Cardiovascular Importance of Hyperglycemia and Hypoglycemia

IVAN TKÁČ, MD, PHD

For addressing the question of cardiovascular importance of hypoglycemia, it is important to clarify its context. First, hypoglycemia is a result of treatment of hyperglycemia by oral insulin secretagogues or insulin. Chronic hyperglycemia usually expressed by HbA_{1c} level is considered a risk factor for cardiovascular disease, although this epidemiological association does not necessarily mean the existence of causal association, so the possibility cannot be excluded that HbA_{1c} may be only a marker of atherosclerotic vascular disease. Thus, in the present review the evidence related to hyperglycemia and hypoglycemia as factors contributing to the development of cardiovascular events will be discussed and the main following issues will be addressed: The relationship of hyperglycemia to cardiovascular disease will be documented based on analysis of epidemiological and clinical interventional studies. Furthermore, the evidence will be summarized that hypoglycemic episodes contribute to the development of cardiovascular events in patients with type 2 diabetes treated by hypoglycemia-inducing drugs. Finally, it will be demonstrated how the conclusions from the described studies translated in practical recommendations for personalized treatment of type 2 diabetes.

Is hyperglycemia related to cardiovascular disease?

The evidence about a relationship between hyperglycemia and cardiovascular disease comes from epidemiological studies and epidemiological post hoc analyses of clinical trials. For consideration of a biological variable, e.g., HbA_{1c}, as a cardiovascular risk factor, it is important to analyze its relationship with cardiovascular disease also outside the diabetic range. The epidemiological study European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) included 4,662 men and 5,570 women. Relative risks for cardiovascular disease (nonfatal or fatal coronary heart disease and strokes) adjusted for age and risk factors were calculated after 6-year follow-up period. An increase in HbA_{1c} of 1% (11 mmol/mol) was associated with relative risk for cardiovascular disease of 1.21 (95% CI 1.13–1.29 for males and 1.11–1.31 for females; $P < 0.001$). Moreover, the increased risk associated with diabetes seemed to be mediated entirely through HbA_{1c} level, since diabetes was no longer a significant predictor when HbA_{1c} was included into multivariate model (1). Very similar results were found by another large prospective epidemiological study—Atherosclerosis Risk in Communities (ARIC)—which included 11,092 adults without history of diabetes or cardiovascular disease. After 15-year follow-up, an increase in HbA_{1c} of 1% (11 mmol/mol) was associated with hazard ratio (HR) of 1.19 (1.11–1.27) for coronary heart disease and 1.34 (1.22–1.48) for stroke (2).

Epidemiological analysis from the UK Prospective Diabetes Study (UKPDS) showed a similar association. A reduction in HbA_{1c} by 1% (11 mmol/mol) was associated with a 14% decrease in fatal and nonfatal myocardial infarction (MI) ($P < 0.0001$), as well as 12% decrease in fatal and nonfatal stroke ($P = 0.035$). The relationship between HbA_{1c} and incidence of cardiovascular end points was linear to the level of HbA_{1c} of 5.5% (37 mmol/mol) (3). On the other hand, an epidemiological analysis from the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study showed that within the range of HbA_{1c} studied (5.5–10.5%; 37–91 mmol/mol), there was evidence for a threshold effect: While for microvascular events this value was 6.5% (48 mmol/mol), for macrovascular events and death the threshold was 7% (53 mmol/mol). Above this threshold, the risks increased significantly so that every 1% (11 mmol/mol) higher HbA_{1c} was associated with a 40% higher risk of microvascular events ($P < 0.0001$), a 38% higher risk of macrovascular outcomes ($P < 0.0001$), and a 38% higher risk of all-cause mortality ($P < 0.0001$) (4). Epidemiological analysis of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study showed that 1% (11 mmol/mol) increase in average HbA_{1c} during 3.4 years' duration of the study was associated with 22% increase in mortality ($P = 0.0001$). Interestingly, the relationship between mortality and HbA_{1c} was linear in the range of 6–9% (42–75 mmol/mol) only in the intensively treated group ($P < 0.0001$), while no significant relationship ($P = 0.17$) was observed in the standard treatment group (5).

Does the reduction of high blood glucose lead to a cardiovascular benefit?

Studies in newly diagnosed patients with type 2 diabetes

University Group Diabetes Program (UGDP). The first study to approach this question in patients with type 2 diabetes was the UGDP. This study included 1,027 patients and was statistically underpowered (with ~200 patients in each treatment category group: placebo, tolbutamide, phenphormin, insulin standard, or insulin variable regimens) to detect beneficial effect of any treatment modality. The first analysis, published in

From the Department of Internal Medicine 4, P.J. Šafárik University, and L. Pasteur University Hospital, Košice, Slovakia.
Corresponding author: Ivan Tkáč, ivan.tkac@upjs.sk.
This publication is based on the presentations from the 4th World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy). The Congress and the publication of this supplement were made possible in part by unrestricted educational grants from Abbott, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Ethicon Endo-Surgery, Janssen, Medtronic, Novo Nordisk, Sanofi, and Takeda.
DOI: 10.2337/dcS13-2044

See accompanying article, p. S264.

1970, showed that despite better glycemic control, a significantly higher cardiovascular mortality was observed in a group treated by tolbutamide in comparison with placebo and both insulin regimens (6). Further analysis from UGDP showed that patients treated with tolbutamide had significantly higher incidence of fatal MI in comparison with patients on placebo (P = 0.01), while patients on variable insulin regimen had borderline significantly higher incidence of fatal MI (P = 0.06) compared with patients treated with placebo. There was no difference in incidence of nonfatal MI events among the four groups (7). With respect to the incidence of hypoglycemia in UGDP, the number of patients who had glucose levels <50 mg/dL was zero for placebo, four for tolbutamide, three for standard insulin regimen, and five for variable insulin regimen.

The UK Prospective Diabetes Study (UKPDS). The UKPDS study included 4,203 patients with newly diagnosed type 2 diabetes. The main results of the UKPDS study were published in 1998 in two articles. UKPDS 33 reports results of 3,867 patients with newly diagnosed type 2 diabetes who were randomized to intensive glycemic control policy with sulfonylureas or insulin or to conventional treatment policy—primarily with diet. More drugs were added in both groups of patients if fasting plasma glucose was ≥15 mmol/L. The patients in the intensive group had median HbA_{1c} of 7.0% (53 mmol/mol) during 10-year follow-up, while patients in the conventional group achieved median HbA_{1c} of 7.9% (63 mmol/mol) (8).

While significant risk reduction by 12% (P = 0.029) in the incidence of any diabetes-related end point in the intensive treatment group was observed, nonfatal and fatal MI incidence was reduced by 16% with a borderline significance (P = 0.052) (8). Major hypoglycemic episodes defined as the mean proportion of patients per year with one or more episode occurred with chlorpropamide (1.0%), glibenclamide (1.4%), insulin (1.8%), and diet (0.7%). Interestingly, after 10-year post-study follow-up as more events occurred, risk reductions for MI (15%, P = 0.01) and all-cause mortality (13%, P = 0.007) became significant (9).

The results of subgroup analysis of 1,704 overweight patients with type 2 diabetes randomized to intensive treatment by metformin or sulfonylurea/insulin or to conventional treatment were published separately (10). Patients treated primarily by intensive metformin treatment had a median HbA_{1c} level of 7.4% (57 mmol/mol) during the follow-up, while patients in the conventional treatment group had median HbA_{1c} level of 8.0% (64 mmol/mol). Patients allocated to metformin compared with the conventional group had significantly reduced risk for diabetes related death by 42% (P = 0.017), as well as for fatal/nonfatal MI by 39% (P = 0.01). Patients allocated to metformin had lower risk for all-cause mortality (P = 0.021) and for stroke (P = 0.032) compared with patients allocated to insulin or sulfonylurea. Major hypoglycemic episodes occurred in 0.6% patients/year treated with metformin (10). One of the explanations of lower cardiovascular preventive effect of sulfonylurea or insulin treatment in comparison with metformin in UKPDS might be that metformin-treated patients had lower incidence of severe hypoglycemic episodes.

Outcome Reduction with an Initial Glargine Intervention (ORIGIN). The ORIGIN study included a total of 12,537 participants, among whom 88% had diabetes and 12% had prediabetic dysglycemias. Patients were assigned either to insulin glargine or to standard care treatment. After the median follow-up of 6.2 years, there was no significant difference in rates of cardiovascular outcomes between the study groups. Rates of severe hypoglycemia were higher in the glargine-treated group (1.00 vs. 0.31/100 person-years) (11).

Studies in patients with long-term duration of diabetes and macrovascular disease

Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive). The PROactive study included 5,238 patients with previous macrovascular disease. The interventional study group patients were given pioglitazone in addition to the previous treatment. This resulted in an on-study difference of HbA_{1c} level by 0.6% (7 mmol/mol) between the pioglitazone-treated and control groups. The patients on pioglitazone had nonsignificantly reduced incidence of a widely defined primary end point (the composite of all-cause mortality, nonfatal MI, stroke, acute coronary syndrome, vascular interventions in the coronary or leg arteries, and amputations above ankle) by 10% (P = 0.095). The incidence of a more commonly used (in the other studies) main secondary end point (total mortality, nonfatal MI, and stroke), which was not predefined in the design of the study, was significantly reduced by 16% (P = 0.027) in the pioglitazone-treated patients. Symptoms compatible with hypoglycemia arose in 28% on pioglitazone and 20% on placebo (P < 0.0001) (12).

ACCORD. In the ACCORD trial, 10,251 patients were randomized to receive intensive glucose-lowering treatment aiming for HbA_{1c} <6% (42 mmol/mol) or standard diabetes treatment targeting HbA_{1c} level in the range 7.0–7.9% (53–63 mmol/mol). No specific treatment was requested in either of the study groups, and multiple drug combinations were allowed to achieve the defined target. In the intensive treatment group a median HbA_{1c} of 6.4% (46 mmol/mol) and in the standard treatment group a median of 7.5% (58 mmol/mol) were achieved, respectively. The study was prematurely stopped after 3.5 years of follow-up in 2008 because of an observed 22% significant increase in all-cause mortality (P = 0.04) and 35% increase in cardiovascular mortality (P = 0.02) in patients with intensive glycemic control (13).

The primary end point of the study (nonfatal MI, nonfatal stroke, or death from cardiovascular causes) was nonsignificantly reduced in the intensive treatment group by 10% (P = 0.16). Significant reduction in the incidence of nonfatal MI by 24% (P = 0.004) was observed in the intensive therapy group. The subgroup analysis revealed a significantly more beneficial effect on primary end point reduction in the intensive treatment group in the patients without previous cardiovascular disease and with better diabetes control with HbA_{1c} <8%, (64 mmol/mol). Hypoglycemia requiring medical assistance was three times more frequent in the intensive therapy group in comparison with standard therapy (10.5 vs. 3.5%, P < 0.001) (13).

ADVANCE. In the ADVANCE trial, 11,140 patients were randomized to intensive treatment defined as use of gliclazide along with other drugs with a target of HbA_{1c} <6.5% (48 mmol/mol) or standard treatment. The standard treatment strategy was based on local guidelines. Median follow-up of patients was 5 years. A nonsignificant 6% reduction in the incidence of macrovascular events—nonfatal MI, nonfatal stroke, and death from cardiovascular causes—was observed (14).

In contrast with the ACCORD trial, no significant increase in all-cause or cardiovascular mortality was observed.

Subgroup analysis suggested that there might be a more pronounced effect on primary end point reduction in the subgroup of patients with no history of macrovascular disease. However, the test of heterogeneity between the groups with and without history of macrovascular disease was not significant. Severe hypoglycemia was much less frequent than in the ACCORD study. However, it was more common in the intensive control group than in the standard control group (2.7 vs. 1.5%, $P < 0.001$) (14).

Veterans Affairs Diabetes Trial (VADT). The VADT had a design similar to those of the ACCORD and ADVANCE trials. A total of 1,791 patients were randomized to intensive diabetes treatment aiming for HbA_{1c} <6% (42 mmol/mol) and to standard treatment aiming for HbA_{1c} <9% (75 mmol/mol). The goal for HbA_{1c} between-group difference was 1.5% (17 mmol/mol). The on-treatment median HbA_{1c} was 6.9% (52 mmol/mol) for the intensive-treatment group and 8.4% (68 mmol/mol) for the standard treatment group (15).

The primary end point was any major cardiovascular event (a composite of MI, stroke, death from cardiovascular disease, congestive heart failure, surgery for vascular disease, inoperable coronary disease, and amputation for ischemic gangrene). After the median follow-up of 5.6 years, a nonsignificant reduction in primary end point in the intensive therapy group by 12% ($P = 0.14$) was observed. Incidence of none of the end points included in the primary end point did not differ significantly between the study groups. Similarly to the ACCORD and ADVANCE studies, significantly more episodes of hypoglycemia were reported in the intensive therapy group than in standard therapy ($P < 0.001$) (15). In a subgroup of 301 patients, coronary artery calcium (CAC) was measured by computed tomography. Those with low CAC, i.e., less extensive calcified coronary atherosclerosis, had significant benefit from glucose-lowering treatment (HR 0.08 [95% CI 0.01–0.77]; $P = 0.03$), while in the patients with CAC >100 no significant benefit of treatment was observed (16).

Studies in patients with type 2 diabetes and recent MI

Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction 2 (DIGAMI 2). The hypothesis that insulin treatment in the postinfarction period prolongs survival of patients was tested in DIGAMI 2 study, which was performed in Scandinavian countries, the Netherlands, and U.K. and included 1,253 patients with type 2 diabetes. Three treatment strategies were compared: Group 1 included patients in whom insulin-glucose infusion was followed by long-term insulin-based regimen. Group 2 included patients who received insulin-glucose infusion followed by standard glucose control, while group 3 had routine metabolic management according to local practice both in hospital and during the posthospitalization period. The median study duration was 2.1 years.

After 24 h of hospitalization, blood glucose was significantly reduced in both groups with insulin-glucose infusion to 9.1 mmol/L, while in group 3 it was reduced to 10.0 mmol/L. Hypoglycemia <3 mmol/L with and without symptoms was more frequent during the initial 24 h in groups 1 and 2 than in group 3. Long-term follow-up data on hypoglycemia incidence were not published in this study. By the end of follow-up, HbA_{1c} levels were reduced in all three groups similarly by 0.5% (6 mmol/mol) to final 6.8% (51 mmol/mol) (17).

Difference in mortality between groups 1 (23.4%) and 2 (22.6%) was the primary end point of the study, and this difference was not statistically significant. The difference in mortality between group 1 and group 3 (19.3%), which was the secondary end point of the study, also was not significant. There were no significant differences in the incidence of reinfarctions or strokes among all three study groups (17).

Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Type 2 Diabetes Mellitus (HEART2D). HEART2D enrolled 1,115 patients with type 2 diabetes and acute MI. Patients were followed on average 2.7 years. The study was designed to compare two treatment strategies: the first strategy was based on use of basal insulin, while the second strategy aimed to achieve the lowest possible postprandial glucose by use of prandial insulins. Patients in the prandial group experienced 174 events, and patients in the basal group experienced 181 events, with HR of 0.98 (95% CI 0.80–1.21). Secondary analyses included various combinations of cardiovascular outcomes, with hard end points such as cardiovascular death, MI, or stroke being of major interest. The groups did not show any difference with respect to these individual outcomes or combinations of outcomes (18).

The two treatment groups had similar HbA_{1c} throughout the trial: 7.7% (61 mmol/mol) vs. 7.8% (62 mmol/mol). Patients in the prandial group had on average lower postprandial blood glucose, while patients in the basal strategy group had lower fasting/premeal blood glucose. However, the difference in postprandial blood glucose between the groups was smaller (7.8 vs. 8.6 mmol/L; $P < 0.01$) than anticipated (2.5 mmol/L) in the study design. The incidence of severe hypoglycemia was similar throughout the trial (prandial group vs. basal group 12.9 vs. 9.5%, respectively; $P = 0.071$), while the incidence of nocturnal hypoglycemia was significantly higher in the basal group than in the prandial group (10.6 vs. 6.1%, $P = 0.007$) (18).

Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D). The study included 2,368 patients with type 2 diabetes and coronary disease who were assigned to undergo either prompt revascularization with intensive medical therapy or intensive medical therapy alone. Intensive medical therapy was achieved by either insulin sensitization or insulin provision. At 5 years, there was no statistically significant difference in the rate of survival between insulin sensitization and insulin provision groups (88.2 vs. 87.9%). Incidence of severe hypoglycemia was significantly higher in the insulin provision group (9.2 vs. 5.9%, $P = 0.003$) (19).

Meta-analyses of the studies aiming for intensive glycemic control. After publication of the results of three large studies in 2008, several meta-analyses were performed to assess cardiovascular benefits of glucose-lowering treatment. These meta-analyses combined in their majority the results of five trials: UKPDS, PROactive, ACCORD, ADVANCE, and VADT. Although their results slightly differed with respect to evaluated end points, the reduction of HbA_{1c} by an average of 0.9% (10 mmol/mol) was shown to reduce incidence of major cardiovascular events by ~10% and of nonfatal MI by ~15%. No significant effect, either beneficial or deleterious was shown on incidence of stroke and both cardiovascular and total mortality (20–23).

The only group-level meta-analysis combined data from UKPDS, ACCORD, ADVANCE, and VADT. Subgroup analysis showed that beneficial effect on reduction of major cardiovascular events was shown only in diabetic patients without history of macrovascular disease (HR 0.84 [0.75–0.94]; P value for group difference of 0.04). Overall, the intensively treated groups had

also significantly—approximately 2.5 times—increased risk of severe hypoglycemia (24).

Is hypoglycemia a risk factor for cardiovascular disease?

The counterintuitive results of the ACCORD study led to several retrospective analyses of data that tried to explain the role of severe hypoglycemia in increased cardiovascular mortality in the intensively treated group. This analysis showed that the participants with at least one episode of severe hypoglycemia requiring assistance had almost twice as high mortality (6.9 vs. 4.1%) than subjects without a hypoglycemic event. Surprisingly, this risk appeared to be higher in the standard group than in the intensive group. Thus, the investigators concluded that previous severe hypoglycemia was not responsible for the difference in mortality rates between the study groups (25). More recent analysis showed that the frequency of hypoglycemic episodes also did not explain increased mortality in the intensively treated group in ACCORD (26).

Similar analysis performed on the data from the ADVANCE study showed that severe hypoglycemia was associated with significant increase in risks of major macrovascular events (HR 2.88 [95% CI 2.01–4.12]), death from cardiovascular disease (2.68 [1.72–4.19]), and all-cause mortality (2.69 [1.97–3.67]); $P < 0.001$ for all comparisons) (27). A meta-regression analysis indicated three significant predictive factors for cardiovascular mortality in intensively treated groups: incidence of severe hypoglycemia, baseline BMI, and the duration of diabetes (20).

Conclusions

Data from physiological studies showed that severe hypoglycemia or repeated episodes of milder hypoglycemia might lead to sudden arrhythmic death, MI, or stroke predominantly in patients with preexisting macrovascular disease (28). Epidemiological studies indicated that reduction of HbA_{1c} by 1% (11 mmol/mol) should lead to reduction of major cardiovascular events by ~20%. In reality, in two studies (UGDP and ACCORD) the use of drugs causing hypoglycemia was associated with an increased cardiovascular mortality. There is also substantial evidence, mainly from the observational studies, that mortality of patients on sulfonylureas is higher than of patients on metformin (29,30). In the other randomized trials mentioned in this review, there was either no effect of intensive glucose lowering on reduction of cardiovascular events or the effect was smaller than expected. The observed reduction in the incidence of cardiovascular events based on meta-analyses of the most important clinical trials was ~10%. Whether this lack of expected effect could be assigned to the increased incidence of hypoglycemia in intensively treated patients is not clear. Other factors such as an increase in body weight, specific side effects of individual antidiabetes drugs, or further nonidentified factors may contribute to hypothesized lack of effect.

Based on the knowledge from the above-mentioned studies related to cardiovascular benefit of decreasing hyperglycemia and taking into the account the cardiovascular risk of hypoglycemia, a rational treatment approach was defined in the recent years leading to creation of personalized guidelines. In general, the treatment goal in diabetes is to achieve HbA_{1c} <7% (53 mmol/mol) (31). More stringent goals (HbA_{1c} 6.0–6.5%; 42–48 mmol/mol) might be considered in patients with short disease duration, long life expectancy, and no significant cardiovascular disease if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Less stringent HbA_{1c} goals (7.5–8.0%; 58–64 mmol/mol) might be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced complications, and extensive comorbid conditions (31–37).

Acknowledgments—This work was supported by research grants from Ministry of Education, Science, Research and Sport of Slovak Republic VEGA 1/0112/11 and VEGA 1/0340/12 and from the Slovakian Agency for Research and Development (APVV-0134-11). I.T. received speaking and/or consulting fees from Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Sanofi, Servier, and Worwag Pharma. No other potential conflicts of interest relevant to this article were reported.

I.T. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Association of hemoglobin A_{1c} with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. Ann Intern Med 2004;141:413–420
2. Selvin E, Steffes MW, Zhu H, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med 2010;362:800–811
3. Stratton IM, Adler AI, Neil HA, et al; UK Prospective Diabetes Study Group. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–412
4. Zoungas S, Chalmers J, Ninomiya T, et al.; ADVANCE Collaborative Group. Association of HbA_{1c} levels with vascular complications and death in patients with type 2 diabetes: evidence of glycaemic thresholds. Diabetologia 2012;55:636–643
5. Riddle MC, Ambrosius WT, Brillon DJ, et al.; Action to Control Cardiovascular Risk in Diabetes Investigators. Epidemiologic relationships between A1C and all-cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. Diabetes Care 2010;33:983–990
6. Goldner MG, Knatterud GL, Prout TE. Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. 3. Clinical implications of UGDP results. JAMA 1971;218:1400–1410
7. Miller M, Knatterud GL, Hawkins BS, Newberry WB. A study of the effects of hypoglycemia agents on vascular complications in patients with adult-onset diabetes. VI. Supplementary report on nonfatal events in patients treated with tolbutamide. Diabetes 1976;25:1129–1153
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. 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
10. 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
11. The ORIGIN Trial Investigators, Gerstein HC, Bosch J, Dagenais GR, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med 2012;367:319–328
12. Dormandy JA, Charbonnel B, Eckland DJA, 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

13. 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
14. 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
15. 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
16. Reaven PD, Moritz TE, Schwenke DC, et al.; Veterans Affairs Diabetes Trial. Intensive glucose-lowering therapy reduces cardiovascular disease events in veterans affairs diabetes trial participants with lower calcified coronary atherosclerosis. Diabetes 2009;58:2642–2648
17. Malmberg K, Rydén L, Wedel H, et al.; DIGAMI 2 Investigators. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. Eur Heart J 2005;26:650–661
18. Raz I, Wilson PWF, Strojek K, et al. Effects of prandial versus fasting glycemia on cardiovascular outcomes in type 2 diabetes: the HEART2D trial. Diabetes Care 2009;32:381–386
19. 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
20. 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
21. Ray KK, Seshasai SRK, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet 2009;373:1765–1772
22. Tkáč I. Effect of intensive glycemic control on cardiovascular outcomes and all-cause mortality in type 2 diabetes: Overview and metanalysis of five trials. Diabetes Res Clin Pract 2009;86S:S57–S62
23. Kelly TN, Bazzano LA, Fonseca VA, Thethi TK, Reynolds K, He J. Systematic review: glucose control and cardiovascular disease in type 2 diabetes. Ann Intern Med 2009;151:394–403
24. Turnbull FM, Abraira C, Anderson RJ, et al.; Control Group. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia 2009;52:2288–2298
25. Bonds DE, Miller ME, Bergenstal RM, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ 2010;340:b4909
26. 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
27. Zoungas S, Patel A, Chalmers J, et al.; ADVANCE Collaborative Group. Severe hypoglycemia and risks of vascular events and death. N Engl J Med 2010;363:1410–1418
28. Frier BM, Schernthaner G, Heller SR. Hypoglycemia and cardiovascular risks. Diabetes Care 2011;34(Suppl. 2):S132–S137
29. Johnson JA, Majumdar SR, Simpson SH, Toth EL. Decreased mortality associated with the use of metformin compared with sulfonylurea monotherapy in type 2 diabetes. Diabetes Care 2002;25:2244–2248
30. Schramm TK, Gislason GH, Vaag A, et al. Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study. Eur Heart J 2011;32:1900–1908
31. Nathan DM, Buse JB, Davidson MB, et al.; American Diabetes Association; European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009;32:193–203
32. Rodbard HW, Trence DL, Mechanick JI. Should the recommendation of the American Association of Clinical Endocrinologists for a hemoglobin A1c target of 6.5% be modified? A critical reappraisal of recent studies of intensive glycemic control. Endocr Pract 2008;14:791–795
33. Rodbard HW, Jellinger PS, Davidson JA, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. Endocr Pract 2009;15:540–559
34. Ismail-Beigi F, Moghissi E, Tiktin M, Hirsch IB, Inzucchi SE, Genuth S. Individualizing glycemic targets in type 2 diabetes mellitus: implications of recent clinical trials. Ann Intern Med 2011;154:554–559
35. Ismail-Beigi F. Clinical practice. Glycemic management of type 2 diabetes mellitus. N Engl J Med 2012;366:1319–1327
36. Riddle MC, Karl DM. Individualizing targets and tactics for high-risk patients with type 2 diabetes: practical lessons from ACCORD and other cardiovascular trials. Diabetes Care 2012;35:2100–2107
37. 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