Original Article

Glycemic Control for Patients With Type 2 Diabetes Mellitus
Our Evolving Faith in the Face of Evidence

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Background—We sought to determine the concordance between the accumulating evidence about the impact of tight versus less tight glycemic control in patients with type 2 diabetes mellitus since the publication of UKPDS (UK Prospective Diabetes Study) 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 past 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 and 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 about 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 mellitus. (***Circ Cardiovasc Qual Outcomes*. 2016;9:00-00. DOI: 10.1161/CIRCOUTCOMES.116.002901.)**

Key Words: blindness ■ complications ■ evidence-based medicine ■ myocardial infarction ■ type 2 diabetes mellitus

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Type 2 diabetes mellitus is a growing pandemic and a leading cause of morbidity and mortality.[1] After the DCCT (Diabetes Control and Complications Trial)[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 mellitus, a consensus, extended to patients with type 1 and type 2 diabetes mellitus, emerged: normalizing glycemia prevents diabetes mellitus 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 mellitus, but they 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, seems to confirm this impression (Table I in the Data Supplement).[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 mellitus and the contemporary statements on the value of tight glycemic

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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 mellitus.
- Practice guideline recommendations, quality improvement programs, and clinical care all promote tight glycemic control.

WHAT THE STUDY ADDS

- The evidence accrued in the past 2 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 mellitus needs to be recalibrated.

control, when compared with less tight control (HbA1c 7.0%–8.5%), with regard to microvascular and macrovascular outcomes, published in the past decade in top medical journals and clinical practice guidelines.

Methods

Identification and Selection of Published Statements Referring to Glycemic Control

On the basis of the 2014 Journal Citation Reports,[31] we identified the 5 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 mellitus. 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 2 reviewers (R.R.-G. and V.M.M.) tested in 20% of the sample was κ=0.93; 95% confidence interval, 0.85 to 1.00.

With the help of an experienced librarian, we developed an environmental scan strategy using the terms for concepts of diabetes, guidelines, and standards of care, to identify clinical practice guidelines about diabetes mellitus 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 macrovascular complications in patients with type 2 diabetes mellitus. Because practice standards from the American Diabetes Association are issued yearly and we believe them to have a broad impact, we included all published in the decade of interest. Chance-adjusted agreement for guideline selection between reviewers was perfect (κ=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 mellitus because 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 (κ=0.87 for journal articles, κ=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 I in the Data Supplement 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 (eg, Kumamoto),[33] tested multifactorial risk factor reduction (eg, Steno-2),[34] or evaluated specific antihyperglycemic agents (eg, 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 2 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 (CIs) from each extension study and conducted a random effects (DerSimonian and Laird) meta-analysis on each outcome of interest. Because UKPDS (UK Prospective Diabetes Study) 33 control patients also participated as controls in UKPDS 34, we constructed 2 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 because 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 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 outcomes from this body of evidence,[38,40] reviewers worked together using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach, taking into account the risk of bias (methodological quality), directness, consistency, precision of estimates, and risk of biased reporting.

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Results

Study Identification

We identified 328 journal articles (Table II in the Data Supplement), 16 guidelines (including 10 American Diabetes Association standards from 2006 to 2015, Tables II and III in the Data Supplement), 11 meta-analyses published between 2009 and 2014, and 5 RCTs[10–14] and their extension studies[41–44] (Figure IA and IB in the Data Supplement; Tables I, II, and III in the Data Supplement).

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 (because of lack of blinding, loss to follow-up in long-term studies; Tables IX through XI in the Data Supplement).[45] However, results were inconsistent for mortality outcomes; also the evidence was sparse for ESRD, renal death, and amputations[46] (Table XII in the Data Supplement).

Relationship Between Statements in Favor of Tight Glycemic Control and the Body of Evidence

Microvascular Complications

Figure 1A shows the relationship between the estimates of treatment effect for each of the included studies and contemporaneous statements about the value of tight glycemic control on microvascular complications (Table V in the Data Supplement). 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, that is, ≤5 fewer ESRD events per 1000 patients treated with tight glycemic control, are still consistent with the data. This imprecision may be because of the lack of effect, the enrollment of low-risk patients, or brief duration of follow-up.[45] Figure 2A 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 1A; Tables II and III in the Data Supplement).

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 1B; Table VI in the Data Supplement), although there is no significant effect of tight glycemic control on all-cause and cardiovascular mortality. That a reduction in the risk of nonfatal MI is not associated with a concomitant reduction in the risk of cardiovascular 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 cardiovascular mortality (by 43%; 95% CI, 11–86) while reporting a significant reduction in the risk of nonfatal 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 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 2B; Figure S4).

Before the ACCORD trial, a majority of statements declared valuable to achieve tight glycemic control to prevent macrovascular complications (47%–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. Although biological reasons, including hypoglycemia (Figure II in the Data Supplement; Table VII in the Data Supplement), 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%–79%) expressing uncertainty and skepticism. Only two of the guidelines examined, the American Diabetes Association standards published in 2003 and in 2004, declared valuable to achieve tight glycemic control to reduce macrovascular complications.

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Discussion

Our Findings

Although 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 (ie, on surrogates of these patient-important outcomes, such as microalbuminuria), but such reliance should reduce their confidence in the value of glycemic control. Although the evidence supports similar cautious skepticism about the impact of glycemic control on mortality and cardiovascular end points, a similarly favorable consensus existed before 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 end points 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 mellitus–related end point 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 few end points (20 versus 7 events), which renders statistical inference fragile.[45,51]

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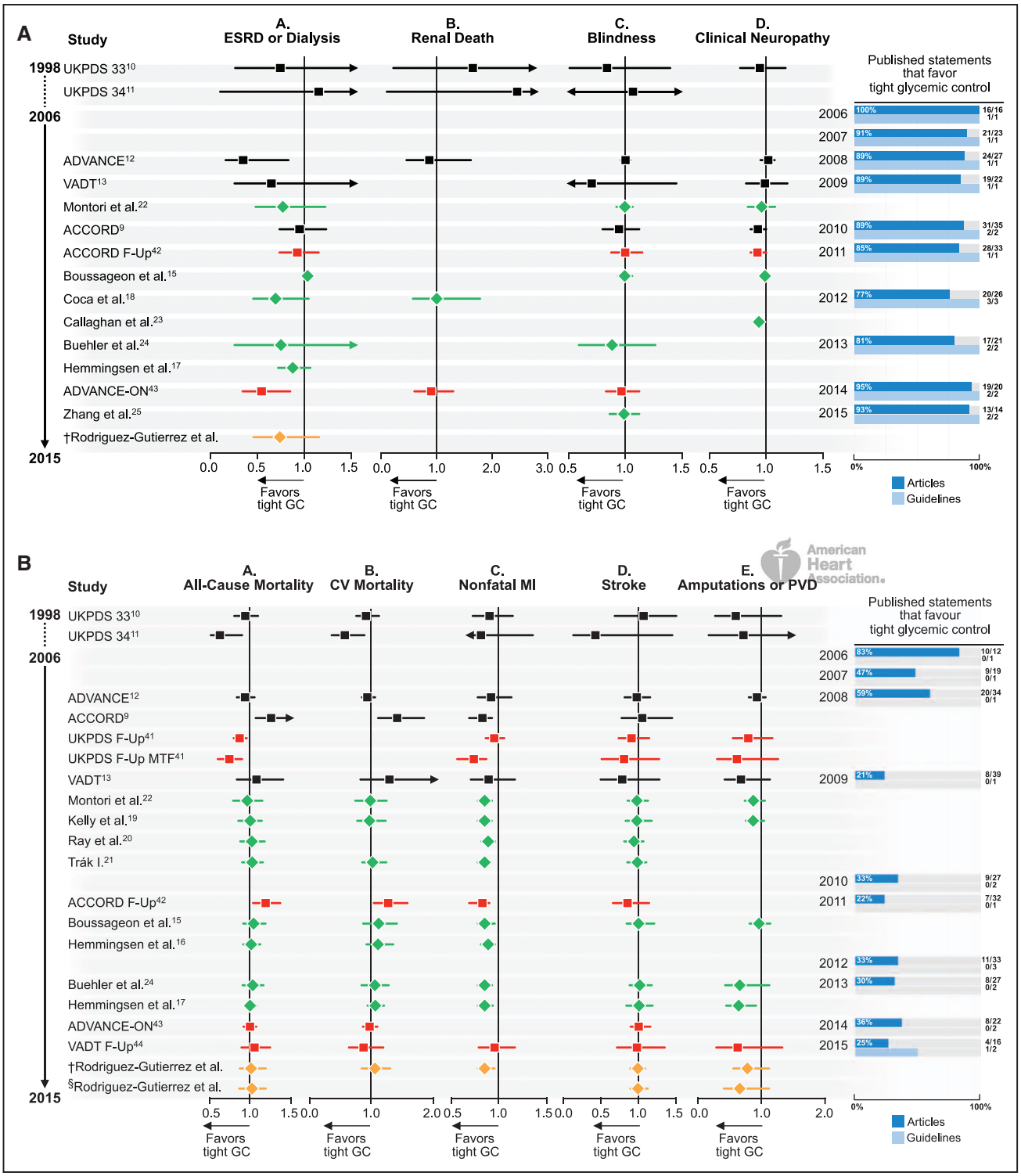

Figure 1. Body of evidence and statements published in journals and guidelines in favor of tight glycemic control in patients with type 2 diabetes mellitus**. A**, Microvascular complications. The number of guideline statements is presented in parenthesis. ESRD indicates end-stage renal disease; and GC, glycemic control. Black, randomized clinical trials; red, follow-up studies of included randomized clinical trials; green, meta-analyses; and orange; meta-analyses of follow-up studies. †Meta-analysis including follow-up UKPDS 33[10] and excluding follow-up UKPDS 34.[11] **B**, Macrovascular complications. The number of guideline statements is presented in parenthesis. CV indicates cardiovascular; GC, glycemic control. Black, randomized clinical trials; red, follow-up studies of included randomized clinical trials; green, meta-analyses; and orange; meta-analyses of follow-up studies. Because UKPDS 33[10] control patients also participated as controls in UKPDS 34,[11] 2 pooled estimates were constructed including either one or the other study. †Meta-analysis including follow-up UKPDS 33[41] and excluding follow-up UKPDS 34.[41] §Meta-analysis including follow-up UKPDS 34[41] and excluding follow-up UKPDS 33.[41] *UKPDS 33.[41] Follow-up (**C**) includes both fatal and nonfatal myocardial infarction (MI). *UKPDS 33,[10] UKPDS 34,[11] Kelly et al,[19] Trák,[21] Boussageon et al,[15] Hemmingsen et al,[16] Buehler et al,[24] and VADT. Follow-up[44] reports only nonfatal strokes. *UKPDS 34[11] 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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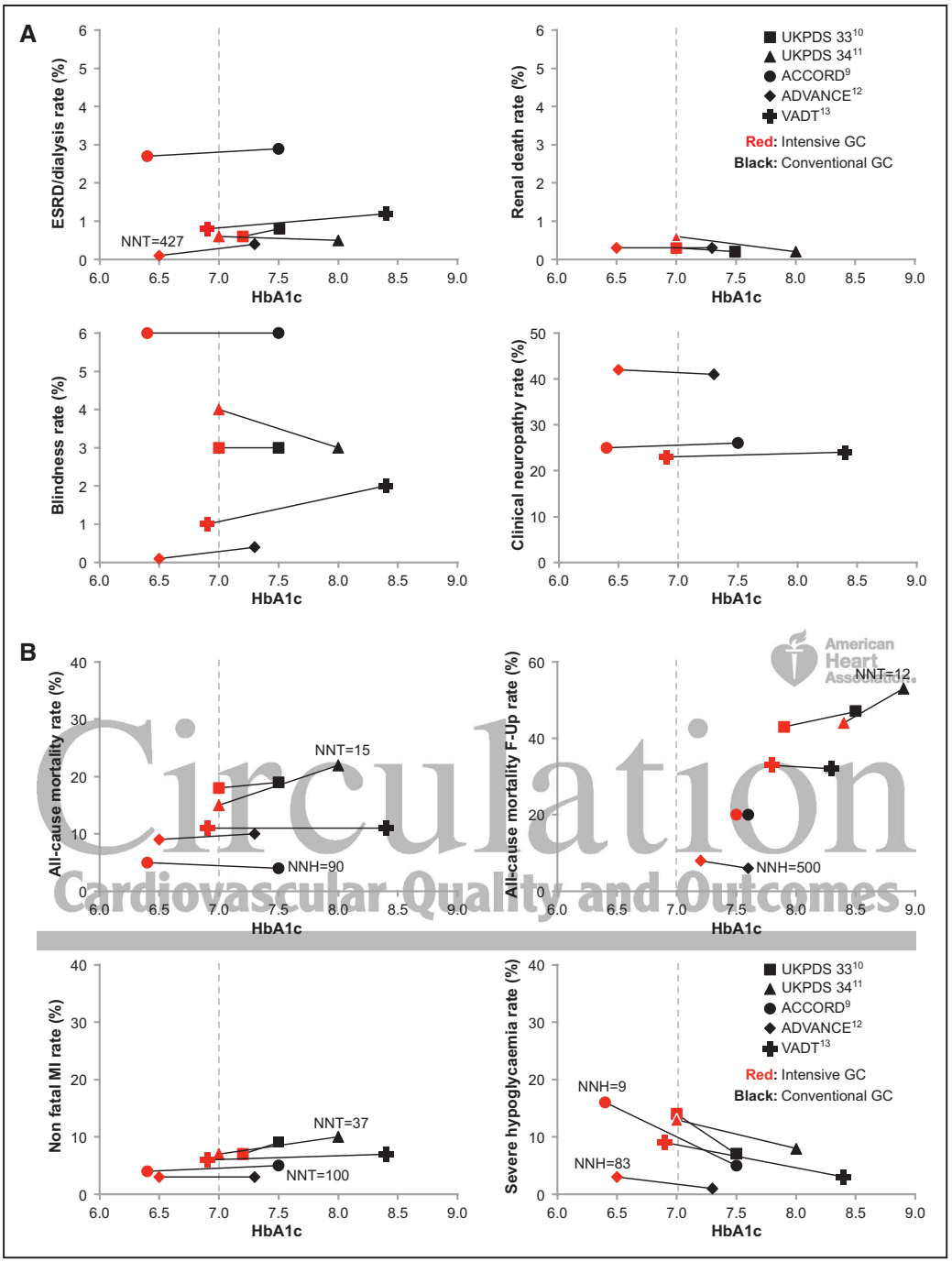

Figure 2. A, End-of-study mean glycohemoglobin A1c (HbA1c) and rate of microvascular complications and macrovascular complications in the tight (red) and less tight (black) glycemic control groups (square: UKPDS 33[10]; triangle: UKPDS 34[11]; circle: ACCORD[9]; diamond: ADVANCE[12]; and Cross: VADT[13]). ESRD indicates end-stage renal disease; GC, glycemic control; NNH, Number needed to harm; and NNT, number needed to treat. **B**, End-of-study mean HbA1c and risk of macrovascular complications and severe hypoglycemia (**B**) in the tight (red) and conventional (black) glycemic control groups of included studies (square: UKPDS 33[10]; triangle: UKPDS 34[11]; circle: ACCORD[9]; diamond: ADVANCE[12]; and Cross: VADT[13]). MI indicates myocardial infarction.

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

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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 past 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 mellitus) and UGDP trials (which was stopped early because of 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 concerns about placing the UKPDS trial alongside the ACCORD, VADT, or ADVANCE trials because the population are different in terms of duration of diabetes mellitus, 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 end points (eg, any diabetes mellitus–related complications; Figure III in the Data Supplement; Table VIII in the Data Supplement). 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 end points have been used in all diabetes mellitus trials and may have contributed to obfuscate their interpretation. The UKPDS used the end point "any diabetes mellitus–related end point," 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 end point, 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 end points 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 end point) cannot be interpreted, that is, the statement that glycemic control significantly reduced all diabetes mellitus–related complications is potentially misleading.[56,57] It is plausible that reliance on surrogate and composite end points 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 mellitus 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 such as the National Institutes of Health–funded GRADE trial comparing antihyperglycemic drugs on their ability to reduce HbA1c, rather than to reduce the risk of diabetes mellitus 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 mellitus care forward. The notion that tight glycemic control is clearly beneficial does not hold in the face of the evidence accrued during the past decade, evidence that has fallen short of confirming this notion. The contributions of >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 mellitus. 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 mellitus complications. Consider the list of evidence-based therapies recommended in guidelines, subject of quality metrics, or routinely prescribed to patients with type 2 diabetes mellitus to prevent retinopathy or neuropathy beyond glycemic control: none. Beyond interventions to improve vascular health that 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 1 National Institutes of Health program announcement calling for RCTs to reduce cardiovascular risk in older adults with diabetes mellitus.[61]

Moderation in expectations about the value of tight glycemic control may help advance the individualization of diabetes mellitus 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

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the point of symptomatic hyperglycemia), and when selecting glycemic control to reduce the residual risk of complications (eg, 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 mellitus, 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 mellitus epidemic. Exciting new questions and new answers may surface as we look beyond glycemic control.

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Disclosures

None.

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

René Rodríguez-Gutiérrez and Victor M. Montori

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SUPPLEMENTAL MATERIAL

Supplemental Material- Table of Contents

Figures

Tables

References

Figure S1a. Articles selection diagram for the statements in articles**.**

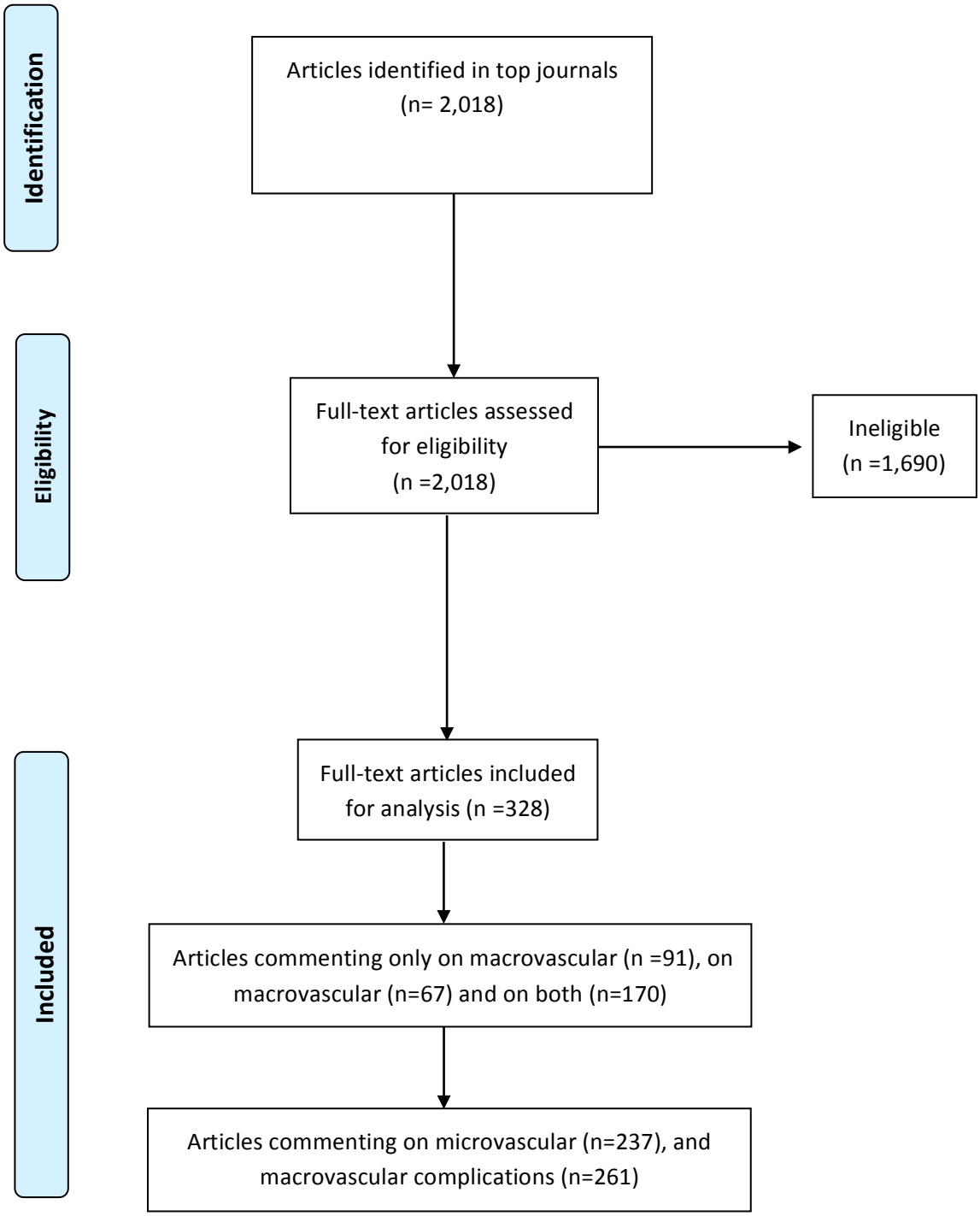
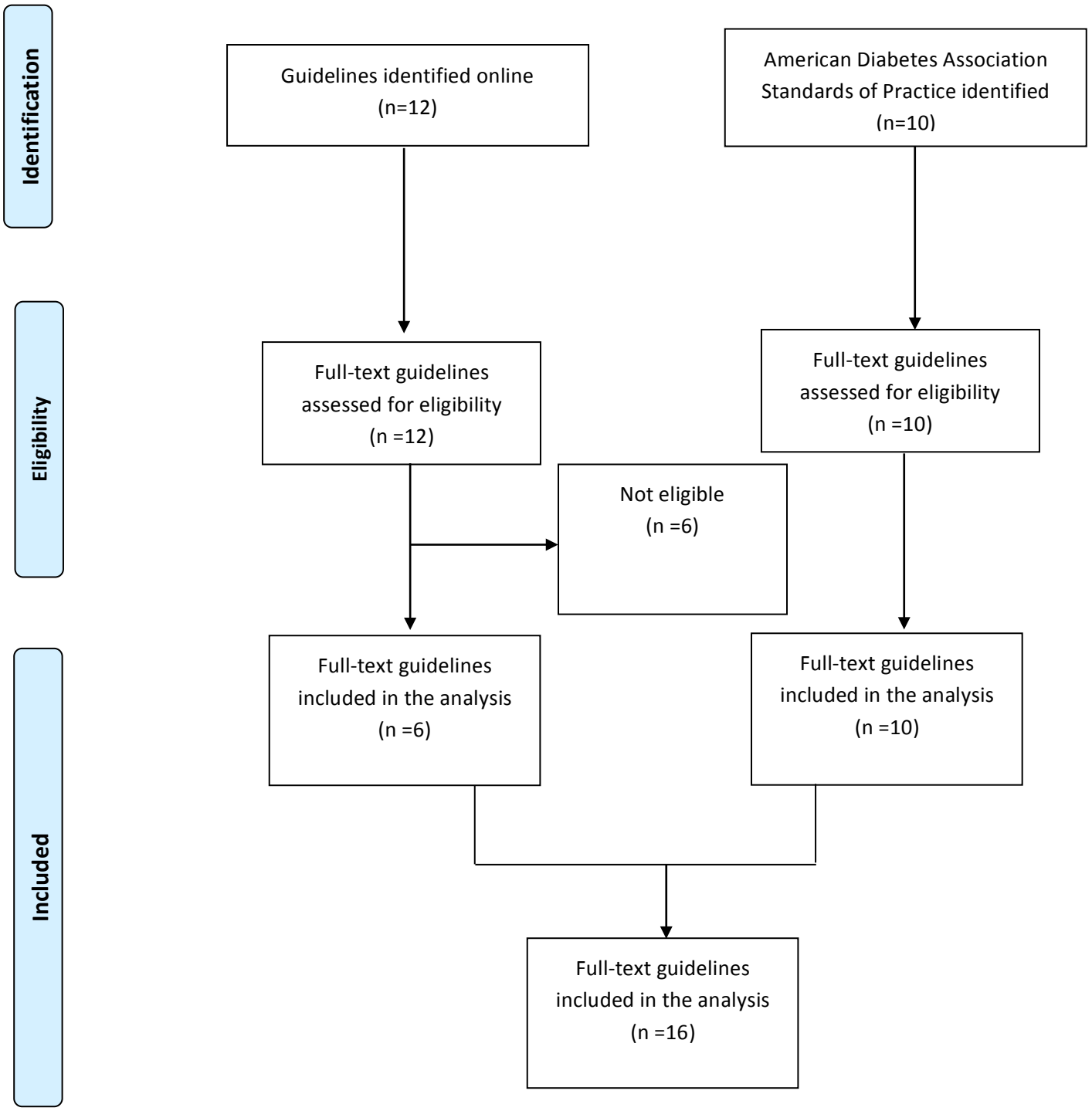
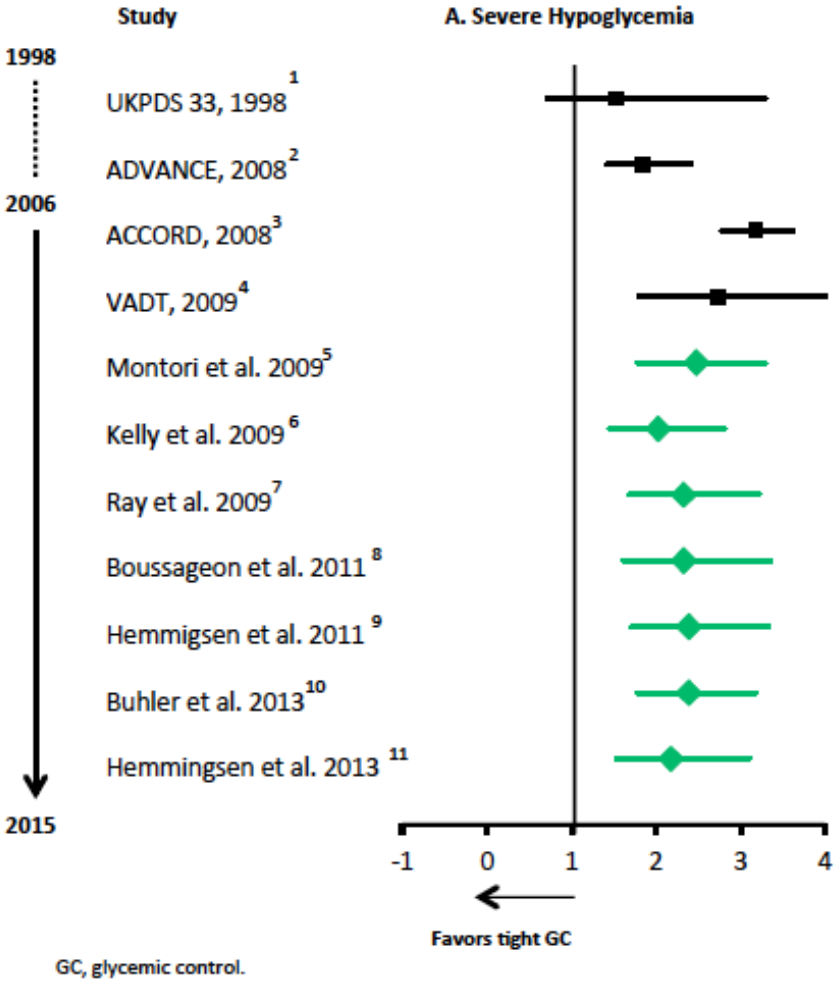


Figure S1b. Clinical practice diabetes guidelines selection diagram**.**



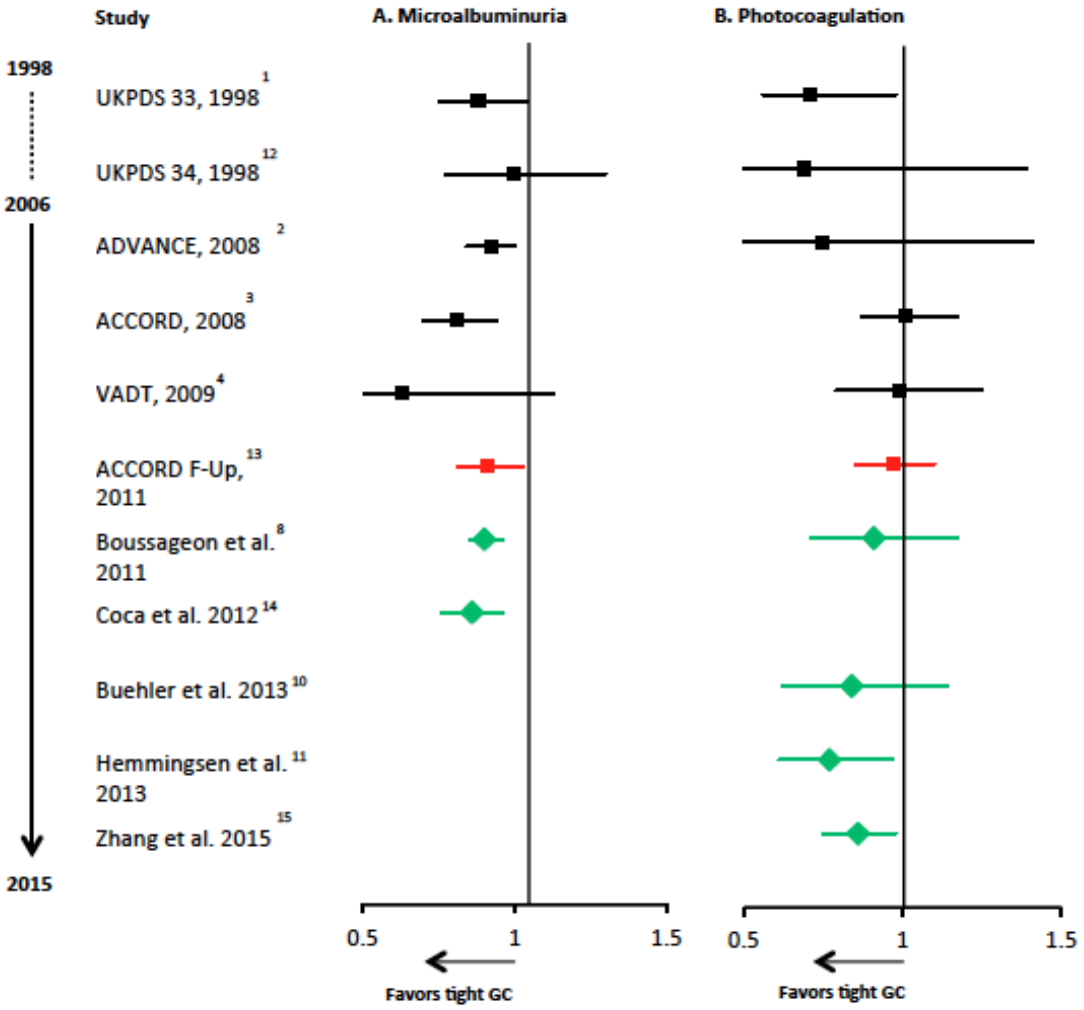
Not eligible guidelines (due to lack of clear statements with regard micro- or macrovascular diabetes outcomes were the National Institute of Health Excellence, The Japan Diabetes Society, Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA), Association Latino Americana de Diabetes (ALAD), Australian Diabetes Society, Joslin Diabetes Center Guidelines

Figure S2. Body of evidence on the effect of glycemic control on severe hypoglycemia.



GC, glycemic control.

Figure S3. Body of evidence and statements in articles and guidelines in favour of tight glycemic control with regard to microalbuminuria and photocoagulation (surrogate markers)



Statements about Tight Control

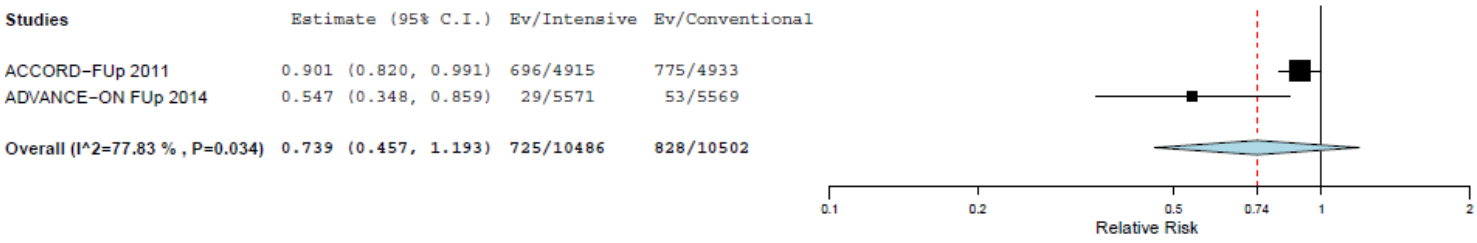
Year	Favorable	Uncertain	%
2006	17 (1)	0	100
2007	22 (2)	2	92
2008	25 (1)	3	89
2009	20 (1)	3	87
2010	32 (2)	4	89
2011	29 (1)	5	85
2012	21 (3)	6	78
2013	18 (2)	4	82
2014	20 (2)	1	95
2015	14 (2)	1	93

F-Up, follow up; GC, glycemic control; F, Favor; NF, not in favor.
In parenthesis the number (n=) of guidelines.

Figure S4. Meta-analysis of extension studies. Including UKPDS 33[1]

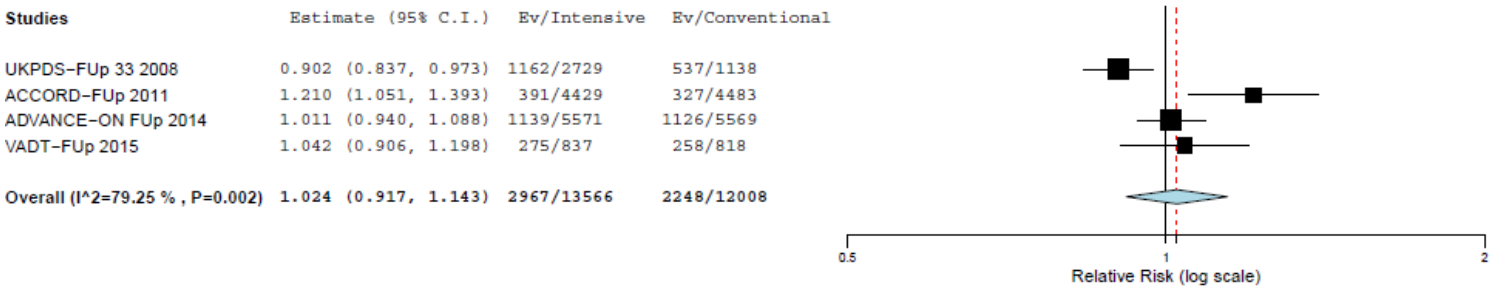
A. ESRD study

Study names	Weights
ACCORD-FUp[13]:	60.7%
ADVANCE-ON FUp[16]:	39.2%



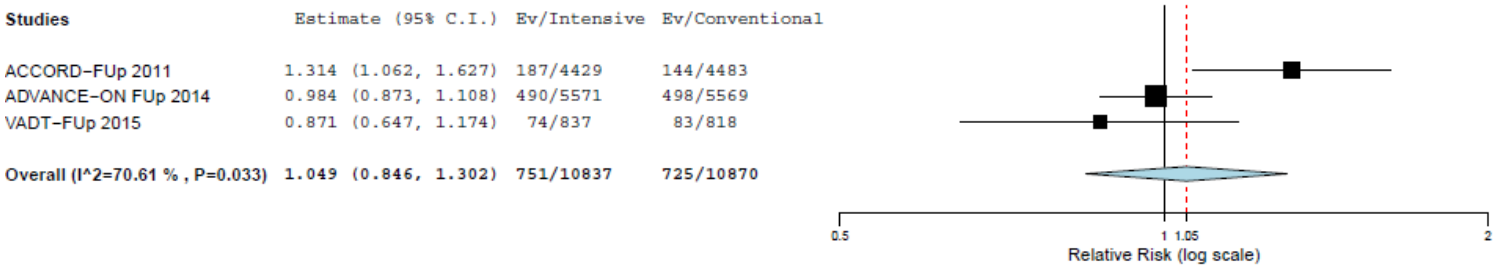
B. All-Cause Mortality

Study names	Weights
UKPDS-FUp 33[17]:	28.4%
ACCORD-FUp[13]:	21.3%
ADVANCE-ON F-Up[16]:	28.6%
VADT-FUp[18]:	21.4%



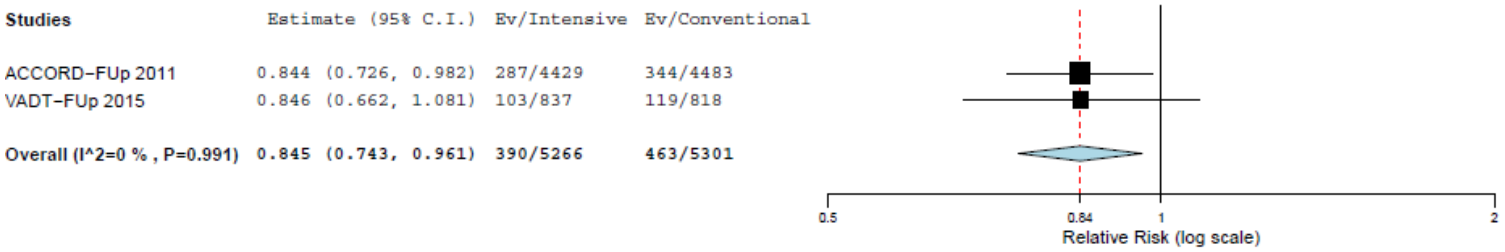
C. CV Mortality†

Study names	Weights
ACCORD-FUp[13]:	33.5%
ADVANCE-ON FUp[16]:	42.1%
VADT-FUp[18]:	24.3%



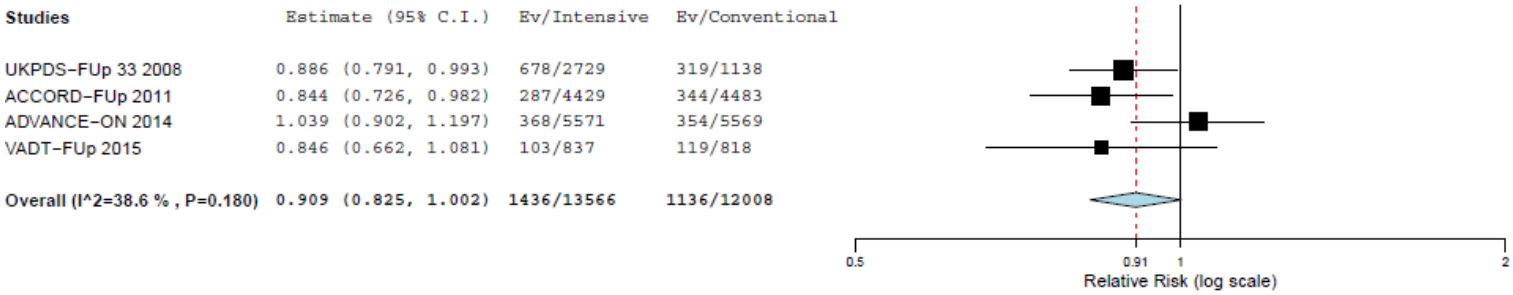
D. Non-Fatal Myocardial Infarctions†

Study names	Weights
ACCORD-FUp[13]:	75.254%
VADT-FUp[18]:	24.746



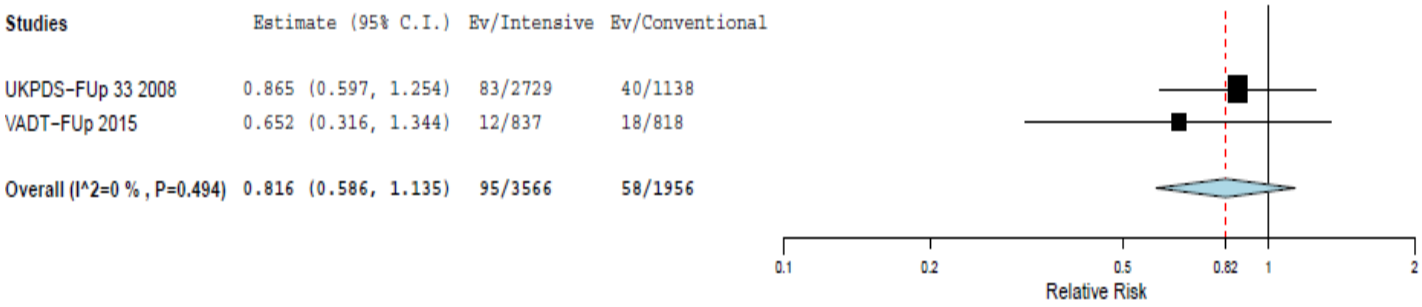
E. Fatal and Non-Fatal Stroke^

Study names	Weights
UKPDS-FUp 33[17]:	19.2%
ACCORD-FUp[13]:	12.7%
ADVANCE-ON FUp[16]:	58.9%
VADT-FUp[18]:	9.0%



F. Amputations

Study names	Weights
UKPDS-FUp 33[17]:	78.665%
VADT-FUp[18]:	21.335%



† Did not include neither UKPDS 33[1] or UKPDS 34[12]

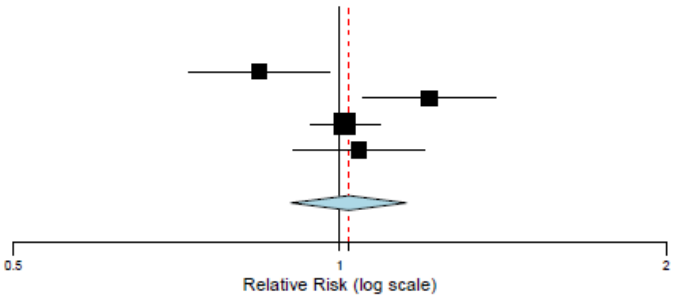
^ Includes analysis of fatal and non-fatal stroke.

Figure S5. Meta-analysis of extension studies. Including UKPDS 34[12]

A. All-Cause Mortality

Study names	Weights
UKPDS-FUp 34[41]:	22.593%
ACCORD-FUp[42]:	23.491%
ADVANCE-ON FUp[43]:	30.323%
VADT-FUp[44]:	23.593%

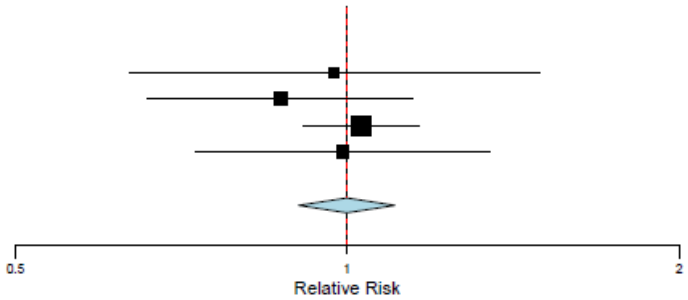
Studies	Estimate (95% C.I.)	Ev/Intensive	Ev/Conventional
UKPDS-FUp 34 2008	0.842 (0.725, 0.978)	152/342	217/411
ACCORD-FUp 2011	1.210 (1.051, 1.393)	391/4429	327/4483
ADVANCE-ON FUp 2014	1.011 (0.940, 1.088)	1139/5571	1126/5569
VADT-FUp 2015	1.042 (0.906, 1.198)	275/837	258/818
Overall (I^2=75.26 % , P=0.007)	**1.019 (0.901, 1.152)**	**1957/11179**	**1928/11281**



B. Fatal and Non-Fatal Stroke^

Study names	Weights
UKPDS-FUp 34[41]:	5.2%
ACCORD-FUp[42]:	14.9%
ADVANCE-ON FUp[43]:	69.1%
VADT-FUp[44]:	10.6%

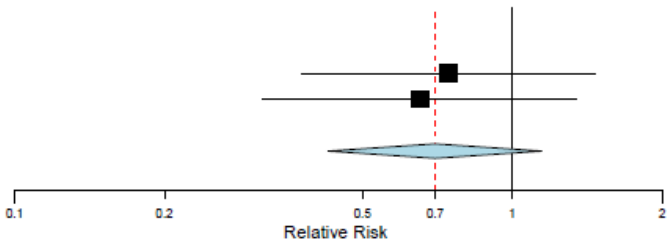
Studies	Estimate (95% C.I.)	Ev/Intensive	Ev/Conventional
UKPDS-FUp 34 2008	0.973 (0.634, 1.494)	34/342	42/411
ACCORD-FUp 2011	0.869 (0.659, 1.146)	91/4429	106/4483
ADVANCE-ON FUp 2014	1.029 (0.912, 1.161)	491/5571	477/5569
VADT-FUp 2015	0.991 (0.729, 1.346)	75/837	74/818
Overall (I^2=0 % , P=0.747)	**0.999 (0.903, 1.105)**	**691/11179**	**699/11281**



C. Amputations

Study names	Weights
UKPDS-FUp 34[41]:	52.064%
VADT-FUp[44]:	47.936%

Studies	Estimate (95% C.I.)	Ev/Intensive	Ev/Conventional
UKPDS-FUp 34 2008	0.744 (0.378, 1.464)	13/342	21/411
VADT-FUp 2015	0.652 (0.316, 1.344)	12/837	18/818
Overall (I^2=0 % , P=0.793)	**0.699 (0.427, 1.147)**	**25/1179**	**39/1229**



^ Includes analysis of fatal and non-fatal stroke.

Table S1. Meta-analysis, RCTs and extension studied included as part of the body of evidence.

S1a. Meta-analysis that included only core studies of glycemic control

Study/ Year Pub.	Included Studies	No. Patients	Outcomes Reported
Montori et al. 2009[5]	UKPDS 33 UKPDS 34 ADVANCE ACCORD VADT	28 753	Microvascular Macrovascular Hypoglycemia
Kelly et al. 2009[6]	UKPDS 33 UKPDS 34 ADVANCE ACCORD VADT	27 802	Macrovascular Hypoglycemia

S1b. Meta-analysis that included other studies besides 5 Core Studies.

Study/ Year Pub.	Included Studies	No. Patients	Outcomes Reported
Ray et al. 2009[7]	UKPDS 33,34 PROactive ADVANCE VADT ACCORD	33 040	Macrovascular Hypoglycemia
Trák I. 2009[19]	UKPDS PROactive ADVANCE ACCORD VADT	32 629	Macrovascular
Boussageon et al. 2011[8]	13 Trials* Including: UGDP (1975,76 and 1982) Kumamoto PROactive HOME	34 533	Microvascular Macrovascular Hypoglycemia
Hemmingsen et al. 2011[9]	14 Trials* Including: UGDP REMBO Service et al. Kumamoto VA CSDM	28 614	Microvascular Macrovascular Hypoglycemia
Coca et al. 2012[14]	Kumamoto UKPDS 33 UKPDS 34 VADT ACCORD ADVANCE VA CSDM	28 065	Microvascular (Renal Endpoints)
Callaghan et al. 2012[20]	ACCORD Azad et al. VADT Tovi et al.	6669	Microvascular (Neuropathy)
Buehler et al. 2013[10]	Kumamoto UKPDS ADVANCE ACCORD VADT VA CSDM	27 654	Microvascular Macrovascular Hypoglycemia
Hemmingsen et al. 2013[11]	28 Trials* Including: UGDP (1975)	34 912	Microvascular Macrovascular Hypoglycemic

	Kumamoto Steno-2 Service et al. ADDITION-Europe, Leicester, Netherlands REMBO IDA DIGAMI 2 VA CSDM		
Zhang et al. 2015[15]	Kumamoto UKPDS 33 UKPDS 34 ADVANCE ACCORD VADT VA CSDM AdRem	32 523	Microvascular (Retinopathy)

*Also included in their analysis UKPDS, ACCORD, ADVANCE and VADT.

Table S1c. Randomized clinical trials included.

Study/ Year Pub.	Location	Total N=	Mean HbA1c	CVD	Lost F-Up	Duration of Diabetes Dx.	Trial Duration	Glycemic Target Intensive	HbA1c Achieved Intensive	Glycemic Target Con.	HbA1c Achieved Con.
UKPDS 33 1998[1]	United Kingdom 23 Centers	3867	7.1%	0%	4%	Recent Diagnosis	10.1 years	FPG <108 mg/dl	7.0%	Best Achievable FPG	7.9%
UKPDS 34 1998[12]	United Kingdom	753	7.2%	0%	3%	Recent Diagnosis	10.7 Years	FPG <108 mg/dl	7.0%	Best Achievable FPG	8.0%
ACCORD 2008[3]	US and CA 77 Centers	10 251	8.3%	35%	9%	10 years	3.7 Years	HbA1c < 6.0%	6.4%	HbA1c 7.0-7.9%	7.5%
ADVANCE 2008[2]	215 Centers 20 Countries	11 140	7.5%	32%	14%	8 years	5 years	HbA1c < 6.5%	6.5%	HbA1c Per Local Guidelines	7.3%
VADT 2009[4]	US 20 Centers	1791	9.4%	40%	4%	11.5	5.6 years	HbA1c < 6.0%	6.9%	HbA1c 8.0-9.0%	8.4%

Table S1d. Extension studies.

Study/ Year Pub.	Total Follow-Up	Post-Trial Follow-Up	No. Initial Patients	No. Patients Follow-Up	HbA1c End of Study Intensive	HbA1c End of Follow-Up Intensive	HbA1c End of Study Conventional	HbA1c End of Follow-Up Conventional
UKPDS 33 2008[17]	16.8 years	8.5 years	3867	2998	7.0%	7.9%	7.4%	8.5%
UKPDS 34 2008[17]	17.7 years	8.8 years	1704	588	7.0%	8.4%	8.0%	8.9%
ACCORD 2011[13]	5.0 years	1.3 years	10 251	8912	6.4%	7.2%	7.5%	7.6%
ADVANCE 2014[16]	9.9 years	5.4 years	11 140	5131	6.5%	7.5%	7.3%	7.5%
VADT 2015[18]	9.8 years	4.2 years	1791	1391	6.9%	7.8%	8.4%	8.3%*

*Exact data only available for 1st year after end of study.

Table S2. Articles included by year and journal.

Journal	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total (%)
NEJM	2	6	7	3	8	1	6	5	3	0	41 (12.5)
The Lancet	1	0	5	11	6	3	4	3	5	2	40 (12.2)
JAMA	2	7	3	5	4	6	2	3	7	1	40 (12.2)
The BMJ	4	2	3	2	5	9	7	6	1	1	40 (12.2)
Annals of IM	0	4	10	9	4	5	9	0	1	2	44 (13.4)
JACC	1	2	1	4	6	1	5	4	0	0	24 (7.3)
Diabetes Care	7	5	10	8	10	18	6	6	13	16	99 (30.2)
Total	17	26	39	42	43	43	39	27	30	22	328

NEJM, New England Journal of Medicine; JAMA, Journal of the American Medical Association; BMJ, British Medical Journal; IM, Internal Medicine; JACC, Journal of the American College of Cardiology

Table S3. American Diabetes Association guidelines 1998-2015 and their position regarding tight glycemic control.

Guideline	Year	Microvascular	Macrovascular	HbA1c Goal
American Diabetes Association[21]	2006	Favourable	Uncertain	<6.0-7.0%
American Diabetes Association[22]	2007	Favourable	Uncertain	<6.0-7.0%
American Diabetes Association[23]	2008	Favourable	Uncertain	<6.0-7.0%
American Diabetes Association[24]	2009	Favourable	Uncertain	<7.0%*
American Diabetes Association[25]	2010	Favourable	Uncertain	<7.0%*
American Diabetes Association[26]	2011	Favourable	Uncertain	<7.0%*
American Diabetes Association[27]	2012	Favourable	Uncertain	<7.0%*
American Diabetes Association[28]	2013	Favourable	Uncertain	<7.0%*
American Diabetes Association[29]	2014	Favourable	Uncertain	<7.0%*
American Diabetes Association[30]	2015	Favourable	Uncertain	<7.0%*

*More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations.

Table S4. Latest version of included guidelines and their position regarding tight glycemic control.

Guideline	Year	Microvascular	Macrovascular	HbA1c Goal
Department of Veterans Affairs and The Department of Defense[31]	2010	Favourable	Uncertain	<7.0%*
American Diabetes Association/European Association for the Study of Diabetes[32]	2012	Favourable	Uncertain	<7.0%*
International Diabetes Federation[33]	2012	Favourable	Uncertain	<7.0%*
Canadian Diabetes Association[34]	2013	Favourable	Uncertain	≤ 7.0%*
The Royal Australian College of General Practitioners[35]	2014-2015	Favourable	Uncertain	≤ 7.0%*
American Association of Clinical Endocrinologists/ American College of Endocrinology[36]	2015	Favourable	Uncertain	≤ 6.5%*

*More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations

Table S5. Point estimates and 95% confidence intervals for microvascular outcomes.

Study/Year	ESRD or Dialysis	Renal Death	Blindness	Clinical Neuropathy
UKPDS 33 1998[1]	0.73 (0.25-2.14)	1.63 (0.21-12.49)	0.84 (0.51-1.40)	0.95 (0.76-1.18)
UKPDS 34 1998[12]	1.14 (0.09-14.94)	2.44 (0.10-57.46)	1.07 (0.38-2.99)	-
ADVANCE 2008[2]	0.35 (0.15-0.83)	0.85 (0.45-1.62)	1.01 (0.97-1.04)	1.02 (0.97-1.06)
VADT 2009[4]	0.64 (0.25-1.64)	-	0.71 (0.35-1.46)	0.99 (0.82-1.20)
Montori et al. 2009[5]	0.76 (0.47-1.23) I2=0%	-	1.00 (0.93-1.07) I2=0%	0.95 (0.84-1.08) I2=50%
ACCORD 2010[3]	0.95 (0.73-1.24)	-	0.95 (0.80-1.13)	0.93 (0.87-1.01)
ACCORD F-Up 2011[13]	0.92 (0.73-1.16)	-	1.01 (0.88-1.16)	0.92 (0.86-1.01)
Boussageon et al. 2011[8]	1.03 (0.98-1.08) I2=0%	-	1.00 (0.96-1.05) I2=0%	0.99 (0.95-1.03) I2=0%
Coca et al. 2012[14]	0.69 (0.46-1.05) I2=43%	0.99 (0.55-1.79) I2=0%	-	-
Callaghan et al. 2012[20]	-	-	-	0.94 (0.90-1.00) I2=0%
Buehler et al. 2013[10]	0.74 (0.33—1.64) I2=NR	-	0.88 (0.60-1.27) I2=NR	-
Hemmingsen et al. 2013[11]	0.87 (0.71-1.06) I2=0%	-	-	-
ADVANCE-ON 2014 [16]	0.54 (0.34-0.85)	0.89 (0.60-1.31)	0.97 (0.83-1.13)	-
Zhang et al. 2015[15]	-	-	0.99 (0.86-1.13) I2=0%	-
Meta-analysis F-Up Studies 2015	0.73 (0.46-1.16) I2=77%	-	-	-

NR, not reported. I^2= Heterogeneity

Table S6. Point estimates and 95% confidence intervals for macrovascular outcomes.

Study/Year	All-Cause Mortality	CV Mortality	Non-Fatal MI	Stroke	Amputations/ PVD
UKPDS 33 1998[1]	0.94 (0.80-1.10)	0.91 (0.75-1.12)	0.79 (0.58-1.09)	1.07 (0.68-1.69)*	0.61 (0.28-1.33)
UKPDS 34 1998[12]	0.62 (0.42-0.90)	0.57 (0.36-0.89)	0.69 (0.35-1.34)	0.42 (0.12-1.45)*	0.74 (0.19-2.89)
ADVANCE 2008[2]	0.93 (0.83-1.06)	0.94 (0.84-1.06)	0.98 (0.79-1.22)	0.97 (0.81-1.15)	0.94 (0.81-1.08)
ACCORD 2008[3]	1.26 (1.06-1.51)	1.43 (1.11-1.86)	0.79 (0.66-0.95)	1.05 (0.77-1.45)	-
UKPDS F-Up 2008[17]	0.87 (0.79-0.96)	-	0.85 (0.74–0.97) §	0.91 (0.73-1.13)	0.82 (0.56-1.19)
UKPDS F-Up MTF 2008[17]	0.73 (0.59-0.89)	-	0.67 (0.51–0.89) §	0.80 (0.50-1.27)	0.63 (0.32-1.27)
VADT 2009[4]	1.08 (0.83-1.41)	1.32 (0.83-2.11)	0.78 (0.55-1.11)	0.78 (0.48-1.27)	0.65 (0.31-1.36)
Montori et al. 2009[5]	0.96 (0.78-1.16) I2=78%	0.97 (0.74-1.26) I2=76%	0.82 (0.74-0.93) I2=0%	0.98 (0.86-1.12) I2=0%	0.89 (0.77-1.04) I2=0%
Kelly et al. 2009[6]	0.98 (0.84-1.15) I2=72%	0.97 (0.76-1.24) I2=76%	0.84 (0.75-0.94) I2=0%	0.98 (0.82-1.17)* I2=0%	0.91 (0.79-1.03) I2=0%
Ray et al. 2009[7]	1.02 (1.02-1.19) I2=NR	-	0.83 (0.75-0.93) I2=NR	0.93 (0.81-1.06) I2=NR	-
Trák I. 2009[19]	1.02 (0.89-1.16) I2=<50%	1.03 (0.84-1.26) I2=>50%	0.84 (0.75-0.93) I2=<50%	0.97 (0.85-1.10)* I2=<50%	-
ACCORD F-Up 2011[13]	1.19 (1.03-1.38)	1.29 (1.04-1.60)	0.82(0.70-0.96)	0.86 (0.65-1.13)	-
Boussageon et al. 2011[8]	1.04 (0.91-1.19) I2=42%	1.11(0.86-1.43) I2=61%	0.85 (0.74-0.96) I2=0%	1.00 (0.83-1.21)* I2=0%	0.98 (0.84-1.13) I2=34%
Hemmingsen et al. 2011[9]	1.02 (0.91-1.13) I2=30%	1.11(0.92-1.35) I2=46%	0.85 (0.76-0.95) I2=0%	-	-
Buehler et al. 2013[10]	1.03 (0.90-1.17) I2=50%	1.04 (0.83-1.29) I2=60%	0.85 (0.76-0.95) I2=0%	1.02 (0.88-1.17)* I2=0%	0.69 (0.44-1.08) I2=0%
Hemmingsen et al. 2013[11]	1.0 (0.92-1.08) I2=16%	1.06 (0.94-1.21) I2=20%	0.87 (0.77-0.98) I2=13%	1.0 (0.84-1.19)* I2=21%	0.65 (0.45-0.94) I2=0%
ADVANCE-ON 2014[16]	1.00 (0.92-1.08)	0.97 (0.86-1.10)	-	1.01 (0.89-1.15)	-
VADT F-Up 2015[18]	1.05 (0.89-1.25)	0.88 (0.64-1.20)	0.85 (0.65-1.11)	0.98 (0.71-1.36)*	0.67 (0.32-1.39)
Meta-analysis F-Up Studies (UKPDS 33[1]) 2015	1.02 (0.91-1.14) I2=79%	1.05 (0.85-1.30) † I2=70%	0.85 (0.74-0.96) † I2=0%	0.99 (0.89-1.08)^ I2=0%	0.82 (0.59-1.14) I2=0%
Meta-analysis F-Up Studies (UKPDS 34[12]) 2015	1.02 (0.90-1.15) I2=75%			0.99 (0.90-1.11)^ I2=0%	0.70 (0.43-1.15) I2=0%

† Did not include neither UKPDS 33[1] or UKPDS 34[12]

* UKPDS 33[1], UKPDS 34[12], Kelly et al[6], Trák I.[19], Boussageon et al[8], Hemmingsen et al.[9], Buehler et al.[10], and VADT F-Up[18] are only non-Fatal Strokes

§ Includes Fatal and Non-Fatal MI

^ Includes analysis of fatal and non-fatal stroke.

NR, not reported. I^2= Heterogeneity

Table S7. Point estimates and 95% confidence intervals for severe hypoglycemia.

Study/Year	Severe Hypoglycemia
UKPDS 33 1998[1]	1.99 (1.58-2.51)
ADVANCE 2008[2]	1.85 (1.42-2.42)
ACCORD 2008[3]	3.18 (2.78-3.63)
VADT 2009[4]	2.74 (1.8-4.17)
Montori et al. 2009[5]	2.48 (1.79-3.29) I2=83%
Kelly et al. 2009[6]	2.03 (1.46-2.81) I2=84%
Ray et al. 2009[7]	2.37 (1.72-3.25) I2=NR
Boussageon et al. 2011[8]	2.33 (1.62-3.36) I2=63%
Hemmingsen et al. 2011[9]	2.39 (1.71-3.34) I2=73%
Buehler et al. 2013[10]	2.39 (1.79-3.18) I2=62%
Hemmingsen et al. 2013[11]	2.18 (1.53-3.11) I2=66%

NR, not reported. I^2= Heterogeneity

Table S8. Point estimates and 95% confidence intervals for microalbuminuria and photocoagulation.

Study/Year	Microalbuminuria	Photocoagulation
UKPDS 33 1998[1]	0.88 (0.75-1.04)	0.71 (0.53-0.98)
UKPDS 34 1998[12]	1.00 (0.77-1.30)	0.69 (0.34-1.39)
ADVANCE 2008[2]	0.92 (0.84-1.00)	0.75 (0.39-1.41)
ACCORD 2008[3]	0.81 (0.70-0.94)	1.01 (0.87-1.17)
VADT 2009[4]	0.63 (0.35-1.13)	0.99 (0.79-1.25)
ACCORD F-Up 2011[13]	0.91 (0.81-1.03)	0.97 (0.85-1.10)
Boussageon et al. 2011[8]	0.90 (0.85-0.96) I2=31%	0.91 (0.71-1.17) I2=57%
Coca et al. 2012[14]	0.86 (0.76-0.96) I2=64%	-
Buehler et al. 2013[10]	-	0.84 (0.62-1.14) I2=73%
Hemmingsen et al. 2013[11]	-	0.77 (0.61-0.97) I2=43%
Zhang et al. 2015[15]	-	0.86 (0.75-0.98) I2=12%

NR, not reported. I2= Heterogeneity

Table S9. Risk of Bias Assessment for randomized included studies

Study	Year	Random Sequence Generation	Allocation Concealment	Blinding Participants and Personnel	Blinding outcome assessment	Incomplete data outcome	Were there any imbalances at baseline?	Reporting Bias	Other bias	% of lost to follow up
UKPDS 33[1]	1998	Yes	Yes	No blinding	Yes	No	No	No	No	Low
UKPDS 34[12]	1998	Yes	Yes	No blinding	Yes	No	No	No	No	Low
ACCORD[3]	2008	Yes	Yes	No blinding	Yes	No	No	No	No	Low
ADVANCE[2]	2008	Yes	Yes	No blinding	Yes	No	No	No	No	Low
VADT[4]	2009	Yes	Yes	No blinding	YEs	No	No	No	No	Low

Cochrane assessment tool for RCTs

Table S10. Risk of bias assessment for extension studies.

Study	Year	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that the outcome of interest was not present at baseline	Comparability of cohorts on the basis of design or analysis	Assessment of the outcome	Was follow up enough for outcomes to occur?	Adequacy of follow up of cohorts
UKPDS[17]	2008	Somewhat representative	Drawn from the same community as exposed cohort	Secure Record	Yes	Study controls	Yes	Yes	Lost of follow up likely to introduce bias >20%
UKPDS[17]	2008	Somewhat representative	Drawn from the same community as exposed cohort	Secure Record	Yes	Study controls	Yes	Yes	Lost of follow up likely to introduce bias >20%
ACCORD[3]	2011	Truly representative	Drawn from the same community as exposed cohort	Secure Record	Yes	Study controls	Yes	Yes	Los of follow up unlikely to introduce bias
ADVANCE[2]	2014	Truly representative	Drawn from the same community as exposed cohort	Secure Record	Yes	Study controls	Yes	Yes	Lost of follow up likely to introduce bias >20%
VADT[4]	2015	Somewhat representative	Drawn from the same community as exposed cohort	Secure Record	Yes	Study controls	Yes	Yes	Lost of follow up likely to introduce bias >20%

Modified Ottawa classification for observational studies

Table S11. Risk of bias assessment for included systematic reviews.

Domain 1: Study eligibility criteria

Study	Year	Did the review adhere to pre-defined objectives and eligibility criteria?	Were the eligibility criteria appropriate for the review question?	Were eligibility criteria unambiguous?	Were all restrictions in eligibility criteria based on study characteristics appropriate?	Were any restrictions in eligibility criteria based on sources of information appropriate?	Concerns regarding specification of study eligibility criteria
Montori et al.[5]	2009	Y	Y	PN	Y	PY	Low
Kelly et al.[6]	2009	Y	Y	PN	Y	PY	Low
Ray et al.[7]	2009	Y	Y	N	Y	Y	Low
Trák I.[19]	2009	PY	N	PY	PN	PN	High
Boussageon et al.[8]	2011	Y	Y	N	Y	Y	Low
Hemmingsen et al.[9]	2011	Y	Y	N	Y	PY	Low
Coca et al.[14]	2012	Y	Y	PN	Y	PY	Low
Callaghan et al.[20]	2012	Y	Y	PN	PY	PY	Low
Buehler et al.[10]	2013	PY	PY	PN	PY	PN	Low
Hemmingsen et al.[11]	2013	Y	Y	N	Y	Y	Low
Zhang et al.[15]	2015	PY	PY	PN	PN	PN	High

Domain 2: Identification and selection of studies

Study	Year	Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Were methods additional to database searching used to identify relevant reports?	Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Were restrictions based on date, publication format, or language appropriate?	Were efforts made to minimize error in selection of studies?	Concerns regarding methods used to identify and/or select studies
Montori et al.[5]	2009	NI	NI	NI	NI	NI	Unclear
Kelly et al.[6]	2009	PN	PY	Y	PN	PN	Low
Ray et al.[7]	2009	Y	Y	Y	PN	Y	Low
Trák I.[21]	2009	PN	N	N	PN	PN	High
Boussageon et al.[8]	2011	Y	Y	Y	Y	Y	Low
Hemmingsen et al.[9]	2011	Y	Y	Y	Y	Y	Low
Coca et al.[14]	2012	Y	Y	Y	Y	Y	Low
Callaghan et al.[20]	2012	Y	Y	Y	Y	Y	Low
Buehler et al.[10]	2013	Y	PY	PY	PY	PY	Low
Hemmingsen et al.[11]	2013	Y	Y	Y	Y	Y	Low
Zhang et al.[15]	2015	PN	PN	PN	PN	PN	High

Domain 3: Data collection and study appraisal

Study	Year	Were efforts made to minimize error in data collection?	Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Were all relevant study results collected for use in the synthesis?	Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Were efforts made to minimize error in risk of bias assessment?	Concerns regarding methods used to collect data and appraise studies
Montori et al.[5]	2009	NI	NI	NI	NI	NI	Unclear
Kelly et al.[6]	2009	PN	Y	Y	PY	Y	Low
Ray et al.[7]	2009	PY	Y	Y	PY	PY	Low
Trák I.[19]	2009	PN	N	PN	PN	N	High
Boussageon et al.[8]	2011	PY	Y	Y	Y	Y	Low
Hemmingsen et al.[9]	2011	PY	Y	Y	Y	Y	Low
Coca et al.[14]	2012	PY	Y	Y	Y	Y	Low
Callaghan et al.[20]	2012	PY	Y	Y	Y	Y	Low
Buehler et al.[10]	2013	PY	PY	PY	Y	Y	Low
Hemmingsen et al.[11]	2013	PY	Y	Y	Y	Y	Low
Zhang et al.[15]	2015	PN	PN	PN	Y	PY	High

Domain 4: Synthesis and findings

Study	Year	Did the synthesis include all studies that it should?	Were all pre-defined analyses reported or departures explained?	Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Were biases in primary studies minimal or addressed in the synthesis?	Concerns regarding the synthesis and findings
Montori et al.[5]	2009	PY	PN	PY	PN	PN	PY	Low-Moderate
Kelly et al.[6]	2009	Y	PY	PY	Y	PY	PY	Low
Ray et al.[7]	2009	Y	Y	PY	PY	Y	PY	Low
Trák I.[19]	2009	PN	PN	PN	PY	PN	PN	High
Boussageon et al.[8]	2011	Y	Y	PY	PY	PY	PY	Low
Hemmingsen et al.[9]	2011	Y	Y	Y	PY	PY	PY	Low
Coca et al.[14]	2012	Y	Y	Y	PY	PY	PY	Low
Callaghan et al.[20]	2012	Y	Y	Y	Y	PY	PY	Low
Buehler et al.[10]	2013	Y	Y	PY	PY	PY	PY	Low

Hemmingsen et al.[11]	2013	Y	Y	Y	PY	PY	PY	Low
Zhang et al.[15]	2015	PN	PY	PN	PN	PY	PY	High

ROBIS tool to assess risk of bias in systematic reviews

Table S12. GRADE assessment of studied outcomes. (Until end-of original study [RCT])

Outcome	Number of Participants (Studies)	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Quality	Best Estimate of TG Effect
ESRD or Dialysis	27 802 (5)	Moderate Limitations	Inconsistent	No serious Limitations	Imprecision	Not Detected	Low to Very-Low	RR 0.87 (0.71-1.06) (Hemmingsen et al.)[11]
Renal Death	15 760 (3)	Moderate Limitations	Consistent	No serious Limitations	Imprecision	Not Detected	Low to Moderate	RR 0.99 (0.55-1.79) (Coca et al)[11]
Blindness	27 802 (5)	Moderate Limitations	Consistent	No serious Limitations	No serious Limitations	Not Detected	Moderate	RR 1.00 (0.96-1.05) (Boussageon et al.)[8]
Clinical Neuropathy	27 049 (4)	Moderate Limitations	Consistent	No serious Limitations	No serious Limitations	Not Detected	Moderate	RR 0.99 (0.95-1.03) (Boussageon et al.)[8]
All-Cause Mortality	27 802 (5)	Moderate Limitations	Inconsistent	No serious Limitations	No serious Limitations	Not Detected	Moderate	RR 1.00 (0.92-1.08) (Hemmingsen et al.)[11]
CV Mortality	27 802 (5)	Moderate Limitations	Inconsistent	No serious Limitations	No serious Limitations	Not Detected	Moderate	RR 1.06 (0.94-1.21) (Hemmingsen et al.)[11]
Non-Fatal MI	27 802 (5)	Moderate Limitations	Consistent	No serious Limitations	No serious Limitations	Not Detected	Moderate To High	RR 0.87 (0.77-0.98) (Hemmingsen et al.)[11]
Stroke	27 802 (5)	Moderate Limitations	Consistent	No serious Limitations	No serious Limitations	Not Detected	Moderate To High	RR 1.00 (0.84-1.19) (Hemmingsen et al.)[11]
Amputation or PVD	17 551 (4)	Moderate Limitations	Inconsistent	No serious Limitations	Imprecision	Not Detected	Moderate To High	RR 0.98 (0.84-1.13) (Boussageon et al.)[8] RR 0.65 (0.45-0.94) (Hemmingsen et al.)[11]
Severe Hypoglycemia	27 049 (4)	Moderate Limitations	Consistent	No serious Limitations	No serious Limitations	Not Detected	Moderate To High	RR 2.18 (1.53-3.11) (Hemmingsen et al.)[11]
*Microalbuminuria	27 802 (5)	Moderate Limitations	Consistent	Moderate to Serious Limitations	No serious Limitations	Not Detected	Moderate	RR 0.86 (0.76-0.96)[14] Coca et al.
*Photocoagulation	27 802 (5)	Moderate Limitations	Consistent	Moderate to Serious Limitations	No serious Limitations	Not Detected	Moderate	RR 0.77 (0.61-0.97) (Hemmingsen et al.)[11]

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