Type 2 Diabetes: Glucose Lowering Medications and Diabetes Related Outcomes
Synopsis of Findings from Clinical Trial Data: Systematic Reviews, Meta Analyses, Single Randomized Controlled Trials (RCTs)

	Retinopathy, Neuropathy Nephropathy	Cardiovascular Outcomes	Mortality
Metformin [1-11]	effect uncertain[i]	effect uncertain[i]	effect uncertain[i]
Sulfonylureas: glyburide, gliclazide, glimepiride [1,2,3,5,6,10-14]	effect uncertain[ii]	effect uncertain[ii]	effect uncertain[ii]
Repaglinide [2,3,6,13,18,19]	effect uncertain	effect uncertain	effect uncertain
Acarbose [3,13,19,20]	effect uncertain	effect uncertain	effect uncertain
Thiazolidinediones: pioglitazone, rosiglitazone [1,2,3,6,13,19,21-31]	effect uncertain	no statistically significant increase or decrease 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; single cardiovascular RCTs)[iii,iv]
See notes on reverse side (i.e., comparators, outcomes, patient populations)			
Additional type 2 diabetes clinical outcome RCTs completed but not yet published: exenatide added to usual care[67] **Additional type 2 diabetes clinical outcome RCTs in progress:** pioglitazone vs. sulfonylureas;[68] linagliptin added to usual care;[69] linagliptin vs. glimepiride;[70] dapagliflozin added to usual care;[71] albiglutide added to usual care;[72] dulaglutide added to usual care[73]			

	Retinopathy, Neuropathy Nephropathy	Cardiovascular Outcomes	Mortality
DPP4 Inhibitors: saxagliptin, linagliptin, sitagliptin, alogliptin [1,2,13,19,32-43]	effect uncertain	2017 systematic review: no statistically significant increase or decrease cardiovascular death, non-fatal myocardial infarction, non-fatal stroke (OR 0.99, 95% 0.92 to 1.07)[42, vii,viii,ix] 2016 systematic review: borderline increase hospital admission for heart failure (OR 1.13, 95%CI 1.00 to 1.26)[43, vii,vii,ix]	2017 systematic review: no statistically significant increase or decrease (OR 1.02, 95% 0.91 to 1.14)[42, vii, viii,ix]
GLP1 Agonists: liraglutide, exenatide, albiglutide, dulaglutide, lixisenatide, semaglutide [1,2,13,19,44-55]	effect uncertain; statistically significant decrease nephropathy composite outcome (liraglutide, semaglutide; cardiovascular safety RCT)[x,xii] statistically significant increase retinopathy composite outcome (semaglutide; cardiovascular safety RCT)[xii]	2017 systematic review: no statistically significant increase or decrease cardiovascular death, non-fatal myocardial infarction, non-fatal stroke (OR 0.88, 95% 0.74 to 1.04)[42,x,xi,xii]	2017 systematic review: borderline decrease (OR 0.89, 95% 0.80 to 0.99)[42,x,xi,xii]
SGLT2 Inhibitors: canagliflozin, dapagliflozin, empagliflozin [56-66]	effect uncertain; statistically significant decrease nephropathy composite outcome (canagliflozin, empagliflozin; cardiovascular safety RCTs)[xiii,xv,xvi]	statistically significant decrease primary cardiovascular composite outcome (canagliflozin; two integrated cardiovascular safety RCTs)[xiii] statistically significant decrease primary cardiovascular composite outcome (empagliflozin; single cardiovascular safety RCT)[xv,xvii]	no statistically significant increase or decrease (canagliflozin; two integrated cardiovascular safety RCTs)[xiii] statistically significant decrease (empagliflozin; single cardiovascular safety RCT)[xv]
	statistically significant increase amputations (canagliflozin; two integrated cardiovascular safety RCTs)[xiii, xiv]		

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):[23] 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*: time to death, 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):[24] 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*: time to first 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;[25] risk noted in Canadian prescribing information[26,27]

[vi] **rosiglitazone, myocardial infarction**: European Medicines Agency recommended removal from market in 2010;[28] Health Canada added prescribing restrictions in 2010;[29] U.S. FDA removed some previous prescribing restrictions in 2013 citing scientific uncertainty;[30] 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[27]

[vii]**saxagliptin** as reported in a single postmarketing safety RCT (SAVOR-TIMI 53):[38,39] 16,492 type 2 diabetes participants *with cardiovascular disease or 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*: time to first 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 cardiovascular safety outcome[38]

[viii]**sitagliptin** as reported in a single postmarketing safety RCT (TECOS):[40] 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*: time to first 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)

[ix]**alogliptin** as reported in a single postmarketing safety RCT (EXAMINE):[39,41] 5380 type 2 diabetes participants *with recent 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*: time to first 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 cardiovascular safety outcome[38]

[x]**liraglutide** as reported in a single postmarketing safety RCT (LEADER):[52] 9340 type 2 diabetes *participants with cardiovascular disease or risk factors for cardiovascular disease*; mean A1C 8.7%; *liraglutide vs. placebo in addition to usual care* (including other glucose lowering medications); followed median 3.8 yrs; *primary outcome*: time to first cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke 13.0% vs. 14.9% (HR 0.87, 95%CI 0.78 to 0.97); hospitalization for heart failure 4.7% vs. 5.3% (HR 0.87, 95%CI 0.73 to 1.05); total mortality 8.2% vs. 9.6% (HR 0.85, 95%CI 0.74 to 0.97); composite of incident or worsening nephropathy (clinical outcomes and biomarkers) 5.7% vs. 7.2% (HR 0.78, 95%CI 0.67 to 0.92); retinopathy composite outcome 2.3% vs 2.0% (HR 1.15, 95%CI 0.87 to 1.52); met U.S. FDA guidance for noninferiority with upper bound of hazard ratio < 1.3 for cardiovascular safety outcome[53]

[xi]**lixisenatide** as reported in a single postmarketing safety RCT (ELIXA):[54] 6068 type 2 diabetes *participants with recent acute coronary syndrome*; mean A1C 7.7%; *lixisenatide vs. placebo in addition to usual care* (including other glucose lowering medications); followed median 2.1 yrs; *primary outcome:* time to first cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or unstable angina 13.4% vs. 13.2% (HR 1.02, 95%CI 0.89 to 1.17); hospitalization for heart failure 4.0% vs. 4.2% (HR 0.96, 95%CI 0.75 to 1.23); total mortality 7.0% vs. 7.4% (HR 0.94, 95%CI 0.78 to 1.13); met U.S. FDA guidance for noninferiority with upper bound of hazard ratio < 1.3 for cardiovascular safety outcome[51]

[xii]**semaglutide** as reported in a single premarketing noninferiority safety RCT designed to rule out a hazard of 1.80 (SUSTAIN-6):[55] 3297 type 2 diabetes *participants with cardiovascular disease, chronic kidney disease or risk factors for cardiovascular disease*; mean A1C 8.7%; *semaglutide vs. placebo in addition to usual care* (including other glucose lowering medications); followed median 2.1 yrs; *primary outcome:* time to first cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke 6.6% vs. 8.9% (HR 0.74, 95%CI 0.58 to 0.95); hospitalization for heart failure 3.6% vs. 3.3% (HR 1.11, 95%CI 0.77 to 1.61); total mortality 3.8% vs. 3.6% (HR 1.05, 95%CI 0.74 to 1.50); composite of incident or worsening nephropathy (clinical outcomes and biomarkers) 3.8% vs. 6.1% (HR 0.64, 95%CI 0.46 to 0.88); retinopathy composite outcome 3.0% vs. 1.8% (HR 1.76, 95%CI 1.11 to 2.78)

[xiii]**canagliflozin** as reported in two integrated pre&postmarketing safety RCTs (CANVAS Program):[60] 10,142 type 2 diabetes *participants with cardiovascular disease or risk factors for cardiovascular disease*; mean A1C 8.2%; *canagliflozin vs. placebo in addition to usual care* (including other glucose lowering medications); followed mean 3.6 yrs; primary outcome: time to first cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke 26.9 vs. 31.5 per 1000 patient-yrs (HR 0.86, 95%CI 0.75 to 0.97); hospitalization for heart failure 5.5 vs. 8.7 per 1000-patient yrs (HR 0.67, 95%CI 0.52 to 0.87); total mortality 17.3 vs. 19.5 per 1000 patient-yrs (HR 0.87, 95%CI 0.74 to 1.01); amputation toes, feet, or legs 6.3 vs. 3.4 per 1000-patient yrs (HR 1.97, 95%CI 1.41 to 2.75); composite of incident or worsening nephropathy (40% reduction in eGFR, renal replacement therapy, or renal death): 5.5 vs. 9.0 per 1000-patient yrs (HR 0.60, 95%CI 0.47 to 0.77)

[xiv]**canagliflozin, amputations**: U.S. FDA concludes canagliflozin increases the risk of amputations based on the CANVAS Program results[61]

[xv]**empagliflozin** as reported in a single postmarketing safety RCT (EMPA-REG OUTCOME):[62] 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*: time to first 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); composite of incident or worsening nephropathy (clinical outcomes and biomarkers) 12.7% vs. 18.8% (HR 0.61, 95%CI 0.53 to 0.70)[63]

[xvi]**empagliflozin, renal outcomes**: U.S. FDA 2016 review renal outcomes "There were too few clinical events to make meaningful conclusions that differences between therapies truly existed"[64]

[xvii]**empagliflozin, cardiovascular indication**: U.S. FDA 2016 approves indication "to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and cardiovascular disease";[65] Health Canada 2016 "indicated as an adjunct to diet, exercise and standard care therapy to reduce the incidence of cardiovascular death in patients with type 2 diabetes mellitus and established cardiovascular disease who have inadequate glycemic control"[66]