle; LVH, left ventricular hypertrophy; MACE, major adverse coronary events; MI, myocardial infarction; miR, micro-RNA; MMP, matrix metalloproteinases; mPTP, mitochondrial permeability transition pore; MRI, magnetic resonance imaging; MVO, microvascular obstruction; NAD, nicotinamide adenine dinucleotide; NLRP3, nucleotide-binding and oligomerization domain (NOD)-like receptor domain-containing protein 3; NO, nitric oxide; NOS:, nitric oxide synthase; PCSK9:, proprotein convertase subtilisin/kexin type 9; PI3K, phosphoinositide-3-kinase; PPCI, primary percutaneous coronary interventions; PreC, preconditioning; PostC, postconditioning; RCT, randomized controlled trial; RIC, remote ischemic conditioning; RISK, reperfusion injury salvage kinase; PKC, protein kinase C; ROS, reactive oxygen species; SHR, spontaneously hypertensive rat; SGLT2, sodium–glucose cotransporter 2; STEMI, ST-segment elevation myocardial infarction; SAFE, survivor activating factor enhancement; STAT, signal transducers and activators of transcription; TIMI, thrombolysis in myocardial infarction; TNF, tumor necrosis factor.

***Abstract*——Preconditioning, postconditioning, and remote conditioning of the myocardium enhance the ability of the heart to withstand a prolonged ischemia/reperfusion insult and the potential to provide novel therapeutic paradigms for cardioprotection. While many signaling pathways leading to endogenous cardioprotection have been elucidated in experimental studies over the past 30 years, no cardioprotective drug is on the market yet for that indication. One likely major reason for this failure to translate cardioprotection into patient benefit is the lack of rigorous and systematic preclinical evaluation of promising cardioprotective therapies prior to their clinical evaluation, since ischemic heart disease in humans is a complex disorder caused by or associated with cardiovascular risk factors and comorbidities. These risk factors and comorbidities induce fundamental alterations in cellular signaling cascades that affect the development of ischemia/reperfusion injury and responses to cardioprotective interventions. Moreover, some of the medications used to treat these comorbidities may impact on cardioprotection by again modifying cellular signaling pathways. The aim of this article is to review the recent evidence that cardiovascular risk factors as well as comorbidities and their medications may modify the response to cardioprotective interventions. We emphasize the critical need for taking into account the presence of cardiovascular risk factors as well as comorbidities and their concomitant medications when designing preclinical studies for the identification and validation of cardioprotective drug targets and clinical studies. This will hopefully maximize the success rate of developing rational approaches to effective cardioprotective therapies for the majority of patients with multiple comorbidities.**

***Significance Statement*——Ischemic heart disease is a major cause of mortality; however, there are still no cardioprotective drugs on the market. Most studies on cardioprotection have been undertaken in animal models of ischemia/reperfusion in the absence of comorbidities; however, ischemic heart disease develops with other systemic disorders (e.g., hypertension, hyperlipidemia, diabetes, atherosclerosis). Here we focus on the preclinical and clinical evidence showing how these comorbidities and their routine medications affect ischemia/reperfusion injury and interfere with cardioprotective strategies.**

I. Introduction

Acute myocardial infarction (AMI) and subsequent heart failure (HF) remain the leading causes of death and disability worldwide. Effective treatment of AMI is based on procedures that promote the return of blood flow to the ischemic zone of the myocardium (i.e., reperfusion therapy). The achievement of prompt and successful

reperfusion to the infarct-related artery has revolutionized the management of ST-segment elevation myocardial infarction (STEMI), which is mostly equivalent to AMI arising from epicardial coronary artery plaque rupture [type I myocardial infarction (MI)] and complete acute coronary artery occlusion and is associated with acute ST-segment elevation on the electrocardiogram (ECG). Nonetheless, there is considerable room for further improvement. Reperfusion, however, may lead to further myocardial cell death, termed lethal myocardial reperfusion injury. Currently, there is no effective drug therapy for ischemia/reperfusion (I/R) injury (IRI) on the market, and routinely used pharmacological agents for ischemic heart disease do not salvage the I/R myocardium when applied at reperfusion. As such, new therapeutic targets are needed to protect the myocardium against the detrimental effects of acute IRI to reduce myocardial infarct size (IS), preserve left ventricular (LV) function and prevent the onset of HF (Heusch et al., 2014; Hausenloy et al., 2017; Heusch and Gersh, 2017; Heusch, 2020).

The heart possesses a remarkable ability to adapt to I/R stress, and this molecular plasticity of the heart in I/R has been the focus of intense research. Over the past 35 years, many cardioprotective strategies against myocardial IRI have been proposed. The cardioprotective strategies can be categorized based on the specific protective modality, time of application, and cellular or intracellular targets. The cardioprotective strategies that have been studied most are based on either (i) the controlled application of episodes of brief I/R (ischemic conditioning by mechanical occlusion and reperfusion of heart and other tissues), (ii) the application of physical measures (e.g., exercise), or (iii) the administration of chemical substances (pharmacological agents) (see Section II) (Fig. 1).

Established pharmacological treatments administered to patients with cardiovascular disease potentially affect the outcome from IRI and the possibility to protect the heart. Additionally, new pharmacological treatments—derived through the better understanding of the underlying signaling cascades involved in endogenous cardioprotection—could be administered either prior to a sustained episode of I/R (i.e., prior to cardiovascular surgery) or as early as possible during reperfusion [in case of patients with STEMI undergoing primary percutaneous coronary interventions (PPCI)] to potentially protect further from IRI.

Ischemic heart disease results from coronary atherosclerosis, which, in turn, develops as a consequence of a number of comorbidities predisposing to atherosclerosis development; it always coexists with other systemic disease states. These comorbidities include systemic arterial hypertension with related LV hypertrophy and metabolic diseases such as hyperlipidemia or diabetes mellitus. In addition, age

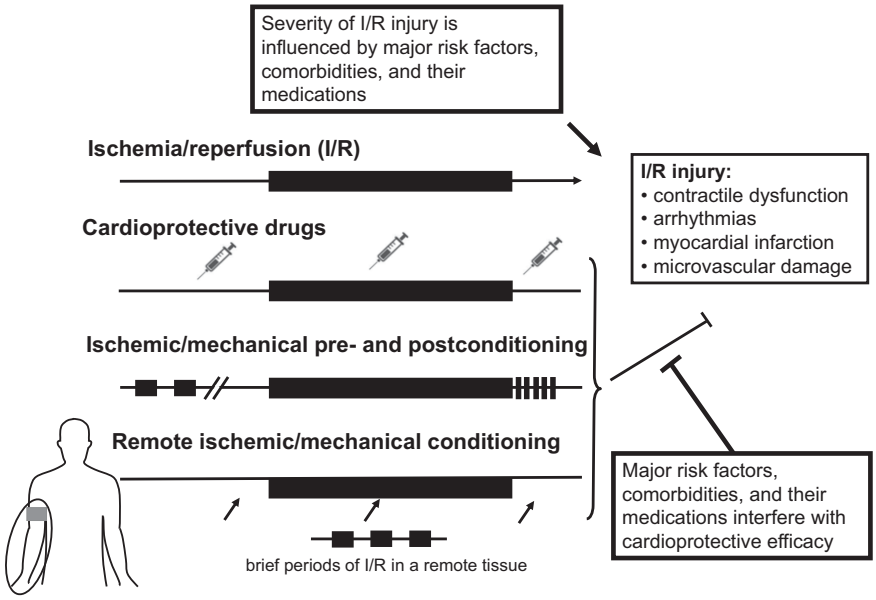

Fig. 1. The concept of ischemia/reperfusion injury and cardioprotection by pre-, post-, and remote conditioning as well as by drugs is expressed graphically (black areas denote periods of ischemia). Myocardial ischemia and reperfusion lead to I/R injury characterized by the development of contractile dysfunction, arrhythmias, tissue necrosis (infarction), and microvascular damage. Ischemic preconditioning is a well-described acute and subacute adaptive response in which brief exposure to I/R by mechanical occlusion of coronary arteries markedly enhances the ability of the heart to withstand a subsequent ischemia/reperfusion injury. In this diagram, 2 brief periods of ischemia are used to precondition the myocardium against a subsequent period of ischemia that is longer than the preconditioning periods. Brief cycles of I/R applied following a longer period of ischemia also confer cardioprotection against the consequences of I/R, a phenomenon termed "ischemic postconditioning." Brief cycles of I/R applied in a remote cardiac tissue or remote organ (in this diagram the upper limb by a pressure cuff) before, during, or right after a longer period of cardiac ischemia also provides cardioprotection, a phenomenon termed "remote conditioning." The cardioprotective effect of conditioning strategies results in attenuation of I/R injury. Major cardiovascular risk factors and their medications influence the severity of ischemia/reperfusion injury and interferes with cardioprotective efficacy.

and sex are major nonmodifiable risk factors affecting the development of ischemic heart disease. These risk factors and comorbidities exert multiple biochemical effects on the heart that affect the development of IRI and interfere with responses to cardioprotective interventions (Figs. 2 and 3).

The aim of this article is to update our previous reviews (Ferdinandy et al., 1998; Ferdinandy et al., 2014; Ferdinandy et al., 2007) on the effect of cardiovascular risk factors and comorbidities on IRI and cardioprotection and to show the ongoing critical need for preclinical studies that model the presence of risk factors and comorbidities and their pharmacological treatments. Such studies are required for the proper validation of molecular targets for cardioprotection as well as the efficacy and safety of potential cardiovascular drugs (Heusch, 2015, 2020), thereby maximizing the chances of success for translation of cardioprotection into the clinical arena and for the benefit of the majority of ischemic heart disease patients who have multiple comorbidities and associated medications.

II. Experimental Approaches to Cardioprotection

An orchestrated communication between the various cell types of the heart is vital for the maintenance of myocardial homeostasis. The human heart contains billions of cardiomyocytes; their activity needs to be coordinated to facilitate contractile activity, supported by fibroblasts, endothelial, and smooth muscle cells (Hausenloy, Chilian, et al., 2019), immune cells, and sympathetic and parasympathetic neurons (Hausenloy, Bøtker, et al., 2019). Intercellular communication in the heart can occur directly through cell–cell contacts, including gap junctions and tunneling nanotubes, or at longer distances involving the release of soluble factors or vesicle-enclosed mediators (for review see Martins-Marques et al., 2021). In stress conditions, such as acute I/R and developing AMI, a finely tuned crosstalk between the different types of cardiac cells assumes particular importance to sustain efficient responses in wound healing and extracellular matrix remodeling (Daiber et al., 2021). Crosstalk between cardiac and inflammatory cell-types also facilitates endogenous adaptive protection against IRI, the so-called conditioning phenomena (Fig. 2).

A. Conditioning Phenomena

1. Ischemia-Related. The "conditioning" phenomena describe the IS reduction after sustained I/R by brief nonlethal periods of I/R, which are performed either before (pre), during (per), or after (post) the sustained ischemia followed by reperfusion. Whereas in ischemic preconditioning (PreC) or ischemic postconditioning (PostC) the heart itself is subjected to the conditioning I/R, in remote ischemic conditioning (RIC) organs or tissues other than the heart (e.g., skeletal muscle) undergo I/R, and this "conditioning at a distance" reduces myocardial IS (for review see Hausenloy et al., 2017; Heusch et al., 2015). As with ischemic PreC, the benefits of RIC appear to be biphasic with a short initial window of protection during the first 12 hours, followed by a period of loss of protection and finally a longer "delayed" or "second" window of

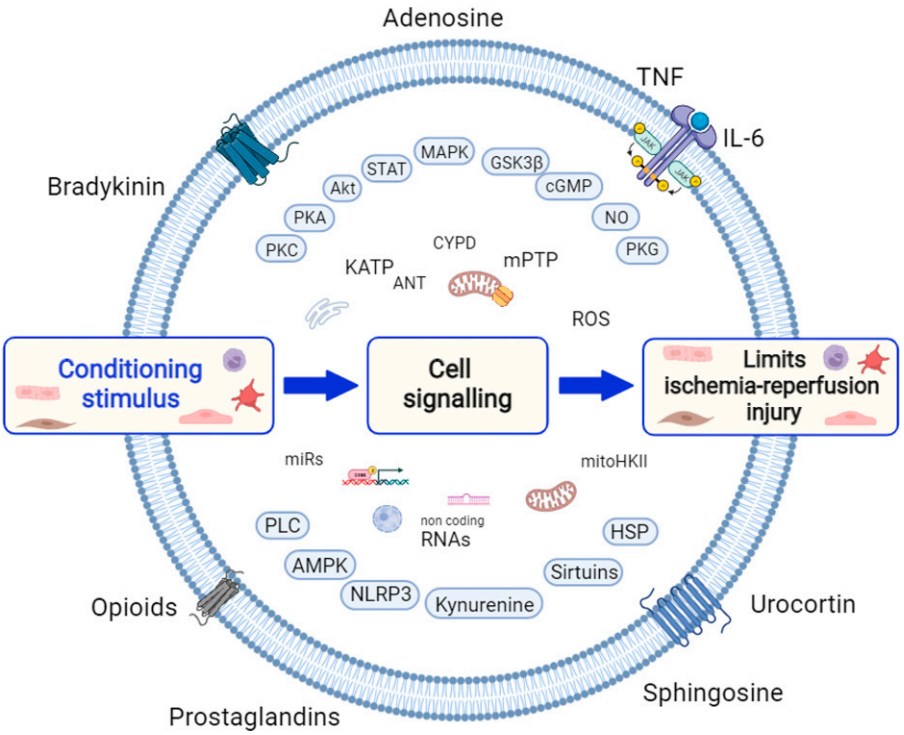

Fig. 2. This diagram shows some of the major cellular mechanisms suspected to contribute to cardioprotection induced by either mechanical or drug-induced conditioning stimulus of different cells of the heart tissue that leads to attenuation of I/R injury of the heart. Most of the cellular mechanisms of cardioprotection seems to be unexplored so far, as conditioning stimuli of cardioprotection is associated with extensive changes in cellular signaling that also includes global cardiac gene expression profile at the coding and noncoding RNA, proteome, and metabolome levels. AMPK, adenosine 5′-monophosphate activated protein kinase; ANT, adenine nucleotide translocase; cGMP, cyclic guanosine monophosphate; CYPD, cyclophilin D; NO, nitric oxide; GSK-3β, glycogen synthase kinase-3β; HSP, heat shock proteins; KATP,ATP-dependent potassium channel; MAPK, mitogen-activated protein kinase; miR, micro-RNA; mitoHKII, mitochondrial hexokinase II; mPTP, mitochondrial permeability transition pore; NLRP3, nucleotide-binding and oligomerization domain (NOD)-like receptor domain-containing protein 3; PKA, protein kinase A; PKC, protein kinase C; PKG, protein kinase G; PLC, phospholipase C; ROS, reactive oxygen species; STAT, signal transducers and activators of transcription; TNF, tumor necrosis factor.

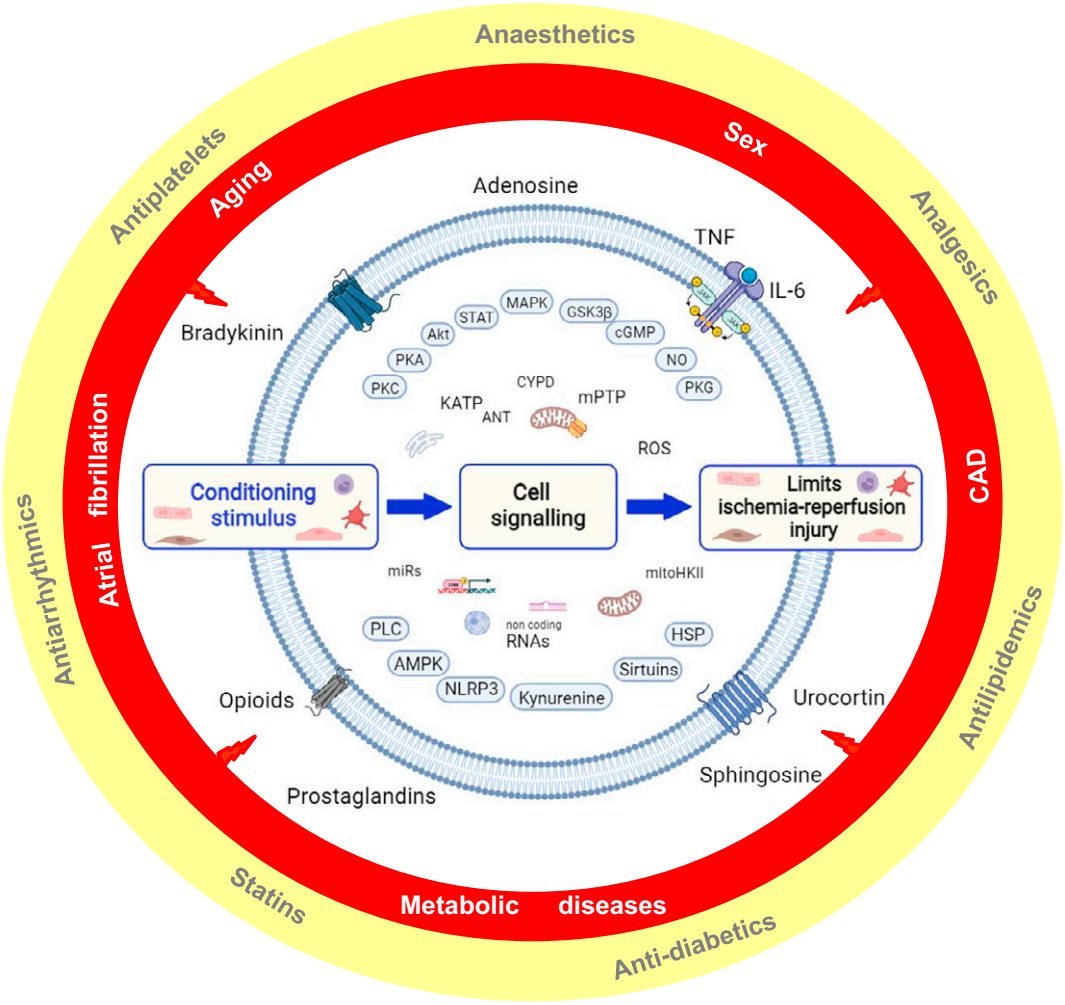

Fig. 3. This diagram shows that different cardiovascular risk factors and comorbidities as well as their routine medications dramatically alter cardiac cellular signaling thereby interfering with cardioprotective mechanisms explored in drug-naive young healthy hearts used in the majority of preclinical studies.

protection lasting as long as 72 hours after RIC exposure (Madias, 2015). When using leg ischemia to induce RIC in mice, leg temperature is decisive for cardioprotection, and leg hypothermia abrogates protection (Penna et al., 2022). The importance of different conditioning strategies to improve patients' outcome is highlighted in Section III.

Repeated administration of RIC over weeks or months (long-term RIC), has been investigated for improving several aspects of cardiovascular health (for review see Epps et al., 2016; Chong et al., 2019). A seminal experimental study demonstrated that RIC repeated daily for 28 days after MI protected against adverse LV remodeling and increased survival in a rat model even though IS was not reduced compared with the single RIC treatment (Wei et al., 2011). This was further supported by a rat study showing survival benefit even when RIC treatment was commenced 4 weeks after MI (Yamaguchi et al., 2015). In a lipopolysaccharide-induced mouse model mimicking bacterial sepsis, RIC reduced circulating and myocardial inflammatory mediators and led to improved LV function, cardiac output, and survival (Honda et al., 2019). Moreover, repeated RIC provided an additional 7 days survival benefit beyond a single-occasion treatment (Honda et al., 2019).

2. Drug-Related. Elucidation of some mechanisms involved in cardioprotection induced by ischemic conditioning strategies has identified a number of signaling pathways, many of which have been targeted by pharmacological agents applied either before the sustained ischemia (pharmacological PreC) or just at the onset of reperfusion (pharmacological PostC) to reduce myocardial IRI (for review see Heusch, 2015, 2020; Calabrese, 2016b; Torregroza et al., 2020). While results from experimental studies were encouraging, translation to the clinical setting again failed to meet the expectations (for review see Heusch, 2017; Roth et al., 2021 and Sections III and V for details).

Apart from ischemic and pharmacological PreC and PostC, another clinically applicable possibility to

precondition the heart against IRI is exercise (for review see Wojcik et al., 2018). Recent clinical investigations confirm that exercise may precondition the human heart (for review see Quindry and Franklin, 2021). Low-load blood flow restricted resistance exercise (Bøtker, Lassen, et al., 2018) improved functional capacity, quality of life, and muscle mitochondrial function in patients (Groennebaek et al., 2019). The mechanisms responsible for exercise-induced cardioprotection include maintenance of endothelial nitric oxide synthase (NOS) coupling (Santana et al., 2018), increased release of circulating hormones (Lu and Pan, 2017; Otaka et al., 2018; Bo et al., 2021), as well as extracellular vesicles (Görgens et al., 2015; Bei et al., 2017), finally leading to preserved mitochondrial dynamics (Ghahremani et al., 2018; Yuan et al., 2018) in cardiomyocytes.

B. Endpoints

As outlined earlier, the heart consists of many different cell types. Therefore, endogenous protection can be directed not only to cardiomyocytes but also to the coronary circulation (including effects on endothelial cells, vascular smooth muscle cells, vessel innervation) (Heusch, 2016, 2019a; Hausenloy, Chilian, et al., 2019) and circulating blood cells, to name a few.

1. Cardiomyocyte Death. To develop strategies to protect the heart from IRI, it is important to define the precise mechanisms by which cardiomyocytes die. Necrosis is known to play a major role in myocardial IRI. Apoptosis is a form of programmed cell death mediated by caspases and characterized by cell shrinkage, chromatin condensation, and blebbing (budding) of the plasma membrane. Despite early studies showing evidence of apoptosis in the heart following I/R, its contribution remains controversial. The protein machinery required for apoptosis is expressed at very low levels in the healthy adult heart, which suggests that the signs of apoptosis that can be detected may be due to cardiac cells other than cardiomyocytes (e.g., fibroblasts, endothelium, leukocytes) (reviewed in Davidson et al., 2020).

Mitochondria play a central role in both of these pathways of cell death, as either a causal mechanism in the case of mitochondrial permeability transition pore (mPTP) opening leading to necrosis or as part of the signaling pathway in mitochondrial cytochrome c release and apoptosis. Autophagy may impact this process by removing dysfunctional proteins or even entire mitochondria through a process called mitophagy (for in-depth review see Gatica et al., 2022). More recently, roles for other programmed mechanisms of cell death such as necroptosis and pyroptosis have been described (for review see Davidson et al., 2020).

Necrosis was previously believed to always be an uncontrolled pathway of cell death. However, it is now evident that there are controlled forms of necrosis, of which necroptosis and pyroptosis are of particular relevance in the heart. Necroptosis involves the recruitment of cytosolic adaptor proteins to complex I, an increase in plasma membrane permeability, re-localization of phosphorylated mixed-lineage kinase domain-like pseudokinase to the plasma membrane, and receptor-interacting-protein 3 activation (Zhang et al., 2016). In the heart, receptor-interacting-protein 3 also causes activation of calmodulin-dependent protein kinase II (Zhang et al., 2016). Necroptotic proteins are also present in the human failing heart due to MI (Szobi et al., 2017). Necroptosis clearly contributes to IRI, because either pharmacological inhibition or deletion of key proteins is cardioprotective (Smith et al., 2007; Newton et al., 2016). Limited evidence suggests that conditioning strategies can reduce necroptosis. For example, ischemic PreC is associated with inhibition of translocation of mixed-lineage kinase domain-like pseudokinase within the plasma membrane, and ischemic PreC is ineffective in hearts where necroptosis is already inhibited (Szobi et al., 2018).

Pyroptosis is a type of programmed necrosis that can be activated in the heart in response to injury. One major difference between pyroptosis and other forms of necrosis is that the proteins involved in pyroptosis are expressed at low levels in the healthy heart, and, as such, in healthy hearts, the contribution of pyroptosis to infarction occurring in the first few hours of reperfusion following ischemia may be limited. However, damage-associated molecular patterns such as interleukin (IL)-1β increase the expression of proteins of the inflammatory and innate immune systems including nucleotide-binding and oligomerization domain-like receptor domain-containing protein 3 (NLRP3), apoptosis-associated speck-like protein containing caspase recruitment domains, and caspase-1, which make up a complex called the NLRP3 inflammasome (Kawaguchi et al., 2011). Following this "priming" stimulus, a stress such as I/R causes rapid assembly and activation of the NLRP3 inflammasome, leading to cleavage and activation of IL-1β and IL-18. Activated caspase-1 also cleaves the protein gasdermin D, which forms cytosolic membrane pores, the lethal and defining feature of pyroptotic cell death (Shi et al., 2015).

Most acute I/R experiments use IS (relative to ischemic area at risk) as a hard endpoint, measured using either tetrazolium staining (postmortem) or late gadolinium cardiac magnetic resonance imaging (MRI) (Bøtker, Hausenloy, et al., 2018). The levels of cardiac proteins such as troponin released by necrotic cells into the blood or perfusate may be used as a supporting measurement. Cardiac contractile function is sometimes used as endpoint but is less robust and less meaningful in the acute period since cardioprotective strategies such as ischemic PreC may have inconsistent effects on ventricular function (Kloner and Jennings, 2001; Gelpi et al., 2002). Since

ventricular fibrillation contributes to deaths following MI, another relevant endpoint measurement, which is a target for ischemic PreC, is cardiac arrhythmia (Hagar et al., 1991).

2. Coronary Microvascular Obstruction. Another target for cardioprotection that has been somewhat overlooked in acute myocardial IRI is the coronary circulation (Heusch, 2016, 2019a; Hausenloy, Chilian, et al., 2019). The function in health and disease of the coronary circulation including the microvasculature is pivotal to our understanding of the complex processes and interactions among myocardial ischemic injury, reperfusion injury, and cardioprotection (Kaski et al., 2018). The putative initiating mechanism in approximately 97% of patients who experience an acute coronary syndrome is plaque erosion or rupture (type I MI), and there is abundant evidence that the response of the microvasculature plays a crucial role in determining the clinical course and final outcome. Moreover, type II MI, which results from changes in systemic hemodynamics and their impact on the matching of coronary blood flow and myocardial metabolism, occurs usually in the presence of significant epicardial coronary atherosclerosis (Ibanez et al., 2018; Thygesen et al., 2018). Finally, MI in the absence of obstructive (<50% diameter reduction on angiography) coronary artery disease still involves in most cases structural or functional alterations of the epicardial or more distal coronary microcirculation (Ibanez et al., 2018; Thygesen et al., 2018). Whereas obstruction of the coronary circulation and reduction of coronary blood flow causes myocardial ischemia (Heusch, 2019b), it is the reopening of the coronary circulation and restoration of coronary blood flow that induces reperfusion and salvages the dependent myocardium from infarction, but this comes at the price of reperfusion injury (Heusch and Gersh, 2017). Type IV MI is defined as any infarction related to interventional reperfusion (Thygesen et al., 2018) including notably microembolization (Heusch, 2016; Kleinbongard and Heusch, 2022). Thus, the coronary circulation in one form or the other is an integral component of the process of myocardial ischemia, microvascular dysfunction, reperfusion, reperfusion injury, and healing.

The coronary microcirculation is as much a victim of myocardial IRI as the cardiomyocytes. The most extreme form of coronary vascular injury following myocardial I/R is no-reflow as recognized in dogs more than 5 decades ago (Krug et al., 1966; Kloner et al., 1974). Such no-reflow, more specifically microvascular obstruction (MVO) (de Waha et al., 2017) and intramyocardial hemorrhage (Reinstadler et al., 2019), determines the prognosis of patients with reperfused AMI independently of IS (Stone et al., 2016). Because morphologic alterations of the coronary microvasculature are difficult to assess in the absence of reperfusion, it is not clear to what extent MVO is a direct consequence of ischemic injury or is caused by the process of reperfusion. Furthermore, since regions of coronary vascular injury typically occur within the infarcted myocardium, the causal relationship and relative contribution of cardiomyocyte and coronary microvascular injury from I/R is not clear. However, multiple mechanisms contribute to coronary microvascular injury from myocardial I/R: endothelial and interstitial edema (Garcia-Dorado et al., 2012; Fernández-Jiménez et al., 2015; Zhou et al., 2017), impaired vasomotion (Ehring et al., 1995; Kleinbongard et al., 2011), leukocyte adherence (Kupatt et al., 2002), erythrocyte stasis (Driesen et al., 2012), platelet aggregation (Pearson et al., 1990; Folts, 1999), extravascular compression by the interstitial edema (Manciet et al., 1994), and ultimately capillary destruction with consequent intramyocardial hemorrhage (Kloner et al., 1974; Higginson et al., 1982; Bulluck et al., 2016). Clinically, coronary microvascular injury is assessed using various imaging modalities, notably in angiography by decreased thrombolysis in MI (TIMI) flow grade and myocardial blush grade, and in cardiac MRI as edema by T2 weighted mapping and lack of contrast medium in gadolinium-hypercontrasted infarcted myocardium or intramyocardial hemorrhage (Heusch, 2016, 2019a; Hausenloy, Chilian, et al., 2019).

What is fortunate is that coronary microvascular injury is not an all-or-none phenomenon but a process subject to modification and damage limitation (Hausenloy, Chilian, et al., 2019; Heusch, 2019a). In the experimental model, mechanical interventions of ischemic conditioning reduced not only IS but also the area of no-reflow (Skyschally et al., 2017). Ischemic PreC reduced endothelial dysfunction (DeFily and Chilian, 1993; Kaeffer et al., 1996), leukocyte adherence (Kurzelewski et al., 1999), edema formation (Zhao et al., 2003), and MVO (Posa et al., 2010) and improved coronary vasodilator responses to adenosine, nitric oxide (NO), and reactive hyperemia (Gattullo et al., 1999), although not all studies have been consistent in demonstrating such benefit (Bauer et al., 1993). Moreover, delayed ischemic PreC provided endothelial protection and improved coronary vasodilation 24 hours later (Kaeffer et al., 1997; Kim et al., 2007). Ischemic PostC improved endothelial function and vasodilator response to acetylcholine and reduced leukocyte adherence, edema, and no-reflow in dogs and pigs (Zhao et al., 2003; Zhao et al., 2007), but again not all studies were positive (Bodi et al., 2014). RIC reduced IS and area of no-reflow in pigs (Skyschally et al., 2017), again with some studies lacking such effects (Baranyai et al., 2017). Hypothermia in rabbits reduced IS and area of no-reflow, and no-reflow was even reduced when hypothermia was delayed later into reperfusion (Hale et al., 2013). Some drugs, when given at reperfusion, reduced IS and no-reflow [e.g., cyclosporine A (CsA)] (Zalewski et al., 2015) and angiopoietin-like peptide 4 (Galaup et al., 2012).

Nitroglycerine can protect both the myocardium and the coronary vasculature but also interferes with RIC (Heusch, 2001; Hauerslev et al., 2018).

The experimental agenda surrounding the reduction of reperfusion injury in the microvasculature has been extensive, but for reasons not clearly understood much has been "lost in clinical translation," and definitive clinical trials demonstrating benefit are conspicuous by their absence (Heusch, 2017; Heusch and Gersh, 2020). More specifically, there is still debate on the role of coronary microvascular dysfunction as cause or consequence of MI and reperfusion injury (Lerman et al., 2007; Heusch, 2019a). Clinical studies evaluating ischemic PreC's effect on coronary MVO do not exist. However, several clinical studies notably using MRI looked not only at IS but also at coronary microvascular injury, including edema, MVO, and intramyocardial hemorrhage, in patients with acute STEMI undergoing either ischemic PostC (Thuny et al., 2012; Dwyer et al., 2013; Mewton et al., 2013; Bodi et al., 2014; Eitel et al., 2015; Kim et al., 2015; Traverse et al., 2019), RIC (Crimi et al., 2013; White et al., 2015; Liu et al., 2016), or both in combination (Eitel et al., 2015). The effects on IS and MVO differed and were partly concordantbut partly not, leaving the issue of causality between the 2 manifestations of myocardial IRI open and a challenge for further studies (Heusch, 2019a). The effects of hypothermia on IS and MVO in patients demonstrated modest benefits at best, and the most recent trial actually pointed in the wrong direction in terms of safety signals (Noc et al., 2021). Metoprolol is 1 exception and demonstrated a modest benefit on the reduction of both IS and MVO in patients with AMI (García-Prieto et al., 2017).

In conclusion, the coronary circulation is both a culprit and a victim of myocardial IRI. Cardioprotection notably reduces cardiomyocyte injury, as reflected by IS, but also coronary microvascular injury, as reflected by the area of no-reflow. The targets are clear, but identifying clinical approaches that favorably influence coronary microvascular obstruction and thereby induce cardioprotection have been difficult and remain the "last frontier" of reperfusion therapy (Heusch, 2019a).

C. Chronic Endpoints

Importantly, the primary endpoints in experimental and clinical studies differ (Bochaton et al., 2019). The most robust primary endpoint in experimental studies on cardioprotection is IS (Bøtker, Hausenloy, et al., 2018), and coronary microvascular injury is also increasingly recognized as a manifestation of IRI and thus a target of cardioprotection (Heusch, 2016, 2019a; Hausenloy, Chilian, et al., 2019) (see previous discussion). However, in clinical studies IS and coronary MVO are major determinants of LV remodeling and prognosis (Stone et al., 2016; de Waha et al., 2017; van der Bijl et al., 2020) but still only surrogate endpoints whereas the primary clinical endpoint is mortality and/or hospitalization for HF (Bøtker, Hausenloy, et al., 2018). In smaller clinical trials, however, adverse LV remodeling, as characterized by an increase in LV end-diastolic volume of 15% to 20% between baseline and follow-up measures, or circulating levels of NH_2-terminal pro-B-type natriuretic peptide, have been used as clinical endpoints (Pryds et al., 2017; Ikonomidis et al., 2021). Thus, when comparing experimental and clinical studies, not only the endpoints per se but also the time frame over which these endpoints are assessed differ (Heusch, 2018; Lecour et al., 2021).

D. Signaling Mechanisms Involved in Cardioprotection

1. Classic Pathways. Timewise, there are 3 key steps in the mechanism of cardioprotection: the trigger step, the mediator step, and the end-effector step, which may or may not involve different signaling pathways. These steps can be clearly distinguished only in ischemic PreC but are more difficult to discern in ischemic PostC and RIC (Heusch, 2015; 2020) (Fig. 2). These have been extensively characterized over the past 35 years and are well established, although some controversies still remain (reviewed in Heusch, 2015; Hausenloy et al., 2016). Moreover, given the fact that none of these pathways have resulted in clinically validated cardioprotective drug targets in the last 30 years suggests the possibility that more systematic research approaches will uncover novel, more druggable targets (Varga et al., 2015; Hausenloy et al., 2017; Perrino et al., 2017). Ischemic PreC causes a localized increase in the extracellular concentration of the autacoid mediators adenosine (Liu et al., 1991), bradykinin (Schulz et al., 1998), opioids (Schulz et al., 2001), and sphingosine (Keul et al., 2016), which bind to receptors on the cardiomyocyte plasma membrane and act additively to initiate the trigger pathway. Ligand-receptor signaling leads to the activation of a sequence of cytosolic kinase pathways that ultimately cause opening of mitochondrial ATP-sensitive potassium channels (K_{ATP}) and allow potassium entry into mitochondria (Liu et al., 1996). Connexin 43 located at the inner mitochondrial membrane forms hemichannels that are also believed to be involved in the passage of potassium into mitochondria and required for cardioprotection by ischemic PreC (Boengler et al., 2005; Heinzel et al., 2005; Miro-Casas et al., 2009; Boengler, Ungefug, Heusch, Leybaert, et al., 2013; Gadicherla et al., 2017; Hirschhäuser et al., 2021). The reperfusion phase of ischemic PreC is crucial for the trigger pathway of cardioprotection, because reoxygenation allows mitochondrial respiration to recommence, which is associated with a small burst of reactive oxygen species (ROS) that activates protein kinase C (PKC) (Liu et al., 1994); the role of PKC in ischemic PreC of larger mammals such as the pig is still contentious (Vahlhaus et al., 1996).

The reperfusion injury salvage kinase (RISK) pathway describes a group of prosurvival kinases that must be

activated at the time of reperfusion for ischemic PreC to protect against IRI (Schulman et al., 2002). The relative importance of different signaling pathways appears to vary between species. In rodents, the ischemic PreC signaling pathway is dependent on both the phosphoinositide-3-kinase (PI3K)α/protein kinase B (Akt) 1 and mitogen-activated protein kinase/extracellular signal related kinase (ERK)1/2 signaling pathways (Hausenloy and Yellon, 2004; Kunuthur et al., 2012; Rossello et al., 2017). In pigs and humans, the salvage activating factor enhancement (SAFE) pathway, consisting of gp 130/tumor necrosis factor (TNF) receptor-mediated activation of janus kinase/signal transducers and activators of transcription (STAT) factors, appears to play a more important role (Lecour, 2009; Heusch et al., 2012; Kleinbongard, Skyschally, Heusch., 2017; Hadebe et al., 2018). Evidence suggests that the RISK and/or SAFE pathways are also involved in ischemic PostC and RIC, although the RISK pathway might not be essential to achieve cardioprotection (Skyschally et al., 2009; Inserte et al., 2013). Similarly, ischemic PreC may activate the RISK and SAFE pathways to limit mPTP opening and reduce IS (Davidson et al., 2006; Hausenloy et al., 2004; Lecour, 2009), but it remains unclear whether cardioprotective kinases protect directly via phosphorylation of end-effector proteins, or indirectly via improved mitochondrial respiration, suppression of mitochondrial calcium overload and oxidative stress (Clarke et al., 2008; Heusch et al., 2011; Skyschally et al., 2018). The NOS/NO-cyclic guanosine monophosphate signaling pathway is also necessary for ischemic PreC (Talukder et al., 2010). NO, being a gaseous molecule, can diffuse between organelles and cells to protect mitochondria from I/R by nitrosylating and inhibit mitochondrial complex I, suppressing the production of damaging ROS during early reperfusion (Chouchani et al., 2013; Rassaf et al., 2014).

Since ischemic PostC is applied at reperfusion, the trigger step is obviously different from ischemic PreC and may or may not involve different signaling pathways. By preventing complete reperfusion, ischemic PostC is believed to maintain an acidic myocardial pH, thereby acting at several cell targets involved in cardioprotection (i.e., preventing hypercontraction, calpain-mediated proteolysis, mPTP opening, and gap junction-mediated spread of injury during the first minutes of reflow) (Cohen et al., 2008; Inserte et al., 2011). However, aspects of the signal transduction and end-effector appear to be similar between ischemic PostC and ischemic PreC (e.g., protein kinases and ROS) (Penna et al., 2006; Barsukevich et al., 2015).

The signaling mechanism for RIC necessitates an additional step to enable communication between the triggering pathway in the remote organ and the end-effector pathway in the heart. A wide range of humoral factors have been proposed to mediate this communication, but there is no consensus on the critical molecule/s, and there may be multiple redundant factors (for review see Kleinbongard, Skyschally A, Gent, et al., 2017; Tsibulnikov et al., 2019). The parasympathetic nervous system is also required for transmission of the cardioprotective signal (Donato et al., 2013), meaning that both neural and hormonal signals are required (Lim et al., 2010). The spleen is an important relay organ between the neuronal and humoral signals of RIC (Lieder, Kleinbongard, et al., 2018; Heusch, 2019c). Interestingly, the various forms of ischemic conditioning (ischemic PreC, ischemic PostC, RIC) may all lead ultimately to the same cellular end-effectors to mediate cardioprotection (Heusch, 2015, 2020; Wolfrum et al., 2002). In this respect, the reduction in myocardial IS by RIC also involves activation of the PI3K/Akt pathway (thereby enhancing autophagy) (Gao et al., 2022), activation of STAT3 (Kleinbongard et al., 2018), and adenosine 5′-monophosphate activated protein kinase (Xu et al., 2022).

2. Mitochondria. Mitochondria are at the crossroads of cell death and survival through a plethora of functions that make them not only triggers but also mediators and end-effectors of cardioprotection due to their multifaceted participation in the pathophysiology of IRI, as extensively reviewed elsewhere (Davidson, Ferdinandy, et al., 2019). During ischemia, the interruption in the generation of mitochondrial adenosine triphosphate by oxidative phosphorylation is the triggering mechanism for the profound ionic and biochemical disturbances of cardiomyocytes (see previous discussion), the duration of which determines the fate of the cells (Piper et al., 1998). Upon reperfusion, the abnormal resumption of mitochondrial respiration (leading to an excessive and unregulated ROS production) and mitochondrial matrix calcium accumulation can synergistically exacerbate energy collapse through the activation of irreversible mPTP, a pathologic disruption of the inner membrane that induces massive matrix swelling and culminates in cell death (Halestrap and Richardson, 2015). In support of this, mice in which mitochondrial calcium overload was inhibited by cardiomyocyte-specific deletion of the mitochondrial calcium uniporter were protected against IRI (Luongo et al., 2015).

However, despite the enormous interest aroused by mPTP as a therapeutic target to prevent mitochondrial failure, its molecular entity remains controversial. Either a change in the dimerization of the FoF1-ATP synthase or a structural alteration within the enzyme holocomplex constitute some of the proposed models of the energy-dissipating channel that have received the most experimental support (Giorgio et al., 2013; Alavian et al., 2014; Bonora et al., 2017). Nevertheless, attempts to prevent mPTP by pharmacological inhibition of cyclophilin D (a regulatory protein known to interact with FoF1-ATP synthase; Giorgio et al., 2013) to desensitize mPTP against calcium resulted in inconsistent effects on cardiomyocyte survival during I/R and failed to confer clinical benefit in

patients (Lim et al., 2012; Cung et al., 2015; Rahman et al., 2018). Of note, the failure of clinical trials to demonstrate cardioprotection using mPTP inhibitors does not negate its role in human heart but is more likely due to incomplete understanding of required dose/target in humans (Shanmuganathan et al., 2005; see Section IIIa3). In contrast, the attenuation of the complex 1-mediated mitochondrial ROS generation by different interventions, including either pharmacological or genetic inhibition of the reverse electron transport from complex II to complex I reduces mPTP opening and limits IS in mice (Chouchani et al., 2014; Valls-Lacalle et al., 2016; Yin et al., 2021) and in the in vivo pig model (Valls-Lacalle et al., 2018). Malonate—as one example—only reduced infarct size in the isolated mouse heart when administered at reperfusion, whereas an acidic malonate formulation was required to affect infarct size with administration before ischemia (Prag et al., 2022; Schulz and Heusch, 2022). However, malonate turned out not to have additive cardioprotective effects on IS reduction in pigs when combined with RIC (Consegal et al., 2021), despite the fact that conditioning strategies had been previously shown to modulate mPTP susceptibility (Heusch et al., 2011).

In a pig model of IRI with or without ischemic PostC, mitochondrial proteome analysis revealed a dual role for ischemic PostC promoting metabolic reprogramming of the myocardium and a protective response mediated by the voltage-dependent anion channel 2 and DJ-1 in the mitochondria (Gallinat et al., 2022). Cardiac mitochondria are dynamic organelles and organize into differentiated populations. As a general rule, interventions capable of decreasing mitochondrial fission (or increasing mitochondrial fusion) reduce IRI (Hernandez-Resendiz et al., 2020). Hence, genetic or pharmacological inhibition of the fission protein dynamin-related protein 1 mitigated cardiac injury in murine models of I/R, although this treatment failed to protect the heart in the more clinically relevant closed-chest pig model of AMI (Ong et al., 2019). Similarly, the beneficial effects of both aerobic exercise conditioning (Ghahremani et al., 2018) and RIC (Cellier et al., 2016) on IS have been attributed to a better maintenance of the elongated mitochondrial morphology in rat models of in vivo I/R. As for their subcellular location, subsarcolemmal mitochondria have a greater contribution to ROS production (Crochemore et al., 2015) and IRI (Lesnefsky et al., 1997) and are more sensitive toward pharmacological and ischemic conditioning than interfibrillar mitochondria (Holmuhamedov et al., 2012; Sun et al., 2015). Moreover, only subsarcolemmal mitochondria contain connexin 43 at their inner membrane (Boengler, Stahlhofen, et al., 2009), a protein involved in the ischemic PreC cardioprotection (Rodriguez-Sinovas et al., 2006; Ruiz-Meana et al., 2014) that has recently been identified as one of the interactors of the FoF1-ATP synthase (Boengler et al., 2018). Also, STAT 3 activation impacts on mitochondrial function; it increases respiration, ATP formation, and calcium retention capacity and decreases ROS formation in rat and mouse mitochondria of myocardium undergoing IRI with ischemic PreC or PostC (Boengler et al., 2008; Boengler et al., 2010; Heusch et al., 2011; Boengler, Ungefug, Heusch, and Schulz, 2013; Skyschally et al., 2018). Taken together, there are multiple available lines of evidence that link the cardioprotective effect of conditioning strategies with better mitochondrial function and integrity, yet the causality between both phenomena is difficult to establish. In part, a more preserved mitochondrial function and network could simply be the consequence of the otherwise well-known beneficial effects of these maneuvers on cellular ionic homeostasis (Inserte et al., 2014; Hausenloy et al., 2016). Furthermore, the effects on mitochondria can vary depending on the conditioning algorithm, the animal species, and the subtype of mitochondria.

3. Metabolism and Metabolomics. It has long been known that cardiac substrate metabolism is a main determinant of the severity of IRI. This is not surprising considering that I/R is in principle a metabolic pathology, with abruptly altered metabolism and thus energy production during the nonhomeostatic transitions from normoxia to ischemia and from ischemia to reperfusion (Guth et al., 1987). One of the first cardioprotective strategies examined against IRI was a metabolic treatment, employing glucose-insulin-potassium infusions to attenuate electrographic disturbances during MI (Sodi-Pallares et al., 1962). It is now known that almost every specific metabolic substrate pathway can affect cardiac IRI (Zuurbier et al., 2020). However, the complex interactions between these metabolic pathways have likely hindered the development of a singular metabolic treatment providing robust cardioprotection against IRI in the clinical condition. Nevertheless, in terms of metabolic approaches, it seems that activation of glycolysis, glucose, and ketone oxidation and inhibition of fatty acid metabolism and oxygen consumption holds the most promise for protecting the heart against IRI (Zuurbier et al., 2020).

Increases in glucose uptake and glycolysis in rodent hearts are mandatory for protecting the heart during low-flow ischemia (Lochner et al., 1996) and for various cardioprotective interventions such as ischemic PreC (Ji et al., 2013), ischemic PostC (Correa et al., 2008), and nicotinamide adenine dinucleotide (NAD) supplementation (Nadtochiy et al., 2018) to be effective.

The coenzyme NAD^+ is critical for many biochemical pathways and the cellular stress response, and it is decreased in aging and many pathologies including cardiovascular diseases (Fang et al., 2017). During cardiac I/R, NAD^+ is acutely decreased in rat heart (Di Lisa et al., 2001), partly due to mPTP opening. NAD^+ is also used by sirtuins, a group of lysine de-acetylation enzymes controlling metabolism (Anderson et al., 2014). Metabolic overloading such as that present in the

metabolic syndrome results in increased acetylation (due to increases in acetyl-coenzyme A) and thereby inhibition of, for example, glucose uptake pathways in rat hearts (Renguet et al., 2017), interfering with cardioprotection. Sirtuins can de-acetylate these pathways and restore cardioprotection. In several studies NAD precursors protected against cardiac IRI (Yamamoto et al., 2014; Nadtochiy et al., 2018; Xiao et al., 2021).

That an activated glucose metabolism is needed for protection is commensurate with the finding that many of the critical signaling molecules (ROS, NO, PKC) triggering and mediating protection (see Fig. 2) are also know activators of glucose metabolism (Tada et al., 2000; Nishino et al., 2004). Metabolomic studies in rat hearts also indicated that protection through PKCε is associated with changes in glucose metabolism (Mayr et al., 2009). It seems that ischemic PreC-activated glucose metabolism (e.g., glycolysis) slows down mitochondrial reactivation following reperfusion (Zuurbier and Ince, 2002), possibly through increased binding of the glycolytic enzyme hexokinase II to mitochondria (Gurel et al., 2009; Nederlof et al., 2017). Glucose and mitochondrially bound hexokinase II are both needed for effective ischemic PreC and reductions in IS and cell death in rodent hearts (Pasdois et al., 2012; Smeele et al., 2011; Sun et al., 2008). Slowing down mitochondrial activity results in decreased oxygen consumption during reperfusion, which has been suggested to contribute to cardioprotection (Burwell et al., 2009). However, the role of mitochondrial function for cardioprotection during reperfusion is somewhat contentious, since STAT3 activation has been shown to mediate cardioprotection by ischemic PostC and RIC through improved mitochondrial function (see previous discussion).

Increased fatty acid uptake and incomplete fatty acid metabolism during ischemia aggravate IRI through the build-up of long-chain acylcarnitines within the mitochondria, resulting in an increase of mitochondrial ROS production (Dambrova et al., 2021). However, although ischemic PreC efficacy is often decreased in conditions of elevated fatty acid metabolism, this is not always observed (Dalgas et al., 2012). Metabolomics studies have suggested that (i) exercise-induced cardioprotection is associated with changes in rat heart ammonia recycling, protein biosynthesis, and pantothenate and coenzyme A biosynthesis (Parry et al., 2018) and (ii) RIC in rats and humans with decreases in plasma ornithine and increases in kynurenine and glycine (Chao de la Barca et al., 2016; Kouassi Nzoughet et al., 2017; Bakhta et al., 2020). Previous work in murine hearts had already indicated the possible important role of alpha-ketoglutarate induced kynurenic acid synthesis in mediating RIC (Olenchock et al., 2016).

Oeing et al. (2021) recently confirmed the importance of glucose metabolism in cardioprotection and ischemic PreC by demonstrating that mechanistic target of rapamycin c1-activated glycolysis at the expense of fatty acid oxidation offers protection of the murine heart against IRI and mediated ischemic PreC protective effects. Lochner et al. (2020) confirmed the mandatory role of glucose in ischemic PreC and that high fatty acid levels prevented ischemic PreC in rat heart.

4. Circulating Cells. Circulating cells can strongly impact on IRI through various mechanisms (for a review, see Davidson, Andreadou, et al., 2019). Among the different circulatory cells, platelets play an important role in myocardial I/R. Platelets, beyond hemostasis and thrombosis, are characterized as versatile cells directly involved in various physiologic and pathophysiological processes (Russo et al., 2017). Several imaging studies have provided evidence that platelets contribute to IRI in in vivo rodent models of cardiac IRI; they are activated early during reperfusion and localized within the ischemic and necrotic areas (von Elverfeldt et al., 2014; Ziegler et al., 2016; Ziegler et al., 2019). Additionally, circulating platelets change their characteristics due to IRI (Eicher et al., 2016; Kaudewitz et al., 2016) as has been shown by proteomic studies in STEMI patients (Ruggeri, 2002).

Platelets also carry and release multiple factors with the potential to reduce IRI (Hjortbak et al., 2021; Kleinbongard et al., 2021), although the role of circulating platelets as signal mediators of cardioprotection is far from being understood. In recent studies, RIC exerted its cardioprotective effect through modulating platelet function by reducing the formation of monocyte-platelet conjugates and thrombus formation (Lanza et al., 2016) and was associated with a reduction in platelet reactivity within the first 48-hour post STEMI (Gorog et al., 2021) (for review see Kleinbongard et al., 2021). More studies are necessary to understand the role of platelets in IRI and their importance for conditioning strategies.

Erythrocyte dysfunction contributes to a reduced NO bioavailability and thereby to increased IS and mortality from IRI in mice (Wischmann et al., 2020); also, erythrocyte stasis contributes to the no-reflow phenomenon (Kyrou et al., 2011).

Neutrophil (polymorphonuclear leukocyte) recruitment to ischemic, and more particularly reperfused, myocardium has been recognized as a pathologic hallmark of AMI for nearly a century. As described earlier, neutrophil adherence and plugging may play a key role in MVO supply and no-reflow. However, a direct causal role of neutrophils in the evolution of myocyte death, at least in the early stages of AMI, has been contentious (Baxter, 2002; Lefer, 2002). There is evidence that effective IS-limiting interventions including ischemic PreC and ischemic PostC result in reduced neutrophil accumulation. One study suggests that neutrophil inhibition is causally related to IS limitation by ischemic PostC (Granfeldt et al., 2012). There is also limited evidence from human

RIC studies to suggest that rapid and long-lasting systemic neutrophil inhibition occurs in response to the RIC stimulus (Kharbanda et al., 2001; Shimizu et al., 2010; Saxena et al., 2013). The extent to which these observations are mechanistically important in cardioprotection is unknown.

5. Innate Immunity and the NLRP3 Inflammasome. Neither circulating monocytes nor cardiac-resident macrophages contribute to acute IRI, although they are crucial for longer term infarct and LV remodeling (Bajpai et al., 2019).

During I/R, resident cardiac mast cells degranulate, releasing their proteolytic and damaging contents. Consequently, mast cell stabilizing compounds are cardioprotective (Wang et al., 1996; Rork et al., 2008; Bajpai et al., 2019). However, mast cell degranulation does not appear to contribute to ischemic PreC (Wang et al., 1996).

Necrosis or pyroptosis of cardiac cells during I/R releases their contents into the extracellular milieu, where they are recognized by the innate immune system as damage-associated molecular patterns. Some damage-associated molecular patterns particularly relevant to cardiac I/R injury include proteins of the extracellular matrix, heat shock proteins, S100 proteins, ATP, histones, high-mobility group box 1 (HMGB1), IL-1α, and mitochondrial deoxyribonucleic acid (Vilahur and Badimon, 2014). For example, heat shock protein 60 can induce apoptosis in cardiomyocytes (Kim et al., 2009). Damage-associated molecular patterns are recognized by toll-like receptors, particularly toll-like receptors 2 and 4, and are targets for reducing IRI. Histones released during I/R damage cardiomyocytes by toll-like receptor 4 related mechanism (Shah et al., 2022). Inhibition of toll-like receptor 2 reduces IS in both mouse and pig models (Arslan et al., 2010; Arslan et al., 2012). Knockout of toll-like receptor 3 (Lu et al., 2014) or 4 (Oyama et al., 2004) reduces IS in mice after I/R. Mitochondria are fundamentally involved in innate immunity and sterile inflammation. After exposure to NLRP3 activators, damaged mitochondria accumulate, leading to increased production of oxidized mtDNA fragments. These associate with the NLRP3 inflammasome in the cytosol and are required for its activation (Zhou et al., 2011; Zhong et al., 2018). The complement system forms an important aspect of the innate immune system. Blocking of either the classic, antibody-activated, complement pathway with a C1 esterase inhibitor or of complement factor C5a in the alternative pathway reduces IS in animals subject to I/R (Buerke et al., 1995; van der Pals et al., 2010) (reviewed in Yasuda et al., 1990).

The NLRP3 inflammasome and innate immunity are potential targets for acute cardioprotection. However, Zuurbier et al. showed that NLRP3 is barely expressed in healthy murine hearts, and deletion of NLRP3 had no effect on IS following I/R either in perfused mouse hearts or in vivo (Zuurbier et al., 2012; Jong et al., 2014). In contrast, Sandanger et al. (2013) reported that isolated mouse hearts lacking NLRP3 had smaller IS following global I/R. Generally, it seems that approximately 24 hours reperfusion time is required for priming (expression) of the NLRP3 inflammasome for pyroptosis to make a significant contribution to IS in wildtype hearts (Merkle et al., 2007; Kawaguchi et al., 2011; Sandanger et al., 2013; Jong et al., 2014; Sandanger et al., 2016). In line with this, an NLRP3 inflammasome inhibitor was able to reduce IS even when administered to mice after 1 hour of reperfusion but only when IS was measured 24 hours following infarction (and not after only 3 hours) (Toldo et al., 2016). The selective NLRP3-inflammasome inhibitor MCC950 reduced IS measured 7 days following I/R in pigs (van Hout et al., 2017). A recent study has implicated an NLRP3-independent, oxidative stress-dependent pathway of caspase-11 mediated cleavage of gasdermin D within cardiomyocytes, and release of Il-18 in IRI, and showed that IS was reduced in gasdermin D knockout mice 24 hours after I/R (Shi et al., 2021).

There is some evidence that the NLRP3 inflammasome may be involved in ischemic PreC, although more studies are required to investigate the role of priming. The benefit of ischemic PreC was lost in NLRP3 knockout but not apoptosis-associated speck-like protein containing caspase recruitment domains knockout hearts in the ex vivo Langendorff model (Zuurbier et al., 2012). Pharmacological preconditioning with a toll-like receptor 2 agonist was also lost in NLRP3 knockout hearts (Sandanger et al., 2016). There is limited evidence that RIC might also affect innate inflammation, as recently reviewed (Pearce et al., 2021). Notably, it has been reported that expression of the NLRP3 inflammasome is higher in infiltrating inflammatory cells and murine cardiac fibroblasts (Kawaguchi et al., 2011; Sandanger et al., 2013), so these may be a target for cardioprotection in addition to cardiomyocytes. An important question remains whether comorbidities can prime expression of NLRP3 inflammasome and gasdermin D, which would increase their relevance to the I/R process in diseased hearts.

Indeed, sterile inflammation has been described in other inflammatory conditions such as gout, pseudogout, type 2 diabetes mellitus, metabolic syndrome, atherosclerosis, asbestosis, silicosis, and Alzheimer's disease (for review see Algoet et al., 2022). There is a growing understanding that these disorders are pathophysiologically linked to and can modulate the course of IRI and its response to treatment. The term "metaflammation" describes a metabolically triggered chronic enhanced systemic inflammatory status that is associated with these conditions (Itoh et al., 2022), and such a chronic inflammatory status is also observed in the elderly population without comorbidities (termed "inflammaging") (Liberale et al., 2022).

6. Exosomes. Since our last substantial review of this topic, there has been an explosion of interest in cell-derived nanoparticles called exosomes (Prakash et al., 2020). These extracellular vesicles are released from all types of cells and are found in the blood of all species. Although they are derived mainly from erythrocytes and platelets, some are derived from the vasculature and some from cardiomyocytes (Hegyesi et al., 2022), and they play a role in cardioprotection (Sluijter et al., 2018). Ischemic PreC increases the release of exosomes from endothelial cells or from the heart, and these exosomes are cardioprotective via a signaling pathway involving ERK1/2 (Davidson, Riquelme, et al., 2018). The potential for exosomes to be involved in RIC was first suggested in 2014 (Yellon and Davidson, 2014), and at the same time the first evidence for this was provided by the demonstration that exosomes could transfer cardioprotection from 1 isolated heart to another (Giricz et al., 2014). RIC was shown in both humans and rats to increase the number of exosomes in the blood, although in this study no additional protection was seen with exosomes after RIC (Vicencio et al., 2015). Another study measured elevated levels of microRNA (miR)144 in the blood of mice and humans following RIC, which they proposed was circulated via exosomes to the heart to induce cardioprotection in mice (Li et al., 2014). In patients undergoing coronary artery bypass grafting (CABG), prior RIC increased the number of circulating exosomes and notably their miR 20 content along with reduced postoperative troponin release (Frey et al., 2019). It was recently proposed that IPost increases the release of miR 423-3p-containing exosomes from cardiac fibroblasts and that these participate in the cardioprotective effects of ischemic PostC, via the downstream effector RAP2C (member of RAS oncogene family) (Luo et al., 2019). In healthy volunteers undergoing RIC, protection was transferred to isolated rat hearts and mediated by extracellular vesicles and their miR cargo of miR 16-5p, 144-3p and 451a (Lassen, Just, et al., 2021). It remains unclear how miRs are able to act rapidly enough on their target transcripts to affect a rapidly developing AMI. Interestingly, diabetes impairs cardioprotection by exosomes (Davidson, Andreadou, et al., 2018; Wider et al., 2018).

7. Cardiac Transcriptome. Rapid development of 'omics technologies in the last 2 decades especially with transcriptomics have enabled the measurement of expression of all known coding and noncoding RNAs. Noncoding RNAs exhibit highly organized spatial and temporal expression patterns and are emerging as critical regulators of differentiation, homeostasis, and pathologic states, including in the cardiovascular system (Abbas et al., 2020; Shah et al., 2022). Unbiased bioinformatics evaluation of such data has led to the discovery of novel mechanisms and promising drug targets for cardioprotection (for reviews see Perrino et al., 2017; Parini et al., 2020). It was shown in the early 2000s that ischemic PreC dramatically altered cardiac gene expression pattern at the mRNA level in rats (Onody et al., 2003) (for review see Perrino et al., 2017). Global cardiac miR expression changes are also observed in pig models of ischemic PreC and ischemic PostC (Spannbauer et al., 2019). In 2013, the first evidence was provided that the expression profile of noncoding miR (fine-tune regulators of mRNA expression) in preconditioned and postconditioned hearts are also altered and several miRs expression changes are associated with cardioprotection—these miRs have been termed protectomiRs (Varga et al., 2014). In particular, a mimic of miR 125b has been shown by several groups to play an important role in ischemic PreC in different models (Wang et al., 2014; Bayoumi et al., 2018; Varga et al., 2018). To date, several miRs have been proposed to be involved in cardioprotective signaling, such as miR 1, miR 144, and miR 221. By unbiased molecular network analysis of miR-mRNA interactions, novel gene targets can be explored (for review see Makkos et al., 2021). Other noncoding RNAs such as circular and long-noncoding are also involved in cardioprotective signaling; however, little is known about their function and possible therapeutic relevance (Wu et al., 2017; Cai et al., 2019; Jusic et al., 2020; Lou et al., 2021).

III. Clinical Approaches to Cardioprotection

A large number of clinical studies have evaluated the cardioprotective effects of ischemic PreC, ischemic PostC, and RIC in patients experiencing acute myocardial IRI during AMI or in cardiac surgery patients. Unfortunately, the results have been variable and overall disappointing (Heusch and Rassaf, 2016) with large multicenter phase 3 studies failing to show any benefit on "hard" clinical outcomes with these cardioprotective interventions and treatments in AMI or cardiac surgery patients (Hausenloy et al., 2015; Meybohm et al., 2015; Hausenloy, Kharbanda, et al., 2019) (see Tables 1 and 2). Apart from providing an overview of recent clinical cardioprotection studies, the challenges facing the translation of cardioprotection for patient benefit will be discussed (Heusch, 2017, 2020), and future opportunities for realizing the clinical potential of cardioprotection will be highlighted.

A. Cardioprotective Strategies

Cardioprotective strategies include mechanical interventions to change blood flow with different clinically approved or novel medical devices as well as with repositioning of drugs on the market and novel drug candidates (Fig. 1). Regulatory and ethical requirements for such clinical studies are not covered in this review.

1. Ischemic Preconditioning and Postconditioning. Clinically, the use of ischemic PreC has been largely restricted to patients undergoing cardiac surgery (for review see Buja, 2022). In this setting, early studies

demonstrated that intermittent cross-clamping of the aorta reduced myocardial injury (assessed by serum cardiac biomarkers such as creatine kinase-MB or troponin T) (Jenkins et al., 1997), and a meta-analysis found potential benefits with RIC with reduced arrhythmias, less inotrope support requirement, and reduced intensive care unit stay (Walsh et al., 2008). However, given the invasive nature of the ischemic PreC stimulus and the potential risk of cerebral thromboembolism from cross-clamping of an atherosclerotic aorta, ischemic PreC has been largely abandoned in cardiac surgery.

In contrast to ischemic PreC, ischemic PostC could be applied at the time of reperfusion in AMI patients undergoing balloon angioplasty at the time of PPCI (Staat et al., 2005). Although shown to be initially promising, with ischemic PostC reducing myocardial IS and preserving cardiac function in a number of small clinical studies (Staat et al., 2005; Thibault et al., 2008), these were followed by several neutral and even negative studies (Freixa et al., 2012; Heusch, 2012; Tarantini et al., 2012). Unfortunately, the large DANAMI-3 trial, which evaluated the effects of ischemic PostC in 1234 STEMI patients undergoing PPCI, failed to report any beneficial effects on clinical outcomes (Engstrøm et al., 2017). The reasons for this failure are not clear but may relate to the ischemic PostC protocol used in the study with the ischemic PostC protocol being delivered within the stent and/or the low-risk patient population (making the study underpowered). Of note, in a post hoc study patients without thrombectomy had reduced risk of all-cause mortality and hospitalization for HF with ischemic PostC (Nepper-Christensen et al., 2020). Ischemic PostC has also been shown to reduce perioperative myocardial injury in the setting of CABG using intermittent cross-clamping of the aorta once the patient has come off cardiopulmonary bypass (Luo et al., 2008; Candilio and Hausenloy, 2017), but, as for ischemic PreC, the invasiveness of the procedure has limited its application. In a recent multicenter trial, ischemic PostC by 3 cycles of normothermic antegrade blood cardioplegia before release of the aortic clamp did not improve cardiac index (primary endpoint) or reduce troponin T or creatine kinase release but reduced a combined secondary endpoint of intraoperative ventricular fibrillation and postoperative atrial fibrillation and suggested hemodynamic differences in the response to PostC between male and female patients undergoing aortic valve replacement (see Kaljusto et al., 2022 and accompanying editorial Podesser and Kiss, 2022). Both ischemic PreC and ischemic PostC require the cardioprotective intervention to be applied directly to the heart, making the procedure invasive and more challenging to apply in the clinical setting. In this regard, RIC, which allows the cardioprotective stimulus to be applied to an organ or tissue away from the heart, has been intensively investigated as a cardioprotective intervention in the clinical setting.

2. Remote Ischemic Conditioning. The ability to apply the cardioprotective stimulus to the arm or leg by simply inflating and deflating a pneumatic cuff on the upper arm/leg or thigh to induce brief nonlethal episodes of I/R, has greatly facilitated the testing of limb RIC in patients at risk of acute myocardial IRI (Heusch et al., 2015). Single-occasion RIC reduces arterial stiffness and LV remodeling after AMI (Ikonomidis et al., 2021) beyond IS reduction alone, but the effect does not unequivocally translate into a reduction of HF admission in patients (Sloth et al., 2014). Several smaller clinical studies have demonstrated that limb RIC (applying 3 to 4 5-minute cycles of cuff inflation and deflation) prior to CABG surgery reduced perioperative myocardial injury (quantified by serum troponin levels) (Hausenloy et al., 2007; Thielmann et al., 2013), although not all studies have been positive (Rahman et al., 2010). Unfortunately, 3 large, multicenter studies in cardiac surgery patients failed to show any improvement in clinical outcomes with limb RIC applied to cardiac surgery patients (Hong et al., 2014; Hausenloy et al., 2015; Meybohm et al., 2015). The reasons for this failure are not clear but have been attributed to the potential confounding effects of certain comedications such as propofol anesthesia (Kottenberg et al., 2012), nitrates (Candilio et al., 2015), or beta-blockers (Cho et al., 2019) (see Section V). Furthermore, the causes of myocardial injury during CABG are not only due to acute myocardial IRI as coronary embolization, direct handling of the heart, and inflammatory injury associated with cardiopulmonary bypass may be etiological and not amenable to RIC cardioprotection. In contrast, an acute STEMI patient treated by reperfusion using PPCI represents a "purer" setting of acute myocardial IRI, which should be more amenable to the cardioprotective effects of limb RIC.

The first study to demonstrate this in STEMI patients was by Bøtker et al. (2010), who showed applying limb RIC patients in the ambulance on the way to the PPCI center, improved myocardial salvage (assessed by myocardial single-photon-emissions-tomography imaging) but did not reduce myocardial IS. Subsequent studies confirmed the cardioprotective effect of limb RIC administered on arrival at the hospital quantified by cardiac MRI (White et al., 2015) and even at the onset of reperfusion (Crimi et al., 2013), although not all studies have been positive (Verouhis et al., 2016). One large clinical study did demonstrate improved clinical outcomes with less HF hospitalization and cardiac death (Gaspar et al., 2018). In addition, follow-up studies of RIC-treated STEMI patients suggested an improvement in major adverse cardiac events at follow-up (Sloth et al., 2014; Stiermaier et al., 2019). However, despite these promising studies, the large, multicenter CONDI-2/ERIC-PPCI trial

of 5401 STEMI patients failed to find any improvement in rates of HF hospitalization and cardiac death at 12 months (Hausenloy, Kharbanda, et al., 2019). The reasons for this failure to translate limb RIC for patient benefit are not clear but may relate to the low-risk population recruited in this trial (Heusch and Gersh, 2020) (see Section IIIa3.).

Most clinical cardioprotective studies with limb RIC have applied 1 stimulus at the time of cardiac surgery or STEMI, but animal studies have suggested that cardioreparative effects of RIC may be induced by repeated daily episodes of limb RIC (Wei et al., 2011). Extended exposure to RIC may add further modulation of myocardial remodeling. Repeated RIC modifies the human inflammatory response and leukocyte adhesion (Shimizu et al., 2010) and improves coronary microcirculation in healthy volunteers and patients with HF (Jones et al., 2014). In contrast to single-occasion RIC, repeated RIC reduces blood pressure (Baffour-Awuah et al., 2021), allowing afterload reduction to modulate myocardial remodeling favorably. Nonetheless, the Daily REmote Ischemic Conditioning Following Acute Myocardial Infarction (DREAM) study demonstrated no effect of 4 weeks of daily RIC-treatment initiated 3 days after PPCI on ventricular function in 73 patients with reduced LV function after the acute coronary event (Vanezis et al., 2018). In pilot studies, repeated RIC as add-on to standard anticongestive treatment in patients with stable chronic HF did not improve LV ejection fraction but decreased circulating NH_2-terminal pro-B-type natriuretic peptide and skeletal muscle function after 28 days of RIC treatment once daily (Pryds et al., 2017), whereas exercise capacity was not different (McDonald et al., 2014). However, prolonged periods of daily limb RIC have been reported to be beneficial in patients with intracranial stenosis at risk of stroke (Meng et al., 2012). Despite the failure to translate the cardioprotective effects of limb RIC into a clinical benefit in cardiac surgery or STEMI patients, it may still have potential in STEMI patients at elevated risk of compromised outcome (Cheskes et al., 2020; Hausenloy et al., 2020) and other settings of acute IRI, such as kidney transplantation (MacAllister et al., 2015).

3. Pharmacological Cardioprotection. A detailed description of comedication administered to treat patients' comorbidities and its impact on IRI as well as cardioprotective interventions will be discussed extensively in Section V. However, some pharmacological approaches derived from a better understanding of the signaling cascades involved in endogenous cardioprotection have also been evaluated in clinical trials (Table 2).

The most promising of these was CsA, a mPTP inhibitor that had been shown in small and large animal studies to reduce IS (Hausenloy et al., 2002; Argaud et al., 2005; Skyschally et al., 2010), although not all studies had been positive (Karlsson et al., 2010; Lim et al., 2012). While initial phase 2 clinical studies with CsA reported reducing myocardial injury in cardiac surgery patients (Chiari et al., 2014; Hausenloy et al., 2014) and smaller IS in STEMI patients (Piot et al., 2008), 1 study did not show cardioprotection with CsA in STEMI patients (Ghaffari et al., 2013). Unfortunately, 2 large, multicenter clinical studies (CIRCUS and CYCLE) (Cung et al., 2015; Ottani et al., 2016) failed to demonstrate improved clinical outcomes with CsA administered prior to reperfusion in STEMI patients. Why these larger clinical trials failed to confirm the benefit of CsA on either reducing IS or clinical outcomes is unclear but may have been due to a type I error, insufficient dosing, the low-risk population, and the presence of $P2Y_{12}$ (chemoreceptor for adenosine diphosphate) inhibitors (see Section V).

Other mitochondrial targeting agents such as MTP-131 (which optimizes mitochondrial energetics and attenuates the production of ROS by selectively targeting cardiolipin in the inner mitochondrial membrane) failed to reduce IS in a phase 2 trial in a carefully selected group of anterior STEMI patients (Gibson et al., 2016). The mitochondrial protective agent, TRO40303, (which binds to the translocator protein in the outer mitochondrial membrane) reduced IS in small animals (Schaller et al., 2010) but not in large animals (Hansson et al., 2015) and did not reduce IS when administered to STEMI patients prior to PPCI (Atar et al., 2015).

While some experimental studies demonstrated cardioprotection with intravenous nitrite administered at the onset of reperfusion (Duranski et al., 2005), the National Heart Lung and Blood Institute Consortium for preclinicAl assESsment of cARdioprotective therapies (CAESAR) Network failed to show IS reduction with nitrite using a multicenter approach in small and large animal I/R models (Lefer and Bolli, 2011; Jones, Tang, et al., 2015; Bolli, 2021). Also, 2 clinical studies failed to demonstrate a significant IS reduction with nitrite administered by either the intravenous (Siddiqi et al., 2014) or intracoronary (Jones, Pellaton, et al., 2015) route in PPCI-treated STEMI patients. The study by Janssens et al. also failed to report any cardioprotective effects with inhaled NO as an adjunct to PPCI in STEMI patients (Janssens et al., 2018), although some benefit was seen in nitrate-naıve patients.

More recently, studies have investigated the cardioprotective effects of targeting interleukin-6 (IL-6), as this cytokine has been shown to contribute to inflammation in coronary artery disease and acute myocardial IRI (Sawa et al., 1998; Interleukin-6 Receptor Mendelian Randomization Analysis Consortium et al., 2012; Ritschel et al., 2013). An initial clinical study in non-ST elevation myocardial infarction patients

reported that pretreatment with a single intravenous 60-minute infusion of tocilizumab (an IL-6 receptor antibody) prior to PCI reduced inflammation and PCI-related myocardial injury when compared with placebo (Kleveland et al., 2016). The recently published ASSAIL-MI study in STEMI patients demonstrated that the same treatment regimen initiated during PCI improved myocardial salvage but did not significantly reduce MI size assessed by cardiac MRI performed on day 3 to 7 post-admission, when compared with placebo (Broch et al., 2021).

The importance of NLRP3 inflammasome-driven IL-1β for cardiovascular events was studied in some clinical trials with anakinra (a recombinant IL-1 receptor antibody) in patients with previous MI (VCU-ART and VCUART2; MRC-ILA-Heart Study). These trials were performed in a relatively small number of patients, and the reported results are contentious. The CANTOS trial, which evaluated the long-term effect of canakinumab (a humanized monoclonal IL-1β antibody) in 10061 MI patients, showed a significant 15% reduction in major adverse coronary events (MACE) compared with the placebo group; however, all-cause mortality did not differ between the canakinumab and placebo groups. Recently, the Colchicine Cardiovascular Outcome Trial using low-dose colchicine in 4745 MI patients as well as the subsequently conducted low-dose colchicine 2 trial in 5522 patients with chronic coronary artery disease confirmed a decrease in MACE (including cardiovascular death). Since colchicine can prevent NLRP3 inflammasome assembly, the clinical efficiency of colchicine supports the notion that NLRP3 inflammasome plays a key role in the pathogenesis of atherosclerosis and subsequent atherothrombotic events (for a detailed review see Takahashi, 2022).

B. Other Mechanical Approaches to Cardioprotection

A number of different mechanical approaches have recently been evaluated in STEMI patients treated by PPCI. Acute ventricular unloading prior to reperfusion has been shown in animal studies to reduce myocardial IS by decreasing myocardial workload (for review see Curran et al., 2019) (Table 1). A recent clinical study has tested the safety and feasibility of unloading the LV for 30 minutes before reperfusion using the percutaneous left ventricular support device, Impella CP, in anterior STEMI patients treated by PPCI. Interestingly, delaying reperfusion by 30 minutes did not increase IS when compared with applying the Impella CP device at the immediate onset of reperfusion (Kapur et al., 2019). The ongoing STEMI-DTU Trial is currently testing the efficacy of this approach on IS assessed by cardiac MRI in 668 anterior STEMI patients (NCT03947619). Therapeutic hypothermia has been reported to reduce IS in animal studies, but this has to be applied during myocardial ischemia, which might explain the lack of cardioprotection seen in clinical studies applying therapeutic hypothermia at reperfusion in STEMI patients treated by PPCI, studies that also showed delays in PPCI and increase adverse events with this intervention (Erlinge et al., 2014; Nichol et al., 2015; Testori et al., 2019; Noc et al., 2021) (for review also see Testori et al., 2019). Prior preclinical studies have demonstrated cardioprotection with intermittent coronary sinus occlusion, a technique that increases myocardial salvage following AMI by improving myocardial perfusion (Guerci et al., 1987; Toggart et al., 1987; Beyar et al., 1989; Rydén et al., 1991). In patients with STEMI, pressure-controlled intermittent coronary sinus occlusion, using a balloon-tipped catheter placed in the coronary sinus that is cyclically inflated and deflated resulting in an intermittent increase in coronary sinus pressure, improved myocardial perfusion. In preliminary studies pressure-controlled intermittent coronary sinus occlusion reduced IS size in anterior STEMI both acutely and at 6 months (De Maria et al., 2018; Egred et al., 2020), and it reduced the index of microcirculatory resistance within 48 hours of revascularization (De Maria et al., 2018; Scarsini et al., 2022).

C. Potential Opportunities for Improving Clinical Translation of Cardioprotection

Overall, the results of clinical cardioprotection studies have been largely disappointing (Heusch, 2017; 2020; Heusch and Rassaf, 2016). In this section we describe some strategies for potentially improving the clinical translation of cardioprotection for patient benefit.

1. Improving Preclinical Assessment of Cardioprotective Strategies. One key reason for the failure to translate cardioprotection into the clinical arena has been the lack of rigorous and systematic preclinical testing of novel cardioprotective therapies, the consequence of which has been the premature clinical evaluation of treatments with inconsistent and less than robust cardioprotective effects (Bolli, 2021). Potential strategies for ensuring that only the most robust and reproducible novel cardioprotective therapies are tested in clinical studies include establishing guidelines and criteria for preclinical evaluation of novel cardioprotective therapies and establishing multicenter research networks for testing of novel cardioprotective therapies. The European Union-CARDIOPROTECTION Cooperation in Science and Technology Action CA16225, a pan-European research network of leading experts in experimental and clinical cardioprotection, aims to address some of these issues. It has already published practical guidelines to ensure rigor and reproducibility in preclinical cardioprotection studies (Bøtker, Hausenloy, et al., 2018) and has established the IMproving Preclinical Assessment of Cardioprotective Therapies (IMPACT) criteria for improving the in vivo preclinical evaluation of the efficacy of novel cardioprotective therapies (Lecour et al., 2021). Finally, the EU-CARDIOPROTECTION

TABLE 1
Major clinical cardioprotection studies of mechanical interventions in patients with AMI

Study	*n*	Patient criteria	Cardioprotection protocol	Main outcome	Notes
Ischemic postconditioning					
Staat et al., 2005	30	LAD/RCA STEMI ≤6 h ischemic time TIMI 0 pre-PPCI	4 × 1 min inflations and deflations of angioplasty balloon upstream of stent Direct stenting	36% reduction in MI size (72 h AUC CK) Better myocardial blush grade	First clinical study to translate ischemic PostC into clinical setting
Staat et al., 2005; Thibault et al., 2008	38	LAD/RCA only ≤6 h ischemic time TIMI 0 pre-PPCI	4 × 1 min inflations and deflations of angioplasty balloon upstream of stent Direct stenting	40% and 47% reductions in MI size (72 h AUC CK and troponin I) 39% reduction in MI size (SPECT at 6 months) 7% increase in LVEF (echo at 1 year)	First clinical study to demonstrate long-term benefit with ischemic PostC
Freixa et al., 2012; Heusch, 2012; Tarantini et al., 2012 POST-AMI	78	All STEMI <6 h ischemic time TIMI 0–1 pre-PPCI No collaterals	4 × 1 min inflations and deflations of angioplasty balloon within the stent Direct stenting and no thrombectomy performed	No difference in MI size (MRI 30 days)—trend to increase with ischemic PostC	First study to suggest possible detrimental effects with ischemic PostC
Freixa et al., 2012; Heusch, 2012; Tarantini et al., 2012	79	All STEMI TIMI 0–1 pre-PPCI No collaterals	4 × 1 min inflations and deflations of angioplasty balloon within the stent Direct stenting	No difference in MI size (MRI at 1 week or 6 months) Less myocardial salvage with ischemic PostC	First study to show detrimental effect of ischemic PostC in terms of less myocardial salvage
Engstrøm et al., 2017 DANAMI 3	1,252	All STEMI TIMI 0–1 pre-PPCI	4 × 0.5 min inflations and deflations of angioplasty balloon at site of lesion	No difference in primary endpoint of all-cause death and HHF at median follow up time of 38 months	Largest outcome study to date with no beneficial effects of ischemic PostC
Remote ischemic conditioning					
Bøtker et al., 2010 CONDI	142	All STEMI	4 × 5 min inflations/deflations of cuff on upper arm in the ambulance before PPCI	Increase in myocardial salvage index at 30 days No difference in MI size (SPECT or peak troponin)	First study to show beneficial effect of RIC on myocardial salvage
Crimi et al., 2013	100	Anterior STEMI only	3 × 5 min inflations/deflation of cuff on thigh at onset of reperfusion	20% reduction in 72 h AUC CK–MB	First study to show beneficial effects of RIC started at onset of reperfusion
White et al., 2015 ERIC-STEMI	83	All STEMI	4 × 5 min inflations/deflations of cuff on upper arm at the hospital before PPCI	27% reduction in MI size by MRI 19% reduction in myocardial edema by MRI	First study to show beneficial effects of RIC on MI size and myocardial edema assessed by MRI
Eitel et al., 2015; Stiermaier et al., 2019 LIPSIA conditioning	333	All STEMI	4 × 5 min inflations/deflations of cuff on upper arm at the hospital before PPCI plus ischemic PostC	Increased myocardial salvage with RIC + ischemic PostC versus control No difference in MI size or MVO	Improved myocardial salvage when ischemic PostC combined with RIC, but effect of RIC alone not tested
Verouhis et al., 2016	93	Anterior STEMI within 6 h chest pain	Variable number of 5 min cycles (7–9) of inflations/deflations of cuff on upper arm	No difference in MI size or myocardial salvage at MRI scan at day 4–7	First neutral study with RIC in STEMI
Vanezis et al., 2018 DREAM	73	STEMI with LVEF <45%	4 × 5 min inflations/deflations of cuff on upper arm in started day 3 post-PPCI and continued daily for 28 days	No difference in MI and LV remodelling at 4 months post-PPCI	First study to test effects of daily RIC post-STEMI
Gaspar et al., 2018 RIC STEMI	516	All STEMI	3 × 5 min inflations/deflations of cuff on thigh before PPCI	Primary endpoint of cardiac mortality and HHF at 12 months reduced by 35% Preserved LVEF at 6 months	First prospective study to show benefits on clinical outcomes
Hausenloy, Kharbanda, et al., 2019 CONDI-2/ERIC-PPCI	5400	All STEMI	4 × 5 min inflations/deflations of cuff on upper arm before PPCI	No difference on primary endpoint of cardiac death and HHF at 12 months	Largest clinical study to investigate the effects of RIC on clinical outcomes

(*continued*)

TABLE 1—*Continued*

Study	*n*	Patient criteria	Cardioprotection protocol	Main outcome	Notes
Cheskes et al., 2020; Hausenloy et al., 2020	1726	All STEMI	4 × 5 min inflations/ deflations of cuff on upper arm before PPCI	No difference in MACE at 90 days although benefit seen in patients presenting with cardiogenic shock or cardiac arrest	Not RCT but pre- and post-implementation designed study
Therapeutic hypothermia					
Erlinge et al., 2014	120	All STEMI within 6 h chest pain	Therapeutic hypothermia using IV infusion of cold saline to achieve <35°C for 1 h	No difference in myocardial salvage Possible benefit in anterior STEMI patients	9 min delay to PPCI with intervention
Nichol et al., 2015 VELOCITY	54	All STEMI	Therapeutic hypothermia using intraperitoneal infusion of cold saline for 3 h post-PPCI	No difference in MI size at 3–5 post-PPCI and significant increase in adverse events at 30 days	15 min delay to PPCI with intervention
Noc et al., 2021 COOL AMI EU Pivotal Trial	111	Anterior STEMI patients	Therapeutic hypothermia using IV infusion of cold saline to achieve 33°C for 1 h post-PPCI	No difference in MI size at 4–6 post-PPCI and significant increase in adverse events (cardiogenic shock) at 30 days	Prematurely stopped due to 44 min delay to PPCI with intervention
LV unloading with Impella CP					
Kapur et al., 2019 DTU STEMI pilot	50	Anterior STEMI patients	LV unloading by using the Impella CP	No difference in MI size with 30-min delay to reperfusion	Feasibility study for efficacy study; DTU STEMI
PICSO					
De Maria et al., 2018; Egred et al., 2020 OXAMI-PICSO	105	Anterior STEMI patients	PICSO	Smaller MI size on MRI at day 2 and 6 months. Improved coronary microvascular perfusion 48 h	
De Maria et al., 2018; Egred et al., 2020	92	Anterior STEMI patients	PICSO	Smaller MI size on MRI at day 5	
De Maria et al., 2018; Scarsini et al., 2022	108	All STEMI patients	PICSO	Improved coronary microvascular perfusion and vasodilatory activity and less MVO and smaller MI size at 48 h on MRI	

AUC, area under curve; CK, creatine kinase; HHF, hospitalization for heart failure; LAD, left anterior descending artery; LV, left ventricle; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events; MI, myocardial infarction; MVO, microvascular obstruction; PISCO, pressure-controlled intermittent coronary sinus occlusion; PostC, postconditioning; PPCI, primary percutaneous coronary intervention; RCA, right coronary artery; RIC, remote ischemic conditioning; SPECT, single-photon emission computed tomography; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombosis in myocardial infarction.

Cooperation in Science and Technology Action is currently establishing a research network for preclinical multicenter testing of novel cardioprotective therapies. The IMPACT small-animal research network is currently being set up to undertake multicenter evaluation of novel cardioprotective therapies in mice and rat models of acute myocardial IRI, and validation of the research network will be undertaken using ischemic PreC. The CIBERCV (the acronym for Spanish Network-Center for Cardiovascular Biomedical Research) has set up the Cardioprotection Large Animal Platform, a Spanish multicenter network of 5 research centers, to perform experimental pig acute myocardial IRI studies testing the efficacy and reproducibility of promising cardioprotective interventions based on a prespecified design and protocols, centralized randomization, blinding assessment, core laboratory analyses of cardiac MRI imaging, histopathology, and proteomics (Rossello et al., 2019). The network is currently being validated using ischemic PreC. Also, it will be necessary in select preclinical studies to perform a more chronic follow-up and use the same endpoints as used in clinical trials (i.e., mortality over 6 to 12 months and the development of HF) (Heusch, 2018).

2. Multitargeted Approaches to Cardioprotection. One potential strategy for improving the clinical translation is to use a multitarget approach using either single agents (that have more than 1 target) or 2 or more therapies with different targets. The multitargeted approach may be a more effective than a single-targeted approach, especially given the complexity and different proponents of acute myocardial IRI (e.g., cardiomyocytes, endothelial cells, immune cells, platelets, microvasculature) (Davidson, Ferdinandy, et al., 2019). The ongoing PITRI study is testing whether administration of the intravenous $P2Y_{12}$ platelet inhibitor, cangrelor, prior to PPCI can prevent microvascular obstruction and reduce

TABLE 2
Major recent clinical cardioprotection studies of pharmacological interventions in patients with AMI

Study	n	Patient criteria	Treatment protocol	Main outcome	Notes
Cyclosporin-A					
Piot et al., 2008	58	All STEMI	IV bolus of CsA administered 10 min prior to PPCI	Reduce MI size assessed by AUC CK. No difference in troponin I. Subset of 37 patients reduce MI size on MRI at day 5 post-PPCI	First clinical study to show cardioprotection with CsA
Cung et al., 2015; Ottani et al., 2016 CIRCUS	970	Anterior STEMI Pre-PPCI TIMI 0/1	IV bolus of CsA administered prior to PPCI	No difference in primary outcome worsening in-pt heart failure, HHF, or adverse LV remodeling at 1 yr	Largest outcome study with CsA
Cung et al., 2015; Ottani et al., 2016 CYCLE	410	All STEMI	IV bolus of CsA administered prior to PPCI	No difference in primary endpoint of ≥70% ST-segment resolution 60 min after TIMI flow grade 3 or MI size (day 4 hs-cTnT) or LV remodeling at 6 mo.	
MTP-131					
Gibson et al., 2016 EMBRACE-STEMI	118	Anterior STEMI Pre-PPCI TIMI 0/1	IV 60-min infusion of MTP-131 started prior to PPCI	No difference in primary endpoint of MI size (72 h AUC CK). No difference in MI size or LV remodeling on MRI at 4 and 30 days	
TRO40303					
Atar et al., 2015 MITOCARE	163	All STEMI within 6 h chest pain Pre-PPCI TIMI 0/1	IV bolus of TRO40303 administered prior to PPCI	No difference in primary endpoint of MI size (72 h AUC CK or hs-cTnI)	There was a significant increase in major adverse events with the study drug compared with placebo
Nitrite					
Siddiqi et al., 2014 NIAMI	229	All STEMI TIMI 0/1	IV bolus of nitrite administered prior to PPCI	No difference in primary endpoint of MI size on MRI at day 6–8. No difference in LV remodeling or MI size by (72 h AUC CK or cTnI)	
Jones, Pellaton, et al., 2015	198	All STEMI	Intracoronary bolus of nitrite administered prior to PPCI	No difference in primary endpoint of MI size (72 h AUC CK or hs-cTnI)	
N-acetylcysteine + Nitroglycerin					
Hausenloy and Yellon, 2017; Pasupathy et al., 2017 NACIAM	75	All STEMI	IV infusion of NAC for 48 h initiated prior to PPCI. On background of IV GTN infusion	Reduction (by 33%) in primary endpoint of MI size by CMR at day 2–3 post-PPCI	
Inhaled nitric oxide					
Janssens et al., 2018 NOMI	250	All STEMI	Inhaled oxygen with NO started 10 min prior to PPCI and continued for 4 h	No difference in primary endpoint of MI size by MRI at day 2–3	
Tocilizumab (IL-6 receptor antibody)					
Kleveland et al., 2016	117	NSTEMI	IV 60-min infusion started prior to PPCI	Reduced hsCRP levels. Reduced median AUC for hs-cTnT by 30%	
Broch et al., 2021 ASSAIL-MI	199	All STEMI	IV 60-min infusion started during PPCI	Increased myocardial salvage by 5.6% on CMR (2–7 days) and less MVO but no difference in MI size	

AUC, area under curve; CMR: cardiac magnetic resonance; CK-MB, creatine kinase MB isoenzyme; GTN, glyceryl trinitrate; hs-cTnT/I, high-sensitive cardiac troponin T/I; HHF, hospitalization for heart failure; IV, intravenous; LAD, left anterior descending artery; MI, myocardial infarction; MVO, microvascular obstruction; NAC, N-acetylcysteine; NSTEMI, non-ST-segment elevation myocardial infarction; PPCI, primary percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

IS in STEMI patients (Bulluck et al., 2019) (Table 1). Cangrelor offers complete platelet inhibition with 1 to 2 minutes of administration, thereby potentially reducing the risk of MVO in STEMI patients, and has also been reported in small and large animal studies to reduce IS when given at reperfusion (Yang, Cui, et al., 2013; Yang, Liu, et al., 2013a, 2013b) (Table 2). The NACIAM study showed that the addition of an intravenous infusion of N-acetylcysteine on a background of nitroglycerin infusion reduced IS when compared with nitroglycerin infusion (Pasupathy et al., 2017) (Table 2).

The combined effects of limb RIC with ischemic PostC have been tested in a clinical study but were shown to have no additional cardioprotective effects in STEMI patients (Prunier et al., 2014). However, the LIPSIA study did report increased myocardial salvage and improved outcomes (less cardiac death, reinfarction, and new congestive HF at 3.6 years) in patients given both limb RIC and ischemic PostC when compared with control or ischemic PostC alone, although the effects of limb RIC alone were not tested (Eitel et al., 2015; Stiermaier et al., 2019). The ongoing CARIOCA (NCT03155022) study is also testing the combination of limb RIC and ischemic PostC in a large STEMI trial (Table 1). Based on the premise that limb RIC and exenatide had different cardioprotective targets (pig study) (Alburquerque-Béjar et al., 2015), the COMBAT MI study recently compared the IS-limiting effects of combining RIC with exenatide to that of limb RIC or exenatide alone in PPCI-treated STEMI patients. Unfortunately, the combination of RIC and exenatide did not translate into a reduction of IS and, more surprisingly, neither limb RIC nor exenatide alone reduced IS (García Del Blanco et al., 2021) (see Section V) (Table 1).

3. Targeting High-Risk Patients. One potential reason for the failure of limb RIC to improve clinical outcomes in STEMI patients in the CONDI2/ERIC-PPCI trial was the low-risk population recruited: they were optimally treated by PPCI and had relatively short ischemic times (median of 3 hours), and 96% of patients presented in Killip Class I and cardiac mortality (2.7%) was low at 12 months (Heusch and Gersh, 2020). RIC may be more effective in higher risk STEMI patients such as those presenting in HF or cardiogenic shock or those who were still treated by thrombolysis (Bøtker, 2020; Heusch and Gersh, 2020). In this regard, the FIRST study in which RIC was implemented in the clinical setting as part of a pre- and post-implementation study reported potential beneficial effects on MACE in those patients with cardiogenic shock or cardiac arrest (Cheskes et al., 2020). The planned RIC-AFRICA trial (NCT04813159) will evaluate RIC in higher risk STEMI patients treated by thrombolysis due to limited availability of PPCI (Hausenloy et al., 2020), and the RIP-HIGH trial will test the combination of RIC and local ischemic PostC in STEMI patients with heart failure (Killip class≥2) (i.e., those with severe hemodynamic impairment or cardiogenic shock) (NCT 04844931).

In summary, the translation of cardioprotection into the clinical setting for patient benefit has been largely disappointing. On the one hand, there is a wealth of preclinical studies unequivocally demonstrating cardioprotection in a variety of species and experimental models with different endpoints, such as arrhythmias, ventricular dysfunction, IS, and coronary MVO. On the other hand, despite several positive proof-of-concept clinical studies in STEMI patients demonstrating cardioprotection by mechanical and pharmacological approaches, there is now an increasing number of recent phase 2 studies showing no benefits on IS and several large phase 3 studies failing to show benefit on clinical outcomes despite positive phase 2 studies. This discrepancy results from the very different approaches inherent to preclinical research and clinical trials. Preclinical studies aim for novel knowledge and mechanistic understanding and therefore regularly use protocols that maximize the cardioprotective efficacy. In contrast, large clinical trials aim to identify a cure for disease in as many patients as possible and therefore regularly use an all-comer approach that does not consider the need of protection or potential confounders. The disappointment about the lack of translation then reflects the very different mutual expectations and a lack of communication between preclinical researchers and clinicians. The present review aims to improve such communication, with a particular focus on confounders.

On the preclinical side, potential reasons for failure in clinical translation include the lack of rigorous preclinical evaluation of novel cardioprotective therapies. Therefore, strategies for improving the preclinical assessment of novel cardioprotective therapies with the introduction of rigorous criteria that need to be fulfilled before proceeding to clinical studies and the use of multicenter networks of small and large animal research centers to blindly evaluate novel cardioprotective therapies are advocated (Lecour et al., 2021; Kreutzer et al., 2022). On the clinical side, targeting high-risk patients at risk of acute myocardial IRI (Heusch and Gersh, 2020) and consideration of confounders may improve the chances of successfully translating cardioprotection for patient benefit. With respect to our focus on confounders, it is important to note that most published clinical cardioprotection studies in AMI patients have not been suitably powered or specifically designed to test the confounding effects of comorbidities and comedications discussed in this article on the efficacy of cardioprotective therapeutic strategies, despite a significant proportion of recruited patients having these potential confounding factors. In an ideal world, we would propose that only those cardioprotective interventions that have fulfilled

stringent criteria and been established in a multicenter network as robust are taken forward from preclinical studies to be tested in a clinical trial, whereas less certain cardioprotective interventions would not even be tested clinically. Conversely, clinical trials for cardioprotection beyond that by reperfusion would be confined to those needing adjunct cardioprotection and not in an all-comer approach; at the least, a prespecified subgroup analysis for STEMI patients with Killip class ≥2 (i.e., those with severe hemodynamic impairment or cardiac shock) would be performed.

IV. Effects of Nonmodifiable Risk Factors and Comorbidities on Ischemia-Reperfusion Injury and Cardioprotective Strategies

A. Nonmodifiable Risk Factors

1. Aging.

a. Aging, IRI, and Cardioprotection. Age is, along with sex, the most prominent disease modifier. Not only does it increase the vulnerability of the heart to IRI, but it also hampers the therapeutic efficiency of several ischemic and pharmacologic conditioning strategies in many (but not all) experimental models and in some clinical studies, as recently reviewed (Ruiz-Meana, Boengler, et al., 2020; Ruiz-Meana, Bou-Teen, et al., 2020). The loss of cardioprotection during aging can be attributed to different factors, among them: (i) the higher burden of comorbidities (e.g., hypertension, metabolic disorders) that may impose additional damage to the heart (Andreadou et al., 2021), (ii) the more frequent use of concomitant medications that can cause therapeutic interferences (Ferdinandy et al., 2014), (iii) the coexistence of a chronic and deleterious proinflammatory myocardial environment (Ramos et al., 2017), (iv) the progressive accumulation of damaged and dysfunctional mitochondria within cardiomyocytes (Ruiz-Meana et al., 2019; Bou-Teen et al., 2022), and (v) the attenuation of some signaling pathways mechanistically involved in cell survival (Boengler, Schulz, et al., 2009). The majority of studies have described a loss of ischemic PreC-induced cardioprotection with age, yet some authors reported myocardial protection by ischemic PreC in old rat hearts (Webster et al., 2017). The cardioprotection provided by ischemic PostC has much greater therapeutic applicability than that afforded by ischemic PreC, but it is, in general, less robust and more dependent on the strength of the ischemic stimulus (Boengler et al., 2008). As in ischemic PreC, experimental evidence indicates an attenuation of its effectiveness with increasing age (Boengler et al., 2008; Przyklenk et al., 2008; Perez et al., 2016).

The age-dependent loss of ischemic PostC protection has also been described for rat hearts and isolated cardiomyocytes from aged rats (Chen, Gao, et al., 2016) and has been attributed to a defective autophagic response. Moreover, the age-dependent attenuation of the cardioprotective properties of PostC appears to be sensitive to sex interaction, as inferred from a recent study in which a specific modality of PostC protocol induced by alternate atrial/ventricular pacing (pacing PostC; see Section IVc2), which was shown to be effective in Langendorff-perfused rat hearts from young animals, remained cardioprotective in the hearts of old females but had no therapeutic benefit in the hearts of old males (Babiker et al., 2019). Regarding the human heart, it seems clear that ischemic PostC can be protective (Staat et al., 2005), but the influence of age on the extent of cardioprotection is more confusing. In a small clinical study of aged patients assigned to receive 2 different ischemic PostC protocols during PPCI (either 4 cycles of 30-second inflation/deflation or 4 cycles of 60-second inflation/deflation), the authors reported a significant beneficial effect on enzyme release (creatine kinase-MB and troponin I) in the postconditioned groups compared with controls, regardless of the ischemic algorithm (Zhang et al., 2018). Although promising, interpretation of clinical data are challenged by substantial interindividual variation in patients and the lack of studies in which the cardioprotective effect has been quantified with hard end-points measurements of IS.

RIC holds the potential of affording simultaneous protection to the heart and other organs susceptible to IRI (like the brain), making it particularly appealing for the systemic protection of elderly patients. Unfortunately, its effectiveness is less consistent than ischemic PreC and other conditioning strategies in rat hearts ex vivo (Lassen, Hjortbak, et al., 2021) and decreases even more with aging, as inferred from preclinical studies in rats in vivo (Behmenburg et al., 2017).

In a more clinically relevant context of patients undergoing CABG surgery with an average age of 76 years, RIC consisting of 4 5-minute inflations and deflations of a standard blood-pressure cuff on the upper arm, prior to anesthesia, did not result in any improvement in clinical outcomes (incidence of AMI, need of coronary revascularization, stroke, and death) (Hausenloy et al., 2015). It has been proposed that such an age-related decline in the ability of RIC to improve clinical outcomes might depend not only on the intrinsic changes developed by the aged heart but also on the loss of the cardioprotective properties of the released humoral factor(s) during aging (Heinen et al., 2018). Moreover, despite the positive results obtained in preclinical and small proof-of-concept clinical trials, the evaluation of its cardioprotective potential as adjunctive to PPCI in appropriately powered randomized controlled (RCT) clinical trials of patients with STEMI yielded neutral results, and RIC added no clinical benefit for outcomes when applied alone (Hausenloy, Kharbanda, et al., 2019) or in combination with exenatide (García Del Blanco et al., 2021), regardless of the subgroup of age.

b. Aging and Cardioprotective Signaling. Reduced expression or altered posttranslational modification of proteins involved in protective signaling cascades, including mitochondrial connexin 43, RISK, and SAFE pathways as well as changes in their subcellular localization, have been shown to participate in the loss of cardioprotection during aging, as extensively reviewed (Boengler et al., 2007; Boengler, Schulz, et al., 2009; Ruiz-Meana, Boengler, et al., 2020; Ruiz-Meana, Bou-Teen, et al., 2020). In addition to this, aged cardiomyocytes develop some idiosyncratic pathophysiological traits that reduce their tolerance to stress and injury and can outweigh the benefits of the therapeutic strategies. Among them, changes in calcium handling, excessive intracellular glycoxidative stress, mitochondrial calcium accumulation, and reduced number of healthy and metabolically competent mitochondria may play a relevant role (Ruiz-Meana et al., 2019; Bou-Teen et al., 2021). A broad spectrum of experimental studies suggests that restoration of the age-dependent loss of cardioprotection is possible through strategies like exercise protocols, dietary interventions (i.e., caloric restriction), and pharmacological agents (Calabrese, 2016a). In agreement with this concept, cardiac supplementation with a hydrogen sulfide donor (a gaseous neurotransmitter) has been recently shown to upregulate the hypoxia-inducible factor-1α/nuclear factor erythroid 2-related factor 2 signaling pathway involved in the late phase of cardioprotection in hearts from aged rats subjected to RIC (left hind limb ischemia) and subsequent ex vivo I/R (Wang, Shi, et al., 2021). In the context of ischemic PostC, exogenous administration of hydrogen sulfide in isolated hearts from aged rats exposed to IRI upregulated the age-dependent reduction in autophagy via the adenosine 5′-monophosphate activated protein kinase adenosine 5′-monophosphate activated protein kinase/mechanistic target of rapamycin pathway and restored the cardioprotective response in the aged hearts (Chen, Gao, et al., 2016). The same line of evidence led to the hypothesis that aged hearts might require a stronger conditioning stimulus (higher number of ischemic cycles or cycles with longer duration) to counteract the defective cytoprotective response. However, the relevance of this approach remains uncertain, as is the relative contribution of the different cytoprotective pathways to the therapeutic success of conditioning during aging.

2. Sex, IRI, and Cardioprotection. Although ischemic heart disease is a major cause of mortality and morbidity in both males and females, sex differences exist in terms of susceptibility, mechanisms, and outcomes to IRI observed between men and women Confounding factors (comorbidities, comedications) in ischemic heart disease may have sex-specific effects, and mechanisms underlying these differences are multiple and include gonadal hormones (for review see Perrino et al., 2021). Despite sex differences in IRI outcome, which occurs in an age-dependent manner, no clinical studies have yet been able to highlight sex as a confounding factor in the cardioprotective strategy of conditioning (Staat et al., 2005). Although most of the preclinical data exploring the cardioprotective effect of ischemic conditioning have been investigated in healthy young male animals, few studies suggest a sex difference in the cardioprotective response of conditioning against IRI in structurally normal myocardium (for review see Querio et al., 2021). As discussed in Section IVc, notable sex-related differences, however, have been noted in hypertrophied myocardium.

In the preclinical setting, some animal studies suggest that ischemic PreC may be less cardioprotective in females than in males, an effect that is also highly dependent on the age of the animals. In mice, ischemic PreC improved the functional outcome of IRI in both 10- and 18-week-old male mice. In contrast, female mice failed to be protected at an age of 10 weeks (Song et al., 2003; Turcato et al., 2006). In Wistar rats, ischemic PreC successfully reduced IS in 12- and 18-week-old males and females but failed to confer an antiarrhythmic effect in 12-week-old females (Ledvenyiova et al., 2013). Whereas both male and female rats can be preconditioned with endotoxin, the protection in females was only observed with higher doses of endotoxin, thus suggesting that the conditioning threshold may differ between males and females (Pitcher et al., 2005). Similarly, delayed pharmacological PreC with isoflurane protected male but not female rabbits (Wang et al., 2006). It is suggested that the apparent lack of protection with ischemic PreC in young female animals is due to estrogen-mediated better tolerance against IRI compared with males (Song et al., 2003).

In contrast, no sex difference in the cardioprotective effect of ischemic PreC was observed in Lewis rats of mixed age ranging between 10 and 20 weeks (Lieder et al., 2019). Also, in anesthetized Göttinger minipigs, there was no difference in IS, area of coronary MVO, and protection by ischemic PreC between young adult female, castrated male, and male pigs (Kleinbongard, Lieder, et al., 2022a; Kleinbongard, Lieder, et al., 2022b).

Similar findings have been reported with ischemic PostC. Ischemic PostC improved cardiac function and IS in both female and male rat hearts, but the protection differed depending on sex and the severity of the IRI (Crisostomo et al., 2006; Penna et al., 2009). Again, the increased effectiveness of ischemic PostC in males versus females is likely a result of overall reduced IRI (lower IS, less oxidative stress and apoptosis) in females versus males (Ciocci Pardo et al., 2018).

The protective effect of RIC may or may not be sex dependent. Whereas RIC of either 1 or 2 limbs in Lewis rats conferred similar protection in both male and female hearts subjected to I/R (Lieder et al., 2019), plasma isolated from male and female volunteers and perfused into

isolated rat hearts subjected to I/R protected the heart in a sex- and age-dependent manner (Heinen et al., 2018). Male but not female plasma collected after RIC protected the isolated rat heart against IRI compared with the non-preconditioned plasma (Heinen et al., 2018).

b. Sex and Cardioprotective Signaling. As observed with aging, differences in the activation of classic cardioprotective signaling pathways are observed between males and females (for review see Perrino et al., 2021). Besides the role of gonadal hormones, multiple cell survival pathways are regulated differently in males and females in a sex hormone–dependent or –independent manner. Increased phosphorylation of protein kinases B or C in female hearts subjected to IRI (Bae and Zhang, 2005) together with an increase in NO and the phosphorylation of aldehyde dehydrogenase and alpha-ketoglutarate dehydrogenase leading to a decrease in ROS (Lagranha et al., 2010; Casin and Kohr, 2020), may be involved in the sex differences in the cardioprotective efficacy of conditioning strategies. Similarly, increased phosphorylation of STAT3 and TNF receptor 2 in females versus males may affect the response to ischemic conditioning (Wang et al., 2007; Wang et al., 2008). Sex-specific downregulation of sirtuins, mitochondrial antioxidative signaling molecules, and modulation of the proinflammatory status in the older hearts are other mechanisms that may influence the outcome of the cardioprotective conditioning therapy in males versus females (Barcena de Arellano et al., 2019).

B. Comorbidities

1. Hypertension.

a. Hypertension and IRI. According to World Health Organization data, the global prevalence of systemic arterial hypertension was estimated to be approximately 30% in the adult population (Mills et al., 2016; Timmis et al., 2022) and ranks first among the leading causes for disability-adjusted life years (GBD 2019 Risk Factors Collaborators, 2020). Systemic arterial hypertension coexists with other major comorbidities discussed elsewhere in this paper. In the presence of any of these comorbidities, elevation of blood pressure contributes powerfully as an additive risk for the development of atherosclerosis and ischemic heart disease (Forouzanfar et al., 2017).

Hypertension promotes structural and biochemical changes in the myocardium. These include the development of left ventricular hypertrophy (LVH), alterations in coronary microvascular perfusion, and myocardial fibrosis. Although arguably imprecise as a diagnostic label, the term "hypertensive heart disease" is applied to describe the coexistence and consequence of coronary vascular changes, myocardial structural alterations, and enhanced risks of morbidity and mortality that occur in uncontrolled hypertension (Diamond and Phillips, 2005; Nwabuo and Vasan, 2020).

Cardiomyocyte hypertrophy, mediated by hemodynamic loading and neurohormonal influences, serves to maintain cardiac output and minimize ventricular wall stress in the presence of increased afterload. While muscle adaptation occurs, microvascular proliferation is mismatched, compounded by interstitial and perivascular fibrosis driven by oxidative stress and hormonal factors (Kong et al., 2014). Ultimately, unless therapeutic intervention stabilizes or reverses the hemodynamic and neurohormonal disturbances, the hypertensive heart is at risk of diastolic and/or systolic failure, re-entrant electrical disturbances, and ischemic changes. Indeed, even moderate hypertension is a determinant of congestive HF, arrhythmias, sudden death, ischemic heart disease, and acute coronary events including AMI. Critically, the presence of LVH is an independent predictor of morbidity and mortality, and LVH regression is a key goal of antihypertensive therapy (Bourdillon and Vasan, 2020).

The response of the hypertrophied myocardium to acute IRI has been the subject of extensive laboratory investigation. Previous literature (Ferdinandy et al., 2007; Pagliaro and Penna, 2017) suggests that hypertrophied myocardium displays greater sensitivity and reduced tolerance to IRI. Various mechanisms have been proposed, including reduced capillary perfusion, increased oxygen consumption, altered intracellular calcium handling, alterations in multiple metabolic pathways, downregulation of cardioprotective signaling pathways, and increased oxidative stress (for reviews see Ferdinandy et al., 2007; Suleiman et al., 2011; Pagliaro and Penna, 2017; Andreadou et al., 2021). There is persuasive evidence from various animal models of hypertension that coronary artery occlusion is associated with the development of more severe arrhythmic disturbances during IRI and that recovery of contractile function is depressed in reperfusion (stunning).

The issue of sensitivity to lethal or irreversible tissue injury (i.e., infarction) has been more contentious. In many experimental studies, standardized protocols to produce infarction reveal an inconsistent picture of IS in hearts with LVH. For example, some rat studies (Ebrahim et al., 2007a, 2007b; Wagner et al., 2013) report no increased IS in LVH, whereas others (Dai et al., 2009; Mølgaard et al., 2016; Yano et al., 2011) reveal moderate to large IS increases. This ambivalence in the experimental literature is not obviously explained by different hypertension models, hypertension duration, heart mass, IRI conditions, animal age, or methods of IS assessment, nNor is there a clear view from experimental studies of an altered pattern of cell death in LVH (necrosis, apoptosis, necroptosis, pyroptosis; see Section II).

In clinical studies, the question of IS in relation to LVH has been difficult to address, due largely to the relative imprecision of traditional methods of LVH

detection (ECG and echocardiography) and IS and risk zone quantification, as well as inconsistencies in the definition of normal LV mass thresholds. However, there are some noteworthy studies that have used cardiac MRI in STEMI patients. While MRI presents challenges in terms of standardization of technique and data interpretation, recent studies support the view that LVH is associated with increased IS in human subjects.

Nepper-Christensen et al. (2017) investigated the relationship between LVH (concentric or eccentric hypertrophy of various causes) and IS in a subgroup of the DANAMI-3 study in patients with STEMI. Despite similar onset-to-reperfusion time and target vessel involvement, patients with LVH showed higher peak troponin concentrations compared with patients without LVH. Acute and final IS were larger in patients with LVH, and the proportion of patients with MVO was higher. During 48 months of follow-up, the combined endpoint of all-cause mortality and hospitalization for HF was higher in the LVH group (9% vs 4%, $P = 0.003$). Similarly, Stiermaier et al. (2018) studied patients with and without LVH in a substudy of the AIDA STEMI trial. They applied MRI to assess IS, LV mass, and other parameters. IS was larger in patients with LVH compared with those without LVH, although clinical outcome (all-cause mortality, reinfarction, or congestive HF) at 12 months was not different between the groups.

Cohort studies are consistent with the broad messages from epidemiologic studies. They point to LVH as a useful risk stratification variable in STEMI, although its potential prognostic value as a determinant of long-term outcome after STEMI remains to be further evaluated in larger trials. Such studies are undoubtedly warranted, given that patients with LVH are at greater risk of AMI and other ischemic events. Moreover, hypertension was found to be an independent factor for underprescription of guideline-directed medical therapy post-AMI in the PROMETHEUS registry, which could further worsen long-term outcome for a substantial proportion of hypertensive patients (Ge et al., 2019).

Considering the increased risk of hypertensive patients developing ischemic heart disease and the greater susceptibility to IRI when LVH is present, cardioprotection of hypertrophied myocardium presents an important scientific and clinical challenge. During the past 3 decades, many experimental studies have reported a number of different approaches with varying degrees of success. More recent studies used IS as a robust endpoint of cardioprotection and reveal potential mechanistic insights.

b. Hypertension and Cardioprotection. Following the earliest description of ischemic PreC in LVH (Speechly-Dick et al., 1994), many further studies confirmed that ischemic or pharmacological PreC protocols may reduce IS in hypertensive animals with LVH (Ferdinandy et al., 2007). However, a number of factors may attenuate the effectiveness of ischemic PreC in LVH. While these factors are not clearly defined, cardioprotection in LVH may be highly model dependent, influenced by the nature of the preconditioning stimulus, modified by hypertension duration, animal sex and age, and the progression to cardiac decompensation. Ebrahim et al. (2007b) showed that ex vivo hearts from male normotensive rats and spontaneously hypertensive rat (SHR) were protected against infarction by 2×5 minute ischemic PreC cycles in 3- to 4-month-old and 7- to 8-month-old animals. However, this was not the case in hearts from 12- to 13-month-old animals, either normotensive or SHR. Although the addition of the angiotensin II converting enzyme (ACE) inhibitor captopril, which enhances tissue kinin concentration, partially restored ischemic PreC efficacy in aged normotensive hearts, it did not do so in aged SHR hearts. In contrast to these findings, Dai et al. (2009) using an in vivo infarct model showed that 3×3 minute ischemic PreC cycles effectively limited IS in 16-month-old female normotensive rats and SHR. Fantinelli et al. (2013) established in an ex vivo infarct model that the threshold for ischemic PreC efficacy is shifted in SHR hearts. A single 5-minute ischemic PreC cycle protected SHR hearts against 35-minute index ischemia but was ineffective against 50-minute index ischemia, whereas a 3×2 minute ischemic PreC protocol was fully effective. Clearly, there are discrepancies in the key findings between closely aligned studies, and these may be related to many factors, including animal sex-related differences in key molecular components of cardioprotective signaling (see Section IVb), infarct model, and ischemic PreC protocol. However, it seems likely that, while key cardioprotective pathways activated by ischemic PreC can be recruited in moderate hypertrophy, the threshold for activation of these mechanisms may require an ischemic PreC stimulus of greater intensity than in normotensive hearts, but this is dependent on duration of hypertension, experimental LVH models, and index ischemia conditions.

Other forms of ischemic conditioning in LVH have received scant attention. Translation of RIC to elective clinical settings, most notably cardiac surgery, has been contentious (see Section III and Heusch et al., 2015; Zaugg and Lucchinetti, 2015). In a small study of patients with cardiac hypertrophy undergoing aortic valve replacement surgery, there was no evidence of benefit (morbidity outcomes, creatine kinase MB release, or troponin T release) in patients receiving RIC (upper limb ischemia), even when propofol was excluded as a confounding factor (Song et al., 2017) (see Section Vb2 for a discussion of anesthetic effects). Also, no cardioprotection was seen in patients undergoing

transcatheter aortic valve implantation for aortic stenosis (Kahlert et al., 2017).

Early evaluation of ischemic PostC in hypertrophied myocardium (Fantinelli and Mosca, 2007) suggested that ischemic PostC (3×30 second cycles) was equally effective in promoting post-ischemic contractile function in normotensive and SHR hearts ex vivo. However, Penna et al. (2010) showed that while ischemic PostC (5×10 second cycles) limited IS in normotensive rat hearts, the same protocol was ineffective in SHR hearts ex vivo. Additionally, 4-week treatment with captopril, while inducing LVH regression, did not restore the ability to postcondition SHR hearts. Similarly, in an in vivo model of AMI, neither of 2 ischemic PostC protocols, 3×30 second or 6×10 second cycles, conferred protection in young SHR with established LVH, although both protocols were effective in normotensive rats (Wagner et al., 2013). Moreover, phosphorylation (inhibition) of glycogen synthase kinase (GSK)-3β was observed 5 minutes after ischemic PostC in normotensive hearts but not in SHR hearts.

As noted for ischemic PreC, it is likely that duration of hypertrophy, animal sex, age, gradual onset of decompensation, and other factors may contribute to discrepant findings for ischemic PostC between laboratories. Hernández-Reséndiz et al. (2013) studied ischemic PostC in rats with either compensated hypertrophy after 7 days angiotensin II treatment or dilated cardiomyopathy/decompensated hypertrophy after 14 days angiotensin II treatment. Perhaps surprisingly, in both groups Ischemic PostC (5×30 second cycles) was effective in limiting IS in LVH, comparable to protection seen in normotensive control rats. However, intriguing alterations in phosphorylation of RISK components occurred between 7 days and 14 days, suggesting that hypertrophy-related downregulation of 1 kinase may be compensated by the parallel upregulation of another kinase pathway.

Babiker et al. (2019) undertook an extensive series of experiments using pacing-induced PostC (3×30 second cycles of alternate atrial/ventricular pacing) in various rat models and explored the interactions of sex, age, and disease states. Interestingly, age and sex were major determinants of PostC efficacy. While effective in young animals of either sex, pacing postconditioning was ineffective in senescent male hearts yet still effective in senescent female hearts. Moreover, the effect of pacing PostC in LVH was preserved in mature female, but not male, SHR. This work underscores the importance of key biologic variables, as well as experimental conditions, which may impede ready interpretation of findings from different laboratories.

c. Hypertension and Cardioprotective Signaling. A similarly controversial and unsettled picture has emerged for a variety of pharmacological preconditioning approaches in LVH. However, many of these studies provide helpful insights into modifications of cardioprotective signaling mechanisms in LVH that may be relevant to our interpretation of contradictory experimental findings and, perhaps more importantly, our ability to make translational advances for clinical cardioprotection in LVH. For example, 10-minute pretreatment with bradykinin (an upstream autacoid trigger of ischemic PreC acting through the G-protein coupled bradykinin B2 receptor) induced concentration-dependent IS reduction in normotensive hearts, but the protective effect in moderate LVH was markedly attenuated (Ebrahim et al., 2007a). González Arbelaez et al. (2016) showed that CsA when given as a short pretreatment prior to index ischemia in SHR hearts was as effective as a single 5-minute cycle of ischemic PreC in limiting IS. Moreover, the effects of ischemic PreC and CsA were PKC-dependent and additive. Yano et al. (2011) investigated the effects of the δ-opioid receptor agonist, (D-Ala2, D-Leu5)-enkephalin, or erythropoietin pretreatment in 3- to 4-month-old normotensive and hypertensive rats (SHR stroke-prone strain). While each of the agonists induced modest IS limitation in normotensive hearts, no protection was observed in hypertrophied hearts, although ischemic PreC (2×5 minute) was highly protective in both groups. Further, they showed that in a different model of pressure-overload hypertrophy (thoracic aorta constriction for 4 weeks), erythropoietin preconditioning was ineffective.

Chen, Wu, et al. (2016) reported that in 9- to 10-month-old SHR with moderate LVH, pharmacological PreC with 30-minute pretreatment with isoflurane was ineffective in limiting IS. Of interest, the efficacy of isoflurane preconditioning in normotensive animals was associated with augmentation of manganese-dependent superoxide dismutase activity, a key mitochondrial antioxidant. Despite higher baseline manganese-dependent superoxide dismutase activity in SHR mitochondria, isoflurane preconditioning did not increase it further.

While delayed ischemic PreC ("second window" preconditioning occurring between 24–72 hours after the preconditioning stimulus) have not been studied in LVH, delayed pharmacological PreC 24 hours after transient (1 hour) exposure to isoflurane (2.1% v/v) was not observed in LVH induced by thoracic aorta constriction (Ma et al., 2014). The loss of delayed protection after isoflurane was associated with a failure of induction of inducible NOS and cyclooxygenase 2, which have been previously implicated in the mechanism of delayed ischemic PreC (Baxter and Ferdinandy, 2001).

As discussed in Section Vb2, pharmacological PostC in LVH has received relatively little attention. Halogenated anesthetic PostC has been shown to be cardioprotective in normal myocardium in many experimental studies, sharing similar mechanisms of protection as ischemic PostC (via the RISK or SAFE pathways and

mPTP inhibition) (for review see Lemoine et al., 2016). However, in LVH induced by suprarenal aortic constriction, the IS-limiting effects of sevoflurane PostC and ischemic PostC were abolished. This was associated with abrogation of phosphorylation of the major RISK pathway components (Ma et al., 2013). The noble gas helium is an interesting and safe conditioning candidate, capable in normal subjects of inducing cardioprotection when substituted for nitrogen in room air and administered by inhalation, either as a PreC protocol (classic and delayed) prior to index ischemia or as a PostC protocol during early reperfusion (Smit et al., 2015). Oei et al. (2012) showed that helium PostC was ineffective at limiting IS in 3-month-old male SHR with rather modest LVH. The combination of delayed helium PreC (brief exposure 24 hours before ischemia), classic helium PreC (exposure immediately before ischemia), and helium PostC (exposure in early reperfusion) induced modest protection in the SHR heart. The loss of protection in SHR myocardium was not obviously associated with changes in GSK-3β or protein PKCε phosphorylation potential.

In summary, the experimental literature reveals an ambivalent picture of the effectiveness of conditioning approaches in LVH. While some studies suggest preservation of PreC and PostC potential in hypertension models, others suggest abrogation of protection, likely associated with perturbation of key cardioprotective signaling pathways. It is reasonable to conclude that a large number of experimental and biologic variables contribute to the discrepancies in experimental findings, notably animal sex, age, and stage of hypertension/hypertrophy. Nevertheless, given the equivocal nature of the experimental literature and the limited number of clinical studies in LVH, conditioning protocols cannot be assumed to be robustly effective in hypertensive patients with LVH (or possibly in patients with other forms of cardiac remodeling where similar structural and molecular maladaptations occur). The clinical picture may be further complicated by the chronic application of antihypertensive agents, barely modeled in experimental studies, which could induce regression of hypertrophy and/or potentiate endogenous cardioprotective mechanisms, independently of conditioning protocols (see Section V). Unfortunately, resolution of the experimental controversies is unlikely to be achieved through further experimental studies. Rather, the imperative is that the design of cardioprotection trials will control rigorously for LV mass, among many other clinical variables, as a key determinant of any measured outcomes. Given the prevalence of hypertension and LVH in the population eligible for cardioprotective intervention, such a cohort could represent a significant number of higher risk subjects in any future trial.

2. Hyperlipidemia.

a. Hyperlipidemia and IRI. Among the different comorbidities that are related to cardiovascular disease, dyslipidemias are present in 40% of patients with ischemic heart disease (Mazo et al., 2019). Hyperlipidemia shows the strongest association with AMI with an odds ratio of 8.39 (95% CI: 8.21–8.58) (Andreadou et al., 2021). The majority of preclinical studies and some small-scale clinical studies have shown that hyperlipidemia per se leads to a significant exacerbation of myocardial IRI. Hyperlipidemia, independently from the development of atherosclerosis, exerts direct myocardial effects such as impaired cardiac performance and diminished adaptation to ischemic stress (for review see Mazo et al., 2019). More recent studies confirm that besides elevated low-density lipoprotein cholesterol (LDL-C), triglycerides and proprotein convertase subtilisin/kexin type 9 (PCSK9) may independently modulate cardiovascular risk. In particular, PSCK9 indirectly affects cardiomyocytes by monitoring the plasma concentration of LDL-C and oxidized low-density lipoprotein (for a review, see Andreadou, Tsoumani, et al., 2020). PCSK9 is also expressed in the myocardium (Wolf et al., 2020) and impacts on IS development and cardiac function as well as on autophagy (Ding et al., 2018). Moreover, hyperlipidemia induces microvascular dysfunction mainly through oxidative stress and inflammation, mechanisms that may also explain the increased susceptibility of the myocardium to I/R (for a review, see Andreadou, Iliodromitis, et al., 2017).

b. Hyperlipidemia and Cardioprotection. The first evidence that comorbidities may hamper the cardioprotective effect of preconditioning maneuvers was published in hypercholesterolemic rodent models in the mid-1990s. Since then, the majority of studies have confirmed these original observations including some small-scale clinical trials (Ferdinandy et al., 2014; Andreadou, Iliodromitis, et al., 2017). Although the loss of the IS-limiting effect of ischemic PreC has been shown in different models of diet-induced hyperlipidemia in rats (for a review, see Ferdinandy et al., 2014), other studies have shown that ischemic PreC (2×5 minute) significantly decreased IS in vivo (Iliodromitis et al., 2006) or in isolated hearts of hypercholesterolemic rabbits (D'Annunzio et al., 2012) (for a review, see Mazo et al., 2019). The divergence in the results could be attributed to different experimental models involving different animal species and different types and duration of diets. Although various animal models of different types of hyperlipidemia exist, only a few of them have been employed and published for studying myocardial IRI and cardioprotection (Andreadou, Schulz, et al., 2020).

A loss of the IS-limiting effect of ischemic PostC has been confirmed by several studies in different animal species such as hypercholesterolemic rats (Kupai et al., 2009; Wu et al., 2014) and rabbits (Iliodromitis et al., 2010; Andreadou et al., 2012).

Preclinical studies have investigated the effects of hyperlipidemia on RIC. Ma et al. demonstrated that RIC failed to reduce myocardial necrosis and apoptosis in hypercholesterolemic rat hearts undergoing I/R (Ma et al., 2017). RIC attenuated IS, delayed cardiomyocyte apoptosis, and improved cardiac systolic function in nonhypercholesterolemic mice, but these beneficial effects were not evident in hypercholesterolemic mice (Hong et al., 2019). In low-density lipoprotein receptor knockout mice with high-fat diet induced atherosclerosis and subjected to I/R with or without anesthesia-induced preconditioning or RIC, IS was reduced (Petermichl et al., 2021); however, lipid levels were not measured.

In summary, further studies are required to investigate at which stage of hyperlipidemia, atherosclerosis, and endothelial dysfunction of the coronary arteries, RIC, and pharmacological conditioning strategies may exert cardioprotective effects.

c. Hyperlipidemia and Cardioprotective Signaling. Explanations for the mechanisms by which hyperlipidemia may interfere with conditioning mechanisms include dysregulation of cardioprotective cascades such as lack of activation or inactivation of the RISK pathway, failure to modulate the K_{ATP} channels activity, impaired NO availability, and a redistribution of the intracellular localization of connexin 43 in cardiomyocytes (reviewed in Andreadou, Iliodromitis, et al., 2017). The dysregulation of the RISK pathway has been recently confirmed, since RIC failed to reduce myocardial necrosis and apoptosis due to a failure of an increase of Akt and GSK-3β phosphorylation in hypercholesterolemic rat myocardium (Ma et al., 2017). Similarly, cardioprotection induced by RIC was lost in cholesterol-fed mice exposed to I/R by alteration of the phosphatase and tensin homolog/Akt signaling pathway that inhibits GSK-3β (Hong et al., 2019). The aforementioned studies suggest that GSK-3β inhibition may be a novel therapeutic strategy for hypercholesterolemic subjects. The activation of the RISK pathway in hypercholesterolemic rat myocardium was restored when lycopene, a type of carotenoid, was given in combination with ischemic PostC, and this led to reduced IS and decreased cardiomyocyte apoptosis by increasing the phosphorylation levels of Akt, ERK1/2, and GSK-3β (Duan et al., 2019). However, in another study, posttranslational activation of ERK, rather than PI3K/Akt, participated in the cardioprotective effect of ischemic PreC and atorvastatin in hyperlipidemia (Sun et al., 2017).

Apart from dysregulation of the RISK pathway, inhibition of myocardial matrix metalloproteinases (MMP), and especially MMP-2, is involved in ischemic PreC-induced cardioprotection. MMP-2 inhibition by ischemic PreC was absent in hyperlipidemia (Giricz et al., 2006), and moderate inhibition of MMP-2 by ilomastat still provided cardioprotection in hyperlipidemia (Bencsik et al., 2018). Although novel inhibitors of MMP-2 dose-dependently reduced IS in an in vivo rat AMI model, their cardioprotective effects at the most effective doses in normal animals were abolished by hypercholesterolemia (Gömöri et al., 2020). Hypercholesterolemia has been shown to alter cardiac gene expression profile including of miRs as demonstrated by a downregulation of cardiac miR 25 in hypercholesterolemic rats (Varga et al., 2013). The attenuated cardioprotective effect of ischemic PreC in hypercholesterolemia correlated to a diminished miR 125b-1-3p induction, indicating that diet-induced hypercholesterolemia blunts the cardiac overexpression of miR 125b-1-3p triggered by ischemic PreC (Szabó et al., 2020). Therefore, modulation of cardiac miR 125b-1-3p could be a feasible target for cardioprotection also in hypercholesterolemia (Varga et al., 2018).

The impact of hypercholesterolemia on mitochondrial membrane fluidity, mitochondrial energetics, and related pathophysiological changes in myocardial injury and function has been investigated in a type 1 diabetes rat model fed with a high fat-cholesterol diet. The authors concluded that the cholesterol enriched diet induced adverse remodeling, which negatively affected mitochondrial function, relating to distortion of the mitochondrial membrane protein lipid interactions, which led to inhibition of endogenously initiated cardioprotective mechanisms (Ferko et al., 2018).

Additional mechanisms refer to the observation that hypercholesterolemia attenuates cardiac autophagy in parallel with the activation of the mechanistic target of rapamycin pathway and an activation of apoptosis, demonstrating a strong relationship between increased cardiac apoptosis and hypercholesterolemia (Giricz et al., 2017). Therefore, the imbalance between prosurvival and death pathways might play a role in the abolishment of cardioprotection in hypercholesterolemia (Giricz et al., 2017).

Some cardioprotective interventions have been studied for their potential to provide cardioprotection or to reestablish cardioprotection in the presence of hyperlipidemia. Zinc supplementation during hyperlipidemia reestablished ischemic PreC (4×5 minute) in rats (Kansal et al., 2015). Pioglitazone restored the cardioprotective effect of ischemic PreC (4×5 minute) in hyperlipidemic rat heart, an effect that may be via PI3K and mechanistic target of rapamycin (Mittal et al., 2016). Preconditioning by dopamine (Gupta et al., 2015) or PreC and PostC by nicorandil (Li et al., 2015) exerted cardioprotection in the presence of hyperlipidemia in rats.

In summary, beyond the known molecular mechanisms that blunt the cardioprotective signaling of conditioning interventions in hyperlipidemia, recent evidence suggests that GSK-3β inhibition, modulation of cardiac miR 125b-1-3p, moderate MMP inhibition,

and cardiac autophagy may represent novel cardioprotective therapeutic interventions for hypercholesterolemic subjects. Whether molecular and metabolic rearrangements in hyperlipidemia may modify the response of cardioprotective maneuvers in the clinic remains to be established.

3. Diabetes.

a. Diabetes and Cardioprotection. According to World Health Organization data, the global prevalence of diabetes mellitus in 2014 was estimated to be 9% (https://www.who.int/nmh/publications/ncd-status-report-2014/en/), with a variation from ≤4% (e.g., in the United Kingdom) to ≥10% (e.g., in Germany) in 2019 (Timmis et al., 2022). High fasting blood glucose ranks third among the leading risk factors for disability-adjusted life years (years lived with severe illness) based on the global burden of disease data for 2019 (GBD 2019 Risk Factors Collaborators, 2020), and patients' mortality increase with the duration of type 2 diabetes depending on the level of glycated hemoglobin achieved (37% increase over 11 years with glycated hemoglobin exceeding 7%) (Joseph et al., 2022).

Protection by ischemic PreC is lost in diabetes when the heart has become insulin resistant, and ischemic PreC cannot further increase glucose uptake (Ji et al., 2013), thereby reinforcing the importance of glucose metabolism for efficient conditioning interventions (see Section II). Several but not all studies reported that the cardioprotective effect of ischemic PreC is reduced in animal models of type 2 diabetes. Ischemic PreC (3×2 minute) failed to protect rat hearts with diabetic cardiomyopathy from IRI probably due to deteriorated mitochondrial function (Ansari and Kurian, 2020a). Pharmacological PreC with inhaled sevoflurane, however, remained cardioprotective during diabetes in mice, via adenosine 5′-monophosphate activated protein kinase-independent activation of a prosurvival mitogen-activated protein kinase member (Xie et al., 2020). In contrast, isoflurane pharmacological PreC failed to induce cardioprotection in obese type 2 diabetic (db/db) mice, and this effect was associated mainly with abnormal regulation of eNOS and mitochondrial respiratory complex I (Ge et al., 2018). Pharmacological PreC with hydrogen sulfide attenuated myocardial injury in diabetic rat hearts via an alternative to the PI3K pathway, although hydrogen sulfide PreC could not attenuate I/R-induced oxidative stress (Ansari and Kurian, 2020b). Hydrogen sulfide PreC also reduced IS in isolated rat hearts with diabetes and with diabetic cardiomyopathy (Ansari and Kurian, 2019). Recent studies have investigated the influence of the duration of type 2 diabetes on the cardioprotective effects of ischemic PreC. The metabolic and endocrine disruption in type 2 diabetes was associated with ischemic intolerance and inhibition of ischemic PreC's cardioprotective effects (Russell et al., 2019). The duration of diabetes may influence the response to cardioprotective maneuvers because early-onset type 2 diabetes is associated with an endogenous cardioprotection characterized by underlying mechanisms distinct from those involved in exogenously induced cardioprotection by conditioning modalities (Povlsen et al., 2013; Kristiansen et al., 2019). However, when male Zucker diabetic fatty rats in different stages of diabetes were subjected to IRI in the Langendorff model and randomized to ischemic PreC stimulus (2×5 minute) or control, ischemic PreC reduced IS in all groups irrespective of the presence of diabetes and its duration (Hjortbak et al., 2018). This cardioprotective effect was associated with an adaptation to myocardial glucose oxidation capacity (Hjortbak et al., 2018).

Hyperglycemia also blunts IS reduction by ischemic PostC (Przyklenk et al., 2011; Chen et al., 2016c) and RIC (Kiss et al., 2014; Baranyai et al., 2015; Tyagi et al., 2019). While alpha-lipoic acid PreC and ischemic PostC did not protect isolated hearts from diabetic rats, adding both interventions reduced IS (Mokhtari et al., 2022). Similarly to alpha-lipoic acid, hydrogen sulfide PostC reduced IS in isolated hearts taken from diabetic rats (Ansari et al., 2022); minocycline given at reperfusion protected isolated hearts from diabetic rats (Sobot et al., 2022).

More recent studies indicate that fluctuations in circulating glucose levels influence the response to cardioprotective maneuvers more in nondiabetic than in diabetic models (Saito et al., 2016; Pælestik et al., 2017; Kristiansen et al., 2019). The clinical implications of these findings remain to be clarified. While clinical studies of ischemic PostC in STEMI patients have yielded mixed results in terms of limiting IS, most studies applying RIC demonstrated such reduction as measured by nuclear imaging or MRI techniques or myocardial biomarker release (Heusch, 2020). Data relying on post hoc analyses indicate that RIC protocols used in clinical settings also yield cardioprotection in patients with type 2 diabetes undergoing PPCI (Sloth et al., 2015). In patients with diabetes undergoing CABG surgery, RIC also induced cardioprotection, but the use of sulfonylureas abrogated protection (Kottenberg et al., 2014). However, it remains to be investigated whether any variation in IS reduction relates to hyperglycemia. Regardless of perturbations in circulating glucose levels, experimental studies indicate that type 2 diabetes blunt the cardioprotective response to ischemic PostC and RIC stimuli by impairing activation of the cardioprotective RISK and SAFE pathways.

In summary, type 2 diabetes appears to abolish the cardioprotective efficacy of both ischemic PreC and PostC, whereas some but not all pharmacological conditioning interventions seem to reduce IS in diabetic animals. Whether the confounding effects of diabetes

on cardioprotection observed in the experimental settings translate into the clinical setting remains to be settled (Kleinbongard et al., 2020). The number of patients that have been enrolled in currently available clinical studies are low, and the methods used to assess IS vary, so further studies are required to define the efficacy of conditioning strategies in humans with diabetes (Reinstadler et al., 2017).

b. Diabetes and Cardioprotective Signaling. Among the underlying mechanisms that may attenuate the effect of cardioprotective maneuvers in diabetic subjects are failure to phosphorylate ERK, PI3K, and Akt (Tsang et al., 2005; Whittington et al., 2013), the maintenance of hexokinase II at the mitochondria (Gurel et al., 2013) and the cytoprotective regulation of the mPTP (Itoh et al., 2012), along with dysfunction of sarcolemma and mitochondrial K_{ATP} channels (Kersten et al., 2001; del Valle et al., 2003), upregulation of mechanistic target of rapamycin (Baranyai et al., 2015), and a decrease in autophagy (Qian et al., 2009; Kobayashi et al., 2012). Many studies have demonstrated that the attenuated response to ischemic PreC may be overcome by an intensified stimulus when a critical level of Akt phosphorylation is achieved to confer protection (Tsang et al., 2005; Hausenloy et al., 2013; Hjortbak et al., 2018; Kristiansen et al., 2019).

Additionally, cardioprotective interventions may also become inefficient when examined in the prediabetic state, knowing that in the early stage of diabetes the heart is often already in a protective state (Zuurbier et al., 2014). This may have implications for clinical studies, where patients are frequently in a nondiagnosed prediabetic state. Impairment in O-linked β-N-acetylglucosamine signaling (Jensen et al., 2013) and release of cardioprotective humoral factors, which depends on intact neural function, may contribute to attenuating RIC-induced cardioprotection (Jensen et al., 2012). Diabetes may increase ROS production (Ansley and Wang, 2013; Su et al., 2013; Baranyai et al., 2015) and inhibit autophagy to attenuate RIC-induced cardioprotection (Baranyai et al., 2015). Diabetes-induced reduction in NO bioavailability may also contribute to decreasing remote RIC-induced cardioprotection (Kiss et al., 2014). Finally, diabetes may reduce the phosphorylation of adenosine 5′-monophosphate activated protein kinase α (Han et al., 2014), with a possible role for elevated adipocyte-released microvessels containing miR 130b-3p for adenosine 5′-monophosphate activated protein kinase downregulation (Gan et al., 2020), and increase the phosphorylation of mechanistic target of rapamycin to attenuate cardioprotection of remote postconditioning (Tyagi et al., 2019). A recent study in Ossabaw minipigs which are prone to develop a full metabolic syndrome, including insulin resistance with progression to type 2 diabetes, hyperlipidemia, obesity, and hypertension with the subsequent development of coronary atherosclerosis and occasional spontaneous myocardial infarction, demonstrated loss of protection by ischemic PreC in these pigs even before they had developed the diseased phenotype; the loss of protection was associated with lack of activation of STAT3 and a primordial genetic difference in mitochondrial function and STAT signaling from other pig strains. Thus, lack of cardioprotection can even become manifest before a metabolic syndrome has developed (Kleinbongard et al., 2022).

In summary, hyperglycemia and diabetes mellitus appear to attenuate the cardioprotective efficacy of mechanical conditioning strategies in experimental animal and human ex vivo heart tissue studies. Underlying mechanisms involve interference with the cardioprotective signaling pathways. The confounding effects of hyperglycemia and diabetes mellitus on cardioprotection can be overcome by increasing the conditioning stimulus. Evidence for these phenomena is not yet available from clinical studies.

4. Interim Coronary Events, IRI, and Cardioprotection. There are 2 principal pathways by which coronary events could interfere with cardioprotection. A coronary event could induce cardioprotection per se and then either be additive to a cardioprotective intervention or limit the potential for a further cardioprotective intervention. Alternatively, a coronary event could attenuate the effect of a cardioprotective intervention by interfering with its mechanisms. Indeed, there is evidence for both these types of interference. In animal experiments, coronary microembolization, which mimics a minor acute coronary syndrome after plaque rupture or erosion, shortly before a sustained myocardial I/R neither induced (Skyschally et al., 2004) nor interfered with ischemic PreC protection in reducing IS (Skyschally et al., 2005); however, the coronary microembolization per se slightly increased IS.

In patients, pre-infarction angina is a prototypic event that is protective per se in that 1 or several episodes of myocardial ischemia in the presence of epicardial coronary atherosclerosis are precipitated by sympathetic activation such as stress or exercise and then exert an ischemic PreC effect on the myocardium for a limited period of time (Heusch, 2001; Rezkalla and Kloner, 2004). Pre-infarction angina in patients decreases IS (Andreotti et al., 1996; Iglesias-Garriz et al., 2001; Kloner et al., 1998; Lønborg, Kelbæk, Vejlstrup, Bøtker, Kim, Holmvang, Jørgensen, Helqvist, Saunamäki, Thuesen, et al., 2012; Reiter et al., 2013) and no-reflow (Karila-Cohen et al., 1999; Colonna et al., 2002; Niccoli et al., 2014), and it improves patients' prognosis (Lorgis et al., 2012; Herrett et al., 2014; Schmidt et al., 2015). However, the protection by pre-infarction angina is attenuated by nonmodifiable risk factors, such as age (Ishihara et al., 2000); modifiable risk factors, such as smoking; and comorbidities, such as

dyslipidemia (Niccoli et al., 2014). Also, the time interval between the prodromal angina and the onset of AMI is decisive and was between 1 (Kloner et al., 1998; Ishihara et al., 2000; Iglesias-Garriz et al., 2001; Reiter et al., 2013) and 7 (Karila-Cohen et al., 1999; Colonna et al., 2002; Lønborg Kelbæk, Vejlstrup, Bøtker, Kim, Holmvang, Jørgensen, Helqvist, Saunamäki, Thuesen, et al., 2012; Herrett et al., 2014) or 14 days (Schmidt et al., 2015) when resulting in a clinical benefit. Prodromal peripheral ischemia in the presence of peripheral artery disease can also elicit a RIC-form of cardioprotection in patients with AMI (Herrett et al., 2014; Schmidt et al., 2015), whereas the presence of a nonculprit stenosis with a significantly reduced fractional flow reserve as such (no evidence for ischemia in this territory was provided) was not associated with better salvage in a larger cohort of STEMI patients (Ekström et al., 2021). Mechanistically, in experiments in pigs, coronary microembolization preceding a sustained myocardial I/R upregulated myocardial TNFα which then reduced IS (Skyschally et al., 2007). Patients with prodromal angina have reduced platelet reactivity (Scalone et al., 2013) and better thrombolysis (Andreotti et al., 1996), suggesting a role for platelet function and coagulation in the protective effects of pre-infarction angina. The clinical observations on the benefits of pre-infarction angina and of prodromal peripheral ischemia underpin the concept of (remote) ischemic PreC as a tool to induce cardioprotection.

Interventional reperfusion obviously involves manipulation of the culprit atherosclerotic lesion and also entails the risk of further release and embolization of atherothrombotic debris into the coronary microcirculation, which there acts to extend the infarct (Heusch and Gersh, 2017). Direct stenting can attenuate the microvascular injury as measured by TIMI flow and ECG resolution (Loubeyre et al., 2002), but thromboaspiration did not reduce IS or microvascular obstruction, as measured by MRI (Desch et al., 2016). Ischemic PreC is not feasible in AMI since the time of its occurrence is not known. Manipulation of the culprit lesion by an ischemic PostC protocol of repeated balloon occlusion/reperfusion entails a further risk for embolization of atherothrombotic debris. In a pig model of reperfused AMI, ischemic PostC reduced IS, but in combination with induced coronary microembolization the IS was larger than without microembolization, reflecting the interference of mechanically induced microembolization with cardioprotection (Skyschally et al., 2013).

In summary, a preceding coronary event characterized by ischemia may induce a degree of cardioprotection, and there are several clinical series to substantiate this. It has yet not been possible to exactly identify the molecular mechanisms of benefit and to harness these into a therapeutic strategy. In contrast, a coronary event characterized by necrosis and microvascular obstruction appears to be universally detrimental.

5. Atrial Fibrillation.

a. Atrial Fibrillation and IRI. Atrial fibrillation (AF) and coronary artery disease frequently coincide, particularly with advanced age. Up to 47% of patients exhibiting any form of AF also present with coronary artery disease, while among patients with coronary artery disease, up to 5% manifest with AF (Lieder, Breithardt, et al., 2018). Many established and emerging risk factors for AF are also fundamental for the development of coronary artery disease and IRI (Kirchhof et al., 2012; Andrade et al., 2014) and the 2 disease entities appear to share a common mechanistic basis that goes both ways (Vermond et al., 2015; Lieder, Breithardt, et al., 2018). Accordingly, the risk factor clusters encompassed by the $CHADS_2$ and CHA_2DS_2-VASc scores for risk of ischemic stroke in nonvalvular AF also predict fatal ischemic heart disease in these patients (Kim et al., 2011). Sympathetic drive is seen as 1 culprit link between AF and IRI (Lieder, Breithardt, et al., 2018), and these 2 diseases are likely to interact at both cellular and molecular levels. A recent study dissecting the differentially expressed genes concurrently associated with coronary artery disease and AF identified 3 highly enriched genes coding for proteins that contribute to the development of both diseases: membrane metalloendopeptidase (neprilysin), transferrin receptor-1, and lysosome-associated membrane glycoprotein-1 (Zheng and He, 2021).

The existence of coronary artery disease and a prior MI are accepted drivers of AF risk. A recently published Mendelian randomization study (Kwok and Schooling, 2021) that aimed to assess the bidirectional causal relationship between AF and major cardiovascular diseases, revealed that genetically predicted ischemic heart disease is positively associated with AF. Two recent Chinese studies further support a causal link between prior IRI and subsequent AF, particularly when associated with concomitant renal dysfunction, higher resting heart rate, and increased left atrial size (Luo et al., 2020; Luo et al., 2021), with each incremental millimeter increase in atrial size raising the risk of AF by 7%. However, the retrospective study design and the lack of clarity of whether AF was truly a first-onset phenomenon or simply the first diagnosis of previously unrecognized AF should be considered when interpreting the outcome of these studies. Conceptually, events occurring during IRI provide putative mechanistic determinants for the onset and perpetuation of AF. Reduced blood flow through the circumflex coronary artery as a result of stenotic or thrombotic occlusion will also cause hypoperfusion and impaired metabolism of the atria. Such punctual alterations may alter impulse conduction and drive electrical and structural remodeling, a constellation that will promote AF and increase its complexity (Opacic et al., 2016; Opacic et al., 2016; Dudink et al., 2021; Van Wagoner,

2021). Chronic atrial ischemia/infarction creates substrates for both spontaneous calcium driven atrial ectopy and sustained reentry due to conduction abnormalities (Nishida et al., 2011). Increased atrial cardiomyocyte excitability along with heterogeneity in atrial conduction could create reentry that could be further amplified by increases in atrial stretch due to the higher atrial pressure secondary to ischemia or ventricular dysfunction and by fibrotic remodeling of the infarcted myocardium (Lieder, Breithardt, et al., 2018; Liang and Wang, 2021). Even subclinical atherosclerosis, defined on the basis of increased intima-media thickness or coronary calcium scores, is significantly associated with incident AF (Willeit and Kiechl, 2014; Kristensen et al., 2020), and the extent of coronary artery disease has been linked to the degree of complexity of induced AF (Dudink et al., 2021).

Conversely, AF may also be seen as prognostic indicator with an increased risk for coronary artery disease and MI (Liang and Wang, 2021), although interpretation of data relating the contribution of AF to coronary artery disease and MI is somewhat hampered by the definition of coronary artery disease. This does not always differentiate clearly between atherosclerotic vessel disease and actual MI. One of the first prospective studies to examine the risk of incident MI in patients with AF and no coronary artery disease at baseline [Reasons for Geographic and Racial Differences in Stroke (REGARD) cohort; Soliman et al., 2014] highlighted AF as an independent risk factor for incident MI, raising the risk by approximately 2-fold even after adjustment for confounders. The Atherosclerosis Risk in Communities study subsequently reported that after multivariate analysis AF diagnosis was associated with a higher (80%) risk of non-ST elevation myocardial infarction but not STEMI (Soliman et al., 2015). More recent systematic reviews and meta-analyses (He and Chu, 2017; Ruddox et al., 2017) further underscore AF as a driver of subsequent MI in patients, although the direct causal relationship is more pronounced in patients who are free of coronary artery disease at baseline. Mendelian randomization did not associate genetically predicted AF with subsequent ischemic heart disease (Kwok and Schooling, 2021), indicating that exposure to environmental risks, lifestyle, and concomitant diseases may be more relevant for the 2-way interaction between AF and cardiac ischemia than random genetic variants at conception. Paroxysmal AF episodes often elicit angina-like symptoms, with mildly elevated troponin, even though no significant coronary artery disease is detected on angiography. Experimental evidence from a porcine model of AF induced by rapid atrial tachypacing implies acute impairment of microcirculatory blood flow in the ventricle as the potential culprit event (Goette et al., 2009). Mechanistically, this can be attributed to oxidative stress induced via the angiotensin II/nicotinamide adenine dinucleotide phosphate oxidase axis, leading to a reduction in coronary flow reserve with subsequent releases of troponin I (Goette et al., 2009). AF fulfills Virchow's Triad of hypercoagulability, hemodynamic perturbation, and endothelial dysfunction and is associated with a chronic state of low-grade inflammation that can be seen as both cause and consequence of AF (Boos et al., 2006; Kallergis et al., 2008). Thus, episodes of uncontrolled AF punctually increase myocardial oxygen consumption while lowering diastolic coronary perfusion (Bertero et al., 2021). Coronary thromboembolism, although a relatively rare cause of myocardial infarction, is, when it occurs, predominantly driven by AF-associated hypercoagulation (Shibata et al., 2015; Borschel and Schnabel, 2019). Concurrent atherosclerotic stenosis of the coronary arteries, driven by AF-associated increases in sympathetic nerve activity, inflammatory signaling, oxidative stress, and endothelial dysfunction, will further exhaust coronary dilator reserve. The additional constellation of burdens that accompany the progression of AF—calcium overload, energy depletion and increased sympathetic drive—promotes a vicious cycle of global cardiac impairment (Korantzopoulos et al., 2018; Borschel and Schnabel, 2019) that will clearly sensitize the myocardium for IRI.

At the cellular and molecular level, priming for IRI in the setting of AF may be seen to encompass, among others, (i) the manifestation of a calmodulin-dependent protein kinase II/NLRP3 inflammasome nexus that induces calcium-handling dysfunction and disseminated inflammatory states (Yao et al., 2018; Liu et al., 2019; Heijman et al., 2020; Nattel et al., 2020; Wang, Chen, et al., 2021), (ii) local injury through increased calpain-mediated proteolysis (Letavernier et al., 2012; Li and Brundel, 2020), (iii) release of mitochondrial deoxyribonucleic acid from cardiomyocytes to the surrounding tissue and the circulation (Wiersma et al., 2020), and (iv) increased local and systemic ROS production (Kim et al., 2005; Reilly et al., 2011).

b. Atrial Fibrillation and Cardioprotection. Data on how AF impacts on cardiac conditioning and cardioprotection are sparse. One RCT examined patients with drug-refractory paroxysmal AF undergoing radiofrequency catheter ablation who received RIC by intermittent arm ischemia prior to ablation. Ablation-stimulated rises in troponin I, high-sensitive-C-reactive protein and IL-6 were notably attenuated by RIC, while early recurrence rates were modestly lowered (Han et al., 2016). These findings were verified in the recent RIPPAF-RTC, which additionally noted lower serum levels of MMP 9 and von Willebrand factor, markers for atrial remodeling and endothelial damage, respectively, in the cohort receiving RIC prior to ablation for paroxysmal AF (Han et al., 2018). Patients undergoing cardiac surgery frequently develop post-surgery AF, the major form of secondary AF. The conceptual model of post-surgery AF encompasses the

presence of a vulnerable substrate provided by an underlying atrial cardiomyopathy created by genetics, risk factors, and comorbidities such as heart failure, diabetes, or hypertension (Goette et al., 2017). Perioperative triggers such as surgery-induced hypoxia, trauma, inflammation, and oxidative stress provide an impetus above a critical threshold that then precipitates post-surgery AF (Dobrev et al., 2019). The incidence of post-surgery AF in patients undergoing CABG is reportedly reduced from 50% to 14% if arm-pressure cuff RIC is applied prior to surgery (Slagsvold et al., 2014). Atrial appendage biopsies collected prior to and after cross-clamping showed that RIC preserved mitochondrial respiratory capacity and prevented the induction of miR 1, while miR 338-3p was upregulated compared with non-RIC samples (Kim et al., 2020). However, a more recent meta-analysis of RCT did not support the notion that RIC protects against post-surgery AF development (Kumar et al., 2019). Whether the cardioprotective window provided by RIC is sufficient to limit future IRI in patients with AF requires further systematic study.

c. Atrial Fibrillation and Cardioprotective Signaling. Little data are available regarding the impact of AF on cardioprotective mediators and pathways. Patients with AF have been noted to show dynamic alterations in critical determinants of NO production and metabolism, specifically arginine, homoarginine asymmetric dimethylarginine, and symmetric dimethylarginine, the levels of which were strictly dependent on acute heart rhythm at blood sampling, the degree of AF progression, and the success rate of sinus rhythm restoration (Büttner et al., 2020). Thus, NO-dependent pathways of cardioprotection will therefore be difficult to predict in patients with AF. Likewise, adenosine represents an important adaptive mediator protecting against myocardial IRI, yet in the context of AF, adenosine, and its receptors promote AF development and its perpetuation (Guieu et al., 2020; Soattin et al., 2020). Adenosine levels in atria and the circulation are elevated in AF, predominantly associated with peripheral blood monocytes (Godoy-Marín et al., 2021), but how this could influence ischemic injury and cardioprotection remains unclear.

Although there are accumulating evidence to support a bidirectional causal relationship between AF and IRI, many aspects remain unclear and require further clarification and verification. The impact of AF on (i) the risk that a myocardial ischemic event will occur in the first place, (ii) the extent of IRI and infarct progression, and (iii) the endogenous cardioprotective pathways that counteract IRI acutely and in the long term all need to be directly addressed in future work.

6. Kidney Failure/Uremia. Kidney failure and uremia are important comorbidities for ischemic heart disease (as reviewed earlier; Ferdinandy et al., 2014). Patients with a chronic kidney disease (CKD) have an increased in-hospital mortality after AMI compared with patients with normal renal function (Gansevoort et al., 2013). Experimentally, hearts from animals with CKD (5/6 nephrectomy) (Guo et al., 2018) or uremia (Dikow et al., 2004) had an increased susceptibility to IRI, even when hypertension was treated pharmacologically (Dikow et al., 2004). The mechanisms behind the increase in irreversible injury following I/R in CKD may be related to mitochondrial uncoupling (Taylor et al., 2015) and/or increased endoplasmic reticulum stress (Guo et al., 2018). Uremic rats also exhibited progressive impairment of LV function following MI (Dikow et al., 2010).

Since sex is an independent nonmodifiable risk factor (see previous discussion), more recently the importance of CKD for myocardial IRI and cardioprotective interventions was compared in males and females. While the severity of CKD was similar in males and females following 5/6 nephrectomy, only CKD males developed more severe LV hypertrophy and increased fibrosis. In both sexes, however, ischemic PreC decreased IS in sham and CKD animals. Interestingly, ischemic PreC increased the phospho-STAT3/STAT3 ratio in sham-operated but not CKD animals in both sexes, while no differences in phospho-AKT/AKT and phospho-ERK/ERK ratios existed (Sárközy et al., 2021). Thus, the underlying signaling events might differ between sham (SAFE-pathway-dependent) and CKD animals (SAFE- and RISK-pathway independent). Surprisingly, the effect of kidney failure on RIC has not been studied yet.

In conclusion, although CKD increases myocardial IRI, ischemic PreC still reduces IS in both female and male hearts; protection in males occurs despite the presence of LV hypertrophy and fibrosis. The underlying signaling events might involve endoplasmic reticulum stress as well as mitochondrial function. Other cardioprotective intervention (PostC or RIC) have not yet been studied in CKD and/or uremic animals. There are no data from humans on CKD and cardioprotective intervention available yet. Therefore, further preclinical studies in long-term experimental uremia models, as well as clinical studies, will be necessary to show if mechanical or pharmacological conditioning can still protect the heart in uremic patients.

V. Effects of Pharmacological Treatment of Comorbidities on Cardioprotection

Previous sections have shown how risk factors and comorbidities can reduce the effectiveness of cardioprotective strategies. However, many patients with risk factors as well as comorbidities will already be receiving multiple medications to treat these comorbidities, even before they experience a MI. Therefore, an additional important consideration is the effect that these comedications

might have on IRI per se and/or cardioprotective interventions. These effects may include attenuation of IRI that may leave less more room to further cardioprotection; however, some medications may negatively affect cardiomyocyte survival in hearts exposed to I/R or attenuate cardioprotective signaling, a phenomenon referred to as "hidden cardiotoxicity" (Ferdinandy et al., 2019). Finally, patients who undergo PPCI or CABG for MI will be administered a number of different analgesics and anesthetics, and these "background drugs" can also potentially affect the response of the heart to I/R and the efficacy of cardioprotective strategies (He et al., 2020; Kleinbongard et al., 2020). The following sections will summarize the current knowledge on different comedications for cardioprotective interventions.

A. Antihypertensive Drugs (Also Used in Part to Treat Heart Failure With Reduced Ejection Fraction)

Effective treatment of hypertension to reduce arterial pressure below guideline thresholds reduces cardiovascular risk, notably from stroke, ischemic events, sudden death, and congestive HF (Soliman et al., 2017; Whelton et al., 2018). Beyond MACE reduction, a number of antihypertensive agents induce regression of LVH. Although blood pressure reduction is a primary determinant of LVH regression, the extent of LV mass reduction by different drug classes may not correlate well with the level of blood pressure reduction, suggesting that hemodynamic effects alone may be insufficient to explain LVH regression. For example, with L-type calcium channel blockers, ACE inhibitors, and angiotensin receptor blockers, LV mass reduction is generally superior to that seen with direct vasodilator agents (Soliman and Prineas, 2017). The question of whether LV mass regression per se, beyond blood pressure lowering, is associated with reduced susceptibility to cardiovascular risk including IRI is unresolved (Soliman et al., 2017).

There is conflicting and inconsistent evidence from experimental and clinical studies suggesting that some antihypertensives either exert direct cardioprotective effects by recruiting cardioprotective signaling pathways or enhance protective conditioning responses, or even attenuate these responses. This may be especially relevant, not only in the context of hypertension being a frequent comorbidity but also because of the use of β-adrenoceptor antagonists and ACE inhibitors as adjuncts in the early management of STEMI and for secondary prevention.

1. β-Adrenoceptor Antagonists. β-adrenoceptor antagonists form a heterogeneous group of drugs, widely applied as antihypertensive agents since the 1960s and thus, with diuretics, the oldest group of antihypertensive agents in current use. A systematic review has suggested inferiority of first-line hypertension management with β-blockers (mainly atenolol or propranolol) on mortality compared with renin-angiotensin system inhibitors (Wiysonge et al., 2017), although hemodynamic benefits of β-blockers are, at least in part, associated with suppression of the renin-angiotensin cascade. They are also used in the management of patients with established coronary artery disease (e.g., as anti-anginal agents) (Bertero et al., 2021). Although under review, US and European guidelines have advocated the use of particular antagonists in early management of acute coronary syndrome in hemodynamically stable patients (Giannakopoulos and Noble, 2021).

There is a wealth of preclinical data on IS reduction by β-blockers in animal studies of I/R, although, as noted later, none have been successfully and reproducibly translated to humans. Studies in pigs have shown MRI-based evidence for cardioprotection by metoprolol (Ibanez et al., 2007; Ibanez et al., 2011; García-Ruiz et al., 2016; Heusch and Kleinbongard, 2020; Lobo-Gonzalez et al., 2020), and histology-based evidence for cardioprotection by carvedilol (Bril et al., 1992; Feuerstein and Ruffolo, 1995), atenolol, and the short-acting β-blocker landiolol (Park et al., 2011). Carvedilol also reduced the area of no-reflow in pigs following I/R, assessed by myocardial contrast echocardiography (Zhao et al., 2008). There are mixed data suggesting that β3 adrenergic receptor stimulation may be cardioprotective. The β3 adrenergic receptor agonist BRL37344 reduces IS in mice and pigs (Aragon et al., 2011; García-Prieto et al., 2014), but mirabegron, a β3-agonist approved for human use, was not cardioprotective in pigs (Rossello et al., 2018).

Clinical studies conducted in the 1980s provided evidence that β-receptor blockade could reduce IS when given within 4 to 7 hours of symptom onset (Peter et al., 1978; Yusuf et al., 1983; International Collaborative Study Group, 1984; MIAMI Trial Research Group 1985); however, this was in the "pre-reperfusion era" before the use even of thrombolysis. A 2020 patient-pooled meta-analysis of randomized clinical trials testing early intravenous β-blockers in patients undergoing PPCI for STEMI, which included 4 trials and 1150 patients, found no difference in the main outcome of 1-year death or biomarker-based IS (Hoedemaker et al., 2020). Although initial studies reported reduced IS with intravenous metoprolol administered prior to reperfusion (Ibanez et al., 2013; Pizarro et al., 2014; Podlesnikar et al., 2020), the larger EARLY BAMI study of 683 STEMI patients failed to report a reduction in myocardial IS (Garcia-Ruiz et al., 2016; Roolvink et al., 2016; Fabris et al., 2020).

A role of endogenous catecholamines in eliciting ischemic PreC has long been recognized in several species, with contributions from α1-adrenoceptor being initially characterized in rabbit and rat heart (Tsuchida et al., 1994; Mitchell et al., 1995). Transient α1-adrenoceptor stimulation induces pharmacological PreC (Bankwala et al., 1994), and transient β1- or β2-adrenoceptor stimulation also induces pharmacological PreC in rat isolated

heart (Salie et al., 2011), with recruitment of similar mechanisms to ischemic PreC. However, the effects of β-blockade on cardioprotective and conditioning responses have been shown in experimental studies to be complex and inconsistent with some but not all studies suggesting a loss of ischemic PreC and ischemic PostC protection, volatile anesthetic PreC, or PostC or RIC in the presence of β-adrenoceptor antagonists (Ferdinandy et al., 2014). There is no obvious or consistent explanation based on the diverse pharmacodynamic profiles of different β-blockers (e.g., lipophilicity, β1 receptor selectivity/cardioselectivity, α receptor antagonism, duration of action, or intrinsic sympathomimetic activity). However, limited evidence from experimental studies suggests that pharmacological PreC or PostC by volatile anesthetic involve recruitment of β-adrenergic signaling (Lange et al., 2009). In more recent clinical studies of conditioning-induced cardioprotection, concomitant β-blockade may be a substantial confounding factor. Cho et al. (2019) examined the effects of limb RIC in healthy human subjects. Plasma dialysate obtained from RIC-treated subjects reduced IS in isolated rat hearts perfused with human RIC dialysate prior to coronary artery occlusion. However, this transfer of protection, likely by some humoral factor in the RIC plasma was abolished if the subjects received RIC in the presence of carvedilol, a β-adrenoreceptor antagonist with ROS-scavenging properties (Feuerstein and Ruffolo, 1995). In a retrospective analysis of a small single-center RCT assessing RIC in patients undergoing CABG surgery, prior use of β-adrenoreceptor antagonists was not found to correlate with troponin I release, a marker of intraoperative IRI (Kleinbongard et al., 2016).

2. ACE Inhibitors and Angiotensin II Receptor Blocker. Inhibitors of the renin-angiotensin system are first-line antihypertensive treatments but are also widely used in the management of established ischemic heart disease and chronic HF. While transient exposure to angiotensin II is known to induce pharmacological PreC via activation of angiotensin II type 1 receptors, and PKC (Liu et al., 1995), several experimental studies have shown ACE inhibitors and angiotensin II receptor blockers (sartans) to be protective in IRI models and to enhance the protective effects of endogenous cardioprotective interventions (ischemic PreC and Ischemic PostC) (Ferdinandy et al., 2014). The mechanisms underlying this beneficial effect are likely to include the potentiation of the production or reduced catabolism of autocrine/paracrine mediators such as bradykinin, prostacyclin, and NO. In pigs with IRI, candesartan pretreatment reduced IS through activation of the angiotensin II type 2 receptor, bradykinin, and prostaglandins, and icatibant or indomethacin abrogated this protection (Jalowy et al., 1998). Sgarra et al. (Sgarra et al., 2014) described differential effects of pharmacological PostC with losartan and irbesartan in a rat isolated heart model of IRI. Losartan given as intermittent pulses during early reperfusion reduced IS whereas continuous losartan perfusion, or intermittent irbesartan treatment, did not. This protective effect was abolished by icatibant (Hoe140), a bradykinin B2 receptor antagonist.

In SHR rats treated with olmesartan for 4 weeks, blood pressure and LV mass were significantly reduced and IS was markedly attenuated after coronary artery occlusion in vivo (Lu, Bi, Chen, and Wang, 2015). In a subsequent study the same group showed that RIC (3×5 minute hind limb ischemia during coronary artery occlusion) was absent in SHR but was restored in animals treated with olmesartan for 4 weeks prior to myocardial ischemia (Lu, Bi, and Chen, 2015).

In a model of rapid pacing-induced PostC in rat isolated heart, the IS limiting effect of PostC was abolished in the presence of irbesartan, an angiotensin II type 1 receptor antagonist, suggesting that activation of the angiotensin II type 1 receptor and signaling via the RISK pathway may be involved in this form of conditioning (Babiker et al., 2016). However, both captopril and chymostatin, which inhibit angiotensin II production by ACE-dependent and ACE-independent pathways, respectively, were protective when administered at reperfusion but did not enhance or abolish the effects of superimposed PostC. Thus, the role of locally produced angiotensin II in mediating IRI and conditioning protection are unclear from this study, and the likelihood is that other peptide mediators are modulated by these drugs.

Acute administration of azilsartan during reperfusion was observed to protect isolated rat hearts against IRI, similarly to ischemic PostC. Whereas the effects of ischemic PostC were abrogated in hypercholesterolemic hearts, azilsartan restored the protective effect, likely through upregulation of eNOS activity (Li et al., 2017).

Clinical studies are limited, but given the widespread guideline-directed use of ACE inhibitors and angiotensin II receptor blocker in the management and prevention of multiple cardiovascular diseases, the drugs are frequently present in patients included in clinical cardioprotection trials. The experimental evidence broadly suggests that these drugs can exert independent cardioprotective effects or augment ischemic PreC and PostC responses and could therefore modify responses in trials of conditioning interventions in a variety of settings. Kleinbongard et al. (Kleinbongard et al., 2016), in further analyzing data from their trial of RIC in CABG patients, concluded that neither ACE inhibitors nor angiotensin II receptor blockers were determinants of the major endpoint of protection (plasma troponin I concentration). However, it seems plausible that further analysis of the use of these pleiotropic drugs as potential confounders in larger trials of conditioning interventions, especially in STEMI patients, is warranted.

More recently, neprilysin inhibitors in particular are gaining recognition as a candidate approach for multitarget cardioprotection, given the spectrum of neprilysin substrates that elicit additive or even synergistic cardioprotective signals, including natriuretic peptides, bradykinin, and apelins, among others (Bellis et al., 2020).

3. L-Type Calcium Channel Blockers. L-type calcium channel blockers are a chemically diverse class of agents used in the management of hypertension, certain arrhythmias, and ischemic heart disease. In the context of cardioprotection, extensive experimental evidence points to the IS-limiting potential of all classes of calcium channel blocker when administered prior to the onset of myocardial ischemia, probably by slowing intracellular calcium overload during ischemia. However, there is no benefit if the drugs are administered immediately prior to or during reperfusion. Thus, there is little rationale for their use as adjuncts to reperfusion in STEMI. However, the question of their potential to interfere with conditioning protocols or to confound interpretation of clinical conditioning interventions remains open. There is a paucity of experimental evidence, but nisoldipine did not interfere with ischemic PreC in pig heart (Wallbridge et al., 1996). However, it is plausible that chronic treatment of patients with calcium channel blocker might confer a reduction in susceptibility to IRI, making it difficult to reveal additive benefits of conditioning interventions. Again, further analysis of data from large trials might be helpful in elucidating ideal protocols and patient populations for targeted cardioprotection.

4. Nitrates (and Nitrate Tolerance). Organic nitrates have been widely used for many decades as one of the main drugs for coronary artery disease treatment. Glyceryl trinitrate (nitroglycerine) is a potent vasodilator that has been used in clinical practice for over a century (Nunez et al., 2005); however, the main constraint of nitrate chronic therapy is the development of rapid tolerance, mainly vascular tolerance, which leads to the loss of clinical efficacy (Csont and Ferdinandy, 2005; Bibli et al., 2019).

Meta-analysis of many experimental studies suggests that IS was limited compared with controls when nitrates were administered through different routes, during ischemia, and/or reperfusion and in different animal species (reviewed in Bice et al., 2016). For example, application of a nitroglycerine patch (designed to deliver 5 mg/d) reduced myocardial IS when applied to mice prior to reperfusion (Yellon et al., 2018). Similarly, low-dose nitroglycerine reduced IS when administered during ischemia both in normal and in animals exhibiting endothelial dysfunction, mainly through the S-nitrosylation and inhibition of cyclophilin D, a component of the mPTP (Bibli et al., 2019). Very recently, administration of a nitrate-functionalized cardiac patch with site-specific delivery of NO directly into the infarcted myocardium demonstrated in a rat model of MI reduced injury at an early stage and suppressed adverse cardiac remodeling, with these results further confirmed in a more clinically relevant porcine model (Zhu et al., 2021).

Clinical trials have provided no consistent evidence of IS limitation associated with nitrate treatment as an adjunct to reperfusion (Bice et al., 2016). However, nitroglycerine showed cardioprotective effects when administered 24 hours before coronary angioplasty compared with patients who received saline (Heusch, 2001; Leesar et al., 2001). This was supported by a study indicating that intracoronary but not intravenous infusion of nitrites reduced IS in STEMI patients with completely occluded arteries (Jones, Pellaton, et al., 2015) and by a recent study indicating that long-term nitrate treatment is cardioprotective, although the mechanism is not fully elucidated (Hauerslev et al., 2018). Additionally, the acute administration of nitrates does not seem to interfere with RIC in patients undergoing CABG surgery under isoflurane anesthesia (Kleinbongard et al., 2013). Interestingly, inhaled NO was able to reduce IS only in a subgroup of nitroglycerine naive STEMI patients (Janssens et al., 2018). This suggests that these patients might be in a nitroglycerine tolerant state that might impair cardioprotection (i.e., an indirect evidence for the hidden cardiotoxic effect of nitroglycerine) (Ferdinandy et al., 2019).

Thus, although tolerance represents a major limitation of the organic nitrates used in the clinic, acute administration and/or site-specific delivery of NO into the myocardium seems to be cardioprotective and may support the translational potential of the use of nitrates as adjunct to reperfusion therapy for IS limitation.

B. Analgesics and Anesthetics

1. Cyclooxygenase Inhibitors. Aspirin may interfere with protection by some forms of ischemic conditioning in experimental studies (Birnbaum et al., 2021). Indomethacin pretreatment abrogates protection from IRI by ACE inhibition and angiotensin II type 1 receptor blockade (Ehring et al., 1994; Jalowy et al., 1998). Thus, cyclooxygenase inhibition can, in principle, interfere with cardioprotection. The cardiac safety of cyclooxygenase 2 inhibitors is still an area of investigation and controversy despite the withdrawal from the market due to increased occurrence of MI (Dubreuil et al., 2018; Abdellatif et al., 2021). Indeed, cyclooxygenase 2 inhibition seems to be cardioprotective in preclinical models; however, its potential hidden cardiotoxic effect has been recently shown in preclinical models of I/R and MI that may hinder their development and indicates safety problems of some cyclooxygenase inhibitors (Brenner et al., 2020).

2. Morphine and Anesthetics. Certain anesthetics are inhibitors of mitochondrial activity (Hanley and

Loiselle, 1998; Chen et al., 2018), and some anesthetics are also strong ROS scavengers (Murphy et al., 1992). Cardiac I/R and protection from it are critically dependent on the presence and type of anesthesia (Zaugg et al., 2014). Anesthesia is likely one of the critical factors hampering successful translation in large clinical trials, considering the often large discrepancies between anesthetic regimen in preclinical models (often pentobarbital, ketamine-xylazine) versus the clinical arena (fentanyl, morphine, volatile anesthetics, benzodiazepines, propofol).

The abrogation by propofol of protection by RIC in patients undergoing CABG surgery was first reported by Kottenberg et al. (Kottenberg et al., 2012). The use of propofol may have interfered with cardioprotection by RIC in the larger phase III trials in CABG patients. Also, RIC was beneficial in rats administered pentobarbital and sevoflurane but not in rats receiving propofol (Behmenburg et al., 2018). Subsequently, the effect of anesthesia using sevoflurane or propofol was studied by perfusing plasma dialysates from patients undergoing CABG into isolated rat hearts with I/R. Here, RIC was only protective when no anesthesia was used, whereas both sevoflurane and propofol abolished RIC protection (Cho et al., 2019). Propofol abrogates not only ischemic conditioning but also various pharmacological types of conditioning (Zuurbier et al., 2014; Lucchinetti et al., 2018; Xiao et al., 2021). It thus seems that analgesic and anesthetic agents used in the clinic (opioids, volatile anesthetics, propofol) can interfere with cardioprotective interventions, mandating the incorporation of these agents in preclinical models to improve translation. Such models were recently developed in rats, 1 showing protection by a caspase inhibitor, but not RIC, on a background of heparin, an opioid agonist, and a platelet-inhibitor (He et al., 2020), and another 1 showing protection by a NAD precursor, but not fingolimod, melatonin, or empagliflozin, on a background of fentanyl, benzodiazepine, and a platelet inhibitor (Xiao et al., 2021).

The opioid receptor system has been shown to represent an important candidate for clinical cardioprotection since it beneficially impacts all major determinants of IRI outcome (infarction/apoptosis, arrhythmogenesis, inflammation). A small number of clinical trials have provided evidence of cardiac benefit from morphine or remifentanil in CABG or coronary angioplasty patients (Headrick et al., 2015). Morphine (Stiermaier et al., 2021) and volatile anesthetics can reduce IS following PPCI or CABG procedures (Zaugg et al., 2014) and thus limit the potential for further protective interventions. However, diabetes mellitus mitigates cardioprotective effects of remifentanil PreC in I/R rat heart in association with antiapoptotic pathways of survival (Kim et al., 2010), and hypertrophy (Weil et al., 2006) may influence opioid receptor responses.

C. Antiplatelets and Anticoagulants

1. Antiplatelets. For use of aspirin see Section Vb1.

Clopidrogel, the first $P2Y_{12}$ inhibitor developed and examined, is now slowly being replaced by the faster-acting prasugrel or ticagrelor. Experimental studies have established that $P2Y_{12}$ receptor blockers reduce IS during cardiac IRI (Yang, Liu, et al., 2013a, 2013b). Cardioprotective signaling by cangrelor and ticagrelor overlap with the signaling pathways used by conditioning strategies such as ischemic PostC (Yang, Liu, et al., 2013a) and RIC (Cohen and Downey, 2017; He et al., 2020; Hjortbak et al., 2021). However, ischemic PreC remained effective in the presence of the $P2Y_{12}$ antagonist ticagrelor (Hjortbak et al., 2021). Pharmacological conditioning has been found to remain effective in the presence of $P2Y_{12}$ agents for the sodium/hydrogen-exchanger inhibitor cariporide (Yang, Cui, et al., 2013), caspase inhibitors (Audia et al., 2018; He et al., 2020), and the NAD^+ precursor nicotinamide riboside (Xiao et al., 2021) but not for NLRP3 inhibitors (Penna et al., 2020).

In patients undergoing PPCI for STEMI, platelet reactivity in response to dual antiplatelet therapy is a key predictor of the extent of both myocardial and microvascular damage (Massalha et al., 2022). Whether $P2Y_{12}$ inhibitors indeed possess direct cardioprotective actions against AMI has not been demonstrated in large prospective clinical trials. However, there is some circumstantial evidence from small clinical or large retrospective studies. A recent study showed reduced IS with ticagrelor versus clopidogrel as indirect evidence that $P2Y_{12}$ agents can reduce IS independent of their platelet inhibitory action (Kim et al., 2017), a finding supported by recent retrospective studies (Hjortbak et al., 2021; Sabbah et al., 2020).

2. Anticoagulants. For decades now, the anticoagulant heparin has been part of the standard of perioperative care during PPCI and cardiac surgical procedures. Experimental studies have established that heparin reduces IS during cardiac IRI (Black et al., 1995; Huang et al., 2017; He et al., 2020). Since 2005, platelet receptor antagonists were added to this standard of care for acute MI patients treated by PCI, and both heparin and $P2Y_{12}$ antagonists possess cardioprotective actions (Roubille et al., 2012; Kleinbongard et al., 2021). Given their protective potential, both heparin and $P2Y_{12}$ antagonists should therefore become part of preclinical models testing for cardioprotection, where these agents have been mostly missing (Cohen and Downey, 2017; He et al., 2020).

While oral anticoagulation is obligatory for thromboembolism prophylaxis in AF and for prevention of deep vein thrombosis and pulmonary embolism, current guidelines also recommend oral anticoagulation with the coumarin-derivative warfarin to prevent LV thrombosis in the 3 to 6 months after AMI (Levine et al.,

2016; Ibanez et al., 2018; Valgimigli et al., 2018). Increasingly, the direct oral anticoagulants (DOAC) are used off-label in this context (Iqbal et al., 2020). Currently available DOAC include the thrombin inhibitor dabigatran; inhibitors of activated coagulation factor X (FXa) are represented by rivaroxaban, apixaban, edoxaban, and betrixaban. A recently published observational study in patients with AMI who received either warfarin or 1 of rivaroxaban, apixaban, or edoxaban (Jones et al., 2021) showed earlier and greater LV thrombus resolution with the FXa inhibitors compared with warfarin, together with lower bleeding rates but comparable systemic thromboembolic events.

The influence of the activated coagulation system on cardiovascular biology and pathophysiology goes beyond thrombosis. The cardioprotection afforded by antithrombin in murine IRI is independent of its hemostatic effect (Wang et al., 2013). Similarly, the beneficial impact of RIC applied pre- and post-off-pump CABG also appears to be unrelated to perioperative improvement in platelet reactivity to adenosine diphosphate or coagulability status (Kim et al., 2020), pointing to existence of coagulation-independent actions. Thrombin and FXa directly promote endothelial dysfunction, oxidative stress, immune cell activation, cell growth and differentiation, as well as inflammation (Fender et al., 2017; Fender et al., 2020; Ten Cate et al., 2021) through cellular protease-activated receptors and thus need to be considered in the context of IRI and cardioprotection.

Regarding the candidate role of DOAC as cardioprotective agents, no benefit could be noted with dabigatran in a rabbit model of no-reflow after myocardial IRI (Hale and Kloner, 2015). In rodent models of cardiac IRI, application of the FXa inhibitor 1 hour prior to occlusion decreased IS by 21% (Guillou et al., 2020). A PostC benefit of rivaroxaban has also been observed in mice subjected to permanent ligation. Here, the cardioprotective window appeared to persist for 24 hours after ischemia; delaying treatment until day 3 after IRI abolished the observed benefits (Bode et al., 2018). If commenced immediately after surgery or up to 24 hours thereafter, rivaroxaban applied in chow prevents intravascular thrombosis, improved cardiac systolic function, and decreased IS and inflammatory markers to variable extents. Within the infarct zone, levels of TNFα, tissue growth factor β, and both protease-activated receptors 1 and 2 are reportedly suppressed, while noninfarcted areas exhibit lower levels of atrial natriuretic peptide and NH_2-terminal pro-B-type natriuretic peptide, activated ERK, and cardiomyocyte hypertrophy (Bode et al., 2018; Nakanishi et al., 2020). Rivaroxaban also improved cardiac function and survival and suppressed transcription of IL-6 and collagens in a mouse model of secondary IRI prevention. Here, rivaroxaban treatment was commenced after IRI evoked by temporary occlusion and continued over 14 days; a second ischemic event was triggered on day 7 with the application of tissue factor (Goto et al., 2016). Mechanistically, the cardioprotective effects afforded by rivaroxaban could be largely attributed to a blunted signaling though FXa/protease-activated receptors 2 (Bode et al., 2018), and given that apixaban could also blunt post-IRI fibrosis in mice (Shi et al., 2018), it is likely that cardioprotection is a class effect of the FXa blockers rather than a phenomenon specific for rivaroxaban.

A recent study in mice with cardiac IRI elegantly demonstrates the apparent superiority of FXa inhibition versus thrombin inhibition (Gadi et al., 2021). Inhibition of thrombin or FXa was commenced 1 week prior to IRI and reinitiated 2 hours post-surgery and continued for 24 hours or 28 days to examine acute and chronic effects. The dose was adjusted to achieve equivalent anticoagulation. IS was markedly and comparably reduced by both interventions. Remarkable differences between the 2 pharmacological strategies were noted in terms of IRI-triggered inflammation. RNA sequencing analysis showed that approximately 75% of genes aberrantly up- or downregulated by IRI were restored by FXa blockade, while thrombin inhibition reversed only one-third of IRI-regulated genes. The most prominently affected pathways included those related to the NLRP3 inflammasome and fibroinflammatory stress, with thrombin inhibition tending to increase, while FXa blockade tending to decrease, expression of IL-1β, IL-6, TNFα, and inflammasome components. The authors proposed that the difference might be related to the unique ability of thrombin to induce the activated protein C pathway, which has previously been shown to protect against myocardial IRI (Wildhagen et al., 2014).

Rivaroxaban exerts a direct cytoprotective action in cardiomyocytes subjected to hypoxia/reoxygenation (Guillou et al., 2020). Possible contributing mechanisms include the preservation of mitochondrial function and metabolism through regulation of key mitophagy proteins including mitochondrial dynamin-related protein 1 and Parkin (López-Farré et al., 2014; Zamorano-Leon et al., 2020). Classic cardioprotective cascades such as the RISK and SAFE pathways do not appear to be modulated by FXa blockers; instead, positive regulation of the Wingless and Int-1β-induced PI3K/AKT-activated protein C system may contribute to the cardioprotective benefits of these agents, as was recently reported for edoxaban (Shan et al., 2019). Additional cardioprotection may arise through upregulation of vascular endothelial NOS (Pham et al., 2019) and suppression of angiotensin II-stimulated inflammatory and fibrotic responses in cardiac fibroblasts. Rivaroxaban attenuated angiotensin II-stimulated signaling through nuclear factor kB and mitogen-activated protein kinase/activator protein 1 pathways in mouse cardiac fibroblasts lowered expression of

inflammatory proteins and concentration-dependently blunted fibroblast migration and proliferation (Hashikata et al., 2015). Potentially, FXa blockade could help to limit IRI-driven fibrosis and remodeling. In line with this concept, apixaban attenuated fibrosis in mouse hearts subjected to permanent ligation (Shi et al., 2018). The underlying mechanism was shown to depend on inhibition of thrombin formation and suppressed signaling through protease-activated receptors 1/Gq/PKC in cardiac fibroblasts. Data related to the effects of the thrombin inhibitor dabigatran are more limited. At the cellular level, dabigatran counterbalances thrombin-stimulated oxidative stress, inflammatory cytokine expression, and sirtuins-driven autophagy in cardiomyocytes in vitro (Wang, Xu, et al., 2021). More recently, an elegant in silico docking study revealed that dabigatran may be a novel candidate inhibitor of c-jun-N terminal kinase (Zulfiqar et al., 2020).

In patients, data on DOAC and myocardial IRI and protection from it are sparse. The main patient population studied are those with AF. However, in anticoagulated patients with AF, the incidence of AMI is relatively low (Connolly et al., 2009). Thus, one could speculate that oral anticoagulation use goes in hand with a generally low risk of AMI. Early studies examining DOAC added to standard antiplatelet therapy include the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome 2–Thrombolysis in Myocardial Infarction 51 (ATLAS ACS 2–TIMI 51) trial. Addition of rivaroxaban (2.5 and 5 mg) reported an approximately 9% reduction in subsequent MI in patients with AMI, albeit at the cost of increased major bleeding, but not fatal cerebral bleeds (Mega et al., 2012). The subsequent Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial (Eikelboom et al., 2017), which added very low-dose rivaroxaban to aspirin in patients with chronic coronary and peripheral artery disease, reported a favorable outcome in terms of thrombotic event reduction but no reduction of MI. Standard-dose rivaroxaban alone showed no benefit regarding primary cardiovascular outcomes but increased bleeding rates compared with aspirin alone. The subsequent A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction, or Stroke in Participants with Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure (COMMANDER-HF) trial corroborated that addition of low-dose rivaroxaban on top of standard antiplatelet therapy lowers the rate of ischemic stroke but does not impact beneficially on MACE endpoints including MI (Zannad et al., 2018). Similarly, the Apixaban for Prevention of Acute Ischemic Events 2 (APPRAISE-2) trial, which examined apixaban added to standard antiplatelet therapy in patients with recent AMI and at least 2 additional ischemic risk factors, was terminated early because of increased major bleeding with no evident reduction in cardiovascular events including MI (Alexander et al., 2011).

Thus, appropriate use of triple therapy remains challenging. FXa blockers on top of standard antiplatelet therapy consistently increase bleeding risk, with no counterbenefit in terms of reduced MI (Khan et al., 2018). At least this is the case if substantial coronary artery disease and prior AMI are already evident. It remains to be determined whether DOAC can modulate either the propensity for a first myocardial event to occur, by influencing the underlying coronary artery disease as indicated by some experimental studies (Hara et al., 2015; van Gorp et al., 2021) or, alternatively, whether DOAC impact on the extent of injury and expansion in the aftermath of the infarct (see previous discussion). Thrombin and FXa are also linked to processes pertaining to post-IRI inflammation and remodeling (Raivio et al., 2009; Fender et al., 2019). The thrombin burst that occurs in the context of IRI despite heparinization (Raivio et al., 2006; Raivio et al., 2009) may therefore contribute adversely and in a long-lasting manner to IRI and its sequelae.

D. Antidiabetic Therapy

The burden of myocardial IRI may be higher in diabetic patients (see Section IVe); therefore, pharmacological therapy to protect the diabetic heart is of significant clinical importance. Experimental and clinical data suggest that antidiabetic therapy may either confer cardioprotection or interfere with cardioprotection elicited by conditioning maneuvers.

1. Sulfonylureas. Preclinical and clinical studies have shown that some sulfonylureas inhibit myocardial protection by conditioning strategies since these drugs have high affinity to myocardial SUR2A/Kir6.2 and smooth muscle SUR2B/Kir6.2 receptors and inhibit the activation of K_{ATP} channels (Gribble and Ashcroft, 1999). The cardiovascular effect of sulfonylureas in humans is inhibition of the cardioprotective effects of RIC (Loukogeorgakis et al., 2007; Kottenberg et al., 2014). At present, there is no evidence that these effects have clinical consequences. Cross-reactivity between pancreatic and cardiac K_{ATP} channels varies with the individual sulfonylureas, and in general the later generation sulphonylureas are more specific for the pancreas and therefore bind less to the cardiac K_{ATP} channels (Gribble and Ashcroft, 1999). The interaction of glimepiride or gliclazide with SUR2 is less than that of glibenclamide, and therefore they do not seem to blunt the cardioprotective effects of ischemic PreC, diazoxide, and nicorandil in isolated rat hearts with I/R (Mocanu et al., 2001; Maddock et al., 2004).

2. Metformin. Pre- and/or post-treatment with metformin protects the heart against IRI and reduces myocardial IS (reviewed in Ye et al., 2011). Metformin PostC reduced IS, attenuated apoptosis, and inhibited

myocardial fibrosis, which was largely dependent on the suppression of NLRP3 inflammasome activation in rat hearts and cardiomyocytes (Zhang et al., 2020). Although meta-analyses have supported the cardiovascular safety of metformin in patients with coronary artery disease and chronic HF independent of its glucose-lowering effects (Varjabedian et al., 2018), no acute protection by metformin during CABG was observed (El Messaoudi et al., 2015), questioning the translatability of metformin for protection against acute I/R settings in the clinical situation. Indeed, in contrast to rodent hearts, PostC with high-dose metformin when administered before reperfusion did not reduce myocardial IS or improve LV function in swine (Techiryan et al., 2018), highlighting the importance of rigorously testing therapies in large animal models to facilitate clinical translation of novel cardioprotective therapies.

3. Thiazolidinediones. The effect of thiazolidinediones on IRI is controversial (Riess et al., 2020). Preclinical studies in small animals have shown that these drugs administered either as PreC or PostC agents protect against IRI and limit myocardial IS. Pioglitazone in nondiabetic and diabetic rats reduced IS (Khodeer et al., 2016) and did so, too, in isolated rat hearts when administered prior to I/R (Wynne et al., 2005). Rosiglitazone, however, was associated with enhanced cardiac injury in a similar model (Riess et al., 2020). Rosiglitazone is associated with increased adverse cardiovascular events in diabetic patients (Lincoff et al., 2007).

4. Glucagon-Like Peptide-1 Receptor Agonists. Glucagon-like peptide 1 (GLP-1) receptor agonists exert diverse actions on distinct target tissues, which lead to reduction of blood glucose level and body weight, and they are approved drugs for consideration as monotherapy or in combination with other oral antihyperglycemics (Peng et al., 2016). GLP-1 receptor agonists administered either as PreC or PostC agents limit myocardial IS in small and large animal models (Bose et al., 2005; Sonne et al., 2008; Timmers et al., 2009). A recent meta-analysis indicated that GLP-1 receptor agonists reduced the incidence of MACE and MI in type 2 diabetes patients and attenuated cardiovascular mortality (Sattar et al., 2021 #3585). In rats with I/R, GLP-1 functions as a humoral factor of RIC, involving activation of vagal nerves and M3-muscarinic receptors (Basalay et al., 2016). In the clinical setting, an intravenous infusion of exenatide initiated prior to PPCI reduced myocardial IS in STEMI patients, especially in those patients presenting with short ischemic times from symptom onset (<132 minutes) (Lønborg, Kelbæk, Vejlstrup, Bøtker, Kim, Holmvang, Jørgensen, Helqvist, Saunamäki, Terkelsen, et al., 2012; Lønborg, Vejlstrup, et al., 2012; Woo et al., 2013). Another GLP-1 analog, liraglutide, when administered prior to PPCI and continued for 7 days, improved LV systolic function (Chen et al., 2015). Exenatide activated cardioprotective pathways different from those of RIC and possessed additive effects with RIC on IS reduction in a pig model of I/R (Alburquerque-Béjar et al., 2015). However, in a 2×2 factorial follow-up study, neither RIC nor exenatide, nor its combination, reduced IS in STEMI patients when administered as an adjunct to PPCI (García Del Blanco et al., 2021), indicating that, although GLP-1 agonists were promising in preclinical models of MI, they failed in RCTs in humans.

5. Dipeptidyl Peptidase-IV Inhibitors. GLP-1 is enzymatically cleaved and inactivated by dipeptidyl peptidase IV (DPP-IV), leading to the development of DPP-IV inhibitors as potential therapeutics. In rodents and pigs, DPP-IV inhibitors (especially sitagliptin and vildagliptin) limited IS when administered either before or after ischemia. Vildagliptin restored the cardioprotective effects of ischemic PostC on diabetic hearts but did not reduce IS per se (Bayrami et al., 2018). A prospective clinical study assessed the effect of repaglinide and vildagliptin on ischemic PreC in patients with type 2 diabetes and coronary artery disease. Although repaglinide eliminated ischemic PreC, probably due to its effect on the K_{ATP} channel, vildagliptin did not cause any impairment of ischemic PreC, suggesting a good alternative treatment in these patients (Rahmi et al., 2013). Clinical trials have shown that hospitalization for HF was increased in saxagliptin-treated patients (Scirica et al., 2013), whereas major adverse cardiovascular events were not increased with alogliptin and sitagliptin as compared with placebo (White et al., 2013; Green et al., 2015). A recent Cochrane analysis did not show any beneficial effect of DPP-IV inhibitors on MACE, MI, or cardiovascular mortality (Kanie et al., 2021). In summary, further preclinical studies especially in large animals with diabetes and clinical trials will be warranted to confirm the myocardial protection afforded by DPP-IV inhibitors.

6. Sodium Glucose Cotransporter 2 Inhibitors. Sodium glucose cotransporter 2 (SGLT2) inhibitors are the newest class of antidiabetic drugs. They markedly reduce MACE in large clinical trials in HF patients (Andreadou, Bell, et al., 2020). SGLT2 inhibitors exert cardioprotective effects in animal models of AMI through reduction of IS (Andreadou, Efentakis, et al., 2017; Tanajak et al., 2018; Lim et al., 2019; Sayour et al., 2019; Uthman et al., 2019; Lahnwong et al., 2020; Nikolaou et al., 2021; Seefeldt et al., 2021) and a subsequent attenuation of HF development (Habibi et al., 2017; Yurista et al., 2019; Connelly et al., 2020). Multiple, parallel protective mechanisms of SGLT2 inhibitors have been proposed, such as the attenuation of cardiac and endothelial inflammation or an inhibition of oxidative stress improving cardiac structure and function (Lee et al., 2017; Ye et al., 2017; Andreadou,

Bell, et al., 2020). The effect of SGLT2 inhibitors on conditioning mechanisms has not yet been evaluated. Clinical trials examining a potential SGLT2 inhibitory effect on cardiac IRI during cardiac surgery or PPCI procedures are currently missing.

E. Statins and Antihyperlipidemic Medications

Statins decrease cardiovascular morbidity and mortality, since apart from their effect on cholesterol levels, they also have pleiotropic effects, which may provide additional benefits (Andreadou, Iliodromitis, et al., 2017; Mendieta et al., 2019). Hyperlipidemia is strongly correlated with increased oxidative stress and interferes with the conditioning cardioprotective mechanisms. Therefore, statins that modulate NO bioavailability and possess antioxidant properties may be beneficial in the hyperlipidemic myocardium (Andreadou et al., 2021). Recently, the pharmacological inhibition of PCSK9 has led to unquestionable benefits in terms of lowering cardiovascular risks, since low LDL-C levels are directly correlated with reduced risk of atherosclerotic cardiovascular disease (Andreadou, Tsoumani, et al., 2020).

Statins protect the heart against I/R but may interfere with the IS-limiting effect of conditioning strategies and, as such, display hidden cardiotoxic effects (Ferdinandy et al., 2014; Brenner et al., 2020). The combined effect of rosuvastatin and ischemic PreC or PostC synergistically protected the in vivo rat heart from IRI (Kelle et al., 2015). Sevoflurane postconditioning that was lost in the diabetic state was rescued by simvastatin through increasing NO levels (Grievink et al., 2019). Intravenous atorvastatin during MI limited cardiac damage, improved cardiac function, and alleviated remodeling to a larger extent than oral administration in a hypercholesterolemic pig model (Mendieta et al., 2020). To the best of our knowledge, the effect of statin treatment on RIC has not been tested yet in preclinical models. Very few studies so far have investigated the role of PCSK9 on myocardial IS in experimental animal models. The PCSK9 inhibitor, Pep2-8 trifluoroacetate, when administered 15 minutes before the onset of ischemia significantly reduced IS and improved LV function mainly due to attenuation of cardiac mitochondrial dysfunction and fission and decrease of the apoptotic process in the ischemic myocardium of rats (Palee et al., 2019). The effect of PSCK9 inhibitors on conditioning strategies has not been evaluated yet.

Statin pretreatment before elective PCI attenuates myocardial injury, as assessed by biomarker release (Herrmann et al., 2002; Patti et al., 2006). Acute statin loading in patients with an acute coronary syndrome before PPCI improves their outcome (Patti et al., 2007). First-time atorvastatin administration in 118 STEMI patients before PPCI prevented the occurrence of postoperative no-reflow and reduced the incidence of MACE (Li et al., 2018). The effect of long-term statin therapy on IS, myocardial salvage index, and microvascular obstruction in consecutive patients with STEMI who underwent PPCI demonstrated that long-term statin therapy was associated with smaller IS and higher myocardial salvage index (Marenzi et al., 2015). Meta-analyses showed an increased effect of RIC in statin users (Sloth et al., 2015), whereas in a retrospective analysis of a randomized, double-blind trial of patients undergoing elective CABG with/without RIC prior to ischemic cardioplegic arrest, statins had no significant impact on RIC-induced cardioprotection (Kleinbongard et al., 2016). Although limited clinical data exist, there is evidence that PCSK9 inhibition is associated with a reduced incidence of MI in patients with increased cardiovascular risk (Andreadou, Tsoumani, et al., 2020). PCSK9 inhibitors have different effects on type and size of myocardial infarcts, since evolocumab had no effect on type 2 events (Wiviott et al., 2020) whereas alirocumab when added to intensive statin therapy attenuated the risk of type 2 MI events (White et al., 2019). A recent meta-analysis of 67 RCTs indicated that PCSK9 inhibitors plus statin treatment significantly reduced the risk of nonfatal MI (Chaiyasothi et al., 2019). Whether PCSK9 inhibitors interfere with conditioning strategies has not been evaluated yet.

F. Antiarrhythmic Drugs

A diverse range of drugs are used in the management of cardiac rhythm disturbances that occur either as a consequence of chronic cardiovascular disease (e.g., hypertensive heart disease, ischemic cardiomyopathy, or HF of any origin) or that present in acute IR settings such as AMI. It is important to consider possible effects of these agents in the context of cardioprotection, specifically IS limitation, since several may have inherent cardioprotective properties or can modify endogenous cardioprotective mechanisms recruited through conditioning interventions. In either case, the use of antiarrhythmic drugs may be a confounding factor in the design and interpretation of clinical cardioprotection trials.

Some agents used for their antiarrhythmic properties may be inherently cardioprotective and limit IS in IRI models. For example, intravenous adenosine or the L-type calcium channel blocker verapamil are used acutely in paroxysmal supraventricular tachycardia. Given the transient nature of paroxysmal supraventricular tachycardia, acute use of adenosine or verapamil is unlikely to present an issue in relation to IRI and cardioprotection. However, recurrent of paroxysmal supraventricular tachycardia and other arrhythmias may require chronic preventative treatment with heart rate-limiting calcium channel blocker (verapamil or diltiazem), which, as described earlier, show cardioprotective effects when given prior to the onset of myocardial ischemia.

Although its efficacy is controversial, the sodium channel blocker lidocaine has been used in the management of malignant ventricular arrhythmias in AMI. Some experimental studies suggest that lidocaine blunts or abrogates conditioning responses. For example, in the rat isolated heart, ischemic PreC (2×5 minute) in the presence of lidocaine was blunted but only at concentrations that could be regarded as beyond the normal therapeutic range (Barthel et al., 2004). It is possible that this effect is related to inhibition of K_{ATP} channels with higher concentrations of the drug (Olschewski et al., 1996). Similarly, in the rat isolated heart, anesthetic PostC (sevoflurane 1.5 MAC for 15 minutes at reperfusion) was abrogated by coadministration with lidocaine at high but not at low concentration (Yan et al., 2008).

Amiodarone is used for a variety of ventricular and supraventricular arrhythmias and has a complex mode of action involving multiple ion channel targets and antiadrenergic activity (Mujović et al., 2020). Amiodarone was shown to improve functional recovery during reperfusion of rat heart subjected to low-flow ischemia (Rochetaing et al., 2001). In a rat isolated working heart preparation, subjected to low-flow ischemia, amiodarone treatment during low-flow ischemia was protective, with IS limitation and reduced arrhythmia severity. However, the protective effects of ischemic PreC (3×5 minute global ischemia) against IS were not enhanced in the presence of amiodarone, and the antiarrhythmic action seen with ischemic PreC and amiodarone individually was lost (Koo et al., 2006). Dronedarone is a structural analog of amiodarone, used primarily for ventricular rate control in paroxysmal or persistent atrial fibrillation and sharing a similarly complex multiple-target mode of action. Dronedarone exerts direct cardioprotective effects. In anesthetized pigs subjected to low-flow ischemia, dronedarone infusion during early ischemia markedly limited IS, although a specific mechanism explaining this powerful effect has not been determined (Skyschally and Heusch, 2011). Whether dronedarone augments or abrogates cardioprotection induced by conditioning protocols is unknown.

Although not a first-line antiarrythmic drug, digoxin may be used in the management of atrial fibrillation and atrial flutter, particularly when congestive HF is present. Several experimental reports suggest that sodium/potassium-ATPase inhibition exerts effects in IRI that impact on cardioprotection. Nawada et al. (Nawada et al., 1997) observed that digoxin blunted the IS-limiting effect of ischemic PreC in rabbit hearts. They proposed that ischemic PreC preserved sodium/potassium-ATPase activity in the early index ischemic period. Since that early report, further studies suggest that low-dose or transient doses of cardiac glycosides (ouabain, digoxin) can pharmacologically PreC or PostC the heart (Pierre et al., 2007; Belliard et al., 2016; Duan et al., 2018; Lauridsen et al., 2018).

Finally, other currently used antiarrhythmic drugs encountered in the management of AMI include flecainide, propafenone, and disopyramide. Whether they exert cardioprotective effects beyond their known antiarrhythmic effects in IRI has not been determined.

VI. Conclusions and Future Perspectives

The discovery of the remarkable cardioprotective effect of innate adaptive responses elicited by different conditioning strategies has fueled intensive research in the past 3 decades to find key cellular mechanisms, drug targets, and novel drug candidates for pharmacological cardioprotection as well as clinically applicable protocols for mechanical cardioprotection elicited by medical devices.

Most of the clinical trials with cardioprotective drugs or medical devices have been unsuccessful so far. One of the reasons might be that validation of drug targets and in vivo preclinical studies aiming to assess cardioprotective efficacy of drug candidates and performance of medical devices as well as their safety have been performed in juvenile, healthy animals subjected to IRI. Here we have summarized some data suggesting that validation of drug targets, assessment of in vivo efficacy of drugs, and performance of medical devices in comorbid animal models would be essential for successful clinical translation. Furthermore, we highlight observations that routine medications for cardiovascular and other diseases may exert undesirable effects on the ischemic heart and cardioprotective signaling mechanisms that should be also taken into account when developing cardioprotective therapies.

The body of evidence we have reviewed here underscores the critical importance of preclinical models and study designs that address cardioprotection specifically in relation to complicating disease states and risk factors. This more sophisticated approach is now an urgent necessity in experimental cardioprotection research to maximize the likelihood of identifying translatable effective approaches to therapeutic protection of the aged or diseased ischemic heart (Lecour et al., 2021).

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