

Pharmacological cardioprotection in diabetes



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Practice points

Diabetes–ischemic heart disease interactions

- Diabetes increases vulnerability to injurious ischemia–reperfusion injury while also increasing the threshold to achieve cardioprotection with modalities such as ischemic conditioning.

Acute cardioprotective strategies

- Ischemic or pharmacological conditioning strategies are well-described phenomena whereby either brief, non-injurious ischemia–reperfusion or acute exposure to a cardioprotective drug results in protection against injurious myocardial ischemia–reperfusion injury.

Pharmacological cardiac conditioning

- Hypoglycemics have pleiotropic effects beyond reducing blood sugar that may be re-purposed to attenuate myocardial injury in diabetic patients.
- Insulin, metformin and incretins appear to possess robust, cardioprotective properties when administered at the time of myocardial reperfusion.

Hypoglycemic drugs that can inhibit cardioprotection

- K_{ATP} channel inhibitors, such as sulfonylureas and meglitinides appear to block ischemic conditioning strategies, and therefore should be avoided at the time of myocardial ischemia.

Conclusion

- Re-purposing existing diabetic management therapies may result in improved outcomes in ischemic heart disease: large-scale trials are now needed to evaluate this exciting potential.

SUMMARY Acute coronary syndrome (ACS) in patients with diabetes continues to present clinical management challenges despite recent improvements in the management of ACS. The diabetic myocardium is more vulnerable to ischemia–reperfusion injury than non-diabetic myocardium and the diabetic patient more likely to develop complications, significant morbidity and death following ACS. Currently, ACS management of diabetic and non-diabetic patients is not sufficiently differentiated to address the additional risk arising from ACS in a diabetic. Here we review the evidence for routine aspects of diabetic management such as glucose control in the context of ACS, and suggest that additional benefit may be derived by tailoring and pre-purposing antiglycemic medications during acute myocardial infarction to make best use of their pleiotropic potential as cardioprotective agents.

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- reperfusion injury

The developed world has seen five decades of mortality reduction in ischemic heart disease (IHD), yet patients with diabetes are subject to the same excess of cardiovascular mortality in the current era as they were in the 1970s [1]. Comparison of cohort studies from the last three decades of the twentieth century suggests that whereas cardiovascular mortality fell by 37% in non-diabetic men, the reduction in diabetics was only 13%; even allowing for the higher prevalence of IHD in diabetes, this is still only half the absolute fall seen in non-diabetics [2]. The persistent residual risk of IHD complicating diabetes (DM-IHD) suggests a direct lethal interaction between these two pathologies. There is a clear, unmet clinical need for new treatments to address the toxicity of diabetes in acute coronary syndrome (ACS), and interestingly there is now an increasing body of evidence to suggest that redeploing existing diabetic therapies may be a valid approach to this challenge.

Diabetes–IHD interactions

DM-IHD differs from IHD related to other, classical non-diabetic cardiac risk factors (ND-IHD) mechanistically, reflected by differences in epidemiology and endpoints of death and heart failure [3,4]. Evidence for this includes earlier demonstrable vascular dysfunction, aggressive development of symptomatic coronary occlusions and more frequent acute ischemic events than in non-diabetics. The high prevalence of heart failure even in the absence of IHD is highly suggestive of direct diabetic myotoxicity, making it attractive to hypothesize that the toxic effects of diabetes upon myocardial viability is responsible for the excess mortality in those diabetic patients presenting with myocardial ischemia [5]. Direct comparison of IHD outcomes between DM-IHD and ND-IHD is challenging because coronary anatomy is typically more complex in DM-IHD, with multi-vessel disease, calcified lesions and lesions with adverse characteristics for percutaneous intervention more common in patients with diabetes [6]. Even allowing for these differences, however, the sequelae of myocardial infarction (MI) in DM-IHD include excess arrhythmia, increased myocyte apoptosis and myocyte hypertrophy, more extensive cardiac fibrosis and higher incidence of heart failure [7,8].

Long-term glycemic control fails to elicit cardioprotection

Current strategies to reduce cardiovascular death in DM-IHD are based on strategies

found to be effective in non-diabetic populations and hence, conventional focus remains on managing hypertension and dyslipidemia. These approaches do not tackle either the primary manifestation of diabetes, hyperglycemia, nor the secondary metabolic sequelae of insulin resistance. Evidence for intervening on blood pressure and lipid levels that would be considered acceptable in the non-diabetic population is strong, but unsurprisingly, even optimal treatment of both these factors fails to erode the residual risk of diabetes [9–12]. One attractive strategy to address this residual risk is to aim for enduring tight glycemic control; however, in contrast to the strong evidence we present later for acute intervention on blood sugar during and immediately after acute myocardial infarction (AMI), long-term intensive glycemic control as a cardioprotective measure in diabetes has proven disappointing. Long-term follow-up data from the UKPDS provides the strongest support for intensive glycemic control for cardiovascular and cardioprotective benefit, with a late divergence in rates of cardiovascular death in those who were initially randomized to tight glycemic control [13]. This contrasts favorably with the lack of benefit shown in the highly powered ACCORD study, and the absence of protection from vascular death shown in ADVANCE [14–16]. Admittedly, the details of ‘tight’ glucose control regimes differed between these trials, and interpretation of ACCORD is beset by excess mortality in the tight glucose control group, which *post hoc* analyses suggest was not causally related to hypoglycemia [17,18]. In summary, while we cannot conclude that intensive glycemic control over the long term is justified as a cardioprotective measure to reduce cardiovascular death, it still has a vital role in reducing morbidity associated with microvascular diabetic complications.

Given that IHD remains the leading cause of mortality in diabetes, we have lately considered whether some of the many anti-hyperglycemics might have more impact on cardiovascular survival if used to target the acute phase of MI, rather than purely as a strategy for long-term glycemic control.

Acute cardioprotective strategies

Conventional cardioprotective drugs such as β -blockers, angiotensin-converting enzyme (ACE) inhibitors and statins are intended to both reduce progression of vascular disease

and to retard the development of a metabolically vulnerable myocardium. Acute treatment, sometimes with the exact same drugs at higher dosages, by contrast, may act over minutes or hours and to induce a temporary state of profound protection in the myocardium. This temporary effect is known as cardiac conditioning, and can modify the sequelae of both ischemia and reperfusion [19].

• Myocardial ischemia

Acute coronary occlusion lasting more than 20 min triggers a wave front of cardiomyocyte death initiated in the sub-endocardium and extends inexorably toward the epicardium unless arrested by timely revascularization and reperfusion. The underlying cause of this ischemic injury is a deficit of ATP and the endpoint is necrotic cell death (reviewed [20]).

• Myocardial reperfusion

While progression of the injurious ischemic wave front is effectively halted by restoration of coronary flow, reinstatement of oxygenated blood supply to still-viable myocardium can paradoxically augment the lethality of the acute myocardial injury. Clinically, this ‘reperfusion injury’ is most apparent as reperfusion arrhythmias and/or transient mechanical dysfunction (stunning) of the affected myocardium. From experimental data, it is clear that ischemia–reperfusion injury also contributes significantly to the total burden of cell death within the heart, potentially contributing up to 50% of final infarct size [20]. With infarct size determining future prognosis, defined largely by sequelae such as ischemic heart failure [21], there remains a prescient need to limit or even attenuate infarct size within this vulnerable diabetic population.

In contrast to necrosis of ATP-depleted myocardium during ischemia, cell death resulting from reperfusion occurs in what would otherwise be a potentially viable population of cardiomyocytes. A key event in reperfusion cell death is the formation of a high conductance pore in the mitochondrial membrane, known as the mitochondrial permeability transition pore (mPTP; **Figure 1**). This allows rapid influx of water and solutes into mitochondria, which then swell, lyse and initiate rapid programmed cell death through apoptosis and necroptosis (see review [20]). Intervening in this cell-death pathway may therefore offer opportunities for reducing the extent of MI resulting

from injurious ischemia–reperfusion injury. One such interventional modality is ischemic conditioning.

• Ischemic conditioning

Ischemic conditioning can reduce cell death from ischemia–reperfusion injury (IRI), chiefly by activation of survival pathways within cardiac myocytes which converge to prevent formation of the mPTP at reperfusion. The exemplar of conditioning strategies is ischemic preconditioning (IPC), where the heart is subjected to repeated short bursts of ischemia and reperfusion, before the onset of injurious (‘index’) ischemia. Variants on IPC include ischemic per-conditioning (where ischemia is intermittently applied typically to a distant organ during the index cardiac ischemia), ischemic post-conditioning (where reperfusion is transiently and repeatedly interrupted) and remote ischemic conditioning (where a distant organ is rendered temporarily ischemic before, during or immediately after index ischemia on the heart). These maneuvers are illustrated in **Figure 2** and have been shown to reduce cell death from IRI across many species, including rodents, rabbit, dog, pig and man [22]. Although not clinically applicable due its invasive nature, direct IPC of the heart has provided a model in which to characterize the response to conditioning stimuli in the laboratory.

• Pharmacological cardiac conditioning

Various drugs have been found to protect the heart from IRI in a similar fashion to ischemic stimuli when given as conditioning agents before, during or immediately following cardiac ischemia (pharmacological pre-, per- or post-conditioning). A complete list is beyond the scope of this review, but among commonly prescribed cardiac drugs, P2Y₁₂ inhibitors, β-blockers, statins, ACE inhibitors and angiotensin-2 receptor blockers have all been shown to reduce infarct size by activating similar intracellular signaling cascades to IPC, prototypically through cell-membrane receptor activation (e.g., bradykinin, angiotensin II) and recruitment of downstream signaling pathways (**Figure 1**; reviewed in [19]).

• Ischemic conditioning signaling

The ultimate target in acute cardiac conditioning is prevention of mPTP opening. Two main intracellular pathways, RISK (reperfusion injury

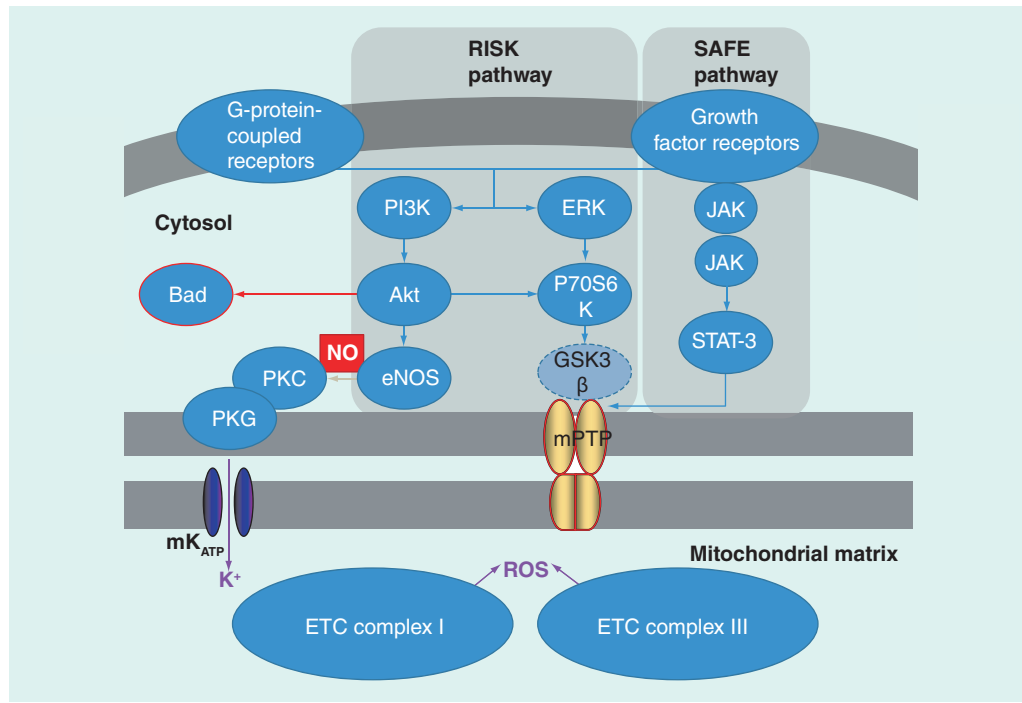


Figure 1. Intracellular pathways involved in classical cardiac conditioning. In response to ligand binding at cell surface G-protein-coupled receptors, the RISK pathway is activated. PI3K is activated, phosphorylating Akt, eNOS. NO activates PKC, PKG. Cross-activation within RISK activates an ERK leading to phosphorylation of P70S6 kinase which may phosphorylate and inhibit GSK3β, though GSK3β's involvement in RISK is now disputed. Separately, binding of growth factors to their cell surface receptors activates the SAFE pathway leading to multiple phosphorylation of JAK and eventually to phosphorylation of STAT-3. SAFE then interacts directly with the mPTP, whereas RISK triggers activation of an mK_{ATP} resulting in a small potassium leak into the mitochondrial matrix and transient ROS release from complexes I and III of the electron transport chain. The signaling ROS then exerts an inhibitory effect on the mPTP. ETC: Electron transport chain; mPTP: Mitochondrial permeability transition pore; RISK: Reperfusion injury salvage kinase; ROS: Reactive oxygen species; SAFE: Survival activating factor enhancement.

salvage kinase) and SAFE (survival activating factor enhancement), converge on the pore to achieve this, as illustrated in **Figure 1**. Each pathway is a cascade of phosphorylation activity, with each reaction activating or inactivating a target kinase. The upstream triggers for these pathways are diverse, but include a range of growth factor receptors and G-protein coupled receptors. The cardioprotective kinase signaling cascades appear to be activated both during the ‘trigger phase’ of conditioning and upon reperfusion, where they exert their protective influence on the mPTP, reducing injurious pore opening.

Events between kinase activation and the mPTP are less well described, but a mitochondrial potassium channel (mK_{ATP}), mitochondrial reactive oxygen species (ROS), and at least two

isoforms of PKC are implicated. For a detailed summary of intracellular cardiac conditioning signaling, see review [23].

Clinical strategies for conditioning in diabetes

Pharmacological intervention during an episode of MI (i.e., pharmacological preconditioning) to reduce tissue death and improve prognosis is a realistic ambition. However, there is good reason to suspect that many forms of conditioning stimuli, be that transient ischemia or drugs, may be less effective in diabetic patients: hyperglycemia, insulin resistance and hyperlipidemia have all been shown to increase the threshold for triggering conditioning; a more robust conditioning signal is required to protect the myocardium in the presence of these co-morbidities [24–26].

Moreover, most diabetic patients will already be on both statins and an ACE inhibitor, and there is good evidence that chronic exposure to these otherwise cardioprotective drugs can erode their acute cardiac conditioning potential [27].

Thus, in considering acute cardiac conditioning of the diabetic patient presenting with an ACS there are three important facets to consider:

- Correction of deleterious hyperglycemia to facilitate cardioprotective signaling;
- Timely prescription and administration of drugs with conditioning potential, cognizant that the efficacy of those drugs may be adversely attenuated where the drugs have already been prescribed as part of a long-term glycemetic control strategy in that patient;
- Discontinuation of any drugs that could block acute cardiac conditioning signals.

• Correction of hyperglycemia

Short-term prevention of hyperglycemia during MI is effective at improving survival. The

DIGAMI study randomized 620 diabetic patients presenting with MI and hyperglycemia (>11 mmol/l; >198mg/dl) to either insulin-glucose infusion in hospital followed by injectable insulin for 6 months post MI, or to standard glucose control. Survival curves of the groups separated in the first few days of the trial, suggesting a powerful effect on IRI or early post-infarct remodeling [28]. It is not clear from human studies whether the observed improved outcomes are a direct effect of insulin on the myocardium as a conditioning agent (as discussed in the next section), or whether restoration of normoglycemia facilitated other acute cardiac conditioning signals. Evidence from studies in non-diabetics, in which insulin-glucose infusions controlled glycemia and yet failed to improve outcome, would suggest that the mechanism is more complicated than purely reversing hyperglycemia [29–32]. Either way, control of glycemia with insulin is mandatory during acute MI in diabetes; this is reflected in UK, European and American national guidelines (see **Table 1**).

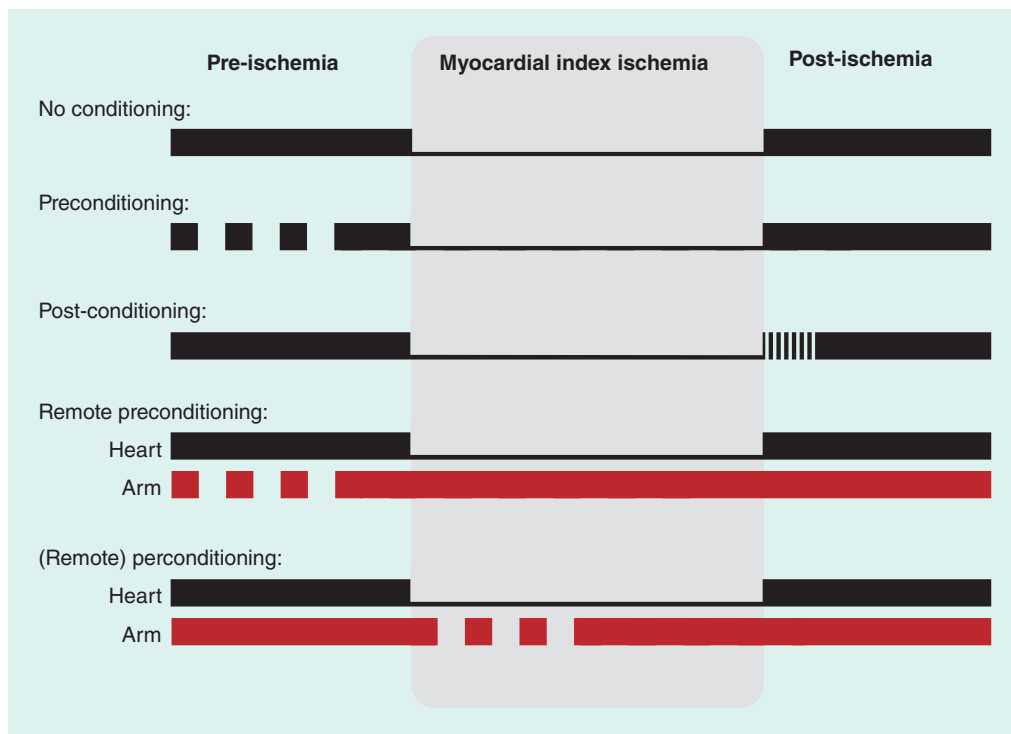


Figure 2. The different possible timings of ischemic conditioning. Preconditioning comprises temporary interruptions to perfusion prior to the index ischemia; postconditioning involves short, rapid cycling interruptions to perfusion following the index ischemia. In remote preconditioning, a distant organ or limb is subjected to interrupted perfusion similar to conventional preconditioning, and the heart is protected from subsequent index ischemia. During perconditioning, the remote organ or limb is subjected to interrupted perfusion during the index ischemia of the heart.

• **Hypoglycemic drugs with conditioning potential**

Insulin

Insulin in basic research studies has been shown to robustly recruit cardioprotective signaling and ameliorate myocardial injury resulting from experimental ischemia–reperfusion injury. Attempting to elucidate the mechanism of insulin-mediated infarct-size reduction in the clinical setting is considerably more challenging; it is extremely difficult to separate the impact of insulin upon conditioning signaling from the effect that insulin therapy has upon correcting hyperglycemia. Trials such as DIGAMI used insulin for acute glycemic control, thus conflating the two effects of cardioprotective signaling and reduction of hyperglycemia: which effect is responsible for the beneficial outcome? Isolated animal heart experiments allow insulin to be added to hearts during ischemia–reperfusion without affecting the concentration of glucose available for cardiac metabolism, and thus the protective effects of normoglycemia and insulin can be examined separately. Results from our lab, amongst others, confirm that insulin exerts a powerful conditioning effect on the heart, mediated by a cascade of pro-survival kinases. The effector, as with classical conditioning by IPC, is inhibition of the mPTP, and enhanced cellular survival at reperfusion [37,38].

The DIGAMI trialists conducted a second trial to address whether insulin’s effect is only during acute IRI, or whether the 6-month intervention with injectable insulin following discharge contributed to the prognostic benefit in DIGAMI. Unfortunately, DIGAMI-2 saw no difference in 1-year mortality between groups randomized to insulin infusion during MI only, insulin infusion followed by long-term injectable insulin, or routine care [39]. Much has been written about possible reasons for failure of this trial, and unmatched baseline patient characteristics between the groups, with a high degree of treatment crossover between groups may both have contributed.

A further factor confounding interpretation of DIGAMI-2 is that it remains unclear what

proportion of patients were diabetic, as opposed to experiencing transient stress hyperglycemia during MI. Trials including a low proportion of diabetic patients have repeatedly proven negative, with GIPS-2, ECLA-GIK and CREATE-ECLA, all producing either conclusively negative or failing to reach statistical significance [29,31–32].

Our interpretation of this conflicting evidence is that there is no strong evidence for use of insulin during MI outside of diabetes, but that acute insulin infusion for diabetics with hyperglycemia on presentation with MI is better supported.

Current clinical guidelines interpret the evidence differently from us, and largely disregard the presence or absence of previous diabetes. All recommend insulin be given to patients with overt hyperglycemia during the acute phase of MI (Table 1). The strategy of routinely giving insulin, glucose and potassium together (GIK infusion) to patients without hyperglycemia at presentation is not currently recommended. Theoretically, GIK infusion should offset the hypoglycemic and hypokalemic effects of insulin, leaving just the direct myocardial conditioning effects, thus allowing insulin to be given to normoglycemic patients. This is not recommended by any current guidelines, due to the negative trials discussed above, but as these trials included only a minority of diabetic patients (10–30%), our view is that the utility of GIK infusion in diabetic patients presenting with normoglycemia during MI remains unproven [29–31,40].

Metformin

Metformin is widely thought to have pleiotropic cardiovascular benefits independent of its role as an oral hypoglycemic agent, hinted at by intriguing additional mortality reductions conferred on obese subjects in the UKPDS trial, though interpretation of subset analyses such as this is fraught with difficulties [41]. Most recently, a retrospective analysis compared infarct sizes in diabetics treated with metformin versus those managed with other hypoglycemic strategies. metformin treatment was associated with smaller infarct sizes as defined by peak

Table 1. Comparison of guidelines for management of hyperglycemia during acute ST-elevation myocardial infarction.

Guideline	Year	Target glucose	Drug strategy	Ref.
ACC/AHA	2008 and 2013	<10 mmol/l ‘avoiding hypoglycemia’	In ICU: insulin infusion; elsewhere: subcutaneous insulin	[33,34]
ESC	2012	5–11 mmol/l	‘May require a dose-adjusted insulin infusion’	[35]
NICE	2011	<11 mmol/l ‘avoiding hypoglycemia’	‘Consider a dose-adjusted insulin infusion’	[36]

ACC: American College of Cardiology; AHA: American Heart Association; ESC: European Society of Cardiology; ICU: Intensive care unit.

blood levels of troponin-T and creatine kinase, and this trend persisted even after correction for other known infarct size determinants such as age, sex, coronary flow status post-percutaneous intervention (PCI) and previous MI [42]. Whilst these data are not prospective or randomized, it is the most persuasive evidence of cardiomyocyte preservation during MI in diabetes by any intervention, save for primary PPCI. Outside the setting of acute MI, a recent prospective, randomized controlled trial in patients with metabolic syndrome undergoing elective PCI has shown similar results, in reducing peri-procedural cardiac enzyme leakage [43]. This study design isolates the effect of metformin on reperfusion, as distinct from any effect it may have on ischemic tolerance, and suggest that metformin confers an important portion of its protection during reperfusion.

Animal data are also strongly supportive of chronic metformin treatment as a measure to reduce IRI, and offer insights into potential mechanisms of protection across a range of diabetic models. Our group has recently shown that chronic treatment of Type 2 diabetic Goto Kakizaki rats with metformin reduces histological infarct size independent of the drug's glucose lowering effects [44]. Streptozotacin-treated (Type 1 diabetic) rats exhibit similar results [45]. This builds on previous work showing that acute treatment of the isolated heart itself could also elicit protection, and is reproduced by others in swine with metabolic syndrome [46,47].

Animal studies reveal that metformin has a range of pro-survival effects on the heart, enabling cardiac myocytes to better withstand both the ischemic and reperfusion phases of IRI. Downstream signaling of acute dosing with metformin is via AMPK and adenosine, which in turn inhibits formation of the mPTP (see **Figure 3**) [46,48–49]. Chronic dosing may act on the mitochondrion via different pathways, upregulating the transcription factor peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α). This in turn promotes mitochondrial elongation and increases mitochondrial organization, presumably by increased transcription of structural mitochondrial components. Interestingly, the classical cardioprotective RISK pathway is not activated by chronic metformin administration, yet this pathway is central to intracellular signaling of acute metformin treatment [44,46].

Building on the combination of improved survival in epidemiological studies and reduced infarct size as outlined above, much interest has surrounded Metformin's potential to reduce heart failure, especially post-infarction. Results following ischemia–reperfusion of the anterior left ventricle wall *in vivo* were promising in non-diabetic rats and mice [50,51], but failed to translate to humans in the GIPS-III study [52]. Similar studies on diabetic animals and humans have yet to be undertaken, but as with the other pharmacological treatments reviewed here, we see more reason for success in the diabetic than in the non-diabetic.

Incretins

Originally identified as an alternative way to control hyperglycemia, the incretin (INtestinal seCRETion of INsulin) hormone modulating drugs not only augment insulin signaling, but also have a range of direct cardiovascular effects, some of which interact with conditioning pathways. The archetypal incretin hormone, glucagon-like peptide-1 (GLP-1), exerts cardiac effects through binding GLP1 receptor (GLP1R) in the myocardium, which, in common with many myocardial G-protein coupled receptors, is capable of activating the pro-survival kinase cascade common in cardiac conditioning [42].

Three broad drug strategies exist to enhance signaling via the GLP1R receptor: GLP1 analogs, direct GLP1R agonists and inhibitors of GLP1 breakdown (dipeptidylpeptidase-4 [DDP-IV] inhibitors). Acute treatment with any of these drug classes has reduced infarct size in diabetic and non-diabetic rodents [42,53–54], though trials in man thus far have been small, and conducted only in non-diabetics. Nonetheless, small benefits to indices of left ventricular function have been seen using all available clinically available incretin therapies as conditioning treatments during MI or experimental coronary artery occlusion in man [55–58]. After the disappointing findings with insulin therapy in non-diabetics [29–32], it might be anticipated that diabetic patients would have more to gain from conditioning with incretins than non-diabetics. Initial placebo-controlled cardiovascular outcome trials of saxagliptin and alogliptin in diabetics have been designed to demonstrate only safety (i.e., non-inferiority to placebo), rather than protection from cardiovascular endpoints [59,60]. Further trials designed to investigate cardioprotective potential are awaited with interest.

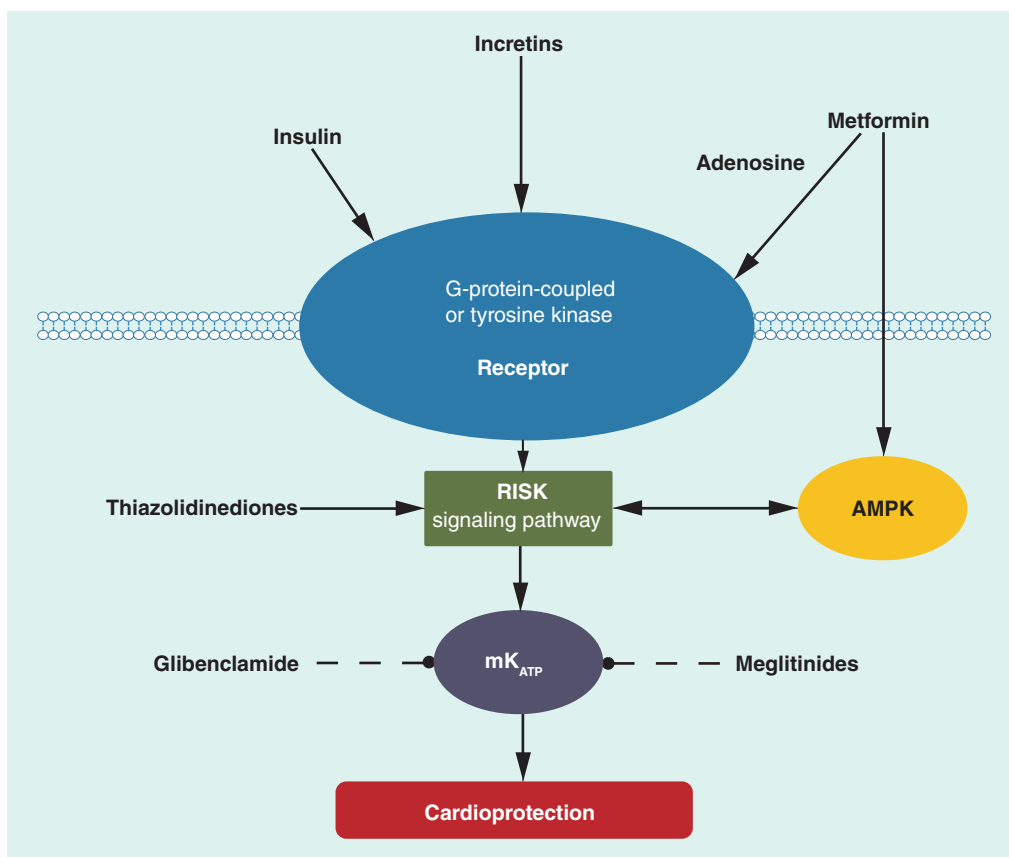


Figure 3. Interactions between conditioning drugs, conditioning blocking drugs and the classical cardiac conditioning signaling pathway. Insulin and incretin-modulating therapies influence signaling through cell surface receptors, whereas thiazolidinediones and metformin have only been thus far shown to have effects on intracellular signaling, though cell surface receptors may be identified in the future. Metformin influences the RISK pathway via AMPK as well as via adenosine receptors. Glibenclamide and the meglitinides block conditioning signaling at the mK_{ATP}. mK_{ATP}: Mitochondrial potassium channel ATPase; RISK: Reperfusion injury salvage kinase.

Thiazolidinediones

Regulators on both sides of the Atlantic have recommended both pioglitazone and rosiglitazone be avoided in patients with established IHD, following reports of excess incidence of heart failure [61,62]. This overshadows the modest finding of the PROactive 05 study that chronic administration of pioglitazone as a cardioprotective agent post-MI in diabetics is associated with a non-significant reduction in subsequent MI and cardiovascular death [63]. A meta-analysis of 19 randomized controlled trials including 16,390 patients randomized to long-term pioglitazone or placebo reached statistical significance for reduction in a composite endpoint of death, MI or stroke. Both these results have only a peripheral bearing on acute cardioprotection in the sense of tissue preservation during MI, though they do suggest that pioglitazone may have a wider role in

cardioprotection at odds with its well-publicized exacerbation of heart failure risk [62].

Of more direct interest here, the thiazolidinediones' effects on cell survival during and immediately after MI have been addressed in animal experiments; in isolated rat hearts, acute pioglitazone pretreatment protects against subsequent IRI, ameliorating infarct size and suppressing reperfusion arrhythmias through activation of the RISK pathway [64,65]. In summary, cardiovascular effects of this class of drug are complex and may be contradictory. We have found that acute administration of some other drug classes in the context of IRI can be quite different to their effects when given chronically (the HMG Co-A reductase inhibitor, atorvastatin, is one such example of this [27]). Thiazolidinediones may also be subject to this paradox, but given the concerns about heart failure causation, further work is

needed to establish their utility and safety in the setting of ACS.

- **Hypoglycemic drugs that can inhibit cardioprotection**

Studies investigating the potential inhibitory interaction of co-prescribed therapies and conditioning drugs (so-called ‘conditioning-mimetics’ and exemplified above) are lacking in both man and laboratory experimental settings. However, blockade of the protection afforded by IPC is well studied, at least in the laboratory. While the reader should be cognizant that drugs which block IPC may not necessarily affect other modes of pharmacological conditioning, both drug classes described here (meglitinide analogs and sulfonylureas) exert their effect through a common target: the mitochondrial potassium ATPase channel (mK_{ATP}), a common signaling component proposed to be involved in many forms of myocardial conditioning (Figure 1). Transient opening of this channel in response to a conditioning stimulus permits a small-scale potassium leakage into the inner mitochondrial space, promoting a transient ROS leak from complexes I and III of the mitochondrial electron transport chain. Signaling via ROS is a vital step in the generation of the protected phenotype, and blockade of myocardial ROS generation or mopping up of ROS by antioxidants blocks the protective effects of conditioning stimuli (reviewed in [66]).

Meglitinide analogs

The meglitinides are novel insulin secretagogues that trigger pancreatic release of insulin via blockade of K_{ATP} channels in pancreatic beta cells. The increased intracellular potassium concentration in turn triggers relative cellular depolarization by calcium influx, and hence increased insulin release [67]. There is clear potential for interaction of meglitinides with K_{ATP} channels in the heart, but their effect upon pro-survival kinase pathways is currently unknown.

Two small clinical studies in diabetic patients have assessed the effect of repaglinide on myocardial ischemic tolerance, using exercise electrocardiographic parameters as surrogate endpoints. Repaglinide administration blocked the usual adaptive response to training so that treadmill performance did not improve over time in patients on repaglinide. When an ischemic conditioning stimulus was used to increase ischemia tolerance, this too was blocked by repaglinide [68,69]. Taken together, these results suggest that not only might

meglitinides block conditioning treatments, but they could have the potential to impair baseline ischemia tolerance within the heart. Further investigation is clearly required to determine whether this apparent detrimental impact upon exercise conditioning translates into increased vulnerability to myocardial ischemia–reperfusion injury. If the latter were proven to be the case, serious consideration should be given to at least temporarily discontinuing these drugs in patients presenting with acute coronary syndrome.

Sulfonylureas

Like the meglitinides, the sulfonylureas are insulin secretagogues targeting the K_{ATP} channel in pancreatic beta cells. In contrast to repaglinide, mechanistic studies demonstrating the interaction between various sulfonylureas and conditioning stimuli are available. Among second-generation sulfonylureas, gliclazide does not block myocardial mK_{ATP} channels, but glibenclamide does [70]. Consistent with this, whereas glibenclamide has been shown to block conditioning by IPC in both isolated non-diabetic rat hearts and diabetic human atrial muscle, gliclazide does not block conditioning [71,72]. Controversially, some studies have suggested that, far from blockade, glimepiride may facilitate IPC via enhanced activation of pro-survival kinases, independent of any action on the mK_{ATP} channel [73–75].

Much has been written on the safety of sulfonylureas for patients with IHD, and the conclusion has generally been that there are insufficient data available from clinical trials. The ongoing CAROLINA study will provide an up-to-date comparison of a modern sulfonylurea with a DPP-IV inhibitor over the long term, but no large-scale peri-infarct mortality outcome studies are planned: this is an important omission from the literature [76]. In the interim, the most evidence-based approach would undoubtedly be to avoid all sulfonylureas other than glibenclamide, and possibly glimepiride, during and immediately after acute MI, substituting these drugs in preference to one of the classes of hypoglycemics described above that is at least cardiovascularly neutral or even beneficial in the context of MI.

Conclusion & future perspective

While novel hypoglycemic agents such as the sodium/glucose transporter (SGLT2) inhibitors offer exciting cardiovascular potential, more

Table 2. Major oral hypoglycemic drugs groups and evidence for their use as acute cardioprotective treatments.

Drug class	Effects in diabetic animals	Effects in diabetic man	Current guidance for use during ACS
Insulin	Acute administration reduces infarct size	Improved early survival post-MI	Use if hyperglycemic [†]
Metformin	Chronic or acute administration reduces infarct size and subsequent heart failure	Chronic use before MI associated with smaller infarct size and enzyme leak	None
Incretins	Acute administration of all incretin modulating drugs reduces infarct size	Not studied	None
Thiazolidinediones	Acute pioglitazone reduces infarct size	Conflicting evidence	Not for use in patients with IHD due to excess CCF
Meglitinides	Not studied	Block exercise conditioning. Other stimuli not studied	None
Sulfonylureas	Glibenclamide blocks ischemic conditioning; glimepiride activates survival signals	Glibenclamide blocks ischemic conditioning of isolated atrial muscle; other drugs not studied	None

Acute administration: Either single *in vivo* dose, or administration to isolated heart preparation.

[†]See **Table 1**.

ACS: Acute coronary syndrome; CCF: Congestive cardiac failure; IHD: Ischemic heart disease; MI: Myocardial infarction; N/A: Not available.

immediate changes can be made to potentially optimize cardiovascular outcomes from ACS by alteration of prescribing patterns of drugs already in everyday use. With the exception of the use of insulin in patients with diabetes, no other glucose lowering intervention is currently advocated in the management of acute hyperglycemia in the context of an acute coronary syndrome within current clinical guidelines (**Table 2**). This appears to be a missed opportunity: every pathophysiological stage in the evolution of DM-IHD presents potential targets to reduce mortality, from asymptomatic hyperglycemia through to post-infarct remodeling of the heart. The current focus of anti-diabetic drug management is primarily to control blood glucose in order to delay or avoid hyperglycemic complications. The sad truth is, however, most diabetic patients will still suffer a myocardial infarct, and too large a proportion will die or be disabled by it.

There is now sufficient evidence for acute administration of insulin and metformin as cardioprotective treatments in diabetic patients presenting with ACS, and clinical trials are needed to clarify whether the newer hypoglycemics

discussed here have similar therapeutic potential, as we suggest. For the meantime we would recommend avoidance of sulfonylurea and meglitinide drugs in the acute phase of ACS. Tantalizingly, such re-purposing of existing therapies offers a new paradigm whereby acute loading doses of the hypoglycemic drugs discussed here become part of standard care during the management of ACS.

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