Hypoglycemia, Diabetes, and Cardiovascular Events

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Diabetes is at epidemic proportions in the U.S. Patients with diabetes are at increased risk for micro- and macrovascular complications. The benefit of glycemic control in decreasing the risk for microvascular disease is well established. However, the role of glycemic control in decreasing macrovascular complications has been controversial. Several large clinical trials looking at this issue have either shown no benefit or even potential harm. The possibility of hypoglycemia as a risk factor for cardiovascular events is a topic of much debate. In this review article, we discuss the evidence for and against this hypothesis and the possible mechanisms that might be involved.

Patients with diabetes have an increased risk of cardiovascular disease. The link between glycemic control and microvascular complications has been firmly established (1,2). However, the association between glycemic control and macrovascular disease is mainly obtained from epidemiological studies, and intensive glucose control has often failed to reduce macrovascular events. Intensive glucose control invariably increases the risk of hypoglycemia and sometimes the severity of hypoglycemia (2) Several epidemiological studies and smaller prospective studies have linked hypoglycemia to increased cardiovascular risk (3–5). Recent large randomized trials looking at intensive glycemic control have either shown no benefit (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation [ADVANCE] and Veterans Affairs Diabetes Trial [VADT]) or increased all cause mortality (Action to Control Cardiovascular Risk in Diabetes [ACCORD]) (6). While the reason for the increased mortality is unclear and hypoglycemia has not been implicated as a cause of death, these studies have increased the debate about the degree of glycemic control required to decrease diabetes complications and the role of hypoglycemia in cardiovascular morbidity and mortality.

DEFINITION, INCIDENCE OF, AND RISK FACTORS ASSOCIATED WITH HYPOGLYCEMIA

— The modern definition of hypoglycemia is plasma glucose <70 mg/dl (7–9). At plasma glucose below this threshold (60–65 mg/dl), the brain becomes neuroglycopenic and promotes secretion of counterregulatory hormones, primarily the adrenomedullary adrenaline and the neurotransmitter norepinephrine (along with glucagons, the "rapid" responses), which have relevant cardiovascular effects (9–11). This occurs in the absence of the warning symptoms of hypoglycemia, which normally occur at lower plasma glucose (<60 mg/dl) (9). If (even mild) hypoglycemia episodes recur often over time (e.g., once a day), the brain adapts to hypoglycemia with symptom responses at a lower-than-usual plasma glucose concentration (9). This shifting of brain glucose thresholds to higher levels (i.e., it takes a lower plasma glucose to activate symptom responses) is dangerous because it masks most of the mild hypoglycemia episodes until blood glucose decreases to ≤50 mg/dl. In turn, failure to sense symptoms of hypoglycemia in an early phase (*hypoglycemia unawareness*) increases the risk of prolonging duration and increasing frequency of hypoglycemia. These events perpetrate a deleterious vicious circle leading to an increase in severe hypoglycemia with brain dysfunction (9,11). The response of adrenaline (and norepinephrine) in individuals with hypoglycemia unawareness is lower than in aware subjects (9), a finding that might be of cardiovascular protection.

The incidence of hypoglycemia is quite varied in the literature (supplementary Table 1, available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc09-2082/DC1) (12), with lack of standardization of definition of hypoglycemia and its classification. The incidence of hypoglycemia in various trials reviewed in this article depends on the definitions of mild, moderate, and severe hypoglycemia. Most recent large trials have defined severe hypoglycemia as severe, whenever help from a third party is required, whereas mild episodes are those that are self-treated (supplementary Table 1 reports severe episodes).

Hypoglycemia has long been recognized as a major barrier to achieving normoglycemia with intensive therapy and has therefore been investigated in terms of its impact (particularly on cognitive function) and physiological counterregulation (7,11). In the Diabetes Control and Complications Trial (DCCT), patients in the intensive arm had a 65% incidence of severe hypoglycemia, compared with 35% in the conventional group (2,13). In the UK Diabetes Prospective Study, the rates of major hypoglycemic episodes were 0.7% in the conventional group, 1.4% in the glibenclamide group, and 1.8% in the group treated with insulin (1). In the 4-T study, median rates of hypoglycemia per patient per year were lowest in the basal insulin group (1.7), higher in the biphasic aspart insulin group (3.0), and highest in the prandial aspart insulin group (5.7) (14). An observational study of 383 patients reported that the duration of diabetes and the duration of insulin treatment were both positively correlated to hypoglycemic episodes (15). Thus, although in general in type 2 diabetes there is less hypoglycemia risk versus type 1 diabetes, the frequency of hypoglycemia increases with increased diabetes and insulin treatment duration in type 2 diabetes, approaching the figures of type 1 diabetes

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(8), primarily because of loss of glucagon responses to hypoglycemia. A retrospective cohort study of Medicaid enrollees, aged ≥65 years, who used insulin or sulfonylureas, identified 586 individuals with an episode of serious hypoglycemia (16). In this cohort, recent hospital discharge was the strongest predictor of subsequent hypoglycemia.

Mild hypoglycemic events are more common but less reported. One prospective study of 267 patients with both type 1 and type 2 diabetes reported 572 hypoglycemic events in 155 patients (17). Patients with type 1 diabetes had a mild hypoglycemic event rate of 42.89 events/patient/year and 1.15 severe hypoglycemic events/patient/year compared with 16.37 mild events/patient/year and 0.35 severe events/patient/year in subjects with type 2 diabetes. Predictors of diabetes in this group included previous hypoglycemia and duration of insulin therapy. A retrospective cross-sectional analysis in 1,055 patients with type 2 diabetes revealed a prevalence of hypoglycemic symptoms in 12% of diet-treated patients, 16% of patients using oral agents, and 30% of patients on insulin (18). Risk factors for hypoglycemia included insulin therapy, lower A1C at follow-up, younger age, and report of hypoglycemia at baseline visit (18).

The estimation of the incidence is complicated by the occurrence of hypoglycemia unawareness, which by its very nature makes it impossible to determine true incidence. Furthermore, many patients in trials may take corrective action to treat hypoglycemia in its early stages, without blood glucose testing, and may not record the occurrence of hypoglycemia. Therefore, all the above rates of hypoglycemia are likely to be underestimates.

Well-known risk factors for the development of hypoglycemia include exercise, alcohol, older age, renal dysfunction, infection, decreased intake of energy, and mental health issues, including dementia, depression, and psychiatric illnesses. In the ADVANCE trial, cognitive dysfunction increased the risk of hypoglycemia (hazard ratio 2.1).

EPIDEMIOLOGICAL EVIDENCE FOR THE ASSOCIATION BETWEEN HYPOGLYCEMIA AND CARDIOVASCULAR MORBIDITY

— Recent studies such as VADT and ACCORD have brought to the forefront the question of the role of hypoglycemia, if any, in increasing the risk for cardiovascular events. There are few studies looking at this question. Broadly, they can be divided into studies that look at the effect of hypoglycemia on cardiac ischemia, arrhythmias, and cerebral ischemia.

MYOCARDIAL ISCHEMIA, INFARCTION, AND ARRHYTHMIAS

— The earliest study in 1932 reported chest pain consistent with myocardial ischemia in two of seven type 1 diabetic patients with known cardiovascular disease (19). However, other similar studies failed to confirm these findings (3,5). More recently, in a retrospective review of 14,670 patients with coronary artery disease, recruited for the Bezafibrate Infarction Prevention study (a secondary prevention prospective multicenter randomized placebo-controlled double-blind trial conducted to assess the efficacy of bezafibrate in reduction of coronary events conducted in Israel) over an 8-year mean follow-up, hypoglycemia (<70 mg/dl) was a predictor of increased all-cause mortality with a hazard ratio of 1.84, but not of increased coronary artery disease mortality (4). The Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes showed that more cardiac events were documented in patients after institution of intensive glycemic control versus standard control (32 vs. 20%) (20). However, this was not significantly different, since the study was inadequately powered to study this question (20). In contrast, in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, although severe hypoglycemia was more frequent in the insulin-provision group (9.2%) than in the insulin-sensitization group (5.9%), major cardiovascular events were not significantly different (21).

A few studies using continuous electrocardiogram monitoring and glucose monitoring have been performed recently. Desouza et al. (22) demonstrated that of 54 episodes of hypoglycemia, 10 were associated with symptoms or electrocardiogram evidence of ischemia, whereas only one episode of chest pain occurred during 59 episodes of hyperglycemia. Less studied is the "dead-in-bed" syndrome, which is defined as sudden nocturnal death in type 1 diabetes. In one study, 24 deaths of patients with type 1 diabetes under the age of 50 years were studied (23). Two patients had irreversible hypoglycemic brain damage and died after artificial ventilation. Nineteen others were sleeping alone at the time of death, and 20 were found lying undisturbed (23). Gill et al. (24) demonstrated that, in patients with type 1 diabetes, severe hypoglycemia was associated with a prolonged corrected QT interval. Eight of those episodes also showed cardiac rate and rhythm abnormalities.

CEREBRAL ISCHEMIA, STROKE, AND DEMENTIA

— Severe hypoglycemia has been known to induce focal neurological deficits and transient ischemic attacks, which are reversible with the correction of blood glucose. However, the question whether hypoglycemia increases the risk for stroke or dementia remains controversial. Recent evidence suggests that recurrent or severe hypoglycemia may predispose to long-term cognitive dysfunction and dementia. Whitmer et al. (25) conducted a longitudinal cohort study of 16,667 patients with type 2 diabetes looking at the relationship between hypoglycemia and dementia. The study found that the attributable risk of dementia between individuals with and without a history of hypoglycemia was 2.4% per year. Patients with multiple episodes of hypoglycemia had a graded increase in dementia risk (25). Conversely, severe cognitive dysfunction has been associated with increased risk of hypoglycemia. In the ADVANCE trial (type 2 diabetes), severe cognitive dysfunction increased the risk of severe hypoglycemia (hazard ratio 2.1) in patients with type 2 diabetes (26). The Fremantle diabetes study (type 2 diabetes) found that dementia was a risk factor for hypoglycemia. However, hypoglycemia itself was not found to increase the risk of getting dementia (27). In type 1 diabetes, some small studies show alterations in regional cerebral blood flow in patients with severe hypoglycemia; however, these are temporary and reversible (28).

In the DCCT, despite frequent hypoglycemia, intensively treated patients with type 1 diabetes did not experience cognitive decline. Some small studies show alterations in regional cerebral blood flow in patients with type 1 diabetes with severe hypoglycemia; however, these are temporary and reversible (28). It is unclear whether this finding can be extrapolated to type 2 diabetes. Thus, the

role of hypoglycemia in increasing the risk for dementia is still controversial.

ROLE OF HYPOGLYCEMIA IN THE RESULTS OF RECENT CLINICAL TRIALS

— Recently, several large randomized trials evaluating the effects of glycemic control on cardiovascular events have published their results (29–31).

The ACCORD trial randomized 10,251 participants with a history of cardiovascular events or significant cardiovascular risk to a strategy of intensive glycemic control or standard glycemic control (29). The ACCORD trial was halted because of a significant increase in all-cause mortality (22%) and cardiovascular mortality (35%) in the intensive treatment group. In both the intensive and standard treatment arms, participants with severe hypoglycemia had a higher mortality rate than those without severe hypoglycemia (29). However, the association between hypoglycemia and mortality is much more complex in this study. The relative risk of death associated with severe hypoglycemia was 1.28 for the intensive arm versus 2.87 for the standard arm in spite of larger number of severe hypoglycemic episodes in the intensive arm. This suggests that severe hypoglycemia in a certain subset of patients may be associated with mortality rather than the strategy of treatment used (intensive versus standard). However, these data are based on post hoc analysis, and the true cause of the increased mortality in these patients may never become obvious. The subset of patients most prone to the detrimental effects of hypoglycemia had several of the following characteristics: they were likely to be women, African American, older patients, or patients with a longer duration of diabetes and have higher A1C and high albumin-to-creatinine ratio.

VADT randomized 1,791 patients with type 2 diabetes to an intensive treatment group and a conventional treatment group (31). At the end of the study, there was no significant difference in cardiovascular events between the two treatment arms. As expected, there was an increased incidence of severe hypoglycemia in the intensive treatment group. Predictors for hypoglycemia included increased duration of diabetes, insulin treatment at baseline, low BMI, previous cardiovascular events, and high albumin-to-creatinine ratio.

The ADVANCE study randomized 11,140 participants to an intensive glycemic control arm and a standard glycemic control arm (30). Although there was an increased risk of hypoglycemia in the intensive treatment arm, there was no association between hypoglycemia and cardiovascular mortality (30). One explanation for the discrepancy between this finding and that in the ACCORD study is the extremely low number of patients (<3%) who had severe hypoglycemia in the intensive treatment arm, during the course of the entire trial.

It is therefore important to seek out the similarities and differences in the study design and patient population of these studies. Patients in the ADVANCE trial had a 2- to 3-year shorter duration of diabetes as well as a lower baseline A1C than patients in the ACCORD trial. The number of patients on insulin in the intensive arm versus the standard arm was 77 versus 55% in the ACCORD trail, 90 versus 74% in the VADT, and 41 versus 24% in the ADVANCE trial. Thus, the ADVANCE trial had a much smaller proportion of patients on insulin than ACCORD or VADT. This could in part account for the low level of hypoglycemia seen in the intensive arm of the ADVANCE trial (<3%) versus the ACCORD trail (16%) and VADT (21%). The DCCT enrolled type 1 diabetic patients on insulin treatment. In contrast to the UK Diabetes Prospective Study, VADT, and ACCORD, the DCCT had a relatively high risk for severe hypoglycemia in the "conventional" treatment group (0.19 episodes/patient-year) and a threefold increased risk in the "intensive" group (0.62 episodes/patient-year). Interestingly, the more frequent severe hypoglycemia in the intensive group was not associated with increased cardiovascular mortality (13) at later follow-up (1). This indirectly highlights the different cardiovascular risk of hypoglycemia in type 2 versus type 1 diabetes. Thus, it is clear that these trials had different treatment strategies to achieve risk factor modification. Perhaps we can now appreciate that the strategy used to achieve risk factor modification is important in how it affects patient outcomes. Moreover, the particular strategy's effect on a risk factor may not predict its effect on patient outcomes (32).

HYPOGLYCEMIA AND INPATIENT GLUCOSE CONTROL

— Hyperglycemia is common in acutely ill patients and is associated with an increased morbidity and mortality (33). This has subsequently led to a large number of trials using various intensive insulin protocols to control inpatient blood glucose. However, results from these trials have increased the controversy over the risks versus benefit of tight inpatient glycemic control. Van den Berghe et al. (34) demonstrated that intensive insulin therapy in critically ill patients reduced morbidity and mortality. The DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) study found that insulin-glucose infusion followed by intensive subcutaneous insulin in diabetic patients with acute myocardial infarction improved long-term survival (35). Conversely, the DIGAMI 2 study did not confirm superiority of insulin versus conventional treatment, but reaffirmed the importance of good glycemic control in prevention of cardiovascular events (36). The recently published NICE-SUGAR (Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation) study found that intensive glucose control increased mortality among adults in the ICU (37). The Glucose Insulin in Stroke Trial (GIST)-U.K. looked at tight control of glucose in patients with acute stroke using an intensive insulin infusion protocol and found no benefit (38). The GIST-UK trial was underpowered to draw any firm conclusions. However, the sub-analysis of the mean change in glucose at 24 h showed that patients who had a decrease in plasma glucose of ≥2 mmol/l had a mortality rate of 34 versus 22% for those who had a <2 mmol/l decrease (38). This raises the question of hypoglycemia having a role in increased mortality in the inpatient setting.

Some recent studies looking at using intensive insulin infusions such as the volume and insulin therapy in severe sepsis and septic shock (VISEP) showed that the incidence of hypoglycemia was higher in the intensively treated group (39). A study by Kosiborod et al. (40), looking at 16,871 patients admitted with myocardial infarction, found that a J-shaped relationship existed between glucose and mortality. Incremental increases above 120 mg/dl and incremental declines below 70 mg/dl were found to be strongly associated with increased mortality. The slopes of these relationships were even steeper in patients with diabetes, suggesting hypoglycemia could contribute to increased mortality, especially in diabetic patients. In another study, a pooled analysis of over 4,200 patients from various myocardial infarction intervention stud-

ies, death occurred in 4.6% of the patients with hypoglycemia versus 1% of those who were considered euglycemic (81–199 mg/dl) (41). In contrast, a subanalysis of the DIGAMI 2 data did not show hypoglycemia to be an independent risk factor for future morbidity or mortality in patients with type 2 diabetes and myocardial infarction (42).

Thus, the role of hypoglycemia in cardiovascular mortality in the inpatient setting is still controversial. Much of the variability in results is due to the different protocols used, differences in definition of hypoglycemia, as well as methodology of its detection and report, presence or absence of safeguards against hypoglycemia in the protocols, local training level of the personnel administering the protocols, and selected patient population. Hence, carefully constructed clinical trails to research this question are required. However, it is prudent to conclude from the available data that severe hypoglycemia should be avoided as much as possible in the inpatient setting.

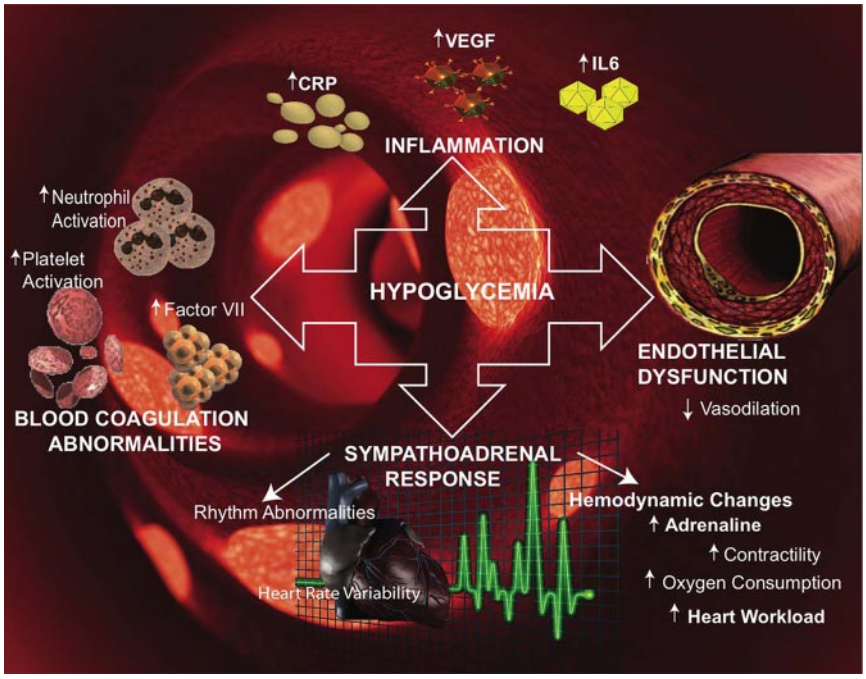

Figure 1—*Mechanisms by which hypoglycemia may affect cardiovascular events. Hypoglycemic events may trigger inflammation by inducing the release of C-reactive protein (CRP), IL-6, and vascular endothelial growth factor (VEGF). Hypoglycemia also induces increased platelet and neutrophil activation. The sympathoadrenal response during hypoglycemia increases adrenaline secretion and may induce arrhythmias and increase cardiac workload. Underlying endothelial dysfunction leading to decreased vasodilation may also contribute to cardiovascular risk.*

MECHANISMS BY WHICH HYPOGLYCEMIA MAY AFFECT CARDIOVASCULAR EVENTS

— Hypoglycemia induces several counterregulatory responses. They include a decrease in pancreatic β-cell insulin secretion, an increase in pancreatic α-cell glucagon secretion, an increased sympathoadrenal response with acute plasma increase in adrenaline and norepinephrine (in addition to its elevated tissue turnover), as well as an increased secretion of ACTH/glucocorticoids. Besides these classical responses, there are several indirect changes induced by hypoglycemia that affect inflammatory cytokine secretion, endothelial function, coagulation, and fibrinolysis. All of these responses have potential adverse effects on cardiovascular morbidity and mortality and will be discussed in this section (Fig. 1).

THE SYMPATHOADRENAL RESPONSE

— Hypoglycemia stimulates the release of catecholamines, which have profound effects on the myocardium and blood vessels. Catecholamines increase myocardial contractility, myocardial workload, and cardiac output (Fig. 1). These effects can induce ischemia in the myocardium in patients with coronary vessel disease (3). The greater oxygen demand is not met because of the rigid vessels, but also because of endothelial dysfunction with failure to vasodilate (Fig. 1).

Several studies have shown that hypoglycemia is associated with a significant lengthening of the corrected QT interval (QT_C) in subjects with and without diabetes (10,24). Other electrocardiographic abnormalities observed during hypoglycemia include a decrease in PR interval and moderate ST segment depressions (10). These changes are likely seen because of increased catecholamine release during hypoglycemia, and QT_C prolongation in particular could lead to a high risk of ventricular tachycardia and sudden death (43). These changes can be prevented or reversed by β blockade (43).

A few studies suggest that hyperinsulinemia and increased secretion of catecholamines may lead to hypokalemia during hypoglycemia, thus potentiating cardiac repolarization abnormalities. These effects can be reversed by β blockade and potassium replacement (43).

Cardiovascular autonomic neuropathy or impairment is associated with increased mortality. Effects of antecedent hypoglycemia on cardiac autonomic regulation may contribute to the occurrence of adverse cardiac events (44). Abnormalities in high-frequency and low-frequency heart rate variability have been associated with hypoglycemia and increases catecholamine release (45). However, other studies did not find any associations between heart rate variability, hypoglycemia, and increased catecholamine release (10,46).

INFLAMMATION, COAGULATION, AND ENDOTHELIAL DYSFUNCTION DURING HYPOGLYCEMIA

— Inflammation has been associated with cardiovascular disease and diabetes. Several inflammatory markers including C-reactive protein, interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)-α, and endothelin-1 have been shown to be increased during hypoglycemia (47,48). This increase in inflammatory cytokines could result in endothelial injury and abnormalities in coagulation, resulting in increased risk for cardiovascular events (Fig. 1). Certain growth factor levels such as vascular endothelial growth factor are also increased locally and in circulation after an episode of hypoglycemia (49). Furthermore, some cytokines such as IL-1 have been shown to increase the severity of hypoglycemia, thus perpetuating a positive feedback cycle (50).

Hypoglycemia induces abnormalities in platelet function and activation of the fibrinolytic system (51,52). Increased epinephrine levels lead to an increase in platelet activation, leukocyte mobilization, and blood coagulability (52). Many of these changes can be reversed by α or β blockade (52).

Recent studies suggest that endothelial function may be compromised during acute hypoglycemia. Vessel wall stiffness was found to be increased during hypoglycemia in patients with type 1 diabetes of longer duration than those with a shorter duration of diabetes (53). Thus, hypoglycemia may increase the risk of cardiovascular events, especially in a subset of patients with longer duration of diabetes. As discussed before, this has been suggested as a possible explanation for the results of ACCORD and VADT.

Inflammation, blood component, and functional abnormalities and endothelial dysfunction are closely interdependent. These abnormalities could potentially be aggravating factors that contribute to increased cardiovascular risk with severe hypoglycemia, especially when applied to the subset of patients with preexisting cardiovascular disease, longer duration of diabetes, and severe autonomic neuropathy (Fig. 1). However, most of these studies are short-duration acute observations and the long-term effects of hypoglycemia on inflammation, coagulation, and endothelial dysfunction are largely unknown and need to be studied.

CONCLUSIONS — The review of the literature and results from large randomized trials suggest that severe hypoglycemia is common during intensive therapy in type 1 and type 2 diabetes. This is true in the outpatient setting as well as the inpatient setting. Although smaller observational and epidemiological studies suggest an association between hypoglycemia and cardiovascular events, there is currently no evidence for causality. Larger clinical trials looking specifically at this question are required. The mechanisms that might be involved also need to be determined further. Our challenge in these patients is to lower blood glucose to near-normal values to lower the risk for long-term complications, but at the same time minimize hypoglycemia- and hypoglycemia-associated morbidity and mortality.

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