The acute reperfusion management of STEMI in patients with impaired glucose tolerance and type 2 diabetes

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Abstract

Diabetes mellitus (DM) remains an important predictor for mortality in patients with ST-segment Elevation Myocardial Infarction (STEMI) although the use of reperfusion therapy has resulted in a considerable improvement of survival. Of importance, newly diagnosed diabetic patients and those with fasting glycaemia in the diabetes range have even worse outcomes compared to patients with known diabetes. Overall, 50% of all patients presenting with STEMI have abnormal glucose metabolism of which fewer than 50% are known diabetics. Obviously, the efficacy of reperfusion therapy in reopening the occluded artery is similar in STEMI patients with or without impaired fasting glycaemia, while the pre-existing decreased myocardial perfusion in STEMI patients with impaired fasting glycaemia persists after successful epicardial revascularisation.

There is no doubt that improving microvascular perfusion within the ischaemic myocardium remains the ultimate goal of managing STEMI patients with impaired glucose metabolism. Identification of defective myocardial perfusion together with an aggressive antithrombotic regimen, reduction of the inflammatory response of the ischaemic myocardium and improvement of glycaemia control represent promising therapeutic approaches that deserve additional specific clinical investigations. This review examines all these important issues.


Key words: myocardial infarction, impaired glucose tolerance, diabetes, fibrinolysis, percutaneous coronary intervention.

Introduction

Diabetes mellitus (DM) is a well-established risk factor for death and cardiac complications such as cardiogenic shock in patients with acute ST-elevation myocardial infarction (STEMI). Although the use of reperfusion therapy in the treatment of STEMI has resulted in a considerable improvement in survival, diabetes remains an important predictor of mortality. Recently, the American Diabetes Association (ADA) guidelines introduced a new category of impaired fasting glucose (IFG) for glucose levels ranging from 6.1 mmol/L to 7 mmol/L (110 mg/dL to 126 mg/dL), below the threshold for DM. Patients with abnormal fasting glycaemia represent a large proportion of the myocardial infarction (MI) population (53%) and the effects of such abnormal glucose metabolism during acute MI are deleterious with regard to short-term clinical outcomes. This review examines the issues that may account for this unfavourable prognosis and discusses measures that may further improve the efficacy of reperfusion therapy and short-term outcome, including the difficult task of glycaemic control in STEMI.

Overview of reperfusion strategies in diabetes mellitus

In patients with the clinical presentation of myocardial infarction and with persistent ST-segment elevation or new or presumed new left bundle branch block, early mechanical or pharmacological reperfusion should be performed to
limit the extent of myocardial damage unless clear contraindications are present.4

**Fibrinolysis in diabetic patients**

Fibrinolytic therapy has undoubtedly improved the outcome of patients after acute myocardial infarction (AMI), saving 35 lives per 1,000 diabetic patients at 35 days compared with 15 per 1,000 non-diabetic patients.3 Thus, the absolute benefit is more than doubled for fibrinolytic therapy among diabetics. Unfortunately, there are three major drawbacks which may account for the poor outcomes of STEMI patients with abnormal glucose metabolism as compared to those with normal fasting glycaemia (figure 1).7

Diabetic patients are less likely to receive fibrinolysis therapy as compared to non-diabetic patients. The Survival and Ventricular Enlargement (SAVE) study clearly showed that the presence of diabetes was one independent variable for not using fibrinolytic therapy, along with age, prior infarction and neurological diseases.8 In 1998, the National Registry of Myocardial Infarction reported that among the 84,663 patients eligible for reperfusion therapy out of a total of 272,651, the odds of patients with DM receiving reperfusion therapy were only half those of non-diabetics.9 The presence of DM remained an independent factor associated with failure to use reperfusion therapy in multivariate analysis (OR 0.67; 95% CI 0.52 to 0.87). Similar findings were recently reported in a contemporary French survey (39% vs. 51%; p = 0.0001).10

There are many reasons accounting for this finding, including the fear of fibrinolysis-related bleeding events. In the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-1) study, there was no increased risk of major bleeding rates. In addition, the rate of intracranial haemorrhage was similar between patients with and without diabetes (0.6% vs. 0.7%, p > 0.05)11 and there were no intraocular haemorrhages among the 6,011 diabetic patients.12 Every DM patient presenting with STEMI should be administered fibrinolytic agents when there are no clear contraindications.

Diabetic patients, when they receive fibrinolytic therapy, receive it later than non-diabetics.13 The impaired sensation of pain may account for atypical and late presentation of diabetic patients.14 Diabetes, in common with age, female gender, history of heart failure and history of previous MI, was a predictive factor of non-revascularisation of STEMI in the large Global Registry of Acute Coronary Events (GRACE).15

Fibrinolytic agents may have reduced efficacy in patients with impaired glucose tolerance. Indeed, the propensity for platelet activation and aggregation, coupled with a tendency for coagulation and impaired intrinsic fibrinolysis, are common features in diabetic patients.16 These may alter the prompt response to fibrinolysis which has been shown to be critical for survival.17 Of interest, in GUSTO-1 there was little difference in the TIMI flow grades and the rates of angiographic reocclusion were similar between patients with and without diabetes.18 However, recurrent ischaemia occurred more commonly among diabetics (22% vs. 20%, p < 0.001)19 and the proportion of patients who died before follow-up angiography was almost three times higher for diabetic patients. These findings suggest that enhanced thrombogenicity among diabetics may have favoured recurrent ischaemic events, which are known to be directly related to the inability to maintain vessel patency.19

Although the risk has decreased with more widespread

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Figure 2. Epicardial and microvascular flow after fibrinolytic therapy for STEMI. TIMI (Thrombolysis In Myocardial Infarction)-3 flow indicates normal flow in the coronary artery. A complete ST-segment resolution indicates a normal microvascular flow.

<table>
<thead>
<tr>
<th>TIMI-3 flow 90 minutes after fibrinolysis</th>
<th>Complete ST-segment resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No history of diabetes</strong></td>
<td><strong>History of diabetes</strong></td>
</tr>
<tr>
<td>59.0%</td>
<td>54.5%</td>
</tr>
<tr>
<td>49.2%</td>
<td>38.6%</td>
</tr>
</tbody>
</table>

*p = 0.04, p = NS*  
Data from Angeja BG,20

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Figure 3. Comparison of myocardial perfusion after successful primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction.

- **Reduced myocardial perfusion grade**
  - No history of diabetes: 10.0%
  - History of diabetes: 20.0%
- **Incomplete ST-segment resolution**
  - No history of diabetes: 55.0%
  - History of diabetes: 35.0%

*p = 0.02*  
Data taken from Timmer JR,24

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Normal myocardial perfusion grade was defined as normal myocardial blush or contrast density or moderate myocardial blush or contrast density but less than that obtained during angiography of the contralateral or ipsilateral non-infarct-related coronary artery. ST-segment resolution was defined as complete when there was ≥70% ST-segment resolution at 180 minutes after the primary percutaneous coronary intervention compared with ST-elevation present on admission.
use of fibrinolytic agents, DM patients still have a higher mortality than those without DM. Recent analysis of epicardial and microvascular flow after fibrinolytic therapy suggests that the link between diabetes and poor clinical outcome may be related to impaired microvascular myocardial perfusion.20 Reassessment of epicardial flow in the Thrombolysis In Myocardial Infarction (TIMI) 4, 10, 10A, 10B and 14 studies (n=2,588) demonstrated no relationship between diabetes and TIMI 3 flow at 90 minutes (55.4% vs 59.0% in those without diabetes). These findings are concordant with the Zwolle Myocardial Infarction Study Group. This group reported on 386 patients who underwent successful primary PCI for STEMI, of whom 64 had DM (figure 3).24 These patients had reduced myocardial perfusion grade (MPG) and incomplete ST-segment resolution more often compared with patients without DM. DM was still associated with impaired ST resolution (odds ratio 2.1, p<0.03) and reduced myocardial perfusion grade (odds ratio 2.2, p<0.03) after the inclusion of all variables, with trends toward a significant difference between patients with and without DM.

This was further confirmed in a substudy of the CADILLAC randomised trial (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications).25 Despite similar high rates of TIMI flow grade 3 after primary PCI in patients with and without diabetes, DM was an independent predictor of absent myocardial perfusion (MPG 0/1) (hazard ratio [HR] 1.63 [95% confidence interval (CI) 1.17 to 2.28], p=0.004) and absent ST-segment resolution (HR 2.94 [95% CI 1.64 to 5.37], p=0.005) by multivariate modelling (figure 4). Diminished microvascular perfusion in diabetics after primary PCI may contribute to adverse outcomes.

**Why do reperfusion therapies fail in diabetics with STEMI?**

Underlying endothelial dysfunction,26 diminished flow reserve27 and structural microvasculature abnormalities in myocardial tissue28 may contribute to the decreased microvascular perfusion and subsequent poorer outcomes observed in DM patients. Furthermore, the negative impact of DM on pre-infarction angina may be related to a greater degree of microvascular damage in diabetic patients.29 Disturbances in glucose metabolism per se may also have a negative impact effect on myocardial reperfusion. Elevated levels of free fatty acids during hyperglycaemia reduce endothelium-derived vasodilation of the myocardial vasculature29 and hyperglycaemia promotes the plugging of leuko-
with abnormal glucose metabolism experience more acute pump failure, which directly contributes to the increased risk of death. A direct role for hyperglycaemia can be suspected, since increased glycaemia is harmful for cardiomyocytes.37

Primary impaired fasting glycaemia is suspected to be directly responsible for acute pump failure since glycosylated haemoglobin levels are significantly higher in IFG, thus confirming the presence of chronic altered glucose metabolism even before the acute ischaemic event.2

Can we extend these findings to all patients with impaired fasting glucose?

The ADA guidelines introduced a new category of IFG for glucose levels ranging from 6.1 mmol/L to 7 mmol/L (110 mg/dL to 126 mg/dL), below the threshold for DM.5 Several recent studies show that patients with abnormal fasting blood glucose represent a large proportion of the MI population (53%). More importantly, the effects of such abnormal glucose metabolism during acute MI have been shown to be deleterious for short-term clinical outcomes.2,6,7,38

In the recent RICO survey, 999 acute MI patients were enrolled, of whom 50% underwent reperfusion therapies. More than half of this population were found to have abnormal fasting glycaemia, including diabetes (38%) or IFG (15%). Patients with IFG had a worse outcome overall, characterised by a higher risk of developing cardiogenic shock during their hospital stay (figure 6). In addition, patients developing cardiogenic shock or ventricular arrhythmia had a significantly higher level of fasting glycaemia (figure 7). In-hospital mortality in the IFG group was double that of the normal fasting glucose (NFG) group. Of interest, the multivariate analysis showed that cardiogenic shock (p<0.0001) and ventricular arrhythmias (p=0.036) explained most in-hospital mortality.

Another important issue is that newly diagnosed diabetic patients after admission for STEMI seem to have a worse outcome compared to patients already known to have DM. The newly diagnosed diabetic patients may represent 25% of the entire DM population.42 In a prospective series of non-diabetic patients (n=735) admitted for STEMI, patients with a
fasting glycaemia in the range of diabetes (≥ 7 mmol/L, [≥ 1.26 g/L]) (n=181, 25% of the whole population study) had worse short-term outcomes. Compared with patients with normal fasting glycaemia, the adjusted OR for 30-day mortality (10.2 [4.4–23.7]) was much higher in patients without a previous diagnosis of diabetes and with fasting glycaemia in the diabetes range (≥ 126 mg/dL [7.0 mmol/L]) compared with patients with known diabetes who were recruited during the same time period (2.4 [1.03–5.5]).

**Can we improve revascularisation in DM patients with STEMI?**

Improvement of myocardial perfusion is obviously a key issue to improve outcomes of AMI patients with abnormal glucose metabolism. Indeed, there is an established association between impaired myocardial perfusion and early and late mortality which may be mediated by improvement in myocardial salvage.35,39 Hyperglycaemia in STEMI is an important predictor of impaired epicardial flow before reperfusion therapy has been initiated.40 In a series of 460 consecutive STEMI patients, TIMI flow grade 3 before primary PCI was observed less often in patients with hyperglycaemia (≥ 7.8 mmol/L) compared to patients without hyperglycaemia (12% vs. 28%, p<0.001). After adjustment for differences in baseline variables, hyperglycaemia was a strong predictor of absence of reperfusion before primary PCI (odds ratio 2.6, 95% CI 1.5 to 4.5). Methods of improving coronary flow before primary PCI or fibrinolysis in these patients was initiated.40 In a series of 460 consecutive STEMI patients, TIMI flow grade 3 before primary PCI was observed less often in patients with hyperglycaemia (≥ 7.8 mmol/L) compared to patients without hyperglycaemia (12% vs. 28%, p<0.001). After adjustment for differences in baseline variables, hyperglycaemia was a strong predictor of absence of reperfusion before primary PCI (odds ratio 2.6, 95% CI 1.5 to 4.5). Methods of improving coronary flow before primary PCI or fibrinolysis in these patients was initiated.40

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Glycoprotein (GP) IIb/IIIa receptor inhibitors may answer this challenge. These agents block the final pathway of platelet aggregation and have been tested successfully in the prevention of coronary complications of elective percutaneous coronary revascularisation. These agents have been shown to reduce mortality in DM patients undergoing elective PCI14-15 (figures 7 and 8). Fewer and smaller randomised studies have been conducted in primary PCI of STEMI. A meta-analysis of this heterogeneous population, including balloon and stent studies, primary and rescue PCI, showed a significant effect of GP IIb/IIIa inhibition on mortality (4.4% vs. 6.2%; OR 0.69; 95% CI 0.52–0.92; p=0.01).41 Early administration of these agents, especially during the pre-hospital management phase, has been shown to improve coronary patency, with favourable trends for clinical outcome.42 Importantly, a recent analysis obtained in a more homogeneous study population representative of modern primary PCI practice (n=1,101)44-45 providing for the first time long-term follow-up to three years, confirmed a reduction in hard clinical outcomes with the use of GP IIb/IIIa receptor antagonists. This risk reduction translates into 50 major events (death or reinfarction) prevented for every 1,000 patients treated: this benefit increases five-fold in diabetic patients treated.

The recent Clopigogrel as Adjunctive Reperfusion TherapY-CIOpigogrel and Metoprolol in Myocardial Infarction Trial (CLARITY-COMMIT) trials will bring new insights on the potential benefit of a dual oral antiplatelet regimen as compared to aspirin alone in STEMI patients with DM. CLARITY enrolled 3,491 patients who presented within 12 hours of the onset of a STEMI and randomly assigned them to receive clopidogrel (300 mg loading dose, followed by 75 mg once daily) or placebo.46 Patients received a fibrinolytic agent, aspirin, and when appropriate heparin (dispensed according to body weight), and were scheduled to undergo angiography 48 to 192 hours after the start of study medication. In total, 17% of patients were diabetic. This study showed that the addition of clopidogrel improves the patency rate of the infarct-related artery and reduces ischaemic complications (figure 9). This was further confirmed by the COMMIT Chinese megatrial in 45,852 MI patients, which reported a significant reduction in mortality.
with clopidogrel treatment without an increase in bleeding. These studies should be helpful to validate the hypothesis that DM patients need a more potent antithrombotic regimen than non-diabetic patients, especially within the first few hours of STEMI.

Other major issues may be critical for DM patients. Post-fibrinolysis strategies are important given the fact that fibrinolysis fails to reopen the occluded artery in 50% of patients. Whether all DM patients should undergo rapid catheterisation is a real question given the fact that complete ST-segment resolution occurs less frequently among diabetic patients after fibrinolysis. Acute and late stent thrombosis is another question. Indeed, DM is an independent predictor of stent thrombosis and the question arises whether the dual oral antiplatelet aggregation regime of aspirin + clopidogrel should ever be withheld from these patients.

The difficult task of glycaemic control
Recent work has further investigated the role of insulin during critical illness, showing that insulin has a powerful anti-inflammatory effect which is associated with improvements in morbidity and mortality. This anti-inflammatory effect has also been demonstrated in STEMI and has been related to a reduction of the extension of MI, which may contribute to its clinical benefit. However, whether the meticulous regulation of DM and glucose levels before or after the restoration of epicardial flow improves myocardial reperfusion is unclear, and further investigation is warranted.

There is no doubt that admission hyperglycaemia in STEMI patients is associated with poor outcomes. The degree of hyperglycaemia may reflect to some extent the underlying stress. It also implies that the acute ischaemic myocardium is in glucose starvation due to increased insulin resistance, with a shift towards free fatty acid metabolism and impaired cardiac performance. On this basis, the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial suggested that optimal glycaemic control with insulin in patients with STEMI was beneficial in allowing intracellular glucose uptake by the ischaemic myocardium. Failure to confirm these results in several recent trials, including DIGAMI 2 and CREATE-ECLA (Clinical Trial of Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation-Estudios Cardiológicos Latinoamérica), however, questions the validity of these concepts.

Obviously, the negative results of glucose-insulin-potassium (GIK) therapy in the very large CREATE-ECLA trial that studied 20,201 patients with STE elevation acute myocardial infarction (AMI) are disappointing, but they can be explained. First, it should be noted that although 83% of patients had reperfusion therapy at a median time of 3.85 hours after symptom onset, randomisation to GIK or control groups occurred almost one hour later (median: 4.7 hours post symptom onset). This late administration may have hampered the GIK’s potential to reduce ischaemic injury. Another important point to emphasise is that the overall AMI mortality rate was relatively high, suggesting ineffective reperfusion in many patients. This is further supported by the fact that GIK administration was found to reduce mortality by 25% in the 9% of patients who had effective reperfusion with percutaneous coronary intervention (PCI) (CI 0.51–1.11). These two issues are probably relevant when looking at the benefit of GIK in the Dutch trial. In this trial, GIK was given relatively early (2.5 hours after symptom onset) and was followed by highly effective primary angioplasty (PCI) and documented reperfusion. GIK reduced mortality by 71% (p<0.01) in the pre-specified ‘no heart failure’ subgroup (n=856), which actually comprised 91% of the entire study population.

These findings do not mean that the benefits of treatment of hyperglycaemia are questionable and that optimal glycaemia may not be warranted. Rather, they indicate that the toxicity of hyperglycaemia on myocardium is complex, not related to the presence of insulin resistance per se but instead representing a direct effect of hyperglycaemia and also an increased inflammatory response. The issue is whether hyperglycaemia, when present during a STEMI, has to be treated with intensive insulin therapy even in non-diabetic patients. It is important to distinguish between a favourable metabolic effect of glucose–insulin infusion and the control of acute hyperglycaemia. Finally, the negative results of the megatrial CREATE-ECLA support early administration of GIK prior to effective myocardial reperfusion, including fibrinolysis, primary PCI and post-fibrinolysis PCI strategies.

As the evidence in support of adverse effects of hyperglycaemia has increased, the treatment of in-hospital hyperglycaemia has become more aggressive. The resulting hypo-glycaemia episodes are common events and hypoglycaemia has been recently shown to be a marker of increased risk in patients with STEMI. Indeed, patients with one episode of hypoglycaemia during hospitalisation had a worse outcome.
than those without hypoglycaemia, and an even higher mortality rate than those with suboptimal glycaemic control (figure 10). These recent findings emphasise that ‘judicious glycaemia management’ should be used for patients with AMI since both suboptimal treatment and overtreatment may be associated with adverse outcomes.

Conclusions
Abnormal glucose metabolism is a very frequent feature in STEMI and is associated with impaired survival. Importantly, patients without a previous diagnosis of diabetes and with fasting glycaemia in the diabetes range have worse outcomes compared to patients with known diabetes. Improvement of the decreased myocardial perfusion is clearly the key issue in order to improve outcomes of STEMI patients with hyperglycaemia. Indeed, the efficacy of reperfusion therapy in reopening the occluded artery is similar in STEMI patients with or without impaired fasting glycaemia, while the pre-existing decreased myocardial perfusion in STEMI patients with impaired fasting glycaemia persists even after successful epicardial revascularisation.

There is no doubt that better glycaemic control is associated with a better general outcome of STEMI patients with IFG. However, there is currently no evidence that it can modify the defective microvascular perfusion of the ischaemic myocardium. Further investigations are warranted.

An aggressive antithrombotic regimen, including early administration of GP IIb/IIIa receptor inhibitors prior to initiation of reperfusion therapy, appears to be very promising for STEMI patients with abnormal glucose metabolism and has been shown to reduce long-term mortality significantly in these high-risk patients. However, the underutilisation of beneficial cardiovascular therapies in the setting of STEMI is of major concern and may also account for the poor outcome of STEMI patients with abnormal glucose metabolism.

Other therapeutic options to reduce the inflammatory response of the ischaemic myocardium are currently being investigated. The Complement inhibition in Myocardial infarction treated with Angioplasty (COMMA) trial has previously shown that blocking activated complement during myocardial ischaemia leads to a reduction of mortality although there was no effect on infarct size.14 Hopefully, the ongoing Assessment of Pexilizumab in Acute Myocardial Infarction (APexMI) trial will confirm the benefit of such a strategy in STEMI patients with hyperglycaemia.

Conflict of interest
None declared.

References


