| **Author Year Study Name** | **Study Design** | **No. of Centers, Country** | **Study Duration Mean Followup** | **Interventions** | **Baseline Demographics** | **Inclusion/Exclusion Criteria** | **Number Screened, Eligible, Enrolled, Analyzed, Withdrawals, Loss to Followup** |
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| **ACCORD** | | | | | | | |
| ACCORD Study Group, 2011128  ACCORD Study Group, 2008127  Calles-Escandon, 2010174 | RCT | 77 centers US, Canada | Mean duration: 3.5 years | A. Intensive glucose control treatment (n=5128) Glucose target: HbA1c < 6.0% B. Standard treatment (n=5123) Glucose target: HbA1c 7.0-7.9% | **A vs. B** Mean age 62 vs. 62 years 39% vs. 38% female 64% vs. 65% White 20% vs. 19% Black 7% vs. 7% Hispanic Duration of diabetes: 10 vs. 10 years Previous CV event: 36% vs. 35% HbA1c: 8.3% vs. 8.3% SBP: 136.2 vs. 136.5 mmHg DBP: 74.8 vs. 75.0 mmHg TC: 183.3 vs. 183.3 mg/dL BMI: 32.3 vs. 32.2 kg/m2 | Age 40-79 years, type 2 diabetes (HbA1c ≥7.5%), previous evidence of CVD or presence of CVD risk factors  Excluded: Frequent/recent serious hypoglycemic events, unwillingness to do home glucose monitoring, BMI >45 kg/m2, serum creatinine >1.5 mg/dL, other serious illness | Screened: NR Eligible: NR Enrolled: 10,251 Analyzed: 10,251 Withdrawals: 162 Loss to followup: 50 |
| Schwartz, 2012139  ACCORD - BONE | RCT | 54 centers, US, Canada | Mean followup: 3.8 years | A. Intensive glucose control treatment (n=3655)  Glucose target: HbA1c <6.0%  B. Standard treatment (n=3632)  Glucose target: HbA1c 7.0-7.9% | **A vs. B**  Mean age 63 vs. 63 years  35% vs. 34% female  70% vs. 71% White  21% vs. 21% Black  9% vs. 9% other  Duration of diabetes 10 vs. 10 years  HbA1c: 8.3% vs. 8.3% | ACCORD patients with self-reported nonspinal fractures | Screened: NA  Eligible: NR  Enrolled: 7287  Analyzed: 6979  Withdrawals: NA  Loss to followup: NA |
| ACCORD Study Group, 201079 ACCORD - BP | RCT | 77 centers US, Canada | Mean followup: 4.7 years | A. Intensive BP lowering treatment (n=2362) Blood pressure target: SBP < 120 mm Hg B. Standard treatment (n=2371) Blood pressure target: SBP <140 mm Hg *Study participants also randomized to intensive (HbA1c <6.0%) or standard (HbA1c 7.0-7.9%) glucose targets; see ACCORD Study Group 2011and 2008* | A. vs. B.  Mean age 62 vs. 62 years 48% vs. 48% female 62% vs. 60% non-Hispanic white 24% vs. 25% Black 7% vs. 7% Hispanic Duration of diabetes 9 vs. 10 years HbA1c 8.4% vs. 8.3% SBP 138.9 vs. 139.4 mmHg DBP 77.5 vs. 77.4 mmHg TC 194.1 vs. 191.4 mg/dL BMI 32.3 vs. 32.1 kg/m2 | Adults with type 2 diabetes (HbA1c ≥7.5%), age >40 years with CVD or age ≥55 years with anatomical evidence of substantial atherosclerosis, albuminuria, LVH or at least two other CVD risk factors.  Excluded: BMI >45, serum creatinine >1/5 mg/dL, other serious illness | Screened: NR Eligible: NR Enrolled: 4733 Analyzed: Withdrawals: unclear Loss to followup: 232/4733 (5%) |
| Ismail-Beigi, 2012140  ACCORD - BP | RCT | 77 centers  US, Canada | Mean followup: 4.7 years | A. Intensive BP lowering treatment (n=2362)  Blood pressure target: SBP <120 mm Hg  B. Standard treatment (n=2371)  Blood pressure target: SBP <140 mm Hg  *Study participants also randomized to intensive (HbA1c <6.0%) or standard (HbA1c 7.0-7.9%) glucose targets; see ACCORD Study Group 2011and 2008* | A. vs. B.  Mean age 62 vs. 62 years  48% vs. 48% female  62% vs. 60% non-Hispanic white  24% vs. 25% Black  7% vs. 7% Hispanic  Duration of diabetes 9 vs. 10 years  HbA1c 8.4% vs. 8.3%  SBP 138.9 vs. 139.4 mmHg  DBP 77.5 vs. 77.4 mmHg  TC 194.1 vs. 191.4 mg/dL  BMI 32.3 vs. 32.1 kg/m2 | Adults with type 2 diabetes (HbA1c ≥7.5%), age >40 years with CVD or age ≥55 years with anatomical evidence of substantial atherosclerosis, albuminuria, LVH or at least two other CVD risk factors. Excluded: BMI >45, serum creatinine >1/5 mg/dL, other serious illness | Screened: NR  Eligible: NR  Enrolled: 4733  Analyzed:  Withdrawals: unclear  Loss to followup: 232/4733 (5%) |
| O'Connor, 2012141 Sullivan, 2007142 ACCORD - BP HRQOL | RCT | Not reported US, Canada | Mean followup 4 years | A. Intensive blood pressure control B. Standard blood pressure control | Not reported | Randomly selected patients included in ACCORD Cost Effectiveness Analysis | Screened: NR Eligible: NR Enrolled: 1028 Analyzed: Unclear |
| ACCORD Study Group, 2010143  ACCORD Eye | RCT | 77 centers  US, Canada |  | A. Intensive glucose control treatment (n=1429)  B. Standard treatment (n=1427)  C. Fenofibrate (n=806)  D. Placebo (n=787)  E. Intensive blood pressure control (n=647)  F. Standard blood pressure control (n=616) | Mean age 62 years  61% male  70% white  30% nonwhite  Duration of diabetes 10 years  HbA1C: 8.2%  LDL: 100.7 mg/dL  HDL: 41.9 mg/dL  SBP: 134.5 mm Hg  DBP: 74.9 mm Hg  BMI 32.4 | ACCORD patients without history of proliferative diabetic retinopathy, lasar photocoagulation or vitrectomy | Screened: NR  Eligible: NR  Enrolled: 3537  Analyzed: 2865  Withdrawals: 65 post randomization exclusions  Loss to followup: 616/3472 (18%) |
| Anderson, 2011144 ACCORD - HRQL | RCT | 77 centers US, Canada; ACCORD HRQL Study included subset of all ACCORD participants |  | A. Intensive glucose control treatment (n=1,024) B. Standard treatment (n=1,029) | *Not stratified by treatment group* Mean age 62 years 40% female 65% non-Hispanic white 20% Black 7% Hispanic Duration of diabetes 10 years HbA1c: 8.3% SBP: 136.2 mmHg DBP: 74.5 mmHg BMI 32.4 kg/m | Randomly selected patients enrolled in ACCORD | *Subgroup analysis of full ACCORD population* Screened: NR Eligible: NR Enrolled: 2053 Analyzed: 1956 Withdrawals: unclear Loss to followup: unclear; 97/2053 (5%) enrolled patients excluded from analysis |
| ACCORD Study Group, 2010129  ACCORD - Lipid | RCT | 77 centers  US, Canada | Mean followup: 4.7 years | A. Intensive lipid control (n=2765)  Lipid target: not reported; intervention simvastatin + fenofibrate  B. Standard treatment (n=2753)  Lipid target: not reported; intervention simvastatin + placebo | A. vs. B.  Mean age 62 vs. 62 years  31% vs. 31% female  69% vs. 68% white  14% vs. 16% Black  8% vs. 7% Hispanic  Duration of diabetes 10 vs. 9 years  HbA1c 8.3% vs. 8.3%  SBP 133.8 vs. 134.0 mm Hg  DBP 73.9 vs. 74.0 mm Hg  TC 174.7 vs. 175.7 mg/dL  BMI 32.2 vs. 32.2 kg/m2 | Adults with type 2 diabetes (HbA1c ≥7.5%), age >40 years with CVD or age ≥55 years with evidence of subclinical CVD or two or more CVD risk factors, LDL 60-180 mg/dL, HDL <55 mg/dL, HDL <55 mg/dL for women or Blacks, HDL <50 mg/dL for all other groups. triglyceride level <750 mg/dL if not receiving lipid therapy or <400 mg/dL if receiving lipid therapy | Screened: NR  Eligible: NR  Enrolled: 5518  Analyzed: 5518 |
| **ADVANCE** | | | | | | | |
| Patel 200780; de Galan, 2009145, Poulter, 2009126 ADVANCE | RCT | 215 centers Asia, Austrailasia, Europe, North America | Mean followup 4.3 years (BP control) and 5.5 years (glucose control) | A. Intensive blood pressure control; addition to existing regimen of fixed-dose combination of perindopril-indapamide; no target set (n=5569) B. Standard blood pressure control; existing regimen with addition of placebo (n=5571) C. Intensive glucose control; target ≤6.5% HbA1c (n=5571) D. Standard glucose control (n=5569) | A vs. B Mean age 66 vs. 66 years 43% vs. 43% female Race not reported Duration of diabetes 8 vs. 8 years HbA1c 7.5% vs. 7.5% History of major macrovascular disease 32% vs. 32% History of major microvascular disease 10% vs. 10% SBP 145 vs. 145 mm Hg DBP 81 vs. 81 mm Hg BMI 28 vs. 28 kg/m2 | Age ≥55 years older with type 2 diabetes with history of major CV disease and at least one other CVD risk factor Excluded: indication for or contraindication to study treatments, definite indication for long-term insulin therapy, participation in another clinical trial | Screened: 12877 Eligible: 12483 Enrolled: 11140 Analyzed: 11140 Withdrawals: 2916/11140 (26%) Loss to followup: 15/11140 (0.1%) |
| Zoungas, 2009130 ADVANCE | RCT | 215 centers Asia, Austrailasia, Europe, North America | Mean followup 4.3 years | A. Intensive glucose control (A1c ≤6.5%) + intensive blood pressure control (addition to existing regimen of fixed-dose combination of perindopril-indapamide; no target set) (n=2783) B. Standard glucose control + standard blood pressure control; existing regimen with addition of placebo (n=2783) | A vs. B Mean age 66 vs. 66 years 33% vs. 33% female Race not reported Duration of diabetes 8 vs. 8 years HbA1c 7.5% vs. 7.5% SBP 145.2 vs. 145.3 mm Hg DBP 80.9 vs. 80.5 mm Hg BMI 28.4 vs. 28.3 kg/m2 | Age ≥55 years older with type 2 diabetes with history of major CV disease and at least one other CVD risk factor Excluded: indication for or contraindication to study treatments, definite indication for long-term insulin therapy, participation in another clinical trial | Screened: 12877 Eligible: 12483 Enrolled: 11140 Analyzed: 11140 (A vs. B: 5566) Withdrawals: 2901/11140 (26%) Loss to followup: 15/11140 (0.1%) |
| Stefansdottir 2011146  ADVANCE | RCT | 215 centers  Asia, Austrailasia, Europe,  North America | Mean followup 5 years | A. Intensive glucose control; HbA1c target <6.5% (n=5571)  B. Standard glucose control (n=5569) | A vs. B  Mean age 67 vs. 67 years  43% vs. 42% female  Race not reported  Duration of diabetes 8 vs. 8 years  HbA1c 7.5% vs. 7.5%  SBP 145.0 mm Hg vs. 145.0 mm Hg  DBP 80.8 mm Hg vs. 80.5 mm Hg  BMI 28 kg/m2 vs. 28 kg/m2 | Age ≥55 years older with type 2 diabetes with history of major CV disease and at least one other CVD risk factor  Excluded: indication for or contraindication to study treatments, definite indication for long-term insulin therapy, participation in another clinical trial | Screened: 12877  Eligible: 12483  Enrolled: 11140  Analyzed: 11140  Withdrawals: 2901/11140 (26%)  Loss to followup: 15/11140 (0.1%) |
| Beulens 2009147 ADVANCE Retinal Measurements Study | RCT | 39 centers Asia, Australia, Europe, North America | Mean followup 4.1 years | A. Intensive blood pressure control; addition to existing regimen of fixed-dose combination of perindopril-indapamide; no target set B. Standard blood pressure control; existing regimen with addition of placebo | A vs. B Mean age 66 vs. 66 years 37% vs. 40% female 49% vs. 47% White 38% vs. 38% Chinese 9% vs. 10% South Asian Mean duration of diabetes 6 vs. 6 years HbA1c 7/3% vs. 7.5% SBP 1431. vs. 142.3 mm Hg DBP 79.5 vs. 79.2 mm Hg BMI 27.7 vs. 27.7 kg/m2 | Age ≥55 years older with type 2 diabetes with history of major CV disease and at least one other CVD risk factor Excluded: indication for or contraindication to study treatments, definite indication for long-term insulin therapy, participation in another clinical trial, previous ophthalmological intervention or unlikely that good quality photos could be obtained due to cataract or pupils that did not adequately dilate | Screened: NR Eligible: 2863 Enrolled: 2130 Analyzed: 1241 Withdrawals: unclear Loss to followup: unclear (528/2130 had no usable baseline photograph; 361/2130 had no valid followup photograph) |
| **JEDIT** | | | | | | | |
| Araki, 2012148 JEDIT | RCT | 39 centers Japan | Study duration: 6 years (mean or median NR) | A. Intensive treatment: targeted HbA1c <6.9%, BMI <25, SBP <130 mmHg, DBP <85 mmHg, HDL-C >40 mg/dL, serum triglycerides <150 mg/dL, serum total cholesterol <180 mg/dL (n=585) B. Usual care: continued baseline treatment for diabetes, hypertension, or dyslipidemia without a specific goal (n=588) | A vs. B Mean age 72 vs. 72 years 54% vs. 54% female Race not reported Duration of diabetes 17 vs. 18 years Mean BMI 24.0 vs. 24.3 kg/m2 HbA1c 8.4% vs. 8.5% | Diabetic outpatients, aged 65-85 years, HbA1c >7.9%, or HbA1c >7.4% with at least one of the following: BMI >25, blood pressure >130/85 mmHg, serum total cholesterol >200 mg/dL Exclude: MI or stroke within previous 6 months, acute or serious illness, aphasia, or severe dementia | Screened: NR Eligible: NR Enrolled: 1,173 Analyzed: 1,173 Withdrawal over 6 years: 8.9% (104/1,173) |
| **JPAD** | | | | | | | |
| Ogawa 2008;149 Okada 2011150 JPAD | RCT | 163 centers Japan | Median follow up 4.4 years | A: Aspirin, 81 mg or 100 mg/day B: No aspirin | A. vs. B.  Mean age 65 vs. 64 years  44% vs. 47% female Race not reported | Type 2 diabetes, age 30-85 years, ability to provide informed consent Excluded: EKG changes consistent with ischemic changes, confirmed history of CAD, history of CVD including TIA, history of atherosclerotic disease, atrial fibrillation, pregnancy, use of antiplatelet or antithrombotic treatments, history of severe gastric of duodenal ulcer, severe CKD or allergy to aspirin | Screened: 2567 Eligible: 2454 Enrolled: 2539 Analyzed: 2539 Withdrawals: NR Loss to followup: 193 |
| **MEGA** | | | | | | | |
| Tajima 2008;84 Nakamura 2006151 MEGA | RCT | 924 centers Japan | Mean followup 5 years | A. Intensive lipid control with diet + pravastatin 10 mg/day; target total cholesterol ≤220 mg/dL (n=1093; 853 diabetes, 240 IFG) B. Standard lipid control with diet only (n=1117; 893 diabetes, 224 IFG) | Not stratified by treatment group - Persons with diabetes: Mean age 59 years 100% Japanese HbA1c 6.9% BMI 24.2 Persons with IFG: Mean age 58 years 100% Japanese HbA1c 5.5% BMI 24.4 | Age 40-70 years with hypercholesterolemia (TC 220-270 mg/dL) with no history of CHD or stroke | Screened: NA Eligible: NA  Enrolled: 2210 (subgroup of persons with diabetes or IFG) Analyzed: 2210 Withdrawals: unclear Loss to followup: unclear |
| **SANDS** | | | | | | | |
| Howard, 2008152 SANDS | RCT | 4 centers United States | 36 months (mean or median NR) | A. Intensive treatment: SBP target <115 mmHg, DBP <75 mmHg, LDL-C <70 mg/dL, non-HDL-C <100 mg/dL (n=276) B. Usual care: SBP target <130 mmHg, DBP <85 mmHg, LDL-C <100 mg/dL, non-HDL-C <130 mg/dL (n=272) | A vs. B Mean age 55 vs. 57 years 66% vs. 65% female 100% Native American Duration of diabetes 9.2 vs. 8.7 years HbA1c 8.2% vs. 7.9% BMI 34 vs. 33 kg/m2 | Native Americans aged >40 years with type 2 diabetes, LDL-C >100 mg/dL, and SBP >130 mmHg within the previous 12 months Exclude: New York Heart Association class III or IV heart failure, SBP >180 mmHg, liver transaminase levels more than twice the upper limit of normal, or diagnosis of primary hyperlipidemia or hypercholesterolemia due to hyperthyroidism or nephrotic syndrome | Screened: 1,067 Eligible: NR Enrolled: 548 Analyzed: 499 |
| **STENO-2** | | | | | | | |
| Gaede, 2008153 Steno-2 | RCT | Single center Denmark | Mean treatment duration: 7.8 years Mean post-treatment followup: 5.5 years Mean total followup: 13.3 years | A. Intensive multifactorial treatment: targets of <6.5% HbA1c, <175 mg/dL fasting serum total cholesterol, <150 mg/dL fasting serum triglyceride, <130 mmHg SBP, and <80 mmHg DBP. Patients received renin-angiotensin blockers and aspirin. (n=80) B. Usual care (n=80) | A vs. B Mean age 55 vs. 55 years Sex not reported 100% vs. 100% White Mean BMI, men: 29.3 vs. 30.3 Mean BMI, women: 31.1 vs. 28.9 HbA1c 8.4% vs. 8.8% | White Danish patients with type 2 diabetes and persistent microalbuminuria | Screened: 315 Eligible: 160 Enrolled: 160 Analyzed: 160 A vs. B Withdrawal: 1.3% (1/80) vs. 2.5% (2/80) Loss to followup: 21.3% (17/80) vs. 16.3% (13/80) |
| **UKPDS** | | | | | | | |
| Holman 2008155 UKPDS | RTC | 23 centers United Kingdom | Initial trial mean duration 8 years Mean post-trial monitoring 8 years | A. Intensive BP control; BP target <150/85 mm Hg (n=758) B. Standard BP control ; <180/105 mm Hg(n=390) | *Not stratified by treatment group* Median age 53 years 41% female 82% white 9% Black 8% Asian 1% other History of retinopathy 21% Prior MI 18% | Newly diagnosed diabetes age 25-65 years referred by general practitioner | Screened: 1544 Eligible: 1292 Enrolled: 1148 Analyzed: 1148 Withdrawals: NA Loss to followup: NA (post-trial monitoring) |
| Holman 2008155  UKPDS (cont.) | RTC | 23 centers  United Kingdom | Initial trial mean duration 10 years  Mean post-trial monitoring 9 years | A. Intensive glucose control with sulfonyurea-insulin <6 mmol/L (n=2729)  B. Intensive glucose control with metformin <6 mmol/L (n=342)  C. Standard glucose control (n=1549) | *Not stratified by treatment group*  Median age 53 years  59% male  82% white  9% Black  8% Asian  1% other  History of retinopathy 21%  Prior MI 18% | Newly diagnosed diabetes age 25-65 years referred by general practitioner | Screened: 5102  Eligible: NR  Enrolled: 4209  Analyzed: 3277  Withdrawals: NA  Loss to followup: NA  (post-trial monitoring) |
| **VADT** | | | | | | | |
| Duckworth, 2009156 VADT | RCT | 20 centers United States | Study duration: accrual over 2.5 years and followup for 5-7.5 years Median followup: 5.6 years | A. Intensive glycemic treatment; if obese, metformin 2000 mg (if lean, glimepiride 8 mg) and rosaglitazone 8 mg; then insulin (n=892) B. Standard care; if obese, metformin 1000 mg (if lean, glimepiride 2 mg) and rosaglitazone 4 mg; then insulin 1 U/4 kg; then metformin 2000 mg or glimepiride 8 mg and rosaglitazone 8 mg; then insulin increase (n=899) | A vs. B Mean age 61 vs. 60 years 3% vs. 3% female 64% vs. 60% non-Hispanic White,  15% vs. 17% Hispanic White  16% vs. 17% non-Hispanic Black,  5% vs. 5% other  Duration of diabetes 12 vs. 12 years Median HbA1c 9.4% vs. 9.4% Mean BMI 31.3 vs. 31.2 kg/m2 Previous CV event 41% vs. 40% | Patients with type 2 diabetes Exclude: HbA1c <7.5, CV events in the prior 6 months, advanced congestive heart failure, severe angina, life expectancy <7 years, BMI >40, serum creatinine >1.6 mg/dL, or transaminase more than 3 times normal | Screened: 17,700 Eligible: 2,231 Enrolled: 1,791 Analyzed: 1,791 A vs. B Withdrawal: 4.8% (43/892) vs. 7.5% (67/899) Loss to followup: 6.5% (58/892) vs. 6.3% (57/899) |

| **Author Year Study Name** | **Outcomes Assessed** | **Clinical Health Outcomes** | **Subgroups** | **Adverse Events** | **Quality Rating** | **Funding Source** | **Comments** |
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| **ACCORD** | | | | | | | |
| ACCORD Study Group, 2011128  ACCORD Study Group, 2008127  Calles-Escandon, 2010174 | Primary outcome - Cardiovascular event (composite outcome including CV mortality, nonfatal MI, nonfatal stroke ) Secondary outcomes - Nonfatal MI Stroke (any; nonfatal) Mortality (all-cause; CV) Primary outcomes + revascularization or nonfatal heart failure Major CHD event | **A vs. B** Pretransition (mean 3.7 years followup) - CV event: 380/5128 (2%) vs. 414/5123 (2%); RR 0.92 (95% CI 0.80 to 1.05); HR 0.9 (95% CI 0.78 to 1.03) Nonfatal MI: 207/5128 (1%) vs. 257/5123 (1%); RR 0.80 (95% CI 0.67 to 0.96); HR 0.79 (95% CI 0.66 to 0.95) Nonfatal stroke: 72/5128 (0.4%) vs. 72/5123 (0.4%); RR 1.0 (95% CI 0.72 to 1.38); HR 0.99 (95% CI 0.72 to 1.38) CV mortality: 140/5128 (0.7%) vs. 109/5123 (0.6%); RR 1.28 (95% CI 1.00 to 1.64); HR 1.27 (95% CI 0.99 to 1.63) All-cause mortality: 283/5128 (1%) vs. 232/5123 (1%); RR 1.22 (95% CI 1.03 to 1.44); HR 1.21 (95% CI 1.02 to 1.44) Revascularization or hospitalization for CHF: 931/5128 (5%) vs. 955/5123 (5%); RR 0.97 (95% CI 0.90 to 1.06); HR 0.96 (95% CI 0.88 to 1.06) Fatal or nonfatal MI or unstable angina: 439/5128 (2%) vs. 490/5123 (3%); RR 0.90 (95% CI 0.79 to 1.01); HR 0.88 (95% CI 0.77 to 1.00) | **A vs. B** All-cause mortality: total risk estimate HR 1.21 (95% CI 1.02 to 1.44) Age - <65 yrs: 125/3397 (4%) vs. 87/3382 (3%); HR 1.39 (95% CI 1.05 to 1.82) 65-69 yrs: 57/938 (6%) vs. 46/947 (5%); HR 1.23 (95% CI 0.84 to 1.82) 70-74: 40/516 (8%) vs. 38/537 (7%); HR 1.01 (95% CI 0.65 to 1.59) >75 yrs: 35/277 (13%) vs. 32/257 (12%); HR 0.90 (95% CI 0.55 to 1.47) Gender - Male: 182/3145 (6%) vs. 146/3154 (5%); HR 1.21 (95% CI 0.97 to 1.50) Female: 75/1983 (4%) vs. 57/1969 (3%); HR 1.23 (95% CI 0.87 to 1.74 | **A vs. B** Pretransition - Serious AEs - hypoglycemia requiring medical assistance: 558/5128 (11%) vs. 189/5123 (4%); RR 2.95 (95% CI 2.51 to 3.46) Other serious AEs: 121/5128 (2%) vs. 84/5123 (2%); RR 1.44 (95% CI 1.09 to 1.90) Through final endpoint - Serious AEs - hypoglycemia requiring medical assistance: 596/5128 (12%) vs. 233/5123 (5%); RR 2.56 (95% CI 2.21 to 2.96) Other serious AEs: 133/5128 (3%) vs. 105/5123 (2%); RR 1.27 (95% CI 0.98 to 1.63) | Good | NHLBI; numerous pharmaceutical companies (Abbott, Amylin, AstraZeneca, Bayer, Closer, GlaxoSmithKline, King, Merck, Novartis, Novo Nordisk, Omron, Sanofi-Aventis, Takeda) |  |
| ACCORD Study Group, 2011128  ACCORD Study Group, 2008127  Calles-Escandon, 2010174 (continued) |  | Fatal or nonfatal stroke: 78/5128 (0.4%) vs. 80/5123 (0.4%); RR 0.97 (95% CI 0.71 to 1.33); HR 0.97 (95% CI 0.71 to 1.33)  Fatal or nonfatal CHF: 189/5128 (1%) vs. 158/5123 (0.8%); RR 1.20 (95% CI 0.97 to 1.47); HR 1.19 (95% CI 0.96 to 1.47) Through final endpoint (mean 4.9 years followup) - CV event: 503/5128 (2%) vs. 543/5123 (2%); RR 0.93 (95% CI 0.82 to 1.04); HR 0.91 (95% CI 0.81 to 1.03) Nonfatal MI: 287/5128 (1%) vs. 344/5123 (1%); RR 0.83 (95% CI 0.72 to 0.97); HR 0.82 (95% CI 0.70 to 0.96) Nonfatal stroke: 82/5128 (0.3%) vs. 94/5123 (0.4%); RR 0.83 (95% CI 0.62 to 1.11); HR 0.87 (95% CI 0.65 to 1.17) CV mortality: 187/5128 (0.7%) vs. 144/5123 (0.6%); RR 1.30 (95% CI 1.05 to 1.60); HR 1.29 (95% CI 1.04 to 1.60) All-cause mortality: 391/5128 (1%) vs. 327/5123 (2%); RR 1.19 (95% CI 1.04 to 1.38); HR 1.19 (95% CI 1.03 to 1.38) Revascularization or hospitalization for CHF: 1159/5128 (5%) vs. 1229/5123 (6%); RR 0.94 (95% CI 0.88 to 1.01); HR 0.93 (95% CI 0.86 to 1.01) | Race/ethnicity - White: 178/3194 (6%) vs. 141/3199 (4%); HR 1.21 (95% CI 0.98 to 1.52) Black: 52/996 (5%) vs. 29/956 (3%); HR 1.60 (95% CI 1.01 to 2.52) Hispanic: 10/358 (3%) vs. 16/380 (4%); HR 0.60 (95% CI 0.27 to 1.33) Asian/other: 17/580 (3%) vs. 17/588 (3%); HR 1.06 (95% CI 0.54 to 2.07) |  |  |  |  |
| ACCORD Study Group, 2011128  ACCORD Study Group, 2008127  Calles-Escandon, 2010174 (continued) |  | Fatal or nonfatal MI or unstable angina: 580/5128 (2%) vs. 627/5123 (3%); RR 0.92 (95% CI 0.83 to 1.03); HR 0.90 (95% CI 0.81 to 1.01) Fatal or nonfatal stroke: 91/5128 (0.4%) vs. 106/5123 (0.4%); RR 0.86 (95% CI 0.65 to 1.13); HR 0.86 (95% CI 0.65 to 1.13) Fatal or nonfatal CHF: 232/5128 (1%) vs. 212/5123 (0.8%); RR 1.09 (95% CI 0.91 to 1.31); HR 1.09 (95% CI 0.91 to 1.32) |  |  |  |  |  |
| Schwartz, 2012139  ACCORD - BONE | Fracture  Falls | **A vs. B**  Nonspinal fracture: 198/3655 (5%) vs. 189/3632 (5%); RR 1.04 (95% CI 0.86 to 1.26); HR 1.04 (95% CI 0.86 to 1.27)  Hip fracture: 11/3655 (0.3%) vs. 8/3632 (0.2%); RR 1.37 (95% CI 0.55 to 3.39); HR 1.35 (95% CI 0.54 to 3.35)  Ankle fracture: 44/3655 (1%) vs. 40/3632 (1%); RR 1.09 (95% CI 0.71 to 1.67); HR 1.09 (95% CI 0.71 to 1.68)  Foot fracture: 19/3655 (0.5%) vs. 26/3632 (0.7%); RR 0.73 (95% CI 0.40 to 1.30); HR 0.71 (95% CI 0.39 to 1.28)  Proximal humerus fracture: 23/3655 (0.6%) vs. 25/3632 (0.6%); RR 0.91 (95% CI 0.52 to 1.60); HR 0.90 (95% CI 0.51 to 1.59)  Distal forearm fracture: 21/3655 (0.5%) vs. 14/3632 (0.4%); RR 1.49 (95% CI 0.76 to 2.93); HR 1.5 (95% CI 0.76 to 2.95)  Falls: 1122/3364 (33%) vs. 1133/3418 (33%); RR 1.01 (95% CI 0.94 to 1.08); HR not reported | NR | NR | Good |  |  |
| ACCORD Study Group, 201079 ACCORD - BP | Primary outcome - Cardiovascular event (composite outcome including CV mortality, nonfatal MI, nonfatal stroke ) Secondary outcomes - All-cause mortality CV mortality Nonfatal MI Nonfatal stroke Fatal or nonfatal congestive heart failure | **A vs. B** Any CV event: 208/2363 (9%) vs. 237/2371 (10%); HR\* 0.88 (95% CI 0.73 to 1.06) Nonfatal MI: 126/2362 (5%) vs. 146/2371 (6%); RR 0.87 (0.69 to 1.09); HR 0.87 (95% CI 0.68 to 1.10) Fatal and nonfatal stroke: 36/2363 (2%) vs. 62/2371 (3%); RR 0.58 (95% CI 0.39 to 0.88); HR 0.59 (95% CI 0.39 to 0.89) Nonfatal stroke: 34/2363 (1%) vs. 55/2371 (2%); HR 0.63 (95% CI 0.41 to 0.96) All-cause mortality: 150/2363 (6%) vs. 144/2371 (6%); RR 1.11 (0.89 to 1.38); AHR 1.07 (95% CI 0.85 to 1.35) CV mortality: 60/2363 (3%) vs. 58/2372 (2%); RR 1.04 (95% CI 0.73 to 1.48); HR 1.06 (95% CI 0.74 to 1.52) Any CV event + revascularization: 521/2363(2%) vs. 551/2371 (2%); HR 0.95 (95% CI 0.84 to 1.07) Major CHD event: 253/2363 (11%) vs. 270/2371 (11%); HR 0.94 (95% CI 0.79 to 1.12) Fatal or nonfatal heart failure: 83/2363 (4%) vs. 90/2371 (4%); HR 0.94 (95% CI 0.70 to 1.26) | NR | **A vs. B** Serious treatment-related adverse events: 77/2362 (3%) vs. 30/2371 (1%); RR 2.58 (95% CI 1.70 to 3.91) Other serious AEs (end-stage renal disease or need for dialysis): 59/2362 (2%) vs. 58/2371 (2%); RR 1.02 (95% CI 0.71 to 1.46) | Good | NHLBI; numerous pharmaceutical companies (Abbott, Amylin, AstraZeneca, Bayer, Closer, GlaxoSmithKline, King, Merck, Novartis, Novo Nordisk, Omron, Sanofi-Aventis, Takeda) |  |
| ACCORD Study Group, 201079 ACCORD – BP (continued) | Primary outcome - Cardiovascular event (composite outcome including CV mortality, nonfatal MI, nonfatal stroke ) Secondary outcomes - All-cause mortality CV mortality Nonfatal MI Nonfatal stroke Fatal or nonfatal congestive heart failure | *\*AHRs adjusted for: assignment to intensive glucose lowering arm, clinical center network, presence/absence of previous CV event* |  |  |  |  |  |
| Ismail-Beigi, 2012140  ACCORD - BP | Primary outcome-  Renal failure, retinal photocoagulation or vitrectomy (to treat retinopathy)  Secondary outcomes–Nephropathy  Diabetic eye complications  Neuropathy | **A vs. B**  Primary outcome: 269/2356 (11%) vs. 258/2370 (11%); HR 1.08 (95% CI 0.91 to 1.28)  Nephropathy outcomes -Microalbuminuria: 306/1473 (21%) vs. 375/1501 (25%); HR 0.84 (95% CI 0.72 to 0.97)  Macroalbuminuria: 116/2038 (6%) vs. 146/2059 (7%); HR 0.81 (95% CI 0.63 to 1.03)  Renal failure: 61/2356 (3%) vs. 64/2370 (3%); HR 1.00 (95% CI 0.71 to 1.43)  Eye outcomes –  Retinal photocoagulation or vitrectomy: 217/2262 (10%) vs. 208/2282 (9%); HR 1.09 (95% CI 0.90 to 1.32)  Cataract surgery: 339/2262 (15%) vs. 361/2282 (16%); HR 0.98 (95% CI 0.85 to 1.14)  Loss of visual acuity (3-line decrease): 819/2339 (35%) vs. 849/2352 (36%); RR 0.97 (0.90 to 1.05); HR 0.98 (95% CI 0.89 to 1.08)  Neuropathy outcomes –  Score >2 on Michigan Neuropathy Screening Instrument: 722/1353 (53%) vs. 781/1388 (56%); RR 0.95 (0.89 to 1.02); HR 0.95 (95% CI 0.86 to 1.05)  Loss of vibratory sensation: 668/1569 (43%) vs. 737/1582 (47%); HR 0.92 (95% CI 0.83 to 1.02)  Loss of light touch: 267/2134 (13%) vs. 294/2115; HR 0.91 (95% CI 0.77 to 1.08) | NR | NR | Good | NR |  |
| O'Connor, 2012141 Sullivan, 2007142 ACCORD - BP HRQOL | Quality of life - 36-Item Short Form Health Survey (SF 36) Diabetes Symptoms Distress Checklist (DSC) World Health Organization Diabetes Treatment Satisfaction Questionnaire (WHO-DTSQ) Patient Health Questionnaire (PHQ-9) | **A vs. B**  *Mean change from baseline (SE)* SF-36 physical component score: -0.8 (0.19) vs. -0.2 (0.19); p=0.02 SF-36 mental component score: 0.5 (0.39) vs. 0.4 (0.40); p=0.77 DSC total score: -1.4 (0.34) vs. -1.1 (0.35); p=0.48 DSC symptom distress: -0.04 (0.02) vs. -0.04 (0.02); p=0.98 DSC treatment satisfaction score: 13.3 (0.54) vs. 13.1 (0.55); p=0.84 PHQ-9 continuous score: -1.1 (0.14) vs. -0.9 (0.14); p=0.29 | NR | NR | Good | NHLBI, National Institute of Diabetes and Digestive and Kidney Diseases, CDC |  |
| ACCORD Study Group, 2010143  ACCORD Eye | Progression of diabetic retinopathy  Moderate vision loss | **A vs. B**  Progression of diabetic retinopathy: 104/1429 (7%) vs. 149/1427 (10%); OR 0.67 (95% CI 0.51 to 0.87)  \*Moderate vision loss: 409/1715 (24%) vs. 457/1737 (26%); OR 0.88 (95% CI 0.77 to 1.01)  **C vs. D**  Progression of diabetic retinopathy: 52/806 (7%) vs. 80/787 (10%); OR 0.60 (95% CI 0.42 to 0.87)  Moderate vision loss: 227/965 (24%) vs. 233/950 (25%); OR 0.95 (95% CI 0.79 to 1.14)  **E vs. F**  Progression of diabetic retinopathy: 67/647 (10%) vs. 54/616 (9%); OR 1.23 (95% CI 0.84 to 10.4)  Moderate vision loss: 221/798 (28%) vs. 185/748 (25%) OR 1.17 (95% CI 0.96 to 1.42)  \*ORs adjusted for other treatments | NR | NR | Good | NR |  |
| Anderson, 2011144 ACCORD - HRQL | Quality of life - 36-Item Short Form Health Survey (SF 36) Diabetes Symptoms Distress Checklist (DSC) World Health Organization Diabetes Treatment Satisfaction Questionnaire (WHO-DTSQ) Patient Health Questionnaire (PHQ-9) | **A vs. B** *Least squares mean, 95% CI\** SF-36 physical component score: -1.1 (-2.0 to -0.2) vs. -1.6 (-2.5 to -0.7); p=0.03 SF-36 mental component score: 0.8 (-1.0 to 2.6) vs. 1.4 (-0.5 to 3.2); p=0.29 DSC total score: -0.4 (-1.9 to 1.0) vs. 0.1 (-1.4 to 1.6); p=0.19 DSC symptom distress: -0.1 (-0.2 to 0.0) vs. 0.0 (-0.1 to 0.1); p=0.15 DTSQ treatment satisfaction scale: 11.1 (8.6 to 13.5) vs. 13.5 (11 to 15.9); p<0.001 DTSQ perceived hyperglycemia: -1.2 (-1.5 to -0.9) vs. -1.7 (-2.0 to -1.5); p<0.0001 DTSQ perceived hypoglycemia: 0.4 (0.1 to 0.6) vs. 0.8 (0.5 to 1.0); p<0.0001 PHQ-9 continuous score: -1.0 (-1.7 to -0.4) vs. -0.9 (-1.5 to -0.3); p=0.44 \*Analyses adjusted for the following variables: previous CVD, secondary trial, secondary trial assignment, age, race, sex, duration of diabetes, smoking, living alone, weight, waist circumference, BMI, baseline HbA1c, fasting blood glucose, SBP and DBP, heart rate, neuropathy, retinal surgery, macro- and microalbuminuria, insulin, sulfonylureas, thiazolidinedione, b-blockers, antihypertensive medication, and triglycerides | NR | NR | Good | NR |  |
| ACCORD Study Group, 2010129  ACCORD - Lipid | Primary outcome -Cardiovascular event (composite outcome including CV mortality, nonfatal MI, nonfatal stroke)  Secondary outcomes -Nonfatal MI  Stroke (any; nonfatal)  Mortality (all-cause; CV)  Hospitalization or death due to heart failure  Primary outcome, revascularization or nonfatal heart failure  Major CHD event (fatal coronary event, nonfatal MI, unstable angina) | **A vs. B**  CV event: 291/2765 (11%) vs. 310/2753 (11%); RR 0.93 (95% CI 0.80 to 1.09); AHR\* 0.92 (95% CI 0.79 to 1.08)  CV event, revascularization or hospitalization for CHF: 641/2765 (23%) vs. 667/2753 (24%); RR 0.96 (95% CI 0.87 to 1.05); AHR 0.94 (95% CI 0.85 to 1.05)  Major CHD event: 332/2765 (12%) vs. 353/2753 (13%); RR 0.93 (95% CI 0.81 to 1.08); AHR 0.92 (95% CI 0.79 to 1.07)  Nonfatal MI: 173/2765 (6%) vs. 186/2753 (7%); RR 0.93 (95% CI 0.76 to 1.13); AHR 0.91 (95% CI 0.74 to 1.12)  Stroke, fatal or nonfatal: 51/2765 (2%) vs. 48/2753 (2%); RR 1.06 (95% CI 0.72 to 1.56); AHR 1.05 (95% CI 0.71 to 1.56)  Stroke, nonfatal: 47/2765 (2%) vs. 40/2753 (1%); RR 1.17 (95% CI 0.77 to 1.78); AHR 1.17 (95% CI 0.76 to 1.78)  All-cause mortality: 203/2765 (7%) vs. 221/2753 (8%); RR 0.91 (95% CI 0.76 to 1.10); AHR 0.91 (95% CI 0.75 to 1.10)  CV mortality: 99/2765 (4%) vs. 114/2753 (4%); RR 0.86 (95% CI 0.66 to 1.13); AHR 0.86 (95% CI 0.66 to 1.12)  Fatal or nonfatal CHF: 120/2765 (4%) vs. 143/2753 (5%); RR 0.84 (95% CI 0.66 to 1.06); AHR 0.82 (95% CI 0.65 to 1.05)  \*Hazard ratios adjusted for number, timing and results of interim monitoring | **A vs. B**  CV event (primary outcome) -Women: 77/851 (9%) vs. 56/843 (7%); RR\* 1.36 (95% CI 0.98 to 1.9)  Men: 214/1914 (11%) vs. 254/1910 (13%); RR 0.84 (95% CI 0.71 to 0.997)  Age <65 years: 149/1838 (8%) vs. 173/1822 (10%); RR 0.85 (0.69 to 1.05)  Age >65 years: 139/927 (15%) vs. 137/931 (15%); RR 1.02 (95% CI 0.82 to 1.27)  Nonwhite race: 83/856 (10%) vs. 73/888 (8%); RR 1.18 (95% CI 0.87 to 1.59)  White race: 208/1909 (11%) vs. 237/1865 (13%); RR 0.86 (95% CI 0.72 to 1.02)  *\*Calculated relative risks; hazard ratios and confidence intervals only reported graphically in text, no data shown.* | **A vs. B**  Serious adverse events: 96/2765 (3%) vs. 74/2753 (3%); RR 1.29 (95% CI 0.96 to 1.74) | Good | NR | Subgroup data reported |
| **ADVANCE** | | | | | | | |
| Patel 200780; de Galan, 2009145, Poulter, 2009126 ADVANCE | Composite outcome: major macrovascular (CV mortality, nonfatal MI, nonfatal stroke) and microvascular (new or worsening nephropathy or retinopathy) events  Macrovascular events Microvascular events All-cause mortality CV mortality Major coronary events (fatal CHD, nonfatal MI) Coronary events (major coronary event, silent MI, coronary revascularization, hospital admission for unstable angina Cerebrovascular events (major cerebrovascular event, TIA, subarachnoid hemorrhage) Heart failure (death, worsening or hospitalization) Peripheral vascular disease New or worsening nephropathy New or worsening retinopathy Microalbuminuria Visual deterioration New or worsening neuropathy Cognitive function Dementia Hospitalization | **A vs. B** Macro- and microvascular outcomes: 861/5569 (16%) vs. 938/5571 (17%); RR 0.92 (95% CI 0.84 to 1.00); Relative Risk Reduction (RRR) 9% (95% CI 0 to 17) Macrovascular outcomes: 480/5569 (9%) vs. 520/5571 (9%); RR 0.92 (95% CI 0.82 to 1.04); RRR 8% (95% CI -4 to 19) Microvascular outcomes: 439/5569 (8%) vs. 477/5571 (9%); RR 0.92 (95% CI 0.81 to 1.04); RRR 9% (95% CI -4 to 20) All-cause mortality: 408/5569 (7%) vs. 471/5571 (9%); RR 0.87 (95% CI 0.76 to 0.98); RRR 14% (95% CI 2 to 25) CV death: 211/5569 (4%) vs. 257/5571 (5%); RR 0.82 (95% CI 0.69 to 0.98); RRR 18% (95% CI 2 to 32) Non-CV death: 197/5569 (7%) vs. 212/5571 (4%); RR 0.93 (95% CI 0.77 to 1.12); RRR 8% (95% CI -12 to 24) Any coronary event: 468/5569 (8%) vs. 535/5571 (10%); RR 0.84 (95% CI 0.75 to 0.95); RRR 14% (95% CI 2 to 24) Major coronary events: 265/5569 (5%) vs. 294/5571 (5%); RR 0.90 (95% CI 0.77 to 1.06); RRR 11% (95% CI -6 to 24) Other coronary events: 283/5569 (5%) vs. 324/5571 (6%); RR 0.87 (95% CI 0.75 to 1.02); RRR 14% (95% CI -1 to 27) Any cerebrovascular event: 286/5569 (5%) vs. 303/5571 (5%); RR 0.94 (95% CI 0.81 to 1.11); RRR 6% (95% CI -10 to 20) Major cerebrovascular events: 215/5569 (4%) vs. 218/5571 (4%); RR 0.99 (95% CI 0.82 to 1.19); RRR 2% (95% CI -18 to 19) Other cerebrovascular events: 79/5569 (1%) vs. 99/5571 (2%); RR 0.80 (95% CI 0.60 to 1.07); RRR 21% (95% CI -6 to 410 Any renal event: 1243/5569 (22%) vs. 1500/5571 (27%); RR 0.83 (95% CI 0.78 to 0.89); RRR 21% (95% CI 15 to 27); HR 0.79 (95% CI 0.73 to 0.85) New or worsening nephropathy: 181/5569 (3%) vs. 216/5571 (4%); RR 0.84 (95% CI 0.69 to 1.02); RRR 18% (95% CI -1 to 32) New microalbuminuria: 1094/5569 (20%) vs. 1317/5571 (24%); RR 0.83 (95% CI 0.77 to 0.89); RRR 21% (95% CI 14 to 27) Any eye event: 2531/5569 (45%) vs. 2611/5571 (47%); RR 0.97 (95% CI 0.93 to 1.01); RRR 5% (95% CI -1 to 10) New or worsening retinopathy: 289/5569 (5%) vs. 286/5571 (5%); RR 1.01 (95% CI 0.86 to 1.19); RRR -1% (95% CI -18 to 15) Visual deterioration: 2246/5569 (44%) vs. 2514/5571 (45%); RR 0.89 (95% CI 0.86 to 0.93); RRR 5% (95% CI -1 to 10) | **A vs. B** Any major macrovascular or microvascular event Age <65 years: 325/2256 (14%) vs. 346/2276(15%); RR 0.95 (95% CI 0.82 to 1.09); RRR 6% (95% CI -10 to 19) Age >65 years: 536/3308 (16%) vs. 592/3295 (18%); RR 0.90 (95% CI 0.81 to 1.00); RRR 11% (95% CI 0 to 21) Men: 546/3212 (17%) vs. 594/3194 (19%); RR 0.91 (95% CI 0.82 to 1.02); RRR 10% (95% CI -5 to 23) Women: 315/2368 (13%) vs. 344/2392 (15%); RR 0.93 (95% CI 0.80 to 1.07); RRR 8% (95% CI -7 to 21) | Withdrawals due to adverse events: 320/5569 (6%) vs. 160/5571 (3%); RR 2.00 (95% CI 1.66 to 2.41) Serious adverse events: 67/5569 (1%) vs. 66/5571 (1%); RR 1.02 (95% CI 0.72 to 1.42) | Good | Servier; National Health and Medical Research Council of Australia |  |
|  |  | **C vs. D**  Macrovascular events: 1009/5571 (18%) vs. 1116/5569 (20%); RR 0.90 (95% CI 0.84 to 0.98); RRR 10% (95% CI 2. to 18)  Microvascular events: 526/5571 (9%) vs. 605/5569 (11%); RR 0.87 (95% CI 0.78 to 0.97); RRR 14% (95% CI 3 to 23)  All-cause mortality: 498/5571 (9%) vs. 533/5569 (11%); RR 0.93 (95% CI 0.83 to 1.05); RRR 7% (95% CI -6 to 17)  CV mortality: 253/5571 (5%) vs. 289/5569 (5%); RR 0.88 (95% CI 0.74 to 1.03); RRR 12% (95% CI -4 to 26)  Major coronary events: 310/5571 (6%) vs. 337/5569 (6%); RR 0.92 (95% CI 0.79 to 1.07); RRR 8% (95% CI -7 to 21)  Nephropathy: 230/5571 (4%) vs. 292/5569 (5%); RR 0.79 (95% CI 0.67 to 0.93); RRR 21% (95% CI 7 to 34) |  |  |  |  |  |
| Zoungas, 2009130 ADVANCE | Composite outcome: major macrovascular (CV mortality, nonfatal MI, nonfatal stroke) and microvascular (new or worsening nephropathy or retinopathy) events  Macrovascular events Microvascular events All-cause mortality CV mortality Major coronary events (fatal CHD, nonfatal MI) Cerebrovascular events (major cerebrovascular event, TIA, subarachnoid hemorrhage) Any renal event New or worsening nephropathy New or worsening retinopathy Microalbuminuria Macroalbuminuria | **A vs. B** Major macrovascular and microvascular events: 431/2783 (15%) vs. 498/2783 (18%); HR 0.85 (95% CI 0.75 to 0.97)  Macrovascular events: 246/2783 (9%) vs. 265/2783 (9%); HR 0.92 (95% CI 0.77 to 1.10) Microvascular events: 213/2783 (8%) vs. 260/2783 (9%); HR 0.81 (95% CI 0.68 to 0.97) All-cause mortality: 198/2783 (7%) vs. 240/2783 (9%); HR 0.82 (95% CI 0.68 to 0.99) CV mortality: 104/2783 (4%) vs. 136/2783 (5%); HR 0.76 (95% CI 0.59 to 0.98) Major coronary events: 133/2783 (5%) vs. 155/2783 (6%); HR 0.92 (95% CI 0.77 to 1.10) Cerebrovascular events: 111/2783 (4%) vs. 107/2783 (4%); HR 1.03 (95% CI 0.79 to 1.35) Any renal event: 590/2783 (21%) vs. 777/2783 (28%); HR 0.72 (95 %CI 0.65 to 0.81) New or worsening nephropathy: 81/2783 (3%) vs. 120/2783 (4%); RR 0.68 (95% CI 0.51 to 0.89); HR 0.67 (95% CI 0.50 to 0.88) New or worsening retinopathy: 147/2783 (5%) vs. 153/2783 (5%); HR 0.96 (95% CI 0.76 to 1.20) Microalbuminuria: 525/2783 (19%) vs. 673/2783 (24%); HR 0.75 (95% CI 0.67 to 0.84) Macroalbuminuria: 44/2783 (2%) vs. 3% (95/2783): HR 0.46 (95% CI 0.32 to 0.65) | NR | NR | Good | Servier; National Health and Medical Research Council of Australia |  |
| Stefansdottir 2011146  ADVANCE | Cancer | **A vs. B**  Cancer mortality: 41/5571 (0.7%) vs. 35/5569 (0.6%); HR 1.17 (95% CI 0.96 to 1.27)  Any neoplasm: 409/5571 (7%) vs. 372/5569 (7%); HR 1.11 (95% CI 0.96 to 1.27)  Malignant neoplasms: 363/5571 (7%) vs. 337/5569 (6%); HR 1.08 (95% CI 0.93 to 1.26)  Malignant neoplasms, except lymphoid, tissue: 328/5571 (6%) vs. 303/5569 (5%); HR 1.09 (95% CI 0.93 to 1.27)  Lip, oral cavity and pharynx: 10/5571 (0.2%) vs. 7/5569 (0.1%); HR 1.43 (95% CI 0.54 to 3.75)  Digestive organs: 119/5571 (2%) vs. 103/5569 (2%); HR 1.16 (95% CI 0.89 to 1.51)  Pancreatic cancer: 16/5571 (0.3%) vs. 16/5569 (0.3%); HR 1.00 (95% CI 0.50 to 2.00)  Respiratory organs: 55/5571 (1%) vs. 61/5569 (1%); HR 0.90 (95% CI 0.63 to 1.30)  Breast cancer: 33/5571 (0.6%) vs. 31/5569 (0.6%); HR 1.07 (95% CI 0.65 to 1.74)  Female genital organs: 6/5571 (0.1%) vs. 10/5569 (0.2%); HR 0.60 (95% CI 0.22 to 1.65)  Male genital organs: 43/5571 (0.8%) vs. 43/5569 (0.8%); HR 1.00 (95% CI 0.66 to 1.53)  Lymphoid, tissue: 21/5571 (0.4%) vs. 19/5569 (0.3%); HR 1.10 (95% CI 0.59 to 2.05) | NR | NR | Good | NR |  |
| Beulens 2009147 ADVANCE Retinal Measurements Study | ETDRS progression ≥2 steps | **A vs. B** ETDRS progression ≥2 steps: 103/796 (13%) vs. 84/806 (10%); adjusted OR 0.78 (95% CI 0.57 to 1.06) | NR | NR | Good | Servier; National Health and Medical Research Council of Australia | Intensive glucose outcomes included in SR ET |
| **JEDIT** | | | | | | | |
| Araki, 2012148 JEDIT | Cardiovascular morbidity and mortality; all-cause mortality | Events and p-values of between-group comparisons (numbers for groups NR) Fatal MI: 12 events (p=0.08) Sudden death: 13 events (p=0.99) Fatal stroke: 6 events (p=0.66) Death due to renal failure: 3 events (p=0.08) Death due to hyper/hypoglycemia: 1 event (p=0.32) Nonfatal MI: 17 events (p=0.998) Coronary revascularization: 18 events (p=0.028) Hospitalization for CHF: 15 events (p=0.19) Nonfatal stroke: 63 events (p=0.28) Diabetic ulcer or gangrene: 12 events (p=0.56) Death due to diabetes: 35 events (p=0.85) Death not related to diabetes: 59 events (p=0.30) Coronary vascular events: 55 events (p=0.99) Any stroke: 67 events (p=0.29) | NR | NR | Fair | Japanese Ministry of Health, Labour, and Welfare; Japan Foundation for Aging and Health | Reduced revascularizations only; no proportions reported by group |
| **JPAD** | | | | | | | |
| Ogawa 2008;149 Okada 2011150 JPAD | Primary outcome -  Any atherosclerotic event (sudden death, death due to coronary, cerebrovascular and aortic causes, nonfatal MI, unstable angina, exertional angina, nonfatal ischemic or hemorrhagic stroke, transient ischemic attack, nonfatal aortic or peripheral vascular disease) Secondary outcomes - Coronary or cerebrovascular mortality Fatal MI Nonfatal MI Unstable angina Stable angina Fatal or nonfatal cerebrovascular disease Fatal stroke Nonfatal ischemic stroke Nonfatal hemorrhagic stroke Transient ischemic attack Peripheral artery disease | **A vs. B** Primary outcome-  Any atherosclerotic event: 68/1262 (5.4%) vs. 8/61277 (6.7%); HR 0.80 (95% CI 0.58 to1.10) Secondary outcomes - Coronary or cerebrovascular mortality: 1/1262 (0.08%) vs. 10/1277 (0.8%); HR 0.10 (95% CI 0.01 to 0.79) Fatal MI: 0/1262 (0%) vs. 5/1277 (0.4%); RR 0.09 (95% CI 0.005 to 1.66) *HR not reported in text, RR calculated* Nonfatal MI: 12/1262 (1%) vs. 9/1277 (0.7%); HR 1.34 (95% CI 0.57 to 3.19) Unstable angina: 4/1262 (0.3%) vs. 10/1277 (0/8%); HR 0.40 (95% CI 0.13 to 1.29) Stable angina: 12/1262 (1%) vs. 11/1277 (0.9%); HR 1.10 (95% CI 0.49 to 2.50) Fatal or nonfatal cerebrovascular disease: 28/1262 (2%) vs. 32/1277 (3%); HR 0.84 (95% CI 0.53 to 1.32) Fatal stroke: 1/1262 (0.08%) vs. 5/1277 (0.4%); HR 0.20 (95% CI 0.02 to 1.74) Nonfatal ischemic stroke: 22/1262 (2%) vs. 24/1277 (2%); HR 0.93 (95% CI 0.52 to 1.66) Nonfatal hemorrhagic stroke: 5/1262 (0.4%) vs. 3/1277 (0.2%); HR 1.68 (95% CI 0.40 to 7.04) Transient ischemic attack: 5/1262 (0.5%) vs. 8/1277 (0.6%); HR 0.63 (95% CI 0.21 to 1.93) Peripheral artery disease: 7/1262 (0.6%) vs. 11/1277 (0.9%); HR 0.64 (95% CI 0.25 to 1.65) | NR | **A vs. B** Serious AEs (GI bleed requiring transfusion): 4/1262 (0.3%) vs. 0/1277 (0%); RR 9.11 (95% CI 0.49 to 169) | Fair | Ministry of Health, Labour, and Welfare |  |
| **MEGA** | | | | | | | |
| Tajima 2008;84 Nakamura 2006151 MEGA | All-cause mortality CHD (fatal and nonfatal MI, cardiac and sudden death, coronary revascularization, angina) Stroke Cardiovascular disease  Cerebral infarction | **A vs. B (Diabetes group)\*** All-cause mortality: 16/853 (2%) vs. 28/893 (3%); RR 0.60 (95% CI 0.33 to 1.10); AHR 0.61 (95% CI 0.33 to 1.12) CHD: 29/853 (3%) vs. 43/893 (5%); RR 0.71 (95% CI 0.45 to 1.12); AHR 0.71 (95% CI 0.44 to 1.13) Stroke: 14/853 (2%) vs. 21/893 (2%); RR 0.70 (95% CI 0.36 to 1.36); AHR 0.70 (95% CI 0.36 to 1.38) CVD events: 46/853 (5%) vs. 68/893 (8%); RR 0.71 (95% CI 0.49 to 1.02); AHR 0.71 (95% CI 0.49 to 1.03) Cerebral infarction: 9/853 (1%) vs. 18/893 (2%); RR 0.52 (95%CI 0.24 to 1.16); AHR 0.52 (95% CI 0.23 to 1.16) **A vs. B (IFG group)\*** All-cause mortality: 4/240 (2%) vs. 1/224 (0.4%); RR 4.07 (95% CI 0.46 to 36); AHR 4.36 (95% CI 0.49 to 39) CHD: 6/240 (3%) vs. 7/224 (3%); RR 0.87 (95% CI 0.30 to 2.56); AHR 0.89 (95% CI 0.30 to 2.66) Stroke: 0/240 (0%) vs. 4/224 (2%); RR 0.10 (95% CI 0.006 to 1.92); AHR not estimated CVD events: 6/240 (3%) vs. 12/224 (5%); RR 0.47 (95% CI 0.18 to 1.22); AHR 0.52 (95% CI 0.20 to 1.39) Cerebral infarction: 0/240 (0%) vs. 4/224 (2%); RR 0.10 (95% CI 0.006 to 1.92); AHR not estimated **A vs. B (Normal glucose group - Contextual Question 2)\*** All-cause mortality: 23/2773 (0.8%) vs. 37/2849 (1%); RR 0.64 (95% CI 0.38 to 1.07); AHR 0.65 (95% CI 0.39 to 1.10) CHD: 22/2773 (0.8%) vs. 35/2849 (1%); RR 0.65 (95% CI 0.38 to 1.10); AHR 0.65 (95% CI 0.38 to 1.11) Stroke: 24/2773 (0.9%) vs. 36/2849 (1%); RR 0.68 (95% CI 0.41 to 1.15); AHR 0.70 (95% CI 0.47 to 1.17) CVD events: 50/2772 (2%) vs. 73/2849 (3%); RR 0.70 (95% CI 0.49 to 1.01); AHR 0.71 (95% CI 0.50 to 1.02) Cerebral infarction: 16/2773 (0.6%) vs. 23/2849 (0.8%); RR 0.71 (95% CI 0.38 to 1.35); AHR 0.73 (95% CI 0.38 to1.37) | NR | NR | Fair | NR |  |
| **SANDS** | | | | | | | |
| Howard, 2008152 SANDS | Cardiovascular events (fatal and nonfatal CVD events, nonfatal MI, nonfatal stroke, unstable angina, revascularization) | **A vs. B** Incidence of primary CV events: 11/252 (4%) vs. 8/247 (3%); RR 1.35 (95% CI 0.55 to 3.29) Incidence of other CV events: 1/252 (0.4%) vs. 3/247 (1%); RR 0.33 (95% CI 0.03 to 3.12) Non-CV death: 2/252 (0.8%) vs. 4/247 (2%); RR 0.49 (95% CI 0.09 to 2.65) | NR | A vs. B Any adverse event: 38.5% (97/252) vs. 26.7% (66/247); RR 1.44, 95% CI 1.11 to 1.87 Any serious adverse event: 26.6% (67/252) vs. 15.4% (38/247); RR 1.73, 95% CI 1.21 to 2.47 | Good | National Heart, Lung, and Blood Institute; National Institutes of Health; First Horizon Pharmacy; Merck and Co; and Prizer | No benefit on clinical health outcomes; Adverse events more common in intensive group |
| **STENO-2** | | | | | | | |
| Gaede, 2008153 Steno-2 | All-cause mortality, cardiovascular morbidity and mortality, amputation, nephropathy, retinopathy, autonomic neuropathy, peripheral neuropathy | **A vs. B** All-cause mortality: 24/80 (30%) vs. 40/80 (50%); ARR 20% (p=0.02); HR 0.54 (95% CI 0.32 to 0.89); RR 0.60 (95% CI 0.40 to 0.90) CV mortality: 9/80 (11%) vs. 19/80 (24%); HR 0.43 (95% CI 0.19 to 0.94); Adjusted HR 0.43 (95% CI 0.19 to 0.95); RR 0.47 (95% CI 0.23 to 0.98) Any CV event: 51 events in 25 patients vs. 158 events in 48 patients; ARR 29%, HR 0.41 (95% CI 0.25 to 0.67) MI: 8/80 (10%) vs. 21/80 (26%); RR 0.38 (95% CI 0.18 to 0.81) Stroke: 6/80 (8%) vs. 18/80 (23%); RR 0.33 (95% CI 0.14 to 0.80) Revascularization: 6/80 (8%) vs. 10/80 (13%); RR 0.60 (95% CI 0.23 to 1.57) Amputation: 6/80 (8%) vs. 14/80 (18%); RR 0.43 (95% CI 0.17 to 1.06)  Nephropathy: 20/80 (25%) vs. 37/80 (46%); RR 0.44 (95% CI 0.25 to 0.77) Retinopathy: 41/80 (51%) vs. 54/80 (68%); RR 0.57 (95% CI 0.37 to 0.88) Blindness in at least one eye: 2/80 (3%) vs. 7/80 (9%); RR 0.51 (95% CI 0.17 to 1.53) Autonomic neuropathy: 39/80 (49%) vs. 52/80 (65%); RR 0.53 (95% CI 0.34 to 0.81) Peripheral neuropathy: 44/80 (55%) vs. 46/80 (58%); RR 0.97 (95% CI 0.62 to 1.51) | NR | A vs. B Symptomatic hypoglycemia: 80% (64/80) vs. 70% (56/80); RR 1.14, 95% CI 0.95 to 1.37 Major hypoglycemic episodes: 13% (10/80) vs. 17% (14/80); RR 0.71, 95% CI 0.34 to 1.51 | Good | Danish Health Research Council | Many significant benefits; All patients counseled at the end of the treatment period about the benefits of intensive intervention |
| **UKPDS** | | | | | | | |
| Holman 2008155 UKPDS | All-cause mortality Diabetes-related endpoint (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal MI, angina, heart failure, fatal or nonfatal stroke, renal failure, amputation, vitreous hemorrhage, retinal photocoagulation, blindness in one eye, cataract extraction) Diabetes-related death (fatal MI, stroke, peripheral vascular disease, renal disease, hyperglycemia, hypoglycemia or sudden death) Fatal or nonfatal stroke Peripheral vascular disease (amputation of at least one digit or death from peripheral vascular disease) Microvascular disease (vitreous hemorrhage, retinal photocoagulation, renal failure)  All-cause mortality  Diabetes-related endpoint (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal MI, angina, heart failure, fatal or nonfatal stroke, renal failure, amputation, vitreous hemorrhage, retinal photocoagulation, blindness in one eye, cataract extraction)  Diabetes-related death (fatal MI, stroke, peripheral vascular disease, renal disease, hyperglycemia, hypoglycemia or sudden death)  Fatal or nonfatal stroke  Peripheral vascular disease (amputation of at least one digit or death from peripheral vascular disease)  Microvascular disease (vitreous hemorrhage, retinal photocoagulation, renal failure) | **A vs. B** All-cause mortality: 373/758 (49%) vs. 211/390 (54%); RR 0.89 (95% CI 0.75 to 1.06) Diabetes-related death: 203/758 (27%) vs. 122/390 (31%); RR 0.84 (95% CI 0.67 to 1.05) Any diabetes-related endpoint: 466/758 (61%) vs. 248/390 (64%); RR 0.93 (95% CI 0.80 to 1.09) MI: 205/758 (27%) vs. 115/390 (29%); RR 0.90 (95% CI 0.71 to 1.13) Stroke: 90/758 (12%) vs. 58/390 (15%); RR 0.77 (95% CI 0.55 to 1.07) Peripheral vascular disease: 21/758 (3%) vs. 21/390 (5%); RR 0.50 (95% CI 0.28 to 0.92) Microvascular disease: 141/758 (19%) vs. 82/390 (21%); RR 0.84 (95% CI 0.64 to 1.10)  **A vs. C**  All-cause mortality: 1162/2729 (43%) vs. 537/1138 (47%); Risk Ratio 0.87 (95% CI 9.79 to 0.96)  Diabetes-related death: 618/2729 (23%) vs. 297/1138 (26%); Risk Ratio 0.83 (95% CI 0.73 to 0.96)  Any diabetes-related endpoint: 1571/2729 (58%) vs. 686/1138 (60%); Risk Ratio 0.91 (95% CI 0.83 to 0.99)  MI: 678/2729 (25%) vs. 319/1138 (28%); Risk Ratio 0.85 (95% CI 0.74 to 0.97)  Stroke: 260/2729 (10%) vs. 116/1138 (10%); Risk Ratio 0.91 (95% CI 0.73 to 1.13)  Peripheral vascular disease: 83/2729 (3%) vs. 40/1138 (4%); Risk Ratio 0.82 (95% CI 0.56 to 1.19)  Microvascular disease: 429/2729 (16%) vs. 222/1138 (20%); Risk Ratio 0.76 (95% CI 0.64 to 0.89)  **B vs. C**  All-cause mortality: 152/342 (44%) vs. 217/411 (53%); Risk Ratio 0.73 (95% CI 0.59 to 0.89)  Diabetes-related death: 81/342 (24%) vs. 120/411 (29%); Risk Ratio 0.70 (95% CI 0.52 to 0.92)  Any diabetes-related endpoint: 209/342 (61%) vs. 262/411 (64%); Risk Ratio 0.79 (95% CI 0.66 to 0.95)  MI: 81/342 (24%) vs. 126/411 (31%); Risk Ratio 0.67 (95% CI 0.51 to 0.89)  Stroke: 34/342 (10%) vs. 42/411 (10%); Risk Ratio 0.80 (95% CI 0.50 to 1.27)  Peripheral vascular disease: 13/342 (4%) vs. 21/411 (5%); Risk Ratio 0.63 (95% CI 0.32 to 1.27)  Microvascular disease: 66/342 (19%) vs. 78/411 (19%); Risk Ratio 0.84 (95% CI 0.60 to 1.17)  **A and B vs. C**  All-cause mortality: 1314/3071 (43%) vs. 754/1549 (49%); RR 0.88 (95% CI 0.82 to 0.94)  Diabetes-related death: 699/3071 (23%) vs. 417/1549 (27%); RR 0.85 (95% CI 0.76 to 0.94)  Any diabetes-related endpoint: 1780/3071 (58%) vs. 948/1549 (61%); RR 0.95 (95% CI 0.90 to 0.995)  MI: 759/3071 (25%) vs. 445/1549 (29%); RR 0.86 (95% CI 0.78 to 0.95)  Stroke: 294/3071 (10%) vs. 158/1549 (10%); RR 0.94 (95% CI 0.78 to 1.13)  Peripheral vascular disease: 96/3071 (3%) vs. 61/1549 (4%); RR 0.79 (95% CI 0.58 to 1.09)  Microvascular disease: 495/3071 (16%) vs. 300/1549 (19%); RR 0.83 (95% CI 0.73 to 0.95) | NR | NR | Good | UK Medical Research Council, UK Department of Health, Diabetes UK, British Heart Foundation, Bristol Meyers Squibb, GlaxoSmithKline, Merck, Novartis, Novo Nordisk, Pfizer |  |
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|  |
| **VADT** | | | | | | | |
| Duckworth, 2009156 VADT | Cardiovascular morbidity and mortality, retinopathy, neuropathy | **A vs. B** All-cause mortality: 102/892 (11%) vs. 95/899 (11%); HR 1.07 (95% CI 0.81 to 1.42) CV mortality: 40/892 (5%) vs. 33/899 (4%); HR 1.32 (95% CI 0.81 to 2.14) Neoplastic mortality: 24/892 (3%) vs. 21/899 (2%); RR 1.15 (95% CI 0.65 to 2.05) Non-CV, non-neoplastic mortality: 38/892 (4%) vs. 41/899 (5%); RR 0.93 (95% CI 0.61 to 1.44) Sudden death: 11/892 (1%) vs. 4/899 (0.4%); RR 2.77 (95% CI 0.89 to 8.67) Incident retinopathy: 54/128 (42%) vs. 66/135 (49%); RR 0.86 (95% CI 0.66 to 1.13) Any increase in albuminuria: 63/693 (9%) vs. 97/703 (14%); RR 0.66 (95% CI 0.49 to 0.89) Any incident neuropathy: 202/464 (44%) vs. 218/498 (44%); RR 0.99 (95% CI 0.86 to 1.15) | NR | A vs. B Any serious adverse event: 24.1% (215/892) vs. 17.6% (158/899); RR 1.37, 95% CI 1.14 to 1.65 Hypoglycemia: 11.0% (98/892) vs. 7.2% (65/899); RR 1.52, 95% CI 1.13 to 2.05 Withdrawal due to adverse event: 0.8% (7/892) vs. 0.3% (3/899); RR 2.35, 95% CI 0.61 to 9.07 | Good | Department of Veterans Affairs Office of Research and Development; National Institutes of Health; American Diabetes Association; Roche Pharmaceuticals; GlaxoSmithKline; sanofi-aventis; Amylin; Novo Nordisk; Roche Diagnostics; Kos Pharmaceuticals; Takeda Pharmaceuticals |  |

**Abbreviations:** ACCORD = Action to Control Cardiovascular risk in Diabetes; ADVANCE =The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; AE=adverse event; AHR = aryl hydrocarbon receptor; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CDC = Centers for Disease Control and Prevention; CHD = coronary heart disease; CHF = coronary heart failure; CI = confidence interval; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DBP = diastolic blood pressure; DSC = diabetes self-care; DTSQ = diabetes treatment satisfaction questionnaire; GI = gastrointestinal ; HbA1c = glycated hemoglobin; HDL = high density lipoprotein; HR = hazard ratio; HRQL = health-related quality of life; HRQOL = health-related quality of life; IFG = impaired fasting glucose; JEDIT = The Japanese elderly Diabetes Intervention Trial; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; LDL = low density lipoprotein; LVH = left ventricular hypertrophy; MEGA = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese ;MI = myocardial infraction; mm Hg = millimeters of mercury; NHLBI = National Heart, Lung and Blood Institute; OR = odds ratio; RCT = randomized, controlled trial; RR = relative risk; SANDS=Stop Atherosclerosis in Native Diabetics Study; SBP = systolic blood pressure; TC = total cholesterol; TIA = transient ischemic attack; UK = United Kingdom; UKPDS = United Kingdom Prospective Diabetes Study; US = United States; VADT = Veterans Affairs Diabetes Trial; WHO = World Health Organization.