Effect of Intensive Versus Standard Blood Glucose Control in Patients With Type 2 Diabetes Mellitus in Different Regions of the World: Systematic Review and Meta-analysis of Randomized Controlled Trials

Partha Sardar, MD;* Jacob A. Udell, MD, MPH, FRCPC;* Saurav Chatterjee, MD; Sameer Bansilal, MD; Debabrata Mukherjee, MD, MS; Michael E. Farkouh, MD, MSc, FRCPC, FACC, FAHA

Background—Regional variation in type 2 diabetes mellitus care may affect outcomes in patients treated with intensive versus standard blood glucose control. We sought to evaluate these differences between North America and the rest of the world.

Methods and Results—Databases were searched from their inception through December 2013. Randomized controlled trials comparing the effects of intensive therapy with standard therapy for macro- and microvascular complications in adults with type 2 diabetes mellitus were selected. We calculated summary odds ratios (ORs) and 95% CIs with the random-effects model. The analysis included 34 967 patients from 17 randomized controlled trials (7 in North America and 10 in the rest of the world). There were no significant differences between intensive and standard therapy groups for all-cause mortality (OR 1.03, 95% CI 0.93 to 1.13) and cardiovascular mortality (OR 1.09, 95% CI 0.90 to 1.32). For trials conducted in North America, intensive therapy compared with standard glycemic control resulted in significantly higher all-cause mortality (OR 1.21, 95% CI 1.05 to 1.40) and cardiovascular mortality (OR 1.41, 95% CI 1.05 to 1.90) than trials conducted in the rest of the world (all-cause mortality OR 0.93, 95% CI 0.85 to 1.03; interaction P=0.006; cardiovascular mortality OR 0.89, 95% CI, 0.79 to 1.00; interaction P=0.007). Analysis of individual macro- and microvascular outcomes revealed no significant regional differences; however, the risk of severe hypoglycemia was significantly higher in trials of intensive therapy in North America (OR 3.52, 95% CI 3.07 to 4.03) compared with the rest of the world (OR 1.45, 95% CI 0.85 to 2.47; interaction P=0.001).

Conclusion—Randomization to intensive glycemic control in type 2 diabetes mellitus patients was associated with increases in all-cause mortality, cardiovascular mortality, and severe hypoglycemia in North America compared with the rest of the world. Further investigation into the pathobiology or patient variability underlying these findings is warranted. (*J Am Heart Assoc*. 2015;4: e001577 doi: 10.1161/JAHA.114.001577)

Key Words: cardiovascular mortality • diabetes mellitus • intensive glycemic control

I ntensive glycemic control has been suggested as a possible modality of therapy for prevention of cardiovascular (CV) events in patients with type 2 diabetes mellitus (T2DM).[1,2] The American Diabetes Association guidelines recommend a glycated hemoglobin (HbA1c) level of ≤7% as a target for nonpregnant adults with T2DM.[3] Based on the mortality benefit in a subgroup of overweight patients receiving metformin in the UK Prospective Diabetes Study (UKPDS), much attention has been focused on intensive glycemic control for prevention of CV events.[4,5] The benefit of such a strategy, however, has not been replicated in dedicated trials.[6–9] Intensive control in trials conducted in

Europe and the Asia–Pacific region did not reduce (or increase) CV events.[6,7] In contrast, North American trials of intensive control resulted in increased mortality with this strategy.[8,9] Several recent meta-analyses of intensive and standard glycemic control trials did not find any mortality benefit with intensive therapy and reported either limited or no benefit for other macro- and microvascular events[10–14]; however, there was high heterogeneity among trial results for all-cause and CV mortality, and the reason for these suggested differences in trial results were not fully explained. Previous reports have highlighted regional and race/ethnicity differences in CV risk-factor profiles among patients with T2DM.[15–20] Significant regional variations in the efficacy of intensive antiplatelet treatment were recently observed in randomized controlled trials (RCTs) of acute coronary syn-

drome.[21,22] Regional variation for major macro- or microvascular disease in patients with T2DM was also seen in 1 RCT.[23] We performed a systematic review and meta-analysis of RCTs to examine regional variation in the efficacy and safety of intensive glycemic control treatment in T2DM patients.

Methods

Data Sources and Searches

We systematically searched PubMed, Cochrane Central, Embase, EBSCO, and Web of Science databases since their inception through December 2013, using the following key words: *diabetes mellitus, type 2 diabetes, cardiovascular diseases, glucose, HbA1c,* and/or *glucose control, glycemic*
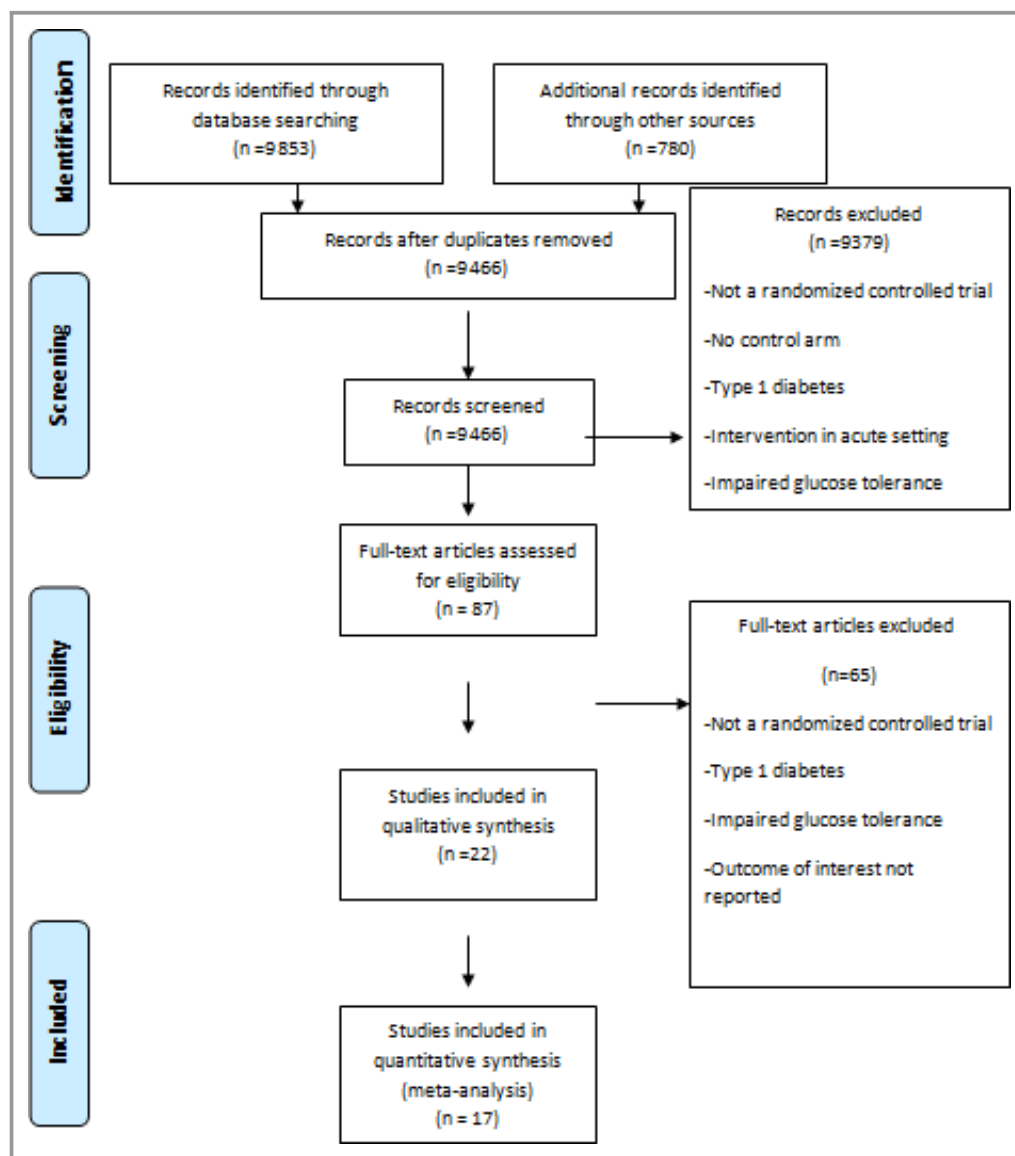

Figure 1. Search strategy and selection of clinical trials included in systematic review and meta-analysis according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist.

Table 1. Baseline Characteristics of Included Trials

Trial	Location	Intensive Group (n)	Standard Group (n)	Follow-up Duration	Intensive Treatment Target	Standard Treatment Target	Intensive Treatment	Standard Treatment
North America								
ACCORD[8,25]	USA and Canada	5128	5123	3.5 years Long term follow up-5 years	HbA1c <6%	HbA1c 7.0% to 7.9%	Therapeutic regimens were individualized at the discretion of the investigators	Available treatments
VADT[9]	USA	892	899	5.6 years	HbA1c ≤6%	HbA1c <9%	Maximal doses of oral agents followed by insulin if target was not achieved	Started on half the maximal doses of oral agents
Veteran Affairs[26,27]	USA	75	78	27 months	HbA1c <7.5%	No specific HbA1c target	One injection of evening intermediate or long-acting insulin, glipizide was added if target was not reached	One insulin injection every morning
UGDP[28,29]	USA	408	205	10 years	—	—	Tolbutamide or phenformin	Placebo
UGDP[30]	USA	204	210	12.5 years	—	—	Intensive insulin	Fixed dose of Insulin
Service et al[31]	USA	10	10	1.75 years	HbA1c to normal range	Eliminate symptoms	Complex insulin treatment	A single daily injection of intermediate acting insulin
Jaber et al[32]	USA	23	22	4 months	Fasting blood glucose ≤6.6 mmol/L	NR	Intensive pharmaceutical care	Routine care with primary care physician

Table 1. Continued

Trial	Location	Intensive Group (n)	Standard Group (n)	Follow-up Duration	Intensive Treatment Target	Standard Treatment Target	Intensive Treatment	Standard Treatment
Europe								
UKPDS 1998 [33,44]	UK	3071	1138	UKPDS 33 10.0 years UKPDS 34 10.7 years Long term follow up-20 years	Fasting blood glucose <6 mmol/L in insulin treated patients	Fasting blood glucose <15 mmol/L without symptoms of hyperglycaemia	Sulfonylureas, or insulin in 1 group Metformin in another separate group	Conventional therapy primarily with diet
REMBO [34]	Russia	41	40	12 months	HbA1c <7% for patients receiving sulfonylurea; HbA1c <6.5% for patients receiving insulin	Not specified	Started with sulfonylurea, metformin followed by insulin was added if not on target	Standard care
PROactive [6]	Multinational	2605	2633	2.9 years	HBA1c concentration below the recommended target (<6.5%)	No predefined target difference with intensive group	Pioglitazone- to achieve the maximum tolerated dose, according to the licensed dose range for pioglitazone and current therapy	Placebo and current therapy
HOME 2009 [35]	Netherlands	196	194	4.3 years	No predefined target	No predefined target	Insulin and metformin	Insulin and placebo
Steno 2003 [36,37]	Denmark	80	80	7.8 years Long term follow up-13.3 years	HbA1c <6.5%, also specific targets for lipids and blood pressure blood pressure	HbA1c <7.5% (1993–1999), HbA1c <6.5% (2000–2001),	Targeted, intensified, multifactorial intervention involving a combination of medications and focused	Conventional multifactorial treatment, consistent with the guidelines of the Danish Medical Association

Table 1. Continued

Trial	Location	Intensive Group (n)	Standard Group (n)	Follow-up Duration	Intensive Treatment Target	Standard Treatment Target	Intensive Treatment	Standard Treatment
							behavior modification	
International/multi-continent								
ADVANCE[7]		5571	5569	5.0 years	HbA1c ≤6.5%	Glycaemic target of HbA1c defined from local guidelines	Glicazide alone or if required sequential addition or increase in dose of metformin, thiazolidinediones, acarbose, or insulin	Standard treatment for glucose control (no glicazide)
Asia								
Kumamoto 1995[38,39]	Japan	55	55	6 years Long term follow up-10 years	HbA1c <7.0%	Fasting blood glucose close to <140 mg/dL	Multiple insulin injection	Conventional insulin injection
Guo et al[40]	China	166	54	6 months	Fasting plasma glucose 4.0 to 7.0 mmol/L, hemoglobin Alc <7%,	No treatment goal	Glipizide, Metformin and α-Glucosidase inhibitors, Bedtime intermediate-acting insulin was added if hemoglobin Alc concentrations ≥7% after the maximum oral hypoglycemic treatment	Traditional or routine outpatient service
Yang et al[41]	China	57	32	2	HbA1c <7.0%	NR	Multiple subcutaneous insulin injections	Routine outpatient treatment.
Other								
Bagg et al[42]	New Zealand	21	22	20 weeks	HbA1c <7%	Avoid symptoms of hyperglycaemia and fortnightly fasting capillary glucose test >17 mmol/L	Oral hypoglycaemic agents and/or insulin	Therapy modified only in case of persistent hyperglycaemia

ACCORD indicates Action to Control Cardiovascular Risk in Diabetes Study; ADVANCE, Action in Diabetes and Vascular disease—PreterAx and DiamicroN MR Controlled Evaluation; HbA1c, glycated haemoglobin A1c; NR, Not reported; PROactive, PROspective pioglitAzone Clinical Trial In macroVascular Events; REMBO, Rational Effective Multicomponent Therapy in the Struggle Against DiaBetes Mellitus in Patients With COngestve Heart Failure; UGDP, University Group Diabetes Program; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

Table 2. Characteristics of Participants

Trials	Age, y	Men (%)	Duration of Diabetes (years)	Previous CVS Events	Initial FPG (mmol/L)	Initial HbA1c (%)—Intensive Group	Initial HbA1c (%)—Standard Group	Initial HbA1c (%)—Median/ Mean	Final HbA1c (%)—Intensive Group	Final HbA1c (%)—Standard Group	Decrease in HbA1c (%)—Intensive Group
North America											
ACCORD[8,25]	62.2	62	10	35%	9.8	8.1	8.1	8.1	6.4	7.5	1.7
VADT[9]	60.4	97	11.5	40%	10.9	9.4	9.4	9.4	6.9	8.4	2.5
Veteran Affairs[26,27]	60.1	100	7.8	38%	11.9	9.3	9.5	9.5	7.0	9.5	2.3
UGDP[28,29]	52	29	<1	9.5%	7.9	NR	NR	NR	NR	NR	NR
UGDP[30]	52	29	<1	9.5%	7.9	NR	NR	NR	NR	NR	NR
Service et al[31]	50.7	60	0.5	NR	8.7	11.4	11.4	11.4	NR	NR	
Jaber et al[32]	62.4	21.8	6.5	NR	12	11.5	12.2	11.9	9.2	11.5	2.3
Europe											
UKPDS*[4,5,33]	53.3	47	<1	NR	8.1	7.1	7.1	7.1	7.0	7.9	0.1
REMBO[34]	64	70	5.5	100%	6.6	7.1	7.2	7.2	—	—	
PROactive[6]	62	67	8	100%	—	7.8	7.9	7.9	7.0	7.6	0.8
HOME 2009[35]	61	50	12	1%	1.58	7.9	7.9	7.9	7.7	7.9	0.2
Steno 2003[36,37]	55	74	5.7	24%	10.3	8.4	8.8	8.6	7.7	8.0	0.7
International/multicontinent											
ADVANCE[7]	66.0	58	8.0	32%	8.5	7.5	7.5	7.5	6.5	7.3	1.0
Asia											
Kumamoto 1995[38,39]	49	50	6.5	0	—	9.3	9	9.2	7.1	9.4	2.2
Guo et al[40]	49	58	Newly diagnosed	NR	8.5	7.1	7.7	7.4	6.3	7.1	0.8
Yang et al[41]	51	NR	1 year	NR	7.2	7.4	6.9	7.2	NR	NR	NR
Other											
Bagg et al[42]	55.9	43	6.9	10%	13.5	10.8	10.5	10.7	NR	NR	NR

All values are either mean or median. ACCORD indicates Action to Control Cardiovascular Risk in Diabetes Study; ADVANCE, Action in Diabetes and Vascular disease—PreterAx and DiamicroN MR Controlled Evaluation; CVS, Cardiovascular; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin A1c; NR, Not reported; PROactive, PROspective pioglitAzone Clinical Trial In macroVascular Events; REMBO, Rational Effective Multicomponent Therapy in the Struggle Against DiaBetes Mellitus in Patients With COngestve Heart Failure; UGDP, University Group Diabetes Program; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.
*Baseline characteristics data from UKPDS 33.

control, tight glucose control, intensive therapy, intensive glucose lowering, intensive blood glucose control, The search was restricted to randomized clinical trials, and we did not apply any language restrictions. Considering the meta-analytic study design, institutional review board approval and informed consent were not required for this project.

Study Selection and Data Extraction

Two authors (P.S. and S.C.) reviewed the identified publications for eligibility and extracted data independently. Eligibility for inclusion was predefined as randomized clinical trials that recruited patients with T2DM who were aged ≥18 years and that assessed the efficacy of intensive blood glucose control versus a standard treatment (placebo or less intensive glycemic control treatment) and reported all-cause or CV mortality data. We excluded trials in which intensive therapy was applied as an acute intervention or in acute care setting. The primary outcome was all-cause mortality, and secondary outcomes included CV mortality, major macrovascular events (composite major macrovascular outcomes, nonfatal myocardial infarction, and stroke), major microvascular events

Table 3. Risk of Bias Assessments for Included Randomized Clinical Trials

Study Name	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Researchers (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome data (Attrition Bias)	Selective Reporting (Reporting Bias)	Other Bias
ACCORD[8,25]	Low	Low	Low	Low	Unclear	Low	Unclear
VADT[9]	Low	Low	Low	Low	Low	Low	Unclear
Veteran Affairs[26,27]	Unclear	Unclear	Low	Low	Low	Low	Unclear
UGDP[28,29]	Low	Low	Low	Low	Low	Low	Low
UGDP[30]	Low	Low	Low	Low	Low	Low	Low
Service et al[31]	Low	Unclear	Low	Low	Low	Low	Low
Jaber et al[32]	Unclear	Unclear	Unclear	Unclear	Low	Low	High
UKPDS[4,5,33]	Low	Low	Low	Low	Low	Low	Unclear
REMBO[34]	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
PROactive[6]	Low	Low	Low	Low	Low	Low	High
HOME 2009[35]	Low	Low	Unclear	Unclear	Low	Low	High
Steno 2003[36,37]	Low	Low	High	High	Low	Low	High
ADVANCE[7]	Low	Low	Low	Low	Low	Low	Unclear
Kumamoto 1995[38,39]	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High
Guo et al[40]	Low	Low	Unclear	Unclear	Low	Unclear	Low
Yang et al[41]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Bagg et al[42]	Unclear	Unclear	Low	Low	Low	Low	Low

ACCORD indicates Action to Control Cardiovascular Risk in Diabetes Study; ADVANCE, Action in Diabetes and Vascular disease—PreterAx and DiamicroN MR Controlled Evaluation; HbA1c, glycated haemoglobin A1c; PROactive, PROspective pioglitAzone Clinical Trial In macroVascular Events; REMBO, Rational Effective Multicomponent Therapy in the Struggle Against DiaBetes Mellitus in Patients With COngestve Heart Failure; UGDP, University Group Diabetes Program; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

(composite microvascular outcomes, new or worsening nephropathy, new or worsening retinopathy, neuropathy and peripheral vascular disease), and severe hypoglycemic events. Risk of bias was assessed using the components recommended by the Cochrane Collaboration.[24]

Categorization of Included Randomized Trials

Among the included trials, 7 were conducted in North America (NA)[8,9,25–32] and 10[4–7,33–42] were conducted in the rest of the world (ROW), including 5 in Europe[4–6,33–37] and 3 in Asia.[38–41] All except 1 European trial[34] were multinational or were conducted in Western Europe. Fifteen trials were published in English, 1 was published in Russian,[34] and 1 was published in Chinese.[41] For our primary analysis, we included data based on initial planned follow-up. Three trials had a factorial design.[4,5,7,8] ADVANCE[7] was a multinational trial with 96% of patients recruited from Europe, Asia, and Australia and New Zealand, with only 4% of patients recruited from Canada and no patients from the United States. Two related University Group Diabetes Program (UGDP) trials (UGDP 1975–1976) used phenformin or

tolbutamide as intensive therapy[28,29]; data from these 2 trials were combined. Separate analysis excluding data from these 2 UGDP trials was performed because phenformin and tolbutamide are no longer in use. The UGDP 1982 trial[30] used insulin as intensive therapy; we regarded this as a separate trial from UGDP 1975–1976. Data from the UKPDS 33 and 34 trials were combined.[4,5] In the ROW group, intensive glycemic control was part of a multimodal multifactorial intervention in 3 RCTs,[36,40,41] and there was no predefined difference in glycemic targets in 2 RCTs.[6,35] Four trials reported long-term follow-up data after the initial published report.[25,33,37,39]

Data Synthesis and Analyses

Analyses were performed according to standard guidelines by intention to treat.[43] Summary odds ratios (ORs) and 95% CIs were calculated with the random-effects model.[44] The random-effects method described by DerSimonian (1986)[44] incorporates an assumption that the different studies are estimating different but related intervention effects. The method is based on the inverse-variance approach and
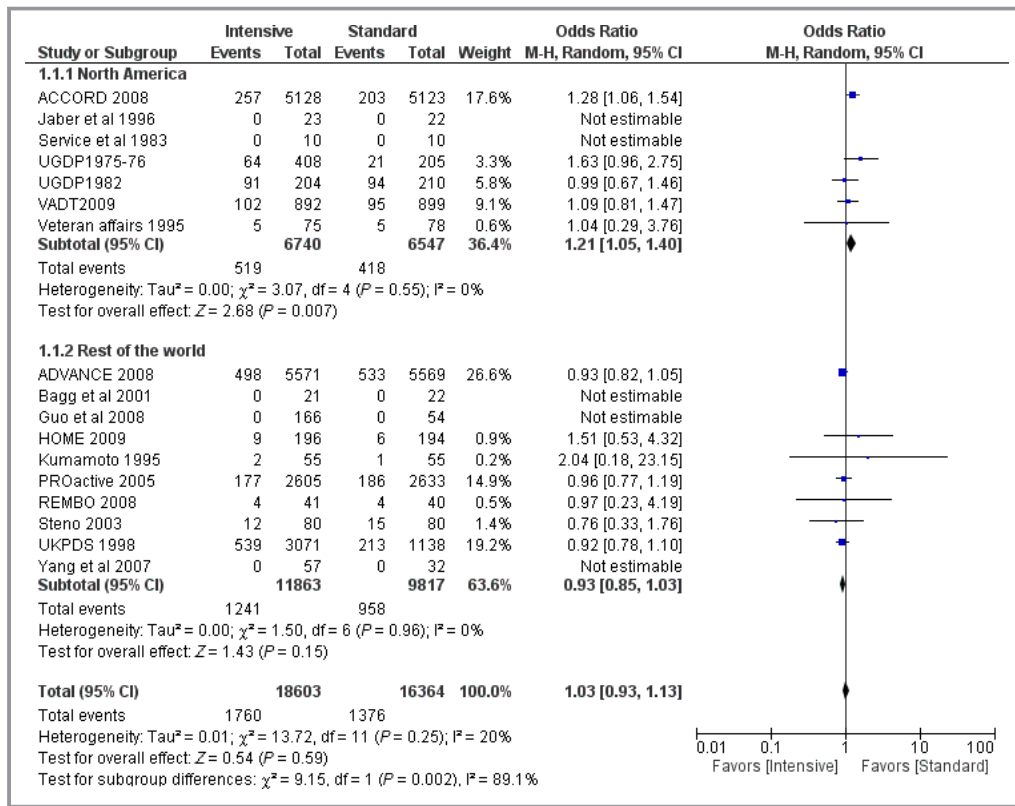
Figure 2. All-cause mortality with intensive therapy for type 2 diabetes mellitus for North America and the rest of the world. ACCORD indicates Action to Control Cardiovascular Risk in Diabetes Study; ADVANCE, Action in Diabetes and Vascular disease—PreterAx and DiamicroN MR Controlled Evaluation; M-H, Mantel-Haenszel; PROactive, PROspective pioglitAzone Clinical Trial In macroVascular Events; REMBO, Rational Effective Multicomponent Therapy in the Struggle Against DiaBetes Mellitus in Patients With COngestve Heart Failure; UGDP, University Group Diabetes Program; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

adjusts the study weights according to the extent of variation, or heterogeneity, among the varying intervention effects. Because we included trials with differently sized patient populations, and there were apparent differences in baseline characteristics and intervention strategies, the random-effects method is more appropriate in this situation. Heterogeneity was assessed with the I^2 statistic,[45] which seeks to determine whether genuine differences underlie the results of the studies (heterogeneity) or whether the variation in findings is compatible with chance alone (homogeneity). We considered $I^2 < 25\%$ as low heterogeneity and $I^2 > 75\%$ as high, with a Cochran Q statistic ($P \leq 0.1$) considered significant for each outcome. Any potential differential association of intensive therapy in patients from NA and the ROW was then tested using a test for interaction, with $P < 0.05$ considered statistically significant.

Publication bias was estimated visually with funnel plots and the weighted regression test of Egger. Additional subgroup analyses categorizing trials conducted in Europe, Western Europe, and Asia were explored. We performed the following sensitivity analyses: excluding studies with a multimodal treatment strategy or multifactorial intervention, excluding the largest trial in both groups (NA and ROW), repeating the analysis with longest available follow-up data of the trials, excluding trials using hypoglycemic agents not currently available, and limiting to trials with low risk of bias. Four trials reported long-term follow-up data after initial published report (ACCORD,[8,25] UKPDS,[4,5] Steno-2,[36,37] Kumamoto[39]). According to trial protocols, intensive therapy was discontinued after the initial planned follow-up period, and patients in both arms of the trials were followed up without any active intensive intervention. We also conducted meta-regression analysis adjusting for potential confounders in our multivariable model, including age, baseline duration of diabetes, baseline proportion with prior CV events, baseline HbA1c, change in HbA1c in the intensive arm, and duration of follow-up. All tests were 2-tailed, with $P < 0.05$ considered significant. We used Review Manager (RevMan), version 5.2.3 (Cochrane Collaboration, 2012) and Stata 11.2 (StataCorp LP) software for analyses.
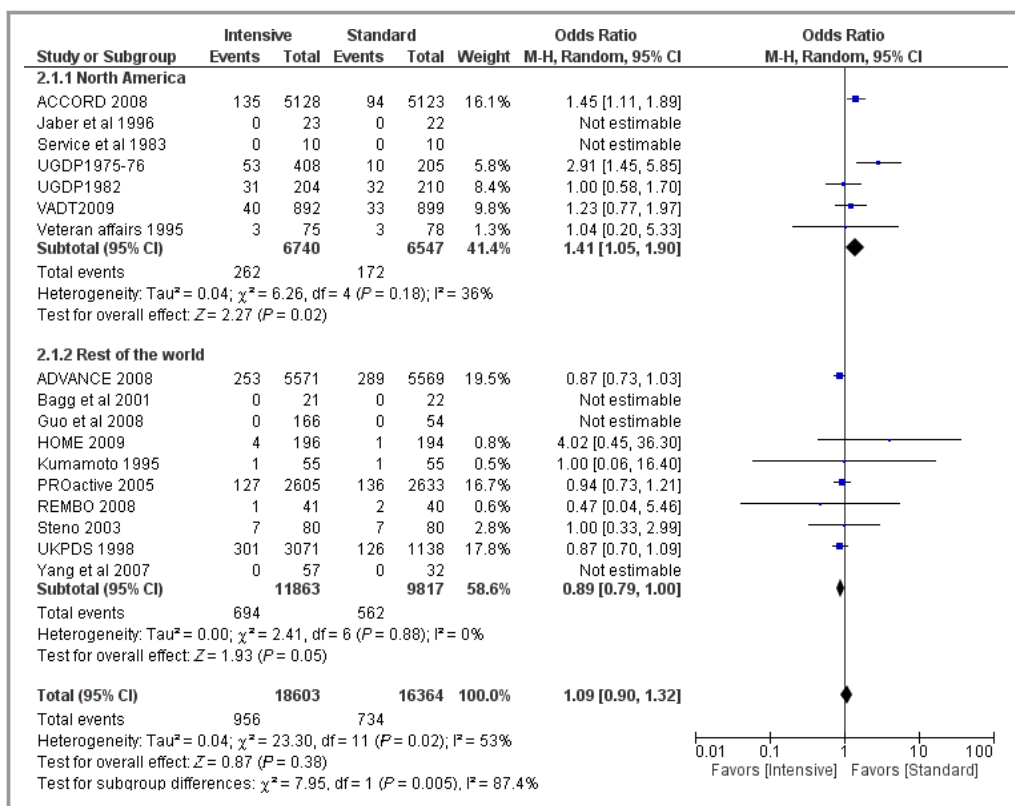
Study or Subgroup	Intensive Events	Total	Standard Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
2.1.1 North America							
ACCORD 2008	135	5128	94	5123	16.1%	1.45 [1.11, 1.89]	
Jaber et al 1996	0	23	0	22		Not estimable	
Service et al 1983	0	10	0	10		Not estimable	
UGDP1975-76	53	408	10	205	5.8%	2.91 [1.45, 5.85]	
UGDP1982	31	204	32	210	8.4%	1.00 [0.58, 1.70]	
VADT2009	40	892	33	899	9.8%	1.23 [0.77, 1.97]	
Veteran affairs 1995	3	75	3	78	1.3%	1.04 [0.20, 5.33]	
Subtotal (95% CI)		**6740**		**6547**	**41.4%**	**1.41 [1.05, 1.90]**	
Total events	262		172				
Heterogeneity: Tau² = 0.04; χ² = 6.26, df = 4 (*P* = 0.18); I² = 36%							
Test for overall effect: *Z* = 2.27 (*P* = 0.02)							
2.1.2 Rest of the world							
ADVANCE 2008	253	5571	289	5569	19.5%	0.87 [0.73, 1.03]	
Bagg et al 2001	0	21	0	22		Not estimable	
Guo et al 2008	0	166	0	54		Not estimable	
HOME 2009	4	196	1	194	0.8%	4.02 [0.45, 36.30]	
Kumamoto 1995	1	55	1	55	0.5%	1.00 [0.06, 16.40]	
PROactive 2005	127	2605	136	2633	16.7%	0.94 [0.73, 1.21]	
REMBO 2008	1	41	2	40	0.6%	0.47 [0.04, 5.46]	
Steno 2003	7	80	7	80	2.8%	1.00 [0.33, 2.99]	
UKPDS 1998	301	3071	126	1138	17.8%	0.87 [0.70, 1.09]	
Yang et al 2007	0	57	0	32		Not estimable	
Subtotal (95% CI)		**11863**		**9817**	**58.6%**	**0.89 [0.79, 1.00]**	
Total events	694		562				
Heterogeneity: Tau² = 0.00; χ² = 2.41, df = 6 (*P* = 0.88); I² = 0%							
Test for overall effect: *Z* = 1.93 (*P* = 0.05)							
Total (95% CI)		**18603**		**16364**	**100.0%**	**1.09 [0.90, 1.32]**	
Total events	956		734				
Heterogeneity: Tau² = 0.04; χ² = 23.30, df = 11 (*P* = 0.02); I² = 53%							
Test for overall effect: *Z* = 0.87 (*P* = 0.38)							
Test for subgroup differences: χ² = 7.95, df = 1 (*P* = 0.005), I² = 87.4%							

Scale: 0.01 0.1 1 10 100 — Favors [Intensive] Favors [Standard]

Figure 3. Cardiovascular mortality with intensive therapy for type 2 diabetes mellitus for North America and the rest of the world. ACCORD indicates Action to Control Cardiovascular Risk in Diabetes Study; ADVANCE, Action in Diabetes and Vascular disease⸺PreterAx and DiamicroN MR Controlled Evaluation; M-H, Mantel-Haenszel; PROactive, PROspective pioglitAzone Clinical Trial In macroVascular Events; REMBO, Rational Effective Multicomponent Therapy in the Struggle Against DiaBetes Mellitus in Patients With COngestve Heart Failure; UGDP, University Group Diabetes Program; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

Results

We identified 9466 articles from our search strategy, of which 17 trials met eligibility criteria and were included in the final analysis (Figure 1).[4–8,25–42] Baseline characteristics and details of the included trials are reported in Table 1. The 17 trials included 34 967 participants, with 18 603 treated with intensive therapy and 16 364 treated with standard therapy.

Characteristics of Included Trials and Patients

The mean duration of diabetes at the entry level was 5.2 years (range 0 to 11.5 years) for the trials conducted in NA and 5.4 years (range 0 to 12.0 years) for the trials conducted in the ROW. Initial (baseline) mean HbA1C level for NA was 10.6% compared with 8.1% for the ROW. Mean duration of follow-up for trials was 5.1 years in NA and 4.1 years in the ROW. The mean decrease in HbA1c level in the intensive group was 2.20% and 0.83% for trials conducted in NA and in the ROW, respectively. Mean age of participants

was 57.1 years for trials in NA and 56.6 years in the ROW. The percentage of male patients in the intensive group for trials conducted in NA was 56.9% and 57.4% in the ROW. Baseline mean fasting plasma glucose level for NA was 9.9 mmol/L compared with 8.0 mmol/L for the ROW (Tables 1 through 3).

Major trials in NA mainly followed an intensive strategy by maximizing doses of oral agents followed by an introduction of insulin (VADT);[9] 1 major trial allowed for an individualized approach at the discretion of the investigators (ACCORD).[8] Major trials in the ROW started with oral agents, and insulin was added if patients were not at the glycemic target, according to details described in Table 1. In 1 trial, PROactive,[6] the comparison was simply pioglitazone to placebo.

Outcomes

There was no significant differences between the intensive and standard therapy groups for all-cause mortality (OR 1.03, 95% CI 0.93 to 1.13) and CV mortality (OR 1.09, 95% CI 0.90

Table 4. Mortality, Macrovascular and Microvascular Outcomes With Intensive Therapy: Regional Variation

Outcomes	North America		Rest of the World		P Interaction
	Events/Total (%)	OR (95% CI)	Events/Total (%)	OR (95% CI)	
All-cause mortality					
Intensive	519/6740 (7.7)	1.21 (1.05 to 1.40)	1241/11 863 (10.5)	0.93 (0.85 to 1.03)	0.006
Standard	418/6547 (6.4)		958/9817 (9.8)		
Cardiovascular mortality					
Intensive	262/6740 (3.9)	1.41 (1.05 to 1.90)	694/11 863 (5.8)	0.89 (0.79 to 1.00)	0.007
Standard	172/6547 (2.6)		562/9817 (5.7)		
Composite macrovascular					
Intensive	608/6095 (10.0)	0.95 (0.77 to 1.17)	729/8376 (8.7)	0.90 (0.73 to 1.10)	0.72
Standard	648/6100 (10.6)		677/6784 (9.9)		
Nonfatal myocardial infraction					
Intensive	302/6707 (4.5)	0.80 (0.68 to 0.93)	514/11 599 (4.4)	0.83 (0.67 to 1.03)	0.79
Standard	356/6515 (5.4)		435/9691 (4.5)		
Nonfatal stroke					
Intensive	89/6020 (1.5)	0.91 (0.58 to 1.43)	431/11 544 (3.7)	0.83 (0.59 to 1.17)	0.75
Standard	93/6022 (1.5)		393/9636 (4.1)		
Composite microvascular					
Intensive	1591/5107 (31.1)	0.94 (0.87 to 1.02)	775/8642 (8.9)	0.82 (0.73 to 0.93)	0.06
Standard	1659/5108 (32.5)		726/6707 (10.8)		
New or worsening nephropathy					
Intensive	2880/6278 (45.8)	1.02 (0.74 to 1.41)	266/8456 (31.4)	0.53 (0.29 to 0.96)	0.06
Standard	2852/6295 (45.3)		353/6864 (51.3)		
New or worsening retinopathy					
Intensive	394/2467 (15.9)	0.74 (0.63 to 0.87)	741/8631 (8.6)	0.78 (0.60 to 1.03)	0.74
Standard	444/2350 (18.9)		591/7036 (8.3)		
Neuropathy					
Intensive	1491/3354 (44.4)	0.92 (0.83 to 1.01)	2793/8284 (33.7)	1.02 (0.95 to 1.09)	0.09
Standard	1568/3367 (46.5)		2533/6857 (36.9)		
Peripheral vascular disease					
Intensive	122/1515 (8.0)	1.03 (0.62 to 1.69)	465/11 443 (4.0)	0.97 (0.81 to 1.17)	0.83
Standard	96/1350 (7.1)		457/9534 (4.7)		
Severe hypoglycemia					
Intensive	911/6118 (14.9)	3.52 (3.07 to 4.03)	207/10 819 (19.1)	1.45 (0.85 to 2.47)	0.0016
Standard	291/6122 (4.7)		112/9497 (11.8)		

OR indicates odds ratio.

to 1.32). A significant interaction was found between the effect of intensive versus standard blood glucose therapy and region (NA versus the ROW) for all-cause mortality (interaction *P*=0.006) and CV mortality (interaction *P*=0.0072), suggesting that the effect of intensive therapy was not uniform across the world; intensive therapy was associated with harm in NA but not in the ROW.

North America

Analysis of the data from trials conducted in NA (7 trials, total of 13 287 patients) showed that intensive therapy compared with standard treatment resulted in significantly higher all-cause mortality among T2DM patients (summary OR 1.21, 95% CI 1.05 to 1.40, *P*=0.007, I^2=0%) (Figure 2). There were 519

Table 5. Distribution of the Main Outcomes in Rest of the World

	Europe	Western Europe*	Asia†
	5 Studies, 10 078 Patients	3 Studies, 4759 Patients	4 Studies, 4550 Patients
	Odds Ratio (95% CI)		
All-cause mortality	0.94 (0.82 to 1.07)	0.93 (0.78 to 1.10)	0.86 (0.68 to 1.08)
Cardiovascular mortality	0.91 (0.77 to 1.07)	0.89 (0.72 to 1.10)	0.86 (0.64 to 1.17)

P interaction between Europe and Asia: 0.5136 for all-cause mortality and 0.7472 for cardiovascular mortality. ADVANCE indicates Action in Diabetes and Vascular disease—PreterAx and DiamicroN MR Controlled Evaluation.
*Western European countries included the United Kingdom, The Netherlands, and Denmark.
†Data also included separate Asia specific data from ADVANCE trial.

deaths (7.70%) in the intensive therapy group compared with 418 (6.38%) in the standard therapy group; this translated into an absolute risk increase of 1.3% (95% CI 0.4 to 2.2) or a number needed to harm of 76 patients (95% CI 45 to 224) treated with intensive therapy to cause 1 additional death. A trend of higher mortality with intensive therapy was observed in almost all NA trials (except UGDP 1982). CV mortality data were reported in all 7 included trials conducted in NA. CV mortality was significantly higher with intensive therapy: 262 patients (3.88%) died in the intensive therapy group versus 172 (2.62%) in the standard therapy group (OR 1.41; 95% CI 1.05 to 1.90; *P*=0.02, I^2=36%); absolute risk increase was 1.2% (95% CI 0.7 to 1.9); number needed to harm was 79 (95% CI 54 to 152) (Figure 3). Again, a trend of higher CV mortality with intensive therapy was observed in almost all NA trials (except UGDP 1982 and Veteran Affairs 1995).

Rest of the World

Pooled analysis of the data from the ROW (10 RCTs, total of 21 680 patients) demonstrated no significant increase in all-cause mortality with intensive therapy compared with standard therapy (OR 0.93, 95% CI 0.85 to 1.03, *P*=0.15, I^2=0%) (Figure 2). Individual trial estimation was possible for 7 of 10 trials (3 trials reported no mortality events). A trend of lower or equal mortality with intensive therapy was observed in 5 of 7 ROW trials. Our analysis for different regions of the ROW for
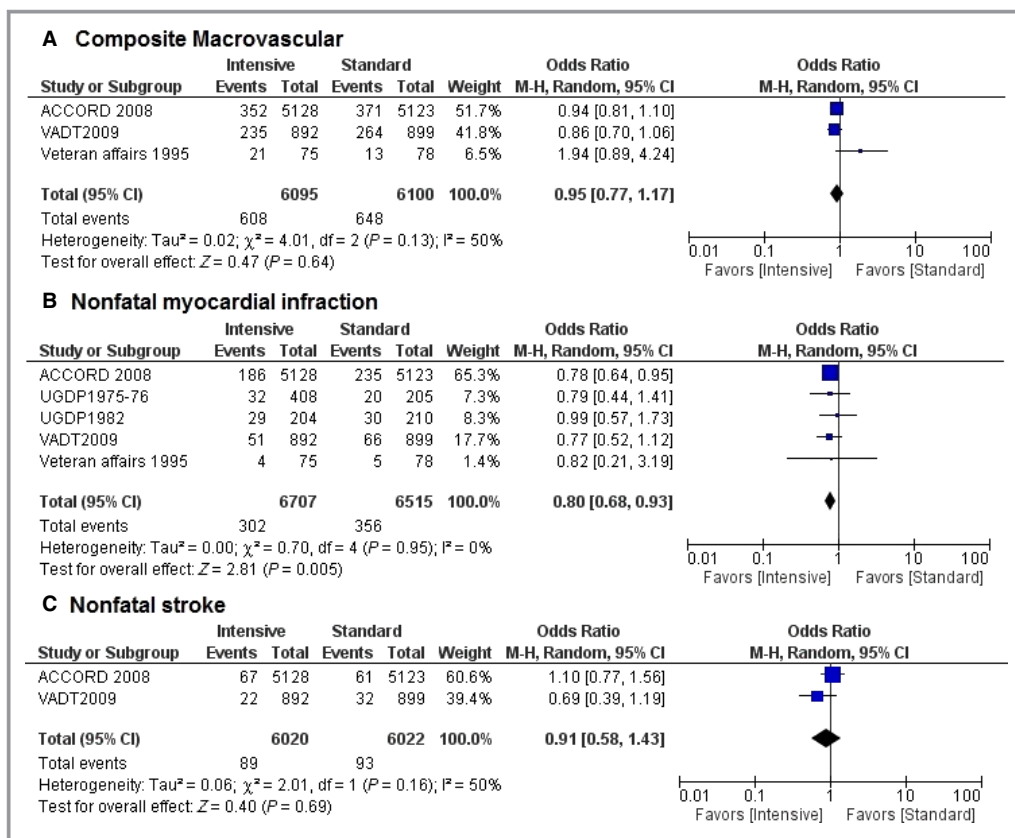

Figure 4. Macrovascular outcomes in North America: composite macrovascular (A), nonfatal myocardial infarction (B), and nonfatal stroke (C). ACCORD indicates Action to Control Cardiovascular Risk in Diabetes Study; M-H, Mantel-Haenszel; UGDP, University Group Diabetes Program; VADT, Veterans Affairs Diabetes Trial.

Europe, Western Europe, and Asia also did not show an increase in all-cause mortality with intensive therapy (interaction $P=0.51$) in comparison with the baseline for the ROW. Data pooled from the 10 RCTs conducted outside NA consistently showed no increased risk for CV mortality with intensive compared with standard therapy (OR 0.89, 95% CI 0.79 to 1.00, $P=0.05$, $I^2=0\%$) (Figure 3). Our analysis for different regions of the ROW for Europe, Western Europe, and

Asia also did not show an increase in CV mortality with intensive therapy (interaction $P=0.75$).

Regional Differences in Macro- and Microvascular Outcomes

No significant differences were observed for macrovascular outcomes between NA and the ROW including composite
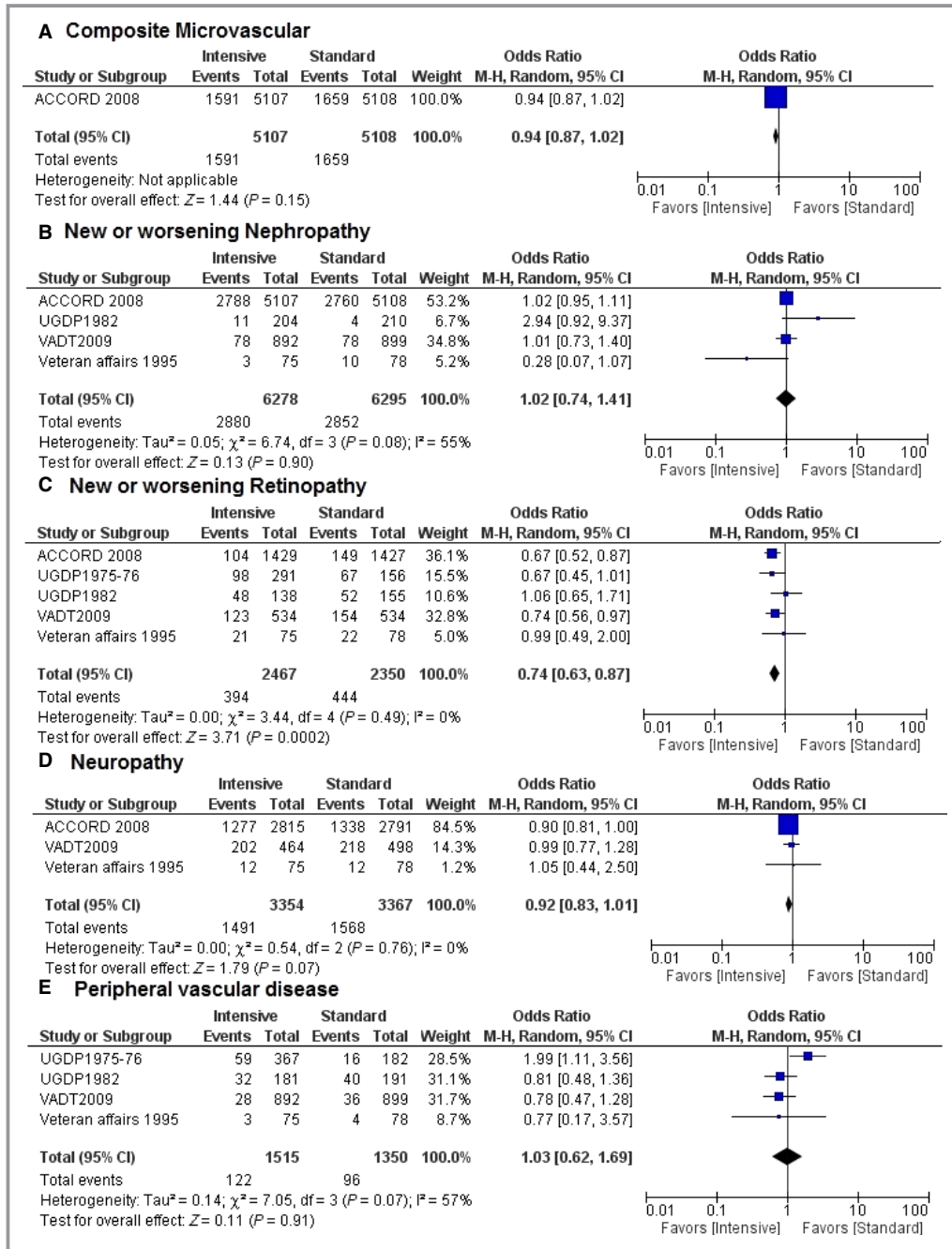
Figure 5. Microvascular outcomes in North America: composite microvascular (A), new or worsening nephropathy (B), new or worsening retinopathy (C), neuropathy (D), peripheral vascular disease (E). ACCORD indicates Action to Control Cardiovascular Risk in Diabetes Study; M-H, Mantel-Haenszel; UGDP, University Group Diabetes Program; VADT, Veterans Affairs Diabetes Trial.

major macrovascular outcomes (interaction *P*=0.72), nonfatal myocardial infarction (interaction *P*=0.79), and nonfatal stroke (interaction *P*=0.75). The risk of microvascular complications also was not significantly different between NA and the ROW for composite microvascular outcomes (interaction *P*=0.06), new or worsening nephropathy (interaction *P*=0.06), new or worsening retinopathy (interaction *P*=0.74), neuropathy (interaction *P*=0.09), and peripheral vascular disease (interaction *P*=0.82). In contrast, there was a significant difference in severe hypoglycemic events, with higher rates among patients assigned to intensive therapy in NA (OR 3.52, 95% CI 3.07 to 4.03) but not in the ROW (OR 1.45, 95% CI 0.85 to 2.47; interaction *P*=0.001) (Tables 4 and 5 and Figures 4 through 8).

Regional Differences With Longer Follow-up

We performed sensitivity analyses including data from the longest reported follow-up in all trials. Inclusion of these additional data extended follow-up by 5.2 years. Data from trials conducted in NA consistently showed significantly higher all-cause mortality (OR 1.18, 95% CI 1.05 to 1.34, *P*=0.008, I^2=0%) and CV mortality (OR 1.35, 95% CI 1.02 to 1.79, *P*=0.04, I^2=45%) for intensive compared with standard therapy. Regional differences between NA and the ROW were statistically significant, with the longest follow-up data for all-cause mortality (interaction *P*=0.0007). In contrast, analysis of long-term data from the ROW trials revealed significantly lower all-cause mortality with intensive therapy (OR 0.88, 95% CI 0.78 to 0.99, *P*=0.04, I^2=27%). The largest trial from the
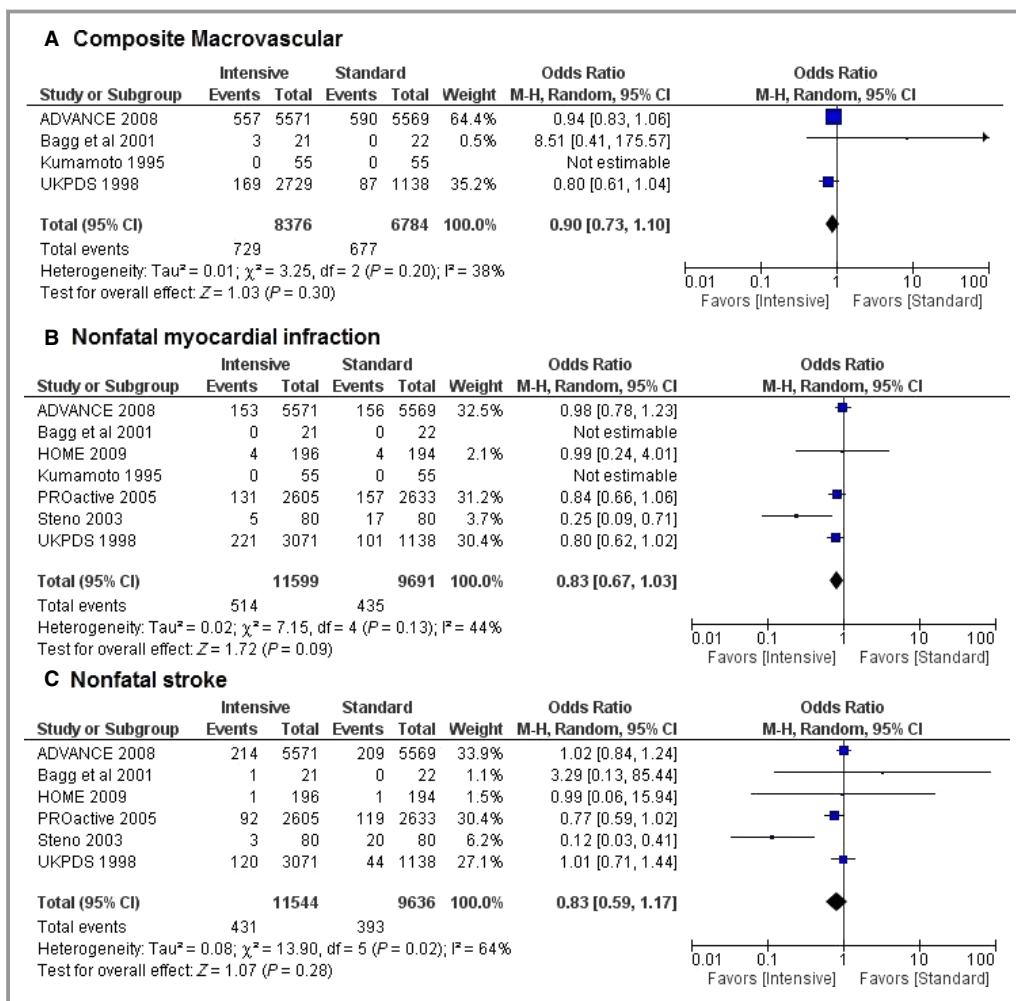

Figure 6. Macrovascular outcomes in the rest of the world: composite macrovascular (A), nonfatal myocardial infarction (B), and nonfatal stroke (C). ADVANCE indicates Action in Diabetes and Vascular disease⸺PreterAx and DiamicroN MR Controlled Evaluation; M-H, Mantel-Haenszel; PROactive, PROspective pioglitAzone Clinical Trial In macroVascular Events; UKPDS, United Kingdom Prospective Diabetes Study.
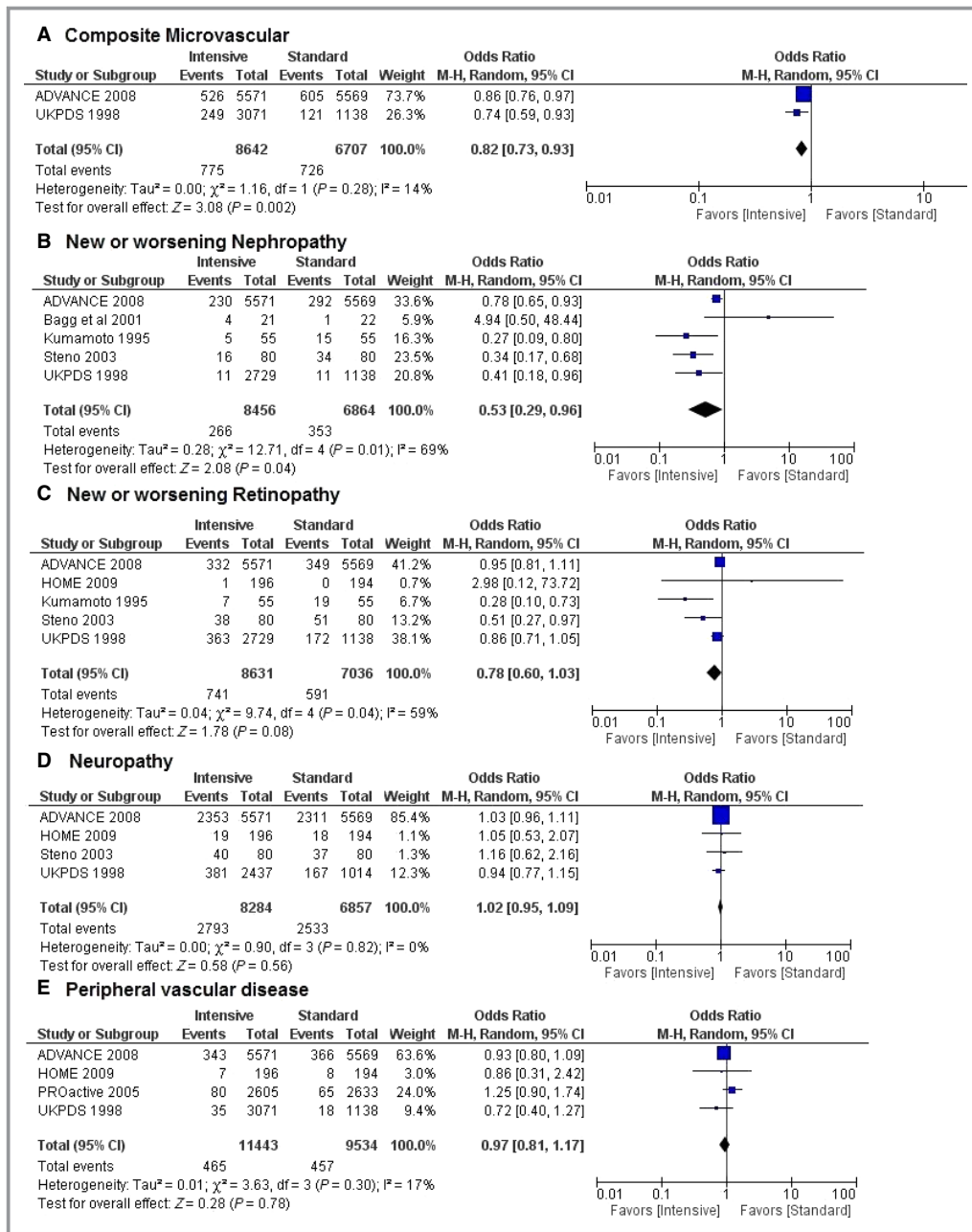
Figure 7. Microvascular outcomes in rest of the world: composite microvascular (A), new or worsening nephropathy (B), new or worsening retinopathy (C), neuropathy (D), peripheral vascular disease (E). ADVANCE indicates Action in Diabetes and Vascular disease—PreterAx and DiamicroN MR Controlled Evaluation; M-H, Mantel-Haenszel; PROactive, PROspective pioglitAzone Clinical Trial In macroVascular Events; UKPDS, United Kingdom Prospective Diabetes Study.

ROW reporting long-term data, UKPDS, did not report separate data for CV mortality (Figure S1).

Sensitivity Analyses

There was no meaningful difference in the results under various other sensitivity analyses exploring the robustness of

the data by region for all-cause mortality (Figures S2 and S3) and CV mortality (Figures S4 and S5). Results limited to trials with low risk of bias were also consistent with our primary analysis (Figure S6). Meta-regression analysis did not detect any confounding factors or effect modifiers in regional variation of results for mortality. No evidence of publication bias was observed (Figure S7).

Discussion

Previous meta-analyses of RCTs of intensive versus standard blood glucose therapy among T2DM patients demonstrated high between-study heterogeneity for mortality outcomes that was insufficiently explained based on differences in patient population alone.[11,13] In this present analysis, we demonstrated that the heterogeneity in results among 17 global RCTs that studied almost 35 000 T2DM participants may derive from patient or treatment-pattern differences, specifically between NA and other regions of the world. There were no major differences between trials conducted in NA and the ROW for mean age, mean duration of diabetes at the entry level, and mean duration of follow-up. Baseline mean HbA1c levels in trials conducted in NA were higher (10.6%) compared with the ROW (8.07%), and mean reductions in HbA1c level in the intensive group were higher in NA (2.20% in NA and 0.83% in ROW). There was no major difference in the treatment regimens used in the trials conducted in NA and the ROW. Most of the trials used oral agents as primary therapy, and insulin was added in cases in which target A1c was not achieved by maximal doses of oral agents. The pooled analysis from trials conducted in NA showed significantly higher all-cause mortality, CV mortality, and severe hypoglycemia with versus without intensive glycemic treatment. In contrast, when data were pooled from trials conducted in the ROW, no significant increase in death or severe hypoglycemia was observed between intensive and standard treatment

groups. In fact, when analyzed within each region separately, we could not detect any statistical heterogeneity between study results for mortality ($I^2=0\%$ for both NA and ROW), which suggested that once region was considered, outcomes were consistent despite variation in trial size. No significant differences were observed for major macro- and microvascular outcomes with intensive therapy between NA and the ROW. Our findings suggest the possibility that the observed differences in mortality and severe hypoglycemia across trials may be associated with underlying design differences in targeting more intensive glycemic control between trials from NA and the ROW, regional variation in background care, or other factors.

Findings in Context With Prior Reviews and Meta-analyses

Previous meta-analyses of trials conducted globally concluded that there was no definite benefit or harm with intensive therapy for all-cause or CV mortality.[10–14] Significant between-trial differences in outcomes persisted after several adjusted analyses,[11,13] and the reason behind this observed heterogeneity could not be fully explained.[11] Our analyses suggest that the effect of intensive therapy was not uniform worldwide and that potential harm (mortality) with intensive therapy may be specific to North American trials, an observation not seen in trials conducted in other regions of the world.
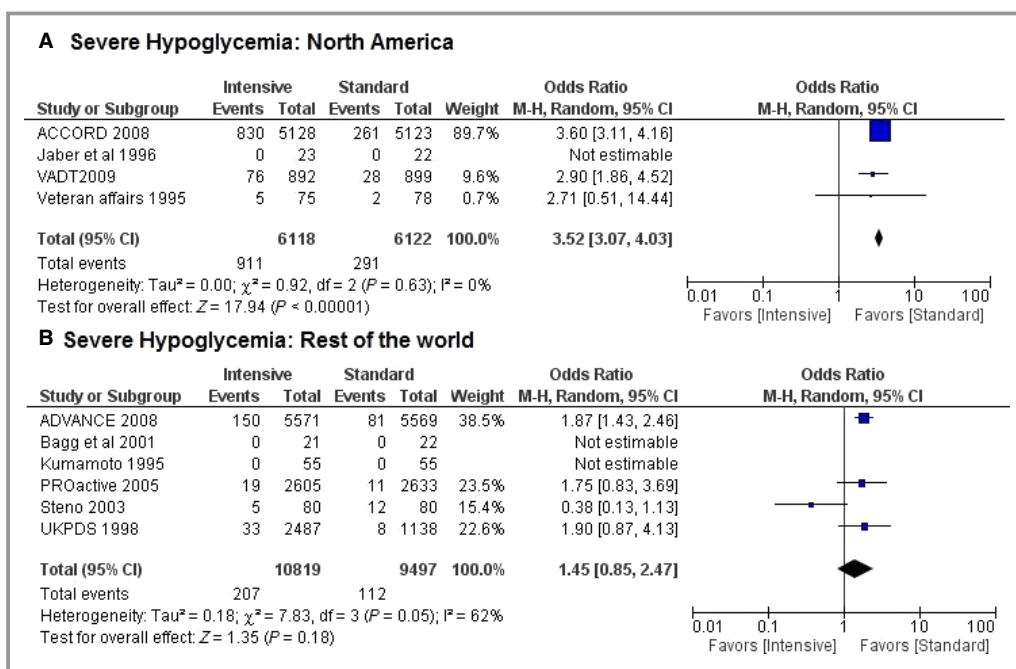

Figure 8. Risk of hypoglycemia with intensive therapy in North America (A) and the rest of the world (B). ADVANCE indicates Action in Diabetes and Vascular disease—PreterAx and DiamicroN MR Controlled Evaluation; M-H, Mantel-Haenszel; PROactive, PROspective pioglitAzone Clinical Trial In macroVascular Events; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

Regional Variation in Intensive Versus Standard Glycemic Control in Diabetes and Outcomes

It is unclear if the differential mortality effect seen across regions may be related to type, dose, or style of introduction of antidiabetic therapies preferentially used in trials from different parts of the world.[4,5,7,8,15,16] Although there was no standardized definition of *intensive therapy*, most trials used oral hypoglycemic agents followed by insulin therapy to titrate intensive control and usual therapy in the control arm; however, there was some variation in therapy, as shown in Table 1. Differences in outcomes may also be related to differences in trial design, such as studying patients with established versus new-onset T2DM or studying elderly and younger patients, 2 groups in which efficacy and safety may be more challenging to discern due to competing risks for all-cause mortality.[46] Both ACCORD[8] and VADT[9] included comparatively older patients and participants with long history of diabetes. In addition, the ACCORD and VADT trials specified an HbA1c target of <6.0%, which was much lower than targets in the studies organized in the ROW. In contrast, long-term follow-up data from UKPDS, which included younger participants with new-onset T2DM, reported a mortality benefit with intensive therapy[33]; however, meta–regression analysis adjusting for age, duration of diabetes, and baseline HbA1c did not reveal any significant attenuation of the effect of intensive therapy on mortality in NA. Nevertheless, because intensive glycemic control did not demonstrate superiority over standard therapy for composite macrovascular events, with mixed results for microvascular events, in either North American RCTs or those conducted in the ROW, current evidence does not support routine intensive glycemic control in patients with T2DM.

Study Limitations

This study has potential limitations inherent to meta-analyses. Retrospective pooling of data from trials conducted in different time periods, with different designs, treatment strategies, targets of glycemic control, patient populations, definitions of outcomes, length of the interventions, and duration of follow-up, are inherently exploratory. Because this study used published data only, we could not explore results using individual patient data. Consequently, our results should be considered hypothesis generating and should be confirmed. We included trials without predefined differences in glycemic targets and trials using multimodal treatment strategies; however, our results remain unchanged when excluding these trials. Diagnostic criteria used for T2DM also varied over time and among trials. Many of the included trials were not double–blinded, and some of them were not designed or powered to assess our predefined primary outcome. We included the ADVANCE trial in the ROW group, although 4% participants were recruited from Canada. There were no participants from the United States, and separate outcomes data for the population from Canada have not been reported. The definition of *intensive therapy* is not standardized, and different trials used different definitions of *intensive therapy* and the target of HbA1C. Future studies to assess an effect of treatment intensity should standardize methods to define intensive therapy and the eligible population that maximizes safety while allowing the opportunity to assess for effectiveness.

Conclusion

Intensive therapy compared with standard glycemic control in patients with T2DM was associated with increased all-cause and CV mortality and severe hypoglycemia in North American RCTs but not in those conducted in the ROW. Regional differences in clinical outcomes may be an artifact that resulted from subtle design differences among trials primarily conducted in NA in contrast with the ROW, particularly with regard to the choice of glycemic target and mean age of the populations studied. Nevertheless, a potential differential regional effect on mortality and hypoglycemia merits further investigation into whether our findings may be a reflection of targeting more intense glycemic control, differences in clinical risk profiles, genetic susceptibility, or differences in disease management protocols.

Author Contributions

Chatterjee and Sardar conceived the analysis. Sardar, Udell and Chatterjee acquired, analyzed, interpreted the data and designed the study with guidance and active participation from Bansilal, Mukherjee and Farkouh. Sardar and Chatterjee drafted the initial manuscript and Udell, Bansilal, Farkouh and Mukherjee critically revised the manuscript for important intellectual content. Mukherjee and Farkouh provided study supervision. The authors accept full responsibility for the content of this article.

Disclosures

None.

References

1. Khaw KT, Wareham N, Luben R, Bingham S, Oakes S, Welch A, Day N. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European prospective investigation of cancer and nutrition (EPIC-Norfolk). *BMJ*. 2001;322:15–18.
2. Sturm G, Lamina C, Zitt E, Lhotta K, Haider F, Neyer U, Kronenberg F. Association of HbA1c values with mortality and cardiovascular events in

diabetic dialysis patients. THE INVOR study and review of the literature. *PLoS One*. 2011;6:e20093.

3. American Diabetes Association. Standards of medical care in diabetes—2012. *Diabetes Care*. 2012;35(suppl 1):S11–S63.

4. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:837–853.

5. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:854–865. Erratum in: Lancet 1998;352:1558.

6. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefèbvre PJ, Murray GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Korányi L, Laakso M, Mokán M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schernthaner G, Schmitz O, Skrha J, Smith U, Taton J; PROactive investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomized controlled trial. *Lancet*. 2005;366:1279–1289.

7. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358:2560–2572.

8. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr, Probstfield JL, Simons-Morton DG, Friedewald WT. *N Engl J Med*. 2008;358:2545–2559.

9. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med*. 2009;360:129–139. Erratum in: N Engl J Med. 2009;361:1028. N Engl J Med. 2009;361:1024-5.

10. Ray KK, Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Preiss D, Erqou S, Sattar N. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet*. 2009;373:1765–1772.

11. Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, Lafont S, Bergeonneau C, Kassaï B, Erpeldinger S, Wright JM, Gueyffier F, Cornu C. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. *BMJ*. 2011;343:d4169.

12. Hemmingsen B, Lund SS, Gluud C, Vaag A, Almdal T, Hemmingsen C, Wetterslev J. Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. *BMJ*. 2011;343:d6898.

13. Wu H, Xu MJ, Zou DJ, Han QJ, Hu X. Intensive glycemic control and macrovascular events in type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. *Chin Med J (Engl)*. 2010;123:2908–2913.

14. Hemmingsen B, Lund SS, Gluud C, Vaag A, Almdal T, Hemmingsen C, Wetterslev J. Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2011;6:CD008143.

15. Rith-Najarian SJ, Gohdes DM, Shields R, Skipper B, Moore KR, Tolbert B, Raymer T, Acton KJ. Regional variation in cardiovascular disease risk factors among American Indians and Alaska Natives with diabetes. *Diabetes Care*. 2002;25:279–283.

16. Hu FB. Globalization of diabetes: the role of diet, lifestyle, and genes. *Diabetes Care*. 2011;34:1249–1257.

17. Chin MH, Auerbach SB, Cook S, Harrison JF, Koppert J, Jin L, Thiel F, Karrison TG, Harrand AG, Schaefer CT, Takashima HT, Egbert N, Chiu SC, McNabb WL. Quality of diabetes care in community health centers. *Am J Public Health*. 2000;90:431–434.

18. Sinclair AJ, Paolisso G, Castro M, Bourdel-Marchasson I, Gadsby R, Rodriguez Mañas L; European Diabetes Working Party for Older People. European Diabetes Working Party for Older People 2011 clinical guidelines for type 2 diabetes mellitus. Executive summary. *Diabetes Metab*. 2011;37(suppl 3):S27–S38.

19. Centre of Clinical Practice at NICE. *Type 2 Diabetes: Newer Agents. NICE Short Clinical Guideline 87*. London: National Institute for Health and Clinical Excellence; 2009.

20. Panagiotou OA, Contopoulos-Ioannidis DG, Ioannidis JP, Ioannidis JP, Rehnborg CF. Comparative effect sizes in randomised trials from less developed and more developed countries: meta-epidemiological assessment. *BMJ*. 2013;346: f707.

21. Mahaffey KW, Wojdyla DM, Carroll K, Becker RC, Storey RF, Angiolillo DJ, Held C, Cannon CP, James S, Pieper KS, Horrow J, Harrington RA, Wallentin L; PLATO Investigators. Ticagrelor compared with clopidogrel by geographic region in the Platelet Inhibition and Patient Outcomes (PLATO) trial. *Circulation*. 2011;124:544–554.

22. Van de Werf F, Topol EJ, Lee KL, Woodlief LH, Granger CB, Armstrong PW, Barbash GI, Hampton JR, Guerci A, Simes RJ, Ross AM, Califf RM. Variations in patient management and outcomes for acute myocardial infarction in the United States and other countries. Results from the GUSTO trial. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. *JAMA*. 1995;273:1586–1591.

23. Woodward M, Patel A, Zoungas S, Liu L, Pan C, Poulter N, Januszewicz A, Tandon N, Joshi P, Heller S, Neal B, Chalmers J. Does glycemic control offer similar benefits among patients with diabetes in different regions of the world? Results from the ADVANCE trial. *Diabetes Care*. 2011;34:2491–2495.

24. Higgins JPT, Altman DG, Sterne JAC, eds. Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 (updated March 2011). Available at: http://www.cochrane-handbook.org. Accessed February 23, 2014.

25. ACCORD Study Group, Gerstein HC, Miller ME, Genuth S, Ismail-Beigi F, Buse JB, Goff DC Jr, Probstfield JL, Cushman WC, Ginsberg HN, Bigger JT, Grimm RH Jr, Byington RP, Rosenberg YD, Friedewald WT. Long-term effects of intensive glucose lowering on cardiovascular outcomes. *N Engl J Med*. 2011;364:818–828.

26. Abraira C, Colwell JA, Nuttall FQ, Sawin CT, Nagel NJ, Comstock JP, Emanuele NV, Levin SR, Henderson W, Lee HS. Veterans Affairs Cooperative Study on glycemic control and complications in type II diabetes (VA CSDM). Results of the feasibility trial. Veterans Affairs Cooperative Study in Type II Diabetes. *Diabetes Care*. 1995;18:1113–1123.

27. Abraira C, Colwell J, Nuttall F, Sawin CT, Henderson W, Comstock JP, Emanuele NV, Levin SR, Pacold I, Lee HS. Cardiovascular events and correlates in the Veterans Affairs Diabetes Feasibility Trial. Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes. *Arch Intern Med*. 1997;157:181–188.

28. The University Group Diabetes Program. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. V. Evaluation of pheniformin therapy. *Diabetes*. 1975;24(suppl 1):65–184.

29. A study of the effects of hypoglycemia agents on vascular complications in patients with adult-onset diabetes. VI. Supplementary report on nonfatal events in patients treated with tolbutamide. *Diabetes*. 1976;25:1129–1153.

30. Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. VIII. Evaluation of insulin therapy: final report. *Diabetes*. 1982;31(suppl 5):1–81.

31. Service FJ, Daube JR, O'Brien PC, Zimmerman BR, Swanson CJ, Brennan MD, Dyck PJ. Effect of blood glucose control on peripheral nerve function in diabetic patients. *Mayo Clin Proc*. 1983;58:283–289.

32. Jaber LA, Halapy H, Fernet M, Tummalapalli S, Diwakaran H. Evaluation of a pharmaceutical care model on diabetes management. *Ann Pharmacother*. 1996;30:238–243.

33. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359:1577–1589.

34. Lapina IuV, Filatov DN, Mareev VIu, Narusov OIu, Bolotina MG, Shestakova MV, Masenko VP, Litonova GN, Baklanova NA, Belenkov IuN. [Effect of strict glycemic control on clinical state and course of the disease in patients with chronic heart failure and type II diabetes mellitus. Results of the REMBO "rational effective multicomponent therapy in the struggle against diabetes mellitus in patients with congestive heart failure" study]. *Kardiologiia*. 2008;48:17–27.

35. Kooy A, de Jager J, Lehert P, Bets D, Wulffelé MG, Donker AJ, Stehouwer CD. Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. *Arch Intern Med*. 2009;169:616–625.

36. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med*. 2003;348:383–393.

37. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med*. 2008;358:580–591.

38. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract*. 1995;28:103–117.

39. Shichiri M, Kishikawa H, Ohkubo Y, Wake N. Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. *Diabetes Care*. 2000;23(suppl 2):B21–B29.

40. Guo LX, Pan Q, Wang XX, Li H, Zhang LN, Chi JM, Wang Y. Effect of short term intensive multitherapy on carotid intima-media thickness in patients with newly diagnosed type 2 diabetes mellitus. *Chin Med J (Engl)*. 2008;121:687–690.

41. Yang JM, Guo XH, Yu X. Long-term intensive glycemic and lipid control ameliorates the carotid intima medial thickness in type 2 diabetes mellitus. *Beijing Da Xue Xue Bao*. 2007;39:649–652.

42. Bagg W, Ferri C, Desideri G, Gamble G, Ockelford P, Braatvedt GD. The influences of obesity and glycemic control on endothelial activation in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2001;86:5491–5497.

43. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med*. 2009;151:W65–W94.

44. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.

45. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.

46. Genuth S, Ismail-Beigi F. Clinical implications of the ACCORD trial. *J Clin Endocrinol Metab*. 2012;97:41–48.