

Cardiovascular disease prevention in diabetes: uncertainties and ethics



Jonathan E Shaw^{*1} & Daniel Fineberg¹

Practice points

- Glucose-lowering therapy shows definite benefits for prevention of microvascular disease, but no clear reduction in cardiovascular disease.
- Blood pressure lowering shows benefits for microvascular and cardiovascular disease, but how aggressively blood pressure should be lowered remains uncertain.
- Statin therapy has strong evidence for prevention of cardiovascular disease, irrespective of cholesterol levels. However, the evidence for the additional value of fibrates is only suggestive, and then only in those with dyslipidemia,
- An ethical approach to diabetes management requires a focus on the individual patient, a recognition that evidence-based guidelines should be instituted in most patients, and a capacity to integrate different levels and strengths of evidence.

SUMMARY: In the last 20 years, there have been a large number of large clinical trials that have informed and improved clinical practice in regard to cardiovascular disease prevention in diabetes. Despite this, there remain a number of areas of uncertainty, some of which are regularly encountered in daily practice. The value of glucose lowering in the prevention of cardiovascular disease is unproven, and the potential for newer glucose-lowering agents to address this gap is uncertain. Although the overall value of blood pressure lowering is well established, the appropriate blood pressure targets remain controversial. Ethical issues arise from this uncertainty, and relate to the means of translating evidence for the average patient into action for an individual, and how to synthesize conflicting evidence.

Cardiovascular risk management is an important component of diabetes management, as cardiovascular disease (CVD) is over twice as common in people with than without diabetes [1]. However, the extent to which the clinician should recommend particular interventions is fraught with a number of challenges. Much has been learnt in recent years about the value of blood pressure lowering and the important role of statins. Nevertheless, many areas

of uncertainty remain in preventing CVD in people with diabetes. These include the potential value of glucose lowering in preventing CVD, appropriate blood pressure targets and the use of non-statin lipid-modifying drugs (Table 1). Due to the significant uncertainties in therapeutic targets, a kind of clinical inertia may ensue. Understanding how to manage these uncertainties in the literature and avoid clinical inertia can lead to ethical challenges in

KEYWORDS

- blood pressure
- cardiovascular disease
- diabetes • ethics
- glycemic control • statin

¹Baker IDI Heart & Diabetes Institute, Melbourne, Australia

^{*}Author for correspondence: jonathan.shaw@bakeridi.edu.au

Table 1. Summary of major areas of more and less certainty in relation to aggressive therapy in diabetes.

Intervention	Relative certainty [†]	Significant uncertainty [‡]
Glucose lowering	Reduction in microvascular disease	Reduction in cardiovascular disease
BP lowering	Benefits for achieving BP >140/90 mmHg	Benefits for achieving BP >130/80 mmHg
Lipid modification	Benefits of statins	Benefits of fibrates
Aspirin	Secondary prevention	Primary prevention

[†]Multiple clinical trials show consistent evidence of benefit.
[‡]Clinical trial findings are inconsistent, or negative, but observational data may suggest a likely benefit.
BP: Blood pressure.

identifying the right intervention for individual patients. To attempt to address this challenge, guidelines have recommended a 'patient centered approach' to diabetes management taking into account not just the nuances of a patient's metabolic issues, but also their preferences and values, in order to ensure that these guide clinical decision-making [2]. This article will describe some of the main areas of uncertainty in the prevention of CVD in people with diabetes, discuss the challenge of clinical inertia and will explore the ethical issues produced by the uncertainty.

Uncertainty in tighter glucose control

Chronic hyperglycemia is associated with an increased risk for cardiovascular outcomes and all-cause mortality, which is independent of other conventional risk factors [3–5].

The UKPDS (United Kingdom Prospective Diabetes Study) demonstrated a clinical benefit for tight glycemic control in Type 2 diabetes (T2D). At the end of the main trial, there was a cardiovascular benefit for tight glycemic control using metformin, and at the end of the 10-year post-trial follow-up, there was also a significant cardiovascular benefit for tight glycemic control achieved with sulphonylureas and insulin [6].

This was consistent with results of the DCCT-EDIC study, a follow-up study involving a cohort of 1441 patients with Type 1 diabetes (T1D) who were randomized to either intensive or conventional glucose lowering [7]. At the end of the randomized phase, the mean HbA_{1c} level was 7.4% in the intensive-therapy group and 9.1% in the conventional therapy group. Patients in the intensive therapy group had a nonsignificant reduction in the risk of macrovascular disease of 41% (95% CI: -10–68%) [8]. However, after a decade of further follow-up, the cardiovascular benefit for the intensive therapy group had become highly significant (risk reduction: 42%; 95% CI: 9–63%; $p = 0.02$).

Although the UKPDS and DCCT follow-up studies had generated considerable enthusiasm for recommending tighter glycemic control to patients, other more recent large clinical trials in T2D including the VADT, ACCORD and ADVANCE have further refined targets and tempered enthusiasm for improved average glycemia at all costs.

The ADVANCE trial included 11,140 patients with T2D. The intensive control group had a mean HbA_{1c} 0.8% lower than that in the control group, but showed a nonsignificant reduction in major macrovascular events of only 6% (95% CI: -6–16) after a median of 5 years of follow-up [9].

The ACCORD trial had 10,251 patients with T2DM [10]. The intensive group was targeted to an HbA_{1c} of less than 6% versus 7.0–7.9% in the standard group. There was a nonsignificant reduction of 10% in the composite primary outcome of nonfatal myocardial infarction, nonfatal stroke and death from cardiovascular causes. However, the trial was stopped after 3.5 years because of an unexplained 22% excess rate of death from any cause ($p = 0.04$) in the intensively treated group. Hypoglycemia requiring assistance from another person and weight gain were also more frequent in the intensive-therapy group.

In addition, a recent Cochrane review of 28 trials with 34,912 T2D participants who were randomized to intensive or conventional glycemic control demonstrated no statistically significant differences between targeting intensive versus conventional glycemic control for all-cause mortality (relative risk [RR]: 1.0; 95% CI: 0.92–1.08) or cardiovascular mortality (RR: 1.06; 95% CI: 0.94–1.21), although a benefit was shown for non-fatal MI (RR: 0.87; 95% CI: 0.77–0.98; $p = 0.02$) [11].

Compared with the DCCT and UKPDS, which involved young people with T1D and people newly diagnosed with T2D, respectively, the ADVANCE and ACCORD trials involved patients at much higher cardiovascular risk. They

were around 8–10 years older than UKPDS participants, and had had diabetes for around 8–10 years at study entry. Approximately one third of patients in ADVANCE and ACCORD had a history of macrovascular disease compared with 7.5% in the UKPDS. It is therefore possible that it is much harder to achieve CVD benefits from glucose lowering in older people with longstanding disease. It is also possible that the relatively short durations of the ACCORD and ADVANCE studies limited the capacity to show a CVD benefit, which might take 10 years or more to emerge. Current guidelines now recommend that due consideration should be given to the time since diagnosis of diabetes, and the presence of comorbidities, in determining HbA_{1c} targets for an individual [2]. It should, nevertheless be noted that there is clear benefit for reduction in microvascular morbidity with glucose lowering. However, even here the life expectancy of the patient is relevant in determining if they are likely to live long enough to reap the microvascular rewards of tight glycaemic control.

Finally, it should be recognized that although HbA_{1c} is associated with cardiovascular morbidity and mortality, it is an imperfect marker of glucose homeostasis and has limited prognostic value for the prediction of cardiovascular morbidity and mortality, which is associated with different disease phenotypes, including cardiac hypertrophy, congestive heart failure, stroke and cardiovascular death [1].

Uncertainty in choice of glucose-lowering therapy

Lifestyle modification, which has been the mainstay of first-line clinical care in most guidelines for diabetes management, has been hit with uncertainty. The LookAHEAD study assessed the effects of an intensive lifestyle intervention in a randomized controlled trial of over 5000 overweight or obese patients with Type 2 diabetes [12]. Despite achieving weight loss of 8.6% after the first year in the intervention group (compared with 0.7% weight loss in the control group) with associated improvements in waist circumference, systolic blood pressure and HbA_{1c} levels, there was no benefit in regard to cardiovascular event rates over the median follow-up of 9.6 years, a finding that was similar in each of the reported subgroups. Part of the explanation for lack of effect may have been the attenuation in weight difference over time, and the slightly lower levels of cardiovascular drugs

used in the intensive lifestyle group than were used in the control group.

Following lifestyle modification, the first line therapeutic agent for glucose lowering is generally metformin. In many cases, however, this is insufficient for glycaemic lowering as a single agent. In addition, there are many patients who cannot tolerate the medication due to gastrointestinal side effects or for whom moderate–severe chronic kidney disease is a contraindication to its use. Until recently the second-line therapy had been the sulphonylureas, which are generally low cost but in which glycaemic control may be associated with the undesirable effects of weight gain and hypoglycaemia. Indeed, there exists uncertainty regarding the durability and long-term CV safety of this class. Potential adverse cardiovascular effects may be related to the fact that SUs not only bind to β -cells, but also bind to cardiac myocytes and to endothelial cells, and thus have direct effects on CV function [13]. There are only a small number of trials designed specifically to examine cardiovascular safety with sulphonylureas. A recent meta-analysis of all studies comparing sulphonylureas to other agents showed no overall difference in major CVD events but a 22% increase in total mortality of borderline statistical significance ($p = 0.047$) [14]. The CAROLINA trial, which has been recruiting since 2010, will provide a head-to-head cardiovascular outcome of the sulphonylurea glimepiride versus the DPP-4 inhibitor linagliptin [15].

The thiazolidinediones showed initial promise as relatively potent oral hypoglycaemic agents. An initial trial with pioglitazone, published as the PROactive Study in 2005, showed a reduction of 10% versus placebo in its primary end point, a complex composite cardiovascular end point that did not, however, reach statistical significance [16]. Rosiglitazone, also a thiazolidinedione, however, began to invoke concern following a limited meta-analysis of small studies with an associated odds ratio for myocardial infarction of 1.43 (95% CI: 1.03–1.98; $p = 0.03$), and the odds ratio for death from cardiovascular causes of 1.64 (95% CI: 0.98–2.74; $p = 0.06$) [17].

Prompted by this meta-analysis, an interim report of the RECORD study comparing rosiglitazone with metformin and with a sulphonylurea, as add-on therapy, was published [18]. The hazard ratio (HR) for a composite of all primary cardiovascular outcomes was 1.11 (95% CI: 0.93–1.32). There were no statistically significant differences between the rosiglitazone group and the control

group regarding myocardial infarction and death from cardiovascular causes or from any cause. There were, however, more patients with heart failure in the rosiglitazone group than in the control group (HR: 2.15; 95% CI: 1.30–3.57). The full publication with 5.5 years of follow-up in 2009 confirmed the lack of difference in the composite cardiovascular outcome, as well as the adverse effects on heart failure. The uncertainty over rosiglitazone in relation to both the harm signaled in the meta-analysis, as well as to challenges regarding the reliability of the RECORD results, led the US FDA to institute a black box warning and the European regulatory body to suspend its use [19]. However, in late 2013, after further analyses of the data, the FDA removed its restrictions and warnings. This changing advice on the use of rosiglitazone can only further add to the difficulties of decision-making for doctors and patients.

Two large cardiovascular outcome trials comparing DPP-4 inhibitors to placebo have recently been published. DPP-4 inhibition with saxagliptin did not increase or decrease the rate of heart attack or stroke in the SAVOR TIMI 53 trial [20]. The trial involved 16,492 patients with T2D who were at high risk for, or had a history of cardiovascular events, and ran for just over 2 years. Although there was no difference in relation to the primary outcome, there was a somewhat surprising finding in relation to heart failure. More patients in the saxagliptin group (3.5%) than in the placebo group (2.8%) were hospitalized for heart failure (HR: 1.27; 95% CI: 1.07–1.51; $p = 0.007$). A similar study of another DPP-4 inhibitor, alogliptin, showed no significant increase or decrease in major adverse cardiovascular events, although there was a nonsignificant trend towards an increase in heart failure in the alogliptin arm [21]. The relevance of the heart failure finding is, as yet, unclear. It was one of many end points, raising the possibility that this happened by chance. Supporting this concept is the fact that most laboratory and short-term clinical studies have suggested that this class of drug ought to improve cardiac function. Results from further studies will be required to clarify this issue. Although the heart failure issue remains to be further assessed, these trials indicate the overall cardiovascular safety of the two DPP-4 inhibitors.

Uncertainty regarding blood pressure targets

The ACCORD BP randomized 4733 patients with T2D to a target systolic blood pressure of less

than 120 mmHg or less than 140 mmHg. After a mean of 4.7 years, mean blood pressures were 119/64 mmHg and 134/71 mmHg in the intensive and moderate treatment groups, respectively. There was no significant difference between the two groups in the primary composite outcome of MI, stroke and death. There was, however, an approximate 40% statistically significant reduction in the risk of stroke (2.6 vs 1.5%). Serious adverse events attributed to antihypertensive treatment occurred in 3.3% of participants in the intensive therapy group and 1.3% of participants in the standard therapy group [22,23].

Concern regarding overzealous blood pressure lowering was also suggested in a *post hoc* observational subgroup analysis of 6400 of the 22,576 participants in the INVEST study [24]. This analysis showed that achieving a systolic blood pressure of lower than 130 mmHg in patients with diabetes and coronary heart disease was associated with a 15–20% increase in risk of all-cause mortality compared with patients with systolic blood pressure lower than 140 mmHg. Caution, however, is required in interpreting this finding. It may be that older and frailer participants whose mortality risk is already high are more likely to show larger reductions in blood pressure, and hence increase the mortality of the groups achieving the lower blood pressures.

Uncertainty regarding lipid-modifying interventions

The use of statin medications to target LDL is possibly the least controversial area of diabetes management. A meta-analysis of 18,686 subjects demonstrated a 9% proportional reduction in all-cause mortality per mmol/l reduction in LDL-cholesterol in participants with diabetes [25]. This confirms the central role of statins in the prevention of CVD for all those in whom absolute risk of a CVD event exceeds 10% over 5 years. This approach works well for the majority of patients with diabetes. However, absolute risk is very dependent on age, and uncertainty remains over how to determine if any of the younger diabetic patients require statin therapy. Consideration of lifetime CVD risk and of treatment based on single risk factors have been suggested for this group, but as yet no widely accepted approach has been developed.

Other lipid-lowering agents have been less impressive. The FIELD study, a placebo-controlled trial of fenofibrate in 9795 participants

aged 50–75 with T2DM, showed mixed cardiovascular results [26]. The primary outcome, defined as coronary heart disease (CHD), death or nonfatal myocardial infarction (MI), was not significantly different (5.9% control vs 5.2% fenofibrate; $p = 0.16$). There was, however, a significant 24% reduction in nonfatal MI ($p = 0.010$) and a nonsignificant increase in CHD mortality ($p = 0.22$). Total CVD events were significantly reduced from 13.9 to 12.5% ($p = 0.035$) and there was a 21% reduction in coronary revascularization ($p = 0.003$). Total mortality was not different – 6.6% in the placebo group and 7.3% in the fenofibrate group ($p = 0.18$).

ACCORD-Lipid also did not suggest much in the way of benefit with combination statin-fibrate therapy [27]. In total, 5518 participants with T2DM and high CVD risk were all treated with simvastatin and randomized to fenofibrate or placebo. After a mean 4.7 years of follow-up, the annual rate of the primary outcome (first occurrence of nonfatal MI, nonfatal stroke or CV death) was not significantly different between the two study arms ($p = 0.32$), and no significant differences between the two study groups with respect to secondary outcomes were noted. Further subgroup analysis suggested a benefit for men and those with more significant dyslipidemia (low HDL, high triglycerides). This finding in the dyslipidemic subgroup was also present in the FIELD trial, suggesting that fenofibrate should be considered in such patients.

Uncertainty regarding aspirin

There is no doubt about the well-established benefit of aspirin in secondary prevention. However, data supporting aspirin use in primary prevention, especially in diabetes, is unclear. Any benefits of reductions in thrombo-embolic disease in primary prevention seem to be offset by increases in hemorrhagic events, leading to lack of benefit for mortality [28]. Current guidelines suggest use in primary prevention if the 10-year cardiovascular risk is greater than 10% [2]. Furthermore, uncertainties concerning the appropriate dose of aspirin and the possibility of increased aspirin resistance in diabetes add yet more confusion to the dilemma. Unsurprisingly, there is the suggestion of significant clinical practice heterogeneity in the use of aspirin in patients with diabetes.

Consequences of clinical uncertainty: clinical inertia – problem or safeguard

Uncertainties regarding the value of therapies

may contribute to ‘clinical inertia’ [29], in which decisions to change therapy according to guidelines are significantly delayed. With the lack of clarity in the literature, guidelines are difficult to produce, and with increasing complexity are difficult for clinicians to follow. Clinicians may therefore resort to using heuristic strategies (pragmatic decisional shortcuts) instead of algorithmic strategies (process based on logical sequences) to overcome this [30]. These strategies, however, may not be evidence based and may vary considerably between clinicians.

The consequences of clinical inertia may be a breakdown in the doctor–patient relationship, lack of adherence to therapies and worsening of the underlying clinical problems. Clinical inertia can delay diagnosis and/or treatment, and put the health of the patient at risk, particularly in the fields of diabetes and cardiovascular disease [31].

Factors contributing to clinical inertia are described by Phillips *et al.* [32]. First, clinicians ‘overestimate the care’ that they provide. For example, lack of review of blood pressure or lipid profile when not the primary focus of the consultation. Second, the clinician may ‘look for excuses’ to avoid intensification of treatment. An example of this may be the patient having been on a holiday in the case of dietary laxity, or poor weather in the case of lack of physical activity. Third, failure to escalate therapy may occur if there is ‘considerable complexity’ to achieve this in which training has not been optimal [33]. An example of this may be the patient on an insulin pump where lack of technological expertise may limit the clinician’s ability to appropriately manage dysglycemia. Avignon *et al.* provides ‘doubt’ as a fourth reason, where clinicians no longer believe in their diabetic therapies, in the studies, guidelines or even concepts such as glycemic control [34].

It is however, important that the doctor–patient interaction is not automatically labeled as clinical inertia just because of a lack of escalation of pharmacologic therapy. The best response to failure of a patient to reach a treatment target may be to identify nonpharmacologic issues that may be causing the problem. In this situation there can be a mistaken perception of inertia (‘false inertia’ or ‘pseudo-inertia’). Furthermore, it should be noted that in instances where guidelines have gone beyond available evidence or are subsequently invalidated by later evidence, clinical inertia may act as a safeguard to protect patients from exposure to unnecessary or harmful interventions [35].

Ethical implications

The ethical principle of 'beneficence' requires clinicians to improve patient well-being by maximizing clinical benefits and minimizing clinical harms. The principle of 'non-maleficence' requires clinicians not to cause or introduce intentional harms for which there is no expectation of resulting greater benefits and to respect patient concerns [36].

These principles can be easy to achieve when the benefits and risks for interventions are clear, but can be challenging in the setting of uncertainty. The lack of clear clinical trial evidence of cardiovascular benefits of glucose lowering might seem to lead to the straightforward clinical decision not to pursue glucose lowering in this setting. However, extensive data from observational studies show that higher blood glucose is associated with a greater risk of cardiovascular disease [5]. Furthermore, there are benefits of glucose lowering for microvascular disease [37]. In addition to these uncertainties regarding the published data, clinicians are also exposed to marketing from pharmaceutical companies, as well as to pressure from peer groups and their employing institutions to achieve certain targets in patient management. Furthermore, government and other payers require costs to be considered, although they are often more interested in interventions that are lower cost than in interventions that are better value for money.

How can a busy clinician consider all of these issues in deciding what to do next for a 65-year-old patient with 10 years of Type 2 diabetes, and an HbA_{1c} of 7.5%? Unfortunately, there is no simple answer. Guidelines are helpful. They give advice applicable to most patients, but not to every individual. However, considering almost every patient to be a case lying outside the guidelines is likely to be at least as harmful as slavishly following the published advice for all. Extrapolating beyond the trial data is usually perceived as being inappropriate, but this may not always be the case. 3–5-year clinical trial data show no CVD benefit for the patient above in regard to lowering HbA_{1c}, but other data suggest that this may simply be because it takes longer than 5 years to demonstrate benefit. Deciding not to treat the patient above may therefore not be an evidence-based decision.

Negotiating the decision path with the patient is difficult, especially when consultation time is short and patient education may be limited. Consideration of actual and potential benefits

that are clinically meaningful to each individual patient is essential. Patients with limited life expectancies are not going to benefit from interventions that take 10 years to show improved outcomes [37], while for younger, healthier patients this may be the most relevant time frame, even though clinical trials of this length are few and far between. The potential for side effects is also an important consideration. People with life-threatening cancer readily agree to have chemotherapy, despite the severity of side-effects, because the benefits are so clear. However, where the benefits are less clear, much more caution is needed for drugs with important side-effects. On the other hand, a good side-effect profile might make a drug more attractive for the case described above. Even if we are not entirely certain of benefit, we might judge the risk of harm to be low, and therefore feel more confident in relying on observational, rather than clinical trial data, on which to base an expectation of benefit.

To overcome uncertainty regarding this, there is a necessity for randomized clinical trials to determine which recommendation is superior. Barriers to appropriate clinical trials include significant cost, uncertainty about whether comparator arms should be placebo, usual care or a single active comparator, and the length of time required to identify relevant clinical outcomes, especially in regard to cardiovascular end points [38]. Without adequately powered clinical trials, practitioners otherwise have an ethical obligation to inform patients of this uncertainty as part of the consent process when initiating and continuing therapy.

A patient-centered approach involves the ethical principle of 'respect for persons', which requires clinicians to respect patient autonomy and to guide care in accordance with patient values, beliefs and preferences. Problems with an overly patient-centric approach include inconsistencies with prescribing guidelines, lack of physician control and a sense of futility in the therapeutic relationship on the side of the clinician. There is arguably also a lack of clinical trial evidence on the patient-centered approach to management.

Conclusion & future perspective

Although cardiovascular data from diabetes-related clinical trials have not always provided clarity for the clinician, newer medications may allow for greater adherence to clinical targets.

The actual targets, however, have shifted since many of these agents have become available and there is greater awareness and emphasis on avoidance of harm, especially with cardiovascular outcomes. Although clinical inertia may be perceived as a limitation in the clinical context, it may also provide a safeguard where uncertainty exists. Ethical principles that consider the patients' values and provide the greatest good with minimization of harm should guide clinical decision-making.

Financial & competing interests disclosure

JE Shaw has received funding for consultancies, honoraria and research from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen-Cilag, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Sanofi-Aventis and Takeda. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

- Selvin E, Steffes MW, Zhu H *et al.* Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *N. Engl. J. Med.* 362(9), 800–811 (2010).
- Standards of medical care in diabetes – 2014. *Diabetes Care* 37(Suppl. 1), S14–S80 (2014).
- Zhang Y, Hu G, Yuan Z, Chen L. Glycosylated hemoglobin in relationship to cardiovascular outcomes and death in patients with Type 2 diabetes: a systematic review and meta-analysis. *PLoS ONE* 7(8), e42551 (2012).
- Barr EL, Zimmet PZ, Welborn TA *et al.* Risk of cardiovascular and all-cause mortality in individuals with diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance: the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). *Circulation* 116(2), 151–157 (2007).
- Selvin E, Marinopoulos S, Berkenblit G *et al.* Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann. Intern. Med.* 141(6), 421–431 (2004).
- 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.* 359(15), 1577–1589 (2008).
- 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.* 329(14), 977–986 (1993).
- Nathan DM, Cleary PA, Backlund JY *et al.* Intensive diabetes treatment and cardiovascular disease in patients with Type 1 diabetes. *N. Engl. J. Med.* 353(25), 2643–2653 (2005).
- 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.* 358(24), 2560–2572 (2008).
- Gerstein HC, Miller ME, Byington RP *et al.* Effects of intensive glucose lowering in Type 2 diabetes. *N. Engl. J. Med.* 358(24), 2545–2559 (2008).
- 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.* 11, CD008143 (2013).
- Wing RR, Bolin P, Brancati FL *et al.* Cardiovascular effects of intensive lifestyle intervention in Type 2 diabetes. *N. Engl. J. Med.* 369(2), 145–154 (2013).
- Ye Y, Perez-Polo JR, Aguilar D, Birnbaum Y. The potential effects of anti-diabetic medications on myocardial ischemia-reperfusion injury. *Basic Res. Cardiol.* 106(6), 925–952 (2011).
- Monami M, Genovese S, Mannucci E. Cardiovascular safety of sulfonylureas: a meta-analysis of randomized clinical trials. *Diabetes Obes. Metab.* 15(10), 938–953 (2013).
- Rosenstock J, Marx N, Kahn SE *et al.* Cardiovascular outcome trials in Type 2 diabetes and the sulphonylurea controversy: rationale for the active-comparator CAROLINA trial. *Diab. Vasc. Dis. Res.* 10(4), 289–301 (2013).
- Dormandy JA, Charbonnel B, Eckland DJ *et al.* 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* 366(9493), 1279–1289 (2005).
- Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N. Engl. J. Med.* 356(24), 2457–2471 (2007).
- Home PD, Pocock SJ, Beck-Nielsen H *et al.* Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet* 373(9681), 2125–2135 (2009).
- Blind E, Dunder K, De Graeff PA, Abadie E. Rosiglitazone: a European regulatory perspective. *Diabetologia* 54(2), 213–218 (2011).
- Scirica BM, Bhatt DL, Braunwald E *et al.* Saxagliptin and cardiovascular outcomes in patients with Type 2 diabetes mellitus. *N. Engl. J. Med.* 369(14), 1317–1326 (2013).
- White WB, Cannon CP, Heller SR *et al.* Alogliptin after acute coronary syndrome in patients with Type 2 diabetes. *N. Engl. J. Med.* 369(14), 1327–1335 (2013).
- Cushman WC, Evans GW, Byington RP *et al.* Effects of intensive blood-pressure control in Type 2 diabetes mellitus. *N. Engl. J. Med.* 362(17), 1575–1585 (2010).
- Allen M, Kelly K, Fleming K. Uncertainty about the systolic blood pressure target in people with diabetes. *Can. Fam. Physician* 59(2), 128–131 (2013).
- Pepine CJ, Handberg EM, Cooper-Dehoff RM *et al.* A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. *JAMA* 290(21), 2805–2816 (2003).
- Kearney PM, Blackwell L, Collins R *et al.* Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet* 371(9607), 117–125 (2008).
- Keech A, Simes RJ, Barter P *et al.* Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with Type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 366(9500), 1849–1861 (2005).
- Ginsberg HN, Elam MB, Lovato LC *et al.* Effects of combination lipid therapy in Type 2 diabetes mellitus. *N. Engl. J. Med.* 362(17), 1563–1574 (2010).

- 28 Baigent C, Blackwell L, Collins R *et al.* Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 373(9678), 1849–1860 (2009).
- 29 Halimi S, Balkau B. Better analyze the determinants of therapeutic inertia to overcome it. *Diabetes Metab.* 38(Suppl. 3), S27–S28 (2012).
- 30 Esposito K, Ceriello A, Giugliano D. Does personalized diabetology overcome clinical uncertainty and therapeutic inertia in Type 2 diabetes? *Endocrine* 44(2), 343–345 (2013).
- 31 Okonofua EC, Simpson KN, Jesri A, Rehman SU, Durkalski VL, Egan BM. Therapeutic inertia is an impediment to achieving the Healthy People 2010 blood pressure control goals. *Hypertension* 47(3), 345–351 (2006).
- 32 Phillips LS, Branch WT, Cook CB *et al.* Clinical inertia. *Ann. Intern. Med.* 135(9), 825–834 (2001).
- 33 Padala PR, Desouza CV, Almeida S *et al.* The impact of apathy on glycemic control in diabetes: a cross-sectional study. *Diabetes Res. Clin. Pract.* 79(1), 37–41 (2008).
- 34 Avignon A, Attali C, Sultan A, Ferrat E, Le Breton J. Clinical inertia: viewpoints of general practitioners and diabetologists. *Diabetes Metab.* 38(Suppl. 3), S53–S58 (2012).
- 35 Giugliano D, Esposito K. Clinical inertia as a clinical safeguard. *JAMA* 305(15), 1591–1592 (2011).
- 36 Gillon R. Medical ethics: four principles plus attention to scope. *BMJ* 309(6948), 184–188 (1994).
- 37 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* 352(9131), 837–853 (1998).
- 38 *Transforming Clinical Research in the United States: Challenges and Opportunities: Workshop Summary*. National Academy of Sciences, Washington, DC, USA (2010).