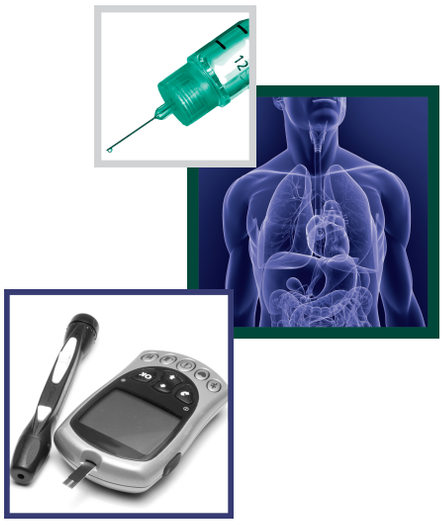
REVIEW

Predicting severe hypoglycemia in the community: a review of recent evidence



Wendy A Davis†

Practice Points

- Severe hypoglycemia is largely preventable.
- Identification of risk factors for severe hypoglycemia should be part of the assessment of diabetic patients taking therapies associated with this complication.
- Significant hypoglycemia may justify less intensive glycemic control, especially in the frail elderly with cognitive impairment or dementia.
- Pregnant women with Type 1 diabetes and a prior history of severe hypoglycemia or hypoglycemia unawareness may require additional monitoring and support so that further episodes are avoided.
- A patient with a low BMI and/or peripheral neuropathy should be considered at risk of severe hypoglycemia.
- A patient with a relatively high HbA1c may have unstable control and an increased risk of severe hypoglycemia.
- Long-term antidepressant use may increase the risk of severe hypoglycemia and should also be considered when planning glycemic management.

SUMMARY The recent literature relating to predictors of severe hypoglycemia in the community is reviewed. Medline and EMBASE databases were searched for English language papers between 2005 and July 2010 using the terms ('severe hypoglyc[a]emia' or 'symptomatic hypoglyc[a]emia') and ('predictor[s]' or 'predict[s]' or 'prediction', 'determinant[s]' or 'determine[s]' or 'marker[s]' or 'factor[s]' or 'indicator[s]'). All studies meeting the inclusion criteria were included. From 186 papers identified, 13 original studies were considered eligible. Another eligible paper became available online during the review process. Of the 14 studies, six were studies of Type 2 diabetes. Two or more of these studies recognized dementia or severe cognitive impairment, higher HbA1c, low BMI and peripheral neuropathy as predictors of severe hypoglycemia in adults with Type 2 diabetes. Renin–angiotensin system-related risk factors independently predicted the frequency of severe hypoglycemia in adults, but not children or adolescents with Type 1 diabetes. An algorithm derived from self-monitoring of blood glucose data predicted imminent severe hypoglycemia in insulin-using diabetic patients.

†University of Western Australia, School of Medicine & Pharmacology, Fremantle Hospital, Fremantle, WA 6160, Australia;
Tel.: +618 9431 3641; Fax: +618 9431 2977; wdavis@meddent.uwa.edu.au

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Diabetes mellitus can be associated with significant morbidity and mortality derived from long-term microvascular and macrovascular complications. The landmark Diabetes Control and Complications Trial (DCCT) in Type 1 diabetes [1] and the UK Prospective Diabetes Study (UKPDS) in Type 2 diabetes [2], and their respective observational poststudy monitoring phases [3,4], have shown that intensive glycemic control can significantly prevent or delay the development and progression of long-term complications. However, intensive glycemic control, particularly with insulin therapy, is associated with an increased incidence of hypoglycemia. Hypoglycemia is an acute complication of diabetes that can have significant clinical impact in terms of mortality, morbidity and quality of life. Hypoglycemia, and the fear of hypoglycemia, are major barriers to the implementation of intensive treatment from both the physician's and patient's perspectives. The cost of severe episodes of hypoglycemia is substantial [5].

Measures to prevent or limit the incidence and effects of hypoglycemia depend on an accurate and detailed knowledge of its determinants [6]. In the DCCT, the number of prior episodes of hypoglycemia was the strongest predictor of the risk of future episodes, followed closely by the current HbA_{1c} value, while males, adolescents and subjects with no residual C-peptide also had a particularly high risk of severe hypoglycemia [7]. The state of awareness of hypoglycemia and autonomic function also predict future risk of severe hypoglycemia [8]. Rewers *et al.* summarized studies of predictors of severe hypoglycemia frequency in children and adolescents in the era after the DCCT [9]. HbA_{1c} (both high and low), higher insulin dose, age (both young and old), male sex, underinsurance and psychiatric disorders were identified as predictors of severe hypoglycemia frequency in prospective studies, as was longer duration of diabetes [9]. A population-based study of 1335 children and adolescents, followed for a mean 4.7 years, confirmed age (younger and older), male sex, longer diabetes duration and lower HbA_{1c} as independent risk factors for frequency of severe hypoglycemia, but added the number of daily insulin injections (independent of insulin dose per unit body weight) and lower socioeconomic status [10]. Two small Scandinavian studies on Type 1 diabetes, one in adults and one in children and adolescents, reported that high serum angiotensin-converting enzyme (ACE) levels were risk factors for higher frequency of severe hypoglycemia [11,12].

A review of hypoglycemia in Type 2 diabetes from 1996 to August 2006 [13] summarized the recognized risk factors. Contributing factors are treatments that increase circulating insulin concentrations (i.e., insulin and its secretagogs) or that augment the effect of blood glucose-lowering therapies, such as renal impairment, impaired counter-regulatory capacity, exercise, irregular meals, alcohol and concurrent medications not used to treat hyperglycemia (e.g., aspirin, allopurinol, nonsteroidal anti-inflammatory drugs, β blockers, warfarin and fibrates). A literature review of, the frequency of and risk factors for, severe hypoglycemia in insulin-treated Type 2 diabetes from 1977 to 2005 [14] identified six pertinent studies (four prospective, two retrospective) that reported possible risk factors. These were older age, sex, BMI, longer diabetes duration, longer duration of insulin therapy, insulin dose, intensive insulin therapy, hypoglycemia unawareness and previous history of severe hypoglycemia. Patient involvement has also been recognized as crucial to optimize glycemic control safely and requires focused self-monitoring of blood glucose, adherence to treatment regimens and knowledge of the interrelationship between physical activity, diet and insulin.

This article describes more recently identified predictors of severe hypoglycemia and discusses their relevance to clinical management.

Methods

■ Search methodology

The question to be addressed by this article is 'What predicts severe hypoglycemia in the community?' The inclusion criteria covered adults, adolescents and children with Type 1 or Type 2 diabetes, regardless of treatment in which severe hypoglycemia was the primary outcome measure, with study designs including randomized controlled trials (RCTs) and observational studies but not case reports. The literature was searched using EMBASE and Medline databases to July 2010 and limited to papers published after 2004 in English. The search protocol included the following key words: ('severe hypoglyc[a]emia' or 'symptomatic hypoglyc[a]emia') and ('predictor[s]' or 'predict[s]' or 'prediction', 'determinant[s]' or 'determine[s]' or 'marker[s]' or 'factor[s]' or 'indicator[s]'). The

references cited in all reviewed papers were also checked for possible studies not identified in primary literature searches. All studies meeting the inclusion criteria were included, as were relevant studies that were available online ahead of print but not identified by the search engines.

Since no RCTs have been undertaken with severe hypoglycemia as the primary end point, it is only possible to determine a causal relationship between potential risk factors and severe hypoglycemia using observational evidence. Therefore, the 'etiology' hierarchy of evidence has been used to grade levels of available evidence [15]. Prospective cohort studies with good follow-up have been ascribed level II, the second highest after a systematic review of level II studies, whilst retrospective studies are level III-2 and case–control studies level III-3. Data from RCTs that are analyzed epidemiologically to address the relationship between exposure(s) and outcome provide level II evidence. Cross-sectional studies and case series (level IV evidence) cannot infer causality and were therefore excluded from this review.

■ Definition of severe hypoglycemia

There is no consensus definition of hypoglycemia in diabetes [13], with threshold levels of plasma glucose ranging from less than 3.9 to less than 3.0 mmol/l. This lack of consensus makes it difficult to compare studies or quantify the frequency of hypoglycemia. However, there is some consensus when defining severe hypoglycemia as an episode in which the mental state of a patient is so disturbed that they are unable to self-treat.

Results

The papers selected are given in **Table 1** together with their characteristics. From 186 papers identified with the database search strategy, 13 papers were considered eligible for this review. Another eligible paper was published online during the review process [16]. Six were studies in Type 1 diabetes [15–21]: two prospective studies in children and adolescents [16,17], two studies in adults [18,19] (one prospective [18] and the other case–control [19]), and two related prospective studies in pregnant women [20,21]. Six were studies in Type 2 diabetes [6,22–26] (two RCTs analyzed epidemiologically [24,25], two related cohort studies [6,23], and two case–control studies [22,26]). The remaining two studies included a case–control study of undifferentiated drug-treated diabetes [27] and a prospective study in Type 1 and insulin-treated Type 2 diabetes [28]. Ten studies provided level II evidence [6,16–18,21,23–25,28] and four level III-3 [19,20,26,27].

■ Definition of severe hypoglycemia

Three studies in Type 1 diabetes [16,17,21], two studies in Type 2 diabetes [22,24] and the study in insulin-treated patients [28] defined severe hypoglycemia broadly as an episode in which the mental state of a patient is so disturbed that the patient is unable to self-treat **(Table 2)**. Two studies in Type 1 diabetes defined severe hypoglycemia with Whipple's triad [18,20], although the blood glucose criterion differed (<3.0 [18] vs ≤3.9 mmol/l [21]) and one required that greater than or equal to two criteria were fulfilled [17] whilst the other considered the event definite if all criteria were fulfilled, probable if two criteria were fulfilled and possible for the rest [20]. Six studies [6,19,23,25–27] relied on health service use to define severe hypoglycemia: hospital attendance only for one [27], admission to the emergency room for two [19,26], and ambulance and/or emergency department attendance and/or hospitalization for three studies **(Table 2)** [6,23,25].

■ Type 1 diabetes in children & adolescents

The aim of the Australian population-based study of 585 children and adolescents with Type 1 diabetes [17] was to determine whether there was a significant relationship between the presence of the deletion (D) allele of the gene encoding ACE and risk of severe hypoglycemia between 1992 and 2004. Children and adolescents with Type 1 diabetes attending the diabetes clinic at the only pediatric referral center for diabetes serving Western Australia were included in the study. Almost all (99.9%) children and adolescents diagnosed with Type 1 diabetes before the age of 16 years in the state are registered and treated at this center. Characteristics of the cohort are described in **Table 1**. After adjusting for sex, younger age and lower HbA_{1c}, but not *ACE I/D* genotype, it independently predicted risk of first severe hypoglycemic event **(Table 3)**. After adjusting for age and sex, longer diabetes duration and lower HbA_{1c}, but not *ACE I/D* genotype, it independently predicted frequency of severe hypoglycemia **(Table 4)** [17].

The prospective Danish study of 1030 children and adolescents with Type 1 diabetes (registrants of the Danish Registry of Childhood Diabetes, established in 1996) was also population-based with 99% ascertainment for the

Table 1. Characteristics of included studies.

Study	Year of study	Number of patients (response rate; %)	Region of study	Source of study population
Type 1 children/adolescents				
Bulsara *et al.*	1992–2004	585 (not stated for this subgroup; 99.9% in parent study [10])	Australia	The only pediatric referral center for diabetes serving Western Australia
Johannessen *et al.*	1996–2007	1037 registrants with DNA and serum (total number of registrants not stated)	Denmark	Danish Registry of Childhood Diabetes (99% ascertainment)
Type 1 adults				
Pedersen-Bjergaard *et al.*	1999–2001	209 (80.4)	Denmark	Consecutive adult outpatients not treated with ACE inhibitors or angiotensin-II-receptor blockers
Pedersen-Bjergaard *et al.*	2000–2001	108 (90.8) cases 262 (86.5) controls	Denmark	Cases: two hospital emergency units Controls: diabetes outpatient clinic
Type 1 pregnant women				
Ringholm Nielsen *et al.*	2004–2006	108 (89.3)	Denmark	Consecutive referents to Center for Pregnant Women with Diabetes
Ringholm Nielsen *et al.*	2004–2006	107 (88.4)	Denmark	Consecutive referents to Center for Pregnant Women with Diabetes
Type 2 adults				
Holstein *et al.*	2000–2003	20 (57.1) cases 337 controls	Germany	Medical emergency department of tertiary care hospital
Bruce *et al.*	2001–2006	302 (51.4% of surviving Fremantle Diabetes Study baseline cohort ≥70 years)	Australia	Community-based observational study
de Galan *et al.*	2001–2008	11,132 (99.9)	International	RCT (ADVANCE)
Davis *et al.*	1999–2006	616 (54.9% of surviving Fremantle Diabetes Study baseline cohort)	Australia	Community-based observational study
Miller *et al.*	2001 and 2003–2005	10,209 (99.6)	USA	RCT (ACCORD)
Duran-Nah *et al.*	2003–2004	94 cases, 188 controls	Mexico	General hospital
Drug treated				
Derijks *et al.*	1991–2002	549 cases, 1897 controls	The Netherlands	PHARMO Record Linkage System
Cox *et al.*	Not stated	100 Type 1, 79 insulin-using Type 2	USA	Responders to regional advertisements

ACCORD: Action to Control Cardiovascular Risk in Diabetes; ACE: Angiotensin-converting enzyme; ADVANCE: Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; RCT: Randomized controlled trial.

Registry and 75% consent to banking of serum and DNA [16]. Besides including the diabetes onset characteristics of all patients, the Registry comprises annual registration of clinical data including hypoglycemia. The overall registration period for the study was 10 years from 1996 with follow-up to 2007. Severe hypoglycemia was recorded annually but no details about ascertainment or validation of events were provided. Longer diabetes duration significantly increased the risk of severe hypoglycemia; however *ACE I/D* genotype, HbA1c prior to the event, the frequency of self-monitoring of blood glucose, the number of injections per day prior to the event, previous hypoglycemia, BMI, age, age at onset and sex, did not. The association

Table 1. Characteristics of included studies (cont.).

Study design	Age of participants (years)	Duration of diabetes (years)	Loss to follow-up for cohort studies (duration of follow-up)	Ref.
Prospective	11.9 ± 4	Mean 4.8	0.5% in parent study [10] (5.8 years)	[17]
Prospective	9.97 ± 3.84	5.10 ± 2.16	Not stated (5.1 ± 2.16 years)	[16]
Prospective	44 ± 12	19 ± 11	31 (14.8%) lost to follow-up, one died, six excluded because they were placed on an ACE inhibitor	[18]
Unmatched case–control	Cases: 45 ± 16 Controls: 44 ± 12	Cases: 21 ± 12 Controls: 24 ± 12	Not applicable	[19]
Prospective	Median (range) 30 (21–42)	Median (range) 15 (1–36)	0% (from before week 14 of pregnancy to postpartum [within 5 days])	[20]
Prospective	Median (range) 30 (21–42)	Median (range) 15 (1–36)	0% (from before week 14 of pregnancy to postpartum [within 5 days])	[21]
Case–control	Cases: Mean (CI: 95%): 74 (67–77) Controls: 65 (64–66)	Cases: 7.6 (4–11) Controls: 10.6 (10–12)	Not applicable	[22]
Prospective	76.0 ± 4.6	Median (interquartile range): 11.2 (8.5–16.5)	0% but 29 died (9.6%) during follow-up (3.7 ± 1.3 years)	[23]
Prospective	65 ± 6.3	7.9 ± 6.3	0% but 1031 (9.3%) died during follow-up (median 4.3–5.0 years)	[24]
Prospective	67.0 ± 9.8	Median (interquartile range): 7.7 (5.2–11.8)	0% but 348 (30.8%) died during follow-up (6.4 ± 2.0 years)	[6]
Prospective	62.2 ± 6.8	Median 10	50 (0.5%) lost to follow-up; 162 (1.6%) withdrew consent; 460 (4.5%) deaths (mean 3.5 years)	[25]
Case–control study	59.2 ± 11.3	13.7 ± 8.3	Not applicable	[26]
Nested case–control study	65.3	Not known	Not applicable	[27]
Prospective	Type 1 40.7 ± 11.2 Type 2 50.2 ± 8.0	Type 1 20.0 ± 10.7 Type 2 12.2 ± 8.5	10 (10.0%) with Type 1 and 9 (11.4%) with Type 2 diabetes (6 and 4 months, respectively)	[28]

between serum ACE and risk of severe hypoglycemia did not reach statistical significance in the absence of the *ACE I/D* genotype (p = 0.0564), but became of borderline significance after adjustment (p = 0.0497) **(Table 3)**. For girls only, serum ACE and insulin dose per kg were independently associated with increased risk of severe hypoglycemia (p < 0.028) [16].

■ Type 1 diabetes in adults

Two Danish studies [18,19] investigated the relationship between the renin–angiotensin system (RAS) and severe hypoglycemia in adults with Type 1 diabetes **(Table 1)**. The first study, conducted between October 1999 and March 2001, was a prospective study of 171 consenting adults attending an outpatient clinic at Hillerød Hospital who were not

Table 2. Definitions of severe hypoglycemia.

Study	Definition of severe hypoglycemia	Definition of frequent severe hypoglycemia	Ref.
Type 1 children/adolescents			
Bulsara *et al.*	A hypoglycemic event leading to loss of consciousness or seizure		[17]
Johannessen *et al.*	Hypoglycemia with either unconsciousness or convulsions		[16]
Type 1 adults			
Pedersen-Bjergaard *et al.*	Hypoglycemic episodes with a need for assistance from other persons in order to restore blood glucose levels. All such events reported within 24 h by telephone and validated according to Whipple's triad: (1) symptoms of hypoglycemia; (2) a blood glucose value lower than 3.0 mmol/l; and (3) adequate response to glucose/glucagon treatment. All events fulfilled two or more criteria		[18]
Pedersen-Bjergaard *et al.*	Medical prehospital or emergency room treatment for documented severe hypoglycemia		[19]
Type 1 pregnant women			
Ringholm Nielsen *et al.*	Whipple's triad: ▪ Symptoms consistent with hypoglycemia ▪ A blood glucose value of 3.9 mmol/l or lower ▪ Adequate response to glucose/glucagon treatment Events fulfilling all criteria were classified as definite, two criteria as probable and the rest as possible		[20]
Ringholm Nielsen *et al.*	Events with symptoms of hypoglycemia requiring assistance from another person to actively administer oral carbohydrate or injection of glucagon or glucose to restore the blood glucose level	Five or more episodes of severe hypoglycemia during pregnancy	[21]
Type 2 adults			
Holstein *et al.*	Symptomatic event requiring treatment with intravenous glucose or glucagon intramuscularly or subcutaneously and confirmed by a blood glucose measurement less than 50 mg/dl (2.8 mmol/l)		[22]
Bruce *et al.*	An episode in which a patient with a subnormal blood glucose required health service use and hypoglycemia was the primary diagnosis		[23]
de Galan *et al.*	The presence of typical symptoms without other apparent cause or a blood glucose value lower than 2.8 mmol/l with CNS dysfunction requiring external assistance		[24]
Davis *et al.*	An episode in which a patient with a subnormal blood glucose required health service use and hypoglycemia was the primary diagnosis		[6]
Miller *et al.*	An episode of hypoglycemia that caused the patient to seek emergency medical care or be admitted to hospital. After March 2003, additional documentation of either a plasma glucose level of less than 2.8 mmol/l or symptoms that promptly resolved with oral carbohydrate, intravenous glucose, or subcutaneous or intramuscular glucagon was also required for a diagnosis of severe hypoglycemia. A total of 85% of reported cases had such documentation		[25]
Duran-Nah *et al.*	Admission to the emergency room with venous blood concentration or fingerstick glucose measurement of 72 mg/dl (4.0 mmol/l) or higher in the presence of a severely confused mental state or unconscious, with clinical response to the administration of intravenous hypertonic glucose		[26]
Drug treated			
Derijks *et al.*	Admission to hospital for hypoglycemia		[27]
Cox *et al.*	Severe neuroglycopenia resulting in stupor, seizure or unconsciousness that precludes self-treatment		[28]

taking ACE inhibitors and who completed 1 year of follow-up for severe hypoglycemia without being placed on ACE inhibitor treatment [18]. The multivariate analysis showed that the number of RAS-related risk factors (fourth quartile of plasma angiotensin and/or fourth quartile of serum ACE activity and/or *AT2R* genotype *A*[*A*]) and the level of hypoglycemia awareness (impaired or

unaware vs aware) were independent predictors of severe hypoglycemia frequency, whilst age, diabetes duration, C-peptide status and HbA_{1c} were not (Table 4).

The second study was a case–control study of 108 (90.8%) Type 1 adults with severe hypoglycemia requiring medical emergency treatment at three sites and 262 (86.5%) consecutive unmatched controls without such events who attended a diabetes outpatient clinic at Steno Diabetes Center (Gentofte, Denmark) and could be genotyped [19]. In multiple logistic regression analysis, after adjusting for sex, hypoglycemia awareness, neuropathy, diabetes duration, insulin regimen and D-allele carriage, increased the risk of severe hypoglycemia threefold (Table 3). BMI, nephropathy and hypertension did not add significantly to the model.

■ Type 1 diabetes in pregnant women

Severe hypoglycemia is a significant problem in pregnant women with Type 1 diabetes. Two papers reported on a prospective cohort of 121 Danish women with pregestational Type 1 diabetes referred to the Center for Pregnant Women with Diabetes before 14 completed gestational weeks with a single living fetus during the study period September 2004 to August 2006 (Table 1). The women were followed from a median 8 weeks into their pregnancy to within 5 days postpartum [20,21].

The first study showed that both a history of severe hypoglycemia in the year preceding the pregnancy and impaired awareness or unawareness of hypoglycemia both independently increased the risk of severe hypoglycemia during pregnancy threefold (Table 3). The second study explored whether frequent severe hypoglycemia was related to placenta growth hormone and IGF-I levels [21]. Only 11 women experienced frequent severe hypoglycemia (defined as ≥5 events; Table 2), so univariate, not multivariate, logistic regression was conducted to identify predictors. Self-estimated impaired hypoglycemia awareness and a history of severe hypoglycemia in the year preceding pregnancy were associated with frequent severe hypoglycemia (Table 4). No associations between IGF-I and placental growth hormone levels at 8 weeks and frequent severe hypoglycemia were found.

■ Type 2 diabetes

Two studies investigated the relationship between severe hypoglycemia and cognitive impairment in patients with Type 2 diabetes [23,24]. The first to be published [23] was a sub-study of the larger Fremantle Diabetes Study [6]. A sample of 302 diabetic patients aged 70 years or older was assessed for dementia, or cognitive impairment without dementia, in 2001–2002 (Table 1). Almost all (99.0%) had Type 2 diabetes. The two-step cognitive assessment comprised an initial screening with the Mini-Mental State Examination (MMSE), the Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE) and a question on subjective memory loss. Those with a MMSE score of less than 28 out of 30 or with an IQCODE rating greater than or equal to 3.31, or who reported subjective memory loss, underwent a detailed cognitive assessment, which was followed by a clinical review to establish the diagnosis of dementia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria. Ratings of functional capacity were conducted by a trained researcher using the Clinical Dementia Rating scale. The Clinical Dementia Rating includes an intermediate state between normal cognition and dementia that was designated cognitive impairment without dementia [23]. Dementia was present in 9.3% and cognitive impairment without dementia in 19.9%. Follow-up for severe hypoglycemia continued until mid-2006 (Table 1). In Cox proportional hazards modeling, with time to first episode of severe hypoglycemia as the dependent variable, in addition to the recognized predictors of severe hypoglycemia, subjects with dementia had a threefold increased risk, those unable to self-manage medications a fourfold increased risk, and those with a BMI less than 22 kg/m^2 a sixfold increased risk of severe hypoglycemia (Table 3). In a negative binomial regression model, a higher frequency of severe hypoglycemia was independently predicted by dementia (20-fold increased risk) (Table 4).

The second study to investigate the relationship between cognitive function and severe hypoglycemia was the multinational Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial [24]. The cognitive function of 11,140 patients aged 55 years or older at study entry with a diagnosis of Type 2 diabetes from the age of 30 years was assessed with the MMSE (Table 1). Severe cognitive dysfunction was defined as a score less than 24 (n = 212 or 1.9%; 31 thought to have dementia). In Cox proportional hazards modeling, with adjustment for potential confounding baseline covariates, severe cognitive dysfunction increased the risk of severe hypoglycemia twofold (Table 3).

Table 3. Predictors of severe hypoglycemia.

Study	Number of patients in final model	Type of analysis	Predictor	Strength of association between predictor and severe hypoglycemia (OR/RR/HR/IRR [95% CI] p-value)	Ref.
Type 1 children					
Bulsara *et al.*	585	Proportional hazards modeling adjusted for sex (and ACE genotype – not significant)	Age (years) HbA_{1c} (%)	0.92 (0.88–0.96), $p < 0.0001$ 0.65 (0.59–0.72), $p < 0.0001$	[17]
Johannessen *et al.*	1030 (7 had not been genotyped)	Negative binomial model with random intercept to take repeated measures into account. Secondary analyses adjusted for ACE genotype, and stratified by sex	Diabetes duration Serum ACE at onset (per 10 U increase) Insulin dose (per increase of 1 U/kg)	RR not presented (nonlinear effect), $p < 0.0001$ 1.11 (1.00–1.22), $p = 0.0497$ after adjusting for ACE genotype; 3.00 (2.10–4.80), $p = 0.0277$ in girls only	[16]
Type 1 adults					
Pedersen-Bjergaard *et al.*	108 cases 262 controls	Multiple logistic regression (sex, insulin regimen, diabetes duration, BMI, hypoglycemia awareness, nephropathy, neuropathy and hypertension)	Male sex Impaired hypoglycemia awareness Neuropathy Duration of diabetes (per year) Insulin regimen (≥4 vs ≥3 injections/day) *D-allele* carriage	3.0 (1.5–5.9), $p = 0.002$ 1.8 (1.1–3.0), $p = 0.020$ 1.8 (1.0–2.9), $p = 0.033$ 0.94 (0.91–0.97), $p < 0.001$ 0.44 (0.31–0.94), $p < 0.001$ 3.2 (1.2–8.0), $p = 0.015$	[19]
Type 1 pregnant women					
Ringholm Nielsen *et al.*	108	Multiple logistic regression	History of severe hypoglycemia in the year preceding pregnancy Impaired hypoglycemic awareness	3.3 (1.2–9.2) 3.2 (1.2–8.2)	[20]
Type 2 adults					
Holstein *et al.*	20 cases 337 controls	Bivariate logistic regression	*CYP2C9*2/*3* or *CYP2C9*3/*3*	5.2 (1.01–27.0)	[22]
Bruce *et al.*	302	Cox proportional hazards modeling (forward conditional variable entry [$p < 0.05$] and removal [$p > 0.10$]) of time to first severe hypoglycemia	Dementia Using insulin BMI <22.0 kg/m^2 Unable to self-manage medication History of self-reported severe hypoglycemia	3.02 (1.07–8.53), $p = 0.037$ 2.77 (1.18–6.46), $p = 0.019$ 5.94 (1.85–19.06), $p = 0.003$ 4.19 (1.43–12.25), $p = 0.009$ 3.51 (1.15–10.76), $p = 0.028$	[23]
de Galan *et al.*	Severe cognitive dysfunction (n = 212) versus normal cognitive function (n = 8689)	Cox proportional hazards modeling (age, sex, treatment allocation, educational status, diabetes duration, SBP, history of currently treated hypertension, HbA_{1c}, LDL-cholesterol, HDL-cholesterol, BMI, history of macro- or micro-vascular disease, current smoking, current alcohol intake and severe cognitive impairment)	Severe cognitive impairment (MMSE <24)	2.10 (1.14–3.87), $p = 0.018$	[24]

ACE: Angiotensin-converting enzyme; ACR: Urinary albumin:creatinine ratio; HDL: High-density lipoprotein; HR: Hazard ratio; IRR: Incidence rate ratio; LDL: Low-density lipoprotein; LGBI: Ratio of low blood glucose index; MMSE: Mini-Mental State Examination; OR: Odds ratio; RR: Relative risk; SBP: Systolic blood pressure; SMBG: Self-monitored blood glucose.

Table 3. Predictors of severe hypoglycemia.

Study	Number of patients in final model	Type of analysis	Predictor	Strength of association between predictor and severe hypoglycemia (OR/RR/HR/IRR [95% CI] p-value)	Ref.
Type 2 adults					
Davis *et al.*	616	Cox proportional hazards modeling (forward conditional variable entry [$p < 0.05$] and removal [$p > 0.10$]) of time to first severe hypoglycemia	Time on insulin (per year) History of severe hypoglycemia eGFR <60 ml/min/1.73 m^2 Peripheral neuropathy Educational attainment > primary level	1.33 (1.15–1.53), $p < 0.001$ 5.66 (2.21–14.50), $p < 0.001$ 2.39 (1.37–4.15), $p = 0.002$ 2.44 (1.33–4.47), $p = 0.004$ 2.34 (1.09–5.04), $p = 0.029$	[6]
Miller *et al.*	10,209	Proportional hazards modeling (age, sex, living arrangement, race, education, alcohol use, BMI, time since diagnosis of diabetes, history of cardiovascular disease, previous amputation of an appendage, history of neuropathy or nerve problems, baseline HbA_{1c}, ACR, serum creatinine, SBP, LDL-cholesterol, use of β-blockers, use of metformin, sulfonylureas, thiazolidinediones, insulin on entry to the trial [prerandomization] plus interactions between treatment arm and each significant variable)	Female African–American vs non-Hispanic white Peripheral neuropathy BMI ≥30 vs <25 kg/m^2 ACR: ▪ Micro- vs normo-albuminuria ▪ Macro- vs normo-albuminuria Creatinine (μmol/l): ▪ 88.4–114.9 vs <88.4 ▪ >114.9 vs <88.4 Age (per 1 year increase) Standard arm only: Education: ▪ <high school vs ≥college graduate ▪ High school vs ≥college graduate ▪ Some college vs ≥college graduate LDL ≥2.59 vs <2.59 mmol/l On any insulin HbA_{1c} (per 1% increase) Intensive arm only: Education: ▪ <High school vs ≥college graduate ▪ High school vs ≥college graduate ▪ Some college vs ≥college graduate On any insulin	1.21 (1.02–1.43), $p = 0.03$ 1.43 (1.20–1.71), $p < 0.0001$ 1.19 (1.02–1.38), $p = 0.03$ 0.65 (0.50–0.85), $p < 0.0001$ 1.20 (1.02–1.43), $p = 0.03$ 1.74 (1.37–2.21), $p < 0.0001$ 1.21 (1.02–1.43), $p = 0.03$ 1.66 (1.25–2.19), $p < 0.0001$ 1.03 (1.02–1.05), $p < 0.0001$ Standard arm only: 1.74 (1.02–2.95), $p = 0.04$ 2.31 (1.46–3.66), $p < 0.0001$ 1.62 (1.01–2.62), $p = 0.05$ 0.59 (0.44–0.80), $p < 0.0001$ 4.08 (2.88–5.76), $p < 0.0001$ 1.30 (1.15–1.47), $p < 0.0001$ Intensive arm only: 1.38 (1.06–1.81), $p = 0.02$ 1.15 (0.90–1.47), $p = 0.26$ 1.02 (0.80–1.31), $p = 0.86$ 1.95 (1.62–2.35), $p < 0.0001$	[25]

ACE: Angiotensin-converting enzyme; ACR: Urinary albumin:creatinine ratio; HDL: High-density lipoprotein; HR: Hazard ratio; IRR: Incidence rate ratio; LDL: Low-density lipoprotein; LGBI: Ratio of low blood glucose index; MMSE: Mini-Mental State Examination; OR: Odds ratio; RR: Relative risk; SBP: Systolic blood pressure; SMBG: Self-monitored blood glucose.

Table 3. Predictors of severe hypoglycemia.

Study	Number of patients in final model	Type of analysis	Predictor	Strength of association between predictor and severe hypoglycemia (OR/RR/HR/IRR [95% CI] p-value)	Ref.
Miller *et al.* (cont.)	10,209	Proportional hazards modeling with time varying glucose control covariates defined as: the updated average HbA_{1c} during follow-up (including the baseline measurement); the most recent HbA_{1c} value; the change in HbA_{1c} from baseline to the updated average (baseline value excluded from the average); and the change in HbA_{1c} from baseline to the 4-month value. Adjusted for the comprehensive baseline model above. Both linear and quadratic effects were fitted for each HbA_{1c} variable. Subsequently,interactions between each variable and treatment arm were investigated	Time varying glucose control Standard arm only: ▪ Updated average HbA_{1c} (per 1% increase) Intensive arm only: ▪ Updated average HbA_{1c} (per 1% increase)	Time varying glucose control Standard arm only: 1.76 (1.50–52.06) Intensive arm only: 1.15 (1.02–1.29)	[25]
Duran-Nah *et al.*	94 cases, 188 controls	Automated binary logistic regression	Age Diabetes duration Lower level of education Attending family physician vs specialist Chronic renal failure Combination antihyperglycemic treatment Fasting or missed meals History of hypoglycemia	0.93 (0.88–0.98), p = 0.008 1.12 (1.05–1.2), p = 0.001 3.7 (1.4–10), p = 0.009 2.8 (1.02–7.9), p = 0.04 3.0 (1.2–7.7), p = 0.01 5.2 (2.3–11.8), p < 0.01 19.8 (9.1–43.1), p < 0.001 2.9 (1.3–6.5), p = 0.01	[26]
Drug treated					
Derijks *et al.*	549 cases, 1897 controls	Conditional logistic regression (age, sex, diabetic comedication, hypo- and hyper-glycemia inducing comedication and CDS score)	Duration of antidepressant use (years): ▪ No antidepressant use ▪ 0–1.00 ▪ 1.01–03.00 ▪ >3.00	 1.00 (reference) 0.88 (0.38–2.05) 0.78 (0.26–2.29) 2.75 (1.31–5.77)	[27]
Cox *et al.*	90 Type 1 70 Type 2	Sliding algorithm	LBGI based on previous 150 SMBG readings to LBGI based on recent readings	58–60% accuracy in predicting imminent (within 24 h) severe hypoglycemia based on three SMBG readings in the 24-h period preceding the episode	[28]

ACE: Angiotensin-converting enzyme; ACR: Urinary albumin:creatinine ratio; HDL: High-density lipoprotein; HR: Hazard ratio; IRR: Incidence rate ratio; LDL: Low-density lipoprotein; LGBI: Ratio of low blood glucose index; MMSE: Mini-Mental State Examination; OR: Odds ratio; RR: Relative risk; SBP: Systolic blood pressure; SMBG: Self-monitored blood glucose.

Table 4. Predictors of frequent severe hypoglycemia.

Study	Number of patients in final model	Type of analysis (variables in model)	Predictor	Strength of association between predictor and frequent severe hypoglycemia (OR or RR [95% CI], p-value) or severe hypoglycemia frequency (regression coefficient, p-value)	Ref.
Type 1 children/adolescents					
Bulsara *et al.*	585	Multivariate negative binomial regression adjusted for age and sex (and ACE genotype – not significant)	Diabetes duration (years)	1.11 (1.06–01.17), $p < 0.0001$	[17]
			HbA_{1c} (%)	0.78 (0.71–70.86), $p < 0.0001$	
Pedersen-Bjergaard *et al.*	171	Frailty model for recurrent events (an extension of the log-linear Poisson model including a γ-distributed variation between patients), backward stepwise entry	Fourth quartile plasma angiotensinogen	2.6 (1.4–4.7), $p = 0.0016$	[18]
			Fourth quartile Serum ACE activity	2.7 (1.5–5.0), $p = 0.004$	
			AT2R genotype *A(A)* and Number of RAS-related risk factors:	1.9 (1.1–3.2), $p = 0.025$	
			1	2.4 (1.3–4.3), $p = 0.006$	
			2	2.5 (1.2–5.1), $p = 0.015$	
			3	16.9 (5.3–54), $p < 0.001$	
			Hypoglycemia awareness:		
			Impaired	4.6 (2.5–8.6), $p < 0.001$	
			Unaware	5.9 (2.7–13.1), $p < 0.001$	
Type 1 pregnant women					
Ringholm Nielsen *et al.*	107	Bivariate logistic regression due to small number (n = 11) with frequent severe hypoglycemia	Impaired hypoglycemic awareness	8.5 (1.1–68.7), $p = 0.004$	[21]
			History of severe hypoglycemia in the year preceding pregnancy	7.6 (1.9–30.8), $p = 0.005$	
Type 2 adults					
Bruce *et al.*	302	Negative binomial regression model	Dementia	20.26 (6.00–68.44), $p < 0.001$	[23]
			On insulin	14.60 (3.49–61.12), $p < 0.001$	
			eGFR <60 ml/min/1.73 m^2	4.70 (1.02–21.70), $p = 0.048$	
Davis *et al.*	616	Zero-inflated negative binomial regression; multiple logistic regression used first to define independent determinants of 1 or more episode of subsequent severe hypoglycemia	Certain zeros	Certain zeros	[6]
			Education > primary level	0.17 (0.04–0.80)	
			Time on insulin	0.34 (0.19–10.62)	
			eGFR <60 ml/min/1.73 m^2	0.22 (0.08–0.59)	
			Peripheral neuropathy	0.19 (0.07–0.50)	
			Count model	Count model	
			HbA_{1c}	1.34 (1.05–1.70)	
			Fasting serum glucose	0.86 (0.76–70.97)	

ACE: Angiotensin-converting enzyme; OR: Odds ratio; RAS: Renin–angiotensin system; RR: Relative rate.

The Fremantle Diabetes Study community-based cohort was recruited between 1993 and 1996. Of 1426 participants, 1294 had clinically defined Type 2 diabetes. Complete data linkage with the ambulance, emergency department and hospital morbidity databases was available from 1999. At the beginning of 1999, 1123 of the participants with Type 2 diabetes were still alive, but only 616 attended a comprehensive physical and biochemical assessment in 1998 (Table 1). Of these, 52 (8.4%) experienced 66 episodes of severe hypoglycemia during a mean 6.4 years' follow-up. Recognized risk factors for the first episode of severe hypoglycemia identified with Cox proportional hazards modeling were a history of severe hypoglycemia, renal impairment and duration of insulin use. In addition, the presence of peripheral neuropathy and education

beyond primary school level were implicated (Table 3). Zero-inflated negative binomial modeling gave the best fit to the count data [6]. Participants who never had severe hypoglycemia (certain zeros) were unlikely to be insulin-treated or, if they were on insulin, they had shorter duration of insulin treatment. They were also unlikely to have renal impairment or peripheral neuropathy or to have been educated beyond primary level (Table 4). Severe hypoglycemia frequency was predicted by higher HbA_{1c} and lower fasting serum glucose (Table 4).

A *post hoc* epidemiological analysis of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, a double 2 × 2 factorial RCT, investigated potential determinants of severe hypoglycemia, including baseline characteristics and the association of severe hypoglycemia with levels of HbA_{1c} achieved during therapy [25]. Of the 10,251 participants enrolled in the ACCORD study with Type 2 diabetes, a HbA_{1c} 7.5% or higher during screening, and aged 40–79 years with established cardiovascular disease or 55–79 years with evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or two or more additional risk factors for cardiovascular disease, 10,209 (99.6%) had any follow-up for hypoglycemia (Table 1).

The incidence of initial episodes of severe hypoglycemia in ACCORD was significantly higher amongst participants assigned to intensive glycemia therapy than in those on standard therapy (log-rank $p < 0.0001$). Forward stepwise proportional hazards regression identified 13 independent determinants of severe hypoglycemia (Table 3). Seven variables had similar associations with severe hypoglycemia in both the intensive and standard treatment groups whilst education, low-density lipoprotein cholesterol, use of any insulin at baseline, and baseline level of HbA_{1c} ($p < 0.05$ for test of interaction) had a different relationship with severe hypoglycemia in the intensive versus the standard group. Baseline covariates associated with an increased risk of severe hypoglycemia in both treatment arms were older age, female gender, African–American race (compared with non-Hispanic whites), history of peripheral neuropathy, lower BMI, higher urine albumin to creatinine ratio, and higher levels of serum creatinine. For those predictors with different relationships according to glycemia treatment group, lower education was associated with an increased risk for severe hypoglycemia in both groups, but to a greater degree in the standard treatment group. Lower levels of low-density lipoprotein-cholesterol and higher HbA_{1c} were associated with an increased risk of severe hypoglycemia among participants in the standard treatment group. Insulin use at randomization was associated with an increased risk of severe hypoglycemia in both treatment groups, but the hazard ratio in the standard treatment arm was double that in the intensive treatment arm (Table 3).

In addition, higher updated average and most recently measured HbA_{1c} levels within each treatment group were associated with a higher annual incidence of severe hypoglycemia, albeit to different degrees. After adjustment for the variables in the comprehensive model described above, for every 1% unit decline in HbA_{1c} concentration from baseline to 4 months, the risk of severe hypoglycemia was reduced by 28% in the standard treatment group and 14% in the intensive treatment group. The effect of the change in HbA_{1c} was not independent of baseline HbA_{1c} ($p = 0.026$ for interaction test), with the magnitude of the reduced risk decreasing with increasing starting HbA_{1c}. Similar results were found for the difference between baseline HbA_{1c} and updated average HbA_{1c}. Overall, a 1% unit decline from baseline was predictive of a 35 and a 15% decrease in the risk of severe hypoglycemia within the standard treatment and intensive treatment groups, respectively, but this was not dependent on the baseline HbA_{1c} ($p = 0.26$ for interaction test).

A Mexican study [26] matched 94 Type 2 patients with a primary diagnosis of symptomatic hypoglycemia with 188 with a diagnosis other than hypoglycemia treated at a general hospital between July 2003 and December 2004 (Table 1) to identify risk factors associated with severe hypoglycemia. In multiple logistic regression, the odds of having a primary diagnosis of severe hypoglycemia increased with younger age, longer diabetes duration, lower education level, family physician (vs specialist physician) attendance, chronic renal failure, combination antihyperglycemic therapy, fasting and a history of hypoglycemia (Table 3).

The genetically polymorphic cytochrome P450 (CYP) enzyme CYP2C9 metabolizes most sulfonylurea drugs. A total of 20 diabetic patients admitted to a German emergency department with severe hypoglycemia during sulfonylurea drug treatment were compared with a control group of 337 patients with Type 2 diabetes but

without a history of severe hypoglycemia [22]. The *CYP2C9* genotypes **3/*3* and **2/*3*, which are predictive of low enzyme activity, were more common in the group with severe hypoglycemia (two [10%] vs seven [2.1%]), with an unadjusted odds ratio of 5.2 (95% CI: 1.01–27.0). The cases were significantly older, more likely to have renal failure and a lower BMI than the controls.

■ Drug-treated diabetes

A nested case–control study among Type 1 or Type 2 diabetes patients treated with insulin and/or oral glucose-lowering medications was used to assess the risk of hypoglycemia requiring hospitalization associated with the use of antidepressants [27]. Patients were selected from the Dutch PHARMO Record Linkage System. Exposure to antidepressants was the primary determinant investigated. From the base cohort (40,600 patients), 549 cases were identified and 1897 controls selected **(Table 1)**. Current use of any antidepressant was not associated with a higher risk of hypoglycemia requiring hospitalization, but the risk was increased 2.75 times after 3 years of use **(Table 3)**.

Finally, a prospective study tested methods to predict imminent (within 24 h) severe hypoglycemia using blood glucose results [28]. A total of 100 adults with Type 1 diabetes were followed for 6 months and 79 insulin-using adults with Type 2 diabetes were followed for 4 months. During this time, subjects' routine selfmonitored blood glucose (SMBG) readings were stored on and retrieved from memory meters, and participants were queried every 2 weeks about the occurrence of severe hypoglycemia **(Table 1)**. The mean age of the Type 1 adults was 40.7 years and the mean age of the Type 2 adults was 50.2 years, mean diabetes duration was 20.0 and 12.2 years, mean HbA_{1c} was 7.6% and 8.8%, and male sex 43% and 39%, respectively. Relative risk of severe hypoglycemia, quantified by the ratio of an individual's low blood glucose index based on the previous 150 readings to the low blood glucose index based on recent SMBG readings, increased significantly in the 24 h before severe hypoglycemia episodes in individuals with Type 1 and Type 2 diabetes. A sliding algorithm detected 58% of imminent severe hypoglycemia in the Type 1 diabetic group and 60% in the Type 2 diabetic group when three SMBG readings were available in the 24 h before an episode. Detection increased to 63 and 75%, respectively, when five SMBG readings were available. The average warning time between a severe hypoglycemia imminent risk increase signal and a subsequent severe hypoglycemic episode was 11 h.

Discussion

This article has identified a further four independent predictors of severe hypoglycemia in Type 2 diabetes that have been recognized by at least two level II studies but not considered in previous reviews: dementia (or severe cognitive impairment), higher HbA_{1c}, low BMI and peripheral neuropathy. Education level was also identified as a predictor of severe hypoglycemia, but inconsistently. In adults with Type 1 diabetes, the RAS system was implicated in risk of severe hypoglycemia. In pregnant women with Type 1 diabetes, a history of severe hypoglycemia in the year before pregnancy and impaired awareness, or unawareness, of hypoglycemia predicted severe hypoglycemia during pregnancy. In drug-treated diabetes of any type, long-term antidepressant use was identified as a risk factor for severe hypoglycemia. Previously identified risk factors for severe hypoglycemia were confirmed. Specifically, in Type 2 diabetes, the use of insulin (or time spent on insulin) [6,23,25,26] and a history of severe hypoglycemia [6,23,26] independently predicted severe hypoglycemia. In Type 1 diabetes, younger age and lower HbA_{1c}, longer diabetes duration, impaired hypoglycemia awareness and insulin regimen were verified as predictors of time to first episode of severe hypoglycemia, whereas longer diabetes duration and lower HbA_{1c} predicted frequency of severe hypoglycemia [17]. *ACE I/D* genotype did not predict severe hypoglycemia in children and adolescents [16,17].

■ Type 1 diabetes

It has been suggested that genetic factors may predispose a susceptibility to severe hypoglycemia. Two case–control studies (level III-3 evidence) suggested that the use of ACE inhibitors may increase the incidence of hypoglycemia in adults [29,30]. However, in the Heart Outcomes Prevention (HOPE) study (a randomized 2 × 2 factorial design trial of the effect of treatment with ramipril (an ACE inhibitor) or placebo and vitamin E or placebo on the occurrence of a combined cardiovascular end point) the rate of admission to hospital due to hypoglycemia did not differ between the ramipril and placebo arms (2 vs 2%) [31]. The prospective, population-based study of children and adolescents (level II

evidence) found that ACE genotype did not predict either first episode or frequency of severe hypoglycemia [16,17]. Renal impairment is a known risk factor for severe hypoglycemia and was adjusted for in the later case–control study of drug-treated diabetic patients [30], but not the earlier one [29]. However, the ACCORD results suggest that micro- and macro-albuminuria are also predictive of severe hypoglycemia [25]. Optimal treatment of albuminuria involves the use of an ACE inhibitor or angiotensin II receptor blocker [32]. Neither case–control study adjusted for the presence of albuminuria. Thus, the association of ACE inhibitor use with severe hypoglycemia in adults may be due to the preferential use of ACE inhibitors by those with nephropathy, which may itself increase the risk of severe hypoglycemia. The two recent studies of RAS-related risk factors in adults with Type 1 diabetes [18,19], nevertheless, add to the evidence that the RAS has a role in the etiology of severe hypoglycemia. The prospective study (level II evidence) showed a strong dose–response relationship between the number of RAS-related risk factors and the frequency of severe hypoglycemia, but did not adjust for albuminuria [18]. A Poisson model was used, which has been shown to be suboptimal [6,33], when the majority of participants have zero events. Replication of these results in large prospective cohorts, in non-Scandinavian countries and in patients with Type 2 diabetes with adjustment for all other possible confounding variables, is required.

Type 1 diabetes in pregnant women

The risk of stillbirth and preterm delivery is increased threefold amongst pregnant women with Type 1 diabetes compared with healthy pregnant women. Management that aims for normal blood glucose levels is of vital importance to prevent these complications. Severe hypoglycemia is the limiting factor for obtaining near-normal blood glucose control in pregnant women with Type 1 diabetes, and occurs in approximately a third of pregnancies complicated with Type 1 diabetes. The study of severe hypoglycemia in pregnant women [21] identified that known predictors in the general Type 1 population were also present in this sub-group. Although expected, these findings may help to reduce severe hypoglycemia in this vulnerable sub-group of women with Type 1 diabetes by identifying those at high risk early in their pregnancy or, preferably, during planning for pregnancy, in order to monitor their glycemic control more intensively to prevent hypoglycemic emergencies. A limitation of this study was the small number of patients having an episode of severe hypoglycemia and consequently the need to use bivariate statistics only.

Type 2 diabetes

Davis *et al.* suggested that the association of higher HbA_{1c} and lower fasting serum glucose with frequency of severe hypoglycemia in Type 2 patients was due to glycemic variability. In agreement with this hypothesis, the ACCORD study found that the risk of severe hypoglycemia increased as the baseline or updated average HbA_{1c} increased [25]. Moreover, in a managed care setting in the USA, bivariate analysis showed that an emergency department or hospital attendance by patients 55 years or older and with Type 2 diabetes with a diagnosis of hypoglycemia was associated with a significantly higher 7-year mean HbA_{1c} [34]. Similarly, the Diabetes Audit and Research in Tayside Scotland (DARTS)/Medicines Monitoring Unit (MEMO) Collaboration, which collects routine record-linked data from the population of Tayside, Scotland, reported, in unadjusted analyses, that for all people with diabetes, people who experienced severe hypoglycemia requiring treatment by the health service emergency facilities had a higher HbA_{1c} ($p < 0.001$) [5]. Davis *et al.* hypothesized that the understandable association of fasting serum glucose with frequency of severe hypoglycemia together with higher HbA_{1c} may reflect unstable control with large glucose swings leading to higher overall average blood glucose levels [6]. This finding implies that patients with Type 2 diabetes with high HbA_{1c} should not be assumed to be at low risk of severe hypoglycemia.

Education beyond primary level was found to double the risk of severe hypoglycemia in Australians with Type 2 diabetes [6], whilst in a small Mexican case–control study of Type 2 patients presenting to a general hospital [26], lower educational attainment was associated with severe hypoglycemia. This disparity may be due to the differing study designs and settings, definition of outcome, methods of statistical analysis and length of follow-up **(Table 1)**. In a managed care setting in the USA, bivariate analysis demonstrated that an emergency department or hospital attendance of patients aged 55 years or older and with Type 2 diabetes

with a diagnosis of hypoglycemia was not associated with education level [34]. However, the ACCORD study found that participants who had graduated from college were significantly less likely to suffer an episode of severe hypoglycemia [25]. This might indicate that well-educated patients are better able to follow the protocol-based glycemic management in clinical trials, a different setting to usual care.

Education level may be a surrogate for socioeconomic status. A systematic literature review to determine whether low socioeconomic status was associated with severe hypoglycemia in Type 1 diabetes in developed countries concluded that low socioeconomic status may be associated with an increased risk of severe hypoglycemia, but that this relationship had been inconsistently observed in the existing literature [35]. There is also some evidence that limited health literacy predisposes to hypoglycemia in insured patients with diabetes in the USA [36].

There are two possible explanations for the apparently contradictory findings relating to educational attainment. First, and consistent with the fact that educational attainment correlates with diabetes knowledge in the Fremantle Diabetes Study cohort [37], better educated Australian adults with Type 2 diabetes may be more aware of the chronic vascular sequelae of poor glycemic control and consequently engage in self-management practices that increase the risk of severe hypoglycemia. Second, Australian diabetic patients with lower educational attainment may not access health services as readily as those who are well educated. In contradiction, the Australian study of severe hypoglycemia in children with Type 1 diabetes found that children from the most socially disadvantaged group had a 40% increased risk of severe hypoglycemia [10].

The opposite findings of these two observational studies from the same geographic location (Western Australia) may be due to when the studies were undertaken and the age differences of the participants. The later time period of the adult study (1999–2006), soon after publication of the results of the UKPDS, proved that intensive glycemic control reduced microvascular complications in people with new-onset Type 2 diabetes [2]. However, the results from the DCCT [1], which showed that intensive therapy effectively delayed the onset and slowed the progression of microvascular complications in patients with Type 1 diabetes, were published soon after the follow-up of the cohort of children began in 1992. The behavior of adults with respect to their own healthcare may be different to their behavior when the patient with diabetes is their child, (i.e., parents of children with diabetes may seek healthcare more readily for their children than adults with diabetes would do for themselves, and/or might attempt to control their child's glycemia more rigorously than adults would their own). In a Scottish prospective cohort study, an association was observed between increasing socioeconomic deprivation and severe hypoglycemia ($p = 0.002$) for the group as a whole, but especially in those with Type 1 diabetes ($p < 0.001$) [5]. Although most evidence points to a low level of education predicting severe hypoglycemia, the study by Davis *et al.* suggests that patients with a higher level of education should not be assumed to be at low risk [6].

Peripheral neuropathy was identified as an independent predictor of first episode of severe hypoglycemia during follow-up [6,25] and recurrent severe hypoglycemia [6]. It was suggested that the significant association between severe hypoglycemia and peripheral but not autonomic neuropathy may reflect the confounding effects of the close relationship between these neurologic complications [6], with the presence of peripheral neuropathy acting as a marker of compromised neuroendocrine defenses. Alternatively, or additionally, since a history of peripheral neuropathy is consistent with a longer duration of diabetes and progressive β-cell dysfunction is a known characteristic of Type 2 diabetes, participants with peripheral neuropathy are likely to have had more severe β-cell failure. Endogenous insulin response to fluctuations in glucose is essentially absent in people with advanced β-cell failure and thus the presence of peripheral neuropathy may be an indicator of a decreased ability to counter-regulate glucose changes precipitated by glucose-lowering medications. The presence of peripheral neuropathy should alert clinicians to intensify patient therapy with care [25].

The presence of dementia or severe cognitive impairment significantly increased the risk of a first episode of severe hypoglycemia during follow-up two- to three-fold [23,24] and the risk of recurrent severe hypoglycemia 20-fold [23]. The smaller, more detailed study also found that an inability to self-manage medications contributed independently to increased risk of

severe hypoglycemia [23]. Management of diabetes is complex and heavily dependent on active involvement of patients with respect to drug compliance, glucose testing, meal planning and insulin dose titration. This is a demanding process that could cause greater difficulties for patients with severe cognitive impairment [24].

Although significant cognitive impairment was an exclusion criterion, the ADVANCE study found that the relative benefits of blood pressure-lowering treatment and risks of intensive glucose control in patients with Type 2 diabetes were largely independent of cognitive function. The greater baseline risk of different outcomes in patients with cognitive dysfunction may translate these similar relative treatment effects into both greater absolute benefits and greater absolute risks (e.g., severe hypoglycemia) [24]. The importance of balancing potential benefits and risks for each patient when making treatment decisions was stressed. Dementia is underdiagnosed by healthcare professionals [38]. The association with severe hypoglycemia adds weight to the need for cognitive screening of older patients with diabetes in order to ensure that they are managed appropriately.

A BMI of less than 22 kg/m^2 has been used to screen for undernutrition in older patients and is associated with several chronic conditions, including dementia [39]. Bruce *et al.* found that the elderly (aged ≥70 years at study entry) participants with a BMI less than 22 kg/m^2 were nearly six-times more likely to suffer severe hypoglycemia during follow-up, independent of dementia status [23]. In the ACCORD study, participants with a BMI less than 25 kg/m^2 were 1.5-times more likely to experience an episode of severe hypoglycemia than those with a BMI greater than or equal to 30 kg/m^2 [25]. These data should ensure that clinicians treating normal or underweight patients with Type 2 diabetes consider their higher risk of severe hypoglycemia when managing their glycemia, especially if they also suffer from cognitive impairment.

These findings are relevant to the 20% of older people living in care homes who have diabetes [40]. Since many of these diabetic patients are treated with oral hypoglycemic medications and/or insulin, hypoglycemia is a concern. Management of this frail population is often complicated by comorbidities (including dementia), disability, polypharmacy and limited life expectancy. Recently published clinical trials [41–43] showed no clear cardiovascular benefit of intensive glycemic control and an increased risk of hypoglycemia. Therefore, it seems reasonable that glycemic control in these frail older patients can be relaxed. Given the short life expectancy of these patients, glycemic targets are better focused on the short-term, day-to-day fluctuations in blood glucose levels, since these fluctuations are responsible for symptoms and poor quality of life, rather than a long-term target such as HbA_{1c}. Quality rather than quantity of life should be the primary goal of diabetes care in these settings [40].

Other risk factors for severe hypoglycemia in Type 2 diabetes were identified in one of the studies reviewed, but need to be replicated in other studies to increase the level of evidence offered (i.e., female sex, African–American racial background, lower low-density lipoprotein-cholesterol, and micro- and macroalbuminuria [25]). The observation that genetically determined low CYP2C9 activity may increase the risk of sulfonylurea-associated severe hypoglycemia [22] needs to be repeated in larger prospective cohorts with the ability to adjust for potential confounders.

■ Drug-treated diabetes

The prevalence of both clinical depression and depressive symptoms in diabetic subjects is double that in the general population [44]. A community-based study of depression in Type 2 diabetes reported that depression was present in 31.5% of subjects at recruitment [45]. Depressed subjects had longer duration of diabetes, more cardiovascular risk factors, more coronary heart disease, cerebrovascular disease and diabetic microvascular complications at baseline, and a higher all-cause and cardiac mortality during follow-up. The finding that long-term (>3 years) use of antidepressants increased the risk of hypoglycemia requiring hospitalization nearly threefold in diabetic patients using oral glucose-lowering medication and/or insulin [27] further complicates management of the patient with diabetes and chronic depression.

In patients with Type 1 diabetes, data from SMBG were found to predict severe hypoglycemia [46]. The low blood glucose index was derived and used to predict imminent severe hypoglycemia in insulin-using patients [28,47,48]. The potential to predict more than half of the imminent episodes of severe hypoglycemia

based on SMBG data has important clinical implications for helping at-risk patients avoid severe hypoglycemia. Given timely warning of imminent severe hypoglycemia, individuals should be able to take preventive action to reduce that risk (e.g., being more vigilant for any signs of hypoglycemia, reducing insulin dose, avoiding strenuous exercise without eating extra carbohydrates, and avoiding delayed meals or missed snacks). This may provide a cost-effective alternative to continuous blood glucose monitors, which cost upwards of US$1000 plus $35 per sensor [101]. Sensors need to be replaced every 3–7 days and monitors have a finite lifetime (0.5–2 years). In addition, continuous systems must be calibrated with a traditional blood glucose measurement (using current technology) and therefore require both the continuous glucose monitoring system and traditional fingerstick measurements (typically twice per day). Patients are also advised to use fingerstick measurements to confirm hypo- or hyper-glycemia before taking corrective action.

Conclusion

Since 2004, four good quality prospective studies have provided consistent level II evidence that in Type 2 diabetes severe hypoglycemia is independently predicted by higher HbA_{1c}, lower BMI, the presence of peripheral neuropathy, and dementia or severe cognitive impairment [6,23–25]. Education level, mostly lower but possibly also higher, may also be a risk factor [6,25,26].

The RAS has been implicated in the etiology of severe hypoglycemia [18,19], but larger prospective cohort studies in different settings with comprehensive ascertainment of all potential confounding variables are required for confirmation.

Further studies of the relationship between antidepressant use and severe hypoglycemia are required to confirm the findings of the case–control study that shows long-term antidepressant use predicts severe hypoglycemia [27].

Patients at risk of severe hypoglycemia who self-monitor their blood glucose at least three times daily may benefit from the sliding algorithm developed by Cox *et al.* that predicts imminent (within 24 h) severe hypoglycemia [28], and therefore allows the patient to take preventive action in a timely, cost-effective manner.

Future perspective

Prevention of severe hypoglycemia

Severe hypoglycemia is largely preventable. Identifying risk factors for severe hypoglycemia can provide guidance to clinicians who attempt to intensify patient therapy and adjust glycemic treatment goals on the basis of individual risk, as has been recommended by the American Diabetes Association [49]. In addition to the conventional risk factors for severe hypoglycemia, patients with Type 2 diabetes and dementia (or severe cognitive impairment), or low BMI, peripheral neuropathy or high HbA_{1c} are at higher risk of severe hypoglycemia and their management should reflect this in order to achieve optimum glycemia in the absence of severe hypoglycemia. These observations in patients with Type 2 diabetes may be applicable to those with Type 1 diabetes, but further research is warranted.

The frail elderly

In balancing the desire for normoglycemia with the threat of severe hypoglycemia, clinicians need to be pragmatic in managing their diabetic patients. Knowledge of their patient's risk profile will help the physician decide which HbA_{1c} target is the safest and most beneficial for the individual patient. Significant hypoglycemia should always warrant consideration of aiming for less intensive control, especially in the frail elderly with short life expectancy for whom glycemic targets are better focused on the short-term, day-to-day fluctuations in blood glucose levels, to reduce symptoms and improve quality of life.

Algorithms

A long-term goal for the optimal management of people with diabetes is the development of a closed-loop system connecting real-time automatic control of an insulin pump based on immediate blood glucose data from a continuous blood glucose sensor. An important step is the development of an algorithm for automatic control allowing the system to function as an artificial pancreas. Such an algorithm would need to be very complex in order to accurately control blood sugar levels without any user input. The expensive technology required means that its use would be limited to those at very high risk of severe hypoglycemia and those in whom severe hypoglycemia is life threatening (e.g., those who live alone, who are prone to

nocturnal hypoglycemia or pregnant women). The sliding algorithm developed by Cox *et al.* based on three or more SMBG readings per day [28] adds value to current self-monitoring and will allow insulin-using patients to be proactive in preventing episodes of severe hypoglycemia. It may also be applicable for people taking insulin secretagogs, but additional research is required.

■ Safer therapies in the treatment of Type 2 diabetes

Progressive loss of β-cell function and mass makes it difficult for patients with Type 2 diabetes to maintain glycemic control. The latest pharmacological agents designed to combat β-cell dysfunction include the glucagon-like peptide-1 (GLP-1) analogs and the dipeptidyl peptidase IV (DPP-4) inhibitors. DPP-4 inhibitors lower blood sugar levels by blocking the DPP-4 enzyme, which is responsible for breaking down the proteins that stimulate the insulin-producing cells and slow gastric emptying time after a meal. If DPP-4 is inhibited, then the proteins can activate the release of insulin for a longer period of time, thereby lowering the glucose level in the blood and slowing the rate of absorption of food. When blood glucose concentrations are normal or elevated, GLP-1 and gastric inhibitory polypeptide increase insulin synthesis and release from pancreatic β cells. GLP-1 also lowers glucagon secretion from pancreatic β cells, leading to reduced hepatic glucose production. This mechanism is unlike the mechanism seen with sulfonylureas; sulfonylureas cause insulin release even when glucose levels are low, which can lead to sulfonylurea-induced hypoglycemia [50]. GLP-1 analogs and DPP-4 inhibitors are associated with a low risk of hypoglycemia and may be more widely deployed in patients at high risk. However, the longer term efficacy, safety and cost–effectiveness of these novel treatments compared with conventional treatments remains to be established.

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