# Treatment of type 2 diabetes: How low do you go?

## Treat early, treat safely!

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**Abstract**
Cardiovascular disease (CVD) represents the major course of death in patients with type 2 diabetes. However, the contribution of improved glycemic control to reduce the individual diabetes-associated risk for CVD is controversially discussed. Although good glycemic control has been shown to reduce the risk of microvascular complications, the potential benefit of intensive glucose lowering in relation to the prevention of cardiovascular events is less clear. Importantly, large clinical trials such as ACCORD, ADVANCE or VADT were not able to show a significant decrease in primary cardiovascular endpoints with intensive glucose control. Since these trials included patients with 8–11.5 years duration of diabetes, the question has been raised whether patients in these trials have been treated early and safely enough. A "bad" metabolic memory effect may have contributed to the lack of effects of good glycemic control in these trials. Supporting the concept that early and safely achievable (i.e. with a low risk of hypoglycaemia and weight gain) glycemic control reduces the CVD in diabetes patients, in the UKPDS early glycemic control of the metformin-based therapy translated into a long-term reduction of the risk of both micro- and macrovascular complications.
In summary, the answer to the question: "How low should we go?" could be: in theory, as low as we can safely achieve without the risk of hypoglycaemia. Preventing the disease should be first priority, but after the manifestation of the disease, early therapeutic interventions with individual targets and personalized (effective and safe) pharmacotherapies.

**Key words:** type 2 diabetes – $HbA_{1c}$, – glucose control – hypoglycemia – weight gain – metabolic memory

## Introduction

Type 2 diabetes (T2D) increases the risk of premature death predominantly due to cardiovascular diseases (CVD). Moreover, the diagnosis of T2D could be seen as an equivalent of CVD, because patients ≥ 30 years of age with diabetes have the same cardiovascular mortality risk as a patient with prior myocardial infarction or otherwise established CVD [1]. Therefore, it has been suggested that T2D patients requiring glucose-lowering therapy should also receive intensive primary prevention for CVD, regardless of other risk factors, sex, or type of diabetes mellitus [1]. Pathogenetic factors which may impair quality of life, but also life expectancy of patients with T2D include chronic hyperglycemia, obesity, impaired lipid metabolism, hypertension, chronic inflammation, oxidative stress, coagulopathy and others [2]. Modern treatment approaches should therefore target all cardiovascular risk factors. Supporting this concept, the results from the extended phase of the STENO-2 trial provide evidence that in at-risk patients with T2D, intensive intervention with multiple drug combinations and behavior modification has sustained beneficial effects on vascular complications and on rates of death from any cause and from CVD [2]. There has been a long debate on the independent contribution of these risk factors (and their control) to CVD risk. Nichols and coworkers recently reported in an observational cohort study including 26,636 T2D patients that control of systolic blood pressure (SBP) and LDL-cholesterol (LDL-C) was significantly associated with reduced CVD hospitalization risk, whereas maintaining $HbA_{1c}$ < 7 % alone was not independently associated with reduced CVD hospitalization risk [3]. Moreover, patients with only SBP or LDL-C in control had the same reduced CVD hospitalization risk as patients with a combination of $HbA_{1c}$ < 7% and low SBP, or $HbA_{1c}$ < 7% and low LDL-C [3]. Such data also raise the question, what do we consider a normal or treatment target $HbA_{1c}$?

In the European prospective investigation into cancer (EPIC) in Norfolk, the relationship between $HbA_{1c}$, cardiovascular disease and total mortality has been investigated in 4662 men and 5570 women in the age group between 45 to 79 years [4]. Although a causal relationship between $HbA_{1c}$ concentrations and cardiovascular disease cannot be concluded from such an observational study, the risk for cardiovascular disease

and total mortality associated with $HbA_{1c}$ concentrations increased continuously [4]. Interestingly, the majority of events occurred in patients with only moderately elevated $HbA_{1c}$ concentrations [4].

In a recent large retrospective cohort study, the survival of patients with T2D has been assessed as a function of $HbA_{1c}$ [5]. Patients were categorized into those whose treatment had been intensified from oral monotherapy to combination therapy with oral blood-glucose lowering agents (n = 27,965) and those with insulin-based treatment (n = 20,005) [5]. Interestingly, an $HbA_{1c}$ of ~ 7.5% was associated with lowest all-cause mortality and lowest progression to CVD and an increase or decrease from this mean $HbA_{1c}$ was associated with increased risk of adverse outcomes [5]. Although the U-shaped pattern of $HbA_{1c}$ dependent risk association was similar in the two treatment cohorts, patients with lower $HbA_{1c}$ had a higher mortality in the insulin compared to the oral antidiabetic treatment group [5], suggesting that adverse effects of insulin treatment such as weight gain and hypoglycaemia may limit the target range of glycemic control. The data further imply that for oral combination therapy without a significant risk of hypoglycaemia a wider $HbA_{1c}$ range is safe with respect to all-cause mortality and CVD events, whereas for insulin-based therapy, a more narrow range might be desirable [5]. Of course, it requires further prospective studies to assess whether intensification of glucose control with insulin therapy alone further heightens risk of death in T2D patients. Taken together, these data open the discussion about setting the right targets for treating chronic hyperglycemia and whether and how we should achieve close to normal glycemic control. Noteworthy, only ~30% of patients with T2D reach their $HbA_{1c}$ treatment goals in Europe [6]. This may further question our treatment practice of "running behind the increased $HbA_{1c}$ value". Should we therefore treat T2D patients earlier or more aggressively or even treat prediabetic states?

## How early is early enough – lessons from type 2 diabetes prevention trials

In the prospective second National Health and Nutrition Examination Survey Mortality Study, undiagnosed diabetes, but also impaired glucose tolerance, which is considered a prediabetic state, have been significantly associated with increased all-cause mortality compared to normoglycemic individuals [7]. However, whether the long-term cardiovascular risk is reduced by the interventions to prevent T2D is still unknown. Recently the ~10 years' follow-up from Diabetes Prevention Program, major improvements were observed for several cardiovascular risk factors, but it was obviously too early to detect any effect of diabetes prevention on CVD mortality [8]. Moreover, a recent meta-analysis of randomized clinical trials in patients with prediabetes elucidated that despite interventions being mostly successful in retarding progression to overt diabetes, this does not translate into reductions in all-cause or cardiovascular mortality [9]. Therefore, the following paragraphs focus on the effects of glycemic control on diabetes complications and mortality in patients with diagnosed T2D.

## Effects of glycemic control on diabetes complications and mortality

The first evidence that a tighter glycemic control significantly reduces the risk for late microvascular complications of T2D has been provided by the results from the United Kingdom Prospective Diabetes Study (UKPDS) [10,11]. The UKPDS included at baseline almost 3,900 patients with newly diagnosed T2D who were randomly assigned to an intensive treatment arm (mainly sulfonylurea or insulin) or to conventional management (mainly based on diet [10,11]. In the intensive treatment group, a mean $HbA_{1c}$ of 7.0% was achieved in the 10-year follow-up, whereas the conventionally treated group reached an $HbA_{1c}$ of 7.9% [10,11]. These differences in long term glycemic control translated into significant reductions of the risk to develop diabetes complications by 12%, for any diabetes-related endpoint by 10%, for any diabetes-related death, by 6% for all causes of mortality, and by 16% for myocardial infarction [11]. Except for the reduction in the incidence of diabetes complications, these endpoint differences were not statistically significant. However, the observed 25% risk reduction for microvascular complications was highly significant [11], but the question whether a better glycemic control may lead to a risk reduction for CVD remained open [12].

Although the Kumamoto study reported a ~50% reduction of cardiovascular (CV) events in patients on intensified compared to conventional insulin treatment, the total number of CV events did allow for formal statistical proof [13]. In the PROactive trial, intensive glycemic control with pioglitazone on top of any existing diabetes medication did not significantly improve the primary CV endpoint [14]. However, pioglitazone treatment caused a significant reduction in a combined secondary endpoint of reduced all-cause mortality, non-fatal myocardial infarction and stroke, which is at least suggestive for aiming at a tighter glycemic control [14].

**Table 1. Benefits of good glycemic control in the United Kingdom Prospective Diabetes Study (UKPDS).** Modified from [10,11].

| | | |
|---|---|---|
| **metformin-based therapy** | | |
| **risk reduction** | | |
| 32% | for any diabetes related endpoint | p = 0.002 |
| 42% | for diabetes related endpoint | p = 0.017 |
| 36% | for all cause mortality | p = 0.021 |
| **sulfonylurea- and insulin-based therapy** | | |
| 12% | for any diabetes related endpoint | p = 0.029 |
| 10% | for diabetes related endpoint | p = 0.34 |
| 6% | for all cause mortality | p = 0.44 |

Noteworthy, the micro- and macrovascular endpoint differences in the UKPDS between intensive and conventional treatment were strongly dependent on the either metformin- or sulfonylurea/insulin- based treatment strategy (Table 1) [11,12]. The better outcomes in the relatively small subgroup of metformin treated patients compared to sulfonylurea/ insulin-based treatment may suggest that avoiding side effects such as weight gain and hypoglycaemia of the latter therapy plays an important role in the consideration of individual T2D management. The hypothesis that better glycemic control leads to a reduced CV outcomes was more recently tested in three large independent trials, which recruited ~23,000 patients with T2D.

## Results from large intensive treatment studies in type 2 diabetes

In 2008 and 2009, the results of three large clinical trials, the ADVANCE study (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) [15], the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study [16], and the Veteran Administration Diabetes Trial (VADT) [17] have provided important insights into the relationship between tight glycemic control and incidence of CV events (Table 2).

In the ADVANCE study, a significantly lower $HbA_{1c}$ in the intensive control group compared to the standard group (6.6% versus 7.3%) significantly reduced the incidence of combined major macro- and microvascular, and major microvascular events (both p = 0.01), but had no significant effect on the number of major macrovascular events, death from CV diseases or any other cause after a median follow-up of 5 years [15]. The ACCORD study (mean follow-up: 3.5 years) with very similar differences in glycemic control between the intensive and standard treatment groups (6.4% versus 7.5%) as in ADVANCE had to be prematurely discontinued because of a 22% increased mortality risk in the intensively treated group, which aimed for a $HbA_{1c}$ below 6.0% [16]. In the intensive treatment group, there were 52 more deaths compared to the standard therapy group [16]. In contrast, parameters of microvascular T2D complications (retinopathy, neuropathy, delayed onset of albuminuria) improved. The VADT achieved a median $HbA_{1c}$ of 6.9% after a median follow-up of 5.6 years in the intensive-therapy group compared to 8.4% in the standard-therapy [17]. This significant difference in chronic hyperglycemia was not associated with differences in the rate of CV events, in the rate of death from any cause and for microvascular complications (except for reduced progression of diabetic nephropathy) between the two intervention groups. In particular the results from the ACCORD study raised concerns about the safety of intensive glycemic control in patients with T2D despite effectiveness [18]. In a recent meta-analysis including 13 studies and data from ~34,500 patients with T2D evaluating the effects intensive glucose lowering on all-cause mortality, cardiovascular death, and vascular events the tighter glucose control was not significantly associated with reduced mortality including CV mortality [19]. These most recent data are in line with several other meta-analyses [reviewed in 18], which do not support the concept that a very good glycemic control causes reduction in CV deaths.

Of course several factors may have contributed to limit the benefit of intensive glucose control on CVD outcomes. The parallel targeting of other – maybe more potent CV risk factors – namely hypertension and dyslipidemia may have masked favourable effects of improved glycemic control. Limited benefit may have been due to the use of glucose-lowering drugs with no favourable impact on CV risk profile or which produced adverse effects on the cardiovascular system by inducing significant weight gain or hypoglycaemic events. In addition, excess mortality in the ACCORD study may have been the result of requiring too many different drugs to achieve tight glycemic control and subsequent adverse and harmful drug-drug interactions [reviewed in 18].

**Table 2. Effects of early versus late glycemic intervention in large clinical trials.** Modified from [12].

| | UKPDS [11, 12] (n =3 ,867) | ADVANCE [15] (n = 11,140) | ACCORD [16] (n = 10,251) | VADT [17] (n = 1,791) |
|---|---|---|---|---|
| disease progression | | | | |
| duration of diabetes (years) | 0 | 8 | 10 | 11.5 |
| mean age (years) | 53 | 66 | 62 | 60 |
| mean baseline $HbA_{1c}$ (%) | 7.1 | 7.5 | 8.3 | 9.4 |
| mean baseline FPG (mmol/L) | 8.0 | 8.5 | 9.7 | 11.4 |
| microvascular complications | reduced | reduced | variable | unchanged |
| macrovascular complications | reduced | unchanged | increased | unchanged |

**UKPDS** – United Kingdom Prospective Diabetes Study **ADVANCE** – Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation **ACCORD** – Action to Control Cardiovascular Risk in Diabetes **VADT** – Veterans Affairs Diabetes Trial **FPG** – fasting plasma glucose

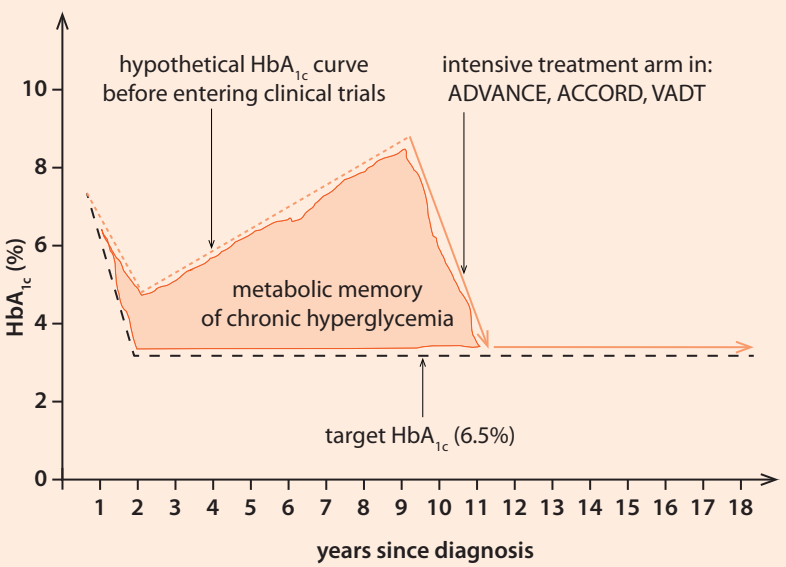
Most importantly, the ADVANCE, ACCORD, and VADT studies included T2D patients with an already high CV risk due to prior CV events in more than one third of the study participants and > 50% with established microvascular complications [reviewed in 12]. Owing to these characteristics of the study populations, the trials initiated an aggressive treatment of CV risk factors resulting in reduced LDL-cholesterol (≈2.3 mmol/l), blood pressure (≈120/70 mmHg), number of active smokers and increased use of anti-platelet therapy (in up to 93%). Such multifactorial intervention has already been proven to be effective [2] and may account for the unexpectedly low mortality rate of 2.2% per year (which is as low as in the general population) [12]. These additional interventions may have dampened the favourable effects of more intensive glucose lowering. This hypothesis is supported by data from subgroups of patients without prior CVD, in whom tight glycemic control was associated with a significant reduction of primary CV outcomes [12,15–17]. Importantly, beneficial effects of intensive glucose lowering on CVD risk was found in T2D patients with a lower $HbA_{1c}$ (≤ 8.0%) at baseline compared to those with higher $HbA_{1c}$ levels [12,15–17]. In ACCORD, the risk of all-cause mortality increased continuously with increased $HbA_{1c}$ from 6–9% and increased risk of premature death mainly occurred in T2D patients with $HbA_{1c}$ > 7% [16]. The absence of a diagnosed CVD, or microvascular complications, and a lower baseline $HbA_{1c}$ may reflect a shorter duration of T2D and opens the question whether there is a "point of no return" in diabetes related CVD prevention. It also suggests that early initiation and maybe intensification of anti-hyperglycemic treatment provides better CV outcomes than optimizing glycemic control in T2D patients with established macro- and microvascular diseases.

## Effects of early versus late glycemic intervention

From the large intervention trials on intensified glycemic control [15–17] it could be concluded that duration of diabetes and established CVD may be the most critical factors influencing the CV outcome of optimizing glucose control. In these trials, good glycemic control was achieved only after years of uncontrolled diabetes [12] (Figure). In contrast to the majority of the study participants in these trials, Bianchi and Del Prato [12] postulated that ideal conditions for good glycemic control prevail when T2D diagnosis is made early and tight glycemic control is ensured from the time of diagnosis (Figure).

The difference between the real glycemia status in patients entering the large T2D trials and the hypothetical ideal $HbA_{1c}$ curve illustrates how a "bad glycemic memory" may built up over the natural course of the disease (Figure). Such glycemic memory also called "legacy effect" has been proposed from post-trial data of the UKPDS [20]. In line with the paradigm that treating patients with T2D early to target reduces adverse outcomes, in the UKPDS 10-year follow up, intensive

**Figure. Schematic representation of a "bad metabolic memory effect"**




Hypothetical individual $HbA_{1c}$ curves representing either the development of the metabolic memory before entering one of the diabetes treatment trials (ADVANCE, ACCORD, VADT) or an early treated to target patient. Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation, ADVANCE; Action to Control Cardiovascular Risk in Diabetes, ACCORD ; Veterans Affairs Diabetes Trial, VADT. Modified from [12].

treatment initiated at the time of diagnosis results in a sustained reduction in the risk of micro- and macrovascular complications [20]: Patients originally randomized into the intensive treatment arm maintained significant reductions in the rates of diabetes-related endpoints, all-cause mortality, risk of myocardial infarction, and microvascular complications 10 years after the active intervention and despite no longer significant differences in $HbA_{1c}$ compared to the conventional treatment group [20]. These data suggest that the legacy of good glycemic control in the initial stages of T2D translated into a permanent benefit related to micro- and macrovascular risk factors.

The impact of a bad glycemic memory is further supported by the relationship between diabetes duration before initiating intensive treatment and CV outcome in different T2D trials [11,12,15–17] (Table 2). The beneficial effects of tight glycemic control on CVD and other complications of diabetes seems to be a clear function of disease duration prior to optimizing treatment (Table 2). The comparison of the outcome of these trials (Table 2) should lead to a paradigm shift towards an early intensive and safe T2D treatment which starts at the time of diagnosis. In addition, early intervention is safer and more effective, because complications of T2D at the time of diagnosis are usually not established and a bad glycemic memory could be avoided. Especially in newly diagnosed patients with T2D, the glycemia targets could be set to a $HbA_{1c}$ as low as possible, because in this stage of the disease, normoglycemia is feasible and necessary. In addition to target hyperglycemia, improvements in all CV risk factors should be achieved by a multifactorial approach. The here requested multimodal treatment strategy has been proven to be successful in the extended phase of the STENO-2 trial. In STENO-2, effective treatment of hyperglycemia, elevated blood pressure and dyslipidemia led to significantly reduced incidence of CV events [2]. Therefore the term glycemic memory should be extended to metabolic memory effect [12]. Both the 10-years follow up of the UKPDS and the extended phase of STENO-2 imply that early (and multifactorial) reducing hyperglycemia and other CV risk factors yield beneficial long term outcomes [2,12,20].

On the other hand, if intensification of T2D treatment is delayed such as in the trials ADVANCE, ACCORD and VADT (Table 2), organ damages including adverse effects on the vasculature may have become irreversible and patients may not significantly benefit from intensive glycemic control with regard to reduced CV mortality. A better understanding of the specific mechanisms linking hyperglycemia to end-organ damage may lead to novel strategies for a better prediction, but more importantly better treatment of diabetes complications.

Taken together, there is evidence that an early (from the time of first diagnosis) and good glycemic control has a protective effect to either prevent or reduce macrovascular complications. In addition to the early initiation of treatment, the ACCORD, ADVANCE and VADT studies demonstrated that safety of the treatment with regard to preventing hypoglycaemia and weight gain is a primary goal in T2D therapy.

## The risk benefit balance in type 2 diabetes treatment

For the individual treatment decision in T2D patients, the risk-benefit ratio of different anti-diabetic pharmacotherapies needs to be carefully considered. Factors limiting tighter glycemic control may include: increased risk hypoglycaemia, weight gain, gastrointestinal side effects, age, comorbidities such as renal impairment and others. Among those, hypoglycaemia seems to the most important factor impairing both quality of life and risk of premature (CV) death. In the earlier stopped than originally planned ACCORD study, the risk of hypoglycaemia was directly related to $HbA_{1c}$, i.e. T2D patient who did not respond well to initial steps of anti-diabetic treatment, the treatment had to me more aggressive associated with a higher hypoglycaemia risk [16]. Indeed, in the ACCORD study, the mortality rate was higher in patients with hypoglycaemia independently of the treatment arm. On the other hand, mortality rate of patients with hypoglycaemia was lower in those with a tighter glycemic control [12]. In VADT, a recent severe hypoglycemic event was an important predictor for CV death (HR 3.72; 95% CI 1.34–10.4; $P < 0.01$) and all-cause mortality (HR 6.37; 95% CI 2.57–15.8; $P = 0.0001$). In contrast, in the ADVANCE study [15], in which the overall occurrence of severe hypoglycemia was much lower than in ACCORD [16], no increase in all-cause or CV mortality was observed in patients randomized to the intensive arm. Nevertheless, severe hypoglycemia was strongly associated with increased risks of various adverse clinical outcomes, and the authors suggested that whereas severe hypoglycemia may contribute to these outcomes, it may alternatively be a marker of vulnerability to these events [21]. Acute hypoglycemia leads to physiological responses as a consequence of the sympatho-adrenal system, and results in end-organ stimulation and a profuse release of epinephrine, which stimulates hemodynamic changes [21]. The consequences of these changes are to maintain the supply of glucose to the brain and promote the hepatic production of glucose. The hemodynamic changes associated with hypoglycemia include an increase in heart rate and peripheral systolic blood pressure, a fall in central blood pressure, reduced peripheral arterial resistance, and increased myocardial contractility, stroke volume, and cardiac output [21]. The workload of the heart is therefore temporarily but markedly increased. This transient cardiac stress is unlikely to be of serious functional importance in healthy young people who have a normal CV system, but may have dangerous consequences in many older people with diabetes, especially individuals with T2D with established CVD [21]. Although not definitely proven, hypoglycemia may in vulnerable patients

**Table 3. Hypoglycemia in patients with type 2 diabetes: risk factors and at-risk groups.** Summarized from [21–23].

| risk factors | at-risk groups |
|---|---|
| exercise | renal impairment |
| irregular eating habits | elderly people |
| alcohol consumption | lower $HbA_{1c}$ |
| periods of fasting (e.g. Ramadan) | prior hypoglycaemia |
| use of insulin and sulfonylureas | long duration of diabetes |
| | hypoglycemia unawareness |

increase the risk for sudden death, cardiac arrhythmias, myocardial infarction, and stroke [21].

The individual risk of hypoglycemia is influenced by several factors and may be increased in specific at-risk groups (Table 3) [22,23]. Therefore it should be recommended that glycemic control must be tailored to the age of the individual patient and in particular should address existing comorbidities and the type of treatment to be used. Accordingly, future diabetes guidelines will have to define a minimum $HbA_{1c}$ value, especially for patients with longstanding diabetes or who have established CVD [21].

In addition to the higher risk of hypoglycemia, intensive T2D anti-hyperglycemic treatment maybe associated with weight gain, especially in patients using insulin, sulfonylurea, glinides and glitazones. However, the impact of increased body weight and fat mass in response to intensified anti-diabetic treatment is still not clear, whereas as a weight reduction has clear beneficial effects on CV outcomes [2]. For both prevention of hypoglycemia and weight gain, T2D treatment should be initiated using pharmacotherapies with a low risk of these side effects including metformin, DPP4 inhibitors, GLP1 receptor agonists or SGLT2 inhibitors. For metformin-based combination therapies it has been demonstrated for the latter three classes of medications that the combination with metformin is as effective as the combination of metformin with a sulfonylurea. For example, vildagliptin added to metformin had a similar efficacy as the metformin-glimepiride combination, but had a significantly lower incidence of hypoglycemia and weight gain over 104 weeks of treatment [24].

## Personalized treatment aims

Modern anti-diabetic pharmacologic treatment options allow for more individualized therapeutic approaches. In each individual, the positive and potential side effects of any medication should be carefully considered. Personalized treatment aims are also suggested by a joint statement of the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD) [25], the ADA and the American Heart Association (AHA) [26], as well as national guidelines such as National Institute of Clinical Excellence (NICE) in the United Kingdom [27]. As an example, the NICE guidelines recommend for the first two treatment steps a target $HbA_{1c}$ of < 6.5% and beyond this a target $HbA_{1c}$ of < 7.5% [28]. The guidelines also suggest to consider adding a DPP4 inhibitor second-line instead of sulfonylurea when blood glucose control is inadequate with metformin alone [28].

The joint ADA/AHA statement paper suggested for patients with a long duration of the disease, limited life expectancy and/or evidence for long-term complications as well as a history of severe hypoglycaemia, target $HbA_{1c}$ should be > 7% [26]. In contrast, patients without these risk factors, tighter glycemic control should be achieved early and maintained below $HbA_{1c}$ of 7% [26].

In clinical practice the risk-benefit-ratio needs to be determined for each patient individually. This approach can only be processed by personalization of treatment targets and "customized" pharmacological therapies [12]. Although personalized treatment is rational, it is not always a simple task and requires experienced physicians and sometimes even changes of guidelines. The current joint ADA/EASD position statement may be used as a basis for a personalized approach [25]. It considers therapeutic decision making including defined aims like differences in efficacy, avoiding hypoglycaemia, and achieving weight loss or weight stability [25].

## How low should we go?

In summary, the answer to the question: "How low should we go?" could be: In theory, as low as we can safely achieve without the risk of hypoglycaemia. For the first two treatment steps a target $HbA_{1c}$ of < 6.5% and beyond this a target $HbA_{1c}$ of < 7.5% should be achieved [28]. Preventing the disease should be first priority, but after the manifestation of the disease, early therapeutic interventions with individual targets and personalized (effective and safe) pharmacotherapies.

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