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
Europe and the Asia-Pacific region did not reduce (or increase) CV events. In contrast, North American trials of intensive control resulted in increased mortality with this strategy. 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, 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. Significant regional variations in the efficacy of intensive antiplatelet treatment were recently observed in randomized controlled trials (RCTs) of acute coronary syndrome. Regional variation for major macro- or microvascular disease in patients with T2DM was also seen in 1 RCT. 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...
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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{28,29} | USA | 408 | 205 | 10 years | — | — | Tolbutamide or phenformin | Placebo |
| UGDP\textsuperscript{30} | USA | 204 | 210 | 12.5 years | — | — | Intensive insulin | Fixed dose of Insulin |
| Service et al\textsuperscript{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\textsuperscript{32} | USA | 23 | 22 | 4 months | Fasting blood glucose ≤6.6 mmol/L | NR | Intensive pharmaceutical care | Routine care with primary care physician |

Continued
| Trial          | Location | Intensive Group (n) | Standard Group (n) | Follow-up Duration | Intensive Treatment Target                                      | Standard Treatment Target                                      | Intensive Treatment | Standard Treatment |
|---------------|----------|---------------------|-------------------|-------------------|----------------------------------------------------------------|----------------------------------------------------------------|--------------------|-------------------|
| **Europe**    |          |                     |                   |                   |                                                                |                                                                |                    |                   |
| UKPDS         | UK       | 3071                | 1138              | 10.0 years        | Fasting blood glucose <6 mmol/L in insulin treated patients    | Fasting blood glucose <15 mmol/L without symptoms of hyperglycaemia |                    |                   |
| UKPDS 34     | UK       | 3071                | 1138              | 10.7 years        | Long term follow up-20 years                                   |                                                                |                    |                   |
| REMBO         | Russia   | 41                  | 40                | 12 months         | HbA1c ~7% for patients receiving sulfonylurea; HbA1c <6.5% for patients receiving insulin | Not specified                                                  |                    |                   |
| PROactive     | 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          | Netherlands | 196               | 194               | 4.3 years         | No predefined target                                           | No predefined target                                           | Insulin and metformin | Insulin and placebo |
| Steno         | Denmark  | 80                  | 80                | 7.8 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 |                   |

Continued
| Trial          | Location         | Intensive Group (n) | Standard Group (n) | Follow-up Duration | Intensive Treatment Target | Standard Treatment Target | Intensive Treatment | Standard Treatment |
|---------------|------------------|---------------------|--------------------|-------------------|---------------------------|---------------------------|---------------------|--------------------|
| **International/multi-continent** |                  |                     |                    |                   |                           |                           |                     |                    |
| ADVANCE⁷      | Japan            | 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 | 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 al⁴⁰  | China            | 166                 | 54                 | 6 months          | Fasting plasma glucose 4.0 to 7.0 mmol/L, hemoglobin A1c <7%, | No treatment goal | Glipizide, Metformin and α-Glucosidase inhibitors, Bedtime intermediate-acting insulin was added if hemoglobin A1c concentrations ≥7% after the maximum oral hypoglycemic treatment | Traditional or routine outpatient service |
| Yang et al⁴¹  | China            | 57                  | 32                 | 2                 | HbA1c <7.0%              | NR                        | Multiple subcutaneous insulin injections | Routine outpatient treatment. |
| **Other**     |                  |                     |                    |                   |                           |                           |                     |                    |
| Bagg et al⁴²  | 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 Congestive Heart Failure; UGDP, University Group Diabetes Program; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.
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 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**              |        |         |                             |                     |                      |                                  |                                 |                                 |                                  |                                 |                                     |
| ACCORD8,25                     | 62.2   | 62      | 10                          | 35%                 | 9.8                  | 8.1                              | 8.1                             | 8.1                             | 6.4                             | 7.5                             | 1.7                                 |
| VADT9                         | 60.4   | 97      | 11.5                        | 40%                 | 10.9                 | 9.4                              | 9.4                             | 9.4                             | 6.9                             | 8.4                             | 2.5                                 |
| Veteran Affairs26,27           | 60.1   | 100     | 7.8                         | 38%                 | 11.9                 | 9.3                              | 9.5                             | 9.5                             | 7.0                             | 9.5                             | 2.3                                 |
| UGDP28,29                      | 52     | 29      | <1                          | 9.5%                | 7.9                  | NR                               | NR                              | NR                              | NR                              | NR                               | NR                                  |
| UGDP30                        | 52     | 29      | <1                          | 9.5%                | 7.9                  | NR                               | NR                              | NR                              | NR                               | NR                               | NR                                  |
| Service et al31                | 50.7   | 60      | 0.5                         | 11.4                | 11.4                 | 11.4                             | NR                              | NR                              | NR                              | NR                               | NR                                  |
| Jaber et al32                  | 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                                 |
| REMBO34                       | 64     | 70      | 5.5                         | 100%                | 6.6                  | 7.1                              | 7.2                             | 7.2                             | —                               | —                               | —                                   |
| PROactive9                     | 62     | 67      | 8                            | 100%                | —                    | 7.8                              | 7.9                             | 7.9                             | 7.0                             | 7.6                             | 0.8                                 |
| HOME 200935                   | 61     | 50      | 12                          | 1%                  | 1.58                 | 7.9                              | 7.9                             | 7.9                             | 7.7                             | 7.9                             | 0.2                                 |
| Steno 200336,37               | 55     | 74      | 5.7                         | 24%                 | 10.3                 | 8.4                              | 8.8                             | 8.6                             | 7.7                             | 8.0                             | 0.7                                 |
| **International/multicontinent**|       |         |                             |                     |                      |                                  |                                 |                                 |                                  |                                 |                                     |
| ADVANCE7                      | 66.0   | 58      | 8.0                         | 32%                 | 8.5                  | 7.5                              | 7.5                             | 7.5                             | 6.5                             | 7.3                             | 1.0                                 |
| **Asia**                      |        |         |                             |                     |                      |                                  |                                 |                                 |                                  |                                 |                                     |
| Kumamoto 199538,39            | 49     | 50      | 6.5                         | 0                   | —                    | 9.3                              | 9                               | 9.2                             | 7.1                             | 9.4                             | 2.2                                 |
| Guo et al40                   | 49     | 58      | Newly diagnosed             | NR                  | 8.5                  | 7.1                              | 7.7                             | 7.4                             | 6.3                             | 7.1                             | 0.8                                 |
| Yang et al41                | 51     | NR      | 1 year                      | NR                  | 7.2                  | 7.4                              | 6.9                             | 7.2                             | NR                              | NR                               | NR                                  |
| **Other**                     |        |         |                             |                     |                      |                                  |                                 |                                 |                                  |                                 |                                     |
| Bagg et al42                 | 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 Congestive Heart Failure; UGDP, University Group Diabetes Program; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

*Baseline characteristics data from UKPDS 33.
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

### 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 |
|-----------------------------|--------------------------------------------|----------------------------------------|------------------------------------------------------------|-----------------------------------------------|----------------------------------------|-------------------------------------|------------|
| ACCORD8,25                  | Low                                       | Low                                    | Low                                                       | Unclear                                      | Low                                    | Unclear                             | Low        |
| VADT9                       | Low                                       | Low                                    | Low                                                       | Unclear                                      | Low                                    | Low                                 | Unclear    |
| Veteran Affairs26,27         | Unclear                                   | Unclear                                | Low                                                       | Low                                           | Low                                    | Low                                 | Unclear    |
| UGDP 28,29                  | Low                                       | Low                                    | Low                                                       | Low                                           | Low                                    | Low                                 | Low        |
| UGDP30                      | Low                                       | Low                                    | Low                                                       | Low                                           | Low                                    | Low                                 | Low        |
| Service et al31             | Low                                       | Unclear                                | Low                                                       | Low                                           | Low                                    | Low                                 | Low        |
| Jaber et al32               | Unclear                                   | Unclear                                | Unclear                                                   | Low                                           | Low                                    | High                                | Low        |
| UKPDS 5,33                  | Low                                       | Low                                    | Low                                                       | Low                                           | Low                                    | Low                                 | Low        |
| REMBO 34                    | Unclear                                   | Unclear                                | Unclear                                                   | Low                                           | Low                                    | Low                                 | Unclear    |
| PROactive 6                 | Low                                       | Low                                    | Low                                                       | Low                                           | Low                                    | Low                                 | High       |
| HOME 2009 35                | Low                                       | Low                                    | Low                                                       | Low                                           | Low                                    | High                                | Low        |
| Steno 2003 36,37            | Low                                       | Low                                    | High                                                      | High                                          | Low                                    | High                                | High       |
| ADVANCE7                    | Low                                       | Low                                    | Low                                                       | Low                                           | Low                                    | Low                                 | Low        |
| Kumamoto 1995 38,39         | Unclear                                   | Unclear                                | Unclear                                                   | Low                                           | Unclear                                | Low                                 | High       |
| Guo et al40                 | Low                                       | Unclear                                | Unclear                                                   | Low                                           | Unclear                                | Low                                 | Low        |
| Yang et al41                | Unclear                                   | Unclear                                | Unclear                                                   | Unclear                                       | Low                                    | Low                                 | Low        |
| Bagg et al42                | Unclear                                   | Unclear                                | Unclear                                                   | Unclear                                       | 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 Congestive Heart Failure; UGDP, University Group Diabetes Program; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

### Categorization of Included Randomized Trials

Among the included trials, 7 were conducted in North America (NA)6,9,25–32 and 104 in the rest of the world (ROW), including 5 in Europe4–6,33–37 and 3 in Asia.38–41 All except 1 European trial34 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 ADVANCE7 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 trial30 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

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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, 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 ($P\leq0.1$) 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, 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 CONgestive Heart Failure; UGDP, University Group Diabetes Program; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial).

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 CONgestive Heart Failure; UGDP, University Group Diabetes Program; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

DOI: 10.1161/JAHA.114.001577

| Study or Subgroup | Intensive Events Total | Standard Events Total | Weight | Odds Ratio | Odds Ratio |
|-------------------|------------------------|-----------------------|--------|------------|------------|
|                   | M-H, Random, 95% CI    | M-H, Random, 95% CI   |
| **1.1 North America** |                        |                       |
| ACCORD 2002       | 267 6128 203 6123 17.6% | 1.26 [1.09, 1.55]     |
| Jardine et al 1995 | 0 23 9 22              | Not estimable         |
| Service et al 1983 | 0 10 9 18              | Not estimable         |
| UGDP(1975-76)     | 84 408 21 205 33.2%    | 1.83 [0.98, 2.76]     |
| UGDP(1982)        | 61 204 21 210 56.6%    | 0.99 [0.67, 1.44]     |
| VADT2000          | 162 892 65 869 41.1%   | 1.96 [0.61, 1.47]     |
| Veteran affairs 1985 | 5 75 5 78 0.6%       | 1.94 [0.23, 1.76]     |
| **Subtotal (95% CI)** | 6740                   | 6547 36.4%            |
| Total events      | 519                    | 419                   |
| Heterogeneity: $I^2 = 3.07$, $df = 1$ ($P = 0.55$), $P = 0.9%$ Test for overall effect: $Z = 2.69$ $\chi^2 = 0.007$ |

| **1.2 Rest of the world** |                        |                       |
| ADVANCE 2006       | 459 557 533 556 26.6%  | 0.93 [0.62, 1.46]     |
| Bagg et al 2007    | 0 21 9 22              | Not estimable         |
| Chief et al 2003   | 0 16 9 64              | Not estimable         |
| HOMEC 2009         | 0 16 8 104 0.9%       | 1.51 [0.83, 3.22]     |
| Karmakar 1995      | 2 25 1 55 0.2%        | 2.64 [0.16, 9.15]     |
| PRoactive 2005     | 177 2655 166 2633 14.8%| 0.96 [0.77, 1.19]     |
| REMBO 2004         | 4 41 4 40 0.5%        | 0.97 [0.22, 4.16]     |
| Silano 2003        | 12 89 15 70 14.4%     | 0.70 [0.33, 1.46]     |
| UKPDS 1986         | 539 1971 213 1388 13.2%| 0.92 [0.79, 1.06]     |
| Yang et al 2007    | 0 57 9 22              | Not estimable         |
| **Subtotal (95% CI)** | 11883                   | 9817 63.6%            |
| Total events       | 1234                   | 959                   |
| Heterogeneity: $I^2 = 1.50$, $df = 1$ ($P = 0.58$), $P = 0.9%$ Test for overall effect: $Z = 1.43$ $\chi^2 = 0.15$ |

| **100%** | **100%** |
|-----------|-----------|
| Intensive | Standard  |

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 CONgestive 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). 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); major trial allowed for an individualized approach at the discretion of the investigators (ACCORD).

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, 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...
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.

### 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 infarction   |                         |                            |                 |
| 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)        |                            | 353/8684 (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.

### 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
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 1.7); 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

| Study or Subgroup | Intensive Events | Total | Weight | Odds Ratio | Odds Ratio | Odds Ratio |
|-------------------|------------------|-------|--------|------------|------------|------------|
|                   |                  |       |        |            | M-H, Random, 95% CI | M-H, Random, 95% CI |
| ACCORD 2000       | 352              | 5120  | 371    | 51.23      | 0.94 [0.91, 1.15] |                     |
| VADT 2008         | 236              | 892   | 284    | 696        | 0.89 [0.76, 1.08] |                     |
| Veteran affairs 1995 | 21           | 75    | 13     | 76         | 1.14 [0.99, 1.24] |                     |
| **Total (95% CI)**| **6095**         | **6100** | **100.0%** | **0.95 [0.77, 1.17]** |                     |                     |

**A Composite Macrovascular**

**B Nonfatal myocardial infarction**

**C Nonfatal stroke**

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.

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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

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**A Composite Microvascular**

| Study or Subgroup | Intensive | Standard | Total | Weight | Odds Ratio M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|-----------|----------|-------|--------|--------------------------------|--------------------------------|
| ACCORD 2000       | 1,659     | 1,659    | 5,108 | 100.0% | 0.84 [0.87, 1.02]              |                                |
| Total (95% CI)    | 5,108     | 5,108    |       | 100.0% | 0.94 [0.87, 1.02]              |                                |
| Total events      | 1,659     | 1,659    |       |         |                                |                                |

**B New or worsening Nephropathy**

| Study or Subgroup | Intensive | Standard | Total | Weight | Odds Ratio M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|-----------|----------|-------|--------|--------------------------------|--------------------------------|
| ACCORD 2000       | 2,760     | 2,760    | 5,520 | 52.2%  | 1.02 [0.95, 1.11]              |                                |
| Total (95% CI)    | 5,520     | 5,520    |       | 100.0% | 1.02 [0.95, 1.11]              |                                |
| Total events      | 2,760     | 2,760    |       |         |                                |                                |

**C New or worsening Retinopathy**

| Study or Subgroup | Intensive | Standard | Total | Weight | Odds Ratio M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|-----------|----------|-------|--------|--------------------------------|--------------------------------|
| ACCORD 2000       | 2,467     | 2,467    | 5,364 | 50.0%  | 0.74 [0.63, 0.87]              |                                |
| Total (95% CI)    | 5,364     | 5,364    |       | 100.0% | 0.74 [0.63, 0.87]              |                                |
| Total events      | 2,467     | 2,467    |       |         |                                |                                |

**D Neuropathy**

| Study or Subgroup | Intensive | Standard | Total | Weight | Odds Ratio M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|-----------|----------|-------|--------|--------------------------------|--------------------------------|
| ACCORD 2000       | 1,297     | 1,297    | 3,534 | 35.3%  | 0.90 [0.81, 1.00]              |                                |
| Total (95% CI)    | 3,534     | 3,534    |       | 100.0% | 0.90 [0.81, 1.00]              |                                |
| Total events      | 1,297     | 1,297    |       |         |                                |                                |

**E Peripheral vascular disease**

| Study or Subgroup | Intensive | Standard | Total | Weight | Odds Ratio M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|-----------|----------|-------|--------|--------------------------------|--------------------------------|
| UGDP 1988-93      | 232       | 232      | 4,648 | 47.7%  | 1.03 [0.92, 1.16]              |                                |
| Total (95% CI)    | 4,648     | 4,648    |       | 100.0% | 1.03 [0.92, 1.16]              |                                |
| Total events      | 232       | 232      |       |         |                                |                                |

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**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

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**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.
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.\(^3\)\(^1\),\(^3\)\(^1\) 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.\(^10\)\(^\text{–}\)\(^14\) 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.
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 anti-diabetic therapies preferentially used in trials from different parts of the world.\(^4,5,7,8,15,16\) Although there was no standardized definition of \textit{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 \textit{intensive therapy} is not standardized, and different trials used different definitions of \textit{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.

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