The burden of type 2 diabetes in Europe: current and future aspects of insulin treatment from patient and healthcare spending perspectives

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Abbreviations

American Diabetes Association – ADA; Cardiovascular Disease – CVD; Conformité Européenne – CE; Continuous glucose monitoring – CGM; Continuous Subcutaneous Insulin Infusion – CSII; European Association for the Study of Diabetes – EASD; Fasting Plasma Glucose – FPG; France – FR; Germany – DE; Glycated Haemoglobin - HbA1c; Healthcare Professional – HCP; International Diabetes Federation – IDF; Italy – IT; Multiple Daily Injections – MDI; Netherlands – NL; Spain – ES; Time in Range – TIR; Type 1 Diabetes Mellitus - T1DM; Type 2 Diabetes Mellitus - T2DM; United Kingdom - UK

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Abstract

Due to the progressive nature of type 2 diabetes (T2DM), initiation of insulin therapy is very likely in the disease continuum. This article aims at highlighting the current situation with regard to insulin therapy in people with T2DM in Europe and at presenting the associated unmet need. Challenges for both people with T2DM and healthcare professionals include clinical inertia also derived from fear of hypoglycaemia, weight gain and injections as well as increased need for a comprehensive diabetes management. We compare national and international guidelines and recommendations for the initiation and intensification of insulin therapy with the real-world situation in six European countries, demonstrating that glycaemic targets are only met in a minority of people with T2DM on insulin therapy. Furthermore, this work evaluates currently recorded numbers of people with T2DM treated with insulin in Europe, the proportion not achieving the stated glycaemic targets and thus in need to enhance insulin therapy e.g. by a change in means of insulin delivery including, but not limited to, insulin pens, wearable mealtime insulin delivery patches, patch pumps, and conventional insulin pumps with continuous subcutaneous insulin infusion.

Objectives and Methodology

The aim of this review is to raise awareness of the status of insulin-treated type 2 diabetes mellitus (T2DM) in Europe. An extensive literature research was conducted on insulin therapy in T2DM, glycaemic targets according to national guidelines, barriers to the initiation of and adherence to insulin therapy as well as costs associated with specific insulin regimens. Country specific data was obtained for six European countries relating to the use of specific insulin regimens in T2DM and the proportion achieving national targets in order to estimate the extent of people inadequately controlled with insulin. Finally, we refer to devices and technologies aimed at improving insulin delivery which may reduce the burden of insulin therapy in those persons sub-optimally controlled.

Section I: Overall understanding of the T2DM health status in Europe

The burden of type 2 diabetes mellitus in Europe

Diabetes mellitus is a major chronic non-communicable disease of our time [1]. In Europe in 2019, around 59 million individuals were estimated to have diabetes mellitus, which is predicted to rise to about 68 million people in 2045 [1]. The recent 9th edition of the Diabetes Atlas of the International Diabetes Federation (IDF) estimated a regional, age-adjusted comparative diabetes prevalence in adults (20-79 years) of 6.3 % in Europe. The national, age-adjusted comparative diabetes prevalence was 4.8 % in France (FR), 10.4 % in Germany (DE), 5.0 % in Italy (IT), 5.4 % in the Netherlands (NL), 6.9 % in Spain (ES), and 3.9 % in the United Kingdom (UK) [1]. Similarly, the estimated number of undiagnosed diabetes cases in adults appears to vary considerably between the European countries: 1,307,700 (FR), 4,528,900 (DE), 1,332,200 (IT), 370,000 (NL), 1,009,700 (ES) and 495,900 (UK) [1]. Around 90 % of people have T2DM which is associated with excess mortality and a variety of comorbidities such as cardiovascular disease (CVD), diabetic kidney disease, diabetic retinopathy, diabetic neuropathy, and many others [1, 2]. By causing around 52 % of diabetes-related mortality, CVD is the major underlying cause of death amongst people with T2DM [3]. Studies have shown that people with T2DM suffer from a 2 to 4-fold increased risk of CVD, which may even increase up to 5-fold if additional risk factors are present at the same time [2]. Thus, diabetes, its comorbidities and complications are not only a major burden for the individual concerned, but also greatly impact health system expenditure. According to the latest edition of the IDF Atlas, total heath expenditure in Europe in 2019 due to diabetes was estimated at USD 161 billion, with mean diabetes related-costs (USD) per person with diabetes estimated at 4859 in France, 4601 in Germany, 2849 in Italy, 5380 in the Netherlands, 2662 in Spain, and up to 5255 in the UK [1]. In 2013 the healthcare resources for people with T2DM in France was estimated to be € 6506 per patient, extrapolating to a nation-wide burden of € 8.5 billion, about 5 % of health expenditures for 2013 [4]. An assessment of a German insurance database estimated direct costs of diabetes in 2001 of € 30.6 billion. This included a difference in costs of € 14.6 billion in people with diabetes compared to a control group, encompassing € 4.9 billion for inpatient care, € 3.3 billion for medication, and € 1.8 billion for physicians' outpatient services [5]. A probabilistic prevalence cost of illness model suggested the direct costs for pharmacologically treated people with diabetes in Italy to be between € 8.11 and € 11.06 billion [6]. In 2016, the economic burden of diabetes in the Netherlands was € 6.5 billion [7].

An earlier study from Spain estimated direct costs of diabetes to range from € 2.4 to 2.7 billion in 2002 [8], while the UK had direct diabetes-related costs of £ 23.7 billion in 2010/2011 [9]. A European analysis indicated higher costs in conjunction with worse outcomes in insulin-treated people with diabetes [10]. Country specific data from economic studies are often outdated, thus not reflecting the current situation.

Glycaemic targets and treatment of T2DM

Adequate glycaemic control is one of the most important factors in the management of T2DM because hyperglycaemia, glycaemic variability as well as hypoglycaemia are considered, amongst blood pressure and lipid control, risk factors for micro- and macrovascular comorbidities (microvascular: e.g. retinopathy, neuropathy, diabetic kidney disease; macro-vascular disease: e.g. CVD) in diabetes [11-15]. Accordingly, the greatest reduction of absolute risk is associated with improvement in glycaemic control, particularly in people poorly controlled with a long life expectancy [12, 16]. According to the American Diabetes Association (ADA), glycaemic control is primarily assessed by the measurement of glycated haemoglobin (HbA1c) [11]. Epidemiological analyses showed that for every 1% reduction in HbA1c, the relative risk for microvascular complications, diabetes-related deaths and myocardial infarction decrease by 37 %, 21 % and 14 %, respectively [17-19]. The joint consensus of ADA and European Association for the Study of Diabetes (EASD) states that *"The goals of treatment for type 2 diabetes are to prevent or delay complications and maintain quality of life"* [12] and focuses on patient-centred care. In this consensus, HbA1c goals of ≤ 7 % (≤ 53 mmol/mol) are stated for most non-pregnant adults when adequate for their life expectancy, whilst also emphasising the need for a patient-centred approach with individual treatment targets [12]. The recently published "Guideline on diabetes, pre-diabetes, and cardiovascular diseases" of the European Society of Cardiology and the EASD similarly recommends a HbA1c < 7 % (< 53 mmol/mol) to decrease microvascular complications [20] (comparison in Table 1). Other surrogate markers aside from HbA1c which have gained importance in recent years are time in range (TIR), defined as (a.) time per day within target glucose range (TIR) defined as 70-180 mg/dL (3.9-10.0 mmol/L), (b.) time per day below glucose target range, and (c.) time per day above target range [13]. TIR has become an important parameter as an isolated assessment of HbA1c does not provide information on acute glycaemic variability i.e. frequency and magnitude of glycaemic variability. It is recommended that individuals with T2DM should spend at least 70 % within TIR which corresponds to a HbA1c of approximately

7 %, and a TIR of 50 % equates to a HbA1c of approximately 8 % [13]. Each 5 % increase in TIR is associated with significant benefits for people with diabetes [13]. First evidence on the clinical relevance of TIR in people with T2DM revealed an association between a lower TIR and the prevalence of diabetic retinopathy [21]. Utilisation of continuous glucose monitoring (CGM) can increase TIR in individuals with T2DM [22].

The level of glycaemic control of T2DM in Europe

National European guidelines recommend similar glycaemic targets for HbA1c as the ADA/EASD consensus (FR HbA1c ≤ 7 % (< 53 mmol/mol) for most people with T2DM [23, 24], DE HbA1c 6.5-7.5 % (48-58 mmol/mol) [25, 26], IT HbA1c < 6.5 % (< 48 mmol/mol) [27], NL HbA1c ≤ 7 % (≤ 53 mmol/mol) [28], ES HbA1c < 7 % (< 53 mmol/mol) [29] UK HbA1c ≤ 6.5 % (≤ 48 mmol/mol) [30]). Recommendations vary according to patient profiles (age, diabetes duration, comorbidities, therapy related risk for hypoglycaemia; comparison in Table 1). Overall, these targets are achieved by less than 50 % of people with T2DM [31], increasing to 63.9 % with an HbA1c > 7 % (> 53 mmol/mol) in people treated with insulin [32]. The high rates of discontinuation of basal insulin therapy [33] might contribute to the high numbers above target. With the more intensive insulin therapy regimens a greater proportion of people with T2DM are above the target of HbA1 > 7 % (> 53 mmol/mol): e.g. in France 82.9 % of multiple daily injections (MDI) [34] and in Italy 72.6 % on basal-bolus therapy [35]. Poor glycaemic control is associated with higher direct medical costs compared to good glycaemic control with every 1 % increase in HbA1c associated with a 2.2 % increase in healthcare costs, as well as the higher costs as a consequence of the increased risk of complications [36-39]. It should be recognised that people with T2DM often do not only have to address glycaemic but also blood pressure and lipid control. The numbers of patients achieving targets for all three risk factors is even lower [40].

Section II: The unmet need of people with T2DM on insulin therapy in Europe

Insulin therapy for T2DM - When it is needed and when is it started in practice?

In general, management of T2DM is based on a stepwise escalation starting from lifestyle modifications over oral glucose lowering medications to injectable therapies. In recent years therapeutic options with a proven CV benefit and positive influence on weight such as SGLT-

2 inhibitors and GLP-1 receptor agonists have enabled a delay in the initiation of insulin therapy. This is also reflected in international guidelines [12, 20]. As T2DM is of a progressive nature, it is nevertheless very likely that many persons will need insulin therapy at some time during disease continuum [41]. The ADA/EASD consensus recommends insulin therapy as 3rd or 4th line therapy when escalating blood glucose lowering therapy [12]. If HbA1c is above target despite dual/triple therapy, injectable combinations i.e. GLP-1 receptor agonists plus basal insulin or prandial plus basal insulin should be considered when HbA1c is above 10 % (> 86 mmol/mol) and/or 2 % (> 23 mmol/mol) above target. Furthermore, insulin should be considered at any stage if HbA1c is very high (> 11 % [> 97 mmol/mol]) and/or if there are symptoms or evidence of catabolism [12]. If basal insulin therapy combined with oral antidiabetics (OADs) is insufficient to achieve guideline-recommended glycaemic targets with reasonable doses of the long-acting insulin [42], therapy may be escalated stepwise to include prandial insulin as part of a multiple daily injections (MDI) regimen i.e. > 1 injection of prandial or premixed insulin in addition to basal insulin, and ultimately a full basal-bolus regime i.e. basal insulin plus ≥ 2 injections of prandial insulin [12, 43].

Several studies have suggested that optimal insulin therapy for T2DM may include the early initiation of a basal insulin regimen, with subsequent addition and intensification of a bolus insulin, much earlier than currently practised [41]. It has been shown that early short-term intensive insulin initiation e.g. MDI and intensive glycaemic control can be beneficial for the preservation of beta-cell function [44]. It needs to be noted however, in contrast to the currently recommended 2nd or 3rd line therapies i.e. GLP-1 receptor agonists, SGLT-2 inhibitors etc., no benefit on all-cause or CV-mortality has been observed with insulins [45]. The risk of hypoglycaemia and body weight increase should be critically addressed in view of alternative therapeutic options. Also the complexity of insulin regimens, e.g. a combination of basal and prandial insulin with varying titration regimens, impose considerable burden on individuals and increase healthcare cost [12, 39, 44, 46]. In support of the earlier recommendation of insulin as a 2nd or 3rd line therapy, was that 1st line basal insulin therapy was associated with significant improvements in glycaemic control and beta-cell function, as compared to metformin [47]. It was also shown that early intervention with insulin as add on to metformin monotherapy results in a more rapid attainment of HbA1c goals [48]. Therefore, insulin therapy should be initiated as soon as indicated by current recommendations, whilst avoiding lengthy periods of clinical inertia resulting in less time in good glycaemic control and at

increased risk of complications. Albeit being one of the most potent blood glucose-lowering substances next to GLP-1 receptor agonists [49, 50], it should be kept in mind that intensification of therapy does not guarantee attainment of glycaemic targets [51, 52]. Several factors such as patient education, patient satisfaction and patient-physician interaction as well as insulin-related treatment aspects are of importance in a patient-centred diabetes management process [12].

Insulin therapy for T2DM – Barriers and enablers to achieving optimal glycaemic control with insulin.

Initiating insulin therapy

Initiation of insulin therapy is subject to a variety of patient- and healthcare professional (HCP)-related barriers. This often results in the phenomenon of clinical inertia which is frequently observed with regard to the initiation of insulin therapy. Although people with T2DM are failing to achieve their glycaemic targets with other therapy regimens, there is hesitation to initiate insulin which is evident from national studies from Germany, Spain and UK [53-55].

Clinical inertia encompasses various aspects, which need to be taken into consideration. From a person with diabetes's view, it should be kept in mind that several factors such as fear of hypoglycaemia, weight gain, injections and associated pain and the need for glucose monitoring can be discouraging and a burden. However, the concern about the risk of hypoglycaemia does vary greatly between the different European countries [56]. Acceptance of insulin therapy largely depends on regimen complexity and the perception of benefits and disadvantages and the individual's emotional well-being [57, 58]. The perception of failure by the person with diabetes should not be neglected, so called "psychological insulin resistance" [59, 60]. However, it has been shown that the initiation of insulin therapy can improve the perception of insulin treatment as a consequence of the improvement in overall quality of life following the introduction of insulin [61, 62].

Even though clinical inertia may be strongly patient driven, it must not be neglected that HCPs also face certain barriers to initiate insulin therapy. These may include lack of time, resources, cost or insufficient experience/expertise with insulin therapy and/or insulin delivery devices [63]. An international survey confirmed that the main barriers for the initiation of insulin

therapy include the lack of experience of HCPs with the available insulin preparations and lack of time available for patient education [64].

Intensification of insulin therapy

Clinical inertia also denotes failure of intensification of therapy when treatment targets are not met [12] and is most pronounced in the management of diabetes after introduction of insulin [65], despite the availability of clear guidelines proposing specific therapeutic targets and treatment regimens. There is evidence of clinical inertia with regard to insulin intensification, revealed by real-world studies showing only modest titration and delay in adjustments of basal insulin therapies.[66-68]. Reluctance and/or inaction of both physicians and patients may well contribute to these observations [69].

A study from the UK showed that in participants with a HbA1c > 7.5 % (> 58 mmol/mol) time to insulin therapy intensification was 3.7 years with only 30 % of people with T2DM eligible for intensification adapting their insulin regimen accordingly [70]. The French INERTIA study also showed a lack of intensification in people with poorly controlled T2DM treated with basal insulin [71].

Prospective follow-up data from European registries reveal that insulin therapy is mostly initiated with a basal insulin formulation only (> 60 %), with an increasing number of patients escalating to basal-bolus regimen in the subsequent 4 years after initiation, although around 50 % remain on their initial regimen [72].

Empowerment of persons with T2DM is a strategy to address titration inertia as shown by multiple studies on patient-driven titration involving either basal insulin [73, 74], premixed insulin [75, 76], or bolus insulin [77, 78] being non-inferior or even superior to HCP-driven titration schedules. In the PREDICTIVE 303 trial lowering of HbA1c was similar in patient- and HCP-driven treatment, while significantly greater reductions in fasting plasma glucose (FPG) levels were observed in the patient-driven treatment group using a simplified self-titration dosing guideline [74]. Similarly in the AT.LANTUS trial, those adopting a patient-driven titration algorithm achieved a significantly greater reduction in HbA1c [73]. In neither studies, a difference was observed in the incidence of severe hypoglycaemia between the groups [73, 74]. In addition, the START trial revealed that a patient-driven treatment algorithm of a bolus insulin resulted in a significantly greater percentage reaching the primary outcome (HbA1c ≤ 7 % [≤ 53 mmol/mol]) [78]. Therefore, with proper education and training, insulin titration

can be entrusted into the patients' hands without the need to rely on HCPs, which may minimise clinical inertia [79].

Adherence to insulin therapy

Apart from clinical inertia, adherence to medication affects glycaemic control in people with T2DM on insulin therapy. Adherence can be affected by factors such as insulin-related beliefs, social influences and psychological factors [57, 80, 81]. Poor medication adherence is very prevalent and ranges from 30 % to 86 %, depending on the patient population and methods used to evaluate medication adherence [82-84]. A French insurance-claims-study showed that treatment persistence varied in relationship to insulin regimen being 61.8 % with basal insulin, 15.0 % with fast-acting insulin and 23.2 % other insulin regimens [33]. Persistence and adherence are also influenced by the frequency of insulin administration [85-87]. Therefore, simplifying insulin therapy by the utilisation of insulin pens or other discrete insulin delivery devices can improve treatment persistence and adherence [83, 88, 89].

Poor medication adherence and persistence, often in conjunction with inadequate glycaemic control, are associated with adverse clinical outcomes, such as increased risk of CV events, morbidity, and premature mortality [90-92]. In contrast, enhanced treatment adherence is associated with improved glycaemic control and decreased healthcare resource utilisation [93].

A multidisciplinary approach involving the person with T2DM, primary and secondary care physicians, nurses and educators can overcome clinical inertia, thus facilitating earlier insulin initiation and intensification, as well as improving diabetes care [64].

Insulin therapy for T2DM - Glycaemic control among European people with T2DM

An analysis was recently published of physicians responses, from eight European countries: when asked about insulin initiation in people, young and old, with T2DM the results implicate insulin initiation according to national guidelines [94]. The situation appears essentially similar throughout Europe with insulin initiation occurring when the mean HbA1c is > 9 % (> 75 mmol/mol) [72]. A study from the UK showed that the median time to initiation of insulin treatment was > 7 years with a mean HbA1c of > 9 % (> 75 mmol/mol) [54]. The French ADHOC survey demonstrated a mean HbA1c at insulin initiation of 9.2 % (77 mmol/mol) [34], while in Germany basal insulin was initiated at a slightly lower mean HbA1c of 8 % (64 mmol/mol) [95]. Between 2005 and 2011, in Italy 43 % of insulin-treated persons with

T2DM started insulin therapy with a HbA1c > 9 % - a situation which appears to be worsening over time [96].

In France, 68.6 % of insulin-treated people with T2DM had a HbA1c > 7 % (> 53 mmol/mol) [97] with similar observations recorded for the Netherlands (75.6 % [98]), Spain (75.2 % [99]), and the UK (63.8 % [100]). In Italy, 18.5 % of insulin-treated people with T2DM had a HbA1c > 9 % (> 75 mmol/mol) [101] (compare Table 2).

Supplementary basal insulin, with or without oral medication, is often not sufficient to achieve good glycaemic control with 16.9 % to 44.7 % of people with T2DM in Europe considered to have uncontrolled glycaemia, with a HbA1c > 7 % (53 mmol/mol) [100]. National data for France, Germany, Italy, the Netherlands, and Spain reveal that 77.1 % [34], 66.6 % [35], 72.6 % [35], 46 % [102], and 76.1 % [35] of people with T2DM on basal insulin therapy have an HbA1c above 7 % (53 mmol/mol), respectively; no data available for the UK (comparison in Table 2).

The low number of people with T2DM achieving glycaemic targets of < 7 % (< 53 mmol/mol) is not only restricted to basal insulin regimens with more than half of the patients on the different insulin regimens having a HbA1c of > 7 % (53 mmol/mol), with increasing numbers treated with complex regimens [10, 103, 104].

The Burden of MDI in T2DM

People with T2DM on MDI therapy are considered to have poorer glycaemic control and incur higher medical costs than those on basal insulin only [105]. An observational study comparing basal and MDI regimens showed that only 15.3 % on MDI had a HbA1c < 7 % (< 53 mmol/mol), compared to 22.4 % on basal insulin therapy [105]. In France 78.2 % of people with T2DM on MDI therapies have a HbA1c above 7 % (53 mmol/mol) [34], 38-54 % in the Netherlands [102], and 73.3 % in the UK [106]. In general MDI regimens are associated with worse clinical outcomes, higher level of dissatisfaction and higher costs compared with less complex insulin treatments.

Combining basal insulin with a GLP-1 receptor agonist is becoming a common alternative to basal-bolus insulin regimens, as it can improve glycaemic control with a lower risk of hypoglycaemia and lesser weight gain with an improved quality of life due to the lowered treatment burden [107].

Current and future opportunities for people with T2DM to improve glycaemic control

Medical devices for insulin delivery, insulin pump treatment for T2DM, and possibilities in insulin therapy for people with T2DM

More than 30 % of people with T2DM have an aversions to intensify insulin regimens even if recommended [41]. Currently there are several options to ease the burden of people with T2DM requiring insulin therapy, which usually encompasses a change in the manner of insulin delivery. This includes, but is not limited to, insulin pens, wearable mealtime insulin delivery patches, patch pumps and conventional insulin pumps with continuous subcutaneous insulin infusion (CSII) [108]. CSII, often coupled with CGM, is amongst the most sophisticated systems for insulin delivery and metabolic monitoring, developed initially for people with type 1 diabetes mellitus (T1DM) in an attempt to achieve good glycaemic control with a reduced risk of hypoglycaemia. For people with T2DM simpler solutions may be sufficient to meet their needs involving easy to follow titration algorithm, dosing aids and easy-to-use insulin delivery devices [56]. Also the use of insulin pens, wearable mealtime insulin delivery patches and patch pumps for either basal insulin, bolus insulin or both might be of advantage for people with T2DM.

Insulin pens

Insulin pens have become increasingly accepted by many people with diabetes and HCPs, considerably reducing clinical inertia and aiding metabolic control. As insulin pens are more portable, less conspicuous than syringes, and dosing is simplified and more accurate the resistance to commencing and adhering to insulin therapy is lowered. [41]. Hypoglycaemic events and emergency room visits are also reduced, both associated with decreased treatment costs [41]. In view of recent digital solutions, insulin pens are currently transformed into “smart” insulin pens which will enable the insulin dosing information to be stored and integrated into digital diabetes management systems, along with CGM. Education of people with T2DM and the HCPs involved is critical for the implementation of these new technological advancements.

Mealtime insulin delivery patches

Wearable mealtime insulin delivery patches are mechanical patches attached to the abdomen which allows easy on-demand bolus subcutaneous insulin delivery [63]. Current bolus insulin

patches can be worn for between 1 and 3 days and reduce the burden of transporting medication [41]. As they require a single insertion only, they substantially reduce the number of subcutaneous injections compared to insulin pens [41]. A recent study comparing mealtime insulin patches and insulin pens observed comparable improvement in HbA1c, FPG, total daily insulin dose, basal insulin dose, body weight, and hypoglycaemic episodes. Patient reported outcomes slightly favoured patches with significantly increased overall satisfaction and ease of use [63]. However, currently the size of the insulin reservoirs may be considered a limitation of these insulin delivery patches.

Patch pumps

Patch pumps for insulin delivery are available with a variety of functionalities and accordingly different complexities. While full-feature devices can supply complex insulin regimens, may also have connectivity to other devices such as CGM, and are comparable to CSII in terms of functionality. Simplified devices are partially or fully disposable and can be used for basal or bolus, or basal and bolus insulin delivery [109]. While mechanic pumping, used in most of todays' insulin pumps, typically is limited to 0.05 U dose step sizes, possibly becoming an issue when high doses of insulin are required. A different technology in patch pumps, the so-called electro-chemiosmotic pumping technology, allows more accurate dosing or even two hormone therapy by continuous subcutaneous infusion using a single patch pump [110]. Patch pumps are devoid of an insulin infusion set, hence have considerably reduced visibility, lack the risk of clogging, air bubbles impairing the pumping and other issues of insulin infusion set systems [summarized in 111]. However, it also has to be taken into account that with increasing simplicity of a system, limitations may arise which are not encountered with the more complex systems, such as the fixed basal and bolus injections component (typically 2 insulin units) [109].

While specifically investigating the efficacy of insulin therapy delivered by a patch pump compared to MDI in 81 people with T2DM in a medium sized trial showed that using a patch pump significantly reduced mean HbA1c, total daily insulin dose, and patient reported (severe) hypoglycaemic events per week, compared to MDI [112]. In addition, there was an 18.8 % increase in the number of subjects achieving HbA1c < 7 % (< 53 mmol/mol) and a 71.4 % more achieved a HbA1c of 7–8 % (53-64 mmol/mol) [112].

Continuous subcutaneous insulin infusion - CSII

In general an increasing body of evidence points towards improved glycaemic control, increased patient satisfaction and reduced insulin requirement when using CSII compared to "traditional" MDI regimes with syringes or insulin pens [63, 112-115]. There is a lack of large randomized controlled trials comparing the efficacy of different insulin delivery systems, particularly in T2DM. Most evidence can be extracted from studies focusing on CSII.

A large trial, the OpT2mise trial, compared CSII to MDI in 331 people with T2DM with uncontrolled glycaemia [114]. Mean baseline patient characteristics in the Opt2mise trial were late-middle age (around 55 years), long-standing duration of diabetes (around 15 years), a high body weight (BMI of around 33 kg/m^2), and a high HbA1c of 9 % (75 mmol/mol) despite intensive treatment [116].

In line with other trials, the OpT2mise trial found significant reductions in HbA1c with CSII compared to MDI [114], with a higher percentage of participants achieving a HbA1c < 7 % (< 53 mmol/mol). When switching participants from MDI to CSII therapy after 6 months, while continuing pump therapy in the comparator group, glycaemic control was aligned between the two study arms [116]. As previously mentioned, there was no increase in the risk of hypoglycaemic events with CSII compared with MDI therapy [117, 118], while patient related outcomes with regard to quality of life and treatment satisfaction improved on CSII [119-122]. A meta-analysis of randomised controlled trials confirmed that insulin pumps, specifically CSII, can achieve better glycaemic control compared to MDI in those with poorly controlled T2DM [123].

The positive impact on glycaemic control when using pump therapy in people with T2DM may additionally be complemented by the development of faster-acting insulins like faster insulin aspart or ultra-rapid insulin lispro, allowing for an even quicker and more accurate control of insulin levels. A recent analysis in patients with T1DM demonstrated that in patients on CSII, use of faster insulin aspart compared to insulin aspart substantially decreased time to 50 % of maximum concentration, as well as time to maximum concentration [124], as well as postprandial glycaemic control [125]. This may also be particularly relevant for patients with T2DM, as the first phase of the prandial insulin response is often impaired and blunted, making post-prandial glucose control of imminent importance also in T2DM [108].

While use of CSII in T2DM still is mostly neglected in national guidelines, presumably to the anticipated cost, ADA/EASD consensus recommendations already acknowledge trials such as Opt2mise [116] and that CSII may also have a place in the treatment of T2DM [12]. Characteristics seen in the Opt2mise trial including late-middle age, long-standing duration of diabetes (~ 15 years), a high body weight (BMI around 33 kg/m^2), and a high HbA1c of 9 % (75 mmol/mol), although not overly common may be sufficient for considering CSII. [126].

Relevance of different insulin delivery systems for individualised, patient-centred therapies

The question arises if and when (new) devices for insulin delivery become available for people with T2DM, which would require well conducted studies to provide the necessary efficacy and safety data. It has been shown that postprandial glucose predominantly contributes to the HbA1c in people with T2DM with a HbA1c < 7.3 % (< 56 mmol/mol) [127]. Therefore, if a patient requires a basal-bolus regimen insulin pens, wearable mealtime insulin delivery devices, or patch pump mediated CSII may be a viable, less complex and less expensive option compared to conventional insulin pump aided CSII. In those subjects with a HbA1c of > 7.3% (> 56 mmol/mol) the basal insulin component increase with increasing HbA1c levels whereas the contribution of the postprandial component remains unchanged at 1% of HbA1c[126]. This can subsequently be optimized by adding bolus insulin [41, 42, 127]. The initiation of such insulin treatment regimens may be facilitated with the use of discrete devices, thereby allowing to overcome barriers in the way of effective diabetes management. This suggests that technologically simplified models may suffice in T2DM, on the one hand conveying benefits of patch pumps for patients and their diabetes management, while not imposing dramatically increased costs on healthcare systems.

The pharmacokinetic comparability of subcutaneous insulin injections with pens and patch pumps is an important aspect which should be discussed, especially in view of the often required high doses of insulin in people with T2DM.

Impact of digitalisation on diabetes management

In recent years, there has been a large influx of digital tools to aid the management of diabetes. The list of applications specifically developed for people with diabetes include mobile applications (apps) supporting lifestyle modifications such as smoking cessation, physical activity or nutritional advice. These can be combined with data from CGM and CSII or smart insulin pens and/or assist with insulin bolus calculations and titration thus improving

self-management [128-131]. Even though the interest in mobile apps continuously increases, it should be kept in mind that only a limited number of the current apps intended for diabetes have clinical outcomes published or a Conformité Européenne (CE) mark [129, 132]. In addition connected and wearable blood glucose meters, telemedicine and mobile platforms [133, 134] can also facilitate glycaemic control and improve self-management. Improvements in glycaemic management driven by CGM might also aid in addressing clinical inertia as well as therapy adherence. The ADA/EASD consensus sees increasing evidence for the use of technology and telemedicine to improve health outcome [12].

Burden of people with uncontrolled insulin-treated T2DM – who could benefit from an improvement in insulin delivery?

As elucidated above, there are several ways to ease and improve the management of diabetes, ranging from overcoming clinical inertia via improved patient and HCP education to patient-driven titration algorithms, as well as simplification of diabetes management through technological advances such as connected insulin pens, wearable insulin patches, and patch pumps. Recent guidelines strongly emphasise a patient-centred approach in treatment of diabetes.

As observed exemplarily for six European countries, more than half of the patients on insulin regimens are above a HbA1c of 7 % (53 mmol/mol) [10, 103, 104] who could benefit from improved insulin delivery (Table 2).

> In France, an estimate of 513,707 people with T2DM treated with insulin do not reach the target HbA1c of 7 % (53 mmol/mol), and 254,038 people with T2DM on a basal insulin regimen and 332,033 people with T2DM on a MDI insulin regimen do not achieve the target HbA1c of 7 % (53 mmol/mol).
>
> In Germany, an estimate of 3,653,970 of the total T2DM population have a HbA1c above 7 % (53 mmol/mol). 225,500 patients on a basal insulin regimen have a HbA1c above 7 % (53 mmol/mol).
>
> Estimated 1,673,931 Italian people with T2DM do not reach the target HbA1c of 7 % (53 mmol/mol). 208,133 of the people with T2DM treated with any insulin regimen

have a HbA1c above 9 % (75 mmol/mol) and 255,653 people treated with basal insulin are above a HbA1c of 7 % (53 mmol/mol).

For the Netherlands, the estimates for people with T2DM above a HbA1c of 7 % (53 mmol/mol) is 258,235 whilst 138,651 patients on any insulin regimen, 32,312 treated with basal insulin and 36,051 on MDI regimens have a HbA1c above 7 % (53 mmol/mol).

In Spain, the target HbA1c of 7 % (53 mmol/mol) is not achieved by an estimate of 371,655 people with T2DM treated with any insulin regimen and 190,571 patients on a basal insulin regimen.

For the UK, the estimated number of people with T2DM above the target HbA1c of 7 .5% (58 mmol/mol) is 267,318, with 498,681 insulin treated patients having a HbA1c > 7 % (> 53 mmol/mol).

These numbers can only be estimates of the actual situation in the respective countries, as publications used for this analysis vary in publication date, investigated population and also target HbA1c. This is also reflected in the heterogeneity of populations with regard to insulin treatment (overall population vs. basal only vs. MDI). History of insulin therapy, reimbursement strategies, and availability of insulins as well as education in the respective countries might contribute to this heterogeneity. Lack of evidence hinders a comparative analysis of potential reasons. Specific data on poorly controlled people with T2DM, irrespective of treatment regimens, are difficult to obtain, as most countries do not have holistic registries. To increase awareness of the poor situation in Europe and address the challenge of improving glycaemic management in people with T2DM, precise numbers of uncontrolled patients are of great importance and should be collected in a more organised and coordinated manner which is essential for the future to conduct meaningful audit and monitor progress and the impact of new therapeutic agents, delivery and monitoring technologies.

Uncontrolled diabetes is not only a burden for those experiencing glycaemic instability with episodes of hyperglycaemia and/or hypoglycaemia, it is also a predictor for comorbidities and therefore a socioeconomic burden for healthcare systems. A literature review for the six European countries (FR, DE, IT, NL, ES and the UK) did not yield specific costs for the different

insulin regimens such as basal insulin only or MDI of insulin, to allow a comparison between countries and enable an estimation of the burden for the European healthcare systems. As stated above, uncontrolled diabetes is associated with high direct medical costs, increasing substantially with the presence of diabetes related complications [36-39]. Thus, it can be assumed that the estimated high numbers of uncontrolled people with insulin-treated T2DM will have strong negative impact on expenditures in the various European healthcare systems.

Conclusion

Even though insulin therapy is very likely to be required in the continuum of T2DM and current guidelines recommend a timely and target optimised patient-centred management to minimise the risk of complications, the situation appears less than optimal in many countries of Europe. Initiation of insulin therapy is hindered by clinical inertia, resulting in long-term exposure to hyperglycaemia with HbA1c of above 9 % (75 mmol/mol). Not only a delay in insulin initiation but inadequate titration, poor adherence to therapy, use of complex regimens are reflected in the high number of people with T2DM on insulin therapy not achieving glycaemic targets as recommended by national and/or international guidelines. Therefore, there is a high need to ease the burden of people with T2DM on insulin therapy. There is evidence that alternatives to current insulin delivery, such as insulin pens, wearable mealtime insulin delivery patches, patch pumps, and conventional insulin pumps ideally in combination with new digital patient-centred diabetes management systems can improve glycaemic control and patient related outcomes in people with T2DM receiving insulin therapy. People with T2DM should therefore be provided with simple solutions and straight forward treatment algorithms, dosing aids, and easy-to-use insulin delivery devices to optimally control their diabetes and reduce its burden on the people with T2DM which will also ultimately reduce the expenditures of European healthcare systems.

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1 Figures and Tables

2 **Table 1: Glycaemic targets as recommended by national guidelines**

Country	Year	Association	HbA1c target
Europe	2019	European Society of Cardiology / European Association for the Study of Diabetes [20]	• **< 7 %** (< 53 mmol/mol) will decrease microvascular complication • tighter glucose control initiated early in younger individuals leads to a reduction in CV outcomes over a 20 year timescale • less rigorous targets should be considered in elderly patients on a personalised basis and in those with sever comorbidities or advanced CVD
US / Europe	2018	American Diabetes Association / European Association for the Study of Diabetes [12]	• **≤ 7 %** (≤ 53 mmol/mol) for most non-pregnant adults with sufficient life expectancy to see microvascular benefits (≈ 10 years) → targets should be individualised
France	2017	Haute Autorité de Santé [23], Société Francophone du Diabète [24]	• **≤ 7 %** (≤ 53 mmol/mol) for most patients with T2DM • **≤ 6.5 %** (≤ 48 mmol/mol) for patients with T2DM who are newly diagnosed, have a life expectancy > 15 years and no cardiovascular history • **< 8 %** (< 64 mmol/mol) for patients with reduced life expectancy, long diabetes duration, risk of hypoglycaemia and associated comorbidities • **≤ 9 %** (≤ 75 mmol/mol) for elderly patients and/or patients in very poor health • The target should be individualised according to the patient profile and can evolve over time
Germany	2018	Deutsche Diabetes Gesellschaft [25, 26]	• **6.5-7.5 %** (48-58 mmol/mol) target corridor for the prevention of complications, avoiding hypoglycaemia.
Italy	2018	Società Italiana di Diabetologia / Associazione Medici Diabetologi [27]	• **< 6.5 %** (< 48 mmol/mol) in patients without an increased risk of hypoglycaemia • **6.5-7.5 %** (48-58 mmol/mol) in patients treated with medications associated with an increased risk of hypoglycaemia • In patients with reduced life expectancy (due to advanced age and / or comorbidity) in which the long-term benefit derived from the prevention of chronic complications is less relevant, higher levels of Hba1c can be tolerated

Netherlands	2013	Nederlands Huisartsen Genootschap [28]	• **≤ 7 %** (≤ 53 mmol/mol) in patients < 70 years, with lifestyle advice only or metformin monotherapy • **≤ 7.5 %** (≤ 58 mmol/mol) in patients > 70 years, other medications than metformin monotherapy and a diabetes duration < 10 years • **≤ 8 %** (≤ 64 mmol/mol) in patients > 70 years, other medications than metformin monotherapy an a diabetes duration > 10 years
Spain	2019	Sociedad Espanola de Endocrinologia y Nutricion [29]	• **< 7 %** (< 53 mmol/mol) general objective • **< 6.5 %** (< 48 mmol/mol) in non-fragile patients, without a risk of hypoglycaemia, without associated comorbidities, high motivation and self-care and high life expectancy • **< 8-8.5 %** (< 64-69 mmol/mol) in fragile patients, with increased risk of hypoglycaemia, associated comorbidities low motivation and self-care and reduced life expectancy
UK	2018	The National Institute for Health and Care Excellence [30]	• **≤ 6.5 %** (48 mmol/mol) T2DM managed either by lifestyle and diet, or by lifestyle and diet combined with a single drug not associated with hypoglycaemia • **< 7 %** (53 mmol/mol) for adults on a drug associated with hypoglycaemia

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Table 2: Number of people with T2DM not reaching glycaemic targets of < 7 % (< 53 mmol/mol) in six European countries

	France	Germany	Italy	Netherlands	Spain	UK
Population	66,992,699[135]	83,073,100[136]	60,359,546[137]	17,356,157[138]	46,934,632[139]	66,435,600[140]
People with diabetes	5 %[141]	9.9 %[142]	6.2 %[143]	15.3 %*[144]	7.8 %[145]	14.4 %*[146]
T2DM (all)						
[%]	92 %[141]	96 %[147]	91.1 %[101]	91 %[144]	90 %[1]	90 %[148]
[number]	3,081,664	7,891,945	3,409,228	1,032,941	3,294,811	3,428,207
[%] above target	/	46.3 %[149]	49.1 %[101]	25 %[102]	/	34.2 %≠[150]
Estimated [number] above target	/	3,653,970	1,673,931	258,235	/	267,318
T2DM insulin therapy						
[%] of T2DM population	24.3 %[151]	22.7 %[152]	33 %[101]	17.8 %*[153]	15 %[99]	22.8 %[10]
[%] above target	68.6 %[97]	/	18.5 %#[101]	75.6 %[98]	75.2 %[99]	63.8 %[100]
Estimated [number] above target	513,707	/	208,133	138,651	371,655	498,681
T2DM basal insulin						
[%] of T2DM population treated with insulin	44 %[151]	18.9 %[154]	31.3 %[155]	38.3 %*[156]	50.67 %[99]	19.7 %[157]
[%] above target	77.1 %[34]	66.6 %[35]	72.6 %[35]	46 %[102]	76.1 %[35]	/
Estimated [number] above target	254,038	225,500	255,653	32,312	190,571	/
T2DM MDI						

[%] of T2DM population treated with insulin	56.7 %[158]	16.3 %[159]	68.7 %[155]	36.4 %*[160]	/	/
[%] above target	78.2 %[34]	/	/	38-54 %[102]	/	73.3 %[106]
Estimated [number] above target	332,033	/	/	36,051	/	/

* calculated according to numbers referenced in respective publications

> 9 % (> 75 mmol/mol)

≠ > 7,5 % (> 58 mmol/mol)

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