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EDITORIAL

Dysglycaemia, cardiovascular outcome and treatment. Is the jury still out?

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This editorial refers to 'Glycaemic control in newly diagnosed diabetes patients and mortality from ischaemic heart disease: 20-year follow-up of the HUNT Study in Norway'†, by A.C. Dale *et al.*, on page 1372

Dale and co-workers have reported on the influence of glycaemic control on long-term mortality from ischaemic heart disease (IHD) in patients with asymptomatic newly detected diabetes mellitus participating in a population-wide health survey in Norway.[1] The annual measurements of glycated haemoglobin A1c (HbA1c) in subjects with newly diagnosed diabetes during the 10 years following recruitment constitute a strength of this study allowing assessment of how risk may vary according to glycaemic burden over time. Considering the high prevalence of undetected diabetes mellitus among patients seen by cardiologists and the widespread dysglycaemia in the general population, the issue raised by this study is indeed relevant for everyday practice.[2,3]

Relationship between higher than optimal glycaemia and cardiovascular diseases

The relationship between cardiovascular disease and glucose regulation abnormalities has been discussed since the first published report on glucosuria in patients with myocardial infarction in 1922.[4] Thanks to individual and collaborative efforts of many research groups, the wealth of knowledge regarding association of dysglycaemia with the incidence of cardiovascular events has increased exponentially in the last decade. Several mechanisms may account for this relationship. Elevated glucose concentrations cause direct damage to vascular endothelium and other tissues owing to oxidative stress. Insulin resistance promotes mobilization of free fatty acids from adipose tissue which reduces HDL and increases LDL. Oxidative stress reduces insulin production by damaging insulin-secreting β-cells. All together these conditions promote pro-inflammatory and pro-thrombotic processes.[5]

Abnormal glucose regulation has serious prognostic implications in patients with coronary artery disease (CAD). Established diabetes is associated with impaired prognosis after myocardial infarction.[6]

According to more recent evidence, the increased risk is already apparent at modestly raised levels of blood glucose below the present threshold for diabetes.[2,7–10] The progressive relationship between cardiovascular mortality and glycaemia is indeed independent of the classical cardiovascular risk factors as confirmed by several large, prospective, population-based studies.[2,10] The accumulated epidemiological data indicate that exposure to higher than optimum blood glucose is a leading cause of cardiovascular mortality worldwide.[2] This analysis, excluding deaths directly related to diabetes, revealed that 21% of IHD deaths are attributable to blood glucose >4.9 mmol/L, compared with 12, 45, and 47% attributable to smoking, elevated cholesterol, and hypertension, respectively.[2] Furthermore, recent data indicate that microvascular lesions, regarded as characteristic for diabetic complications, are already present in ∼8% of patients with impaired glucose tolerance and in >12% of participants who developed diabetes within the last 3 years.[11]

Abnormal glucose metabolism is substantially more common than previously acknowledged both in patients with acute myocardial infarction[3,12] and in those with stable CAD.[3] Newly detected abnormal glucose tolerance was recently reported as a strong, independent risk factor for mortality and morbidity after a myocardial infarction.[13] Thus, available evidence underlines the importance of appropriate glucometabolic characterization.

In agreement with large epidemiological studies,[2,9] Dale *et al.* found a relationship between updated HbA1c and mortality from IHD during 20 years follow-up, showing a 20% risk increase per 1% increment of HbA1c.[1] Interestingly, the mortality was even higher in patients without known cardiovascular disease at baseline [hazard ratio (HR) 1.3, 95% confidence interval (CI) 1.1–1.5]. An important question is emerging from this observation, i.e. whether the increased risk is related to hyperglycaemia or to a less adequate control of classical risk factors among patients without known CAD.

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Potential targets for risk reduction in patients with dysglycaemia

Dysglycaemia is commonly associated with other well known cardiovascular risk factors.[2,5,8] Focusing primarily on glycaemic control is justified especially in young people without any other cardiovascular risk factors, such as the patients with type 1 diabetes included in the DCCT trial.[14] Early intensive insulin treatment, during the first 6.5 years, improved HbA1c at the end of the DCCT trial (7.4% vs. 9.1%) and reduced the risk of any cardiovascular event by 42% (95% CI 9–63) after 17 years of follow-up (DCCT/EDIC[14]). A 10% lower HbA1c (7.2 vs. 8.0%) was associated with 20% reduction in the risk of a cardiovascular event (95% CI 9–30%). In the UKPDS 75, including hypertensives with newly diagnosed type 2 diabetes, the highest risk reduction was achieved in those who met the most stringent glucose (HbA1c <6.0%) and systolic blood pressure control (<130 mmHg) leading to 4.1 (95% CI 2.6–6.6) and 6.7 (3.8–12.0) relative risk reduction for myocardial infarction and diabetes-related death, respectively.[15]

In the STENO-2 patients with known type 2 diabetes and microalbuminuria, a multifactorial intensive treatment strategy resulted in 59% risk reduction of any cardiovascular events and 57% reduction of cardiovascular mortality (*Figure 1*).[16] Taking into account these studies and the underutilization of evidence-based treatment among patients treated with glucose-lowering drugs, there is a substantial potential for improvement by optimal use of the available medication.[17] Accordingly the recent report from the Euro Heart Survey on Diabetes and the Heart clearly indicated that only a comprehensive management of diabetes mellitus patients is highly rewarding.[18]

Recent evidence

Three recent clinical trials: Action to Control Cardiovascular Risk in Diabetes Study Group (ACCORD), Action in Diabetes and Vascular Disease—Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE), and the Veterans Affairs Diabetes Trial (VADT), sought to determine the effect of lowering

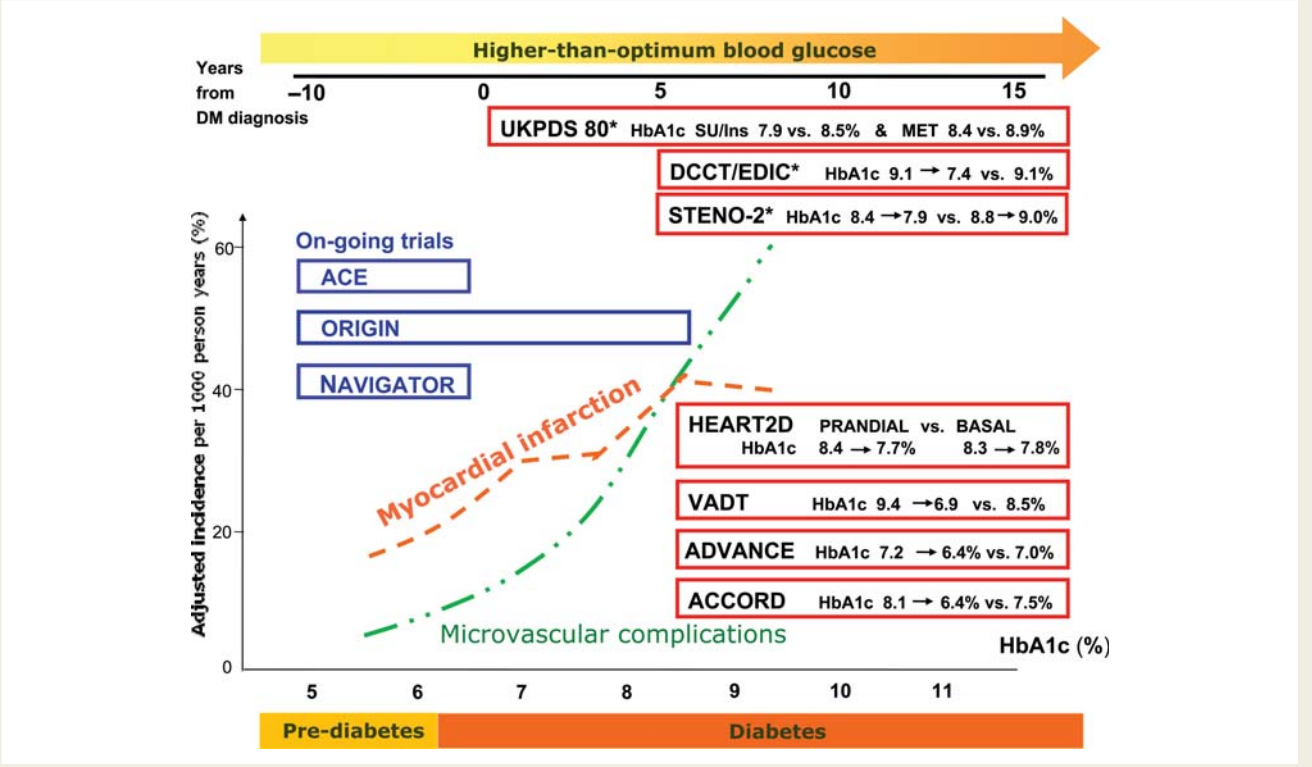

Figure 1 Dysglycaemia, vascular complications and impact of glucose-lowering treatment in clinical trials. Horizontal bars include acronyms of the clinical trials and the glycaemic control described as glycated haemoglobin (HbA1c) at baseline and at the end of the treatment trial in the intensive glucose-lowering arm vs. the conventional therapy, if not stated otherwise. The dashed lines represent the adjusted incidence of myocardial infarction (orange) and microvascular complications (green) as a function of HbA1c (modified from Stratton *et al.*[24]). DM, diabetes mellitus; SU/Ins, sulfonylurea and insulin; MET, metformin; FPG, fasting plasma glucose. *[As known, a significant reduction of cardiovascular (CV) events and mortality induced by intensive glucose lowering was shown only after a long follow-up which is available for the following trials. Results are presented as hazard ratio (95% CIs): STENO-2 after 13.3 years: ↓ CV deaths by 57% (CI 6–81, $P = 0.04$) and ↓ any CV events by 59% (CI 33–75, $P < 0.001$).[16] DCCT after 17 years: ↓ non-fatal myocardial infarction or stroke or CV deaths by 57% (CI 12–79, $P = 0.02$) and ↓ any CV events by 42% (CI 9–63, $P = 0.02$).[14] UKPDS 80 after 17–18 years: ↓ CV mortality by 13% in SU/Ins (CI 4–21, $P = 0.007$) and by 33% in MET (CI 11–49, $P = 0.005$) and ↓ myocardial infarction by 15% in SU/Ins (CI 3–26, $P = 0.01$) and by 33% in MET (CI 11–49, $P = 0.005$).[22]]

of glucose to near-normal levels on cardiovascular risk.[19–21] These studies included a large number of participants with complete follow-up for a median of ~3.5–5.6 years. The baseline characteristics were typical for adults with type 2 diabetes mellitus: mean age 60–66 years and duration of diabetes 8–11 years. Approximately one-third of patients in each study had a history of cardiovascular disease, so these trials assessed the effect of intensive glycaemic control in patients with and in those without pre-existing atherosclerotic vascular disease. In ADVANCE, the microvascular, but not macrovascular, complications were improved during 5 years follow-up while ACCORD was prematurely stopped after 3.4 years due to increased mortality in the intensive treatment arm. VADT had no significant effect on the rates of major cardiovascular events, death, or microvascular complications. There are several possible explanations for these negative results. First, follow-up was too short to demonstrate an effect on macrovascular complications, as previously shown by the DCCT and UKPDS investigators.[14,22] Secondly, many of the participants were at high risk of cardiovascular events perhaps beyond the stage where tight glycaemic control could exert any protective effect. Thirdly, glucose-lowering treatment was too rapidly and aggressively instituted, with an increased risk of severe hypoglycaemia. Taken as a whole, these recent large trials indicate that the effect on cardiovascular events of intensive glucose control, aiming at near normoglycaemia, in patients with long-standing type 2 diabetes mellitus still remains to be confirmed.[19–21] The trial 'Hyperglycemia and Effects After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus (HEART2D)', investigating the effect of a reduction in post-prandial glycaemia (2 h post-prandial blood glucose <7.5 mmol/L) vs. targeting basal glycaemia (fasting/pre-meal blood glucose <6.7 mmol/L) was recently stopped for lack of efficacy.[23] After 2.7 years, the risk for the first combined cardiovascular event in type 2 diabetic patients with a recent acute myocardial infarction was similar in both groups (HR 0.98; 95% CI 0.8–1.21). It is important to mention that the differences in post-prandial blood glucose (<2.5 mmol/L) achieved during the study were lower than expected and the overall glycaemic control (HbA1c 7.7 vs. 7.8%) was suboptimal (*Figure 1*).[23]

Concluding remarks

On the basis of extensive trial evidence, it seems that glucose-lowering therapy may require many years to yield apparent benefits. Retarding the progression of advanced atherosclerosis is difficult, while reduction of other risk factor may, within a shorter time, provide more pronounced effects on cardiovascular outcomes.[17,22] Hence, the final statement in Dale *et al.* 'good glucose control is a key to reduce the risk of coronary complications in patients with diabetes' does not seem to be corroborated by currently available evidence. The potential of lowering blood pressure and lipid targets for reduction of cardiovascular complications has gradually emerged in the last 20 years. In contrast, the increase of cardiovascular risk attributable to higher than optimum glycaemia has been recognized only recently.[2,7–9,13]

It is of utmost importance that evidence-based medicine is implemented and treatment goals are achieved, as outlined in the guidelines on diabetes, pre-diabetes, and cardiovascular diseases.[10] However, further evidence is needed from studies with extended follow-up before we can assess the true benefits of achieving a near normoglycaemia in patients with type 2 diabetes mellitus and whether this may apply for all patients or only for subgroups. It remains to be proven whether early introduction of glucose-lowering treatment may enhance cardiovascular risk reduction in patients with newly recognized impairment of glycaemic control below the diagnostic criteria for diabetes mellitus. Ongoing clinical trials will provide additional clarification on this matter (*Figure 1*).[25–27]

Eventually we will have more data endorsing our treatment decisions. For the time being, patients with type 2 diabetes mellitus or abnormal glucose regulation should be managed according to a multifactorial treatment strategy in which glucose-lowering treatment, aiming at the lowest glycaemia that can safely be sustained, is one of several components.

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