Drug Class Review

Cardiovascular Harms of Newer Diabetes Medications and Combinations

Supplement†

September 2016

†Supplement to Newer Diabetes Medications and Combinations Update 2 Report (July 2016)

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STRUCTURED ABSTRACT

Purpose. We examined the risk of major cardiovascular events and all-cause mortality with newer diabetes medications in patients with type 2 diabetes mellitus.

Data Sources. We searched Ovid Medline for systematic reviews and randomized trials that reported heart failure, myocardial infarction, stroke, cardiovascular mortality, and/or all-cause mortality with newer diabetes medications.

Review Methods. One reviewer assessed titles and abstracts, and 2 reviewers assessed full-text articles for relevance. Two reviewers quality rated included studies.

Results. Four good-quality and 2 fair-quality systematic reviews were included. Treatment with DPP-4 inhibitors was found to decrease the risk of heart attack (RR 0.91, 95% CI 0.84 to 1.00) but increase hospitalizations for heart failure (OR 1.13, 95% CI 1.00 to 1.26), although there was no evidence to suggest that DPP-4 inhibitors increased the risk of heart failure overall (OR 0.97, 95% CI 0.61 to 1.56). Treatment with SGLT-2 inhibitors appeared to decrease the risk of cardiovascular mortality (OR 0.43, 95% CI 0.36 to 0.53), especially canagliflozin (OR 0.50, 95% CI 0.27 to 0.95) and empagliflozin (OR 0.42, 95% CI 0.34 to 0.52), while dapagliflozin was found to decrease the risk of myocardial infarction (OR 0.48, 95% CI 0.26 to 0.87). All-cause mortality was decreased with SGLT-2 inhibitor therapy (OR 0.70, 95% CI 0.59 to 0.83), especially with empagliflozin (OR 0.68, 95% CI 0.56 to 0.82). However, there was a signal for possible increased risk of stroke with SGLT-2 inhibitor treatment. Treatment with GLP-1 receptor agonists did not appear to increase the risk of major cardiovascular events or all-cause mortality. However, there was less evidence available for GLP-1 agonists compared with DPP-4 and SGLT-2 inhibitors.

Conclusion. With the currently available evidence on cardiovascular safety, treatment with GLP-1 inhibitors appears to be safe. DPP-4 inhibitors treatment may decrease the risk of heart attack but may also increase the risk for hospitalization for heart failure. SGLT-2 inhibitor therapy appears to decrease the risk of cardiovascular mortality but may also increase the risk of stroke.

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Funding
The funding source, the Center for Evidence-based Policy, is supported by 13 state Medicaid programs. These organizations selected the topic and had input into the Key Questions for this review. The content and conclusions of the review are entirely determined by the Evidence-based Practice Center researchers. The authors of this report have no financial interest in any company that makes or distributes the products reviewed in this report.

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INTRODUCTION

In June 2016, the drug class review for Newer Diabetes Medications and Combinations was completed. Since this review employed streamlined methods, placebo-controlled trials (i.e., trials without head-to-head comparisons) and systematic reviews of placebo-controlled trials were not included. However, it was felt that the excluded placebo-controlled trials may provide additional information on cardiovascular safety that was not being captured adequately in head-to-head trials. Therefore, the participating organizations commissioned a supplement to the recent review of newer diabetes medications to assess cardiovascular safety of these medications (Table 1).

Table 1. Characteristics of included drugs

Class	Generic Name	Trade Name	Delivery
DPP-4 Inhibitors	Sitagliptin	Januvia®	Oral
	Saxagliptin	Onglyza®	Oral
	Linagliptin	Tradjenta®	Oral
	Alogliptin	Nesina®	Oral
GLP-1 Analogs (incretin mimetics)	Albiglutide	Tanzeum™	Injection
	Dulaglutide	Trulicity®	Injection
	Exenatide	Byetta®	Injection
	Exenatide XR	Bydureon®	Injection
	Liraglutide	Victoza®, Saxenda®	Injection
SGLT-2 Inhibitors	Canagliflozin	Invokana®	Oral
	Dapagliflozin	Farxiga®	Oral
	Empagliflozin	Jardiance®	Oral

Abbreviations: DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; GLP-1 analogs, glucagon-like peptide-1 analogs; SGLT2 inhibitors, sodium glucose co-transporter-2 inhibitors

Scope

The purpose of this supplement is to assist healthcare providers, researchers, and policy makers in making clinical decisions, creating formularies, and developing policies regarding newer medications for the treatment of diabetes based on the most current available literature. We specifically focused on the cardiovascular harms of newer diabetes medications and combinations.

METHODS

We searched Medline for trials and systematic reviews of newer diabetes medications (i.e., dipeptidyl peptidase-4 [DPP-4] inhibitors, glucagon-like peptide-1 [GLP-1] analogs, and sodium glucose co-transporter-2 [SGLT-2] inhibitors) that specifically addressed cardiovascular safety. We searched for drug names and drug classes in conjunction with terms for cardiovascular events (e.g., “stroke”, “myocardial infarct”, and “cardiovascular”) within the titles of published articles. We excluded studies of drug combinations and other potential harms of drug treatment.

One reviewer conducted the searches and reviewed abstracts. Two reviewers assessed full-text articles for relevance and quality rated included publications.

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RESULTS

Cardiovascular Events by Drug Class

A good-quality systematic review compared classes of newer diabetes drugs regarding risk of major cardiovascular events (e.g., cardiovascular mortality, myocardial infarction, and stroke) and all-cause mortality.[1] Heart failure or hospitalization for heart failure were not included outcomes. Additionally, there were no trials of a GLP-1 receptor agonist given as monotherapy, regardless of comparator, and several drugs included in the review are not approved in the United States (Appendix Table A1). Including all 4 outcomes listed above and including monotherapy, dual therapy (with metformin), and triple therapy (with metformin and a sulfonylurea), there were only 40 events in head-to-head comparisons of interest. In all cases, confidence intervals were wide, and, in all but 1 instance (Appendix Table A2), odds ratios were not statistically significant. Event rates were too low (i.e., evidence too sparse) to conclude that there were no differences in cardiovascular risk or all-cause mortality between DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors based on the this review alone. However, 1 signal for concern was in the possible increased risk of stroke with dual therapy with an SGLT-2 inhibitor and metformin compared with metformin and a sulfonylurea (OR 2.75, 95% CI 0.76 to 10.00; Appendix Table A2).

DPP-4 Inhibitors

Heart Failure and Hospitalization for Heart Failure

A good-quality systematic review examined the association between treatment with DPP-4 inhibitors and the risk of heart failure in patients with type 2 diabetes and included evidence from 43 trials (N=68,775) and 12 observational studies (N=1,777,358).[2] Since the observational studies provided only very low-quality evidence, only the trial evidence is reported here (Appendix Table A2). The authors pooled results from 38 trials and found no increased risk of heart failure with DPP-4 inhibitor treatment, but cardiovascular events were few (42/15,701 vs. 33/12,591; OR 0.97, 95% CI 0.61 to 1.56). These results were consistent with another review of 41 trials of DPP-4 inhibitors that also found no difference between treatment with a DPP-4 inhibitor and control treatment in risk of new onset heart failure (RR 1.08, 95% CI 0.97 to 1.20) (Appendix Table A2).[3]

However, when the authors pooled the results from the 5 trials that reported admissions to hospital for heart failure, they found that treatment with a DPP-4 inhibitor was associated with increased risk of hospital admission for heart failure (622/18,554 vs. 552/18,474; OR 1.13, 95% CI 1.00 to 1.26). The meta-analysis included 1 trial each of saxagliptin (N=16,492), alogliptin (N=5,380), sitagliptin (N=14,671), linagliptin (N=233), and vildagliptin (N=252). When the data from the small trial of vildagliptin (which is not approved in the United States) were removed from the meta-analysis, the results were little changed, although no longer statistically significant (EPC analysis: 3.3% vs. 3.0%; OR 1.12, 95% CI 0.999 to 1.26). Additionally, these trials were all conducted in patients with significant cardiovascular morbidity. The only individual trial that reported a significant increase in risk for hospital admission for heart failure in patients treated with a DPP-4 inhibitor found greater risk with saxagliptin (SAVOR-TIMI 53)[4] in patients with renal impairment and cardiovascular disease or several risk factors for cardiovascular disease

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(OR 1.27, 95% CI 1.06 to 1.51). Confidence intervals for the other trials of other drugs included 1 (range of ORs: 1.00 to 1.29).

Major Cardiovascular Events (MACE) and All-cause Mortality

A fair-quality systematic review (rated fair due to lack of quality rating of individual trials) included 107,100 patients in 114 randomized controlled trials.[3] Eligibility criteria included enrollment of more than 200 patients and report of at least 1 event among: cardiovascular or all-cause mortality, myocardial infarction, stroke, or new onset heart failure. Patients averaged 57 years of age and 55% were male. Twenty-seven trials included vildagliptin, which is not approved in the United States, for a total sample size of 19,806 patients. The results from meta-analyses indicated no differences between treatment with a DPP-4 inhibitor and all controls (i.e., placebo and active comparators) in cardiovascular mortality (43 trials; 2.2% vs. 2.5%; RR 0.98, 95% CI 0.89 to 1.07), stroke (67 trials; 1.0% vs. 1.2%; RR 0.93, 95% CI 0.82 to 1.06), or all-cause mortality (66 trials; 2.7% vs. 3.0%; RR 1.01, 95% CI 0.93 to 1.09; Appendix Table A2). There was very little statistical heterogeneity among trials (I^2=0% for all comparisons). Analyses were dominated by the TECOS trial of sitagliptin (N=14,735),[5] the EXAMINE trial of alogliptin (N=5,380),[6] and the SAVOR-TIMI 53 trial of saxagliptin (N=16,492).[4] However, treatment with a DPP-4 inhibitor was associated with a borderline lower risk of myocardial infarction (74 trials; 1.7% vs. 2.3%; RR 0.91, 95% CI 0.84 to 1.00). Only 1 trial of 74 total trials reported reduced risk of myocardial infarction with a DPP-4 inhibitor (the ENDURE trial of alogliptin added to metformin versus glipizide plus metformin, N=2,639).[7]

GLP-1 receptor agonists

Heart Failure

A good-quality systematic review examined the relationship between treatment with a GLP-1 agonist and the development of heart failure and included 20 randomized controlled trials of at least 12 weeks' duration (N=17,519).[8] Treatment duration in most trials was at least 1 year and was at least 2 years in 7 trials (2 of liraglutide and 5 of albiglutide). There were 6 trials each of albiglutide and liraglutide, 4 trials of dulaglutide, and 5 of exenatide. One trial included a drug not approved in the U.S. (taspoglutide; N=751). There was no difference in risk for heart failure with GLP-1 receptor agonists compared with control, but events were few (17/7441 vs. 19/4317; OR 0.62, 95% CI 0.31 to 1.22; Appendix Table A2). No individual trial reported a decreased risk of heart failure with a GLP-1 agonist, with minimal statistical heterogeneity among trials (I^2=0%).

Major Cardiovascular Events (MACE) and All-cause Mortality

A good-quality systematic review that included 13 trials (N=11,943) reported no difference in the risk of having a major cardiovascular event (MACE) between treatment with a GLP-1 agonist and treatment with placebo.[9] However, the largest trial (N=6,068) was of lixisenatide, which is not approved in the United States. Since the population included in this trial was of individuals at high risk for cardiovascular disease, the authors analyzed the data with and without this trial. Effect estimates reported here and in Appendix Table A2 reflect the data without this trial. The review included 1 trial of albiglutide (N=663), 1 trial of dulaglutide (N=884), 5 trials of exenatide (N=1,941), and 3 trials of liraglutide (N=1,535). There were 2 trials of drugs not

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approved in the United States (1 of lixisenatide [N=484] and 1 of taspoglutide [N=368]) that were also included in the meta-analyses. The review found no difference in the risk of MACE with GLP-1 treatment compared with placebo (10 trials; RR 0.85, 95% CI 0.62 to 1.15) but found a lower risk of all-cause mortality with GLP-1 inhibitors (4 trials; RR 0.28, 95% CI 0.08 to 0.93; Appendix Table A2). However, both estimates were imprecise. There was no statistical heterogeneity among trials (I^2=0%) for either analysis, and no individual trial reported a statistically significant effect, although individual trial point estimates for all-cause mortality consistently favored GLP-1 inhibitors.

SGLT-2 inhibitors

Heart Failure

A fair-quality systematic review mentioned previously under DPP-4 inhibitors provided evidence for the risk of new onset heart failure in patients treated with an SGLT-2 inhibitor compared with control treatment.[3] The review included 23 trials that reported at least 1 heart failure event. Heart failure was less likely among participants taking SGLT-2 inhibitors compared with participants in the control groups (RR 0.72, 95% CI 0.61 to 0.84; Appendix Table A2). A fair-quality meta-analysis of individual patient data from 21 trials (N=9,339 patients; 10,550 patient-years) of dapagliflozin found a lower risk of heart failure (10/2,576 vs. 16/1,780; event rate/100 patient-years: hazard ratio [HR] 0.36, 95% CI 0.16 to 0.84),[10] but no difference in risk of cardiovascular mortality, myocardial infarction, stroke, unstable angina, or unplanned coronary revascularization with dapagliflozin compared with control. Hospitalization or death from heart failure were also less likely with empagliflozin based on data from the large EMPA-REG OUTCOME trial (N=7,020), the only trial of SGLT-2 inhibitors with long-term cardiovascular safety data, compared with placebo (2.8% vs. 4.5%; HR 0.61, 95% CI 0.47 to 0.79).[11]

Major Cardiovascular Events (MACE) and All-cause Mortality

A good-quality systematic review of SGLT-2 inhibitors included 71 randomized controlled trials (N=47,287) that assessed the risk of MACE with SGLT-2 inhibitors compared with control treatment and found that SGLT-2 inhibitors were associated with lower risk of cardiovascular mortality, myocardial infarction, and all-cause mortality, but not stroke (Appendix Table C1).[12] Seventy-one trials of at least 12 weeks' duration (mean duration of treatment: 40.2 weeks) met inclusion criteria, but many trials did not report any included events or reported that there were zero events, reducing the number of trials actually analyzed. Canagliflozin, dapagliflozin, and empagliflozin were included in the review, along with 3 SGLT-2 inhibitors not approved in the United States (ipragliflozin, ertugliflozin, and luseogliflozin). However, only 6 trials were of unapproved drugs (N=2,265). Meta-analyses were dominated by the event-driven, cardiovascular safety EMPA-REG OUTCOME trial (discussed in greater detail in the appendix)[13] of empagliflozin (N=7,020), which accounted for 79% of the relative weight for all-cause mortality, for example, followed by a trial of canagliflozin (N=2,072), which accounted for only 6% of the relative weight.[14] The risk of cardiovascular mortality was reduced with SGLT-2 inhibitors overall (23 trials; OR 0.43, 95% CI 0.36 to 0.53) and with canagliflozin (7 trials; OR 0.50, 95% CI 0.27 to 0.95) and empagliflozin (7 trials; OR 0.42, 95% CI 0.34 to 0.52), but not dapagliflozin, when analyzed separately. All-cause mortality was also lower with SGLT-2 inhibitors (32 trials; OR 0.70, 95% CI 0.59 to 0.83) and with empagliflozin in particular (12 trials; OR 0.68, 95% CI 0.56 to 0.82) but not canagliflozin or dapagliflozin. The risk of having a

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myocardial infarction was lower with dapagliflozin (14 trials; OR 0.48, 95% CI 0.26 to 0.87) and SGLT-2 inhibitors when pooled together (36 trials; OR 0.77, 95% CI 0.63 to 0.94), but not with canagliflozin and empagliflozin. Although this review found that the risk of stroke was not significantly different between individual SGLT-2 inhibitors and control treatment, point estimates were greater than 1 with canagliflozin (8 trials; OR 1.36, 95% CI 0.54 to 3.40) and empagliflozin (15 trials; OR 1.13, 95% CI 0.87 to 1.46), which suggested a possible signal of increased risk. This was consistent with another systematic review that found increased risk of stroke with SGLT-2 inhibitors for nonfatal stroke (RR 1.30, 95% CI 1.00 to 1.68).[15]

One cardiovascular event-driven trial of dapagliflozin (DECLARE) and 1 of canagliflozin (CANVAS) have estimated completion dates of April 2019 and February 2017, respectively, and should shed additional light on cardiovascular safety with the SGLT-2 inhibitors.

SUMMARY

With the currently available evidence on cardiovascular safety, treatment with GLP-1 inhibitors appears to be safe. DPP-4 inhibitors treatment may decrease the risk of heart attack but may also increase the risk for hospitalization for heart failure. SGLT-2 inhibitor therapy appears to decrease the risk of cardiovascular mortality but may also increase the risk of stroke.

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APPENDIXES

Appendix A

Appendix Table A1. Drugs included in drug class review not in DERP review

Drugs	Drug Classes
Anagliptin	Alpha glucosidase inhibitors
Ertugliflozin	Insulins
Gemigliptin	Meglitinides
Lixisenatide	Sulfonylureas
Omarigliptin	Thiazolidinediones
Pramlintide	
Semaglutide	
Taspoglutide	
Teneligliptin	
Tofogliflozin	
Vildagliptin	

Appendix Table A2. Direct and network comparisons of effect estimates from JAMA review

Comparison	Type of Evidence	Number of Trials	Intervention n/N	Comparison n/N	Odds Ratio (95% CI)
Monotherapy: Cardiovascular Mortality					
DPP-4 vs. SGLT-2	Direct	1	0/135	1/270	0.66 (0.03, 16.33)
DPP-4 vs. SGLT-2	Network				1.33 (0.23, 7.67)
Monotherapy: All-cause Mortality					
DPP-4 vs. SGLT-2	Direct	2	0/358	3/717	0.58 (0.05, 6.43)
DPP-4 vs. SGLT-2	Network				0.87 (0.23, 3.33)
DPP-4 vs. GLP-1	Direct	1	0/163	0/248	1.52 (0.03, 77.01)
DPP-4 vs. GLP-1	Network				0.80 (0.16, 4.04)
Monotherapy: Myocardial Infarction					
DPP-4 vs. SGLT-2	Direct	1	1/223	1/447	2.00 (0.13, 31.89)
DPP-4 vs. SGLT-2	Network				1.42 (0.17, 11.98)
Monotherapy: Stroke					
DPP-4 vs. SGLT-2	Direct	1	1/223	1/447	2.00 (0.13, 31.89)
DPP-4 vs. SGLT-2	Network				2.04 (0.17, 24.49)
Add-on to Metformin: Cardiovascular Mortality					
DPP-4 vs. SGLT-2	Direct	1	1/128	1/277	2.16 (0.04, 108.95)
DPP-4 vs. SGLT-2	Network				0.94 (0.16, 5.57)
DPP-4 vs. GLP-1	Direct	3	2/700	1/1205	2.24 (0.35, 14.25)
DPP-4 vs. GLP-1	Network				1.54 (0.28, 8.49)
Add-on to Metformin: All-cause Mortality					
DPP-4 vs. SGLT-2	Direct	2	0/494	2/1012	0.69 (0.07, 6.76)
DPP-4 vs. SGLT-2	Network				0.91 (0.37, 2.22)
DPP-4 vs. GLP-1	Direct	4	3/1002	5/1507	0.88 (0.22, 3.55)
DPP-4 vs. GLP-1	Network				0.87 (0.38, 2.00)
Add-on to Metformin: Myocardial Infarction					
DPP-4 vs. SGLT-2	Direct	1	0/366	1/735	0.67 (0.03, 16.45)
DPP-4 vs. SGLT-2	Network				1.39 (0.37, 5.20)
DPP-4 vs. GLP-1	Direct	4	1/1002	5/1507	0.48 (0.11, 2.15)
DPP-4 vs. GLP-1	Network				0.66 (0.26, 1.68)
Add-on to Metformin: Stroke					
DPP-4 vs. SGLT-2	Direct	1	0/366	2/735	0.40 (0.02, 8.40)
DPP-4 vs. SGLT-2	Network				**0.17 (0.05, 0.61)**
DPP-4 vs. GLP-1	Direct	3	1/783	2/1068	0.87 (0.16, 4.60)
DPP-4 vs. GLP-1	Network				0.54 (0.16, 1.81)

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Comparison	Type of Evidence	Number of Trials	Intervention n/N	Comparison n/N	Odds Ratio (95% CI)
Add-on to Metformin + Sulfonylurea: Cardiovascular Mortality					
DPP-4 vs. SGLT-2	Direct	1	0/378	2/378	0.20 (0.01, 4.06)
DPP-4 vs. SGLT-2	Network				0.20 (0.01, 4.08)
Add-on to Metformin + Sulfonylurea: All-cause Mortality					
DPP-4 vs. SGLT-2	Direct	1	0/378	2/378	0.20 (0.01, 4.06)
DPP-4 vs. SGLT-2	Network				0.21 (0.01, 3.04)
DPP-4 vs. GLP-1	Direct	1	1/326	0/324	2.99 (0.12, 74.10)
DPP-4 vs. GLP-1	Network				2.89 (0.18, 46.00)

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Appendix B

EMPA-REG OUTCOME trial

Since much of the review data on cardiovascular safety with SGLT-2 inhibitors was from the EMPA-REG OUTCOME trial, we discuss the trial briefly here.

On June 28, 2016, the FDA Advisory Committee voted 12-11 to approve an addition to the empagliflozin label stating that the drug reduces cardiovascular mortality, based on the results from the EMPA-REG OUTCOME trial.[16] This randomized, double-blind, placebo-controlled trial was an event-driven, cardiovascular safety study that dominated meta-analyses in which it was included. The primary outcome was a composite of major adverse cardiovascular events (MACE), defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. The trial continued until 691 participants had experienced the primary outcome, in order to achieve 80% power to detect a 21.5% risk reduction in MACE events. EMPA-REG OUTCOME participants received empagliflozin 10 mg (N=2,345), empagliflozin 25 mg (N=2,342), or placebo (N=2,333). Participants were largely male (71%) and white (72%), with a mean age of 63 years, and the duration of diabetes was greater than 10 years for 57% of participants.[17] More than 99% of participants had at least 1 high-risk factor for cardiovascular disease; most patients (75%) had a history of coronary artery disease. Baseline characteristics were similar between groups**.** The hazard ratio of combined empagliflozin doses compared with placebo for the primary composite event of cardiovascular death, heart attack, or stroke was 0.86 (95% CI 0.74 to 0.99). Most of the reduced risk of MACE was due to the difference between groups in risk of cardiovascular death (172/4,687 vs. 137/2,333; HR 0.62, 95% CI 0.49 to 0.78). Risk estimates for nonfatal myocardial infarction and nonfatal stroke were not significant (HR 0.87, 95% CI 0.70 to 1.09 and HR 1.24, 95% CI 0.92 to 1.67, respectively), although the point estimate for stroke was greater than 1. The risk of all-cause mortality also favored empagliflozin (5.7% vs. 8.3%; HR 0.68, 95% CI 0.57 to 0.82).

Concerns with the label addition include:[18]

- A suggestion of possible increased risk of stroke with empagliflozin compared with placebo
- EMPA-REG OUTCOME was not designed to assess cardiovascular efficacy
- Cardiovascular death was not a primary outcome of the trial
- Mechanism for reduction in cardiovascular death is unknown
- Findings from the EMPA-REG OUTCOME trial have not been validated with a second trial
- Deaths that were categorized as “non-assessable” were considered CV deaths (71 deaths with empagliflozin vs. 53 with placebo); when these deaths removed, empagliflozin not better than placebo for the primary composite outcome (HR 0.90, 95% CI 0.77 to 1.06); however, CV death and all-cause mortality remained significant (HR 0.59, 95% CI 0.44 to 0.79 and HR 0.68, 95% CI 0.57 to 0.82, respectively).[17]

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Appendix C

Appendix Table C1. Characteristics and results of included systematic reviews

Author, Year (Quality rating)	Search Dates Minimum Duration	Intervention	Patient N Study N	Populations of included trials
Ding, 2016[1] (Good)	2/1/2016 24 weeks	GLP-1 receptor agonists	11,943 patients 12 RCTs	Mean % Male: 51.1-69.4 Mean age: 52.3-63.6 Mean diabetes duration: 5.3-17.2 yrs Mean HbA1c: 7.7-9.0 Mean BMI: 30.2-34.1
Li, 2016[2] (Good)	6/25/2015 12 weeks	DPP-4 inhibitors	68,775 patients 38 RCTs	Mean % Male: 42.3-70.7 Mean age: 49.7-72.6 yrs Mean diabetes duration: 1.7-17.5 yrs Mean HbA1c: 7.1-9.9 Mean BMI: 24.0-32.8
Li, 2016[3] (Good)	6/25/2015 12 weeks	GLP-1 receptor agonists	17,519 patients 20 RCTs	Mean % Male: 43.7-72-8 Mean age: 52.9-97.2 yrs Mean diabetes duration: 2.6-11.5 yrs Mean HbA1c: 7.6-8.5 Mean BMI: 25.6-33.3
Monami, 2016[4] (Good)	11/16/2015 12 weeks	SGLT-2 inhibitors	47,287 patients 71 RCTs	Mean Age: 51-67 yrs Mean diabetes duration: 1-17 yrs Mean HbA1c: 7.2-9.2 Mean BMI: 25.3-35.5

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Appendix Table C1. Characteristics and results of included systematic reviews

Author, Year (Quality rating)	Results (Intervention vs. Control)	Comments
Ding, 2016[1] (Good)	*GLP-1 vs Placebo:* MACE (10 trials): RR 0.85 (0.62 to 1.15) **All-cause mortality (4 trials): RR 0.28 (0.08 to 0.93)**	
Li, 2016[2] (Good)	Heart failure (38 trials): OR 0.97 (0.61 to 1.56) **Admission for heart failure (5 trials): OR 1.13 (1.00 to 1.26)**	
Li, 2016[3] (Good)	Heart failure (20 trials): 0.23% vs 0.44%; OR 0.62 (0.31 to 1.22)	
Monami, 2016[4] (Good)	**Cardiovascular mortality (23 trials): OR 0.43 (0.36 to 0.53)** **CV mortality: canagliflozin (7 trials): OR 0.50 (0.27 to 0.95)** CV mortality: dapagliflozin (9 trials): OR 0.46 (0.20 to 1.07) **CV mortality: empagliflozin (7 trials): OR 0.42 (0.34 to 0.52)** **Myocardial infarction (36 trials): OR 0.77 (0.63 to 0.94)** MI canagliflozin (6 trials): OR 0.57 (0.26 to 1.24) **MI dapagliflozin (14 trials): OR 0.48 (0.26 to 0.87)** MI empagliflozin (15 trials): OR 0.83 (0.67 to 1.04) Stroke (34 trials): OR 1.09 (0.86 to 1.38) Stroke canagliflozin (8 trials): OR 1.36 (0.54 to 3.40) Stroke dapagliflozin (11 trials): OR 0.68 90.31 to 1.46) Stroke empagliflozin (15 trials) OR 1.13 (0.87 to 1.46) **All-cause mortality (32 trials): OR 0.70 (0.59 to 0.83)** All-cause mortality canagliflozin (7 trials): OR 0.80 (0.45 to 1.42) All-cause mortality dapagliflozin (13 trials): OR 0.78 (0.41 to 1.48) **All-cause mortality empagliflozin (12 trials): OR 0.68 (0.56 to 0.82)**	

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Appendix Table C1. Characteristics and results of included systematic reviews

Author, Year (Quality rating)	Search Dates Minimum Duration	Intervention	Patient N Study N	Populations of included trials
Palmer, 2016[5] (Good)	3/21/2016 24 weeks	DPP-4 inhibitors GLP-1 agonists SGLT-2 inhibitors others	118,094 patients 1,417,367 patient- months 301 RCTs	Mean HbA1c: 8.2% mono and dual therapy trials; 8.4% triple therapy trials Median diabetes duration: 5.7 yrs

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Appendix Table C1. Characteristics and results of included systematic reviews

Author, Year (Quality rating)	Results (Intervention vs. Control)	Comments
Palmer, 2016[5] (Good)	Monotherapy compared with metformin: CV mortality DPP-4: OR 1.00 (0.37 to 2.65) CV mortality SGLT-2: OR 0.75 (0.14 to 3.96) MI DPP-4: OR 0.90 (0.36 to 2.23) MI SGLT-2: OR 0.63 (0.06 to 6.24) Stroke DPP-4: OR 1.43 (0.50 to 4.09) Stroke (SGLT-2): OR 0.70 (0.05 to 9.71) All-cause mortality DPP-4: OR 0.73 (0.41 to 1.30) All-cause mortality SGLT-2: OR 0.84 (0.22 to 3.21) Dual therapy with metformin vs metformin with sulfonylurea: CV Mortality DPP-4: OR 0.81 (0.36 to 1.82) CV mortality SGLT-2: OR 0.86 (0.14 to 5.27) CV mortality GLP-1: OR 0.52 (0.08 to 3.43) MI DPP-4: OR 0.59 (0.32 to 1.09) MI SGLT-2: OR 0.42 (0.12 to 1.48) MI GLP-1: OR 0.89 (0.35 to 2.22) Stroke DPP-4: OR 0.47 (0.23 to 0.95) Stroke SGLT-2: OR 2.75 (0.76 to 10.0) Stroke GLP-1: OR 0.88 (0.26 to 2.97) All-cause mortality DPP-4: OR 0.75 (0.45 to 1.24) All-cause mortality SGLT-2: OR 0.83 (0.37 to 1.86) All-cause mortality GLP-1: OR 0.87 (0.39 to 1.91)	

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Appendix Table C1. Characteristics and results of included systematic reviews

Author, Year (Quality rating)	Search Dates Minimum Duration	Intervention	Patient N Study N	Populations of included trials
Savarese, 2016[6] (Fair*)	1/1/2016 4 weeks (DPP-4 inhibitors) 12 weeks SGLT-2 inhibitors	DPP-4 inhibitors SGLT-2 inhibitors	DPP-4: 107,100 patients 114 RCTs SGLT-2: 33,370 patients 43 RCTs	Mean age: 57 years % Male: 55 Mean diabetes duration: 1-16.9 yrs Mean BMI: 24-35

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Appendix Table C1. Characteristics and results of included systematic reviews

Author, Year (Quality rating)	Results (Intervention vs. Control)	Comments
Savarese, 2016[6] (Fair*)	*DPP-4:* CV mortality (43 trials): 2.2% vs 2.5%; RR 0.98 (0.89 to 1.07) **MI (74 trials): 1.7% vs 2.3%; RR 0.91 (0.84 to 1.00)** Stroke (67 trials): 1.0% vs 1.2%; RR 0.93 (0.82 to 1.06) Heart failure (41 trials): 1.9% vs 1.9%; RR 1.08 (0.97 to 1.20) All-cause mortality (66 trials): 2.7% vs 3.0%; RR 1.01 (0.93 to 1.09) *SGLT-2:* **Cardiovascular mortality (12 trials): RR 0.87 (0.54 to 0.82)** **MI (30 trials): RR 0.80 (0.67 to 0.97)** Stroke (23 trials): RR 1.16 (0.91 to 1.47) **Heart failure (23 trials): RR 0.65 (0.52 to 0.82)** **All-cause mortality (30 trials): RR 0.72 (0.61 to 0.84)**	*Did not evaluate trials for quality

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Appendix Table C2. Quality assessment of included systematic reviews

Author, Year	Report clear review question, state inclusion and exclusion criteria of primary studies?	Substantial effort to find relevant research?	Adequate assessment of validity of included studies?	Sufficient detail of individual studies presented?
Ding, 2016[1]	Yes	Yes	Yes	Yes
Li, 2016a[2]	Yes	Yes	Yes	Yes
Li, 2016b[3]	Yes	Yes	Yes	Yes
Monami, 2016[4]	Yes	Yes	Yes	Yes
Palmer, 2016[5]	Yes	Yes	Yes	Yes
Savarese, 2016[6]	Yes	Yes	No	Yes

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Appendix Table C2. Quality assessment of included systematic reviews

Author, Year	Primary studies summarized appropriately?	Overall Rating
Ding, 2016[1]	Yes	Good
Li, 2016a[2]	Yes	Good
Li, 2016b[3]	Yes	Good
Monami, 2016[4]	Yes	Good
Palmer, 2016[5]	Yes	Good
Savarese, 2016[6]	Yes	Fair

Appendix C References

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