Controversies in cardiovascular medicine

Diabetes clinical trials: helped or hindered by the current shift in regulatory requirements?


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Glycaemic control is an inadequate surrogate marker of cardiovascular event reduction in patients with type 2 diabetes. Clinical trials to date have been unsuccessful in identifying a therapeutic approach that addresses the underlying problem in diabetes (glycaemic control) and reduces cardiovascular risk. The potential for some agents to increase the risk of cardiovascular events has led to substantial changes in regulatory requirements for new anti-diabetic therapies. These requirements, while key to ensuring the cardiovascular safety of new agents, fail to emphasize the need to show clinical benefits, such as less visual impairment, less need for dialysis, or fewer cardiovascular events and deaths. Changes in test results such as glycaemic control, serum creatinine, micro-albuminuria, or retinopathy are inadequate surrogates. Regulators should consider the potential advantages of offering extended patent protection in order to encourage companies to conduct long-term trials in diabetes and many other chronic medical conditions. Cooperative efforts among physicians, clinical trialists, regulators, and sponsors are needed to address unresolved issues including re-defining therapeutic targets that are meaningful to patients with diabetes, determining the appropriate length of follow-up for future trials, and considering the ethical and operational challenges of non-inferiority designs.

Keywords

Diabetes mellitus • Cardiovascular disease • Clinical trials

Introduction

Significant changes in the approach to the clinical trial methodology for type 2 diabetes therapeutics have occurred in recent years. Traditionally, glycaemic control [as defined by glycated haemoglobin (HbA1c)] has been the target of new therapeutic interventions in diabetes mellitus and the basis for regulatory approval. Although the prevention of microvascular and macrovascular complications has also long been recognized as an important objective of treatment, no trial has produced overwhelming evidence of a benefit on macrovascular outcomes.1,2 Indeed, the results of recent trials raise the concern that certain anti-diabetic drugs or treatment strategies may increase the cardiovascular risk. This recognition led regulatory bodies to issue new methodology requirements. Improvement in glycaemic control is no longer an acceptable surrogate for efficacy (or safety) with regard to cardiovascular outcomes.3–5 Safety must be formally demonstrated in adequately powered trials that accrue a sufficient number of cardiovascular events.6–9

During the 7th Global Cardiovascular Clinical Trialists Forum in December 2010, a group of cardiovascular clinical trialists, biostatisticians, National Institutes of Health (NIH) scientists, US and
European government regulators, and pharmaceutical industry researchers discussed the challenges related to cardiovascular risk assessment of new drugs for the treatment of type 2 diabetes mellitus. This manuscript summarizes the results of the presentations and discussions on the scientific, statistical, and clinical challenges facing clinical research in type 2 diabetes.

**Glycaemic control in diabetes**

Worldwide age-standardized prevalence of diabetes increased from 8.3 to 9.8% in men and from 7.5 to 9.2% in women between 1980 and 2008. A reported 347 million people worldwide had diabetes in 2008. Preventing cardiovascular events in patients with type 2 diabetes mellitus is important, although whether diabetes is just a risk marker (i.e. other comorbidities common in patients with diabetes are the main driver of cardiovascular risk rather than dysglycaemia per se) or a risk factor (i.e. abnormal glucose metabolism is the primary driver of risk) is still unknown.

Epidemiological and experimental studies have reported an association between elevated HbA1c and both microvascular and macrovascular complications in patients with type 2 diabetes mellitus. The relative risk of coronary heart disease or stroke has been estimated at 1.18 (95% CI: 1.10–1.26) for each 1% increase in HbA1c.

**Optimal intensity of glycaemic control**

Several clinical trials have compared the effects of intensive vs. standard glycaemic control in both type 1 and type 2 patients. These studies demonstrated a reduction in some microvascular complications with more intensive glycaemic control, although the studies were limited by small numbers, few events, and open-label designs. The data supporting a role for intensive glycaemic control in reducing macrovascular complications are even less compelling. The United Kingdom Prospective Diabetes Study (UKPDS) revealed a marginally significant reduction in non-fatal myocardial infarction (MI) (P = 0.052) among patients randomized to intensive control after 10 years of follow-up. In a 10-year post-interventional follow-up analysis, patients in the intensive therapy group showed persistent risk reduction in microvascular disease, MI, and all-cause mortality despite the fact that there was no difference in HbA1c after the first year. It is important to note that UKPDS was unblinded. It enrolled only newly diagnosed patients with type 2 diabetes and was initiated before aspirin, lipid-lowering drugs, and ACE inhibitors were commonly used. Additionally, non-fatal MI was one of 21 pre-defined endpoints with no correction for multiplicity.

Three more recent clinical trials designed to compare intensive vs. standard glycaemic control, ADVANCE (Action in Diabetes and Vascular Disease-Preterax and Diamicron Modified Release Controlled Evaluation), VADT (Veterans Affairs Diabetes Trial), and ACCORD (Action to Control Cardiovascular Risk in Diabetes), showed that intensive glycaemic control did not reduce the incidence of the primary composite endpoints (Appendix Table 1). ACCORD was stopped early because of increased mortality in the intensive-treatment arm (HR: 1.22, 95% CI: 1.01–1.46 after 3.5 years of follow-up), despite a reduction in the risk of non-fatal MI (HR: 0.76, 95% CI: 0.62–0.92, P = 0.004). The increased mortality persisted through the 5-year follow-up, even after patients in the intensive therapy arm were switched to the standard glycaemia-treatment approach (HR: 1.19, 95% CI: 1.03–1.38, P = 0.02). The reasons for this mortality increase have been widely debated.

A systematic review of trials investigating intensive vs. standard glycaemic control found a small relative reduction in cardiovascular disease events (RR: 0.90, 95% CI: 0.83–0.98) associated with intensive control, but no conclusive evidence of benefit or harm for stroke (RR: 0.98, 95% CI: 0.86–1.11), cardiovascular mortality (RR: 0.97, 95% CI: 0.76–1.24), or all-cause mortality (RR: 0.98, 95% CI: 0.84–1.15). As with all systematic reviews, publication bias may have influenced these findings. Additionally, many of the studies included in the systematic review were open-label designs and had other methodological limitations. Significant heterogeneity was noted across trials (UKPDS 33, UKPDS 34, ACCORD, ADVANCE, and VADT) for cardiovascular mortality and all-cause mortality. Another meta-analysis included one additional trial (PROACTIVE) for a total of 33 040 patients with 163 000 person-years of follow-up: intensive glycaemic control was associated with a reduction in coronary heart disease events (OR: 0.85, 95% CI: 0.77–0.93), but not stroke (OR: 0.93, 95% CI: 0.81–1.06) or all-cause mortality (OR: 1.02, 95% CI: 0.87–1.19). However, these results were mainly driven by PROACTIVE, which, contrary to the other trials in the meta-analysis, was not a comparison of intensive vs. standard glucose control. Therefore, the results of the two meta-analyses are qualitatively similar, but they differ in trial selection, outcomes assessed, and interpretation of results. The most recent meta-analysis included 13 randomized controlled trials (representing 34 533 patients) that assessed the effect of intensive glucose lowering on cardiovascular events and microvascular complications in patients with type 2 diabetes. The relative risk for the effect of intensive glucose lowering on all-cause mortality was 1.04 (99% CI: 0.91–1.19) and, for cardiovascular death, it was 1.11 (99% CI: 0.86–1.43). Significant heterogeneity in these endpoints was observed across the included trials. Intensive glycaemic control did appear to reduce the risk of non-fatal MI (RR: 0.85, 99% CI: 0.74–0.96, P < 0.001) and microalbuminuria (RR: 0.9, 95% CI: 0.85–0.96, P < 0.001), but it increased the risk of severe hypoglycaemia (RR: 2.33, 99% CI: 1.62–3.36, P < 0.001). On the basis of these analyses, the benefit, or lack thereof, and the potential for harm associated with intensive glycaemic control is uncertain.

These findings call into question the appropriateness of linking glycaemic control, per se, with cardiovascular and microvascular

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**Table 1** Estimated number of primary cardiovascular events needed to meet regulatory requirements

<table>
<thead>
<tr>
<th>Non-inferiority margin</th>
<th>80% power</th>
<th>90% power</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.8</td>
<td>91</td>
<td>122</td>
</tr>
<tr>
<td>1.3</td>
<td>456</td>
<td>611</td>
</tr>
</tbody>
</table>

Assumes true relative risk is 1.0, one-sided, α = 0.025.
risk reduction. The complex pathophysiological continuum of diabetes mellitus, and the multiple factors related to the treatment of elevated blood glucose (length of time from diabetes diagnosis, extent of exposure to elevated blood glucose before and after diagnosis, anti-diabetic drug therapy, hypoglycaemia, weight gain, concomitant diseases, and others) likely influence the cardiovascular risk profile of patients with diabetes mellitus in a complex, integrated manner.

**Optimal endpoints in diabetes clinical trials**

**Adequacy of glycaemic control as a surrogate endpoint**

Potential surrogate endpoints may fail to reflect the true clinical outcome for several reasons. They may track with the clinical outcome, but lie on a different causal pathway, i.e. interventions that target the surrogate may not necessarily influence the outcome because the pathophysiological processes may differ. Also, a clinical outcome may be influenced by multiple pathways, which may or may not be reflected by the potential surrogate (e.g. coronary heart disease is related to both cholesterol and blood pressure). Indeed, an intervention may adversely affect the outcome independent of the supposed surrogate measure (e.g. inotropic agents to increase cardiac contractility in heart failure and anti-arrhythmic drugs to reduce sudden death after MI).

On the basis of the three recent intensive vs. standard glycaemic control trials, ACCORD, ADVANCE, and VADT, more intense glycaemic control is not a reliable surrogate marker for the reduction in cardiovascular events, a finding that has important implications for future trials. Other trials that evaluated various pharmacological strategies in type 2 diabetes mellitus have also failed to demonstrate improvements in clinical outcomes. These trials generally enrolled patients with long-standing diabetes; it is possible that the response may be different in a newly diagnosed population, but this hypothesis remains to be tested. Some have argued that glycemic control might have been a good surrogate if only the right drug had been used, greater HbA1c separation had been achieved, or if excessive HbA1c lowering had been avoided. Whether or not these contentions are true remains to be proved. Clearly, the optimal level of glycemic control among patients with type 2 diabetes mellitus has yet to be defined, although the ACCORD data suggest that 7–7.9% may be reasonable for this population.

**Measuring disease progression: microvascular vs. macrovascular endpoints**

Microvascular endpoints are important measures of disease progression and morbidity. The development of retinopathy, nephropathy, neuropathy, and peripheral microvascular disease is associated with serious morbidity including blindness, cataracts, end-stage renal disease, amputation, foot trauma, and diabetic ulcers. Measuring these events individually as secondary endpoints in clinical trials is reasonable and provides an assessment of the intervention’s impact on clinically relevant outcomes, but there is inconsistency of how they are defined across clinical trials (Appendix Table A1). Nephropathy, retinopathy, and neuropathy are often combined into a single composite endpoint, and definitions of each can vary markedly. Worsening nephropathy may include albuminuria, increasing creatinine levels, need for renal-replacement therapy, or death due to renal disease. Retinopathy may be defined as need for photocoagulation, vitreous haemorrhage, macular oedema, or diabetes-related blindness. Even if a composite outcome is used, whether or not the treatment intervention has a directionally similar effect on the individual components of the composite must be determined. Endpoints that give rise to symptoms (e.g. foot ulcers, loss of visual acuity) should generally be ranked in clinical importance over those that do not.

Since definitions vary across trials, interpreting the totality of evidence can be difficult. In UKPDS, the 25% reduction in microvascular events was primarily driven by retinal photocoagulation; there were few cases of renal failure. In ADVANCE, microvascular events were mainly the development of macroalbuminuria. In ACCORD, intensive therapy was associated with less micro- or macroalbuminuria, but, within the relatively short-time frame of the trial, it did not affect the development of end-stage renal disease. Thus, albuminuria did not adequately reflect renal risk, which brings into question the clinical relevance of albuminuria as a surrogate microvascular renal endpoint, particularly in trials with short follow-up and few renal events as in ACCORD, or in patients with low levels of proteinuria at baseline as in ONTARGET.

Microvascular complications clinically manifest themselves many years after the onset of diabetes. Elevated HbA1c up to 5 years previously can predict the onset of retinopathy progression. Microvascular outcomes that accrue during a trial’s follow-up (usual 5 years) may have a stronger association with the level of glycemic control at enrollment rather than during randomized treatment. The clinical benefit of improved glycemic control may not be evident until several years of later. Thus, extended follow-up is required to adequately assess the microvascular or macrovascular effects of an intervention. The median follow-up of the ADVANCE and VADT trials were 5 and 5.6 years, respectively, and only 3.7 years in ACCORD (Appendix Table A1). In all three trials, there were no effects on microvascular endpoints, except for a decrease in albuminuria and, in ACCORD, retinopathy. Would other outcomes, such as end-stage renal disease, have been reduced with longer follow-up? In UKPDS, the proportion of patients with retinopathy progression was 38% in the intensive group compared with 31% in the conventional group (P = 0.012), but the median follow-up was 10 years. The size of a clinical trial may be no substitute for the length of follow-up with regard to diabetes mellitus. A large trial lasting <5 years may be much less able to show benefits than a smaller trial lasting 10 years. In UKPDS, the reduction in non-fatal MI was marginally significant after 10 years of follow-up, but there was no significant reduction in all-cause death, stroke, or the composite of any diabetes-related endpoint. After an additional 10 years of post-
interventional trial follow-up, significant risk reductions in microvascular disease, MI, and all-cause mortality were observed.\textsuperscript{22} The planned follow-up of ongoing trials ranges from 3 to 5.5 years (Appendix Table A2).\textsuperscript{43} ACCORD plans to follow participants for a total of 10 years to assess whether there are long-term effects of the 3.7 years of randomized therapy.

**Challenges associated with combining microvascular and macrovascular events**

Combining microvascular and macrovascular outcomes into a composite endpoint introduces several challenges. The interaction of microvascular and macrovascular disease is complex.\textsuperscript{44} Combining microvascular with macrovascular events may mask a neutral or even harmful effect on the macrovascular outcome because the number of, often minor, microvascular events that accrue will generally be larger. Because the total number of events in the composite is greater than the number of events in each individual component, it is easier to obtain statistical significance in the overall composite, even if some of the individual components are not significant. It is also possible for the components to be directionally opposite, resulting in a neutral composite. For this reason, the components must be considered individually in secondary analyses. Trials must also be large enough and follow-up long enough to accrue a sufficient number of macrovascular endpoints to assure cardiovascular safety. The individual components of the macrovascular composite must be represented in numbers sufficient to support analysis of the treatment effect across components.

The ADVANCE study reported a statistically significant 10\% reduction in the primary composite endpoint of major macrovascular (cardiovascular death, non-fatal MI, or non-fatal stroke) or microvascular events (new or worsening nephropathy or retinopathy) in favour of intensive glycaemic control (HR: 0.90, 95\% CI: 0.82–0.98, \(P = 0.01\)). When analysed separately, the effect on macrovascular outcomes was not significant (HR: 0.94, 95\% CI: 0.84–1.06), but the effect on microvascular events persisted (HR: 0.86, 95\% CI: 0.77–0.97).\textsuperscript{1} This example illustrates how the components can differ and highlights the need for a separate assessment of the components in a primary composite endpoint.

**Major adverse cardiovascular events and mortality endpoints**

Accelerated atherosclerosis is one mechanism underlying the increased cardiovascular risk observed in patients with type 2 diabetes. Hence, the cardiovascular endpoints for most diabetes trials focus on cardiovascular death, MI, and stroke. Regulatory agencies now require an assessment of these specific endpoints (at a minimum) to evaluate the cardiovascular safety of therapies to treat type 2 diabetes mellitus.

It is relevant to decide whether non-atherosclerotic cardiovascular endpoints, particularly heart failure, should also be studied in diabetes trials.\textsuperscript{45} The incidence of heart failure is often similar to that of MI in patients with diabetes,\textsuperscript{1} and in some studies, higher.\textsuperscript{32} Thiazolidinediones have been associated with an increased risk for heart failure.\textsuperscript{4,47–51} In the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes) trial, rosiglitazone was associated with a higher risk of death or heart failure hospitalization (HR: 2.10, 95\% CI: 1.35–3.27) and heart failure death alone, based on a few events (10 vs. 2). There was no increase in the risk of cardiovascular mortality or hospitalization (HR: 0.99, 95\% CI: 0.85–1.16) or cardiovascular deaths (HR: 0.84, 95\% CI: 0.59–1.18). The evidence regarding MI was inconclusive (HR: 1.14, 95\% CI: 0.80–1.63).\textsuperscript{36,51} Based on these data, heart failure should be included as an endpoint in trials of diabetes mellitus. Heart failure should be specifically defined (i.e. limited to hospitalization events) and events adjudicated to increase the robustness of the endpoint. Of the 12 ongoing trials, only one includes heart failure as a component of the primary endpoint (based on information available in clinical trial registries) (Appendix Table A2), although it is listed as a secondary endpoint in the majority.

**Measuring cardiovascular safety of anti-diabetic drugs**

In 2007, a meta-analysis that caused some controversy was published. The analysis included 42 rosiglitazone trials involving 27,843 patients and reported an increased risk of MI (RR: 1.43, 95\% CI: 1.03–1.98, \(P = 0.03\)) with the use of rosiglitazone.\textsuperscript{7} This finding, despite the data quality and resulting methodological limitations of the analysis, along with an earlier ‘near miss’ with a related drug,\textsuperscript{52–54} are believed to have contributed to the change in the US Food and Drug Administration (FDA) regulatory requirements for new anti-diabetic therapies.\textsuperscript{6,57–59} The European Medicines Agency (EMA) regulations are under development. On the basis of these changes, it is possible that cardiovascular safety (i.e. not producing more cardiovascular events) will dominate future research of anti-diabetic medicines, potentially at the expense of obtaining efficacy data (i.e. prevention of cardiovascular events). This would be an unfortunate consequence since drug approval should be based on improvements in outcomes that are important to patients, as well as safety.

Based on the new guidelines, each treatment programme requires an independent cardiovascular endpoints committee to conduct a blinded adjudication of cardiovascular events during all phase 2 and phase 3 trials. The FDA guidance\textsuperscript{6} stipulates that cardiovascular mortality, MI, and stroke should be evaluated, and other endpoints may also be included. Prior to submitting a new drug application, a meta-analysis of all phase 2 and 3 data must rule out an 80\% excess risk, i.e. the two-sided 95\% confidence interval for the estimated risk ratio must exclude 1.8. If the confidence interval includes 1.3, then a large post-marketing safety trial is required to rule out a 30\% excess risk.

These rules create a number of challenges that need to be addressed. Some of the ongoing trials are testing both the 1.8 and 1.3 margins in a single study/programme, which raises the issue of how to test the 1.8 margin without compromising the integrity of the rest of the ongoing study/programme. Marketing a drug while a placebo-controlled trial is ongoing with the drug in the same target population is another issue that may impede the completion of the trial. If 1.8 and 1.3 margins are tested in two separate trials, one may need to frame a time limit on how long a sponsor has to initiate and complete the second (1.3 margin) trial.
These requirements present important considerations for future diabetes trials. Firstly, improvements in glycaemic control have not been shown to reduce cardiovascular events.\(^3\) On this basis, should future diabetes trials studying cardiovascular outcomes be designed for superiority (i.e. the intervention is better than placebo/standard therapy) or for non-inferiority (i.e. the intervention is not worse than placebo/standard therapy), or for both? The non-inferiority approach, which is the minimum FDA requirement, raises ethical concerns and logistical challenges with regard to enrolling thousands of patients in a trial whose objective is to demonstrate safety rather than efficacy. Does the principle of beneficence apply when patients are randomized into a trial that is not powered to show benefit on a meaningful outcome, only to rule out harm? From a clinical perspective, it is inadequate only to exclude harm. It is a reasonable expectation that a new drug will improve some pre-defined meaningful outcome in order to be approved. On the basis of results from previous clinical trials, it can be argued that lowering HbA1c is not, in and by itself a meaningful outcome.

The FDA guidance also raises a number of statistical issues, particularly regarding alpha penalties. An alpha penalty is a reduction in the required alpha level to declare significance, which is often necessary when multiple hypotheses are tested. It is likely that the FDA will not impose an alpha penalty to test the hypothesis that the relative risk is \(< 1.8\), unless multiple looks at the data are taken for efficacy, but an alpha penalty may well be incurred if multiple looks at the data are taken to determine whether the relative risk \(< 1.3\) threshold has also been met. However, no specific assurances on this issue have been made by the agency. Further, no alpha penalty should be incurred if the intent shifts from demonstrating non-inferiority to claiming superiority. Clearly, the need for consensus on the statistical aspects of these studies is needed. Finally, there is debate about whether it is permissible to add studies to a completed meta-analysis in order to accrue the number of events needed to attain the relative risk targets, if the original meta-analytic results fall short of the stipulated relative risk thresholds. Should such additions require an alpha penalty? Can the regulatory agencies guide such decisions, or should they be made on an individual trial basis in consultation with regulatory agencies?

Clinical trials must be of substantial size to achieve these regulatory requirements. Keys are the size of the database and the time needed to detect potential safety signals for relatively uncommon cardiovascular events. A long-term cardiovascular safety trial with several years follow-up would be expected as a part of the clinical development programme. Table 1 shows the number of primary cardiovascular events needed to meet the FDA-required non-inferiority margins. Many diabetes outcome trials achieved a lower primary event rate than expected, suggesting that the problems in designing a trial to achieve a specific risk profile are often underestimated.\(^6\) Enhancing population risk can be achieved by including patients with pre-existing cardiovascular disease or proteinuria,\(^6\) or as suggested by the FDA guidance document, including patients with advanced disease, the elderly, or patients with renal impairment.\(^6\) Using cardiovascular risk scores such as Framingham, EuroScore, or other validated instruments, may help in identifying high-risk patients.

However, this practice of enhancing risk may also be problematic. Firstly, it is possible that the highest risk patients will not benefit from interventions since the disease may be impossible to modify at the advanced stage. The best opportunity to detect clinical benefits may be in lower risk patients with extended follow-up. Secondly, the ethical conduct of clinical research requires that the potential for harm does not outweigh the potential for benefit. This criterion may not be satisfied, particularly when a non-inferiority design is applied to a group of patients at high cardiovascular risk. Even when high-risk populations are targeted, estimated sample sizes for these trials are quite large.\(^6\) Ongoing and future trials will be competing for similar patients, a factor that may prolong recruitment and the overall study timeline. Whether there exist sufficient patients willing to participate in these trials remains to be seen (Appendix Table A2).

Longer follow-up is one approach that would allow for better characterization of efficacy and safety profiles for drugs intended for chronic diseases. However, current patent regulations are a disincentive for pharmaceutical companies to conduct trials with extended follow-up. Regulators should consider the potential advantages of offering longer patent protection, particularly for companies who commit to a scientifically robust drug development programme.\(^6\)

These large safety trials generate other interpretative challenges. There will be disparity in the ancillary therapies used between treatment arms, since HbA1c could be less well controlled in the placebo group, making placebo group patients more likely to receive insulin, sulfonylureas, or other drugs. This may confound the treatment comparison or result in greater placebo drop-out rates. Additionally, existing drugs for type 2 diabetes mellitus were not required to prove long-term efficacy or safety. Thus, the differential use of these agents in future trials may further confound the interpretation of results.

The methodology for the required meta-analyses presents new challenges. Multiple trials will be analysed, most being small with short-term follow-up, with the exception of the large safety trial. The included trials will have both active and placebo controls, and the validity of including both in a meta-analysis is debatable. Additionally, the trials may have different HbA1c inclusion thresholds, and differential use of other anti-diabetic therapies. This heterogeneity of trial designs may lead to significant challenges in interpretation.

Finally, large safety trials represent new territory for data monitoring. If event rates are lower than expected, then sample sizes may need to be increased, the population risk further enriched, or follow-up extended. The FDA has not ruled out the possibility of using adaptive designs such that a trial follow-up can be increased or decreased based on unblinded interim results. Release of information from the pre-marketing meta-analysis by the FDA also poses a threat to maintaining clinical equipoise and integrity of the large post-marketing safety trial, as well as the overall likelihood that it will be completed as planned.

**Conclusion: current challenges and future directions for diabetes clinical research**

Clinical research in the field of type-2 diabetes is facing many challenging scientific issues. The FDA guidelines for new anti-diabetic agents, while addressing a very important and real issue of drug
safety for drugs given chronically to individuals for many years, may have created a number of problems that have been highlighted in this overview. These guidelines should be considered as a work in progress. The EMA should carefully evaluate the implications of the FDA’s approach before implementing their own policy on this issue.

Several areas of uncertainty remain. These include but are not limited to determining the adequate length of follow-up for future trials; developing appropriate analytic methodology to address the influence of differences in background or ancillary therapy; mechanisms to robustly evaluate the contribution of adverse effects such as hypoglycaemia or weight gain to observed clinical outcomes; considering the ethical and operational challenges of non-inferiority designs; scientifically robust methodology for meta-analyses of studies with different methodology or design characteristics; and processes to deal with multiple competing clinical trials and the potential for a limited availability of subjects. Addressing these issues is a key component to improving the outcomes of the millions of current and future patients with diabetes mellitus.

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### Table A1  Recent trials of intensive vs. standard glycaemic control in type 2 diabetes mellitus

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment regimens</th>
<th>Primary endpoint</th>
<th>Secondary endpoint</th>
<th>Length of F/U</th>
<th>Results</th>
<th>End of follow-up HbA1C and comments</th>
</tr>
</thead>
</table>
| **ADVANCE**<sup>3</sup>  
(n = 11 140) | Intensive glucose control (HbA<sub>1c</sub>) ≤ 6.5% using gliclazide + metformin, TZD, acarbose, or insulin at physician’s discretion vs. standard control (defined as target HbA<sub>1c</sub> level according to local guidelines) using a sulfonylurea other than gliclazide if needed + metformin, TZD, acarbose, or insulin at physician’s discretion | Composite of macro- and microvascular events, considered jointly and separately  
Macrovasc: CV death, NFMI, NF stroke  
Microvasc: New or worsening nephropathy (macroalbuminuria, doubling of SCr to at least 2.26 mg/dL, need for RRT, or death due to renal disease) or retinopathy (proliferative retinopathy, macular oedema, diabetes-related blindness, or the use of retinal photocoagulation therapy) | Median 5 years | Composite 18.1% intensive vs. 20% standard control (HR: 0.9, 95% CI: 0.82–0.98, P = 0.01)  
Macrovascular: HR for intensive 0.94, 95% CI: 0.84–1.06, P = 0.32  
Microvascular: HR for intensive 0.86, 95% CI: 0.77–0.97, P = 0.01 (driven by effect in microalbuminuria) | Intensive control: 6.3% (median)  
Standard control: 7% (median)  
Significant increase in hospitalization with more intensive therapy |
| **VADT**<sup>4</sup>  
(n = 1791) | Intensive glucose control (HbA<sub>1c</sub>) < 6% using metformin or glimepiride plus rosiglitazone (at maximal dose), plus insulin if needed. Further changes were at the physician’s discretion vs. Standard control using metformin or glimepiride plus rosiglitazone (at half maximal dose) for those with HbA<sub>1c</sub> < 9  
Goal was absolute reduction in 1.5 percentage points in intensive control compared with standard control | Time to the first occurrence of the composite of CV events: MI, stroke, CV death, new or worsening HF, surgical intervention for cardiac, cerebrovascular, or PVD; inoperable CAD, amputation for ischaemic gangrene  
Microvascular complications  
Retinopathy: progression of retinopathy or clinically important macular oedema  
Nephropathy: doubling of SCr, SCr > 3.0 mg/dL, or GFR < 15 mL/min. Progression of albuminuria defined as increase for 2 consecutive annual visits without reversion to improved level  
First neuropathy outcome: mononeuropathy, peripheral neuropathy, or autonomic neuropathy | Median 5.6 years | HR for the intensive group 0.88, 95% CI 0.74–1.05, P = 0.14  
No significant difference in any component  
No difference in all-cause mortality (HR: 1.07, 95% CI: 0.81–1.42, P = 0.62)  
No difference in microvascular outcomes | Intensive control: 6.9%  
Standard control: 8.4% |
| **ACCORD**<sup>5</sup>  
(n = 10 251) | Intensive glucose control (HbA<sub>1c</sub>) < 6% using individualized discretion of investigators and patients vs. standard control (HbA<sub>1c</sub>, 7–7.9%) using individualized discretion of investigators and patients | First occurrence of NF MI or NF stroke or CV death  
First composite: development of renal failure (initiation of dialysis or ESRD, renal transplantation, or rise of SCr > 3.3 mg/dL), or retinal photocoagulation or vitrectomy to treat retinopathy  
Second composite: peripheral neuropathy or first composite | Mean 3.7 years  
Primary outcome HR for intensive (0.9, 95% CI: 0.78–1.03)  
All-cause mortality HR for intensive 1.21, 95% CI: 1.02–1.44 | Intensive control: 6.4% (median)  
Standard control: 7.5% (median) |
<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Inclusion</th>
<th>Background therapy</th>
<th>Primary endpoint superiority or non-inferiority</th>
<th>HF included as secondary endpoint?</th>
<th>Planned length of follow-up</th>
<th>Number of patients</th>
<th>Estimated start and completion dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP4 inhibitors</td>
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<tr>
<td>EXAMINE</td>
<td>Alogliptin vs. placebo</td>
<td>Type 2 DM, ≥18 years, HbA1c 6.5–11% (or 7–9% if on insulin), ACS</td>
<td>Monotherapy or combination anti-diabetic therapy</td>
<td>CV death, MI, or stroke</td>
<td>No</td>
<td>4.75 years</td>
<td>5400</td>
<td>9/2009–12/2014</td>
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<tr>
<td>TECOS</td>
<td>Sitagliptin vs. placebo</td>
<td>Type 2 DM, ≥50 years, HbA1c 6.5–8%, CVD</td>
<td>Monotherapy or combination anti-hyperglycaemic agents</td>
<td>CV death, MI, unstable angina, or stroke</td>
<td>Yes</td>
<td>Minimum 4</td>
<td>14 000</td>
<td>12/2008–12/2014</td>
</tr>
<tr>
<td>SAVOR (TIMI-53)</td>
<td>Saxagliptin vs. placebo</td>
<td>Type 2 DM, ≥40 years, HbA1c ≥6.5%, CVD/CV risk factors</td>
<td>Monotherapy or combination anti-diabetic therapy, except for DPP4 inhibitors and/or GLP-1 mimetics</td>
<td>CV death, MI, or stroke</td>
<td>No</td>
<td>5 years</td>
<td>16 500</td>
<td>5/2010–5/2015</td>
</tr>
<tr>
<td>CAROLINA</td>
<td>Glimepiride vs. linagliptin</td>
<td>Type 2 DM, ≥40 years, HbA1c 6.5–8.5%, CVD/CV risk factors</td>
<td>Monotherapy or combination therapy with metformin or alpha-glucosidase inhibitor; TZD, GLP-1 mimetics, DPP-IV inhibitors, or insulin not allowed</td>
<td>CV death, MI, stroke, or unstable angina; Non-inferiority, then superiority if non-inferiority met</td>
<td>No</td>
<td>8 years</td>
<td>6000</td>
<td>10/2010–9/2018</td>
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<td>GLP-1 analogues</td>
<td></td>
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<td>REWIND</td>
<td>Dulaglutide</td>
<td>Type 2 DM, HbA1c 6–10%, ACS</td>
<td>Information not available</td>
<td>CV death, MI, or stroke, hospitalization for unstable angina</td>
<td>Yes</td>
<td>Median 2 years</td>
<td>9600</td>
<td>6/2010–10/2013</td>
</tr>
<tr>
<td>ELIXA</td>
<td>Lixisenatide vs. placebo</td>
<td>Type 2 DM, HbA1c 6–10%, ACS</td>
<td>Information not available</td>
<td>CV death, MI, or stroke, hospitalization for unstable angina</td>
<td>Yes</td>
<td>Median 2 years</td>
<td>6000</td>
<td>6/2010–10/2013</td>
</tr>
<tr>
<td>EXSCEL</td>
<td>Exenatide vs. placebo</td>
<td>Type 2 DM, HbA1c 7–10%, CVD in 60%</td>
<td>Monotherapy or combination (up to 3) oral anti-hyperglycaemic therapy (no insulin)</td>
<td>CV death, MI, or stroke</td>
<td>Yes</td>
<td>5.5 years</td>
<td>9500</td>
<td>6/2010–3/2017</td>
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<tr>
<td>LEADER</td>
<td>Liraglutide vs. placebo</td>
<td>Type 2 DM, HbA1c ≥7%, ≥50 years + CVD, ≥60 years + CV risk factors</td>
<td>Anti-diabetic drug naive or with 1 or more oral anti-diabetic drugs, or insulin</td>
<td>CV death, MI, or stroke</td>
<td>Yes</td>
<td>5 years</td>
<td>8754</td>
<td>8/2010–1/2016</td>
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<td>SGLT2 inhibitors</td>
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<tr>
<td>BI 10773</td>
<td>BI 10773 (low) vs. BI 10773 (high) vs. placebo</td>
<td>Type 2 DM, ≥18 years, HbA1c 7–10%, (7–8% drug naive) CVD (CHD, stroke, PAD)</td>
<td>Drug naive or any background therapy</td>
<td>CV death, MI, or stroke</td>
<td>No</td>
<td>4 years</td>
<td>4000</td>
<td>7/2010–8/2014</td>
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<tr>
<td>Study</td>
<td>Description</td>
<td>Type 2 DM</td>
<td>Age</td>
<td>HbA1c</td>
<td>History of/CVD</td>
<td>Background standard of care for diabetes</td>
<td>Endpoint</td>
<td>Years</td>
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<td>CANVAS</td>
<td>Canagliflozin 100 mg vs. canagliflozin 300 mg vs. placebo</td>
<td>≥ 30 years, HbA1c 7–10.5%, History of high risk of CVD</td>
<td>Background standard of care for diabetes</td>
<td>CV death, MI, unstable angina, or stroke</td>
<td>No</td>
<td>4</td>
<td>4500</td>
<td>12/2009–4/2013</td>
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<tr>
<td>Glitazones/glitazars</td>
<td>ALECARDIO Aleglitazar PPARα and γ vs. placebo</td>
<td>≥ 18 years, HbA1c 6–10%, ACS</td>
<td>CV death, MI, or stroke</td>
<td>Not specified</td>
<td>4.5</td>
<td>6000</td>
<td>2/2010–7/2015</td>
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<tr>
<td>IFG/IGT/insulin resistance</td>
<td>ORIGIN45</td>
<td>2 × 2 factorial, insulin glargine vs. N-3 fatty acids vs. placebo</td>
<td>IGT/IFG, Early Type 2 DM, ≥ 50 years, CVD or CVD risk factors</td>
<td>Drug naive or monotherapy</td>
<td>(i) CV death, MI, or stroke (ii) CV death, MI, stroke, revasc, or HF</td>
<td>Superiority</td>
<td>4.5–5</td>
<td>12 612</td>
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<tr>
<td></td>
<td>ACE</td>
<td>Acarbose vs. placebo</td>
<td>IGT, ≥ 50 years, CHD</td>
<td>CV death, MI, or stroke</td>
<td>Yes</td>
<td>4</td>
<td>7500 (until 904 adjudicated events)</td>
<td>2/2009–10/2014</td>
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<tr>
<td></td>
<td>IRIS</td>
<td>Pioglitazone 45 mg vs. placebo</td>
<td>Insulin resistance (HOMA-IR &gt; 3.0) ≥ 40 years, 2 weeks—6 months after stroke/TIA</td>
<td>Fatal/non-fatal stroke Fatal/non-fatal MI</td>
<td>Yes</td>
<td>3</td>
<td>3136</td>
<td>2/2005–8/2014</td>
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</tbody>
</table>


