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Review

Glycaemic control in people with diabetes following acute myocardial infarction

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ABSTRACT

Diabetes is a highly prevalent disease associated with considerable cardiovascular end organ damage and mortality. Despite significant changes to the management of acute myocardial infarction over the last two decades, people with diabetes remain at risk of complications and mortality following a myocardial infarct for a multitude of reasons, including increased coronary atherosclerosis, associated coronary microvascular dysfunction, and diabetic cardiomyopathy. Dysglycaemia causes significant endothelial dysfunction and upregulation of inflammation within the vasculature and epigenetic changes mean that these deleterious effects may persist despite subsequent efforts to tighten glycaemic control. Whilst clinical guidelines advocate for the avoidance of both hyper- and hypoglcyaemia in the *peri*-infarct period, the evidence base is lacking, and currently there is no consensus on the benefits of glycaemic control beyond this period. Glycaemic variability contributes to the glycaemic milieu and may have prognostic importance following myocardial infarct. The use of continuous glucose monitoring means that glucose trends and parameters can now be captured and interrogated, and its use, along with newer medicines, may provide novel opportunities for intervention after myocardial infarction in people with diabetes.

1. Introduction

Despite significant changes to the management of acute myocardial infarction (AMI) over the last 20 years, with the introduction of early revascularisation as standard of care, people with diabetes sustaining an AMI persist as a subgroup at high risk of complications. These include death, heart failure, stroke and nonfatal re-infarction, whilst an inpatient [1–2], within 30 days [1], at 6–12 months [1], and in the longer term [3–5]. Concerningly, in people with a background of polyvascular disease, or in people experiencing an AMI complicated by clinical signs of heart failure or left ventricular dysfunction, who have a high baseline risk for complications following AMI [6], diabetes independently confers additional risk of complications and mortality [6–7].

Dysglycaemia causes significant oxidative stress, endothelial and platelet dysfunction, and upregulation of inflammation within the vasculature following AMI (Fig. 2). It is strongly associated with adverse outcomes [8–10]. However currently there is no consensus on the benefits of glycaemic control beyond the acute *peri*- infarct period and the evidence base to support current in-patient guidance is small. Recent new insights from studies [11–12] looking at epigenetic changes following acute and sustained hyperglycaemia throw weight behind the concept of the vascular hyperglycaemic memory where end organ damage from dysfunctional glucose control is irreversible. This questions therefore how much is to be gained from subsequent efforts to obtain glucose control, following AMI, on cardiac structure and function, and associated morbidity and mortality. On the other hand, a number of studies (detailed in Table 1) find direct evidence of reduction in oxidative stress, cell apoptosis and increased markers of myocardial regeneration in ventricular specimens (taken at the time of *peri*- infarct coronary artery bypass grafting) when tight glucose control is achieved in the context of hyperglycaemia shortly following infarct [13–14].

This review aims to provide an overview of the associations between hyperglycaemia, hypoglycaemia and glycaemic variability (GV), and prognosis after AMI, emphasising the evidence gaps that exist in clinical

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Table 1
Key randomised control trials investigating glucose control following AMI. Statistical significance defined as $p < 0.05$ in all, pPCI = primary percutaneous coronary intervention.

Key randomised control trials investigating glucose control following AMI								
Clinical trial (year)	**# of participants (% without known diabetes)**	**Admission glycaemia**	**Glucose control method in intervention and control groups**	**Acute glucose control- mean (SD) over 24 h of infusion, or mean (SD) 24 h of infusion**	**Outpatient glucose difference intervention vs control group**	**Primary endpoint**	**Results**	**Comments**
Randomised control trials that inform current clinical guidance								
DIGAMI 1 (1995) [30]	620 with AMI (13 %)	>11 mmol/L	Intervention group: acute phase IV insulin-glucose infusion followed by long term subcutaneous insulin based treatment Control group: standard care	Significant. Intervention group: 9.6 (3.3) mmol/L Control group: 11.7 (4.1) mmol/L	Significant at 3 and 12 months	Mortality at 3 months	Primary endpoint not significant	- Significant mortality benefit at 12 months in intervention group. - The only RCT to show survival benefit following intensive glucose control. - Unable to differentiate between effects of acute phase, and longer term, glucose control. - Mortality lower than expected overall. - Significantly higher number of in-patient hypoglycaemic episodes in the intervention group than in the control group.
DIGAMI 2 (2005) ([31])	1,253 with AMI (N/A)	Known type 2 diabetes or admission blood glucose > 11 mmol/L	Intervention group 1: acute phase insulin-glucose infusion followed by long term subcutaneous insulin based treatment with a treatment goal of fasting glucose level of 5–7 mmol/L and non-fasting glucose level of < 10 mmol/L Intervention group 2: acute phase insulin-glucose infusion followed by standard care Control group: standard care	Statistically significant difference comparing groups 1 and 2 with group 3, but difference small (absolute difference comparing groups 1 and 2 with group 3 of 0.9 mmol/L)	Not significant	All-cause mortality over median 2.1yrs follow up (interquartile range 1.03-3yrs) between groups 1 and 2	Primary endpoint not significant	- Lower baseline glucose at randomisation than in DIGAMI 1 (15.5 mmol/L in DIGAMI 1 versus 12.8 mmol/L in DIGAMI 2). - Initial decrease in glucose in infusion groups smaller in DIGAMI 2 (-3.4 mmol/L) compared with DIGAMI 1 (-5.8 mmol/L). - Outpatient glucose targets not reached in group 1, and long term glucose control did not differ between the groups. Therefore study underpowered for outcomes. - Overall longer term glucose control better in DIGAMI 2 than DIGAMI 1. Of note, combined 2 year mortality was 18.4 % (lower than expected)- speculatively may be related to better glucose control across the trial. - Trend towards fewer secondary events in groups 2 and 3 compared with group 1. - 70 % of participants on statin at the time of discharge

(*continued on next page*)

Table 1 (*continued*)

	Key randomised control trials investigating glucose control following AMI							
								following their AMI compared with none in the DIGAMI 1 trial. - Hypoglycaemia defined as glucose < 3 mmol/L. Hypoglycaemia in the first 24 h more frequent in the groups receiving the insulin glucose infusion (groups 1 and 2) compared to group 3.
HI-5 (2006) ([32])	240 with AMI (52 %)	>7.8 mmol/L	Intervention group: acute phase IV insulin- glucose infusion Control group: standard care	Not significant. Intervention group: 8.3 (2.2) mmol/L Control group: 9.0 (2.8) mmol/L	N/A	Mortality during the index hospital admission and after 3 and 6 months	Primary endpoint not significant	- Recruitment glucose cut off lower than DIGAMI 1 and 2 trials. - Glucose difference between the groups not established. - Lower than expected overall mortality. - Borderline statistically significant incidence of heart failure in the in-patient period and of reinfarction within 3 months in the insulin-glucose infusion group. - Glucose of ≥ 8.1 mmol/L or above at 24 h associated with significantly higher mortality than in those with glucose ≤ 8 mmol/L. - Hypoglcyaemia defined as glucose < 3.5 mmol/L. Significantly more hypoglycaemic episodes in the intervention group.
Other notable trials								
BIOMarKS2 (2013) ([33])	294 with AMI (90.4 %) Exclusion of people with insulin-dependent diabetes	7.8–13.6 mmol/L	Intervention group: Insulin-glucose infusion Control group: Standard care	Significant. Median glucose of 6.2 (IQR 5.4 – 7.2) mmol/L in infusion group at 24 h	N/A	High-sensitivity troponin 72 h after admission	Primary endpoint not significant	- Admission to infusion start time median 5.0 h (3.9–7.7) and so lower than DIGAMI 1 and HI-5. - Intervention group did not have significantly different troponin measurements or infarct size.
Marfella (2009) ([14])	50 with AMI and CABG (58 %)	≥7.8 mmol/L	Intervention group: Insulin-glucose infusion/subcutaneous insulin Control group 1: Standard care Control group 2: Additional n = 38 normoglycaemic participants	Significant. Intervention group: 9 (1.3) mmol/L Control group 1: 10.7 (1.2) mmol/L	N/A	Left ventricular ejection fraction, oxidative stress and apoptosis	Significant	- Ventricular specimens taken at *peri* infarct coronary artery bypass grafting procedure. - Higher oxidative stress and increased inflammation and apoptosis in those receiving standard care compared with the intervention group.
Marfella (2012) ([13])	50 with AMI and CABG (62 %)	≥7.8 mmol/L	Intervention group: Insulin-glucose infusion/subcuta-	Significant. Intervention group:	N/A	Myocardial regeneration	Significant	- Ventricular specimens taken at *peri* infarct coronary

(*continued on next page*)

guidelines, particularly those pertaining to the prognostic benefits of glycaemic control beyond the period of hospital admission, in the weeks and months after an AMI. We discuss why people with diabetes are at high risk of complications following AMI, review the evidence for the vascular hyperglycaemic memory, and consider the extent to which glycaemic control may be expected to impact on prognosis in the context of end organ (cardio)vascular disease. We also discuss the role of diabetes sensor technology in both detecting clinically relevant glycaemic parameters in this cohort and highlight the use of this technology as a potential interventional therapeutic tool following AMI in those with both type 1 and 2 diabetes.

2. Outcomes following AMI for people with diabetes

There are many reasons for poor outcomes in those with diabetes following AMI (Fig. 1). Anatomically, people with diabetes have a higher burden of coronary artery disease, and at the time of presentation with AMI can be expected to have increased rates of multivessel disease [15]. They also have a higher incidence of left mainstem disease and total occlusions, longer lesions, diminished collateral vessel development and increased coronary artery calcification [16]. In addition, an enduring insult to the heart's microvascular system may lead to varying degrees of cardiomyopathy, combining with the burden of advanced atherosclerosis and additional comorbidities, to markedly increase the risk of heart failure following myocardial infarction [6,17–18].

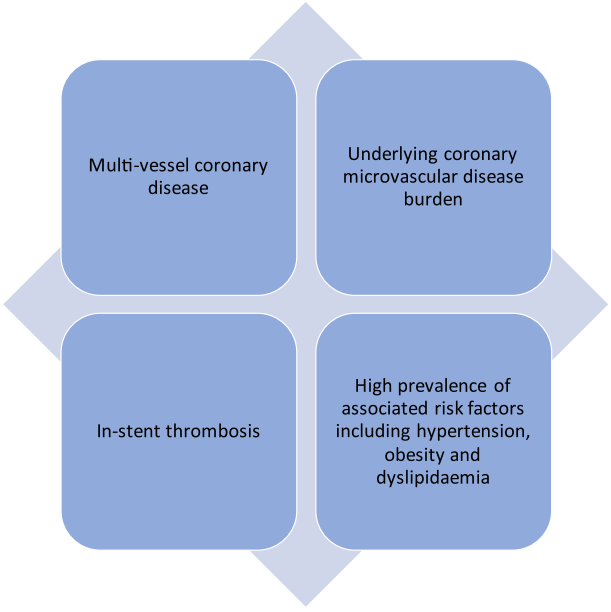

Fig. 1. Recognised drivers of adverse outcomes in those with diabetes following myocardial infarction.

Table 1 (*continued*)

	Key randomised control trials investigating glucose control following AMI							
			neous insulin Control group 1: Standard care Control group 2: Additional n = 25 normoglycaemic participants	8.9 (1.3) mmol/L Control group 1: 10.8 (1.2) mmol/L				artery bypass grafting procedure. - Numbers of myocyte precursor cells, and myocyte proliferation, significantly increased when a tight glycaemic control was achieved early.
Marfella (2012) ([34])	165 with STEMI and pPCI (53 %)	≥7.8 mmol/L	Intervention group: Insulin-glucose infusion/subcutaneous insulin Control group: Standard care	Significant differences between the intervention and control groups *peri*-procedure.	Not significant at 6 months	In-stent restenosis	Significant	- Significantly lower coronary restenosis rate at 6 months in the intervention group compared to the standard care group.
Marfella (2013) [35]	106 with STEMI and pPCI (62 %)	≥7.8 mmol/L	Intervention group: Insulin-glucose infusion/subcutaneous insulin Control group: Standard care	Significant differences between the intervention and control groups *peri*-procedure.	Not significant at 6 months	Myocardial salvage	Significant	- Increased peripheral endothelial precursor cell number and differentiation following tight glycaemic control. Number of endothelial precursor cells and differentiation at day one associated with myocardial salvage at 6 months. - *Peri*-procedural tight glycaemic control significantly increased the area of myocardial salvage accompanied with a reduction of the ischaemic area and greater recovery of LV function at 6 months after stenting.

Diabetes is associated with an increased rate of in stent thrombosis, target lesion revascularisation, stent thrombosis and major adverse cardiac events (MACE) when using bare metal stents and first- generation drug eluting stents (DES). The introduction of second generation DES has shown clear benefit in those with diabetes [19], but whether their introduction has helped to ameliorate the excess risk of re-stenosis related to underlying diabetes status is controversial, with some studies continuing to report diabetes as a major risk factor for DES failure [20–21], and others refuting this [22–23].

Whether prognosis following AMI is impacted by glycaemic control in the weeks and months after AMI remains unclear. Guidelines from the National Institute and Health and Care Excellence [24], American Heart Association [25] and European Society of Cardiology [26] recommend that plasma glucose should be kept at < 10–11 mmol/L in the *peri*-infarct period, with avoidance of hypoglycaemia, but offer limited recommendations beyond this period. Arguably clinical attention has now shifted to exploiting the robust cardiovascular (CV) benefits of SGLT-2 inhibitors and GLP-1 analogues in this arena [5,27–29] alongside aggressive lipid modification and blood pressure control. The DIGAMI-1 trial [30] (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction), published in 1995, is the only randomised control trial to show survival advantage in those with intensive glycaemic control post infarct. The trial recruited 620 in-patients with an AMI in the previous 24 h and a blood glucose level > 11 mmol/L with or without the presence of confirmed diabetes. It then randomised 306 participants to treatment with an insulin glucose infusion for at least 24 h as an in-patient with a further minimum three months of multidose insulin and 314 participants to standard care. In the latter group, a glucose-insulin infusion was started at the discretion of the cardiac care team. At randomisation both groups had comparable mean blood sugars (control group = 15.7 mmol/L+/- 4.2 mmol/L and intervention group 15.4 mmol/L +/- 4.1 mmol/L) and the study aimed to achieve a glycaemic target of 7–10.9 mmol/L using the glucose-insulin infusion. At 24 h, the intervention group, who had received the insulin glucose infusion achieved a glucose in this range (mean 9.6 mmol/L +/- 3.3 mmol/L), and the control group had a significantly higher glucose that was outside this range (mean 11.7 mmol/L +/- 4.1 mmol/L).

At three months there were significant differences in the HbA1c between the groups (7.0 +/- 1.6 % in the intervention group and 7.5 +/- 1.8 % in the control group, $p < 0.010$) and the HbA1c decreased significantly more in the infusion group at both 3 and 12 months (1.1 +/- 1.6 % vs 0.4 +/- 1.5 % after 3 months, $p < 0.0001$, and 0.9 +/- 1.9 % vs 0.35 +/- 1.8 % after one year, $p < 0.05$). A significant reduction in mortality in relation to these changes in HbA1c was identified at 1 year, with no difference in in-hospital mortality or mortality at 3 months, the 3 month timepoint being the primary outcome of the study.

The study suffered from a number of limitations related to its methodology and event numbers. Given that the change in A1c remained significantly larger in the intervention group at 3 and 12 months, crucially it could not differentiate if the advantages of glycaemic control were secondary to the acute insulin glucose infusion, or to the continued use of insulin during the 12 months after the AMI, or both. In addition, there was a considerably lower than expected mortality rate overall, meaning that the study had little statistical power to address its outcomes.

Attempting to build on the DIGAMI-1 trial, the DIGAMI 2 trial (2005) randomised participants with an AMI and known type 2 diabetes or plasma glucose of > 11 mmol/L to 3 groups: Group 1 ($n = 474$) received a glucose-insulin infusion followed by insulin based long term glucose control, group 2 ($n = 473$) received a glucose-insulin infusion followed by standard glucose control, and group 3 ($n = 306$) received routine metabolic management according to local practice. The endpoints were all cause mortality between groups 1 and 2, and groups 2–3.

There was a small but significant difference in blood glucose level at 24 h in those who received a glucose-insulin infusion (groups 1 and 2) and those who did not (group 3), but there was no difference in mortality over the time of follow up (mean 2 years) between those who received the glucose-insulin infusion alone, those who received the infusion and the longer term subcutaneous insulin (group 2) and group 3, that received neither. In addition, because long term glycaemic control between the groups did not differ, DIGAMI-2 was unable to meaningfully assess the impact on longer term glucose control in relation to the short term intervention (acute glucose-insulin infusion *peri*-infarct), or in relation to routine glucose management. Of note both DIGAMI 1 and DIGAMI 2 trial saw higher hypoglycaemia exposure in their glucose-insulin infusion groups, and its prognostic impact is explored in the hypoglycaemia section.

The Hyperglycaemia: Intensive Insulin Infusion in Infarction (HI-5) Study (2006) aimed to investigate intensive glycaemic control in the 24 h after an infarct with the use of a glucose-insulin infusion in the first 24 h without further glycaemic intensification in the months after. Unlike DIGAMI 1 and 2 which only recruited patients with admission hyperglycaemia (AH) of 11 mmol/L or above, the HI-5 study recruited 240 participants with or without known diabetes with a blood glucose of ≥ 7.8 mmol/L. The HI-5 study found no difference in in-patient, 3 month or 6 month mortality between the groups, with a lower incidence of in-patient heart failure and of reinfarction within 3 months in the infusion group. However, although the infusion group did have a lower mean blood glucose over the first 24 h, it was not statistically different from the control group, hampering assessment of outcomes by glucose levels.

It is worth noting that within DIGAMI 1 no participants were receiving statins and only a third were taking angiotensin-converting enzyme inhibitors at the time of discharge from hospital, highlighting the role of glycaemic control independent of associated risk factor management in type 2 diabetes. In contrast in the DIGAMI-2 trial [31], 70 % were taking statins at the time of discharge with an average systolic blood pressure of 135 mmHg. Further trials, with the inclusion of people with diabetes not limited to those experiencing AH, are required.

3. The vascular hyperglycaemia memory hypothesis

The concept of an imprinted 'vascular hyperglycaemic memory' where vascular inflammation may persist despite restoration of normoglycaemia after a period of exposure to chronic hyperglycaemia, posited as an explanation for vascular complications in diabetes, emerged in the late 1980s after a report that dogs with diabetes experienced the same rates of retinopathy regardless of whether they experienced poorly controlled glycaemia or a period of poor control preceding good control [36]. Following this in 1990, Roy et al [37] showed that in vitro and in diabetic rats, enhanced expression of fibronectin and collagen IV driven by a high glucose concentration was measurable despite the removal of the hyperglycaemic stimulus. The evolving field of epigenetics, examining the role of DNA methylation, histone modification and noncoding DNA, may provide clues as to the mechanisms behind this memory.

In 2016 for the first time microRNA profiling identified the dysregulation of 316 of 1007 microRNAs examined in left ventricular specimens from mice with diabetes when compared with controls. Expression of 268 of these microRNAs remained significantly altered in mice with diabetes despite restoration of normoglycaemia [11]. The microRNAs identified were involved in apoptosis, fibrosis, hypertrophic growth and oxidative stress. Vascular inflammation in those with diabetes also results from activation of cytokines, chemokines and adhesions molecules from the NF-Kb p65 gene (RELA) activation in endothelial cells secondary to hyperglycaemia, and also from the action of advanced glycation product on p53, driving endothelial dysfunction [38]. Ventricular biopsy specimens from people presenting with unstable angina who underwent a coronary artery byass grafting (CABG) procedure highlighted evidence of upregulation of the Ubiquitin-proteasome system with secondary upregulation of NFkB-dependent inflammation in those with diabetes, which was associated with a reduction in ejection fraction [12]. Plausibly, therefore upregulation of the inflammatory process via

the hyperglycaemic memory in the context of AMI may hamper recovery of the myocardium following AMI and could be associated with increased ischaemic reperfusion injury. However, in one of the largest studies looking at infarct size following the introduction of primary percutaneous coronary intervention (PPCI) as standard of care after AMI of nearly 800 STEMI patients (20 % with diabetes), no differences in the myocardial salvage index, area at risk, or infarct size were found in those with diabetes [39].

Additional support for the hyperglycaemic memory hypothesis stems from large clinical trials. Whilst the UKPDS [40] and DCCT [41] studies led to a proposed legacy effect of early tight glycaemic control on complications, the VADT [42], ACCORD [43]and ADVANCE [44] trials combined did not show this, with just a minor, non statistically significant, trend toward reduction in CV events following intensive glycaemic control versus standard control and an increase in mortality in the intensively treated group in the ACCORD study.

Follow up of these trials has not demonstrated a delayed reduction in (CV) morbidity or mortality. In the VADT study, the fall in CVD risk was no longer appreciable when the between group glycaemic control differences became insignificant [45]. Follow up of the ADVANCE study for 6 years post trial, did not identify a difference in mortality or death from major macrovascular events between treatment groups [46]. Nine year follow up of the ACCORD trial found an increase in CV -related death, but no change in all-cause death and non-fatal CV events [47].

Finally, microvascular complications of diabetes are well-recognised to increase the risk of CV events [48]. The pathological mechanism(s) by which microvascular disease increases this risk have not been fully elucidated. The 'Micro/Macro Interaction' concept proposes that microvascular disease instigates the pathological chain of events along the vascular continuum that results in atherosclerotic cardiovascular disease . It is the chronic and worsening disruption in the microvascular bed from altered glycaemic control that eventually leads to upstream secondary irreversible subsequent endothelial disruption and atherosclerosis. Neovascularisation following microvascular insult in the adventitia and outer medical layer of larger arteries and the aorta has also been found to promote atherosclerosis and contribute to clot rupture [49]. Recent work by Montone et al [50] suggests that the presence of recognised diabetic microvascular complications may actually correlate with a different pathological coronary artery disease phenotype. For the first time using optical coherence tomography imaging they show that atherosclerotic features in the culprit cardiac vessel differ depending on the background presence of retinopathy. Those with a history of microvascular disease have a higher prevalence of fibrous plaques and healed plaques with larger calcifications whereas in people without microvascular complications, lipid plaques are seen more frequently, with higher prevalence of spotty calcifications and fewer healed plaques.

It is also unclear whether the presence of microvascular disease modifies CV outcomes following intensive glucose control. Interestingly, the ACCORDION study [51], a prospective observational follow up of the ACCORD cohort, reported in 2021 that pre-existing diabetic retinopathy identified a subgroup of people in the ACCORD trial with type 2 diabetes that experienced a larger absolute risk reduction in primary outcome following intensive glucose control.

4. Glucose abnormalities in the context of AMI

Much attention has focused on the role of AH at the time of myocardial infarction, and this provided a key recruitment criterion for the major randomized controls that inform contemporary *peri*-infarct glucose management guidelines. However in the *peri*-infarct period, a U-shaped relationship exists between glucose value and mortality rates for both those with and without diabetes. Hyperglycaemia, hypoglycaemia and GV are each associated with adverse impacts on the CV system following AMI, exerting effects on the inflammatory response and on the cardiac conduction system, and causing abnormalities of clotting and platelet function (Fig. 2). Mechanisms are considered first, followed by clinical implications.

4.1. Mechanistic insights

The deleterious effects of cardiac glucotoxicity are induced by a supra-physiological glucose insult to cardiomyocytes, cardiac endothelial cells and the clotting system. Hyperglycaemia reduces endothelium dependent vasodilatation and impairs endothelial repair [52], and is thought to directly impact the remodelling of infarcted cardiac tissue. It has been shown to directly magnify oxidative stress and inflammatory immune reaction in cardiac tissue following ischaemia, with higher levels of myocardial TNF-alpha, NFkB-activated captase-3 and nitrotyrosine levels found in ventricular specimens taken at the time of CABG surgery following AMI [14]. In addition, hyperglycaemia is associated with a reduction in release of endothelial progenitor cells following infarct, the latter of which are mobilised after an ischaemic insult to augment neovascularisation of the infarcted area [34]. People with type 2 diabetes show a reduction in expression in several angiogenic factors thought important in myocardial recovery following ischaemia, including hypoxia-inducible factor-1alpha and vascular endothelial growth factor in ventricular specimens [53].

Hyperglycaemia enhances the reactivity of platelets by several mechanisms. It is associated with an upregulation of platelet receptors including glycoprotein and P2Y12 [54], a reduction in the membrane fluidity from glycation, also leading to receptor overexpression and activity, and higher platelet activation markers [55–56]. Oxidative stress also contributes by increasing production of certain isoprostanes which activate the thromboxane receptors on the platelets and increase platelet aggregation [57]. In addition, calcium homeostatic in platelets is interrupted by hyperglycaemia leading to changes in the cytoskeleton and exaggerated release of pro-aggregatory granules [58]. There are also marked disturbances in the coagulation- fibrinolytic system. An increased level of tissue factor, prothrombin, factor VII and fibrinogen lead to densely packed thrombi [59–61], which are rendered resistant to fibrinolysis because of the inclusion in the clot of anti-fibrinolytic proteins (completement C3 and plasmin inhibitor), elevated levels of anti-fibrinolytic proteins and antihyperglycaemic driven alterations in plasminogen's fibrinolytic activity [60,62–63].

Hypoglycaemia also has significant prothrombotic and proinflammatory effects. Acutely hypoglcyaemia enhances platelet reactivity and aggregation in both people with and without diabetes. In those with diabetes, clot lysis times however may be prolonged following resolution of the hypoglycaemia for as long as 7 days, with an accompanying rise in complement C3 levels [64]. In parallel there is significant elevation of inflammatory cells following hypoglycaemia with significant elevation of circulating lymphocytes, monocytes and high sensitivity C-reactive protein, sustained over 7 days following the hypoglycaemic episode [65]. Additionally, using assessment of flow mediated dilatation with two-dimensional Doppler ultrasound Joy et al. found that hypoglycaemia significantly impaired endogenous nitric oxide (NO)-mediated endothelial function [66].

Both hyper and hypoglycaemia are pro-arrythmogenic. AH at the time of AMI increases the risk of arrythmia regardless of diabetes status. It is recognised to prolong the QT interval, rendering the heart vulnerable to ventricular arrythmia, and may also promote atrial fibrillation [67]. Experimentally induced hypoglycaemia in people with type 1 and type 2 diabetes also prolongs the corrected QT interval [68–69], and individuals with type 2 diabetes show greater repolarisation abnormalities for a given hypoglycaemic stimulus despite similar sympathoadrenal responses compared to matched controls without diabetes [70].

Both in vitro and in vivo GV induces oxidative stress [71–72], and inflammation in human coronary artery endothelial cells [73–74]. GV has been found to advance atherosclerosis independent of cholesterol levels in apolipoprotein E deficient mice, by increasing macrophage adhesion at the area of the lesion; the introduction of an alpha-

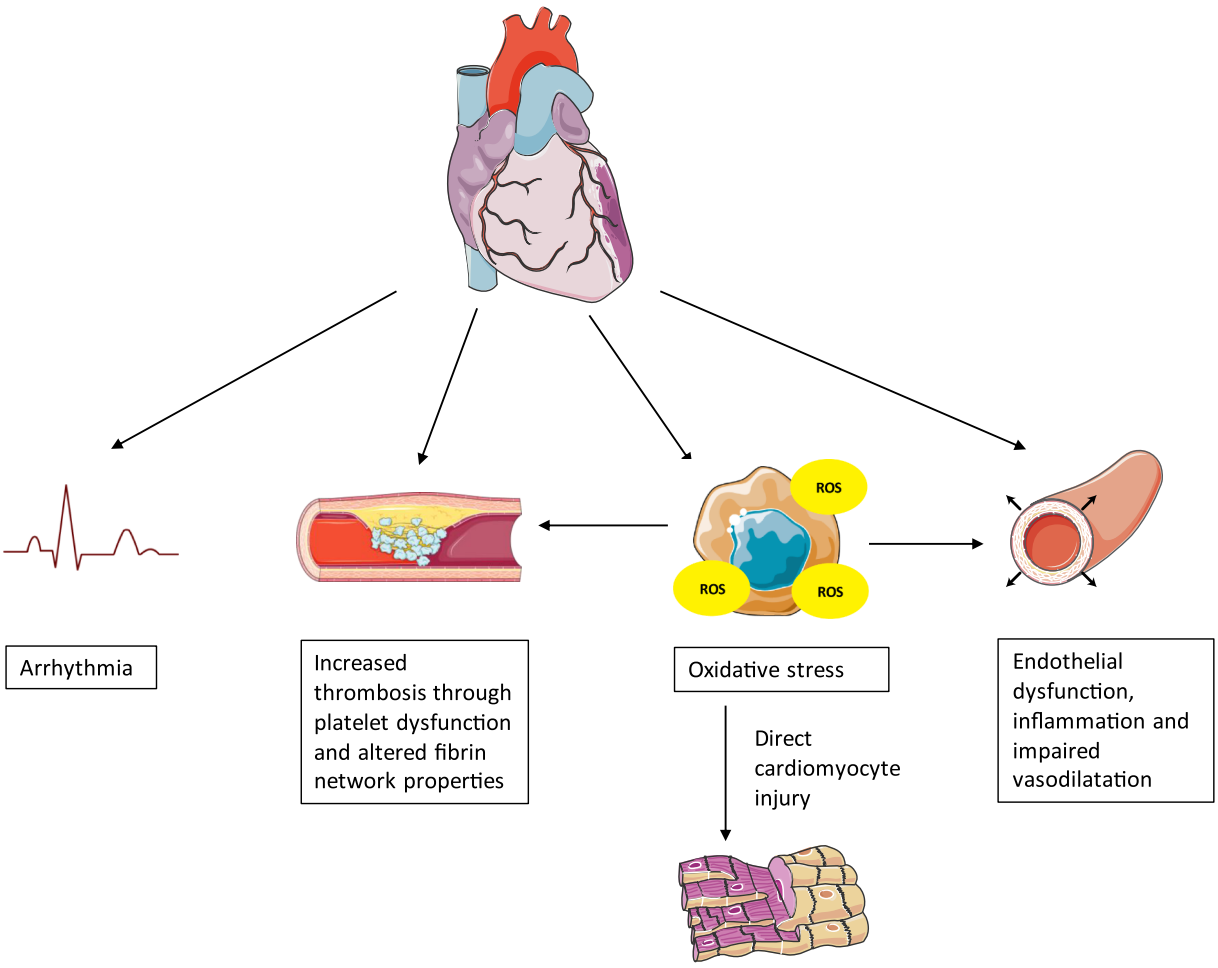

Fig. 2. Effects of hyperglycaemia, hypoglycaemia and glycaemic variability following myocardial infarction. ROS- reactive oxygen species.

glucosidase inhibitor to reduce GV in this setting controlled the atherosclerosis [71]. There is also in vitro evidence that both brief (4 day) and longer term (21 day) GV, more than constant hyperglycaemia can hasten apoptosis of endothelial cells [75]. In the culprit vessel in AMI, GV is also associated with increased lipid and decreased fibrous contents in coronary plaques in those with AMI, and a larger plaque burden [76]. GV has also been found to alter the balance of CD14++/CD16 + monocytes, rendering coronary plaques more vulnerable to rupture [77].

4.2. Clinical implications

4.2.1. Hyperglycaemia

4.2.1.1. Admission hyperglycaemia. AH is associated with a near four-fold increase in 30 day mortality [8–9] following AMI, although the association between AH and longer term outcomes is less clear [78–79]. The introduction of timely PPCI has not ameliorated the increased mortality risk [8]. AH is relatively poorly defined because the severity and length of hyperglycaemia that define it as a pathological entity, are unknown [80], but the prognostic impact of glucose is recognized to extend throughout a hospital admission period following AMI [81]. AH may also have a multifactorial aetiology. It may be secondary to stress hyperglycaemia, which can be defined as "the relative increase in glucose due to the inflammatory and neurohormonal derangements that occur during a major illness" [82], or due to poorly controlled underlying diabetes in the presence or absence of a known diabetes diagnosis, or a due to a combination of both. In addition, differentiating between the acute effects of glucotoxicity and the relationship between AH and other traditional predictors of worse outcomes means that there is controversy as to whether AH represents a cause or a marker of mortality [8].

4.2.1.2. The stress hyperglycaemia ratio. Evidence from an RCT [83] and from observational studies [84–85] supports separate in-patient hyperglycaemia cut off values for those with and without diabetes, but such a distinction is not made in guidelines. The last 10 years however, have seen attempts to redefine how hyperglycaemia is characterised in acute illness to enable discrimination between an 'absolute' and a 'relative' hyperglycaemia for a given patient, using new concepts such as the stress hyperglycaemia ratio (SHR) [82]. The SHR controls for background glycaemia by dividing the admission glucose by the estimated average glucose, calculated using the person's HbA1c. The evidence to support the use of this measurement is drawn mostly from critically unwell patients in the intensive care setting [82], where it has been found to better identify patients at risk of progression to critical illness than absolute hyperglycaemia, but its application in the context of AMI is an area of active research. Recent retrospective analysis suggest that the SHR is superior to admission glucose following AMI in predicting MACE events in the 30 days following infarct [86–87] and in the longer term [87–88]. Additionally post hoc analysis of the HI-5 trial suggests that relative hyperglycaemia, calculated using the SHR, rather than absolute hypoglycaemia is associated with in-patient complications following an AMI [89].

4.2.2. Hypoglycaemia

Collectively large clinical trials and epidemiological studies show that hypoglycaemia is associated with a 1.5–1.6 times increased risk of CV events and mortality compared to those without hypoglycaemia [90]. It is also associated with poor prognosis in the post AMI setting [91–92]. However, establishing whether hypoglycaemia is a risk marker or true risk factor for CV events, or mortality, is challenging. Currently no direct evidence shows that a reduction in hypoglycaemic events translates directly into a meaningful reduction in CV events. However, individualised structured intervention following a severe hypoglycaemic episode in type 2 diabetes has been shown to reduce CV mortality at 1 year [93]. Of note the DEVOTE trial [94] in which people with type 2 diabetes were randomised to the use of insulin degludec versus insulin glargine U100 did show that the use of insulin degludec resulted in a reduction of severe hypoglycaemia by 40% with a non–significant 9 % reduction in incidence of CV events in a time to event analysis.

In addition, the effect of confounding in this population given the marked association between comorbidity and hypoglycaemia is still unclear. In the ADVANCE study, it was concluded that confounding was in large part responsible for the association between hypoglycaemia and mortality [95]. Three subsequent systematic reviews [96–98] of both observational studies and RCTs have suggested a causal link between hypoglycaemia and CV events and mortality, with two reviews concluding that comorbid severe illness was not prevalent enough to explain the association [96–97].

Knowledge gaps exist as to the impact of the duration, severity and frequency of a hypoglycaemic episode on the CV system, the role of previous exposure to hypoglycaemia on blunting of systematic sympatho-aderenal responses, and the potentially deleterious effects of the rebound hyperglycaemia phenomenon [90]. Thus, whilst the analysis of the impact of hypoglycaemia in the post AMI period from observational and interventional studies provides some clues to its associations, meaningful assessment of its impact is likely to be more complex. Rebound hyperglycaemia, the phenomenon of hyperglycaemia secondary to treatment or overtreatment of hypoglycaemia, impairs endothelial function more than hypoglycaemia alone [99], possibly because it facilitates a bigger inflammatory response. In people without diabetes, exposure to an episode of acute hypoglycaemia blunts autonomic responses to experimentally induced hypotensive stress for several hours [100], and in those with diabetes, recurrent hypoglycaemia reduces sympatho-adrenal response [101] and beta adrenergic sensitivity [102] so that the consequences of hypoglycaemia itself may be less profound in those who may be at highest risk of it.

Analysis of the implications of hypoglycaemia following AMI have primarily focused on the prognostic impact of in-patient hypoglycaemia only. DIGAMI 1 [30] reported significantly higher number of hypoglycaemic episodes in the infusion group during admission but no correlation with any increased morbidity or mortality. In DIGAMI 2 [31], in the first 24 h, 12 % of insulin treated and 1 % of routinely treated participants were recorded to have experienced hypoglycaemia, with symptoms in only 23 % and 33 % respectively [103]. The relationship between hypoglycaemia and mortality and CV morbidity disappeared following adjustment for potential confounders, and diabetes duration and body weight were independent risk predictors of hypoglycaemia. Furthermore in the the CREATE-ECLA and OASIS-6 trials, two randomised controlled trials of glucose-insulin-potassium therapy in AMI in those without AH, hypoglycaemia at the time of admission only, and not at any other time during admission, predicted 30 day mortality [104], whilst Kosiborod et al [105] in an analysis of a large cohort of people hospitalised with AMI found that the risk of mortality associated with hypoglycaemia was restricted to spontaneous hypoglycaemia only, in contrast to iatrogenic hypoglycaemia, suggesting that hypoglycaemia is a marker for more severe illness and not a cause of mortality itself.

In a critical care setting, the NICE-SUGAR study [106] reported that hypoglycaemia was robustly associated with mortality at 3 months, despite adjustment for baseline confounders, with moderate hypoglycaemia increasing the risk of death by 40 % and severe hypoglycaemia doubling the risk [107]. Notably the NICE-SUGAR study, using an intensive IV insulin regime to target a blood glucose range of 4.5–6 mmol/L compared to conventional glucose control with a target of < 10 mmol/L identified a high incidence of hypoglycaemia in their study population: 40.5% of all patients experienced moderate hypoglycaemia, and severe hypoglycaemia was observed in 3.7%, with higher rates in the intensive glucose control group [107], although as Hirsch notes [108], the limitations of the frequency of glucose monitoring (the protocol called for 1 hourly monitoring which could be relaxed to 2–4 hourly) may mean that the documented incidence is an underestimate. Other barriers to accurate identification of hypoglycaemia include the inability of timing of self monitored blood glucose (SMBG) to detect the travel of direction of blood glucose, a reliance on the person actively testing to identify hypoglycaemia, impairment or loss of hypoglycaemia awareness and the fact that nocturnal hypoglycaemia, accounts for over 50 % of hypoglycaemic episodes in insulin treated diabetes [109].

4.2.3. Glucose variability

GV can be defined as “the measurement of fluctuations of glucose over a given interval of time” [110]. Short term GV refers to within day and between day GV, which can be calculated using SBMG or more recently from continuous glucose monitoring (CGM) sensor data. Long term GV usually reflects serial HbA1c, or less often, serial fasting plasma glucose and postprandial glucose measurements [110]. GV has emerged as an important risk factor for hypoglycaemia [111–113] and diabetes-related complications, with long term GV independently predicting the risk of CV disease, including subclinical coronary atherosclerosis [114]. Post hoc analysis of the DIGAMI-2 trial [115], and the HEART- 2 study [116] (Hyperglycemia and Its Effect after Acute Myocardial Infarction on Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus), reliant on 7 point SMBG and regression methods suggested no relationship between GV and outcomes following AMI. However Gerbaud et al [10] found that an elevated GV (standard deviation) ($>$2.7 mmol/L) during hospitalisation was the strongest independent predictor of midterm MACE following infarction. More recent studies using CGM technology in the *peri*-infarct period have identified relationships between GV and major adverse cardiac events after AMI [117–118], impairment of myocardial salvage after AMI [119–120] and reduced healing after coronary artery stent insertion [121].

5. The role of diabetes technology

Since the DIGAMI 1 [30], DIGAMI-2 [31] and HI-5 [32] trials, the landscape of diabetes management has changed markedly. The introduction of CGM means that a wealth of glycaemic metrics can be captured throughout a 24 period, beyond HbA1c and regular SMBG measurements, the latter which does not have an evidence base in those with type 2 diabetes not administering insulin [122–123]. These metrics include, but are not limited to, time in a targeted glycaemic range, time below a targeted range (indicating hypoglycaemia of varying degrees), time above a targeted range, and various measures of GV.

Time in range (TIR), defined by International Consensus [124] as between 3.9 and 10 mmol/L for the majority of people with diabetes is a key CGM metric, and is increasingly used to guide management in diabetes, with accumulating evidence that it is linked to both micro and macrovascular complications [125]. It is also increasingly used as a primary outcome in diabetes trials. Recently Lu et al [126], in the first longitudinal study examining TIR in relation to all cause and CV mortality, found a significant association with TIR (measured for 3 days only) in 6225 people with type 2 diabetes. There was an inverse relationship between CV mortality and TIR with HRs of 1.35 (0.90–2.04, $p = 0.02$) in those with TIR 71–85%, 1.47 (0.99–2.19, $p = 0.02$) in those with TIR 51–70%, and 1.85 (1.25–2.72, $p = 0.02$) in those with TIR

51–70% for CVD mortality (p for trend = 0.015, 85% TIR as reference). In addition, the HR for each 10% decrease in TIR was 1.05 (1–1.11, p = 0.02). TIR is also associated with an abnormal carotid intima media thickness [127], a surrogate marker for CV disease, and a greater aortic stiffness, an independent risk factor for CV disease [128]. It is currently unknown whether TIR, and for what time period, is associated with MACE outcomes following AMI.

In addition to measuring these glycaemic parameters, the application of CGM is an intervention that improves glycaemic control, reduces hypoglycaemia in type 1 diabetes, and decreases the mean duration and severity of rebound hyperglycaemia events [129–132]. In type 2 diabetes, sensor technology is currently reserved in the UK for a small subgroup of people at highest risk of hypoglycaemia [133]. The CGM devices allow the user to track their glucose in detail with the ability to set alarms for impending hypo and hyperglycaemia, and the user is provided with arrows to inform the direction and speed of change in interstitial glucose. Burgeoning evidence also supports the use of CGM as a core constituent of self management in people with type 2 diabetes, in both people taking insulin and those taking oral anti-glycaemic treatment alone, because of its ability to facilitate beneficial behavioural and lifestyle changes, enhancing self efficacy and self-engagement behaviour [134–138]. The recently published LIBERATES randomised control trial [139] of intermittently scanned glucose monitoring (Libre-Pro) or SMBG following AMI in those with type 2 diabetes at risk of hypoglycaemia found a significant reduction in time below range (time < 3.9 mmol/L) and a small increase in time in range at three months. The forthcoming GLAM trial [140] will assess real time CGM versus standard care in people with type 2 diabetes for 6 months following AMI.

6. Conclusion

CGM provides a new and exciting approach to measuring glycaemic parameters, and its application in a sub-population of patients following AMI provides an opportunity to re-examine if and how glucose affects prognosis after AMI, and which glycaemic parameters matter the most. This is important because, although extremes of glucose are acknowledged to be detrimental post AMI, there is currently a lack of evidence to support the appropriate level of glycaemic control in contemporary management strategies. Understanding which parameters are the most important will help in the design of future clinical trials which will likely use CGM both for monitoring and for enhancing glycaemic control in the active arm. CGM has the potential to enhance glucose control by facilitating increased self-efficacy, positive behavioural change and better diabetes self-management in this cohort. Trials using CGM in this population may overcome the previous difficulties that the main interventional trials have had in achieving significant differences in glycaemic control between the interventional and control groups.

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Figure 2 was generated using pictures with adaptation (additional markings) from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/, accessed 5th February 2023).

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