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; I²: 53.95%, tau²: 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; I²: 43.74%, tau²: 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 the dipeptyl-dipeptidase-4 inhibitors (DPP-4Is) and the subsequent blanket labelling of hHF to all the four approved DPP-4Is in 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 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
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; \( P = 0.007 \)). 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.

| Trial eponyms/Authors | DPP-4 inhibitors | Control | Median duration (weeks) |
|-----------------------|------------------|---------|------------------------|
| **Type** | **Events/n** | **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 | Oramiglipitin | 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

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\( P \) = 0.026.

\( P \) = 0.26.

\( P \) = 0.007.

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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 \( (N = 43,522; \Gamma:53.95%, \tau^2:0.012, P = 0.089) \) did not find significant increase in hHF [Figure 1] with DPP-4 inhibitors (fixed model RR 1.06; 95% CI, 0.96–1.17; \( P = 0.25/\text{random model RR 1.06; 95% CI}, 0.91–1.22; P = 0.48 \)). Meta-analysis of all RCTs [Figure 2] that explicitly looked for hHF for ≥52 weeks \( (N = 48,199; \Gamma:43.74%, \tau^2:0.016, P = 0.10) \) 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](image1)

![Figure 2: Meta-analysis of hHF with DPP-4Is in RCTs](image2)

**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 | Sitagliptin (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 | Sitagliptin (US) | Active        | 5027 | HF | 0.75 | 0.38–1.46 | 0.40  |
| Chang et al., 2016 | Sitagliptin (Taiwan) | Acarbose      | 290,130 | hHF | 1.03 | 0.98–1.08 | NS     |
| Toh et al., 2016 | Sitagliptin (US) | SU            | 642,529 | hHF | 0.86 | 0.77–0.95 | NA     |
| Toh et al., 2016 | Saxagliptin (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
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]. 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). However, other meta-analysis that was done with RCTs of gliptins including three CVOTs showed conflicting results on HF/hHF finding [Table 3]. So were the findings from the meta-analysis conducted with RCTs of gliptins that excluded three CVOTs [Table 4]. 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].

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 I 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. There remains a possibility that apparent deviation from the initial statistical analysis may have caused an insufficient Bonferroni correction that may have caused type I 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. 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.

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.
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Conflicts of interest
There are no conflicts of interest.

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