Title: Glucocentric risk factors for macrovascular complications in diabetes - Glucose "legacy" and "variability": What we see, know and try to comprehend.

Running title: Glucose legacy and variability in diabetes

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Abstract

Recognising 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 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 (beyond 10 years) of patients included in the UKPDS and the DCCT (DCCT/EDIC). These studies have led to the concept of the glucose-lowering legacy effect ("metabolic memory"), which depends on the duration and magnitude of glucose lowering and not a forever phenomenon as demonstrated in the 15 years follow-up of the VADT. The relatively weak evidence for linking long- and short- term glycaemic variability to vascular complications in persons with diabetes is mainly due to the reliance on observational and retrospective studies and the lack of randomised interventional trials. However, hypoglycaemia may contribute an intermediary role to accentuate the link between glycaemic variability and vascular events.

Key words: chronic hyperglycaemia; metabolic memory; glycaemic variability; macrovascular diseases in diabetes

During the latter half of the last century, epidemiologic surveys such as the Framingham study [1,2] and the Multiple Factor Interventional Trial (MRFIT) [3] established that, everything else being equal, people suffering from diabetes exhibited a 3-to 4-fold increase in death rates from cardiovascular events when compared with non-diabetic individuals. However, many short-or medium-term randomized interventional trials compared intensive with standard management of chronic glucose disorders: the United Kingdom Prospective Diabetes Study (UKPDS) [4], Action in Diabetes and Vascular disease: preterax and diamicronN modified release Controlled Evaluation (ADVANCE) [5], Action to Control Cardiovascular Risk in Diabetes (ACCORD) [6],Veterans Affairs Diabetes Trial [7] and the Diabetes Control and Complications Trial (DCCT) [8]. All these studies 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 provided in support of the benefit of implementing intensive glycaemic control in the extended follow-up of some of the aforementioned randomised trials: the extension of the UKPDS [9], the VADT [10] and of the DCTT (DCCT/EDIC) [11,12], The findings led to the introduction of the concept of the "legacy effect" also referred to as "metabolic memory" of glucose-lowering. However, this concept has been recently disputed based on the 15 years data from the VADT. Similarly, there is continuing debate on the role of glycaemic variability on vascular outcome compounded by the inconsistencies in the definition of glycaemic variability [13,14]. Researchers and clinicians are continuing to search for a consensus thus permitting a clear cut distinction between short-term glucose variability, which corresponds to acute within-or between-day glucose fluctuations and the long-term variability of glucose homeostasis, which is usually depicted as monthly or quarterly variations in markers of glucose control such as fasting plasma glucose or HbA1c levels [15]. Therefore, we need to gain more insight into the respective roles of chronic hyperglycaemia, "metabolic memory" and glycaemic variability as risk factors for macrovascular diseases in diabetes. To address these controversies this review will allocate "What we know" and "What we comprehend" according to a high, moderate or low grade of probability to be correct.

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

After a long interval of time from the mitigated results of earlier epidemiologic research [1-3] the causal relationship between ambient hyperglycaemia, micro- and macro-vascular complications in both type 1 or type 2 diabetes became progressively evident from randomised double blind health policy clinical interventional studies with no commercial gain. The design of such randomised clinical trials (RCTs) [16-18] is relatively simply based on comparisons between intensive and standard management groups which in diabetes means reducing the overall exposure to hyperglycaemia in the intensively treated group versus a control group. One of the goals is achieving a stable difference in HbA1c levels of approximately 1 to 2% and the selection of appropriate

primary or secondary end points for cardiovascular outcomes. RCTs should then provide an answer to the question as to whether intensive therapy exerts superiority or not compared with standard treatment in terms of protection against atherosclerotic complications at different arterial sites. However, we should acknowledge that implementing such studies are complex due to several reasons including the need for large number of patients to be recruited, selection of medical centres/expertise across different countries and the need for careful and consistent monitoring of participants over several years. It should also be noted that the pre-specified HbA1c difference of 1 to 2% is not always attained. In the UKPDS [4] the difference between the intensively treated and control groups was less than 1% even though the duration of the "active" interventional period was more prolonged (10 years) than in other trials [5-7] (figure 1). In the population of newly diagnosed persons with type 2 diabetes in the UKPDS [4], the intensively managed group benefited having a reduced risk of any diabetes-related events (P = 0.029). The achievement over almost 10 years of sustained HbA1c differences of 0.9% between the intensive-therapy group (mean HbA1c =7%) and the conventional group (mean HbA1c = 7.9%) was associated with a reduction in the incidence of microvascular complications (37%, p = 0.0099) [4]. By contrast, the relative risk reduction for myocardial infarction did not reach statistical difference (- 16%, p = 0.052) with the intensive treatment (figure 2) [4]. 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 this time frame. The absence of any significant reduction in the incidence of macrovascular events was also a common finding in other studies, when intensive and standard cares were compared, including ADVANCE [5], ACCORD [6] and VADT [7] (figure2). In these latter trials, the "active" interventional period was approximately half that in the UKPDS: 5 years in ADVANCE [5], 3.6 years in ACCORD [6] and 5.6 years in VADT [7] (figure 1). It should also be mentioned that the finding of a higher mortality rate in the intensive therapy group of the ACCORD study led the investigators to halt the intensive policy earlier than expected [6]. Therefore, from a general point of view, all these studies showed disappointing results on primary cardiovascular endpoints such as major adverse cardiovascular events (MACE) considered as a whole and on secondary end points such as myocardial infarction, stroke and heart failure when considered individually. These observations have led a

number of clinicians to consider that reducing the overall glucose exposure was not a priority relative to controlling blood pressure and cholesterol levels in the management of type 2 diabetes. However the beneficial impact of intensive glucose-lowering therapies emerged to be likely in terms of protection against occurrence of cardiovascular events when studies extending beyond 10 years [9] were published. Furthermore, it is necessary to integrate the experience from the DCCT/EDIC [11,12] with its extended follow-up even though this trial was conducted exclusively in type 1 diabetes. Presently the DCCT/EDIC remains the longest follow-up study extending up to 30 years after the initial intensive interventional period of 6.5 years [12]. When considering the time from initial randomisation, patients were assigned to continuous follow-up for 9 years in ACCORD (ACCORDION) [19], 10.4 years in ADVANCE (ADVANCE-ON) [20], 10 and 15 years in VADT [10], 20 years in the UKPDS [9] and from 20 to 30 years in the DCCT/EDIC [11,12] (figure 1).

In these studies, significant reductions in incidence of cardiovascular events occurred only when the magnitude of the difference in HbA1c between intensive-and standard-therapy groups was > 0.9% in the UKPDS [4] and 2% in the DCCT [8] and the duration of follow-up exceeded 10 years (UKPDS [9], DCCT/EDIC [11,12]). These observations indicate that both the magnitude and duration of the early improvements in overall glucose exposure are major determinants of the long-term cardiovascular outcome. Figure 3 represents the relationship between the reduction in the incidence of cardiovascular events (Y axis) and the overall glucose exposure (X axis), which was estimated from the magnitude of the difference in HbA1c (ΔHbA1c) between the intensive- and control- treatment groups multiplied by the duration of the "active" interventional period. For example in the VADT the difference in HbA1c was 1.5% throughout the 5.6-year "active" intervention period [7]. Consequently, the product is equal to 8.4% -year. Utilising this formula revealed that the incidence of cardiovascular events was not lowered in ADVANCE-ON after 10.4 years of follow-up [20], decreased by 5% in ACCORDION after 9 years (ns) [19], 17% ($p = 0.04$) and 9% (ns) in the VADT at 10 and 15 years, respectively [10], 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 the existence of "metabolic memory" with a prolonged latency period needed to show cardiovascular benefit from early intensive glycaemic control. Although this review article is focused 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 type 2 diabetes in an attempt to limit both micro- and macrovascular disease. The Steno-2 study [21], conducted 10 years ago, demonstrated a long-lasting reduction in the risk of death and cardiovascular events in a small population of 160 patients when submitted to a multifactorial risk control regimen. This approach has recently been re-affirmed in a much larger cohort of 271,174 patients with type 2 diabetes followed for 5.7 years [22] where the risk of death, myocardial infarction or stroke was similar to the general population when five risk factor were maintained within the target ranges, i.e. HbA1c ≤ 7%, systolic and diastolic blood pressure < 140 and 80 mmHg, respectively, LDL-cholesterol ≤ 97 mg/dL, absence of elevated albuminuria and abstinence from smoking. This study also observed that a HbA1c level outside the defined target represented the strongest predictor for stroke and acute myocardial infarction, confirming that retaining tight glycaemic control safely over a prolonged period, with the avoidance of hypoglycaemia, is a major objective in the management of persons with diabetes.

What we see and try to comprehend

1. Duration of the "metabolic memory": long or rapidly "evanescent"?

Whereas the concept of "metabolic memory" is strongly supported by the extended follow-up of patients included in the UKPDS [9] and DCCT/EDIC cohorts [11,12], there remains uncertainty concerning the duration of benefit following a period of intensive glucose lowering therapy. The VADT was designed to compare the occurrence of major cardiovascular events in 1791 persons with type 2 diabetes recruited among military veterans randomised to either intensive or standard glucose control. The participants were initially follow-up at the end of 5.6-year period of "active" intervention [7] and then at approximately 10 years [10] and 15 years after randomisation .The latest updated results of the extended newly follow-up at 15 years were subject to an oral presentation at the 2018 annual meeting of the American Diabetes Association held in Orlando (USA) (figure 1). As previously mentioned, the mean absolute reduction in

HbA1c levels was 1.5% throughout the initial 5.6 years period of intervention in the intensive-therapy group (mean HbA1c = 6.9%) as compared with the control group (mean HbA1c = 8.4%) [7]. At the end of the first period, there was no significant reduction (hazard ratio [HR] = 0.88, 95% confidence interval [CI] = 0.74-1.05, p = 0.14) in the 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) [figure 4] or death from any cause [7]. Following the conclusion of the initial clinical trial, the participants were then reviewed at regular time-intervals for a further 5 years during which the median HbA1c levels rapidly converged (figure 5). The intensive-therapy group achieved a small but statistically significant lower risk for the primary outcome compared to the control group (HR = 0.83, 95% CI =0.70-0.99, p = 0.04) [10]. However, this statistical difference in the primary outcome was no longer evident after another 5- year period, i.e. 15 years after randomisation (HR= 0.91, 95% CI = 0.78-1.06). It should be noted that the small significant differences in HbA1c between the groups (- 0.2 to -0.3%) observed at 10 years did not persist after 15 years (figure 5). This observation indicates or at least suggests that the "metabolic memory" in the intensive treated cohort is therefore time limited.

Reverting to the results of the UKPDS [9] and the DCCT/EDIC [11,12] a "legacy effect" was predominantly observed when the reduction of the overall glucose exposure quantified by the derived product of HbA1c decrement and duration of improvement during the "active" interventional period was ranging from -9 to -15 expressed as %-year (figure 3). This means that a "legacy effect" will be evident only after 10 years when the HbA1c decrements from baseline are limited to 1% during periods of intensive therapy. Appearance within a shorter period of time would necessitate a greater improvement in HbA1c level. In the VADT a decline in "metabolic memory" appears evident in persons with type 2 diabetes, the longer the post intervention period [10]. A similar trend has been seen in the DCCT/EDIC [11,12] intensively treated cohort as the reduction of any cardiovascular event after initial intensive therapy period fell from -47% after 20 years to -30% at 30 years (figure 3). The prolonged maintenance of this beneficial effect may be due in part to the modest persistent difference in HbA1c (0.4%) between the original intensive and conventional treatment groups.

The role of other factors should also be considered as the intensive glucose lowering therapies were implemented in young adults with recent-onset type 1 diabetes in the DCCT [8] and DCCT/EDIC [11,12] and in newly diagnosed type 2 diabetes in UKPDS [4], at early stages of the disease when clinical evidence of the atherosclerosis process would be unlikely. This remark does not however apply to individuals with older-onset type 2 diabetes involved in the VADT [7], ADVANCE [5] and ACCORD [6] studies. Macrovascular lesion is a protracted process consisting of increased glycation of the protein matrix of arterial walls in response to sustained increases in circulating glucose [23-25]. Collagen fibres in vessel walls have a slow turnover rate. Therefore alterations in plasma glucose concentrations require several years to result in significant harmful or beneficial clinical outcomes. Other mechanisms that involve epigenetic changes have also been proposed to explain the "metabolic memory" hypothesis [26]. The findings of the VADT after 15 years of follow-up has permitted further insight into the pathogenesis of the "metabolic memory" despite the absence of cardiovascular benefit. This finding when considered in isolation has led some to conclude that "metabolic memory" does not exist in response to intensive glycaemic control. A more detailed analysis has shown that the "metabolic memory" is a true entity although it is subject to the time interval since the intensive therapeutic intervention. For instance any prolonged discontinuation of the efforts made for achieving a satisfactory glycaemic control results in a loss of beneficial effects on cardiovascular outcomes.

2. Is glycaemic variability an ancillary or a key player in cardiovascular risks?

As previously reported, glycaemic variability (GV) is defined by fluctuations of glucose or other related parameters of glucose homeostasis over a short - or long -time interval [13,14]. Short-term glycaemic variability is characterized by sudden and rapid upward or downward glucose changes usually within or between consecutive days. The second category, long-term variability is determined from markers of glucose homeostasis, either serial measurements of postprandial and/or fasting plasma glucose concentrations at weekly or monthly frequency or from visit-to-visit determinations of HbA1c levels at quarterly or even longer time-intervals [15].
Reverting to short-term glycaemic variability, its assessment can be calculated using either self-monitoring of plasma glucose (SMPG) [27,28] or continuous interstitial

glucose monitoring (CGM) [29-33]. However, CGM has many advantages due to the fact that this technology permits measurements at 5-min time-intervals, i.e. 288 per day, thus providing a more comprehensive view compared with SMPG. Many indices are proposed for estimating short-term glucose variability but for routine practice two metrics seem to be most useful, and which can be obtained by simple computation. For the within-day glucose variability, the most reliable index seems to be the coefficient of variation for glucose (%CV = [SD of glucose/mean glucose] x 100), which has the advantage of being adjusted on the 24-h mean glucose concentration. A cut-off value of 36%, has been established as a threshold that separates stable from labile glucose control [30], and recently adopted by the international consensus on the use of continuous glucose monitoring [29]. For between-day glucose variability, the Mean Of Daily Difference (MODD) is 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 appears able to separate stable from unstable control [13].

Therefore, it is important to recognise the difference between short-and long-term variabilities, which are sometimes wrongly included as a single entity.

a) Short-term glycaemic variability

At present, due to the lack of interventional trials, there is no hard evidence that short-term glycaemic variability is an independent factor for the risk of adverse cardiovascular events [14]. The possible role of acute glucose fluctuations as risk factor for cardiovascular diseases is based on laboratory and observational studies that have demonstrated that oxidative stress and inflammatory cytokines , which are key players for diabetic complications [24,25], is activated by glycaemic variability [35]. Oscillating glucose concentrations is more deleterious to vascular endothelial cell function than continuous hyperglycaemia in both healthy subjects and non-insulin treated type 2 diabetes [36]. Others have failed to reproduce a similar relationship in type 1 diabetes [37]. In a cross-sectional study we have shown that the activation of oxidative stress in insulin-treated patients with either type 2 or type 1 diabetes remained within the normal range while those with type 2 diabetes treated only with oral antidiabetic agents exhibited higher urinary excretion rates of isoprostanes, a marker of oxidative stress

[38]. These findings strongly suggest that insulin per se exerts an inhibitory effect on the activation of oxidative stress. The FLAT SUGAR trial [39] was designed to test whether adding exenatide in contrast to prandial insulin when added to ongoing basal insulin therapy reduces short-term glycaemic variability and improves the level of biomarkers for cardiovascular disease in persons with insulin-requiring type 2 diabetes and an already elevated cardiovascular risk. Glycaemic variability was slightly improved in participants who received add-on therapy with exenatide, but the inflammatory and cardio-metabolic risk markers did not differ between the active and control groups. These neutral findings could be 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 to hypothesize that hypoglycaemia is an inherent link within the pathophysiological sequence commencing with excess glycaemic variability and ending with cardiovascular diseases. At present, the contribution of short-term variability to the risk of hypoglycaemia, is well recognized, especially when the mean blood glucose concentration is low [8,41-43]. We have recently been able to established that there exists a relationship between the frequency of all types of hypoglycaemia when considered as a whole (symptomatic or silent) and the coefficient of variation for glucose (%CV) in persons with type 1 and type 2 diabetes [30]. The participants were ranked into groups ranging from type 2 diabetes treated with diet and/or oral antidiabetic agents such as insulin sensitizers, theoretically devoid of hypoglycaemic risk (group 1), DPP-4 inhibitors (group 2) to those requiring sulfonylureas (group 3) or insulin (group 4) and type 1 diabetes (group 5). The frequency of hypoglycaemia increased exponentially, i.e. none in groups 1 and 2, once weekly in groups 3 and 4, and once daily in group 5 which 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 [13,30]. However, the mean glucose levels in the different groups were found to be similar. In support of these findings, the CONCEPTT [44], DIAMOND [45] and two other studies [46,47] have shown that the use of a continuous glucose monitoring (CGM) for prolonged periods of time can improve short-term glycaemic variability and also reduces the frequency of hypoglycaemic episodes in either type 1 [44-46] or insulin-treated type 2 [47] diabetes.

In contrast, the second sequential step in the catenary chain, i.e. the potential causal link between hypoglycaemic episodes and the risk of chronic cardiovascular diseases/events

has never been clearly established. The ACCORD Study [6] showed that intensive therapy was associated with an increased frequency of hypoglycaemia and risk of cardiovascular death, although a causative relationship between the hypoglycaemic episodes and chronic cardiovascular diseases has not been established [48]. Post-hoc analyses of the ADVANCE data base [49] has led to a similar conclusion suggesting that hypoglycaemia is more likely a marker of cardiovascular vulnerability than a causative factor for adverse vascular outcomes. However, there is increasingly convincing evidence that hypoglycaemic events are responsible for acute vascular events by inducing harmful pro-arrhythmic cardiac disorders [52-54] and enhancing platelet aggregation [50,51]. Therefore, presently, the relationship between hypoglycaemic episodes and chronic cardiovascular complications may be considered the weakest link for completing 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].

b) The long-term variability

The impact of long-term variability in glucose homeostasis has been extensively reviewed in two recent reviews [14,15]. Despite the abundant literature devoted to the adverse effects of long-term variability interpretation should be viewed with caution. The first concern is that variability in overall glycaemic control represented by HbA1c may only serve as an "umbrella" for heterogeneous glycaemic disorders [59]. An analysis of the DCCT data based on quarterly fluctuations of HbA1c, found a weak association between HbA1c variability and the development of diabetic retinopathy [60]. The same investigators failed to find any association with quarterly 7-point glycaemic profiles recorded over 3 consecutive days [61]. Therefore, long- and short-term glucose variability represent different aspects of dysglycaemia. A meta-analysis involving persons with type 1 diabetes (7 studies) and type 2 diabetes (13 studies) showed that long-term variability based on quarterly HbA1c was positively correlated with HbA1c ($r = 0.55$) [60], thereby representing poor overall glycaemic control and perhaps resulting from a loose adherence to dietary and pharmacologic measures

[62,63]. One of the most recent analysis of the VADT data has suggested the existence of a relationship between long-term glycaemic variability and cardiovascular risk [64]. However, this relationship was only observed in the intensively treated group, leading the investigators to imply that those exhibiting a satisfactory overall glycaemic control are more sensitive to fluctuations of glucose homeostasis than those less well controlled. However, the results of this study does not help to clarify whether long-term variability is a simple biomarker or a risk factor for cardiovascular disease due to the lack of any association between HbA1c measures and cardiovascular risk regardless of the group considered (intensive- or standard-therapy group).

Concluding remarks

In summary (figure 6), the role of different elements of dysglycaemia as risk factors for macrovascular diseases in persons with diabetes appears to be evident but there is a relative disparity in clinical expression, which is listed as follows:

- The decrease in cardiovascular risk requires long-lasting periods of intensive therapy resulting in good glycaemic control (clear evidence)
- When the magnitude of HbA1c decrements is suboptimal a longer duration of exposure to reduced plasma glucose concentrations is required (clear evidence).
- The concept of metabolic memory is one possible mechanism that explains the reduction of macrovascular diseases in both type 1 and type 2 diabetes (clear evidence). However its “legacy effect” is lost if the duration of good glycaemic control is inadequate (supportive evidence)
- Glycaemic variability exerts either a direct or indirect influence on cardiovascular disease according to whether we consider its short- or long -term components. The benefit of a reduced short-term variability can be mediated via a reduction in the frequency of hypoglycaemic episodes (supportive evidence), which in turn results in a lower risk for adverse cardiovascular events (low evidence). Long-term variability on the other hand may simply reflect the overall glucose exposure because an association between these two glycaemic disorders cannot be excluded (low evidence).

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Legends of figures

Figure 1: Durations of "active" interventional and post interventional periods of extended follow-up in the following randomised controlled trials (RCTs): ACCORD (ACCORDION), ADVANCE (ADVANCE-ON), VADT, UKPDS and DCCT/EDIC.

Figure 2: Hazard Ratios (HR) and 95% Confidence Intervals (95% CI) (intensive therapy vs standard therapy) of a composite of Major Adverse Cardiovascular Events in the following RCTs: ACCORD, VADT, ADVANCE and UKPDS, at the end of the "active" interventional period. In the UKPDS, cardiovascular events are limited to myocardial infarctions. The ΔHbA1c corresponds to the differences in the HbA1c levels between the intensive-and standard-therapy groups.

Figure 3: Relationship between: (i) reduction in incidence of adverse cardiovascular events during the long-term extensions of the ADVANCE (ADVANVE-ON), ACCORD (ACCORDION), VADT, UKPDS and DCCT/EDIC studies (Y axis) and (ii) reduction in the overall chronic exposure to glucose throughout the "active" interventional periods (X axis). This exposure was assessed using the product: [magnitude of the differences in HbA1c levels between the intensive and standard arms during the "active" interventional period] multiplied by [the duration of the interventional period]. The result of the product is expressed as percentage-year and as negative units because the differences in HbA1c levels (ΔHbA1c) are always negative. The time elapsed from randomisation (years) is indicated on the horizontal oblique axis. The reduction in incidence of cardiovascular events is expressed on the Y axis, using negative units. The higher the columns, the greater the reduction in the risk of cardiovascular events. Reductions are statistically significant in the VADT at 10 years ($P = 0.04$), the UKPDS ($P = 0.01$) and in the DCCT/EDIC at 20 and 30 years ($P = 0.005$ and $P = 0.016$).

Figure 4: Hazard ratios (HR) and 95% Confidence Intervals (95% CI) (intensive therapy vs standard therapy) of a composite of Major Adverse Cardiovascular Events in the VADT at end point of the "active" interventional period (5.6 years) and at 10 and 15 years after randomisation during the extended follow-up.

Figure 5: Changes in median HbA1c levels according to year since the start of the VADT. Open circles: standard-therapy group. Close circles: intensive-therapy group.

Figure 6: Respective roles of glycaemic disorders (ambient hyperglycaemia, "metabolic memory" and short- or long-term variability) on the risk of cardiovascular (CV) events. Effects are depicted according to whether they are direct (spokes in a wheel) or indirect (links in a chain). Solid thick, solid thin and broken arrows represent the effects/actions with clear, supportive and low evidence, respectively.