| **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** | **Outcomes Assessed** |
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| **ADDITION** | | | | | | | | |
| Griffin, 201168; Simmons 201269; van der Donk 2013138 ADDITION-Europe | RCT | 343 general practices Denmark, UK, the Netherlands | Mean followup: 5.3 years | A. Intensive multifactorial treatment (n=1678) Glucose target: HbA1c ≤7.0% BMI target: ≤27 kg/m2 Blood pressure target: ≤135/85 mm Hg Cholesterol target: ≤5.0 mmol/L in patients with no history of CVD; ≤4.5 mmol/L in patients with history of CVD Lifestyle education B. Routine care (n=1379) Standard level of care according to each center's recommendations | **A vs. B** Mean age 60 vs. 60 years 41% vs. 43% female 96% vs. 93% white (other races/ ethnicities not reported) Duration of diabetes: N/A; screen-detected HbA1c 6.5 v 6.6% SBP 149 vs. 150 mmHg DBP 86 vs. 87 mmHg TC 5.5 vs. 5.6 mmol/L BMI 31.6 vs. 31.6 kg/m2 7% vs. 6% history of MI 28% vs. 27% smoker | Newly diagnosed type 2 diabetes without: contraindications or intolerance to study medication, conditions likely to invalidate ability to give informed consent, malignant disease with a poor prognosis, pregnancy or lactation | Screened: N/A Eligible: N/A Enrolled: 3057 Analyzed: 3055 | Cardiovascular event (composite outcome including CV mortality, nonfatal MI, nonfatal stroke, revascularization, nontraumatic amputation) |
| Charles, 2011135 ADDITION-Denmark | RCT | 190 general practices Denmark | Duration: 5 years Mean followup: 6 years | A. Intensive multifactorial treatment (n=702) Glucose target: HbA1c ≤7.0% BMI target: ≤27 kg/m2 Blood pressure target: ≤120/80 mmHg Cholesterol target: ≤5.0 mmol/L in patients with no history of CVD; ≤4.5 mmol/L in patients with history of CVD Lifestyle education B. Routine care (n=459) Standard level of care in Denmark | **A vs. B** Mean age 60 vs. 60 years 41% vs. 40% female Race not reported Duration of diabetes: N/A; screen-detected SBP 149.8 vs. 147.0 mmHg DBP 88.3 vs. 87.3 mmHg Weight (men) 93.7 vs. 94.2 kg Weight (women) 82.8 vs. 84.6 kg BMI (men) 30.4 vs.  30.4 BMI (women) 31.2 vs. 31.5 HDL 1.4 vs. 1.4 mmol/L  TC 5.8 vs. 5.6 mmol/L | Newly diagnosed type 2 diabetes without: contraindications or intolerance to study medication, conditions likely to invalidate ability to give informed consent, malignant disease with a poor prognosis, pregnancy or lactation | Screened: 1,533 Eligible: 1,278 Enrolled: 1,161 Analyzed: Varied by outcome | Neuropathy |
| van den Donk, 2010136;  Janssen, 2009137 ADDITION-Netherlands | RCT | 79 general practices The Netherlands | Mean duration: 4.7 years (for certain outcomes) | A. Intensive multifactorial treatment: Glucose target: HbA1c <7.0% Blood pressure target: ≤120/80 mm Hg Cholesterol target: <5.0 mmol/L or <4.5 mmol/L in patients with known history of CVD+ lifestyle education (n=255) B. Routine care: Glucose target: HbA1c <8.5% Blood pressure target: <150/85 mmHg Cholesterol target: Any participant with CVD risk >25% within 10 years; patients with known CVD <5.0 mmol/L (n=243) | **A vs. B** Mean age 60 vs. 60 years 44% vs. 48% female 99% vs. 98% white Duration of diabetes: N/A; screen-detected SBP 163 vs. 166 mmHg DBP 89 vs. 90 mmHg HDL 1.1 vs. 1.1 mmol/L TC 5.6 vs. 5.6 mmol/L BMI 30.4 vs. 31.2 kg/m2 | Screen-detected diabetes without: contraindications or intolerance to study medication, conditions likely to invalidate ability to give informed consent, malignant disease with a poor prognosis | Screened: NR Eligible: 586 Enrolled: 498 Analyzed: 498 | Quality of life - Medical Outcomes Study 36-Item Short Form Health Survey (SF-36; scale 0-100, higher score = better QoL) European Quality of Life-5 Dimensions (EQ5D; scale -0.5 to 1; higher score = better QoL) Diabetes Treatment Satisfaction Questionnaire (DTSQ; scale 0-36; higher score = greater treatment satisfaction) Problem Areas in Diabetes scale (PAID; scale 0-100; higher score = more emotional distress, lower QoL) |

| **Author Year Study Name** | **Treatment: Mean Baseline and Achieved Values** | **Clinical Health Outcomes** | **Adverse Events** | **Quality Rating** | **Funding Source** |
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| **ADDITION** | | | | | |
| Griffin, 201168; Simmons 201269, van der Donk 2013138 ADDITION - Europe | **A vs. B** HbA1c - Baseline: 7.0% vs. 7.0% Achieved: 6.6% vs. 6.7% Blood pressure - Baseline: 149/86 vs. 150/87 mmHg Achieved: 135/80 vs. 138/81 mmHg Total cholesterol - Baseline: 5.5 vs. 5.6 mmol/L Achieved: 4.2 vs. 4.4 mmol/L BMI - Baseline: 31.6 vs. 31.6 kg/m2 Achieved: 31.1 vs. 31.0 kg/m2 | **A vs. B** First CV event: 121/1678 (7%) vs. 117/1377 (8%); RR 0.85 (95% CI 0.67 to 1.08); HR 0.83 (95% CI 0.65 to 1.05) All-cause mortality: 104/1678 (6%) vs. 92/1377 (7%); RR 0.93 (95% CI 0.71 to 1.22); HR 0.91 (95% CI 0.69 to 1.21) CV mortality: 26/1678 (2%) vs. 22/1377 (2%); RR 0.97 (95% CI 0.55 to 1.70); HR 0.88 (95% CI 0.51 to 1.51) MI: 29/1678 (2%) vs. 32/1377 (2%); RR 0.74 (95% CI 0.45 to 1.22); HR 0.70 (95% CI 0.41 to 1.21) Stroke: 22/1678(1%) vs. 19/1377 (1%); RR 0.95 (95% CI 0.52 to 1.74); HR 0.98 (95% CI 0.57 to 1.71) Revascularization: 44/1678 (3%) vs. 44/1377 (3%); RR 0.82 (95% CI 0.54 to 1.24); HR 0.79 (95% CI 0.53 to 1.18) A vs. B; stratified by country (n/N not reported): CV events - -Denmark: HR 0.83 (95% CI 0.59 to 1.16) -UK: HR 0.80 (95% CI 0.55 to 1.17) -The Netherlands: HR 0.96 (95% CI 0.45 to 2.03) All-cause mortality - -Denmark: HR 1.15 (95% CI 0.80 to 1.66) -UK: HR 0.59 (95% CI 0.35 to 0.98) -The Netherlands: HR 0.85 (95% CI 0.35 to 2.06) CV mortality - -Denmark: HR 1.46 (95% CI 0.69 to 3.12) -UK: HR 0.45 (95% CI 0.19 to 1.06) -The Netherlands: HR 0.97 (95% CI 0.14 to 6.82) MI - -Denmark: HR 0.55 (95% CI 0.28 to 1.09) -UK: HR 1.09 (95% CI 0.40 to 2.94) -The Netherlands: HR 0.95 (95% CI 0.14 to 6.52) Stroke - -Denmark: HR 0.84 (95% CI 0.34 to 2.04) -UK: HR 1.11 (95% CI 0.52 to 2.35) -The Netherlands: HR 0.95 (95% CI 0.14 to 6.56) Revascularization - -Denmark: HR 0.81 (95% CI 0.49 to 1.35) -UK: HR 0.68 (95% CI 0.32 to 1.46) -The Netherlands: HR 0.95 (95% CI 0.30 to 3.00) | None reported | Fair | Novo Nordisk; GlaxoSmithKline; Pfizer |
| Griffin, 201168; Simmons 201269, van der Donk 2013138 ADDITION - Europe (cont.) |  | Second CV event - CVD mortality: 5/1678 (0.3%) vs. 3/1377 (0.2%); RR 0.82 (95% CI 0.54 to 1.24) MI: 0/1678 (0%) vs. 5/1377 (0.3%); RR 0.07 (95% CI 0.004 to 1.35) Stroke: 1/1678 (0.06%) vs. 1/1377 (0.07%); RR 0.82 (95% CI 0.05 to 13) Revascularization: 27/1678 (2%) vs. 28/1377 (2%); RR 0.79 (95% CI 0.47 to 1.34) Amputation: 0/1678 (0%) vs. 1/1377 (0.07%); RR 0.27 (95% CI 0.01 to 6.72) Pooled risk second event: HR 0.70 (95% CI 0.43 to 1.12) Third CV event - CVD mortality: 1/1678 (0.05%) vs. 3/1377 (0.2%); RR 0.27 (95% CI 0.03 to 2.63) MI: 0/1678 (0%) vs. 3/1377 (0.2%); RR 0.12 (95% CI 0.006 to 2.27) Stroke: 2/1678 (0.01%) vs. 0/1377 (0%); RR 4.10 (95% CI 0.20 to 85) Revascularization: 4/1678 (0.2%) vs. 11/1377 (0.8%); RR 0.30 (95% CI 0.10 to 0.94) Amputation: 1/1678 (0.05%) vs. 0/1377 (0%); RR 2.46 (95% CI 0.10 to 60) Pooled risk third event: HR 0.30 (95% CI 0.10 to 0.97) Pooled risk any event: HR 0.77 (95% CI 0.58 to 1.02) *Individual outcome RRs calculated; pooled HRs reported in text*  Quality of life measures - A (n=1,574) vs. B (n=1,287), mean between-group difference at followup SF-36 mental component score (scale 0 to 100): -0.01 (95% CI -0.03 to 0.02) SF-36 physical component score (scale 0 to 100): -0.01 (95% CI -1.2 to 1.0) Euroquel Visual Analog Scale score (scale 0 to 100): -1.17 (95% CI -4.2 to 1.9) Euroquel 5 Dimensions score (scale -0.6 to 1.0): -0.01 (95% CI -0.03 to 0.02) Well-Being Questionnaire - General score (scale 0 to 36): -0.32 (95% CI -1.31 to 0.66) Well-Being Questionnaire - Negative score (scale 0 to 12): 0.01 (95% CI -.025 to 0.27) Well-Being Questionnaire - Positive score (scale 0 to 12): -0.19 (95% CI -0.53 to 0.15) | None reported | Fair | Not reported. |
| Griffin, 201168; Simmons 201269, van der Donk 2013138 ADDITION - Europe (cont.) |  | Well-Being Questionnaire - Energy score (scale 0 to 12): -0.04 (95% CI -0.38 to 0.31) Audit of Diabetes-Dependent Quality of Life score (scale -9 to 3): -0.04 (95% CI -0.20 to 0.13)  Diabetes Treatment Satisfaction Questionnaire score (scale 0 to 36): -0.85 (95% CI -1.76 to 0.07) | None reported | Fair | Not reported |
| Charles, 2011135 ADDITION - Denmark | **A vs. B** HbA1c - Baseline: 6.4% vs. 6.4% Achieved: No significant change in either group (data not reported) Blood pressure - Baseline: 147/87 vs. 150/88 mmHg Achieved: Significant reduction in both groups (data not reported) Total cholesterol - Baseline: 5.5 vs. 5.6 mmol/L Achieved: Significant reduction in both groups (data not reported) BMI - Baseline: 31.5 vs. 31.2 kg/m2 Achieved: No significant change in either group (data not reported) | **A vs. B** Ankle brachial index ≤0.9%: 37/507 (7.3%) vs. 30/329 (9.1%); RR 0.80 (95% CI 0.50 to 1.27) Measures of peripheral diabetic neuropathy: -Light touch 1/8: 69/387 (17.8%) vs. 47/231 (20.3%); RR 0.88 (95% CI 0.63 to 1.22) -VDT >95% percentile: 53/235 (22.6%) vs. 35/136 (25.7%); RR 0.88 (95% CI 0.60 to 1.27) -Light touch + VDT: 69/229 (30.1%) vs. 47/135 (34.8%): RR 0.87 (95% CI 0.64 to 1.17)  -MNSI Qst, cut ≥7: 57/656 (8.7%) vs. 40/430 (9.3%); RR 0.93 (95% CI 0.64 to 1.37)  Pain: 27/581 (4.6%) vs. 18/400 (4.5%); RR 1.03 (95% CI 0.58 to 1.85) | None reported | Fair | NovoNordisk, Glaxo Smith Kline, Merck |
| van den Donk, 2010136; Janssen, 2009137 ADDITION - Netherlands | **A vs. B (at 1 year followup)** HbA1c - Baseline: 7.3% vs. 7.4% Achieved: 6.5% vs. 7.2% Blood pressure - Baseline: 166/90 vs. 163/83 mm Hg Achieved: 133/78 vs. 144/82 mm Hg Total cholesterol - Baseline: 5.6 vs. 5.6 mmol/L Achieved: 4.4 vs. 5.1 mmol/L | **A vs. B** SF-36 at 1 year: -General health: 63.3 (SD 18.4) vs. 64.4 (SD 18.1); p=0.63 -Vitality: 64.8 (SD 20.4) vs. 67.1 (SD 18.4); p=0.81 -Mental health: 75.9 (SD 17.9) vs. 79.0 (SD 15.6); p=0.56 -Physical functioning: 80.1 (SD 21.2) vs. 78.1 (SD 23.2); p=0.22 -Role physical: 80.3 (SD 35.0) vs. 81.1 (SD 33.5); p=0.93 -Bodily pain: 79.2 (SD 22.7) vs. 82.2 (22.4); p=0.97 -Social functioning: 83.0 (SD 22.0) vs. 85.7 (SD 19.2); p=0.37 -Role emotional: 86.2 (SD 30.9) vs. 89.9 (SD 26.0); p=0.25 SF-36 at 3 years: -General health: 64.2 (SE 1.5) vs. 65.8 (SE 1.5); p=0.45 -Vitality: 65.6 (SE 1.6) vs. 67.7 (SE 1.6); p=0.35 -Mental health: 75.9 (SE 1.4) vs. 79.7 (SE 1.2); p=0.04 -Physical functioning: 77.3 (SE 1.8) vs. 79.1 (SE 1.7); p=0.46 -Role physical: 76.6 (SE 2.7) vs. 83.4 (SE 2.4); p=0.06 -Bodily pain: 78.0 (SE 1.8) vs. 81.1 (SE 1.6); p=0.20 -Social functioning: 83.2 (SE 1.7) vs. 86.2 (SE 1.6); p=0.20 -Role emotional: 84.8 (SE 2.4) vs. 87.0 (SE 2.4); p=0.52 EQ5D at 3 years: 0.81 (SE 0.02) vs. 0.82 (SE 0.02); p=0.72 DTSQ at 5 years: 32.7 (SE 0.3) vs. 32.7 (SE 0.3); p=1.00 PAID at 5 years: 9.8 (SE 1.0) vs. 8.4 (SE 0.9); p=0.30 | Serious AEs (hypoglycemic event requiring assistance): 1/255 (0.4%) vs. 0/243 (0%); RR 2.86 (95% CI 0.12 to 70) | Fair | NovoNordisk, Glaxo Smith Kline, Merck |

**Abbreviations:** ADDITION = Anglo-Danish-Dutch Study of Intensive Treatment in People With Screen-Detected Diabetes; BMI = body mass index; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; DTSQ = Diabetes Treatment Satisfaction Questionnaire; HbA = glycated hemoglobin; HR = heart rate; QoL = quality of life; RR = relative risk; SD = standard deviation; UK = United Kingdom