Diabetes Ther (2024) 15:897–915
https://doi.org/10.1007/s13300-024-01556-z

REVIEW

Expert Opinion on Current Trends in the Use of Insulin in the Management of People with Type 2 Diabetes from the South-Eastern European Region and Israel

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Received: December 18, 2023 / Accepted: February 14, 2024 / Published online: March 12, 2024
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ABSTRACT

Despite the availability of various antihyperglycaemic therapies and comprehensive guidelines, glycaemic control in diabetes management has not improved significantly during the last decade in the real-world clinical setting. Treatment inertia arising from a complex interplay among patient-, clinician- and healthcare-system-related factors is the prime reason for this suboptimal glycaemic control. Also, the key factor leading to inadequate glycaemic levels remains limited communication between healthcare professionals (HCPs) and people with type 2 diabetes (PwT2D). Early insulin administration has several advantages including reduced glucotoxicity, high efficacy and preserved β-cell mass/function, leading to lowering the risk of diabetes complications. The current publication is based on consensus of experts from the South-Eastern European region and Israel who reviewed the existing evidence and guidelines for the treatment of PwT2D. Herein, the experts emphasised the timely use of insulin, preferably second-generation basal insulin (BI) analogues and intensification using basal-plus therapy, as

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the most-potent glucose-lowering treatment choice in the real-world clinical setting. Despite an increase in the use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs), the experts urged timely insulin initiation for inadequate glycaemic control in PwT2D. Furthermore, the combination of BI and GLP-1 RA addressing both fasting plasma glucose and post-prandial excursions as a free- or fixed-ratio combination was identified to reduce treatment complexity and burden. To minimise discontinuation and improve adherence, the experts reiterated quality, regular interactions and discussions between HCPs and PwT2D/carers for their involvement in the diabetes management decision-making process. Clinicians and HCPs should consider the opinions of the experts in accordance with the most recent recommendations for diabetes management.

Keywords: Clinical practice; Insulin initiation; Intensification; Titration; Type 2 diabetes; South-Eastern European region; Israel

Key Summary Points
Clinical inertia, poor drug adherence and low disease awareness are crucial challenges in achieving glycaemic targets, especially in the real-world clinical setting
Experts from six European countries and Israel reviewed current evidence on the status of insulin initiation in insulin-naïve people with type 2 diabetes, along with considerations in special populations
Early initiation of a combination therapy, without undue delay of insulin initiation, can be instrumental in achieving and sustaining glycaemic targets as well as attenuating the development of chronic complications
A less complex treatment regimen that requires fewer adjustments and measurements may facilitate timely achievement of glycaemic targets in routine clinical practice

INTRODUCTION

Type 2 diabetes (T2D) is a complex metabolic disorder involving impaired β-cell function and decreased insulin sensitivity [1]. It is associated with increased risk of morbidity (long-term microvascular and macrovascular complications) and mortality [2], and the increasing incidence poses a significant health burden [3]. The prevalence of diabetes in Europe is about 9.2% with about 61.4 million people living with diabetes and is expected to increase up to 10.4% by the year 2025 [4].

Besides glycaemic control, the updated T2D management guidelines emphasise simultaneous management of glycaemia and body weight with use of medications that provide cardiorenal protection [5, 6]. Most of the guidelines recommend individualising medication choice and treatment targets/goals based on patient characteristics [such as cardiovascular (CV) risk, comorbidities, and psychosocial determinants] as well as patient preferences [5–9]. Timely initiation and intensification of basal insulin (BI) is further recommended in case of inappropriate glycaemic control. However, real-world evidence indicates that despite an increasing use of non-insulin medications like glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter 2 inhibitors (SGLT-2i), BI remains a fundamental part of T2D management [10].

Early use of insulin may modify the disease course by restoring residual β-cell function [11] and by attenuating the risk of microvascular and long-term macrovascular complications [12, 13]. In newly diagnosed people with type 2 diabetes (PwT2D), early intensive insulin therapy reduces the level of tumour necrosis factor-alpha (TNF-α) and improves endothelial function [12]. These findings altogether indicate that insulin could have pleiotropic effects on putative CV risk factors and endothelial dysfunction [12].

Optimal therapy in T2D management requires a balance between the benefits of glycaemic control and the risk of hypoglycaemia, which may improve adherence and quality of life and result in reduced morbidity and healthcare resource utilisation [14–16]. However, many individuals

experience years of inadequate glycaemic control because of delays in treatment initiation/intensification, especially during transition from oral antidiabetic drugs (OADs) to insulin [17]. A complex interplay among patient-, clinician-, and healthcare-system-related factors leads to treatment inertia. Furthermore, adequate titration after initiating insulin remains a challenge, driven by multiple physician- and patient-related factors, including fear of hypoglycaemia, weight gain or impact on daily life and lack of time or resources for healthcare professionals (HCP), assistance and education on effective titration [17].

Herein, the experts reviewed the current evidence on insulin use, defined its position in T2D management and provided medical recommendations for timely use of insulin in PwT2D uncontrolled with non-insulin therapy, including people with diabetes-related complications.

METHODS

This article is based on the discussion among endocrinology and diabetology experts from South-East Europe and Israel during an advisory board meeting held in Bucharest, Romania, on 10 June 2023, which was facilitated by Sanofi. Prior to the meeting, a set of topics related to insulin treatment in T2D (timing of insulin initiation, right insulin treatment choice in T2D, in chronic kidney disease [CKD], in cardiovascular disease [CVD], in the elderly, in those with high risk of hypoglycaemia, and ways to improve treatment adherence) were circulated to all the experts. The experts considered publications from the last 5 years, which included meta-analyses, systematic reviews, RCTs, RWE studies and national and international diabetes guidelines. The published evidence on specific topics was gathered and presented during the meeting. The presentations were followed by roundtable discussion that highlighted local differences in clinical practice and led to resolution of any disagreements between experts. The recommendations presented in this article are based on the evidence presented and discussions summarised in the minutes of the meeting.

Given that this expert opinion article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors, no ethical approval was sought.

DISCUSSION

During the expert meeting, participants reviewed the routine clinical practice, current diabetes management guidelines and recommendations followed in the South-Eastern European region and Israel, which particularly focused on patient characteristics and other factors to be considered for selecting a diabetes treatment regimen. During the meeting, the experts univocally agreed that glycaemic control in PwT2D is far from target and that treatment inertia plays a major role in suboptimal glycaemic control. Furthermore, considering the real-world scenarios, the experts sought to provide recommendations for diabetes management based on available clinical evidence and their real-time experience in clinical settings.

Right Time for Insulin Initiation

Timely initiation of insulin in PwT2D has been associated with multi-faceted benefits, such as decreasing glucotoxic effects of hyperglycaemia, preserving β-cell mass/function, improving insulin sensitivity and long-term protection from chronic complications [18]. In clinical practice, the timing of insulin treatment initiation is mostly based on diabetes duration and if glycaemic targets are not attained with the use of OADs (single/multiple) or other injectables (Table 1).

Newly Diagnosed T2D

Multiple studies have shown that early short-term intensive insulin therapy in newly diagnosed individuals with T2D can improve β-cell function and insulin resistance by eliminating glucotoxicity and lead to drug-free glycaemic

Table 1 Indication for insulin initiation or intensification in people with type 2 diabetes

Circumstance	Remark	Therapy	Potential for de-escalation
Acute glycaemic emergency			
Diabetic ketoacidosis Hyperglycaemic hyperosmolar state		i.v. pump, followed by MDI/sc. pump	After treatment
Acute glycaemic deterioration			
Acute stress (i.e., stroke, sepsis) Surgery Steroid therapy	Severe or symptomatic hyperglycaemia	BI/MDI/sc. pump	After cause is treated
Chronic hyperglycaemia			
Newly diagnosed diabetes	Independent of glycaemia levels (to induce remission)	MDI/sc. pump	After days/weeks
	Severe or symptomatic hyperglycaemia	BI/MDI /sc. pump	After weeks/months
On single non-insulin agent	Severe or symptomatic hyperglycaemia	BI/MDI /sc. pump	After days/weeks
On multiple non-insulin agents including injectables	Glycaemia above personal target	BI	Possible on long term
	Severe or symptomatic hyperglycaemia	BI/MDI /sc. pump	After weeks/months
On combination of BI and non-insulin agents including injectables	Glycaemia above personal target	MDI /sc. pump	Possible on long term

Severe or symptomatic hyperglycaemia—unexpected weight loss, polyuria, polydyspia, HbA1c > 10%, blood glucose > 16.7 mmol/l

BI basal insulin, *i.v. pump* continuous intravenous insulin pump therapy, *MDI* multiple daily insulin injection, *sc. pump* continuous subcutaneous insulin pump therapy

remission for up to 2 years [19]. Furthermore, insulin as a treatment option is used in cases of severe hyperglycaemia (blood glucose [BG] levels > 300 mg/dl [16.7 mmol/l], HbA_{1c} > 10%) [7, 20, 21].

However, the experts agreed that de-escalation to OADs/SGLT-2i/GLP-1 RA after early insulin treatment is possible to preserve long-lasting glycaemic control, considering the disease pathophysiology and recommendations from current guidelines [6, 21].

Individuals on Single OAD with Uncontrolled Glycaemic Target

In instances where HbA_{1c} remains above target for 3 months after initiating OAD, the American Diabetes Association (ADA)/ American Association of Clinical Endocrinology

(AACE) guidelines recommend adding a second antidiabetic agent [6, 7]. The choice should be based on multiple factors including hypoglycaemia risk, obesity, access/cost and comorbidities. Individuals with a history of/at high risk of hypoglycaemia should preferentially be initiated with GLP-1 RA, SGLT2i, dual gastric inhibitory polypeptide (GIP)/GLP-1 RA, thiazolidinedione or DPP-4i. Furthermore, dual GIP/GLP-1 RA, GLP-1 RA or SGLT2i class is preferred in individuals with the additional goal of weight loss. BI is advised in instances of severe hyperglycaemia (HbA_{1c} > 10%), with or without initiation/titration of GLP-1 RAs. However, it should be noted that for early combination therapy, incretin-based therapies are not recommended [7].

Apart from the use of BI in case of very high (symptomatic) levels of fasting plasma glucose (FPG) and HbA_{1c}, the experts also suggested to include BI in individuals where the use of GLP-1 RAs is contraindicated, there is lack of direct indication for using SGLT-2i or treatment targets are unlikely to be achieved with a single agent.

Individuals on Multiple OADs

Herein, if the individualised HbA_{1c} goal is not achieved or the glycaemic control is not maintained after 3 months of dual or triple non-insulin therapy (including a GLP-1 RA), the experts recommended initiating a BI treatment [5, 6].

Indications for Insulin Treatment in T2D

Absolute Indications for Insulin Treatment in T2D

The experts identified indications when insulin is required for appropriate diabetes management including diabetic ketoacidosis (DKA), pregnancy (uncontrolled glycaemia with lifestyle intervention) and extreme glycaemia [22–24].

Hyperglycaemic hyperosmolar state (HHS), which is more prevalent in PwT2D, and DKA are two cases of significant decompensation among the metabolic emergencies that may require management in the intensive care unit. In critically ill and mentally obnubilated individuals with DKA or HHS, continuous intravenous insulin is the standard of care followed by transition to subcutaneous (SC) insulin regimens [25].

In case of acute medical/surgical conditions, where individuals previously not treated with insulin demonstrate a need for insulin during the postoperative period, a SC regimen totalling 0.5–0.7 U/kg of body weight can be used [26]. Insulin also remains the first-line therapy for individuals hospitalised for acute illness with significant hyperglycaemia or among those on steroid therapy [26].

During pregnancy, although metformin is commonly prescribed, insulin remains the preferred option for treating hyperglycaemia in gestational diabetes mellitus or pre-gestational T2D as it does not cross the placenta and is effective in controlling glycaemic levels if sufficient dosage is administered [27].

However, given the above medical conditions, all the experts agreed that in routine clinical practice, glycaemic levels are the most prominent reasons for initiation and intensification of insulin treatment.

Glycaemic Levels—Main Criteria for Insulin Initiation

The experts mentioned that even today, glycaemic levels remain the main criteria for initiating insulin. Furthermore, with high FPG and $HbA_{1c} \geq 9.0\%$ and/or symptomatic hyperglycaemia, insulin should be initiated with or without OADs independent of the duration of diabetes. However, the limitation associated with the HbA_{1c} parameter includes lack of information on glycaemic variability (GV) or hypoglycaemia and its unreliability in situations such as older age or renal failure [28]. The experts highlighted that various clinical scenarios may lead to inappropriate HbA_{1c} values. An elevated HbA_{1c} level might be observed in case of anaemia, vitamin-B12 and folate deficiency anaemia, asplenia or severe hyper-bilirubinaemia, whereas false decline in HbA_{1c} may be reported in acute and chronic blood loss, haemolytic anaemia,

end-stage renal disease, splenomegaly or during pregnancy [29].

Considering the above-mentioned interfering factors that might yield false results and misinterpretation of the glycaemic status, the experts asserted the need to have a comprehensive approach using a combination of HbA_{1c} and FPG levels as main parameters for insulin initiation, switching and titration in T2D management.

Additional, Non-mandatory Conditions for Initiating Insulin

Apart from the glycaemic levels, the experts also discussed the use of C-peptide levels and disease duration as indicators for insulin treatment. It has been reported that a stimulated C-peptide concentration of < 0.2 nmol/l may be used as a cut-off for poor β-cell reserve and indicative of requirement of insulin therapy. Additionally, a fasting C-peptide < 0.25 nmol/l alone or in combination with islet cell antibody positivity is a strong predictor for future insulin treatment [30].

Conversely, the experts suggested using C-peptide measurements only at the stage of diabetes diagnosis, i.e., to differentiate type 1 diabetes from T2D. The rationale is that in classical T2D cases, even after many years of onset, C-peptide measurements could be characterised by more-or-less similar insulin secretion corresponding to a close-to-normal C-peptide level leading to misinterpretation of the necessity to initiate insulin. Moreover, lower C-peptide levels can also be observed in PwT2D and glucotoxicity or already on large doses of insulin (e.g., during a hypoglycaemic event) [30, 31]. Hence, the experts recommended that C-peptide levels should be interpreted with caution and in the relevant clinical context.

Recommended Type of Insulin and Regimen

As specified in the 2023 ADA Standards of Care, BI alone is the most convenient initial insulin treatment and can be added to metformin or other OADs and non-insulin injectables [6]. Moreover, the recent ADA/EASD consensus suggests that in case of severe hyperglycaemia (HbA_{1c} > 10%) or evidence of catabolism, BI is preferred as first injectable or as an intensifying option in case of suboptimal control with OADs/GLP-1 RAs [5].

Based on the treatment algorithm from various guidelines, the experts recommended that BI treatment should be initiated in a timely manner, preferably within 3–6 months of inadequate control, with optimal use of single-, dual- or triple OADs and GLP-1 RAs. Additionally, the experts highlighted that compared to neutral protamine Hagedorn (NPH) insulin, all BI analogues have similar or greater reduction in HbA_{1c}/FPG with a reduced risk of overall/nocturnal hypoglycaemia and no differences in body mass index (BMI) [32–34].

In addition to the right choice of insulin preparation, education on appropriate insulin injection technique is also an important determinant of therapeutic success that should be recognised by physicians. This includes administration into appropriate body areas, injection cite rotation and proper care of injection sites to prevent infections or other complications. As per the ADA guidelines, the best practices of insulin administration include insulin injection into subcutaneous tissue in abdomen, thigh, buttock and upper arm. Use of short needles (e.g., 4-mm pen needles) has been recognised as effective and well tolerated compared with longer needles. Additionally, injection site rotation is also extremely important to avoid lipohypertrophy, erratic insulin absorption, increased GV and unexplained hypoglycaemic episodes. Thus, the key elements of a thorough diabetes medical evaluation and treatment plan should include regular assessment of insulin injection sites for lipohypertrophy and evaluating injection technique and device use [6].

Basal-Supported Non-insulin Therapy

Basal-supported non-insulin therapy (previously basal-supported oral therapy [BOT]), comprising BI and non-insulin agents, is an alternative option in clinical settings usually prescribed for outpatients as a once-daily (OD) injection and is preferred over multiple daily injections (MDI)

[35]. The conventional BOT mainly controls FPG with low risk of hypoglycaemia and does not necessarily correct post-prandial glycaemia; hence adequate glycaemic control is not always attained [35].

Several studies have shown strong benefits for glycaemic control and other outcomes upon addition of BI to any non-insulin agent [12, 36]. A simple and easy way to initiate BI and GLP-1 RA is the fixed-ratio combination (FRC) [6, 7] where FRCs have more potent glucose-lowering action with less weight gain and hypoglycaemia compared with intensified insulin regimens [6].

A network meta-analysis and systematic review in PwT2D has confirmed that, compared to NPH, all BI analogues led to a significant reduction in HbA_{1c}/fasting BG and reduced risk of overall/nocturnal hypoglycaemia with no differences in BMI [34, 37]. Furthermore, compared to first-generation analogues (glargine [Gla]-100/insulin detemir [IDet]), second-generation analogues (Gla-300/insulin degludec [IDeg]-100) with a prolonged duration of action and greater flexibility have demonstrated comparable glycaemic control with enhanced safety [38–40].

Herein, the experts agreed with the ADA Standards of Care and recommended initiating GLP-1 RA as the first injectable therapy and BI analogues over NPH as first insulin choice, followed by advancing to combination injectable therapy using GLP-1 RA or dual GIP or GLP-1 RA added to BI. Based on the clinical evidence, the experts emphasised the use of second-generation BI with equivalent glycaemic control and reduced risk of hypoglycaemia compared with first-generation BI.

Notably, apart from selecting the appropriate insulin type, initial dose and titration are key to obtain optimal glycaemic control, with adequate dose titration being the crucial step [6]. In diabetes management, the starting BI doses can be estimated as 10 U/day or based on body weight (0.1–0.2 U/kg/day), which can be individualised according to the degree of hyperglycaemia (AACE recommends 0.2–0.3 U/kg/day for $HbA_{1c} > 8\%$) and titration over days to weeks as needed [6, 7]. Simple regimens of insulin dose self-titration with 1 U/day evaluated for Gla-100 in the INSIGHT study [36] and for Gla-300 in the TITRATION study [41] showed comparable efficacy and safety to titration based on the average 3-day FPG values. This 1 U/day titration regimen, being simple for PwT2D, is preferred by HCPs [36, 41]. However, BI titration in the real-world setting is generally less stringent compared to clinical setup [42].

Experts emphasised that following BI initiation the physicians should empower PwT2D for titrating BI dose to achieve individualised treatment goals.

Meal-Time Insulin (MTI)

People with diabetes have several unmet needs associated with their use of MTI, which mainly include effect on glycaemic levels/variability and associated impacts on optimal management [43]. If injectable therapy is required to reduce HbA_{1c} levels, the AACE guidelines suggest rapid-acting analogues as preferred prandial insulin which can be initiated at the largest meal at 10% of the BI dose or 5U with stepwise addition to other meals as additional glycaemic control is needed [7].

The experts highlighted the advantages of the basal-plus strategy which combines BI with one rapid-acting insulin before the meal that causes the maximal postprandial spike in cases when GLP-1 RA is contraindicated/not accepted or when GLP-1 RA is already used at maximal tolerated dose. Furthermore, the results of the SoliMix randomised controlled trial (RCT) comparing the clinical outcomes with a FRC of Gla-100 and lixisenatide iGlarLixi versus premix biphasic insulin aspart 30 (BIAsp 30; 30% insulin aspart and 70% insulin aspart protamine) showed better glycaemic control with weight benefit and less hypoglycaemia with OD iGlarLixi compared with twice-daily premixed BIAsp 30 [44]. However, studies indicate that advancing to basal-plus strategy increases the risk of hypoglycaemia and body weight gain compared with BOT [45]. It is considered that changing BI to a biphasic (premixed) insulin preparation might strengthen the treatment and may be suitable for individuals reluctant to move to MDI [46]. Based on these factors, the experts recommended restricting the use of the basal-bolus strategy among PwT2D because of the complexity associated with the

need for carbohydrate counting and increased risk of hypoglycaemia and weight gain.

Insulin Treatment Choice for Older Adults with T2D

Older adults (≥ 65 years) with T2D have an increased risk of mortality [47] and higher risk of hypoglycaemia, cognitive impairment, depression, urinary incontinence, persistent pain and frailty than younger adults [48]. The widespread prevalence of multimorbidity complicates the management of T2D in older adults, necessitating individualised approaches [49]. To avoid hypoglycaemia and minimise adverse events (AEs), the glycaemic targets in older adults with T2D are less intense than in younger adults with T2D [50]. Some pros and cons of the use of available insulin regimens in older adults with T2D are listed in Table 2.

The ADA guidelines recommend that for adults ≥ 65 years, glycaemic goals should be individualised depending on personal goals, life expectancy and overall health status and suggest the use of BI in this group [6]. Based on the available evidence and expert consensus, second-generation analogues (Gla-300/IDeg) provide additional benefits over first-generation analogues (Gla-100/IDet) and NPH regarding hypoglycaemia incidence [51, 52].

The results from RCTs comparing the efficacy and safety of first-generation vs second-generation BI analogues (post-hoc analysis of EDITION trials; SENIOR, both comparing Gla-300 vs Gla-100) indicated that Gla-300 provides glycaemic control similar to Gla-100 with reduced risk of nocturnal hypoglycaemia in adults aged ≥ 65 years [53], while significant reduction in hypoglycaemia was seen in adults aged ≥ 75 years [54]. The results from the SWITCH 2 study demonstrated that, compared to Gla-100, IDeg was associated with similar reductions in HbA_{1c} and AEs with a lower risk of hypoglycaemia [55]. This is also evident in pooled analysis from real-world studies where switching to or initiating second-generation analogues is associated with significant improvement in HbA_{1c}, with a low incidence of symptomatic and severe hypoglycaemia [52, 56].

The experts highlighted a simpler treatment regimen and safety as the two most important pillars for improving glycaemic levels in older adults with T2D and emphasised minimising

Table 2 Pros and cons of various insulin regimen in older people with type 2 diabetes

Insulin regimen	Pros	Cons
NPH	Established efficacy Inexpensive	Requires resuspension High risk of hypoglycaemia and weight gain Variable glucose-lowering effect per injection
First-generation BI analogues (Gla-100, IDet)	Lower risk of hypoglycaemia than NPH insulin Once-daily injection possible Less variable absorption and longer duration of action	Requirement of injection at same time each day may be troublesome
Second-generation BI analogues (Gla-300, IDeg)	Less GV and prolonged duration of action Increased dosing flexibility Lower hypoglycaemia risk compared to Gla-100	More expensive than other BI (possibly offset by reduced need for nurse visits ± and longer-lasting pens)

BI Basal insulin, *Gla-100* insulin glargine 100 U/ml, *Gla-300* insulin glargine 300 U/ml, *GV* glycaemic variability, *IDeg* insulin degludec, *IDet* insulin detemir, *NPH* Neutral Protamine Hagedorn, *PwT2D* people with type 2 diabetes

hypoglycaemic events in this group. Flexibility of timing of BI injection might be important since older people may tend to forget about getting insulin on time. Furthermore, initiating BI in this group with comorbidities can reduce the number of OADs and may improve treatment adherence.

Based on available data from RCTs and real-world studies, the experts concluded that free-ratio or FRC of BI and GLP-1 RA should be preferred for older adults with T2D over a basal-bolus insulin regimen in instances where BI/BOT is not effective [57, 58]. Furthermore, the experts also advised considering simplification or deintensification to free ratio or FRC of BI and GLP-1 RA and regular re-assessment of individuals receiving a complex insulin therapy regimen aiming to improve clinical outcomes and overall quality of life.

Insulin Treatment Choice for PwT2D and CKD

The prevalence of CKD has increased significantly over decades. Moreover, CKD in PwT2D is also associated with increased risk of hypoglycaemia, CV events and hospitalisation, resulting in a significant burden on healthcare system [59]. The number of OADs to treat hyperglycaemia in people with advanced CKD is limited because of decreased drug clearance and adverse/side effects [60]. Therefore, the use of some OADs, such as SU, is limited in people with CKD because of higher risk of hypoglycaemia while metformin and SGLT-2i are contraindicated in people with eGFR < 30 and < 25 ml/min, respectively [61, 62]. Meanwhile, insulin therapy remains a viable therapeutic option for PwT2D and with early to advanced stages of CKD [61].

The sub-analysis of the BRIGHT study (Gla-300 vs IDeg-100) and post-hoc analysis from the EDITION program (Gla-300 vs Gla-100) indicated that Gla-300 provided glycaemic control similar to Gla-100 with a reduced overall risk of hypoglycaemia, while Gla-300 provided better glycaemic control compared with IDeg-100 in insulin-naïve PwT2D and with impaired renal function [61, 63]. In addition, the results from the REALI CKD pooled analysis also showed that individuals with inadequately controlled T2D and renal impairment who were initiated on or switched to Gla-300 achieved a clinically important improvement in glycaemic control with a low risk of hypoglycaemia [64].

The experts agreed that there are limited therapeutic options for PwT2D and CKD and recognised the importance of avoiding hypoglycaemia in this high-risk group. Considering the evidence from clinical studies, all the experts agreed that second-generation analogues (Gla-300/IDeg) have demonstrated comparable efficacy to first-generation analogues in reducing HbA_{1c} levels—with reduced incidence of hypoglycaemia—and are the best fit for this group.

Insulin Treatment Choice in PwT2D and CVD

PwT2D have a high incidence of macrovascular complications such as stroke, myocardial infarction (MI), heart failure (HF), coronary artery disease and mortality due to accelerated atherosclerosis [65].

A recent network meta-analysis and systematic review of RCTs comparing 13 drug treatment classes used in PwT2D indicated that addition of SGLT-2i or a GLP-1 RA to ongoing OADs for diabetes treatment reduced all-cause mortality, CV death, non-fatal MI, hospitalisation for HF and CKD; moreover, with GLP-1 RAs, reduced risk of non-fatal stroke was also reported [66].

In addition, achieving optimal glycaemic control during the course of T2D (with/without insulin) has a 'legacy effect' which reduces the risk of macrovascular complications [67]. Moreover, the data from a Swedish registry estimating the strength of association between various risk factors and the incremental risks of death and CV outcomes associated with T2D identified HbA_{1c} as the most important predictor for acute MI and stroke [68]. Also, in the United Kingdom Prospective Diabetes Study (UKPDS), early glucose control demonstrated sustained benefit on macrovascular risk, even when glycaemic levels deteriorated during the post-trial monitoring phase. The participants treated

with insulin/SU in the UKPDS study experienced not only a reduced risk of microvascular complications in the short term but also reduced risk of macrovascular disease during long-term follow-up [69].

The ORIGIN trial showed that in individuals with dysglycaemia at high risk of CVD, addition of exogenous BI (as insulin glargine) sufficient to normalise FPG had a neutral effect compared to standard care without insulin on CV events, cancers and other serious outcomes [70].

Based on the results from a population-based retrospective cohort study, long-acting analogues were associated with modestly reduced risk of major adverse cardiovascular events (MACEs) compared to NPH [71]. In addition, in a double-blind, treat-to-target, event-driven CV outcomes trial in PwT2D receiving either IDeg or Gla-100 OD, IDeg was found to be non-inferior to Gla-100 regarding the incidence of MACE in people at high risk of CV events [72].

The experts argued that achieving good glycaemic control significantly reduces the risk of diabetic complications (including CV events), and this may include the use of insulin to achieve good control as the most potent glucose-lowering medication. Furthermore, all the experts recommended the use of second-generation analogues (Gla-300/IDeg) with careful initiation and slow titration to attain optimal glycaemic control with minimal risk of hypoglycaemia in PwT2D and associated risk of CV events.

Insulin Treatment Choice in PwT2D and High Risk of Hypoglycaemia

Individuals who have a history of severe hypoglycaemia (requiring assistance in managing symptoms), impaired awareness of hypoglycaemia or medical conditions (such as renal [discussed above] and hepatic failure) that make them more susceptible to severe hypoglycaemia are at high risk of hypoglycaemia [73]. Hypoglycaemia unawareness (HU) is more common in elderly people with a long history of diabetes (diabetes duration > 10 years) and in individuals with autonomic neuropathy. Moreover, HU is linked to an increased risk of severe hypoglycaemia by nine-fold in PwT2D [74]. The episodes of severe hypoglycaemia or HU were shown to be associated with increased mortality in both the Action to Control Cardiovascular Risk in Diabetes (ACCORD) [75] and the Action in Diabetes and Vascular Disease (ADVANCE) trials [76]. The Endocrine Society clinical practice guidelines suggest the use of long-acting analogues over NPH among individuals on BI therapy and rapid-acting analogues over regular (short-acting) human insulins among those on basal-bolus insulin therapy in individuals at high risk of hypoglycaemia [73].

Furthermore, fewer hypoglycaemic events were reported in clinical trials evaluating first- and second-generation insulins [77]. In PwT2D on insulin therapy and with ≥ 1 hypoglycaemia risk factor, the SWITCH 2 study demonstrated that 32 weeks of treatment with IDeg vs Gla-100 decreased the overall rate of symptomatic hypoglycaemia [78]. Also, the CONCLUDE trial reported no significant difference in the rate of overall symptomatic hypoglycaemia with IDeg-200 vs Gla-300 and nominally lower rates of nocturnal symptomatic and severe hypoglycaemia with IDeg-200 vs Gla-300 [79]. Compared to the basal-bolus regimen, FRC of IDeg and liraglutide (IDegLira) in PwT2D and HbA_{1c} ≥ 9.0–15.0% led to a similar reduction in HbA_{1c} and less hypoglycaemia and weight gain compared with the basal-bolus regimen [80]. The findings from DELIVER-High Risk study showed that participants on Gla-300 had numerically lower incidences and event rates for all hypoglycaemia and mainly significantly lower incidences and event rates for hypoglycaemia associated with inpatient/ED contacts compared to Gla-100 or IDet [81]. Similar results have also been reported based on the real-world data from Optum Humedica United States electronic health record database [82]. In addition, a meta-analysis evaluating the efficacy and safety of rapid-acting analogues with short-acting analogues and OADs showed a slight reduction in the rates of nocturnal and overall hypoglycaemia with rapid-acting analogues, with similar effect on glycaemic parameters [83].

Continuous glucose monitoring (CGM), measuring glucose levels in the interstitial fluid, provides a more comprehensive picture of glycaemic levels [28]. It is an indispensable tool to gather insights about GV and is useful for the detection and prevention of asymptomatic hypoglycaemia [28, 84]. Higher GV and lower glucose levels in older adults with T2D have been associated with high hypoglycaemia risk, which is difficult to evaluate based on HbA_{1c} levels alone [84]. The results from a multicentre, open-label RCT showed that the use of CGM in insulin-treated PwT2D led to improved glycaemic control and reduced ED visits due to hypoglycaemia [85].

Based on the clinical evidence and available literature [81, 82], the experts recommended substituting short-acting analogues with rapid-acting ones (aspart, lispro or glulisine) to reduce the frequency of daytime hypoglycaemia and switching intermediate-acting insulin (NPH or premix) with second-generation basal analogues (Gla-300 or IDeg-100) to reduce the frequency of anytime hypoglycaemia. Herein, the experts also emphasised the importance of CGM in insulin-treated PwT2D to detect hypoglycaemia. By measuring glucose levels in the interstitial fluid with data readouts in real-time or via intermittent scanning, CGM devices can provide a visual representation of BG data in the form of an ambulatory glucose profile for the identification of glycaemic trends and patterns. The experts highlighted that PwT2D should be encouraged to regularly review their trend graphs and self-assess their glycaemia to avoid hypoglycaemia risk and duration. A collaborative approach to data interpretation involving clinicians and the individuals can allow for the identification of abnormal glycaemic patterns, potential reasons for these patterns and appropriate actions to address the identified causes of glucose excursions and can empower PwT2D and guide personalised goal setting.

Ways to Increase Adherence to Insulin Treatment

Diabetes treatment adherence in PwT2D is associated with lesser rates of microvascular and/or macrovascular outcomes, inpatient hospitalisation and lower or budget-neutral total healthcare expenditure [86]. Furthermore, non-adherence to diabetes treatment can be attributed to factors like socioeconomic and demographic factors, treatment cost, lifestyle, existing health comorbidities and financial and diabetes care factors. These factors can pose a considerable barrier to effective diabetes management, often leading to poor health outcomes and increased healthcare resource utilisation in PwT2D [87].

A recent retrospective analysis evaluating the association between hypoglycaemia and adherence to and persistence of BI treatment showed that experiencing a hypoglycaemic event early after initiating BI treatment was associated with decreased adherence over the 36-month follow-up [88]. A systematic review and meta-analysis comparing the adherence and persistence rates across different medication classes for diabetes reported better adherence and persistence with the use of long-acting analogues than with human insulins [89]. Another retrospective observational analysis showed that continuing second-generation analogues was associated with a lower risk of discontinuation than first-generation analogues [90].

Barriers associated with initiating or advancing insulin-based therapy include fear of injection pain and of hypoglycaemia [91]. Table 3 describes these barriers and plausible solutions to improve overall adherence and treatment outcomes. Moreover, treatment advancement from BI involving the stepwise addition of a new glucose-lowering agent or switching to a more complex insulin regimen can further increase treatment burden and chances of non-adherence. Current guidelines such as ADA/EASD and AACE support the concept of simplifying the treatment regimen to decrease treatment complexity and burden, particularly

Table 3 Challenges associated with insulin use and possible solutions to improve overall adherence

Issue with insulin treatment	Solutions to improve adherence
Frequency of injections (daily/multiple)	BI analogues with once-daily administration compared with NPH or IDet Preference of BOT or FRC of BI + GLP-1RA to MDI regimen
Hypoglycaemia risk	Second-generation analogues (Gla-300 or IDeg) with lower risk of hypoglycaemia vs NPH and first- generation analogues (Gla-100 or IDet)
Weight gain	BI insulin analogues vs NPH Preference of BI to MDI Preference of FRC of BI + GLP-1RA to MDI after BI failure or as de-escalation of current MDI regimen
Impact on lifestyle	Second-generation analogues (Gla-300 or IDeg) with once-daily administration and flexibility in daily injection time compared with NPH and first-generation analogues (Gla-100 or IDet) Preference of BOT or FRC of BI + GLP-1RA to MDI regimen
Difficulties with devices	Prefer insulin pre-filled pens to syringe/vials or reusable pens
Complicated insulin dose titration	Select simple titration schemas (+ 1 U/day) Use of CGM for timely insulin dose change
Fear of insulin use and fear of needles/pain	Regular and quality interactions between the HCPs and individuals and caregivers; Patient education

BI basal insulin, *BOT* basal-supported oral therapy, *CGM* continuous glucose monitoring, *FRC* fixed-ratio combination, *Gla-100* insulin glargine 100 U/mL, *Gla-300* insulin glargine 300 U/mL, *GLP-1* RA glucagon-like peptide-1 receptor agonist, *HCP* healthcare professional, *IDeg* insulin degludec, *IDet* insulin detemir, *MDI* multiple daily injection, *NPH* neutral protamine Hagedorn

for insulin therapy, which may in turn improve adherence and glycaemic control [5, 7, 21, 92].

The experts agreed that a less complex treatment regimen that requires fewer adjustments and glycaemic measurements may facilitate timely achievement of glycaemic control in routine clinical practice and stressed the strategies to overcome common barriers and foster healthy self-management behaviours to improve medication adherence. Furthermore, the experts recommended to overcome fear of insulin at initiation stage by selecting the most appropriate and simple regimen as the preferred option. Effective and regular communication between HCP and PwT2D may help patients to continue with their insulin treatment and provide better understanding of any causes of non-adherence. The experts emphasised the importance of involvement of PwT2D in decision-making and setting the right expectations, which can prevent discontinuation and increase adherence for better glycaemic control.

Strengths and Limitations

The broad strengths of these recommendations, as endorsed by the experts from South-East Europe and Israel, are that they reflect both a nuanced understanding of the diverse group of PwT2D within these regions and the extensive literature search on the current treatment landscape regarding guidance and published evidence on insulin initiation and positioning.

This paper also has limitations that must be acknowledged. First, not all aspects of insulin

treatment in PwT2D were discussed. Second, high-quality data were lacking for some aspects of insulin treatment of T2D and especially for special populations (e.g., the elderly, those with CKD). Moreover, this paper is based on the opinion of experts from only six countries of the South-Eastern European region and Israel, which may limit its generalisability across countries.

CONCLUSION

Despite an increasing availability and use of newer non-insulin medications, glycaemic control of PwT2D is still suboptimal, and thus insulin treatment remains an important option for the treatment of PwT2D and addresses insulin resistance and absolute insulin deficiency. The experts from the South-Eastern European region and Israel agreed that insulin treatment has a significant role in all stages of the course of T2D. Early short-term intensive insulin therapy in new-onset PwT2D can lead to drug-free glycaemic remission for up to 2 years; moreover, BI analogues can be used as second-line glucose-lowering agents in case of high glycaemia or as third-line agents if individualised HbA_{1c} goal is not achieved after 3–6 months on dual/triple non-insulin therapy.

In agreement with most guidelines, the experts recommend BI analogues over NPH as first insulin treatment and second-generation analogues over first-generation analogues based on pharmacokinetic/pharmacodynamic profile, longer duration of action and lower risk of hypoglycaemia. Second-generation analogues provide HCPs with better treatment options and easier titration algorithms for achieving targeted glycaemic control. If further intensification is required, the experts recommend basal-plus or FRC therapy and suggest limiting the use of basal-bolus therapies. The available evidence suggests that the benefits of second-generation BI analogues extend to special populations such as the elderly and those with CKD or macrovascular disease. Furthermore, free-ratio or FRC of BI and GLP-1 RA could replace more complex insulin therapy regimens in older adults with T2D. The experts found that timely achievement of good glycaemic control may include using insulin as the most potent glucose-lowering medication. Notably, the views expressed by the experts should be considered by the clinicians/HCPs in line with the current diabetes treatment and management guidelines.

Furthermore, the experts agreed that less complex treatment regimens requiring fewer adjustments, as well as effective and regular communication between HCP and individuals, may help PwT2D continue with their insulin treatment and improve adherence. Moreover, partnering with PwT2D can prevent discontinuation and increase adherence for better glycaemic control.

These recommendations, as endorsed by the experts from the South-Eastern European region and Israel, reflect a nuanced understanding of the diverse group of PwT2D within these regions. The strength lies in the extensive literature search to provide the current treatment landscape regarding guidance, published evidence on insulin initiation and positioning. Additionally, the experts emphasised the importance of personalised goals, recognising that individual responses to insulin therapy may vary. However, challenges may arise in translating recommendations into consistent clinical practice because of variations in healthcare infrastructure and resources across countries. Nevertheless, the insights presented in this article contribute valuable guidance for the management of T2D.

Medical Writing and Editorial Assistance. Manuscript writing assistance was provided by Sneha Sinha and Amol Gujar, both employees of Sanofi.

Author Contributions. All authors were involved in writing and editing various drafts of the manuscript, and they meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work, and have given their approval for this version to be published. Adam G Tabak: was not a member of the expert meeting, was invited as

author of publication by all other participants, provided the draft of the manuscript based on expert meeting minutes, leading the manuscript preparation, approving the final draft of the manuscript. Peter Kempler: contribution to forming the expert opinion, participation in the manuscript preparation, approving the final draft of the manuscript. Cristian Guja: contribution to forming the expert opinion, leading the manuscript preparation, approving the final draft of the manuscript. Roy Eldor: contribution to forming the expert opinion, leading the manuscript preparation, approving the final draft of the manuscript. Martin Haluzik: contribution to forming the expert opinion, participation in the manuscript preparation, approving the final draft of the manuscript. Tomasz Klupa: contribution to forming the expert opinion, participation in the manuscript preparation, approving the final draft of the manuscript. Nikolaos Papanas: contribution to forming the expert opinion, participation in the manuscript preparation, approving the final draft of the manuscript. Anca Pantea Stoian: contribution to forming the expert opinion, participation in the manuscript preparation, approving the final draft of the manuscript. Boris Mankovsky: contribution to forming the expert opinion, participation in the manuscript preparation, approving the final draft of the manuscript.

Funding. The expert meeting was funded by Sanofi. The authors received no payment from Sanofi related to the development of this publication. The journal's Rapid Service Fee was funded by Sanofi.

Data Availability. The authors make themselves available to readers in case of any doubt, suggestion, or question. Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Declarations

Conflict of Interest. Adam G Tabak was supported by the Ministry of Innovation and Technology of Hungary from the National Research, Development and Innovation Fund (2021 Thematic Excellence Programme funding scheme, TKP2021-NKTA-47) and has received consultancy and advisory board fees from 77 Elektronika, Lilly Hungária, and Sanofi; and speaker fees from AstraZeneca, Berlin-Chemie, Eli Lilly, Novo Nordisk, and Sanofi. Cristian Guja has participated in scientific advisory boards for and received lecturing fees from AstraZeneca, Berlin Chemie Mennarini, Boehringer Ingelheim, Eli Lilly, Krka, Novo Nordisk, Pfizer, Sandoz, Sanofi, Servier and Viatris. Nikolaos Papanas has been an advisory board member of Astra-Zeneca, Boehringer Ingelheim, MSD, Novo Nordisk, Pfizer, Takeda and TrigoCare International; has participated in sponsored studies by Astra-Zeneca, Eli-Lilly, GSK, MSD, Novo Nordisk, Novartis and Sanofi-Aventis; has received honoraria as a speaker for Astra-Zeneca, Boehringer Ingelheim, Eli-Lilly, ELPEN, Galenica, MSD, Mylan, Novo Nordisk, Pfizer, Sanofi-Aventis, Takeda and Vianex; and attended conferences sponsored by TrigoCare International, Eli-Lilly, Galenica, Novo Nordisk, Pfizer and Sanofi-Aventis. Nikolaos Papanas is a member of the Editorial Board for Diabetes Therapy. Nikolaos Papanas was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Boris Mankovsky has received speaker bureau for Astra Zeneca, Boehringer Ingelheim, Novo Nordisk, Sanofi, Servier, Bayer and member of advisory board from Sanofi, Bayer, Woerwag-pharma, Boehringer Ingelheim. Peter Kempler has been an advisory board member of AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Richter, Wörwag Pharma, Sanofi; has been provided the speaker service to AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Richter, Wörwag Pharma, Sanofi. Roy Eldor has been an ad hoc speaker and consultant to Sanofi, Lilly, Novo Nordisk, Bayer, Boehringer Ingelheim, Novartis; consultant to Oramed. Martin Haluzik has been an advisory panel member of: Novo Nordisk, Eli Lilly, Sanofi, Merck, Pfizer, Astra-Zeneca, Berlin Chemie; has received the consulting fees and grants/research support from Sanofi; has received the speakers honoraria for speakers bureau from Sanofi, Novo Nordisk, Eli Lilly, Sanofi, Pfizer, Astra-Zeneca, Berlin Chemie. Tomasz Klupa has received speakers honorarium from Sanofi, Eli

Lilly, Novo Nordisk, Bioton and served on an advisory panel for Sanofi, Eli Lilly, Bioton. Anca Pantea Stoian is currently President of Romanian National Diabetes Committee, and has given lectures, received honoraria and research support, and participated in conferences, advisory boards and clinical trials sponsored by pharmaceutical companies including AstraZeneca, Amgen, Boehringer Ingelheim, Coca-Cola, Eli Lilly, Merck Medtronic, MSD, Medochemie, Novo Nordisk, Novartis, Roche Diagnostics, Servier, Sandoz, Sanofi.

Ethical Approval. Given that this expert opinion manuscript is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors, no ethical approval was sought.

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