Is Glucose Control Important for Prevention of Cardiovascular Disease in Diabetes?

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Patients affected by diabetes show an increased risk of cardiovascular disease (CVD) and mortality that reduces their life expectancy by 5–15 years (depending on the age at diagnosis). An 18-year follow-up study from Finland demonstrated a similar impact of type 1 and type 2 diabetes on cardiovascular mortality, with an increased risk of 5.2 and 4.9 times for type 1 and type 2 diabetes, respectively (1). In type 1 diabetes, follow-up results from a large randomized clinical trial suggest that the improvement of metabolic control, obtained through intensive insulin treatment, can prevent CVD in the long term. On the other hand, despite some encouraging results (2,3), the results of trials assessing the long-term cardiovascular effects of improving metabolic control in type 2 diabetes are controversial. Here, we will present the main points supporting and will illustrate the main counterpoints challenging the importance of glucose control for prevention of CVD in diabetic patients.

Pros
Pathophysiological effects of hyperglycemia on cardiovascular system.
There is convincing evidence from epidemiological and pathophysiological studies that hyperglycemia has a detrimental effect on cardiovascular risk profile in its own right. It is well known that among patients with type 2 diabetes, those with higher levels of blood glucose and HbA$_{1c}$ are at greater risk for CVD. Glycemic fluctuations and chronic hyperglycemia are triggers for inflammatory responses via increased endoplasmic reticulum stress and mitochondrial superoxide production. The molecular pathways underlying hyperglycemia, low-grade inflammation, and oxidative stress have been widely recognized in the pathogenesis of endothelial dysfunction, which represents the first step of atherogenesis. Through this pathway, hyperglycemia-induced early atherogenesis may lead to an increased probability of cardiovascular events later in life. Direct effects of glucose toxicity, oxidative stress, and low-grade inflammation act in a vicious cycle that determines impaired insulin sensitivity, β-cell loss, and endothelial dysfunction, thus leading to micro- and macrovascular complications (4,5).

Effects of glucose lowering on CVD morbidity and mortality.
Whereas epidemiological and pathophysiological growing evidence demonstrated a direct link between hyperglycemia and cardiovascular morbidity and mortality in diabetic patients, the results of large clinical trials, investigating the efficacy of improving glycemic control in both type 1 and type 2 diabetes to reduce cardiovascular events, have not been convincing. The Diabetes Control and Complications Trial (DCCT) showed a trend toward a 41% risk reduction of cardiovascular events in type 1 diabetes (6). Moreover, during the posttrial 9-year follow-up observational period of the DCCT-Epidemiology of Diabetes Interventions and Complications (EDIC) trial, despite the loss of original difference in HbA$_{1c}$ as a consequence of conventional treatment switching to intensive approach and the less tight glycemic control in patients intensively treated, a risk reduction for any cardiovascular event (42%; P = 0.02) and for nonfatal myocardial infarction, stroke, or death for CVD (57%; P = 0.02) was fully achieved (7). Some conditions, such as the baseline young age of the study sample, the low mortality, and the cardiovascular incidence rate reported during the observation, may have contributed to reveal cardiovascular benefits in the long term only.

A benefit for long-term cardiovascular risk profile has also been described for type 2 diabetes. The UK Prospective Diabetes Study (UKPDS) reported a 16% reduction in the risk of myocardial infarction, with borderline statistical significance (P = 0.052) (8). In the 10-year posttrial follow-up, patients originally randomized to receive intensified glucose treatment achieved a significant reduction in the incidence of myocardial infarction (risk ratio reduction 15%; P = 0.0014) and all-cause mortality (13%; P = 0.007) (2). In the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) trial, which compared pioglitazone with placebo, with HbA$_{1c}$ difference of ~0.5%, a reduced risk for the main secondary end point—a composite of all-cause mortality, nonfatal myocardial infarction, and stroke (hazard ratio 0.84; P = 0.027)—was observed in the intervention group (3).

On the other hand, no significant improvement in cardiovascular risk was observed with intensification of diabetes therapy in the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE)

(9) and the Veterans Affairs Diabetes Trial (VADT) (10); in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (11), the reduction in cardiovascular morbidity in the intensified therapy group did not reach statistical significance, due to the premature interruption because of increased mortality. The negative results of these trials on cardiovascular events may have been determined by the insufficient sample size. It should be considered that one of these trials (i.e., ACCORD), which was specifically designed for cardiovascular outcomes, was prematurely interrupted (before reaching the target number of events) because of an unexpected excess of mortality in the intervention group, whereas two other studies (e.g., UKPDS and ADVANCE) were designed for a composite end point including macro- and microvascular complications, which obviously has a higher incidence than cardiovascular events alone, thus resulting in an undersized study sample for CVD as a separate end point.

When several insufficiently powered studies fail to provide clear results, they should be combined in a meta-analysis to retrieve relevant information, which would otherwise remain hidden because of statistical reasons. The efficacy of the improvement of glycemic control on the cardiovascular risk profile can be easily demonstrated by combining the results of all trials exploring cardiovascular end points and comparing treatment groups with an HbA$_{1c}$ difference of at least 0.5%. Intensified treatment for type 2 diabetes is associated with a significant reduction of all cardiovascular events (overall odds ratio 0.89; $P = 0.001$) and myocardial infarction (0.84; $P < 0.001$) (12). The reduction of cardiovascular morbidity induced by diabetes treatment should theoretically produce a decrease in cardiovascular mortality; however, no such improvement is observed when combining the results of large-scale trials (12). The lack of effect of improvement of glucose control on mortality is largely driven by the negative result of the ACCORD trial, with other studies (particularly UKPDS and PROactive) showing nonsignificant trends toward improvement. Excess mortality in ACCORD could be explained, in part, by the aggressive therapeutic approach in the intensified treatment group, thus leading to a remarkable increase of hypoglycemia. Intensive glycemic control is related to an increased hypoglycemic risk, as observed both in individual trials

and in their meta-analysis. A positive correlation between incidence of severe hypoglycemia and cardiovascular mortality has been documented (12,13). There is evidence that hypoglycemia may adversely affect the cardiovascular risk profile, in particular in subjects affected by a longer duration of diabetes. Hypoglycemia triggers a cascade of physiologic effects, inducing adrenergic activation, oxidative stress, and cardiac arrhythmias, and may contribute to sudden death and ischemic cerebral damage (14). Overall, available trials show that reduction of hyperglycemia reduces the incidence of major cardiovascular events, whereas severe hypoglycemia may increase cardiovascular mortality. In fact, even in the acute phase of major cardiovascular events, a very aggressive treatment of hyperglycemia determining a high hypoglycemic risk increases mortality (15). If this is the case, hypoglycemia-inducing agents (such as insulin or sulfonylureas) could have a less favorable cardiovascular profile than glucose-lowering drugs, which do not induce hypoglycemia.

Growing evidence-based importance of different cardiovascular outcomes with different glucose medications. The hypothesis that irrespective of the extent of the improvement of glycemic control, different glucose-lowering drugs may exert varying effects on cardiovascular risk profile has been repeatedly suggested. From available data, any overall harmful effect of metformin on the incidence of myocardial infarction, stroke, or heart failure has been ruled out, suggesting possible benefits in monotherapy and a detrimental effect when combined with sulfonylureas (16).

On the contrary, sulfonylureas, insulin, and thiazolidinediones have been suspected of adverse cardiovascular effects, although some data of specific drugs were not confirmed by subsequent investigations. A meta-analysis of retrospective cohort studies reported a significant excess risk for all-cause mortality associated with first-generation sulfonylureas (17). In observational studies, insulin therapy has been associated with increased cardiovascular morbidity and mortality, supporting the hypothesis of a proatherogenic effect of insulin therapy in type 2 diabetes (18). On the other hand, the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial failed to detect any difference in cardiovascular effect of insulin in comparison with oral drugs (mainly metformin and sulfonylureas) in

earlier stages of diabetes (19). Among thiazolidinediones, rosiglitazone has been withdrawn because of a supposed increase in the risk of myocardial infarction. On the other hand, pioglitazone seems to be considerably safer in this respect, and it could produce a glucose-independent reduction of cardiovascular risk (20–22), although it has been associated with increased risk of heart failure (20).

Some of the newer drugs might be associated with cardiovascular benefits. In particular, meta-analyses of adverse events reported in available trials have shown significant reductions in cardiovascular morbidity after treatment with dipeptidyl peptidase-4 inhibitors (23), even when used in monotherapy (24). These meta-analytical findings should be considered with caution because they were obtained from trials designed for other purposes (usually efficacy on glucose control) without any clear definition of methods for screening and criteria for diagnosis of cardiovascular events. However, there is wide experimental evidence suggesting that incretin-based drugs could be associated with cardiovascular protection, even through glucose-independent mechanisms (25).

It is likely that individual drugs used for blood glucose control in type 2 diabetes can have different effects (either beneficial or detrimental) on cardiovascular risk, irrespective of their action on glycemia. This possibility complicates the analysis of results of available trials on the long-term effects of improvement of metabolic control. In some of the available studies, there was widespread use of drugs possibly associated with cardiovascular harm (e.g., rosiglitazone in ACCORD), which could have masked some of the benefits of lower HbA$_{1c}$; conversely, in future trials, the use of drugs with glucose-independent beneficial actions may produce an overestimation of the protection conferred by strict metabolic control in type 2 diabetes.

Cons
The pathophysiology of accelerated atherosclerosis and CVD risk in diabetes is complex (26). Several risk factors for CVD, including insulin resistance/hyperinsulinemia, hyperglycemia, overweight/obesity, hemorreological abnormalities, dyslipidemia, and hypertension, are often present in varying combinations in patients with type 2 diabetes. Although some studies have shown that

hyperglycemia is an independent risk factor for CVD in subjects with or without diabetes (1,27), the complex interaction of several risk factors justifies the difficulty in determining whether the treatment of hyperglycemia really improves the risk of macrovascular complications, as observed with microangiopathic complications. The role of nonglycemic factors that accompany the vast majority of patients with type 2 diabetes is much better understood and seems to be independent of glycemia. In addition, there have been studies demonstrating that interventions addressed to control these other factors in patients with diabetes effectively reduce cardiovascular risk (28,29). In contrast, to date, the positive effect of intensive glucose management in comparison with nonintensive glucose control on CVD outcomes is still far from proven.

The milestone study evaluating glucose control improvement and diabetes complications in type 1 diabetes is the DCCT (6). Because of the low rate of macrovascular events during the follow-up, the study lacked the power to evaluate the effect of glucose control on CVD (30). The DCCT/EDIC study followed up 1,341 initial participants evaluating cardiovascular events (17 years in total after entry in the DCCT). There was a 42% reduction for any cardiovascular event and a 57% reduction for cardiovascular death, myocardial infarction, or stroke in the group originally assigned to intensive management (7). The authors attributed this positive finding to the DCCT period of intensive glucose control despite an increase in body weight. While promising, these results need confirmation. We should not forget that CVD risk in long-standing type 1 diabetes may be related to weight gain (31,32) that may result from many years of sustained peripheral hyperinsulinemia. However, the latter may be less relevant than expected in determining CVD. Alternatively, higher rates of CVD in subjects with many years of type 1 diabetes, especially in older studies, really reflect the adverse effects of diabetic microangiopathy on CVD risk (31,32). It should also be considered that the impact of hyperglycemia on cardiovascular risk could be different in type 1 and type 2 diabetes. In a large Finnish study, an increment of 1 unit (%) of HbA_{1c} increased cardiovascular mortality by 52% and 7% in type 1 and 2 diabetic subjects, respectively (1).

Among clinical trials assessing the long-term effect of diabetes treatment on CVD in type 2 diabetes, the UKPDS (8) was the largest one. In this study, no differences were observed for macrovascular disease: aggregate end points, including diabetes-related deaths, all-cause mortality, myocardial infarction, stroke, or amputations or death from peripheral vascular disease, did not reach statistical significance. Moreover, the cardioprotective action of metformin is based on the observations collected in a cohort of only 342 overweight patients with diabetes included in the UKPDS (33), which is a very small population compared with that of the most recent studies that have not been able to highlight a safe cardiovascular protective effect of intensive treatment.

In the PROactive study (3), it was claimed that the use of pioglitazone was associated with a positive and significant reduction in secondary composite end points of death, stroke, and myocardial infarction. However, in that study pioglitazone ameliorated other risk factors beyond blood glucose; a post hoc analysis suggests that HDL could have been a more important mediator of cardiovascular benefits than HbA_{1c} (22).

More recently, in the ACCORD study (11) >10,000 patients with type 2 diabetes at high risk for CVD were randomly assigned to intensive therapy (aimed at HbA_{1c} ≤6.0%) or standard therapy (HbA_{1c} goal of 7.0–7.9%). The results showed no significant difference in the primary end points (nonfatal myocardial infarction, nonfatal stroke, or death from CV causes) between the two groups, whereas all-cause mortality was 22% higher in the intensive therapy group (95% CI 1.01–1.46; $P = 0.04$). The causes of excess deaths in the ACCORD trial remain to be explained definitively. It is plausible, however, that excess mortality was due to serious hypoglycemia, which was significantly more frequent in the intensive control group.

In the ADVANCE study (8), ~11,000 patients with multiple CVD risk factors were followed for 5 years. The data showed that intensive glucose control (HbA_{1c} goal <6.5%) did not provide greater macrovascular protection than did standard therapy. The VADT (10) also did not show significant differences in the primary outcome, a first cardiovascular event (hazard ratio 0.88 [95% CI 0.74–1.05]; $P = 0.14$), or all-cause mortality (1.07 [0.81–1.42]; $P = 0.62$).

Furthermore, the results of the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) study (34) showed the difficulty of demonstrating

beneficial effects of intensive glycemic control on CVD prognosis. There was no difference in the survival rate in the insulin-sensitization therapy versus the insulin provision group (88.2 vs. 87.9%, respectively; difference 0.3% [95% CI –2.2 to 2.9]; $P = 0.89$), despite a 0.5% difference in HbA_{1c} (7.0 vs. 7.5%; $P = 0.001$) (30).

In recent meta-analyses of phase 2 and 3 studies on a small number of events, the possibility was raised that some of the newer drugs, such as dipeptidyl peptidase-4 inhibitors and GLP-1 analogs, showed significant cardiovascular protective effects in type 2 diabetes (23,24), but these benefits could be due to vasculo- or cardioprotective actions (e.g., myocardial protection from ischemia, improvement of endothelial function, etc.), independent of glucose control (35,36).

The comparisons of results of different intervention studies are complex because of diversities in characteristics of enrolled subjects and in concomitant therapies. For example, the UKPDS trial was performed before the widespread use of statin therapy in type 2 diabetes and in subjects with newly diagnosed diabetes free from cardiovascular complications; conversely, PROactive, ACCORD, ADVANCE, and VADT enrolled subjects with high CVD risk. In fact, subgroup analyses of data from these trials suggested that patients with a shorter duration of diabetes, a lower HbA_{1c}, or lack of established CVD might have benefited significantly from more intensive glycemic control (37).

More recently, the ORIGIN trial was designed to determine whether insulin can reduce cardiovascular morbidity in people with prediabetic hyperglycemia or early type 2 diabetes. Interestingly, in patients without prior CVD, insulin treatment was associated with a higher yearly incidence of CV events (2.21 vs. 1.89%), despite a similar glycemic control (19).

Few studies are available on the long-term CV effects of multifactorial interventions, in which treatment of hyperglycemia was associated with accurate therapy for associated risk factors. In the Steno-2 study (38), on a relatively small sample of subjects with type 2 diabetes, the intensive treatment of hyperglycemia, hypertension, dyslipidemia, and microalbuminuria reduced CV risk by >50%, demonstrating the need for a multifactorial intervention.

Presently, in type 2 diabetes, the use of statins, ACE inhibitors or angiotensin receptor blockers, and antiplatelet agents is an essential component of the clinical management. It is possible that the

remarkable efficacy of other therapies in cardiovascular prevention makes it difficult to demonstrate an additional benefit of glucose-lowering interventions in clinical trials (38). For example, patients with CVD or CVD risk factors in the ACCORD, ADVANCE, and VADT trials also received statins, antihypertension agents, and aspirin as appropriate/needed, all of which have robust cardiovascular risk reduction properties.

Patients with type 2 diabetes are heterogeneous for age, duration of disease, comorbidity, and genetic background. Glucose-lowering therapy should be adapted to this complexity, with an attempt at improving, or at least avoidance of worsening, associated cardiovascular risk factors.

Conclusions

The assumption that treatment of hyperglycemia can prevent all diabetes complications, including CVD, has been an "act of faith" in the diabetological community for many decades. The contrasting results of available clinical trials in recent years have generated perplexity amid concerns that glucose-lowering therapies, under certain circumstances, might even be detrimental. When all available evidence to date is considered, which includes a fair number of large-scale clinical trials, the improvement of glycemic control appears to be associated with a reduction in the incidence of major cardiovascular events, whereas hypoglycemia could increase cardiovascular mortality. The pursuit of accurate glycemic control, avoiding both hyper- and hypoglycemia, should be recommended for preventing CVD in diabetes, and thus an individualized approach for achievement of target HbA$_{1c}$ in type 2 diabetic patients should be adopted (39,40). At the same time, it should also be clearly recognized that the control of other risk factors (such as hypertension and hypercholesterolemia) is more effective than glucose-lowering therapy in reducing the incidence of cardiovascular events. As a consequence, diabetes care implies a comprehensive management of cardiovascular risk, which includes other factors beyond glycemia.

References

1. Juutilainen A, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Similarity of the impact of type 1 and type 2 diabetes on cardiovascular mortality in middle-aged subjects. Diabetes Care 2008;31:714–719
2. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589
3. Dormandy JA, Charbonnel B, Eckland DJ, et al.; PROactive investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366:1279–1289
4. Bornfeldt KE, Tabas I. Insulin resistance, hyperglycemia, and atherosclerosis. Cell Metab 2011;14:575–585
5. Reusch JE, Wang CC. Cardiovascular disease in diabetes: where does glucose fit in? J Clin Endocrinol Metab 2011;96:2367–2376
6. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
7. Nathan DM, Cleary PA, Backlund JY, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643–2653
8. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853
9. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–2572
10. Duckworth W, Abraira C, Moritz T, et al.; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–139
11. Gerstein HC, Miller ME, Byington RP, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559
12. Mannucci E, Monami M, Lamanna C, Gori F, Marchionni N. Prevention of cardiovascular disease through glycemic control in type 2 diabetes: a meta-analysis of randomized clinical trials. Nutr Metab Cardiovasc Dis 2009;19:604–612
13. Seaquist ER, Miller ME, Bonds DE, et al.; ACCORD Investigators. The impact of frequent and unrecognized hypoglycemia on mortality in the ACCORD study. Diabetes Care 2012;35:409–414
14. Snell-Bergeon JK, Wadwa RP. Hypoglycemia, diabetes, and cardiovascular disease. Diabetes Technol Ther 2012;14(Suppl. 1):S51–S58
15. Finfer S, Liu B, Chittock DR, et al.; NICE-SUGAR Study Investigators. Hypoglycemia and risk of death in critically ill patients. N Engl J Med 2012;367:1108–1118
16. Lamanna C, Monami M, Marchionni N, Mannucci E. Effect of metformin on cardiovascular events and mortality: a meta-analysis of randomized clinical trials. Diabetes Obes Metab 2011;13:221–228
17. Tzoulaki I, Molokhia M, Curcin V, et al. Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. BMJ 2009;339:b4731
18. Gamble JM, Simpson SH, Eurich DT, Majumdar SR, Johnson JA. Insulin use and increased risk of mortality in type 2 diabetes: a cohort study. Diabetes Obes Metab 2010;12:47–53
19. ORIGIN Trial investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med 2012;367:319–328
20. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA 2007;298:1180–1188

21. Nissen SE, Nicholls SJ, Wolski K, et al.; PERISCOPE Investigators. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. JAMA 2008 2;299:1561–1573

22. Ferrannini E, Betteridge DJ, Dormandy JA, et al. High-density lipoprotein-cholesterol and not HbA1c was directly related to cardiovascular outcome in PROactive. Diabetes Obes Metab 2011;13:759–764

23. Monami M, Ahrén B, Dicembrini I, Mannucci E. Dipeptidyl peptidase-4 inhibitors and cardiovascular risk: a meta-analysis of randomized clinical trials. Diabetes Obes Metab 2013;15:112–120

24. Patil HR, Al Badarin FJ, Al Shami HA, et al. Meta-analysis of effect of dipeptidyl peptidase-4 inhibitors on cardiovascular risk in type 2 diabetes mellitus. Am J Cardiol 2012;110:826–833

25. Mannucci E, Dicembrini I. Incretin-based therapies and cardiovascular risk. Curr Med Res Opin 2012;28:715–721

26. Mazzone T, Chait A, Plutzky J. Cardiovascular disease risk in type 2 diabetes mellitus: insights from mechanistic studies. Lancet 2008;371:1800–1809

27. Barr EL, Boyko EJ, Zimmet PZ, Wolfe R, Tonkin AM, Shaw JE. Continuous relationships between non-diabetic hyperglycaemia and both cardiovascular disease and all-cause mortality: the Australian Diabetes, Obesity, and Lifestyle (AusDiab) study. Diabetologia 2009;52:415–424

28. Huang ES, Meigs JB, Singer DE. The effect of interventions to prevent cardiovascular disease in patients with type 2 diabetes mellitus. Am J Med 2001;111:633–642

29. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICROHOPE substudy. Lancet 2000;355:253–259

30. Effect of intensive diabetes management on macrovascular events and risk factors in the Diabetes Control and Complications Trial. Am J Cardiol 1995;75:894–903

31. Libby P, Nathan DM, Abraham K, et al.; National Heart, Lung, and Blood Institute; National Institute of Diabetes and Digestive and Kidney Diseases Working Group on Cardiovascular Complications of Type 1 Diabetes Mellitus. Report of the National Heart, Lung, and Blood Institute-National Institute of Diabetes and Digestive and Kidney Diseases Working Group on Cardiovascular Complications of Type 1 Diabetes Mellitus. Circulation 2005;111: 3489–3493

32. Orchard TJ, Costacou T, Kretowski A, Nesto RW. Type 1 diabetes and coronary artery disease. Diabetes Care 2006;29: 2528–2538

33. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352: 854–865

34. Frye RL, August P, Brooks MM, et al.; BARI 2D Study Group. A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med 2009; 360:2503–2515

35. Anagnostis P, Athyros VG, Adamidou F, et al. Glucagon-like peptide-1-based therapies and cardiovascular disease: looking beyond glycaemic control. Diabetes Obes Metab 2011;13:302–312

36. Ban K, Noyan-Ashraf MH, Hoefer J, Bolz SS, Drucker DJ, Husain M. Cardioprotective and vasodilatory actions of glucagon-like peptide 1 receptor are mediated through both glucagon-like peptide 1 receptor-dependent and -independent pathways. Circulation 2008;117:2340–2350

37. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 2008;358:580–591

38. Skyler JS, Bergenstal R, Bonow RO, et al.; American Diabetes Association; American College of Cardiology Foundation; American Heart Association. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. Diabetes Care 2009;32:187–192

39. Pozzilli P, Leslie RD, Chan J, et al. The A1C and ABCD of glycaemia management in type 2 diabetes: a physician's personalized approach. Diabetes Metab Res Rev 2010;26:239–244

40. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2012;55:1577–1596