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COMMENT

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Clinical perspectives of new insights and tools to minimize the hypoglycaemia burden connected with type 2 diabetes pharmacotherapy

Eberhard Standl[1,5*], Antonio Ceriello[2], Darren K. McGuire[3], Oliver Schnell[1,5] and Rury R. Holman[4]

Abstract

- *Current state of affairs*: The potential for hypoglycaemia is a 100-year-long challenge that can complicate blood glucose lowering therapy in people with type 2 diabetes. This omnipresent imminent risk continues to the present day, particularly with insulin or sulfonylurea treatment.

- *Specific objective*: This clinical perspective seeks to synthesize new insights and tools to help reduce the hypoglycaemic burden related to type 2 diabetes pharmacotherapy by suggesting a synergistic triad approach: Guidance using an innovative approach based on comprehensive network analyses evaluating differential risk of diabetes medications for severe hypoglycaemic events (SHEs) observed in randomized controlled trials. These show an estimated background risk of 60 SHEs per 1000 patients over five years in the trial control populations allocated to standard treatments. Adopting this approach, the data indicate that the highest risk (~fivefold higher) relates to therapy with sulfonylureas or with basal-bolus insulin regimens, whereas novel therapies with sodium-glucose transport protein 2 inhibitors (SGLT2is) or glucagon-like peptide-1 receptor agonists (GLP1-RAs) have minimal risk of SHEs, with the non-steroidal mineralocorticoid receptor antagonist finerenone showing a potential risk reduction.Recognition of these insights and translating them into treatment guidance should underpin the approach to minimizing the risk of hypoglycaemia, as they likely reflect drug related hypoglycaemia risk more broadly across all degrees of hypoglycaemia. Following this approach would be particularly helpful in those either with specific risk factors for hypoglycaemia (Fig. 1) or with the recently established frail phenotype at dual risk of SHEs and cardiovascular (CV) events in the context of multiple co-morbidities including heart failure, frailty or cancer and a high Charlson Co-Morbidity Index. Also the acute CV risk related to arrhythmias and mortality must not be ignored.

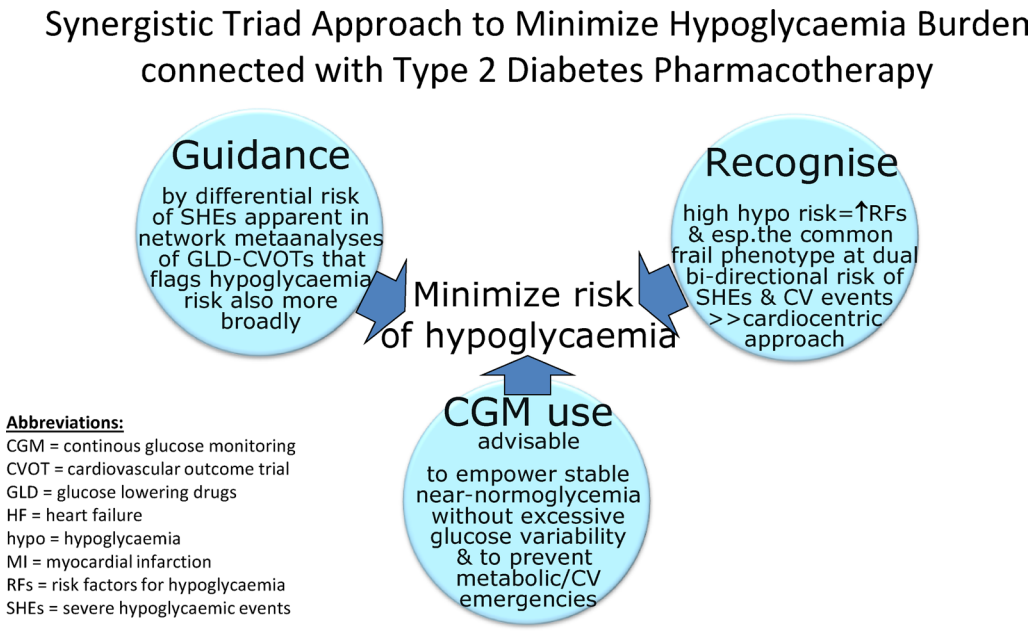
*Correspondence:
Eberhard Standl
Eberhard.Standl@lrz.uni-muenchen.de

Full list of author information is available at the end of the article

- Continuous glucose monitoring (CGM) for people with type 2 diabetes is advisable given it has been shown convincingly to provide a powerful new tool in those at dual risk of hypoglycaemia and CV events by reducing related hospitalization emergencies by ~50%.*Conclusion*: Each of these new insights and tools comprise an important step forward in their own right. Used together in a synergistic manner they, for the first time in over one hundred years, appear to provide the capacity to mitigate the threats of hypoglycaemia related to type 2 diabetes pharmacotherapy.

Keywords Type 2 diabetes pharmacotherapy, Hypoglycaemia, Cardiovascular events, Bi-directional association, Phenotype at dual risk, Continuous glucose monitoring

Graphical abstract



Introduction

Following the epochal life-saving introduction of insulin into diabetes therapy over 100 years ago, hypoglycaemia soon emerged as a concerning side effect due to accidental overdosing of this first effective blood glucose lowering therapy for people with diabetes mellitus [1]. As it is well recognized today, dependent upon the degree of hypoglycaemia, symptoms may range from mild, though unpleasant, to more severe cognitive impairment and mental confusion, to coma and seizures, with the risk of fatal outcomes or permanent neurologic disablement, as well as of cardiovascular or microvascular damage [1, 2]. Even less severe hypoglycemic events, however, can seemingly align with important societal, medical, and psychosocial consequences and may be associated with unfavorable effects on the brain, cognitive function, or depressive disorders longer term [1–4]. Prevention of hypoglycaemia, therefore, quickly evolved as a strategic component of any treatment with insulin since the early days of this therapy [1–3].

The challenge of hypoglycaemia continues to the present day as an omnipresent imminent risk of insulin therapy, regardless of the type of diabetes. This challenge expanded from the 1950s with the introduction of insulin secretagogues such as sulfonylureas in people with type 2 diabetes [1–5]. Dealing with the risk of hypoglycaemia in this type of diabetes may be particularly complex in view of progressive loss of beta cell function evolving over time that requires more intensive insulinotropic therapy, yet at the expense of increasing glycemic variability associated with increased risk of hypoglycaemia [6]. Early intervention to prevent beta cell loss, therefore, is important [2]. Based on recent position statements and recommendations from scientific organizations and working groups on both sides of the Atlantic, Fig. 1 outlines contemporary definitions of hypoglycaemia and established appropriate precautions in clinical use, especially for type 2 diabetes [1–5]. Following this background, our paper focuses exclusively on type 2 diabetes, as the global epidemic of this condition. In 2025, the global prevalence of diabetes was estimated at 589 million adults aged 20–79, a figure expected to increase to 853 million by 2050, with approximately 90% being type 2 diabetes, exposing millions of individuals to a potential hypoglycemic burden

Definition	• Level 1: Threshold for neuro-endocrine responses of plasma glucose <3.9 mmol/L (<70 mg/dL) & ≥3.0 mmol/L (≥54 mg/dL) • Level 2: Threshold at which neuroglycopenic symptoms begin to occur of plasma glucose <3.0 mmol/L (<54 mg/dL) • Level 3: Severe event characterized by altered mental and/or physical status requiring third party assistance for treatment of hypoglycaemia
Risk factors	• Use of insulin or sulfonylureas • Previous (severe) hypoglycaemia • Impaired awareness of hypoglycaemia • Older age & high glycaemic variability • Long duration of diabetes • Chronic kidney disease • Alcohol use • Liver disease • Frailty • Cancer • High comorbidity load
Detection	• Continuous glucose monitoring recommended, if possible, rather than capillary blood glucose monitoring in at-risk patients • Ask patients about any hypoglycaemia incidents at every visit
Prevention	• Delay use of insulin or/and insulinotropic medications, e.g. sulfonylureas, until other treatment options have been exhausted • Consider switching patients on insulin and/or sulfonylureas to other glucose-lowering modalities or de-escalate therapy
Education	• Teach patients about causes, signs, symptoms and management of hypoglycaemia • Advise family members and other close associates, e.g. friends or colleagues at work, about the use of glucagon and hypoglycaemia management
Treatment	• Use enough oral glucose or sugar containing drinks/food • Consider prescribing glucagon to all patients at risk and advise about its use

Fig. 1 Addressing hypoglycaemia related to type 2 diabetes pharmacotherapy. Modified from [1–6]

related to glucose lowering therapy [7–9]. With many people diagnosed with type 2 diabetes still being treated with sulfonylureas in many parts of the world, notably in Asia, current global estimates of those treated with insulin range from 150 to 200 million, typically with a diabetes duration of more than 10 years, coexisting complications and multiple comorbidities [8, 9]. In aggregate, the insulin and/or sulfonylurea treated type 2 diabetes phenotype represents a truly sizable group of people with an intrinsic potential risk of hypoglycaemia, warranting a fresh clinical (triad) approach based on new insights and tools to reduce the hypoglycaemia burden connected with type 2 diabetes pharmacotherapy in general, but not least also addressing the relationship with cardiovascular disease (CVD).

Guidance to pharmacotherapy by differential risk of diabetes medications for severe hypoglycaemia observed in randomized controlled trials

The era of cardiovascular outcome trials (CVOTs) [10, 11], mandated by the American Food and Drug Administration (FDA) in 2008 for any new blood glucose lowering medication [12, 13] has revolutionized modern therapy for people with type 2 diabetes. These CVOTs, designed to exclude cardiovascular harm considering previous unexpected negative experience, collected a wide spectrum of well-defined and adjudicated cardiovascular (CV) outcomes, e.g. a composite of major adverse CV events (MACE) defined as non-fatal myocardial infarction, non-fatal stroke, or CV death (3-point MACE). Outcomes were soon expanded to include hospitalisation for unstable angina, acute coronary syndromes, re-vascularisation, and hospitalisation for heart failure (hHF) [10, 11, 14]. Furthermore, microvascular renal and retinal

outcomes were assessed as well as level 3 severe hypoglycemic events (SHEs) (Fig. 1) relating to the randomised blood glucose lowering medication [1–3, 10, 11, 14–23]. Level 1 and 2 hypoglycaemic events were also often evaluated, especially in insulin or sulfonylurea/gliptin CVOTs [1, 3, 4, 15–18, 22, 23].

Meanwhile, some 30 such trials have reported their outcome results [24]. Together with shorter term randomized metabolic trials with a minimum of 24 weeks follow-up, including also cardio-metabolically unhealthy people without diagnosed diabetes, they have opened new avenues for the guidance of targeted safe and successful pharmacotherapy of type 2 diabetes. To establish a living data base of randomized controlled trials in type 2 diabetes for continuous evaluation of drug specific benefits and harms, we recently have been able to study a substantial data set involving 481,914 participants, 13 different drug classes and 26 outcomes by network meta-analysis [24]. Information has also been collected concerning the comparative risk of SHEs connected with the randomized administration of blood glucose lowering drugs. Notably, against an estimated background risk of 60 SHEs per 1000 patients over five years seen in the control populations on standard treatments, Table 1 shows the absolute and relative changes in risk for SHEs together with the HbA_{1c} lowering efficacy associated with the randomized use of the different drug classes or treatment strategies in relation to the observed CV benefit and drug adverse events [24].

Taking this analytical network approach as a useful new tool for guidance to minimize the hypoglycaemia burden of diabetes pharmacotherapy, the data indicate (Table 1) that the highest risk (about fivefold higher) relates to therapy with sulfonylureas and basal-bolus insulin regimens, whereas novel therapies with sodium-glucose transport protein 2 inhibitors (SGLT2is) or glucagon-like peptide-1 receptor agonists (GLP1-RAs) have minimal risk of hypoglycaemia, or even show a potential reduction with the non-steroidal mineralocorticoid receptor antagonist finerenone (see chapter "Considering Potential Pathogenetic Factors"). Moreover, all latter compounds yield a significant reduction of all cause death along with a broad cardiorenal benefit, whilst GLP1-RAs/SGLT2is provide a robust HbA_{1c}-lowering effect. It seems reasonable, therefore, to conclude that the more recent drug therapy options, if possible, should be integrated preferentially into the multifactorial risk management of people with type 2 diabetes, particularly in those with the high-risk hypoglycaemia phenotype (see chapter "Recognising high hypoglycaemic risk").

These suggestions are also in line with results of the randomised, controlled Glycaemia Reduction Approaches in Type 2 Diabetes: A Comparative Effectiveness (GRADE) Study [25–27] that reported frequencies for SHEs with the sulfonylurea glimepiride of 2.2% versus 1.0% with the GLP-1 RA liraglutide, 0.7% with the dipeptidyl peptidase 4 (DPP-4) inhibitor, sitagliptin, and 1.3% with long acting glargine insulin in individuals with short-term type 2 diabetes at low CV risk over a five year follow-up [25]. Given the close correlation between SHEs and less severe level 1 or 2 hypoglycaemic events [1–4, 15], the findings of the network meta-analysis on SHEs (Table 1) should also apply to estimating the overall hypoglycaemia risk more broadly, helping to reduce the number of persons at risk for hypoglycaemia as well as the numbers of hypoglycaemic events in general, though costs and availability, are of course always an issue for a balanced approach.

Recognising high hypoglycaemic risk and embracing the bi-directional association between SHEs and CV outcomes as indicating a common at-risk phenotype

Striving for a clinically sound, but also cost-oriented approach, it is important to recognise individuals at high risk of hypoglycaemia proactively, based on assessing the presence of specific risk factors as listed in Fig. 1 and starting by asking patients about any hypoglycaemic incidents at every clinic visit. As apparent, a wide spectrum from high glycaemic variability, hypoglycaemia unawareness, to alcohol use, liver or renal disease, older age, high comorbidity load, frailty and cancer may signal risk, especially in the context of insulin, sulfonylurea or other insulinotropic therapies. The information obtained should then be used for individual patient education and potential drug treatment adaptation according to the insights derived from updated network meta-analyses [24] discussed above.

Beyond that, the recently recognised high-risk hypoglycaemia phenotype at dual bi-directional risk may pose particular challenges. Based on post hoc analyses of the Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS) [19], we described a robust bi-directional association between SHEs and CV events. These findings not only showed greater risk of CV events after SHEs, as reported in previous publications [1, 3, 4, 16–18, 22, 23, 28–30], but conversely, also greater risk of SHEs after non-fatal CV events, suggesting a common at-risk type 2 diabetes frail phenotype of patients who are susceptible to both events. Thus, SHEs in many, if not most, instances—rather than being causative of MACE, hospitalization for hHF, or all-cause mortality (ACM)—may simply be indicative of patients with a frail type 2 diabetes phenotype who are at high risk of both outcomes likely due to a multitude of coexisting risk factors [19, 20].

In subsequent post hoc analyses of the Exenatide Study of Cardiovascular Event Lowering (EXSCEL),

Table 1 Benefits and harms of pharmacotherapy for type 2 diabetes

Interventions	All-cause death (OR, 95%CI)	Non-fatal myocardial infarction (OR, 95%CI)	Non-fatal stroke (OR, 95%CI)	Hospitalisation for heart failure (OR, 95%CI)	3-P MACE (OR, 95%CI)	kidney progression (OR, 95%CI)	Health-related Quality of life score (SMD, 95%CI)	Haemoglobin A1c change (MD, 95%CI)	Severe hypoglycaemia (Absolute risk change from a reference of 60 per 1000 patients x 5yrs)	Severe hypoglycaemia (OR, 95%CI)	Drug specific adverse events (OR, 95%CI)
SGLT2 inhibitors	**0.88 (0.83 to 0.94)**	**0.90 (0.82 to 0.98)**	0.99 (0.88 to 1.11)	**0.66 (0.60 to 0.73)**	**0.89 (0.82 to 0.95)**	**0.61 (0.55 to 0.68)**	**0.31 (0.11 to 0.52)**	**-0.59 (-0.63 to -0.54)**	6 fewer (12 fewer to 1 more)	0.90 (0.79 to 1.02)	**Genital infection 3.32 (2.90 to 3.80)** **Ketoacidosis due to diabetes 2.08 (1.45 to 2.99)**
GLP-1 receptor agonists	**0.88 (0.82 to 0.93)**	**0.92 (0.85 to 0.98)**	**0.85 (0.77 to 0.94)**	**0.91 (0.83 to 0.99)**	**0.86 (0.80 to 0.92)**	**0.84 (0.75 to 0.94)**	**0.19 (0.09 to 0.30)**	**-0.85 (-0.90 to -0.80)**	1 fewer (6 fewer to 3 more)	0.98 (0.90 to 1.06)	**Severe gastrointestinal events 2.01 (1.44 to 2.80)**
Finerenone	**0.89 (0.79 to 1.00)**	0.91 (0.74 to 1.12)	1.00 (0.82 to 1.22)	**0.78 (0.66 to 0.92)**	—	**0.84 (0.74 to 0.94)**	—	0.09 (-0.30 to 0.48)	**21 fewer (33 fewer to 2 fewer)**	**0.64 (0.43 to 0.96)**	**Hyperkalaemia leading to hospitalisation 5.92 (3.02 to 11.62)**
Tirzepatide	0.81 (0.47 to 1.37)	0.69 (0.08 to 6.10)	—	0.65 (0.17 to 2.44)	0.88 (0.26 to 3.06)	0.60 (0.09 to 4.14)	**0.47 (0.20 to 0.73)**	**-1.74 (-1.93 to -1.56)**	7 more (34 fewer to 101 more)	1.12 (0.42 to 3.01)	**Severe gastrointestinal events 4.49 (1.93 to 10.43)**
Metformin	0.83 (0.67 to 1.04)	0.86 (0.68 to 1.09)	0.97 (0.71 to 1.33)	1.45 (0.28 to 7.36)	—	1.61 (0.36 to 7.27)	0.06 (-0.25 to 0.37)	**-0.78 (-0.91 to -0.65)**	39 more (6 fewer to 116 more)	1.73 (0.89 to 3.35)	—
Alpha-glucosidase inhibitors	0.60 (0.21 to 1.77)	0.33 (0.06 to 1.92)	9.41 (0.76 to 116.23)	3.25 (0.13 to 82.49)	—	—	0.04 (-0.35 to 0.43)	**-0.61 (-0.72 to -0.50)**	16 more (41 fewer to 197 more)	1.29 (0.31 to 5.41)	—
Thiazolidinediones	0.95 (0.83 to 1.09)	0.97 (0.81 to 1.15)	0.85 (0.70 to 1.03)	**1.54 (1.27 to 1.88)**	0.91 (0.73 to 1.14)	0.95 (0.70 to 1.29)	0.22 (-0.13 to 0.56)	**-0.65 (-0.73 to -0.57)**	22 more (2 fewer to 57 more)	1.40 (0.96 to 2.07)	**Major osteoporotic fractures 1.60 (1.03 to 2.48)**

Table 1 (continued)

DPP-4 inhibitors	1.01 (0.95 to 1.08)	1.01 (0.92 to 1.11)	0.91 (0.80 to 1.03)	1.05 (0.95 to 1.17)	1.01 (0.92 to 1.12)	1.03 (0.91 to 1.17)	0.04 (-0.12 to 0.20)	**-0.56 (-0.60 to -0.52)**	**6 more (0 more to 13 more)**	**1.11 (1.00 to 1.24)**	—
Sulfonylureas	1.10 (0.96 to 1.26)	1.00 (0.82 to 1.21)	1.05 (0.83 to 1.32)	1.00 (0.80 to 1.25)	1.06 (0.86 to 1.31)	0.94 (0.75 to 1.18)	0.23 (-0.21 to 0.66)	**-0.97 (-1.18 to -0.77)**	**186 more (134 more to 246 more)**	**5.11 (3.78 to 6.90)**	**Neuropathy 1.22 (1.02 to 1.45)**
Meglitinides	1.52 (0.49 to 4.72)	0.28 (0.05 to 1.59)	1.70 (0.25 to 11.37)	—	—	—	0.19 (-0.31 to 0.68)	**-0.68 (-0.91 to -0.45)**	109 more (3 fewer to 345 more)	3.19 (0.95 to 10.67)	—
Basal insulin	1.10 (0.81 to 1.48)	0.98 (0.47 to 2.06)	0.83 (0.37 to 1.88)	0.97 (0.65 to 1.44)	—	0.97 (0.77 to 1.22)	0.13 (-0.09 to 0.34)	**-0.73 (-0.94 to -0.52)**	**72 more (44 more to 106 more)**	**2.38 (1.82 to 3.11)**	—
Basal-Bolus insulin	0.79 (0.19 to 3.32)	0.33 (0.03 to 3.27)	0.60 (0.10 to 3.48)	—	—	—	—	**-0.69 (-0.89 to -0.49)**	**179 more (3 more to 534 more)**	**4.93 (1.06 to 22.92)**	—
Bolus insulin	0.48 (0.15 to 1.59)	1.18 (0.40 to 3.51)	0.86 (0.16 to 4.48)	0.64 (0.07 to 6.22)	—	2.68 (0.11 to 66.18)	-0.07 (-0.26 to 0.12)	**-0.74 (-0.91 to -0.56)**	**76 more (17 more to 168 more)**	**2.47 (1.31 to 4.64)**	—
Standard treatments	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference

High to moderate certainty evidence	**Low to very low certainty evidence**
Among the most effective	Possibly among the most effective
Among the intermediate effective	Possibly among the intermediate effective
Not convincingly different from standard treatment	Possibly not convincingly different from standard treatment
Among the intermediate harmful	Possibly among the intermediate harmful
Among the most harmful	Possibly among the most harmful

Modified from [24]

we were able to confirm the bi-directional relationship between SHEs and CV events and validate this particularly vulnerable frail type 2 diabetes phenotype with high Charlson-Co-Morbidity scores [21]. Individuals at dual risk of SHEs and CV events were further characterized by being older (in their late sixties), having a 4-year longer duration of diabetes (more than 15 years), and were more likely (80% vs. 37%) to be insulin treated (and with a higher dose) at study entry, with a further increase of insulin users within the trial [21]. Almost all had a prior CV event either at study baseline preceding the first SHE in the study or occurring before an SHE during the study. Some 43% had stage 3 chronic kidney disease at study entry, and more than one-third had a history of heart failure, with all these factors adding up to increased SHE risk and risk of fatal and nonfatal CV events, hHF events, but also a higher risk for non-CV events, cancer events and ACM [21].

The bi-directional nature of the hypoglycaemia-CV-events-relationship has also been confirmed in a combined analysis of the Cardiovascular and Renal Microvascular Outcome Study with Linagliptin (CARMELINA) trial in patients with a long duration of type 2 diabetes and prevalent chronic kidney disease, and the

Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients with Type 2 Diabetes (CAROLINA) in patients with type 2 diabetes and elevated cardio-renal risk [31]. Both studies also assessed less severe levels of hypoglycaemia. Moreover, this new dual-risk concept has recently been recognised in the 2023 ESC-Guidelines for the management of cardiovascular disease in patients with diabetes [32]. In addition, patient characteristics of the Hypoglycaemia REdefining SOLutions for better liVEs (Hypo-RESOLVE) project and data extracted from electronic patient records of a hospital emergency department in UK seem to underpin the key importance of a multitude of adverse prognostic markers or comorbidities being present in those with hypoglycaemia including in those with less severe events [4, 33]. Though hypoglycaemia in many cases may not be a causative factor for cardiovascular complications, its occurrence nevertheless should be understood as a potential warning signal of complex risks [notably also of cancer 18, 21, 34, 35] requiring special attention by the healthcare providers [19, 21, 31, 32].

Interestingly, scoring patients' individual overall hypoglycaemic risk based on similar characteristics as we observed in the vulnerable frail phenotype at dual risk for CV events and SHEs in EXSCEL [21, see above], the DEVOTE trialists recently demonstrated in a post-hoc analysis that the highest rates of SHEs, MACE and ACM occurred in those participants within the highest hypoglycaemic risk score quartile [36]. Not unexpectedly, however, this quartile also encompassed higher proportions with pre-existing CVD, reduced GFR, longer diabetes duration, higher age, obesity and female sex [36], again alluding to the clinical reality of the complex association between hypoglycaemia and adverse vascular events in type 2 diabetes. In essence, the association obviously may not entirely be explained by comorbid illness alone, as on top also causative linkages may play a role on the individual level (see also next chapter below).

At any rate, embracing these new insights, the key consequences likely should be: Recognise proactively individuals with high hypoglycaemic risk based on specific risk factors and especially the patient phenotype at dual risk for SHEs and CV events (due to prior CVD, HF, CKD, high comorbidity, frailty, cancer), go for a cardiocentric approach as for patients with established CVD, choose GLP1-RAs &/or SGLT2is for blood glucose lowering therapy as available, regardless of HbA_{1c} concentration, and avoid use of insulin/sulfonylureas as much as possible, thereby minimising the risk of hypoglycaemia both in terms of number of patients being exposed as well as number of hypoglycaemic events (see also Fig. 1 and Table 1). In settings with economical constraints for novel glucose lowering drugs, the alternate use of basal insulins and/or insulin secretagogues with relatively lower hypoglycaemic risk such as generic gliptins or gliclazide MR may offer reasonable options [2, 17, 19, 29], as underscored also in Table 1.

Considering potential pathogenetic factors and acute and longer-term interrelationships

Having emphasized the utility of a common at-risk phenotype concept for therapeutic considerations in the longer term, one also must not ignore the acute CVD risks of hypoglycaemia, especially in those alluded to above with a multitude of risk factors for hypoglycaemia (Fig. 1). Figure 2 provides a comprehensive list of pathogenic mechanisms on the heart and vasculature. Cardiac autonomic dysfunction may be exacerbated and sustained proinflammatory or prothrombotic effects be induced [37–46]. SHEs in particular have been associated with hypokalaemia, prolongation of the electrocardiographic QTc interval, and neuro-sympathetic overdrive with marked increase of blood pressure, tachycardia, and various kinds of arrhythmias, often necessitating emergency hospitalization for life-threatening complications [37–46]. In line with this, a recent meta-analysis based on 12 studies, though many of these being observational, sought to evaluate associations between reported hypoglycaemic events and the risks of a broad spectrum of arrhythmias, i.e. from QTc-prolongation, to bradycardia or ectopic beats, to atrial fibrillation, and found a 27% increase, yet with moderate heterogeneity and usually not in a close time relationship with hypoglycaemia [47]. Opportunistic arrhythmia monitoring of individuals with a hypoglycaemic event might be useful, perhaps with available inexpensive devices, as arrhythmia risk was, not surprisingly, also aligned with an 80 to 90% increase of both ACM and CV mortality [47]. In addition, looking for early signs and symptoms of heart failure is advisable in this particularly vulnerable patient phenotype with complex comorbidities.

The mutual inter-relationship between hypoglycaemia and heart failure events is particularly evident in terms of consistency and strength in all publications looking at the bi-directional association of hypoglycaemia before and after CV events [19, 21, 31]. Mechanistically, it should be noted that brain natriuretic peptides (BNPs) released from the dysfunctional failing heart also have insulin sensitizing effects at the level of skeletal muscle and adipose tissue, potentially increasing the risk of hypoglycaemia in the context of relative hyperinsulinemia [48–51]. Reduction of circulating BNP levels by finerenone may well explain the reduced risk of severe hypoglycaemia apparent in the CVOTs of this drug seen in our network analysis (Table 1) [24]. Though more proactive studies on these pathophysiological linkages are needed, there appears to be an opportunity to augment the earlier detection of heart failure, as recently recommended by all

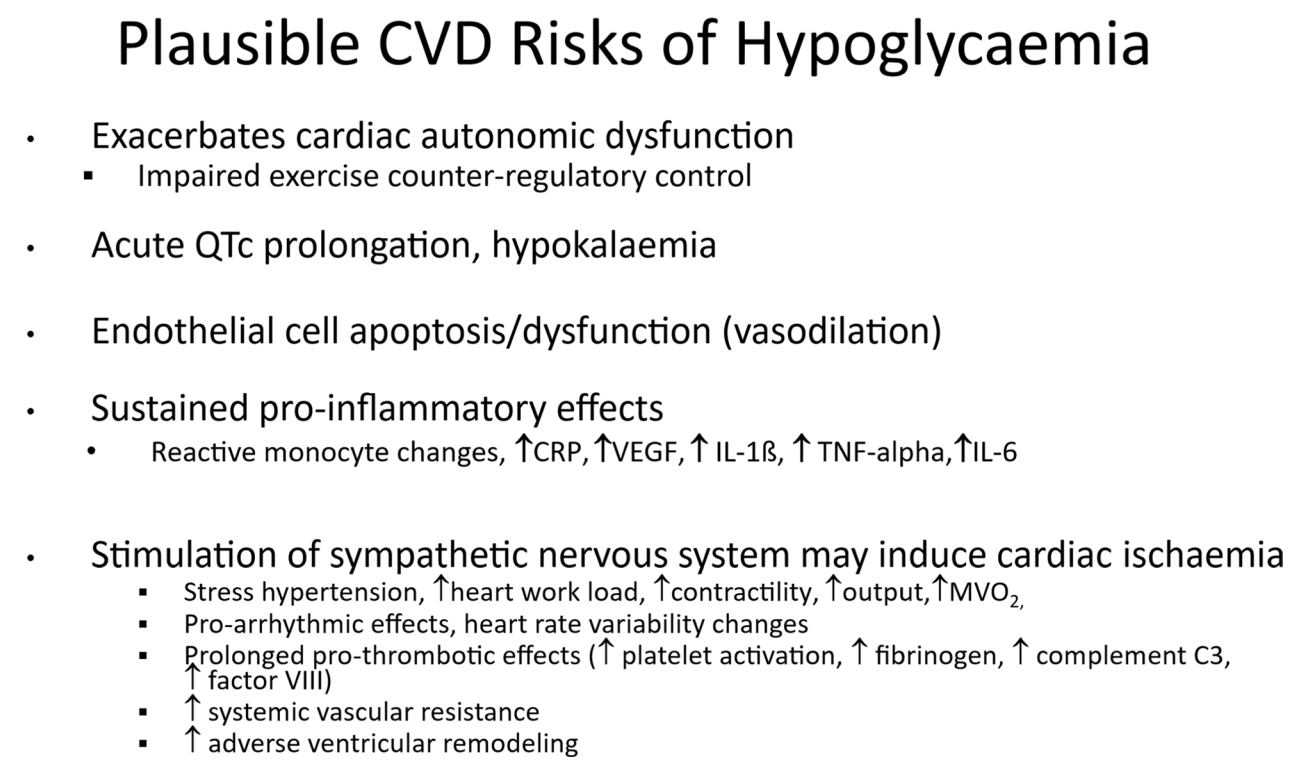


Fig. 2 *Abbreviations* CRP, C-reactive protein; IL-1ß, interleukin-1ß; IL-6, interleukin-6; MVO^2, myocardial volume oxygen; QTc, QTc interval on ECG; TNF-alpha, tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor

international heart failure guidelines. Moreover, abnormal mitochondrial metabolomic signatures indicative of developing CV and HF events seem to be reversible by appropriate drug treatment [52].

Attempts to further elucidate putative mechanisms by looking at the temporal relationships between hypoglycaemic events, especially SHEs, and CV events, have yielded variable results. Undoubtedly, both events may occur closely interrelated in time including acute CV and non-CV death [1, 3, 4, 15, 18, 21, 36–46]. In our own EXSCEL database of 116 double event cases, four participants exhibited both a SHE and a CV event on the same day [21]. Of those, three were taking insulin at baseline and the other had commenced insulin therapy prior to the events. Two died within 2 days from a CV death and a non-CV death, while the other two remained free from further events during the trial [21], underpinning the huge variation of outcomes on the individual level.

Population based temporal relationships have been described ranging from a median lag interval of 1.56 years (interquartile range, 0.84 to 2.41) between SHEs and a first MACE in the original report on severe hypoglycaemia from the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial [29] to—and in marked contrast—an association between hypoglycaemic episodes of any kind in the previous 10 days and death, acute CVD and retinal disorders in both type 1 and type 2 diabetes in the Hypo-RESOLVE cohort [4]. Moreover, within the range of hypoglycaemia defined by levels 1, 2 and 3 (as shown in Fig. 1), no evidence of a threshold was found in Hypo-RESOLVE at which risk of these consequences suddenly became pronounced [4]. Concluding in aggregate from the wide array of temporal relationships observed, all factors compiled in Fig. 2 remain on the list as plausible explanations for the association between hypoglycaemia and CV events, likely operating in a personal mix on the individual level including sustained proinflammatory, prothrombotic and proarrhythmic effects. Importantly, this adverse pathogenic setting may deploy the potential to further aggravate any coexisting, often high, comorbidity load and to complicate preexisting established cardiovascular and microvascular complications.

Of further note in the context of considering the temporal relationships, of 87 patients in ADVANCE with both a SHE & MACE, 40 exhibited a SHE before MACE vs 47 had SHEs after MACE, though only the first sequential order has been analysed in detail [29]. These figures are quite comparable with our own experience confirming the bi-directional nature of this relationship in EXSCEL which showed that of the 116 participants with double events as mentioned above, 66 had these events after an SHE during the trial and 50 participants

had an SHE after a nonfatal CV or hHF event during the trial [21], suggesting also in the ADVANCE population the existence of a bi-directional relationship between SHEs and CV events.

In terms of the temporal relationships in EXSCEL, the figures indicated in general about a doubling of hazards (after adjustment for the full list of covariates) regarding combined CV events (MACE/hospitalisaton for acute coronary syndrome = hACS/hHF) following SHEs and of SHEs following combined nonfatal CV events (nonfatal MACE/hACS/hHF) that were approximately constant over time, the latter being compatible with the BNP-hypothesis discussed above. The hazard for ACM following hypoglycaemia, however, changed over time ($p < 0.001$), being greatest (~ fivefold) soon after an SHE, decreasing over the first 2 years to about normal levels and increasing again after 3 years post-SHE, although the numbers at risk beyond 3 years decreased and 95% Confidence Intervals widened substantially [21].

Continuous glucose monitoring as an empowering tool to minimise hypoglycaemic emergencies as well as the need for other hospitalisations

Most recently, the UKPDS 44-year outcome results have once and for all reinforced the paramount importance of establishing early good glycaemic control to assure the best possible long-term survival for people with type 2 diabetes [53]. Hence, maintaining near-normoglycaemia in these individuals is a prerequisite and plays a central role within the established multispecialty care of people with cardio-renal and metabolic diseases [2, 5, 54]. At the same time, however, it requires appropriate glycaemic monitoring. Initiation of CGM, both real time or intermittently scanned, i.e. isCGM, represents a major advance for improved clinical management—superior to capillary blood glucose monitoring (BGM)—not only in type 1 diabetes, but also in type 2 diabetes, especially if insulin treated [54–56]. A retrospective observational cohort study comprising people with insulin treated type 2 diabetes within the Veterans Affairs Health Care System, demonstrated convincingly that CGM use was linked to significantly lower HbA_{1c} levels by about 0.4% (vs. non-use), as well as to fewer clinical events requiring hospitalisation or emergency room visits for hypoglycaemia, hyperglycaemia, or any cause over a 12 month follow-up (Hazard Ratio = 0.89; 95% CI 0.82–0.97; $p = 0.004$) in this cohort of some 15 000 individuals [55].

Of note, very similar data were obtained from the Swedish National Diabetes Register [56]. The baseline-adjusted difference in the mean HbA_{1c} change for isCGM vs BGM control participants in the type 2 diabetes subgroup on multiple daily insulin injections was − 3.7 mmol/mol (− 0.34%) at 6 months, and this was maintained at 24 months. In addition, this cohort experienced a significantly lower relative risk (RR) of admission for severe hypoglycaemia (0.51; 95% CI 0.27–0.95; $p = 0.034$), stroke (0.54; 95% CI 0.39–0.73; $p < 0.001$), acute non-fatal myocardial infarction (0.75; 95% CI 0.51–0.99; $p = 0.047$) or hospitalisation for any reason (0.84; 95% CI 0.77–0.90; $p < 0.001$). For those using basal insulin alone (T2D-B), the baseline-adjusted difference in the change in HbA_{1c} for isCGM-users vs BGM control participants was − 3.5 mmol/mol (− 0.32%) at 6 months and maintained at 24 months. Alongside the metabolic improvement, isCGM-users in the T2D-B cohort had a lower RR of hHF (0.63; 95% CI 0.46–0.87; $p = 0.006$) or hospitalization for any reason (0.76; 95% CI 0.69–0.84; $p < 0.001$).

These results strongly underpin the overall utility of using CGM in type 2 diabetes [57, 58]. Beyond that, they also specifically appear to suggest CGM use as a powerful new tool in those at dual risk of hypoglycaemia and CV events, particularly in the context of insulin therapy (see also Fig. 1), with a substantial impact in terms of effectively reducing the need for hospitalisations, including for hypoglycaemic and CVD emergencies. Thus, CGM has emerged as a strong contender to help minimise the burden of hypoglycaemia, although the costs involved may be considerable. They appear justifiable, however, at least in settings of serious life-threating dangers of severe hypoglycaemia or advanced CV complications, with careful selection of individuals and, if required, perhaps for time limited periods and confined to those experiencing complex and rapidly evolving disease changes, as those in particular may show refractory recurrence of hypoglycaemic episodes, especially if they need to continue on intensified insulin therapies or sulfonylureas for various reasons.

Perspectives

Each of the new insights and tools detailed above comprise important steps forward in their own right, while used together in a synergistic manner synthesizing a strategic triad approach, they for the first time in over 100 years appear to provide the capacity to mitigate the threats of hypoglycaemia related to type 2 diabetes pharmacotherapy (Fig. 1). Meanwhile, curing type 2 diabetes by preventing it at the level of pre-diabetes, or even reversing it years after its overt manifestation, may be within reach during the second quarter of the twenty-first century given the major new advances in diabetology [59–63]. Effectively reducing body weight of obese and overweight people with and without type 2 diabetes by some 10 to 30% plays a pivotal role in this endeavour, first demonstrated by bariatric surgery [59, 60], followed by studies successfully exercising comprehensive and rigid life style management, e.g. the DiRECT study [63], and most recently seen with GLP1-RAs or co-agonists like semaglutide and tirzepatide with the development of

further co-agonists pending [61, 62]. So, perhaps paving the way towards a world without overt type 2 diabetes and, hence, without the need of treatment with insulin or sulfonylureas may also envisage a world where the burden of hypoglycaemia related to type 2 diabetes pharmacotherapy has been consigned to history.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

Author details
[1]Forschergruppe Diabetes E.V. at the Helmholtz Center, Munich, Neuherberg, Germany
[2]IRCCS MultiMedica, Milan, Italy
[3]Division of Cardiology, University of Texas Southwestern Medical Center, Dallas, USA
[4]Diabetes Trials Unit, Radcliffe Department of Medicine, University of Oxford, Oxford, UK
[5]Diabetes Research Group Inc. at Munich Helmholtz Center, Ingolstaedter Landstr. 1, 85764 Neuherberg, Munich, Germany

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