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Glycemic Control for Patients with Type 2 Diabetes: Our Evolving Faith in the Face of Evidence

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Abstract

Background—We sought to determine the concordance between the accumulating evidence about the impact of tight vs. less tight glycemic control in patients with type 2 diabetes since the publication of UKPDS in 1998 until 2015 with the views about that evidence published in journal articles and practice guidelines.

Methods and Results—We searched in top general medicine and specialty journals for articles referring to glycemic control appearing between 2006 and 2015 and identified the latest practice guidelines. To summarize the evidence, we included all published systematic reviews and meta-analyses of contemporary randomized trials of glycemic control measuring patient-important microvascular and macrovascular outcomes, and completed a meta-analysis of their follow-up extensions. We identified 16 guidelines and 328 statements. The body of evidence produced estimates warranting moderate confidence. This evidence reported no significant impact of tight glycemic control on the risk of dialysis/transplantation/renal death, blindness, or neuropathy. In the last decade, however, most published statements (77–100%) and guidelines (95%) unequivocally endorsed benefit. There is also no significant effect on all-cause mortality, cardiovascular mortality, or stroke; however, there is a consistent 15% relative-risk reduction of nonfatal myocardial infarction. Between 2006–2008, most statements (47–83%) endorsed the benefit; after 2008 (ACCORD), only a minority (21–36%) did.

Conclusions—Discordance exists between the research evidence and academic and clinical policy statements regarding the value of tight glycemic control to reduce micro- and macrovascular complications. This discordance may distort priorities in the research and practice agendas designed to improve the lives of patients with type 2 diabetes.

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Keywords

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Background

Type 2 diabetes mellitus is a growing pandemic and a leading cause of morbidity and mortality.¹ After the Diabetes Control and Complications Trial (DCCT)² found that tight glycemic control – a glycohemoglobin A1c (HbA1c) < 7% (53 mmol/mol) – could prevent or slow the progression of nephropathy, retinopathy, and neuropathy in patients with type 1 diabetes, a consensus, extended to patients with type 1 and type 2 diabetes, emerged: normalizing glycemia prevents diabetes complications. Guidelines, quality improvement interventions, quality-of-care measures and patient-directed marketing have since focused on achieving tight glycemic control.^{3–5} Experts labeled clinicians' failure to intensify therapy to achieve this target as clinical inertia and a quality gap.^{6–8}

As large randomized clinical trials (RCTs) and their follow-up extensions accrued, experts have interpreted their results as confirming that tight glycemic control prevented microvascular complications of type 2 diabetes, but may only prevent cardiovascular complications and mortality in some patients, perhaps those newly diagnosed with this condition.^{9–14} The body of evidence, previously summarized in meta-analyses of large RCTs, appears to confirm this impression (Table S1).^{15–25} This evidence has contributed to a consensus reflected in universal guideline recommendations, quality improvement efforts, and clinical decisions all promoting tight glycemic control (HbA1c <6.5 or 7.0%).^{26–28} The same evidence, however, has led some critics to question this consensus.^{22, 29, 30}

Given the impact on patients, healthcare delivery, and policymaking, the extent to which the consensus about the value of tight glycemic control is consistent with the body of evidence merits clarification. Accordingly, we sought to systematically examine the relationship between the body of evidence about glycemic control in type 2 diabetes and contemporary statements on the value of tight glycemic control, when compared to less tight control (HbA1c 7.0–8.5%), with regard to microvascular and macrovascular outcomes, published in the last decade in top medical journals and clinical practice guidelines.

Methods

Identification and selection of published statements referring to glycemic control

Based on the 2014 Journal Citation Reports³¹, we identified the five general medical journals (New England Journal of Medicine, the Lancet, the Journal of the American Medical Association (JAMA), the BMJ, and Annals of Internal Medicine), and clinical diabetes (Diabetes Care) and cardiology (Journal of the American College of Cardiology) journals with the highest impact factor within these categories.

Using the search engine for each journal's online site, we searched for “glycemic control” and alternative spellings in original articles, reviews, letters, commentaries, and editorials

appearing between January 2006 and March 2015. Eligible articles offered any statement about the effect of glycemic control on microvascular or macrovascular complications in patients with type 2 diabetes. We included all eligible articles from general medicine journals, and, because of the large volume of pertinent articles, only those published in the first trimester (January to March) of each year for the specialty journals. Article selection was reproducible: chance-adjusted agreement between the two reviewers (RRG, VMM) tested in 20% of the sample was $\kappa = 0.93$, 95% CI 0.85 – 1.00.

With the help of an experienced librarian, we developed an environmental scan strategy using terms for concepts of “diabetes”, “guidelines”, and “standards of care”, to identify clinical practice guidelines about diabetes without language restriction. This was strengthened with a search in the National Guideline Clearinghouse. We also consulted Mayo Clinic experts in the field to identify guidelines missed by our search strategy. Eligible guidelines were the latest version published and included statements about the effect of glycemic control on microvascular and/or macrovascular complications in patients with type 2 diabetes. Because practice standards from the American Diabetes Association (ADA) are issued yearly and we believe have broad impact, we included all published in the decade of interest. Chance-adjusted agreement for guideline selection between reviewers was perfect ($\kappa=1.0$).

Classification of statements in articles and guidelines

We classified the statements in each article and guideline about the causal relationship between achieving tight glycemic control and the prevention of microvascular and macrovascular complications in patients with type 2 diabetes as either clearly favorable or uncertain/skeptical. For example, we classified as *clearly favorable* for microvascular complications and *uncertain* for macrovascular complications the following statement: “Data from randomized trials indicate early and aggressive antihyperglycemic therapy significantly reduces the risk of long-term microvascular outcomes. Although the effects of tight glucose control on macrovascular disease are less clear”.³² This classification was reproducible ($\kappa=.87$ for journal articles, $\kappa=1.0$ for guidelines). Within each year – 2006 to 2015 – we estimated the proportion of articles with statements clearly in favor of tight glycemic control to prevent micro- and macrovascular outcomes.

Body of evidence about glycemic control

The body of large randomized trial evidence about glycemic control has been previously summarized, except for the published follow-up extensions of these RCTs. Table S1 describes contemporary large RCTs, their corresponding follow-up extensions and the meta-analyses that include these RCTs. At the individual trial level, we excluded trials that did not test contemporary treatment approaches (e.g. Kumamoto)³³, tested multifactorial risk factor reduction (e.g. Steno-2)³⁴, or evaluated specific antihyperglycemic agents (e.g. PROactive)³⁵. However, some reviews included some or all of these studies, and we retained their summaries in our analyses of the body of evidence, subject to sensitivity analyses. When necessary data were not discernible from published studies, as was the case with two extension studies, we attempted to contact authors without success. We did not impute any data.

Because the follow-up extension studies have not been summarized, we conducted a meta-analysis. To this end, we extracted the reported hazard or risk ratios and their 95% confidence intervals (CI) from each extension study and conducted a random-effects (DerSimonian and Laird) meta-analysis on each outcome of interest. As UKPDS 33 control patients also participated as controls in UKPDS 34, we constructed two pooled estimates including either one or the other study. Analyses were conducted using the OpenMeta Analyst Software.³⁶

Examined outcomes were those patients experience and consider important.^{37–39} We selected the following microvascular outcomes as important to patients: end-stage renal disease (ESRD) or dialysis, renal death, blindness, and clinical neuropathy. We also included microalbuminuria and retinal photocoagulation as they are often cited as surrogate outcomes of patient-important microvascular complications and are consistently reported in RCTs. We selected the following macrovascular outcomes as important to patients: all-cause mortality, cardiovascular (CV) mortality, nonfatal myocardial infarction (MI), fatal and nonfatal stroke, and peripheral vascular events or amputations. To rate the confidence (high, moderate, low or very low) in the estimates about the impact of glycemic control on each micro- and macrovascular outcome from this body of evidence,^{38, 40} reviewers worked together using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, taking into account risk of bias (methodological quality), directness, consistency, precision of estimates, and risk of biased reporting.

Results

Study Identification

We identified 328 journal articles (Table S2), 16 guidelines (including 10 American Diabetes Association standards from 2006 to 2015, Table S3 and S4), 11 meta-analyses published between 2009 and 2014, and 5 RCTs^{10–14} and their extension studies^{41–44} (Figures S1a and S1b and Table S1, S2 and S3).

Reliability of the body of evidence about microvascular and macrovascular outcomes

Using GRADE, we rated the body of evidence as warranting moderate confidence in estimates; it rendered precise (with >400 events for most outcomes) and consistent estimates of direct applicability at moderate risk of bias (due to lack of blinding, loss to follow-up in long-term studies, Tables S9–S11).⁴⁵ However, results were inconsistent for mortality outcomes; also the evidence was sparse for ESRD, renal death and amputations⁴⁶ (Table S12).

Relationship between statements in favor of tight glycemic control and the body of evidence

Microvascular complications—Figure 1A (Table S5) shows the relation between estimates of treatment effect for each of the included studies and contemporaneous statements about the value of tight glycemic control on microvascular complications. Since 1998, evidence warranting moderate confidence reports no significant impact of tight glycemic control on the risk of ESRD, renal death, blindness, and clinical neuropathy. The

exception was the ADVANCE trial that reported a reduction of 65% (95% CI 17 – 85) in the risk of ESRD or dialysis. These estimates are imprecise (very wide CI): important but small benefits, i.e., up to 5 fewer ESRD events per 1000 patients treated with tight glycemic control, are still consistent with the data. This imprecision may be due to lack of effect, the enrollment of low-risk patients or brief duration of follow-up.⁴⁵ Figure 2, panel A also shows a very low (<6%) incidence of all microvascular outcomes and no apparent HbA1c threshold effect on microvascular complications. In contrast, practice guidelines and published statements offer a consistent and confident consensus, with 100% of the guidelines, and 77% to 100% of the statements in favor of tight glycemic control to prevent microvascular complications (Figure 1, panel A, tables S2 and S3).

Macrovascular complications—The picture with regard to macrovascular complications is more complex. Tight glycemic control reduces the risk of nonfatal MI by 15%, a consistent finding across the included studies (Figure 1, panel B and Table S6), although there is no significant effect of tight glycemic control on all-cause and CV mortality. That a reduction in the risk of nonfatal MI is not associated with a concomitant reduction in the risk of CV death complicates its interpretation. In fact, the ACCORD study reported significant increases in the risks of all cause-mortality (by 26%, 95% CI 6–51) and of CV mortality (by 43%, 95% CI 11–86) while reporting a significant reduction in the risk of non-fatal MI (by 21%, 95% CI 5–34). These is evidence of no significant effect of tight glycemic control on the risk of strokes. The effect on amputations is imprecise in part due to very few events. Recent RCTs have enrolled lower risk participants, reducing the chance of detecting differences if they exist (Figure 2). Long-term follow-up studies that accrued more events, however, could not maintain HbA1c < 7% in the intervention arm limiting their relevance to current guideline targets (Figure 2, panel B, Figure S4).

Before the ACCORD trial, a majority of statements declared valuable to achieve tight glycemic control to prevent macrovascular complications (47% to 59%). Uncertainty clearly emerged after the publication of the results of ACCORD in 2008:¹⁴ only 21% of statements favored tight glycemic control in 2009. While biological reasons, including hypoglycemia (Figure S2 and Table S7) have been proposed and rejected,^{14, 47, 48} chance remains an explanation, the estimate likely an exaggeration produced by the trialists' decision to truncate the trial.^{49, 50} After ACCORD, the consensus about the value of tight glycemic control to prevent macrovascular complications withered, with most statements (64% to 79%) expressing uncertainty and skepticism. Only two of the guidelines examined, the ADA standards published in 2003 and in 2004, declared valuable to achieve tight glycemic control to reduce macrovascular complications.

Discussion

Our findings

While no significant impact of tight glycemic control on the risks of patient-important nephropathy, retinopathy, or neuropathy is evident, most published statements and practice guidelines endorse its value to prevent microvascular complications. It is possible that these statements rely on indirect evidence (i.e., on surrogates of these patient-important outcomes

such as microalbuminuria), but such reliance should reduce their confidence in the value of glycemic control. While the evidence supports similar cautious skepticism about the impact of glycemic control on mortality and cardiovascular endpoints, a similarly favorable consensus existed prior to the ACCORD trial (2008). Since then, the prevailing skepticism, while appropriate, may have failed to account for the consistent apparent benefits of tight glycemic control on the risk of nonfatal MI.

The use of composite endpoints that include both patient-important and surrogate outcomes may have contributed to this consensus. The UKPDS was a landmark study that reported a significant decrease in the risk of the composite “any diabetes-related endpoint” with tight glycemic control,¹⁰ although 85% of the effect was limited to one component: retinal photocoagulation. Similarly, ADVANCE investigators reported a 14% relative reduction in the risk of a composite microvascular outcome, with almost all of the effect limited to reductions in the risk of new micro- and macroalbuminuria.^{9, 12} ADVANCE researchers also reported a 65% reduction in the risk of ESRD, but this was based on very few endpoints (20 vs. 7 events) which renders statistical inference fragile.^{45, 51} ACCORD reported benefits such as delayed onset of macroalbuminuria, of 3-line worsened visual acuity, of loss of ankle jerk, and of loss of sensation to light touch, but no significant reduction in the risk of patient-important microvascular complications. The VADT also reported reduction in the risk of progression to albuminuria, but no significant impact on important microvascular outcomes.¹³ This pattern persists in meta-analyses of these RCTs and of their extensions (Figure 1A). Thus, the consensus favoring glycemic control may narrowly reflect evidence of benefit of tight glycemic control on surrogate markers of microalbuminuria and retinal photocoagulation.

Limitations and strengths of our analysis

Several concerns may reduce confidence in our analyses. We limited our review of journals to those with highest impact factor, which may capture a consensus that exists only among an elite of researchers and clinicians. That these statements agree with contemporary guidelines strengthen our sense that they represent dominant and influential, rather than fringe, views. Our focus on the last decade (2006–2015), while arbitrary, offers complete coverage: after the UKPDS, before the ACCORD, ADVANCE and VADT, before and after the publication of the respective extension reports, and present time. As others, we have excluded the Kumamoto (which tested the DCCT intervention in patients with type 2 diabetes) and UGDP trials (which was stopped early due to harm marred in controversy over its data handling) as individual trials, although their data were represented in some of the included meta-analyses. In addition, the timeframe of our systematic search for meta-analyses of RCTs (2009 to present time) offers complete coverage of all major trials: UKPDS, ACCORD, ADVANCE, and VADT, the latter published last in January 2009.

There is some concern about placing the UKPDS trial alongside the ACCORD, VADT or ADVANCE trials because the populations are different in terms of duration of diabetes, glycemic targets, antihyperglycemic agents used, comorbidities, and use of statins. Described as supportive of early aggressive intervention to reduce macrovascular complications, statements often expressed uncertainty about the applicability of the UKPDS

results to older patients with comorbidities and more advanced disease.^{48, 52} Inspection of Figure 2, however, reveals how most results of UKPDS, particularly of UKPDS 33, are similar to those of more recent RCTs for both micro- and macrovascular outcomes. Furthermore, a consistent beneficial effect on nonfatal MI is seen across all of these trials, even ACCORD. These findings should reduce our confidence that the results of the UKPDS trial are different to those of latter trials and enable us to consider these trials together as forming a body of evidence.

Our focus on outcomes important to patients may have artificially introduced uncertainty that perhaps is not as evident when one focuses on the effect of glycemic control on surrogate markers or composite endpoints (e.g., any diabetes-related complications) (Figure S3, Table S8). Surrogate markers, to be valid, need to capture all of the effect of treatment on the outcomes of interest.^{53, 54} In the ON-TARGET trial, for example, dual renin-angiotensin-aldosterone blockade prevented albuminuria, but worsened renal outcomes and mortality.⁵⁵ The inconsistencies observed in diabetes trials between the effect of glycemic control on surrogates and on outcomes important to patients should lower our confidence in relying on these surrogates for decision-making and support the case for larger and longer-term investigations.

Composite endpoints have been used in all diabetes trials and may have contributed to obfuscate their interpretation. The UKPDS used the endpoint “any diabetes-related endpoint” which included 14 components and was reduced significantly with glycemic control by 3.2%. Almost all of this reduction, 2.7%, was on the retinal photocoagulation endpoint, with almost no effect on the other components of greater importance to patients such as mortality, stroke, amputation, blindness, or need for dialysis.¹⁰ Composite endpoints that exhibit large gradients of treatment effects and of importance to patients (death and cataract extraction while very different in their importance to patients were both included in the same UKPDS endpoint) cannot be interpreted, i.e., the statement that glycemic control significantly reduced all-diabetes related complications is potentially misleading.^{56, 57} It is plausible that reliance on surrogate and composite endpoints has contributed to the observed consensus.

Implications for policy and practice

We find the overwhelming consensus in favor of tight glycemic control to prevent microvascular complications to be stronger than warranted by the evidence. This consensus likely drives guidelines and quality-of-care interventions focused on glycemic control. It also supports the US Food and Drug Administration policy to approve diabetes drugs only on the basis of their antihyperglycemic effect without requiring evidence of reduction in the risk of complications. This consensus is also driving studies like the NIH-funded GRADE trial comparing antihyperglycemic drugs on their ability to reduce HbA1c, rather than to reduce the risk of diabetes complications.⁵⁸ Given the uncertain relationship between tight glycemic control and outcomes that matter to patients, this consensus and its downstream consequences to practice, policy and research deserve review.

As of 2015, the evidence suggests that a skeptical view may be necessary to move diabetes care forward. The notion that tight glycemic control is clearly beneficial does not hold in the

face of the evidence accrued over the last decade, evidence that has fallen short of confirming this notion. The contributions of more than 27,000 patients participating in RCTs of glycemic control, their clinicians, and the investigators that designed and conducted these trials, question our confident reliance on tight glycemic control as the main or, in some cases only, strategy to prevent complications in patients with type 2 diabetes. Perhaps as a result, guideline developers are now advocating for selecting less stringent HbA1c targets in patients with recurrent severe hypoglycemia, high-comorbidity burden, or limited-life expectancy.^{52, 59}

Embracing this skeptical view may spur research to discover new therapeutic approaches to prevent diabetes complications. Consider the list of evidence-based therapies recommended in guidelines, subject of quality metrics, or routinely prescribed to patients with type 2 diabetes to prevent retinopathy or neuropathy beyond glycemic control: none. Beyond interventions to improve vascular health which may be helpful,⁶⁰ our narrow focus on hyperglycemia has kept this list empty. In this sense, we could not find in clinicaltrials.gov any ongoing trials exploring interventions to prevent microvascular complications. In contrast, where we are skeptical, there is at least one NIH program announcement calling for RCTs to reduce cardiovascular risk in older adults with diabetes.⁶¹

Moderation in expectations about the value of tight glycemic control may help advance the individualization of diabetes care protocols, whispered in recent guidelines,⁵² using shared decision making to select glycemic targets and treatments.^{62, 63} This, however, will require further research to clarify the tradeoffs involved when selecting different targets (below the point of symptomatic hyperglycemia), and when selecting glycemic control to reduce residual risk for complications (e.g., nonfatal MI) after implementing other evidence-based interventions, such as statins.⁶⁴ Recognizing the nature of the evidence also requires the revision of model-based estimates of the economic impact of tight glycemic control^{65, 66} and moderation of the exuberant support for policies of tight glycemic control with consequent overtesting and overtreatment.^{67, 68} Any moderation will have to be delicately balanced against the risk of therapeutic nihilism. A careful and thoughtful recalibration is likely to promote patient trust in our efforts to advance their best interest. Today, patients with type 2 diabetes, at least in certain parts of the world, seem to live longer lives with fewer complications.^{69–72} The evidence summarized here requires us to explore factors other than tight glycemic control to explain this improvement and better address the diabetes epidemic. Exciting new questions and new answers may surface as we look beyond glycemic control.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What Is Known

- Tight glycemic control is considered an essential strategy to prevent chronic complications in patients with type 2 diabetes.
- Practice guideline recommendations, quality improvement programs, and clinical care all promote tight glycemic control.

What the Study Adds

- The evidence accrued in the last two decades consistently demonstrates no significant benefit of tight glycemic control on patient-important micro- and macrovascular outcomes, with the exception of a 15% relative risk reduction in nonfatal myocardial infarction.
- Despite this, most published statements and all guidelines unequivocally endorse tight glycemic control to prevent microvascular complications, although the benefits for macrovascular outcomes have been tempered after one trial was stopped early because of increased cardiovascular mortality.
- The widespread consensus about the value of tight glycemic control to prevent complications in patients with type 2 diabetes needs to be recalibrated.

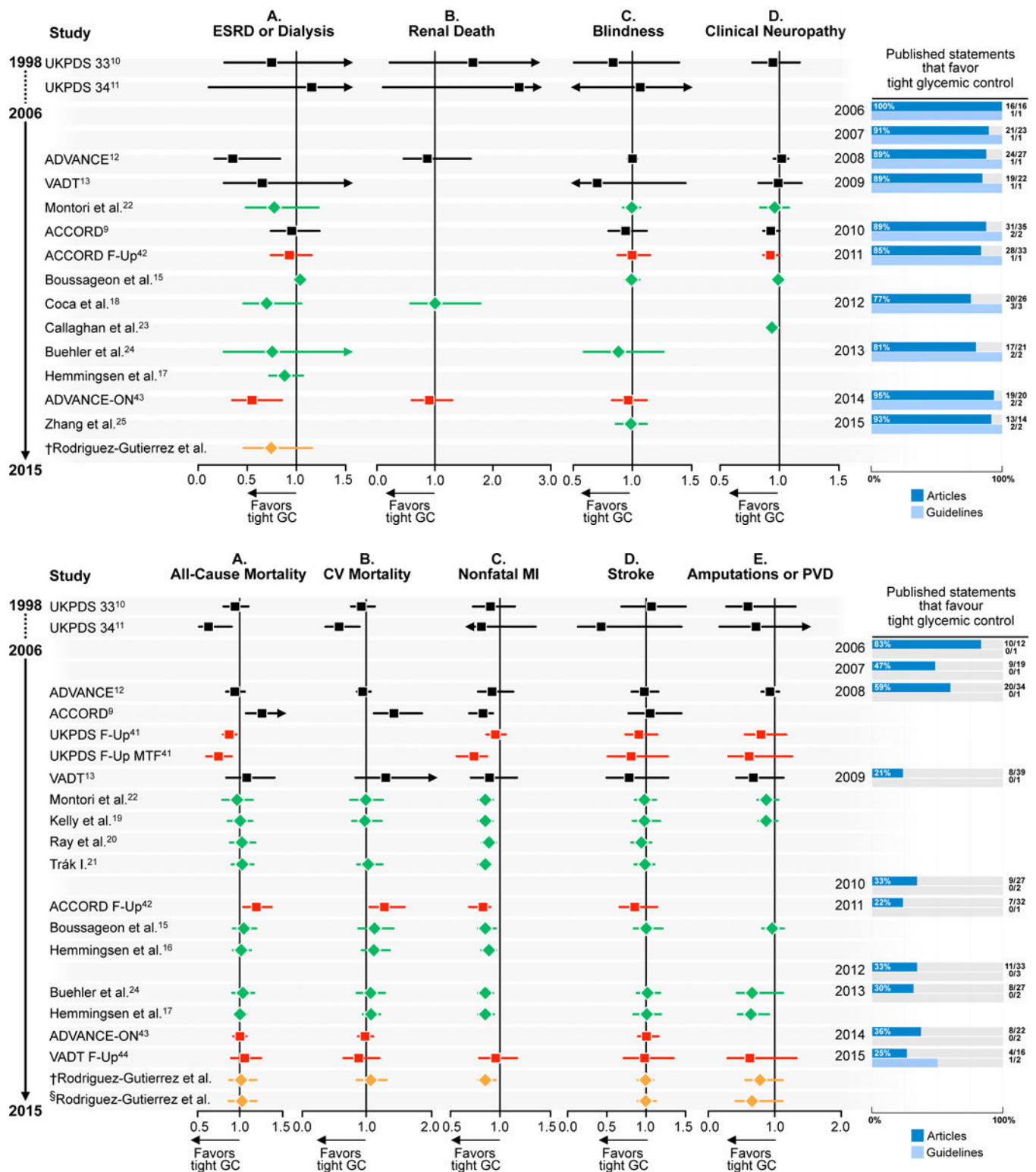
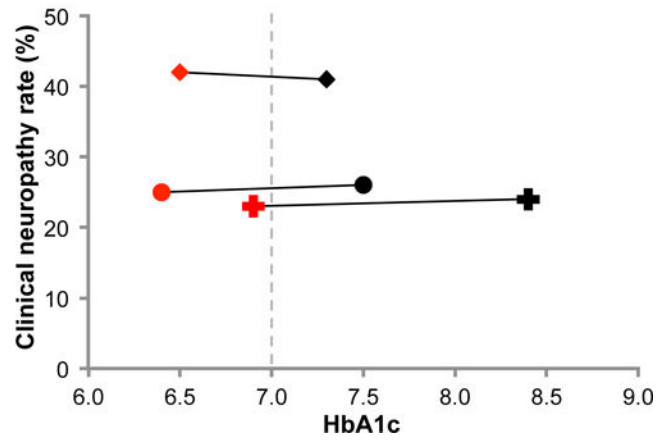
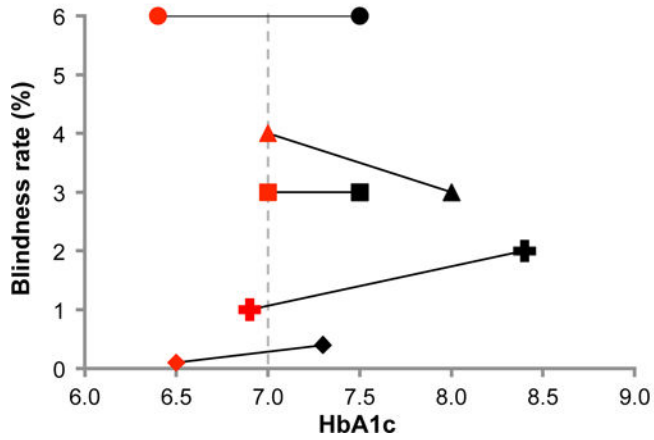
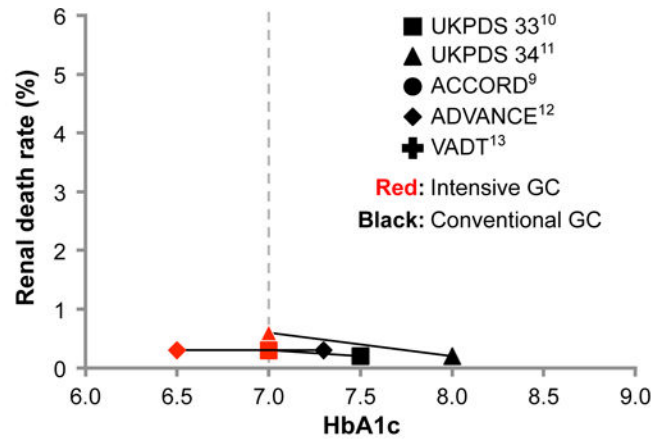
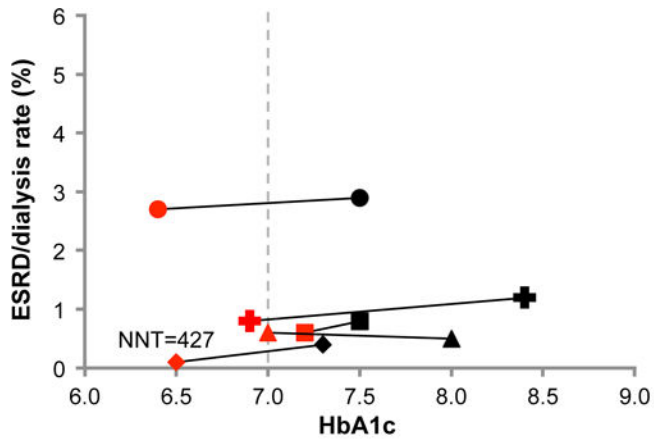


Figure 1. Body of evidence and statements published in journals and guidelines in favor of tight glycemic control in patients with type 2 diabetes mellitus. A. Microvascular complications.

The number of guideline statements is presented in parenthesis. ESRD, end-stage renal disease; GC, glycemic control. Black, randomized clinical trials; red, follow-up studies of included randomized clinical trials; green, meta-analyses; orange; meta-analyses of follow-up studies. † Meta-analysis including follow-up UKPDS 33¹⁰ and excluding follow-up UKPDS 34¹¹. B. Macrovascular complications. The number of guideline statements is presented in parenthesis. CV, cardiovascular; GC, glycemic control; MI, myocardial infarction; PVE, peripheral vascular events. Black, randomized clinical trials; red, follow-up studies of included randomized clinical trials; green, meta-analyses; orange; meta-analyses of follow-up studies. As UKPDS 33¹⁰ control patients also participated as controls in UKPDS 34¹¹, two pooled estimates were constructed including either one or the other study. †Meta-analysis including follow-up UKPDS 33⁴¹ and excluding follow-up UKPDS 34⁴¹ §Meta-analysis including follow-up UKPDS 34⁴¹ and excluding follow-up UKPDS 33⁴¹. *UKPDS 33⁴¹ Follow-up (c) includes both fatal and nonfatal-MI. *UKPDS 33¹⁰, UKPDS 34¹¹, Kelly et al.¹⁹, Trák I.²¹, Boussageon et al.¹⁵, Hemmingsen et al.¹⁶, Buehler et al.²⁴ and VADT Follow-Up⁴⁴ report only nonfatal strokes. *UKPDS 34¹¹ was not included in the 2015 meta-analysis of follow-up studies for cardiovascular mortality and nonfatal MI outcomes, as these outcomes were not reported.



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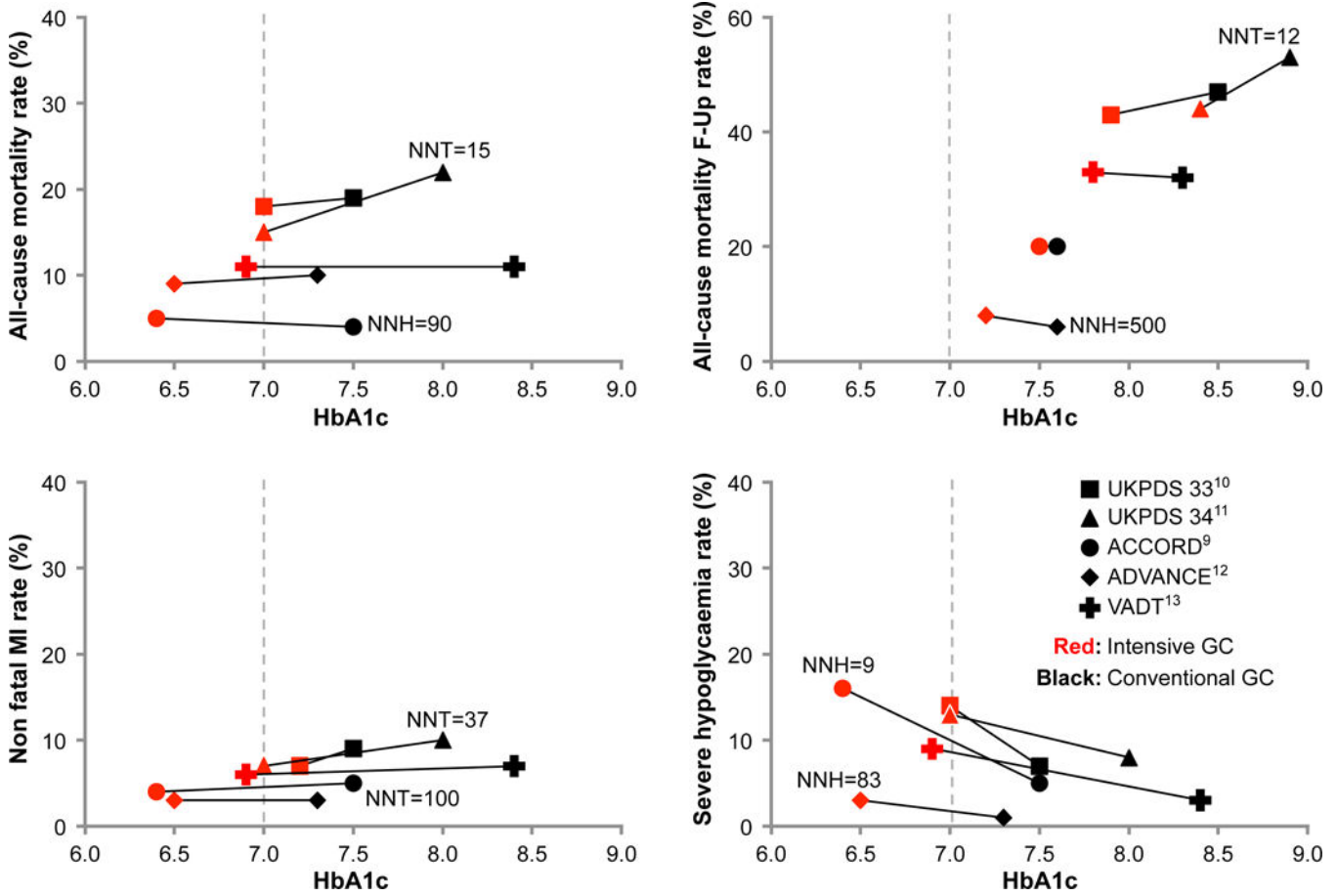


Figure 2.

A. End-of-study mean HbA1c and rate of microvascular complications and macrovascular complications in the tight (red) and less tight (black) glycemic control groups (square: UKPDS 33¹⁰; triangle: UKPDS 34¹¹; circle: ACCORD⁹; diamond: ADVANCE¹²; Cross: VADT¹³). GC, glycemic control; ESRD, end-stage renal disease; NNH, Number needed to harm; NNT, number needed to treat. B. End-of-study mean HbA1c and risk of macrovascular complications and severe hypoglycemia (Panel B) in the tight (red) and conventional (black) glycemic control groups of included studies (square: UKPDS 33¹⁰; triangle: UKPDS 34¹¹; circle: ACCORD⁹; diamond: ADVANCE¹²; Cross: VADT¹³). GC, glycemic control; MI, myocardial infarction; NNH, number needed to harm; NNT, number needed to treat.