**Table D5. Characteristics of studies evaluating effects of diabetes medications on long-term outcomes**

| **Author, year**  **Country**  **Registered Protocol** | **Study design** | **Enrollment period**  **Follow-up duration** | **Run-in period** | **Industry support** | **Number screened/ enrolled**  **Source population** | **Exclusion criteria** |
| --- | --- | --- | --- | --- | --- | --- |
| Agarwal, 2005 [189](#_ENREF_189)  US  Not extracted | RCT | Start year: 2001  End year: 2003  16 Wks | No run-in period | Yes | 102/54  Outpatient: subspecialty care setting | Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), BMI >40 kg/m2, class III or IV heart failure, NSAID use |
| Ahren, 2014[2](#_ENREF_2)  Country NR  NCT00838903 | RCT | 2009  2013  104 wks | Yes | Yes | NR/1049  NR | Adequate glycemic control while taking background metformin (>=1500mg or maximum tolerated dose) >=3 months before screening. Any liver disease. Any kidney disease. Abnormal thyroid-stimulating hormone concentration and not clinically euthyroid. Ongoing symptomatic biliary disease. History of pancreatitis. Recent clinically significant cardiovascular and/or cerebrovascular disease (<=2 months before screening). Treated gastroparesis. History of GI surgery thought to significantly affect upper GI function. History of most cancers not in remission for at least 3 years. Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2. Resting systolic blood pressure (SBP)>160mmHg and/or diastolic blood pressure(DBP)>100mmHg. Additional exclusion criteria: hemoglobinopathy that could affect HbA1c,lipase> ULN. "any liver disease": ALT or AST more than 2.5 times the ULN."any kidney disease": creatinine clearance <=60ml/min using the Cockcroft-Gault formula. withdrawal criteria: loss to follow-up, protocol violation, noncompliance, withdrawal of consent,  Also stated that did race subgroup analysis in methods but not reported in results. withdrawal criteria: an AE/lab result requiring withdrawal (QTc prolongation, elevation of liver function test results, severe potential allergic reactions, confirmed pancreatitis, severe or repeated hypoglycemia, calcitonin>100pg/ml). |
| Alba, 2013[3](#_ENREF_3)  Multi-continent  NCT00511108 | RCT | Neither year reported  12 | Yes | Yes | Not Extracted/  211    NR | Age <30 or >65 yrs, HbA1c >10% if drug naive, 9% if on antihyperglycaemic agent monotherapy or low-dose combination therapy or <7% if drug naive, 6.5% if on antihyperglycaemic agent monotherapy or low-dose combination therapy, Any liver disease, Any kidney disease, History of CVD, current use of sitagliptin, vildagliptin, exenatide, PPARr agonist within the prior 12 wks  fasting fingerstick glucose <7.2mmol/l or 14.4mmol/l at week -2 |
| Amador-Licona, 2000[186](#_ENREF_186)  Mexico  Not extracted | RCT | 12 wks (planned duration) | Not extracted | No | Not extracted | Age >65 years, any liver disease, history of CVD, other |
| Andersson, 2010[190](#_ENREF_190)  Denmark   No | Retrospective cohort | 1997  2006     844 days | Not applicable | Yes | 10,920 / 5,852    Administrative database, The Danish National Patient Register - The Danish Register of Medicinal Product Statistics and The National Causes of Death Register  Inpatient diagnosis/procedures, Inpatient pharmacy records, Outpatient pharmacy records, Death registry | Age <= 30 yrs, No diagnosis/hospitalization for CHF, not using MET, SU and/or Insulin, Use of other glucose lowering meds, patients with previous hospitalisations for HF during the period from 1978 until 1996 (diagnosis codes [ICD-10] I50, I42, J81, I11.0 and [ICD-8] 425, 4270, 4271) were excluded from the study, not alive 30 days after discharge for CHF, not receiving drug of interest 30 days after discharge for CHF, use of study drug within 90 days of hospitalization fro CHF |
| Arechavaleta, 2011[5](#_ENREF_5)  multi-national  NCT00701090 | RCT | Neither year reported  30 | Yes | Yes | Not Extracted/  1035    NR | Age <18 years, HbA1c >9% or <6.50%, Not on a stable dose of metformin (ΓëÑ1500 mg/day) as well as diet and exercise for past 12 wks, history of type 1 diabetes, used any Anti Hypoglycemic Agent besides metformin within 12 wks of the screening visit, renal function impairment prohibiting the use of metformin, fasting fingerstick glucose of <6.1 or >13.3 mmol/l at randomization, stable meds for HTN, thyroid dz, HRT, OCPs |
| Arjona Ferreira, 2013[6](#_ENREF_6)  Multinational  NCT00509262 | RCT | Neither year reported  58 | Yes | Yes | Not Extracted/  426      NR | Age <30 yrs, HbA1c >9.00% or <7.00%, Prior or current use of insulin, Any liver disease, did NOT have moderate to severe chronic renal insufficiency (eGFR>=50 ml/min/1.73m2 using the Modification of Diet in Renal Disease equation), on dialysis or likely to require dialysis for the duratoin of the study, acute renal disease, history of renal transplant, history of ketoacidosis, recent (within 3 months) cardiovascular event, thyroid stimulating hormone outside the reference range, triglycerides>600mg/dl, visit2, FPG>260mg/dl, unlikely to improve with diet/exercise, visite 3, FPG>250mg/dl consistently (i.e., measure=ment repeated and confirmed within 7 days); visite 4, FPG>240mg/dl consistently  visit5, finger-stick glucose > 240 or <120mg/dl |
| Aschner, 2010[7](#_ENREF_7)  Multi-continent  Not extracted | RCT | Neither year reported  24 wks | Run-in period but number of participants excluded NR | Yes | 2068/1050  NR | Age <18 or >78 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g., myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <6.5% or >9%, treatment naive, no Type 2 DM, FPG <120 or >250 mg/dL, triglycerides >600 mg/dL, CK > 2x upper limit normal |
| Aschner, 2012[8](#_ENREF_8)  Multi-continent  NCT00751114 | RCT | 2008  2011    24 | No | Yes | Not Extracted/  515    NR | Age <35 - >70 yrs, HbA1c >=11% or <7%, BMI <25 - >45, Any liver disease, Any kidney disease, FPG >14.4 mmol/L, tx'd w/ oral other than metformin in past 3 mo, received SU+MET In past year  prior use of GLP-1 or DPP-4, any disorder that the investigator felt woudl compromise the patient's safety, unwilling to self-monitor BG or keep diary |
| Bailey, 2005[9](#_ENREF_9)  UK, 14 European countries  Not extracted | RCT | 24 wks (planned duration) | Not extracted | Yes | Not extracted | Age <18 or >70 years, history of CVD, no Type 2 DM, other |
| Bailey, 2013[10](#_ENREF_10)  Multi-continent  NCT00528879 | RCT | 2007  2008    102 | Yes | Yes | Not Extracted/  546      NR | Age <18 and >77 yrs, HbA1c >10% or 7%, BMI >45 kg/m^2, Any liver disease, Any kidney disease, History of CVD, C-peptide concentration <0.34 nmol/L, not taking stable dose of metformin for at least 8 wks prior to enrollment, creatine kinase more than 3 times upper limit of normal, symptoms of poorly controlled diabetes, systolic blood pressure >=180 mmHG, diastolic blood pressure >=110 mmHG, clinically significant haematological, oncological, endocrine, psychiatric, or rheumatic disease, New York Heart Association class III or IV congestive heart failure |
| Bakris, 2003[11](#_ENREF_11)  likely US and  UK  Not extracted | RCT | 52 wks (planned duration) | Not extracted | Yes | Not extracted | NR |
| Bakris, 2006[12](#_ENREF_12)  US, Multi-continent, South America, Europe  Not extracted | RCT | Neither year reported  32 Wks | Yes | Yes | 560/514  NR | Age <40 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), BMI < 22 kg/m2, use of any TZD in the 3 months prior to screening, use of insulin for ≥6 months at any time prior to screening, anemia, severe angina, SBP >159 mm Hg (can't adjust the BP meds during the trial), DBP >99 mm Hg |
| Barnett, 2012[13](#_ENREF_13)  Multi-continent  NCT00740051 | RCT | 2008  2010    52 | Yes | Yes | Not Extracted/  227    NR | Age <18 or >80 yr, HbA1c: If treatment naive: L10.0%(9.0% for Canada); If receiving an oral antidiabetes drug: 9.0%, HbA1c: If treatment naive: <7.0%; If receiving an oral antidiabetes drug: 6.5%, BMI >40kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing, Not using adequate contraception, MI, stokre, or TIA in last 6 months, changed glucose-lowing treatment <10 wks prior to informed consent, hereditary galactose intolerance, treatment with GLP-1 analogue, TZD, or an antiobesity drug within the previous 3 months, or any investigational agent within the previous 2 months, hypersensitivity or allergy to the investigational drugs |
| Bergenstal, 2010[14](#_ENREF_14)  Multi-continent  NCT00637273 | RCT | 2008  2008    26 | No | Yes | Not Extracted/  514    Outpatient: primary care | Age <18years, HbA1c >11% or <7.10%, BMI <25 and greater than 45kg/m2, Prior or current use of insulin, Prior or current use of study drug, Pregnant, Nursing, Not using adequate contraception, not treated with a stable metformin regimen for at least 2 months before screening, no type 2 diabetes, fasting plasma glucose >/= 280 mg/dL (15.5 mmol/L), clinically significant laboratory test values, physical examination, or electrocardiogram results, clinically significant medical condition (e.g., hepatic disease, renal disease, cardiovascular disease, gastroparesis, malignant disease, macular edema, chronic infections), drug or alcohol abuse, donated blood within 60 days of screening or planning to donate blood during study, major surgery or blood transfusion within 2 months of screening, current treatment with alpha-glucosidase inhibitors, meglitinide, nateglinide, or pramlintide, systemic corticosteroids or intrapulmonary steroids, drugs interacting with the CYP2C8 enzyme system, or any investigational drug, known allergies or hypersensitivity to any component of study treatment, or previously experienced a clinically significant adverse event related to TZD or DPP-4 inhibitor use |
| Bolinder, 2012[17](#_ENREF_17)  Europe  NCT00855166 | RCT | 2009  2011    102 | Yes | Yes | Not Extracted/  182    NR | Women age <55 or >75 years. Men <30 or >75 years, HbA1c >8.50% or <6.50%, BMI <25kg/m^2 and body weight >120 kg, Prior or current use of insulin, Any liver disease, Any kidney disease, Pregnant, Nursing, Fasting plasma glucose >240 mg/dl (>13.2 mmol/liter), diabetes treatment includes other drugs besides metformin, metformin treatment <1500 mg/d, not on stable metformin treatment at least 12 wks before enrollment, perimenopausal women, body weight change >5% within 3 months, serum total bilirubin >34 ╬╝mol/L; hemoglobin (Hb) Γëñ105 g/L (10.5 g/dL) for men and Γëñ95 g/L (9.5 g/dL) for women; abnormal thyroid stimulating hormone level; 25-hydroxyvitamin D level <12 ng/mL (<30 nmol/L), history of osteoporotic fracture, bilateral hip replacement, spinal deformity or spinal surgery, metabolic bone disease or disease known to significantly influence bone metabolism or use of medication known to significantly influence bone metabolism within 6 months of enrolment, T-score less than ΓêÆ2.0 for bone mineral density at lumbar spine, femoral neck, or total hip at baseline DXA measurement, systolic blood pressure ΓëÑ180 mmHg and/or diastolic blood pressure ΓëÑ110 mmHg; cardiovascular event within 6 months of enrolment; congestive heart failure  significant respiratory, hematological, oncological, endocrine, immunological (including hypersensitivity to study medications)  alcohol and/or substance misuse disorders; a history of bariatric surgery; use of weight loss medication within 30 days of enrolment |
| Borges, 2011[18](#_ENREF_18)  Multi-continent  NCT00386100 | RCT | 2006  2008    80 | No | Yes | Not Extracted/  688    NR | Age <18 - >75 yrs, HbA1c >10.5% or <7.5%, BMI < =25  Prior use of any diabetes treatment  fasting glucose <7 mmol/l |
| Brownstein, 2010  [191](#_ENREF_191)  United States  Not extracted | Cohort | Start year: 2000  End year: 2006  7 years | NA | No | NA/34252  Inpatient/hospital, Outpatient: primary care, Outpatient: subspecialty care setting | Age ≤18 years, HbA1c ≤ 6.0%, no diagnosis of DM with ICD-9 code of 250.XX |
| Cefalu, 2013[20](#_ENREF_20)  Multi-continent  NCT00968812 | RCT | 2009  2011    52 | Yes | Yes | Not Extracted/  1452    NR | Age <18, >80 yrs, HbA1c >9.5 or <7%, Any kidney disease, Not on stable metformin therapy (ΓëÑ2000 mg per day or ΓëÑ1500 mg per day if unable to tolerate a higher dose) for at least 10 wks, prior TZD use in 16 wks before screening, h/o more than 1 severe hypoglycemic episode within 6 months, repeated measurements of fasting plasma glucose or fasting self-monitored blood glucose, or both, of 15┬╖0 mmol/L or more during the pretreatment phase; |
| Comaschi, 2007[25](#_ENREF_25)  Italy  Not extracted | RCT | Neither year reported  6 Months | Run-in period but number of participants excluded was NR | Yes | 398/250  NR | Age <35 years, HbA1c <7.5% or >11%, had not received SU or metformin as a monotherapy at a stable dose for at least 3 months, fasting C-peptide <0.33 nmol/L |
| Corrao, 2011[192](#_ENREF_192)  Italy | Retrospective cohort | 2001  2003     4.8-5.1 | Not applicable | No | Not Extracted/  70,437    Administrative database, health service databases of Lombardy, Inpatient diagnosis/procedure, Outpatient pharmacy records, database for regional National Health demographic and administrative data | Age <40, >90 yrs, Prior use of any diabetes treatment, Prior or current use of insulin, History of CVD, macrovascular disease hospitalization, resident of Lombardy region, < 1 year FU, started treatment on combination therapy of MET + SU, received fewer than 2 prescriptions for diabetes drugs during follow up |
| DeFronzo, 1995[27](#_ENREF_27)  US  Not extracted | RCT | 29 wks (planned duration) | Not extracted | No | Not extracted | Age <40 or >70 years, any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other |
| DeFronzo, 2012[31](#_ENREF_31)  Multi-continent  NCT00328627 | RCT | Neither year reported  26 | Yes | Yes | Not Extracted/  1554      NR | Age <18 or >80 yr, HbA1c >10% before and after run-in/stabilization period or <7.5% before and after run-in/stabilization period, BMI <23 or >45kg/m2, Any liver disease, Any kidney disease, Retinopathy, Not using adequate contraception, fasting C-peptide <0.26nmol/l, not on met monotherapy (stable met dose >1500mg/d for >=2 months), SBP/DBP>160/100mmHg, hemoglobin < 12g/dl for men, <10g/dl for women, class 3 or 4 CHF, cardiac surgery or acute MI within last 6 months, TSH > ULN, treated diabetic gastroparesis, no willingness or ability to perform self-monitoring of blood glucose or to provide written informed consent, FPG>16.7mmol/l after run-in/stabilization period, oral or systemically injected glucocorticoids or weight-loss drugs within 3 months of randomization |
| Del Prato, 2015[32](#_ENREF_32)  Multi-continent  NCT00660907 | RCT | Neither year reported  208 wks | No | Yes | NR/814  NR | NR |
| Del Prato, 2014[33](#_ENREF_33)  Mutli-continent  NCT00856284 | RCT | Neither year reported  104 wks | Yes | Yes | NR/2639  NR | Systolic blood pressure >150mm hg. Diastolic blood pressure >90 mm hg. History of cancer. Prior use of any other diabetes drug for the last 2 months. |
| Diamant, 2010[44](#_ENREF_44)  Multi-continent  NCT00641056 | RCT | 2008  2009    26 | Yes | Yes | Not Extracted/  321    NR | Age <18 years or older, HbA1c >11% or <7.1%, BMI <25kg/m2 and >45kg/m2. Unstable body weight within 3 months, more than three episodes of major hypoglycaemia within 6 months of screening, treatment within 4 wks of screening with systemic glucocorticoids, treatment for longer than 2 wks with insulin, thiazolidinediones, ╬▒-glucosidase inhibitors, meglitinides, exenatide twice-aday formulation, dipeptidyl peptidase-4 inhibitors, or pramlintide acetate within 3 months of screening, not treated with a stable dose of metformin of 1500 mg or more per day for at least 8 wks prior to screening |
| Ekstrom, 2012[193](#_ENREF_193)  Sweden | Retrospective cohort | 2004  2010    3.9 | Not applicable | No | Not Extracted/  51675    Outpatient: primary care and subspecialty care setting, National Diabetes Register, prescribed drug register, the patient register and the cause of death register, Inpatient diagnosis/procedures, Outpatient diagnosis/procedures, Inpatient pharmacy records, Outpatient pharmacy records, Death registry | Age >=85 or <45 yrs, not registered in Nat'l diabetes Register 1 yr prior to and 1 yr following first prescription of glucose-lowering tx, less then 3 prescriptions or less than 18 fills of mulidose dispensed drugs during 12 months of continuous use of glucose-lowering med |
| Erem, 2014[47](#_ENREF_47)  Turkey  Not Extracted | RCT | Neither year reported  52 | Yes | No | Not Extracted/  60    NR | Age <30 or >70 yr, HbA1c <8% when FPG<126mg/dl, <7% if FBG is 126 -139 mg/dl and HOMA-IR>3, not newly diagnosed, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Nursing, COPD, ketoacidosis or ketonuria  NYHAC Class 3/4 CHF, history of lactic acidosis, malignancy, thyroid disease or chronic inflammatory diseases or rheumatic disease, substance abuse, steroid treatment, active infection |
| Esposito, 2011[48](#_ENREF_48)  Italy  Not Extracted | RCT | Neither year reported  24 | No | Yes | Not Extracted/  110    investigators' practices | Age <30 and >75 years, HbA1c >10% or 7%, BMI </=25kg/m2 and unstable weight in last 6 months or evidence of participation in weight reduction programs, "Newly diagnosed", Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Pregnant, Nursing, any investigational drug in past 3 mo, use of agents affecting glycaemic control (such as systemic glucocorticoids and weight loss drugs), acute disease or infection, recent (within 3 months) cardiovascular events or surger, immunological disorders, any condition that might compromise adherence to the study, patients with positive antibodies to glutamate decarboxylase, participation in weight loss program or unstable wt in past 6 mo, patients with C-peptide levels less than 0.25 pmol/l (<0.76 ng/l) |
| Farcasiu, 2011[51](#_ENREF_51)  Multi-continent  Not Extracted | RCT | 2006  2009    16 | Yes | Yes | Not Extracted/  302    NR | Age <30 - >75 yrs, HbA1c >1.8 X ULN or <1.2 X ULN, BMI >40 kg/m2, Any liver disease, metformin <1500mg, on other oral dm med besides metformin, history of severe hypoglycemia within 6 months, CHF, renal transplantation, irregular sleep-wake cycle |
| Ferrannini, 2013[194](#_ENREF_194)  Multi-continent  NCT00789035 | RCT | Neither year reported  12 | Yes | Yes | Not Extracted/  408    NR | Age, <18 or >79 years, HbA1c> 9% if on antidiabetic drug, >10 if tx naïve or <6.5 if on antidiabetic drug, <7 if treatment naïve, BMI >40 kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing, Not using adequate contraception, not treatment naive or on stable dose of more than one antidiabetic drug (except GLP1, insulin, TZDs) in past 10 wks, myocardial infarction, stroke or transient ischaemic attack Γëñ6 months prior, unstable or acute congestive heart failure, acute or chronic acidosis; disease of CNS, psychiatric d/o or clinically relevant neuro d/o, chronic or clinically relevant acute infection, current or chornic urogenital tract inf, dehydration, hereditary galactose intolerance, tx with antiobesity drugs, systemic steroids, alchol abuse, tx with investigational drug <=2 m prior, neurologic/psychiatric issues that might interfere with participation |
| Fonseca, 2000[55](#_ENREF_55)  US  Not extracted | RCT | 26 wks (planned duration) | Not extracted | No | Not extracted | Age <40 or >80 years, any liver disease, any kidney disease, history of CVD, treatment experienced, neuropathy, no Type 2 DM, other |
| Fonseca, 2012[56](#_ENREF_56)  US and Latin America  NCT00960076 | RCT | 2009  2010    18 | Yes | Yes | Not Extracted/  282      NR | Adults, HbA1c >11% or <7.5%, BMI >45 kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Not using adequate contraception, weight loss >10% in 3 mo before screening, unable to finish lead-in period (stabilitized on met 1500 mg/d), history of ketoacidosis, alcohol or drug abuse or unstable psychiatric disorder, hemoglobinopathy, blood/plasma donation in past 3 mo, anemia or significant lab/ecg abnormalities, investigational drugs or partiipation in a clinical trial in last mo, treatment with any other diabetes med (besides met) in past 8 wk, tx with potent CYP 450 3A drug or contradind to / h/o tx w/ saxa |
| Forst, 2010[57](#_ENREF_57)  Europe  NCT00309608 | RCT | Neither year reported  12 | Yes | Yes | Not Extracted/  333      NR | Age <21 or >75 yr, HbA1c>9.0% for patients previously treated with met and one other oral anti-diabetic drug; 10.0% for patients perviously treated with met alone; 10% for all patients after run-in phase or HbA1c >7.0% for patients previously treated with met and one other oral anti-diabetic drug; 7.5% for patients previously treated with met alone; 7.5% for all patients after run-in phase, BMI <25 or >40 kg/m2, Prior or current use of insulin, previously treated with therapy other than 1. met alone; 2. met and one other oral hypoglycaemic agent other than rosi or pio., anti-diabetic therapy changed within 10 wks prior to screening, FPG concentrations > 13.3mmol/l (measured on 2 separate days), treated with rosi or pio within 6 months prior to screening, one or more of a list of specified clinical lab abnormalities (not specified in article), clinically relevant stroke, MI, TIA within 6 months |
| Gallwitz, 2012[61](#_ENREF_61)  Multi-continent  NCT00622284 | RCT | 2008  2010    104 | Yes | Yes | Not Extracted/  1552    Outpatient: primary care, Outpatient: subspecialty care setting | Age <18, >80 years, BMI >40 kg/m^2, Prior or current use of insulin, Any liver disease, History of CVD, Not on stable metformin dose >= 1500mg/day (alone or with another antidiabetic drug), HbA1c <6.5% or >10% if participant on metformin alone prior to enrollment, HbA1c <6% or >9% if participant on metformin and another anti-diabetic medication prior to enrollment, myocardial infarction, stroke, transient ischemic attack 6 months prior to screening, treatment with rosiglitazone, pioglitazone, GLP-1 analogue or agonist 3 months prior to screening, On anti-obesity drug in 3 months prior to screening |
| Gallwitz, 2012[62](#_ENREF_62)  Multi-continent  NCT00359762, EudraCT 2005-005448-21 | RCT | 2006  2011    48 | No | Yes | Not Extracted/  1029    NR | Age <18 or >85 yrs, HbA1c >9% or <6.5%, BMI <25 or >=40  prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Retinopathy, adequate response to metformin based on HbA1c criteria, contraindication to glimepiride, active/untreated cancer or cancer in remission <5 yrs, hemoglobinopathy or significant anemia, severe GI disease, on drugs affecting motility, glucocorticoids, weight loss drugs in last 3 mo, treatment for more than 2 wks in past 3 mo with insulin, TZDs, alpha glucosidase inhib, SUs, meglitinides |
| Garber, 2003[64](#_ENREF_64)  US  Not extracted | RCT | 16 wks (planned duration) | Not extracted | Yes | Not extracted | Age < 20 or >79 years, any liver disease, any kidney disease, treatment experienced, HbA1c >7% or <12%, no Type 2 DM, other |
| Garber, 2011[67](#_ENREF_67)  US Mexico  NCTC00294723 | RCT | 2006  2008    104 | No | Yes | Not Extracted/  746    NR | Age <18 or >80, HbA1c >11% if on diet/exercise or >10% if on monotherapy or <7%, BMI >45 kg/m2, Prior or current use of insulin, Any liver disease, treatment with systemic corticosteroids, hypoglycemia unawareness or recurrent severe hypoglycemia |
| Genovese, 2013[68](#_ENREF_68)  Italy  NCT00772174 | RCT | Neither year reported  24 | Yes | Yes | Not Extracted/  213    NR | Age <35 or >75 yr, Any liver disease, Any kidney disease, Pregnant, Nursing, Not using adequate contraception, not taking metformin (2000-30000mg/day) for at least 3 months, HDL-C levels >=40mg/dl in males and >=50mg/dl in females irrespective of statin tx, anemia of any etiology (Hb<10.5g/dl) or any other hematological disease; diagnosis or suspicion of neoplastic disease, no central obesity (excluded if waist circumference <94 cm for men and <80 cm for women), using oral anti-diabetic drugs other than met or insulin in the 3 months preceding study entry, treatment with fibrates or rifampicin, acute or chronic pancreatitis or familial polyposis, history of chronic alcohol or drug/substance abuse, satisfactory drug compliance (compliance ranging between 80-120%) during run-in, medical history of MI, transient ischemic attacks or stroke in the past 6 months, designation of class 1-4 heart failure according to NYHA criteria |
| Genovese, 2013[69](#_ENREF_69)  NR  ACTRN12608000534381 | RCT | Neither year reported  16 | Yes | Yes | Not Extracted/  58    Outpatient: subspecialty care setting | Age <35 or >75 yr, HbA1c >9.00%, Prior use of any diabetes treatment, Prior or current use of insulin, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Nursing, lack of cooperative attitude and ability to be treained to use the investigational drugs correctly or to attain the study procedures, participation in another trial in the 3 months preceding study entry, any disease with malabsorption, or familial polyposis or pancreatitis, congestive heart failure (NYHA class 1-4), anemia of any etiology (hemoglobin level < 10.5g/dl) or any other clinically relevant hematologic disease, diagnosis or suspicion of any neoplastic disease, history of chronic alcohol or drug/substance abuse, or presence of other conditions potentially able to affect study stubjects compliance, concomitant therapy with statins, antioxidant drugs (e.g. vitamins, Q10 coenzyme), beta-blockers, nonsteroidal anti-inflammatory drugs, aspirin, corticosteroids,, known allergy, sensitivity, ,or intolerance to study drugs and/or study drugs' formulation ingredients ( pioglitazone, met marked above) |
| Goke, 2010[70](#_ENREF_70)  Multi-continent  NCT00575588 | RCT | 2007  2010    104 | Yes | Yes | Not Extracted/  858    NR | Age <18 years, HbA1c >10% or <6.50%, Prior or current use of insulin, Prior or current use of study drug, Any liver disease, Any kidney disease, no type 2 diabetes, not on stable metformin monotherapy >=1500mg/day for at least 8 wks prior to enrollment, type 1 diabetes, history of diabetic ketoacidosis or hyperosmolar non-ketotic coma, donation of blood, plasma or platelets within the 3 months prior to enrolment, history of haemoglobinopathies; significant alcohol or drug abuse within the year prior to enrolment, treatment with human immunodeficiency virus Γüä antiviral drugs or cytochrome P450 3A4 (CYP450 3A4) inducers, treatment with a thiazolidinedione within 12 wks prior to enrollment, congestive heart failure, significant cardiovascular history within the past 6 months |
| Goldstein, 2003[71](#_ENREF_71)  US  Not extracted | RCT | 18 wks (planned duration) | Not extracted | Yes | Not extracted | Any liver disease, any kidney disease, history of CVD, HbA1c <7.5% or >12.0%, other |
| Gomez-Perez, 2002[73](#_ENREF_73)  Mexico  Not extracted | RCT | 26 wks (planned duration) | Not extracted | Yes | Not extracted | Age <40 or >80 years, any liver disease, any kidney disease, history of CVD, treatment experienced, no Type 2 DM, other |
| Haak, 2012[77](#_ENREF_77)  Multi-continent  NCT00798161 | RCT | 2008  2010    24 | Yes | Yes | Not Extracted/  791    NR | Age <18 or >80 years, HbA1c >10.5% if on OAD or >=11% if treatment naïve or <7.0% if on OAD or <7.5% if treatment naïve, BMI > 40 kg/m2, Prior or current use of insulin, Any kidney disease, History of CVD, Pregnant, Nursing, neither treatment naive nor had been treated with OAD monotherapy, prior treatment with rosiglitazone, pioglitazone, GLP-1 analogs, or anti-obesity drugs in the previous 3 months, receiving treatment with systemic steroids or had a change in dosage of thyroid hormones in the previous 6 wks, had undergone gastric bypass, Had known hypersensitivity or allergy to linagliptin or its excipients, metformin or placebo, had a history of alcohol or drug abuse in the previous 3 months, had acute or chronic metabolic acidosis, had hereditary galactose intolerance, had experienced a myocardial infarction, stroke, or transient ischemic attack in the previous 6 months |
| Haak, 2013[78](#_ENREF_78)  Multi-continent  NCT00915772 | RCT | 2009  2011    52 | Yes | Yes | Not Extracted/  567    NR | Pregnant, Nursing, Not using adequate contraception, completed the previous 6-month trial, were not on rescue medication, alcohol abuse within the past 3 months or drug abuse that would have interfered with trial participation |
| Hallsten, 2002[79](#_ENREF_79)  Finland  Not extracted | RCT | 26 wks (planned duration) | Not extracted | Yes | Not extracted | Any liver disease, any kidney disease, history of CVD, no Type 2 DM, other |
| Hamann, 2008[80](#_ENREF_80)  Multinational Europe, Mexico  Not extracted | RCT | Neither year reported  52 Wks | Yes | NR | 818/596  NR | Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <7% or >10%, BMI <25 kg/m2, used any ODM other than metformin in the prior 12 wks, or insulin at any time other than during pregnancy or for emergency treatment, history of metabolic acidosis, edema requiring pharmacological treatment (either ongoing or within the prior 12 months), anemia (hemoglobin < 11.0 g/dl for men and < 10.0 g/dl for women), C-peptide <0.5nmol/L, SBP >170 mmHg, DBP >100 mmHg |
| Hanefeld, 2004[81](#_ENREF_81)  Canada, UK, Hungary, Finland, Slovak Republic, Belgium, Estonia, Lithuania, Denmark, Italy, Greece, Sweden, and Netherlands  Not extracted | RCT | NR | Not extracted | Yes | Not extracted | Age <35 or >75 years, history of CVD, HbA1c <7.5% or >11%, no Type 2 DM, other |
| Hanefeld, 2007[82](#_ENREF_82)  Multinational Europe  Not extracted | RCT | Neither year reported  52 Wks | Run-in period but number of participants excluded was NR | Yes | NR/598  NR | Age <40 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), BMI <22 kg/m2 or >38 kg/m2, pregnant, patient on insulin therapy, patient with diabetic complications requiring treatment, hematologic impairment, FPG: <7 mmol/l or >15 mmol/l, C-peptide <0.27 nmol/l |
| Haring, 2014[83](#_ENREF_83)  Multi-continent  NCT01159600 | RCT | 2010  2012    24 | Yes | Yes | Not Extracted/  638    NR | Age <18 yrs, HbA1c >10% or <7%, BMI >45 kg/m2, Any liver disease, Contraindication or history of intolerance to metformin, not on stable MFM IR unchanged >=12 wks prior to randomization, uncontrolled hyperglycemia (glu> 13.3mmol/L) after overnight fast confirmed by 2nd measurement, ACS, stroke, TIA within 3 mo, bariatric surgery or other GI surgeries that induce chronic malabsorption, cancer (except basal cell ca) or tx for CA within last 5 yrs, blood dyscrasias, hemolysis, unstable erythrocytes, tx with antiobesity drugs 3m prior, use of tx leading to unstable body weight, tx with systemic steroids, change in dose of thyroid hormones within 6w, alcohol or drug abuse within 3m, investigational drug in another trial with 30d, eGFR<30 |
| Henry, 2012[84](#_ENREF_84)  Multi-continent  NCT00643851 | RCT | 2008  2009    24 | Yes | Yes | Not Extracted/  603  Inpatient/hospital  Outpatient: primary care, Outpatient: subspecialty care setting | Age <18 or >77, HbA1c >12 or <7.5, BMI >45, Any liver disease, Any kidney disease, creatine kinase > 3 times ULN;, h/o diabetes insipidus, symptoms of poorly controlled diabetes (including marked polyuria and polydipsia with > 10% weight loss during 3 months before enrollment), New York Heart Association Class III or IV congestive heart failure, systolic blood pressure ΓÇí 180 or diastolic blood pressure ΓÇí 110 mmHg., a cardiovascular event within 6 months, other significant renal, hepatic, hematologic, oncologic, endocrine, psychiatric, or rheumatic disease |
| Henry, 2012[84](#_ENREF_84)  Multi-continent  NCT00859898 | RCT | 2009  2010    24 | Yes | Yes | Not Extracted/  641  Inpatient/hospital  Outpatient: primary care, Outpatient: subspecialty care setting | Age <18 or >77 yrs, HbA1c >12% or <7.5%, BMI >45 kg/m2, Any liver disease, Any kidney disease, History of CVD, creatine kinase > 3 times ULN;, h/o diabetes insipidus, symptoms of poorly controlled diabetes (including marked polyuria and polydipsia with > 10% weight loss during 3 months before enrollment), New York Heart Association Class III or IV congestive heart failure, systolic blood pressure ΓÇí 180 or diastolic blood pressure ΓÇí 110 mmHg., a cardiovascular event within 6 months |
| Hermann, 1994[86](#_ENREF_86)  Sweden  Not extracted | RCT | 6 months (planned duration) | Not extracted | Yes | Not extracted | No Type 2 DM, other |
| Hermans, 2012[87](#_ENREF_87)  Europe  NCT01006590 | RCT | Neither year reported  24 | Yes | Yes | Not Extracted/  286    NR | Age <18 yrs, HbA1c >10, HbA1c <7, Prior or current use of insulin, Contraindication or history of intolerance to metformin, Pregnant, Nursing, type 1 DM, history of DKA or HONC, prior use of injectable GLP-1 analogues within 3mo of study, treatment with systemic glu- cocorticoids other than replacement therapy (inhaled, local injected and topical use of glucocorticoids were allowed), treatment with cytochrome P450 3A4 inducers, not on stable tx with metfomrin 1500-1700 mg/d |
| Home, 2009[89](#_ENREF_89)  Multinational Europe  Not extracted | RCT | Start year: 2001  End year: 2003  7.5 Years | Run-in period but number of participants excluded was NR | Yes | 7428/4458  Outpatient: primary care | Age <40 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), contraindication or history of intolerance to metformin, HbA1c < 7% or >9%, BMI <25 kg/m2, pregnant, nursing, not using adequate contraception, recent CAD event, heart failure |
| Hong, 2013[195](#_ENREF_195)  China  NCT00513630 | RCT | 2004  2007    36 | Yes | Yes | Not Extracted/  304  clinical centers | Age >80yr, Prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing, not diagnosed as CAD (either having a history of acute myocardial infarction diagnosed by a representative set of electrocardiograms, cardiac enzyme values, and typical symptoms or by angiographically identified stenosis of >50% of lumen diameter in at le, severe dysfunction of the heart (NYHA class > phase 3), other severe organic heart diseases, including but not limited to congenital heart disease, rheumatic heart disease, hypertrophic or dilated cardiomyopathy; psychiatric disease, severe infection, severe anemia, Neutropenia, allergic to study drugs, fasting plasma glucose>=15 mmol/l, recent drug or alcohol abuse |
| Horsdal, 2011[196](#_ENREF_196)  Denmark  Not Extracted | Case-control | 1996  2004    6 | No | Yes | Not Extracted/  101313    Administrative database, Danish National Patient Registry, Registry of Medicinal Product Statistics, National Health Insurance Service Registry, Inpatient diagnosis/ procedures, Outpatient diagnosis/  procedures, Inpatient pharmacy records, Outpatient pharmacy records, Death registry | Age <30, controls matched up to 10:1 to the cases based on age and gender |
| Hsiao, 2009  [197](#_ENREF_197)  Taiwan  Not extracted | Cohort | Start year: 2000  End year: 2005  6 years | NA | NR | NA/20450  Inpatient/hospital, Outpatient: primary care, Outpatient: subspecialty care setting | Type 1 DM, prescribed insulin only during study period, new diagnosis of Type 2 DM during the year before index date, switch between rosiglitazone and pioglitazone or combined use of both drugs during study period, prescribed ODM less than three times during study period |
| Hung, 2012[198](#_ENREF_198)  US  Not extracted | Retrospective cohort | 2001  2008    0.7-0.9 | Not applicable | No | Not Extracted/  93577  Inpatient/hospital  Outpatient: primary care, Outpatient: subspecialty care setting, VA health system, VA health system, Inpatient diagnosis/procedures, Outpatient diagnosis/procedures, Inpatient pharmacy records, Outpatient pharmacy records, Death registry | Age <18, Any liver disease, Any kidney disease, less than 365 days of active use of VHA pharmacy services with diabetes drug filled, unknown birthdate, gender, race, less than 365 days of baseline data, missing eGFR, missing creatinine, CHF, HIV/AIDS, cancer except non-melanoma skin ca, transplant, cocaine use, baseline Cr>1.5, eGFR<60, combo therapy |
| Hung, 2013[199](#_ENREF_199)  Taiwan  Not extracted | Retrospective cohort | 1998  2007    3.1-3.8 | Not applicable | No | Not Extracted/  1159    Administrative database, Taiwan National Health Insurance Research Database, Inpatient diagnosis/procedures, Outpatient diagnosis/procedures | Age <30 yrs, Prior use of any diabetes treatment, Prior or current use of insulin, Any liver disease, Any kidney disease, cancer, followup <0.5 yr, Use of concomitant DM2 medications |
| Hung, 2013[200](#_ENREF_200)  US  Not extracted | Retrospective cohort | 1999  2008    About 1 year | Not applicable | No | Not Extracted/  13238  Inpatient/hospital, Outpatient: primary care, Outpatient: subspecialty care setting, VA Mid-South VISN 9 Data Warehouse, VA Mid-South VISN 9 Data Warehouse, Inpatient diagnosis/procedures, Outpatient diagnosis/procedures, Inpatient pharmacy records, Outpatient pharmacy records, Death registry | Age <18, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, receive regular care in Veterans Health, Administration healthcare system, HIV/AIDS, cancer, end stage respiratory disease, organ transplant during baseline yr, CHF, ESRD, end stage liver disease |
| Jadzinsky, 2009 [91](#_ENREF_91)  Multi-continent  Not extracted | RCT | Start year: 2006  End year: 2007  24 wks | Fewer than 10% participants excluded | Yes | 2936/1394  Outpatient: primary care, Outpatint: subspecialty care | Age <18 or >77 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g. "failed initial treatment"), HbA1c < 8% or >12%, BMI >40 kg/m2, prior treatment, diabetic ketoacidosis or nonketotic hyperosmolar coma, CVD events 6 months prior, LVEF <40%, psychiatric history, alcohol or drug abuse, abnormal metabolic or hematologic test |
| Jain, 2006[92](#_ENREF_92)  US, Puerto Rico  Not extracted | RCT | Neither year reported  56 Wks | Run-in period but number of participants excluded was NR | NR | NR/502  NR | Age <18 or >80 years, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), poorly controlled on prior treatments (e.g. failed initial treatment), HbA1c< 7.5% or >11.5%, pregnant, nursing, duration of DM > than 2 years, intolerance to Rosi, Pio or Troglitazone, drug or alcohol abuse, previous treatment with meglitinide analog, alpha glucosidase inhibitor, metformin, insulin, SU for 3 months or more, use of hydrochlorothiazide, joint injections, niacin greater than 250 mg/day, oral antidiabetic drugs, concurrent participation in another investigational study, serum creatinine level > 1.5mg/dl of men, 1.4 mg/dl for women, 1 + proteinuria , anemia (< 10g/dl women, < 12g/dl men), BMI ≤20kg/m2 or >45kg/m2, hypertension, chronic pulmonary disease, history of cancer not in remission for at least 5 years |
| Johnson, 2005[201](#_ENREF_201)  Canada  Not extracted | Cohort | Median follow-up periods for each group ranged from 4.6 to 5.6 yeas | Not extracted | No | Not extracted | Age < 30 years, no Type 2 DM, other |
| Jones, 2003[202](#_ENREF_202)  US  Not extracted | RCT | Neither year reported  6 Months | Run-in period but number of participants excluded was NR | NR | NR | Age <40 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), neuropathy, CHF, history chronic insulin, FPG <140 or >300 mg/dL, prior rosiglitazone study, use on any investigational drug within 30 days |
| Kadowaki, 2013[96](#_ENREF_96)  Japan  NCT00363948 | RCT | 2006  2008    12 | Yes | Yes | Not Extracted/  149    NR | Age <20 or >=75yr, HbA1c >9.4% for patients receiving an OHA other than met at screening, 10.5% for patients with met only at screening, 10.5% for all patients completing the run-in period, HbA1c <6.4% for patients receiving an OHA other than met at screening, 6.9% for patients with met only at screening, 6.9% for all patients completing the run-in period, Any kidney disease, high serum creatinine levels (male > 100.8umol/l, female>78.7umol/l), FPG>15.0mmol/l at the beginning of the placebo run-in period, not on stable diet and exercise therapy for at least 8 wks, not on met monotherapy for at least 12 wks |
| Kahler, 2007[203](#_ENREF_203)  US  Not extracted | Cohort | Start year: 1998  End year: 2001  3 Years | NA | No | > 1500000/39721  VHA Medical facilities | Age <18 years, non-respondents to 1999 LHSVE survey, medical facilities that do not have assays certified by the National Glycohemoglobin Standardization Program, less than 15 month window period after 1 year exposure to drug, alive as of 31 December 2000, fixed one year window of drug exposure |
| Kahn, 2006[97](#_ENREF_97)  Multi-continent  Not extracted | RCT | Start year: 2000  End year: 2006  6 Years | No run-in period | Yes | 6676/4360  NR | Age <30 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), uncontrolled hypertension, FPG <126 or > 180 mg/dL, history of lactic acidosis |
| Kaku, 2011[99](#_ENREF_99)  Japan  NCT00393718 | RCT | 2006      52 | Yes | Yes | Not Extracted/  411      NR | Age <20 yrs, HbA1c >10.4%, HbA1c <7.4%, not able to self monitor blood glucoses |
| Kikuchi, 2012[101](#_ENREF_101)  Japan  NCT00297063 | RCT | 2005  2007    28 | No | Yes | Not Extracted/  373    NR | Age <20 - >75, HbA1c <7.4, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Retinopathy, hyperlipidemia w/o statin tx, SBP >=160 or DBP >=100, FPG >=270, BNP >= 60, hemoglobinopathy, edema, unstable or serious angina, MI in past yr, h/o or current heart failure, serious arrhythmia, valvular dis, cardiomyopathy, serious neuropathy requiring tx |
| Kvapil, 2006[105](#_ENREF_105)  Multinational Europe  Not extracted | RCT | Neither year reported  16 Wks | No run-in period | NR | NR/341  NR | Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), retinopathy, recurrent severe hypoglycemia, anemia, change in dose of meds known to interfere with glucose metabolism, inclusion criteria includes not adequately controlled on metformin |
| Lavalle-Gonzalez, 2013[106](#_ENREF_106)  Multi-continent  NCT01106677 | RCT | Neither year reported  56 | Yes | Yes | Not Extracted/  1284  NR | Age <18 or >80, HbA1c >10.5, HbA1c <7, Prior or current use of insulin, Any kidney disease, not on MFM (ΓëÑ2,000 mg/day [or ΓëÑ1,500 mg/day if unable to tolerate higher dose], repeated FPG and/or fasting self-monitored blood glucose (SMBG), ΓëÑ15.0 mmol/l during the pretreatment phase, Type 1 diabetes, treatment with a peroxisome proliferator-activated receptor ╬│ agonist, insulin, another SGLT2 inhibitor or any other AHA (except metformin as monotherapy or in combination with a sulfonylurea) in the 12 wks before screening; cardiovascular disease (including myocardial infarction, unstable angina, revascularisation procedure or cerebrovascular accident) in the 3 months before screening  uncontrolled HTN |
| Lawrence, 2004[107](#_ENREF_107)  UK  Not extracted | RCT | 12 titration, 12 week maintenance (planned duration) | Not extracted | Yes | Not extracted | Age <45 or >80 years, any liver disease, any kidney disease, history of CVD, HbA1c for diet treated diabetes: <7% or >10% for low-dose ODM: >7.5%, no Type 2 DM, other |
| List, 2009[109](#_ENREF_109)  US Canada Mexico, Puerto Rico  NCT00263276 | RCT | 2005  2006    12 | Yes | Yes | Not Extracted/  389  "98 clinical centers" | Age <18, >79, HbA1c >10, HbA1c >7, BMI >40, Prior use of any diabetes treatment, Any kidney disease, C peptide>1.0 ng/ml |
| Malone, 2003[112](#_ENREF_112)  14 countries not specified  Not extracted | randomized, open-label, 2 arm parallel prospective study | Neither year reported  16 Wks | Fewer than 10% of participants were excluded during run-in | Yes | NR/597  subgroup completing test meals | Age <30 or >75 years, HbA1c <125% of upper limit of normal by local lab within 4 wks prior to entry, BMI >40 kg/m2, not Type 2 DM, not use of single oral agent (metformin or SU) for 3 months prior to study at maximum clinically effective dose for previous 30 days |
| Malone, 2004[204](#_ENREF_204)  US  Not extracted | RCT | Neither year reported  32 Wks | Yes | Yes | 145/111  NR | Not extracted Age <30 or >80 years, HbA1c <1.3 or >2.0 times normal, BMI >40 kg/m2, HbA1c value that is less than or greater than 1.3 and 2.0 times the ULN within 30 days before the study, while using 1 or more ODM without insulin for 30 or more days before study start |
| Malone, 2005 [205](#_ENREF_205)  Multinational Europe  Not extracted | RCT | Neither year reported  32 wks | Yes | Yes | 119/97  NR | Age <30 or >75 years, HbA1c >2.0 times the upper limit of normal, HbA1c <1.3 times the upper limit of normal, used glitazones within 30 days prior to the study, used NPH QD or BID 30-days prior to entry, expected to benefit from prandial control |
| Masica, 2013[206](#_ENREF_206)  US  Not extracted | Retrospective cohort | 1998  2009    2.8 - 3.2 | Not applicable | No | Not Extracted/  1921  electronic health record encounters, Baylor Health Care System (BHCS; Dallas, TX) and Christiana Care Health System (CCHS; Newark, DE), Outpatient diagnosis/procedures | Age <21, Prior use of any diabetes treatment, Prior or current use of insulin, ΓÇóPatients with a T2D-related bill with a date of serviceΓëÑ90 days before EHR problem onset date were designated as pre-existing and excluded from the cohort, <90 days of exposure to metformin, sulfonylureas, or thiazolidinediones (or any combination of those three agents) over the study period |
| Mogensen, 2014[207](#_ENREF_207)  Denmark  Not extracted | Retrospective cohort | 2007  2011    2.1 | Not applicable | No | Not Extracted/  40028  National databases of inpatient, outpatient, medication and mortality information  Administrative database, Danish National Patient Registry, Danish Registry of Medicinal Product Statistics, Danish National Population Registry, National Causes of Death Register, Inpatient diagnosis/procedures, Inpatient pharmacy records, Outpatient pharmacy records, Death registry | Age <18, Users of glucose lowering treatment before 1 January 1997 with unknown treatment duration, Prior myocardial infarction (ICD-10: I21-I22, ICD-8: 410), Prior stroke (ICD-10: I61-I64, ICD-8: 431ΓÇô434) |
| Nakamura, 2000[115](#_ENREF_115)  Japan  Not extracted | RCT | 3 months (planned duration) | Not extracted | No | Not extracted | Any liver disease, history of CVD, treatment experienced, HbA1c <6.5%, no Type 2 DM, other |
| Nakamura, 2004[116](#_ENREF_116)  Japan  Not extracted | RCT | Neither year reported  12 Months | No run-in period | NR | NR/45  Inpatient/hospital | Any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c > 6.5%, BP <140/90 mm Hg, controlled on diet alone, no history ketoacidosis, c peptide <0.33mmol/L, creatinine <1.5, no BP meds, malignancy, no microalbuminuria, collagen vascular disease, non-diabetic renal disease |
| Nakamura, 2006  [185](#_ENREF_185)  Japan  Not extracted | RCT | Neither year reported  12 months | No run-in period | NR | NR/68  NR | HbA1c >6.5%, history of ketoacidosis, treatment other than by diet alone, fasting C-peptide level < 0.33 mmol/L, hematuria, non-diabetic renal disease, microalbuminura defined as a median urinary albumin excretion of 20 to 200 ug/min |
| Nauck, 2007[118](#_ENREF_118)  US, Multinational Europe, Multi-continent  Not extracted | RCT | Neither year reported  52 Wks | Yes | Yes | 2141/1172  NR | Age <18 or >78 years, any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), FPG >15 mmol/L, insulin use within 8 wks of screening, history of Type 1 DM, other treatments for hypoglycemia |
| Nauck, 2009[119](#_ENREF_119)  Multi-continent  NCT00286442 | RCT | Neither year reported  26 | Yes | Yes | Not Extracted/  527      NR | Age<18 or >80 yr, HbA1c >10.00%, HbA1c <7.00%, BMI <23 or >45 kg/m2, Any kidney disease, used antidiabetic agents other than met within the 3 months prior to screening, or not on ongoing (>=3 months) stable metformin monotherapy regimen (>=1500mg per day for at least 8 wks), C-PEPTIDE CONCENTRATION <0.26 nmol/l, use of steroids or weight loss meds in last 3 months  after run-in/stabilisation period FPG>=275mg/dl, during run-in/stabilisation peiod <75% compliance with the single-blind placebo regimen, h/o cardiac surgery or cardiovascular disease in last 6 months, history of cancer (other than squamous cell or basal cell carcinoma of the skin that had not been in full remission for at least 5 years), laser treatment for proliferative diabetic retinopathy within 6 months, history of treated diabetic gastroparesis, New York Heart Association Class 3 or 4 heart failure |
| Nauck, 2011[120](#_ENREF_120)  Multi-continent  NCT00660907 | RCT | 2008      52 | Yes | Yes | Not Extracted/  814    NR | Age < 18 years, HbA1c >10%, HbA1c <6.50%, BMI > 45.0 kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, Pregnant, Nursing, not taking metformin +/- another oral antidiabetes drug, FPG > 15 mmol/L; C-peptide < 0.33 nmol/L, history of diabetic ketoacidosis or hyperosmolar non-ketotic coma; polyuria/polydipsia with > 10% weight loss, calculated creatinine clearance < 60 mL/min; urine albumin:creatinine ratio > 203.4 mg/mmol, AST and/or ALT and/or creatine kinase >= 3x ULN; serum total bilirubin > 34 micromol/L, Hb <= 11 g/dL for men and <= 10 g/dL for women; abnormal thyroid stimulating hormone level, SBP >= 180 mmHg and/or DBP >= 110 mmHg, cardiovascular event in last 6 months, CHF, significant respiratory, hematological, oncological, endocrine, immunological, and alcohol and/or substance misuse disorders, use of systemic corticosteroids equivalent to >10 mg of oral prednisolone within 30 days of enrolment, history of bariatric surgery; use of weight loss medication within 30 days or enrolment |
| Nauck, 2014[121](#_ENREF_121)  NR  NCT00734474 | RCT | Neither year reported  52 | Yes | Yes | Not Extracted/  1098    NR | Age<18 or >75 years, HbA1c >= 9.5%, HbA1c <8% if on diet and exercise alone or <7% if on OAD monotherapy or combination therapy, BMI <25 or >40 kg/m2, Duration of diabetes <6 months, Prior or current use of insulin, Prior or current use of study drug, unstable weight during the 3-months prior to study entry |
| Pantalone, 2009 [208](#_ENREF_208)  United States  Not extracted | Cohort | Start year: 1998  End year: 2006  8 years | NA | Yes | NA/20450  Inpatient/hospital, Outpatient: primary care, Outpatient: subspecialty care setting | Age <18 years, history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), on dialysis, on combination ODM, on insulin or other injectible antidiabetics, history of CHF |
| Pantalone, 2012[209](#_ENREF_209)  US  Not extracted | Retrospective cohort | 1998  2006     2.2 | Not applicable | Yes | Not Extracted/  23915  Inpatient/hospital  Outpatient: primary care, Outpatient: subspecialty care setting, Cleveland Clinic EMR including main campus or family health centres, Cleveland Clinic EMR including main campus or family health centres, Inpatient diagnosis/procedure, Outpatient diagnosis/procedures, Inpatient pharmacy records, Outpatient pharmacy records, Death registry | Age <18, Prior or current use of insulin, Prior or current use of study drug, Any kidney disease, does not have at least two encounters for diabetes after visiting the Cleveland Clinic main campus or family health centres, Patients prescribed insulin or other injectable diabetes medications (as monotherapy or in conjunction with oral agents), and those on multiple oral agents at baseline, were excluded. |
| Petrica, 2009[126](#_ENREF_126)  Romania  Not extracted | RCT | Neither year reported  12 | No | No | Not Extracted/  44    Outpatient: subspecialty care setting | HbA1c <7%, < 5 years, no poor glycemic control with previous medication, no stable therapy with metformin for at least 6 months  CKD of non-diabetic origin, symptoms or history of, cerebrovascular disease (TIA, stroke), micro/macroalbuminuria, thyroid dysfunction, abnormal albuminuria, microangiogrpahic complications |
| Pfutzner, 2011[128](#_ENREF_128)  Germany (assumed based on author affiliations)  NCT00770653 | RCT | Neither year reported  24 | No | Yes | Not Extracted/  305      NR | Age <18 - >75, HbA1c <6.5, Any liver disease, Any kidney disease, History of CVD, Pregnant, patients without dyslipidemia, Prior use of any diabetes treatment except for metformin, no current treatment MET, respiratory, neurological or hematlogical disease, not on individually-determined maximal metformin, hypersensitivity to study drugs, history of severe or multiple allergies, h/o significant CVD (greater than NYHA stages II-IV) |
| Pfutzner, 2011[129](#_ENREF_129)  Multi-continent  NCT00327015 | RCT | Neither year reported  76 | Yes | Yes | Not Extracted/  1306    Community  outpatient settings (unspecified) | Age <18 or >77 years, HbA1c >12.00%, HbA1c <8.00%, BMI >40 kg/m2, Prior use of any diabetes treatment, Prior or current use of insulin, Any liver disease, Any kidney disease, fasting C-peptide < 1.0 ng/ml, symptoms of poorly controlled diabetes, history of diabetic ketoacidosis or hyperosmolar non-ketotic coma, CVD event within the prior 6 months or NYHA stage III/IV congestive heart failure and/or LVEF </= 40%, psychiatric disorder, alcohol or drug abuse within previous year, treatment with potential CYP3A4 inhibitors or inducers, immunocompromised individuals, clinically signficant abnormal hepatic, renal, endocrine, metabolic or hematological screening tests |
| Pratley, 2010  [130](#_ENREF_130)  Multi-continent, Europe, USA and Canada  Not extracted | RCT | Neither year reported  2 years | No run-in period | Yes | 1302/665  “office based”- possibly outpatient | Age <18 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >7.5% or <10%, BMI >45 kg/m2, no Type 2 DM, cancer, contraindication to trial drugs, recurrent hypoglycemia or hypoglycemia unawareness, not on metformin for at least 3 months, on any non-metformin ODM in past 3 months |
| Pratley, 2014[131](#_ENREF_131)  Multi-continent  NCT01023581 | RCT | Neither year reported  26 | Yes | Yes | Not Extracted/  784    NR | Age <18yr or >80 yr, HbA1c >10%, HbA1c <7.50%, BMI <23 or >45 kg/m2, <20 or >35 kg/m2 for Asian participants, Prior use of any diabetes treatment, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Retinopathy, Not using adequate contraception, class 3 or 4 CHF OR recent CVD event in last 3 months such as MI, stent, bypass, adequate controlled glycemia following treatment with diet and exercise alone for at least 2 months prior to screening, fasting C-peptide concentration < 0.8ng/ml (0.26nmol/l), lack of ability or willingness to monitor blood glucose using a home glucos monitor and keep a glucose diary, at week-1 of the placebo run-in/stabilization period prior to randomization: HbA1c<7.5% or >10%, at week-1 of the placebo run-in/stabilization period prior to randomization: study drug compliance < 75% or >125%, at week-1 of the placebo run-in/stabilization period prior to randomization: use of oral or systemically injected glucocorticoids or weight-loss drugs, low hemoglobin levels (Γëñ 12 and Γëñ 10 g/dL for men and women, respectively), elevated blood pressure (ΓëÑ 150 and ΓëÑ 90 mm Hg for systolic and diastolic, respectively), hemoglobinopathy; |
| Qiu, 2014[132](#_ENREF_132)  Multi-continent  NCT01340664 | RCT | Neither year reported  22 | Yes | Yes | Not Extracted/  279    NR | Age <18 or >80, HbA1c >10.5 or <7, Any kidney disease, FPG and/or fasting self-monitored blood glucose 15.0 mmol/L during the pretreatment phas, diabetic ketoacidosis, history of cardiovascular disease (including myocardial infarction, unstable angina, revascularization procedure or cerebrovascular accident) within 3 months before screening, un- controlled hypertension, not on metformin monotherapy at protocol-specified doses (at least 1500 mg/d (>2000 mg/d preferred), on any other diabetes medication within last 12 wks, not completing the placebo run-in period |
| Raz, 2008[188](#_ENREF_188)  Multi-continent  Not extracted | RCT | Neither year reported  30 Wks | Run-in period but number of participants excluded was NR | Yes | 544/190  NR | Age <18 or >78 years, HbA1c <8% after run-in or HbA1c >11% after run-in, BMI <20 kg/m2 or >43 kg/m2, pregnant, nursing, insulin within 8 wks prior to screening, PPAR-G or incretin mimetics within 12 wks prior to screening, Type 1 DM, FPG <7.2 mmol/l or >15.6 mmol/L consistently during run-in, no Type 2 DM |
| Reasner, 2011[135](#_ENREF_135)  US  NCT00482729 | RCT | 2007  2009    44 | Yes | Yes | Not Extracted/  1250    NR | Age <18 or >78 years, HbA1c <7.5%, Prior use of any diabetes treatment, Any liver disease, History of CVD, Contraindication or history of intolerance to metformin, No type 2 diabetes, Not on diet/exercise regimen, Finger stick glucose test <7.2 or >17.8 mmol/l, Type 1 diabetes |
| Ridderstrale, 2014[136](#_ENREF_136)  Multi-continent  NCT01167881 | RCT | 2010  2011    104 | Yes | Yes | Not Extracted/  1549    NR | Age <18, HbA1c >10 or <7, BMI>45, Any kidney disease, not on stable dose of MFM IR (>=1500mg/day or max tolerated dose, or max dose according to local label) for at least 12 wks prior to randomization, blood glucose concentration greater than 13┬╖3 mmol/L after an overnight fast during the placebo run-in, confi rmed by a second measurement, use of antidiabetes drugs other than metformin immediate release any time during the 12 wks before randomisation |
| Rigby, 2010  [137](#_ENREF_137)  United States, Multi-continent  Not extracted | RCT | Start year: 2007  End year: 2008  16 wks | No run-in period | Yes | 356/169  NR | Age <18 or >80 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c >10% (9.5% if on metformin combination therapy), HbA1c < 7% (6.5% if on metformin combination therapy), BMI > 40 kg/m2, LDL<50mg/dl or TG > = 500 mg/dL, weight loss program with ongoing weight loss or starting an intensive exercise program within 4 wks of screening, need for oral corticosteroids, bile acid sequestrants, or any antidiabetes medications other than metformin, >2 months insulin, not on metformin for >=3 months (1500-2550 mg/day, Type 1 DM and/or ketoacidosis, dysphagia/swallowing disorders, intestinal motility disorders, pancreatitis, HIV/AIDS, drug/alcohol abuse within 2 years, any serious disorder including pulmonary, hepatic, gastrointestinal, uncontrolled endocrine/metabolic, hematologic/oncologic (within 5 years), neurologic, or psychiatric diseases, current treatment with TZD/combo with metformin/colesevelam/fixed-dose combination product including metformin, hospitalization within 14 days of screening |
| Roden, 2013[139](#_ENREF_139)  Multi-continent  NCT01177813. | RCT | 2010  2012    24 | Yes | Yes | Not Extracted/  899  Inpatient/hospital  Outpatient: primary care, Outpatient: subspecialty care setting, academic medical ctrs, hospitals, and private practices | Age <18, <20 in Japan, <18 or >65 in India  HbA1c >10 or 9 in Germany or <7, BMI >45, Any kidney disease, diabetes treatment in 12 wks before randomization, uncontrolled hyperglycaemia (glucose concentration >13┬╖3 mmol/L after an overnight fast during the placebo run-in phase and confi rmed by a second measurement),, contraindications to sitagliptin according to the local label,, treatment with antiobesity drugs within 3 months before informed consent, treatment with systemic steroids at time of informed consent, change in dose of thyroid hormones within 6 wks before informed consent, any uncontrolled endocrine disorder apart from type 2 diabetes., did not meet inclusion criteria after placebo run-in |
| Rosenstock, 2006[140](#_ENREF_140)  Multi-continent  Not extracted | RCT | Start year: 2003 to 2004  32 Wks | Yes | Yes | 1252/468  multicenter | Age <18 or >70 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c < 7% or > 11%, FPG >15 mmol/l, hematological disease, uncontrolled hypertension while on antihypertensive treatment, intermittent or chronic use of oral or intravenous corticosteroids, investigators discretion, use of investigational agent within 30 days of the study (or five half live of the investigational drug if longer than 30 days), previous history of severe edema or medically serious fluid related event associated with TZD, acute or chronic metabolic acidosis, history of diabetic ketoacidosis |
| Rosenstock, 2013[143](#_ENREF_143)  Multi-continent  NCT00707993 | RCT | Neither year reported  52 | Yes | Yes | Not Extracted/  441    NR | Age <65 or >90 yr, HbA1c> 9.0% for patients on diet and exercise therapy alone, 8.0% for patients on oral antidiabetic monotherapy & 9.0% after washout period without medications within 2 wks  6.50%, not able or unwilling to self-monitor blood glucose with a home glucose monitor |
| Rosenstock, 2013[144](#_ENREF_144)  Multi-continent  NCT00749190 | RCT | Neither year reported  12 | Yes | Yes | Not Extracted/  495    NR | Age <18 or >80, HbA1c >9 if on MFM and one other OAD or >10 if on MFM monotherapy or < 6.5 if on MFM and one other OAD, <7 if on MFM monotherapy, BMI >40, Any liver disease, Any kidney disease, prior treatment that didn't include MFM and one other oral OAD, unchanged antidiabetic therapy for <10 wks prior to screening including stable metformin therapy (ΓëÑ1500 mg/day or maximum tolerated dose); diseases of the central nervous system; chronic or clinically relevant acute infections; history of clinically relevant allergy/hypersensitivity; treatment with thiazolidinediones, glucagon-like peptide-1 (GLP-1) analogues or insulin within 3 months. h/o of MI, CVA, or TIA in past 6 mo HbA1c <7 or >10 at start of placebo run-in history of clinically relevant allergy/hypersensitivity treatment with thiazolidinediones, glucagon-like peptide-1 (GLP-1) analogues or insulin within 3 months |
| Ross, 2012[146](#_ENREF_146)  Multi-continent  NCT01012037 | RCT | 2009  2010    12 | Yes | Yes | Not Extracted/  491    NR | Age <18 or > 80yr, HbA1c> 10.0% when taking met alone; 9.5% when taking met and no more than one other oral antidiabetic drug (SU, meglitinide, DPP-4 inhibitor or a-glucosidase inhibitor with unchanged dose for 12 wks prior to informed consent); 10% after the placebo run-in or < 7.00%, BMI > 45kg/m2, Prior or current use of insulin, Any liver disease, Any kidney disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing, Not using adequate contraception total daily dosage of met was not >=1500mg/day or maximum tolerated dose b.i.d., or was on unstable dose (changed within 12 wks prior to randomisation or during the study) treatment within the prevous 3 months with a thiazolidinedione, a GLP-1 receptor agonist, or an antiobesity drug, major cvd event in last 6 months |
| Roumie, 2012[210](#_ENREF_210)  US | Retrospective cohort | 2001  2008     0.78 (metformin), 0.61 (sulfonylurea) | Not applicable | No | Not Extracted/  253690  VA databases linked to Medicare files, VA databases linked to Medicare files, Inpatient diagnosis/ procedures, Outpatient diagnosis/  procedures, Inpatient pharmacy records, Outpatient pharmacy records | Age <18, Prior use of any diabetes treatment, Prior or current use of insulin, Any kidney disease, initiating oral monotherapy before 10/1/2001 or after 9/30/2008, not receiving regular VHA care (a VHA encounter or prescription fill at least once every 180 days) for at least the past 365 days, not a new user (<365 days since filled prescription for oral or injectable diabetic drug), serious mental illness, serious medical conditions identi∩¼üed at baseline (heart failure, HIV, cancer except for nonmelanoma skin cancer, organ transplantation, end-stage kidney or liver disease, or respiratory failure), baseline serum creatinine level of 133 mol/L (1.5 mg/dL) or greater, cocaine use, combination therapy |
| Russell-Jones, 2012[147](#_ENREF_147)  Multi-continent  NCT00676338 | RCT | 2008  2010    36 | No | Yes | Not Extracted/  820    NR | Adults, HbA1c >11 or <7.1, BMI <23 - >45, Prior use of any diabetes treatment, unstable weight |
| Scheller, 2014[211](#_ENREF_211)  Denmark | Retrospective cohort | 2007  2011    0.9-1.8 | Not applicable | No | Not Extracted/  84756    Administrative database, The Danish National Patient Register - The Danish Register of Medicinal Product Statistics and the National Causes of Death Register, Inpatient diagnosis/procedures, Inpatient pharmacy records, Outpatient pharmacy records, Death registry | Age <20, The metformin group was restricted to patients who had not received glucose-lowering drugs prior to the therapy with metformin, DPP-IV inhibitor users were only included if they had not received a glucose-lowering drug, except for metformin, prior to the treatment with sitagliptin, excluded if the duration of treatment with sitagliptin or metformin monotherapy was less than 30 days |
| Schernthaner, 2015[148](#_ENREF_148)  Multi-continent  NCT 01215097 | RCT | 2009  2012  52 wks | Yes | Yes | NR/720  NR | Age <65, HbA1c>9, HbA1c7, any liver disease, any kidney disease, type 1 diabetes, any antihyperglycaemic therapy other than metformin <8 wks before enrollment, glucocorticoids, cytochrome P450 3A4 inducers, history of ketoacidosis or hyperosmolar non-ketonic coma, haemoglobinopathies, cognitive function problems, alcohol or illegal drug abuse |
| Schernthaner, 2004[149](#_ENREF_149)  Europe  Not extracted | RCT | 12 months (planned duration) | Not extracted | No | Not extracted | Age <35 or >75 years, treatment experienced, HbA1c <7.5% or >11%, no Type 2 DM |
| Schramm, 2011[212](#_ENREF_212)  Denmark | Retrospective cohort | 1997  2006    3.3 | Not applicable | No | Not Extracted/  107806    Administrative database, The National Patient Registry (Denmark) and The Danish Registry of Medicinal Product Statistics Inpatient diagnosis/ Procedures, Outpatient pharmacy records, Death registry | Age >20, initiated single-agent treatment with an IS or metformin |
| Schumm-Draeger, 2015[151](#_ENREF_151) | RCT | 2010  2011  20 wks | Yes | Yes | NR/400  NR | Not on stable dose of MET >=1500mg/day for >= 10 weeks. Weight loss (sx of uncontrolled dm). BP>=160/100. Clinically significant haematological or oncological conditions. Symptoms of poorly-controlled diabetes. |
| Scott, 2008[153](#_ENREF_153)  Multi-continent  Not extracted | RCT | Neither year reported  18 Wks | Run-in period but number of participants excluded was NR | Yes | 486/273  NR | Age <18 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), HbA1c < 7% or >11%, not on 10 wks on stable dose of metformin, insulin use, Type 1 DM, glucose > 270 mg/dL |
| Seck, 2010  [154](#_ENREF_154)  NR  Not extracted | RCT | Neither year reported  2 years | Run-in period but number of participants excluded NR | Yes | 2141/1172  NR | Age <17 or >78 years |
| Seino, 2010[155](#_ENREF_155)  Japan  Not extracted | RCT | Neither year reported  24 wks | Yes | Yes | NR/464  NR | Age <20 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), retinopathy, HbA1c < 7% or >10%, BMI >35 kg/m2, treated with insulin within 12 wks of the start of the study, receiving or expecting to receive systemic corticosteroids, known hypoglycemia unawareness or recurrent major hypoglycemia unawareness or recurrent major hypoglycemia, no Type 2 DM, treated with diet therapy for less than 8 wks, on more than 1/2 of the recommended maximum dose of an SU (e.g., on more than 2.5 mg of glibenclamide) |
| Seino, 2012[156](#_ENREF_156)  Japan  NCT01318109 | RCT | 2008  2009    12 | Yes | Yes | Not Extracted/  288  outpatient, but not specified | Age <20 or >=65years, HbA1c >=10.4% after 8 wks of observation or <6.9% after 8 wks of observation, Prior or current use of insulin, Any liver disease, Any kidney disease, History of CVD, Contraindication or history of intolerance to metformin, Pregnant, Nursing, HbA1c >=10% variation in A1c between week 4 and 8, not receiving metformin at a stable dosage for at least 12 wks plus specific dietary and exercise therapies, administration of any investigational drug, orhter than met, within 12 wks of study initiation, a history/symptoms of lactic acidosis, h/o drug abuse/dependency, severe cardiovascular or pulmonary function impairment or severe pancreatic, cerebrovascular, or hematologic diseases, dehydration, gastrointestinal disorders, malignant tumours, elevated blood pressure (>=180 / 110mmHg |
| St John Sutton, 2002[159](#_ENREF_159)  US  Not extracted | RCT | 52 wks (planned duration) | Not extracted | Yes | Not extracted | Age <40 or age >80 years, any liver disease, any kidney disease, history of CVD, no Type 2 DM, other |
| Stenlof, 2014[213](#_ENREF_213)  NR  NCT01081834 | RCT | Neither year reported  52 | Yes | Yes | Not Extracted/  587    NR | Age <18 or >80, HbA1c >10 or <7, Prior or current use of study drug, Any kidney disease, if on AHA other than PPAR agonist or combination MFM+SU, FPG >15 mmol/l, h/o type 1 dm, history of cardiovascular disease (including myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident) within 3 months before screening |
| Stewart, 2006[160](#_ENREF_160)  Multinational Europe  Not extracted | RCT | Start year: 2003 to 2004  32 Wks | Yes | Yes | 1397/526  NR | Age <18 or >70 years, history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c < 7% or > 9%, drug naive patients with FPG <7 mmol/l or >9 mmol/l, patient on monotherapy with FPG < 6.0 mmol/l or > 8 mmol/l, prior history of exposure to thiazolidinediones within previous 6 months, use of insulin anytime in the past, uncontrolled hypertension |
| Suzuki, 2014[161](#_ENREF_161)  Japan  Not extracted | RCT | 2009  2012  6 months | No | No | NR/56  Outpatient: subspecialty care setting | Type 1 diabetes. Severe complication of diabetes. Severe renal and liver dysfunction. Pregnant or nursing women and those who might be pregnant. Alcoholism. A history of stroke and cardiovascular events. Any patient whom the investigator judged to be inappropriate for this study. |
| Umpierrez, 2014[171](#_ENREF_171)  Multi-continent  NCT01126580 | RCT | 2010  2012    52 | Yes | Yes | NR | Age <18 years, HbA1c >9.50% or <6.50%, <3 months or >5 years, Prior or current use of insulin, Prior or current use of study drug, on more than one oral antihyperglycemic medication(OAM) or on one OAM for <3 months prior to screening., receiving an OAM and taking >50% of the approved maximum daily dose per respective labels in participating countries, have been taking thiazolidinediones or GLP-1 receptor agonists during the 3 months prior to screening, on one oral medication < 3 months |
| Weissman, 2005[174](#_ENREF_174)  US  Not extracted | RCT | Neither year reported  24 wks (planned duration) | Run-in period but number of participants excluded was NR | Yes | 1270/766  NR | Age <18 or >75 years, any liver disease (such as elevated aminotransferases (ALT, AST, SGOT, SGPT)), any kidney disease (such as microalbuminuria, macroalbuminuria or elevated creatinine, low GFR or creatinine clearance), history of cardiovascular disease (e.g. myocardial infarction, stroke, transient ischemic attack, coronary artery disease, angina), HbA1c <6.5% for subjects having received prior combination treatment (metformin + SU), HbA1c >8.5% for subjects having received prior combination treatment (Metformin + SU), BMI <27 kg/m2, HbA1c < 7% for drug naive or prior monotherapy subjects, HbA1c > 10% for drug naive or prior monotherapy subjects, FPG < 126 mg/dL or >270 mg/dL, anemia, severe edema, prior insulin use within 3 months of study start, non -compliant patient with metformin up-titration |
| Wheeler, 2013[214](#_ENREF_214)  US | Retrospective cohort | 2004  2009     1.4-1.7 | Not applicable | No | Not Extracted/  193,172  Inpatient/hospital, Outpatient: primary care, Outpatient: subspecialty care setting, VA, Inpatient diagnosis/procedures, Outpatient diagnosis/  procedures, Inpatient pharmacy records, Outpatient pharmacy records, Death registry | Prior use of any diabetes treatment, less than 2 consecutive prescription of SU, MFM or rosi within 200 days between 1/1/2004 and 12/31/2009, veterans who did not have prescriptions for non-diabetes medications during the year before this first prescription for an oral diabetes medication, because for these individuals we could not distinguish whether they were new users of oral diabetes therap, persons without an outpatient visit to a VHA facility in the year before the first prescription for an oral diabetes medication., renal allograft, type 1 diabetes, history of CHF, serum creatinine level ΓëÑ132.6 ╬╝mol/l (or were missing values), initial dm2 prescription not a study drug or started on dual therapy, other medical exclusions including ketoacidosis, diabetic coma, kidney transplant |
| White, 2014[175](#_ENREF_175)  Multi-continent  NCT00885378 | RCT | 2009  2010    12 | Yes | Yes | Not Extracted/  160  outpatient | Age <18 and >78 years, HbA1c >10% or <7%, BMI >45, Pregnant  Nursing, not on metformin monotherapy at >=1500 mg for >=8 wks prior to study start, marked polydipsia and polyuria and >10% weight loss<3 months before screening, h/o DKA or HHNC or insulin use in the last year, h/o CVD within 3 months of screening, CHF class 3 or 4 or known EF<=40%, h/o hemoglobinopathies |
| Williams-Herman, 2010[177](#_ENREF_177)  Multi-continent  NCT00103857 | RCT | Neither year reported  104 | Yes | Yes | Not Extracted/  1091    NR | Age <18 or >78 years, HbA1c >11% or <7.50%, Any liver disease, Any kidney disease, History of CVD, completed the 54-week base study, >/= 75% compliant in taking study medication, had not developed contraindication to study medication |
| Xu, 2015[178](#_ENREF_178)  China  NCT01147627 | RCT | 2010  2012  48 wks | No | Yes | NR/416  NR | Acute or severe chronic diabetic complications or illnesses (ketoacidosis, hyperosmotic state, lactic acidosis, severe microand macro-vascular complications, and hepatic dysfunction). Presence of glutamic acid decarboxylase antibodies. Use of drugs affecting gastrointestinal motility, weight and glycaemia. History of pancreatitis. Triglyceride (TG) levels ΓëÑ5 mmolL-1. Dody weight not atble over the last 3 months. |
| Yang, 2011[180](#_ENREF_180)  Multinational Asia (China - India – SouthKorea  NCT00661362 | RCT | Neither year reported  24 | Yes | Yes | Not Extracted/  570    NR | Age <18, HbA1c >10 or <7, Any liver disease, Any kidney disease, Pregnant, Nursing, not on stable dose of metformin; C-peptide <0.33 nmol/l, history of diabetic ketoacidosis or hyperosmolar coma, symptoms of poorly controlled dm, CHF - NYHA III-IV, use of sysetmic steroids or CYP 3A4 inducersHemoglobinopathies, signiifcant cardiovasc illness within 6 mo of enrollment, autoimmune skin d/o, GI surgery that could affect absorpotion, immunocompromised, drug or alcohol abuse in past 12 mo, abnormal lab, exam, ECG that would compromise safe, successful participation - investigator discretion, insulin in past yr, Prior use of any diabetes treatment besides metformin within 8 wks, ever used DPP4 inhib |
| Yang, 2012[182](#_ENREF_182)  China  NCT00813995 | RCT | 2009  2010    24 | Yes | Yes | Not Extracted/  395    NR | Age <18 - >78, HbA1c >11 or <7.5, Any liver disease, Contraindication or history of intolerance to metformin, Pregnant, Nursing, Diabetes type 1, history of ketoacidosis, CHF, unstable CHD, not Chinese, able to get off other diabetes meds during run-in prior use of TZDs |
| Zhang, 2012[187](#_ENREF_187)  China  Not extracted | RCT | Neither year reported  16 | Yes | Yes | Not Extracted/  42  check up center at hospital | HbA1c >10.00% or <7.00%, Prior or current use of insulin, Any liver disease, History of CVD, did NOT have a 24h urinary albumin level <30 or >300 mg/24h after determination from 2 samples, statins, angiotensin II receptor blocker, angiotensin-converting enzyme inhibitors in the previous 2 wks, had primary nephropathy or secondary kidney disease besides diabetic nephropathy, had rheumatic disease, had acute diabetic complications, patients failed to keep FPG between 4.4-8.0mmol/l and maintain 2h-PG<11.1mmol/l |
|  |  |  |  |  |  |  |

ACEI = angiotensin-converting enzyme inhibitors; ADA = American Diabetes Association; ALT = alanine aminotransferase; AST = asparate aminotransferase; BG = blood glucose, BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CHF = congestive heart failure; CK = creatine phosphokinase; CVD = cardiovascular diseases; DBP = diastolic blood pressure; DM = diabetes mellitus; FBG = fasting blood glucose; FPG = fasting plasma glucose; g/day = grams per day; g/dl = grams per deciliter; GFR = glomerular filtration rate; GI r = gastrointestinal; HbA1c = hemoglobin A1c; kg = kilogram; kg/m2 = kilograms per meter squaredlbs = pounds; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; met = metformin; mg = milligram; mg/d = milligrams per day; mg/dL = milligrams per deciliter; MI = myocardial infarction ; mm Hg = millimeters of mercury; mmol/l =millimoles per liter; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel IIIng/ml = nanograms per milliliter; nmol/l = nanomoles per liter; NR = Not reported; NYHA = New York Heart Association; ODM = oral diabetes medications; pmol/l = picomoles per liter; SBP = systolic blood pressure; SGOT = serum glutamyl oxaloacetic transaminase; SGPT = serum glutamyl pyruvic transaminase; SU = sulfonylurea; TIA = Transient ischemic attack; TZD = thiazolidinedione; U/kg = units per kilogram; UKPDS = The UK Prospective Diabetes Study; US = United States; WHO = World Health Organization; yrs = years

Some data may have not been extracted because the question was not asked.