**Table D7. Results of studies evaluating effects of diabetes medications on long-term clinical outcomes**

| **Author, year****Study design** | **Intervention** | **Overall mortality, n (%)** | **CVD mortality, n (%)** | **CVD morbidity, n (%)** | **Cerebrovascular disease, n (%)** |
| --- | --- | --- | --- | --- | --- |
| Ahren, 2014[2](#_ENREF_2) | Grp1: Metformin + placeboFixed >=1500 mgGrp2: Metformin + glimepiride + placeboFixed >=1500 mgTitrated 2 mg qdup-titration to 4mg qd | Def: All-cause mortalityIncidence Grp1: 1Incidence Gp2: 3 |  |  |  |
| Ahren, 2014[2](#_ENREF_2) | Grp1: Metformin + placeboFixed >=1500 mgGrp2: Metformin + sitagliptin + placeboFixed >=1500 mgFixed 100 mg qd | Def: All-cause mortalityIncidence Grp1: 1Incidence Grp2: 1 |  |  |  |
| Ahren, 2014[2](#_ENREF_2) | Grp1: Metformin + placeboFixed >=1500 mgGrp2: Metformin + albiglutide + placeboFixed >=1500 mgTitrated 30 mg qwup-titration to 50 mg qw | Def: All-cause mortalityIncidence Grp1: 1Incidence Grp2: 3 |  |  |  |
| Alba, 2013[3](#_ENREF_3)RCT | Grp1: PioglitazoneFixed (30mg)Grp2: SitagliptinFixed (100mg)ITT: YesFollowup (wks): 52 NR/unclear | Def:All-cause mortalityIncidence Grp1: 0   Persons p NR Incidence Grp2: 0   Persons p NR  |  |  |  |
| Andersson, 2010[190](#_ENREF_190)Retrospective cohort | Grp1: MetforminNot specified  Grp2: SUNot specified  ITT: YesFollowup (wks): 52 NR/unclear | Def:All-cause mortalityIncidence Grp1: 0   Persons p NR Incidence Grp2: 0   Persons p NR  |  |  |  |
| Andersson, 2010[190](#_ENREF_190)Retrospective cohort | Grp1: MetforminNot specified  Grp2: SUNot specified  ITT: YesFollowup (wks): 26 | Def:All-cause mortalityIncidence Grp1: 0  177 Persons p NR Incidence Grp2: 0  315 Persons p NR  |  |  |  |
| Andersson, 2010[190](#_ENREF_190)Retrospective cohort | Grp1: MetforminNot specified  Grp2: Metformin + suNot specified  Not specified  ITT: YesFollowup (wks): 52 | Def:All-cause mortalityIncidence Grp1:   Persons p NR Incidence Grp2: 2  315 Persons p NR  |  |  |  |
| Andersson, 2010[190](#_ENREF_190)Retrospective cohort | Grp1: MetforminNot specified  Grp2: Metformin + suNot specified  Not specified  ITT: YesFollowup (wks): 26 | Def:All-cause mortalityIncidence Grp1: 0  177 Persons p NR Incidence Grp2: 0  302 Persons p NR  |  |  |  |
| Andersson, 2010[190](#_ENREF_190)Retrospective cohort | Grp1: SUNot specified  Grp2: Metformin + suNot specified  Not specified  ITT: YesFollowup (wks): 52 | Def:All-cause mortalityIncidence Grp1:   Persons p NR Incidence Grp2: 0  302 Persons p NR  |  |  |  |
| Andersson, 2010[190](#_ENREF_190)Retrospective cohort | Grp1: SUNot specified  Grp2: Metformin + suNot specified  Not specified  ITT: YesFollowup (wks): 52 | Def:All-cause mortalityIncidence Grp1:   Persons p NR Incidence Grp2: 1  304 Persons p NR  |  |  |  |
| Arechavaleta, 2011[5](#_ENREF_5)RCT | Grp1: Metformin + glimepiride + placeboNot specified (on stable metformin >=1500 mg at screening for the past 12 wks)Titrated (Median: 2.1mg/day after wk 18 (at end of titration period)Max: 6mg/day)Grp2: Metformin + sitagliptin + placeboNot specified (on at least 1500 mg daily for 12 wks prior to screening at stable dose)Fixed (100mg daily)ITT: YesFollowup (wks): 26 | Def:All-cause mortalityIncidence Grp1: 0  177 Persons p NR Incidence Grp2: 1  304 Persons p NR  |  |  |  |
| Arechavaleta, 2011[5](#_ENREF_5)RCT | Grp1: Metformin + glimepiride + placeboNot specified (on stable metformin >=1500 mg at screening for the past 12 wks)Titrated (Median: 2.1mg/day after wk 18 (at end of titration period)Max: 6mg/day)Grp2: Metformin + sitagliptin + placeboNot specified (on at least 1500 mg daily for 12 wks prior to screening at stable dose)Fixed (100mg daily)ITT: YesFollowup (wks): 26 | Def:All-cause mortalityIncidence Grp1: 0  315 Persons p NR Incidence Grp2: 0  302 Persons p NR  |  |  |  |
| Arjona Ferreira, 2013[6](#_ENREF_6)RCT | Grp1: Glipizide + placeboTitrated (Mean: 7.7mgMax: 20mg as considered appropriate by the investigator based on the pateint's glycemic controlstarting dose of 2.5mg, the dose could also be reduced or interrupted to prevent hypoglycemia)Grp2: Sitagliptin + placeboFixed (50mg for pateitns with moderate renal insufficiency, 25mg for patients with severe renal insufficiency, dose was reduced from 50 to 25mg for patients whose renal status changed from moderate to severe during the study)  ITT: YesFollowup (wks): 52  | Def:All-cause mortalityIncidence Grp1: 2  315 Persons p NR Incidence Grp2: 0  302 Persons p NR  |  |  |  |
| Arjona Ferreira, 2013[6](#_ENREF_6)RCT | Grp1: Glipizide + placeboTitrated (Mean: 7.7mgMax: 20mg as considered appropriate by the investigator based on the pateint's glycemic controlstarting dose of 2.5mg, the dose could also be reduced or interrupted to prevent hypoglycemia)Grp2: Sitagliptin + placeboFixed (50mg for pateitns with moderate renal insufficiency, 25mg for patients with severe renal insufficiency, dose was reduced from 50 to 25mg for patients whose renal status changed from moderate to severe during the study)ITT: YesFollowup (wks): 52  | Def:All-cause mortalityIncidence Grp1: 2  315 Persons p NR Incidence Grp2: 1  304 Persons p NR  |  |  |  |
| Arjona Ferreira, 2013[6](#_ENREF_6)RCT | Grp1: Glipizide + placeboTitrated (Mean: 7.7mgMax: 20mg as considered appropriate by the investigator based on the pateint's glycemic controlstarting dose of 2.5mg, the dose could also be reduced or interrupted to prevent hypoglycemia)Grp2: Sitagliptin + placeboFixed (50mg for pateitns with moderate renal insufficiency, 25mg for patients with severe renal insufficiency, dose was reduced from 50 to 25mg for patients whose renal status changed from moderate to severe during the study)ITT: YesFollowup (wks): 26 | Def:All-cause mortalityIncidence Grp1: 0  315 Persons p NR Incidence Grp2: 1  304 Persons p NR  |  |  |  |
| Arjona Ferreira, 2013[6](#_ENREF_6)RCT | Grp1: Glipizide + placeboTitrated (Mean: 7.7mgMax: 20mg as considered appropriate by the investigator based on the pateint's glycemic controlstarting dose of 2.5mg, the dose could also be reduced or interrupted to prevent hypoglycemia)Grp2: Sitagliptin + placeboFixed (50mg for pateitns with moderate renal insufficiency, 25mg for patients with severe renal insufficiency, dose was reduced from 50 to 25mg for patients whose renal status changed from moderate to severe during the study)ITT: NoFollowup (wks): 26 Active | Def:All-cause mortalityIncidence Grp1: 0   NA p Incidence Grp2: 0   NA p  |  |  |  |
| Arjona Ferreira, 2013[6](#_ENREF_6)RCT | Grp1: Glipizide + placeboTitrated (Mean: 7.7mgMax: 20mg as considered appropriate by the investigator based on the pateint's glycemic controlstarting dose of 2.5mg, the dose could also be reduced or interrupted to prevent hypoglycemia)Grp2: Sitagliptin + placeboFixed (50mg for pateitns with moderate renal insufficiency, 25mg for patients with severe renal insufficiency, dose was reduced from 50 to 25mg for patients whose renal status changed from moderate to severe during the study)ITT: NoFollowup (wks): 26 Active | Def:All-cause mortalityIncidence Grp1: 0   NA p Incidence Grp2: 0   NA p  |  |  |  |
| Arjona Ferreira, 2013[6](#_ENREF_6)RCT | Grp1: Glipizide + placeboTitrated (Mean: 7.7mgMax: 20mg as considered appropriate by the investigator based on the pateint's glycemic controlstarting dose of 2.5mg, the dose could also be reduced or interrupted to prevent hypoglycemia)Grp2: Sitagliptin + placeboFixed (50mg for pateitns with moderate renal insufficiency, 25mg for patients with severe renal insufficiency, dose was reduced from 50 to 25mg for patients whose renal status changed from moderate to severe during the study)ITT: NoFollowup (wks): 26 Active | Def:All-cause mortalityIncidence Grp1: 0   NA p Incidence Grp2: 0   NA p  |  |  |  |
| Aschner, 2010[7](#_ENREF_7)RCT | Grp1: MetforminVaried, prespecified target doseStart: 500 mg, Max: 2000 mg, Mean: 1903D: 5 wksGrp2: SitagliptinFixedMean: 100 mg | Grp1: 0 (0)Grp2: 1 (<1) |  |  |  |
| Aschner, 2012[8](#_ENREF_8)RCT | Grp1: Metformin + sitagliptinNot specified (baseline dose of metformin was 1835 mg)Fixed (100 mg)Grp2: Metformin + insulin glargineNot specified (mean baseline dose 1852 mg)Titrated (0.5 U/kg at 24 wks)ITT: NoFollowup (wks): 26 Active | Def:All-cause mortalityIncidence Grp1: 0   NA p Incidence Grp2: 0   NA p  |  |  |  |
| Aschner, 2012[8](#_ENREF_8)RCT | Grp1: Metformin + sitagliptinNot specified (baseline dose of metformin was 1835 mg)Fixed (100 mg)Grp2: Metformin + insulin glargineNot specified (mean baseline dose 1852 mg)Titrated (0.5 U/kg at 24 wks)ITT: NoFollowup (wks): 26 Active | Def:All-cause mortalityIncidence Grp1: 0   NA p Incidence Grp2: 0   NA p  |  |  |  |
| Aschner, 2012[8](#_ENREF_8)RCT | Grp1: Metformin + sitagliptinNot specified (baseline dose of metformin was 1835 mg)Fixed (100 mg)Grp2: Metformin + insulin glargineNot specified (mean baseline dose 1852 mg)Titrated (0.5 U/kg at 24 wks)ITT: NoFollowup (wks): 26 Active | Def:All-cause mortalityIncidence Grp1: 0   NA p Incidence Grp2: 0   NA p  |  |  |  |
| Aschner, 2012[8](#_ENREF_8)RCT | Grp1: Metformin + sitagliptinNot specified (baseline dose of metformin was 1835 mg)Fixed (100 mg)Grp2: Metformin + insulin glargineNot specified (mean baseline dose 1852 mg)Titrated (0.5 U/kg at 24 wks)ITT: NoFollowup (wks): 26 Active | Def:All-cause mortalityIncidence Grp1: 0   NA p Incidence Grp2: 0   NA p  |  |  |  |
| Bailey, 2005[9](#_ENREF_9)RCT | Grp1: MetforminVariedStart: 2500 mg, Max: 3000 mgGrp2: Metformin + rosiglitazoneFixed; VariedStart: 2500mg; Start: 4 mg, Max: 8 mg | Grp1: 0 (0)Grp2: 1 (<1) | Def: CVD mortality/sudden cardiac deathGrp1: 0 (0)Grp2: 1 (<1) | Def: CVD morbidity/MI (non-fatal) + pulmonary edema with MIGrp1: 0 (0)Grp2: 1 (<1) |  |
| Bailey, 2013[10](#_ENREF_10)RCT | Grp1: Metformin + placeboFixed (Mean: 1861 mgMedian: 1500 mg)Grp2: Metformin + dapagliflozin + placeboFixed (Mean: 1792 mgMedian: 1500 mg)Fixed (2.5 mg)ITT: NoFollowup (wks): 26 Active | Def:All-cause mortalityIncidence Grp1: 0   NA p Incidence Grp2: 0   NA p  |  |  |  |
| Bailey, 2013[10](#_ENREF_10)RCT | Grp1: Metformin + placeboFixed (Mean: 1861 mgMedian: 1500 mg)Grp2: Metformin + dapagliflozinFixed (Mean: 1854 mgMedian: 2000 mg)Fixed (5.0 mg)ITT: YesFollowup (wks): 52 Passive | Def:All-cause mortalityIncidence Grp1: 1   Incidence Grp2: 2    |  |  |  |
| Bailey, 2013[10](#_ENREF_10)RCT | Grp1: Metformin + placeboFixed (Mean: 1861 mgMedian: 1500 mg)Grp2: Metformin + dapagliflozin + placeboFixed (Mean: 1800 mgMedian: 1500 mg)Fixed (10.0 mg)ITT: YesFollowup (wks): 52 Passive | Def:All-cause mortalityIncidence Grp1: 1   Incidence Grp2: 1    |  |  |  |
| Bailey, 2013[10](#_ENREF_10)RCT | Grp1: Metformin + placeboFixed (Mean: 1861 mgMedian: 1500 mg)Grp2: Metformin + dapagliflozin + placeboFixed (Mean: 1792 mgMedian: 1500 mg)Fixed (2.5 mg)ITT: NoFollowup (wks): 26 Active | Def:All-cause mortalityIncidence Grp1: 1 (0.6) NR p NR Incidence Grp2: 0 (0) NR p NR  |  |  |  |
| Bailey, 2013[10](#_ENREF_10)RCT | Grp1: Metformin + placeboFixed (Mean: 1861 mgMedian: 1500 mg)Grp2: Metformin + dapagliflozinFixed (Mean: 1854 mgMedian: 2000 mg)Fixed (5.0 mg)ITT: NoFollowup (wks): 26 Active | Def:All-cause mortalityIncidence Grp1: 1 (0.6) NR p NR Incidence Grp2: 0 (0) NR p NR  |  |  |  |
| Bailey, 2013[10](#_ENREF_10)RCT | Grp1: Metformin + placeboFixed (Mean: 1861 mgMedian: 1500 mg)Grp2: Metformin + dapagliflozin + placeboFixed (Mean: 1800 mgMedian: 1500 mg)Fixed (10.0 mg)ITT: YesFollowup (wks): 52 Passive | Def:All-cause mortalityIncidence Grp1:   Persons p NR Incidence Grp2: 1 (0.3) Persons p NR  |  |  |  |
| Bailey, 2013[10](#_ENREF_10)RCT | Grp1: Metformin + placeboFixed (Mean: 1861 mgMedian: 1500 mg)Grp2: Metformin + dapagliflozin + placeboFixed (Mean: 1792 mgMedian: 1500 mg)Fixed (2.5 mg)ITT: YesFollowup (wks): 52 Passive | Def:All-cause mortalityIncidence Grp1:   Persons p NR Incidence Grp2: 0 (0) Persons p NR  |  |  |  |
| Bailey, 2013[10](#_ENREF_10)RCT | Grp1: Metformin + placeboFixed (Mean: 1861 mgMedian: 1500 mg)Grp2: Metformin + dapagliflozinFixed (Mean: 1854 mgMedian: 2000 mg)Fixed (5.0 mg)ITT: YesFollowup (wks): 52 Passive | Def:All-cause mortalityIncidence Grp1:   Persons p NR Incidence Grp2: 1 (0.3) Persons p NR  |  |  |  |
| Bailey, 2013[10](#_ENREF_10)RCT | Grp1: Metformin + placeboFixed (Mean: 1861 mgMedian: 1500 mg)Grp2: Metformin + dapagliflozin + placeboFixed (Mean: 1800 mgMedian: 1500 mg)Fixed (10.0 mg)ITT: YesFollowup (wks): 52 Passive | Def:All-cause mortalityIncidence Grp1: 1 (0.3) Persons p NR Incidence Grp2: 0 (0) Persons p NR  |  |  |  |
| Bakris, 2006[12](#_ENREF_12)RCT | Grp1: Metformin + rosiglitazoneVaried, NS; Varied, glucose: ≤ 6.6 mmol/LUnclear; Start: 4mgD: 3 wksGrp2: Metformin + glyburideVaried, NS; Varied, glucose: ≤ 6.6mmol/LUnclear; Start: 5 mgD: 3 wks | Grp1: 1 (1)Grp2: 0 (0) |  |  |  |
| Barnett, 2012[13](#_ENREF_13)RCT | Grp1: GlimepirideTitrated (Max: 4mg qdplacebo for 1st 18 wks then only for 19-52 wks, initiated at 1mg qd and uptitrated in 1mg increments every 4 wks to 4mg qd max if fassting blood glucose was >110mg/dl (6.1mmol/l))Grp2: LinagliptinFixed (5mg qdstarted this at randomization and on for all 52 wks)ITT: YesFollowup (wks): 52 Passive | Def:All-cause mortalityIncidence Grp1: 1 (0.3) Persons p NR Incidence Grp2: 1 (0.3) Persons p NR  |  |  |  |
| Barnett, 2012[13](#_ENREF_13)RCT | Grp1: GlimepirideTitrated (Max: 4mg qdplacebo for 1st 18 wks then only for 19-52 wks, initiated at 1mg qd and uptitrated in 1mg increments every 4 wks to 4mg qd max if fassting blood glucose was >110mg/dl (6.1mmol/l))Grp2: LinagliptinFixed (5mg qdstarted this at randomization and on for all 52 wks)ITT: NoFollowup (wks): 52 NR/unclear | Def:All-cause mortalityIncidence Grp1: 2   Incidence Grp2: 0    |  |  |  |
| Bergenstal, 2010[14](#_ENREF_14)RCT | Grp1: Metformin + pioglitazone + placeboFixed (Mean: 1480mg)Fixed (45mg daily)Grp2: Metformin + sitagliptin + placeboFixed (Mean: 1583mg)Fixed (100mg daily)ITT: NoFollowup (wks): 52 NR/unclear | Def:All-cause mortalityIncidence Grp1: 2   Incidence Grp2: 2    |  |  |  |
| Bergenstal, 2010[14](#_ENREF_14)RCT | Grp1: Metformin + pioglitazone + placeboFixed (Mean: 1480mg)Fixed (45mg daily)Grp2: Metformin + sitagliptin + placeboFixed (Mean: 1583mg)Fixed (100mg daily)ITT: YesFollowup (wks): 102 NR/unclear | Def:All-cause mortalityIncidence Grp1: 1 (0.7) Incidence Grp2: 2 (1.5)  |  |  |  |
| Bergenstal, 2010[14](#_ENREF_14)RCT | Grp1: Metformin + pioglitazone + placeboFixed (Mean: 1480mg)Fixed (45mg daily)Grp2: Metformin + sitagliptin + placeboFixed (Mean: 1583mg)Fixed (100mg daily)ITT: YesFollowup (wks): 102 NR/unclear | Def:All-cause mortalityIncidence Grp1: 1 (0.7) Incidence Grp2: 0 (0)  |  |  |  |
| Bergenstal, 2010[14](#_ENREF_14)RCT | Grp1: Metformin + pioglitazone + placeboFixed (Mean: 1480mg)Fixed (45mg daily)Grp2: Metformin + sitagliptin + placeboFixed (Mean: 1583mg)Fixed (100mg daily)ITT: YesFollowup (wks): 102 NR/unclear | Def:All-cause mortalityIncidence Grp1: 1 (0.7) Incidence Grp2: 0 (0)  |  |  |  |
| Bergenstal, 2010[14](#_ENREF_14)RCT | Grp1: Metformin + pioglitazone + placeboFixed (Mean: 1480mg)Fixed (45mg daily)Grp2: Metformin + sitagliptin + placeboFixed (Mean: 1583mg)Fixed (100mg daily)ITT: YesFollowup (wks): 104  | Def:All-cause mortalityIncidence Grp1: 4 (1) Incidence Grp2: 4 (1)  |  |  |  |
| Bergenstal, 2010[14](#_ENREF_14)RCT | Grp1: Metformin + pioglitazone + placeboFixed (Mean: 1480mg)Fixed (45mg daily)Grp2: Metformin + exenatide + placeboFixed (Mean: 1504mg)Fixed (2mg weekly)ITT: NoFollowup (wks): 24 NR/unclear | Def:All-cause mortalityIncidence Grp1: 0   Incidence Grp2: 1 (0.5)  |  |  |  |
| Bergenstal, 2010[14](#_ENREF_14)RCT | Grp1: Metformin + pioglitazone + placeboFixed (Mean: 1480mg)Fixed (45mg daily)Grp2: Metformin + exenatide + placeboFixed (Mean: 1504mg)Fixed (2mg weekly)ITT: NoFollowup (wks): 24 NR/unclear | Def:All-cause mortalityIncidence Grp1: 0   Incidence Grp2: 0    |  |  |  |
| Bergenstal, 2010[14](#_ENREF_14)RCT | Grp1: Metformin + pioglitazone + placeboFixed (Mean: 1480mg)Fixed (45mg daily)Grp2: Metformin + exenatide + placeboFixed (Mean: 1504mg)Fixed (2mg weekly)ITT: NoFollowup (wks): 24 NR/unclear | Def:All-cause mortalityIncidence Grp1: 1 (0.5) Incidence Grp2: 0    |  |  |  |
| Bergenstal, 2010[14](#_ENREF_14)RCT | Grp1: Metformin + pioglitazone + placeboFixed (Mean: 1480mg)Fixed (45mg daily)Grp2: Metformin + exenatide + placeboFixed (Mean: 1504mg)Fixed (2mg weekly)ITT: YesFollowup (wks): 24  | Def:All-cause mortalityIncidence Grp1: 1   Incidence Grp2: 0    |  |  |  |
| Bergenstal, 2010[14](#_ENREF_14)RCT | Grp1: Metformin + pioglitazone + placeboFixed (Mean: 1480mg)Fixed (45mg daily)Grp2: Metformin + exenatide + placeboFixed (Mean: 1504mg)Fixed (2mg weekly)ITT: YesFollowup (wks): 24  | Def:All-cause mortalityIncidence Grp1: 0   Incidence Grp2: 0    |  |  |  |
| Bergenstal, 2010[14](#_ENREF_14)RCT | Grp1: Metformin + sitagliptin + placeboFixed (Mean: 1583mg)Fixed (100mg daily)Grp2: Metformin + exenatide + placeboFixed (Mean: 1504mg)Fixed (2mg weekly)ITT: YesFollowup (wks): 24  | Def:All-cause mortalityIncidence Grp1: 1   Incidence Grp2: 0    |  |  |  |
| Bergenstal, 2010[14](#_ENREF_14)RCT | Grp1: Metformin + sitagliptin + placeboFixed (Mean: 1583mg)Fixed (100mg daily)Grp2: Metformin + exenatide + placeboFixed (Mean: 1504mg)Fixed (2mg weekly)ITT: YesFollowup (wks): 24  | Def:All-cause mortalityIncidence Grp1: 0   Incidence Grp2: 0    |  |  |  |
| Bergenstal, 2010[14](#_ENREF_14)RCT | Grp1: Metformin + sitagliptin + placeboFixed (Mean: 1583mg)Fixed (100mg daily)Grp2: Metformin + exenatide + placeboFixed (Mean: 1504mg)Fixed (2mg weekly)ITT: YesFollowup (wks): 24  | Def:All-cause mortalityIncidence Grp1: 0   Incidence Grp2: 0    |  |  |  |
| Bergenstal, 2010[14](#_ENREF_14)RCT | Grp1: Metformin + sitagliptin + placeboFixed (Mean: 1583mg)Fixed (100mg daily)Grp2: Metformin + exenatide + placeboFixed (Mean: 1504mg)Fixed (2mg weekly)ITT: YesFollowup (wks): 24  | Def:All-cause mortalityIncidence Grp1: 1   Incidence Grp2: 0    |  |  |  |
| Bergenstal, 2010[14](#_ENREF_14)RCT | Grp1: Metformin + sitagliptin + placeboFixed (Mean: 1583mg)Fixed (100mg daily)Grp2: Metformin + exenatide + placeboFixed (Mean: 1504mg)Fixed (2mg weekly)ITT: YesFollowup (wks): 24 | Def:All-cause mortalityIncidence Grp1: 0   Incidence Grp2: 0    |  |  |  |
| Bolinder, 2012[17](#_ENREF_17)RCT | Grp1: Metformin + placeboFixed (Patients continued open-label metformin dosage from prior to enrollment)Grp2: Metformin + dapagliflozin (Patients continued open-label metformin dosage from prior to enrollment)Fixed (10 mg)ITT: YesFollowup (wks): 24  | Def:All-cause mortalityIncidence Grp1: 0   Incidence Grp2: 0    |  |  |  |
| Bolinder, 2012[17](#_ENREF_17)RCT | Grp1: Metformin + placeboFixed (Patients continued open-label metformin dosage from prior to enrollment)Grp2: Metformin + dapagliflozin (Patients continued open-label metformin dosage from prior to enrollment)Fixed (10 mg)ITT: YesFollowup (wks): 102  | Def:All-cause mortalityIncidence Grp1: 0   Incidence Grp2: 1 (1.1)  |  |  |  |
| Bolinder, 2012[17](#_ENREF_17)RCT | Grp1: Metformin + placeboFixed (Patients continued open-label metformin dosage from prior to enrollment)Grp2: Metformin + dapagliflozin (Patients continued open-label metformin dosage from prior to enrollment)Fixed (10 mg)ITT: YesFollowup (wks): 104 Active | Def:All-cause mortalityIncidence Grp1: 4 (1) 408 Persons p Incidence Grp2: 0 (0) 406 Persons p  |  |  |  |
| Borges, 2011[18](#_ENREF_18)RCT | Grp1: MetforminTitrated (Max: 2000 mg/dStart 500mg/d)Grp2: Metformin + rosiglitazoneTitrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg)Titrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg)ITT: YesFollowup (wks): 26 Active | Def:All-cause mortalityIncidence Grp1: 0   Incidence Grp2: 0    |  |  |  |
| Borges, 2011[18](#_ENREF_18)RCT | Grp1: MetforminTitrated (Max: 2000 mg/dStart 500mg/d)Grp2: Metformin + rosiglitazoneTitrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg)Titrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg)ITT: YesFollowup (wks): 26 Active | Def:All-cause mortalityIncidence Grp1: 0   Incidence Grp2: 1    |  |  |  |
| Borges, 2011[18](#_ENREF_18)RCT | Grp1: MetforminTitrated (Max: 2000 mg/dStart 500mg/d)Grp2: Metformin + rosiglitazoneTitrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg)Titrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg)ITT: YesFollowup (wks): 12  | Def:All-cause mortalityIncidence Grp1: 0   Incidence Grp2: 0    |  |  |  |
| Borges, 2011[18](#_ENREF_18)RCT | Grp1: MetforminTitrated (Max: 2000 mg/dStart 500mg/d)Grp2: Metformin + rosiglitazoneTitrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg)Titrated (Max: AVM 8mg/2000mgstart AVM 4mg/500mg)ITT: YesFollowup (wks): 12  | Def:All-cause mortalityIncidence Grp1: 0   Incidence Grp2: 0    |  |  |  |
| Brownstein, 2010[191](#_ENREF_191)Cohort | Grp1: MetforminNSGrp2: RosiglitazoneNS |  |  | Def: Hospitalization for acute MIGrp1: refGrp2: HR: 3.0 (CI: 2.4-3.7) |  |
| Brownstein, 2010[191](#_ENREF_191)Cohort | Grp1: RosiglitazoneNSGrp2: Sulfonylurea |  |  | Def: Hospitalization for acute MIGrp1: HR: 1.3 (CI: 1.0-1.7)Grp2: ref |  |
| Cefalu, 2013[20](#_ENREF_20)RCT | Grp1: Metformin + glimepirideFixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory)Titrated (Mean: 5.6 mg (mean maximum dose achieved)Max: 6 mg or 8 mg (on the basis of maximum approved dose in the country of the investigational site))Grp2: Metformin + canagliflozinFixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory)Fixed (100mg)ITT: YesFollowup (wks): 12  | Def:All-cause mortalityIncidence Grp1: 0 (0) Incidence Grp2: 0 (0)  |  |  |  |
| Cefalu, 2013[20](#_ENREF_20)RCT | Grp1: Metformin + glimepirideFixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory)Titrated (Mean: 5.6 mg (mean maximum dose achieved)Max: 6 mg or 8 mg (on the basis of maximum approved dose in the country of the investigational site))Grp2: Metformin + canagliflozinFixed (prior metformin dose up-titrated if needed during screening (no change during intervention period after rz reported); seems that goal of >=2000 mg/d ideal but not mandatory)Fixed (300mg)ITT: YesFollowup (wks): 12  | Def:All-cause mortalityIncidence Grp1: 0 (0) Incidence Grp2: 0 (0)  |  |  |  |
| Chien, 2007[24](#_ENREF_24)RCT | Grp1: MetforminVaried, glucose: 140 mg/dLStart: 1000mg, Mean: 1910 mg, Max: 2000 mgD: 4 wksGrp2: GlyburideVaried, glucose: 140Start: 10 mg, Mean: 19 mg, Max: 20 mgD: 4 wks | Grp1: 0 (0)Grp2: 0 (0) |  |  |  |
| Chien, 2007[24](#_ENREF_24)RCT | Grp1: MetforminVaried, glucose: <140 mg/dLStart: 1000 mg, Max: 2000 mg, Final mean: 1910 mgD: 4 wksGrp2: Metformin + glyburideVaried, glucose: <140 mg/dLStart: 1000 mg, Max: 2000 mg, Final mean: 1680 mg; Start: 5 mg, Max: 10 mg, Final mean: 8.4 mgD: 4 wks | Grp1: 0 (0)Grp2: 0 (0) |  |  |  |
| Corrao, 2011[192](#_ENREF_192)Retrospective cohort | Grp1: MetforminNot specified  Grp2: SUNot specified  ITT: YesFollowup (wks): 12  | Def:All-cause mortalityIncidence Grp1: 0 (0) Incidence Grp2: 0 (0)  |  |  |  |
| Corrao, 2011[192](#_ENREF_192)Retrospective cohort | Grp1: MetforminNot specified  Grp2: SUNot specified  ITT: YesFollowup (wks): 12  | Def:All-cause mortalityIncidence Grp1: 0 (0) Incidence Grp2: 0 (0)  |  |  |  |
| DeFronzo, 1995[27](#_ENREF_27)RCT | Grp1: MetforminVariedStart: 500 mg, Max: 2500 mgGrp2: GlyburideVariedStart: 5 mg bid, Max: 10 mg bid | Grp1: 1 (0.5)Grp2: 0 (0) | Def: CVD mortality/Fatal MIGrp1: 1 (0.5)Grp2: 0 (0) |  |  |
| DeFronzo, 1995[27](#_ENREF_27)RCT | Grp1: MetforminVariedStart: 500 mg, Max: 2500 mgGrp2: Metformin + glyburideVariedStart: 500 mg, Max: 2500 mg; Start: 10 mg, Max: 20 mg | Grp1: 1 (1))Grp2: 0 (0) |  |  |  |
| DeFronzo, 2012[31](#_ENREF_31)RCT | Grp1: Metformin + placeboFixed (Mean: 1937mgwas fixed after stabilization/run-in)Grp2: Metformin + pioglitazone + placeboFixed (Mean: 1893mgfixed dose after run-in)Fixed (15mg)ITT: NoFollowup (wks): 24  | Def:All-cause mortalityIncidence Grp1: 0 (0) Incidence Grp2: 0 (0)  |  |  |  |
| DeFronzo, 2012[31](#_ENREF_31)RCT | Grp1: Metformin + placeboFixed (Mean: 1937mgwas fixed after stabilization/run-in)Grp2: Metformin + pioglitazone + placeboFixed (Mean: 1854mgfixed after run-in)Fixed (30mg)ITT: NoFollowup (wks): 24  | Def:All-cause mortalityIncidence Grp1: 0 (0) Incidence Grp2: 0 (0)  |  |  |  |
| DeFronzo, 2012[31](#_ENREF_31)RCT | Grp1: Metformin + placeboFixed (Mean: 1937mgwas fixed after stabilization/run-in)Grp2: Metformin + pioglitazone + placeboFixed (Mean: 1919mgfixed after run in)Fixed (45mg)ITT: YesFollowup (wks): 12  | Def:All-cause mortalityIncidence Grp1: 0   Incidence Grp2: 0    |  |  |  |
| DeFronzo, 2012[31](#_ENREF_31)RCT | Grp1: Metformin + placeboFixed (Mean: 1937mgwas fixed after stabilization/run-in)Grp2: Metformin + pioglitazone + placeboFixed (Mean: 1893mgfixed dose after run-in)Fixed (15mg)ITT: NoFollowup (wks): 104 NR/unclear | Def:All-cause mortalityIncidence Grp1: 5   Persons p NR Incidence Grp2: 5   Persons p NR  |  |  |  |
| DeFronzo, 2012[31](#_ENREF_31)RCT | Grp1: Metformin + placeboFixed (Mean: 1937mgwas fixed after stabilization/run-in)Grp2: Metformin + pioglitazone + placeboFixed (Mean: 1854mgfixed after run-in)Fixed (30mg)ITT: YesFollowup (wks): 18  | Def:All-cause mortalityIncidence Grp1: (0) Incidence Grp2: (0)  |  |  |  |
| DeFronzo, 2012[31](#_ENREF_31)RCT | Grp1: Metformin + placeboFixed (Mean: 1937mgwas fixed after stabilization/run-in)Grp2: Metformin + pioglitazone + placeboFixed (Mean: 1919mgfixed after run in)Fixed (45mg)ITT: YesFollowup (wks): 18  | Def:All-cause mortalityIncidence Grp1: (0) Incidence Grp2: 1 (1.1)  |  |  |  |
| DeFronzo, 2012[31](#_ENREF_31)RCT | Grp1: Metformin + placeboFixed (Mean: 1937mgwas fixed after stabilization/run-in)Grp2: Metformin + alogliptin + placeboFixed (Mean: 1902mgfixed after run in)Fixed (12.5mg)ITT: NoFollowup (wks): 24  | Def:All-cause mortalityIncidence Grp1: (0) Incidence Grp2: (0)  |  |  |  |
| DeFronzo, 2012[31](#_ENREF_31)RCT | Grp1: Metformin + placeboFixed (Mean: 1937mgwas fixed after stabilization/run-in)Grp2: Metformin + alogliptin + placeboFixed (Mean: 1851mgfixed after run in)Fixed (25mg)ITT: NoFollowup (wks): 24  | Def:All-cause mortalityIncidence Grp1: (0) Incidence Grp2: (0)  |  |  |  |
| DeFronzo, 2012[31](#_ENREF_31)RCT | Grp1: Metformin + placeboFixed (Mean: 1937mgwas fixed after stabilization/run-in)Grp2: Metformin + alogliptin + placeboFixed (Mean: 1902mgfixed after run in)Fixed (12.5mg)ITT: NoFollowup (wks):  NR/unclear | Def:All-cause mortalityIncidence Grp1: 0   p Incidence Grp2: 0   p  |  |  |  |
| DeFronzo, 2012[31](#_ENREF_31)RCT | Grp1: Metformin + placeboFixed (Mean: 1937mgwas fixed after stabilization/run-in)Grp2: Metformin + alogliptin + placeboFixed (Mean: 1851mgfixed after run in)Fixed (25mg)ITT: NoFollowup (wks):  NR/unclear | Def:All-cause mortalityIncidence Grp1: 0   p Incidence Grp2: 0   p  |  |  |  |
| DeFronzo, 2012[31](#_ENREF_31)RCT | Grp1: Metformin + pioglitazone + placeboFixed (Mean: 1919mgfixed after run in)Fixed (45mg)Grp2: Metformin + alogliptin + placeboFixed (Mean: 1902mgfixed after run in)Fixed (12.5mg)ITT: Not applicable (e.g., cohort)Followup (wks):   | Def:All-cause mortalityIncidence Grp1: 23  3246 Person-years p Rate ratio (poisson) 0.77Incidence Grp2: 304  6916 Person-years p Rate ratio (poisson) 1.95 |  |  |  |
| DeFronzo, 2012[31](#_ENREF_31)RCT | Grp1: Metformin + pioglitazone + placeboFixed (Mean: 1854mgfixed after run-in)Fixed (30mg)Grp2: Metformin + alogliptin + placeboFixed (Mean: 1902mgfixed after run in)Fixed (12.5mg)ITT: Not applicable (e.g., cohort)Followup (wks):   | Def:All-cause mortalityIncidence Grp1: 644  31497 Person-years p Rate ratio (poisson) 1 (ref)Incidence Grp2: 23  3246 Person-years p Rate ratio (poisson) 0.77 |  |  |  |
| DeFronzo, 2012[31](#_ENREF_31)RCT | Grp1: Metformin + pioglitazone + placeboFixed (Mean: 1893mgfixed dose after run-in)Fixed (15mg)Grp2: Metformin + alogliptin + placeboFixed (Mean: 1902mgfixed after run in)Fixed (12.5mg)ITT: Not applicable (e.g., cohort)Followup (wks):   | Def:All-cause mortalityIncidence Grp1: 644  31497 Person-years p Rate ratio (poisson) 1 (ref)Incidence Grp2: 118  11619 Person-years p Rate ratio (poisson) 0.65 |  |  |  |
| DeFronzo, 2012[31](#_ENREF_31)RCT | Grp1: Metformin + pioglitazone + placeboFixed (Mean: 1919mgfixed after run in)Fixed (45mg)Grp2: Metformin + alogliptin + placeboFixed (Mean: 1851mgfixed after run in)Fixed (25mg)ITT: Not applicable (e.g., cohort)Followup (wks):   | Def:All-cause mortalityIncidence Grp1: 644  31497 Person-years p Rate ratio (poisson) 1 (ref)Incidence Grp2: 304  6916 Person-years p Rate ratio (poisson) 1.95 |  |  |  |
| DeFronzo, 2012[31](#_ENREF_31)RCT | Grp1: Metformin + pioglitazone + placeboFixed (Mean: 1854mgfixed after run-in)Fixed (30mg)Grp2: Metformin + alogliptin + placeboFixed (Mean: 1851mgfixed after run in)Fixed (25mg)ITT: Not applicable (e.g., cohort)Followup (wks):   | Def:All-cause mortalityIncidence Grp1: 118  11619 Person-years p Rate ratio (poisson) 0.65Incidence Grp2: 23  3246 Person-years p Rate ratio (poisson) 0.77 |  |  |  |
| DeFronzo, 2012[31](#_ENREF_31)RCT | Grp1: Metformin + pioglitazone + placeboFixed (Mean: 1893mgfixed dose after run-in)Fixed (15mg)Grp2: Metformin + alogliptin + placeboFixed (Mean: 1851mgfixed after run in)Fixed (25mg)ITT: Not applicable (e.g., cohort)Followup (wks):   | Def:All-cause mortalityIncidence Grp1: 118  11619 Person-years p Rate ratio (poisson) 0.65Incidence Grp2: 304  6916 Person-years p Rate ratio (poisson) 1.95 |  |  |  |
| DeFronzo, 2012[31](#_ENREF_31)RCT | Grp1: Metformin + pioglitazone + placeboFixed (Mean: 1854mgfixed after run-in)Fixed (30mg)Grp2: Metformin + alogliptin + placeboFixed (Mean: 1902mgfixed after run in)Fixed (12.5mg)ITT: YesFollowup (wks):   | Def:All-cause mortalityIncidence Grp1: 0   Incidence Grp2: 0    |  |  |  |
| DeFronzo, 2012[31](#_ENREF_31)RCT | Grp1: Metformin + pioglitazone + placeboFixed (Mean: 1919mgfixed after run in)Fixed (45mg)Grp2: Metformin + alogliptin + placeboFixed (Mean: 1902mgfixed after run in)Fixed (12.5mg)ITT: Not applicable (e.g., cohort)Followup (wks):   | Def:All-cause mortalityIncidence Grp1:  222258 Person-years p NR RH 1Incidence Grp2:  5263 Person-years p NR RH 1.19 (males); 4.36 (1.34-14.20) females) |  |  |  |
| DeFronzo, 2012[31](#_ENREF_31)RCT | Grp1: Metformin + pioglitazone + placeboFixed (Mean: 1893mgfixed dose after run-in)Fixed (15mg)Grp2: Metformin + alogliptin + placeboFixed (Mean: 1902mgfixed after run in)Fixed (12.5mg)ITT: Not applicable (e.g., cohort)Followup (wks):   | Def:All-cause mortalityIncidence Grp1:  222258 Person-years p NR RH 1Incidence Grp2:  47604 Person-years p NR RH 1.55 |  |  |  |
| DeFronzo, 2012[31](#_ENREF_31)RCT | Grp1: Metformin + pioglitazone + placeboFixed (Mean: 1893mgfixed dose after run-in)Fixed (15mg)Grp2: Metformin + alogliptin + placeboFixed (Mean: 1851mgfixed after run in)Fixed (25mg)ITT: Not applicable (e.g., cohort)Followup (wks):   | Def:All-cause mortalityIncidence Grp1:  222258 Person-years p NR RH 1Incidence Grp2:  48238 Person-years p NR RH 1.38 |  |  |  |
| DeFronzo, 2012[31](#_ENREF_31)RCT | Grp1: Metformin + pioglitazone + placeboFixed (Mean: 1919mgfixed after run in)Fixed (45mg)Grp2: Metformin + alogliptin + placeboFixed (Mean: 1851mgfixed after run in)Fixed (25mg)ITT: Not applicable (e.g., cohort)Followup (wks):   | Def:All-cause mortalityIncidence Grp1:  47604 Person-years p NR RH 1.55Incidence Grp2:  5263 Person-years p NR RH 1.19 (males); 4.36 (1.34-14.20) females) |  |  |  |
| DeFronzo, 2012[31](#_ENREF_31)RCT | Grp1: Metformin + pioglitazone + placeboFixed (Mean: 1854mgfixed after run-in)Fixed (30mg)Grp2: Metformin + alogliptin + placeboFixed (Mean: 1851mgfixed after run in)Fixed (25mg)ITT: Not applicable (e.g., cohort)Followup (wks):   | Def:All-cause mortalityIncidence Grp1:  48238 Person-years p NR RH 1.38Incidence Grp2:  5263 Person-years p NR RH 1.19 (males); 4.36 (1.34-14.20) females) |  |  |  |
| Del Prato, 2015[32](#_ENREF_32) | Grp1: Metformin + glipizideTitrated 5,10,20mgGrp2: Metformin + dapagliflozinTitrated 2,5,10mg | Def: All-cause mortalityIncidence Grp1: 5 (1.2)Incidence Grp2: 2 (0.5) |  | Def: UnspecifiedIncidence Grp1: 0Incidence Grp2: 0 |  |
| Del Prato, 2014[33](#_ENREF_33) | Grp1: Metformin + glipizideTitrated 1823.4 mgTitrated 5 mgGrp2: Metformin + alogliptinTitrated 1825.2 mgFixed 12.5 mg | Def: All-cause mortalityIncidence Grp1: 5(0.6)Incidence Grp2: 3(0.3) | Def: UnspecifiedIncidence Grp1: NR(0.5)Incidence Grp2: NR(0.2) | Def: Composite outcomeIncidence Grp1: NR(1.3)Incidence Grp2: NR(0.7)Def: Nonfatal MIIncidence Grp1: Nr(0.5)Incidence Grp2: NR(0.1)Def: Nonfatal strokeIncidence Grp1: NR(0.3)Incidence Grp2: NR(0.3) |  |
| Del Prato, 2014[33](#_ENREF_33) | Grp1: Metformin + glipizideTitrated 1823.4 mgTitrated 5 mgGrp2: Metformin + alogliptinTitrated 1837.2 mgFixed 25 mg | Def: All-cause mortalityIncidence Grp1: 5(1.2)Incidence Grp2: 2(0.5) | Def: UnspecifiedIncidence Grp1:NR(0.5)Incidence Grp2: NR(0.2) | Def: Composite outcomeIncidence Grp1: NR(1.3)Incidence Grp2: NR(0.9)Def: Nonfatal MIGrp1: NR(0.5)Grp2: NR(0.5)Def: Nonfatal strokeIncidence Grp1: NR(0.3)Incidence Grp2: NR(0.2) |  |
| Diamant, 2010[44](#_ENREF_44)RCT | Grp1: Metformin + exenatideNot specified (continued stable dose)Fixed (2mg weekly)Grp2: Metformin + insulin glargineNot specified (continued stable dose)Titrated (started at 10 IU per day but adjusted by patient to keep glucose at 4-5.5mmol/L)ITT: YesFollowup (wks): 12 Active | Def:All-cause mortalityIncidence Grp1: 0   Incidence Grp2: 0    |  |  |  |
| Diamant, 2010[44](#_ENREF_44)RCT | Grp1: Metformin + exenatideNot specified (continued stable dose)Fixed (2mg weekly)Grp2: Metformin + insulin glargineNot specified (continued stable dose)Titrated (started at 10 IU per day but adjusted by patient to keep glucose at 4-5.5mmol/L)ITT: YesFollowup (wks): 24 Passive | Def:All-cause mortalityIncidence Grp1: 0   Incidence Grp2: 0    |  |  |  |
| Ekstrom, 2012[193](#_ENREF_193)Retrospective cohort | Grp1: MetforminNot specified (Median: 1100mg)Grp2: Metformin + basal insulinNot specified (Median: 1700mg)Not specified  ITT: YesFollowup (wks): 12  | Def:All-cause mortalityIncidence Grp1: 0   Incidence Grp2: 0    |  |  |  |
| Ekstrom, 2012[193](#_ENREF_193)Retrospective cohort | Grp1: MetforminNot specified (Median: 1100mg)Grp2: Metformin + basal insulinNot specified (Median: 1700mg)Not specified  ITT: NoFollowup (wks): 58  | Def:All-cause mortalityIncidence Grp1: 7   Incidence Grp2: 3    |  |  |  |
| Ekstrom, 2012[193](#_ENREF_193)Retrospective cohort | Grp1: MetforminNot specified (Median: 1100mg) Grp2: Metformin + basal insulinNot specified (Median: 1700mg)Not specified  ITT: YesFollowup (wks): 144  | Def:All-cause mortalityIncidence Grp1: 7   NA p 0.55 Incidence Grp2: 14   NA p  |  |  |  |
| Erem, 2014[47](#_ENREF_47)RCT | Grp1: MetforminTitrated (Max: 2000mg4-8 wks of titration then fixed after that - article reported all patients ended up on 2000 mg)Grp2: PioglitazoneTitrated (Max: 45mg according to glycemic controlinitiated at 15mg/day and titrated in first 4-8 wks then fixed after that (ended up 6 pts on 15 mg, 12 pts on 30 mg and 1 pt on 45 mg))ITT: YesFollowup (wks): 24 NR/unclear | Def:All-cause mortalityIncidence Grp1: 1 (0.7) Persons p Incidence Grp2: 1 (0.7) Persons p  |  |  |  |
| Erem, 2014[47](#_ENREF_47)RCT | Grp1: MetforminTitrated (Max: 2000mg4-8 wks of titration then fixed after that - article reported all patients ended up on 2000 mg)Grp2: PioglitazoneTitrated (Max: 45mg according to glycemic controlinitiated at 15mg/day and titrated in first 4-8 wks then fixed after that (ended up 6 pts on 15 mg, 12 pts on 30 mg and 1 pt on 45 mg))ITT: Not applicable (e.g., cohort)Followup (wks):  NR/unclear | Def:All-cause mortalityIncidence Grp1: 971   NA p NR RH 1.00 REFIncidence Grp2: 818   NA p NR RH 1.25 |  |  |  |
| Esposito, 2011[48](#_ENREF_48)RCT | Grp1: MetforminTitrated (Max: 1000mg twice dailyend of titration: 36% on 1500 mg/d and 64% on 2000 mg/d)Grp2: PioglitazoneTitrated (Max: 45 mgend of titration period: 27% on 30 mg/d and 72% on 45 mg/d)ITT: NoFollowup (wks):  NR/unclear | Def:All-cause mortalityIncidence Grp1: 5   Persons p NR Incidence Grp2: 5   Persons p NR  |  |  |  |
| Ferrannini, 2013[194](#_ENREF_194)RCT | Grp1: MetforminTitrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose)Grp2: EmpagliflozinFixed (10mg)ITT: NoFollowup (wks): 24 NR/unclear | Def:All-cause mortalityIncidence Grp1: 0 (0) p Incidence Grp2: 0 (0) p  |  |  |  |
| Ferrannini, 2013[194](#_ENREF_194)RCT | Grp1: MetforminTitrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose)Grp2: EmpagliflozinFixed (25mg)ITT: Not applicable (e.g., cohort)Followup (wks): 114.4  | Def:All-cause mortalityIncidence p RH Incidence p RH 1.64 |  |  |  |
| Ferrannini, 2013[194](#_ENREF_194)RCT | Grp1: MetforminTitrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose)Grp2: EmpagliflozinFixed (10mg)ITT: Not applicable (e.g., cohort)Followup (wks): 114.4  | Def:All-cause mortalityIncidence p RH Incidence p RH 1.59 |  |  |  |
| Ferrannini, 2013[194](#_ENREF_194)RCT | Grp1: MetforminTitrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose)Grp2: EmpagliflozinFixed (25mg)ITT: Not applicable (e.g., cohort)Followup (wks): 114.4  | Def:All-cause mortalityIncidence p RH Incidence p RH 1.68 |  |  |  |
| Ferrannini, 2013[194](#_ENREF_194)RCT | Grp1: MetforminTitrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose)Grp2: EmpagliflozinFixed (10mg)ITT: NoFollowup (wks): 36 NR/unclear | Def:All-cause mortalityIncidence Grp1: 1   p Incidence p  |  |  |  |
| Ferrannini, 2013[194](#_ENREF_194)RCT | Grp1: MetforminTitrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose)Grp2: EmpagliflozinFixed (10mg)ITT: NoFollowup (wks): 36 NR/unclear | Def:All-cause mortalityIncidence Grp1: 1   p Incidence p  |  |  |  |
| Ferrannini, 2013[194](#_ENREF_194)RCT | Grp1: MetforminTitrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose)Grp2: EmpagliflozinFixed (10mg)ITT: NoFollowup (wks): 36 NR/unclear | Def:All-cause mortalityIncidence Grp1: 1   p Incidence p  |  |  |  |
| Ferrannini, 2013[194](#_ENREF_194)RCT | Grp1: MetforminTitrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose)Grp2: EmpagliflozinFixed (25mg)ITT: NoFollowup (wks): 36 NR/unclear | Def:All-cause mortalityIncidence p Incidence p  |  |  |  |
| Ferrannini, 2013[194](#_ENREF_194)RCT | Grp1: MetforminTitrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose)Grp2: EmpagliflozinFixed (25mg)ITT: NoFollowup (wks): 36 NR/unclear | Def:All-cause mortalityIncidence p Incidence p  |  |  |  |
| Ferrannini, 2013[194](#_ENREF_194)RCT | Grp1: MetforminTitrated (Mean: 1567 mg/dayMax: a maximum of 1000 mg twice daily or the maximum tolerated dose1668 mg is mean final dose)Grp2: EmpagliflozinFixed (25mg)ITT: NoFollowup (wks): 36 NR/unclear | Def:All-cause mortalityIncidence p Incidence p  |  |  |  |
| Fonseca, 2000[55](#_ENREF_55)RCT | Grp1: MetforminFixedStart: 2500 mgGrp2: Metformin + rosiglitazoneFixedStart: 2500 mg; Start: 8 mg | Grp1: 0 (0)Grp2: 1 (1) | Def: CVD mortality/unclear mortality + Fatal MIGrp1: 0 (0)Grp2: 0 (0) |  |  |
| Fonseca, 2012[56](#_ENREF_56)RCT | Grp1: MetforminTitrated (Max: 2000 mg/duptitration from 1500 to 2000 mg/d)Grp2: Metformin + saxagliptinFixed (1500 mg/d)Fixed (5mg/d)ITT: NoFollowup (wks): 52 NR/unclear | Def:All-cause mortalityIncidence p Incidence Grp2: 1   p  |  |  |  |
| Forst, 2010[57](#_ENREF_57)RCT | Grp1: Metformin + placeboFixed (17of 70 patients receiving <1500 mg and 53 of 70 receiving >=1500 mg)Grp2: Metformin + glimepirideFixed  Titrated (Max: 3 mgstarted from 1mg for 4 wks, thereafter uptitrate the daily dose up to 3mg according to investigator's discretion)ITT: YesFollowup (wks): 24 NR/unclear | Def:All-cause mortalityIncidence p Incidence p  |  |  |  |
| Forst, 2010[57](#_ENREF_57)RCT | Grp1: Metformin + placeboFixed (17of 70 patients receiving <1500 mg and 53 of 70 receiving >=1500 mg)Grp2: Metformin + linagliptinFixed (11 of 62 were on <1500 mg met; 51 of 62 were on >=1500 mg metformin)Fixed (5mg)ITT: NoFollowup (wks): 80  | Def:All-cause mortalityIncidence Grp1: 1   p Incidence Grp2: 2   p  |  |  |  |
| Forst, 2010[57](#_ENREF_57)RCT | Grp1: Metformin + glimepirideFixed  Titrated (Max: 3 mgstarted from 1mg for 4 wks, thereafter uptitrate the daily dose up to 3mg according to investigator's discretion)Grp2: Metformin + linagliptinFixed (11 of 62 were on <1500 mg met; 51 of 62 were on >=1500 mg metformin)Fixed (5mg)ITT: Not applicable (e.g., cohort)Followup (wks): 91.52 NR/unclear | Def:All-cause mortalityIncidence Grp1: 1548   p RH 1Incidence Grp2: 1546   p RH 1.19 |  |  |  |
| Gallwitz, 2012[61](#_ENREF_61)RCT | Grp1: Metformin + glimepiride + placeboFixed (stable dose of 1500mg per day or more (or a maximum tolerated dose less than 1500mg per day))Titrated (Mean: 3.0 mgMax: 4 mg once daily)Grp2: Metformin + linagliptin + placeboFixed (stable dose of 1500mg per day or more (maximum tolerated dose less than 1500mg per day))Fixed (5 mg once daily)ITT: Not applicable (e.g., cohort)Followup (wks):  NR/unclear | Def:All-cause mortalityIncidence Grp1: 213   p RH 1Incidence Grp2: 265   p RH 1.47 |  |  |  |
| Gallwitz, 2012[61](#_ENREF_61)RCT | Grp1: Metformin + glimepiride + placeboFixed (stable dose of 1500mg per day or more (or a maximum tolerated dose less than 1500mg per day))Titrated (Mean: 3.0 mgMax: 4 mg once daily)Grp2: Metformin + linagliptin + placeboFixed (stable dose of 1500mg per day or more (maximum tolerated dose less than 1500mg per day))Fixed (5 mg once daily)ITT: Not applicable (e.g., cohort)Followup (wks): 91.52 NR/unclear | Def:All-cause mortalityIncidence Grp1: 1548   p RH 1Incidence Grp2: 947   p RH 1.27 |  |  |  |
| Gallwitz, 2012[61](#_ENREF_61)RCT | Grp1: Metformin + glimepiride + placeboFixed (stable dose of 1500mg per day or more (or a maximum tolerated dose less than 1500mg per day))Titrated (Mean: 3.0 mgMax: 4 mg once daily)Grp2: Metformin + linagliptin + placeboFixed (stable dose of 1500mg per day or more (maximum tolerated dose less than 1500mg per day))Fixed (5 mg once daily)ITT: Not applicable (e.g., cohort)Followup (wks):  NR/unclear | Def:All-cause mortalityIncidence Grp1: 213   p RH 1Incidence Grp2: 141   p RH 1.53 |  |  |  |
| Gallwitz, 2012[61](#_ENREF_61)RCT | Grp1: Metformin + glimepiride + placeboFixed (stable dose of 1500mg per day or more (or a maximum tolerated dose less than 1500mg per day))Titrated (Mean: 3.0 mgMax: 4 mg once daily)Grp2: Metformin + linagliptin + placeboFixed (stable dose of 1500mg per day or more (maximum tolerated dose less than 1500mg per day))Fixed (5 mg once daily)ITT: Not applicable (e.g., cohort)Followup (wks):  NR/unclear | Def:All-cause mortalityIncidence Grp1: 213   p RH 1Incidence Grp2: 737   p RH 1.3 |  |  |  |
| Gallwitz, 2012[61](#_ENREF_61)RCT | Grp1: Metformin + glimepiride + placeboFixed (stable dose of 1500mg per day or more (or a maximum tolerated dose less than 1500mg per day))Titrated (Mean: 3.0 mgMax: 4 mg once daily)Grp2: Metformin + linagliptin + placeboFixed (stable dose of 1500mg per day or more (maximum tolerated dose less than 1500mg per day))Fixed (5 mg once daily)ITT: Not applicable (e.g., cohort)Followup (wks): 91.52 NR/unclear | Def:All-cause mortalityIncidence Grp1: 1548   p RH 1Incidence Grp2: 4081   p RH 1.32 |  |  |  |
| Gallwitz, 2012[61](#_ENREF_61)RCT | Grp1: Metformin + glimepiride + placeboFixed (stable dose of 1500mg per day or more (or a maximum tolerated dose less than 1500mg per day))Titrated (Mean: 3.0 mgMax: 4 mg once daily)Grp2: Metformin + linagliptin + placeboFixed (stable dose of 1500mg per day or more (maximum tolerated dose less than 1500mg per day))Fixed (5 mg once daily)ITT: YesFollowup (wks): 44 Active | Def:All-cause mortalityIncidence Grp1: 2 (0.3) Incidence Grp2: 1 (0.2)  |  |  |  |
| Gallwitz, 2012[61](#_ENREF_61)RCT | Grp1: Metformin + glimepiride + placeboFixed (stable dose of 1500mg per day or more (or a maximum tolerated dose less than 1500mg per day))Titrated (Mean: 3.0 mgMax: 4 mg once daily)Grp2: Metformin + linagliptin + placeboFixed (stable dose of 1500mg per day or more (maximum tolerated dose less than 1500mg per day))Fixed (5 mg once daily)ITT: YesFollowup (wks): 76  | Def:All-cause mortalityIncidence Grp1: 5 (1.5) Incidence Grp2: 2 (0.6)  |  |  |  |
| Gallwitz, 2012[62](#_ENREF_62)RCT | Grp1: Metformin + glimepirideNot specified (Mean: 1989 mg)Titrated (Mean: 2.01 mginitial dose 1 mg; could be titrated per attending physician every 4 wks based on maximum tolerated dose and country guidelines)Grp2: Metformin + exenatideNot specified (Mean: 1956 mg)Titrated (Mean: 17.35 micgrogramsMax: 20 microgramsstarted at 5 microgm bid and titrated if possible based on GI sxs)ITT: YesFollowup (wks): 76  | Def:All-cause mortalityIncidence Grp1: 5 (1.5) Incidence Grp2: 1 (0.3)  |  |  |  |
| Garber, 2003[64](#_ENREF_64)RCT | Grp1: MetforminVariedStart: 500 mg, max: 2000 mgGrp2: GlyburideVariedStart: 2.5 mg, max: 10 mg | Grp1: 0 (0)Grp2: 0 (0) |  |  |  |
| Garber, 2003[64](#_ENREF_64)RCT | Grp1: MetforminVariedStart: 500 mg, Max: 2000 mgGrp2: Metformin + glyburideVariedStart: 500 mg, Max: 2000 mg; Start: 1.25 mg, Max: 20 mg | Grp1: 0 (0)Grp2: 2 (1) |  |  |  |
| Garber, 2011[67](#_ENREF_67)RCT | Grp1: Glimepiride + placeboTitrated (Max: 8mg)Grp2: Liraglutide + placeboTitrated (Max: 1.2 mg)ITT: YesFollowup (wks): 76  | Def:All-cause mortalityIncidence Grp1: 5 (1.5) Incidence Grp2: 2 (0.6)  |  |  |  |
| Garber, 2011[67](#_ENREF_67)RCT | Grp1: Glimepiride + placeboTitrated (Max: 8mg)Grp2: Liraglutide + placeboTitrated (Max: 1.8 mg)ITT: YesFollowup (wks): 76  | Def:All-cause mortalityIncidence Grp1: 2 (0.6) Incidence Grp2: 1 (0.3)  |  |  |  |
| Garber, 2011[67](#_ENREF_67)RCT | Grp1: Glimepiride + placeboTitrated (Max: 8mg)Grp2: Liraglutide + placeboTitrated (Max: 1.2 mg)ITT: YesFollowup (wks): 76  | Def:All-cause mortalityIncidence Grp1: 2 (0.6) Incidence Grp2: 2 (0.6)  |  |  |  |
| Garber, 2011[67](#_ENREF_67)RCT | Grp1: Glimepiride + placeboTitrated (Max: 8mg)Grp2: Liraglutide + placeboTitrated (Max: 1.2 mg)ITT: YesFollowup (wks): 24  | Def:All-cause mortalityIncidence Grp1: 0   Persons p NR Incidence Grp2: 0   Persons p NR  |  |  |  |
| Garber, 2011[67](#_ENREF_67)RCT | Grp1: Glimepiride + placeboTitrated (Max: 8mg)Grp2: Liraglutide + placeboTitrated (Max: 1.8 mg)ITT: YesFollowup (wks): 104 NR/unclear | Def:All-cause mortalityIncidence Grp1: 1   Incidence Grp2: 0    |  |  |  |
| Garber, 2011[67](#_ENREF_67)RCT | Grp1: Glimepiride + placeboTitrated (Max: 8mg)Grp2: Liraglutide + placeboTitrated (Max: 1.8 mg)ITT: YesFollowup (wks): 104 NR/unclear | Def:All-cause mortalityIncidence Grp1: 1   Incidence Grp2: 1    |  |  |  |
| Garber, 2011[67](#_ENREF_67)RCT | Grp1: Glimepiride + placeboTitrated (Max: 8mg)Grp2: Liraglutide + placeboTitrated (Max: 1.2 mg)ITT: NoFollowup (wks): 30  | Def:All-cause mortalityIncidence Grp1: 1   Persons p NR Incidence Grp2: 0   Persons p NR  |  |  |  |
| Garber, 2011[67](#_ENREF_67)RCT | Grp1: Glimepiride + placeboTitrated (Max: 8mg)Grp2: Liraglutide + placeboTitrated (Max: 1.8 mg)ITT: Not applicable (e.g., cohort)Followup (wks):   | Def:All-cause mortalityIncidence p RH Incidence p RH 1.37 |  |  |  |
| Genovese, 2013[68](#_ENREF_68)RCT | Grp1: Metformin + placeboFixed (2550 mg)Grp2: Metformin + pioglitazoneFixed (2550 mg)Fixed (45titrated from 30 mg to 45 mg in first four wks then fixed at 45 for 20 wks)ITT: YesFollowup (wks): 104  | Def:All-cause mortalityIncidence Grp1: 2 (0.5) Incidence Grp2: 4 (0.9)  |  |  |  |
| Genovese, 2013[69](#_ENREF_69)RCT | Grp1: MetforminTitrated (starting dose of 850mg/day, up-titrated to 1700mg or 2550mg in later visits depending on the glycemic response)Grp2: Pioglitazone + placeboTitrated (Max: 45mgstarting dose of 30mg qd, up-titrated to 45mg qd in later visits in the case of poor response)ITT: Not applicable (e.g., cohort)Followup (wks):  NR/unclear | Def:All-cause mortalityIncidence Grp1: 239 (35) 1533 Person-years p NR 0.85Incidence Grp2: 2344 (65) 9570 Person-years p NR 1.00 REF |  |  |  |
| Goke, 2010[70](#_ENREF_70)RCT | Grp1: Metformin + glipizideFixed (>/= 1500 mgMean: 1883 mg)Titrated (Mean: 14.7 mg/dayMax: 20 mg/day)Grp2: Metformin + saxagliptin (>/= 1500 mgMean: 1938 mg)Fixed (5 mg Γüä day)ITT: Not applicable (e.g., cohort)Followup (wks):  NR/unclear | Def:All-cause mortalityIncidence Grp1: 239 (35) 1533 Person-years p NR 0.85Incidence Grp2: 759 (49) 4280 Person-years p NR 0.89 |  |  |  |
| Goke, 2010[70](#_ENREF_70)RCT | Grp1: Metformin + glipizideFixed (>/= 1500 mgMean: 1883 mg)Titrated (Mean: 14.7 mg/dayMax: 20 mg/day)Grp2: Metformin + saxagliptin (>/= 1500 mgMean: 1938 mg)Fixed (5 mg Γüä day)ITT: Not applicable (e.g., cohort)Followup (wks):  NR/unclear | Def:All-cause mortalityIncidence Grp1: 2344 (65) 9570 Person-years p NR 1.00 REFIncidence Grp2: 759 (49) 4280 Person-years p NR 0.89 |  |  |  |
| Goke, 2010[70](#_ENREF_70)RCT | Grp1: Metformin + glipizideFixed (>/= 1500 mgMean: 1883 mg)Titrated (Mean: 14.7 mg/dayMax: 20 mg/day)Grp2: Metformin + saxagliptin (>/= 1500 mgMean: 1938 mg)Fixed (5 mg Γüä day)ITT: YesFollowup (wks): 26  | Def:All-cause mortalityIncidence Grp1: 0 (0) Incidence Grp2: 0 (0)  |  |  |  |
| Goke, 2010[70](#_ENREF_70)RCT | Grp1: Metformin + glipizideFixed (>/= 1500 mgMean: 1883 mg)Titrated (Mean: 14.7 mg/dayMax: 20 mg/day)Grp2: Metformin + saxagliptin (>/= 1500 mgMean: 1938 mg)Fixed (5 mg Γüä day)ITT: NoFollowup (wks): 26  | Def:All-cause mortalityIncidence Grp1: 0   Persons p Incidence Grp2: 0   Persons p  |  |  |  |
| Goke, 2010[70](#_ENREF_70)RCT | Grp1: Metformin + glipizideFixed (>/= 1500 mgMean: 1883 mg)Titrated (Mean: 14.7 mg/dayMax: 20 mg/day)Grp2: Metformin + saxagliptin (>/= 1500 mgMean: 1938 mg)Fixed (5 mg Γüä day)ITT: YesFollowup (wks): 26 NR/unclear | Def:All-cause mortalityIncidence Grp1:   Incidence Grp2: 1    |  |  |  |
| Goldstein, 2003[71](#_ENREF_71)RCT | Grp1: MetforminVariedStart: 500 mg, Max: 2000 mgGrp2: GlipizideFixedStart: 15mg bid | Grp1: 0 (0)Grp2: 0 (0) |  |  |  |
| Goldstein, 2003[71](#_ENREF_71)RCT | Grp1: MetforminVariedStart: 500 mg, Max: 2000 mgGrp2: Metformin + glipizideVariedStart: 500 mg, Max: 2000 mg; Start: 5 mg, Max: 20 mg | Grp1: 0 (0)Grp2: 0 (0) |  |  |  |
| Gomez-Perez, 2002[73](#_ENREF_73)RCT | Grp1: MetforminFixedStart: 2500 mgGrp2: Metformin + rosiglitazoneFixedStart: 2500 mg; Start: 2 mg bid |  |  | Def: CVD morbidity/ischemic heart disease + bundle branch block + tachycardiaGrp1: 1 (3)Grp2: 1 (3) |  |
| Gomez-Perez, 2002[73](#_ENREF_73)RCT | Grp1: MetforminFixedStart: 2500 mgGrp2: Metformin + rosiglitazoneFixedStart: 2500 mg; Start: 4 mg bid |  |  | Def: CVD morbidity/ischemic heart disease + bundle branch block + tachycardiaGrp1: 1 (3)Grp2: 2 (5) |  |
| Haak, 2012[77](#_ENREF_77)RCT | Grp1: MetforminTitrated (Max: 2000 mg)Grp2: LinagliptinFixed (5 mg)ITT: YesFollowup (wks): 26 NR/unclear | Def:All-cause mortalityIncidence Grp1:   Incidence Grp2:    |  |  |  |
| Haak, 2012[77](#_ENREF_77)RCT | Grp1: MetforminFixed (1000 mg)Grp2: LinagliptinFixed (5 mg)ITT: YesFollowup (wks): 26 NR/unclear | Def:All-cause mortalityIncidence Grp1: 1   Incidence Grp2:    |  |  |  |
| Haak, 2012[77](#_ENREF_77)RCT | Grp1: MetforminFixed (1000 mg)Grp2: LinagliptinFixed (5 mg)ITT: YesFollowup (wks): 104  | Def:All-cause mortalityIncidence Grp1: 0 (0) Incidence Grp2: 0 (0)  |  |  |  |
| Haak, 2012[77](#_ENREF_77)RCT | Grp1: MetforminTitrated (Max: 2000 mg)Grp2: LinagliptinFixed (5 mg)ITT: YesFollowup (wks): 104  | Def:All-cause mortalityIncidence Grp1: 1 (0.5) Incidence Grp2: 0 (0)  |  |  |  |
| Haak, 2012[77](#_ENREF_77)RCT | Grp1: MetforminTitrated (Max: 2000 mg)Grp2: Metformin + linagliptinFixed (1000 mg)Fixed (5 mg)ITT: YesFollowup (wks): 104  | Def:All-cause mortalityIncidence Grp1: 2 (1.1) Incidence Grp2: 0 (0)  |  |  |  |
| Haak, 2012[77](#_ENREF_77)RCT | Grp1: MetforminFixed (1000 mg)Grp2: Metformin + linagliptinFixed (1000 mg)Fixed (5 mg)ITT: YesFollowup (wks): 104  | Def:All-cause mortalityIncidence Grp1: 2 (1.1) Incidence Grp2: 1 (0.6)  |  |  |  |
| Haak, 2012[77](#_ENREF_77)RCT | Grp1: MetforminFixed (1000 mg)Grp2: Metformin + linagliptinTitrated (Max: 2000 mg)Fixed (5 mg)ITT: YesFollowup (wks): 104  | Def:All-cause mortalityIncidence Grp1: 0 (0) Incidence Grp2: 1 (0.6)  |  |  |  |
| Haak, 2012[77](#_ENREF_77)RCT | Grp1: MetforminTitrated (Max: 2000 mg)Grp2: Metformin + linagliptinTitrated (Max: 2000 mg)Fixed (5 mg)ITT: YesFollowup (wks): 104  | Def:All-cause mortalityIncidence Grp1: 1 (0.5) Incidence Grp2: 1 (0.6)  |  |  |  |
| Haak, 2012[77](#_ENREF_77)RCT | Grp1: MetforminTitrated (Max: 2000 mg)Grp2: Metformin + linagliptinFixed (1000 mg)Fixed (5 mg)ITT: YesFollowup (wks): 104  | Def:All-cause mortalityIncidence Grp1: 2 (1.1) Incidence Grp2: 1 (0.6)  |  |  |  |
| Haak, 2012[77](#_ENREF_77)RCT | Grp1: MetforminFixed (1000 mg)Grp2: Metformin + linagliptinFixed (1000 mg)Fixed (5 mg)ITT: YesFollowup (wks): 104  | Def:All-cause mortalityIncidence Grp1: 1 (0.5) Incidence Grp2: 1 (0.6)  |  |  |  |
| Haak, 2012[77](#_ENREF_77)RCT | Grp1: MetforminFixed (1000 mg)Grp2: Metformin + linagliptinTitrated (Max: 2000 mg)Fixed (5 mg)ITT: YesFollowup (wks): 104  | Def:All-cause mortalityIncidence Grp1: 0 (0) Incidence Grp2: 1 (0.6)  |  |  |  |
| Haak, 2012[77](#_ENREF_77)RCT | Grp1: MetforminTitrated (Max: 2000 mg)Grp2: Metformin + linagliptinTitrated (Max: 2000 mg)Fixed (5 mg)ITT: YesFollowup (wks): 104  | Def:All-cause mortalityIncidence Grp1: 0 (0) Incidence Grp2: 1 (0.6)  |  |  |  |
| Haak, 2012[77](#_ENREF_77)RCT | Grp1: LinagliptinFixed (5 mg)Grp2: Metformin + linagliptinFixed (1000 mg)Fixed (5 mg)ITT: YesFollowup (wks): 104  | Def:All-cause mortalityIncidence Grp1: 0 (0) Incidence Grp2: 1 (0.6)  |  |  |  |
| Haak, 2012[77](#_ENREF_77)RCT | Grp1: LinagliptinFixed (5 mg)Grp2: Metformin + linagliptinTitrated (Max: 2000 mg)Fixed (5 mg)ITT: Not applicable (e.g., cohort)Followup (wks):   | Def:All-cause mortalityIncidence Grp1: 3024 (3.6) p NR RR 1.0 REFIncidence Grp2: 49 (4) p NR RR 1.25 |  |  |  |
| Haak, 2012[77](#_ENREF_77)RCT | Grp1: LinagliptinFixed (5 mg) Grp2: Metformin + linagliptinFixed (1000 mg)Fixed (5 mg)ITT: NoFollowup (wks): 24 NR/unclear | Def:All-cause mortalityIncidence Grp1: 1 (0.5) Incidence Grp2: 0    |  |  |  |
| Haak, 2012[77](#_ENREF_77)RCT | Grp1: LinagliptinFixed (5 mg)Grp2: Metformin + linagliptinTitrated (Max: 2000 mg)Fixed (5 mg)ITT: NoFollowup (wks): 24 NR/unclear | Def:All-cause mortalityIncidence Grp1: 1 (0.5) Incidence Grp2: 0    |  |  |  |
| Haak, 2013[78](#_ENREF_78)RCT | Grp1: MetforminTitrated (Max: 2000 mg)Grp2: Metformin + linagliptinFixed (1000 mg)Fixed (5.0 mg)ITT: NoFollowup (wks): 24 NR/unclear | Def:All-cause mortalityIncidence Grp1: 0   Incidence Grp2: 0    |  |  |  |
| Haak, 2013[78](#_ENREF_78)RCT | Grp1: MetforminTitrated (Max: 2000 mg)Grp2: Metformin + linagliptinTitrated (Max: 2000 mg)Fixed (5 mg)ITT: YesFollowup (wks): 26  |  |  |  | Def:CerebrovascularFatal strokeIncidence Grp1: 0  177 Persons p NR Incidence Grp2: 0  315 Persons p NR  |
| Haak, 2013[78](#_ENREF_78)RCT | Grp1: MetforminTitrated (Max: 2000 mg)Grp2: Metformin + linagliptinFixed (1000 mg)Fixed (5.0 mg)ITT: YesFollowup (wks): 26  |  |  |  | Def:CerebrovascularFatal strokeIncidence Grp1: 0  177 Persons p NR Incidence Grp2: 0  302 Persons p NR  |
| Haak, 2013[78](#_ENREF_78)RCT | Grp1: MetforminTitrated (Max: 2000 mg)  Grp2: Metformin + linagliptinTitrated (Max: 2000 mg)Fixed (5 mg)ITT: YesFollowup (wks): 26  |  |  |  | Def:CerebrovascularFatal strokeIncidence Grp1: 0  177 Persons p NR Incidence Grp2: 1  304 Persons p NR  |
| Haak, 2013[78](#_ENREF_78)RCT | Grp1: MetforminTitrated (Max: 2000 mg)Grp2: Metformin + linagliptinFixed (1000 mg)Fixed (5.0 mg)ITT: YesFollowup (wks): 26  |  |  |  | Def:CerebrovascularFatal strokeIncidence Grp1: 0  315 Persons p NR Incidence Grp2: 0  302 Persons p NR  |
| Haak, 2013[78](#_ENREF_78)RCT | Grp1: MetforminTitrated (Max: 2000 mg)Grp2: Metformin + linagliptinFixed (1000 mg)Fixed (5.0 mg)ITT: YesFollowup (wks): 26  |  |  |  | Def:CerebrovascularFatal strokeIncidence Grp1: 0  315 Persons p NR Incidence Grp2: 1  304 Persons p NR  |
| Haak, 2013[78](#_ENREF_78)RCT | Grp1: MetforminTitrated (Max: 2000 mg)Grp2: Metformin + linagliptinTitrated (Max: 2000 mg)Fixed (5 mg)ITT: NoFollowup (wks): 26 Active |  |  |  | Def:CerebrovascularNot-fatal stroke (ischemic stroke and cerebrovascular accident)Incidence Grp1: 1 315  Incidence Grp2:    |
| Haak, 2013[78](#_ENREF_78)RCT | Grp1: MetforminTitrated (Max: 2000 mg)Grp2: Metformin + linagliptinTitrated (Max: 2000 mg)Fixed (5 mg)ITT: NoFollowup (wks): 26 Active |  |  |  | Def:CerebrovascularNot-fatal stroke (ischemic stroke and cerebrovascular accident)Incidence Grp1:  1 315 Incidence Grp2:    |
| Haak, 2013[78](#_ENREF_78)RCT | Grp1: MetforminTitrated (Max: 2000 mg)Grp2: Metformin + linagliptinFixed (1000 mg)Fixed (5.0 mg)ITT: NoFollowup (wks): 26 Active |  |  |  | Def:CerebrovascularNot-fatal stroke (ischemic stroke and cerebrovascular accident)Incidence Grp1:  1 315 Incidence Grp2:  1 304  |
| Haak, 2013[78](#_ENREF_78)RCT | Grp1: MetforminTitrated (Max: 2000 mg)Grp2: Metformin + linagliptinTitrated (Max: 2000 mg)Fixed (5 mg)ITT: NoFollowup (wks): 26 Active |  |  |  | Def:CerebrovascularNot-fatal stroke (ischemic stroke and cerebrovascular accident)Incidence Grp1: 1 315Incidence Grp2:    |
| Hamann, 2008[80](#_ENREF_80)RCT | Grp1: Metformin + rosiglitazoneVaried, glucose: 6.1 mmol/lStart: 2 g; Start: 4 mgD: 12 wksGrp2: Metformin + sulfonylureaVaried, glucose: 6.1 mmol/lStart: 2 g; Start: 5 mgD: 12 wks | Grp1: 2 (1)Grp2: 2 (1) |  |  |  |
| Hanefeld, 2004[81](#_ENREF_81)RCT | Grp1: Metformin + sulfonylureaVaried; NRStart: 850 mg, Max: 850 mg tid; NRGrp2: Pioglitazone + sulfonylureaVaried; NRStart: 15 mg, Max: 45 mg; NR | Grp1: 2 (1)Grp2: 1 (<1) |  | Def: Coronary heart diseases/cardiac disordersGrp1: (3.1)Grp2: (4.1) |  |
| Hanefeld, 2007[82](#_ENREF_82)RCT | Grp1: RosiglitazoneFixedStart: 4 mgD: 12 wksGrp2: GlibenclamideVariedStart: 2.5 mg, Max: 15 mgD: 12 wks | Grp1: 0 (0)Grp2: 0 (0) |  |  |  |
| Hanefeld, 2007[82](#_ENREF_82)RCT | Grp1: RosiglitazoneFixedStart: 8 mgD: 12 wksGrp2: GlibenclamideVariedStart: 2.5 mg, Max: 15 mgD: 12 wks | Grp1: 0 (0)Grp2: 0 (0) |  |  |  |
| Haring, 2014[83](#_ENREF_83)RCT | Grp1: Metformin + placeboNot specified (prior MFM therapy (>=1500mg/day, max tolerated dose or max dose according to local label))Grp2: Metformin + empagliflozinNot specified (prior MFM therapy (>=1500mg/day, max tolerated dose or max dose according to local label))Fixed (10mg)ITT: NoFollowup (wks): 26 Active |  |  |  | Def:CerebrovascularNot-fatal stroke (ischemic stroke and cerebrovascular accident)Incidence Grp1:   Incidence Grp2:    |
| Haring, 2014[83](#_ENREF_83)RCT | Grp1: Metformin + placeboNot specified (prior MFM therapy (>=1500mg/day, max tolerated dose or max dose according to local label))Grp2: Metformin + empagliflozinNot specified (prior MFM therapy (>=1500mg/day, max tolerated dose or max dose according to local label))Fixed (25mg)ITT: NoFollowup (wks): 26 Active |  |  |  | Def:CerebrovascularNot-fatal stroke (ischemic stroke and cerebrovascular accident)Incidence Grp1:   Incidence Grp2:    |
| Henry, 2012[84](#_ENREF_84)RCT | Grp1: Metformin + placeboTitrated (Mean: 1843.6 mgMedian: 2000 mgMax: 2000mg)Grp2: Dapagliflozin + placeboFixed (5mg)ITT: NoFollowup (wks): 26 Active |  |  |  | Def:CerebrovascularNot-fatal stroke (ischemic stroke and cerebrovascular accident)Incidence Grp1:   Incidence Grp2:    |
| Henry, 2012[84](#_ENREF_84)RCT | Grp1: Metformin + placeboTitrated (Mean: 1843.6 mgMedian: 2000 mgMax: 2000mg)Grp2: Metformin + dapagliflozinTitrated (Mean: 1773.5 mgMax: 2000mg)Fixed (5 mg)ITT: NoFollowup (wks): 26 Active |  |  |  | Def:CerebrovascularNot-fatal stroke (ischemic stroke and cerebrovascular accident)Incidence Grp1:   Incidence Grp2:    |
| Henry, 2012[84](#_ENREF_84)RCT | Grp1: Dapagliflozin + placeboFixed (5mg)Grp2: Metformin + dapagliflozinTitrated (Mean: 1773.5 mgMax: 2000mg)Fixed (5 mg)ITT: YesFollowup (wks): 52 Passive |  |  |  | Def:CerebrovascularNot-fatal stroke (non-fatal stroke)Incidence Grp1: 1   Incidence Grp2: 1    |
| Henry, 2012[84](#_ENREF_84)RCT | Grp1: Metformin + placeboTitrated (Mean: 1949.7 mgMedian: 2000 mgMax: 2000 mg)  Grp2: Dapagliflozin + placeboFixed (10 mg) ITT: YesFollowup (wks): 52 Passive |  |  |  | Def:CerebrovascularNot-fatal stroke (non-fatal stroke)Incidence Grp1: 1   Incidence Grp2:    |
| Henry, 2012[84](#_ENREF_84)RCT | Grp1: Metformin + placeboTitrated (Mean: 1949.7 mgMedian: 2000 mgMax: 2000 mg)Grp2: Metformin + dapagliflozinTitrated (Mean: 1928.6 mgMedian: 2000 mgMax: 2000 mg)Fixed (10 mg)ITT: YesFollowup (wks): 104  |  |  |  | Def:CerebrovascularOther cerebrovascular (cerebral infarction)Incidence Grp1: 4 (0.5) Incidence Grp2: 0 (0)  |
| Henry, 2012[84](#_ENREF_84)RCT | Grp1: Dapagliflozin + placeboFixed (10 mg)Grp2: Metformin + dapagliflozinTitrated (Mean: 1928.6 mgMedian: 2000 mgMax: 2000 mg)Fixed (10 mg)ITT: YesFollowup (wks): 104  |  |  |  | Def:CerebrovascularNot-fatal stroke (not defined)Incidence Grp1: 11   NA p NR RR Incidence Grp2: 3   NA p NR RR 0.27 |
| Hermann, 1994[86](#_ENREF_86)RCT | Grp1: MetforminVariedStart: 1000 mg, Max: 3000 mgGrp2: GlyburideVariedStart: 3.5 mg, Max: 10.5 mg |  |  | Def: CVD morbidity/unclear CHDGrp1: 2 (5)Grp2: 3 (9) |  |
| Hermann, 1994[86](#_ENREF_86)RCT | Grp1: MetforminVariedStart: 1000 mg, Max: 3000 mgGrp2: Metformin + glyburideVariedStart: 500 mg, Max: 1500 mg; Start: 1.75mg, Max: 5.25 mg |  |  | Def: CVD morbidity/unclear CHDGrp1: 2( 5)Grp2: 10 (14) |  |
| Hermans, 2012[87](#_ENREF_87)RCT | Grp1: MetforminTitrated (1500mgMean: mean additional dose (on top of 1500 mg) was 904 mgadded 500mg qd or bid depending on clinical determination)Grp2: Metformin + saxagliptinFixed (1500 mg)Fixed (5 mg)ITT: NoFollowup (wks): 26 NR/unclear |  |  |  | Def:CerebrovascularNot-fatal stroke (cerebrovascular accident, not defined)Incidence Grp1: 1   Incidence Grp2:    |
| Home, 2009[89](#_ENREF_89)RCT | Grp1: Metformin + sulfonylureaVaried, HgbA1c: ≤7.0%Max: 2550 mg;Glibenclamide, Max: 15 mg, Glimepiride, Max: 4 mgD: 8 wksGrp2: Rosiglitazone + metformin or sulfonylureaVaried, HgbA1c: ≤7.0%Start: 4 mg, Max: 8 mg; Metformin, Max: 2550 mg, Glibenclamide, Max: 15 mg, Glimepiride, Max: 4 mgD: 8 wks | Grp1: 157Grp2: 136HR: 0.86 (CI: 0.68 to 1.08), p: 0.19 | Grp1: 71Grp2: 60HR: 0.84 (CI: 0.59 to 1·18), p: 0.32 | Def: Fatal and non-fatal MIGrp1: 56Grp2: 64HR: 1.14 (CI: 0.80 to 1·63), p: 0.47 | Def: Fatal and non-fatal strokeGrp1: 63Grp2: 46HR: 0.72 (CI: 0.49 to 1·06), p: 0.10 |
| Hong, 2013[195](#_ENREF_195)RCT | Grp1: Metformin + placeboTitrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g, titrated to 1.5g within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l))Grp2: Glipizide + placeboTitrated (Mean: 28.3mgMax: 30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l))  ITT: NoFollowup (wks): 26 NR/unclear |  |  |  | Def:CerebrovascularNot-fatal stroke (cerebrovascular accident, not defined)Incidence Grp1: 1   Incidence Grp2:    |
| Hong, 2013[195](#_ENREF_195)RCT | Grp1: Metformin + placeboTitrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g, titrated to 1.5g within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l))Grp2: Glipizide + placeboTitrated (Mean: 28.3mgMax: 30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l))ITT: NoFollowup (wks): 26 NR/unclear |  |  |  | Def:CerebrovascularNot-fatal stroke (cerebrovascular accident, not defined)Incidence Grp1: 1   Incidence Grp2:    |
| Hong, 2013[195](#_ENREF_195)RCT | Grp1: Metformin + placeboTitrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g, titrated to 1.5g within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l))Grp2: Glipizide + placeboTitrated (Mean: 28.3mgMax: 30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l))ITT: NoFollowup (wks): 26 NR/unclear |  |  |  | Def:CerebrovascularNot-fatal stroke (cerebrovascular accident, not defined)Incidence Grp1: 1   Incidence Grp2:    |
| Hong, 2013[195](#_ENREF_195)RCT | Grp1: Metformin + placeboTitrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g, titrated to 1.5g within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l))Grp2: Glipizide + placeboTitrated (Mean: 28.3mgMax: 30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l))ITT: NoFollowup (wks): 26 NR/unclear |  |  |  | Def:CerebrovascularNot-fatal stroke (cerebrovascular accident, not defined)Incidence Grp1: 1   Incidence Grp2:    |
| Hong, 2013[195](#_ENREF_195)RCT | Grp1: Metformin + placeboTitrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g, titrated to 1.5g within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l))Grp2: Glipizide + placeboTitrated (Mean: 28.3mgMax: 30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l))ITT: NoFollowup (wks): 26 NR/unclear |  |  |  | Def:CerebrovascularNot-fatal stroke (cerebrovascular accident, not defined)Incidence Grp1:   Incidence Grp2:    |
| Hong, 2013[195](#_ENREF_195)RCT | Grp1: Metformin + placeboTitrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g, titrated to 1.5g within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l))Grp2: Glipizide + placeboTitrated (Mean: 28.3mgMax: 30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l))ITT: NoFollowup (wks): 26 NR/unclear |  |  |  | Def:CerebrovascularNot-fatal stroke (cerebrovascular accident, not defined)Incidence Grp1:   Incidence Grp2:    |
| Hong, 2013[195](#_ENREF_195)RCT | Grp1: Metformin + placeboTitrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g, titrated to 1.5g within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l))  Grp2: Glipizide + placeboTitrated (Mean: 28.3mgMax: 30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l))  ITT: NoFollowup (wks): 26 NR/unclear |  |  |  | Def:CerebrovascularNot-fatal stroke (cerebrovascular accident, not defined)Incidence Grp1:   Incidence Grp2:    |
| Hong, 2013[195](#_ENREF_195)RCT | Grp1: Metformin + placeboTitrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g, titrated to 1.5g within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l))Grp2: Glipizide + placeboTitrated (Mean: 28.3mgMax: 30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l))ITT: NoFollowup (wks): 26 NR/unclear |  |  |  | Def:CerebrovascularNot-fatal stroke (cerebrovascular accident, not defined)Incidence Grp1:   Incidence Grp2:    |
| Hong, 2013[195](#_ENREF_195)RCT | Grp1: Metformin + placeboTitrated (Mean: 1.4gMax: 1.5ginitial dose was 0.75g, titrated to 1.5g within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l))Grp2: Glipizide + placeboTitrated (Mean: 28.3mgMax: 30mginitial dose was 15mg, titrated to 30 mg within 3 months if not to target (HbA1c<7.0%, FBG concentration < 7mmol/l, postload 2-h BG < 10mmol/l))ITT: NoFollowup (wks): 26 NR/unclear |  |  |  | Def:CerebrovascularNot-fatal stroke (cerebrovascular accident, not defined)Incidence Grp1:   Incidence Grp2:    |
| Horsdal, 2011[196](#_ENREF_196)Case-control | Grp1: MetforminNot specified  Grp2: SUNot specified   ITT: NoFollowup (wks): 26 NR/unclear |  |  |  | Def:CerebrovascularNot-fatal stroke (cerebrovascular accident, not defined)Incidence Grp1:   Incidence Grp2:    |
| Hsiao, 2009[215](#_ENREF_215)Cohort | Grp1: MetforminNSGrp2: PioglitazoneNS |  |  | Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalizationGrp1: 1367 (2.97)Grp2: 22 (4.51) HR: 1.15 (CI: 0.6 to 2.21) p: 0.6753Def: ICD-9-CM diagnostic codes of hospitalizationGrp1: 484 (1.02)Grp2: 44 (8.89) HR: 1.0 (CI: 0.26 to 3.89) p: 0.9954 | Def: ICD-9-CM diagnostic codes of hospitalizationGrp1: 116 (0.25)Grp2: 2 (0.41)Def: TIA defined by ICD-9-CM diagnostic codes of hospitalizationGrp1: 285 (0.63)Grp2: 5 (1.03) |
| Hsiao, 2009[215](#_ENREF_215)Cohort | Grp1: MetforminNSGrp2: RosiglitazoneNS |  |  | Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalizationGrp1: 1367 (2.97)Grp2: 154 (7.52) HR: 1.79 (CI: 1.39 to 2.3)Def: ICD-9-CM diagnostic codes of hospitalizationGrp1: 484 (1.02)Grp2: 266 (12.71) HR: 2.09 (CI: 1.36 to 3.24) p: 0.0007 | Def: ICD-9-CM diagnostic codes of hospitalizationGrp1: 116 (0.25)Grp2: 16 (0.8)Def: TIA defined by ICD-9-CM diagnostic codes of hospitalizationGrp1: 285 (0.63)Grp2: 23 (1.14) |
| Hsiao, 2009[215](#_ENREF_215)Cohort | Grp1: MetforminNSGrp2: SulfonylureaNS |  |  | Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalizationGrp1: 1367 (2.97)Grp2: 3721 (3.87)Def: ICD-9-CM diagnostic codes of hospitalizationGrp1: 484 (1.02)Grp2: 1678 (1.76) | Def: ICD-9-CM diagnostic codes of hospitalizationGrp1: 116 (0.25)Grp2: 318 (0.34)Def: TIA defined by ICD-9-CM diagnostic codes of hospitalizationGrp1: 285 (0.63)Grp2: 940 (0.99) |
| Hsiao, 2009[215](#_ENREF_215)Cohort | Grp1: MetforminNSGrp2: Metformin + rosiglitazoneNS |  |  | Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalizationGrp1: 1367 (2.97)Grp2: 103 (4.26)Def: ICD-9-CM diagnostic codes of hospitalizationGrp1: 484 (1.02)Grp2: 25 (1.03) | Def: ICD-9-CM diagnostic codes of hospitalizationGrp1: 116 (0.25)Grp2: 12 (0.49)Def: TIA defined by ICD-9-CM diagnostic codes of hospitalizationGrp1: 285 (0.63)Grp2: 11 (0.45) |
| Hsiao, 2009[215](#_ENREF_215)Cohort | Grp1: MetforminNSGrp2: Metformin + sulfonylureaNS |  |  | Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalizationGrp1: 1367 (2.97)Grp2: 5910 (2.2)Def: ICD-9-CM diagnostic codes of hospitalizationGrp1: 484 (1.02)Grp2: 11435 (4.27) | Def: ICD-9-CM diagnostic codes of hospitalizationGrp1: 116 (0.25)Grp2: 588 (0.22)Def: TIA defined by ICD-9-CM diagnostic codes of hospitalizationGrp1: 285 (0.63)Grp2: 1637 (0.61) |
| Hsiao, 2009[215](#_ENREF_215)Cohort | Grp1: RosiglitazoneNSGrp2: PioglitazoneNS |  |  | Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalizationGrp1: 154 (7.52)Grp2: 22 (4.51) Def: ICD-9-CM diagnostic codes of hospitalizationGrp1: 266 (12.71)Grp2: 44 (8.89) | Def: ICD-9-CM diagnostic codes of hospitalizationGrp1: 16 (0.8)Grp2: 2 (0.41)Def: TIA defined by ICD-9-CM diagnostic codes of hospitalizationGrp1: 23 (1.14)Grp2: 5 (1.03) |
| Hsiao, 2009[215](#_ENREF_215)Cohort | Grp1: PioglitazoneNSGrp2: SulfonylureaNS |  |  | Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalizationGrp1: 22 (4.51)Grp2: 3721 (3.87) Def: ICD-9-CM diagnostic codes of hospitalizationGrp1: 44 (8.89)Grp2: 1678 (1.76) | Def: ICD-9-CM diagnostic codes of hospitalizationGrp1: 2 (0.41)Grp2: 318 (0.34)Def: TIA defined by ICD-9-CM diagnostic codes of hospitalizationGrp1: 5 (1.03)Grp2: 940 (0.99) |
| Hsiao, 2009[215](#_ENREF_215)Cohort | Grp1: RosiglitazoneNSGrp2: SulfonylureaNS |  |  | Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalizationGrp1: 154 (7.52)Grp2: 3721 (3.87) Def: ICD-9-CM diagnostic codes of hospitalizationGrp1: 266 (12.71)Grp2: 1678 (1.76) | Def: ICD-9-CM diagnostic codes of hospitalizationGrp1: 16 (0.8)Grp2: 318 (0.34)Def: TIA defined by ICD-9-CM diagnostic codes of hospitalizationGrp1: 23 (1.14)Grp2: 940 (0.99) |
| Hsiao, 2009[215](#_ENREF_215)Cohort | Grp1: Metformin + rosiglitazoneNSGrp2: Metformin + sulfonylureaNS |  |  | Def: Angina pectoris defined by ICD-9-CM diagnostic codes for hospitalizationGrp1: 103 (4.26)Grp2: 5910 (2.2)Def: ICD-9-CM diagnostic codes of hospitalizationGrp1: 25 (1.03)Grp2: 11435 (4.27) | Def: ICD-9-CM diagnostic codes of hospitalizationGrp1: 12 (0.49)Grp2: 588 (0.22)Def: TIA defined by ICD-9-CM diagnostic codes of hospitalizationGrp1: 11 (0.45)Grp2: 1637 (0.61) |
| Hung, 2012[198](#_ENREF_198)Retrospective cohort | Grp1: MetforminNot specified  Grp2: RosiglitazoneNot specified  ITT: YesFollowup (wks): 24  |  |  |  | Def:CerebrovascularOther cerebrovascular (transient ischemic attack NOS)Incidence Grp1:   Incidence Grp2: 1   NA p NR |
| Hung, 2012[198](#_ENREF_198)Retrospective cohort | Grp1: MetforminNot specified  Grp2: RosiglitazoneNot specified  ITT: NRFollowup (wks): 24 NR/unclear |  |  |  | Def:CerebrovascularOther cerebrovascular (CVA)Incidence Grp1:   Incidence Grp2: 1    |
| Hung, 2012[198](#_ENREF_198)Retrospective cohort | Grp1: MetforminNot specified  Grp2: RosiglitazoneNot specified    ITT: NRFollowup (wks): 24 NR/unclear |  |  |  | Def:CerebrovascularOther cerebrovascular (CVA)Incidence Grp1:   Incidence Grp2:    |
| Hung, 2012[198](#_ENREF_198)Retrospective cohort | Grp1: MetforminNot specified  Grp2: RosiglitazoneNot specified  ITT: YesFollowup (wks): 144  |  |  |  | Def:CerebrovascularNot-fatal stroke (no specific definition but confirmed by medical record)Incidence Grp1: 10   Incidence Grp2: 15    |
| Hung, 2012[198](#_ENREF_198)Retrospective cohort | Grp1: MetforminNot specified  Grp2: RosiglitazoneNot specified   ITT: YesFollowup (wks): 168  |  |  |  | Def:CerebrovascularOther cerebrovascular (cerebrovascular incident)Incidence Grp1:   Incidence Grp2: 1 (4)  |
| Hung, 2012[198](#_ENREF_198)Retrospective cohort | Grp1: MetforminNot specified  Grp2: SUNot specified  ITT: NoFollowup (wks): 80  |  |  |  | Def:CerebrovascularOther cerebrovascular (not clearly predefined (just said 'cerebrovascular events'stem infarction)Incidence Grp1: 3   Persons p Incidence Grp2: 5 (1) Persons p  |
| Hung, 2012[198](#_ENREF_198)Retrospective cohort | Grp1: MetforminNot specified  Grp2: SUNot specified  ITT: YesFollowup (wks): 76  |  |  |  | Def:CerebrovascularOther cerebrovascular (death due to ischemic stroke or cerebrovascular accident)Incidence Grp1: 1   p Incidence Grp2: 1   p  |
| Hung, 2012[198](#_ENREF_198)Retrospective cohort | Grp1: MetforminNot specified  Grp2: SUNot specified  ITT: YesFollowup (wks): 76  |  |  |  | Def:CerebrovascularOther cerebrovascular (death due to ischemic stroke or cerebrovascular accident)Incidence Grp1: 1   p Incidence p  |
| Hung, 2012[198](#_ENREF_198)Retrospective cohort | Grp1: MetforminNot specified  Grp2: SUNot specified  ITT: YesFollowup (wks): 76  |  |  |  | Def:CerebrovascularOther cerebrovascular (death due to ischemic stroke or cerebrovascular accident)Incidence Grp1: 1   p Incidence p  |
| Hung, 2012[198](#_ENREF_198)Retrospective cohort | Grp1: MetforminNot specified  Grp2: SUNot specified  ITT: YesFollowup (wks): 76  |  |  |  | Def:CerebrovascularOther cerebrovascular (death due to ischemic stroke or cerebrovascular accident)Incidence Grp1: 1   p Incidence p  |
| Hung, 2012[198](#_ENREF_198)Retrospective cohort | Grp1: SUNot specified  Grp2: RosiglitazoneNot specified  ITT: YesFollowup (wks): 76  |  |  |  | Def:CerebrovascularOther cerebrovascular (death due to ischemic stroke or cerebrovascular accident)Incidence Grp1: 1   p Incidence p  |
| Hung, 2012[198](#_ENREF_198)Retrospective cohort | Grp1: SUNot specified  Grp2: RosiglitazoneNot specified  ITT: NoFollowup (wks): 30  |  |  |  | Def:CerebrovascularFatal strokeIncidence Grp1: 1   p Incidence p  |
| Hung, 2012[198](#_ENREF_198)Retrospective cohort | Grp1: SUNot specified  Grp2: RosiglitazoneNot specified  ITT: YesFollowup (wks): 104  |  |  |  | Def:CerebrovascularOther cerebrovascular (transient ischemic attack)Incidence Grp1: 1   Incidence Grp2:    |
| Hung, 2012[198](#_ENREF_198)Retrospective cohort | Grp1: SUNot specified  Grp2: RosiglitazoneNot specified  ITT: YesFollowup (wks): 104  |  |  |  | Def:CerebrovascularFatal strokeIncidence Grp1: 1   Incidence Grp2:    |
| Hung, 2012[198](#_ENREF_198)Retrospective cohort | Grp1: SUNot specified  Grp2: RosiglitazoneNot specified  ITT: NoFollowup (wks): 26  |  |  |  | Def:CerebrovascularOther cerebrovascular (Cerebrovascular accident)Incidence Grp1: 1 (1) Persons p Incidence Grp2: 1 (1) Persons p  |
| Hung, 2013[199](#_ENREF_199)Retrospective cohort | Grp1: MetforminNot specified   Grp2: GlyburideNot specified  ITT: NoFollowup (wks): 26  |  |  |  | Def:CerebrovascularOther cerebrovascular (Cerebrovascular accident)Incidence Grp1: 1 (1) Persons p Incidence Grp2: 0 (0) Persons p  |
| Hung, 2013[199](#_ENREF_199)Retrospective cohort | Grp1: MetforminNot specified  Grp2: GlimepirideNot specified  ITT: NoFollowup (wks): 26  |  |  |  | Def:CerebrovascularOther cerebrovascular (Cerebrovascular accident)Incidence Grp1: 1 (1) Persons p Incidence Grp2: 0 (0) Persons p  |
| Hung, 2013[200](#_ENREF_200)Retrospective cohort | Grp1: MetforminNot specified  Grp2: SUNot specified  ITT: NoFollowup (wks): 26 Active |  |  | Def:CVD morbidityNonfatal MI (unspecified)Incidence Grp1:   Incidence Grp2: 1    |  |
| Hung, 2013[200](#_ENREF_200)Retrospective cohort | Grp1: MetforminNot specified   Grp2: SUNot specified  ITT: NoFollowup (wks): 26 Active |  |  | Def:CVD morbidityNonfatal MI (unspecified)Incidence Grp1:   Incidence Grp2: 1    |  |
| Hung, 2013[200](#_ENREF_200)Retrospective cohort | Grp1: MetforminNot specified  Grp2: SUNot specified  ITT: NoFollowup (wks): 26 Active |  |  | Def:CVD morbidityNonfatal MI (unspecified)Incidence Grp1:   Incidence Grp2:    |  |
| Hung, 2013[200](#_ENREF_200)Retrospective cohort | Grp1: MetforminNot specified  Grp2: Metformin + suNot specified  Not specified  ITT: NoFollowup (wks): 26 Active |  |  | Def:CVD morbidityNonfatal MI (unspecified)Incidence Grp1:   Incidence Grp2:    |  |
| Hung, 2013[200](#_ENREF_200)Retrospective cohort | Grp1: MetforminNot specified  Grp2: Metformin + suNot specified  Not specified  ITT: NoFollowup (wks): 26 Active |  |  | Def:CVD morbidityNonfatal MI (unspecified)Incidence Grp1:   Incidence Grp2:    |  |
| Hung, 2013[200](#_ENREF_200)Retrospective cohort | Grp1: MetforminNot specified  Grp2: Metformin + suNot specified  Not specified  ITT: NoFollowup (wks): 26 Active |  |  | Def:CVD morbidityNonfatal MI (unspecified)Incidence Grp1:   Incidence Grp2:    |  |
| Hung, 2013[200](#_ENREF_200)Retrospective cohort | Grp1: SUNot specified  Grp2: Metformin + suNot specified  Not specified  ITT: NoFollowup (wks): 26 Active |  |  | Def:CVD morbidityNonfatal MI (unspecified)Incidence Grp1:   Incidence Grp2: 1    |  |
| Hung, 2013[200](#_ENREF_200)Retrospective cohort | Grp1: SUNot specified  Grp2: Metformin + suNot specified  Not specified  ITT: NoFollowup (wks): 26 Active |  |  | Def:CVD morbidityNonfatal MI (unspecified)Incidence Grp1:   Incidence Grp2: 1    |  |
| Hung, 2013[200](#_ENREF_200)Retrospective cohort | Grp1: SUNot specified  Grp2: Metformin + suNot specified  Not specified  ITT: YesFollowup (wks): 52 Active |  |  | Def:CVD morbidityNonfatal MI (non-fatal MI)Incidence Grp1: 1   Incidence Grp2: 3    |  |
| Jadzinsky, 2009[91](#_ENREF_91)RCT | Grp1: MetforminVaried, NSStart: 500 mg, Max: 1000 mgD: 1 weekGpr2: SaxagliptinFixed | Grp1: 3 (1)Grp2: 0 (0) |  |  |  |
| Jadzinsky, 2009[91](#_ENREF_91)RCT | Grp1: Metformin + saxagliptinVaried, prespecified target dose; FixedStart: 500 mg, Max: 1000 mg; Mean: 10 mgD: 1 weekGrp2: MetforminVaried, NSStart: 500 mg, Max: 1000 mgD: 1 week | Grp1: 0 (0)Grp2: 3 (1) |  |  |  |
| Jadzinsky, 2009[91](#_ENREF_91)RCT | Grp1: Metformin + saxagliptinVaried, prespecified target dose; FixedStart: 500 mg, Max: 1000 mg; Mean: 5 mgGrp2: MetforminVaried, NSStart: 500 mg, Max: 1000 mgD: 1 week | Grp1: 0 (0)Grp2: 3 (1) |  |  |  |
| Jain, 2006[92](#_ENREF_92)RCT | Grp1: PioglitazoneVaried, glucose: 69-141 mg/dLStart: 15 mg, Median: 45 mg, Max: 45 mgD: 12 wksGrp2: GlyburideVaried, glucose: 69-141 mg/dLStart: 5 mg, Median: 10 mg, Max: 15 mgD: 12 wks | Grp1: 0 (0)Grp2: 2 (0.8) |  | Def: Non-fatal MIGrp1: 2 (0.8)Grp2: 2 (0.8) |  |
| Johnson, 2005[201](#_ENREF_201)Cohort | Grp1: MetforminVariedMin: 250 mgGrp2: SulfonylureaVaried |  | Def: CVD mortality/CVD mortality registry + CVD mortality + ICD-9 codes 410, 411-414, 420-427, 429, 428, 430-432, 433-434, 436-438, 440Grp1: 14.4/1000 patient-yearsGrp2: 25.5/1000 patient-years | Def: Non-fatal cardiovascular hospitalization/used ICD-9 codes 410-414, 420-427, 429, 428, 440, 430-432, 433-434, 436-438Grp1: 53.7/1000 patient-yearsGrp2: 75.3/1000 patient-years |  |
| Jones, 2003[202](#_ENREF_202)RCT | Grp1: MetforminFixedStart: 2.5 gGrp2: Metformin + rosiglitazoneFixed; Varied, NSStart: 2.5 g; Max: 8 mg | Grp1: 0 (0)Grp2: 1 (1) |  |  |  |
| Kadowaki, 2013[96](#_ENREF_96)RCT | Grp1: Metformin + placeboFixed (maintained previous dosage40% on 500 mg/day; 56% on 750 mg/day; 3% on 1000 mg/day; 1.4% on 1500 mg/day)Grp2: Metformin + sitagliptinFixed (maintained previous dosage43% on 500 mg/day; 51% on 750 mg/day; 3% on 1000mg/day; 4% on 1500 mg/day)Fixed (50mg qd)ITT: YesFollowup (wks): 52 Active |  |  | Def:CVD morbidityOther CVD morbidity (unstable angina)Incidence Grp1:   Incidence Grp2: 2    |  |
| Kadowaki, 2013[96](#_ENREF_96)RCT | Grp1: Metformin + placeboFixed (maintained previous dosage40% on 500 mg/day; 56% on 750 mg/day; 3% on 1000 mg/day; 1.4% on 1500 mg/day)Grp2: Metformin + sitagliptinFixed (maintained previous dosage43% on 500 mg/day; 51% on 750 mg/day; 3% on 1000mg/day; 4% on 1500 mg/day)Fixed (50mg qd)ITT: YesFollowup (wks): 52 Active |  |  | Def:CVD morbidityNonfatal MI (non-fatal MI)Incidence Grp1: 1   Incidence Grp2:    |  |
| Kahler, 2007[203](#_ENREF_203)Cohort | Grp1: MetforminNRGrp2: SulfonylureaNR | Grp1: 82 (2.7)Grp2: 1005 (5.3) |  |  |  |
| Kahler, 2007[203](#_ENREF_203)Cohort | Grp1: MetforminNRGrp2: Metformin + sulfonylureaNR | Grp1: 82 (2.7)Grp2: 468 (3.4) |  |  |  |
| Kahn, 2006[97](#_ENREF_97)RCT | Grp1: MetforminVaried, glucose: 140 mg/dLStart: 500 mg, Max: 2000 mgGrp2: RosiglitazoneVaried, glucose: 140 mg/dLStart: 4 mg, Max: 8 mg | Grp1: 31 (2)Grp2: 34 (2) | Def: Fatal MIGrp1: 2 (0.1)Grp2: 2 (0.1) | Grp1: 21 (1.4)Grp2: 25 (1.7) | Def: Stroke not definedGrp1: 19 (1.3)Grp2: 16 (1.1) |
| Kahn, 2006[97](#_ENREF_97)RCT | Grp1: MetforminVaried, glucose: 140 mg/dLStart: 500 mg, Max: 2000 mgGrp2: GlyburideVaried, glucose: 140 mg/dLStart: 2.5 mg, Max: 15 mg | Grp1: 31 (2)Grp2: 31 (2) | Def: Fatal MIGrp1: 2 (0.1)Grp2: 3 (0.2) | Def: Not definedGrp1: 21 (1.4)Grp2: 15 (1) | Def: Stroke not definedGrp1: 19 (1.3)Grp2: 17 (1.2) |
| Kahn, 2006[97](#_ENREF_97)RCT | Grp1: RosiglitazoneVaried, glucose: 140 mg/dLStart: 4 mg, Max: 8 mgGrp2: GlyburideVaried, glucose: 140 mg/dLStart: 2.5 mg, Max: 15 mg | Grp1: 34 (2)Grp2: 31 (2) | Def: Fatal MIGrp1: 2 (0.1)Grp2: 3 (0.2) | Def: Non-fatal MIGrp1: 25 (1.7)Grp2: 15 (1) | Def: Stroke not definedGrp1: 16 (1.1)Grp2: 17 (1.2) |
| Kaku, 2011[99](#_ENREF_99)RCT | Grp1: GlibenclamideFixed (1.25 -2.5 mg/d)Grp2: LiraglutideTitrated (Max: 0.9 mg/d)ITT: YesFollowup (wks): 52 Active |  |  | Def:CVD morbidityOther CVD morbidity (unstable angina)Incidence Grp1:   Incidence Grp2: 2    |  |
| Kaku, 2011[99](#_ENREF_99)RCT | Grp1: GlibenclamideFixed (1.25 -2.5 mg/d)Grp2: LiraglutideTitrated (Max: 0.9 mg/d)ITT: NoFollowup (wks): 26  |  |  | Def:CVD morbidityCVD morbidity composite outcome (see comments)Incidence p Incidence p  |  |
| Kaku, 2011[99](#_ENREF_99)RCT | Grp1: GlibenclamideFixed (1.25 -2.5 mg/d)Grp2: LiraglutideTitrated (Max: 0.9 mg/d)ITT: NoFollowup (wks): 26  |  |  | Def:CVD morbidityCVD morbidity composite outcome (see comments)Incidence p Incidence p  |  |
| Kaku, 2011[99](#_ENREF_99)RCT | Grp1: GlibenclamideFixed (1.25 -2.5 mg/d)Grp2: LiraglutideTitrated (Max: 0.9 mg/d)ITT: NoFollowup (wks): 26  |  |  | Def:CVD morbidityCVD morbidity composite outcome (see comments)Incidence p Incidence p  |  |
| Kvapil, 2006[105](#_ENREF_105)RCT | Grp1: Metformin + sulfonylureaFixed; VariedStart: 1660 mg; Start: 1.75 mg, Max: 10.5, Mean: 6.58Grp2: Metformin + aspart 70/30Fixed; VariedStart: 1660 mg; Start: 0.2 U/kg BID, Mean: 0.3 BID | Grp1: 0 (0)Grp2: 1 | Def: Fatal MIGrp1: 0 (0)Grp2: 1 |  |  |
| Lavalle-Gonzalez, 2013[106](#_ENREF_106)RCT | Grp1: Metformin + placeboFixed ((ΓëÑ2,000 mg/day [or ΓëÑ1,500 mg/day if unable to tolerate higher dose]))Grp2: Metformin + sitagliptinFixed ((ΓëÑ2,000 mg/day [or ΓëÑ1,500 mg/day if unable to tolerate higher dose]))Fixed (100mg)ITT: YesFollowup (wks): 52 Active |  |  | Def:CVD morbidityNonfatal MI (not specified)Incidence Grp1: 1   Incidence Grp2: 0    |  |
| Lavalle-Gonzalez, 2013[106](#_ENREF_106)RCT | Grp1: Metformin + placeboFixed ((ΓëÑ2,000 mg/day [or ΓëÑ1,500 mg/day if unable to tolerate higher dose]))Grp2: Metformin + canagliflozinFixed ((ΓëÑ2,000 mg/day [or ΓëÑ1,500 mg/day if unable to tolerate higher dose]))Fixed (100mg)ITT: YesFollowup (wks): 104  |  |  | Def:CVD morbidityNonfatal MI (not defined)Incidence Grp1: 10   NA p NR RR Incidence Grp2: 6   NA p NR RR 0.6 |  |
| Lavalle-Gonzalez, 2013[106](#_ENREF_106)RCT | Grp1: Metformin + placeboFixed ((ΓëÑ2,000 mg/day [or ΓëÑ1,500 mg/day if unable to tolerate higher dose]))  Grp2: Metformin + canagliflozinFixed ((ΓëÑ2,000 mg/day [or ΓëÑ1,500 mg/day if unable to tolerate higher dose]))Fixed (300mg)ITT: YesFollowup (wks): 104  |  |  | Def:CVD morbidityCVD morbidity composite outcome (Must have one of following: cardiovascular death, myocardial infarction, stroke, admission to hospital due to unstable angina)Incidence Grp1: 26   NA p NR RR Incidence Grp2: 12   NA p NR RR 0.46 |  |
| Lavalle-Gonzalez, 2013[106](#_ENREF_106)RCT | Grp1: Metformin + sitagliptinFixed ((ΓëÑ2,000 mg/day [or ΓëÑ1,500 mg/day if unable to tolerate higher dose]))Fixed (100mg)Grp2: Metformin + canagliflozinFixed ((ΓëÑ2,000 mg/day [or ΓëÑ1,500 mg/day if unable to tolerate higher dose]))Fixed (100mg)ITT: YesFollowup (wks): 104  |  |  | Def:CVD morbidityOther CVD morbidity (Admission to hospital due to unstable angina)Incidence Grp1: 3   NA p NR RR Incidence Grp2: 3   NA p NR RR 1 |  |
| Lavalle-Gonzalez, 2013[106](#_ENREF_106)RCT | Grp1: Metformin + sitagliptinFixed ((ΓëÑ2,000 mg/day [or ΓëÑ1,500 mg/day if unable to tolerate higher dose]))Fixed (100mg)Grp2: Metformin + canagliflozinFixed ((ΓëÑ2,000 mg/day [or ΓëÑ1,500 mg/day if unable to tolerate higher dose]))Fixed (300mg)ITT: NoFollowup (wks): 50  |  |  | Def:CVD morbidityOther CVD morbidity (acute MI)Incidence Grp1:   Incidence Grp2:    |  |
| Lawrence, 2004[107](#_ENREF_107)RCT | Grp1: MetforminVariedStart: 500 mg bid, Max: 1000 mg tidGrp2: PioglitazoneVariedStart: 30 mg, Max: 45 mg | Grp1: 1 (5)Grp2: 0 (0) | Def: CVD mortality/Fatal MIGrp1: 1 (5)Grp2: 0 (0) | Def: CVD morbidity/MI (non-fatal)Grp1: 0 (0)Grp2: 0 (0) |  |
| List, 2009[109](#_ENREF_109)RCT | Grp1: MetforminTitrated (Max: 1500 mg/d)Grp2: DapagliflozinFixed (5mg)ITT: YesFollowup (wks): 12 Active |  |  | Def:CVD morbidityUnspecified CVD morbidity outcomeincreased blood glucoseIncidence Grp1: 0   Incidence Grp2: 0    |  |
| List, 2009[109](#_ENREF_109)RCT | Grp1: MetforminTitrated (Max: 1500 mg/d)Grp2: DapagliflozinFixed (10 mg)ITT: YesFollowup (wks): 12 Active |  |  | Def:CVD morbidityUnspecified CVD morbidity outcomeincreased blood glucoseIncidence Grp1: 0   Incidence Grp2: 0    |  |
| Malone, 2003[112](#_ENREF_112)RCT | Grp1: Metformin + glibenclamideVaried; Varied, fasting and pre-meal goal <7mmol/L, 2-hour post-prandial goal <10mmol/LMax: 2550 mg, Mean: 1968 mg; Mean: 14.2 mgD: 4 wks; 16 wksGrp2: Metformin + lispro 75/25Varied; Varied, fasting and pre-meal goal <7mmol/L, 2-hour post-prandial goal <10mmol/LMax: 2550 mg; Mean: 0.19 U/kg in am and 0.14 U/kg in eveningD: 4 wks; 16 wks | Grp1: 0 (0)Grp2: 1 (<1) |  |  |  |
| Malone, 2005[205](#_ENREF_205)RCT | Grp1: Metformin + lispro 75/25Varied, pre-meal glucose 90-126 mg/dL; 2-hr postprandial 144-180 mg/dLStart: 1500 mg, Max: 2550 mg, Mean: 2146 mg; Mean: 0.42 U/kg BIDD: 4 wks, 16 wksGrp2: Metformin + glargineVaried, pre-meal glucose 90-126 mg/dL Start: 1500 mg, Max: 2500 mg, Mean: 2146 mg; Mean: 0.36 U/Kg QDD: 4 wks, 16 wks | Grp1: 1 (2)Grp2: 1 (2) | Grp1: 1 (2)Grp2: 0 (0) |  |  |
| Masica, 2013[206](#_ENREF_206)Retrospective cohort | Grp1: MetforminNot specified  Grp2: TZDNot specified  ITT: YesFollowup (wks): 12 Active |  |  | Def:CVD morbidityUnspecified CVD morbidity outcomeincreased blood glucoseIncidence Grp1: 0   Incidence Grp2: 0    |  |
| Masica, 2013[206](#_ENREF_206)Retrospective cohort | Grp1: MetforminNot specified  Grp2: TZDNot specified  ITT: YesFollowup (wks): 26 Passive |  |  | Def:CVD morbidityOther CVD morbidity (discontinuation due to hypertensive heart disease. Discontinuation because of serious adverse event.)Incidence Grp1:   Incidence Grp2:    |  |
| Masica, 2013[206](#_ENREF_206)Retrospective cohort | Grp1: MetforminNot specified  Grp2: SUNot specified  ITT: YesFollowup (wks): 26 Passive |  |  | Def:CVD morbidityOther CVD morbidity (discontinuation due to hypertensive heart disease. Discontinuation because of serious adverse event.)Incidence Grp1:   Incidence Grp2: 1    |  |
| Masica, 2013[206](#_ENREF_206)Retrospective cohort | Grp1: MetforminNot specified  Grp2: SUNot specified  ITT: YesFollowup (wks): 12  |  |  | Def:CVD morbidityOther CVD morbidity (CEC-confirmed cardiovascular event - ST elevation myocardial infarction)Incidence Grp1:   Incidence Grp2: 1    |  |
| Masica, 2013[206](#_ENREF_206)Retrospective cohort | Grp1: SUNot specified  Grp2: TZDNot specified  ITT: YesFollowup (wks): 12  |  |  | Def:CVD morbidityOther CVD morbidity (acute MI)Incidence Grp1: 0   Incidence Grp2: 2    |  |
| Masica, 2013[206](#_ENREF_206)Retrospective cohort | Grp1: SUNot specified  Grp2: TZDNot specified  ITT: NoFollowup (wks): 12 NR/unclear |  |  | Def:CVD morbidityOther CVD morbidity (Prinzmetal angina)Incidence Grp1: 1   Incidence Grp2:    |  |
| Mogensen, 2014[207](#_ENREF_207)Retrospective cohort | Grp1: Metformin + glp-1 agonistNot specified  Not specified  Grp2: Metformin + basal insulinNot specified  Not specified  ITT: NoFollowup (wks): 12 NR/unclear |  |  | Def:CVD morbidityOther CVD morbidity (Prinzmetal angina)Incidence Grp1: 1   Incidence Grp2:    |  |
| Mogensen, 2014[207](#_ENREF_207)Retrospective cohort | Grp1: Metformin + glp-1 agonistNot specified  Not specified  Grp2: Metformin + basal insulinNot specified  Not specified  ITT: NoFollowup (wks): 48  |  |  | Def:CVD morbidityNonfatal MI (no definition)Incidence Grp1: 0   Incidence Grp2: 0    |  |
| Mogensen, 2014[207](#_ENREF_207)Retrospective cohort | Grp1: Metformin + suNot specified  Not specified  Grp2: Metformin + glp-1 agonistNot specified  Not specified  ITT: YesFollowup (wks):  Active |  |  | Def:CVD morbidityNonfatal MI (non ST segment myocardial infarction with pulmonary edema and stent placed)Incidence Grp1:   Incidence Grp2: 1    |  |
| Mogensen, 2014[207](#_ENREF_207)Retrospective cohort | Grp1: Metformin + suNot specified  Not specified  Grp2: Metformin + glp-1 agonistNot specified  Not specified  ITT: Not applicable (e.g., cohort)Followup (wks):   |  |  | Def:CVD morbidityCVD morbidity composite outcome (ICD9 410-413, 414-414.05, 414.8, 414.9, 428.9, 430-438, 440-448 (Except 440 and 440.1))Incidence Grp1:  2241 Person-years p NR RH 0.31Incidence Grp2:  1017 Person-years p NR RH ref |  |
| Mogensen, 2014[207](#_ENREF_207)Retrospective cohort | Grp1: Metformin + suNot specified  Not specified  Grp2: Metformin + dpp-4 inhibitorNot specified  Not specified  ITT: Not applicable (e.g., cohort)Followup (wks):   |  |  | Def:CVD morbidityCVD morbidity composite outcome (ICD9 410-413, 414-414.05, 414.8, 414.9, 428.9, 430-438, 440-448 (Except 440 and 440.1))Incidence Grp1:  2241 Person-years p NR RH 0.31Incidence Grp2:  745 Person-years p NR RH 0.52 |  |
| Mogensen, 2014[207](#_ENREF_207)Retrospective cohort | Grp1: Metformin + suNot specified  Not specified  Grp2: Metformin + dpp-4 inhibitorNot specified  Not specified  ITT: YesFollowup (wks): 16 NR/unclear |  |  | Def:CVD morbidityNonfatal MI (Discontinuation due to myocardial ischemia - did not specify as fatal or nonfatal)Incidence Grp1: 1   Incidence Grp2:    |  |
| Mogensen, 2014[207](#_ENREF_207)Retrospective cohort | Grp1: Metformin + suNot specified  Not specified  Grp2: Metformin + basal insulinNot specified  Not specified  ITT: NoFollowup (wks): 58  |  |  | Def:CVD morbidityCVD morbidity composite outcome (vascular events)Incidence Grp1: 11   Incidence Grp2: 8    |  |
| Mogensen, 2014[207](#_ENREF_207)Retrospective cohort | Grp1: Metformin + suNot specified  Not specified  Grp2: Metformin + basal insulinNot specified  Not specified  ITT: NoFollowup (wks): 58  |  |  | Def:CVD morbidityCVD morbidity composite outcome (vascular event)Incidence Grp1:  100 Person-years p NR Incidence Grp2:  100 Person-years p NR  |  |
| Mogensen, 2014[207](#_ENREF_207)Retrospective cohort | Grp1: Metformin + dpp-4 inhibitorNot specified  Not specified  Grp2: Metformin + glp-1 agonistNot specified  Not specified  ITT: YesFollowup (wks): 144  |  |  | Def:CVD morbidityCVD morbidity composite outcome (including nonfatal myocardial infarction, nonfatal stroke, or arterial revascularization by PTCA or by coronary artery bypass graft, death from a cardiovascular cause, and death from any cause, obtained and confirmed by thIncidence Grp1: 39   NA p NR RH 0.54Incidence Grp2: 52   NA p NR RH |  |
| Mogensen, 2014[207](#_ENREF_207)Retrospective cohort | Grp1: Metformin + dpp-4 inhibitorNot specified  Not specified  Grp2: Metformin + glp-1 agonistNot specified  Not specified  ITT: YesFollowup (wks): 144 Active |  |  | Def:CVD morbidityOther CVD morbidity (new peripheral vascular disease events not further specified but confirmed by medical record)Incidence Grp1: 1   NA p NR RH 0.13Incidence Grp2: 6   NA p NR RH |  |
| Mogensen, 2014[207](#_ENREF_207)Retrospective cohort | Grp1: Metformin + dpp-4 inhibitorNot specified  Not specified  Grp2: Metformin + basal insulinNot specified  Not specified  ITT: YesFollowup (wks): 144  |  |  | Def:CVD morbidityOther CVD morbidity (new or worsening angina confirmed by medical record)Incidence Grp1: 77   NA p NR RH 1.07Incidence Grp2: 71   NA p NR RH |  |
| Mogensen, 2014[207](#_ENREF_207)Retrospective cohort | Grp1: Metformin + dpp-4 inhibitorNot specified  Not specified  Grp2: Metformin + basal insulinNot specified  Not specified  ITT: YesFollowup (wks): 144  |  |  | Def:CVD morbidityOther CVD morbidity (new critical cardiac arrhythmia confirmed by medical record)Incidence Grp1: 30   NA p NR RH 1.01Incidence Grp2: 27   NA p NR RH |  |
| Nauck, 2007[118](#_ENREF_118)RCT | Grp1: Metformin + glipizideNRGrp2: Metformin + sitagliptinNR | Grp1: 2 (0.3)Grp2: 1 (0.2) | Def: Fatal MIGrp1: 1 (0.2)Grp2: 0 (0) |  |  |
| Nauck, 2009[119](#_ENREF_119)RCT | Grp1: Metformin + placeboFixed (Mean: 1868mg>=1500mg or maximum tolerated dose)Grp2: Metformin + alogliptinFixed (Mean: 1846mg>=1500mg or maximum tolerated dose)Fixed (25mg)ITT: YesFollowup (wks): 144  |  |  | Def:CVD morbidityNonfatal MI (no specific definition - confirmed by medical records at each institution)Incidence Grp1: 5   Incidence Grp2: 6    |  |
| Nauck, 2009[119](#_ENREF_119)RCT | Grp1: Metformin + placeboFixed (Mean: 1868mg>=1500mg or maximum tolerated dose)Grp2: Metformin + alogliptinFixed (Mean: 1837mg>=1500mg or maximum tolerated dose)Fixed (12.5mg)ITT: YesFollowup (wks): 144  |  |  | Def:CVD morbidityOther CVD morbidity (arterial revascularization by PTCA or by coronary artery bypass graft confirmed by medical records)Incidence Grp1: 21   Incidence Grp2: 25    |  |
| Nauck, 2009[119](#_ENREF_119)RCT | Grp1: Metformin + placeboFixed (Mean: 1868mg>=1500mg or maximum tolerated dose)  Grp2: Metformin + alogliptinFixed (Mean: 1846mg>=1500mg or maximum tolerated dose)Fixed (25mg)ITT: Not applicable (e.g., cohort)Followup (wks): 260  |  |  | Def:CVD morbidityCVD morbidity composite outcome (AMI and stroke events only)Incidence Grp1:  179351 Person-years p NR RH 1.00 (ref)Incidence Grp2:  101125 Person-years p NR RH 1.15 |  |
| Nauck, 2009[119](#_ENREF_119)RCT | Grp1: Metformin + placeboFixed (Mean: 1868mg>=1500mg or maximum tolerated dose)Grp2: Metformin + alogliptinFixed (Mean: 1837mg>=1500mg or maximum tolerated dose)Fixed (12.5mg)ITT: Not applicable (e.g., cohort)Followup (wks): 260  |  |  | Def:CVD morbidityCVD morbidity composite outcome (hospitalization for acute myocardial infarction (AMI) or stroke, or death)Incidence Grp1:  179351 Person-years p NR RH 1.00 (Ref)Incidence Grp2:  101125 Person-years p NR RH 1.21 |  |
| Nauck, 2009[119](#_ENREF_119)RCT | Grp1: Metformin + placeboFixed (Mean: 1868mg>=1500mg or maximum tolerated dose)Grp2: Metformin + alogliptinFixed (Mean: 1846mg>=1500mg or maximum tolerated dose)Fixed (25mg)ITT: Not applicable (e.g., cohort)Followup (wks):   |  |  | Def:CVD morbidityCVD morbidity composite outcome (hospitalization for acute myocardial infarction (AMI) or stroke, or death)Incidence p RH 1Incidence p RH 1.18 |  |
| Nauck, 2009[119](#_ENREF_119)RCT | Grp1: Metformin + placeboFixed (Mean: 1868mg>=1500mg or maximum tolerated dose)Grp2: Metformin + alogliptinFixed (Mean: 1837mg>=1500mg or maximum tolerated dose)Fixed (12.5mg)ITT: Not applicable (e.g., cohort)Followup (wks):   |  |  | Def:CVD morbidityCVD morbidity composite outcome (hospitalization for acute myocardial infarction (AMI) or stroke, or death)Incidence p RH 1Incidence p RH 1.28 |  |
| Nauck, 2011[120](#_ENREF_120)RCT | Grp1: Metformin + glipizideFixed (1500 - 2500 mg)Titrated (Mean: 16.4 mgMax: 20 mg)Grp2: Metformin + dapagliflozinFixed (1500 - 2500 mg)Titrated (Mean: 9.2 mgMax: 10 mg)ITT: Not applicable (e.g., cohort)Followup (wks):   |  |  | Def:CVD morbidityOther CVD morbidityIncidence p RH 1Incidence p RH 1.24 |  |
| Nauck, 2011[120](#_ENREF_120)RCT | Grp1: Metformin + glipizideFixed (1500 - 2500 mg)Titrated (Mean: 16.4 mgMax: 20 mg)Grp2: Metformin + dapagliflozinFixed (1500 - 2500 mg)Titrated (Mean: 9.2 mgMax: 10 mg)ITT: Not applicable (e.g., cohort)Followup (wks):   |  |  | Def:CVD morbidityCVD morbidity composite outcome (hospitalization for acute myocardial infarction (AMI) or stroke, or death)Incidence p RH 1Incidence p RH 1.18 |  |
| Nauck, 2014[121](#_ENREF_121)RCT | Grp1: Metformin + placeboFixed (>=1500 mg/day)Grp2: Metformin + sitagliptinFixed (>=1500 mg/day)Fixed (100 mg)ITT: Not applicable (e.g., cohort)Followup (wks):  NR/unclear |  |  | Def:CVD morbidityCVD morbidity composite outcome (diagnosis of myocardial infarction, angina pectoris, intracerebral haemorrhage, cerebral infarction, unspecified stroke, peripheral vascular disease, or intervention with percutaneous coronary intervention or coronary arteIncidence Grp1: 1734   p RH 1.00 REFIncidence Grp2: 1338   p RH 1.28 |  |
| Nauck, 2014[121](#_ENREF_121)RCT | Grp1: Metformin + placeboFixed (>=1500 mg/day)Grp2: Metformin + sitagliptinFixed (>=1500 mg/day)Fixed (100 mg)ITT: NoFollowup (wks): 25 NR/unclear |  |  | Def:CVD morbidityOther CVD morbidity (UNstable angina)Incidence Grp1: 0   p NR Incidence Grp2: 2   p NR  |  |
| Nauck, 2014[121](#_ENREF_121)RCT | Grp1: Metformin + placeboFixed (>=1500 mg/day)Grp2: Metformin + sitagliptinFixed (>=1500 mg/day)Fixed (100 mg)ITT: NoFollowup (wks): 25 NR/unclear |  |  | Def:CVD morbidityOther CVD morbidity (carotid artery occlusion)Incidence Grp1: 0   p Incidence Grp2: 1   p  |  |
| Nauck, 2014[121](#_ENREF_121)RCT | Grp1: Metformin + placeboFixed (>=1500 mg/day)Grp2: Metformin + dulaglutideFixed (>=1500 mg/day)Fixed (0.75 mg/week)ITT: NoFollowup (wks): 25 NR/unclear |  |  | Def:CVD morbidityNonfatal MI (Acute myocardial infarction)Incidence Grp1: 1   Incidence Grp2: 0    |  |
| Nauck, 2014[121](#_ENREF_121)RCT | Grp1: Metformin + placeboFixed (>=1500 mg/day)Grp2: Metformin + dulaglutideFixed (>=1500 mg/day)Fixed (0.75 mg/week)ITT: Followup (wks): 25 NR/unclear |  |  | Def:CVD morbidityOther CVD morbidity (Angina pectoris)Incidence Grp1: 1   Persons p NR Incidence Grp2: 1   Persons p NR  |  |
| Nauck, 2014[121](#_ENREF_121)RCT | Grp1: Metformin + placeboFixed (>=1500 mg/day)Grp2: Metformin + dulaglutideFixed (>=1500 mg/day)Fixed (1.5 mg/week)ITT: NoFollowup (wks): 18 NR/unclear |  |  | Def:CVD morbidityNonfatal MI (Acute cardiovascular event- Myocardial ischemia or MI)Incidence Grp1: 1   Persons p Incidence Grp2: 1   Persons p  |  |
| Nauck, 2014[121](#_ENREF_121)RCT | Grp1: Metformin + placeboFixed (>=1500 mg/day)Grp2: Metformin + dulaglutideFixed (>=1500 mg/day)Fixed (1.5 mg/week)ITT: NoFollowup (wks): 52 NR/unclear |  |  | Def:CVD morbidityOther CVD morbidity (Vascular Disorders')Incidence Grp1: 10 (7.6) p Incidence Grp2: 17 (6.3) p  |  |
| Nauck, 2014[121](#_ENREF_121)RCT | Grp1: Metformin + placeboFixed (>=1500 mg/day)Grp2: Metformin + dulaglutideFixed (>=1500 mg/day)Fixed (0.75 mg/week)ITT: NoFollowup (wks): 52 NR/unclear |  |  | Def:CVD morbidityOther CVD morbidity (Cardiac disorders')Incidence Grp1: 14 (10.6) NA p Incidence Grp2: 17 (6.3) NA p  |  |
| Nauck, 2014[121](#_ENREF_121)RCT | Grp1: Metformin + placeboFixed (>=1500 mg/day)Grp2: Metformin + dulaglutideFixed (>=1500 mg/day)Fixed (1.5 mg/week)ITT: YesFollowup (wks): 24  |  |  | Def:CVD morbidityOther CVD morbidity (defined as 'acute cardiovascuar event')Incidence Grp1: 1   p Incidence Grp2: 1   p  |  |
| Nauck, 2014[121](#_ENREF_121)RCT | Grp1: Metformin + sitagliptinFixed (>=1500 mg/day)Fixed (100 mg)Grp2: Metformin + dulaglutideFixed (>=1500 mg/day)Fixed (0.75 mg/week)ITT: NoFollowup (wks): 80 NR/unclear |  |  | Def:CVD morbidityCVD morbidity composite outcome (ischemic events')Incidence Grp1: 4 (1) p Incidence Grp2: 6 (2) p  |  |
| Nauck, 2014[121](#_ENREF_121)RCT | Grp1: Metformin + sitagliptinFixed (>=1500 mg/day)Fixed (100 mg)Grp2: Metformin + dulaglutideFixed (>=1500 mg/day)Fixed (0.75 mg/week)ITT: Not applicable (e.g., cohort)Followup (wks):  NR/unclear |  |  | Def:CVD morbidityCVD morbidity composite outcome (MI, Stroke and CV death based on ICD-10 codes composite of MI (I21â€“I22), stroke (I61â€“I64) cardiovascular death (I00 â€“I99))Incidence Grp1: 1646   p RH 1Incidence Grp2: 1376   p RH 1.12 |  |
| Nauck, 2014[121](#_ENREF_121)RCT | Grp1: Metformin + sitagliptinFixed (>=1500 mg/day)Fixed (100 mg)Grp2: Metformin + dulaglutideFixed (>=1500 mg/day)Fixed (1.5 mg/week)ITT: Not applicable (e.g., cohort)Followup (wks):  NR/unclear |  |  | Def:CVD morbidityCVD morbidity composite outcome (MI, Stroke and CV death based on ICD-10 codes composite of MI (I21â€“I22), stroke (I61â€“I64) cardiovascular death (I00 â€“I99))Incidence Grp1: 245   p RH 1Incidence Grp2: 267   p RH 1.29 |  |
| Nauck, 2014[121](#_ENREF_121)RCT | Grp1: Metformin + sitagliptinFixed (>=1500 mg/day)Fixed (100 mg)Grp2: Metformin + dulaglutideFixed (>=1500 mg/day)Fixed (1.5 mg/week)ITT: Not applicable (e.g., cohort)Followup (wks):  NR/unclear |  |  | Def:CVD morbidityCVD morbidity composite outcome (MI, Stroke and CV death based on ICD-10 codes composite of MI (I21â€“I22), stroke (I61â€“I64) cardiovascular death (I00 â€“I99))Incidence Grp1: 1646   p RH 1Incidence Grp2: 820   p RH 1.17 |  |
| Nauck, 2014[121](#_ENREF_121)RCT | Grp1: Metformin + sitagliptinFixed (>=1500 mg/day)Fixed (100 mg)Grp2: Metformin + dulaglutideFixed (>=1500 mg/day)Fixed (0.75 mg/week)ITT: Not applicable (e.g., cohort)Followup (wks):  NR/unclear |  |  | Def:CVD morbidityCVD morbidity composite outcome (MI, Stroke and CV death based on ICD-10 codes composite of MI (I21â€“I22), stroke (I61â€“I64) cardiovascular death (I00 â€“I99))Incidence Grp1: 245   p RH 1Incidence Grp2: 154   p RH 1.46 |  |
| Nauck, 2014[121](#_ENREF_121)RCT | Grp1: Metformin + sitagliptinFixed (>=1500 mg/day)Fixed (100 mg)Grp2: Metformin + dulaglutideFixed (>=1500 mg/day)Fixed (1.5 mg/week)ITT: Not applicable (e.g., cohort)Followup (wks):  NR/unclear |  |  | Def:CVD morbidityCVD morbidity composite outcome (MI, Stroke and CV death based on ICD-10 codes composite of MI (I21â€“I22), stroke (I61â€“I64) cardiovascular death (I00 â€“I99))Incidence Grp1: 245   p RH 1Incidence Grp2: 751   p RH 1.29 |  |
| Pantalone, 2009[208](#_ENREF_208)Cohort | Grp1: MetforminNRGrp2: RosiglitazoneNR | Grp1: refGrp2: HR: 1.33 (CI: 0.93 to 1.91) p: 0.11 |  | Def: CABG, PTCA, MI, or diagnosis of CAD by ICD-9 after baselineGrp1: refGrp2: HR: 0.96 (CI: 0.76 to 1.21) p: 0.74 |  |
| Pantalone, 2009[208](#_ENREF_208)Cohort | Grp1: MetforminNRGrp2: PioglitazoneNR | Grp1: refGrp2: HR: 1.08 (CI: 0.78 to 1.51) p: 0.64 |  | Def: CABG, PTCA, MI, or diagnosis of CAD by ICD-9 after baselineGrp1: refGrp2: HR: 1.11 (CI: 0.91 to 1.34) p: 0.32 |  |
| Pantalone, 2009[208](#_ENREF_208)Cohort | Grp1: Metformin NRGrp2: SulfonylureaNR | Grp1: HR: 0.54 (CI: 0.46 to 0.64) p: <0.001Grp2: ref |  | Def: CABG, PTCA, MI, or diagnosis of CAD by ICD-9 after baselineGrp1: HR: 0.94 (CI: 0.85 to 1.05) p: 0.23Grp2: ref |  |
| Pantalone, 2009[208](#_ENREF_208)Cohort | Grp1: Rosiglitazone NRGrp2: PioglitazoneNR | Grp1: refGrp2: HR: 0.81 (CI: 0.52 to 1.27) p: 0.36 |  | Def: CABG, PTCA, MI, or diagnosis of CAD by ICD-9 after baselineGrp1: refGrp2: HR: 1.15 (CI: 0.87 to 1.53) p: 0.32 |  |
| Pantalone, 2009[208](#_ENREF_208)Cohort | Grp1: RosiglitazoneNRGrp2: SulfonylureaNR | Grp1: HR: 0.73 (CI: 0.51 to 1.02) p: 0.08Grp2: ref |  | Def: CABG, PTCA, MI, or diagnosis of CAD by ICD-9 after baselineGrp1: HR: 0.90 (CI: 0.71 to 1.14) p: 0.41Grp2: ref |  |
| Pantalone, 2009[208](#_ENREF_208)Cohort | Grp1: PioglitazoneNRGrp2: SulfonylureaNR | Grp1: HR: 0.59 (CI: 0.43 to 0.81) p: <0.001Grp2: ref |  | Def: CABG, PTCA, MI, or diagnosis of CAD by ICD-9 after baselineGrp1: HR: 1.04 (CI: 0.86 to 1.26) p: 0.69Grp2: ref |  |
| Pantalone, 2012[209](#_ENREF_209)Retrospective cohort | Grp1: MetforminNot specified  Grp2: GlipizideNot specified  ITT: Not applicable (e.g., cohort)Followup (wks):  NR/unclear |  |  | Def:CVD morbidityCVD morbidity composite outcome (MI, Stroke and CV death based on ICD-10 codes composite of MI (I21â€“I22), stroke (I61â€“I64) cardiovascular death (I00 â€“I99))Incidence Grp1: 1646   p RH 1Incidence Grp2: 3517   p RH 1.21 |  |
| Pantalone, 2012[209](#_ENREF_209)Retrospective cohort | Grp1: MetforminNot specified  Grp2: GlyburideNot specified  ITT: NoFollowup (wks): 24  |  |  | Def:CVD morbidityCVD morbidity composite outcome (not prespecified as a composite outcome but this is what is reported on - CAD, carotid artery stenosis, peripheral artery disease)Incidence p Incidence p  |  |
| Pantalone, 2012[209](#_ENREF_209)Retrospective cohort | Grp1: MetforminNot specified  Grp2: GlimepirideNot specified  ITT: Not applicable (e.g., cohort)Followup (wks):   |  |  | Def:CVD morbidityNonfatal MI (ï¬rst-time discharge diagnosis of MI)Incidence Grp1: 599  5927 Persons p OR 0.86Incidence Grp2: 3080  26778 Persons p OR 1 REF |  |
| Petrica, 2009[126](#_ENREF_126)RCT | Grp1: Metformin + rosiglitazoneFixed (1700 mg/day)Fixed (4 mg/day)Grp2: Metformin + glimepirideFixed (1700 mg/day)Fixed (4 mg/day)ITT: YesFollowup (wks): 76 NR/unclear |  |  | Def:CVD morbidityOther CVD morbidity (acute CVD adverse events (unspecified))Incidence Grp1: (2.1) Incidence Grp2:    |  |
| Petrica, 2009[126](#_ENREF_126)RCT | Grp1: Metformin + rosiglitazoneFixed (1700 mg/day)Fixed (4 mg/day)Grp2: Metformin + glimepirideFixed (1700 mg/day)Fixed (4 mg/day)ITT: YesFollowup (wks): 76 NR/unclear |  |  | Def:CVD morbidityOther CVD morbidity (acute CVD adverse events (unspecified))Incidence Grp1: (2.1) Incidence Grp2: (0.3)  |  |
| Pfutzner, 2011[128](#_ENREF_128)RCT | Grp1: Metformin + pioglitazoneFixed (1700 mg/d)Fixed (30 mg/d)Grp2: Metformin + glimepirideFixed (1700 mg/d)Fixed (2mg/d)ITT: YesFollowup (wks): 76 NR/unclear |  |  | Def:CVD morbidityOther CVD morbidity (acute CVD adverse events (unspecified))Incidence Grp1: (2.1) Incidence Grp2:    |  |
| Pfutzner, 2011[129](#_ENREF_129)RCT | Grp1: Metformin + placeboTitrated (Max: 2000 mg)Grp2: Saxagliptin + placeboFixed (10 mg)ITT: YesFollowup (wks): 76 NR/unclear |  |  | Def:CVD morbidityOther CVD morbidity (acute CVD adverse events (unspecified))Incidence Grp1:   Incidence Grp2: (0.3)  |  |
| Pfutzner, 2011[129](#_ENREF_129)RCT | Grp1: Metformin + placeboTitrated (Max: 2000 mg)Grp2: Saxagliptin + placeboFixed (10 mg)ITT: YesFollowup (wks): 76 NR/unclear |  |  | Def:CVD morbidityOther CVD morbidity (acute CVD adverse events (unspecified))Incidence Grp1:   Incidence Grp2:    |  |
| Pfutzner, 2011[129](#_ENREF_129)RCT | Grp1: Metformin + placeboTitrated (Max: 2000 mg)Grp2: Saxagliptin + placeboFixed (10 mg)ITT: YesFollowup (wks): 104  |  |  | Def:CVD morbidityNonfatal MI (myocardial infarction, judged to have a possible relationship to trial drug by investigator)Incidence Grp1: 1   Incidence Grp2: 1    |  |
| Pfutzner, 2011[129](#_ENREF_129)RCT | Grp1: Metformin + placeboTitrated (Max: 2000 mg)Grp2: Saxagliptin + placeboFixed (10 mg)ITT: Followup (wks): 104  |  |  | Def:CVD morbidityOther CVD morbidity (cardiac disorders)Incidence Grp1: 14 (6) Incidence Grp2: 8 (3)  |  |
| Pfutzner, 2011[129](#_ENREF_129)RCT | Grp1: Metformin + placeboTitrated (Max: 2000 mg)Grp2: Metformin + saxagliptinTitrated (Max: 2000 mg)Fixed (5 mg)ITT: Followup (wks): 104  |  |  | Def:CVD morbidityOther CVD morbidity (cardiac disorders)Incidence Grp1: 14 (6) Incidence Grp2: 11 (5)  |  |
| Pfutzner, 2011[129](#_ENREF_129)RCT | Grp1: Metformin + placeboTitrated (Max: 2000 mg)Grp2: Metformin + saxagliptinTitrated (Max: 2000 mg)Fixed (10 mg)ITT: YesFollowup (wks): 104  |  |  | Def:CVD morbidityNonfatal MI (myocardial infarction, judged to have a possible relationship to trial drug by investigator)Incidence Grp1: 1   Incidence Grp2: 1    |  |
| Pfutzner, 2011[129](#_ENREF_129)RCT | Grp1: Metformin + placeboTitrated (Max: 2000 mg)Grp2: Metformin + saxagliptinTitrated (Max: 2000 mg)Fixed (5 mg)ITT: Not applicable (e.g., cohort)Followup (wks):   |  |  | Def:CVD morbidityCVD morbidity composite outcome (death from any cause or first hospitalization for myocardial infarction (ICD-9 code 410-412.99 and 414. xx), cerebrovascular disease (430â€“437.1 and procedure code 38.12), coronary artery bypass graft (36.10â€“36.16 and 3Incidence p RH Incidence p RH 1.15 |  |
| Pfutzner, 2011[129](#_ENREF_129)RCT | Grp1: Metformin + placeboTitrated (Max: 2000 mg)Grp2: Metformin + saxagliptinTitrated (Max: 2000 mg)Fixed (10 mg)ITT: NRFollowup (wks): 104  |  |  | Def:CVD morbidityCVD morbidity composite outcome (CV AEs (qualitatively reported))Incidence p Incidence p  |  |
| Pfutzner, 2011[129](#_ENREF_129)RCT | Grp1: Metformin + placeboTitrated (Max: 2000 mg)Grp2: Metformin + saxagliptinTitrated (Max: 2000 mg)Fixed (5 mg)ITT: NoFollowup (wks): 26  |  |  | Def:CVD morbidityOther CVD morbidity (Unstable Angina)Incidence Grp1: 1 (1) Persons p Incidence Grp2: 0 (0) Persons p  |  |
| Pfutzner, 2011[129](#_ENREF_129)RCT | Grp1: Metformin + placeboTitrated (Max: 2000 mg)Grp2: Metformin + saxagliptinTitrated (Max: 2000 mg)Fixed (10 mg)ITT: NoFollowup (wks): 26  |  |  | Def:CVD morbidityOther CVD morbidity (Coronary artery occlusion)Incidence Grp1: 2 (1) Persons p NR Incidence Grp2: 0 (0) Persons p NR  |  |
| Pfutzner, 2011[129](#_ENREF_129)RCT | Grp1: Metformin + placeboTitrated (Max: 2000 mg)Grp2: Metformin + saxagliptinTitrated (Max: 2000 mg)Fixed (5 mg)ITT: NoFollowup (wks): 26  |  |  | Def:CVD morbidityOther CVD morbidity (Unstable Angina)Incidence Grp1: 1 (1) Persons p Incidence Grp2: 0 (0) Persons p  |  |
| Pfutzner, 2011[129](#_ENREF_129)RCT | Grp1: Metformin + placeboTitrated (Max: 2000 mg)Grp2: Metformin + saxagliptinTitrated (Max: 2000 mg)Fixed (10 mg)ITT: NoFollowup (wks): 26  |  |  | Def:CVD morbidityOther CVD morbidity (Coronary artery occlusion)Incidence Grp1: 2 (1) Persons p NR Incidence Grp2: 0 (0) Persons p NR  |  |
| Pfutzner, 2011[129](#_ENREF_129)RCT | Grp1: Saxagliptin + placeboFixed (10 mg)Grp2: Metformin + saxagliptinTitrated (Max: 2000 mg)Fixed (5 mg)ITT: NoFollowup (wks): 26  |  |  | Def:CVD morbidityOther CVD morbidity (Unstable Angina)Incidence Grp1: 0 (0) Persons p Incidence Grp2: 0 (0) Persons p  |  |
| Pfutzner, 2011[129](#_ENREF_129)RCT | Grp1: Saxagliptin + placeboFixed (10 mg)Grp2: Metformin + saxagliptinTitrated (Max: 2000 mg)Fixed (10 mg)ITT: NoFollowup (wks): 26  |  |  | Def:CVD morbidityOther CVD morbidity (Coronary artery occlusion)Incidence Grp1: 0 (0) Persons p NR Incidence Grp2: 0 (0) Persons p NR  |  |
| Pfutzner, 2011[129](#_ENREF_129)RCT | Grp1: Saxagliptin + placeboFixed (10 mg)Grp2: Metformin + saxagliptinTitrated (Max: 2000 mg)Fixed (5 mg)ITT: Not applicable (e.g., cohort)Followup (wks):   |  |  | Def:CVD morbidityCVD morbidity composite outcome (all-cause mortality, AMI and stroke)Incidence Grp1: 4286 (5.1) p RR REFIncidence Grp2: 62 (5) p RR 1.22 |  |
| Pfutzner, 2011[129](#_ENREF_129)RCT | Grp1: Saxagliptin + placeboFixed (10 mg)Grp2: Metformin + saxagliptinTitrated (Max: 2000 mg)Fixed (10 mg)ITT: YesFollowup (wks): 102  |  | Def:CVD mortalityOther CVD mortality (cardiopulmonary arrest and myocardial infarction)Incidence Grp1:   Incidence Grp2: 2    |  |  |
| Pfutzner, 2011[129](#_ENREF_129)RCT | Grp1: Saxagliptin + placeboFixed (10 mg)Grp2: Metformin + saxagliptinTitrated (Max: 2000 mg)Fixed (5 mg)ITT: YesFollowup (wks): 102  |  | Def:CVD mortalityOther CVD mortality (cardiopulmonary arrest and myocardial infarction)Incidence Grp1:   Incidence Grp2:    |  |  |
| Pfutzner, 2011[129](#_ENREF_129)RCT | Grp1: Saxagliptin + placeboFixed (10 mg)Grp2: Metformin + saxagliptinTitrated (Max: 2000 mg)Fixed (10 mg)ITT: YesFollowup (wks): 102  |  | Def:CVD mortalityOther CVD mortality (cardiopulmonary arrest and myocardial infarction)Incidence Grp1:   Incidence Grp2:    |  |  |
| Pfutzner, 2011[129](#_ENREF_129)RCT | Grp1: Saxagliptin + placeboFixed (10 mg)Grp2: Metformin + saxagliptinTitrated (Max: 2000 mg)Fixed (5 mg)ITT: YesFollowup (wks): 52 Active |  | Def:CVD mortalityFatal MIIncidence Grp1: 0   Incidence Grp2: 1    |  |  |
| Pfutzner, 2011[129](#_ENREF_129)RCT | Grp1: Saxagliptin + placeboFixed (10 mg)Grp2: Metformin + saxagliptinTitrated (Max: 2000 mg)Fixed (10 mg)ITT: YesFollowup (wks): 104  |  | Def:CVD mortalityComposite CVD mortality outcome (sudden cardiac death, fatal myocardial infarction, and fatal stroke)Incidence Grp1: 2   NA p NR RR Incidence Grp2: 2   NA p NR RR 1 |  |  |
| Pratley, 2010[130](#_ENREF_130)RCT | Grp1: Metformin + sitagliptinNS; Max: 100 mgGrp2: Metformin + liraglutideVaried, HgbA1c: 7.5-10%NS; Start: 0.6 mg, Max: 1.8 mg |  | Def: Fatal cardiac arrestGrp1: 1 (<1)Grp2: 0 (0) |  |  |
| Pratley, 2010[130](#_ENREF_130)RCT | Grp1: Metformin + sitagliptinNS; Max: 100 mgGrp2: Metformin + liraglutideVaried, HgbA1c: 7.5-10%NS; Start: 0.6 mg, Max: 1.2 mg |  | Def: Fatal cardiac arrestGrp1: 1 (<1)Grp2: 0 (0) |  |  |
| Pratley, 2014[131](#_ENREF_131)RCT | Grp1: MetforminFixed (2000 mg)Grp2: + alogliptinFixed (25mg qd)ITT: NoFollowup (wks): 26 NR/unclear |  | Def:CVD mortalityOther CVD mortality (sudden cardiac death)Incidence Grp1:   Incidence Grp2:    |  |  |
| Pratley, 2014[131](#_ENREF_131)RCT | Grp1: MetforminFixed (1000 mg)Grp2: + alogliptinFixed (25mg qd)ITT: NoFollowup (wks): 26 NR/unclear |  | Def:CVD mortalityOther CVD mortality (sudden cardiac death)Incidence Grp1:   Incidence Grp2:    |  |  |
| Pratley, 2014[131](#_ENREF_131)RCT | Grp1: MetforminFixed (2000 mg)Grp2: + alogliptinFixed (25mg qd)ITT: NoFollowup (wks): 26 NR/unclear |  | Def:CVD mortalityOther CVD mortality (sudden cardiac death)Incidence Grp1:   Incidence Grp2: 1    |  |  |
| Pratley, 2014[131](#_ENREF_131)RCT | Grp1: MetforminFixed (1000 mg)Grp2: + alogliptinFixed (25mg qd)ITT: NoFollowup (wks): 26 NR/unclear |  | Def:CVD mortalityOther CVD mortality (sudden cardiac death)Incidence Grp1:   Incidence Grp2:    |  |  |
| Pratley, 2014[131](#_ENREF_131)RCT | Grp1: MetforminFixed (1000 mg)Grp2: + alogliptinFixed (25mg qd)ITT: NoFollowup (wks): 26 NR/unclear |  | Def:CVD mortalityOther CVD mortality (sudden cardiac death)Incidence Grp1:   Incidence Grp2:    |  |  |
| Pratley, 2014[131](#_ENREF_131)RCT | Grp1: MetforminFixed (2000 mg)Grp2: + alogliptinFixed (25mg qd)ITT: NoFollowup (wks): 26 NR/unclear |  | Def:CVD mortalityOther CVD mortality (sudden cardiac death)Incidence Grp1:   Incidence Grp2:    |  |  |
| Pratley, 2014[131](#_ENREF_131)RCT | Grp1: MetforminFixed (1000 mg)Grp2: Metformin + alogliptinFixed (1000 mg)Fixed (25 mg)ITT: NoFollowup (wks): 26 NR/unclear |  | Def:CVD mortalityOther CVD mortality (sudden cardiac death)Incidence Grp1: 1   Incidence Grp2:    |  |  |
| Pratley, 2014[131](#_ENREF_131)RCT | Grp1: MetforminFixed (2000 mg)Grp2: Metformin + alogliptinFixed (1000 mg)Fixed (25 mg)ITT: NoFollowup (wks): 26 NR/unclear |  | Def:CVD mortalityOther CVD mortality (sudden cardiac death)Incidence Grp1:   Incidence Grp2:    |  |  |
| Pratley, 2014[131](#_ENREF_131)RCT | Grp1: MetforminFixed (1000 mg)Grp2: Metformin + alogliptinFixed (2000 mg)Fixed (25 mg)ITT: NoFollowup (wks): 26 NR/unclear |  | Def:CVD mortalityOther CVD mortality (sudden cardiac death)Incidence Grp1:   Incidence Grp2:    |  |  |
| Pratley, 2014[131](#_ENREF_131)RCT | Grp1: MetforminFixed (2000 mg)Grp2: Metformin + alogliptinFixed (2000 mg)Fixed (25 mg)ITT: NoFollowup (wks): 26 NR/unclear |  | Def:CVD mortalityOther CVD mortality (sudden cardiac death)Incidence Grp1: 1   Incidence Grp2:    |  |  |
| Pratley, 2014[131](#_ENREF_131)RCT | Grp1: MetforminFixed (2000 mg)Grp2: Metformin + alogliptinFixed (1000 mg)Fixed (25 mg)ITT: NoFollowup (wks): 26 NR/unclear |  | Def:CVD mortalityOther CVD mortality (sudden cardiac death)Incidence Grp1:   Incidence Grp2:    |  |  |
| Pratley, 2014[131](#_ENREF_131)RCT | Grp1: MetforminFixed (1000 mg)Grp2: Metformin + alogliptinFixed (1000 mg)Fixed (25 mg)ITT: YesFollowup (wks): 24  |  | Def:CVD mortalityFatal MIIncidence Grp1: 0   Incidence Grp2: 0    |  |  |
| Pratley, 2014[131](#_ENREF_131)RCT | Grp1: MetforminFixed (2000 mg)Grp2: Metformin + alogliptinFixed (2000 mg)Fixed (25 mg)ITT: YesFollowup (wks): 24  |  | Def:CVD mortalityFatal MIIncidence Grp1: 1   Incidence Grp2: 0    |  |  |
| Pratley, 2014[131](#_ENREF_131)RCT | Grp1: MetforminFixed (1000 mg)Grp2: Metformin + alogliptinFixed (2000 mg)Fixed (25 mg)ITT: YesFollowup (wks): 24  |  | Def:CVD mortalityFatal MIIncidence Grp1: 1   Incidence Grp2: 0    |  |  |
| Pratley, 2014[131](#_ENREF_131)RCT | Grp1: MetforminFixed (2000 mg)Grp2: Metformin + alogliptinFixed (1000 mg)Fixed (25 mg)ITT: YesFollowup (wks): 24  |  | Def:CVD mortalityFatal MIIncidence Grp1: 0   Incidence Grp2: 0    |  |  |
| Pratley, 2014[131](#_ENREF_131)RCT | Grp1: MetforminFixed (1000 mg)Grp2: Metformin + alogliptinFixed (1000 mg)Fixed (25 mg)ITT: YesFollowup (wks): 24  |  | Def:CVD mortalityFatal MIIncidence Grp1: 0   Incidence Grp2: 0    |  |  |
| Pratley, 2014[131](#_ENREF_131)RCT | Grp1: MetforminFixed (2000 mg)Grp2: Metformin + alogliptinFixed (2000 mg)Fixed (25 mg)ITT: YesFollowup (wks): 24  |  | Def:CVD mortalityFatal MIIncidence Grp1: 1   Incidence Grp2: 0    |  |  |
| Pratley, 2014[131](#_ENREF_131)RCT | Grp1: MetforminFixed (1000 mg)Grp2: Metformin + alogliptinFixed (2000 mg)Fixed (25 mg)ITT: YesFollowup (wks): 24  |  | Def:CVD mortalityFatal MIIncidence Grp1: 0   Incidence Grp2: 0    |  |  |
| Pratley, 2014[131](#_ENREF_131)RCT | Grp1: Metformin + alogliptinFixed (2000 mg)Fixed (25 mg)Grp2: + alogliptinFixed (25mg qd)ITT: YesFollowup (wks): 24  |  | Def:CVD mortalityFatal MIIncidence Grp1: 0   Incidence Grp2: 0    |  |  |
| Pratley, 2014[131](#_ENREF_131)RCT | Grp1: Metformin + alogliptinFixed (1000 mg)Fixed (25 mg)Grp2: + alogliptinFixed (25mg qd)ITT: YesFollowup (wks): 104  |  | Def:CVD mortalityFatal MIIncidence Grp1: 1  408 Persons p NR Incidence Grp2: 0  406 Persons p NR  |  |  |
| Pratley, 2014[131](#_ENREF_131)RCT | Grp1: Metformin + alogliptinFixed (2000 mg)Fixed (25 mg)Grp2: + alogliptinFixed (25mg qd)ITT: YesFollowup (wks): 12  |  | Def:CVD mortalityOther CVD mortality (no fatal adverse events were reported)Incidence Grp1: 0   Incidence Grp2: 0    |  |  |
| Pratley, 2014[131](#_ENREF_131)RCT | Grp1: Metformin + alogliptinFixed (1000 mg)Fixed (25 mg)Grp2: + alogliptinFixed (25mg qd)ITT: Not applicable (e.g., cohort)Followup (wks):   |  | Def:CVD mortalityOther CVD mortality (ICD-10: I00-I99)Incidence Grp1: 10  3246 Person-years p Rate ratio (poisson) 0.89Incidence Grp2: 91  6916 Person-years p Rate ratio (poisson) 1.57 |  |  |
| Pratley, 2014[131](#_ENREF_131)RCT | Grp1: Metformin + alogliptinFixed (1000 mg)Fixed (25 mg)Grp2: + alogliptinFixed (25mg qd)ITT: Not applicable (e.g., cohort)Followup (wks):   |  | Def:CVD mortalityOther CVD mortality (ICD-10: I00-I99)Incidence Grp1: 256  31497 Person-years p Rate ratio (poisson) 1 (Ref)Incidence Grp2: 10  3246 Person-years p Rate ratio (poisson) 0.89 |  |  |
| Pratley, 2014[131](#_ENREF_131)RCT | Grp1: Metformin + alogliptinFixed (2000 mg)Fixed (25 mg)Grp2: + alogliptin  Fixed (25mg qd)ITT: Not applicable (e.g., cohort)Followup (wks):   |  | Def:CVD mortalityOther CVD mortality (ICD-10: I00-I99)Incidence Grp1: 256  31497 Person-years p Rate ratio (poisson) 1 (Ref)Incidence Grp2: 38  11619 Person-years p Rate ratio (poisson) 0.57 |  |  |
| Qiu, 2014[132](#_ENREF_132)RCT | Grp1: Metformin + placeboFixed (Mean: 2131mg>= 2000mg/day,or >= 1500mg/day ifunable to tolerate a higher dose) for >=8 wks prior to screening)Grp2: Metformin + canagliflozinFixed (Mean: 2137mg>= 2000mg/day,or >= 1500mg/dayifunable to tolerate a higher dose) for >= 8 wks prior to screening)Fixed (50mg BID)ITT: Not applicable (e.g., cohort)Followup (wks):   |  | Def:CVD mortalityOther CVD mortality (ICD-10: I00-I99)Incidence Grp1: 256  31497 Person-years p Rate ratio (poisson) 1 (Ref)Incidence Grp2: 91  6916 Person-years p Rate ratio (poisson) 1.57 |  |  |
| Qiu, 2014[132](#_ENREF_132)RCT | Grp1: Metformin + placeboFixed (Mean: 2131mg>= 2000mg/day,or >= 1500mg/day ifunable to tolerate a higher dose) for >=8 wks prior to screening)Grp2: Metformin + canagliflozinFixed (Mean: 2128mg>= 2000mg/day,or >= 1500mg/dayifunable to tolerate a higher dose) for >= 8 wks prior to screening)Fixed (150mg BID)ITT: Not applicable (e.g., cohort)Followup (wks):   |  | Def:CVD mortalityOther CVD mortality (ICD-10: I00-I99)Incidence Grp1: 38  11619 Person-years p Rate ratio (poisson) 0.57Incidence Grp2: 10  3246 Person-years p Rate ratio (poisson) 0.89 |  |  |
| Qiu, 2014[132](#_ENREF_132)RCT | Grp1: Metformin + placeboFixed (Mean: 2131mg>= 2000mg/day,or >= 1500mg/day ifunable to tolerate a higher dose) for >=8 wks prior to screening)Grp2: Metformin + canagliflozinFixed (Mean: 2137mg>= 2000mg/day,or >= 1500mg/dayifunable to tolerate a higher dose) for >= 8 wks prior to screening)Fixed (50mg BID)ITT: Not applicable (e.g., cohort)Followup (wks):   |  | Def:CVD mortalityOther CVD mortality (ICD-10: I00-I99)Incidence Grp1: 38  11619 Person-years p Rate ratio (poisson) 0.57Incidence Grp2: 91  6916 Person-years p Rate ratio (poisson) 1.57 |  |  |
| Qiu, 2014[132](#_ENREF_132)RCT | Grp1: Metformin + placeboFixed (Mean: 2131mg>= 2000mg/day,or >= 1500mg/day ifunable to tolerate a higher dose) for >=8 wks prior to screening)Grp2: Metformin + canagliflozinFixed (Mean: 2128mg>= 2000mg/day,or >= 1500mg/dayifunable to tolerate a higher dose) for >= 8 wks prior to screening)Fixed (150mg BID)ITT: NoFollowup (wks): 48  |  | Def:CVD mortalityUnspecified CVD mortalityIncidence Grp1: 0   Incidence Grp2: 0    |  |  |
| Raz, 2008[188](#_ENREF_188)RCT | Grp1: MetforminFixedGrp2: Metformin + sitagliptinFixedMax: 2550 mg; Mean: 100 mg | Grp1: 1 (1)Grp2: 0 (0) | Def: Fatal MIGrp1: 1 (1)Grp2: 0 (0) |  |  |
| Reasner, 2011[135](#_ENREF_135)RCT | Grp1: MetforminTitrated (Max: 2000 mg)Grp2: Metformin + sitagliptinTitrated (Max: 2000 mg)Titrated (Max: 100 mg)ITT: NoFollowup (wks): 58  |  | Def:CVD mortalityFatal MIIncidence Grp1: 2   Incidence Grp2:    |  |  |
| Reasner, 2011[135](#_ENREF_135)RCT | Grp1: MetforminTitrated (Max: 2000 mg)Grp2: Metformin + sitagliptinTitrated (Max: 2000 mg)Titrated (Max: 100 mg)ITT: YesFollowup (wks): 144  |  | Def:CVD mortalityOther CVD mortality (not specified but confirmed by medical record and death certificates at each institution)Incidence Grp1: 7   Incidence Grp2: 11    |  |  |
| Ridderstrale, 2014[136](#_ENREF_136)RCT | Grp1: Metformin + glimepirideFixed (Mean: 2.71 mg/day (mean max titrated dose of glimep(ΓëÑ1500 mg/day, maximum tolerated dose, or maximum dose according to the local label)Titrated (Max: 4mg)Grp2: Metformin + empagliflozinFixed ((ΓëÑ1500 mg/day, maximum tolerated dose, or maximum dose according to the local label)Fixed (25mg)ITT: Not applicable (e.g., cohort)Followup (wks):  NR/unclear |  | Def:CVD mortalityComposite CVD mortality outcome (death within 28 days of CVD was defined as diagnosis of myocardial infarction (ICD â€ 10 code I21), angina pectoris (ICD â€ 10 code I20.0), intracerebral haemorrhage, cerebral infarction, unspecified stroke (ICD â€ 10 cIncidence Grp1: 264   NA p NR RH 1.00 REFIncidence Grp2: 276   NA p NR RH Non-Proportional hazard, excluded from analysis |  |  |
| Ridderstrale, 2014[136](#_ENREF_136)RCT | Grp1: Metformin + glimepirideFixed (Mean: 2.71 mg/day (mean max titrated dose of glimep(ΓëÑ1500 mg/day, maximum tolerated dose, or maximum dose according to the local label)Titrated (Max: 4mg)Grp2: Metformin + empagliflozinFixed ((ΓëÑ1500 mg/day, maximum tolerated dose, or maximum dose according to the local label)Fixed (25mg)ITT: NoFollowup (wks): 80 NR/unclear |  | Def:CVD mortalityOther CVD mortality (fata MI)Incidence p Incidence p  |  |  |
| Rigby, 2009[137](#_ENREF_137)RCT | Grp1: Metformin + rosiglitazoneFixedNS; Mean: 4 mgGrp2: Metformin + sitagliptinNS: Mean: 100 mg |  |  | Def: Transient ischemic cerebrovascular accidentGrp1: 1 (2)Grp2: 0 (0) |  |
| Roden, 2013[139](#_ENREF_139)RCT | Grp1: SitagliptinFixed (100 mg)Grp2: EmpagliflozinFixed (10 mg)ITT: Not applicable (e.g., cohort)Followup (wks):  NR/unclear |  | Def:CVD mortalityOther CVD mortality (cardiovascular death (ICD-10 I00 â€“I99))Incidence Grp1: 169   p RH 1Incidence Grp2: 207   p RH 1.5 |  |  |
| Roden, 2013[139](#_ENREF_139)RCT | Grp1: SitagliptinFixed (100 mg)Grp2: EmpagliflozinFixed (25 mg)ITT: Not applicable (e.g., cohort)Followup (wks):  NR/unclear |  | Def:CVD mortalityOther CVD mortality (cardiovascular death (ICD-10 I00 â€“I99))Incidence Grp1: 827   p RH 1Incidence Grp2: 876   p RH 1.14 |  |  |
| Roden, 2013[139](#_ENREF_139)RCT | Grp1: SitagliptinFixed (100 mg)Grp2: EmpagliflozinFixed (10 mg)ITT: Not applicable (e.g., cohort)Followup (wks):  NR/unclear |  | Def:CVD mortalityOther CVD mortality (cardiovascular death (ICD-10 I00 â€“I99))Incidence Grp1: 827   p RH 1Incidence Grp2: 559   p RH 1.25 |  |  |
| Roden, 2013[139](#_ENREF_139)RCT | Grp1: SitagliptinFixed (100 mg)Grp2: EmpagliflozinFixed (25 mg)ITT: Not applicable (e.g., cohort)Followup (wks):  NR/unclear |  | Def:CVD mortalityOther CVD mortality (cardiovascular death (ICD-10 I00 â€“I99))Incidence Grp1: 169   p RH 1Incidence Grp2: 115   p RH 1.63 |  |  |
| Rosenstock, 2006[140](#_ENREF_140)RCT | Grp1: MetforminVaried, glucose: 6.1 mmol/lStart: 500 mg, Mean: 1847 mg, Max: 2000 mgD: 32 wksGrp2: RosiglitazoneVaried, glucose: 6.1 mmol/lStart: 4 mg, Mean: 7.7 mg, Max: 8 mgD: 32 wks | Grp1: 0 (0)Grp2: 0 (0) |  | Def: Not defined ischemic heart diseaseGrp1: 2 (1)Grp2: 2 (1) |  |
| Rosenstock, 2006[140](#_ENREF_140)RCT | Grp1: MetforminVaried, glucose: 6.1 mmol/lStart: 500 mg, Max: 2000 mg, Mean: 1847 mgD: 32 wksGrp2: Metformin + rosiglitazoneVaried, glucose: 6.1 mmol/lStart: 500 mg, Mean: 1799 mg, Max: 2000 mg; Start: 2 mg, Max: 8 mg, Mean: 7.2mgD: 32 wks | Grp1: 0 (0)Grp2: 0 (0) |  | Def: Not defined ischemic heart diseaseGrp1: 2 (1)Grp2: 1 (1) |  |
| Rosenstock, 2013[144](#_ENREF_144)RCT | Grp1: Metformin + placeboNot specified (prestudy dose: ΓëÑ1500 mg/day or maximum tolerated dose)Grp2: Metformin + sitagliptinNot specified (prestud dose: ΓëÑ1500 mg/day or maximum tolerated dose)Fixed (100mg)ITT: Not applicable (e.g., cohort)Followup (wks):  NR/unclear |  | Def:CVD mortalityOther CVD mortality (cardiovascular death (ICD-10 I00 â€“I99))Incidence Grp1: 827   p RH 1Incidence Grp2: 2251   p RH 1.28 |  |  |
| Rosenstock, 2013[144](#_ENREF_144)RCT | Grp1: Metformin + placeboNot specified (prestudy dose: ΓëÑ1500 mg/day or maximum tolerated dose)Grp2: Metformin + empagliflozinNot specified (prestudy dose: ΓëÑ1500 mg/day or maximum tolerated dose)Fixed (10mg)ITT: Not applicable (e.g., cohort)Followup (wks):  NR/unclear |  | Def:CVD mortalityOther CVD mortality (cardiovascular death (ICD-10 I00 â€“I99))Incidence Grp1: 169   p RH 1Incidence Grp2: 591   p RH 1.32 |  |  |
| Rosenstock, 2013[144](#_ENREF_144)RCT | Grp1: Metformin + placeboNot specified (prestudy dose: ΓëÑ1500 mg/day or maximum tolerated dose)Grp2: Metformin + empagliflozinNot specified (prestudy dose: ΓëÑ1500 mg/day or maximum tolerated dose)Fixed (25mg)ITT: YesFollowup (wks): 44  |  | Def:CVD mortalityComposite CVD mortality outcome (fatal acute myocardial infarction and cario-respiratory arrest)Incidence Grp1: 1   Incidence Grp2: 1    |  |  |
| Rosenstock, 2013[144](#_ENREF_144)RCT | Grp1: Metformin + sitagliptinNot specified (prestud dose: ΓëÑ1500 mg/day or maximum tolerated dose)Fixed (100mg)Grp2: Metformin + empagliflozinNot specified (prestudy dose: ΓëÑ1500 mg/day or maximum tolerated dose)Fixed (10mg)ITT: YesFollowup (wks): 76  |  | Def:CVD mortalityOther CVD mortality (sudden death, cardiac arrest, coronary artery arteriosclerosis, cardiac failure, AMI)Incidence Grp1: 3   Incidence Grp2: 1    |  |  |
| Rosenstock, 2013[144](#_ENREF_144)RCT | Grp1: Metformin + sitagliptinNot specified (prestud dose: ΓëÑ1500 mg/day or maximum tolerated dose)Fixed (100mg)Grp2: Metformin + empagliflozinNot specified (prestudy dose: ΓëÑ1500 mg/day or maximum tolerated dose)Fixed (25mg)ITT: YesFollowup (wks): 76  |  | Def:CVD mortalityOther CVD mortality (sudden death, cardiac arrest, coronary artery arteriosclerosis, cardiac failure, AMI)Incidence Grp1: 3   Incidence Grp2: 0    |  |  |
| Ross, 2012[146](#_ENREF_146)RCT | Grp1: Metformin + placeboFixed (Mean: 1963.6mgMax: 1500mg or maximum tolerated dose)Grp2: Metformin + linagliptin + placeboFixed (Mean: 1811.6mgMax: 1500mg or maximum tolerated dose)Fixed (5mg)ITT: YesFollowup (wks): 76  |  | Def:CVD mortalityOther CVD mortality (sudden death, cardiac arrest, coronary artery arteriosclerosis, cardiac failure, AMI)Incidence Grp1: 3   Incidence Grp2: 2    |  |  |
| Ross, 2012[146](#_ENREF_146)RCT | Grp1: Metformin + placeboFixed (Mean: 1963.6mgMax: 1500mg or maximum tolerated dose)Grp2: Metformin + linagliptin + placeboFixed (Mean: 1811.6mgMax: 1500mg or maximum tolerated dose)Fixed (5mg)ITT: YesFollowup (wks): 76  |  | Def:CVD mortalityOther CVD mortality (sudden death, cardiac arrest, coronary artery arteriosclerosis, cardiac failure, AMI)Incidence Grp1: 1   Incidence Grp2: 0    |  |  |
| Ross, 2012[146](#_ENREF_146)RCT | Grp1: Metformin + placeboFixed (Mean: 1963.6mgMax: 1500mg or maximum tolerated dose)Grp2: Metformin + linagliptin + placeboFixed (Mean: 1811.6mgMax: 1500mg or maximum tolerated dose)Fixed (5mg)ITT: YesFollowup (wks): 76  |  | Def:CVD mortalityOther CVD mortality (sudden death, cardiac arrest, coronary artery arteriosclerosis, cardiac failure, AMI)Incidence Grp1: 1   Incidence Grp2: 2    |  |  |
| Ross, 2012[146](#_ENREF_146)RCT | Grp1: Metformin + placeboFixed (Mean: 1963.6mgMax: 1500mg or maximum tolerated dose)Grp2: Metformin + linagliptin + placeboFixed (Mean: 1811.6mgMax: 1500mg or maximum tolerated dose)Fixed (5mg)ITT: YesFollowup (wks): 104  |  | Def:CVD mortalityComposite CVD mortality outcome (cardiac failure, myocardial infarction)Incidence Grp1: 1   Incidence Grp2: 1    |  |  |
| Roumie, 2012[210](#_ENREF_210)Retrospective cohort | Grp1: MetforminNot specified  Grp2: SUNot specified  ITT: Not applicable (e.g., cohort)Followup (wks):   |  | Def:CVD mortalityOther CVD mortality (death from cardiovascular causes (ICD- 10 codes I00â€“I99))Incidence Grp1: 109  1533 Person-years p 0.79Incidence Grp2: 1378  9570 Person-years p 1 REF |  |  |
| Roumie, 2012[210](#_ENREF_210)Retrospective cohort | Grp1: MetforminNot specified  Grp2: SUNot specified    ITT: Not applicable (e.g., cohort)Followup (wks):   |  | Def:CVD mortalityOther CVD mortality (death from cardiovascular causes (ICD- 10 codes I00â€“I99))Incidence Grp1: 109  1533 Person-years p 0.79Incidence Grp2: 447  4280 Person-years p 0.94 |  |  |
| Roumie, 2012[210](#_ENREF_210)Retrospective cohort | Grp1: MetforminNot specified  Grp2: SUNot specified  ITT: Not applicable (e.g., cohort)Followup (wks):   |  | Def:CVD mortalityOther CVD mortality (death from cardiovascular causes (ICD- 10 codes I00â€“I99))Incidence Grp1: 1378  9570 Person-years p 1 REFIncidence Grp2: 447  4280 Person-years p 0.94 |  |  |
| Roumie, 2012[210](#_ENREF_210)Retrospective cohort | Grp1: MetforminNot specified  Grp2: SUNot specified  ITT: YesFollowup (wks): 104  |  | Def:CVD mortalityOther CVD mortality (sudden cardiac death or worsening CAD)Incidence Grp1:   Incidence Grp2:    |  |  |
| Roumie, 2012[210](#_ENREF_210)Retrospective cohort | Grp1: MetforminNot specified  Grp2: SUNot specified  ITT: YesFollowup (wks): 104  |  | Def:CVD mortalityOther CVD mortality (sudden cardiac death or worsening CAD)Incidence Grp1:   Incidence Grp2:    |  |  |
| Roumie, 2012[210](#_ENREF_210)Retrospective cohort | Grp1: MetforminNot specified  Grp2: SUNot specified  ITT: YesFollowup (wks): 104  |  | Def:CVD mortalityOther CVD mortality (sudden cardiac death or worsening CAD)Incidence Grp1: 1   Incidence Grp2:    |  |  |
| Russell-Jones, 2012[147](#_ENREF_147)RCT | Grp1: Metformin + placeboTitrated (Max: 2500 mg based on glycemic controltarget 2000 mg)Grp2: Pioglitazone + placeboTitrated (Max: 45 mgtarget dose 45 mg/d)ITT: YesFollowup (wks): 104  |  | Def:CVD mortalityOther CVD mortality (sudden cardiac death or worsening CAD)Incidence Grp1:   Incidence Grp2: 1    |  |  |
| Russell-Jones, 2012[147](#_ENREF_147)RCT | Grp1: Metformin + placeboTitrated (Max: 2500 mg based on glycemic controltarget 2000 mg)Grp2: Sitagliptin + placeboFixed (100 mgimplies fixed daily dose and makes sense clinically for sita)ITT: YesFollowup (wks): 104  |  | Def:CVD mortalityOther CVD mortality (sudden cardiac death or worsening CAD)Incidence Grp1: 1   Incidence Grp2: 1    |  |  |
| Russell-Jones, 2012[147](#_ENREF_147)RCT | Grp1: Metformin + placeboTitrated (Max: 2500 mg based on glycemic controltarget 2000 mg)Grp2: Exenatide + placeboFixed (2.0 mg subcut weeklyEQW)ITT: YesFollowup (wks): 104  |  | Def:CVD mortalityOther CVD mortality (sudden cardiac death or worsening CAD)Incidence Grp1:   Incidence Grp2: 1    |  |  |
| Russell-Jones, 2012[147](#_ENREF_147)RCT | Grp1: Pioglitazone + placeboTitrated (Max: 45 mgtarget dose 45 mg/d)Grp2: Sitagliptin + placeboFixed (100 mgimplies fixed daily dose and makes sense clinically for sita)ITT: YesFollowup (wks): 104  |  | Def:CVD mortalityOther CVD mortality (sudden cardiac death or worsening CAD)Incidence Grp1:   Incidence Grp2:    |  |  |
| Russell-Jones, 2012[147](#_ENREF_147)RCT | Grp1: Pioglitazone + placeboTitrated (Max: 45 mgtarget dose 45 mg/d)Grp2: Exenatide + placeboFixed (2.0 mg subcut weeklyEQW)ITT: YesFollowup (wks): 104  |  | Def:CVD mortalityOther CVD mortality (sudden cardiac death or worsening CAD)Incidence Grp1:   Incidence Grp2:    |  |  |
| Russell-Jones, 2012[147](#_ENREF_147)RCT | Grp1: Sitagliptin + placeboFixed (100 mgimplies fixed daily dose and makes sense clinically for sita)  Grp2: Exenatide + placeboFixed (2.0 mg subcut weeklyEQW)  ITT: YesFollowup (wks): 104  |  | Def:CVD mortalityOther CVD mortality (sudden cardiac death or worsening CAD)Incidence Grp1: 1   Incidence Grp2:    |  |  |
| Scheller, 2014[211](#_ENREF_211)Retrospective cohort | Grp1: MetforminNot specified  Grp2: SitagliptinNot specified  ITT: YesFollowup (wks): 104  |  | Def:CVD mortalityOther CVD mortality (sudden cardiac death or worsening CAD)Incidence Grp1:   Incidence Grp2: 1    |  |  |
| Scheller, 2014[211](#_ENREF_211)Retrospective cohort | Grp1: MetforminNot specified  Grp2: SitagliptinNot specified  ITT: YesFollowup (wks): 104  |  | Def:CVD mortalityOther CVD mortality (sudden cardiac death or worsening CAD)Incidence Grp1:   Incidence Grp2:    |  |  |
| Schernthaner, 2015[148](#_ENREF_148) | Grp1: Metformin + glimepiride + placeboMean: 1572 mg/dTitrated (Mean: 3.3 mg/d Max: 6mg/d)Grp2: Metformin + saxagliptin + placeboMean: 1647Fixed (5 mg/d)ITT: NoFollowup (wks): 52 | Def: All-cause mortalityIncidence Grp1: 1Incidence Grp2: 1 | Fatal MIIncidence Grp1: NRIncidence Grp2: 1 |  |  |
| Schernthaner, 2004[149](#_ENREF_149)RCT | Grp1: MetforminVariedMax: 850 mg tidGrp2: PioglitazoneVariedStart: 30 mg, Max: 45 mg | Grp1: 2 (0.3)Grp2: 3 (0.5) |  |  |  |
| Schumm-Draeger, 2015[151](#_ENREF_151) | Grp1: Metformin + placeboFixed (adjusted to 1500, 2000, 2500 mg/d)Grp2: Metformin + dapagliflozinFixed 5 mg twice daily | Grp1: 0 (0)Grp2: 0 (0) |  |  |  |
| Schumm-Draeger, 2015[151](#_ENREF_151) | Grp1: Metformin + placeboFixed (adjusted to 1500, 2000, 2500 mg/d)Grp2: Metformin + dapagliflozinFixed 10 mg/d | Grp1: 0 (0)Grp2: 0 (0) |  |  |  |
| Seck, 2010[154](#_ENREF_154)RCT | Grp1: Metformin + sitagliptinFixedGrp2: Metformin + glipizideFixed; Varied, glucose > 110 mg/dlNR; Start: 5 mg, Max: 20 mg, Mean: 9.2 mg | Grp1: 8 (1.4)Grp2: 1 (0.2) | Def: Sudden cardiac deathGrp1: 2 (<1)Grp2: 0 (0) |  |  |
| St John Sutton, 2002[159](#_ENREF_159)RCT | Grp1: RosiglitazoneFixedStart: 4 mg bidGrp2: GlyburideVariedMax: 20 mg |  |  | Def: CVD morbidity/heart diseaseGrp1: 9 (9)Grp2: 5 (5) |  |
| Stewart, 2006[160](#_ENREF_160)RCT | Grp1: MetforminVariedStart: 500 mg, Mean: 2627.9 mg, Max: 3000 mgD: 20wksGrp2: Metformin + rosiglitazoneVariedStart: 500 mg, Mean: 1812.9 mg, Max: 2000 mgD: 18 wks |  |  | Def: MI, angina pectoris, myocardial ischemic, coronary artery insufficiencyGrp1: 0 (0)Grp2: 4 (2) |  |
| van der Meer, 2009[172](#_ENREF_172)RCT | Grp1: Metformin + glimepirideFixedStart: 1000 mg, Max: 2000 mg; Start: 15 mg, Max: 30 mgD: 8 wksGrp2: Pioglitazone + glimepirideVariedNot specifiedD: 8 wks |  | Def: CVD eventGrp1: 0 (0)Grp2: 0 (0) |  |  |
| Wang, 2015[173](#_ENREF_173)RCT | Grp1: Metformin + placeboFixed >=1500 mg/day or maximum tolerated doseGrp2: Metformin + lingliptinFixed >=1500 mg/day or max tolerated doseFixed 5mg |  |  | Nonfatal MI (suspected Myocardial Ischemia)Incidence Grp1: 0Incidence Grp2: 1 | Nonfatal stroke (lacunar infarction)Incidence Grp1: 1Incidence Grp2: 0 |
| Weissman, 2005[174](#_ENREF_174)RCT | Grp1: MetforminVariedStart: 1000mg, Max: 2000mgGrp2: Metformin + rosiglitazoneFixed; VariedStart: 1000 mg; Start: 4 mg, Max: 8 mg | Grp1: 0 (0)Grp2: 1 (<1) |  | Def: CVD morbidity/MI (non-fatal)Grp1: 0 (0)Grp2: 2 (1) |  |
| Weissman, 2005[174](#_ENREF_174)RCT | Grp1: MetforminVariedStart: 1000mg, Max: 2000mgGrp2: Metformin + rosiglitazoneFixed; VariedStart: 1000 mg; Start: 4 mg, Max: 8 mg |  |  | Def: CVD morbidity/MI (non-fatal) + pulmonary edema with MIGrp1: 3 + 1 withdrew (1)Grp2: 5 (1) |  |
| Xu, 2015[178](#_ENREF_178) | Grp1: PioglitazoneTitrated 45 mg/dGrp2: ExenatideTitrated 10ug twice daily |  |  |  | Def: Other cerebrovascular (cerebral infarction)Grp1:NR(1)Grp2: NR(1) |

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.