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Review

Glucocentric risk factors for macrovascular complications in diabetes: Glucose 'legacy' and 'variability'-what we see, know and try to comprehend

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ABSTRACT

Recognizing the role of dysglycaemia, 'ambient' hyperglycaemia, 'metabolic memory' and glycaemic variability as risk factors for macrovascular diseases is mandatory for effective diabetes management. Chronic hyperglycaemia, also referred to as 'ambient hyperglycaemia', was only fully acknowledged as a risk factor for adverse cardiovascular events when the beneficial effects of intensive glucose-lowering strategies were consolidated in the extended follow-up (> 10 years) of patients included in the United Kingdom Prospective Diabetes Study (UKPDS) and Diabetes Control and Complications Trial (DCCT)/ Epidemiology of Diabetes Interventions and Complications (EDIC) Study. These studies led to the concept of the glucose-lowering 'legacy effect' (metabolic memory), which depends on the duration and magnitude of glucose-lowering, and is not a 'forever' phenomenon, as demonstrated in the 15-year follow-up of the Veterans Affairs Diabetes Trial (VADT). The relatively weak evidence for linking long- and short-term glycaemic variability to vascular complications in patients with diabetes is mainly due to a reliance on observational and retrospective studies, and the lack of randomized interventional trials. However, hypoglycaemia may play an intermediary role in accentuating the link between glycaemic variability and vascular events.

Introduction

During the latter half of the 20th century, epidemiological surveys, such as the Framingham study [1,2] and Multiple Risk Factor Intervention Trial (MRFIT) [3], established that, with everything else being equal, people with diabetes exhibited a three- to fourfold increase in deaths due to cardiovascular events compared with non-diabetic individuals. In addition, many short- or medium-term randomized interventional trials compared intensive with standard management of chronic glucose disorders, including the United Kingdom Prospective Diabetes Study (UKPDS) [4], Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) [5], Action to Control Cardiovascular Risk in Diabetes (ACCORD) [6], Veterans Affairs Diabetes Trial (VADT) [7] and Diabetes Control and Complications Trial (DCCT) [8]. Yet, these studies all failed to demonstrate any clear benefits in terms of macrovascular outcomes, even though intensive therapy delayed the onset and progression of microvascular complications such as diabetic retinopathy and nephropathy.

Fortunately, longer-term evidence-based data were also found in support of the benefits of implementing intensive glycaemic control in extended follow-ups of some of the above-mentioned randomized trials – specifically, the UKPDS [9], VADT [10] and DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) Study [11,12]. Such findings introduced the concept of the 'legacy effect', also referred to as the 'metabolic memory' of lowering glucose. However, this idea has recently been disputed based on 15-year data from the VADT. Similarly, there is still continuing debate over the role of glycaemic variability on vascular outcomes, compounded by inconsistencies in the definition of glycaemic variability [13,14]. Thus, researchers and clinicians have continued to search for a consensus that will permit making a clear-cut distinction between short-term glucose variability,

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which corresponds to acute within- or between-day glucose fluctuations, and long-term variability of glucose homoeostasis, usually defined as monthly or quarterly variations in markers of glucose control, such as fasting plasma glucose and HbA_{1c} levels [15].

Therefore, more insight needs to be gained as to the respective roles of chronic hyperglycaemia, metabolic memory and glycaemic variability as risk factors for macrovascular diseases in diabetes. To address these controversies, the present review has considered what we know and what we comprehend according to their high, moderate and low grades of probability of being correct.

What we know about chronic ('ambient') hyperglycaemia and metabolic memory as risk factors of vascular disease in diabetes

After a long time interval, according to the mitigating results of earlier epidemiological research [1–3], the causal relationship between ambient hyperglycaemia and micro- and macrovascular complications in both type 1 (T1D) and type 2 diabetes (T2D) became progressively more evident, as per randomized double-blind health-policy clinical interventional studies performed for no commercial gain. The design of such randomized clinical trials (RCTs) [16–18] is relatively simple, based on comparisons between intensive and standard patient management that, in diabetes, means reducing overall exposure to hyperglycaemia with intensive treatment vs. a control. One goal is to achieve a stable difference in HbA_{1c} levels of around 1–2% and to select appropriate primary or secondary endpoints for cardiovascular outcomes. RCTs should then provide an answer to the question of whether intensive therapy is superior or not, compared with standard treatment, in protecting against atherosclerotic complications at different arterial sites.

However, it should be acknowledged that implementing such studies can be complex for several reasons, including the need to recruit large numbers of patients, to appropriately select medical centres/expertise across different countries, and to carefully and consistently monitor participants over a number of years. It should also be noted that the prespecified HbA1c difference of 1–2% may not always be attained. In the UKPDS [4], the difference between the intensively treated and control groups was < 1% even though the 'active' interventional period was more prolonged (10 years) than in other trials (Fig. 1) [5–7]. In newly diagnosed patients with T2D in the UKPDS [4], the intensively managed group benefitted by having a reduced risk of any diabetes-related events ($P = 0.029$): the achieved and sustained HbA_{1c} difference of 0.9% over almost 10 years between the intensively treated (mean HbA_{1c} = 7%) and conventionally treated (mean HbA_{1c} = 7.9%) groups was associated with a reduced incidence of microvascular complications (37%, $P = 0.0099$) [4]. In contrast, the relative risk reduction of myocardial infarction did not reach statistical significance (−16%, $P = 0.052$) despite intensive therapy (Fig. 2) [4], and a similar lack of significance was observed for any event related to macrovascular complications.

Such results confirm that microvascular complications are more responsive to intensive glucose control than macrovascular disease within that time frame. In fact, the absence of any significant reduction in incidence of macrovascular events was a common finding in other studies in which intensive and standard regimes were compared, including the ADVANCE [5], ACCORD [6] and VADT [7] (Fig. 2). In those three trials, the active interventional period was around half that of the UKPDS: 5 years in ADVANCE [5]; 3.5 years in ACCORD [6]; and 5.6 years in VADT [7] (Fig. 1). It should also be mentioned that the higher mortality rate found in the intensive therapy group of the ACCORD study led the investigators to halt the intensive protocol earlier than expected [6]. Therefore, in general, these studies all showed disappointing results for primary cardiovascular endpoints such as major adverse cardiovascular events (MACE) when evaluated as a whole, and for secondary endpoints like myocardial infarction, stroke and heart failure when such events were considered individually.

These observations have led a number of clinicians to consider that reducing overall glucose exposure may not be a priority in comparison to controlling blood pressure and cholesterol levels in the management of T2D. Nevertheless, the beneficial impact of

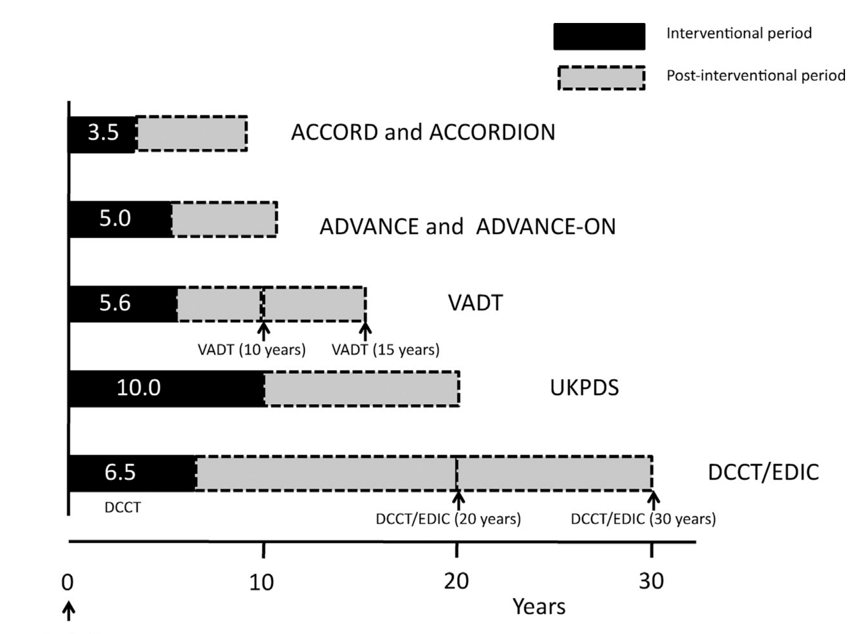

Fig. 1. Durations of active interventional and post-interventional periods of extended follow-up in five randomized controlled trials (RCTs): Action to Control Cardiovascular Risk in Diabetes (ACCORD) and its extended study (ACCORDION); Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) and its extension (ADVANCE-ON); Veterans Affairs Diabetes Trial (VADT); United Kingdom Prospective Diabetes Study (UKPDS); and Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study.

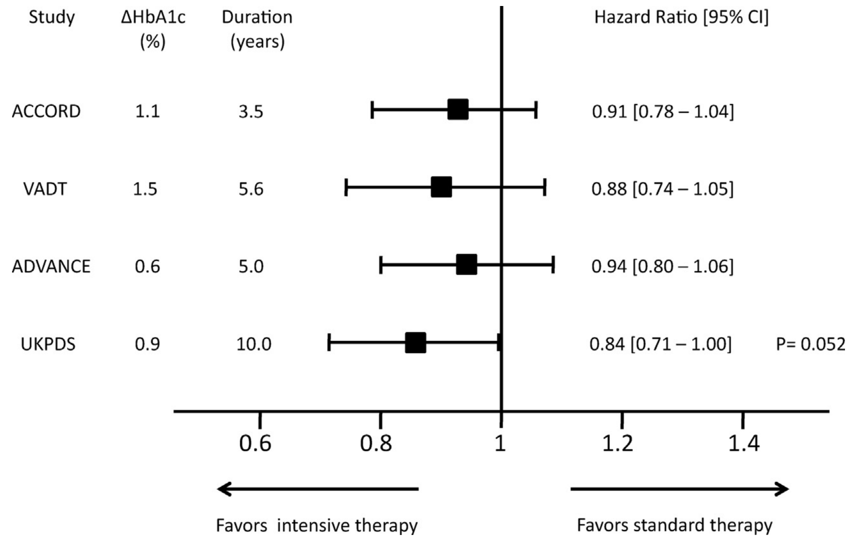

Fig. 2. Hazard ratios and 95% confidence intervals (CI) of intensive *vs* standard therapy in a composite of major adverse cardiovascular events at the end of active interventional periods in four randomized controlled trials: Action to Control Cardiovascular Risk in Diabetes (ACCORD); Veterans Affairs Diabetes Trial (VADT); Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE); and United Kingdom Prospective Diabetes Study (UKPDS), in which cardiovascular events were limited to myocardial infarction. Differences (Δ) in HbA_{1c} were between levels in the intensive- and standard-treatment groups.

intensive glucose-lowering therapies does appear likely in terms of protecting against cardiovascular events when studies are extended for > 10 years [9]. Moreover, it is important to integrate the experience of the DCCT/EDIC [11,12] and its extended follow-up, even though this trial was conducted exclusively in T1D patients. At present, the DCCT/EDIC remains the longest follow-up study, lasting from 20–30 years beyond the initial intensive interventional period of 6.5 years [11,12].

If the time lag from initial randomization is taken into consideration, patients underwent continuous follow-up for 9 years in the ACCORD extended study (ACCORDION) [19], 10.4 years in the extended ADVANCE (ADVANCE-ON) study [20], 10 and 15 years in the VADT [10], and 20 years in the UKPDS [9] (Fig. 1). In these studies, significant reductions in the incidence of cardiovascular events manifested only when the magnitude of the HbA1c difference between the intensive and standard therapy groups was > 0.9% (UKPDS [4]) and 2% (DCCT [8]), and the duration of follow-up was > 10 years (UKPDS [9] and DCCT/EDIC [11,12]). These observations indicate that both the magnitude and duration of early improvement in overall glucose exposure are major determinants of long-term cardiovascular outcomes. Fig. 3 shows the relationship between reduced incidence of cardiovascular events (*y*-axis) and overall glucose exposure (*x*-axis), as estimated from the magnitude of the HbA_{1c} difference (Δ) between intensive- and control-treatment groups multiplied by the duration of the active interventional period. Thus, in the VADT, the ΔHbA_{1c} was 1.5% throughout the 5.6-year active intervention period [7] and, consequently, the product was 8.4% per year. Using this formula, the incidence of cardiovascular events was not lower in ADVANCE-ON after 10.4 years of follow-up [20], but did decrease by 5% in ACCORDION after 9 years [not significant (ns)] [19], by 17% (P = 0.04) and 9% (ns) in the VADT at 10 and 15 years, respectively [10], by 15% (P = 0.01) in the UKPDS after 20 years [9], and by 47% and 30% in the DCCT/EDIC at 20 (P = 0.005) and 30 (P = 0.016) years, respectively [11,12]. These results are in agreement with the concept of metabolic memory and a prolonged latency period in order to show cardiovascular benefit from early intensive glycaemic control.

While the present review focuses on the role of glucose control, it is well accepted that consideration to other risk factors, such as hypertension, dyslipidaemia, albuminuria and smoking, is necessary in the multifactorial management of T2D in the attempt to limit both micro- and macrovascular disease. The Steno-2 study [21], conducted 10 years ago, demonstrated long-lasting reductions in the risk of death and cardiovascular events in a small population of 160 patients subjected to a multifactorial risk-control regimen. This approach was recently reaffirmed in a much larger cohort of 271,174 patients with T2D followed for 5.7 years [22], wherein the risk of death, myocardial infarction or stroke was similar to that of the general population when five risk factors were maintained within target ranges: $HbA_{1c} \leq 7\%$; systolic and diastolic blood pressure < 140 mmHg and < 80 mmHg, respectively; low-density lipoprotein (LDL) cholesterol ≤ 97 mg/dL; absence of elevated albuminuria; and cessation of smoking. The study also noted that an HbA_{1c} level outside of the defined target represented the strongest predictor of stroke and acute myocardial infarction, thereby confirming that maintaining tight glycaemic control over a prolonged period safely with avoidance of hypoglycaemia is a major objective in the management of people with diabetes.

What we see and try to comprehend

Duration of metabolic memory: long or rapidly 'evanescent'?

Although the idea of metabolic memory is strongly supported by the extended follow-up of patients in the UKPDS [9] and DCCT/EDIC cohorts [11,12], there is still uncertainty over the duration of benefit following periods of intensive glucose-lowering therapy. The VADT was designed to compare the occurrence of major cardiovascular events in 1791 patients with T2D recruited among military veterans randomized to either intensive or standard glucose control. Participants were initially followed to the end of a 5.6-year period of active intervention [7], then at approximately 10 years [10] and 15 years after randomization. In fact, the latest updated results of the newly extended 15-year follow-up constituted an oral presentation at the 2018 Annual Clinical Conference on Diabetes of the American Diabetes Association held in Orlando, Florida (Fig. 1). As previously mentioned, the mean

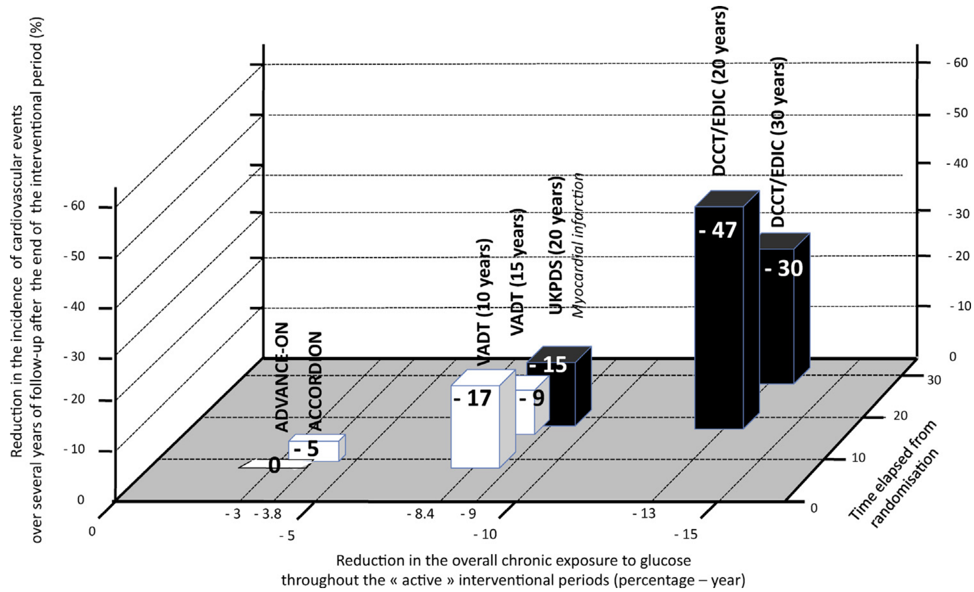

Fig. 3. Relationship between: (*i*) reduced incidence of adverse cardiovascular events during long-term extended follow-ups of the ADVANCE (ADVANCE-ON), ACCORD (ACCORDION), VADT, UKPDS and DCCT/EDIC studies (*y*-axis); and (*ii*) reduced overall chronic exposure to glucose throughout active interventional periods (*x*-axis), as assessed by the [product of magnitude of differences (Δ) in HbA_{1c} levels between intensive- and standard-therapy arms during active interventional period] multiplied by [duration of interventional period]. The result is expressed as percentage-years and negative units because ΔHbA_{1c} is always negative. Time elapsed from randomization (years) is indicated by the horizontal oblique axis (right). Reduced incidences of cardiovascular events are expressed on the *y*-axis (negative units). The higher the bars, the greater the reduction in risk of cardiovascular events. Decreases are statistically significant in the VADT at 10 years (P = 0.04), UKPDS (P = 0.01), and DCCT/EDIC at 20 and 30 years (P = 0.005 and P = 0.016, respectively).

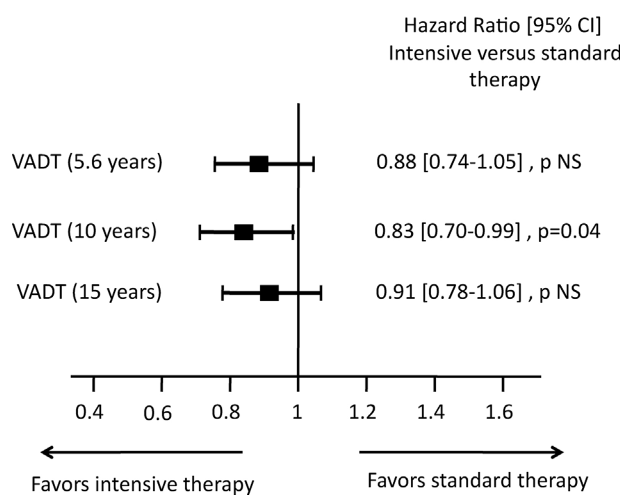

Fig. 4. Hazard ratios and 95% confidence intervals (CI) for intensive *vs* standard therapy in a composite of major adverse cardiovascular events in the Veterans Affairs Diabetes Trial (VADT) at the end of the active interventional period (5.6 years), and at 10 and 15 years after randomization.

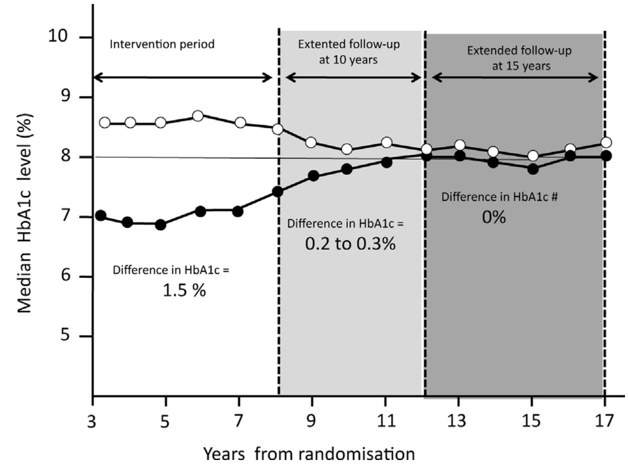

Fig. 5. Changes in median HbA1c levels according to number of years since starting the Veterans Affairs Diabetes Trial (VADT). White circles: standard-treatment group; black circles: intensive-treatment group.

absolute reduction in HbA_{1c} levels was 1.5% throughout the initial 5.6-year intervention in the intensive-treatment group (mean HbA_{1c} = 6.9%) compared with the control group (mean HbA_{1c} = 8.4%) [7]. At the end of the first intervention, there was no significant reduction [hazard ratio (HR): 0.88, 95% confidence interval (CI): 0.74–1.05; P = 0.14] in primary outcome (composite of myocardial infarction, stroke, death from cardiovascular causes, congestive heart failure, surgery for vascular disease, inoperable coronary disease and amputation for ischaemic gangrene; Fig. 4) or death from any cause [7].

Following the conclusion of the initial clinical trial, the participants were then reviewed at regular intervals for a further 5 years, during which time their median HbA_{1c} levels rapidly converged (Fig. 5). The intensive-treatment group achieved a small but statistically significant lower risk for the primary outcome compared with the control group (HR: 0.83, 95% CI: 0.70–0.99; P = 0.04) [10]. However, this statistically significant difference in primary outcome was no longer evident after a further 5 years (in other words, 15 years) after randomization (HR: 0.91, 95% CI: 0.78–1.06). It should also be noted that the small yet significant differences in HbA_{1c} between the two groups (−0.2% to −0.3%) observed at 10 years did not persist after 15 years (Fig. 5). This observation indicates, or at least suggests, that the metabolic memory in the intensively treated cohort was actually time-limited.

Returning to the results of the UKPDS [9] and DCCT/EDIC [11,12], a legacy effect was predominantly observed when the reduction in overall glucose exposure, as quantified by the derived product of

HbA_{1c} decrement and duration of improvement during the active intervention, ranged from −9 to −15 percentage-years (Fig. 3). This suggests that such an effect will only be evident after 10 years if HbA_{1c} decrements from baseline are 1% during periods of intensive therapy; for this to happen within a shorter time period would require a greater improvement in HbA_{1c} levels. In the VADT, a decline in metabolic memory was only evident the longer the post-intervention period in those with T2D [10]. A similar trend was seen in the DCCT/EDIC [11,12] intensively treated cohort when a reduction of any cardiovascular event after the initial intensive-treatment period fell from −47% after 20 years to −30% at 30 years (Fig. 3). Prolonged maintenance of this beneficial effect may be due in part to the modest but persistent difference in HbA_{1c} (0.4%) between the original intensively and conventionally treated groups.

The role of other factors may also be possible, as suggested when intensive glucose-lowering therapies were implemented in young adults with recent-onset T1D in the DCCT [8] and DCCT/EDIC Study [11,12], and in newly diagnosed T2D patients in the UKPDS [4], whose early stages of disease rendered clinical evidence of the atherosclerosis process unlikely. This, however, did not apply to those with older-onset T2D in the VADT [7], ADVANCE [5] and ACCORD [6] studies. Macrovascular lesions involve a protracted process of increased glycation of protein matrix in arterial walls in response to sustained increases in circulating glucose [23–25]. As collagen fibres in vessel walls have a slow turnover rate, alterations in plasma glucose concentrations then require several years to result in either significant harmful or beneficial clinical outcomes.

Other mechanisms involving epigenetic changes have also been proposed to explain the metabolic-memory hypothesis [26], while findings of the VADT after 15 years of follow-up have brought further insights into the pathogenesis of metabolic memory despite the absence of cardiovascular benefit. Such findings, when considered in isolation, have led some to conclude that metabolic memory is not a response to intensive glycaemic control. Nevertheless, more detailed analyses have shown that metabolic memory is indeed a true entity, albeit dependent on time since the intensive therapeutic intervention. Indeed, any prolonged discontinuation of effort towards achieving satisfactory glycaemic control will result in loss of beneficial effects for cardiovascular outcomes.

Is glycaemic variability an ancillary or key player in cardiovascular risk?

As previously reported, glycaemic variability is defined as fluctuations in glucose or other related parameters of glucose homoeostasis over either short or long time intervals [13,14]. Short-term glycaemic variability is characterized by sudden and rapid upward or downward glucose changes usually within or between consecutive days, whereas long-term variability is determined by markers of glucose homoeostasis, such as serial measurements of post-prandial and/or fasting plasma glucose concentrations at weekly or monthly intervals, or by visit-to-visit determinations of HbA_{1c} levels at quarterly or even longer time intervals [15].

Regarding short-term glycaemic variability, its assessment may be calculated using either self-monitoring of plasma glucose (SMPG) [27,28] or continuous interstitial glucose monitoring (CGM) [29–33]. The latter has many advantages due to the fact that the technology permits measurements at 5-min intervals, or 288 per day, thereby providing a more comprehensive view than SMPG. While many indices have been proposed for estimating short-term glucose variability, two metrics appear to be particularly useful for routine practice and can be obtained by simple computation. For within-day glucose variability, the most reliable index seems to be the percent coefficient of variation for glucose: % CV = (SD of glucose/mean glucose) $\times$100; this has the advantage of being adjusted on 24-h mean glucose concentrations. Also, a cut-off value of 36% has been established as the threshold separating stable from labile glucose control [30], and was recently adopted by an international consensus on the use of CGM [29]. For between-day glucose variability, the mean of daily difference (MODD) can be calculated by averaging the absolute differences between two glucose values at the same time on two consecutive days [34]. There is evidence to suggest that a value of 60 mg/dL may be able to separate stable from unstable control [13].

Thus, it is important to recognize the difference between short- and long-term glucose variability, which are sometimes wrongly considered a single entity.

Short-term glycaemic variability

At present, due to a lack of interventional trials, there is no hard evidence that short-term glycaemic variability is an independent risk factor for adverse cardiovascular events [14]. Nevertheless, the possible role of acute glucose fluctuations as a risk factor for cardiovascular disease can be based on laboratory and observational studies demonstrating that oxidative stress and inflammatory cytokines, both key players in diabetic complications [24,25], are activated by glycaemic variability [35]. Oscillating glucose concentrations are more deleterious to vascular endothelial cell function than continuous hyperglycaemia in both healthy subjects and non-insulin-treated T2D patients [36]. However, other research has failed to find a similar relationship in T1D [37]. One cross-sectional study showed that activation of oxidative stress in insulin-treated patients with either T2D or T1D stayed within the normal range, whereas those with T2D treated only with oral antidiabetic drugs (OADs) exhibited higher urinary excretion rates of isoprostanes, markers of oxidative stress [38].

These findings strongly suggest that insulin per se exerts an inhibitory effect on activation of oxidative stress. For this reason, the Fluctuation Reduction with Insulin and Glucagon-Like Peptide-1 Agonist (GLP-1) Added Together (FLAT-SUGAR) trial [39] was designed to test whether adding exenatide rather than prandial insulin to ongoing basal insulin therapy reduced short-term glycaemic variability and improved levels of biomarkers of cardiovascular disease in patients with insulin-requiring T2D already at high cardiovascular risk. While glycaemic variability was slightly improved in those receiving exenatide as add-on therapy, neither inflammatory nor cardiometabolic risk markers differed between active and control groups. These neutral findings may have been due to the inhibitory action of insulin on inflammation, thrombosis and activation of oxidative stress in both arms of the study [40].

Another consideration is the hypothesis that hypoglycaemia is an inherent link in the pathophysiological sequence that begins with excess glycaemic variability and ends with cardiovascular disease. At present, the contribution of short-term variability to risk of hypoglycaemia is well recognized, especially when mean blood glucose concentrations are low [8,41–43]. Indeed, a relationship has recently been established between the frequency of any type of hypoglycaemia considered as a whole (symptomatic or silent) and % CV for glucose in those with either T1D or T2D [30]. T2D patients were ranked into groups treated with diet and/or OADs as follows: (group 1) insulin sensitizers, theoretically devoid of hypoglycaemic risk; (group 2) dipeptidyl peptidase (DPP)-4 inhibitors; (group 3) sulphonylureas; (group 4) insulin; and (group 5) those with T1D. The frequency of hypoglycaemia increased exponentially, with none in groups 1 and 2, once a week in groups 3 and 4, and once daily in group 5, and was associated with increasing glycaemic variability (median % CV) of 18.1%, 18.6%, 23.7%, 27.8% and 37.2% in groups 1, 2, 3, 4 and 5, respectively

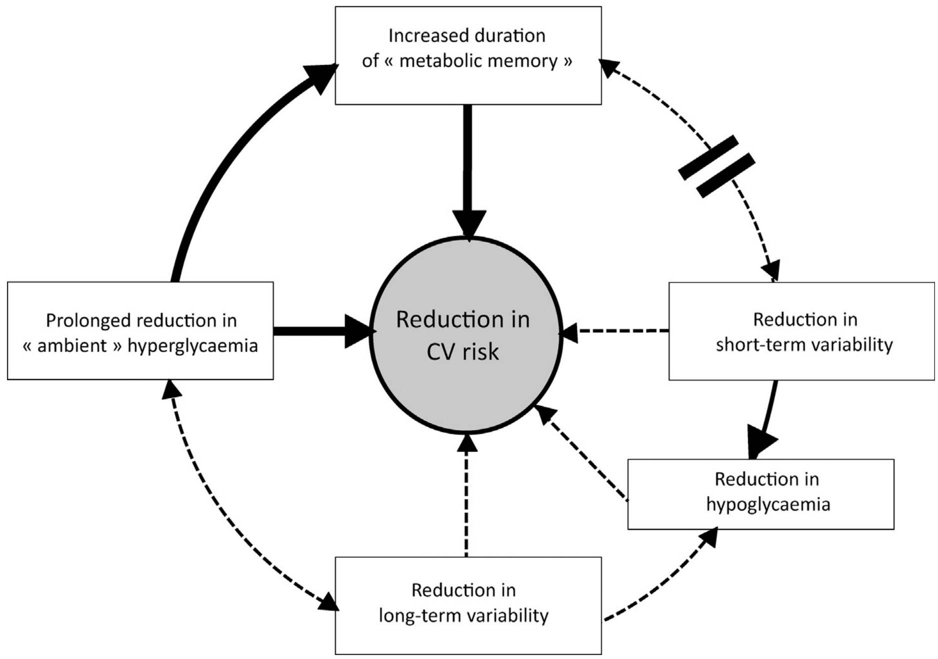

Fig. 6. Effects of glycaemic disorders (ambient hyperglycaemia, metabolic memory, short- and long-term variability) on risk of cardiovascular (CV) events according to whether they are direct (arrows pointing towards centre) or indirect (arrows along the periphery). Solid thick, solid thin and dotted arrows represent the effects/actions with clear, supportive and low evidence, respectively.

[13,30]. However, the mean glucose levels in these five groups were similar. In support of these findings, the Continuous Glucose Monitoring in Pregnant Women with Type 1 Diabetes (CONCEPTT) [44], DIAMOND [45] and two other studies [46,47] have demonstrated that the use of CGM for prolonged periods of time can improve short-term glycaemic variability, and also reduce the frequency of hypoglycaemic episodes, in either T1D [44–46] or insulin-treated T2D [47] patients.

The second sequential step in the catenary chain—the potential causal link between hypoglycaemic episodes and risk of chronic cardiovascular diseases/events – has never been clearly established. Whereas the ACCORD study [6] showed that intensive therapy was associated with an increased frequency of hypoglycaemia and risk of cardiovascular death, a causal relationship between hypoglycaemic episodes and chronic cardiovascular disease has not been established [48]. Post-hoc analyses of the ADVANCE database [49] have led to a similar conclusion, suggesting that hypoglycaemia is more likely a marker of cardiovascular vulnerability than a causative factor for adverse vascular outcomes. Yet, there is increasingly convincing evidence that hypoglycaemic events are responsible for acute vascular events by inducing harmful proarrhythmic cardiac disorders [52–54] and enhancing platelet aggregation [50,51].

Thus, at present, the relationship between hypoglycaemic episodes and chronic cardiovascular complications may be considered the weakest link in the proposed catenary chain from short-term glycaemic variability to chronic cardiovascular events. Nevertheless, it is currently advocated that stringent glucose-lowering strategies should be avoided in vulnerable patients [55–58], partly based on the fact that, when glycaemic fluctuations are excessive, there is an increased risk of hypoglycaemia [14,30,42].

Long-term glycaemic variability

The impact of long-term variability on glucose homoeostasis was extensively reviewed in two recent reviews [14,15]. However, despite the abundance of literature devoted to the adverse effects of long-term variability, its interpretation should be viewed with caution. The first concern is that the variability in overall glycaemic control represented by HbA_{1c} values may be only an ‘umbrella’ for heterogeneous glycaemic disorders [59]. Indeed, analysis of DCCT data based on quarterly fluctuations in HbA_{1c} found a weak association between HbA_{1c} variability and development of diabetic retinopathy [60], and failed to find any association with quarterly seven-point glycaemic profiles recorded over 3 consecutive days [61].

Therefore, long- and short-term glucose variability may be referring to different aspects of dysglycaemia. One meta-analysis including T1D (seven studies) and T2D (13 studies) found that long-term variability based on quarterly HbA_{1c} was positively correlated with HbA_{1c} ($r = 0.55$) [60], thereby representing poor overall glycaemic control perhaps as a result of poor adherence to dietary and pharmacological regimes [62,63]. A more recent analysis of VADT data has suggested a relationship between long-term glycaemic variability and cardiovascular risk [64]. However, the relationship was observed only in the intensively treated group, leading the investigators to suggest that those exhibiting satisfactory overall glycaemic control were more sensitive to fluctuations of glucose homoeostasis than those who were less well controlled. In any case, the results of the study failed to clarify whether long-term variability is a simple biomarker or a risk factor of cardiovascular disease, as there was no association between HbA_{1c} values and cardiovascular risk regardless of the study group (intensive- or standard-treatment) considered.

Conclusion

In summary (Fig. 6), the role of different elements of dysglycaemia as risk factors of macrovascular disease in people with diabetes seems evident, although there is a relative disparity in clinical expression based on the following:

- the decrease in cardiovascular risk requires long-lasting periods of intensive therapy resulting in good glycaemic control (clear evidence);

- when the magnitude of HbA_{1c} decrements is suboptimal, a longer duration of exposure is required to reduce plasma glucose concentrations (clear evidence);
- the concept of metabolic memory is one possible mechanism to explain the reduction of macrovascular disease in both T1D and T2D (clear evidence), although the legacy effect is lost if the duration of good glycaemic control is inadequate (supportive evidence); and;
- glycaemic variability exerts either direct or indirect effects on cardiovascular disease depending on whether short- or long-term components are considered, as the benefits of less short-term variability can be mediated *via* a lower frequency of hypoglycaemic episodes (supportive evidence) which, in turn, results in a lower risk of adverse cardiovascular events (low evidence), whereas long-term variability may simply reflect overall glucose exposure, as an association between these two glycaemic disorders cannot be excluded (low evidence).

Disclosure of interest

The authors declare that they have no competing interest.

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