Original Article

Heart Failure Hospitalization with DPP-4 Inhibitors: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Abstract

Background: Heart failure hospitalization (hHF) with dipeptyl-dipeptidase-4 inhibitors (DPP-4Is) remains at the center stage since the publication of Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction (SAVOR-TIMI) in 2013 showing significant increase with saxagliptin, compared to placebo. This outcome led to additional label of hHF to both saxagliptin and alogliptin in April 2016 and eventual labelling of hHF to all the four approved DPP-4Is in United States in August 2017, by US Food Drug Administration. To note, neither Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS), nor Cardiovascular and Renal Microvascular Outcome Study with Linagliptin (CARMELINA), showed any signals of hHF with these two agents. These developments have seriously generated an uncertainty among clinicians with regards to hHF effect of DPP-4Is in type 2 diabetic patients with high risk of cardiovascular (CV) disease. **Aims and Objectives:** We systematically searched the database of PubMed, Embase, Cochrane Central library, ClinicalTrials.gov, and International conference presentation from the inception up to October 25, 2018 using MeSH and specific key words. We retrieved all those studies that explicitly looked for hHF as a prespecified end point and were conducted for ≥52 weeks. Subsequently, we conducted the meta-analysis using comprehensive meta-analysis software Version 3, using different sensitivity analysis to study the effect of DPP-4Is on hHF in both dedicated CV outcome trials as well as randomized controlled trials. **Results:** The meta-analysis of four exclusive dedicated CV outcome trials ($N = 43,522$) did not find significant increase in hHF with DPP-4 inhibitors (Fixed model Relative Risk [RR] 1.06; 95% Confidence Interval [CI], 0.96-1.17; $P = 0.25$; I^2: 53.95%, tau^2: 0.012, $P = 0.089$). Meta-analysis of all randomized controlled trials that explicitly looked for hHF for ≥52 weeks ($N = 48,199$) also did not show any significant increase in hHF (fixed model peto odds ratio 1.05; 95% CI 0.95–1.15, $P = 0.36$; I^2: 43.74%, tau^2: 0.016, $P = 0.10$). **Conclusions:** This meta-analysis suggests no significant increase in hHF with DPP-4 inhibitors, although a nonsignificant heterogeneity across the trials might limit this observation.

Keywords: Cardiovascular outcomes, DPP-4 inhibitors, gliptins, heart failure, heart failure hospitalization

Introduction

One of the uncertainties in pharmacotherapy is treating patients of type 2 diabetes with heart failure (HF). This aspect was further complicated due to increase in heart failure hospitalization (hHF) observed with some of dipeptyl-dipeptidase-4 inhibitors (DPP-4Is) and the subsequent blanket labelling of hHF in August 2017 to the entire class of DPP-4Is approved by United States Food Drug Administration (USFDA).

The fall out started after rosiglitazone controversy in 2007 and subsequent mandatory cardiovascular safety outcome trials (CVOT) of antidiabetic drugs issued in 2008 at the behest of USFDA and later on by European Medicine Agency (EMA).[1,2] This directive resulted in a boom of cardiovascular outcomes trials, and DPP-4Is were the first to get off in the block. The first two DPP-4Is trial that was presented and published was SAVOR-TIMI 53 with saxagliptin (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction), and EXAMINE by alogliptin (Examination of Cardiovascular Outcomes with Alogliptin in Acute coronary syndrome).[3,4] In both the trials conducted in diabetic patients with established cardiovascular (CV) disease or high CV risk, the safety of

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saxagliptin and alogliptin was clearly established. However, surprisingly the SAVOR-TIMI raised the issue of hHF in saxagliptin arm compared to placebo (Hazard Ratio [HR] 1.27; 95% Confidence Interval [CI], 1.07-1.51; $P = 0.007$).[3] This was surely an unexpected outcome, since there were no such previous signals indicative of the same through either experimental or across the phase 2–3 developmental program, conducted with saxagliptin. Curiously, at the same time other CVOT with alogliptin in EXAMINE also raised a similar trend of hHF which was not statistically significant (HR 1.19; 95% CI, 0.89–1.58; $P = 0.24$), although in a subgroup analysis there was a significant increase in hHF in patients without base line HF (HR 1.76; 95% CI, 1.07–2.90; $P = 0.026$).[4,5] Perhaps, this led USFDA to put an additional label of hHF with both the saxagliptin and alogliptin in April 2016, which suggested avoiding both of these drugs in patients with established CV and or chronic kidney disease.[6] Since then, entire medical fraternity eagerly waited for the result of the third CVOT being conducted with sitagliptin in Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS). Sitagliptin did not show any signals of hHF risk (HR 1.00; 95% CI 0.83–1.20; $P = 0.98$) irrespective of the type of statistical analysis used and thus TECOS put some reassurance on the ongoing controversies of hHF with DPP-4Is.[7] Intriguingly, 2016 scientific statement by American Heart Association and 2016 European Society of Cardiology HF guidelines both warned about hHF with the entire class of DPP-4Is, despite knowing well that there were no signals of hHF with sitagliptin in TECOS published in 2015.[8,9] This move was criticized by a group of authors in Lancet.[10] Even more surprising stand came from USFDA when they put the label of hHF with sitagliptin (TECOS data available) as well as linagliptin (CARMELINA [Renal Microvascular Outcome Study with Linagliptin in Patients With Type 2 Diabetes Mellitus], results not available) in August 2017 alongside of saxagliptin and alogliptin.[11]

Meanwhile, a truncated data of omarigliptin CV outcome trial (OMNEON) from Japan did not find any signals of hHF (HR 0.60; 95% CI 0.35–1.05; *P*-not reported) with omarigliptin, compared to placebo.[12] The only HF trial with DPP-4 inhibitors that is conducted till date is with vildagliptin in VIVIDD (Effects of Vildagliptin on Ventricular Function in Patients with Type 2 Diabetes Mellitus and Heart Failure). VIVIDD did not find any significant difference in left ventricular ejection fraction (LVEF) in vildagliptin arm, compared to placebo (Δ LVEF 0.62%; 95% CI 2.21–3.44; $P = 0.67$) over 1 year as measured by echocardiography, thereby suggestive of no detrimental effect on HF. Although, there was a significant increase in left ventricular end-diastolic volume in vildagliptin arm (Δ 17.1 mL, 95% CI, 4.6–29.5; $P = 0.007$) compared to placebo in VIVIDD.[13] Finally, the fourth and the last CVOT of the DPP-4I class comparing linagliptin to placebo in CARMELINA was very recently presented at EASD 2018 and linagliptin was not found to be associated with any increase in hHF (HR 0.90; 95% CI 0.74–1.08; $P = 0.26$).[14]

Materials and Methods

We systematically searched the database of Medline (via PubMed), Embase (via OvidSP), Cochrane Central library (Trials only), ClinicalTrials.gov, and International conference presentation since inception up to October 25, 2018 with a prespecified inclusion criteria using MeSH and free text terms related to our research. The inclusion criteria for this study include both randomized and observational trials that explicitly looked for hHF for ≥52 weeks. We included only studies that reported hospitalization due to HF. Although we have reported the studies which looked for incidental HF in this article but this have been excluded from the meta-analysis. While both hospitalization due to heart failure (hHF) and incidental HF events sound similar, inclusion of former is clinically meaningful for both clinicians, patients, payers, and society, while the latter could be subclinical and might not be diagnosed many a times, and thus excluded in this meta-analysis. Nevertheless, with the extensive review of literature, we found only seven studies that fulfilled our inclusion criteria (studies that were conducted for ≥52 weeks and explicitly reported hHF with DPP-4Is) as summarized in Supplementary Figure 1 and Table 1.[3,4,7,12-15]

Subsequently, we conducted two meta-analysis using different sensitivity analysis on effect measures (risk ratio versus odds ratio), pooling methods (Peto versus Mantel–Hanszel method), heterogeneity analysis (fixed versus random model), using comprehensive meta-analysis software Version 3. The first meta-analysis included only four dedicated CV outcome trials using risk ratio and log risk ratio, considering that the number of events for hHF was considerably higher in these studies.

Table 1: Trials that reported hHF with DPP-4 inhibitors conducted for ≥52 weeks

Trial eponyms/ Authors	DPP-4 inhibitors		Control		Median duration (weeks)
	Type	Events/*n*	Type	Events/*n*	
SAVOR-TIMI	Saxagliptin	289/8280	Placebo	228/8212	109
EXAMINE	Alogliptin	85/2701	Placebo	79/2679	78
TECOS	Sitagliptin	228/7332	Placebo	229/7339	156
CARMELINA	Linagliptin	209/3494	Placebo	226/3485	115
OMNEON	Omarigliptin	20/2092	Placebo	33/2100	96
VIVIDD	Vildagliptin	13/128	Placebo	10/124	52 (EOT)
Laakso *et al*.	Linagliptin	7/113	Placebo/Glimepiride	6/120	52 (EOT)

hHF: Hospitalization due to heart failure, EOT: End of trial

To our knowledge, this would be the first meta-analysis to include all the four dedicated CVOTs. In addition, we also conducted the meta-analysis on the effect of DPP-4Is on hHF seen across all the randomized control trials (RCTs). In the second meta-analysis we used Peto odds ratio, considering the smaller number of events in some of the RCTs.

Results and Conclusions

The meta-analysis of four dedicated CV outcome trials (N = 43,522; I^2:53.95%, tau^2:0.012, P = 0.089) did not find significant increase in hHF [Figure 1] with DPP-4 inhibitors (fixed model RR 1.06; 95% CI, 0.96–1.17; P = 0.25/random model RR 1.06; 95% CI, 0.91–1.22; P = 0.48). Meta-analysis of all RCTs [Figure 2] that explicitly looked for hHF for ≥52 weeks (N = 48,199; I^2:43.74%, tau^2:0.016, P = 0.10) also did not show any significant increase in hHF (fixed model Peto odd ratio 1.05; 95% CI 0.95–1.15, P = 0.36 and random model Peto odds ratio 1.03, 95% CI 0.88–1.20; P = 0.72).

This meta-analysis suggests that there is no significant increase in hHF with DPP-4 inhibitors, although a nonsignificant heterogeneity across the trials might limit this observation.

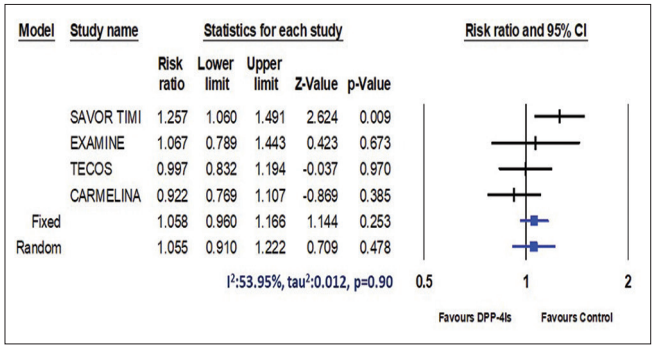

Figure 1: Meta-analysis of hHF with DPP-4Is in dedicated CVOTs

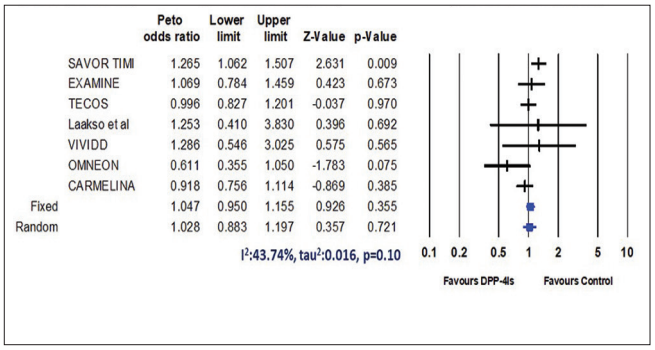

Figure 2: Meta-analysis pf hHF with DPP-4Is in RCTs

Table 2: Observational studies on hHF/HF with DPP-4Is versus active comparators

Author, year	Study drug (country)	Compared with	*n*	Outcome	HR/OR	95% CI	*P*
Wang *et al*., 2014	Sita (Taiwan)	Active	16,576	hHF	1.21	1.04-1.42	0.017
Ou *et al*., 2015	DPP-4Is (Taiwan)	SU	20,178	hHF	0.78	0.57-1.06	NS
Seong *et al*., 2015	DPP-4Is (Korea)	SU	328,283	HF	0.93	0.62-1.41	NS
Fadini *et al*., 2015	DPP-4Is (Italy)	SU	110,757	hHF	0.78	0.62-0.97	0.026
Eurich *et al*., 2016	Sita (US)	Active	5027	HF	0.75	0.38-1.46	0.40
Chang *et al*., 2016	Sita (Taiwan)	Acarbose	290,130	hHF	1.03	0.98-1.08	NS
Toh *et al*., 2016	Sita (US)	SU	642,529	hHF	0.86	0.77-0.95	NA
Toh *et al*., 2016	Saxa (US)	SU	510,904	hHF	0.69	0.54-0.87	NA
Ekstrom *et al*., 2016	DPP-4Is (Sweden)	SU	10,923	HF	0.54	0.38-0.76	<0.05
Kannan *et al*., 2016	DPP-4Is (US)	SU	10,906	HF	1.10	1.04-1.17	0.001
Fu *et al*., 2016	DPP-4Is with CVD (US)	SU	54,518	hHF	0.95	0.78-1.15	0.580
Fu *et al*., 2016	DPP-4Is without CVD (US)	SU	164,038	hHF	0.59	0.38-0.89	0.013
Gokhale *et al*., 2017	DPP-4Is (US)	SU	98,512	hHF	0.87	0.77-0.97	NA
Kim *et al*., 2017	DPP-4Is (Korea)	SU	511,382	hHF	0.78	0.67-0.86	NA

CVOTs: Cardiovascular outcome trials, RCTs: Randomized controlled trials, HF: Heart failure, HHF: Hospitalization due to heart failure, HR: Hazard ratio, OR: Odd ratio, CI: Confidence interval, NS: Not significant, NA: Not available, Sita: Sitagliptin, Saxa: Saxagliptin, DPP-4Is: DPP-4 inhibitors, SU: Sulfonylureas, Active: Active comparators, CVD: Cardiovascular diseases, US: United States

Table 3: Meta-analysis of CVOTs on hHF/HF with DPP-4Is with or without inclusion of other RCTs

Author, year	Studies analyzed	Compared with	*n*	Outcome	HR/OR	95% CI	*P*
Abbas *et al*., 2016	3 CVOT only	Placebo	36,543	hHF	1.12	1.00-1.25	0.05
Li *et al*., 2016	5 RCTs (including 3 CVOT)	Placebo	37,028	hHF	1.13	1.00-1.26	0.05
Elgendy *et al*., 2017	90 RCTs (including 3 CVOT)	Placebo	66,730	HF	1.11	0.99-1.25	0.07
Verma *et al*., 2017	29 RCTs + 3 CVOT	Placebo/active	54,640	HF	1.13	1.01-1.26	0.03

CVOTs: Cardiovascular outcome trials, RCTs: Randomized controlled trials, HF: Heart failure, HHF: Hospitalization due to heart failure, HR: Hazard ratio, OR: Odd ratio, CI: Confidence interval, DPP-4Is: DPP-4 inhibitors

Table 4: Meta-analysis of RCTs on hHF/HF with DPP-4Is without inclusion of CVOTs

Author, year	Studies analyzed	Compared with	*n*	Outcome	HR/OR	95% CI	*P*
Li *et al*., 2016	36 RCTs	Placebo/active	28,292	HF	0.97	0.61-1.56	NS
Kongwatcharapong *et al*., 2016	54 RCTs	Placebo/active	74,737	HF	1.11	0.99-1.23	0.062
Rehman *et al*., 2017	36 RCTs	Placebo	54,664	HF	1.13	1.01-1.26	NA

CVOTs: Cardiovascular outcome trials, RCTs: Randomized controlled trials, HF: Heart failure, HHF: Hospitalization due to heart failure, HR: Hazard ratio, OR: Odd ratio, CI: Confidence interval, DPP-4Is: DPP-4 inhibitors, NA: Not available

Table 5: Observational studies showing hHF outcome with saxagliptin versus sitagliptin

Author, year	Study drug (country)	Compare with	*n*	Outcome	HR/OR	95% CI	*P*
Toh *et al*., 2016	Saxa (US)	Sita	288,731	hHF	0.83	0.70-0.99	NA
Fu *et al*., 2016	Saxa in patients with CVD (US)	Sita	26,084	hHF	0.95	0.70-1.28	0.712
Fu *et al*., 2016	Saxa in patients without CVD (US)	Sita	86,804	hHF	0.99	0.56-1.75	0.972
Chang *et al*., 2016	Saxa (Taiwan)	Sita	197,891	hHF	0.98	0.91-1.06	NS
Fadini *et al*., 2017	Saxa (Italy)	Sita	12,856	hHF	1.04	0.55-1.95	NS

hHF: Hospitalization due to heart failure, HR: Hazard ratio, OR: Odd ratio, CI: Confidence interval, NS: Not significant, NA: Not available, Sita: Sitagliptin, Saxa: Saxagliptin, DPP-4Is: DPP-4 inhibitors, CVD: Cardiovascular diseases, US: United States

Discussion

Several observational studies and meta-analysis have yielded a conflicting result on HF/hHF outcome with DPP-4Is. First, the observational studies comparing DPP-4Is to other active comparators have yielded an inconsistent result on both HF and hHF outcomes [Table 2].[16-27] Second, a meta-analysis of three CVOTs revealed a 12% increased risk of hHF with gliptins with borderline significance (HR 1.12; 95% CI, 1.00–1.25; $P = 0.05$).[28] However, other meta-analysis that was done with RCTs of gliptins including three CVOTs showed conflicting results on HF/hHF finding [Table 3].[29-31] So were the findings from the meta-analysis conducted with RCTs of gliptins that excluded three CVOTs [Table 4].[29,32,33] Finally, while a meta-analysis of nine RCTs of saxagliptin by Kongwatcharapong *et al.* have suggested a significant increase in HF signals (HR = 1.22; 95% CI 1.028–1.437; $P = 0.02$), data from observational studies that compared saxagliptin to sitagliptin head-on, did not find increased hHF with the former [Table 5].[21,22,25,34]

Our findings suggest that the more CV outcomes data we seem to add on to SAVOR-TIMI for analysis of hHF, the more the statistical significance appears to disappear. We feel if this trend of diminishing negative effect continues, we might consider the initial adverse effect size of hHF could be unique to saxagliptin or an effect emerged by a chance or type 1 error (statistical noise). It is also possible that hHF issue with saxagliptin could be due to statistical error and not the reality, as raised and questioned by several authors in recent past.[35-37] There remains a possibility that apparent deviation from the initial statistical analysis may have caused an insufficient Bonferroni correction that may have caused type 1 error. This could be further supported by the fact that by applying the Bradford Hill criteria, this association of hHF and saxagliptin use no longer remains highly significant.[35,36] Moreover, by applying an alternative measure to the hazard ratio, there seems to be no substantial clinically relevant differences in the risk of hHF between saxagliptin, alogliptin, or sitagliptin versus placebo in SAVOR-TIMI, EXAMINE, and TECOS, respectively.[37]

As with any meta-analysis, our study has strength and limitations. First, the strength includes the rigorous methods of systematically identifying the data from both randomized and observational studies that examined risk of HF and hospitalization with DPP-4Is. Second, we analyzed only studies that explicitly looked for hHF as prespecified endpoint and were conducted for reasonably longer time (at least 1 year). Finally, we meta-analyzed all the four dedicated CVOTs with DPP-4Is including linagliptin (CARMELINA). The limitations include absence of GRADE application to assess the quality of evidence. Moreover, we are unable to confirm whether the increased hHF seen in previous meta-analysis is a class effect of DPP-4Is or a specific effect of saxagliptin. Furthermore, no increase in hHF with DPP-4Is in our meta-analysis may have been compounded by the heterogeneity across the trials.

While there may be a difference in selectivity to other DPP-4 substrate between saxagliptin and other DPP-4Is and their long-term inhibitory consequences, no apparent mechanistic reason exists currently that may explain as to why saxagliptin would have increased HF. Only long-term head-to-head trials of different DPP-4Is could perhaps answer these questions.

Mechanistic Evaluation of Glucose-lowering Strategies in Patients with Heart Failure (MEASURE-HF) is a 24-week, double-blind, randomized, multicentric placebo-controlled study ($N = 330$) is currently undergoing which is investigating the effects of saxagliptin and sitagliptin on cardiac dimensions and function (change in Left Ventricular End-diastolic Volume (LVEDV) index measured by Magnetic Resonance Imaging (MRI)) in patients with type 2 diabetes and HF. This study might enlighten us about differential hHF between two gliptins, once it is completed in 2019.[38]

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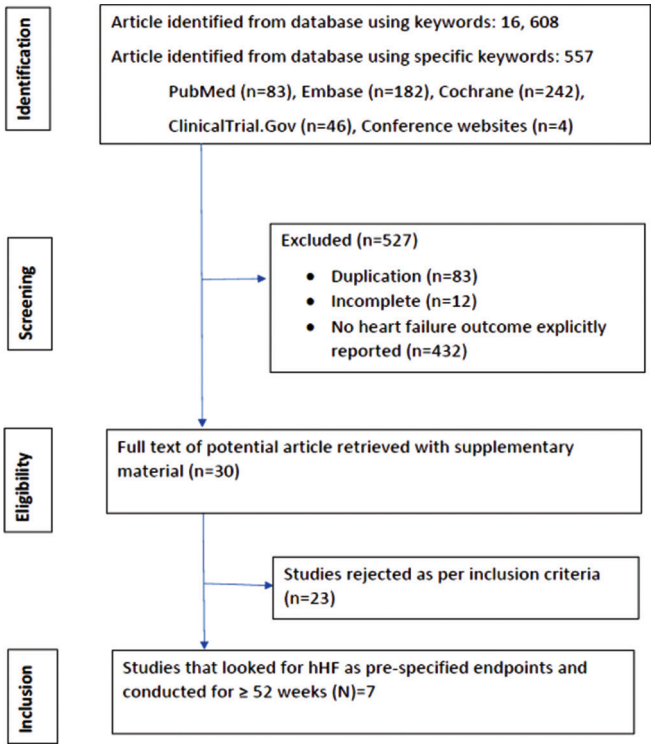
Nil.

Conflicts of interest
There are no conflicts of interest.

References
1. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457-71.
2. U.S. Department of Health and Human Services and Food and Drug Administration Center for Drug Evaluation and Research (CDER), Guidance for Industry Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes, 2008, http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627 pdf. [Last accessed on 2018 Oct 25]
3. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirschberg B, *et al*. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013;369:1317-26.
4. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, *et al*. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013;369:1327-35.
5. Zannad F, Cannon CP, Cushman WC, Bakris GL, Menon V, Perez AT, *et al*. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: A multicentre, randomised, double-blind trial. Lancet 2015;385:2067-76.
6. FDA Drug Safety Communication: FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin. Available from: https://www.fda.gov/Drugs/DrugSafety/ucm486096.htm. [Last accessed on 2018 Oct 25].
7. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, *et al*. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015:373:232-42.
8. Page RL 2nd, O'Bryant CL, Cheng D, Dow TJ, Ky B, Stein CM, *et al*. Drugs that may cause or exacerbate heart failure: A scientific statement from the American Heart Association. Circulation 2016;134:e32-69.
9. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, *et al*. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129-200.
10. Rydén L, Van de Werf F, Armstrong PW, McGuire DK, Standl E, Peterson ED, *et al.* Corrections needed to 2016 ESC and AHA guidelines on heart failure. Lancet Diabetes Endocrinol 2017;5:325-6.
11. Available from: http://www.diabetesincontrol.com/heart-failure-warning-added-to-the-dpp-4-inhibitor-class-of-drugs/. [Last accessed on 2018 Oct 25].
12. Gantz I, Chen M, Suryawanshi S, Ntabadde C, Shah S, O'Neill EA, *et al*. A randomized, placebo-controlled study of the cardiovascular safety of the once-weekly DPP-4 inhibitor omarigliptin in patients with type 2 diabetes mellitus. Cardiovasc Diabetol 2017;16:112.
13. McMurray JJV, Ponikowski P, Bolli GB, Lukashevich V, Kozlovski P, Kothny W, *et al*. Effects of vildagliptin on ventricular function in patients with type 2 diabetes mellitus and heart failure: A randomized placebo controlled trial. JACC Heart Fail 2018;6:8-17.
14. Rosenstock J, Perkovic V, Johansen OE, Cooper ME, Kahn SE, Marx N, *et al*. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: The CARMELINA randomized clinical trial. JAMA 2018 Nov 9. doi: 10.1001/jama. 2018.18269.
15. Laakso M, Rosenstock J, Groop PH, Barnett AH, Gallbitz B, Hehnke U, *et al*. Treatment with the dipeptidyl peptidase-4 inhibitor linagliptin or placebo followed by glimepiride in patients with type 2 diabetes with moderate to severe renal impairment: A 52-week, randomized, double-blind clinical trial. Diabetes Care 2015;38:e15-7.
16. Wang KL, Liu CJ, Chao TF, Huang CM, Wu CH, Chen SJ, *et al*. Sitagliptin and the risk of hospitalization for heart failure: A population-based study. Int J Cardiol 2014;177:86-90.
17. Ou SM, Shih CJ, Chao PW, Chu H, Kuo SC, Lee YJ, *et al*. Effects on clinical outcomes of adding dipeptidyl peptidase-4 inhibitors versus sulfonylureas to metformin therapy in patients with type 2 diabetes mellitus. Ann Intern Med 2015;163:663-72.
18. Seong JM, Choi NK, Shin JY, Chang Y, Kim YJ, Lee J, *et al*. Differential cardiovascular outcomes after dipeptidyl peptidase-4 inhibitor, sulfonylurea, and pioglitazone therapy, all in combination with metformin, for type 2 diabetes: A population-based cohort study. PLoS One 2015;10:e0124287.
19. Fadini GP, Avogaro A, Degli Esposti L, Russo P, Saragoni S, Buda S, *et al*. Risk of hospitalization for heart failure in patients with type 2 diabetes newly treated with DPP-4 inhibitors or other oral glucose lowering medications: A retrospective registry study on 127,555 patients from the Nationwide OsMed Health-DB Database. Eur Heart J 2015;36:2454-62.
20. Eurich DT, Weir DL, Simpson SH, Senthilselvan A, McAlister FA. Risk of new-onset heart failure in patients using sitagliptin: A population-based cohort study. Diabet Med 2016;33:621-30.
21. Chang CH, Chang YC, Lin JW, Caffrey JL, Wu LC, Lai MS, *et al.* No increased risk of hospitalization for heart failure for patients treated with dipeptidyl peptidase-4 inhibitors in Taiwan. Int J Cardiol 2016;220:14-20.
22. Toh S, Hampp C, Reichman ME, Graham DJ, Balakrishnan S, Pucino F, *et al*. Risk for hospitalized heart failure among new users of saxagliptin, sitagliptin, and other antihyperglycemic drugs: A retrospective cohort study. Ann Intern Med 2016;164:705-14.
23. Ekstrom N, Svensson AM, Miftaraj M, Franzen S, Zethelius B, Eliasson B, *et al*. Cardiovascular safety of glucose lowering agents as add-on medication to metformin treatment in type 2 diabetes: Report from the Swedish National Diabetes Register. Diabetes Obes Metab 2016;18:990-8.
24. Kannan S, Pantalone KM, Matsuda S, Wells BJ, Karafa M, Zimmerman RS. Risk of overall mortality and cardiovascular events in patients with type 2 diabetes on dual drug therapy including metformin: A large database study from the Cleveland Clinic. J Diabetes 2016;8:279-85.
25. Fu AZ, Johnston SS, Ghannam A, Tsai K, Cappell K, Fowler R, *et al*. Association between hospitalization for heart failure and dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes: An observational study. Diabetes Care 2016;39:726-34.
26. Gokhale M, Buse JB, Jonsson Funk M, Lund J, Pate V, Simpson RJ, *et al*. No increased risk of cardiovascular events in older adults initiating dipeptidyl peptidase-4 inhibitors vs therapeutic alternatives. Diabetes Obes Metab 2017;19:970-8.
27. Kim YG, Yoon D, Park S, Han SJ, Kim DJ, Lee KW, *et al*. Dipeptidyl peptidase-4 inhibitors and risk of heart failure in patients with type 2 diabetes mellitus: A population-based cohort study. Circ Heart Fail 2017;10. pii: e003957. doi: 10.1161/CIRCHEARTFAILURE.117.003957.
28. Abbas AS, Dehbi HM, Ray KK. Cardiovascular and non-cardiovascular safety of dipeptidyl peptidase-4 inhibition: A meta-analysis of randomized controlled cardiovascular outcome trials. Diabetes Obes Metab 2016;18:295-9.
29. Li L, Li S, Deng K, Liu J, Vandvik PO, Zhao P, *et al*. Dipeptidyl peptidase-4 inhibitors and risk of heart failure in type 2 diabetes: Systematic review and meta-analysis of randomised and observational studies. BMJ 2016;352:i610.
30. Elgendy IY, Mahmoud AN, Barakat AF, Elgendy AY, Saad M, Abuzaid A, *et al*. Cardiovascular safety of dipeptidylpeptidase IV inhibitors: A meta-analysis of placebo-controlled randomized trials. Am J Cardiovasc Drugs 2017;17:143-55
31. Verma S, Goldenberg RM, Bhatt DL, Farkouh ME, Quan A, Teoh H, *et al*. Dipeptidyl peptidase-4 inhibitors and the risk of heart failure: A systematic review and meta-analysis. CMAJ Open 2017;5:E152-77.
32. Kongwatcharapong J, Dilokthornsakul P, Nathisuwan S, Phrommintikul A, Chaiyakunapruk N. Effect of dipeptidyl peptidase-4 inhibitors on heart failure: A meta-analysis of randomized clinical trials.

Int J Cardiol 2016;211:88-95.
33. Rehman MB, Tudrej BV, Soustre J, Buisson M, Archambault P, Pouchain D, *et al*. Efficacy and safety of DPP-4 inhibitors in patients with type 2 diabetes: Meta-analysis of placebo-controlled randomized clinical trials. Diabetes Metab 2017;43:48-58.
34. Fadini GP, Saragoni S, Russo P, Degli Esposti L, Vigili de Kreutzenberg S, Melazzini M, *et al*. Intraclass differences in the risk of hospitalization for heart failure among patients with type 2 diabetes initiating a dipeptidyl peptidase-4 inhibitor or a sulphonylurea: Results from the OsMed Health-DB registry. Diabetes Obes Metab 2017;19:1416-24.
35. Cebrian-Cuenca AM, Nunez E, Nunez-Villota J, Consuegra-Sanchez L. What would be the fate of the association between saxagliptin and heart failure admission in the SAVOR-TIMI 53 trial if appropriate statistical methods should have been applied? Diabetes Res Clin Pract 2017;126:320-1.
36. Cebrian-Cuenca AM, Orozco-Beltran D, Navarro-Perez J, Franch-Nadal J, Nunez-Villota J, Consuegra-Franchez L. Saxagliptin and risk of heart failure hospitalization: Concern or miscalculation? Int J Cardiol 2016;220:573-4.
37. Kaneko M, Narukawa M. Assessment of the risk of hospitalization for heart failure with dipeptidyl peptidase-4 inhibitors, saxagliptin, alogliptin, and sitagliptin in patients with type 2 diabetes, using an alternative measure to the hazard ratio. Ann Pharmacother 2017;51:570-6.
38. Mechanistic Evaluation of Glucose-lowering Strategies in Patients With Heart Failure (MEASURE-HF). [Online] Available from: https://clinicaltrials.gov/ct2/show/NCT02917031. [Last accessed on 2018 Oct 25].



Supplementary Figure 1: Study selection process