Dipeptidyl peptidase-4 (DPP-4) inhibitors and the risk of heart failure: A systematic review and meta-analysis of randomized trials

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Abstract

Background: Given recent discrepant results from randomized trials (RCTs), we examined the totality of RCT evidence assessing DPP-4 inhibitors' association with heart failure (HF).

Methods: MEDLINE, EMBASE and ClinicalTrials.gov were searched to August 2016 for RCTs comparing DPP-4 inhibitors to placebo/no therapy for ≥24 weeks. Pooled analyses used random-effects.

Results: We identified 100 RCTs (n=79,867) - 3 large cardiovascular-safety RCTs (SAVOR-TIMI 53[saxagliptin]/n=16,492, EXAMINE[alogliptin]/n=5,380, and TECOS[sitagliptin]/n=14,735), and 97 smaller RCTs with primary outcome that was usually change in A1C. Virtually all were high-quality multi-center placebo-controlled trials. 1192/1244(96%) of HF events were pre-specified, blindly adjudicated, and required hospitalization. Pooled results suggested a 13% HF increase (RR 1.13, 95%CI 1.01–1.26,P=0.03, I^2=0%; 32 RCTs, n=54,640, 1,244 events). When including only the 3 large RCTs, the increase was similar but not statistically significant (RR 1.14, 95%CI 0.97–1.32,P=0.10; 3 RCTs, n=36,543, 1,169 adjudicated events, number needed to harm 246) due to heterogeneity (I^2=42%) leading to wider confidence intervals since SAVOR-TIMI 53 showed increased HF (RR 1.26, 95%CI 1.06-1.49,P=0.009) and TECOS no effect (RR 1.00, 95%CI 0.83-1.19,P=0.97). Paired differences between agents did not achieve statistical significance (e.g., interaction P=0.07-0.13 for saxagliptin vs. sitagliptin). Results from the two ongoing DPP-4 inhibitor vs. placebo cardiovascular-safety RCTs (CARMELINA [linagliptin]/n=8,300, MK-3102-018 [omarigliptin]/n=4,000) could result in different pooled risk estimates for HF among the cardiovascular-safety RCTs.

Interpretation: Despite pooled data from 79,867 patients, whether DPP-4 inhibitors increase HF overall, or exhibit within-class differences, remains unresolved highlighting the importance of ongoing trials which will address the overall but not class difference question.

Abbreviations

CI	confidence intervals
DPP-4	dipeptidyl peptidase-4
eGFR	estimated glomerular filtration rate
EMPA-REG OUTCOMES	Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes
EXAMINE	Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care
FDA	Food and Drug Administration
HF	heart failure
MACE	major adverse cardiovascular events
NNH	number needed to harm
RCTs	randomized trials
RR	relative risks
SAVOR-TIMI 53	Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR) – Thrombolysis in Myocardial Infarction (TIMI) 53
SGLT2	sodium–glucose cotransporter 2
TECOS	Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin

Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors are integral in the management of patients with diabetes given their effective glucose lowering with low risk for hypoglycemia or weight gain.[1] Since heart failure (HF) remains a common complication of diabetes, and is associated with poor long-term prognosis,[2,3] understanding the potential effects of antihyperglycemic agents on risk for HF is of critical and immediate importance. The first large DPP-4 inhibitor vs. placebo randomized trial (RCT). Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction(TIMI) 53 (SAVOR-TIMI 53)(n=16,492 patients with a history of, or at risk for cardiovascular events) unexpectedly found a significantly higher rate of heart failure (HF) requiring hospitalization.[4,5] The second was the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE)(n=5,380 patients post-acute coronary syndrome) found a numerical but non-statistically significant higher rate of HF requiring hospitalization.[6,7] In contrast, Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin (TECOS), enrolled (n=14,735 patients with cardiovascular disease and longer follow up [median 3.0 years vs. 1.5 and 2.1 years for EXAMINE and SAVOR-TIMI 53]) found almost identical rates of hospitalization for HF in the sitagliptin and placebo groups.[8]

The potential safety issue arising from SAVOR-TIMI 53 and EXAMINE led to the FDA's recent recommendation[9] to consider discontinuing saxagliptin and alogliptin in patients that develop HF. Given the apparent discrepant results from TECOS,[3,10,11] we felt it was important to inform clinicians who are concerned about the potential increased HF signal by providing them with the totality of the available randomized controlled trial evidence in the field. In addition, the recent publication of the EMPA-REG OUTCOMES trial[12] showing that HF hospitalization was significantly reduced with the use of an oral antihyperglycemic agent of a different class, empagliflozin, a sodium–glucose cotransporter 2 (SGLT2)

inhibitor, has increased the importance of quantifying the risk of increased HF for DPP-4 inhibitors. The two specific questions addressed by this systematic review and meta-analysis are whether 1) DPP-4 inhibitors, as a class, compared to placebo or no therapy increases HF in patients with Type 2 diabetes, and 2) whether there are significant within-class differences.

Methods

Data Sources and Study Selection

We systematically searched MEDLINE and EMBASE (inception-to August 2016) and ClinicalTrials.gov in duplicate for RCTs comparing treatment of any DPP-4 inhibitor vs. placebo or no therapy(active comparator RCTs were excluded) that enrolled adult patients with type 2 diabetes for at least 24 weeks. For multiple treatment group RCTs we included only randomized groups in which treatments differed by DPP-4 inhibitor treatment. Groups with different DPP-4 inhibitor doses were combined within the same trial. RCTs in which placebo-treated groups were subsequently switched to open-label active therapy were only included if this switch occurred after 24 weeks of therapy.

Data Extraction and Risk of Bias Assessment

For each RCT, baseline patient characteristics, intervention, outcome definitions and events were collected in duplicate (discrepancies resolved by consensus). Risk of bias (patient, caregiver, and outcome assessor blinding; allocation concealment; intention-to-treat analysis; early stopping for benefit;[13] loss to follow up) were also assessed in duplicate.[14]

Data Analysis

In the primary analysis we included all heart failure outcomes when listed either as a serious adverse event (SAE) or adverse event, though all were listed as SAEs. As secondary analysis, we included only RCTs in which cardiovascular outcomes were the primary outcome and hospitalization for HF was an adjudicated primary or secondary outcome. Additional data analysis details are provided in the on-line appendix. We did not register or publish a review protocol.

Results

Search results

One hundred twenty-one RCTs were identified in which treatment between randomized groups differed only by DPP-4 inhibitor treatment. Of these, 11 RCTs listed only on ClinicalTrials.gov provided no results (NCT00683735,NCT01356381,NCT01582230,NCT01697592,NCT01704261,NCT01792518,NCT01890122, NCT01990469,NCT02015299,NCT02099110,NCT02104804) and 10 RCT publications did not provide HF data[15-24] leaving 100 RCTs that reported the number of patients with HF (Supplementary Table 1, Figure 1) and these enrolled 79,867 patients into groups that differed only in DPP-4 inhibitor therapy.[4-8,25-136]

RCT patient characteristics

Only the three RCTs discussed in the Introduction (SAVOR-TIMI 53, EXAMINE, and TECOS) had cardiovascular outcomes as the primary outcome and enrolled 46% (36,543/79,867) of all patients in the included RCTs (Tables 1 and 2). Enrolled patients in these three RCTs had a mean age of 61–66 years old, two-thirds of whom were men and ~70% were of white race. Median BMI was approximately 30 kg/m^2. The patients had type 2 diabetes for median durations that ranged from 7–10 years with a mean baseline A1C of 8.0% (SAVOR-TIMI 53, EXAMINE) or 7.2% (TECOS), and with a mean of 23–41% also taking insulin in addition to oral antihyperglycemic agents. A large majority of patients had other cardiovascular risk factors including hypertension and dyslipidemia, and most had a previous myocardial infarction or revascularization, while a minority had a previous stroke (Table 2). Most patients were receiving ASA and/or another anti-platelet therapy as well as a statin, angiotensin converting enzyme inhibitors or angiotensin receptor antagonists, and beta-blockers or other antihypertensive medications. Patients with pre-existing HF ranged from 13–28% among the included larger RCTs.

The primary outcome for the vast majority of the smaller RCTs (n=89/97) was glycemic control. One small trial, presented only in abstract form,[104] enrolled patients with class I–III NYHA HF and measured change in left-ventricular ejection fraction as its primary outcome. Enrolled patients in these smaller trials had variable characteristics (Table 1). Mean age was typically in the mid-50's, with >50% men, and >50% of white race, and median BMI approximately 30 kg/m^2. The mean duration of type 2 diabetes ranged from 0–17 years with the majority of mean baseline A1C levels between 8.0–8.5%. No patients were using insulin therapy in the vast majority of smaller RCTs. Few data were provided on the prevalence of other cardiovascular risk factors or cardiovascular medication use in the smaller RCTs.

Risk of Bias Assessment

Included RCTs generally had low risk of bias. The three large RCTs and all trials with events were blinded using placebos with concealed allocation, intention-to-treat analysis, no stopping early for benefit and had low numbers (typically <1–5%) of randomized patients with missing HF outcome data (Table 3). Only six of the smaller trials, each with zero events, were not blinded or had unclear allocation concealment,[75,96,120,129,130,135,136] and only four had >5% of randomized patients lost to follow up.[83,116,120,136] The three larger trials as well as the small trial that enrolled patients with class I–III NYHA HF ,[104] defined HF requiring hospitalization as a pre-specified secondary outcome that was adjudicated by outcome assessors blinded to treatment allocation. The three larger trials used virtually identical HF definitions (Table 2 footnote). Virtually all RCTs were pharmaceutical company funded.

Quantitative Data Synthesis

Pooling HF data from the three larger RCTs and the 29 smaller RCTs with at least one patient with HF suggested a 13% increased risk of HF with DPP-4 inhibitors which achieved statistical significance (pooled RR 1.13, 95% CI 1.01–1.26, P=0.03; 32 RCTs, 54,640 patients, 1,244 events) with no significant

heterogeneity (I^2=0%) (Figure 2). 94% (1169/1244) of the events came from the three larger RCTs, and 23 of the remaining 75 (31%) events reported in the 29 smaller RCTs occurred in the one RCT that enrolled patients with class I–III NYHA HF. Thus, in total 1,192/1,244 (96%) of HF outcomes occurred in RCTs that pre-specified that these i) required hospitalization and ii) were subject to blinded adjudication. Including also the results from the 68 smaller RCTs (n=25,227) with no patients with HF and thus RR equal to 1.00 (or no effect), as the pre-planned sensitivity analysis, did not change the pooled result (pooled RR 1.12, 95% CI 1.01–1.25, P=0.03, I^2=0%; 100 RCTs, 79,867 patients, 1244 events).

Pooling data from only the three large RCTs with cardiovascular primary outcomes and blinded outcome adjudication, as the pre-planned secondary analysis, resulted in a similar effect size, however, this did not achieve statistical significance (pooled RR 1.14, 95% CI 0.97–1.32, P=0.10; 3 RCTs, 36,543 patients, 1,169 [adjudicated] events) due in part to heterogeneity (I^2=42%) resulting in wider confidence intervals (the pooled result would be statistically significant if fixed effects meta-analysis, which ignores heterogeneity, is used: pooled RR 1.14, 95% CI 1.01–1.27, P=0.03). Adding the results of the smaller trial that enrolled patients with class I–III NYHA HF, and also defined HF requiring hospitalization as a pre-specified secondary outcome that was adjudicated by outcome assessors blinded to treatment allocation, gives a pooled result that just achieves statistical significance (pooled RR 1.139, 95% CI 1.002–1.293, P=0.046; 4 RCTs, 36,796 patients, 1,192 [adjudicated] events). There was no difference in the pooled result of the 3 larger RCTs with cardiovascular primary outcomes and the pooled result of the smaller RCTs (interaction P=0.54) (Figure 2).

Differences between pooled RR for individual DPP-4 inhibitors (Figure 3) did not achieve statistical significance. The most extreme difference was between saxagliptin, dominated by the results of SAVOR-TIMI 53, suggesting a statistically-significant increased risk of HF requiring hospitalization (pooled RR 1.22, 95% CI 1.03-1.44, P=0.02, I^2=0%; 9 RCTs, 20,880 patients, 536 events), and sitagliptin,

dominated by the results of TECOS, suggesting no difference in risk (pooled RR 1.01, 95% CI 0.85-1.21, P=0.89, I^2=0%; 10 RCTs, 21,218 patients, 468 events); however, even this difference in pooled RR between saxagliptin and sitagliptin did not achieve statistical significance (interaction P=0.13 [interaction P=0.07 comparing RR for only SAVOR-TIMI 53 vs. RR for only TECOS]).

In *post hoc* analysis, only SAVOR TIMI-53 and EXAMINE provided data for patients with and without a prior history of HF. HF requiring hospitalization rates were considerably higher in patients with (359/3638[9.9%]) vs without (353/3638[1.9%]) prior history of HF but the increase was concentrated in patients without (RR 1.42, 95%CI 1.15-1.74) rather than with (RR 1.08, 95%CI 0.89-1.31) prior history of HF (interaction p=0.06)(Figure 4); though cautious interpretation is needed given the limited data.

Interpretation

Pooled data from all RCTs (n=79,867) in which intervention and control patients differed only by DPP-4 inhibitor therapy suggest that DPP-4 inhibitors increase the risk of HF requiring hospitalization by 13%. This increase is statistically significant if data from both large and small high-quality RCTs are included, or if data from the 3 large RCTs[4-8] and 1 smaller RCT[104] that defined HF requiring hospitalization as a pre-specified secondary outcome adjudicated by outcome assessors blinded to treatment allocation are included. If however, data from only the 3 large RCTs with primary cardiovascular outcomes are included,[4-8] the magnitude remains numerically similar but is no longer statistically significant, largely due to heterogeneity between the risk of HF with saxagliptin and sitagliptin. Unfortunately, the current data do not have sufficient statistical power to definitively answer either 1) the question of whether DPP-4 inhibitors as a class increase HF given pooled treatment effect p-values ranging from 0.03-0.10 depending on whether or not the smaller RCT data are included, or 2) whether DPP-4 inhibitors exhibit

significant within class differences (in which case pooling would not be appropriate) given interaction p-values ranging from 0.07-0.13 comparing results between the two medications with the most extreme safety (sitagliptin) or harm (saxagliptin) results. Results from the two ongoing DPP-4 inhibitor vs. placebo cardiovascular-safety RCTs will be important as they could have an impact on the pooled risk estimates for HF among the cardiovascular-safety RCTs (see Additional Results in on-line appendix) which emphasizes the importance of ongoing trials to resolve the question whether DPP-4 inhibitors as a class increase HF. Because there are only single large cardiovascular safety RCTs for each specific DPP-4 inhibitor and few head-to-head comparisons (our search identified eleven small short-term RCTs[23,128,137-145] directly comparing agents but none reported any HF events), the ongoing cardiovascular-safety trials will be less helpful in identifying differential effects among DPP-4 inhibitors.

In comparison to previous systematic reviews,[146-151] ours is the only one to focus on RCTs in which randomized groups differed by DPP-4 inhibitor treatment to avoid the confounding effect of other medications, some of which are known to independently increase or decrease the risk of HF,[12,152] and the only one to statistically compare differences in HF outcomes between different agents. Our meta-analysis includes from 4 to 29 more RCTs enrolling 1,639-19,339 more patients than other meta-analyses (Table 4). Moreover, we avoided inadvertently double counting RCTs and used all HF events for EXAMINE and the most recently published data for VIVIDD, unlike some of the previously published meta-analyses (Table 4). With the larger number of included RCTs, our pooled results demonstrate statistically higher overall HF risk, unlike other post-TECOS meta-analyses, but only if data from all (placebo-controlled) RCTs are included. Ours is also the first to compare pooled HF hospitalization rates by previous HF history suggesting, based on limited data, that increased risk from DPP-4 inhibitors may be concentrated in patients without previous HF.

Our meta-analysis has limitations. It included relatively small trials with variable inclusion criteria, short follow-up times (though we specified minimum of 24 weeks which is longer than the 12 weeks follow-up used in some other meta-analyses[147,148,150]) and non-adjudicated outcomes. However, 96% of the HF outcomes were blindly adjudicated and pooled results are dominated by the large cardiovascular safety trials with adjudicated outcomes: point estimates are similar regardless of whether the data from the smaller trials are included (1.14 vs. 1.13), though inclusion of the additional data from the smaller RCTs narrows the confidence intervals resulting in statistical significance being achieved. This is in contrast to a highly-cited rosiglitazone meta-analysis[153] where smaller RCTs with non-adjudicated outcomes drove overall results and the effect on both myocardial infarction and cardiovascular death changed depending on how the analysis was conducted.[154] Nevertheless, the absolute increase in risk during follow up, even limiting the analysis only to the three cardiovascular safety RCTs is small at around 0.4%(= 623/18313-546/18230)(Figure 2) corresponding to a number needed to harm of (1/0.004=)246 (median follow up 2.4y). Studies in patients with previous HF, and longer follow up data may uncover higher risks, and are needed to explore longer-term safety of these lifelong therapies. Although we limited our analysis to placebo-controlled trials, in trials targeting A1C, placebo-treated patients would likely have received more non-DPP-4 inhibitor medications.

In summary, our updated systematic review includes more RCTs than others and is the only post-TECOS meta-analysis to demonstrate statistically higher, albeit small, overall HF risk, but only if data from all placebo-controlled RCTs are included. It is also the only meta-analysis to statistically compare differences in HF outcomes by different agents and by previous history of HF. However, despite pooled data from 79,867 patients, whether DPP-4 inhibitors increase HF overall, or exhibit within-class differences (which would make pooling between agents inappropriate), remains unresolved highlighting the importance of ongoing trials which will address the overall but not class difference

question. Nevertheless, given the current data, it seems prudent to follow the FDA's Drug Safety Communication[9] and be cautious about prescribing saxagliptin and alogliptin in patients with established HF, or at high risk of developing HF (previous HF, low eGFR and/or elevated NT-proBNP), and consider discontinuing these medications in any patient who develops heart failure.

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Table 1: Description of Included Randomized Controlled Trials

First Author Year of Publication	Trial Registration Number	Inclusion Criteria		Trial Duration (wks)	Baseline Patient Characteristics								Patients w/ Heart Failure (n/N)	
		Other Anti-hyperglycemic agent(s)	A1C range (%)		Prim. Outcome	Mean Age (yrs)	% Male	% Caucasian	BMI (kg/m^2)	DM (yrs)	Mean A1C (%)	On Insulin (%)	DPP4 Inhibitor	Placebo
Trials with Primary Cardiovascular Outcomes														
Scirica 2013, 2014 (SAVOR-TIMI 53)[4,5] (saxagliptin)	NCT01107886	--	6.5-12	110 (med)	MACE	65	67%	75%	31	10.3 (med)	8.0	41%	289/ 8280	228/ 8212
White 2013 (EXAMINE)[6,7] (alogliptin)	NCT00968708	--	6.5-11 (7-11)	76 (med)	MACE	61 (med)	68%	73%	29 (med)	7.2 (med)	8.0	30%	106/ 2701	89/ 2679
Green 2015 (TECOS)[8,25] (sitagliptin)	NCT00790205	--	6.5-8	156 (med)	MACE	66	71%	68%	30	9.4 (med)	7.2	23%	228/ 7332	229/ 7339
Trials with Primary Metabolic Outcomes														
Alogliptin														

Nauck 2009[26]	NCT00286442	Met	7-10	26	A1C	55	50%	77%	32	6	7.9	0%	1/ 423	0/ 104
DeFronzo 2008[27]	NCT00286455	--	7-10	26	A1C	53	53%	67%	n/r	n/r	7.9	0%	0/ 264	0/ 64
Pratley 2009[29]	NCT00286468	Sulf	7-10	26	A1C	57	52%	71%	30	7.7	8.1	0%	1/ 401	0/ 99
Pratley2009[30]	NCT00286494	Pio	7-10	26	A1C	55	58%	74%	33	7.6	8.0	0%	2/ 397	0/ 97
Rosenstock 2009[31]	NCT00286429	Ins	≥8	26	A1C	55	41%	65%	32	12.6	9.3	100%	0/ 261	0/ 129
Rosenstock 2010[28]	NCT00395512	Pio 30	7.5-11	26	A1C	53	49%	80%	31	3.2	8.8	0%	0/ 327	0/ 163
Pratley 2014[32]	NCT01023581	±Met	7.5-10	26	A1C	54	54%	68%	31	4	8-8.5	0%	0/ 442	0/ 326
DeFronzo 2012[33]	NCT00328627	Met ±Pio	7.5-10	26	A1C	54	45%	71%	3	6.2	8.5	0%	0/ 1037	2/ 516
Mita 2016[136]	UMIN000005311	+Var	7-9.3	104	Intimal thick-	65	58%	0%(Japanese)	25	8.6	7.3	0%	0/ 161	0/ 161

					ness									
Linagliptin														
Gomis 2011[34]	NCT00641043	±Met	7.5-10 (11)	24	A1C	55	54%	67%	29	n/r	8.6	0%	0/ 259	0/ 130
Haak 2012[35]/Haak 2013[36]	NCT00798161 /NCT00915772	±Met	7.5-10 (11)	24	A1C	55	54%	67%	29	2.5	8.7	0%	2/ 428	0/ 363
Owens 2011[37]	NCT00602472	+Met & Sulf	7-10	24	A1C	58	47%	47%	28	>5	8.1	0%	0/ 792	0/ 263
Taskinen 2011[38]	NCT00601250	+Met	7-10	24	A1C	57	54%	76%	30	5	8.1	0%	0/ 523	0/ 177
Thrasher 2014[39,127]	NCT01194830	--	7.5-11	24	A1C	54	54%	0% (Black)	33	5-6	8.7	0%	0/ 106	0/ 120
Barnett 2013[40]	NCT01084005	--	≥7 (age ≥70)	24	A1C	75	68%	97%	30	10-12	7.8	21%	0/ 162	0/ 79
Bajaj 2014[41]	NCT00996658	+Met &Pio	7.5-10	24	A1C	54	49%	27%	28	1-2	8.4	0%	0/ 183	0/ 89
Del Prato	NCT00621140	--	7-10	24	A1C	56	48%	54%	29	n/r	8	0%	0/	0/

2011[42]													336	167
McGill 2013[43]	NCT00800683	--	7-10 (CRI)	52	A1C	64	60%	74%	32	>5	8.2	82%	2/68	1/65
Yki-Jarvinen 2013[44]	NCT00954447	--	7-10	52	A1C	60	52%	80%	31	>5	8.3	100%	3/ 631	2/ 630
ClinicalTrials.gov[48]	NCT01183013	+Pio	7-10.5	84	A1C	57	53%	n/r	n/r	n/r	8.1	0%	0/ 392	1/ 409
Chen 2015[155]	NCT01214239	--	7-10	24	A1C	54	59%	0% (Asian)	25	n/r	8.0	0%	0/ 200	0/ 99
ClinicalTrials.gov[50]	NCT01215097	+Met	7-10	24	A1C	56	50%	0% (Asian)	26	n/r	8.0	0%	0/ 205	0/ 100
DeFronzo 2015[45]/Lewin 2015[46]	NCT01422876	±Met	7-10.5	24	A1C	55	54%	74%	31	~5	8.0	0%	0/ 545	0/ 551
ClinicalTrials.gov[47]	NCT01708902	+Met	7.5-11	24	A1C	51	62%	n/r	n/r	n/r	n/r	n/r	0/ 294	0/ 289
Wu 2015[134]	n/r	--	7-10	24	A1C	52	59%	0%(Chinese)	24	0	8.0	0%	0/33	0/22
ClinicalTrials.	NCT01778049	+Empa	7-10.5	24	A1C	57	57%	n/r	n/r	n/r	n/r	n/r	0/	0/

gov[133]		&Met											238	240
Saxagliptin														
Pfützner 2011[51]/ Jadzinsky 2009[52]	NCT00327015	+Met	8-12	76	A1C	52	49%	76%	30	1.7	9.4	0%	1/ 643	2/ 328
Barnett 2013[53]	NCT00757588	+Ins ±Met	7.5-11	52	A1C	57	41%	78%	32	12	8.7	100%	2/ 304	0/ 151
Chacra 2011[54]	NCT00313313	+Sulf	7.5-10	76	A1C	55	45%	59%	29	7	8.4	0%	1/ 501	0/ 267
DeFronzo 2009[55]/ Rosentock 2013[56]	NCT00121667	+Met	7-10	24 (208 for mort)	A1C	55	51%	82%	31	6.5	8.0	0%	3/ 564	2/ 179
Frederich 2012[57]	NCT00316082	--	7-10	24	A1C	55	46%	70%	31	1.7	8.0	0%	0/ 291	0/ 74
Hollander 2011[58]	NCT00295633	+TZD	7-10.5	76	A1C	54	50%	55%	30	5.2	8.3	0%	0/ 381	1/ 184
Nowicki 2011[59]	NCT00614939	+var	7-11 (CRI)	52	A1C	67	43%	100%	31	16.6	8.3	75%	1/85	2/85

Pan 2012[60]	NCT00698932	--	7-10	24	A1C	51	55%	0% (Asian)	26	1	8.1	0%	0/ 284	0/ 284
Rosenstock 2009[61]/Rosenstock 2013[56]	NCT00121641	--	7-10	24 (208 for mort)	A1C	53	51%	85%	32	2.6	7.9	0%	1/ 306	0/ 95
Moses 2014[62]	NCT01128153	+Met &Sulf	7-10	24	A1C	57	60%	45%	29	n/r	8.3	0%	0/ 129	0/ 128
Rosenstock 2015[63]	NCT01606007	+Met &dap	8-12	24	A1C	54	49%	70%	32	7.3	8.9	0%	0/ 179	0/ 179
Matthaei 2015[132]	NCT01619059	+Met& dap	8-11.5	24	A1C	55	47%	88%	31	7.7	7.9	0%	1/ 153	2/ 162
Sitagliptin														
Charbonnel 2006[64]	NCT00086515	+Met	7-10	24	A1C	55	57%	64%	31	4.6	8.0	0%	1/ 464	0/ 237
Hermansen 2007[65]	NCT00106704	+Sulf ±Met	7.5-10.5	24	A1C	56	53%	63%	31	8.8	8.3	0%	1/ 222	0/ 219
Henry 2014[66]	NCT00722371	+Pio	7.5-11	54	A1C	52	56%	67%	31	3.9	8.9	0%	2/ 691	0/ 693

Raz 2008[67]	NCT00337610	+Met	8-11	30	A1C	55	46%	44%	30	7.9	9.2	0%	0/96	0/94
Vilsbøll 2011[68]	NCT00395343	+Ins ±Met	7.5-11	24	A1C	58	51%	70%	31	12	8.7	100%	0/ 322	2/ 319
Williams-Herman 2010[69]/ Goldstein 2007[70]	NCT00103857	±Met	7.5-11	104	A1C	53	49%	52%	32	4.5	8.8	0%	1/ 372	0/ 364
Yoon 2012[71]/Yoon 2011[72]	NCT00397631 / NCT01028391	+Pio	8-12	54	A1C	51	54%	52%	30	2.3	9.5	0%	0/ 261	0/ 259
ClinicalTrials.gov[73]	NCT00918879	--	7-10	24	A1C	49	56%	0% (India)	n/r	n/r	n/r	0%	0/ 107	0/ 106
Yang 2011[74]	NCT00661362	+Met	7-10	24	A1C	54	48%	0% (Asian)	26	5.1	7.8	0%	0/ 283	0/ 287
ClinicalTrials.gov[75]	NCT00875394	+Met	6.5-11	24	A1C	55	26%	n/r	29	8.4	8.5	0%	0/36	0/9
Barzilai 2011[76]	NCT00305604	--	7-10 (age ≥65)	24	A1C	72	47%	79%	31	7.1	7.8	0%	0/ 102	0/ 104
Yang 2012[77]	NCT00813995	+Met	7.5-11	24	A1C	55	51%	0%(Chi-	25	6.9	8.5	0%	0/	0/

								nese)					197	198
Rosenstock 2006[78]	NCT00086502	+Pio	7-10	24	A1C	56	56%	73%	31	6.1	8.0	0%	0/ 175	0/ 178
Aschner 2006[79]	NCT00087516	--	7-10	24	A1C	54	52%	51%	30	4.4	8.0	0%	0/ 488	0/ 253
Fonseca 2013[80]	NCT00885352	+Met +Pio	7.5-11	26	A1C	56	62%	50%	30	9.8	8.7	0%	0/ 157	0/ 156
Olansky 2011[81]	NCT00482729	+Met	≥7.5	44	A1C	50	57%	80%	33	3.4	9.9	0%	1/ 625	0/ 621
ClinicalTrials.gov[82]	NCT00420511	+Met	6/6.5-9	44	β-cell func-tion	61	67%	62%	33	3.0	6.1	0%	0/10	0/11
Dobs 2013[83]	NCT00350779	+Met &Rosi	7.5-11	54	A1C	55	58%	51%	30	9.3	8.8	0%	0/ 170	0/ 92
Moses 2016[156]	NCT01076075	+Met &Sulf	7.5-10.5	24	A1C	55	46%	n/r	n/r	n/r	8.4	0%	0/ 210	0/ 212
Lavalle-González 2013[85]	NCT01106677	--	7-10.5	26	A1C	55	48%	72%	32	6.8	7.9	0%	1/ 366	0/ 183

Mathieu 2015[86]	NCT01462266	+Glar ±Met	7.5-11	24	A1C	59	48%	70%	32	13.5	8.7	100%	0/ 329	0/ 329
Roden 2013[87]	NCT01177813 / NCT01289990	--	7-10	76	A1C	55	59%	34%	28	<5	7.9	0%	1/ 223	0/ 223
ClinicalTrials.gov[88]	NCT01177384	+Acar	n/r	24	A1C	57	51%	n/r	n/r	n/r	8.1	0%	0/ 191	0/ 189
Skrivanek 2014[89]	NCT00734474	+Met	7-9.5	26	A1C	54	49%	51%	31	7	8.1	0%	0/ 355	0/ 177
ClinicalTrials.gov[90]	NCT00838903	+Met	n/r	156	A1C	55	47%	72%	n/r	n/r	n/r	n/r	1/ 302	0/ 101
Ji 2016[157]	NCT01076088	±Met	7(.5)-10(11)	24	A1C	53	61%	0%(Chinese)	n/r	n/r	8.7	0%	0/ 367	0/ 376
ClinicalTrials.gov[92]	NCT01519674	+Met &Ins	7-10	24	A1C	56	52%	49%	29	9.1	8.4	100%	0/ 383	0/ 192
ClinicalTrials.gov[93]	NCT01590771	+Sulf ±Met	7.5-11	24	A1C	57	50%	n/r	n/r	n/r	8.6	0%	0/ 248	0/ 249
ClinicalTrials.	NCT01590797	+Ins	7.5-11	24	A1C	58	53%	0%(Chi-	n/r	n/r	n/r	100%	0/	0/

gov[94]		±Met						nese)					234	233
ClinicalTrials.gov[95]	NCT01652729	+Met	7.1-11	28	A1C	54	56%	81%	32	8.2	8.5	0%	0/ 122	0/ 61
Ishikawa 2014[96]	UMIN000006432	--	<6.5	52	Carotid artery intima thickness	71	85%	0%(Japanese)	25	n/r	5.6	0%	0/37	0/39
	*UMIN Clinical Trials Registry													
Derosa 2012[97-99]	n/r	+Met	>8.0	52	A1C	55	48%	100%	29	0.5	8.1	0%	0/91	0/87
Derosa 2014[100]	n/r	+Var	>7.0	104	A1C	n/r	49%	100%	29	n/r	8.1	0%	0/ 102	0/ 103
Chien 2011[130]	n/r	+Var	≥7.0	24	A1C	73	58%	0%(Chinese)	26	13.6	9.7	0%	0/49	0/48
Weinstock 2015[131]	NCT00734474	+Met	7/8-9.5%	26	A1C	54	49%	51%	31	7.0	8.1	0%	0/ 315	0/ 177
Mita 2016[135]	UMIN000007396	+Var	≥6.6	104	Intimal thickness	64	60%	0%(Japanese)	25	17.3	8.1	100%	0/ 137	0/ 137

ClinicalTrials.gov[128]	NCT01703221	--	n/r	24	A1C	60	69%	0%(Japanese)	n/r	n/r	n/r	0%	0/ 164*	0/ 82
Vildagliptin														
Bosi 2007[101]	NCT00099892	+Met	7.5-11	24	A1C	54	57%	74%	33	6.3	8.4	0%	0/ 360	0/ 181
Bosi 2009[102]	NCT00382096 / NCT00468039	+Met	7.5-11	24	A1C	53	58%	73%	31	4.1	8.7	0%	0/ 292	0/ 292
Fonseca 2007[103]	NCT00099931	+Ins	7.5-11	24	A1C	59	51%	71%	33	14.7	8.4	100%	0/ 144	0/ 152
VIVIDD 2014[104]	NCT00894868	--	6.5-10 (EF <40)	52	LVEF	63	77%	n/r	29	n/r	7.8	34%	13/ 128	10/ 125
Scherbaum 2008[105,106]	NCT00300285[106] / NCT00101712[106]	--	6.2-7.5	104	A1C	63	59%	99%	30	2.6	6.7	0%	0/ 156	0/ 150
Strain 2013[107]	NCT01257451	--	7-10 (age >70)	24	A1C	75	45%	97%	30	11.4	7.9	0%	1/ 139	1/ 139
Vollmer 2009[108]	NCT00494884	+Met	6.5-8	24	A1C	61	46%	96%	n/r	n/r	7.2	0%	0/ 274	0/ 131

Garber 2007[109]	NCT00099853	+Pio	7.5-11	24	A1C	54	43%	69%	32	4.7	8.7	0%	1/305	1/158
Garber 2008[110]	NCT00099944	+Sulf	7.5-11	24	A1C	58	59%	69%	31	7.1	8.5	0%	0/339	0/176
Yang 2015[111]	NCT01357252	+Sulf	7.5-11	24	A1C	59	57%	0%(Chinese)	25	6.9	8.7	0%	0/143	0/136
Foley 2011[112]/ Bunck 2012[113]	NCT00260156	--	≤7.5	52	□-cell function	57	59%	93%	30	1.0	6.0	0%	0/29	0/30
Pan 2012[114]	NCT00822211	+Met	7-10	24	A1C	54	47%	0%(Chinese)	25	5	8.1	0%	0/294	0/144
Lukashevich 2014[115]	NCT01233622	+Met ±Sulf	7.5(8.5)-11	24	A1C	55	48%	23%	28	7.3	8.8	0%	0/157	0/160
Macauley 2015[116]	NCT01356381	+Met	≤7.6	26	Liver TG + Ins Sens	61	64%	n/r	30	1.0	6.0	0%	0/20	0/19
Ahren 2004[117]/Ahre	Pre-dated registration	+Met	7-9.5	52	A1C	57	37%	99%	30	5.6	7.7	0%	0/56	0/51

n 2005[118]														
Goodman 2009[119]	n/r	+Met	7.5-11	24	A1C	55	58%	66%	32	n/r	8.6	0%	0/ 248	0/ 122
Ito 2011[120]	n/r	--	>7.0 (ESRD)	24	A1C	67	69%	0%(Japanese)	23	n/r	6.7	0%	0/30	0/21
Derosa 2012[121-123]	n/r	+Met	8.1-10.9	52	A1C+ β-cell function	53	51%	100%	28	0.5	8.2	0%	0/84	0/83
Zografou 2015[129]	n/r	+Met	7-9	26	Arter. stiffness	54	59%	n/r	32	n/r	8.1	0%	0/32	0/32
Gemigliptin														
Yang 2013[124]	NCT01601990	--	7-11	24	A1C	53	58%	0%(Ind/ Korean)	26	3	8.3	0%	0/87	0/87
Teneligliptin														
ClinicalTrials.gov[125]	NCT00971243	+Met	7-10	24	A1C	58	56%					0%	0/ 359	0/ 88
Anagliptin														
Yang 2015[126]	NCT01529528	--	6.5-10	24	A1C	56	54%	0% (Korean	25	3.6	7.1	0%	0/	1/

								)					68	40

Abbreviations: acar, acarbose; BMI, body mass index; dap, dapagliflozin;DPP-4, dipeptidyl peptidase-4 ; EF, left ventricular ejection fraction; empa, empagliflozin; glar, glargine; Ind, Indian; ins, insulin; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; med, median; met, metformin; n/N, number of patients with heart failure/total number of patients; n/r, not reported; pio, pioglitazone; rosi, rosiglitazaone; sulf, sulfonylurea; TZD, thiazolidinedione; var, various hypoglycemic agents; wks, weeks; yrs, years.

*Randomized patients to three groups comparing both sitagliptin and omarigliptin to placebo. 0/166 heart failure events in the omarigliptin group.

Table 2: Trial and baseline patient comorbidities and medications for RCTs with primary cardiovascular outcomes*

Trial Name	SAVOR-TIMI 53	EXAMINE	TECOS
Trial Characteristics			
DPP-4 Inhibitor	Saxagliptin	Alogliptin	Sitagliptin
Number of Patients	16492	5380	14724
Enrolment period	Oct 2009 – Mar 2013	May 2010 – Dec 2011	Dec 2008 – Jul 2012
Median Follow Up (y)	2.1	1.5	3.0
Main Inclusion Criteria -A1C -Clinical	 6.5-12.0% Established CV disease or age>55/60 (male/female) and one other CV risk factor	 6.5-11.0% (7-11% if on insulin) ACS in previous 15-90d	 6.5-8.0% Established CV disease and ≥50 years old
Patient Comorbidities			
Hypertension	81%	83%	86%
Dyslipidemia	71%	n/r	77%
Current Smoker	13%	14%	11%
Prior MI	38%	88%**	43%
Prior PCI	27%	63%**	39%
Prior CABG	24%	13%**	25%
Heart Failure	13%	28%	18%
Atrial Fibrillation	7%	n/r	8% (incl AFlutter)
Stroke	13%	7%	17% (+4% TIA)
Peripheral Arterial Disease	12%	10%	17%
eGFR (mL/min/1.73 m^2)	73 (excluded dialysis)	71 (excluded dialysis)	75 (excluded <30)
Medications			
ASA	75%	91%	79%
Any Anti-platelet	81%	n/r (80% thienopyridine)	n/r (22% clopidogrel/ ticlopidine, 7% vit K antagonist)
Statin	78%	90%	80%
ACE Inhibitor/ARB	79% (total)	82% (total)	79%
Beta-Blocker	61%	82%	64%
Other antihypertensive agents	41%	22% CCB 37% diuretic	34% CCB 41% diuretic

*The three trials used virtually identical HF definitions: patients were required to be admitted to hospital or have an emergency department visit of more than 12h with clinical manifestations of heart failure, defined as at least one of new or worsening dyspnea, orthopnea, paroxysmal nocturnal dyspnea,

peripheral edema, bibasilar rales on pulmonary examination, jugular venous distention, new third heart sound, or radiographic evidence of heart failure; and receive at least one of intravenous treatment with a diuretic, inotrope, or vasodilator therapy, ultrafiltration or dialysis, or mechanical or surgical intervention (including heart transplant) specifically directed as treatment for their heart failure. The other smaller RCTs did not provide definitions, or specify whether the patients with HF required hospitalization or whether this outcome was subject to blinded adjudication.

** includes index event prior to enrolment

Abbreviations: ACE, angiotensin converting enzyme; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; AFlutter, atrial flutter; ASA, aspirin; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCB, calcium channel blocker; CV, cardiovascular; eGFR, estimated glomerular filtration rate; kg, kilogram (body weight); min, minute; MI, myocardial infarction; mL, milliliter; N, number of patients; no., number; n/r, not reported; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; vit, vitamin; y, years.

Table 3: Study Risk of Bias

First Author Year of Publication	Trial Registration Number (ClinTrials.gov)	Total Number of Patients Randomized	Number of Centres	Trial Duration (wks)	Blinded **	AC	ITT	No Early Stopping for Benefit	<5% Loss to Follow Up
Primary Cardiovascular Outcomes									
Scirica 2013 (SAVOR-TIMI 53)[4,5] (saxagliptin)	NCT01107886	16492	788	110*	Yes	Yes	Yes	Yes	Yes (0.9%)
White 2013 (EXAMINE)[6,7] (alogliptin)	NCT00968708	5380	898	76*	Yes	Yes	Yes	Yes	Yes (0.9%)
Green 2015 (TECOS)[8,25] (sitagliptin)	NCT00790205	14724	673	156*	Yes	Yes	Yes	Yes	Yes (0.4%)
				* median					
Alogliptin									
DeFronzo 2008[27]	NCT00286455	329	67	26	Yes	Yes	Yes	Yes	Yes (0.3%)
Nauck 2009[26]	NCT00286442	527	115	26	Yes	Yes	Yes	Yes	Yes (0%)
Pratley 2009[29]	NCT00286468	500	124	26	Yes	Yes	Yes	Yes	Yes (0%)
Pratley 2009[30]	NCT00286494	493	125	26	Yes	Yes	Yes	Yes	Yes (0%)
Rosenstock 2009[31]	NCT00286429	390	110	26	Yes	Yes	Yes	Yes	Yes (0%)

Rosenstock 2010[28]	NCT00395512	490	161	26	Yes	Yes	Yes	Yes	Yes (0%)
Pratley 2014[32]	NCT01023581	784	198	26	Yes	Yes	Yes	Yes	Yes (2.0%)
DeFronzo 2012[33]	NCT00328627	1554	327	26	Yes	Yes	Yes	Yes	Yes (0.1%)
Mita 2016[136]	UMIN000005311	341	11	104	No	Yes	Yes	Yes	No (5.6%)
Linagliptin									
Gomis 2011[34]	NCT00641043	389	43	24	Yes	Yes	Yes	Yes	Yes (0%)
Haak 2012[35]/Haak 2013[36]	NCT00798161/ NCT00915772	791/567	133/112	24/54	Yes	Yes	Yes	Yes	Yes (0%/0.2%)
Owens 2011[37]	NCT00602472	1058	100	24	Yes	Yes	Yes	Yes	Yes (0.3%)
Taskinen 2011[38]	NCT00601250	701	82	24	Yes	Yes	Yes	Yes	Yes (0.1%)
Thrasher 2014[39,127]	NCT01194830	226	93	24	Yes	Yes	Yes	Yes	Yes (0.0%)
Barnett 2013[40]	NCT01084005	241	33	24	Yes	Yes	Yes	Yes	Yes (0.0%)
Bajaj 2014[41]	NCT00996658	272	52	24	Yes	Yes	Yes	Yes	Yes (0.0%)
Del Prato 2011[42]	NCT00621140	503	66	24	Yes	Yes	Yes	Yes	Yes (0.0%)
McGill 2013[43]	NCT00800683	133	53	52	Yes	Yes	Yes	Yes	Yes (0.0%)
Yki-Jarvinen 2013[44]	NCT00954447	1261	167	52	Yes	Yes	Yes	Yes	Yes (0.0%)

ClinicalTrials.gov[48]	NCT01183013	936	132	84	Yes	Yes	Yes	Yes	Yes (0.0%)
Chen 2015[155]	NCT01214239	300	19	24	Yes	Yes	Yes	Yes	Yes (0.3%)
ClinicalTrials.gov[50]	NCT01215097	306	19	24	Yes	Yes	Yes	Yes	Yes (0.3%)
DeFronzo 2015[45]/ Lewin 2015[46]	NCT01422876	1404	211	24	Yes	Yes	Yes	Yes	Yes (3.0%)
ClinicalTrials.gov[47]	NCT01708902	730	56	24	Yes	Yes	Yes	Yes	Yes (0.0%)
Wu 2015[134]	n/r	57	1	24	Yes	Yes	Yes	Yes	Yes (3.5%)
ClinicalTrials.gov[133]	NCT01778049	708	114	24	Yes	Yes	Yes	Yes	n/r
Saxagliptin									
Pfützner 2011[51]/Jadzinsky 2009[52]	NCT00327015	1306	211	76	Yes	Yes	Yes	Yes	Yes (0.2%)
Barnett 2013[53]	NCT00757588	457	80	52	Yes	Yes	Yes	Yes	Yes (0.4%)
Chacra 2011[54]	NCT00313313	768	115	76	Yes	Yes	Yes	Yes	Yes (0.0%)
DeFronzo 2009[55]/Rosenstock 2013[56]	NCT00121667	743	154	24 (208 for mor-tality)	Yes	Yes	Yes	Yes	Yes (0.0%)
Frederich 2012[57]	NCT00316082	366	72	24	Yes	Yes	Yes	Yes	Yes (0.3%)
Hollander 2011[58]	NCT00295633	565	133	76	Yes	Yes	Yes	Yes	Yes (0.0%)

Nowicki 2011[59]	NCT00614939	170	75	52	Yes	Yes	Yes	Yes	Yes (0.0%)
Pan 2012[60]	NCT00698932	568	40	24	Yes	Yes	Yes	Yes	Yes (0.0%)
Rosenstock 2009[61]/Rosenstock 2013[56]	NCT00121641	401	135	24 (208 for mor-tality)	Yes	Yes	Yes	Yes	Yes (0.0%)
Moses 2014[62]	NCT01128153	257	35	24	Yes	Yes	Yes	Yes	Yes (0.0%)
Rosenstock 2015[63]	NCT01606007	534	139	24	Yes	Yes	Yes	Yes	Yes (0.0%)
Matthaei 2015[132]	NCT01619059	315	84	24	Yes	Yes	Yes	Yes	Yes (0.0%)
Sitagliptin									
Charbonnel 2006[64]	NCT00086515	701	100	24	Yes	Yes	Yes	Yes	Yes (0.0%)
Hermansen 2007[65]	NCT00106704	441	74	24	Yes	Yes	Yes	Yes	Yes (0.0%)
Henry 2014[66]	NCT00722371	1615	256	54	Yes	Yes	Yes	Yes	Yes (0.0%)
Raz 2008[67]	NCT00337610	190	24	30	Yes	Yes	Yes	Yes	Yes (0.0%)
Vilsbøll 2011[68]	NCT00395343	641	100	24	Yes	Yes	Yes	Yes	Yes (0.0%)
Wiiliams-Herman 2010[69]/Goldstein 2007[70]	NCT00103857	1091	140/117	104	Yes	Yes	Yes	Yes	Yes (0.0%)
Yoon 2012[71]/Yoon 2011[72]	NCT00397631/	520	60/28	54	Yes	Yes	Yes	Yes	Yes (0.0%)

	NCT01028391								
ClinicalTrials.gov[73]	NCT00918879	213	9	24	Yes	Yes	Yes	Yes	Yes (0.0%)
Yang 2011[74]	NCT00661362	570	40	24	Yes	Yes	Yes	Yes	Yes (0.0%)
ClinicalTrials.gov[75]	NCT00875394	68	1	24	No	n/r	n/r	n/r	n/r
Barzilai 2011[76]	NCT00305604	206	52	24	Yes	Yes	Yes	Yes	Yes (0.0%)
Yang 2012[77]	NCT00813995	395	17	24	Yes	Yes	Yes	Yes	Yes (0.0%)
Rosenstock 2006[78]	NCT00086502	353	71	24	Yes	Yes	Yes	Yes	Yes (0.0%)
Aschner 2006[79]	NCT00087516	741	111	24	Yes	Yes	Yes	Yes	Yes (0.0%)
Fonseca 2013[80]	NCT00885352	313	58	26	Yes	Yes	Yes	Yes	Yes (0.0%)
Olansky 2011[81]	NCT00482729	1250	209	44	Yes	Yes	Yes	Yes	Yes (0.3%)
ClinicalTrials.gov[82]	NCT00420511	21	1	44	Yes	Yes	Yes	Yes	Yes (0.0%)
Dobs 2013[83]	NCT00350779	278	41	54	Yes	Yes	Yes	Yes	No (5.8%)
Moses 2016[156]	NCT01076075	427	Multi	24	Yes	Yes	Yes	Yes	Yes (1.2%)
Lavalle-González 2013[85]	NCT01106677	1284	169	26	Yes	Yes	Yes	Yes	Yes (0.0%)
Mathieu 2015[86]	NCT01462266	660	Multi	24	Yes	Yes	Yes	Yes	Yes (0.3%)
Roden 2013[87]	NCT01177813/ NCT01289990	899	124	76	Yes	Yes	Yes	Yes	Yes (1.1%)

ClinicalTrials.gov[88]	NCT01177384	381	Multi	24	Yes	Yes	Yes	Yes	Yes (0.0%)
Skrivanek 2014[89]	NCT00734474	1202	99	26	Yes	Yes	Yes	Yes	Yes (0.0%)
ClinicalTrials.gov[90]	NCT00838903	1049	386	156	Yes	Yes	Yes	Yes	Yes (3.5%)
Ji 2016[157]	NCT01076088	744	Multi	24	Yes	Yes	Yes	Yes	Yes (0.1%)
ClinicalTrials.gov[92]	NCT01519674	582	60	24	Yes	Yes	Yes	Yes	Yes (1.2%)
ClinicalTrials.gov[93]	NCT01590771	498	Multi	24	Yes	Yes	Yes	Yes	Yes (0.2%)
ClinicalTrials.gov[94]	NCT01590797	467	28	24	Yes	Yes	Yes	Yes	Yes (0.0%)
ClinicalTrials.gov[95]	NCT01652729	366	60	28	Yes	Yes	Yes	Yes	Yes (0.3%)
Ishikawa 2014[96]	UMIN000006432	80	1	52	No	Uncl.	Yes	Yes	Yes (3.8%)
	UMIN Clinical Trials Registry								
Derosa 2012[97-99]	n/r	178	1	52	Yes	Yes	Yes	Yes	n/r
Derosa 2014[100]	n/r	205	Multi	104	Yes	Yes	Yes	Yes	n/r
Chien 2011[130]	n/r	97	1	24	No	Uncl.	Yes	Uncl.	Yes (0.0%)
Weinstock 2015[131]	NCT00734474	1098	111	26	Yes	Yes	Yes	Yes	Yes (0.0%)
Mita 2016[135]	UMIN000007396	282	12	104	No	Yes	Yes	Yes	Yes (2.8%)
ClinicalTrials.gov[128]	NCT01703221	414	Multi	24	Yes	Yes	Yes	Yes	Yes (0.5%)

Vildagliptin									
Bosi 2007[101]	NCT00099892	544	106	24	Yes	Yes	Yes	Yes	Yes (0.6%)
Bosi 2009[102]	NCT00382096/ NCT00468039	1179	>250	24	Yes	Yes	Yes	Yes	Yes (0.8%)
Fonseca 2007[103]	NCT00099931	296	68	24	Yes	Yes	Yes	Yes	Yes (0.0%)
VIVIDD 2014[104]	NCT00894868	254	94	52	Yes	Yes	Yes	Yes	Yes (0.4%)
Scherbaum 2008[105,106]	NCT00300287[105]/ NCT00101712[106]	306	69	52/ 104	Yes	Yes	Yes	Yes	Yes/No (0%/57%)
Strain 2013[107]	NCT01257451	278	45	24	Yes	Yes	Yes	Yes	Yes (0.0%)
Vollmer 2009[108]	NCT00494884	405	94	24	Yes	Yes	Yes	Yes	Yes (0.0%)
Garber 2007[109]	NCT00099853	463	123	24	Yes	Yes	Yes	Yes	Yes (0.0%)
Garber 2008[110]	NCT00099944	515	114	24	Yes	Yes	Yes	Yes	Yes (0.0%)
Yang 2015[111]	NCT01357252	279	18	24	Yes	Yes	Yes	Yes	Yes (0.0%)
Foley 2011[112]/Bunck 2012[113]	NCT00260156	59	1	52	Yes	Yes	Yes	Yes	Yes (0.0%)
Pan 2012[114]	NCT00822211	438	17	24	Yes	Yes	Yes	Yes	Yes (0.0%)
Lukashevich 2014[115]	NCT01233622	318	55	24	Yes	Yes	Yes	Yes	Yes (0.3%)

Macauley 2015[116]	NCT01356831	44	1	26	Yes	Yes	Yes	Yes	No (11.4%)
Ahren 2004[117]/Ahren 2005[118]	Pre-dated Registration	107	4	52	Yes	Yes	Yes	Yes	Yes (0.0%)
Goodman 2009[119]	n/r	370	67	24	Yes	Yes	Yes	Yes	Yes (0.0%)
Ito 2011[120]	n/r	60	1	24	No	Yes	Yes	Yes	No (11.7%)
Derosa 2012[121-123]	n/r	167	4	52	Yes	Yes	Yes	Yes	Yes (0.0%)
Zografou 2015[129]	n/r	64	1	26	No	Uncl.	Yes	Uncl.	n/r
Gemigliptin									
Yang 2013[124]	NCT01601990	182	14	24	Yes	Yes	Yes	Yes	Yes (4.2%)
Teneligliptin									
ClinicalTrials.gov[125]	NCT00971243	448	45	24	Yes	Yes	Yes	Yes	Yes (0.2%)
Anagliptin									
Yang 2015[126]	NCT01529528	109	25	24	Yes	Yes	Yes	Yes	Yes (0.9%)

** Patient, caregiver, and outcome assessor blinding for HF outcome.

Abbreviations : AC, allocation concealment; ITT, intention-to-treat analysis; multi, multi-center; n/r, not reported; uncl, unclear; wks, weeks.

Table 4: Comparison of current meta-analysis and previously published meta-analyses

Previously Published Meta-Analyses	Analysis Included Only RCTs in which randomized groups differ by DPP-4 inhibitor treatment to avoid the confounding effect of other medications	Statistically Compared HF Outcomes Between Different DPP-4 Inhibitors	Additional ≥24 week follow up DPP-4 Inhibitor vs Placebo RCTs/ Enrolled Patients With HF Events Included in the Current Meta-Analysis	Avoidance of Inadvertent Double Counting of Some Included RCTs	Inclusion of all* HF outcomes for EXAMINE Trial[7]	Inclusion of most recently published HF results for VIVIDD Trial[104]	Main Conclusions
Including TECOS							
Current Meta-Analysis	**Yes**	**Yes**	**(reference)**	**Yes**	**Yes**	**Yes**	**--13% increase in HF risk only statistically significant (P=0.03) if results of smaller RCTs added to large cardiovascular safety RCTs --differences between agents not statistically significant (interaction P=0.07-0.12)**
Li 2016[148]	No	No	10 RCTs/ 5,541 patients	Yes	No	Yes	--12% increase in HF risks¶ (P=0.05) pooling HF hospitalization outcomes from 5 RCTs only; no significant increase in HF for the remaining RCTs vs all comparators
Abbas 2016[146]	Yes†	No	29 RCTs/ 18,097 patients†	Yes	No	--‡	--non-significant 11% increase in HF risk (P=0.19) pooling only the 3 large cardiovascular safety RCTs but not including

							all HF outcomes for EXAMINE
Kongwat-charapong 2016[147]	No	No	4 RCTs/ 1,639 patients	Yes	Yes	No	--non-significant 11% increase in HF risk (P=0.06) vs all comparators --highlighted increase in HF for saxagliptin but differences not statistically compared to other agents
Pre-TECOS							
Monami 2014[149]	No	No	8 RCTs/ 17,463 patients	No (double counted NCT01028391[71] which was an extension of NCT00397631[72])	No	--‡	--19% increase in HF odds (P=0.015) vs all comparators --highlighted increase in HF for saxagliptin but differences not statistically compared to other agents
Wu 2014[151]	No§	No	15 RCTs/ 19,339 patients	No (double counted two publications for NCT00327015[51,52])	No	No	--16% increase in HF risk (P=0.04) vs all comparators and 17% increase (P=0.03) vs only placebo comparators
Savarse 2015[150]	No	No	9 RCTs/ 18,055 patients	No (double counted NCT00915772[36] which was an extension of NCT00798161[35])	No	No	--16% increase in HF risk (P=0.03) vs all comparators pooling long-term follow up RCTs but no increase pooling short-term follow up RCTs

*Some of the previously published meta-analyses[146,148-151] included only HF hospitalizations that were counted in the analysis of the composite endpoint reported in the abstract of the follow-up publication for EXAMINE focusing on HF outcomes,[7] instead of all HF hospitalizations reported in the main body of this publication. Including all HF hospitalization events results in a higher HF hospitalization risk for alogliptin for this RCT (RR 1.18 vs. RR 1.07).

†Abbas 2016[146] only included the three large cardiovascular RCTs (SAVOR-TIMI 53,[4,5] EXAMINE[6,7] and TECOS[8]).

‡VIVIDD[104] was not included in Monami 2014[149]and Abbas 2016[146].

§For Wu 2014,[151] comparison to placebo trials was included as a secondary analysis.

¶Li 2016[148] actually reported 13% increase in odds using Peto odds ratios (P=0.05) which corresponds to a 12% increase in risk using risk ratios (P=0.05).

FIGURE LEGENDS

Figure 1: Search Strategy and Trial Flow

Flow chart for the systematic review and meta-analysis showing the number of studies retained and number of studies excluded with reason for exclusion at each stage of the study selection process.

Figure 2: Forest Plot for Heart Failure: Large vs. Small Trials

Individual and pooled risk ratios (RR) with 95% confidence intervals (CI) for randomized controlled trials (RCTs) with a primary outcome that included cardiovascular outcomes and reported the number of patients in each treatment group that were hospitalized for HF as an adjudicated primary or secondary outcome, as well as smaller RCTs reporting at least one patient with HF for which outcomes were not necessarily adjudicated and patients not necessarily hospitalized. The pooled RRs with 95% CI were calculated using random-effects models. Weight refers to the contribution of each study to the overall pooled estimate of treatment effect. Each square and horizontal line denotes the point estimate and 95% CI for each trial's RR. The diamonds signify the pooled RR; the diamond's centre denotes the point estimate and width denotes the 95% CI.

Figure 3: Forest Plot for Heart Failure by DPP-4 Inhibitor

Individual and pooled risk ratios (RR) with 95% confidence intervals (CI) for larger and smaller randomized controlled trials (RCTs) by DPP-4 inhibitor. Interaction p-values comparing RRs between pairs of subgroups of RCTs using different DPP-4 inhibitors were all non-significant. For the most extreme difference between saxagliptin RCTs and sitagliptin RCTs, interaction P=0.13 (interaction P=0.07 comparing RR for only SAVOR-TIMI 53 vs. TECOS). The pooled RRs with 95% CI were calculated using random-effects models. Interaction p-values were calculated using Z tests. Weight refers to the

contribution of each study to the overall pooled estimate of treatment effect. Each square and horizontal line denotes the point estimate and 95% CI for each trial's RR. The diamonds signify the pooled RR; the diamond's centre denotes the point estimate and width denotes the 95% CI.

Figure 4: Forest Plot for Heart Failure Requiring Hospitalization by Previous History of Heart Failure

Individual and pooled risk ratios (RR) with 95% confidence intervals (CI) for the outcome of heart failure requiring hospitalization in subgroups of patients with vs without previous heart failure in SAVOR TIMI-53 and EXAMINE, the only RCTs that provided this data. Average rates of HF requiring hospitalization were 9.9% ([124+107+63+65]/[1056+1049+771+762]=359/3638) in patients with vs 1.9% ([165+121+43+24]/[7224+7163+1930+1917]=353/18234) in patients without a prior history of HF. In this analysis, the heterogeneity in the overall analysis (I^2=43%) is reduced (I^2=0%) within each subgroup. The pooled RRs with 95% CI were calculated using random-effects models. Interaction p-values were calculated using Z tests. Weight refers to the contribution of each study to the overall pooled estimate of treatment effect. Each square and horizontal line denotes the point estimate and 95% CI for each trial's RR. The diamonds signify the pooled RR; the diamond's centre denotes the point estimate and width denotes the 95% CI.

ONLINE APPENDIX

More Detailed Methods

Data Analysis

Analyses were performed using Review Manager (Cochrane Collaboration, Oxford, UK). Review Manager includes continuity corrections of 0.5 in RCTs to allow inclusion of RCTs with no events in one treatment arm. Traditionally, RCTs with no events in either the intervention or control groups are excluded in binary outcome meta-analysis using RR; however, as a sensitivity analysis, continuity corrections were also used in RCTs with no events in either treatment arm to allow their inclusion as previously described.[158] These latter calculations were carried out using standard equations in Microsoft Excel and continuity corrections based on the reciprocal of the group (i.e., treatment or control) opposite the zero cell as proposed by Sweeting and colleagues[159] rather than 0.5 to minimize bias. (A recently published statistical simulation study suggests other approaches to inclusion of such studies.[160]) Random effects models[161] which incorporate between-trial heterogeneity and give wider and more conservative confidence intervals (CI) when heterogeneity is present were used for all analyses. Statistical heterogeneity among trials was assessed using the I^2 statistic, defined as the percentage of total variability across studies attributable to heterogeneity rather than chance.[162] Relative risks (RR) were used to pool outcomes. Individual trial and summary results are reported with 95% CIs. *A priori*, Z-tests of interaction were used to calculate interaction p-values comparing RRs between the larger trials with cardiovascular primary outcomes to the smaller trials, and between pairs of subgroups of RCTs using different DPP-4 inhibitors to determine whether treatment effects differed between agents; and *post hoc* between subgroups of patients with and without a previous history of HF. To assess for publication bias, a funnel plot comparing effect measure for the primary outcome of HF requiring

hospitalization to study precision was examined for evidence of asymmetry and this was tested statistically using both the Egger[163] regression and Begg and Mazumdar[164] rank correlation tests as implemented in Comprehensive Meta Analysis, Version 3.3.070 (available at www.Meta-Analysis.com).

Supplementary Results

Visual inspection of the funnel plot showed no evidence of asymmetry (Supplementary Figure 1) and there was no statistical evidence for publication bias (P=0.44 using the Egger regression test and P=0.59 using the Begg and Mazumdar rank correlation test).

ClinicalTrials.gov was also systematically searched using the same search strategy but limited to "Interventional" "Recruiting" (n=147) and "Active, not Recruiting" (n=35) studies. The search identified three ongoing RCTs with primary cardiovascular outcomes of which one is comparing a DPP-4 inhibitor to active control (CAROLINA, linagliptin vs. glimepiride, n=6115, estimated completion March 2019; ClinicalTrials.gov, NCT01243424), and two that are comparing DPP-4 inhibitors to placebo: 1) CARMELINA (linagliptin vs. placebo, n=8,300, targeted completion January 2018; ClinicalTrials.gov, NCT01897532) and 2) MK-3102-018 (omarigliptin vs. placebo, n=4,202, stopped in May 2016 but results currently unpublished; ClinicalTrials.gov, NCT01703208). Assuming baseline HF rates requiring hospitalization in the control group similar to the average of the large RCTs of 3.1% (2.8% for SAVOR-TIMI 53, 3.3% for EXAMINE, 3.1 % for TECOS), then an average RR of as little as 1.03 for both CARMELINA and MK-3102-018 would make the relative risk for HF requiring hospitalization statistically significant pooling only data from the large RCTs with primary cardiovascular outcomes (Supplementary Figure 2A, which assumes RR=1.03 for both CARMELINA and MK-3102-018). These hypothetical results are similar even if one uses baseline HF rates requiring hospitalization half or double the average rate of 3.1% as long as the RR of the two ongoing RCTs are similar. Alternatively, if the RRs are different, for example if the smaller RCT (MK-3102-018) has a RR of 0.9, then the larger RCT (CARMELINA) would have to have a RR at least as high as EXAMINE (RR=1.18), for the pooled random-effects RR for HF requiring hospitalization of all five cardiovascular safety RCTs to be statistically significant (Supplementary Figure 2B, which assumes RR 0.90 for MK-3102-018 and RR 1.18 for CARMELINA). (This is due to the effects of

heterogeneity: similar trial results for the ongoing RCTs lower overall heterogeneity and narrow confidence intervals when pooling the results of all five RCTs, while non-similar trial results increase heterogeneity leading to wider confidence intervals.) In any case, these calculations illustrate that the results from the two ongoing DPP-4 inhibitor vs. placebo cardiovascular-safety RCTs will be important as they could have an impact on the pooled risk estimates for HF among the cardiovascular safety RCTs.

Supplementary Table 1: Search Strategies

I) Medline Search Strategy:
Database: Ovid MEDLINE(R) <1946 to August Week 2 2016>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <August 19, 2016>
Search Strategy:
1 Dipeptidyl-Peptidase 4 Inhibitors.mp. or exp Dipeptidyl-Peptidase IV Inhibitors/ (3124)
2 sitagliptin.mp. (1572)
3 saxagliptin.mp. (451)
4 vildagliptin.mp. (757)
5 linagliptin.mp. (399)
6 alogliptin.mp. (310)
7 gemigliptin.mp. (24)
8 teneligliptin.mp. (51)
9 anagliptin.mp. (27)
10 omarigliptin.mp. (10)
11 or/1-10 (4081)
12 limit 11 to (clinical trial, phase iii or clinical trial, phase iv or clinical trial or randomized controlled trial) (614)

II) Supplementary Embase Search Strategy:
Database: Embase <1980 to 2016 Week 34> <August 19,2016>
Search Strategy:
1 Dipeptidyl-Peptidase 4 Inhibitors.mp. or exp Dipeptidyl-Peptidase IV Inhibitors/ (11779)
2 sitagliptin.mp. (5883)
3 saxagliptin.mp. (2104)
4 vildagliptin.mp. (2916)
5 linagliptin.mp. (1452)
6 alogliptin.mp. (1159)
7 gemigliptin.mp. (79)
8 teneligliptin.mp. (120)
9 anagliptin.mp. (97)
10 omarigliptin.mp. (36)
11 or/1-10 (11916)
12 limit 11 to (clinical trial or randomized controlled trial or phase 3 clinical trial or phase 4 clinical trial) (2104)
13 limit 12 to exclude medline journals (349)

III) ClinicalTrials.gov Search Strategy: <August 22, 2016>
"dipeptidyl peptidase 4 inhibitors" OR "alogliptin" OR “SYR-322” OR "linagliptin" OR “BI-1356” OR "saxagliptin" OR “BMS-477118” OR "sitagliptin” OR “MK-0431” OR "vildagliptin" OR “LAF237” OR “gemigliptin” OR “LC15-0444” OR “teneligliptin” OR “”MP-513” OR “anagliptin” OR “CWP-0403” OR “omarigliptin” OR “MK-3102” OR “gosogliptin” OR “PF-00734200” | Interventional Studies | Completed | (528)

SUPPLEMENTARY FIGURE LEGENDS

Supplementary Figure 1: Funnel Plot

Funnel plot comparing the effect measure, relative risk (RR), for the heart failure outcome for the large RCTs with primary cardiovascular outcomes (SAVOR-TIMI 53, EXAMINE, and TECOS) and the 28 smaller RCTs with at least one patient with heart failure on the x-axis, with its precision, expressed as the standard error of the natural logarithm of RR, SE(log[RR]), on the y-axis to assess for asymmetry. There was no statistical evidence of publication bias (P=0.44 using the Egger regression test and P=0.59 using the Begg and Mazumdar rank correlation test).

Abbreviations: RCTs, randomized controlled trials; RR, relative risk; SE, standard error.

Supplementary Figure 2: Forest Plot for Heart Failure of Large Randomized Controlled Trials with Primary Cardiovascular Outcomes: Potential Impact of Ongoing Trials

Individual and pooled risk ratios (RR) with 95% confidence intervals (CI) for completed and ongoing randomized controlled trials (RCTs) with a primary outcome that included cardiovascular outcomes and reported the number of patients in each treatment group that were hospitalized for heart failure as an adjudicated primary or secondary outcome. For the ongoing trials, CARMELINA and MK-3102-018, baseline event rates were assumed similar to SAVOR-TIMI 53, EXAMINE, and TECOS (3.1%). Panel A shows that if the average RRs for the ongoing RCTs are identical, RRs of as little as 1.03 results in a statistically significant increased heart failure rate. Panel B shows that if the RRs for the ongoing RCTs are different, then for a RR of 0.90 for MK-3102-018, the RR for CARMELINA needs to be at least 1.18 to produce a significantly increased pooled heart failure rate for all five cardiovascular safety RCTs combined. The pooled RRs with 95% CI were calculated using random-effects models. Weight refers to the contribution of each study to the overall pooled estimate of treatment effect. Each square and

horizontal line denotes the point estimate and 95% CI for each trial's RR. The diamonds signify the pooled RR; the diamond's centre denotes the point estimate and width denotes the 95% CI.

FIGURE 1

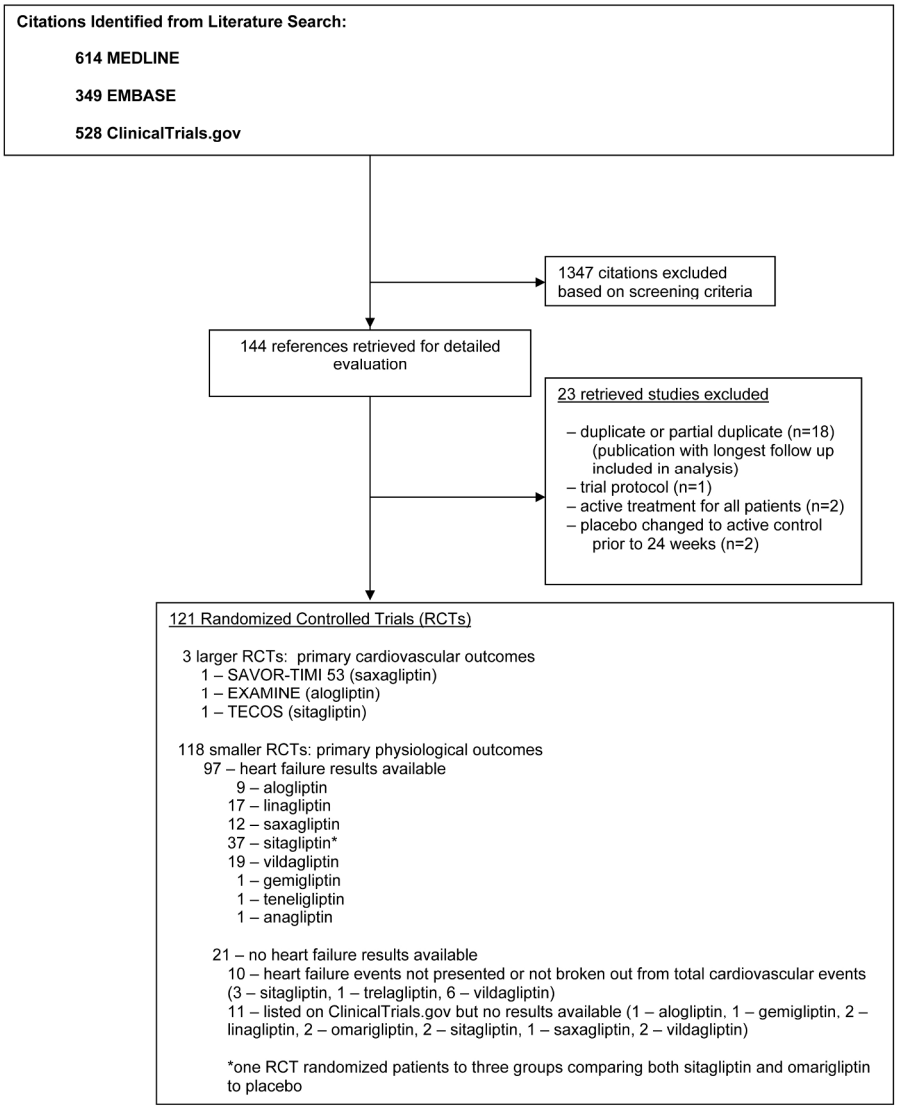

Figure 1: Search Strategy and Trial Flow
Flow chart for the systematic review and meta-analysis showing the number of studies retained and number of studies excluded with reason for exclusion at each stage of the study selection process.

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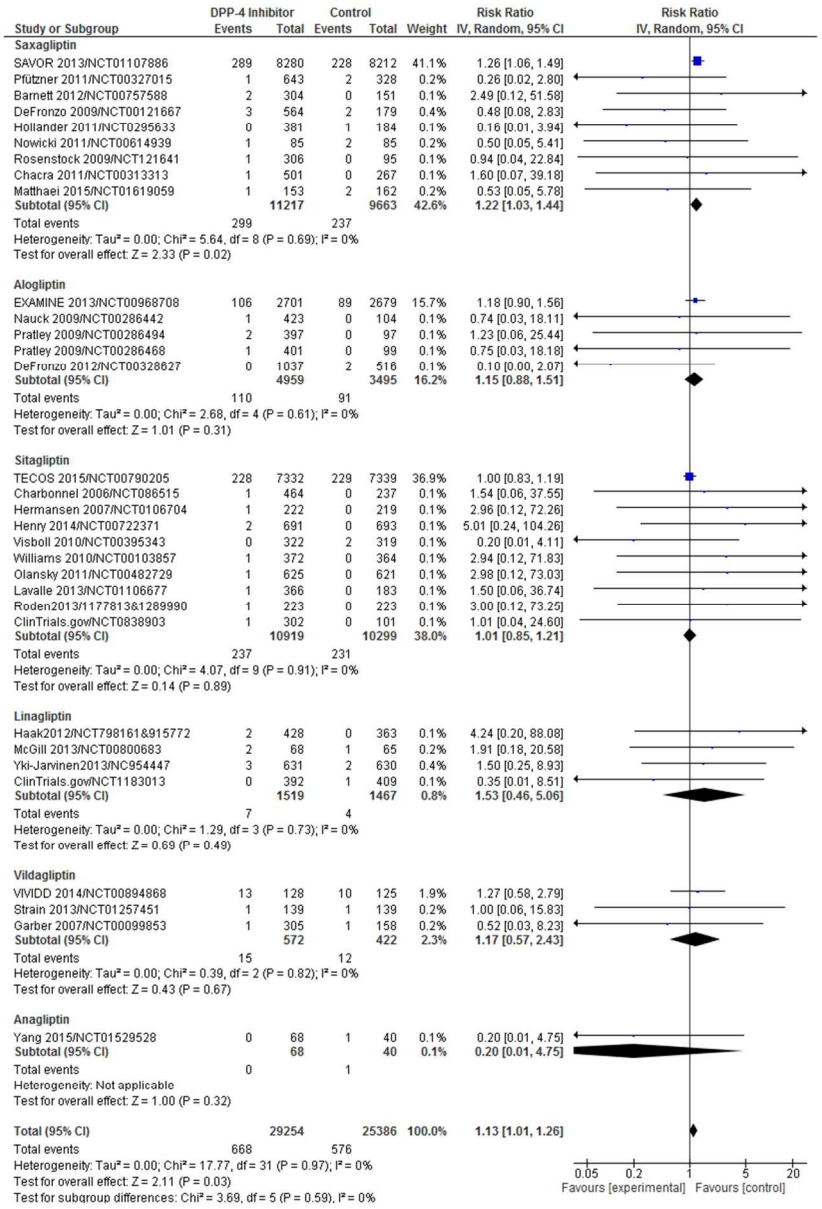

Figure 2: Forest Plot for Heart Failure: Large vs. Small Trials

Individual and pooled risk ratios (RR) with 95% confidence intervals (CI) for randomized controlled trials (RCTs) with a primary outcome that included cardiovascular outcomes and reported the number of patients in each treatment group that were hospitalized for HF as an adjudicated primary or secondary outcome, as well as smaller RCTs reporting at least one patient with HF for which outcomes were not necessarily adjudicated and patients not necessarily hospitalized. The pooled RRs with 95% CI were calculated using random-effects models. Weight refers to the contribution of each study to the overall pooled estimate of treatment effect. Each square and horizontal line denotes the point estimate and 95% CI for each trial's RR. The diamonds signify the pooled RR; the diamond's centre denotes the point estimate and width denotes the 95% CI.

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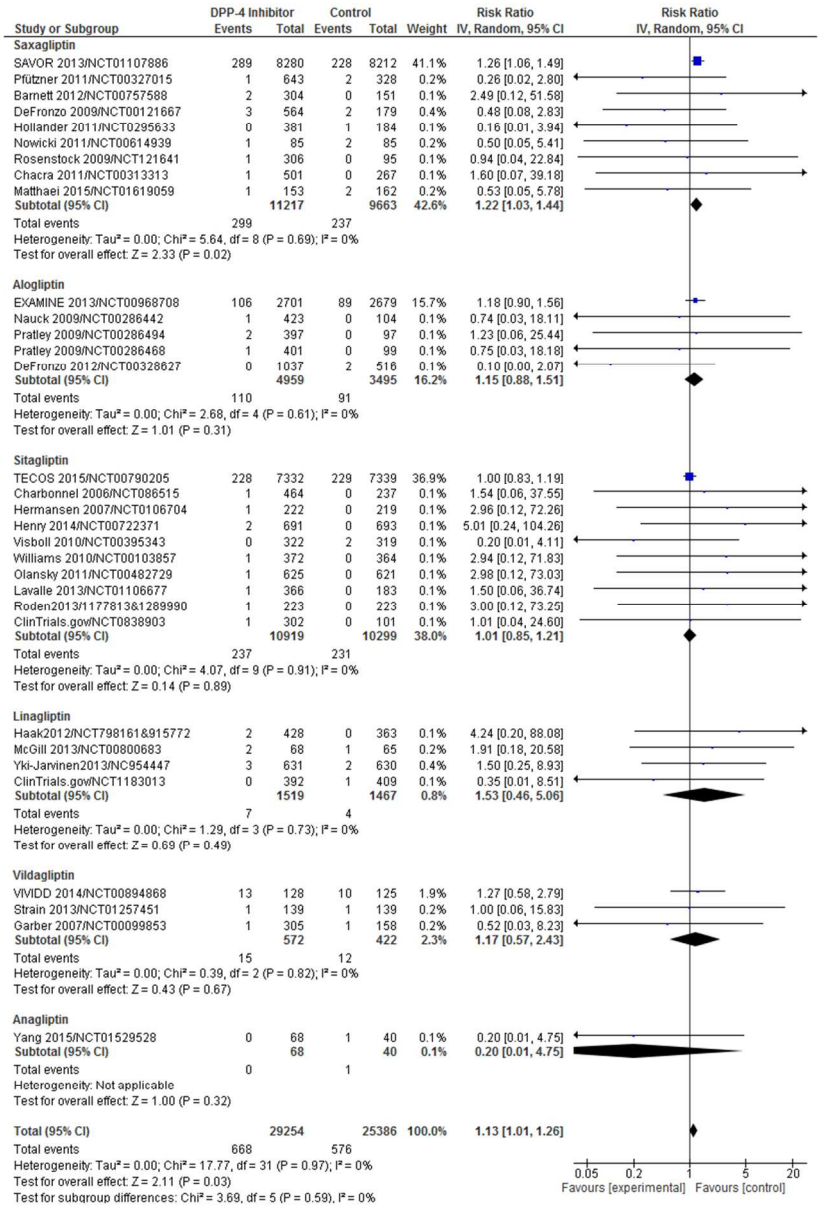

Figure 3: Forest Plot for Heart Failure by DPP-4 Inhibitor

Individual and pooled risk ratios (RR) with 95% confidence intervals (CI) for larger and smaller randomized controlled trials (RCTs) by DPP-4 inhibitor. Interaction p-values comparing RRs between pairs of subgroups of RCTs using different DPP-4 inhibitors were all non-significant. For the most extreme difference between saxagliptin RCTs and sitagliptin RCTs, interaction P=0.13 (interaction P=0.07 comparing RR for only SAVOR-TIMI 53 vs. TECOS). The pooled RRs with 95% CI were calculated using random-effects models. Interaction p-values were calculated using Z tests. Weight refers to the contribution of each study to the overall pooled estimate of treatment effect. Each square and horizontal line denotes the point estimate and 95% CI for each trial's RR. The diamonds signify the pooled RR; the diamond's centre denotes the point estimate and width denotes the 95% CI.

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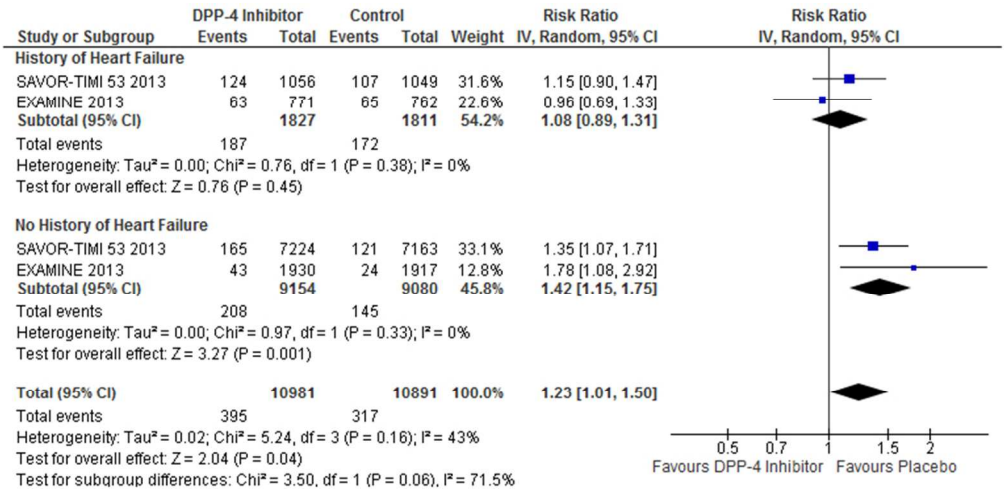

Figure 4: Forest Plot for Heart Failure Requiring Hospitalization by Previous History of Heart Failure
Individual and pooled risk ratios (RR) with 95% confidence intervals (CI) for the outcome of heart failure requiring hospitalization in subgroups of patients with vs without previous heart failure in SAVOR TIMI-53 and EXAMINE, the only RCTs that provided this data. Average rates of HF requiring hospitalization were 9.9% ([124+107+63+65]/[1056+1049+771+762]=359/3638) in patients with vs 1.9% ([165+121+43+24]/[7224+7163+1930+1917]=353/18234) in patients without a prior history of HF. In this analysis, the heterogeneity in the overall analysis (I2=43%) is reduced (I2=0%) within each subgroup. The pooled RRs with 95% CI were calculated using random-effects models. Interaction p-values were calculated using Z tests. Weight refers to the contribution of each study to the overall pooled estimate of treatment effect. Each square and horizontal line denotes the point estimate and 95% CI for each trial's RR. The diamonds signify the pooled RR; the diamond's centre denotes the point estimate and width denotes the 95% CI.

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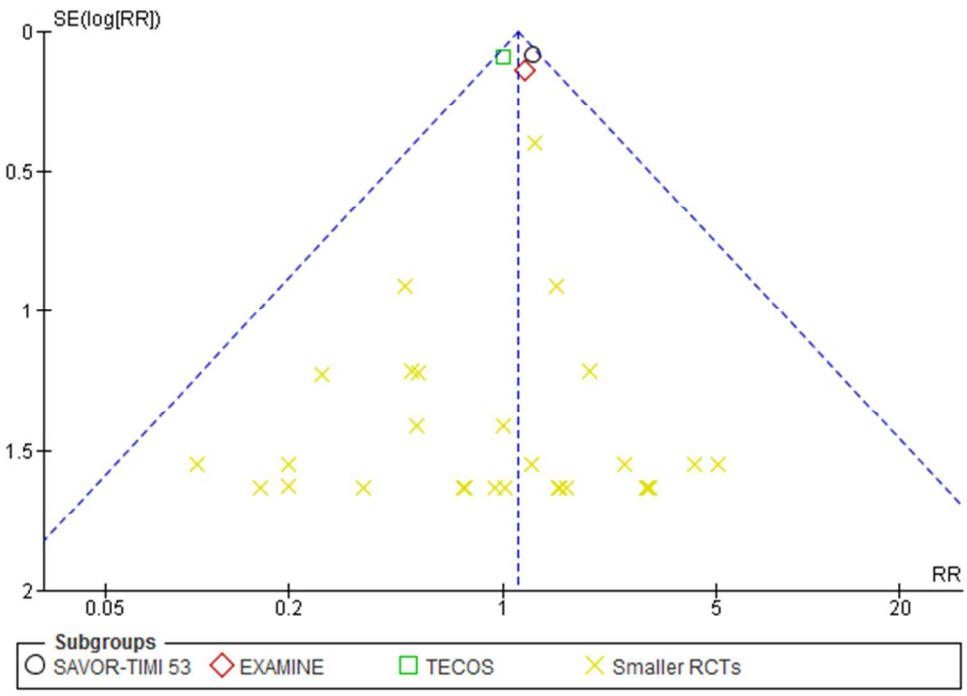

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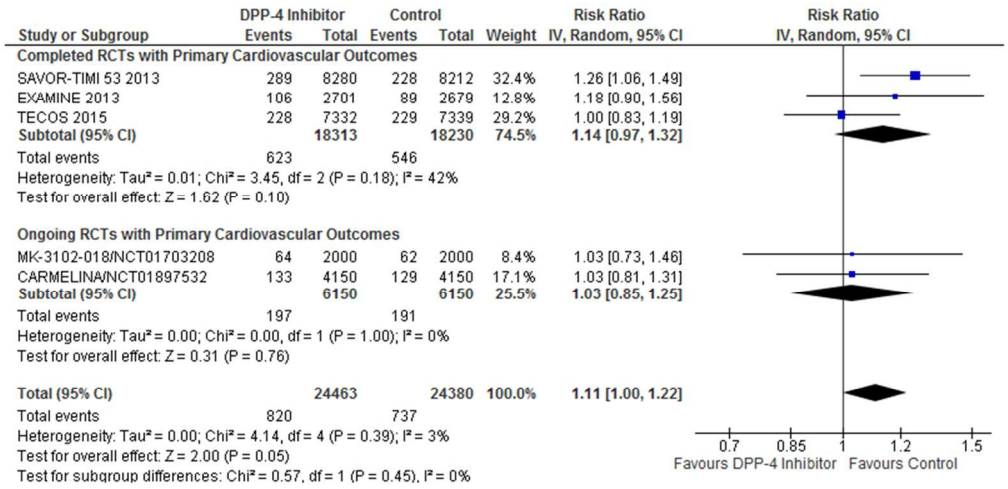

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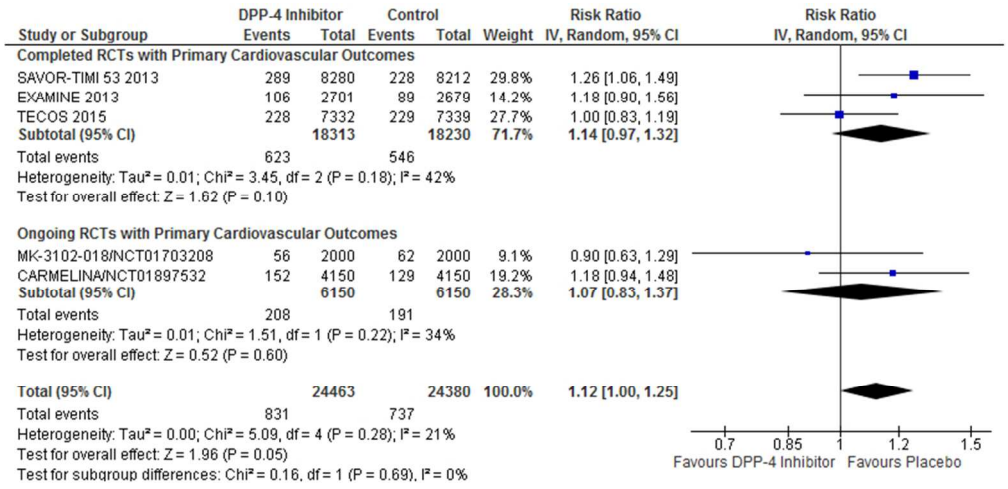

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7, Fig 1, Supp Table 1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Figure 1, Supp Table 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Supp

PRISMA 2009 Checklist

			p.55
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Supp p.55

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Supp p.55
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Supp p. 55
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1, Supp Table 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-9 Tables 1-2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9, Table 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-11, Figs 2-3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-11, Figs 2-3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supp p.56, Supp Fig 1
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-11, Figs 2-4
DISCUSSION			

PRISMA 2009 Checklist

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13-14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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