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Hypoglycemia among Patients with Type 2 Diabetes: Epidemiology, Risk Factors, and Prevention Strategies

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Abstract

Purpose of the review: Hypoglycemia is the most common and often treatment-limiting serious adverse effect of diabetes therapy. Despite being potentially preventable, hypoglycemia in type 2 diabetes incurs substantial personal and societal burden. We review the epidemiology of

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Conflict of Interest

Richard Silbert, Alejandro Salcido-Montenegro, Rene Rodriguez-Gutierrez, and Abdulrahman Katabi declare that they have no conflict of interest.

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hypoglycemia in type 2 diabetes, discuss key risk factors, and introduce potential prevention strategies.

Recent findings: Reported rates of hypoglycemia in type 2 diabetes vary widely as there is marked heterogeneity in how hypoglycemia is defined, measured, and reported. In randomized controlled trials, rates of severe hypoglycemia ranged from 0.7 to 12 per 100 person-years. In observational studies, hospitalizations or emergency department visits for hypoglycemia were experienced by 0.2 (patients treated without insulin or sulfonylurea) to 2.0 per 100 person-years (insulin- or sulfonylurea-users). Patient-reported hypoglycemia is much more common. Over the course of 6 months, 1-4% non-insulin users reported need for medical attention for hypoglycemia; 1-17%, need for any assistance; and 46-58%, any hypoglycemia symptoms. Similarly, over a 12-months period, 4-17% of insulin-treated patients reported needing assistance and 37-64% experienced any hypoglycemic symptoms. Hypoglycemia is most common among older patients with multiple or advanced comorbidities, patients with long diabetes duration, or patients with a prior history of hypoglycemia. Insulin and sulfonylurea use, food insecurity, and fasting also increase hypoglycemia risk. Clinical decision support tools may help identify at-risk patients. Prospective trials of efforts to reduce hypoglycemia risk are needed, and there is emerging evidence supporting multidisciplinary interventions including treatment deintensification, diabetes self-management, and social support.

Summary: Hypoglycemia among patients with type 2 diabetes is common. Patient-centered multidisciplinary care may help proactively identify at-risk patients and address the multiplicity of factors contributing to hypoglycemia occurrence.

Keywords

Type 2 diabetes mellitus; hypoglycemia; epidemiology; patient-reported outcome; patient-centered care

Introduction

Diabetes mellitus is one of the most common and increasing chronic health conditions in the U.S. and around the world, affecting an estimated 30.2 million (12.2%) U.S. adults [1] and 422 million (8.4%) adults worldwide.[2, 3] Most, approximately 95%, have type 2 diabetes. [1] Diabetes is a major cause of blindness, kidney failure, heart attacks, strokes, and lower extremity amputations and is the seventh leading cause of death in the U.S.[1] To reduce these risks, diabetes management has prioritized lowering blood glucose levels through lifestyle modifications and glucose-lowering medications. In the U.S., 83% of the 23 million adults who have been diagnosed with diabetes (9.3% of the total U.S. adult population) are treated with glucose-lowering medications [1]. However, glucose-lowering pharmacotherapy can lead to iatrogenic hypoglycemia, the most common and often treatment-limiting adverse effect of diabetes therapy [4]. While commonly accepted by patients and their healthcare providers as an inevitable consequence of preventing long-term diabetes complications, hypoglycemia is increasingly recognized an important and potentially preventable cause of morbidity, mortality, high costs, diminished productivity, and impaired quality of life. [5–14]

Real-world data on hypoglycemia rates and risk factors are necessary to inform patients and healthcare providers about the benefits and potential harms of glucose-lowering therapies, facilitate shared decision making, and guide clinical practice. In this review, we discuss the epidemiology of hypoglycemia among adults with type 2 diabetes as revealed by studies conducted in diverse clinical settings and patient populations. We focus specifically on type 2 diabetes because the risk of hypoglycemia in this population is more heterogeneous, treatment-dependent, and ultimately less inevitable than in type 1 diabetes. We conclude by offering insights into some of the risk factors for hypoglycemia and introducing potential prevention strategies.

Defining Hypoglycemia

An important barrier to quantifying and understanding the burden of hypoglycemia is the marked heterogeneity in how it is defined, documented, and ascertained. Since 2005, the American Diabetes Association (ADA) has defined *confirmed hypoglycemia* as symptomatic or asymptomatic blood glucose ≤ 70 mg/dL (3.9 mmol/L), *probable hypoglycemia* as symptoms typical of hypoglycemia in the absence of blood glucose measurements, and *relative hypoglycemia* as typical symptoms accompanied by blood glucose >70 mg/dL (3.9 mmol/L).[15] *Severe hypoglycemia* was defined as hypoglycemia requiring assistance of another person for management and symptom recovery after treatment.[15] In 2013, the ADA began to explicitly recommend that providers routinely ask at-risk patients about symptomatic and asymptomatic hypoglycemia,[16] thereby acknowledging the importance of patient-reported events. In 2017, the ADA reclassified blood glucose ≤ 70 mg/dL (3.9 mmol/L) as a *hypoglycemia alert value* warranting treatment with fast-acting carbohydrate and adjustment of glucose-lowering therapy; added the category of *clinically significant hypoglycemia* with blood glucose <54 mg/dL (3.0 mmol/L); and reaffirmed *severe hypoglycemia* as the presence of severe cognitive impairment requiring external assistance for recovery irrespective of the glucose level.[17, 18] However, these definitions are difficult to operationalize in population-based and clinical research. Most hypoglycemic events occur outside the confines of the healthcare system [19–21] and we lack efficient mechanisms to detect and document such events. Indeed, while low blood glucose values are captured by self-monitoring of blood glucose and continuous glucose monitors as part of routine or symptom-responsive testing, this data is not routinely incorporated into the electronic health record. As a result, hypoglycemic events occurring in the real-world setting and outside of prospectively defined research studies or registries cannot be easily or consistently detected.

Research studies generally focus on either *documented* hypoglycemia (confirmed by a laboratory result, a patient-measured glucose value that is directly visible to the research or clinical team, or a clinical encounter with the diagnosis of hypoglycemia) or *patient-reported* hypoglycemia (reported by the patient without explicit confirmation by laboratory data). Often, hypoglycemia is reported without a clear definition of how it was measured or defined. The type of hypoglycemia reported is typically contingent on study design and data source. Cross-sectional (e.g. survey or interview) studies commonly assess patient-reported events, whereas retrospective studies using administrative or electronic health record data focus on healthcare utilization events with the diagnosis codes of hypoglycemia. While there

are validated claims-based algorithms to identify hypoglycemic encounters using ICD-9[22] and ICD-10[23] codes, studies vary widely in their choice of diagnosis codes and types of encounters (e.g. ambulatory visits, emergency department visits, hospitalizations) used to capture events. Some retrospective and many prospective studies also report hypoglycemic events confirmed by laboratory results, which can be patient-reported or documented in the electronic health record, with qualifying glucose values ranging between 36 mg/dL (2.0 mmol/L) and 70 mg/dL (3.9 mmol/L).

All of these approaches to identifying hypoglycemic events have limitations. Self-report of hypoglycemia is affected by accuracy of patient recall, which can be poor, particularly for non-severe events.[24] It is further contingent on the patient's ability to recognize hypoglycemia when it occurs, which is limited by impaired hypoglycemia awareness, and to correctly differentiate them from symptoms unrelated to hypoglycemia. On the other hand, exclusive reliance on documented low blood glucose values will fail to identify events during which patients did not, or could not, measure their blood glucose. Furthermore, approximately 95% of hypoglycemic events are managed outside the healthcare system, either by the patient, caregivers, or emergency medical services.[19–21] These events do not precipitate a clinical encounter or billing claim and as are therefore missed by methods that rely on administrative or electronic health record data. The probability that a hypoglycemic event is brought to medical attention is confounded by multiple factors including patient access to healthcare, availability of resources (e.g. food, medications, and third party assistance) to manage hypoglycemia, and the ability to recognize and effectively treat hypoglycemic events when they occur. For example, in a study of ambulance calls for hypoglycemia, 13.5% of patients with hypoglycemia (blood glucose <60 mg/dL [3.3 mmol/L]) were managed on the scene without transport to the emergency department.[25] Patients brought to the emergency department were more likely to be older, residents of skilled nursing or assisted living facilities, or have altered consciousness or weakness (both potential signs of frailty).[25] Thus, all reports of hypoglycemia need to be considered in the context of the methodology used to identify and measure these events.

Frequency of Hypoglycemia in Randomized Controlled Trials

Severe hypoglycemia occurred rarely in the two landmark randomized controlled trials conducted among patients with newly diagnosed type 2 diabetes or prediabetes. The UK Prospective Diabetes Study (UKPDS) of intensive glucose-lowering therapy in type 2 diabetes enrolled adults with newly diagnosed type 2 diabetes who had no significant microvascular or macrovascular disease between 1977 and 1991. Participants were treated with metformin, sulfonylurea, or insulin to maintain fasting plasma glucose <108 mg/dL (6 mmol/L), or received standard treatment of diet alone as long as fasting plasma glucose remained <270 mg/dL (15 mmol/L) and participants were asymptomatic.[26, 27] Severe hypoglycemia, defined by need for third party assistance, occurred each year, on average, in 0.1/100 patients treated with diet, 0.4-0.6/100 of patients treated with sulfonylurea, 2.3/100 of patients treated with insulin.[27] Non-severe hypoglycemia was more common, with at least one hypoglycemic event per year experienced by 0.8/100 persons treated with diet, 1.7/100 persons treated with metformin, 7.9/100 persons treated with sulfonylurea, 21.2/100 persons treated with basal insulin, and 32.6/100 persons treated with basal plus prandial

insulin.[28] More recently, the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial compared intensive glucose-lowering therapy with insulin glargine (targeting fasting plasma glucose ≤ 95 mg/dL [5.3 mmol/L]) vs. standard treatment among older patients with cardiovascular disease risk factors and either prediabetes or early type 2 diabetes.[29] The incidence rates of severe hypoglycemia requiring third party assistance were 1.00/100 person-years in the insulin glargine group and 0.31/100 person-years in the standard treatment group.[29]

The paradigm of type 2 diabetes management began to shift a decade ago after three large randomized controlled trials of intensive glycemic control conducted among adults with long-standing type 2 diabetes at high cardiovascular disease risk did not demonstrate meaningful improvements in cardiovascular events or mortality, yet had much higher rates of hypoglycemia than both UKPDS and ORIGIN trials.[30–33] In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, intensive treatment also resulted in higher cardiovascular and all-cause mortality,[31] thereby raising awareness of potential risks associated with intensive glucose-lowering therapy, polypharmacy, and overtreatment. These trials sought to lower HbA_{1c} much more aggressively than either UKPDS or ORIGIN, with the intensive treatment arms targeting HbA_{1c} levels below 6% [31, 32] or 6.5%, [30] often using multiple glucose-lowering medications. As a result, intensive treatment more than doubled the risk of hypoglycemia compared to standard treatment.[30–32] While hypoglycemia itself was not the immediate cause of excess death in these trials, it was associated with a 2-3-fold increase in major macrovascular and microvascular events and all-cause mortality irrespective of the treatment arm.[5, 8]

The absolute rates of severe hypoglycemia observed in these trials varied widely, demonstrating how much hypoglycemia risk is contingent on patient characteristics, treatment modality, and approach to ascertainment and monitoring during the trial. In the intensive vs. standard treatment arms, rates of severe hypoglycemia were 0.7 vs. 0.4/100 patient-years in the Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation (ADVANCE) trial (defined by symptoms or blood glucose <50 mg/dL [2.8 mmol/L] resulting in transient central nervous system dysfunction and need for any third party assistance); [30] 3.1 vs. 1.0/100 patient-years in ACCORD (defined by requiring medical assistance); [31] and 12 vs. 4/100 patient-years in the Veterans Affairs Diabetes Trial (VADT; defined by impaired or complete loss of consciousness). [32] Non-severe hypoglycemia was much more common with 120 vs. 90 events/100 patient-years in ADVANCE, [30] while rates of any hypoglycemia in VADT were 1,566 vs. 432/100 patient-years, in the intensive vs. standard treatment arms, respectively. [32]

More recent large randomized controlled trials of glucose-lowering therapies have focused primarily on the cardiovascular safety of newly approved glucose-lowering medications rather than intensive glycemic control. These trials include EMPA-REG OUTCOME (empagliflozin), [34] CANVAS (canagliflozin), [35] LEADER (liraglutide), [36] SAVOR-TIMI 53 (saxagliptin), [37] TECOS (sitagliptin), [38] EXAMINE (alogliptin), [39] ELIXA (lixisenatide), [40] SUSTAIN-6 (semaglutide), [41] and DEVOTE (insulin degludec). [42] Most patients had baseline HbA_{1c} above 8% (except TECOS and ELIXA, where baseline HbA_{1c} was 7.2% [38] and 7.6%, [40] respectively) and patients were treated to “standard”

HbA_{1c} targets in all treatment arms; differences in HbA_{1c} levels achieved with study drugs vs. placebo were less than 0.5%. Hypoglycemia was infrequent in these trials, though there was variability in how hypoglycemia was reported (e.g. the percent of patients with at least one hypoglycemic event during the study period vs. annualized event rates). Severe hypoglycemia requiring third-party assistance occurred in 1.3% of empagliflozin-treated patients (vs. 1.5% in placebo group; median 3.1 years of observation), [34] 2.4% of liraglutide-treated patients (vs. 3.3% in placebo group; median 3.8 years of observation), [36] 2.1% of saxagliptin-treated patients (vs. 1.7% in placebo group; median 2.1 years of observation), [37] and 0.7% of alogliptin-treated patients (vs. 0.6% in placebo group; median 1.5 years of observation).[39] In the TECOS trial, severe hypoglycemia occurred at the rate of 0.8/100 person-years in the sitagliptin group and 0.7/100 person-years in the placebo group.[38] Non-severe hypoglycemia with blood glucose ≥ 54 mg/dL (3.0 mmol/L) occurred in 14.2% of saxagliptin-treated patients (vs. 12.5% in placebo group) [37] and <70 mg/dL (3.9 mmol/L) in 27.9% of empagliflozin-treated patients (vs. 27.8% in placebo group).[34] Any hypoglycemia occurred in 6.7% of alogliptin-treated patients (vs. 6.5% in placebo group) [39] and 21.7%-23.1% of semaglutide-treated patients (vs. 21-21.5% in placebo group; median 2.1 years of observation).[41] In the CANVAS trial, rates of any hypoglycemia were 5.0/100 person-years in the canagliflozin group and 4.6/100 person-years in the placebo group.[35] Finally, in the DEVOTE trial (the only cardiovascular outcome trial of an insulin agent), rates of severe hypoglycemia were 3.7/100 person-years in the insulin degludec group and 6.3/100 person-years in the insulin glargine group.[42]

Results from trials may not immediately generalize to real-world practice. Large, randomized trials often select motivated patients who are adherent to their recommended treatments, are less likely to experience socioeconomic barriers to care, are closely monitored, and may have their treatment regimens promptly adjusted in the event of adverse events. None of the studies discussed above included patients with history of severe hypoglycemia, poor health status, or with major non-cardiovascular comorbidities. As a result, the rates and nature of hypoglycemia reported in trials likely differ substantially from real-world practice.[43]

Frequency of Hypoglycemia in Real-World Studies

Iatrogenic hypoglycemia is one of the most common adverse drug events requiring emergency department care or hospitalization.[44] The Centers for Disease Control and Prevention estimates that there were 245,000 emergency department visits for hypoglycemia in 2014, or 1.12 visits/100 person-years, exceeding the number of hyperglycemic crises managed in the emergency department (0.95 events/100 person-years).[1] Between 2007 and 2009, insulin and oral glucose-lowering medications were implicated in nearly 14% and 10.7% of emergent hospitalizations among diabetes patients ≥ 65 years, respectively,[44] though hypoglycemia was not necessarily the primary reason for admission. In a claims-based study of commercially-insured and Medicare Advantage beneficiaries across the U.S., hypoglycemia was the primary reason for hospitalization among 1.2% of 594,146 hospitalized adults with diabetes between 2009 and 2014.[45] However, these estimates, which include patients with type 1 and type 2 diabetes, likely represent a small fraction of

hypoglycemic events, as hypoglycemia rarely necessitates emergency care and even less often culminates in hospital admission.[19–21]

When patients were asked about their experience of severe hypoglycemia, the rate of self-reported events varied widely. Multiple studies have assessed the rates of self-reported hypoglycemia, most often during the preceding 6-months period, among non-insulin treated patients with type 2 diabetes. Rates of severe hypoglycemia, defined by requiring third party assistance, were highly variable, ranging from 1% (questionnaire completed by 412 patients in Sweden; mean age 69 years, 71% with diabetes duration >7 years, mean HbA_{1c} 6.3%, all on metformin/sulfonylurea combination therapy),[46] 9% (questionnaire completed by 392 patients in Germany; mean age 62.7 years, 60.3% with diabetes duration >7 years, HbA_{1c} 7.2%, all on metformin/sulfonylurea combination therapy),[47] 12% (questionnaire completed by 2,257 patients in China, Korea, Taiwan, Malaysia, and Thailand; mean age 58.7 years, HbA_{1c} 7.5%, 13.9% on metformin monotherapy and 46% using sulfonylureas), [48] 13% (internet survey completed by 1984 non-insulin-treated patients in the U.S.; mean age 58.1 years, diabetes duration 7.3 years, 50% treated with sulfonylurea),[49] and 17% (postal survey completed by 326 patients with type 2 diabetes in the U.S.; mean age 69.3 years, diabetes duration 15.7 years, HbA_{1c} 7.4%, 66% insulin-treated)[14]. In the same studies, severe hypoglycemia requiring medical assistance was reported by 1%, [46] 6%, [47] 8%, [48] and 4% [49] of respondents. Non-severe events were much more frequent. Mild events, defined by symptoms causing little disruption to patients' activities, were reported by 51%, [47] 58%, [48] and 46% [49] of participants. Similarly, moderate severity events, defined by symptoms causing disruption but self-managed, were reported by 17%, [46] 46%, [47] 22%, [48] and 37%. [49]

Patients treated with insulin have higher self-reported rates of hypoglycemia. Studies conducted in this population commonly asked patients treated with insulin for 1 year about hypoglycemic events in the preceding 12 months. Self-reported severe hypoglycemia, defined by requiring third party assistance, was reported by 4% (interview of 1667 patients in the Netherlands; mean age 67.2 years, diabetes duration 11.5 years, using insulin for 4.6 years), [50] 15% (interview of 215 patients in Scotland; mean age 68 years, HbA_{1c} 8.6%, diabetes duration 13 years, using insulin for 4 years), [51] and 17% (survey completed by 401 patients in Denmark; mean age 66 years, HbA_{1c} 8.3%, diabetes duration 15 years, using insulin for 7 years) [52] of patients. Once again, non-severe hypoglycemic events were more common, reported by 37% [50] and 64% of patients [51] in these studies.

More recently, the InHypo-DM Study of patient-reported hypoglycemia examined hypoglycemia rates among patients treated with insulin and/or insulin secretagogues. An online survey was completed by 458 patients with self-identified type 2 diabetes (mean age 53.4 years, diabetes duration 10.0 years, HbA_{1c} 7.1%) who reported taking insulin (34.7%), insulin secretagogues (47.4%), or both (17.9%); it included questions about non-severe (symptoms of hypoglycemia managed by the patient) and severe (symptoms requiring any third party assistance) hypoglycemic events in the preceding 30 days and 12 months, respectively. Non-severe hypoglycemia was reported by 54% of patients (12.1 events per person year) and severe hypoglycemia was reported by 38% (2.5 events per person year). [53]

Reliability of self-reported measures of hypoglycemia is contingent on confidence in patients' hypoglycemia awareness, willingness to report events, and ability to differentiate true hypoglycemia from pseudo-hypoglycemia. In a study of 6,273 insulin-treated adults with type 2 diabetes (median age 58 years, diabetes duration 12 years, HbA_{1c} 8.6%, using insulin for 5 years) 48.1% of patients blood glucose <3.1 mmol/L (56 mg/dL) over a 4-week period (1.6 events/patient/month). However, analysis of continuous glucose monitor data revealed that in fact 95.3% had experienced episodes of hypoglycemia (2.4 events/patient/month). Furthermore, just 1.7% were hospitalized for hypoglycemia during the 4-week period (0.026 events/patient/month),[54] reinforcing the small fraction of hypoglycemic events captured by hospitalization encounters.

Continuous glucose monitoring detects substantially more hypoglycemic events than identified and reported by patients. This was demonstrated in the continuous glucose monitor sub-study of the Treating to Target in Type 2 Diabetes Trial (4-T), where 106 patients with insulin-dependent type 2 diabetes (mean age 61.8 years, diabetes duration 8.9 years, HbA_{1c} 8.5%) underwent continuous glucose monitoring. During the 3-day study period, 10% reported hypoglycemia with glucometer glucose <3.1 mmol/L (56 mg/dL), yet continuous glucose monitor data showed that 42% had glucose <3.0 mmol/L (54 mg/dL) and 18% had glucose <2.2 mmol/L (40 mg/dL).[55] In another study of 108 patients with type 2 diabetes (both insulin and non-insulin treated), continuous glucose monitoring detected glucose <70 mg/dL [3.9 mmol/L] in 49.1% of participants over 5 days (1.74 episodes/patient per 5 days); 75% of those with hypoglycemia had at least one asymptomatic event.[56] Despite its incompleteness, glucometer data is still informative, particularly as continuous glucose monitors are used infrequently by patients with type 2 diabetes. In a study of 165 insulin-treated adults with type 2 diabetes (mean age 67, diabetes duration 18 years, HbA_{1c} 7.6%) an electronic diabetes management system was retrospectively used to capture patients' home glucometer data at the time of clinical encounters. Over a 3-months period, 19% of patients had episodes with glucose <45 mg/dL (2.5 mmol/L) and 82% with glucose <70 mg/dL (3.9 mmol/L), corresponding to annualized rates of 2.9 and 37 events/person-year, respectively.[57]

Clinicians are often unaware of their patients' hypoglycemic events, potentially due to patient reluctance to report events and lack of direct questioning about hypoglycemia in between and during clinical encounters. Patients may underreport report hypoglycemia due to fear of repercussions such as loss of driving privileges.[58] In a Japanese web survey of 230 insulin-treated adults with type 2 diabetes (mean age 55 years, diabetes duration 15 years), 90% of respondents reported at least one episode of non-severe daytime hypoglycemia and 34% reported at least one episode of non-severe nighttime hypoglycemia over the prior 3 months. However, only 60% of patients experiencing daytime hypoglycemia and 42% experiencing nighttime hypoglycemia had notified their healthcare provider.[59] In another online survey of 3,042 insulin-adults with type 2 diabetes (mean age 61 years, diabetes duration 11 years, using insulin for 5 years) in the U.S., Canada, Japan, Germany, UK, and Denmark, 36% endorsed non-severe (i.e. self-treated) hypoglycemia during the preceding 30 days (3.1 events/person/30 days), but only 2% of those with hypoglycemia were seen by their healthcare provider for it, 1% emailed their healthcare provider, 1% saw a diabetes specialist, and fewer than 1% were evaluated in the emergency department.[60]

This has important research and clinical implications, because if patients do not report or discuss their hypoglycemic events with their healthcare providers, precipitating factors cannot be identified, treatment is unlikely to be modified, and future hypoglycemic events are less likely to be prevented.

Hypoglycemic events requiring emergency department care or hospitalization are, by definition, most severe, as they represent the need for the highest level of medical assistance. In a UK study of 17,604 sulfonylurea-treated patients (mean age 68 years, diabetes duration 1.6 years), there were 0.42/100 person-years hospitalizations for hypoglycemia.[61] In a more recent U.S. study of 206,435 adults with type 2 diabetes (mean age 64; 35% treated with sulfonylurea and 20% treated with insulin), the rate of emergency department visits or hospitalizations for hypoglycemia was 0.49/100 person-years.[62] And in a German study of 29,485 sulfonylurea-treated patients (median age 71 years, diabetes duration 8.2 years), which defined severe hypoglycemia more broadly as requiring external help, causing altered mental status or seizure, and/or requiring hospitalization, there were 3.9 severe hypoglycemic events/100 patient-years.[63] In this study, severe hypoglycemia rates by treatment regimen were, per 100 patient-years, 6.7 (sulfonylurea plus insulin), 4.9 (sulfonylurea plus insulin plus other non-insulin drug), 3.1 (sulfonylurea plus other non-insulin drug) and 3.8 (sulfonylurea only).[63]

Despite the recent availability and use of new classes of glucose-lowering medications that have a lower risk of hypoglycemia (e.g. glucagon-like peptide 1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium-glucose transport protein 2 (SGLT2) inhibitors),[64] rates of severe hypoglycemia do not appear to be decreasing. In a claims-based study of 1.66 million U.S. commercially-insured and Medicare Advantage beneficiaries with type 2 diabetes, emergency department visits and hospitalizations for hypoglycemia remained stable at 1.3 events/100 person-years between 2006 and 2013.[65] There was, however, marked variation in hypoglycemia rate as a function of patient age, medications used, and comorbidity status. In 2016, patients aged ≥75 years experienced 2.3 events/100 person-years, compared to 1.3 events/100 person-years among patients aged 65-74 years, and 0.9 events/100 person-years among patients aged 45-64 years and 18-44 years. Patients with ≥2 comorbidities experienced 3.5 events/100 person-years, while patients with one and no comorbid conditions had 1.1 and 0.4 events/100 person-years, respectively. Patients treated with insulin or sulfonylurea experienced 2.0 events/100 person-years, compared to 0.2 events/100 person-years among patients treated with other glucose-lowering drugs. [65] Comparable rates were observed in a longitudinal study conducted in a different patient population in the U.S., though that study included patients with both type 1 and type 2 diabetes.[66]

There is limited data regarding diabetes management and hypoglycemia among people living in long-term care facilities, despite their high clinical complexity and, presumably, hypoglycemia risk. Approximately one third of nursing home residents in the U.S. have diabetes[67]. In a cohort study of 200 patients ≥65 years (mean age 80 years) in two U.S. skilled nursing facilities, the majority of patients were treated with hypoglycemia-prone drugs: 71% were treated with insulin, 15.5% with insulin and non-insulin drugs, and 13.5% with only non-insulin drugs; 78% of the non-insulin drugs were sulfonylureas. During up to

30 days of observation, 38% of patients in the study experienced events with glucose <70 mg/dL (3.9 mmol/L; 3.4% of patient-days) and 3.5% with glucose <40 mg/dL (2.2 mmol/L; 0.1% of patient-days).[68] Hypoglycemia rates were similar among patients treated with insulin and non-insulin medications. Two other studies that focused on nursing home residents in the U.S. [69] and India [70] demonstrated comparable rates of hypoglycemia.

Risk Factors for Hypoglycemia

Precipitating events for hypoglycemia are rarely ascertained, documented, and reported in the literature. In a UK online survey of 1,329 adults with type 2 diabetes (mean age 58.8 years, diabetes duration 9.6 years, HbA1c 7.3%, 76.2% treated only with non-insulin medications) most hypoglycemic events were ascribed to dietary factors: delayed meals (29%), irregular or inadequate carbohydrates (25%), or skipped meals or snacks (20%).[71] Other commonly cited factors were excessive physical activity (16%) and stress (13%). Medication misadventures were implicated less often; 10% of patients blamed a miscalculated insulin dose and 5% a newly started glucose-lowering medication. [71] Similar factors were cited by participants in the ACCORD trial, including delayed or missed meals (31% of patients in the intensive treatment arm and 44% of patients in the standard treatment arm), eating fewer carbohydrates than usual (26% and 25%, respectively), more or unplanned exercise (15% and 12%, respectively), use of more insulin than prescribed or usually administered (5% and 7%, respectively), and illness (4% and 3%, respectively).[72] In the SAVOR-TIMI 53 trial of saxagliptin therapy, there was an identifiable precipitant in 47.3% of hypoglycemic events in the saxagliptin arm and 48.4% in the placebo arm, including illness (2.5 % and 3.1%, respectively), overdose of hypoglycemic agent (9.8% and 7.8%, respectively), and missed meals (50.7% and 48.7%, respectively).[73]

The risk of hypoglycemia in type 2 diabetes is influenced by many patient- and treatment-related factors (Figure 1). One of the strongest predictors of future hypoglycemia is history of prior hypoglycemia, both severe and non-severe.[74, 45, 62, 75] A large U.S. claims-based case control study of adults with type 2 diabetes found that an emergency department visit for hypoglycemia within prior 180 days increased the risk of subsequent hospitalization for hypoglycemia by 9.5-fold.[76] In a U.S. claims-based cohort study, history of an ambulatory visit for hypoglycemia increased the risk of subsequent hypoglycemia requiring emergency department or hospital care by 3-fold.[77] Similarly, in the prospective Fremantle Diabetes Study, the risk of ambulance use, emergency department care, or hospitalization for hypoglycemia during 6.4 years of follow-up increased more than 6-fold with prior history of severe hypoglycemic events.[78]

A strong and potentially modifiable risk factor for hypoglycemia is the choice of glucoselowering therapy, with insulin or insulin secretagogues (e.g. sulfonylureas and meglitinides) posing the highest risk.[44, 65, 66, 79, 74, 80] In the ORIGIN trial, the risk of severe hypoglycemia increased 2-fold with sulfonylureas and 4.5-fold with insulin.[81] In observational studies, the risk of severe hypoglycemia was increased 2- to 3-fold with sulfonylureas [76–78] and 3- to 4-fold with insulin [77, 78]. The risk of hypoglycemia is highest with prolonged insulin use, as demonstrated by a UK study that prospectively quantified rates of hypoglycemia (glucose <54 mg/dL [3.0 mmol/L]) in sulfonylurea- and

insulin-treated adults over a 9-12 months observation period.[82] Rates of severe hypoglycemia requiring third party assistance were 10/100 person-years among sulfonylurea-treated patients (mean age 60.8 years, diabetes duration 6 years, HbA_{1c} 7.5%) and patients treated with insulin for <2 years (mean age 59.7 years, diabetes duration 7 years, HbA_{1c} 7.4%), and 70/100 person-years among patients treated with insulin >5 years (mean age 62.4 years, diabetes duration 14.2 years, HbA_{1c} 7.7%). Non-severe events were more common: 192/100 person-years, 408/100 person-years, and 1020/100 person-years among patients treated with sulfonylurea, insulin <2 years, and insulin >5 years, respectively. At the same time, 7-day CGM detected interstitial glucose <40 mg/dL (2.2 mmol/L) in 14% of sulfonylurea-treated patients (0.25 event/person/week), 13% of patients treated with insulin for <2 years (0.29 event/person/week), and 26% of patients treated with insulin for >5 years (0.73 event/person/week)[82]. In the Fremantle Diabetes Study, the risk of severe hypoglycemia requiring ambulance, emergency department, and hospital care increased by 42% with each additional year of insulin therapy.[78] Still, glucose-lowering polypharmacy in high risk patients (e.g. the elderly or those with multiple comorbidities) can lead to hypoglycemia even without the use of sulfonylurea or insulin.[5, 77, 78, 83]

Importantly, while sulfonylurea and insulin medications do carry the highest risk of hypoglycemia, they can be used safely and should not be avoided if clinically necessary. Indeed, patients may be limited to using insulin or sulfonylurea drugs for a variety of clinical and non-clinical reasons, including intolerance or contraindication to other medications or cost considerations. Metformin is the only generic medication at low risk for hypoglycemia that is part of the World Health Organization list of essential medicines and available through low cost generic drug programs in the U.S.[84], together with human insulin and sulfonylureas. If patients do not tolerate metformin, have contraindications for its use, or metformin monotherapy is not sufficient, sulfonylureas and insulin may be the only affordable treatment options.

Other commonly cited risk factors for hypoglycemia in type 2 diabetes include older age, [5, 57, 65, 66, 79, 83, 85, 86] longer duration of diabetes, frailty, and multimorbidity. The chronic health conditions most often implicated in increasing hypoglycemia risk are kidney disease,[5, 66, 74, 76, 78, 85] cognitive impairment, [81, 87–89] cardiovascular disease,[66, 77] depression,[66, 79] and heart failure.[66, 77, 79] Post-hoc analyses of both ACCORD and ADVANCE found a direct association between hypoglycemia risk and rising serum creatinine.[5, 85] Furthermore, in the ADVANCE trial, history of microvascular disease was the strongest predictor of hypoglycemia (HR 2.62), with greater impact on hypoglycemia than allocation to the intensive treatment arm (HR 1.86) or use of 2 glucose-lowering medications (HR 1.79)[5]. Impaired hypoglycemia awareness, which affects up to 10% of insulin-treated patients with type 2 diabetes, further increases the risk of hypoglycemia by nearly five-fold.[90]

Social determinants of health also contribute to hypoglycemia risk, including food insecurity,[91–93] socioeconomic deprivation, and poor health literacy.[19] A population-based study in California, which included all adults with diabetes as it could not subset patients by diabetes type, found that hospitalizations for hypoglycemia were much more common among lower income adults (0.27 events/100 person-years) compared to higher

income adults (0.20 events/100 person-years). Furthermore, lower-income, but not higher-income, adults experienced a 27% increase in hypoglycemia admissions in the last week of the month (period of greater food insecurity and financial hardship) compared to the first.[91] Even among commercially-insured adults, patients with diabetes (once again, not subset by diabetes type) earning less than the median household income had a significantly higher rate of emergency department visits and hospitalizations for hypoglycemia than higher income patients (0.20 events/100 person-years vs. 0.15 events/100 person-years), with greatest probability of events during the last week of the month.[94] There have been no studies of food insecurity exclusively in type 2 diabetes. Several studies also found increased risk of hypoglycemia among racial/ethnic minorities, particularly African Americans,[77, 85, 86, 95, 96] though this may be confounded by differences in access to healthcare, food insecurity, and financial burden –factors that are known to increase hypoglycemia risk yet are poorly ascertained in many research studies.

An often overlooked hypoglycemia risk factor is fasting, whether planned or unplanned. Continuing to take glucose-lowering medications while fasting for medical tests or procedures can lead to hypoglycemia.[97] Patients who observe Ramadan are at increased risk for hypoglycemia while fasting, particularly when treated with insulin or sulfonylurea drugs.[98–100]

The association between HbA_{1c} and hypoglycemia risk is complex, partly because HbA_{1c} reflects the average glycemic control over a 3 month period and does not convey glycemic variability and excursions. Recent studies have suggested that low HbA_{1c} may predict hypoglycemia risk in type 1 but not type 2 diabetes.[101] While hypoglycemia rates were higher among patients with type 2 diabetes achieving low HbA_{1c} targets with intensive glucose-lowering therapy in the ADVANCE,[30] ACCORD,[31] and VADT[32] trials, these episodes may be the result of intensive treatment and polypharmacy rather than low glycemic levels themselves.[5] In a survey of patients with diabetes, the relationship between HbA_{1c} and severe hypoglycemia was U-shaped, and the association became less significant once other key patient- and treatment-related factors were taken into consideration (specifically: patient age, sex, comorbidities, polypharmacy, diabetes medications used, history of prior hypoglycemia).[20] In the UKPDS trial, hypoglycemia was more common at lower HbA_{1c} levels among patients treated with metformin or sulfonylureas, and at higher HbA_{1c} levels among patients treated with insulin.[28] In most studies, however, the risk of hypoglycemia increased progressively with higher, not lower, HbA_{1c}. [5, 78, 85]

Preventing Hypoglycemia

Preventing hypoglycemia is a priority for patients, healthcare providers, and policy makers. [102] Diabetes agents and iatrogenic hypoglycemia are part of the U.S. Department of Health and Human Services Adverse Drug Event Action Plan. These initiatives may provide counterbalance to existing incentives and performance metrics rewarding intensive glycemic control and low HbA_{1c} targets. Incorporation of patient-reported outcomes into diabetes management and use of individualized glycemic targets can further raise awareness about hypoglycemia and align financial incentives with patient safety.[103]

The first step in preventing hypoglycemia is identifying patients at highest risk for these events, engaging them in conversation about contributing and/or exacerbating factors, and identifying strategies to mitigate these risks (Figure 2). Through shared decision-making, patients and clinicians can apply scientific evidence regarding the benefits and risks of glucose-lowering therapy to each patient's unique circumstance, context, and preferences for care.[104] Clinical decision support tools can facilitate this process by integrating a variety of data sources to compute an individualized hypoglycemia risk and alert providers when an intervention may be necessary.[105, 106] Ideally, clinical decision support tools would also guide interventions, signaling need to change or de-escalate glucose-lowering therapy, and/or make appropriate referrals.[107]

Two recently published hypoglycemia prediction models can help identify at-risk patients. [62, 108] Developed and validated in different populations, these models were reliable, accurate, and efficient. The model proposed by Karter and colleagues stratifies patients with type 2 diabetes on the basis of their 12-months risk for hypoglycemia-related utilization (emergency department use, hospitalization) and is predicated on 6 variables: total number of prior hypoglycemia-related emergency department visits or hospitalizations, number of emergency department visits for any cause in the prior year, insulin use, sulfonylurea use, presence of stage 4 or 5 chronic kidney disease, and age ≥ 77 years.[62] Schroeder and colleagues developed two models, a marginally more accurate 16 variable model and a parsimonious 6 variable model, to predict emergency department use or hospitalization for hypoglycemia over 6 months among adults with type 1 or type 2 diabetes. The 6-variable model includes patient age (U-shaped relationship), diabetes type (nearly doubled risk with type 1 diabetes), HbA_{1c} (U-shaped relationship), creatinine clearance (small increase in risk with worse renal function), severe hypoglycemia within the prior year (4-fold higher risk), and insulin use (2.3-fold higher risk).[108]

While clinical practice guidelines recommend raising glycemic targets for patients at high risk for hypoglycemia,[17] this strategy alone may not be sufficient.[109, 110] A more effective approach may be to proactively de-intensify treatment regimens of overtreated patients.[111, 112] Potential overtreatment of adults with type 2 diabetes is common, including among older adults, patients with advanced kidney disease and dementia, and patients with high clinical complexity.[83, 113–115] These patients are at highest risk for hypoglycemia, yet because of their multi-morbidity and limited life expectancy they also derive less benefit from intensive glycemic control. De-escalation of glucose-lowering therapy, simplification of treatment regimens, and preferential use of medications with lower risk of hypoglycemia may moderate their risk of hypoglycemia, reduce polypharmacy and burden of treatment, and improve quality of life.[111, 112]

Indeed, change of glucose-lowering therapy, if clinically and logistically feasible, may be the simplest way to lower hypoglycemia risk. For example, patients with chronic kidney disease are at high risk for hypoglycemia,[5, 66, 74, 76, 78, 85] yet are often treated with insulin or sulfonylureas as both are approved for use with estimated glomerular filtration rate (eGFR) <15 mL/min/1.73m². However, other glucose-lowering medications may also be considered in the setting of renal impairment, which may lower the patients' hypoglycemia risk. Metformin may be used, at reduced doses, as long as eGFR is above 30 mL/min/1.73m².

DPP-4 inhibitors may be used at reduced doses with eGFR <30 mL/min/1.73m² and GLP-1 receptor agonists can be used without dose reduction as long as eGFR is above 15 mL/min/1.73 m² (except for liraglutide and dulaglutide, where there is limited evidence for use at lower eGFR, and lixisenatide, which may be considered even with eGFR 15-29 mL/min/1.73m²). SGLT-2 inhibitors are contraindicated in patients with eGFR<30 mL/min/1.73m² and caution is advised during use in patients with moderate kidney disease (eGFR 30-45 mL/min/1.73m²) due to limited data supporting safety and efficacy in this population.[116] Still, in clinical practice, access to these medications may be limited by financial considerations and formulary restrictions, which would need to be addressed as part of a systems-wide effort to promote safe, effective, and equitable diabetes care.

Engagement and coordination of multi-disciplinary clinical teams may also improve diabetes management and reduce hypoglycemia risk (Figure 2). Patients experiencing or at risk for hypoglycemia may benefit from diabetes self-management education focused on glucose monitoring, medication management, recognition of precipitating events, and treatment of hypoglycemia. Training in hypoglycemia awareness, though studied primarily in patients with type 1 diabetes,[117] may benefit patients with type 2 diabetes and hypoglycemia unawareness. While continuous glucose monitoring can help patients identify asymptomatic or undetected hypoglycemic events, and they are approved for patients with type 2 diabetes on the basis of lowering HbA1c,[118] evidence for hypoglycemia reduction with continuous glucose monitoring in type 2 diabetes (in contrast to type 1 diabetes) is inconsistent.[118–122] Dieticians can help address hypoglycemia related to dietary miscalculations, while mental health professionals can focus on diabetes distress, fear of hypoglycemia, and treatment burden. Patients with complex treatment regimens may benefit from pharmacist engagement to identify safer, simpler, or more affordable treatment options. While pharmacist-led interventions have not been studied in relation to hypoglycemia, there is evidence for improved HbA1c, medication adherence, and access to care[123]. Finally, real-time integration of patient-generated glycemic data and self-reported events into the electronic health record for clinical review, followed by bidirectional flow of information between the clinical setting and the patient's home, may help identify, treat, and ultimately prevent hypoglycemic events. In a pilot study, real-time evaluation of blood glucose data obtained using a connected glucometer by a diabetes educator lowered the probability of hypoglycemia (glucose <70 mg/dL [3.9 mmol/L]) by 18%.[124]

Provider awareness of the patient's situation is also necessary to gauge hypoglycemia risk and identify strategies to reduce it. This includes cultural practices, eating and physical activity habits, and socioeconomic realities. For instance, fasting increases the risk for hypoglycemia during a predefined time period, and proactive focused patient education and treatment modification may reduce this risk ahead of medical tests or procedures [97] and during Ramadan.[125] Community health workers show promise in improving diabetes management in immigrant groups,[126, 127] though their impact on hypoglycemia has not been assessed. Similarly, enhancing financial and social support may help lower hypoglycemia risk in vulnerable patients. In a study of commercially-insured people with diabetes, the end-of-month increase in emergency department visits and hospitalizations for hypoglycemia that was likely driven by food insecurity was lessened by an increase in Supplemental Nutrition Assistance Program benefits,[94] reinforcing access to food as an

important component of diabetes management. Enhancing caregiver support and supervision can also help, particularly if patients need assistance with food preparation, medication administration, and treatment of hypoglycemia before it becomes very severe. Identifying these non-clinical factors, engaging patients and social support networks, and acknowledging the realities of each patient's situation are important aspects of patient-centered diabetes care that need to be evaluated in prospective studies and, if successful, implemented into practice.

CONCLUSIONS

Many patients with type 2 diabetes experience hypoglycemia, increasing their risk of adverse health outcomes including death, high costs, and impaired quality of life. Yet, few events are brought to medical attention or elicited by healthcare providers, which hinders identification of precipitating and contributing causes and, ultimately, prevention of future hypoglycemic events. Understanding, managing, and preventing hypoglycemia is particularly important for patients with type 2 diabetes, whose risk may be lessened through use of safer treatment regimens. Furthermore, evidence demonstrating benefits of intensive glucose-lowering therapy is weaker and less consistent for type 2 diabetes compared to type 1 diabetes, whereas the risk of hypoglycemia is often increased due to older age and higher comorbidity burden.

Prospective clinical trials focused specifically on reducing hypoglycemia among high risk patients with type 2 diabetes are needed. There are several barriers to such trials, including heterogeneity of hypoglycemia risk and risk factors, need for different interventions at varying points in time and contexts, and lack of consensus about how hypoglycemia is defined, measured, and recorded. Both interventional and non-interventional studies should be encouraged to use standard definitions of hypoglycemia and to ascertain/report hypoglycemia in all trials that enroll patients with diabetes. Healthcare providers should ask patients about their experience of hypoglycemia, how this hypoglycemia is detected and managed, and what events predated or precipitated its occurrence. This information, and glycemic data from patient devices and diabetes technologies, can then be incorporated into the electronic health record to facilitate hypoglycemia detection, management, and prevention strategies. Finally, both clinical guidelines and quality/accountability measures need to reflect the importance of hypoglycemia in the management of diabetes and to consider patients' treatment goals and anticipated benefits and harms of treatment.[103]

Patient-centered diabetes care is predicated on identifying and promoting safe and effecting treatment strategies that minimize patient burden, improve quality of life, and reduce risks of both immediate and long-term complications. Addressing hypoglycemia by leveraging advances in diabetes technologies, patient engagement, multi-disciplinary team-based care, and alignment of reimbursement and policy decisions is an essential part of this effort.

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among 917,440 adults with diabetes (not separated by diabetes type) within a large integrated healthcare delivery system in the U.S. between 2005-2011. Annual rates of severe hypoglycemia ranged from 1.4 to 1.6/100 person-years and were higher among older patients, patients treated with insulin, sulfonylurea, and beta-blockers, and patients with chronic kidney disease, heart failure, cardiovascular disease, depression, and higher HbA1c

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Intern Med. 2016 7 1;176(7):969–78. doi: 10.1001/jamainternmed.2016.2275. [PubMed: 27273792] This study quantified the prevalence of diabetes overtreatment among commercially-insured and Medicare Advantage beneficiaries with non-insulin-requiring type 2 diabetes across the U.S. and established the association between overtreatment and severe hypoglycemia. McCoy et al found that 18.7% of clinically complex and 26.5% of non-clinically complex patients were potentially overtreated, which increased the risk-adjusted probability of severe hypoglycemia among clinically complex patients from 1.7% over two years to 3.0%. Non-clinically complex patients were able to tolerate potential overtreatment without significant increase in hypoglycemia risk (1.02% versus 1.30% over two years)

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year, any emergency department visit in past year, severe hypoglycemic event in past year, retinopathy, cardiovascular disease, depression, heart failure, insulin, metformin, number of classes of glucose lowering medications. The simplified model was comprised of patient age, diabetes type, HbA1c, eGFR, history of a hypoglycemic event in the prior year, and insulin use

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Figure 1. Risk factors for hypoglycemia among patients with type 2 diabetes.
 DSME, diabetes self-management education. EHR, electronic health records. HbA_{1c}, hemoglobin A_{1c}. PROs, patient-reported outcomes.

Figure 2. Strategies to reduce hypoglycemia risk among patients with type 2 diabetes. DSME, diabetes self-management education. EHR, electronic health records. HbA_{1c}, hemoglobin A_{1c}. PHR, patient health records. PROs, patient-reported outcomes.