Glucose Lowering Medications and Diabetes Related Outcomes

Synopsis of Findings from Clinical Trial Data: Systematic Reviews, Meta Analyses, Single Randomized Controlled Trials (RCTs)

Current as of October 5, 2015

	Microvascular Outcomes (e.g., nephropathy, retinopathy)	Macrovascular Outcomes (e.g., cardiovascular morbidity, cardiovascular mortality)	Mortality
metformin 1-10	effect uncertain[i]	effect uncertain[i]	effect uncertain[i]
glyburide, gliclazide, glimepiride [1,2,4,5,9-13]	effect uncertain[ii]	effect uncertain[ii]	effect uncertain[ii]
repaglinide 1,2,5,12,17,18	effect uncertain	effect uncertain	effect uncertain
acarbose 2,12,18,19	effect uncertain	effect uncertain	effect uncertain
pioglitazone, rosiglitazone 1,2,5,12,18,20-30	effect uncertain	no statistically significant increase or decrease in primary cardiovascular composite outcome (pioglitazone, rosiglitazone; single RCTs);[iii,iv] statistically significant increase heart failure (pioglitazone, rosiglitazone; systematic review);[v] statistically significant increase myocardial infarction (rosiglitazone; meta analysis)[vi]	no statistically significant increase or decrease (pioglitazone, rosiglitazone; secondary outcome, single cardiovascular RCTs)[iii,iv]
saxagliptin, linagliptin, sitagliptin, alogliptin 1,12,18,31-40	effect uncertain	no statistically significant increase or decrease in primary cardiovascular composite outcome (saxagliptin, sitagliptin, alogliptin; single RCTs);[vii,viii,ix] statistically significant increase heart failure (saxagliptin; secondary outcome, single RCT)[vii]	no statistically significant increase or decrease (saxagliptin, sitagliptin, alogliptin; secondary outcome, single cardiovascular RCTs)[vii,viii,ix]
canagliflozin, dapagliflozin, empagliflozin 41-45	effect uncertain	statistically significant decrease in primary cardiovascular composite outcome (empagliflozin; single RCT)[x]	statistically significant decrease (empagliflozin; secondary outcome, single cardiovascular RCT)[x]
liraglutide, exenatide 1,12,18,46-49	effect uncertain	effect uncertain	effect uncertain
See notes on reverse side (e.g., comparators, outcomes, patient populations)			
Additional type 2 diabetes cardiovascular outcome RCTs in progress: pioglitazone vs. sulfonylureas;[50] linagliptin vs. placebo;[51] linagliptin vs. glimepiride;[52] canagliflozin vs. placebo;[53] dapagliflozin vs. placebo;[54] liraglutide vs. placebo;[55] exenatide vs. placebo[56]			

Notes:

[i] **metformin**: UKPDS 34, a small RCT subgroup referenced to describe a macrovascular and mortality benefit for metformin;[8] 342 type 2 diabetes participants (> 120% ideal body weight) received open label metformin as their initial therapy;[8] the specific effect of metformin on microvascular, macrovascular outcomes, mortality cannot be firmly confirmed or rejected when systematically reviewed[1-7]

[ii] **glyburide, gliclazide, glimepiride**: UKPDS 33, an RCT referenced to describe a microvascular benefit for sulfonylureas;[13] 1573 type 2 diabetes participants received open label sulfonylurea (chlorpropamide, glyburide, or glipizide) as their initial therapy;[13] the specific effect of glyburide, gliclazide, or glimepiride on microvascular, macrovascular outcomes, mortality cannot be firmly confirmed or rejected when systematically reviewed;[1,2,4,5,11,12] RCT evidence of an increased risk of cardiovascular mortality with tolbutamide vs. placebo;[11] Canadian prescribing information for glyburide, gliclazide, and glimepiride advise close monitoring for cardiovascular complications[14-16]

[iii] **pioglitazone** as reported in a single RCT (PROactive):[22] 5238 type 2 diabetes participants *with cardiovascular disease*; median A1C 7.8%; randomized to *pioglitazone vs. placebo in addition to usual care* (including other glucose lowering medications); followed mean 2.9 yrs; *primary outcome*: total mortality, nonfatal myocardial infarction, stroke, acute coronary syndrome, endovascular or surgical intervention coronary or leg arteries, amputation above ankle 19.7% vs. 21.7% (HR 0.90, 95%CI 0.80 to 1.02); total mortality 6.8% vs. 7.1% (HR 0.96, 95%CI 0.78 to 1.18)

[iv] **rosiglitazone** as reported in a single RCT (RECORD):[23] 4447 type 2 diabetes participants on metformin or a sulfonylurea; mean A1C 7.9%; randomized to the *open label addition of rosiglitazone to metformin or sulfonylurea vs. the combination of metformin plus sulfonylurea*; followed mean 5.5 yrs; *primary outcome*: cardiovascular death or cardiovascular hospitalization 14.5% vs. 14.5% (HR 0.99, 95%CI 0.85 to 1.16); total mortality 6.1% vs. 7.0% (HR 0.86, 95%CI 0.68 to 1.08)

[v] **rosiglitazone & pioglitazone, heart failure**: systematic review, thiazolidinediones vs. placebo 5.3% vs. 3.7% (OR 1.59, 95%CI 1.34 to 1.89) over a mean of 1.9 years;[24] risk noted in Canadian prescribing information[25,26]

[vi] **rosiglitazone, myocardial infarction**: European Medicines Agency recommended removal from market in 2010;[27] Health Canada added prescribing restrictions in 2010;[28] U.S. FDA removed some previous prescribing restrictions in 2013 citing scientific uncertainty;[29] Canadian prescribing information meta analysis: myocardial infarction (OR 1.80, 95%CI 1.03 to 3.25), total mortality (OR 1.38, 95%CI 0.72 to 2.72) over a mean of 6 months[26]

[vii] **saxagliptin** as reported in a single RCT (SAVOR-TIMI 53), a postmarketing safety requirement:[37,38] 16,492 type 2 diabetes participants *with cardiovascular disease or multiple risk factors for cardiovascular disease*; mean A1C 8.0%; randomized to *saxagliptin vs. placebo in addition to usual care* (including other glucose lowering medications); followed median 2.1 yrs; *primary outcome*: cardiovascular death, nonfatal myocardial infarction, or nonfatal ischemic stroke 7.3% vs. 7.2% (HR 1.00, 95%CI 0.89 to 1.12); hospitalization for heart failure 3.5% vs. 2.8% (HR 1.27, 95%CI 1.07 to 1.51); total mortality 4.9% vs. 4.2% (HR 1.11, 95%CI 0.96 to 1.27); met U.S. FDA guidance for noninferiority with upper bound of hazard ratio < 1.3 for primary outcome[38]

[viii] **sitagliptin** as reported in a single RCT (TECOS), a postmarketing safety requirement:[39] 14,671 type 2 diabetes participants *with cardiovascular disease*; mean A1C 7.2%; randomized to *sitagliptin vs. placebo in addition to usual care* (including other glucose lowering medications); followed median 3 yrs; *primary outcome*: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina 11.4% vs. 11.6% (HR 0.98, 95%CI 0.89 to 1.08); hospitalization for heart failure 3.1% vs. 3.1% (HR 1.00, 95%CI 0.83 to 1.20); total mortality 7.5% vs. 7.3% (HR 1.01, 95%CI 0.90 to 1.14); results not reviewed by U.S. FDA

[ix] **alogliptin** as reported in a single RCT (EXAMINE), a postmarketing safety requirement:[38,40] 5380 type 2 diabetes participants *with acute coronary syndrome*; mean A1C 8.0%; *alogliptin vs. placebo in addition to usual care* (including other glucose lowering medications); followed median 1.5 yrs; *primary outcome*: cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke 11.3% vs. 11.8% (HR 0.96, upper boundary 99%CI ≤ 1.16); hospitalization for heart failure 3.9% vs. 3.3% (HR 1.19, 95%CI 0.90 to 1.58); total mortality 5.7% vs. 6.5% (HR 0.88, 95%CI 0.71 to 1.09); met U.S. FDA guidance for noninferiority with upper bound of hazard ratio < 1.3 for primary outcome[38]

[x] **empagliflozin** as reported in a single RCT (EMPA-REG), a postmarketing safety requirement:[45] 7020 type 2 diabetes participants *with cardiovascular disease*; mean A1C 8.1%; *empagliflozin vs. placebo in addition to usual care* (including other glucose lowering medications); followed median 3.1 yrs; *primary outcome*: cardiovascular death, nonfatal myocardial infarction (excluding silent myocardial infarction), or nonfatal stroke 10.5% vs. 12.1% (HR 0.86, 95%CI 0.74 to 0.99); hospitalization for heart failure 2.7% vs. 4.1% (HR 0.65, 95%CI 0.50 to 0.85); total mortality 5.7% vs. 8.3% (HR 0.68, 95%CI 0.57 to 0.82); results not reviewed by U.S. FDA