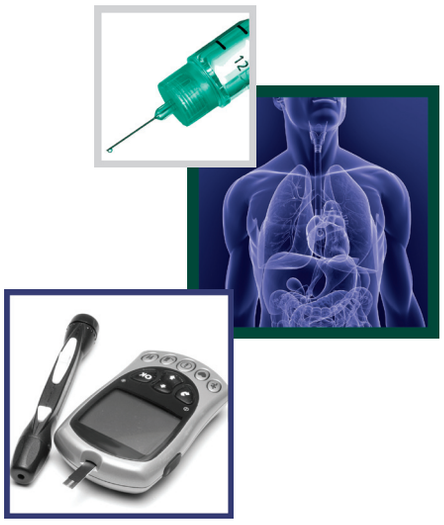
MANAGEMENT PERSPECTIVE

Effects of glucose-lowering drugs in patients with diabetes and myocardial infarction



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Summary Points

- Glucose-lowering strategies in acute myocardial infarction patients
  - Two main strategies have been employed to improve the prognosis in such patients.
  - Metabolic modulation, in which fixed doses of glucose/insulin/potassium are infused, has failed to show any benefit on mortality or morbidity in randomized controlled trials.
  - Metabolic control uses insulin to lower glucose to a prespecified level. The first study using this strategy, Diabetes and Insulin–Glucose Infusion in Acute Myocardial Infarction (DIGAMI), found that intensive insulin treatment in patients with Type 2 diabetes and acute myocardial infarction provided better metabolic control and significantly reduced mortality compared with conventional therapy.
  - A second DIGAMI study found no difference in glucose control between different glucose-lowering modalities and no difference in total mortality or nonfatal cardiovascular events.
- Glucose-lowering treatment & prognosis in an outpatient setting
  - Glucose-lowering treatment reduces long-term microvascular complications and may also reduce macrovascular complications in patients with Type 2 diabetes who have not had a cardiovascular event. However, the optimal strategy for glucose lowering has not yet been defined.
  - In high-risk patients with established diabetes, intensive glycemic control has either failed to show any significant reduction in cardiovascular outcomes or has been associated with increased mortality.
  - *Post-hoc* analyses and registry-based studies found that the agent used to achieve glucose control has prognostic implications, with insulin seemingly associated with an increase in nonfatal myocardial infarction and stroke, and metformin appearing to be protective.
  - Potential mechanisms that may contribute to the harmful effects of insulin include hypoglycemia, direct effects of insulin on the vessel wall and hemodynamics, endothelial dysfunction, increased inflammatory activation and platelet dysfunction.
- Glucose-lowering agents & malignancies
  - Insulin may be associated with a greater risk of malignancies than noninsulin-based therapy, whereas metformin appears to reduce malignancies.
- Conclusion & future perspective
  - New management strategies that can improve the poor prognosis in patients with diabetes and myocardial infarction are needed.

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SUMMARY Patients with diabetes have a higher risk for fatal and nonfatal complications of cardiovascular (CV) disease, and a worse prognosis following a CV event than patients without diabetes. Lowering glucose levels appears to prevent CV events in patients with newly detected diabetes, but data are conflicting in patients with longer diabetes duration and in patients with established CV disease. Furthermore, the optimal strategy for glucose lowering has not yet been defined, either in the setting of an acute CV event or for long-term glucose-lowering treatment. Recent data suggest that insulin may be associated with an increased rate of nonfatal myocardial infarctions in patients who have suffered an acute coronary event. This article provides an overview of the impact of different glucose-lowering agents on CV morbidity and mortality, and on malignant diseases in patients with diabetes and myocardial infarction.

Cardiovascular disease is the leading cause of mortality, accounting for more than 4.35 million deaths each year in the 53 states comprising the WHO European region and more than two million deaths in the EU [101]. The proportion is higher in women (54% of all deaths) than in men (43% of all deaths) and among those living in poor socioeconomic conditions [101]. A high rate of cardiovascular deaths is seen in all parts of the industrialized world, and cardiovascular disease as a cause of death is increasing rapidly in developing countries [1]. Patients with diabetes are particularly prone to developing atherosclerosis and various manifestations of cardiovascular disease, including myocardial infarction (MI) [2–4], and are at considerably higher risk for fatal and nonfatal complications of cardiovascular disease than patients without diabetes [5,6]. Patients with diabetes also have a worse prognosis than those without diabetes following a cardiovascular event [7,8], and a meta-analysis of in-hospital mortality or congestive heart failure rates after an MI revealed that patients with hyperglycemia at hospital admission had an impaired prognosis whether or not they had diabetes [9]. The impact of hyperglycemia during hospitalization on short- and long-term prognosis has subsequently been confirmed in a large number of studies [10–18], with several reports suggesting that there is a J- or U-shaped relationship between blood glucose and prognosis, implying that not only high but also low levels of blood glucose are related to increased mortality in patients with MI [12,13,19].

Several mechanisms may explain how acute hyperglycemia leads to a more dismal outcome after an acute coronary event in patients with diabetes [20]. Hyperglycemia may reduce ischemic preconditioning and enhance the development of ischemia/reperfusion injury, decrease collateral circulation, enhance platelet aggregation and reduce spontaneous thrombolytic capacity (thereby contributing to lower rates of spontaneous reperfusion) and may be behind a no-reflow phenomenon caused by microvascular dysfunction. High free fatty acid concentrations may further aggravate myocardial ischemia and trigger malignant arrhythmias. This article is not intended as a systematic literature review, but aims to provide the practicing physician with an overview of the impact of various glucose-lowering treatments on factors of prognostic importance in patients with diabetes and MI.

Glucose-lowering strategies in patients with acute MI

Two main strategies have been employed to improve the prognosis of patients with an acute MI with or without diabetes: metabolic modulation and metabolic control.

■ Metabolic modulation

Metabolic modulation focuses on the potential beneficial effects of insulin and potassium during acute stress, without any particular attention to blood glucose. This strategy, in which fixed doses of glucose/insulin/potassium (GIK) are infused in order to facilitate transportation of potassium into the cells, was based on the belief that an increase in intracellular potassium would stabilize cardiomyocytes, thereby reducing the risk of arrhythmias. It was also believed that GIK would improve glucose oxidation and decrease β oxidation of free fatty acids by improving both aerobic and anaerobic myocardial energy metabolism [21]. Unfortunately, randomized trials failed to show any benefit on mortality or morbidity. One plausible explanation for this finding is that the GIK solutions enhance blood glucose, a known risk factor, and that the rather high infused volume load required was harmful [22,23].

Metabolic control

The concept of metabolic control uses insulin to lower glucose to a prespecified level in order to reduce the harmful effects of acute hyperglycemia and to take advantage of the beneficial effects of insulin on myocardial metabolism (as described above). This was first studied in the Diabetes and Insulin–Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial, which compared an intensive insulin-treatment regimen (24-h insulin–glucose infusion followed by subcutaneous insulin) with routine glucose-lowering therapy [24]. Results from the study showed that intensive insulin treatment provided better metabolic control than routine therapy. Mortality was also significantly reduced after 1 year in patients treated with intensive insulin therapy both during the acute phase and long-term follow-up compared with those treated with conventional therapy [25].

A second DIGAMI trial (DIGAMI 2) was conducted in patients with Type 2 diabetes and acute MI with the objective of determining whether the benefit was linked to the initial insulin–glucose infusion or to the continued insulin-based glucose control [26]. Patients (n = 1253) were randomized to one of three glucose-lowering strategies:

- Acute insulin–glucose infusion followed by short- and long-acting insulin (initiated during hospitalization and continued over the complete follow-up period), with the aim of reaching a fasting blood glucose level of 5–7 mmol/l and a nonfasting blood glucose level of <10 mmol/l;
- The same initial insulin–glucose infusion followed by glucose-lowering treatment according to local practice without any protocol-stated target glucose level;
- Glucose-lowering treatment according to local practice. After a median follow-up of 2.1 years (range: 1–3 years), there was no difference in glucose control between the different glucose-lowering modalities and no difference in total mortality or nonfatal cardiovascular events. It was speculated that the lack of a difference in glucose control accounted for the latter result, but effects related to the different glucose-lowering management strategies (insulin vs oral drugs or lifestyle) cannot be excluded. Thus, glucose control rather than insulin treatment *per se* seems to be important in patients with acute MI. The current recommendation is that patients with diabetes and MI benefit from tight glycemic control, which may be accomplished by different treatment strategies but insulin is usually the drug of choice in the acute setting.

Hypoglycemia

One potential problem with insulin treatment during the acute phase of a MI is the risk of induction of hypoglycemia, which may enhance catecholamine release that may aggravate myocardial ischemia. Fear of inducing hypoglycemia has been reported as an obstacle to the use of sufficient insulin to reach target glucose levels [27], although Kosiborod and coworkers have reported that, in patients with acute MI, it is spontaneous, rather than iatrogenic hypoglycemia that is associated with increased mortality [28]. The impact of insulin-induced hypoglycemia during acute coronary care was studied in the DIGAMI 2 trial. Results showed that symptomatic hypoglycemia was related to mortality, but this difference disappeared following adjustment for potential confounders (hazard ratio [HR]: 1.09; 95% CI: 0.64–1.87; p = 0.7403). Importantly, body weight (odds ratio: 0.97; 95% CI: 0.95–0.98; p < 0.0001) and diabetes duration (odds ratio: 1.03; 95% CI: 1.01–1.05; p = 0.0085) were independent predictors of hypoglycemia. Thus, hypoglycemia during hospitalization was not a risk factor for mortality or cardiovascular events in patients with Type 2 diabetes and MI; however, hypoglycemic episodes seemed to identify patients at high risk for other reasons [29]. It should be noted that the relationship between hypoglycemia and outcome may be different with episodes of hypoglycemia during long-term treatment.

Glucose-lowering treatment & prognosis in an outpatient setting

In addition to the benefits of lowering glucose in the setting of an acute MI, glucose-lowering strategies may also be beneficial over the long term in reducing micro- and macro-vascular complications in patients with Type 2 diabetes. However, the optimal strategy for such long-term glucose lowering has not yet been defined. Different drugs have different target tissues and their effects on the cardiovascular system remain uncertain to a large extent. Until recently, most studies on glucose-lowering drugs focused on

their ability to control hyperglycemia. Few clinical trials studied the effects on mortality and cardiovascular events, and it is only during the last few years that their impact on cardiovascular morbidity and mortality has attracted interest.

Intensive glucose-lowering therapy (with insulin, metformin or sulfonylureas) has been shown to reduce the risk of microvascular complications in patients with rather newly established Type 2 diabetes [30,31]. In high-risk patients with diabetes established for several years, intensive glycemic control either failed to show any significant reduction in cardiovascular outcomes or was actually associated with impaired prognosis [32]. An explanation may be a variable cardiovascular profile of different glucose-lowering agents.

■ Thiazolidinediones

Thiazolidinediones, as an example, are associated with fluid retention and an increased risk of heart failure, and at least some of the drugs in this class have been claimed to provoke MI [33,34]. Because of the importance of clearly understanding the potential cardiovascular benefits or drawbacks of glucose-lowering agents, the US FDA issued recommendations to the industry to evaluate the impact of all new glucose-lowering drugs on mortality and cardiovascular events. Pending prospective trials designed and powered to assess mortality and morbidity outcomes, information must be derived from available data such as the *post-hoc* information from the DIGAMI 2 study. Although the results of such analyses should be interpreted with caution, analysis of the study population of patients with MI and diabetes revealed that the agent used to achieve glucose control had prognostic implications.

■ Insulin

In DIGAMI 2 insulin was seemingly associated with an increased rate of nonfatal MI, whereas metformin appeared protective **(Figure 1)** [35]. During the initial 2.3-year follow-up period, nonfatal cardiovascular events (MI and stroke) were significantly more common in patients receiving insulin even after adjustments for a number of confounders, including: updated glucose control and concomitant treatment, with a HR of 1.73 (95% CI: 1.26–2.37; p = 0.0007) in insulin-treated patients; a beneficial HR of 0.63 (95% CI: 0.42–0.95; p = 0.03) in patients receiving metformin; and a neutral HR of 0.81 (95% CI: 0.57–1.14; p = 0.23) in patients receiving sulfonylureas. Further analyses were performed to rule out the effect of already ongoing insulin treatment in study subjects, which may reflect a more long-standing or severe diabetes. However, the risk seemed to be even stronger in patients on newly instituted insulin (HR: 1.95; 95% CI: 1.35–2.82; p = 0.0003) and in those who, according to the protocol, were randomized to insulin treatment (HR: 2.22; 95% CI: 1.46–3.35; p = 0.0002). None of the glucose-lowering treatments influenced mortality during the initial 2.3-year follow-up, and it was speculated that an effect on mortality may take longer to become apparent. An extended follow-up study (median: 4.1 years, maximum: 8 years) was performed and the observations remained with regard to an increase in MI and stroke, but mortality was still not increased [36].

These findings consolidate observations from registry-based reports that exogenous insulin may increase the risk of MI and impair prognosis in patients with Type 2 diabetes [37–39]. For example, the Euro Heart Survey on Diabetes and the Heart enrolled 4676 patients with coronary artery disease, of whom 1425 had known diabetes. The impact of different glucose-lowering modalities on cardiovascular mortality was followed over 1 year. Insulin-treated patients with known diabetes had an adjusted HR of 2.23 (95% CI: 1.24–4.03; p = 0.006) compared with those on oral glucose-lowering drugs [39]. Insulin treatment has also been associated with an increased risk for heart failure and increased mortality in patients with heart failure [40,41]. However, it is difficult to interpret data from registry and *post-hoc* trials due to the possibility that the use of insulin may be a marker of more advanced disease, or so-called confounding by indication [36–41]. Several potential mechanisms may contribute to the possible harmful effects of insulin. As described above, hypoglycemia may be one explanation. Another mechanism may relate to the direct effects of insulin on the vessel wall and hemodynamics. Patients with Type 2 diabetes who require insulin treatment are in an insulin-resistant state, with high levels of endogenous insulin to which exogenous insulin is added. Insulin may act via the MAPK pathway, leading to anabolic, vasoconstrictive and, subsequently, pro-atherosclerotic effects. Moreover, exogenous insulin has been related to endothelial dysfunction [42], increased inflammatory activation [43] and platelet dysfunction [44]. Finally, insulin may act on the IGF-1 receptor with subsequent anabolic effects [45].

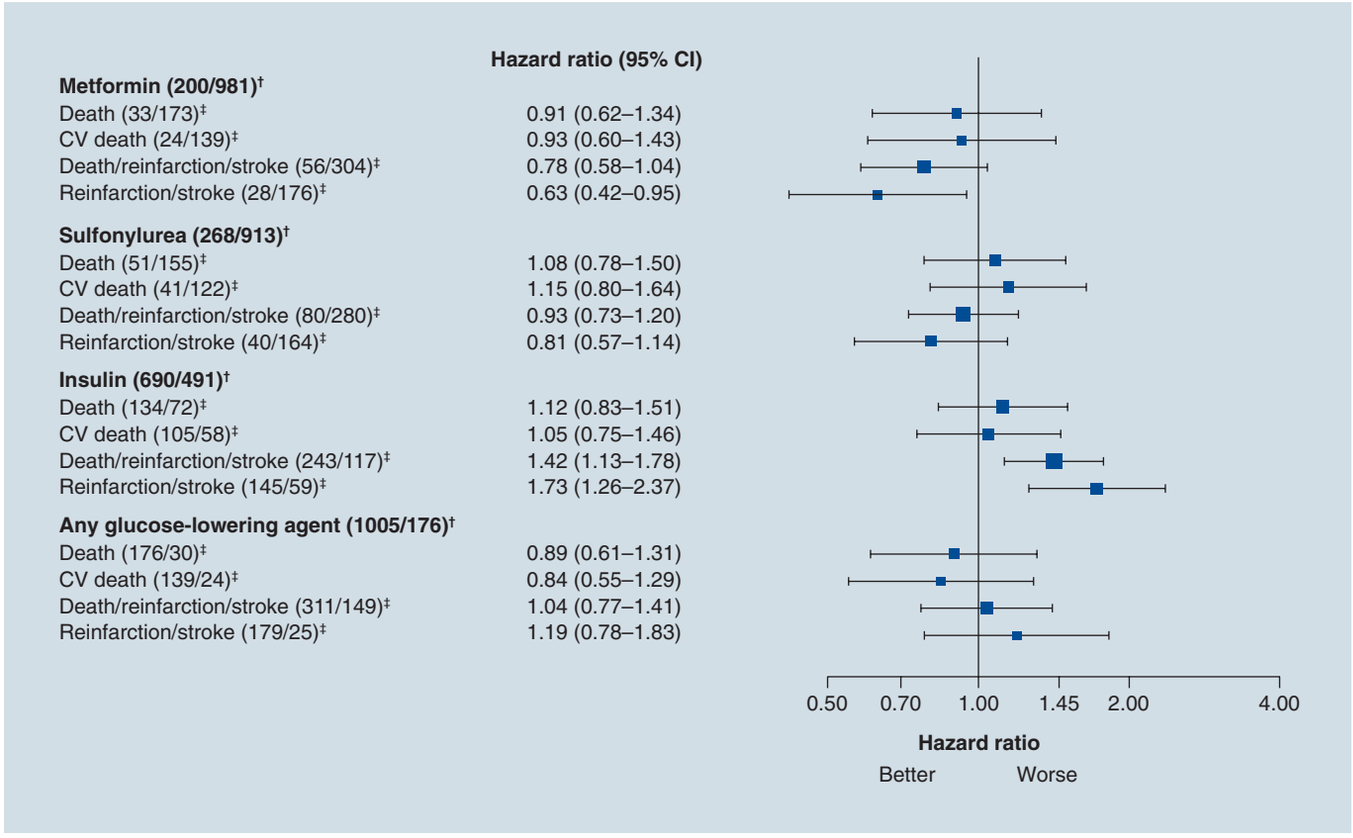

Figure 1. Effect of different glucose-lowering treatments on morbidity and mortality.
†Number of patients using drug/number of patients not using drug.
‡Number of end points for patients using drug/number of end points for patients not using drug.
CV: Cardiovascular.
Reproduced with permission from [35].

■ Sulfonylureas

Because of the negative effects of high exogenous insulin levels, concerns have also been raised regarding drugs that increase endogenous insulin, such as the sulfonylureas [37,38,46,47]. Sulfonylureas, which act via opening of ATP-sensitive potassium channels in the pancreatic β cells, may have direct negative effects on the myocardium by inhibiting these channels even in myocytes, thereby interacting with ischemic preconditioning, coronary vasorelaxation and diminishing myocardial contractile strength [48]. Although it is claimed that second-generation sulfonylureas act more specifically at the pancreatic level and less in myocardial and vascular tissue [49,50], data have, so far, been inconclusive for patients with MI. The findings of the *post-hoc* analysis of the DIGAMI 2 trial support the notion that sulfonylureas do not affect the prognosis compared with other compounds such as insulin and metformin.

■ Metformin

Of the different glucose-lowering alternatives analyzed within the context of DIGAMI 2, metformin was the most beneficial. Although this observation originates from a nonrandomized *post-hoc* analysis, it strongly supports previous reports on beneficial effects of metformin in patients with newly diagnosed diabetes [30] and extends these effects to patients with established cardiovascular complications. In addition to the decreased risk of nonfatal cardiovascular events, patients on metformin had a lower mortality during prolonged follow-up in DIGAMI 2 [36]. The UK Prospective Diabetes Study (UKPDS) Group was the first to report on the mortality benefits of metformin in overweight patients with newly diagnosed Type 2 diabetes [30]. Patients randomized to metformin had lower all-cause mortality and fewer strokes than those receiving chlorpropamide, glibenclamide or insulin. Further support was provided by the 10-year extended

follow-up of this study, which reported a highly significant 33% reduction in MI (p = 0.005) and a 27% reduction in total mortality (p = 0.002) in patients originally treated with metformin compared with conventional treatment [51]. It is most likely that this beneficial effect of metformin is related to a combination of mechanisms. Metformin may have anti-atherosclerotic effects independent of glucose control [52]. It stimulates the AMP-activated kinase (AMPK), a key regulator of cellular energy balance and substrate metabolism, thereby inhibiting hepatic gluconeogenesis, contributing to improved endothelial function and increased insulin sensitivity in adipose tissue and peripheral muscles [53–56]. It has been suggested that the AMPK effect in endothelial cells is mediated by an activation of the PI3K pathway [54].

Glucose-lowering agents & malignancies

Diabetes is related to malignant diseases [57–60], and several reports have advocated that insulin might further increase this risk [61,62]; however, these suspicions were not supported by other studies [63,64]. A finding of concern in DIGAMI 2 was the higher rate of death due to malignancies among patients randomized to insulin-based treatment [26]. An extended follow-up analysis was thus performed to determine if this increased risk remained over time. Although total mortality was similar in the three treatment groups, patients randomized to insulin had a trend toward increased mortality from malignant diseases compared with those randomized to noninsulin-based glucose-lowering therapy. By contrast, patients on metformin had a significantly lower risk of death from malignancies [36].

High levels of circulating insulin caused by insulin resistance may change the cellular response to insulin-altering growth signals, perhaps via MAPK or activation of IGF-1 receptors. It may also cause resistance to apoptosis, which predisposes to the survival and proliferation of malignant cells [65–67]. An alternate interpretation of these findings is that the seemingly negative impact of insulin on malignant diseases may be explained by a beneficial effect of the drugs to which insulin is compared. Both alternatives have support from mechanistic investigations. Metformin has been reported to protect against cancer [61,68,69]. The beneficial effects are thought to be mediated by the AMPK pathway, perhaps via growth inhibition [56,70,71]. These observations show that it is of great importance to further study the impact of glucose-lowering agents not only on their capacity to lower glucose, but also their influence on cardiovascular morbidity, mortality and malignant conditions.

Conclusion

The high mortality rate in the DIGAMI 2 cohort further emphasizes the need for new management strategies that can improve the poor prognosis in patients with diabetes and MI [5,6]. The impressive overall mortality rate in the original follow-up (21%) [26] increased to 31% in the extended follow-up [36\]. The majority of deaths (72%) were caused by cardiovascular events, but other factors such as malignancies were also important.

The finding of the *post-hoc* analysis of DIGAMI 2 may also illustrate how difficult it is to improve the prognosis of these patients despite the extensive use of evidence-based therapy [26]. Still, the STENO-2 study demonstrated that early institution of multifactorial treatment in patients with established Type 2 diabetes without MI is remarkably rewarding [72,73]. In addition, the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial showed that patients with diabetes and stable angina pectoris eligible for revascularization had a similar prognosis if managed with optimal medical treatment (including lipid lowering, antihypertensive treatment, lifestyle interventions, and insulin sensitizers or insulin providers) compared with early revascularization (i.e., coronary artery bypass graft or percutaneous coronary intervention within 4 weeks) [74,75].

The prognosis for patients with diabetes and MI remains poor, underscoring the need to improve management strategies, especially with regard to glucose-lowering drugs as part of a comprehensive and target-driven multifactorial intervention.

Future perspective

The potential differences in the effect of glucose-lowering agents on the prognosis of patients with Type 2 diabetes and MI highlights the importance of evaluating the cardiovascular effects of such drugs as soon as possible during drug development and marketing. The potentially negative effects of insulin deserve further evaluation. In the meantime, it is important to lower glucose sufficiently when insulin is used so as not to end up with the possible negative effects in addition to the known negative effects of hyperglycemia. Since metformin seems to have positive effects

on the cardiovascular system and also on cancer prevention, drugs involving similar mechanisms, such as insulin sensitization, probably via the AMPK pathway, are of interest.

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