Role of Intensive Glucose Control in Development of Renal Endpoints in Type 2 Diabetes: Systematic Review and Meta-analysis

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Abstract

Background—Aggressive glycemic control has been hypothesized to prevent renal disease in type 2 diabetics. A systematic review was conducted to summarize the benefits of intensive versus conventional glucose control on kidney-related outcomes for adults with type 2 diabetes.

Methods—Three databases were systematically searched (January 1950 to December 2010) with no language restrictions to identify randomized trials that compared surrogate renal endpoints (micro and macroalbuminuria) and clinical renal endpoints (doubling of serum creatinine, End Stage Renal Disease [ESRD] and death from renal disease) in patients with type 2 diabetes receiving intensive glucose control versus receiving conventional glucose control.

Results—Seven trials involving 28,065 adults who were followed-up for 2 to 15 years. Compared with conventional control, intensive glucose control reduced the risk for microalbuminuria (risk ratio [RR], 0.86 [95% CI, 0.76 to 0.96]) and macroalbuminuria (RR 0.74 [95% CI, 0.65–0.85]), but not doubling of serum creatinine (RR 1.06 [95% CI, 0.92 to 1.22]),

ESRD (RR 0.69 [95% CI, 0.46–1.05]), or death from renal disease (RR 0.99 [95% CI 0.55–1.79]). Meta-regression revealed that larger differences in HbA1C between intensive and conventional therapy at the study level were associated with greater benefit for both micro- and macroalbuminuria. The pooled cumulative incidence of doubling of creatinine, ESRD, and death from renal disease was low ($< 4\%$, $<1.5\%$, and $<0.5\%$, respectively) compared with the surrogate renal endpoints of micro- (23%) and macroalbuminuria (5%).

Conclusion—Intensive glucose control reduces the risk for microalbuminuria and macroalbuminuria but evidence is lacking that intensive glycemic control reduces the risk for significant clinical renal outcomes such as doubling of creatinine, ESRD or death from renal disease during the years of follow-up of the trials.

Keywords

Proteinuria; creatinine; chronic kidney disease; end-stage renal disease; prognosis

INTRODUCTION

Epidemiologic studies have demonstrated an association between poor glycemic control and microvascular complications in patients with type 2 diabetes.[1, 2] Randomized controlled trials have demonstrated that intensive glycemic control reduces albuminuria.[3–5] Less clear, however, is whether intensive glycemic control actually prevents clinical renal endpoints (e.g., progressive loss in glomerular filtration rate) beyond albuminuria in type 2 diabetics. Despite the lack of strong evidence, expert panels and guidelines continue to recommend a target HbA1C < 7.0% for prevention of renal disease and other microvascular complications. The 2007 National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease (CKD)[6] endorse intensive glycemic control, and these recommendations are reinforced by the 2011 American Diabetes Association (ADA) guidelines. As stated in the guidelines, recommendations for intensive glycemic control for prevention of renal disease are based on studies that have demonstrated an improvement in albuminuria, a surrogate endpoint.

Furthermore, in light of the fact that intensive glycemic control increased the risk for death by 22% in the ACCORD trial,[7] and, pooling the data from all studies did not reduce cardiovascular-related death or all-cause mortality,[8] it is increasingly problematic for clinicians to continue aggressive glycemic control for the treatment of renal outcomes. The reasons for the lack of clinical benefits are unclear. A recent study demonstrated that despite substantial increases in the use of glucose-lowering medications (and inhibitors of the renin-angiotensin-aldosterone system) from 1988 to 2008, the prevalence of CKD in diabetics actually increased.[9]

The recent publication of several large randomized controlled multicenter trials of intensive glycemic control in type 2 diabetes[7, 10, 11] may allow an assessment of the effects intensive glycemic control on clinical renal endpoints. Thus, in the context of strategies employed in these studies for intensive control of glycemia, we sought to examine whether this form of therapy was associated with benefits on clinically relevant renal outcomes among patients with type 2 diabetes via a systematic review and meta-analysis.

METHODS

Data Sources and Searches

In collaboration with an expert librarian, we searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials to identify randomized controlled trials that compared the effects of intensive glucose control and conventional glucose control on renal events in patients with type 2 diabetes. Inclusion criteria and methods of analysis were specified in advance and documented in a protocol available on request. Investigators searched the PUBMED central for publications (January 1950 through December 2010) using the Medical Subject Headings(MeSH) *chronic kidney disease; diabetes mellitus type 2; hypoglycemic agents; creatinine* as well as keywords *chronic kidney disease, albuminuria, proteinuria, protein to creatinine ratio, albumin to creatinine ratio, glucose control*, and *glycemic control*. The search was restricted to randomized, controlled trials conducted among human adults (age 19 years), with no journal group, language or gender restrictions. We also checked the reference lists of identified articles, previous meta-analyses, and original studies identified by the electronic search to find other potentially eligible studies. We searched review articles and the Web of Science database to find all relevant follow-up articles.

Study Selection

Two investigators independently reviewed the contents of 751 abstracts or full text manuscripts identified through the literature search to determine whether they met the eligibility criteria. He predefined inclusion criteria required the clinical trials to: (1) randomly assign individuals with type 2 diabetes mellitus either to an intensive lowering of glucose versus a standard regimen (placebo, standard care, or glycemic control of reduced intensity), (2) address the progression or development of kidney disease either as a primary or a surrogate outcome, and report complete information about effect measures or provide information to allow calculation of effect estimates for progression or new diagnosis of kidney disease, and (3) involve stable patients in the outpatient setting only, excluding studies in an acute hospital setting. The risk of bias was assessed by using the components recommend by the Cochrane Collaboration: sequence generation by allocation; allocation concealment; blinding of participants, staff and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias.

Data Extraction and Risk of Bias in Included Studies

We entered data from the trials into an electronic database with validity checks. The data abstraction and data entry were confirmed by a second reviewer who cross-checked 100% of selected articles.

Variables including details of the trials, details of the intervention, renal end-points were abstracted. The corresponding primary author of the article was contacted to clarify details or confirm outcomes for two trials.[7, 10]

The surrogate endpoints were development of microalbuminuria and macroalbuminuria. The clinical endpoints included doubling of serum creatinine, end-stage renal disease (ESRD), and death from renal disease.

Statistical Analysis

We examined the relationship between intensive glucose control and risk for all the study outcomes using relative risk and risk difference measures. Forest plots were created to determine pooled measures. Heterogeneity was assessed with I^2 statistics, ranging from 0% to 100%. I^2 demonstrates the percentage of total variation across studies due to

heterogeneity and was used to judge the consistency of evidence. I^2 values of 50% and more indicate a substantial level of heterogeneity.[12] Random effects models were used to combine data on outcomes in Review Manager 5.0 (The Cochrane Collaboration). The meta-analysis was performed in line with recommendations from the Cochrane Library. A *P*-value <0.05 was considered statistically significant. Analyses were stratified by risk of bias in subsequent analyses. We also performed meta-regression using SAS 9.1 (Cary, NC) on the 5 study-level variables (median date of enrollment, years since diabetes diagnosis, duration of therapy, difference in achieved HbA1C, and median achieved HbA1C) to determine the relationship between these variables and the relative risk for each endpoint. Regression lines were plotted and bubbles were weighted for the inverse of the variance of the individual relative risks of each endpoint in each trial via Microsoft Excel 2007 (Redmond, Washington).

RESULTS

Figure 1 depicts the study selection process. The current meta-analysis included a total of seven trials conducted among 28,065 participants.

Description of Studies

Table 1 presents the characteristics of the 7 randomized, controlled trials and trial participants.[4, 5, 7, 10, 11, 13–16] The number of trial participants ranged from 110 to 11,140. Mean baseline serum creatinine ranged from 81 to 88.4 μmol/L in the trials. Mean duration of diabetes before enrollment ranged from 8 to 18 years with the exception of UKPDS 33 and UKPDS 34, which enrolled patients with newly-diagnosed T2DM. The interventions to achieve glycemic control varied across studies (Table 1). HbA1C (or FPG) targets varied as well in all of the studies. The highest HbA1C target in the intensive arms of the trials was < 7%,[4] and the lowest HbA1C targets were < 6% in the ACCORD study[13] and VADT[10] and 5.1% in the Veterans Affairs (VA) Diabetes Feasibility Trial.[5]

The median HbA1C values during the trials were lower in the intensive group in all studies, and 4 studies achieved HbA1C difference of > 1% compared to the control group (Table 2).[4, 5, 10, 13] Three studies achieved median HbA1C < 7% in the intensive glycemic control group. Follow-up time was shortest in the VA Diabetes Feasibility Trial (2 years),[5] and was 5 years or more in all other studies. UKPDS 33 and 34 had the longest follow-up times (up to 15 years).[14, 15] The cumulative incidence of renal endpoints were as follows: microalbuminuria, range 5.8–53%; macroalbuminuria, range from 2.6–8.5%; doubling of serum creatinine, 1.1–8.8%; and ESRD 0.5–2.8% (Table 3). The cumulative incidence of morality was lowest in ACCORD (5.0% and 3.9% in intensive and standard therapy groups, respectively), and highest in UKPDS 34 (14.6% and 21.7%, respectively).

Outcomes

Figure 2 presents the individual and pooled relative risks and risk differences of microalbuminuria (Panel A) and macroalbuminuria (Panel B). Figure 3 presents the same for the clinical renal endpoints of doubling of serum creatinine (Panel A), renal failure/ESRD (Panel B), and death from renal disease (Panel C). Overall analyses indicated that patients randomly assigned to intensive glucose control had reduced risk for microalbuminuria (7 studies: risk ratio [RR], 0.86 [95% CI, 0.76 to 0.96; risk difference [RD] −0.04 [CI −0.08 to −0.01]) and macroalbuminuria (6 studies: 0.74 [CI, 0.65–0.85]; RD −0.01 [CI −0.02 to −0.01]); but not doubling of serum creatinine (4 studies: RR, 1.06 [CI, 0.92 to 1.22]; RD 0.0 [CI 0.0 to 0.1]; ESRD (5 studies: RR, 0.69 [CI, 0.46–1.05]; RD 0.0 [CI −0.01 to 0.0]), or death from renal disease (3 studies: RR, 0.99 [95% CI 0.55–1.79]; RD 0.0 [CI 0.0 to 0.0]) compared with participants in the conventional treatment groups. We identified possible

heterogeneity for the endpoint of microalbuminuria ($I^2 = 69\%$), whereas statistical heterogeneity was low for all other analyses.

Sensitivity Analyses & Meta-Regression

In order to determine the reasons for heterogeneity for our analyses of the effect on intense glucose therapy on the outcome of microalbuminuria, we excluded each study one by one. Elimination of the VA Diabetes Feasibility Trial[5] from the microalbuminuria analysis reduced the I^2 to 0%. This study was one of the smallest studies and had a short duration of follow-up (2 years). However, even after exclusion of VA Diabetes Feasibility Trial, the pooled RR was not measurably different (RR 0.91, CI 0.85–0.96).

We formally examined the relationship between the 5 study level variables as continuous variables and the risk for each of the renal endpoints (eFigure 1). The median year of enrollment, the years since diabetes diagnosis, and the duration of therapy (eFigure 1A–C) were only associated with one endpoint: risk for doubling of serum creatinine. Furthermore, these three meta-regressions were largely driven by UKPDS 33, as this study had the earliest median year (1984), the shortest duration of years since diagnosis (zero), and the longest duration of therapy (11 years). The difference in achieved HbA1C was associated with greater benefit from intensive glycemic control for both microalbuminuria ($\beta = -0.401$ for every percent difference in HbA1C, $p = 0.01$) and macroalbuminuria ($\beta = -0.474$, p=0.008; eFigure 1D). The median HbA1C achieved in the intensive glycemic group was not associated with magnitude of the relative risk for any of the endpoints (eFigure 1E).

Risk of Bias Assessment

The studies were generally of good methodological quality (eFigure 2 and 3).

Allocation

Two[4, 5] of the seven trials did not clearly state their methods for allocation concealment. The results were not quantitatively or qualitatively changed when those two trials were excluded from the analyses.

Blinding

Only UKPDS 33 and 34 ensured blinding of participants and personnel. Participants in the intensive glycemic control arms in the other five trials[4, 5, 7, 10, 11] had more frequent study visits with personnel than participants in the control arms. When only UKPDS 33 and 34 were considered, the results were not qualitatively different for ESRD (RR 0.80, 95% CI 0.38–1.69), however the benefit of intensive glycemic control for the endpoint of macroalbuminuria was lost (RR 0.91, 95% CI 0.79–1.05). Blinding of outcome assessment was reported in all included studies except one.[4]

Incomplete outcome data

There was a significant amount of incomplete outcome data from several of the studies. For example, between 20–40% of participants were not assessed for the endpoints of micro and macroalbuminuria in ACCORD, UKPDS 33, UKPDS 34, and VADT. However, the proportions with assessment of these endpoints were equal in both arms of each of these studies, indicating low risk of bias. Sensitivity analyses with exclusion of the 4 aforementioned studies resulted in similar results for micro and macroalbuminuria.

The proportion missing serum creatinine values in follow-up was < 5% in ACCORD and VADT, but was 45% at 9 years in UKPDS 33. Again, however, the proportion that were missing values were equal in both arms, thus the risk of bias was low. Due to the fact that

patients are unaware of either subnephrotic proteinuria levels or of serum creatinine values, and the equal proportions of missingness, we felt that the missing data occurred at random and was not due to differences in the outcomes themselves in those without the assessments. Nevertheless, a sensitivity analysis excluding UKPDS 33 from the analysis did not change the results qualitatively or quantitatively. The ascertainment for the outcome of ESRD was complete in all of the studies that reported the endpoint.

Selective reporting

There was no evidence of selective reporting in the included studies.

Other potential sources of bias

There was evidence of publication bias by funnel plot analysis for the outcomes of microalbuminuria, macroalbuminuria, and doubling of serum creatinine, as small studies with risk ratio greater than the summary estimates were missing for these outcomes.

COMMENT

In this systematic review and meta-analysis of 7 RCTs of intensive glycemic control in type 2 diabetes, a statistically significant reduction in micro and macroalbuminuria occurred with intensive therapy. However, the data were inconclusive in regards to the effect of intensive glycemic control on clinical renal outcomes defined as doubling of serum creatinine, ESRD, or death from renal disease. Our analysis demonstrates that after 163,828 patient-years of follow-up in the 7 studies examined, intensive glycemic control improves albuminuria but data is lacking for evidence of a benefit for clinically important renal endpoints. There was a non-significant trend towards reduction of the endpoint of ESRD, a surprising observation given the very tight precision and null findings for the endpoint of doubling of creatinine which must temporally precede ESRD. However, it is worth noting that that the absolute rate of clinical renal outcomes in the published studies is relatively low: the pooled cumulative incidence of doubling of creatinine in the standard treatment group of all of the trials that measured these outcomes was only 4.1%[10, 11, 13, 14] and for ESRD was only 1.6%.[10, 11, 13–15] The low incidence of these endpoints may render the number needed to treat too large to justify intensive insulin therapy (even assuming a treatment effect) given the risks of severe hypoglycemia and minimal benefit for cardiovascular outcomes and potential for increased risk of death.[7]

As further detailed below, multiple reasons may underlie the lack of evidence for a beneficial effect of tight glycemic control on clinically significant renal endpoints (i.e., doubling of serum creatinine or ESRD) in this setting. These include A) intensive glycemic control may have started too late in the course of the disease; B) the duration of glycemic treatment may have been insufficient; C) HbA1C levels were not reduced to normal; D) there may be a "ceiling effect" that once HbA1C is reduced to a moderate degree (e.g., < 7%), further reduction does not benefit the patient, especially in the setting of other interventions including use of statins and antihypertensive medications; E) competing risk of death; F) inadequate statistical power to detect a difference.

Is it possible that the glycemic interventions started too late in the disease process to prevent the development of clinical renal outcomes? More years since diagnosis of T2DM at time of enrollment trended towards less benefit for doubling of serum creatinine. In fact, the only RCT that did not have a relative risk 1 for doubling of creatinine enrolled NEWLY-diagnosed type 2 diabetics exclusively (UKPDS 33).[14] The other studies had a mean duration of diabetes of 8–12 years at the time of enrollment.[10, 11, 13] Thus, it is possible that despite normal GFR at the time of enrollment, there was already a significant amount of

subclinical kidney damage that occurred over the 8+ years of "non-intensive" glycemic control, making it too late to change the natural history of the kidney disease despite aggressive glycemic management.

Alternatively, is it possible that the duration of intensive glycemic therapy (or the duration of follow-up) was too short to witness improvement in progressive CKD? Because the duration of therapy was not exceedingly long in any of the RCTs that enrolled patients with prevalent type 2 diabetes (generally ~5 years), it is impossible to answer this question with any degree of certainty. It is conceivable that longer duration of intensive therapy is required to demonstrate an effect on CKD or ESRD. Longer duration of therapy was associated with a reduction in doubling of serum creatinine, however, this was again driven by UKDPS 33, which also enrolled newly-diagnosed type 2 diabetics. Furthermore, there was no reduction in ESRD in UKPDS 33 or 34, despite the long duration of treatment. Regardless, given that a small and nearly equal percentage of participants in both glycemic treatment arms of all the studies examined developed CKD or ESRD, it can be surmised that any potential differential benefit from intensive treatment must be quite small. In contrast, data from patients with type 1 diabetes from the DCCT/EDIC study demonstrate that intensive glycemic control for 6.5 years reduced the incidence of impaired GFR by 50% over a median follow-up period of 22 years.[17] An analysis at 14 years after the start of DCCT was not able to demonstrate a difference in the number of patients with doubling of serum creatinine.[18] Thus, it may take 20+ years to witness the impact of intensive glycemic control on clinical renal outcomes.

Was the reduction in HbA1C achieved in the trials of sufficient magnitude? Four RCTs achieved a difference in HbA1C of > 1% with intensive therapy vs. standard therapy.[4, 5, 10, 13] While there was a strong association between the difference in HbA1C in the intensive vs. standard groups and the risk for both micro- and macroalbuminuria, there was no association for the endpoints of doubling of serum creatinine or ESRD. Furthermore, although median HbA1C achieved in the intensive group was not statistically associated with any of the renal endpoints, qualitatively there was no greater benefit for development of micro- and macroalbuminuria and a trend towards harm for the endpoint of doubling of creatinine in studies with lower achieved median HbA1C values. This suggests that avoidance of excessive hyperglycemia is necessary, but aggressive glycemic control offers little advantage and may be deleterious when one accounts for risk for severe hypoglycemic events. Furthermore, given the multifactorial nature and complexity of mechanisms underlying the pathogenesis of T2DM, it is of importance to investigate whether control of other pathogeneic mechanisms - in addition to intensive treatment of hyperglycemia, hypertension, and dyslipidemia - might help prevent progressive CKD in patients with T2DM.

Could the lack of apparent convincing benefit for hard renal outcomes be due to competing risk of death? For this to be it operative, it would presume that those at risk of developing the renal endpoint are the same patients who are dying prematurely, and thus when outcomes are examined at the study level, the higher rate of death in one group vs. the other does not allow more participants in that group sufficient time to manifest the renal endpoint of interest. However, the pooled risk of death not different between the two groups (RR 0.98, 95% CI 0.84–1.15).[8] If mortality was higher in the standard treatment group, there may have been a chance for competing risk of death to mask the renal benefit.

Finally, despite nearly 30,000 patients included in this meta-analysis, we may have lacked adequate statistical power to detect a difference in clinical renal endpoints between the two groups. The incidence of doubling of creatinine was 503 events in 12383 participants in the standard therapy group (4.1%). Given the number of patients and a 2-sided alpha of 0.05, we

would have been able to detect at least a 16% difference in the relative risk of the outcome between the two groups with 80% power, if there would have been a difference. The incidence of ESRD was 204 in 13117 (1.55%) in the standard therapy group and 147 in 14643 participants (1.0%) in the intensive therapy group, yielding 98% power at a 2-sided alpha of 0.05 to detect whether this 31% relative risk reduction was statistically significant. Regardless, with a baseline rate of ESRD so low in the standard therapy group, and the overall lack of benefit for cardiovascular or all-cause mortality,[8] it does not seem prudent to expose patients to this therapy to achieve an absolute risk reduction for ESRD that will be < 1% in a best-case scenario.

In conclusion, our systematic review and meta-analysis suggests that intensive glycemic control reduces albuminuria but evidence is lacking that it prevents clinically meaningful renal outcomes such as CKD, ESRD and renal-related death in patients with T2DM measured during the 3.5 to 10.7 years of the published trials. Acknowledging the low incidence of clinical renal outcomes coupled with the apparent lack of convincing benefit of intensive glycemic control to prevent CKD and ESRD in patients with newly-diagnosed or prevalent type 2 diabetes, there is little compelling reason to initiate intensive glycemic control in mid-stage of the disease with the aim of preventing renal failure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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│ Reports identified in literature search  │
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Figure 1. Literature search and selection

A. Microalbuminuria

Study or Subgroup	Intensive Therapy Events	Intensive Therapy Total	Standard Therapy Events	Standard Therapy Total	Weight	Risk Ratio M-H, Random, 95% CI
ACCORD	720	3250	828	3273	27.3%	0.88 [0.80, 0.96]
ADVANCE	1318	5571	1434	5569	29.3%	0.92 [0.86, 0.98]
Kumamoto	5	52	11	50	1.3%	0.44 [0.16, 1.17]
UKPDS 33	368	2277	172	938	19.6%	0.88 [0.75, 1.04]
UKPDS 34	79	342	95	411	12.2%	1.00 [0.77, 1.30]
VADT	43	442	61	463	7.6%	0.74 [0.51, 1.07]
VADT Feasibility Trial	7	42	30	46	2.5%	0.26 [0.13, 0.52]
Total (95% CI)		**11976**		**10750**	**100.0%**	**0.86 [0.76, 0.96]**
Total events	2540		2631			

Heterogeneity: Tau² = 0.01; Chi² = 16.71, df = 6 (P = 0.01); I² = 64%
Test for overall effect: Z = 2.60 (P = 0.009)

Risk Ratio M-H, Random, 95% CI (0.01 0.1 1 10 100) — Favors intensive   Favors standard

B. Macroalbuminuria

Study or Subgroup	Intensive Therapy Events	Intensive Therapy Total	Standard Therapy Events	Standard Therapy Total	Weight	Risk Ratio M-H, Random, 95% CI
ACCORD	195	4397	272	4424	39.3%	0.72 [0.60, 0.86]
ADVANCE	230	5571	292	5569	42.5%	0.79 [0.67, 0.93]
Kumamoto	0	52	4	50	0.2%	0.11 [0.01, 1.94]
UKPDS 33	72	2277	33	938	10.4%	0.90 [0.60, 1.35]
VADT	20	693	36	703	6.2%	0.56 [0.33, 0.96]
VADT Feasibility Trial	3	24	10	28	1.4%	0.35 [0.11, 1.13]
Total (95% CI)		**13014**		**11712**	**100.0%**	**0.74 [0.65, 0.85]**
Total events	520		647			

Heterogeneity: Tau² = 0.00; Chi² = 5.73, df = 5 (P = 0.33); I² = 13%
Test for overall effect: Z = 4.24 (P < 0.0001)

Risk Ratio M-H, Random, 95% CI (0.01 0.1 1 10 100) — Favors intensive   Favors standard

Figure 2. Pooled Risk Ratios, with 95% CI, by trial for end-points of micro and macroalbuminuria

Footnote: Data on the incidence of micro- and macroalbuminuria from UKPDS 33 was reported in 3 year intervals. Due to the marked drop-off of patients with outcomes reported at 9 years and beyond, the data from the 6 year time-point was chosen for the endpoints of micro- and macroalbuminuria. The incidence of microalbuminuria at 9, 12, and 15 years were 19.2%, 23.0%, and 27.1% in the intensive group and 25.4%, 34.2%, and 39% in the conventional group. The incidence of macroalbuminuria at 9, 12, and 15 years was 4.4%, 6.5%, and 7.9% in the intensive group and 6.5%, 10.3%, and 12.6% in the conventional group. Intensive therapy was stopped earlier than planned in ACCORD. Data on renal outcomes were reported at transition to standard therapy (median follow-up 3.5 years) and at study end (median follow-up 5 years). The incidence of outcomes was taken from study end for the main analyses. Utilization of data from transition did not change the results for macroalbuminuria (pooled RR 0.83, 95% CI 0.72–0.95, I² = 68%) or macroalbuminuria (pooled RR 0.74, 95% CI 0.65–0.84, I² = 17%).

A. Doubling of Serum Creatinine

Study or Subgroup	Intensive Therapy Events	Total	Standard Therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
ACCORD	392	5041	357	5035	62.5%	1.10 [0.96, 1.26]	
ADVANCE	67	5571	61	5569	15.6%	1.10 [0.78, 1.55]	
UKPDS 33	7	2150	7	895	1.9%	0.42 [0.15, 1.18]	
VADT	78	882	78	884	20.0%	1.00 [0.74, 1.35]	
Total (95% CI)		13644		12383	100.0%	1.06 [0.92, 1.22]	
Total events	544		503				

Heterogeneity: Tau² = 0.00; Chi² = 3.46, df = 3 (P = 0.33); I² = 13%
Test for overall effect: Z = 0.76 (P = 0.44)

Favors intensive Favors standard

B. ESRD

Study or Subgroup	Intensive Therapy Events	Total	Standard Therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
ACCORD	138	5119	151	5115	43.2%	0.91 [0.73, 1.15]	
ADVANCE	11	5571	31	5569	21.2%	0.35 [0.18, 0.70]	
UKPDS 33	16	2729	9	1138	17.3%	0.74 [0.33, 1.67]	
UKPDS 34	2	342	2	411	4.2%	1.20 [0.17, 8.49]	
VADT	7	882	11	884	14.1%	0.64 [0.25, 1.64]	
Total (95% CI)		14643		13117	100.0%	0.69 [0.46, 1.05]	
Total events	174		204				

Heterogeneity: Tau² = 0.09; Chi² = 7.08, df = 4 (P = 0.13); I² = 43%
Test for overall effect: Z = 1.72 (P = 0.09)

Favors intensive Favors standard

C. Death from Renal Disease

Study or Subgroup	Intensive Therapy Events	Total	Standard Therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
ADVANCE	16	5571	19	5569	79.3%	0.84 [0.43, 1.64]	
UKPDS 33	8	2728	2	1138	14.6%	1.67 [0.35, 7.85]	
UKPDS 34	2	342	1	411	6.1%	2.40 [0.22, 26.39]	
Total (95% CI)		8641		7118	100.0%	0.99 [0.55, 1.79]	
Total events	26		22				

Heterogeneity: Tau² = 0.00; Chi² = 1.19, df = 2 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.03 (P = 0.98)
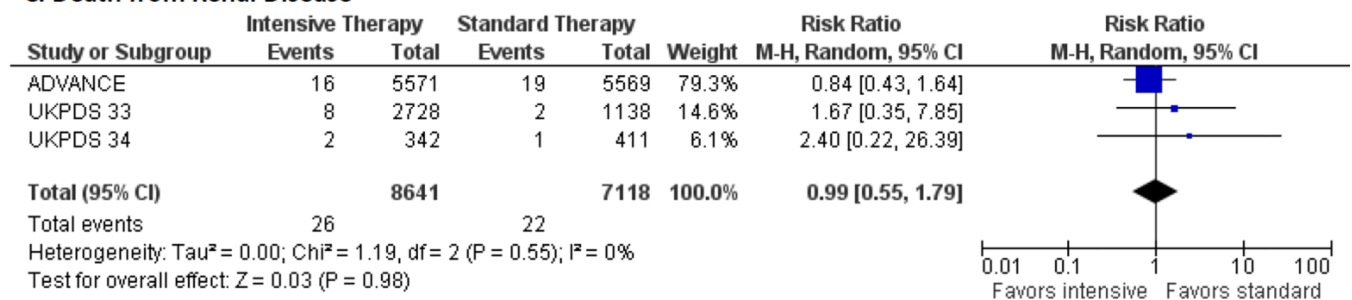
Favors intensive Favors standard

Figure 3. Pooled Risk Ratios, with 95% CI, by trial for clinical renal endpoints (doubling of serum creatinine and ESRD)

Footnote: Data on the incidence of doubling of serum creatinine from UKPDS 33 was reported in 3 year intervals. Due to the marked drop-off of patients with outcomes reported at 9 years and beyond, the data from the 6 year time-point (n= 3,045) was chosen for inclusion in the summary data above. There was no difference in the magnitude or direction of effect at 9 and 12 years. At 9 years (n= 2,172), 0.71% vs. 1.76% (RR 0.40, 95% CI 0.14–1.20), and at 12 years (n=1,054), 0.91% and 3.5% (RR 0.25, 95% CI 0.07–0.91)had doubling of serum creatinine in the intensive vs. conventional groups. At 15 years (n=170), 3.52% in the intensive group and 2.8% in the convention group had doubling of serum creatinine (RR 1.25, 95% 0.16–9.55). Data on the incidence of ESRD and Death from Renal Disease are reported from the end of the study period. Intensive therapy was stopped earlier than planned in ACCORD. Data on renal outcomes were reported at transition to standard therapy (median follow-up 3.5 years) and at study end (median follow-up 5 years). The incidence of outcomes was taken from study end for the main analyses. Utilization of data

from transition did not change the results for doubling of serum creatinine (pooled RR 1.08, 95% CI 0.95–1.23, I^2 = 19%) or ESRD (pooled RR 0.70, 95% CI 0.45–1.08, I^2 = 45%).

Table 1

Characteristics of Randomized, Controlled Trials of Intensive Glucose Control

CHARACTERISTIC	Kumamoto[4]	UKPDS 33[14]	UKPDS 34[15]	VA Diabetes Feasibility Trial[5]	ACCORD[7]	ADVANCE[11]	VADT[10]
Year of Publication	1995	1998	1998	2000	2008	2008	2009
Participants, *n*	110	3867	753	153	10,251	11,140	1791
Country	Japan	UK	UK	USA	USA & Canada	Multi-national	USA
Median Year of Enrollment	1991	1984	1984	1991	2003	2002	2002
Age (mean, yrs)	49	53.3	53	60.1	62.2	66	60.4
Race-ethnicity (%)							
Non-Hispanic white	0	81	85	…	64	…	62
Hispanic white	0	…	…	…	7	…	16
Black	0	8	10	…	19	…	17
Asian	100	10	4	…	…	…	…
Mean duration of diabetes (years)	6.5/10.2	0	0	8	10	8	12
Men (%)	45	61	46	100	61	58	97
Current Smokers (%)	…	31	39	26	14	14	17
Hypertension (%)	…	12	16	…	85	…	72
Hx of CVD (%)	…	…	…	13	35	32	40
SBP (mm Hg)	120/122	135	140	135	136	145	132
DBP (mm Hg)	70/70	82	85	81	75	80	76
Mean LDL (mmol/L)	2.7	3.5	3.7	…	2.7	3.1	2.8
Body weight (kg)	…	77.5	87	…	94	78	97
BMI (kg/sq meter)	21.4/19.3	27.5	31.6	31	32.2	28	31.3
HbA1C (%)	9.1/9.2	7	7.3	9.7	8.3	7.2	9.4
Creatinine (μmol/L)	…	81	77	83	80	87	88.4
Macroalbuminuria (%)	0	1.6%	2%	…	6	3.6	…
Microalbuminuria (%)	0	10.5%	<7.6%	38	27	25.6	…
Urine Alb:creat	13/43	…	…	0.042	1.54	…	…
Fasting plasma glucose (mmol/L)	…	8	8.1	11	9.3	7.9	…

CHARACTERISTIC	Kumamoto[4]	UKPDS 33[14]	UKPDS 34[15]	VA Diabetes Feasibility Trial[5]	ACCORD[7]	ADVANCE[11]	VADT[10]
GFR (ml/min)	…	…	…	…	90	…	…
ARB/ACEI (%)	…	…	…	37	53	…	…
Statins (%)	…	…	…	…	62	28	…
Target HbA1C% in intensive glucose group	<7%	FPG < 6 mmol/L	FPG < 6 mmol/L	5%	<6%	6.5%	< 6% and 1.5% less than conventional
Target HbA1C% in conventional glucose group	*	FPG 6.1–15 mmol/L	FPG 6.1–15 mmol/L	Avoidance of excessive hyperglycemia	7–7.9%	Local standards	<9% and 1.5% higher than intensive
Primary agent in intensive arm	Insulin	Sulfonylurea or insulin	Metformin plus sulfonylurea	Insulin	Multiple Drugs	Gliclazide	BMI 27: metformin & rosiglitazone BMI <27: glimerpiride & rosiglitazone
Median duration of treatment (years)	6	11.1	10.7	2	3.7	5	5.6
Median follow-up (years)	8	11.1	10.7	2	5	5.0	5.6

*
2 separate numbers reported for primary prevention arm (n=55 in each); The clinical and glycemic goals for the intensive therapy group in the Kumomato study was to maintain the blood glucose control as close to the fasting blood glucose concentration of < 140 mg/dL, 2 hour post-prandial blood glucose concentration < 200 mg/dL, HbA1C < 7.0% and mean amplitude of glycemic excursions < 100 mg/dL.. The goals in the conventional arm was to show no symptoms of hyperglycemia or hypoglycemia, and glycemic control as close to the fasting glucose concentration of < 140 mg/dL.

…= Not Reported

Abbreviations: CAD- coronary artery disease, SBP- systolic blood pressure, DBP- diastolic blood pressure, LDL- low density lipoprotein, BMI- body mass index, GFR- glomerular filtration rate, ARB- angiotensin receptor blocker, ACEI- angiotensin converting enzyme inhibitor; FPG- fasting plasma glucose.

Table 2

Risk factors for renal disease in trial participants after the intervention

	Kumamoto	UKPDS 33	UKPDS 34	VA Diabetes Feasibility Trial	ACCORD	ADVANCE	VADT
Median HbA1C (%)							
Intensive	7.1	7.0	7.4	7.1	6.4	6.5	6.9
Standard	9.4	7.9	8.0	9.1	7.5	7.3	8.4
Mean LDL (mmol/L)							
Intensive	…	3.26	3.37	…	2.59	2.64	2.07
Standard	…	3.26	3.34	…	2.61	2.65	2.07
Mean SBP (mm Hg)							
Intensive	…	139	141	135	135	135.5	127
Standard	…	138	139	142	135	138	125
Mean DBP (mm Hg)							
Intensive	…	77	78	82	75	73.5	68
Standard	…	77	77	82	75	74.3	69

…= Not Reported

Abbreviations: SBP- systolic blood pressure, DBP- diastolic blood pressure, LDL- low density lipoprotein

Table 3

Cumulative Incidence of Renal Outcomes in the Trials (Combined incidence in treatment and control arms)

	Kumamoto	UKPDS 33	UKPDS 34	VA Diabetes Feasibility Trial	ACCORD	ADVANCE	VADT
Median length of follow-up (yrs)	6	10	10.7	2	5	5	6
Microalbuminuria	15.6%	21.0% [*]	23%	44%	23.5%	24.7%	11.5%
Macroalbuminuria	3.9%	5.0% [*]	...	8.5%	4.6%	3.5%	4.0%
Doubling of Creatinine	...	1.0% [*]	...	...	7.4%	1.1%	8.8%
ESRD	...	0.6% [†]	0.5%	...	2.8%	0.5%	1.0%
Death from Renal Failure	...	0.3% [†]	0.4%	...	...	0.5%	...

[*] At 9 years follow-up

[†] At study end (median 11.1 years of follow-up)

...=Not Reported