Controversies in cardiovascular medicine

Blood pressure, lipids and glucose in type 2 diabetes: how low should we go? Re-discovering personalized care

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Epidemiological studies have clearly shown a direct relationship between the levels of blood pressure, glycaemia and LDL-cholesterol, and the complications of diabetes. Although ‘lower should be better’, the results of recent clinical trials examining the benefits of normalizing risk factor levels have been counter-intuitive and, at times, disturbing, and have called into question this notion. This review focuses on patients with type 2 diabetes who make up 90% of patients with diabetes. It aims to provide a clear summary and interpretation of recent trials to help clinicians to set targets for cardiovascular risk factors in individual patients. It highlights areas of agreement and disagreement between current guidelines. Recent data indicate that some patient subgroups might respond differently to aggressive risk factor management. Our challenge is how to identify these patients and deliver truly personalized diabetes care that maximizes benefit, and minimizes harm. Guidelines and position statements stress the value of setting personalized targets. We explore what this means, and how this might be achieved in practice by outlining some solutions to issues that currently limit the delivery of personalized care. We call for further research assessing the overall clinical impact of cardiovascular risk factor intervention by finding appropriate ways of combining data on mortality, complications, side-effects, quality of life, and cost-effectiveness.

Keywords

Diabetes • Blood pressure • Glucose • Lipids • Target level • Cardiovascular risk

Introduction and aims

Cardiovascular disease (CVD) is responsible for approximately half of all deaths in patients with type 2 diabetes,¹², and at a population level an increasing proportion of all cardiovascular events is being attributed to the presence of diabetes.³

Epidemiological studies have clearly shown a direct relationship between the levels of blood pressure, glycaemia and LDL-cholesterol, and the complications of diabetes.⁴–⁷ Although ‘lower should be better’, the results of recent clinical trials examining the benefits of normalizing risk factor levels have been counter-intuitive and, at times, disturbing, and have called into question this notion.⁸–¹⁰

Here we present data to guide physicians regarding how low to go with blood pressure targets by examining diabetes trials that have randomized patients to different blood pressure targets.²⁶ – ³² We believe that these results are more likely to provide relevant information than extrapolating from the blood pressure levels achieved in trials that used alternative designs,³³– ⁴³ although these important trials have highlighted major clinical benefits, and have rightly influenced blood pressure guidelines, as reviewed recently.⁴⁴

Blood pressure

Epidemiological evidence from the general population suggests that cardiovascular risk starts to increase above a blood pressure of 115/75 mmHg and then it doubles for every 20 mmHg rise in systolic pressure, and for every 10 mmHg rise in diastolic blood pressure.²⁵

Here we present data to guide physicians regarding how low to go with blood pressure targets by examining diabetes trials that have randomized patients to different blood pressure targets.²⁶ – ³²

We believe that these results are more likely to provide relevant information than extrapolating from the blood pressure levels achieved in trials that used alternative designs,³³– ⁴³ although these important trials have highlighted major clinical benefits, and have rightly influenced blood pressure guidelines, as reviewed recently.⁴⁴
Early trials

In the ‘pre-ACCORD era’ several important trials informed the debate about blood pressure targets. The relationships of these targets, and achieved blood pressures with total mortality and the primary outcomes of these trials are presented in Table 1.

The United Kingdom Prospective Diabetes Study (UKPDS) blood pressure trial was the first major trial to randomize hypertensive patients with type 2 diabetes to conventional or to intense blood pressure targets.26,27 In this trial, ‘intensive’ blood pressure lowering was associated with major reductions in important clinical endpoints including a 32% reduction for diabetes-related death; a 44% reduction in stroke; and a 37% reduction in microvascular endpoints—predominantly retinal photocoagulation.

The Hypertension Optimal Treatment (HOT) trial, which reported around the same time, randomized hypertensive patients to different diastolic blood pressure targets (Table 1). A post-hoc diabetes subgroup analysis showed that major cardiovascular events were reduced by half, and cardiovascular death was reduced by two-thirds in the group randomized to the lowest vs. the highest blood pressure target.31

These early trials changed clinical practice, but now have limited clinical relevance because target blood pressures, and achieved levels, were well above those that are currently acceptable (Table 1). Trials published since these have shown less impressive additional benefits associated with lower blood pressure targets.

The Appropriate Blood Pressure Control in Diabetes (ABCD) trial was the first to compare the benefits of normal blood pressure levels (target diastolic blood pressure 75 mmHg) with moderate blood pressure control (80–89 mmHg) on the progression of microvascular complications in patients with type 2 diabetes.28 After 5 years, intensive therapy did not reduce the risk for the primary outcome or for cardiovascular endpoints, but it was associated with lower total mortality (5.5 vs. 10.7%). This is the only early trial that achieved an on-treatment blood pressure of <130/80 mmHg in the intensive therapy group (Table 1).

**ACCORD blood pressure trial**

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial randomized patients with type 2 diabetes to a normal target systolic pressure target (<120 mmHg), or to standard therapy with the goal of reducing cardiovascular endpoints.32

The trial achieved an impressive blood pressure separation between the two groups, but this did not translate into a significant reduction in the primary outcome or the risk of death (Table 1). However, the annual rate of stroke was 39% lower in the intensive treatment group (P = 0.01), which yielded an estimated number needed to treat (NNT) to prevent one stroke over 5 years of 89 patients.

The most obvious reason why the ACCORD blood pressure trial was negative for the primary endpoint is that targeting near-normal levels of blood pressure has limited clinical benefit, with most of the benefits being achieved by targeting a level of <140 mmHg, as earlier trials have shown. However, cardiovascular event rates were much lower than expected, in part because patients with dyslipidaemia were recruited into the ACCORD lipid trial and higher-risk patients with renal impairment were excluded. This meant that the study was somewhat underpowered to detect differences between groups and therefore it was unable to exclude a 27% benefit for the primary endpoint.

Another possible explanation is that a u-shaped relationship exists between achieved blood pressure and coronary (but not cerebrovascular) risk such that the minimum coronary risk is achieved when the systolic pressure is reduced to somewhere between 120 and 130 mmHg.45 Previous trials have suggested that lowering blood pressures to <120/70 mmHg can cause harm.46–49 Although there was no suggestion that aggressive blood pressure lowering caused increased coronary risk in the ACCORD blood pressure trial, it is possible that the optimal blood pressure level was missed because of the wide separation of on-treatment systolic pressures in the intensive therapy group.45 Unfortunately, the cost of performing a trial to identify this optimal blood pressure level may be prohibitive, and moreover, if this hypothesis was confirmed, then current blood pressure targets would probably remain unchanged (see below).

Intensive blood pressure lowering was generally well tolerated, but there have been some concerns raised about potential harm associated with this intervention. Serious adverse events attributed to antihypertensive treatment that included hypotension, bradycardia, and hyperkalaemia, occurred in 3.3% of the intensively treated patients and in 1.3% in the standard therapy group (P < 0.001).

The ACCORD blood pressure trial showed that intensive blood pressure lowering was associated with lower albumin excretion rates. There was no increase in the risk of end-stage renal disease or the need for dialysis, but there was a significant reduction in estimated glomerular filtration rate associated with intensive therapy. The long-term clinical impact of these changes in renal function is uncertain.

**Current blood pressure guidelines in diabetes**

The main conclusion that can be drawn from the ACCORD blood pressure trial is that a systolic blood pressure target of <120 mm Hg cannot be recommended for the majority of patients with type 2 diabetes. Current guidelines and position statements show a remarkable consistency in setting a target blood pressure level at 130/80 mm Hg (Table 3). Based on current evidence, this is probably an appropriate blood pressure target for most patients. However, a lower blood pressure target level might be justifiable in patients with a prior history of transient ischaemic attack or stroke, and in other high-risk groups such as South Asians.50 Further information refining the optimal individualized target blood pressure may come from post-hoc analyses of this trial.

**How to lower blood pressure in patients with dysglycaemia**

The clinical benefits of most classes of blood pressure-lowering medication have been demonstrated in trials involving patients with diabetes.51

Some,5,38,51,52 but not all,53 data indicate that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) possess reno-protective benefits that are
### Table 1: Selected clinical trials of blood pressure-, glucose-, and lipid-lowering in patients with type 2 diabetes: target levels (when available) and achieved risk factor levels and their associated outcomes

<table>
<thead>
<tr>
<th>Trials</th>
<th>Study and reference</th>
<th>Primary endpoint</th>
<th>Target risk factor level or treatment allocation</th>
<th>Achieved risk factor level</th>
<th>HR (95% CI) for 1º endpoint</th>
<th>HR (95% CI) for total mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>UKPDS 33</td>
<td></td>
<td>Composite 1</td>
<td>BP (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOT</td>
<td></td>
<td>CVD death, non-fatal MI, non-fatal stroke</td>
<td>BP ≤ 80</td>
<td>150/85</td>
<td>0.76 (0.62–0.92)</td>
<td>0.82 (0.62–1.08)</td>
</tr>
<tr>
<td>ABCD</td>
<td></td>
<td>24-h creatinine clearance</td>
<td>SBP 75</td>
<td>154/87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCORD BP</td>
<td></td>
<td>CVD death, non-fatal MI, non-fatal stroke</td>
<td>SBP &lt; 120</td>
<td>144/82</td>
<td></td>
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<tr>
<td><strong>Glucose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>UKPDS 33: insulin, SU</td>
<td>Composite 1</td>
<td>FPG &lt; 6 mmol/L</td>
<td>7.0</td>
<td>7.9</td>
<td>0.88 (0.79–0.99)</td>
<td>0.94 (0.90–1.20)</td>
</tr>
<tr>
<td>UKPDS 80: 10 years, insulin, SU</td>
<td>Composite 1</td>
<td>Usual care</td>
<td>~8.5</td>
<td>~8.5</td>
<td>0.91 (0.83–0.99)</td>
<td>0.87 (0.79–0.96)</td>
</tr>
<tr>
<td>UKPDS 34: metformin</td>
<td>Composite 1</td>
<td>FPG &lt; 6 mmol/L</td>
<td>7.4</td>
<td>8.0</td>
<td>0.68 (0.53–0.87)</td>
<td>0.64 (0.45–0.91)</td>
</tr>
<tr>
<td>UKPDS 80: 10 years, metformin</td>
<td>Composite 1</td>
<td>Usual care</td>
<td>~8.5</td>
<td>~8.5</td>
<td>0.79 (0.66–0.95)</td>
<td>0.73 (0.59–0.89)</td>
</tr>
<tr>
<td>ACCORD</td>
<td>CVD death, non-fatal MI, non-fatal stroke</td>
<td>&lt;6.0%</td>
<td>6.4</td>
<td>7.5</td>
<td>0.90 (0.78–1.04)</td>
<td>1.22 (1.01–1.46)</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>CVD death, non-fatal MI, non-fatal stroke</td>
<td>&lt;6.5%</td>
<td>6.5a</td>
<td>7.3c</td>
<td>0.94 (0.84–1.06)</td>
<td>0.93 (0.83–1.06)</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>New/worse nephropathy or retinopathy</td>
<td>&lt;6.5%</td>
<td>6.5b</td>
<td>7.3c</td>
<td>0.86 (0.77–0.97)</td>
<td>NA</td>
</tr>
<tr>
<td>VADT</td>
<td>Composite 2</td>
<td></td>
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<tr>
<td><strong>Lipids</strong></td>
<td></td>
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</tr>
<tr>
<td>HPS</td>
<td>Composite 3</td>
<td>Simvastatin</td>
<td>LDL 2.3</td>
<td>0.78 (0.70–0.87)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>CARDS</td>
<td>Composite 4</td>
<td>Atorvastatin</td>
<td>LDL 1.8</td>
<td>0.63 (0.48–0.83)</td>
<td>0.73 (0.52–1.01)</td>
<td></td>
</tr>
<tr>
<td>FIELD</td>
<td>MI or CHD death</td>
<td>Fenofibrate</td>
<td>TG 1.8; LDL 4.2</td>
<td>0.89 (0.75–1.03)</td>
<td>1.11 (0.95–1.29)</td>
<td></td>
</tr>
<tr>
<td>ACCORD lipid</td>
<td>CVD death, non-fatal MI, non-fatal stroke</td>
<td>Fenofibrate</td>
<td>TG 1.7; LDL 2.1</td>
<td>0.92 (0.79–1.08)</td>
<td>0.91 (0.75–1.10)</td>
<td></td>
</tr>
</tbody>
</table>

Composite endpoint 1: Any diabetes-related endpoint (sudden death, death from hyperglycaemia or hypoglycaemia, fatal or non-fatal MI, angina, HF, stroke, renal failure, amputation, vitreous haemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction).

Composite endpoint 2: CVD death, MI, stroke, HF, surgery for vascular disease, inoperable coronary disease, or amputation for ischaemic gangrene.

Composite outcome 3: Coronary death, non-fatal myocardial infarction, stroke or revascularization.

Composite outcome 4: Acute coronary heart disease event (myocardial infarction including silent infarction, unstable angina, acute coronary heart disease death, resuscitated cardiac arrest), coronary revascularization procedure or stroke.

ABCD: Appropriate Blood Pressure Control in Diabetes; ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and DiaMicron Modified Release Controlled Evaluation; CARDS, Collaborative Atorvastatin Diabetes Study; CVD, cardiovascular disease; dBP, diastolic blood pressure; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes; FPG, fasting plasma glucose; HF, heart failure; HOT, Hypertension Optimal Treatment; HR, hazard ratio; HPS, Heart Protection Study; LDL, low-density lipoprotein cholesterol; MI, myocardial infarction; NA, not available or not applicable; NA*, HR and 95% CI not available but mortality was lower in intensive therapy (5.5 vs. 10.7%, \( P = 0.037 \)); NS, not significant (HR, 95% CI not presented); SU, sulphonylurea therapy; TG, triglycerides; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

*a Insulin-treated patients also aimed to keep pre-meal glucose values 4–7 mmol/l.

*b Local target: ‘x’ is based on the target HbA1c, from local guidelines.

c BP target changed after 5 years.
independent of their blood pressure-lowering effects. Here we highlight two recent trials that have provided additional information about the potential benefits of ACE inhibitors and ARBs in patients with diabetes or non-diabetic hyperglycaemia.

First, the Action in Diabetes and Vascular Disease Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) trial compared clinical outcomes associated with an ACE inhibitor–diuretic combination (perindopril/indapamide) vs. placebo in middle-aged, high-risk patients with diabetes, one-third of whom had established CVD.\(^5\) After 4.3 years, active therapy was associated with an average blood pressure lowering of 6/2 mm Hg; a 9% reduction in the relative risk of macrovascular or microvascular complications (absolute risk reduction 1.3%); a 14% reductions in all-cause mortality; an 18% reduction in cardiovascular death; and a 21% reduction in total renal events. It is uncertain whether the observed clinical benefits can be explained simply by blood pressure lowering, or by ‘off-target’ effects of perindopril or indapamide.\(^5\) Pleotropic effects of perindopril seem unlikely because more than half the placebo-treated patients were taking perindopril by the time the trial concluded. The mechanism of benefit is important because the cost of this fixed dose combination may be prohibitive for large-scale clinical use despite claims of cost-effectiveness.\(^5\)

Perhaps more importantly, this trial emphasizes the clinical benefits of achieving a systolic blood pressure of $<140$ mmHg in high-risk patients with type 2 diabetes. Over 5 years, the NNT to prevent one death was $\approx 79$ patients, with greater absolute benefits in older patients and in those with chronic kidney disease.\(^6\)

Second, the blood pressure-lowering arm of the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial assessed whether the ARB valsartan could reduce the risk of incident diabetes or CVD in high-risk patients with non-diabetic hyperglycaemia. During a 5-year follow-up, active therapy reduced incident diabetes by 14%, but failed to have any effect on CVD outcomes despite a blood pressure difference of 6/4 mmHg.\(^5\) The reduction in diabetes risk was probably a real effect because other randomized and non-randomized studies have suggested a similar degree of benefit, although the mechanism is unknown. The modest clinical benefit with valsartan (NNT $\approx 26$ to prevent one case of diabetes) may have been limited by a high proportion of therapy crossovers, and the effects of a lifestyle intervention which was offered to all participants. Since the benefit of lifestyle intervention in preventing diabetes is much greater than that observed with valsartan, diet and physical activity will remain the cornerstone of diabetes prevention for most people. However, when choosing an antihypertensive agent, it is useful to know that valsartan has modest beneficial effects on diabetes risk when other agents may not.\(^1\)

In conclusion, these recent data support the use of ACE inhibitors or ARBs as first-line anti-hypertensive agents in patients with dysglycaemia.\(^1\) However, in practice, this recommendation is somewhat arbitrary because most patients with hypertension and diabetes require more than one agent.\(^2\)

**Glucose**

Several studies have assessed the benefits of glucose lowering in patients with type 2 diabetes.\(^1,8\)–\(^10,61\)–\(^65\) The most important trials that randomized patients to different glycaemia targets will be discussed here (Table 1).

**Early trials**

The UKPDS was a landmark study that had a major impact on clinical care when it showed that in newly diagnosed patients with type 2 diabetes, intensive glucose-lowering reduced the risk for clinically important diabetes-related endpoints (Table 1).\(^6\) Mortality and cardiovascular events were not reduced in the main trial, but important benefits emerged during a 10-year post-trial monitoring.\(^1\) These benefits included a 24% reduction in microvascular disease, a 15% reduction in myocardial infarction and lower mortality (Table 1).

In a subgroup of overweight patients randomized to metformin or conventional therapy, metformin reduced the risk for any diabetes-related endpoint, myocardial infarction and all-cause mortality by approximately one-third,\(^6\) and these benefits were maintained during 10-year monitoring.\(^1\)

It is important to note that glycaemia targets and the levels of glycaemia achieved in UKPDS were significantly higher than the near-normal levels associated with more recent studies (Table 1).\(^3\)–\(^10\)

**ACCORD glucose trial**

The most controversial of recent trials is the ACCORD trial, which tested the hypothesis that when compared with conventional therapy, normalizing glucose levels [target glycylated haemoglobin (HbA\(_1c\)) $<6.0\%$] would reduce incident cardiovascular death or events in high-risk patients with type 2 diabetes.\(^8\) After 3.5 years, the trial was stopped prematurely because of a 22% higher mortality in the intensive-therapy group (Table 1).\(^8\)

![Figure 1](https://academic.oup.com/eurheartj/article-abstract/32/18/2247/498015)

**Figure 1** Primary and secondary outcomes for ACCORD trial participants in intensive therapy and standard therapy groups. The primary outcome was CVD death, non-fatal MI or stroke (non-fatal stroke $P$-value: 0.74). $P$-values have been calculated using Cox proportional-hazards regression analyses. CVD, cardiovascular; MI, myocardial infarction.
Figure 1). Several reasons might explain these findings, but it is difficult to prove or disprove any because of the study design:

(a) Hypoglycaemia
The most obvious explanation for the increased mortality in ACCORD is hypoglycaemia. Severe episodes of hypoglycaemia, requiring third-party assistance, were more frequent in intensively treated patients (16 vs. 5%). In support of the hypoglycaemia hypothesis, the mortality among intensively treated patients was 2.8% per year in those who had one or more episodes of hypoglycaemia requiring any assistance compared with 1.2% for those with no episodes of hypoglycaemia. Similar results were seen in the VA diabetes trial (see below).10

However, some additional observations from ACCORD suggest that hypoglycaemia might not be the explanation. First, only 1 out of 451 deaths in ACCORD were definitely caused by hypoglycaemia.66 Second, among participants with at least one episode of hypoglycaemia requiring assistance, a non-significant lower risk of death was seen in patients in the intensive therapy arm compared with the standard therapy arm.66 This might be explained by improved management and training of intensively managed patients,66 and it also makes some sense from a physiological perspective because repeated episodes of hypoglycaemia could reduce the adrenergic response and the ischaemic and arrhythmogenic potential of subsequent hypoglycaemic episodes.

However, it remains a real possibility that hypoglycaemia was largely responsible for the increased mortality in ACCORD. Patients who died, and those who had the greatest experience of hypoglycaemia, tended to have higher HbA1c values at baseline and during the trial, and they were more likely to be receiving intensive therapy.67,68 For example, intensively treated patients had a higher risk of death than standard therapy patients at all average HbA1c values >7% during the trial.

The ACCORD data are entirely consistent with unexpected isolated fatal episodes of hypoglycaemia occurring without prior warning in patients who were struggling to improve poor glycaemic control using intensive glucose-lowering therapies. Unfortunately, it is not possible to test this hypothesis retrospectively.

(b) Rapid reduction of glycosylated haemoglobin
Since the achieved HbA1c was similar in intensively treated patients in ACCORD and in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation trial (ADVANCE, presented below), the difference in mortality between these studies might be explained by the rapidity of the fall in HbA1c. During the first 6 months of the study, HbA1c fell by 1.5% in ACCORD compared with 0.5% in ADVANCE.

Although ‘too-rapid’ glucose lowering seems an attractive hypothesis, the epidemiological assessment of ACCORD mentioned above has shown that a higher mean HbA1c during the trial was associated with a higher, and not a lower, mortality.68 Patients who experienced the largest fall in HbA1c experienced the lowest risk of hypoglycaemia and the lowest risk of death. Therefore, HbA1c being low or being lowered too quickly does not appear to explain the excess mortality in the intensively treated group.

(c) Other explanations
The higher mortality in intensively treated patients in ACCORD might be due to unmeasured drug effects or perhaps by unwanted interactions between multiple glucose-lowering agents. A greater proportion of intensively treated participants received rosiglitazone than in the standard therapy group (92 vs. 58%), but a preliminary analysis has identified no link between this drug and increased mortality. It has been postulated that the increased mortality could be caused by particular harmful drug combinations, but these may be impossible to identify due to the large number of potential combinations.

In the intensive therapy arm of ACCORD, 28% of the subjects gained >10 kg, but a preliminary analysis of weight change as a predictor of mortality has been negative.

The mortality rate difference between intensive and standard therapy appeared to be greatest at 3 years and varied randomly for the duration the trial. When the P value for the difference in mortality between intensive and standard therapy groups is adjusted for multiple endpoints (N ≈ 3) and the number of sequential interim analyses (N ~ 10), then the probability that the observed result occurred by chance has been estimated to be as high as 50%.69

Other recent glucose-lowering trials
In the ADVANCE trial, high-risk patients with type 2 diabetes were randomized to receive either intensive glucose-lowering therapy with gliclazide or standard therapy without gliclazide.9 The main outcome in this trial was a composite macrovascular and microvascular endpoint (Table 1). The relative risk of the primary endpoint was reduced by 14% because of a reduced risk of nephropathy (absolute risk: 4.1 vs. 5.2%). There were no between-group differences in mortality or cardiovascular events.

In the Veterans Affairs Diabetes Trial (VADT), high-risk poorly controlled patients with type 2 diabetes were randomized to an intensive treatment regime designed to lower HbA1c by 1.5% compared with a standard therapy.10 The main outcome measure was a composite cardiovascular endpoint as shown in Table 1. After 5.6 years, there was no significant difference in the risk of incident CVD or microvascular complications (except for the progression of albuminuria) in the two groups. There was a non-significant 7% higher mortality in the intensively treated patients.

Comparison of glucose-lowering trials
When compared with UKPDS patients, those enrolled in recent trials were older, more obese, with a longer duration of diabetes, and had a higher proportion of patients with established vascular disease (Table 2). At baseline, ACCORD patients had worse glycaemic control, but better management of lipids and blood pressure. Comparisons between UKPDS and ADVANCE or VADT give similar results.

Subgroup analyses of recent randomized trials suggest that patient selection might influence the benefits of aggressive glucose lowering: a preliminary post-hoc subgroup analysis of VADT has suggested cardiovascular benefit in patients with diabetes duration <12 years, but not in those with longer duration of diabetes.70 In ACCORD, patients with no prior CVD history, and baseline HbA1c of <8% experienced CVD benefit,8 and in
**Table 2  Baseline patient characteristics in ACCORD and UKPDS**

<table>
<thead>
<tr>
<th></th>
<th>‘Average’ ACCORD patient</th>
<th>‘Average’ UKPDS patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62</td>
<td>53</td>
</tr>
<tr>
<td>Known diabetes duration (years)</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Established vascular disease</td>
<td>One-third of patients</td>
<td>No</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>32</td>
<td>28</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>136/75</td>
<td>135/82</td>
</tr>
<tr>
<td>Diabetes medication</td>
<td>Metformin, gliclazide</td>
<td>Diet</td>
</tr>
<tr>
<td>Other therapy</td>
<td>Aspirin, statin, ACE inhibitor</td>
<td>Nil</td>
</tr>
<tr>
<td>Baseline HbA₁c (%)</td>
<td>8.3</td>
<td>7.1</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>2.7</td>
<td>3.5</td>
</tr>
</tbody>
</table>

ACCORD, Action to Control Cardiovascular Risk in Diabetes; HbA₁c, glycosylated haemoglobin; UKPDS, United Kingdom Prospective Diabetes Study.

VADT, patients with low coronary and aortic calcium scores experienced benefit from aggressive glucose lowering, while those with higher scores did not.71

**Reasons why recent trials failed to show cardiovascular benefits**

Skyler et al.18 have highlighted several possible reasons why recent glucose-lowering trials8–10 failed to show cardiovascular benefits. Importantly, they pointed out that these trials were operating in a relatively flat part of the curve relating cardiovascular risk to glycaemia, and they explained that other cardiovascular risk factors were generally well managed, and CVD event rates were lower than predicted.

**Other data**

A recent large retrospective observational study of type 2 diabetic patients from a UK-based General Practice Research Database has related patient mortality to observed HbA₁c levels.72 The study showed a u-shaped relationship between these variables with a minimum risk of death associated with an HbA₁c level of ≏7.5%. Intensifying treatment with insulin was associated with a greater risk of death than intensifying treatment with oral hypoglycaemic agents. We highlight this study because it has been used to justify higher HbA₁c targets,73 but we are concerned that these data have several limitations: This was on observational retrospective study and differences among the patients and their other therapies might explain the different outcomes. Moreover, the focus of this analysis was on CVD, and it is important that the benefits of glucose lowering with respect to reducing microvascular complications are included in decisions about glycaemia targets.1,9,62,65,74,75

**Guidelines and glucose targets**

There is some variation in the HbA₁c targets recommended by expert groups (Table 3). The American Diabetes Association, the American College of Cardiology Foundation, the American Heart Association, and Australian guidelines have made recommendations following the publication of recent trials,8–10 and therefore they deserve special mention.18,24 These expert bodies recommended that the target HbA₁c should remain at <7.0% and the main justification for this has been the benefits of reduced risk of microvascular complications associated with lower HbA₁c levels.1,9,62,65,74,75 The ADA has suggested that an HbA₁c target of <7.0% would be appropriate for patients with short duration of diabetes, long life expectancy, no significant CVD, and in whom there was a major focus on the primary prevention of complications.19 They stated that a higher HbA₁c target would be appropriate for those with a history of severe hypoglycaemia, limited life expectancy, advanced microvascular or macrovascular complications, or extensive co-morbid conditions and those with longstanding diabetes.19 In these individuals, the general HbA₁c goal of <7% may be difficult to achieve despite diabetes self-management education, appropriate glucose monitoring and effective doses of multiple glucose-lowering agents including insulin. Australian guidelines also stress the importance of an individualized target HbA₁c.24

National Institute for Health and Clinical Excellence guidelines were published before the results of recent studies were available.8–10 They have rightly emphasized that patients should be involved in setting their HbA₁c target, and that they maintain this target unless side-effects (including hypoglycaemia) impair quality of life.22

**Lipids**

In contrast to the data available on glucose and blood pressure lowering in diabetes, there is little evidence to guide clinicians regarding the most appropriate target levels for lipids. However, good-quality trial data have highlighted the clinical benefits of statin therapy. For this reason, the main target of lipid-lowering therapy has become LDL-cholesterol. Here, we highlight several important statin and fibrate trials that have influenced clinical practice.

**Standard-dose statin trials**

The Heart Protection Study (HPS) randomized middle-aged or elderly patients with diabetes and high LDL-cholesterol levels to simvastatin or placebo.76 The 22% reduction in coronary death or vascular events associated with simvastatin therapy was not influenced by diabetes duration, type or control; or by age, blood pressure, or lipids (Table 1).

In the Collaborative Atorvastatin Diabetes Study (CARDS) middle-aged or elderly patients with type 2 diabetes, without high LDL-cholesterol, were randomized to atorvastatin or placebo.77 This trial was terminated 2 years early because of a 37% reduction in vascular events after 3.9 years (Table 1). The study also showed that the risk of stroke was reduced by half, and that the benefits of statin therapy were not related to the baseline LDL-cholesterol level.

The publication of these trials contributed to statin therapy becoming a standard of care for all but the lowest-risk patients with type 2 diabetes. Subsequent trials have focused on the clinical benefits of achieving very low cholesterol levels and the benefits of additional therapy.
## Table 3  Target levels of blood pressure, HbA1c, and lipids in patients with diabetes according to current guidelines and position statements

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>ESC/EASD 11</th>
<th>European 12–14</th>
<th>IDF 15</th>
<th>JNC 7 16</th>
<th>NCEP 2004 17</th>
<th>ADA 18–20</th>
<th>AHA 18, 20</th>
<th>JBS2 21</th>
<th>NICE 12</th>
<th>Canadian 23</th>
<th>Australian 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure (mmHg)</td>
<td>130/80</td>
<td>130/80</td>
<td>138/80</td>
<td>130/80</td>
<td>130/80</td>
<td>130/80</td>
<td>130/80</td>
<td>130–140/80</td>
<td>130/80</td>
<td>130/80</td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.5–7.0</td>
<td>6.5–7.0</td>
<td>6.5</td>
<td>7.0</td>
<td>7.0</td>
<td>7.0</td>
<td>6.5</td>
<td>6.5</td>
<td>6.5</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>Lipids (mmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>3.5</td>
<td>4.0–4.5</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td>2.0–2.5</td>
<td>2.5</td>
<td>1.8–2.6–3.4</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>1.0</td>
<td>1.15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG</td>
<td>2.0</td>
<td>2.3</td>
<td>1.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-HDL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.4</td>
<td></td>
</tr>
</tbody>
</table>

ADA, American Diabetes Association; AHA, American Heart Association; CVD, cardiovascular disease; ECS, European Society of Cardiology; EASD, European Association for the Study of Diabetes; HbA1c, glycosylated haemoglobin; HDL-cholesterol, high-density lipoprotein; IDF, International Diabetes Federation; JBS, Joint British Societies; JNC, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; LDL, low-density lipoprotein; NCEP, National Cholesterol Education Program; NICE, National Institute for Health and Clinical Excellence; TG, triglycerides.

130/80 if eye, kidney or cerebrovascular disease.

1If feasible.

2The goal for individual patients is as close to normal (6%) as possible without causing significant hypoglycaemia, this glycaemia target was also set by American College of Cardiology Foundation.

3With avoidance of hypoglycaemia.

4Involving the person in the setting of targets, and ‘avoiding highly intensive management to levels <6.5%’.

5General target is <7.0%; individualized target is 6–8% depending on clinical circumstances.

6Lower target if feasible.

7Or a 25% reduction in total cholesterol and a 30% reduction in LDL cholesterol, whichever gets the person to the lowest absolute level.

81.8 in the presence of CVD, 2.6 in most patients and 3.4 in low-risk patients.

9If age >40 or high CVD risk.

10In women consider HDL target of 1.3 mmol/L.

11Fenofibrate advised as first-line therapy if TG >4.5 mmol/L and as second-line therapy after statin initiated if TG remain elevated (2.3–4.5 mmol/L).

12Non-HDL cholesterol (total HDL) is a secondary target if TG levels 2.3–5.6 mmol/L (200–499 mg/dL), but if TG levels >5.6 mmol/L (500 mg/dL) then consider TG-lowering therapy before LDL-lowering therapy with a statin.
High-dose statin trials in high-risk patients with diabetes

While there are only limited data suggesting that lowering cholesterol to very low levels with statin therapy might have clinical benefits, we believe that this might be a fruitful area for future clinical trials.

In acute coronary syndrome patients, a post-hoc diabetes subgroup analysis of the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) TIMI 22 study was performed. Cardiac event rates were much higher in patients with diabetes, but events were reduced similarly by high-dose statin therapy vs. conventional statin therapy in those with or without diabetes.

In the non-acute setting, a post-hoc subgroup analysis of the Treating to New Targets (TNT) study suggested macrovascular and microvascular benefits of aggressive statin therapy in patients with type 2 diabetes. In this study, high-dose atorvastatin (80 mg daily) compared with low-dose therapy (10 mg daily) reduced the risk of major cardiovascular events by 35% in patients with diabetes and chronic kidney disease (21 vs. 14%, P = 0.04). In these patients, the NNT over 4.8 years to prevent one major cardiovascular event was ~14. The study also suggested that there were important renal benefits for diabetic patients treated with both low- and high-dose atorvastatin.

Early fibrate trials

Here we highlight several clinical trials that have assessed the benefits of fibric acid therapy in patients with diabetes. These agents have a potent effect on lowering triglycerides, which is also an important component of diabetic dyslipidemia (raised triglyceride and low HDL-cholesterol).

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial randomized patients with type 2 diabetes to fenofibrate or placebo. The primary outcome was not significantly influenced by fenofibrate therapy (Table 1), but total cardiovascular events were significantly reduced by 11% (from 13.9 to 12.5%, P = 0.035). Moreover, a post-hoc analysis of this study suggested that fenofibrate might benefit those patients with both elevated triglycerides and low HDL-cholesterol levels.

Fenofibrate therapy was also associated with reduced progression of albuminuria and the number of patients requiring laser therapy, but of some concern, there was a modest reversible elevation of serum creatinine (11 μmol/l). While FIELD was an important study, two limitations should be noted: First, a higher proportion of placebo-treated patients received a statin compared with the fenofibrate group, which may have significantly masked beneficial effects of fenofibrate. Finally, fenofibrate led to a ~13% reduction in LDL-cholesterol, and it is possible that the modest cardiovascular benefits observed could be explained by LDL lowering.

Following publication of the impressive results of HPS and CARDS, statin therapy became a standard of care for the majority of patients with diabetes, and fibrate therapy became less important. Meanwhile, other studies reported the effect of fibrate therapy in subgroups of patients with diabetes or in those without diabetes. These studies did not address the role of fibrate therapy in statin-treated patients, and therefore they are of less relevance to current clinical practice and will not be discussed.

ACCORD lipid trial

The ACCORD lipid trial tested the hypothesis that the addition of fenofibrate would reduce cardiovascular risk in statin-treated patients with type 2 diabetes. There were no significant differences between the two study groups with respect to the primary or secondary outcomes (Table 1), and therefore the authors concluded that there was no role for the routine use of fenofibrate with simvastatin to reduce CVD risk in high-risk patients with type 2 diabetes.

Although the overall results of ACCORD lipid were negative, some pre-specified subgroups appeared to derive clinical benefit. These groups were men (P = 0.01 for interaction), and possibly those with both a high baseline triglyceride and low baseline HDL-cholesterol (P = 0.057 for interaction). The significant treatment interaction by sex was in contrast to the results of the FIELD study that showed no similar interaction. However, the benefits observed in the group with diabetic dyslipidemia were observed in the FIELD trial, and post-hoc subgroup analyses of two other fibrate trials.

As observed in the FIELD trial, mean serum creatinine levels in ACCORD lipid increased modestly in the fenofibrate group within the first year and remained relatively stable thereafter. Reassuringly, there was no increased risk of end-stage renal disease or dialysis. Moreover, there was a reduction in albuminuria and retinopathy in fenofibrate-treated patients, as shown in other trials. Furthermore, there was no increased risk of myositis or rhabdomyolysis when fenofibrate was added to the statin therapy.

Current guidelines and potential future trials of lipid-lowering therapy in diabetes

As shown in Table 3 there is quite a wide variation in the target lipid levels set by various expert organizations mainly because lipid trials have not been designed to evaluate one lipid target over another. However, there is general agreement that a desirable LDL-cholesterol level is in the region of 2.0 – 2.6 mmol/l.

It is clear is that standard-dose statin therapy has major benefits for patients with diabetes and, in general, guidelines agree that these agents should be prescribed in all but the lowest-risk patients with type 2 diabetes. As mentioned above, the authors believe that there are some higher-risk patients, such as those with diabetic dyslipidemia, who might benefit from aggressive lipid lowering with statin therapy. Further trials are called for to explore this possibility.

Since the results of the ACCORD lipid trial were negative, the routine use of fibrates in statin-treated patients cannot be recommended. The authors believe that fenofibrate may be beneficial in statin-treated patients with diabetic dyslipidemia as suggested by guidelines. However, we need at least one dedicated trial confirming this, before fenofibrate can be recommended routinely in this subgroup of patients.
Setting personalized targets

Recent guidelines and position statements have stressed the value of setting personalized targets, but what this means in practice and how this might be achieved is often unclear. Here we outline some solutions (mostly technological) to issues that currently limit the delivery of personalized care.

Computer-based systems could help clinicians to prioritize therapy in a way that minimizes individual patient risk. Systems could identify which risk factor is contributing most to patient risk, and which risk factor, when treated, might yield the greatest benefit. Similar systems could help identify the highest-risk patients who appear to derive the greatest benefit from a treat-to-target strategy.89 The importance of identifying and reducing global cardiovascular risk is emphasized by several European guidelines12–14—an approach that has been shown to have major clinical benefits.90,91

Software systems could help identify subgroups of patients who might benefit or be harmed by specific therapies or aggressive treatment goals. For example, identifying those with established CVD and hypoglycaemia unawareness in whom an HbA1c target of <7.0% might be inappropriate; identifying those with declining renal function who might be harmed by metformin; or identifying those with a history of prior transient ischaemic attack or stroke might benefit from a lower blood pressure target.86

Involving patients in decisions about their care could yield important benefits.92 A practice-linked online system that involves patients in the writing of a Diabetes Care Plan has shown clinical benefits,93 as have other shared electronic decision-support systems.94

Finally, improving personalized care by enhancing the quality of the consultation through education and training could have more emphasis.95,96 For example, physician training in behaviour change counselling techniques could be particularly beneficial in diabetes clinics.97

Conclusions

In the management of glucose, blood pressure and lipids, recent clinical trials have clearly established that lower is not always better in type 2 diabetes. Although the optimal targets for these risk factors have not been firmly established by these trials, they have provided vital information and a better understanding of what targets are appropriate. However, at the time of writing, these trials have mostly reported data on mortality, and macrovascular and microvascular outcomes. Data on health-related quality of life and cost-effectiveness expected from ACCORD98 and other studies might also influence patient care.

Recent clinical trials have suggested that some patient subgroups might respond differently to aggressive risk factor management. Our challenge is how to identify these patients and deliver truly personalized diabetes care that maximizes benefit and minimizes harm (Figure 2).

Further research should assess the overall clinical impact of these interventions by finding appropriate ways of combining data on mortality, complications, side-effects, quality of life, and cost-effectiveness.

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