Hypoglycemia and Adverse Outcomes: Marker or Mediator?

Kasia J. Lipska, MD,[1] Mikhail Kosiborod, MD[2]

[1]Robert Wood Johnson Clinical Scholars Program, Yale University School of Medicine, New Haven, CT; [2]Mid America Heart Institute of Saint Luke's Hospital, University of Missouri, Kansas City, MO

Multiple studies have shown that hypoglycemia is associated with increased mortality and a variety of adverse outcomes. Whether hypoglycemia is a mediator of adverse outcomes or simply represents a marker of critical illness has been unclear until now. Based on observational data, spontaneous (but not iatrogenic) hypoglycemia is associated with increased mortality during hospitalization for acute myocardial infarction. In the recent ADVANCE trial of patients with diabetes, intensive glucose lowering was associated with increased risk of hypoglycemia. Hypoglycemia was, in turn, associated with increased risk of macro- and microvascular events and death, and also with increased risk of noncardiac adverse events, including disorders of the digestive, respiratory, and skin systems. Based on available evidence, hypoglycemia does not appear to directly lead to death or cardiovascular events and is likely a marker for more severe illness and comorbidity burden. Nevertheless, continued efforts to avoid hypoglycemia are clearly warranted.

[Rev Cardiovasc Med. *2011;12(3):132-135 doi: 10.3909/ricm0586*]

Key words: Hypoglycemia • Microvascular events • Macrovascular events

The pursuit of strict glucose control is frequently hampered by concerns over hypoglycemia. In randomized controlled trials of both acute and long-term glycemic control, hypoglycemia occurs more frequently in patients treated intensively with insulin or insulin secretagogues, as compared with patients assigned to conventional glucose control strategies.[1-9] Several observational studies suggest that hypoglycemia during acute hospitalization is associated with increased mortality.[10-12] In addition, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, excess mortality risk observed in the intensive glucose control group raised the possibility that hypoglycemia may directly contribute to adverse outcomes.[3] Despite post hoc analyses of this

study, which suggest that hypoglycemia did not explain the excess mortality risk, questions remain with regard to the association between hypoglycemia and adverse events. Specifically, it has been unclear whether hypoglycemia is a mediator of adverse outcomes or simply represents a marker of critical illness.

In the inpatient setting, this issue was directly addressed in a large retrospective cohort of patients with acute myocardial infarction (AMI).[13] In this study, hypoglycemia (random blood glucose < 60 mg/dL) was associated with increased in-hospital mortality, but only among patients who experienced spontaneous hypoglycemia, defined as hypoglycemia occurring without administration of any insulin during hospital stay. In contrast, there was no significant association between hypoglycemia and in-hospital death among patients who experienced iatrogenic hypoglycemia, defined as occurring in the presence of any insulin treatment during hospitalization. Based on this study, hypoglycemia is more likely to be a marker, rather than a cause, for increased mortality, at least in the setting of AMI hospitalization.

The recent Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial provided another opportunity to investigate the relationship between hypoglycemia and adverse outcomes, specifically among diabetic patients.[4] ADVANCE was a factorial trial with randomized comparisons of blood pressure and glucose lowering on the risk of vascular outcomes and death in patients with type 2 diabetes. In this trial, intensive glucose lowering with gliclazide (and other therapies as required) was compared with conventional glucose control among 11,140 patients with major macro- or microvascular disease or at least one cardiovascular risk factor. There were no significant differences in major macrovascular outcomes or death between the groups after a median follow-up of 5 years, but intensive glucose therapy was associated with increased risk of severe hypoglycemia (2.7% vs 1.5% in the intensive versus conventional arms, respectively; $P < .001$). Severe hypoglycemia was defined as any blood glucose < 50 mg/dL accompanied by transient neurologic dysfunction and requiring administration of treatment by someone else.

Recent analysis of the ADVANCE trial by Zoungas and colleagues[14] specifically examined the association between severe hypoglycemia and the risks of macro- and microvascular events and death. The median time from severe hypoglycemia to the first major macrovascular event was 1.56 years (interquartile range [IQR], 0.84-2.41), to the major microvascular event was 0.99 years (IQR 0.40-2.17), and to death was 1.05 years (IQR, 0.34-2.41). Patients reporting severe hypoglycemic episodes were at higher risk for major macrovascular events (adjusted hazard ratio [HR] 3.45, 95% confidence interval [CI], 2.34-5.08), major microvascular events (adjusted HR 2.07, 95% CI, 1.32-3.26), and death from any cause (adjusted HR 3.30, 95% CI, 2.31-4.72). Moreover, severe hypoglycemia was associated with increased risk of a wide range of noncardiac adverse events, including disorders of the digestive, respiratory, and skin systems. Importantly, the association between severe hypoglycemia and these adverse outcomes was similar among patients assigned to intensive and conventional treatment strategies.

Although there were a number of limitations to this analysis (including the relatively small number of hypoglycemic episodes and inability to account for unreported hypoglycemia), the study suggests that hypoglycemia may be a strong marker of sicker patients. Coexisting conditions and health factors may make these individuals more vulnerable to both hypoglycemia and subsequent adverse outcomes. In fact, patients experiencing hypoglycemia in the ADVANCE study were older, had longer duration of diabetes, lower body mass index, and other risk factors associated with severe illness, compared with patients who did not report hypoglycemia (Table 1). The temporal

Table 1
Risk Factors for Hypoglycemia in Patients With Diabetes

Patient Factors
Older age
Longer duration of diabetes
Lower body mass index
Higher creatinine levels
Lower cognitive function
History of smoking or microvascular disease
History of severe hypoglycemia or hypoglycemia unawareness
Treatment Factors
Use of two or more glucose-lowering drugs
Use of insulin therapy or insulin secretagogues
Assignment to intensive glucose control
Other Factors
Alcohol use

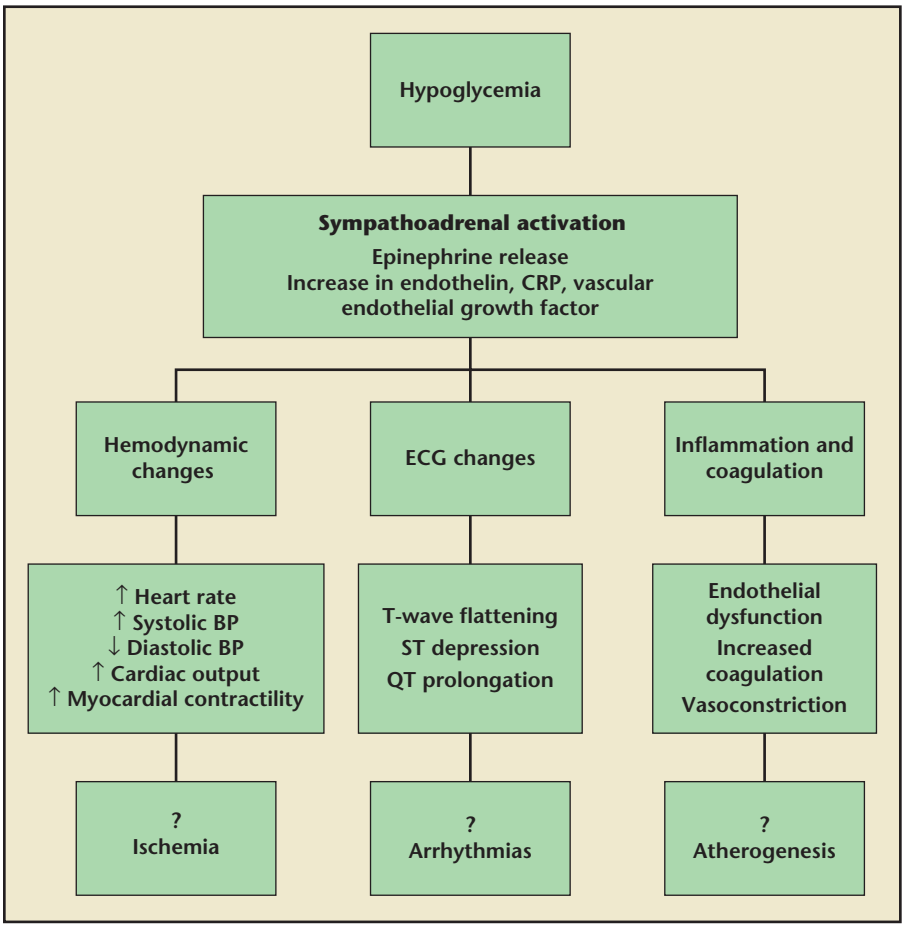

Figure 1. *Potential mechanisms by which hypoglycemia may trigger cardiovascular events. BP, blood pressure; CRP, C-reactive protein; ECG, electrocardiography.*

relationship between hypoglycemia and outcomes with long duration of time between the two events also supports the notion that hypoglycemia is a marker of critical illness. In addition, the broad increases in risks across various conditions (particularly skin and respiratory disorders, for which no clear causative mechanisms related to hypoglycemia exist) make it less likely that hypoglycemia directly leads to these adverse events (Figure 1).

This study provides further evidence that hypoglycemia does not appear to directly lead to death or cardiovascular events, either in the hospital or in the outpatient setting; it is likely just a marker for more severe illness and comorbidity burden. Nevertheless, there is certainly no benefit associated with hypoglycemia, and efforts to avoid it are still warranted. ■

References

1. United Kingdom Prospective Diabetes Study 24: a 6-year, randomized, controlled trial comparing sulfonylurea, insulin, and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy. United Kingdom Prospective Diabetes Study Group. *Ann Intern Med*. 1998; 128:165-175.
2. Duckworth W, Abraira C, Moritz T, et al; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med*. 2009;360:129-139.
3. Gerstein HC, Miller ME, Byington RP, et al; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008; 358:2545-2559.
4. Patel A, MacMahon S, Chalmers J, et al; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358:2560-2572.
5. Malmberg K, Rydén L, Efendic S, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol*. 1995; 26:57-65.
6. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med*. 2001;345:1359-1367.
7. Malmberg K, Rydén L, Wedel H, et al. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J*. 2005;26:650-661.
8. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med*. 2006;354:449-461.

Main Points

- Hypoglycemia is associated with increased mortality and adverse outcomes.
- Prior observational studies in hospitalized patients show that spontaneous (but not iatrogenic) hypoglycemia is associated with increased mortality during hospitalization for acute myocardial infarction, suggesting that hypoglycemia is a marker of sicker patients.
- Recent analysis of the ADVANCE trial demonstrates that hypoglycemia is associated with a broad range of adverse outcomes without a clear causal pathway or temporal relationship. These data provide additional evidence that hypoglycemia is likely not a direct cause of adverse events in patients with type 2 diabetes.

9. Finfer S, Chittock DR, Su SY, et al; NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360:1283-1297.
10. Svensson AM, McGuire DK, Abrahamsson P, Dellborg M. Association between hyper- and hypoglycaemia and 2 year all-cause mortality risk in diabetic patients with acute coronary events. *Eur Heart J*. 2005;26:1255-1261.
11. Kosiborod M, Inzucchi SE, Krumholz HM, et al. Glucometrics in patients hospitalized with acute myocardial infarction: defining the optimal outcomes-based measure of risk. *Circulation*. 2008;117:1018-1027.
12. Pinto DS, Skolnick AH, Kirtane AJ, et al. U-shaped relationship of blood glucose with adverse outcomes among patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol*. 2005;46:178-180.
13. Kosiborod M, Inzucchi SE, Goyal A, et al. Relationship between spontaneous and iatrogenic hypoglycemia and mortality in patients hospitalized with acute myocardial infarction. *JAMA*. 2009;301:1556-1564.
14. Zoungas S, Patel A, Chalmers J, et al. Severe hypoglycemia and risks of vascular events and death. *N Engl J Med*. 2010;363:1410-1418.