

## Intensive glucose control in patients with type 2 diabetes mellitus and incidence of cardiovascular events Has this issue been resolved?

K. Kaitanidis,<sup>1</sup> Chr. Boutari,<sup>1</sup> A. Lazaridis,<sup>1</sup>  
M. Doumas,<sup>1,2</sup> K. Tziomalos,<sup>3</sup> V.G. Athyros<sup>1</sup>

<sup>1</sup>2nd Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, “Hippocrates” Hospital, Thessaloniki, Greece,

<sup>2</sup>“Veteran Affairs” Medical Center and George Washington University, Washington, DC, USA,

<sup>3</sup>1st Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, “AHEPA” Hospital, Thessaloniki, Greece

## Εντατική ρύθμιση των επιπέδων γλυκόζης ασθενών με σακχαρώδη διαβήτη τύπου 2 και η επίπτωση των καρδιαγγειακών συμβαμάτων Έχει αυτό το ζήτημα επιλυθεί;

K. Καϊτανίδης,<sup>1</sup> Χρ. Μπουτάρη,<sup>1</sup> Α. Λαζαρίδης,<sup>1</sup>  
Μ. Δούμας,<sup>1,2</sup> Κ. Τζιόμαλος,<sup>3</sup> Β.Γ. Άθυρος<sup>1</sup>

<sup>1</sup>Β' Προπαιδευτική Πλαθολογική Κλινική, Ιατρική Σχολή, Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης, «Ιπποκράτειο» Νοσοκομείο, Θεσσαλονίκη,

<sup>2</sup>Ιατρικό Κέντρο “Veteran Affairs” και Πλανεπιστήμιο George Washington, Washington, DC, USA,

<sup>3</sup>Α' Προπαιδευτική Πλαθολογική Κλινική, Ιατρική Σχολή, Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης, Νοσοκομείο «ΑΧΕΠΑ», Θεσσαλονίκη

Diabetes is one of the major public health burdens worldwide: according to the International Diabetes Federation, more than 371 million people (8.3% of the earth's adult population) have diabetes; it was predicted that by 2030, the number of people with diabetes in the world will have risen to 552 million.<sup>1</sup> Patients with type 2 diabetes mellitus (T2DM) exhibit an increased risk of cardiovascular disease (CVD) events leading to an increased CVD morbidity and mortality compared to relevant population without T2DM; 70% of T2DM patients die because of CVDs.<sup>2</sup> Observational studies report a relationship between reduced blood glucose and reduced risk of both micro- and macrovascular complications in patients with T2DM.<sup>2</sup> In the

UK Prospective Diabetes Study (UKPDS), intensive glycemic control [median glycated haemoglobin (HbA<sub>1c</sub>), 7.0%], was found to reduce the overall microvascular complication rate of T2DM by 25% compared with conventional treatment (median HbA<sub>1c</sub>, 7.9%), while there was a 16% reduction ( $p=0.052$ ) in CVD events (macrovascular complications) in the intensive glycemic control arm in the original RCT period.<sup>3</sup> However, in a subgroup of overweight patients in UKPDS, treatment with metformin decreased the risk of myocardial infarction (MI) by 39% ( $p=0.01$ ) and the risk of death from any cause by 36% ( $p=0.01$ ) during a median follow-up of 10.7 years.<sup>4</sup> After an additional 10 years of follow-up for the UKPDS, the entire population originally assigned to

Vasilios G. Athyros, MD, FESC, FRSPH, FASA, FACS  
15 Marmara street, GR-551 32 Thessaloniki, Greece  
Tel: (+30) 2310-892 606, Fax: (+30) 2310-835 955  
e-mail: vathyros@gmail.com – athyros@med.auth.gr

Βασίλειος Γ. Άθυρος, MD, FESC, FRSPH, FASA, FACS  
Μαρμαρά 15, 551 32 Θεσσαλονίκη  
Τηλ: 2310-892 606, Fax: 2310-835 955  
e-mail: vathyros@gmail.com – athyros@med.auth.gr

intensive glycemic control had significant long-term reductions in incident MI (15%,  $p=0.01$ ) and death from any cause (13%,  $p=0.007$ ), despite the loss of glycaemic control differences with the group on conventional hypoglycaemic treatment.<sup>5</sup> Several other randomized controlled trials (RCTs), however, did not show a significant reduction in macrovascular complications in the intensive glycemic treatment arm among patients with T2DM.<sup>6–8</sup> In the Action in Diabetes and Vascular Disease: Pretezax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial,<sup>6</sup> a strategy of intensive glucose control that lowered the HbA<sub>1c</sub> value to 6.5% yielded a 10% relative reduction in the combined outcome of major macrovascular and microvascular events, primarily as a consequence of a 21% relative reduction in nephropathy;<sup>6</sup> however, there were no significant effects of the type of glucose control on major macrovascular events, death from CVD causes, or death from any cause.<sup>6</sup> The Veteran Administration Diabetes Trial (VADT) reported that intensive glucose control in patients with previously poorly controlled T2DM had no significant effect on the rates of major CVD events, death, or microvascular complications, with the exception of progression of albuminuria ( $p=0.01$ ).<sup>7</sup> Moreover, the results of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial suggested that as compared with standard therapy, the use of intensive therapy not only failed to reduce major CVD events significantly, but it appears that it increased CVD risk and all cause mortality.<sup>8</sup> These results led the American Diabetes Association (ADA), the American Heart Association (AHA), and the American College of Cardiology (ACC) to provide a conservative class IIb recommendation with level of evidence A for the benefit of glycaemic control on CVD, while microvascular complications of T2DM received a superior level recommendation of class I.<sup>9</sup>

A very recent post hoc analysis of the ACCORD trial evaluated the effect of intensive glycaemic control by kidney function status.<sup>10</sup> Renal function data were available on 10,136 patients of the original ACCORD cohort. Of those, 3,636 met the criteria for mild-to-moderate chronic kidney disease (CKD) and 6,506 were free of CKD at baseline.<sup>10</sup> Participants were randomly assigned to a treatment strategy of either intensive or standard glycemic goal. Risk for the primary outcome (all-cause and CVD mortality) was 87% higher in patients with CKD than in those without it (hazard ratio of 1.87; 95% confidence interval: 1.65–2.11). All prespecified secondary outcomes were 1.5 to 3 times more frequent in patients with CKD than in those without it.<sup>10</sup> The compari-

son of CKD patients with those without CKD showed that these were older, had higher body mass index, fasting glucose, HbA<sub>1c</sub>, and systolic blood pressure, as well as higher rates for history of CVD, congestive heart failure, and duration of T2DM.<sup>10</sup> Moreover, CKD patients used insulin at higher doses and most anti-hypertensive agents more frequently and oral hypoglycemic agents less frequently compared with patients without CKD.<sup>10</sup> In addition, patients with CKD had higher triglyceride and lower high-density lipoprotein levels compared with non-CKD patients.<sup>10</sup> Intensive glucose lowering was significantly associated with both 31% higher all-cause mortality (1.31:1.06–1.60) and 41% higher CVD (1.41:1.05–1.89) in patients with CKD, as compared with standard therapy.<sup>10</sup> No significant (positive or negative) effects of tight glycemic ( $HbA_1c \approx 6.5\%$ ) control were found in patients without CKD.<sup>10</sup> Thus, in high-risk patients with T2DM, mild (stage I and II) and moderate (stage III) CKD was associated with increased CVD risk for CVD events and total mortality; patients with stage IV and V of CKD were excluded from the ACCORD trial.<sup>10</sup> The author of this post hoc analysis state that the management of patients with T2DM and CKD is difficult and intensive glucose lowering seems to be hazardous.<sup>10</sup> This calls for new approaches for altering the CVD outcome of this patient population.<sup>10</sup> Given the above it is of vital importance to establish CKD status in all newly diagnosed and existing patients with T2DM and this should be taken into account when designing their hypoglycemic treatment.<sup>10</sup>

Another recent analysis has shown that intensive glucose control is associated with increased rates of severe hypoglycaemia but not increased rates of CV or all-cause mortality.<sup>11</sup> Aiming for HbA<sub>1c</sub> levels of <7.0% still remains the general target for effective glucose control. Under certain circumstances, aiming for lower HbA<sub>1c</sub> levels may be appropriate.<sup>11</sup> This applies in the setting of newly diagnosed T2DM in relatively young individuals without significant co-morbidities and in patients treated with agents that minimize the risk of severe hypoglycaemia such as metformin.<sup>11</sup> Whether this also applies to newer glucose-lowering agents that target the incretin system or the SGLT-2 inhibitors will depend on CVD outcomes of long-term studies which are in progress.<sup>11</sup> It has been shown, for example, that adding dapagliflozin, a sodium-glucose co-transporter 2 (SGLT-2) inhibitor, to currently available treatment options is projective for further decrease the CVD and microvascular complications associated with T2DM.<sup>11</sup> In any case, the improvement of CVD

outcomes in patients with T2DM will probably come from other than hypoglycaemic effects of newer drugs for the treatment of diabetes [dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, and SGLT-2 inhibitors].<sup>12–14</sup> For example, SGLT-2 inhibitors exhibit a favorable impact on glucose metabolism in patients with T2DM and emerge as a hopeful hypoglycemic treatment.<sup>15</sup> The resultant negative energy balance caused by glucosuria results in long-term weight loss, significantly reduced HbA<sub>1c</sub> levels (by 0.5–1.0%) with a low risk for hypoglycaemia, and may in addition exert beneficial effects on blood pressure, reactive oxygen products and inflammatory mediators, even in patients with T2DM and CKD.<sup>15</sup> Clinical and experimental studies with all these newer hypoglycaemic agents (DPP-4 inhibitors, GLP-1 agonists, and SGLT-2 inhibitors) have also shown favorable effects on CVD risk factors such as dyslipidaemia, arterial hypertension, and improvements in endothelial function and cardiac contractility.<sup>16</sup>

All the above suggest that we should aim for a glycemic control with an HbA<sub>1c</sub> just below 7%. We should be more careful in patients with both T2DM and CKD and aim for a higher HbA<sub>1c</sub> to avoid the excess CVD and all cause morbidity and mortality. Further reduction in CVD event rate could be achieved in patients with T2DM, with or without CKD, with the use of other secondary prevention means. The use of statins, especially atorvastatin,<sup>16</sup> not only halts the progression to CKD in T2DM (diabetic nephropathy) but might even reverse it, substantially reducing the CVD morbidity and mortality, with an independent action on top of its hypolipidaemic effect; after adjustment for 25 predictors of all CVD related events, multivariate analysis revealed a hazards ratio of 0.84 (confidence interval 0.73–0.95; p=0.003) with every 5% increase in glomerular filtration rate (GFR).<sup>17</sup> In the Collaborative Atorvastatin in Diabetes Study (CARDS), atorvastatin (10 mg/dL) treatment was associated with increased GFR in comparison with placebo, and a modest beneficial effect was observed, particularly in patients with albuminuria.<sup>18</sup> Moreover, atorvastatin was effective at decreasing CVD by 42% in patients with a moderately decreased e-GFR (30–60 mL/min per 1.73 m<sup>2</sup>), and this treatment effect was higher of the 37% reduction in CVD observed in the entire CARDS population, mostly with normal e-GFR.<sup>18</sup> Furthermore, a meta-analysis showed that statin therapy was associated with decreased albuminuria compared to a placebo.<sup>19</sup>

The cautious administration of fibrates, in combination with statins, in patients with T2DM and mixed hyperlipidaemia might be also beneficial. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study demonstrated that fenofibrate (200 mg/dL) reduced CVD events, reduced albuminuria, and slowed e-GFR loss over 5 years; although it initially and reversibly increased plasma creatinine levels.<sup>20</sup> In a meta-analysis, fibrates reduced the risk of albuminuria progression in patients with diabetes and also reduced the risk of major CVD events and CVD death in patients with an e-GFR of 30–60 mL/min per 1.73 m<sup>2</sup>.<sup>21</sup>

In the very recent Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial among 5,380 patients with T2DM who had had a recent acute coronary syndrome, the rates of major adverse CVD events and heart failure hospitalizations were not increased with the DPP-4 inhibitor alogliptin as compared with placebo.<sup>22,23</sup>

In conclusion, the treatment target for HbA<sub>1c</sub> in older patients with T2DM should be around 7% and in younger around 6.6%. This is in agreement with recently published studies that included a verity of T2DM patients with comorbidities.<sup>22–26</sup> Going lower does not offer substantial improvement of CVD outcomes; on the contrary this might be hazardous in patients with CKD. Further reduction of the excess CVD risk related to diabetes should be attempted with other secondary CVD preventive measures such as renin-angiotensin axis inhibition, statins, and in specific cases fibrates. If the newer antidiabetic agents will contribute to a further reduction in CVD morbidity and mortality with their “pleiotropic” effects should be shown in well designed prospective RCT with hard endpoints; some of them are on the way already.

#### *Declaration of interest*

There is no conflict of interest for all authors.

#### References

1. International Diabetes Federation. *IDF Diabetes Atlas*. 5th ed. International Diabetes Federation, 2011. Available at: <http://www.idf.org/diabetesatlas>
2. Hemmingsen B, Lund SS, Gluud C et al. Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. Cochrane Database Syst Rev 2011, 6:CD008143
3. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications

- in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998, 352:837–853
4. 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): UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998, 352:854–865
  5. Holman RR, Paul SK, Bethel MA et al. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008, 359:1577–1589
  6. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008, 358:2560–2572
  7. 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
  8. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008, 358:2545–2559
  9. Skyler JS, Bergenfelz R, Bonow RO et al. 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. *Circulation* 2009, 119:351–357
  10. Papademetriou V, Lovato L, Doumas M et al. Chronic kidney disease and intensive glycemic control increase cardiovascular risk in patients with type 2 diabetes. *Kidney Int* 2014, Sep 17. doi: 10.1038/ki.2014.296 (Epub ahead of print)
  11. Macisaac RJ, Jerums G. Intensive glucose control and cardiovascular outcomes in type 2 diabetes. *Heart Lung Circ* 2011, 20:647–654
  12. Mogensen UM, Andersson C, Fosbøl EL et al. Cardiovascular safety of combination therapies with incretin-based drugs and metformin compared with a combination of metformin and sulphonylurea in type 2 diabetes mellitus—a retrospective nationwide study. *Diabetes Obes Metab* 2014, 16:1001–1008
  13. DeNicola M, Du J, Wang Z et al. Stimulation of glucagon-like peptide-1 receptor through exendin-4 preserves myocardial performance and prevents cardiac remodeling in infarcted myocardium. *Am J Physiol Endocrinol Metab* 2014, 307:E630–E643
  14. Dziuba J, Alperin P, Racka J et al. Modeling effects of SGLT-2 inhibitor dapagliflozin treatment versus standard diabetes therapy on cardiovascular and microvascular outcomes. *Diabetes Obes Metab* 2014, 16:628–635
  15. Vlotides G, Mertens PR. Sodium-glucose co-transport inhibitors: mechanisms, metabolic effects and implications for the treatment of diabetic patients with chronic kidney disease. *Nephrol Dial Transplant* 2014, Sep 17. pii: gfu299 (Epub ahead of print)
  16. Jayawardene D, Ward GM, O'Neal DN et al. New Treatments for Type 2 Diabetes: Cardiovascular Protection Beyond Glucose Lowering? *Heart Lung Circ* 2014, Jun 10. pii: S1443–9506(14)00503-4. doi: 10.1016/j.hlc.2014.05.007 (Epub ahead of print)
  17. Athyros VG, Mikhailidis DP, Papageorgiou AA et al. The effect of statins versus untreated dyslipidaemia on renal function in patients with coronary heart disease. A subgroup analysis of the Greek atorvastatin and coronary heart disease evaluation (GREACE) study. *J Clin Pathol* 2004, 57:728–734
  18. Colhoun HM, Betteridge DJ, Durrington PN et al. Effects of atorvastatin on kidney outcomes and cardiovascular disease in patients with diabetes: an analysis from the Collaborative Atorvastatin Diabetes Study (CARDS). *Am J Kidney Dis* 2009, 54:810–819
  19. Sandhu S, Wiebe N, Fried LF et al. Statins for improving renal outcomes: a meta-analysis. *J Am Soc Nephrol* 2006, 17:2006–2016
  20. ACCORD Study Group, Ginsberg HN, Elam MB, Lovato LC et al. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 2010, 362:1563–1574
  21. Jun M, Zhu B, Tonelli M et al. Effects of fibrates in kidney disease: a systematic review and meta-analysis. *J Am Coll Cardiol* 2012, 60:2061–2071
  22. Zannad F, Cannon CP, Cushman WC et al for the EXAMINE Investigators. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. *Lancet* 2015, 385: 2067–2076
  23. White WB, Cannon CP, Heller SR et al; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 2013, 369:1327–1335
  24. White WB, Cannon CP, Heller SR et al; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 2013, 369:1327–1335
  25. Gerstein HC, Miller ME, Ismail-Beigi F et al. Effects of intensive glycemic control on ischemic heart disease: analysis of data from the randomized, controlled ACCORD trial. *Lancet* 2014, 384:1936–1941
  26. Green JB, Angelyn Bethel M, Armstrong PW et al, for the TECOS Study Group. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2015, June 8, doi: 10.1056/NEJMoa1501352 (Epub ahead of print)

Ημερομηνία Υποβολής 17/04/2015  
Ημερομηνία Αποδοχής 08/06/2015