

Role of Intensive Glucose Control in Development of Renal End Points in Type 2 Diabetes Mellitus

Systematic Review and Meta-analysis

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

Methods: Three databases were systematically searched (January 1, 1950, to December 31, 2010) with no language restrictions to identify randomized trials that compared surrogate renal end points (microalbuminuria and macroalbuminuria) and clinical renal end points (doubling of the serum creatinine level, end-stage renal disease [ESRD], and death from renal disease) in patients with type 2 diabetes receiving intensive glucose control vs those receiving conventional glucose control.

Results: We evaluated 7 trials involving 28 065 adults who were monitored for 2 to 15 years. Compared with conventional control, intensive glucose control reduced the risk for microalbuminuria (risk ratio, 0.86 [95% CI, 0.76-0.96]) and macroalbuminuria (0.74 [0.65-0.85]),

but not doubling of the serum creatinine level (1.06 [0.92-1.22]), ESRD (0.69 [0.46-1.05]), or death from renal disease (0.99 [0.55-1.79]). Meta-regression revealed that larger differences in hemoglobin A_{1c} between intensive and conventional therapy at the study level were associated with greater benefit for both microalbuminuria and macroalbuminuria. The pooled cumulative incidence of doubling of the serum creatinine level, ESRD, and death from renal disease was low (<4%, <1.5%, and <0.5%, respectively) compared with the surrogate renal end points of microalbuminuria (23%) and macroalbuminuria (5%).

Conclusions: 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 the serum creatinine level, ESRD, or death from renal disease during the years of follow-up of the trials.

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EPIDEMIOLOGIC STUDIES^{1,2} have demonstrated an association between poor glycemic control and microvascular complications in patients with type 2 diabetes mellitus (T2DM). Randomized controlled trials³⁻⁵ have demonstrated that intensive glycemic control reduces albuminuria. Less clear, however, is whether intensive glycemic control prevents clinical renal end points (eg, progressive decrease in glomerular filtration rate) beyond albuminuria in patients with T2DM. Despite the



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lack of strong evidence, expert panels and guidelines continue to recommend a target hemoglobin A_{1c} (HbA_{1c}) of less than 7.0% for prevention of renal disease and

other microvascular complications. The 2007 National Kidney Foundation Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease (CKD)⁶ endorse intensive glycemic control, and

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these recommendations are reinforced by the 2011 American Diabetes Association guidelines.⁷ 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 end point.

Furthermore, in light of the fact that intensive glycemic control increased the risk for death by 22% in the Action to Control Cardiovascular Risk in Diabetes (ACCORD)

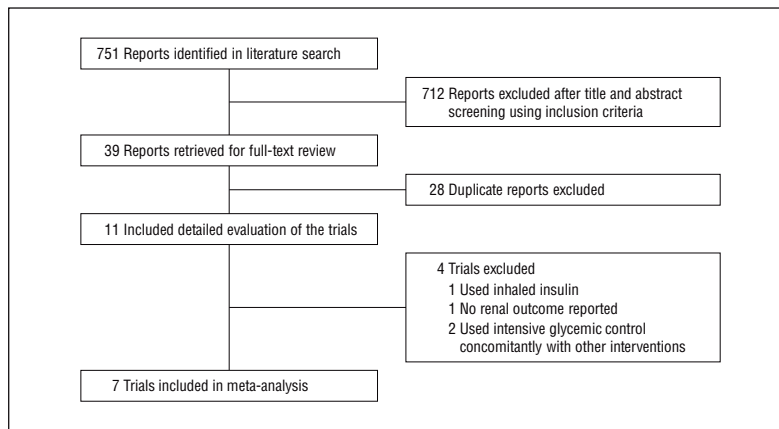


Figure 1. Literature search and selection.

trial,⁸ and pooling the data from all studies did not reduce cardiovascular-related death or all-cause mortality,⁹ it is increasingly problematic for clinicians to continue aggressive glycemic control for the treatment of renal outcomes related to T2DM. The reasons for the lack of clinical benefits are unclear. A recent study¹⁰ 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 individuals with diabetes increased.

The recent publication of several large, randomized, controlled, multicenter trials of intensive glycemic control in T2DM^{8,11,12} may allow an assessment of the effects of intensive glycemic control on clinical renal end points. Thus, in the context of strategies used in these studies, we sought to examine whether this form of therapy was associated with benefits on clinically relevant renal outcomes among patients with T2DM 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 T2DM. Inclusion criteria and methods of analysis were

specified in advance and documented in a protocol available on request. Investigators searched the PubMed central database for publications (January 1, 1950, through December 31, 2010) using the Medical Subject Headings *chronic kidney disease*, *diabetes mellitus type 2*, *hypoglycemic agents*, and *creatinine*, as well as the key words *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 sex 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 (S.G.C. and N.H.) independently reviewed the contents of 751 abstracts or full-text manuscripts identified through the literature search to determine whether they met the eligibility criteria. The predefined inclusion criteria required the clinical trials to (1) randomly assign individuals with T2DM either to an intensive lowering of glucose vs 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 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 patients with stable disease 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 (C.R.P.) who cross-checked all selected articles.

Variables including details of the trials, details of the intervention, and renal end points were abstracted. The corresponding primary author of the article was contacted to clarify details or confirm outcomes for 2 trials.^{8,11}

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

STATISTICAL ANALYSIS

We examined the relationship between intensive glucose control and risk for all study outcomes using risk ratio (RR) and risk difference (RD) measures. Forest plots were created to determine pooled measures. Heterogeneity was assessed with I^2 statistics, ranging from 0% to 100%. The I^2 value demonstrates the percentage of total variation across studies resulting from heterogeneity and was used to judge the consistency of evidence. Any I^2 values of 50% or more indicate a substantial level of heterogeneity.¹³ 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. $P < 0.05$ was considered statistically significant. Analyses were stratified by risk of bias in subsequent analyses. We also performed meta-regression using commercial software (SAS 9.1; SAS Institute, Inc) on the 5 study-level variables (median date of enrollment, years since T2DM diagnosis, duration of therapy, difference in achieved HbA_{1c}, and median achieved HbA_{1c}) to determine the relationship between these variables and the RR for each end point. Regression lines were plotted and bubbles were weighted for the inverse of the variance of the individual RRs of each end

Table 1. Characteristics of Randomized Controlled Trials of Intensive Glucose Control

Characteristic	Kumamoto ^{4,15}	UKPDS 33 ¹⁶	UKPDS 34 ¹⁷	VA Diabetes Feasibility Trial ⁵	ACCORD ^{8,14}	ADVANCE ¹²	VADT ¹¹
Year of publication	1995	1998	1998	2000	2008	2008	2009
Participants, No.	110	3867	753	153	10 251	11 140	1791
Country	Japan	United Kingdom	United Kingdom	United States	United States and Canada	Multinational	United States
Year of enrollment, median	1991	1984	1984	1991	2003	2002	2002
Age, mean, y	49	53.3	53	60.1	62.2	66	60.4
Race/ethnicity, %							
Non-Hispanic white	0	81	85	NR	64	NR	62
Hispanic white	0	NR	NR	NR	7	NR	16
Black	0	8	10	NR	19	NR	17
Asian	100	10	4	NR	NR	NR	NR
Duration of diabetes, mean, y	6.5/10.2 ^a	0	0	8	10	8	12
Male sex, %	45	61	46	100	61	58	97
Current smoker, %	NR	31	39	26	14	14	17
Hypertension, %	NR	12	16	NR	85	NR	72
History of CVD, %	NR	NR	NR	13	35	32	40
SBP, mean, mm Hg	120/122 ^a	135	140	135	136	145	132
DBP, mean, mm Hg	70/70 ^a	82	85	81	75	80	76
LDL-C, mean, mg/dL	104	135	143	NR	104	120	108
Body weight, mean, kg	NR	77.5	87	NR	94	78	97
BMI, mean	21.4/19.3 ^a	27.5	31.6	31.0	32.2	28.0	31.3
HbA _{1c} , %	9.1/9.2 ^a	7.0	7.3	9.7	8.3	7.2	9.4
Serum creatinine, mean, mg/dL	NR	0.9	0.9	0.9	0.9	1.0	1.0
Macroalbuminuria, mean, %	0	1.6	2.0	NR	6.0	3.6	NR
Microalbuminuria, mean, %	0	10.5	<7.6	38	27	25.6	NR
Urine albumin to creatinine ratio, mean	13/43 ^a	NR	NR	0.042	1.54	NR	NR
FPG, mean, mg/dL	NR	144	146	198	168	142	NR
GFR, mean, mL/min	NR	NR	NR	NR	90	NR	NR
ARB/ACEI, % ^b	NR	NR	NR	37	53	NR	NR
Statins, %	NR	NR	NR	NR	62	28	NR
Target HbA _{1c} in intensive glucose group, %	<7	FPG <6 mg/dL	FPG <6 mg/dL	7.1	<6	≤6.5	<6 and 1.5 less than conventional
Target HbA _{1c} in conventional glucose group, %	NR ^c	FPG 6.1-15 mg/dL	FPG 6.1-15 mg/dL	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 and rosiglitazone; BMI <27: glimepiride and rosiglitazone
Duration of treatment, median, y	6	11.1	10.7	2	3.7	5.0	5.6
Follow-up, median, y	8	11.1	10.7	2	5.0	5.0	5.6

Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; ACEI, angiotensin-converting enzyme inhibitor; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation; ARB, angiotensin receptor blocker; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CVD, cardiovascular disease; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GFR, glomerular filtration rate; HbA_{1c}, hemoglobin A_{1c}; LDL-C, low-density lipoprotein cholesterol; NR, not reported; SBP, systolic blood pressure; UKPDS, United Kingdom Prospective Diabetes Study; VA, Veterans Affairs; VADT, Veterans Affairs Diabetes Trial.

SI conversion factors: To convert LDL-C to millimoles per liter, multiply by 0.0259; HbA_{1c} to a proportion of total hemoglobin, multiply by 0.01; serum creatinine to micromoles per liter, multiply by 88.4; and FPG to millimoles per liter, multiply by 0.0555.

^aThe first value represents the result in the primary-prevention cohort; the second value, in the secondary-prevention cohort.

^bData indicate the percentage of patients taking an ARB or an ACEI.

^cTwo separate numbers reported for primary prevention arm (55 patients in each). The clinical and glycemic goals for the intensive therapy group in the Kumamoto study was to maintain the blood glucose control as close to the fasting blood glucose concentration of less than 140 mg/dL; 2-hour postprandial blood glucose concentration, less than 200 mg/dL; HbA_{1c}, less than 7.0%; and mean amplitude of glycemic excursions, less than 100 mg/dL. The goals in the conventional arm were to show no symptoms of hyperglycemia or hypoglycemia, and glycemic control as close to the fasting glucose concentration of less than 140 mg/dL.

point in each trial (Microsoft Excel 2007; Microsoft Corporation).

RESULTS

Figure 1 depicts the study selection process. The meta-analysis included 7 trials conducted among 28 065 participants.

DESCRIPTION OF STUDIES

Table 1 presents the characteristics of the 7 randomized controlled trials and trial participants.^{4,5,8,11,12,14-17}

The number of participants in each trial ranged from 110 to 11 140. Mean baseline serum creatinine levels ranged from 0.9 to 1.0 mg/dL (to

convert to micromoles per liter, multiply by 88.4) in the trials. Mean duration of T2DM before enrollment ranged from 6.5 to 12 years, with the exception of United Kingdom Prospective Diabetes Study (UKPDS) 33 and UKPDS 34, which enrolled patients with newly diagnosed T2DM. The interventions to achieve glyce-

Table 2. Risk Factors for Renal Disease in Trial Participants After the Intervention

Characteristic	Kumamoto ⁴	UKPDS 33 ¹⁶	UKPDS 34 ¹⁷	VA Diabetes Feasibility Trial ⁵	ACCORD ⁸	ADVANCE ¹²	VADT ¹¹
HbA _{1c} , median, %							
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
LDL-C, mean, mg/dL							
Intensive	NR	126	130	NR	100	102	80
Standard	NR	126	129	NR	101	102	80
SBP, mean, mm Hg							
Intensive	NR	139	141	135	135	135.5	127
Standard	NR	138	139	142	135	138	125
DBP, mean, mm Hg							
Intensive	NR	77	78	82	75	73.5	68
Standard	NR	77	77	82	75	74.3	69

Abbreviations: See Table 1.

SI conversion factors: See Table 1.

Table 3. Cumulative Incidence of Renal Outcomes in the Trials^a

Characteristic	Kumamoto ⁴	UKPDS 33 ¹⁶	UKPDS 34 ¹⁷	VA Diabetes Feasibility Trial ⁵	ACCORD ⁸	ADVANCE ¹²	VADT ¹¹
Length of follow-up, median, y	6	10	10.7	2	5	5	6
Microalbuminuria	15.6	21.0 ^b	23	44	23.5	24.7	11.5
Macroalbuminuria	3.9	5.0 ^b	NR	8.5	4.6	3.5	4.0
Doubling of serum creatinine level	NR	1.0 ^b	NR	NR	7.4	1.1	8.8
ESRD	NR	0.6 ^c	0.5	NR	2.8	0.5	1.0
Death from renal failure	NR	0.3 ^c	0.4	NR	NR	0.5	NR

Abbreviations: ESRD, end-stage renal disease. For other abbreviations, see Table 1.

^a Combined incidence in treatment and control arms.^b At 9-year follow-up.^c At study's end (median follow-up, 11.1 years).

mic control varied across studies (Table 1). The HbA_{1c} (or fasting plasma glucose) targets also varied in all studies. The highest HbA_{1c} target in the intensive arms of the trials was 7.1%,⁵ and the lowest HbA_{1c} target was less than 6% in the ACCORD study^{8,14} and VADT (Veterans Affairs Diabetes Trial).¹¹

The median HbA_{1c} values during the trials were lower in the intensive group in all studies, and 4 studies^{4,5,8,11} achieved an HbA_{1c} difference of more than 1% compared with the control group (Table 2). Three studies^{8,11,12} achieved median HbA_{1c} of less than 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. The UKPDS 33 and 34 trials had the longest follow-up times (up to 15 years).^{16,17} The cumulative incidence of renal end points was as follows: microalbuminuria, range

11.5% to 44%; macroalbuminuria, 3.5% to 8.5%; doubling of the serum creatinine level, 1.0% to 8.8%; and ESRD, 0.5% to 2.8% (Table 3). The cumulative incidence of mortality was lowest in ACCORD (5.0% and 3.9% in the 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 RRs of microalbuminuria (Figure 2A) and macroalbuminuria (Figure 2B). Figure 3 presents the same for the clinical renal end points of doubling of the serum creatinine level (Figure 3A), renal failure/ESRD (Figure 3B), and death from renal disease (Figure 3C). Overall analyses indicated that patients randomly assigned to intensive glucose control had reduced risk for microalbuminuria (7 studies: RR,

0.86 [95% CI, 0.76 to 0.96]; RD, −0.04 [95% CI, −0.08 to −0.01]) and macroalbuminuria (6 studies: RR, 0.74 [95% CI, 0.65 to 0.85]; RD, −0.01 [95% CI, −0.02 to −0.01]), but not doubling of the serum creatinine level (4 studies: RR, 1.06 [95% CI, 0.92 to 1.22]; RD, 0.0 [95% CI, 0.0 to 0.1]), ESRD (5 studies: RR, 0.69 [95% CI, 0.46 to 1.05]; RD, 0.0 [95% CI, −0.01 to 0.0]), or death from renal disease (3 studies: RR, 0.99 [95% CI, 0.55 to 1.79]; RD, 0.0 [95% CI, 0.0 to 0.0]) compared with participants in the conventional treatment groups. We identified possible heterogeneity for the end point of microalbuminuria ($I^2 = 64\%$), whereas statistical heterogeneity was low for all other analyses.

SENSITIVITY ANALYSES AND META-REGRESSION

To determine the reasons for heterogeneity for our analyses of the ef-

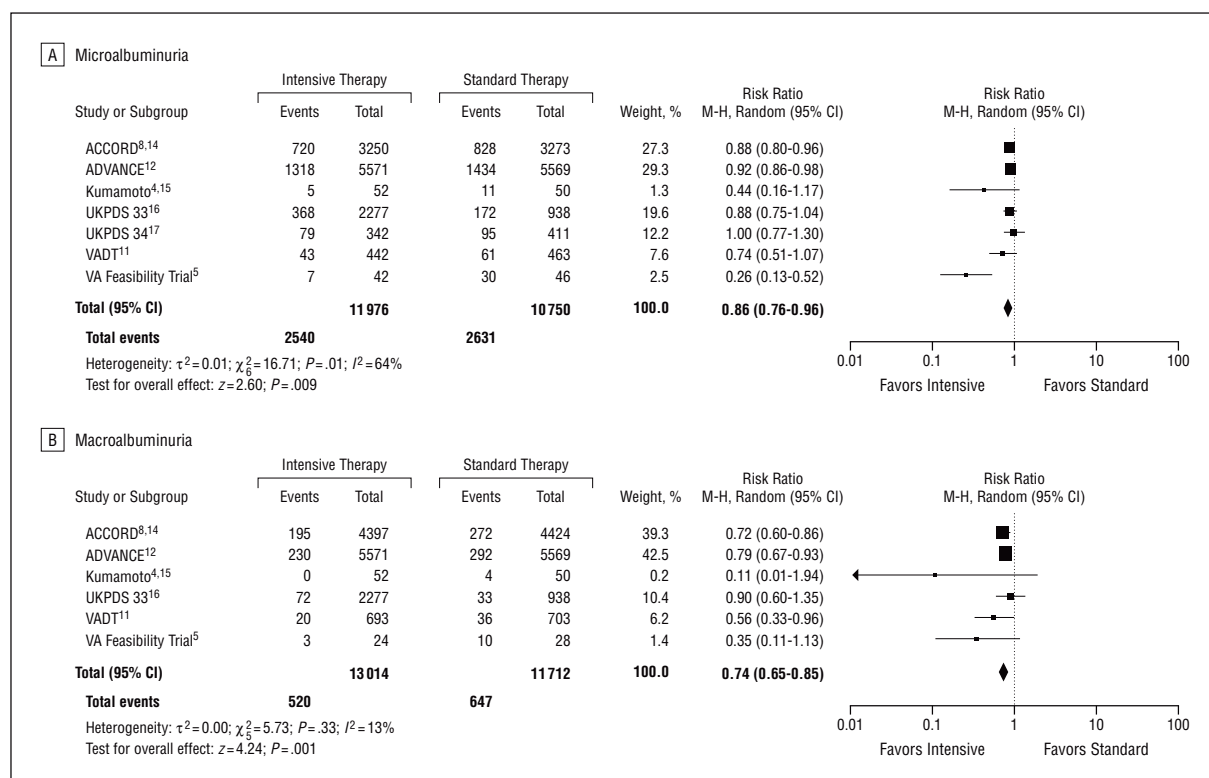


Figure 2. Pooled risk ratios (RRs), with 95% CI, by trial for end points of microalbuminuria and macroalbuminuria. Data on the incidence of microalbuminuria and macroalbuminuria from United Kingdom Prospective Diabetes Study (UKPDS) 33 was reported in 3-year intervals. Because of the marked drop-off of patients with outcomes reported at 9 years and beyond, data from the 6-year time point were chosen for the end points of microalbuminuria and macroalbuminuria. The incidences 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 39.0% in the conventional group, respectively. The incidences of macroalbuminuria at 9, 12, and 15 years were 4.4%, 6.5%, and 7.9% in the intensive group and 6.5%, 10.3%, and 12.6% in the conventional group, respectively. Intensive therapy was stopped earlier than planned in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. 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. Use of data from transition did not significantly change the results for macroalbuminuria (pooled RR, 0.83; 95% CI, 0.72-0.95; $I^2 = 68\%$) or microalbuminuria (pooled RR, 0.74; 95% CI, 0.65-0.84; $I^2 = 17\%$). Bars represent the 95% CIs, the squares are proportional to the study weight, and the diamond is the summary measure, with the lateral points indicating the 95% CI for this estimate. ADVANCE indicates Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation; M-H, Mantel-Haenszel; VA, Veterans Affairs; and VADT, Veterans Affairs Diabetes Trial.

fect on intense glucose therapy on the outcome of microalbuminuria, we excluded each study one by one. Elimination of the VA Diabetes Feasibility Trial⁵ from the microalbuminuria analysis reduced the I^2 to 0%. This study was one of the smallest and had a short duration of follow-up (2 years). However, even after exclusion of the VA Diabetes Feasibility Trial, the pooled RR was not measurably different (RR, 0.91; 95% 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 end points (eFigure 1; available at <http://www.archinternmed.com>). The median year of enrollment, the years since diabetes diagnosis, and the duration of therapy (eFigure 1A-C) were associated with only one end point: risk for doubling of the se-

rum creatinine level. Furthermore, these 3 meta-regressions were largely driven by UKPDS 33, as this study had the earliest median year (1984), the shortest duration of years since diagnosis (<1), and the longest duration of therapy (11 years). The difference in achieved HbA_{1c} was associated with greater benefit from intensive glycemic control for both microalbuminuria ($\beta = -0.40$ for every percentage point of difference in HbA_{1c} , $P = .01$) and macroalbuminuria ($\beta = -0.47$, $P = .008$; eFigure 1D). The median HbA_{1c} achieved in the intensive glycemic group was not associated with magnitude of the RR for any of the end points (eFigure 1E).

RISK OF BIAS ASSESSMENT

The studies were generally of good methodologic quality (eFigure 2 and

eFigure 3). The individual components of The Cochrane Collaboration's tool for assessing risk of bias are described in the subsections that follow.

ALLOCATION

Two^{4,5} of the 7 trials did not clearly state their methods for allocation concealment. The results were not quantitatively or qualitatively changed when those trials were excluded from the analyses.

BLINDING

None of the studies were blinded; all were open label after randomization. Blinding of outcome assessment was reported in all but one⁴ of the included studies.

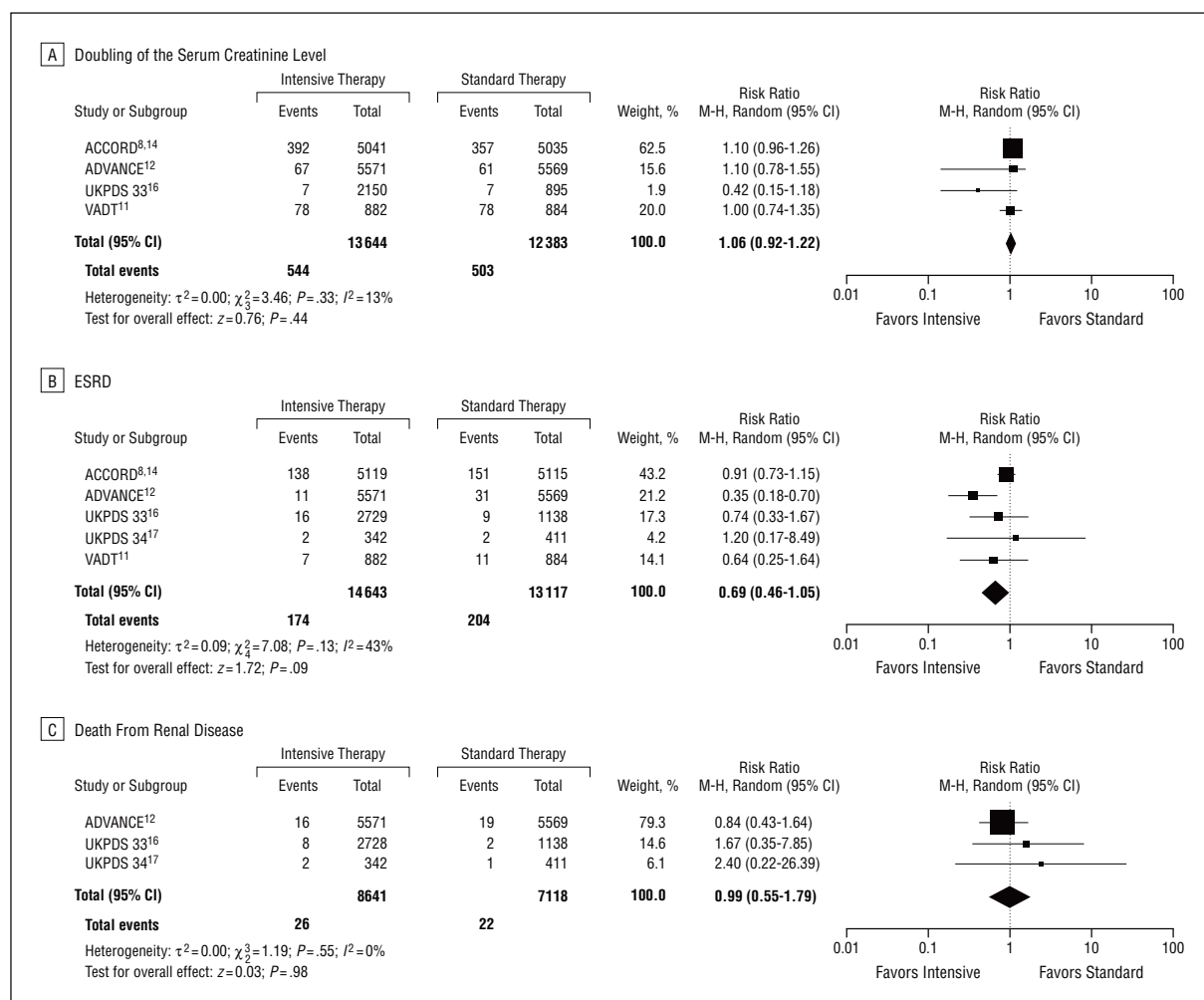


Figure 3. Pooled risk ratios (RRs), with 95% CI, by trial for clinical renal end points (doubling of the serum creatinine level and end-stage renal disease [ESRD]). Data on the incidence of doubling of the serum creatinine level from United Kingdom Prospective Diabetes Study (UKPDS) 33 was reported in 3-year intervals. Because of the marked drop-off of patients with outcomes reported at 9 years and beyond, the data from the 6-year time point ($n=3045$) were chosen for inclusion in the summary data. There was no significant difference in the magnitude or direction of effect at 9 and 12 years. At 9 years ($n=2172$), 0.71% vs 1.76% (RR, 0.40; 95% CI, 0.14-1.20) and at 12 years ($n=1054$), 0.91% and 3.50% (RR, 0.25; 95% CI, 0.07-0.91) patients had doubling of the serum creatinine level in the intensive vs conventional groups. At 15 years ($n=170$), 3.52% of patients in the intensive group and 2.80% of those in the convention group had doubling of the serum creatinine level (RR, 1.25; 95% CI, 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. Use of data from transition did not significantly change the results for doubling of the serum creatinine level (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; $I^2=45\%$). Other abbreviations and the graph elements are defined in the legend to Figure 2.

INCOMPLETE OUTCOME DATA

There was a significant amount of incomplete outcome data from several of the studies. For example, between 20% and 40% of the participants were not assessed for the end points of microalbuminuria and macroalbuminuria in ACCORD, UKPDS 33, UKPDS 34, and VADT. However, the proportions with assessment of these end points 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 microalbuminuria and macroalbuminuria.

The proportion of missing serum creatinine values during follow-up was less than 5% in ACCORD and VADT but was 45% at 9 years in UKPDS 33. Again, however, the proportion of studies that were missing values was equal

in both arms; thus, the risk of bias was low. Because patients were unaware of either subnephrotic proteinuria levels or serum creatinine values and because of the equal proportions of missingness, we believed that the missing data occurred at random and were not the result of differences in the outcomes in the patients without the assessments. Nevertheless, a sensitivity analysis excluding UKPDS 33 did not change the results qualitatively or

quantitatively. The ascertainment for the outcome of ESRD was complete in all the studies that reported the end point.

SELECTIVE REPORTING

There was evidence of selective reporting only by the UKPDS 34 study. The UKPDS 34 study did not report on the end point concerning the doubling of the serum creatinine level, whereas the UKPDS 33 study did so.

OTHER POTENTIAL SOURCES OF BIAS

There was evidence of publication bias by funnel plot analysis. This was shown for the outcomes of microalbuminuria, macroalbuminuria, and doubling of the serum creatinine level, as small studies with a 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 T2DM, a statistically significant reduction in microalbuminuria and macroalbuminuria occurred with intensive therapy. However, the data were inconclusive regarding the effect of intensive glycemic control on clinical renal outcomes defined as doubling of the serum creatinine level, 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 lessens albuminuria, but data are lacking for evidence of a benefit for clinically important renal end points. There was a nonsignificant trend toward reduction of the end point of ESRD, a surprising observation given the very tight precision and null findings for the end point of doubling of the serum creatinine level that must precede ESRD. However, the absolute rate of clinical renal outcomes in the published studies was relatively low: the pooled cumulative incidence of doubling of the serum creatinine level in the standard treatment group of all trials that measured these outcomes was only 4.1%,^{11,12,14,16} and for

ESRD, it was only 1.6%.^{11,12,14,16,17} The low incidence of these end points 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.⁸

As further detailed in the section, multiple reasons may underlie the lack of evidence for a beneficial effect of tight glycemic control on clinically significant renal end points (ie, doubling of the serum creatinine level or ESRD) in this setting. These include (1) intensive glycemic control may have started too late in the course of the disease; (2) the duration of glycemic treatment may have been insufficient, (3) HbA_{1c} levels were not reduced to normal; (4) there may be a “ceiling effect” that once HbA_{1c} is reduced to a moderate degree (eg, <7%), further reduction does not benefit the patient, especially in the setting of other interventions, including use of statins and antihypertensive medications; (5) competing risk of death; and (6) inadequate statistical power to detect a significant 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 toward less reduction of doubling of the serum creatinine level. In fact, the only randomized controlled trial that did not have an RR of 1 or more for doubling of the serum creatinine level enrolled only patients with newly diagnosed T2DM (UKPDS 33).¹⁶ Participants in the other studies had a mean duration of diabetes of 8 to 12 years at the time of enrollment.^{11,12,14} Thus, it is possible that, despite normal glomerular filtration rate at the time of enrollment, there was already a significant amount of subclinical kidney damage that occurred during the 8 or more years of “nonintensive” glycemic control, making it too late to change the usual progression of 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 randomized controlled trials that enrolled patients with prevalent T2DM (generally approximately 5 years), it is impossible to answer this question with any degree of certainty. It is conceivable that a 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 the serum creatinine level; however, this was again driven by UKPDS 33, which enrolled patients with newly diagnosed T2DM. 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 small. In contrast, data from patients with type 1 diabetes from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications follow-up study¹⁸ demonstrate that intensive glycemic control for 6.5 years reduced the incidence of impaired glomerular filtration rate by 50% over a median follow-up period of 22 years. An analysis at 14 years after the start of The Diabetes Control and Complications Trial was not able to demonstrate a significant difference in the number of patients with doubling of the serum creatinine level.¹⁹ Thus, it may take 20 or more years to witness the effect of intensive glycemic control on clinical renal outcomes.

Was the reduction in HbA_{1c} achieved in the trials of sufficient magnitude? Four randomized controlled trials^{4,5,11,14} achieved a difference in HbA_{1c} of more than 1% with intensive therapy vs standard therapy. Although there was a strong association between the difference in HbA_{1c} in the intensive vs standard groups and the risk of both microalbuminuria and macroalbuminuria, there was no association for the end points of doubling of the serum creatinine level or ESRD. Fur-

thermore, although median HbA_{1c} achieved in the intensive care group was not significantly associated with any of the renal end points, there was no greater qualitative benefit for development of microalbuminuria and macroalbuminuria and a trend toward harm for the end point of doubling of the serum creatinine level in studies with lower achieved median HbA_{1c} 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 the risk of severe hypoglycemic events. Furthermore, given the multifactorial nature and complexity of mechanisms underlying the pathogenesis of T2DM, it is important to investigate whether control of other pathogenic 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 definite renal outcomes be the result of competing risk of death? For this to be operative, it would presume that patients at risk of developing the renal end point are the same as those 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 for more participants in that group sufficient time to manifest the renal end point of interest. However, the pooled risk of death was not significantly different between the 2 groups (RR, 0.98; 95% CI, 0.84-1.15).⁹ 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 significant difference in clinical renal end points between the 2 groups. The incidence of doubling of the serum creatinine level was 503 events in 12 383 participants (4.1%) in the standard therapy group. Given the number of patients and a 2-sided α value of .05, we would have been able to detect at least a 16% difference in the RR of the outcome between the 2 groups with 80% power

if there had been a significant difference. The incidence of ESRD was 204 in 13 117 patients (1.6%) in the standard therapy group and 147 in 14 643 participants (1.0%) in the intensive therapy group, yielding 98% power at a 2-sided α value of .05 to detect whether this 31% RR 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,⁹ it does not seem prudent to expose patients to this therapy to achieve an absolute risk reduction for ESRD that will be less than 1% in a best-case scenario.

In conclusion, results of our systematic review and meta-analysis suggest 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 existing T2DM, there is little compelling reason to initiate intensive glycemic control in midstage of the disease with the aim of preventing renal failure.

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INVITED COMMENTARY

Understanding the Long-term Benefits and Dangers of Intensive Therapy of Diabetes

One of the major challenges of studying and treating diabetes mellitus, a chronic degenerative disease, is the extremely long time horizon involved in the development of its complications. Our understanding of this time course has largely been through the study of type 1 diabetes mellitus (T1DM), in which the onset of abnormal glycemia can be accurately timed and there are relatively few co-incident mediators of disease.

The earliest clinically detectable signs of retinopathy, such as microaneurysms, do not usually occur until at least 5 years after development of T1DM. More advanced stages of retinopathy, including preproliferative retinopathy, require at least 10 years, and macular edema and proliferative retinopathy, which can lead to loss of vision, do not usually occur until 15 to 20 years of T1DM duration. Similarly, nephropathy and neuropathy usually manifest initially subclinically, with microalbuminuria and abnormal electrophysiologic findings, respectively.¹ They advance over time to albuminuria and physical findings including diminished thresholds for vibration and light touch sensation. These subclinical and early clinical findings are by themselves not clinically significant; however, with time they can progress to further injury and loss of function with severe clinical consequences. The development of end-stage kidney disease requiring dialy-

sis or a transplant usually takes 25 years or more of T1DM duration.

In contrast to T1DM, type 2 diabetes mellitus (T2DM) often has an onset that is difficult to pinpoint, with a duration that is frequently at least 5 years longer than that reflected by clinical history, a surfeit of nonglycemic risk factors for the microvascular complications and nonspecific cardiovascular complications, and competing comorbidities.¹ Nevertheless, the clinical course of the long-term microvascular complications is largely similar in T2DM as in T1DM, with the major shared risk factors being the level of chronic glycemia and duration of exposure to hyperglycemia.^{2,3} Diabetes is the major cause of blindness, renal failure, and amputations in adults.

The introduction of intensive therapy, with the goal of achieving near-normal HbA_{1c} levels and usual achievement of a level of approximately 7%, has altered the clinical course of retinopathy, nephropathy, and neuropathy. The vast majority of the clinical trials that established the worth of intensive therapy in T1DM and T2DM have been too brief to provide more than a snapshot of the relatively early stages of diabetes complications. The 2 seminal studies, the Diabetes Control and Complications Trial (DCCT) in T1DM⁴ and the UKPDS in T2DM,⁵ reported average follow-up periods of 6.5 and 11 years, respectively. The DCCT included primary prevention and secondary intervention cohorts (mean diabetes du-

rations of 3 and 9 years, respectively), and the UKPDS included patients with “newly-diagnosed” diabetes. Both studies demonstrated consistent major salutary effects of intensive therapy on microvascular complications compared with conventional therapy, with the benefits roughly proportional to the degree of HbA_{1c} separation achieved. In the DCCT, the relative benefits of intensive therapy for all complications were greater in the primary prevention cohort, reinforcing the notion that intensive treatment should be initiated as early in the course of diabetes as practical.⁴ Moreover, long-term follow-up of the DCCT⁶ and UKPDS⁷ cohorts has shown durable effects of early intervention even after the differences in glycemia between the original intervention groups had dissipated, referred to as *metabolic memory* (DCCT) and *legacy effect* (UKPDS). Finally, and most importantly from the clinical point of view, long-term follow-up of the DCCT and UKPDS cohorts (for a total of approximately 25 and 22 years, respectively) has shown beneficial effects of intensive therapy on the development of more advanced clinical outcomes, including cardiovascular events.⁶⁻⁸ These data are the most persuasive argument that intensive therapy, especially when initiated early in the course of diabetes, is effective in reducing the otherwise common clinical consequences of long-term complications.