Appendix 1. CADTH review.

Table 1- 1. Summary of CADTH inclusion/exclusion criteria

| **Inclusion criteria** |  |
| --- | --- |
| ***Population*** | Adults inadequately controlled (HbA1c >6.5%, FPG > 7mmol/L or 2-hour PPG > 10 mmol/L) despite therapy with MET + SU, at any dose |
| ***Intervention/comparator*** | MET + SU + Placebo  MET + SU + ≥1 drug from Table 1- 2  MET + ≥1 drug from Table 1- 2  Drug from Table 1- 2  Increased dose of MET + increased dose of SU |
| ***Study design*** | Active or placebo-controlled RCTs (parallel and cross-over studies) |
| ***Outcomes*** | Glycemic control: hemoglobin HbA1C  Long-term clinical complications of diabetes: congestive heart failure; ischemic heart disease; stroke/transient ischemic attack; peripheral vascular disease; retinopathy; nephropathy; neuropathy; mortality  Short-term complications of diabetes or anti-diabetes treatment: overall hypoglycemia; severe hypoglycemia; nocturnal hypoglycemia; hyperosmolar hyperglycemic non-ketotic coma  Quality-of-life: health-related quality-of-life (generic or diabetes specific)  Patient satisfaction: patient satisfaction with diabetes care; patient satisfaction with diabetes treatment  Other: weight, body mass index; serious/severe adverse events; pancreatitis; upper extremity fractures; macular edema |
| **Exclusion criteria** |  |
|  | > 15% of patients used a therapeutic regimen other than combination therapy with MET and SUs at baseline  Studies evaluating the switch from combination therapy to another anti-diabetes drug(s) in which the comparator was placebo or no anti-diabetes therapy (i.e., no active comparator)  Non-English publications |
|  | RCTs <4 weeks duration |

From the CADTH reports14,15

Abbreviations: FPG = fasting plasma glucose; MET = metformin; PPG = post-prandial plasma glucose; RCT = randomized controlled trial; SU = sulfonylurea

Table 1- 2. Summary of drugs for inclusion in the CADTH review

|  |  |
| --- | --- |
| **Drug class** | **Agent** |
| Biguanides | Metformin |
| Sulfonylureas | |  | | --- | | Gliclazide/Gliclazide MR | | Glimepiride | | Glyburide | | Chlorpropamide | | Glipizide | | Tolbutamide | |
| Thiazolidinediones | |  | | --- | | Pioglitazone | | Rosiglitazone | |
| Meglitinides | |  | | --- | | Nateglinide | | Repaglinide | |
| Alpha-glucosidase inhibitors | |  | | --- | | Acarbose | | Miglitol | |
| DPP-4 inhibitors | |  | | --- | | Sitagliptin | | Vildagliptin | | Saxagliptin | | Linagliptin | |
| GLP-1 analogues | |  | | --- | | Exenatide | | Liraglutide | |
| Bolus insulin | |  | | --- | | Insulin Aspart | | Insulin Lispro | | Insulin Glulisine | | Regular Human Insulin | |
| Basal insulin | |  | | --- | | Insulin NPH | | Insuln detemir | | Insulin glargine | | Insulin NPL | |
| Biphasic insulin | |  | | --- | | Premixed regular NPH | | Biphasic insulin aspart | | Biphasic insulin lispro | |

aAdapted from CADTH review reports14,15

***Abbreviations****: MR = modified release; NPH =* *neutral protamine Hagedorn ; NPL = neutral protamine lispro;*

**Appendix 2. PICOS table for NMA.**

Table 2-1. Inclusion/exclusion criteria

|  |  |
| --- | --- |
| **Inclusion criteria** |  |
| ***Population*** | Adults inadequately controlled despite therapy with MET + SU, at any dose. Inadequate controlled defined as: HbA1c >6.5%, Fasting plasma glucose > 7mmol/L or 2-hour postprandial glucose > 10 mmol/L |
| ***Intervention/comparator*** |  |
| ***Class*** | ***Drug*** |
| Reference treatment | MET + SU + placebo |
| DPP-4 inhibitors | MET + SU + saxagliptin  MET + SU + sitagliptin  MET + SU + linagliptin  MET + SU + vildagliptin |
| TZDs | MET + SU + pioglitazone |
|  | MET + SU + rosiglitazone |
| SGLT-2 inhibitor | MET + SU + dapagliflozin  MET + SU + canagliflozin |
| GLP-1 analogues | MET + SU + liraglutide  MET + SU + exenatide |
| Insulin | MET + SU + basal insulin  MET + SU + bolus insulin  MET + SU + biphasic insulin |
| ***Study design*** | Active or placebo-controlled randomized controlled trials >4 weeks duration |
|  | Continued treatment with MET plus SU throughout follow-up period  Comparison between at least two drugs (or placebo) |
| **Outcomes** | Reported at least one of the following:  Efficacy:  Mean change in HbA1c (%) from baseline  Mean change in weight (kg) from baseline  Mean change in systolic blood pressure (mmHg) from baseline  Safety:  Proportion of subjects with at least one hypoglycemic episode (n/N; %) |
| **Exclusion criteria** |  |
| ***Population*** | > 15% of patients used a therapeutic regimen other than combination therapy with MET and SU at baseline |
| ***Population*** | All patients have high cardiovascular risk  All patients have renal or hepatic impairment |

***Abbreviations****: DPP = Dipeptidyl peptidase; GLP = Glucagon-like peptide; MET = metformin;*

*SGLT = sodium-glucose linked transporter; SU = sulfonylurea; TZD = Thiazolidinedione*

**Appendix 3. Details of Included Studies**

**Table 3- 1. Bibliographic references for RCTs included in the network meta-analysis**

| **Author, Year** | **Full bibliographic reference** |
| --- | --- |
| Al-Shaikh et al., 2006a;54 | Al-shaikh AR. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. Pak J Med Sci 2006;22:14-7. |
| Aljabri et al., 2004a;49 | Aljabri K, Kozak SE, Thompson DM. Addition of pioglitazone or bedtime insulin to maximal doses of sulfonylurea and metformin in type 2 diabetes patients with poor glucose control: A prospective, randomized trial. American Journal of Medicine 116 (4) (pp 230-235), 2004 Date of Publication: 15 Feb 2004:15. |
| Bell et al., 201151 | Bell DSH, Dharmalingam M, Kumar S, et al. Triple oral fixed-dose diabetes polypill versus insulin plus metformin efficacy demonstration study in the treatment of advanced type 2 diabetes (TrIED study-II). Diabetes, Obesity and Metabolism. 13 (9) (pp 800-805), 2011. Date of Publication: September 2011. |
| Bergenstal et al., 2009a;41 | Bergenstal R, Lewin A, Bailey T, et al. Efficacy and safety of biphasic insulin aspart 70/30 versus exenatide in subjects with type 2 diabetes failing to achieve glycemic control with metformin and a sulfonylurea. Curr Med Res Opin 2009;25:65-75. |
| Charpentier and Halimi, 2009a;45 | Charpentier G, Halimi S. Earlier triple therapy with pioglitazone in patients with type 2 diabetes. Diabetes, Obesity and Metabolism 11 (9) (pp 844-854), 2009 Date of Publication: 2009:2009. |
| Study 626 | AstraZeneca and Bristol-Myers Squibb. A 24-week, Multicentre, Randomized, Double-Blind, Placebo-Controlled Phase IIIb Study to Evaluate the Efficacy and Safety of Saxagliptin in Combination with Metformin and Sulfonylurea in Subjects with Type 2 Diabetes who have Inadequate Glycaemic Control with the Combination of Metformin and Sulfonylurea. 2012 Apr 24.  ***Additional reference***: Saxagliptin Triple Oral Therapy. Identifier NCT01128153. ClinicalTrials.gov[internet] . 2013. Bethesda (MD).  ***Additional reference***: Moses R, Kalra S, Brook D, et al. Saxagliptin Effectively Reduces HbA1c and Is Well Tolerated When Added to a Combination of Metformin and Sulfonylurea (1094-P). American Diabetes Association 72nd Scientific Sessions June 8-12; 2012. |
| Davies et al., 2007a;42 | Davies MJ, Thaware PK, Tringham JR, et al. A randomized controlled trial examining combinations of repaglinide, metformin and NPH insulin. Diabet Med 2007;24:714-9. |
| Diamant et al., 201027 | Diamant M, Gaal LV, Stranks S, et al. Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. Lancet (375) Date of Publication: June 26, 2010. |
| Dorkhan et al., 2009a;52 | Dorkhan M, Dencker M, Stagmo M, Groop L. Effect of pioglitazone versus insulin glargine on cardiac size, function, and measures of fluid retention in patients with type 2 diabetes. Cardiovasc Diabetol 2009;8:15. |
| Goudswaard et al., 2004a;53 | Goudswaard AN, Stolk RP, Zuithoff P, et al. Starting insulin in type 2 diabetes: Continue oral hypoglycemic agents? A randomized trial in primary care. Journal of Family Practice 2004;53:393-9. |
| Hartemann-Heurtier et al., 2009a;46 | Hartemann-Heurtier A, Halbron M, Golmard JL, et al. Effects of bed-time insulin versus pioglitazone on abdominal fat accumulation, inflammation and gene expression in adipose tissue in patients with type 2 diabetes. Diabetes Res Clin Pract 2009;86:37-43. |
| Heine et al., 2005a;28 | Heine RJ, Van Gaal LF, Johns D, et al. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: A randomized trial. Annals of Internal Medicine 143 (8) (pp 559-569+I30), 2005 Date of Publication: 18 Oct 2005:18. |
| Herman et al., 2011a;43 | Herman WH, Buse JB, Arakaki RF, et al. Concomitant oral antihyperglycemic agent use and associated treatment outcomes after initiation of insulin therapy. Endocr Pract 2011;17:563-7. |
| Hermansen et al., 2007a;29 | Hermansen K, Kipnes M, Luo E, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. Diabetes, Obesity and Metabolism 9 (5) (pp 733-745), 2007 Date of Publication: Sep 2007:Sep. |
| Holman et al., 2007a;50 | Holman RR, Thorne KI, Farmer AJ, et al. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. New England Journal of Medicine 357 (17) (pp 1716-1730), 2007 Date of Publication: 25 Oct 2007:25. |
| Home et al. 201330 | Home P, Stewart M, Yang F, Perry B, Carr MC. 52-Week Efficacy of Albiglutide vs Placebo and vs Pioglitazone in Triple Therapy (Background Metformin and Glimepiride) in People with Type 2 Diabetes: HARMONY5 Study. American Diabetes Association 73rd Scientific Sessions; June 21-25 Chicago, IL. 58-LB (Abstract).  ***Additional reference:*** Stewart M, Home P, Yang F, Perry B, Carr MC. 52-week efficacy of albiglutide vs placebo and vs pioglitazone in triple therapy (background metformin and glimepiride) in patients with type 2 diabetes: HARMONY 5 study. 49th European Association for the Study of Diabetes; Barcelona 23-27 September, 2013. #905 (Abstract) |
| Janka et al., 2005a;31 | Janka HU, Plewe G, Riddle MC, et al. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. Diabetes Care 2005;28:254-9. |
| Kendall et al., 2005a;44 | Kendall DM, Riddle MC, Rosenstock J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. Diabetes Care 28 (5) (pp 1083-1091), 2005 Date of Publication: May 2005:May. |
| Liu et al., 201347 | Liu SC, Chien KL, Wang CH, et al. Efficacy and safety of adding pioglitazone or sitagliptin to patients with type 2 diabetes insufficiently controlled with metformin and a sulfonylurea. Endocrine Practice. 19 (6) (pp 980-988), 2013. Date of Publication: 01 Nov 2013. |
| Lu et al, 201348 | Lu CH, Wu TJ, Shih KC, et al. Safety and efficacy of twice-daily exenatide in Taiwanese patients with inadequately controlled type 2 diabetes mellitus. Journal of the Formosan Medical Association. 112 (3) (pp 144-150), 2013. Date of Publication: March 2013. |
| Lukashevich et al., 201332 | Lukashevich V, Prato SD, Araga M, et al. Efficay and safety of vildagliptin in patients with type 2 diabetes mellitus inadequately controlled with dual combination of metformin and sulphonylurea. Diabetes, Obesity & Metabolism. Date of Publication: 29 October 2013. |
| Nauck et al., 2007a;33 | Nauck MA, Duran S, Kim D, et al. A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. Diabetologia 50 (2) (pp 259-267), 2007 Date of Publication: Feb 2007:Feb. |
| Owens et al., 2011a;34 | Owens DR, Swallow R, Dugi KA, Woerle HJ. Efficacy and safety of linagliptin in persons with type 2 diabetes inadequately controlled by a combination of metformin and sulphonylurea: a 24-week randomized study. Diabet Med 2011;28:1352-61. |
| Round et al., 201335 | Round E, Shentu Y, Golm GT, et al. Safety and Efficacy of Sitagliptin Added to the Combination of Sulfonylurea and Metformin in Patients With Type 2 Diabetes Mellitus and Inadequate Glycemic Control. American Diabetes Association 73rd Scientific Sessions; June 21-25 Chicago, IL. 1148-P (Abstract). |
| Russell-Jones et al., 2009a;36 | Russell-Jones D, Vaag A, Schmitz O, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): A randomized controlled trial. Diabetologia 52 (10) (pp 2046-2055), 2009 Date of Publication: October 2009:October. |
| Schernthaner et al., 201337 | Schernthaner G, Gross JL, Rosenstock J, et al. Canagliflozin Compared With Sitagliptin for Patients With Type 2 Diabetes Who Do Not Have Adequate Glycemic Control With Metformin Plus Sulfonylurea: A 52-week randomized trial. Diabetes Care (2013) 36 (2508-2515). |
| Stehouwer et al. 2003a;55 | Stehouwer MH, DeVries JH, Lumeij JA, et al. Combined bedtime insulin--daytime sulphonylurea regimen compared with two different daily insulin regimens in type 2 diabetes: effects on HbA1c and hypoglycaemia rate--a randomised trial. Diabetes Metab Res Rev 2003;19:148-52. |
| Strojek et al., 2009a;38 | Strojek K, Bebakar WMW, Khutsoane DT, et al. Once-daily initiation with biphasic insulin aspart 30 versus insulin glargine in patients with type 2 diabetes inadequately controlled with oral drugs: An open-label, multinational RCT. Current Medical Research and Opinion 25 (12) (pp 2887-2894), 2009 Date of Publication: December 2009:December. |
| Matthaei et al., 201339 | AstraZeneca and Bristol-Myers Squibb. A 24-week, Multicentre, Randomized, Double-Blind, Placebo-Controlled, International Phase III Study with a 28-week Extension Period to Evaluate the Safety and Efficacy of Dapagliflozin 10mg once daily in Patients with Type 2 Diabetes who have Inadequate Glycemic Control on a background combination of Metformin and Sulfonylurea (D1693C00005). 2013 May 27.  ***Additional reference:*** Evaluation of Safety and Efficacy of Dapagliflozin in Subjects With Type 2 Diabetes Who Have Inadequate Glycaemic Control on Background Combination of Metformin and Sulfonylurea. Identifier NCT01128153. ClinicalTrials.gov[internet] . 2013. Bethesda (MD).  ***Additional reference:*** Matthaei S, Rohwedder K, Grohl A, et al. Dapagliflozin Improves Glycaemic Control and Reduces Body Weight as Add-On Therapy to Metformin Plus Sulphonylurea (PS-073). Diabetologia 56[S1]. 2013. |
| Wilding et al., 201340 | Wilding JPH, Charpentier G, Hollander P, et al. Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sulphonylurea: A randomised trial. International Journal of Clinical Practice. 67 (12) (pp 1267-1282), 2013. Date of Publication: December 2013. |

adata from the CADTH report15

**Table 3- 2. Overview of articles included in the network meta-analysis**

| **Author, Year** | **Country** | **Number randomized** | **Treatment duration (weeks)** | **Intervention** |
| --- | --- | --- | --- | --- |
| Al-shaikh et al., 2006a;54 | Saudi Arabia | 221 | 26 | * Glargine (HS) + Met + SU * Biphasic (30% regular insulin + 70% NPH) 2/3 in am, 1/3 in pm |
| Aljabri et al., 2004a;49 | Canada | 62 | 17 | * Pioglitazone (30-45 mg/d) + Met + SU * NPH insulin (titrated to FG <6.0 mg/dl) + Met + SU |
| Bell et al., 201151 | India | 101 | 12 | * Pioglitazone (15 mg/d) + Met + glimepiride [polypill] * Biphasic insulin 70/30 + Met |
| Bergenstal et al., 2009a;41 | US | 372 | 26 | * Exenatide (titrated to 10 µg BID) + Met + SU * BIAsp30 (QD) + Met + SU |
| Charpentier and Halimi, 2009a;45 | France | 299 | 30 | * Pioglitazone (30-45 mg/day) + Met + SU * Placebo + Met + SU |
| Study 6a;26 | Multinational | 257 | 24 | * Saxagliptin+ Met + SU * Placebo + Met + SU |
| Davies et al., 2007a;42 | US | 82 | 16 | * 30/70 human insulin+Met * NPH+Repaglinide+ Met * NPH Insulin (HS) + Met |
| Diamant et al. 201027 | Multinational | 135 | 26 | * Exenatide (2 mg QW) + Met + SU * Insulin glargine + Met + SU |
| Dorkhan et al., 2009a;52 | Sweden | 30 | 28 | * Pioglitazone + Met + SU * Insulin (glargine) + Met + SU |
| Goudswaard et al., 2004a;53 | Netherlands | 69 | 52 | * NPH (8 IU) QD + Met + SU * Biphasic (12 IU/6 IU; 70/30 BID) |
| Hartemann-Heurtier et al., 2009a;46 | France | 28 | 26 | * Pioglitazone + Met + SU * NPH insulin + Met + SU |
| Heine et al., 2005a;28 | Multinational | 551 | 26 | * Exenatide (10 µg BID) + Met + SU * Insulin glargine + Met + SU |
| Herman et al., 2011a;43 | US | 1274 | 26 | * Biphasic insulin lispro (75/25) + Met + SU * Insulin glargine + Met + SU |
| Hermansen et al., 2007a;29 | US and Denmark | 219 | 26 | * Sitagliptin (100 mg/day) + Met + SU * Placebo + Met + SU |
| Holman et al., 2007a;50 | Ireland, UK | 708 | 52 | * Insulin aspart (TID) + Met + SU * Insulin determir (HS or BID) + Met + SU * Biphasic insulin aspart 30 (BID) + Met + SU |
| Home et al., 201330 | Multinational | 404 | 52 | * Pioglitazone (30-45mg QD) + Met + SU * Placebo + Met + SU |
| Janka et al., 2005a;31 | European multinational | 364 | 24 | * Insulin glargine + Met + SU * NPH (30/70) + placebo |
| Kendall et al., 2005a;44 | US | 734 | 32 | * Exenatide (5 µg BID) + Met + SU * Exenatide (10 µg BID) + Met + SU * Placebo + Met + SU |
| Liu et al., 201347 | Taiwan | 120 | 24 | * Pioglitazone (30 mg) + Met + SU * Sitagliptin(100 mg) + Met + SU |
| Lu et al., 201348 | Taiwan | 51 | 16 | * Exenatide (5 to 10 µg BID) + Met + SU * Placebo + Met +SU |
| Lukashevich et al., 201332 | Multinational | 318 | 24 | * Vildagliptin (50 mg BID) + Met + glimepiride * Placebo + Met + glimepiride |
| Nauck et al., 2007a;33 | Multinational | 505 | 52 | * Exenatide (10 µg BID) + Met + SU * Biphasic insulin aspart 30/70 |
| Owens et al., 2011a;34 | Multinational | 1058 | 24 | * Linagliptin+ M + S * Placebo + M + S |
| Round et al., 201335 | Multinational (Asia-Pacific) | 427 | 24 | * Sitagliptin (100 mg) + Met + SU * Placebo + Met + SU |
| Russell-Jones et al., 2009a;36 | Multinational | 581 | 26 | * Liraglutide (1.8 mg/day) + Met + glimepiride * Insulin glargine + Met + glimepiride * Placebo + Met + glimepiride |
| Schernthaner et al., 201337 | Multinational | 756 | 52 | * Canagliflozin (300 mg) + Met +SU * Sitagliptin (100 mg) + Met + SU |
| Stehouwer et al., 2003a;55 | Multicentre | 261 | NR | * NPH + SU * NPH (BD) * NPH+30/70 |
| Strojek et al., 2009a;38 | Multinational | 480 | 26 | * Insulin glargine + Met + SU * BIAsp30 + Met + SU |
| Matthaei et al., 201339 | Multinational | 216 | 24 | * Dapagliflozin (10 mg) + Met + SU * Placebo + Met + SU |
| Wilding et al., 201340 | Multinational | 469 | 26 | * Canagliflozin (100 mg) + Met +SU * Canagliflozin (300 mg) + Met +SU * Placebo + Met + SU |

Abbreviations: BIAsp = Biphasic insulin aspart; FG = fasting glucose; MET = metformin; NPH = neutral protamine Hagedorn; UK = United Kingdom; US = United States; SU = sulfonylurea

adata from the CADTH report15

**Table 3- 3. Patient characteristics of included studiesa**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Author, Year** | **Average age (years)** | **% Male** | **Average duration of DM (years)** | **Average HbA1c (%)** |
| Al-shaikh et al., 2006a;54 | 56.3 | 56.1 | NR | 11.3 |
| Aljabri et al., 2004a;49 | 58.0 | 60.3 | 10.0 | 9.9 |
| Bell et al., 201151 | 52.5 ± 11.0 | 57.4 | 4.7 ± 2.7 | 9.2 ± 1.4 |
| Bergenstal et al., 2009a;41 | 52.6 | 48.4 | 9.0 | 10.2 |
| Charpentier and Halimi, 2009a;45 | 59.7 | 75.4 | 12.3 | 8.1 |
| Study 6a;26 | 57.0 | 59.9 | NR | 8.3 |
| Davies et al., 2007a;42 | 57.2 | 43.9 | 8.7 | 9.7 |
| Diamant et al., 201027 | NRb | NRb | NRb | NRb |
| Dorkhan et al., 2009a;52 | 61.2 | 66.7 | 10.3 | 8.2 |
| Goudswaard et al., 2004a;53 | 58.5 | 48.4 | 7.4 | 8.5 |
| Hartemann-Heurtier et al., 2009a;46 | 60.1 | 59.3 | 12.0 | 8.4 |
| Heine et al., 2005a;28 | 58.9 | 61.1 | 9.6 | 8.2 |
| Herman et al., 2011a;43 | 57.2 | 48.5 | 9.8 | 7.4 |
| Hermansen et al., 2007a;29 | 57.3 | 52.4 | 10.2 | 8.3 |
| Holman et al., 2007a;50 | 61.7 ± 9.8 | 64.1 | Median: 9.0 | 8.5 ± 0.8 |
| Home et al., 201330 | 55.7± 9.5 | 55.6 | 9.2 ± 6.1 | 8.3± 0.9 |
| Janka et al., 2005a;31 | 60.6 | 59.1 | 9.9 | 8.8 |
| Kendall et al., 2005a;44 | 55.3 | 58.1 | 8.9 | 8.5 |
| Liu et al., 201347 | 59.1 ± 8.6 | 37.5 | 7.8 ± 4.1 | 8.4 ± 0.9 |
| Lu et al., 201348 | 50.9 ± 9.4 | 54.0 | 7.6 ± 4.9 | 8.1 ± 1.0 |
| Lukashevich et al., 201332 | 55.1 ± 10.6 | 47.8 | 7.3 ± 6.1 | 8.8 ± 0.9 |
| Nauck et al., 2007a;33 | 58.5 | 51.1 | 9.9 | 8.6 |
| Owens et al., 2011a;34 | 58.1 | 47.2 | 73.3% > 5 years | 43.3 % with HbA1c ≥ 8.5% |
| Round et al., 201335 | 54.9 ± 9.9 | 45.7 | 7.8 ± 5.3 | 8.4 ± 0.85 |
| Russell-Jones et al., 2009a;36 | 57.5 | 56.6 | 9.4 | 8.3 |
| Schernthaner et al., 201337 | 56.7 ± 9.5 | 55.9 | 9.6 ± 6.2 | 8.1 ± 0.9 |
| Stehouwer et al., 2003a;55 | 57.9 | 50.2 | 7.9 | 9.4 |
| Strojek et al., 2009a;38 | 56.0 | 43.9 | 9.3 | 8.5 |
| Matthaei et al., 201339 | 61.0 | 49.1 | 9.5 | 8.2 |
| Wilding et al., 201340 | 56.8 ± 9.3 | 51.0 | 9.6 ± 6.3 | 8.1 ± 0.9 |

*adata from the CADTH report15;  bdata not reported for subgroup of subjects on Met + SU. Estimates for full population enrolled in trial were: mean age: 58 years; % male: 53.3%; average duration of DM: 7.9 years; Average HbA1c: 8.3%;*

***Abbreviations****: DM = diabetes mellitus; NR = not reported*

**Table 3- 4. Combination therapy – baseline mean, SU as per inclusion criteria, and duration of stable therapy**

| **First Author** | | **Year** | **Mean dose (mg/day) of combination therapy, at baseline/screening** | | | **Allowable SU and dose as per study criteria**  **(mg/day)a** | **Duration of stable**  **combination**  **therapy prior to study entry (months)** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Metformin** | **Sulfonylurea** | |
| **Agent** | **Dose** |
| Al-shaikha;54 | | 2006 | NR | NR | NR | Any SU - MD | ≥3 |
| Aljabria;49 | | 2004 | 2050  2210 | glyburide | 20 | Any SU -- MTD | ≥3 |
| Bell51 | | 2011 | NR | glimepiride | NR | Glimepiride - 1 or 2 mg | NR |
| Bergenstala;41 | | 2009 | NR |  | NR | Any SU - ≥ ½ MD | 3 |
| Charpentiera;45 | | 2009 | 2584 | glimepiride  glyburide  gliclazide  glipizide carbutamide | 5.2  15.1  146  20  1000 | Any SU – MTD | ≥3 |
| Study 6a;26 |  | 1957 | Saxagliptin  glibenclamide  gliclazide  glimepiride  glipizide  Placebo  glibenclamide  gliclazide  glimepiride glipizide | Saxagliptin  14.5  157.9  5.2  20.0  Placebo  16.5  161  4.9  15.0 | Any SU- stable dose | ≥2 |
| Daviesa;42 | 2007 | MTD | NR | NR | N/A | NR |
| Diamant27 | 2010 | ≥1500 | NR | NR | NR | ≥2 |
| Dorkhana;52 | | 2009 | NR | NR | NR | Any SU - > ½ MRD | NR |
| Goudswaarda;53 | | 2004 | NR | NR | NR | Any SU - MTD | NR |
| Hartemann-Heurtiera;46 | | 2009 | NR | NR | NR | Any SU – MTD | 6 |
| Heinea;28 | | 2005 | NR | NR | NR | Any SU – MED | ≥3 |
| Hermana;43 | | 2011 | NR | NR | NR | Any SU – ½ MD |  |
| Hermansena;29 | | 2007 | NR | NR | NR | Any OAD, or no agent at all | 2.5 |
| Holmana;50 | | 2007 | NR | NR | NR | Any SU – MTD | ≥4 |
| Home30 | | 2013 | >1500 | glimepiride | 4mg | Glimepiride 4mg/day | NR |
| Jankaa;31 | | 2005 | NR | Glimepiride | 3-4 | Any SU – stable dose | ≥1 |
| Kendalla;44 | | 2005 | NR | NR | NR | Any SU - ≥MED | ≥3 |
| Liu47 | | 2013 | ≥1500 | gliclazide MR  glimepiride | 60-120  4-8 | ≥ ½ MD | ≥2.5 |
| Lu48 | | 2013 | 1706 (exenatide)  1692 (placebo) | NR | NR | NR | ≥3 |
| Lukashevich32 | | 2013 | ≥1500 | glimepiride | ≥4 | Glimepiride ≥4 mg | ≥3 |
| Naucka;33 | | 2007 | NR | NR | NR | Any SU – optimally effective dose | ≥3 |
| Owensa;34 | | 2011 | NR | NR | NR | Any oral glucose-lowering drug | ≥3 |
| Round35 | | 2013 | ≥1500 | Glimepiride  Gliclazide | ≥2  ≥50% of the max registered dose | ≥2  ≥50% of the max registered dose | ≥2.5 |
| Russell-Jonesa;36 | | 2009 | NR | NR | NR | Any oral glucose-lowering drug | ≥0.75 |
| Schernthaner37 | | 2013 | ≥2000  Or ≥1500 if unable to tolerate a higher dose. | Glipizide  Glipizide XR Glyburide/  glibenclamide  Glimepiride  Gliclazide  Gliclazide MR  Glyburide micronized  Tolazamide | 20  10  10  4  160  60  0 | ≥ ½ maximal labeled dose | NR |
| Stehouwera;55 | | 2003 | 1000 | Glimepiride | 6 | Glimepiride ≤6 | 3 |
| Strojeka;38 | | 2009 | NR | NR | NR | Glimepiride ≤8 | ≥1 |
| Matthaei39 | | 2013 | ≥1500 and MTD | NR | ½ MD | ½ MD | ≥2 |
| Wilding40 | | 2013 | ≥2000  Or ≥1500 if unable to tolerate a higher dose. | Glipizide  Glipizide XR Glyburide/  glibenclamide  Glimepiride  Gliclazide  Gliclazide MR | 20  10  10  4  160  60 | ≥ half-maximal labeled dose | NR |

*adata from the CADTH report15;* b*As reported at the study-level. In some randomized controlled trials, only extracted data from a subgroup of subjects who received MET + SU.*

***Abbreviations****: N/A = Not applicable; NR = Not reported; MD = maximum dose; MRD = maximum recommended dose; MR = modified release; MTD = maximum tolerated dose; MED = maximum effective dose; OAD = oral antidiabetic agent; SU = sulfonylurea; XR = extended release*

**Table 3- 5. Summary of insulin titration among included trials involving an insulin treatment arm\***

| **Author, Year** | **Intervention** | **Insulin dose and titration** | **Summary of titration** |
| --- | --- | --- | --- |
| Aljabri et al., 2004a;49 | NPH + Met + SU | Insulin patients were started on a dose of 0.3 unit/kg in addition to their hypoglycemic agents. They were instructed on how to increase the dose to achieve a fasting glucose level 108 mg/dL, and were contacted weekly for help with insulin adjustment | Starting dose: 0.3U/kg  Increase: to attain FPG of 108mg/dL |
| Al-Shaikh et al., 2006a;54 | Glargine (HS) + MET + SU | The starting dose of Glargine insulin was 14 units per day titrated up weekly according to the fasting blood glucose levels. Fasting blood glucose was more than 200 mg/dl. The dose was in-creased by 8 units. In case of less than 200 and more than 140 mg/dl the dose was increased by 4 units per week. | Starting dose: 14U/day  Increase: 8U weekly if FPG >200mg/dL; 4U weekly if FPG >140mg/dL, but <200mg/dL |
| Biphasic 30/70  2/3 in am, 1/3 in pm | The doses of mixed insulin were one unit per kg in the beginning di-vided to two third in the morning and one third in the evening. The morning dose was in-creased weekly by 4 units if the postprandial level was more than 200 mg/dl and the evening dose was increased by 4 units if the fasting blood glucose was more than 140 mg/dl. | Starting dose: 1U/kg  Increase: 4U for morning dose if postprandial BG >200mg/dL; 4U for evening dose if FBG >140mg/dL |
| Bell et al., 201151 | Biphasic insulin 70/30 + Met | Insulin 70/30 mix twice daily (dose titrated based on fasting and evening plasma glucose with goals of 80-120 mg/dl which maximizes control while avoiding hypoglycemia) along with 500 mg SR metformin twice daily for 12 weeks. This group eventually utilized an average of 12.8 units in the morning and 12.3 units in the evening of 70/30 mix (0.43 units per kg per day). | Starting dose: NR  Increase: to attain FPG of 80-120 mg/dl |
| Bergenstal et al., 2009a;41 | BIAsp30 (QD) + Met + SU | Subjects initiated insulin therapy with 12 U before supper in the BIAsp 30 QD group, and with 12 U divided equally between pre-breakfast and pre-supper in the BIAsp 30 BID group. Subjects randomized to BIAsp 30 treatment were instructed to adjust their insulin dose every 3–4 days based on an insulin titration algorithm. Insulin dose titration was based on the average self-monitored blood glucose (SMBG) results for the 3 days preceding the visit, unless hypoglycemia occurred. If hypoglycemia occurred, titration was postponed and the insulin dose remained unchanged. Subjects randomized to BIAsp 30 BID group could not increase the total daily dose by more than 10 U at any time. After visit 2 (week 0), insulin doses were titrated weekly for the first 12 weeks, then every 2 weeks thereafter according to the titration algorithm. | Starting dose: 12U/day  Increase: based on SMBG |
| BIAsp30 (BID) + Met + SU |
| Davies et al., 2007a;42 | Biphasic insulin 70/30 (BID) + Met  NPH insulin + Met  NPH insulin + Met + Repaglinide | The initial bedtime NPH insulin dose was 10 IU, while the premixed insulin dose (Human Mixtard 30ge) was 10 IU twice daily. The bedtime insulin was titrated in 2-unit increments to achieve fasting blood glucose <6.0 mmol/l. The twice daily premixed insulin was titrated at 2-unit increments, with the morning dose increased to achieve post breakfast glucose <8.0 mmol/l and pre-evening meal glucose <6.0 mmol/l. The evening premixed insulin dose targets were bedtime glucose <8.0 mmol/l and fasting glucose <6.0mmol/l. Insulin was titrated over the first 6 weeks and then patiens were followed up monthly for 4 months. | Starting dose: 10 IU BID  Increase: 2-unit increments to achieve post breakfast glucose <8.0 mmol/l; 2-unit increments to achieve pre-evening meal glucose <6.0 mmol/L  Starting dose: 10 IU OD  Increase: 2-unit increments to achieve FBG <6.0 mmol/l |
| Diamant et al., 201027 | Insulin glargine + Met + SU | The 26-week treatment duration allowed for implementation of the INITIATE (Initiate Insulin by Aggressive Titration and Education) dosing algorithm for insulin glargine. Patients started insulin glargine treatment with 10 IU per day, measured fasting blood glucose concentrations every morning, and were instructed to adjust insulin doses to achieve a target glucose of 4.0-5.5 nmol/L. Patients and investigators were asked to adhere to titration targets; however, there was no central supervision to enforce titration. Insulin glargine was injected at the same time every day, preferably at bedtime. Patients continued their stable metformin dosing until week 26. For patients who had confirmed hypoglycaemia, we recommended reduction of the sulphonylurea dose. Specific instructions for eight-point self monitored blood-glucose profiles (measured before and 2 hours after morning, midday, and evening meals, at bedtime, and at 0300 h) were given. | Starting dose: 10 U/day  Increase: to achieve a target glucose of 4.0-5.5 mmol/L |
| Dorkhan et al., 2009a;52 | Glargine + Met + SU | Insulin was up-titrated to achieve fasting plasma glucose < 6 mmol/l. | Starting dose:  Increase: to achieve FPG <6mmol/L |
| Goudswaard et al., 2004a;53 | NPH QD + MET + SU | Insulin therapy was initiated with 8 IU (NPH) before bedtime in the IC group, and with 12 and 6 IU before breakfast and dinner in the IM (Biphasic) group, respectively. Insulin dosages were adjusted twice weekly by telephone contact with the diabetes nurse (adjusting phase), aiming for a target fasting blood glucose of 4.0–7.0 mmol/L and a target postprandial glucose of 4.0–10.0 mmol/L. When these targets were achieved and had proved stable, the insulin dose was fixed and telephone contacts were decreased to once monthly (stable phase). | Starting dose: NPH 8 IU/day; biphasic 18 IU/day;  Increase: twice weekly until FPG of 4.0-7.0mmol/L and PPG of 4.0-10.0mmol/L |
| Biphasic 70/30 BID |
| Hartemann-Heurtier et al., 2009a;46 | NPH + Met + SU | Human NPH insulin (0.2 IU/kg/day) (Umuline NPH; LILLY) at bedtime for 24 weeks, The target fasting plasma glucose (FPG) was < 110 mg/dl (<6.1 mmol/l). Insulin treated patients were con-tacted weekly by phone to discuss dosage changes. | Starting dose: 0.2 IU/kg/day   Increase: weekly until FPG <6.1 mmol/L |
| Heine et al., 2005a;28 | Insulin glargine+ M + S | Insulin glargine, 1 daily dose titrated to maintain fasting blood glucose levels of less than 5.6 mmol/L (<100 mg/dL); A second group of patients was assigned to receive insulin glargine at an initial dosage of 10 U/d; then, using a fixed-dose algorithm to adjust the dose, they self-titrated the dose in 2-U increments every 3 days to achieve a fasting blood glucose target level of less than 5.6 mmol/L ( 100 mg/dL) on daily glucose monitoring. | Starting dose: 10U/day  Increase: 2U every 3 days until FPG <5.6mmol/L |
| Herman et al., 2011a;43 | MET +SU+Lispro 75/25 | Either twice-daily insulin lispro mix 75/25 (75% insulin lispro protamine suspension and 25% lispro); Total daily insulin dose (U/kg) 0.50 ± 0.22 | Starting dose: 0.5U/kg  Increase: NR |
|  | MET +SU+Glargine | Once-daily insulin glargine therapy; Total daily insulin dose (U/kg) 0.42 ± 0.23 | Starting dose: 0.42U/kg    Increase: NR |
| Holman et al., 2007a;50 | Biphasic insulin aspart + M + S | Patients injected biphasic insulin twice daily, prandial insulin immediately before meals, and basal insulin at bedtime. For each visit and telephone contact, patients were asked to perform in advance three capillary glucose profiles (Medisense Optium, Abbott) obtained before break -fast and before the evening meal for patients in the biphasic and basal groups and before meals and 2 hours after meals and at bedtime in the prandial group. Using these glucose readings and self-reported hypoglycemia, the trial management system suggested changes in insulin doses, aiming for values before meals of 72 to 99 mg per deciliter (4.0 to 5.5 mmol per liter) and values 2 hours after meals of 90 to 126 mg per deciliter (5.0 to 7.0 mmol per liter). | Mean Starting dose: biphasic 16U/day; prandial 18 U/day; basal 16U/day;   Increase: to achieve preprandial glucose 4.0-5.5mmol/L and postprandial glucose 5.0-7.0mmol/L |
|  | Insulin aspart + M + S |
|  | Insulin detemir + M + S |
| Janka et al., 2005a;31,62 | Insulin glargine + MET + SU | The starting dose for insulin glargine was 10 IU in the morning and, for pre-mixed insulin, 10 IU before breakfast and 10 IU before dinner. These starting doses could be lowered if considered clinically necessary by the investigator. Insulin doses were adjusted by a forced titration regimen calling for weekly adjustments for 8 weeks and at 2-week intervals there-after for both groups, according to daily self-monitored capillary whole blood glucose measurements using meters (AccuChek Sensor; Roche Diagnostics). For both groups, the FBG target was 100 mg/dl (5.6 mmol/l), and the before dinner blood glucose target for the 70/30 group was 100 mg/dl (5.6 mmol/l), with a step-wise increase of insulin depending on the blood glucose values as follows: blood glucose 100 –120 mg/dl, increased by 2 IU/day; blood glucose 120 –140 mg/dl, increased by 4 IU/day; blood glucose 140 –160 mg/dl, increased by 6 IU/day; and blood glucose 160 mg/dl, increased by 8 IU/day, unless symptoms of hypoglycaemia occurred. | Starting dose: glargine 10 IU/day: NPH 20 IU/day  Increase: 2 IU/day if FBG 100-200mg/dL; 4 IU/day if FPG 120-140mg/dL; 6 IU/day if FPG 140-160mg/dL weekly for 8 weeks, then every two weeks until FPG of 100mg/dL (5.6mmol/L) |
| NPH + placebo |
| Nauck et al., 2007a;33 | Biphasic insulin aspart 30/70 + M + S | Investigators chose the starting insulin dose for patients following randomisation, and contacted patients at regular intervals to discuss glycaemic control. A forced titration schedule was not used in this trial. Investigators were instructed to adjust insulin doses to achieve an optimal balance between glycaemic control and risk of hypoglycemia as dictated by best clinical practice. The decision to adjust insulin therapy, and the mode of patient empowerment to self-adjust insulin doses, was ultimately left up to each investigator ’s clinical judgement. Multiple options were available to guide intensification of insulin therapy including : (1) ongoing analysis of the patient’s diary and home glucose monitoring results; and (2) a titration guideline outlining minimum targets for fasting glucose (<7 mmol/l [126 mg/ dl]) and 2-h postprandial glucose (<10 mmol/ l [180 mg/ dl]). In addition, the importance of optimising insulin doses was discussed with investigators at both study initiation and mid-study meetings where they were encouraged to optimise glucose control by titrating insulin doses as high as clinically possible | Starting dose: at discretion of investigator  Increase: at discretion of investigator; FPG target of <7 mmol/L [126 mg/ dl] |
| Russell-Jones et al., 2009a;36 | Insulin+ M + S | Insulin glargine (100 IU/ml injected once daily with OptiSet ; sanofi aventis) was titrated by patients following instruction by the investigator according to a specific and widely adopted dosing algorithm for insulin glargine based on fasting concentration of blood glucose (adapted from A Trial comparing Lantus Algorithms to achieve Normal blood glucose Targets in patients with Uncontrolled blood Sugar [AT-LANTUS]). The starting dose of insulin glargine was numerically equivalent to the highest FPG value in mmol/l over the previous 7 days (e.g. if the FPG measure was 10 mmol/l, the initial glargine dose would be 10 IU). This facilitated ease of initiation in this patient-driven titration. During the first 8 weeks of treatment, the dose was titrated twice weekly by the participant, based on self-measured FPG, aiming for a target value of FPG ≤ 5.5 mmol/l. After 8 weeks of treatment, the frequency of monitoring and titration was at the investigator ’s discretion, but at minimum the insulin glargine dose was adjusted at the 12 and 18 week visits. The investigator reviewed the doses and these could be changed at his/her discretion. The injection could be administered at any time of the day, but the selected time of the day remained the same throughout the trial. | Starting dose: sliding scale; 10 IU/mL if FPG 10mmol/L; 9 IU/mL if FPG 9mmol/L  Increase: twice weekly for 8 weeks to attain FPG ≤ 5.5mmol/L, then at discretion of investigator |
| Stehouwer et al., 2003a;55 | NPH + SU (OD)  NPH (BID)  NPH+30/70 (BID) | Glycaemic targets were 4.0 to 7.4 mmol/L for fasting blood-glucose levels. The insulin dose was adjusted twice a week in steps of 2-4 IU by the diabetes nurse educator or diabetologist until glycaemic targets were reached. | Starting dose: NR  Increase: 2-4 IU to achieve 4.0–7.4 mmol/L |
| Strojek et al., 2009a;38 | Insulin - BIAsp+ M + S | Half of the subjects were treated with BIAsp 30 (through use of a FlexPen [Novo Nordisk A/S, Bagsværd, Denmark] device; 100 units/mL), starting with 12 units administered subcutaneously once daily 0–5 minutes before dinner. | Starting dose: BIAsp 30 12U/day; Glargine 12U/day  Increase: weekly for 10 weeks, then every 2 weeks to achieve FPG 5-6.1mmol/L |
|  | Insulin - Glargine+ M + S | The remaining subjects were treated with insulin glargine (OptiSet [Sanofi– Aventis, Paris, France] device; 100 units/mL), starting with 12 units administered subcutaneously once daily at bedtime. Both treatments were given in combination with metformin and glimepiride. The trial was designed as a treat-to-target trial; the insulin dose was titrated weekly (based on pre-breakfast plasma glucose values measured on three consecutive days) for the first 10 weeks, and every 2 weeks for the remainder of the treatment period, with the aim of reaching a fasting plasma glucose level of 5 to 6.1 mmol/L. The trial was open-labeled, as blinding of the two treatments would require more injections because of the difference in administration time |

***Abbreviations****: BIAsp = Biphasic insulin aspart; FPG = fasting plasma glucose; IU = international units; MET = metformin; NPH = neutral protamine Hagedorn; NR = Not reported; PPG = Postprandial plama glucose; SMBG = self-monitored blood glucose; SMBG = Self-monitored blood glucose; SR = Slow release; SU = sulfonylurea*

*aunless otherwise stated, data were derived from the CADTH report15*