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REVIEW ARTICLE

One size does not fit all glycemic targets for type 2 diabetes

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ABSTRACT

The United Kingdom Prospective Diabetes Study, and Diabetes Control and Complications Trial have shown that aggressive glucose control, especially early in the natural history of the disease, might result in a significant reduction of microvascular as well as macrovascular complications. However, more recent trials have increased the level of complexity of the relationship between 'tight glucose control/chronic complications', with several factors influencing the risk-to-benefit ratio to be considered, such as age, presence of established complications and diabetes duration. According to this strategy, a more intensive goal is desirable for young patients with no cardiovascular disease, whereas less stringent control is suitable for all people who are relatively late in the natural history of diabetic complications. Numerous calls for an individualized therapy have been proposed during the past years, but still debated is the level of glucose lowering necessary to reduce complications balanced by the risk and costs of the means used. The present paper briefly reviews the rationale and the clinical trials that support specific glycemic goals towards a 'tailored' approach for the management of hyperglycemia in diabetes.

INTRODUCTION

Nowadays, the chronic complications of diabetes are a major burden for both individuals with the disease and health systems. It is well known that as much as 60–70% of costs related to diabetes are currently attributable to chronic complications, mainly hospitalization[1]. It is recognized that hyperglycemia has a pathogenic role in micro- and macrovascular complications. Cardiovascular disease (CVD) is independently associated with hyperglycemia[2,3], and predictive markers of CVD are also often elevated in diabetes[4]. Furthermore, some varieties of retinopathy, nephropathy and neuropathy are diabetes specific, and do not occur in the absence of diabetes. Still debated, however, is the level of glucose lowering necessary to reduce complications balanced by the risk and costs of the means used. Even more controversial is the threshold below which a benefit does not occur despite an antidiabetic treatment – this threshold being the goal of therapy in most cases. Quite intriguingly, indeed, data from epidemiological studies and from interventional trials are somewhat discordant. This raises the question of glycemic goals, especially in type 2 diabetes. The present paper briefly reviews the rationale and the clinical trials that support specific glycemic goals towards a 'tailored' approach for the management of hyperglycemia in diabetes.

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GLUCOCENTRIC DOGMA: 'THE LOWER, THE BETTER'

The core data for target setting of blood glucose in type 1 and type 2 diabetes initially came from three main trials published in the 1990s, which aimed to prove the benefit of tight glucose control in terms of diabetic complications[5–7].

The Diabetes Control and Complications Trial (DCCT) compared intensive insulin therapy with conventional treatment in 1,441 patients with type 1 diabetes after an average follow up of 6.5 years. The intensive therapy group was targeted to achieve near-to-normal blood glucose control, including glycated hemoglobin (HbA1c) within the normal range. Results showed that a 2% HbA1c absolute difference between the two groups reduced the risk of new-onset retinopathy by 76% (95% confidence interval [CI] 62–85), as well as the risk of progression by 54% (95% CI 39–66). The appearance of microalbuminuria, proteinuria or neuropathy was also significantly reduced[5] (Table 1). Similar evidence came a few years later from the United Kingdom Prospective Diabetes Study

Table 1 | Effect of intensive vs standard blood glucose control on major microvascular outcomes in type 1 and type 2 diabetes

Study	DCCT	Kumamoto study	UKPDS 33	EDIC (post-DCCT)	UKPDS 80 (post-UKPDS 33)	ACCORD	ADVANCE	VADT	ORIGIN
Population	1,441 T1D	110 T2D	4,209 T2D	1,421 T1D	3,277 T2D	10,251 T2D	11,140 T2D	1,791 T2D	11,085 T2D 1,452 IGR
Age (years)	27	47–52	53			62	66	60	
BMI (kg/m^2)	23	19–21	28			32	28	31	
Complications	–/+	–/+	–/+			++	++	++	++
Disease duration (years)	<15	6–10	0			10	8	11.5	5
Baseline HbA1c (%)	8.8–9	8.9–9.4	7.1			8.3	7.5	9.4	6.4
Post-trial HbA1c (intensive vs standard;%)	7.0 vs 9.0	7.1 vs 9.4	7.0 vs 7.9			6.3 vs 7.5	6.5 vs 7.3	7.0 vs 8.5	6.2 vs 6.5
Microvascular end-points									
Retinopathy	0.37 (0.29–0.48) ≥3-step sustained retinopathy	0.31 (0.13–0.76) ≥2-step cumulative change	0.75 (0.60–0.98) Any micro-vascular outcome	0.47 (0.39–0.57) 3-step progression	0.76 (0.64–0.89) Any microvascular outcome	0.67 (0.51–0.87)† 3-step progression	0.72 (0.44–1.17)† 3-step progression	0.77 (0.58–1.02) 2-step progression	0.97 (0.90–1.05) Any micro-vascular outcome
Nephropathy	0.61 (0.48–0.79) Incident micro-albuminuria	0.30 (0.11–0.86) New or worsening nephropathy		0.41 (0.27–0.61)† Incident micro-albuminuria		0.72 (0.61–0.84) Incident macro-albuminuria	0.79 (0.66–0.93) New or worsening nephropathy	0.65 (0.49–0.89) Any increase in albuminuria	
Neuropathy	0.40 (0.26–0.62) Clinical neuropathy			0.70 (0.52–0.93)† Clinical neuropathy		0.92 (0.86–0.99) Neuropathy (MNSI>2)		0.99 (0.87–1.14) Any new neuropathy	
References	5	7	6	40–42	14	[17,19,20]	18,21	16	24

†Data are relative risk (95% confidence interval) or odds ratio. EDIC, Epidemiology of Diabetes Interventions and Complications; HbA1c, glycated hemoglobin; IGR, impaired glucose regulation (impaired glucose tolerance or impaired fasting tolerance); MNSI, Michigan Neuropathy Screening Instrument; T1D, type 1 diabetes; T2D, type 2 diabetes.

(UKPDS). A total of 4,209 participants with recently diagnosed type 2 diabetes were randomly allocated to two treatment policies of conventional treatment (diet only) or intensive treatment (with either a sulphonylurea or insulin, or metformin in overweight patients)[6,8]. Patients assigned to intensive treatment experienced a risk reduction of 25% (95% CI 7–40) for any microvascular end-points (Table 1)[6], but a benefit in terms of mortality or cardiovascular events was shown only in overweight patients treated with metformin[8]. As expected, the cost for tight glucose control was an increase in severe hypoglycemia and bodyweight.

The Kumamoto Study also showed similar risk reduction of retinopathy and nephropathy in 110 lean Japanese participants with insulin-requiring type 2 diabetes. Participants were randomly assigned to intensive insulin therapy with three or more daily insulin injections or conventional insulin treatment with one or two daily intermediate-acting insulin injections. The intensive therapy group was targeted to maintain the fasting blood glucose <140 mg/dL, 2-h postprandial blood glucose <200 mg/dL and HbA1c <7%[7]. After 8 years, the intensive therapy reduced the risk of retinopathy development or progression by 68% and 57%, respectively, and the risk of microalbuminuria by 74%. No worsening of retinopathy or nephropathy was shown in those patients whose HbA1c levels were lower than 6.5%[9]. No clear effect on mortality or cardiovascular events[7,9,10] was observed, but carotid intima-media thickness and oxidative stress were lower in the intensive group[11]. These results showed the efficacy of blood glucose control in individuals with clinical and ethnic features different from those in the DCCT and UKPDS.

Although tight glucose control was already suspected to be beneficial in terms of chronic complications, these three studies formally demonstrated such a hypothesis. Since then, the evidence provided by those studies has guided clinical practice and medical decisions for several years. The DCCT, UKPDS and the Kumamoto Study were targeted to achieve a near normalization of blood glucose control. In both the DCCT and UKPDS, the rate of complications appeared to follow a positive linear relationship to HbA1c values. Risk reduction was proportional to the HbA1c differences in the two studies between the intensive therapy and control group, and there was no clear glucose concentration or HbA1c level below which the complication risk no longer decreased[5,6,12]. Although the trials did not show a clear benefit in terms of cardiovascular events or death, this possibility was supported by subsequent observational analyses instead. In the UKPDS population, a strong relationship between the appearance of diabetic complications, including mortality, and blood glucose was evident. Each 1% reduction in HbA1c value decreased microvascular complications by 37%, risk of death related to diabetes by 21% and vascular event rates were lower at HbA1c values as low as 5.5%[12]. No threshold of glycemia was evident for a substantial change in risk for any of the clinical outcomes studied, showing that the lower the glycemia, the lower the risk of complications.

LEGACY EFFECT: 'THE EARLIER, THE BETTER'

Additional insight into the relationship between blood glucose control and chronic complications was provided by the post-trial monitoring of the DCCT and UKPDS cohorts[13,14]. The main objective of these observational studies was the prospective evaluation of long-term effects of the differences in treatment policies, intensive vs conventional, several years after the cessation of the original trials. As expected, after the end of the two trials, the differences in HbA1c values tended to narrow in the intensive-treatment and conventional-treatment groups. Despite the similar level of HbA1c, rates of complications were significantly lower in patients who were enrolled in the intensive groups. Importantly, after a timeframe as long as 11 years from the close of the DCCT, patients in the intensive group reached a risk reduction of 42% (95% CI 9–63) for cardiovascular events and 57% (95% CI 12–79) for severe clinical events, including non-fatal myocardial infarction, stroke or death from CVD[13]. This percentage was even higher than that obtained with other proven interventions, such as drugs targeting cholesterol levels and blood pressure. Similarly, the 10-year post-UKPDS observational study confirmed the presence of this legacy effect of prior tight glucose control on complications. Relative reduction in risk persisted at 10 years for any diabetes-related outcome (9%, 95% CI 1–17) and microvascular complications (24%, 95% CI 11–36; Table 1). More importantly, risk reduction emerged for diabetes-related mortality (17%, 95% CI 4–27) and myocardial infarction (15%, 95% CI 3–26)[14]. These results implemented the experimental evidence that early metabolic environment is remembered by target organs[15], and therefore gave credit to the idea, 'the earlier the better'.

FROM A 'GLUCOCENTRIC' APPROACH TO 'PERSONALIZED' GLUCOSE CONTROL

However, a major turning point came a few years ago, when the results of three large trials unexpectedly reduced the enthusiasm generated by the aforementioned follow-up studies. The Veteran Affairs Diabetes Trial (VADT)[16], the Action to Control Cardiovascular risk in Diabetes (ACCORD)[17], and the Action in Diabetes and Vascular Disease (ADVANCE)[18] tested the ambitious hypothesis that close-to-normal glucose control would benefit type 2 diabetes patients at very high risk of CVD. The rationale was based on the assumption that a possible reason for the lack of cardiovascular benefit during the original UKPDS trial was the relatively low cardiovascular risk of the population selected for the study; patients from the UKPDS were newly diagnosed, with neither prior cardiovascular events nor cardiovascular risk factors other than diabetes.

Lessons from the ACCORD

The ACCORD was designed to test the hypothesis that a very ambitious glycemic control (HbA1c <6%) could yield an additional benefit vs standard control. In this study, however, older and long standing patients with type 2 diabetes with high

cardiovascular risk (prior CVD in more than 30% of cases) were recruited (Table 1), and they received a very aggressive treatment of accompanying risk factors, along with a diabetes treatment quite often based on the concomitant use of insulin and three to four oral agents. In this study, there was a quick decline of HbA1c of almost 2% (absolute value) in 4 months. Throughout the study, HbA1c averaged 6.4% in the intensive control group vs 7.5% in the conventional control group. The primary outcome (combined end-point of fatal and not fatal myocardial infarction or stroke) was not significantly reduced in participants who had a 1.0% lower HbA1c, and a greater risk of all cause and CVD mortality was observed (Table 2)[17]. As for microvascular complications, intensive control yielded an improvement of some neurological end-points (loss of ankle jerks, loss of sensation of light touch, neuropathy score), less cataract surgery and a reduced incidence of micro- and macroalbuminuria, but no change in renal function or visual acuity[19,20]. It is worth mentioning that when participants of the ACCORD were stratified into those with very poor control at baseline (HbA1c >8%) and those in fair control (HbA1c ≤8.0%), the latter had a significant reduction of the primary (cardiovascular) endpoints (fatal and not fatal myocardial infarction or stroke and CVD death), whereas the former did not. A further difference in the effect of intensive treatment was observed in participants without prior CVD, who had a significant benefit from intensive control, and in those with prior CVD, who had no such benefit. In conclusion, the ACCORD suggested that intensive glycemic control can be harmful in many patients with type 2 diabetes, whereas others can have a beneficial effect from particularly low glucose concentrations. This was a major contribution to the concept that glycemic goals should be personalized.

Lessons from the ADVANCE

The ADVANCE study also aimed at exploring the hypothesis that more intensive glycemic control could translate into a more favorable outcome in type 2 diabetes. The participants under study were similar to those in the ACCORD in terms of age, duration of diabetes and prior CVD, but were less frequently obese and had a lower baseline HbA1c (Table 1). In this study, the glycemic goal in the more intensive control arm was HbA1c <6.5%, and this goal was pursued less aggressively (it was reached in 3 years and not in 4 months). The absolute HbA1c difference in intensive vs conventional treatment was 0.8%. The primary outcome was a composite of micro- and macrovascular end-points, and intensive treatment was able to improve it significantly, although not dramatically (relative risk reduction 10%, 95% CI 2–18). When examining the different end-points separately, it was found that nephropathy (microalbuminuria), but not CVD, was significantly prevented by intensive control[18]. Subgroup analyses showed that the benefit of intensive control on primary outcome was greater in subjects aged <65 years. Subsequent analyses on different end-points were unable to detect a beneficial effect of intensive control on retinopathy[21].

Table 2 | Effect of intensive vs standard glycemic control on cerebrovascular disease end-points in trials carried out in type 2 diabetes

End-points	ACCORD	ADVANCE	VADT
Composite CVD end-point	0.90 (0.78–1.04)	0.94 (0.84–1.06)	0.87 (0.73–1.04)
CVD death	1.35 (1.04–1.76)	0.88 (0.76–1.04)	1.25 (0.77–2.05)

Data are hazard ratios (95% confidence interval). Composite end-points: Action to Control Cardiovascular risk in Diabetes (ACCORD) = cardiovascular disease (CVD) death + non-fatal acute myocardial infarction (AMI) and stroke; Action in Diabetes and Vascular Disease (ADVANCE) = CVD death + non-fatal AMI and stroke; Veteran Affairs Diabetes Trial (VADT) = CVD death + non-fatal AMI and stroke + congestive heart failure + severe coronary heart disease + any revascularization + vascular amputation.

Lessons from the VADT

The VADT had the same aim as the other recent trials, but it examined type 2 diabetes participants with very poor control (baseline HbA1c 9.4%; Table 1). As in the other two trials, the duration of the study was approximately 5 years, but HbA1c averaged 7.0% in the intensive control arm vs 8.5% in the standard treatment arm in the VADT, a greater difference than in the ACCORD and ADVANCE. The intensive control did not achieve any CVD advantage in the VADT and increased, although not significantly, CVD death, consistent with the ACCORD data (Table 2)[16]. Subgroup analyses showed a cardiovascular benefit in participants with shorter duration of diabetes, and a clear harm was observed in those with longer duration[22]. In addition, the VADT examined several microvascular end-points, and only albuminuria progression was significantly improved and only in participants with prior retinopathy or higher body mass index or lower diastolic blood pressure[23].

BACK TO THE ORIGIN

These results strongly suggested that optimal glucose control should be personalized according to patients' differences in terms of phenotype. Additional support for this idea is provided by the recent Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial[24]. Although the ORIGIN was not a study of more intensive vs less intensive glucose lowering, additional clues on the relationship between glucose control and complications might be extrapolated. The study, by far the largest of its kind, compared the effectiveness of insulin glargine vs standard therapy with diet or oral hypoglycemic agents in 12,537 people who showed evidence of CVD in addition to diabetes (88%) or prediabetes (12%). A total of 50% of the insulin glargine group achieved the fasting plasma glucose target of 95 mg/dL or less, but cardiovascular outcomes remained similar between groups. Previous studies have shown some benefit of early insulin treatment in term of β-cell function[25] and post-

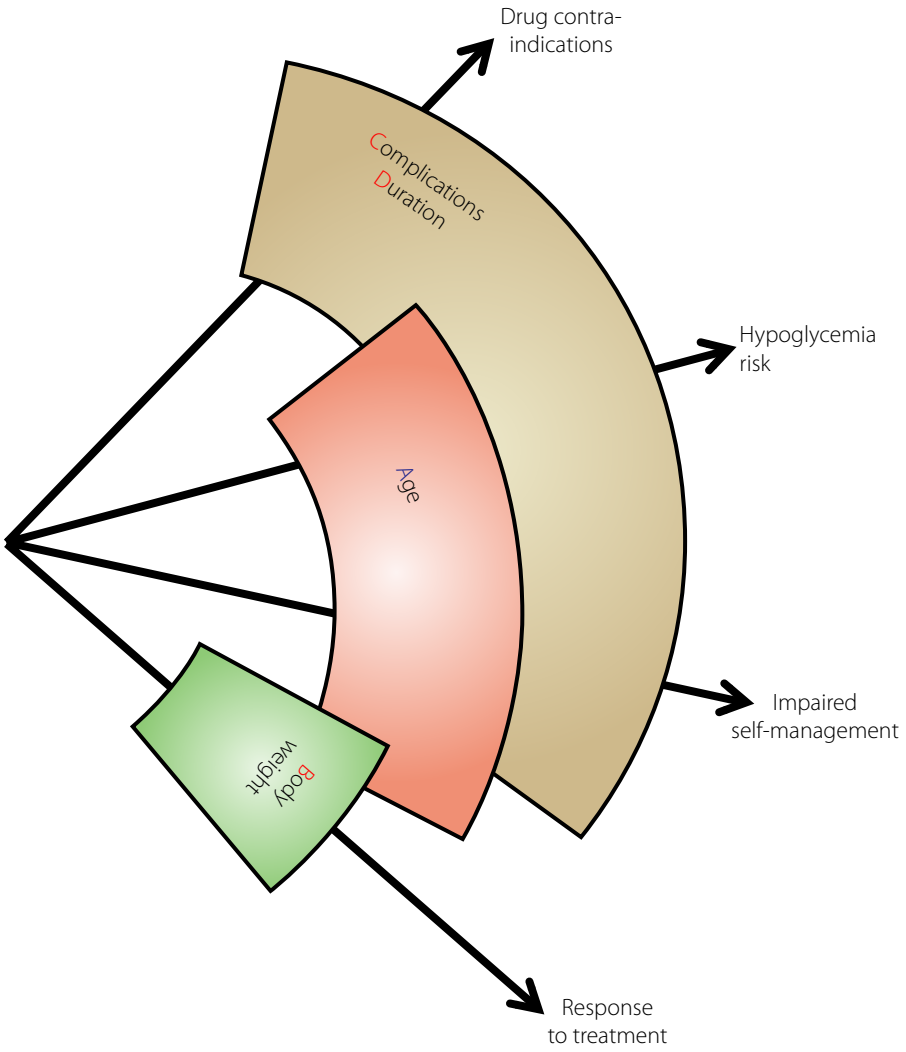
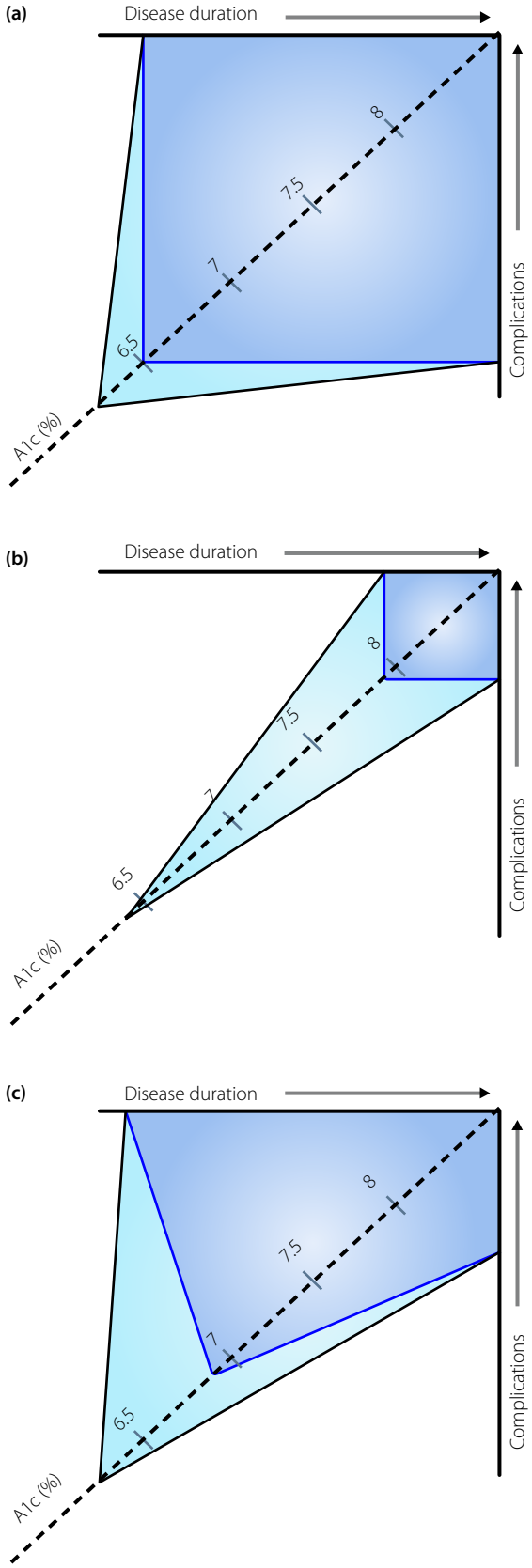


Figure 1 | The ABCD of type 2 diabetes: age, bodyweight, complications and disease duration can further influence diabetes treatment. Risk of hypoglycemia is increased in older patients and people with additional comorbidities (e.g., autonomic, kidney or liver failure). Specific complications limit drug choice and might increase the hypoglycemic risk linked to some drugs. Bodyweight is a determinant of treatment response as well as hypoglycemic drugs, which can often induce weight changes.

prandial fluctuation[26], but the effect of this treatment on CVDs was not fully evaluated until the ORIGIN trial. The ORIGIN is the largest study available for cardiovascular outcome prevention in type 2 diabetes. It is worth noting that this study targeted a population with features in between the UKPDS, and those in the ADVANCE, ACCORD and VADT, as it studied patients that were early in the natural history of their dysglycemic course, but relatively late in terms of cardiovascular risk. However, examining data from other studies, the absence of benefit in the ORIGIN is not completely unexpected. The post-trial difference between groups in term of HbA1c was the smallest compared with previous trials (Table 1). Furthermore, a closer comparison between newer and older trials shows that the rate of cardiovascular events, as well as microvascular complications, is relatively low in the present compared with decades ago (for example, 5% of the ORIGIN patients experienced myocardial infarction vs 10–16% in the UKPDS, despite higher cardiovascular risk and similar disease duration). It is worth noting that almost all patients in the ORIGIN were treated with statin, antihypertensive or antiplatelet drugs, compared with approximately 12% in the UKPDS, possibly narrowing the residual risk reduction for glucose intervention. Indeed, it is clear that intensive intervention with multiple drug combinations has beneficial effects with respect to vascular complications and mortality[27].

WHAT LESSON?

The UKPDS and DCCT have shown that aggressive glucose control, especially early in the natural history of the disease, might result in a significant reduction of microvascular as well



as macrovascular complications. However, the more recent trials have increased the level of complexity of the relationship between 'tight glucose control/chronic complications', with several factors influencing the risk-to-benefit ratio to be considered, and numerous calls for an individualized therapy have been proposed during the past years[28–30].

We have recently proposed an easy approach to determine appropriate HbA_{1c} targets in type 2 diabetes based on age, bodyweight, complications and disease duration, namely the 'A1c and ABCD' of type 2 diabetes[31]. Age, complications and disease duration share some interdependency, and can further influence issues that are relevant to diabetes treatment (Figure 1). Older people experience more frequent and severe hypoglycemic events[32], whereas the presence of specific complications can reduce hypoglycemia awareness[33], and increase the hypoglycemic risk linked to some drugs; similarly, drug choices and self-management abilities are limited in patients with complications or additional comorbidities[34]. Accordingly, a more intensive goal is desirable for young patients with no CVD, whereas less stringent control is suitable for all people who are relatively late in the natural history of diabetic complications. Importantly, tight blood glucose control must be implemented early in the course of the disease in order to maximize its effect and reduce the rate of complications, which would make such intervention less effective or even harmful later on (Figure 2). For example, an early course of intensive insulin treatment in selected patients might restore β-cell function[25,35,36], reverse diabetes[25], recover hypoglycemia awareness[37] and is cost-effective[10], whereas a late introduction of such intervention is likely to increase the rate of serious hypoglycemic events and, in the presence of additional comorbidities, the rate of dysrhythmia and possibly death. Additional factors, such as bodyweight, can

Figure 2 | Minimal graphic model of the relationship between disease duration and he presence of prior complications in determining the optimal glycated hemoglobin (A1c) target balancing risks and benefits. Right and upper axes refer to the natural history of diabetic complications and dysglycemia, respectively. Blue and sky blue areas denote the magnitude of benefit or risk, respectively. The threshold of benefit (blue line) derives from the perpendicular crossing of the lines coming from the two axes. (a) Patients who are early in the natural history of dysglycemia and complications, such as those in the United Kingdom Prospective Diabetes Study, and Diabetes Control and Complications Trial, are likely to benefit from very tight glucose control. (b) In patients who are late both in the natural history of dysglycemia and complications, such as those in Action in Diabetes and Vascular Disease, Action to Control Cardiovascular risk in Diabetes, and Veteran Affairs Diabetes Trial, the benefit of tight glucose control is limited, and a less stringent control should be allowed. (c) In patients who are early in the natural history of dysglycemia, but relatively late in terms of complications, such as those in the Outcome Reduction with Initial Glargine Intervention trial, the benefit of tight glucose control could still overcome the risk depending on the degree of complications.

influence response to treatment or drug choice; high body mass index is associated with a greater response to some drugs, such as thiazolidinediones, but not others[38], and most of the drugs used in diabetes have an effect on bodyweight *per se*[39].

Therefore, patients' characterization has become a crucial step in the management of diabetes. In order to minimize risk and maximize benefits of tight glucose control, clinical trials are required to compare the effectiveness of phenotype-based approaches vs the traditional 'one-size-fits-all' strategy.

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