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Meta-analyses of the effects of DPP-4 inhibitors, SGLT2 inhibitors and GLP1 receptor analogues on cardiovascular death, myocardial infarction, stroke and hospitalization for heart failure

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ABSTRACT

Aim: To assess the effects DPP-4i; SGLT2-i & GLP1-RA on CV death, MI, stroke and hHF. This is probably the first meta-analysis to assess the effects of these drugs on MI and stroke in totality, including non-fatal & fatal MI and stroke.

Methods: Scientific databases were searched for RCTs with pre-specified inclusion criteria and each end-point from the selected 13 studies was reported as an effect size (M H odds ratio) with a 95% confidence interval P value.

Results: The pooled analysis of all the 5 available CVOT with DPP-4i resulted in a neutral effect on MI, stroke, the combined end points of MI & Stroke, CV death and hHF. The pooled analysis of all the 5 available CVOTs with GLP1-RA resulted in a neutral effect on MI. However, there was a statistically significant 12% reduction in CV death (P = 0.01), 13% reduction in stroke (P = 0.02) and 11% reduction the combined end points of MI & Stroke (P = 0.001). The impact of GLP1-RA inhibitors on hHF was neutral. The pooled analysis of all the 3 available CVOTs with SGLT2-i resulted in a neutral effect on MI, stroke, the combined end points of MI & Stroke and CV death. There was however a statistically significant 28% reduction in hHF (P < 0.001).

Conclusion: DPP-4i & SGLT-2i are neutral as far as all aspects of CV outcomes are concerned except for hHF which is significantly reduced by the latter. GLP1-RA as a class reduce risk of ASCVD showing a significant reduction in MI and stroke.

Abbreviations: T2D, type 2 diabetes; DPP-4i, dipeptidyl peptidase 4 inhibitor; SGLT2-i, sodium glucose linked transporter inhibitor; GLP1-RA, glucagon like peptide 1 receptor analogues; hHF, hospitalization for heart failure; MI, myocardial infarction; RCT, randomized controlled trial; CVOT, Cardiovascular Outcomes Trial; FDA, Food and Drugs Administration; MACE, Major Adverse Cardiac Events; CVD, cardiovascular death; ASCVD, atherosclerotic cardiovascular disease

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1. Introduction

The last two decades have seen a paradigm shift in the management of type 2 diabetes (T2D) from "glucocentricity" to an approach which takes into consideration the side effects of the drugs like hypoglycemia and weight gain, the pathophysiology of the disease and most importantly the cardiovascular outcomes of the drugs used to treat this disease. The latter was brought into minute focus following the seminal publication which showed an increased risk of myocardial infarction and cardiovascular death with the popular drug Rosiglitazone [1].

The Food and Drugs Administration (FDA) mandated that any new drug used for the treatment of T2D must have a cardiovascular outcome trial (CVOT) to demonstrate its safety [2]. If the pooled analysis of phase 2 & 3 data of the cardiovascular events showed an upper boundary of confidence interval between 1.3 & 1.8, a well-designed cardiovascular outcome trial was necessary to demonstrate safety of these drugs. Therefore, the newer groups of drugs namely the incretin mimetics (Dipeptidyl Peptidase 4 inhibitor (DPP-4i) & Glucagon like Peptide 1 Receptor Analogues (GLP1-RA) and the sodium glucose linked transporter inhibitor (SGLT2-i) drugs have all been through these large, scientifically robust and stringent CVOTs. The results of these studies have revealed much about these drugs while at the same time raised a few doubts about their safety as groups and their effects on the individual aspects of cardiovascular disease. Amongst dipeptidyl peptidase 4 inhibitor (DPP-4i); Sitagliptin and Linagliptin have shown cardiovascular neutrality from all aspects but not Saxagliptin and Alogliptin, which have shown a higher risk of hospitalization for heart failure [3–6]. It is extremely confusing for clinicians' now, as to how to place these drugs in their patients, as there is a black box warning from FDA for increased hospitalization for heart failure ascribed to the entire DPP-4i class [7].

All glucagon like peptide 1 receptor analogues (GLP1-RA) trials have shown a uniform reduction in the major adverse cardiovascular events (MACE) with the studied drugs except Lixisenatide and Exenatide LAR, which have shown neutrality [8,9]. However, the driving force in the published data would suggest that these drugs have reduced MACE by either reduction of cardiovascular deaths (Liraglutide) or by reduction of myocardial infarctions (Albiglutide) or by reduction of non-fatal strokes (Semaglutide), a completely non-uniform finding, across the various GLP1-RA studied [10–12]. Again, the clinician is left confused as to whether GLP1-RA as a group produces these benefits or are the benefits individualized to the drugs. GLP1-RA have shown no effect on heart failure, an entity of great significance in patients of T2D.

Similarly, the CVOTs with the SGLT2-i have uniformly indicated an improvement in the rates of hospitalization for heart failure but except for Empagliflozin which showed a reduction in cardiovascular death, such results have not been replicated with neither Canagliflozin nor Dapagliflozin [13–15].

A non-significant increase in non-fatal strokes seen in the EMPA REG outcome study has not been seen in either CANVAS or DECLARE – TIMI outcomes studies.

With the publication of all the recent CVOTs, there was a substantial increase in the total number of patients available for analysis, who could be pooled to perform a meta-analysis of all these groups of drugs (DPP-4i, GLP1-RA and SGLT2-i) and ascertain the positive and negative signals, as far as cardiovascular death (CVD), myocardial infarction (MI), stroke, a combination of MI and stroke (hitherto not analyzed yet

Table 1 – Baseline characteristics of studies included in the meta-analysis.

Group	Drug	Studies	Mean DM duration (years)*	Median follow-up (years)	Mean change in HBA1C (%)	Established CVD (%)
GLP-1RA						
	Lixisenatide	ELIXA	9.2 ± 8.2	2.1	−0.27	100
	Liraglutide	LEADER	12.8 ± 8.0	3.8	−0.40	81
	Semaglutide+	SUSTAIN-6	14.1 ± 8.2	2.1	−1.4	83
	Exenatide-LAR	EXSCEL	12	3.2	−0.53	73
	Albiglutide	HARMONY	14.1	1.6	−0.52	71
DPP-4i						
	Saxagliptin	SAVOR-TIMI 53	10–15	2.1	−0.2	68–86#
	Alogliptin	EXAMINE	7.1	1.5	−0.36	88
	Sitagliptin	TECOS	11.6	3	−0.29	74
	Linagliptin	CARMELINA	15	2.2	−0.36	57
	Omarigliptin	Omarigliptin CVOT	12	1.8	−0.3	∼100
SGLT-2i						
	Canagliflozin	CANVAS PROGRAM	13.5	3.6	−0.58	64.8
	Dapagliflozin	DECLATE-TIMI-58	11	4.2	−0.42	40.6
	Empagliflozin	EMPAREG	>10 (57%)	3.1	−0.36 (25 mg)–0.24 (10 mg)	99.5

* Taken from the treatment arm.
\+ With 1 mg semaglutide.
\# Depending on eGFR.

pertinent) and hospitalization for heart failure (hHF) that emanate from these drugs as groups.

2. Materials & methods

2.1. Search strategy and selection criteria

We performed a database search for title, abstract & keywords, without any language restriction. Search terms included ""dipeptidyl peptidase-4 inhibitors", "saxagliptin", "alogliptin", "sitagliptin", "linagliptin", "vildagliptin", "sodium-glucose linked transporter-2 inhibitors", "canagliflozin", "dapagliflozin","empagliflozin","ertugliflozin ","glucagon-likepeptide-1 receptor agonist", "lixisenatide", "liraglutide", "exenatide", "exenatide-LAR", "dulaglutide", "albiglutide", "semaglutide", "placebo", "myocardial infarction", "cardiovascular death", "stroke", and "hospitalization for heart failure". The search was conducted clubbing the flozins with cardiovascular end points, gliptins with cardiovascular end points and GLP1-RA with cardiovascular end points independently (3 groups of data). The initial search yielded a sum total of articles (in each group) consisting of a combination of citations from Cochrane library, Embase & PubMed. (Supplementary appendix 1) Subsequent screening involved applying additional filters in the form of cardiovascular outcomes trial (CVOT) and date of publication from March 2008 (time of first formulation of FDA guidelines for the industry) till date. The final selection was based on the pre-defined inclusion criteria, a criterion derived from all previously published meta-analysis in this area:

- Studies with at least 1000 patients above 18 years of age.
- Studies with at least 18 months follow up.
- Studies with 3-P MACE and/or 4-P MACE as a primary end point with at least 611 events included for the primary end-point analysis.

A total of 13 studies (42,920 patients from the GLP1-RA trials, 47,645 patients from the gliptin trials and 34,312 patients from the SGLT-2i trials) were finally selected for this meta-analysis.

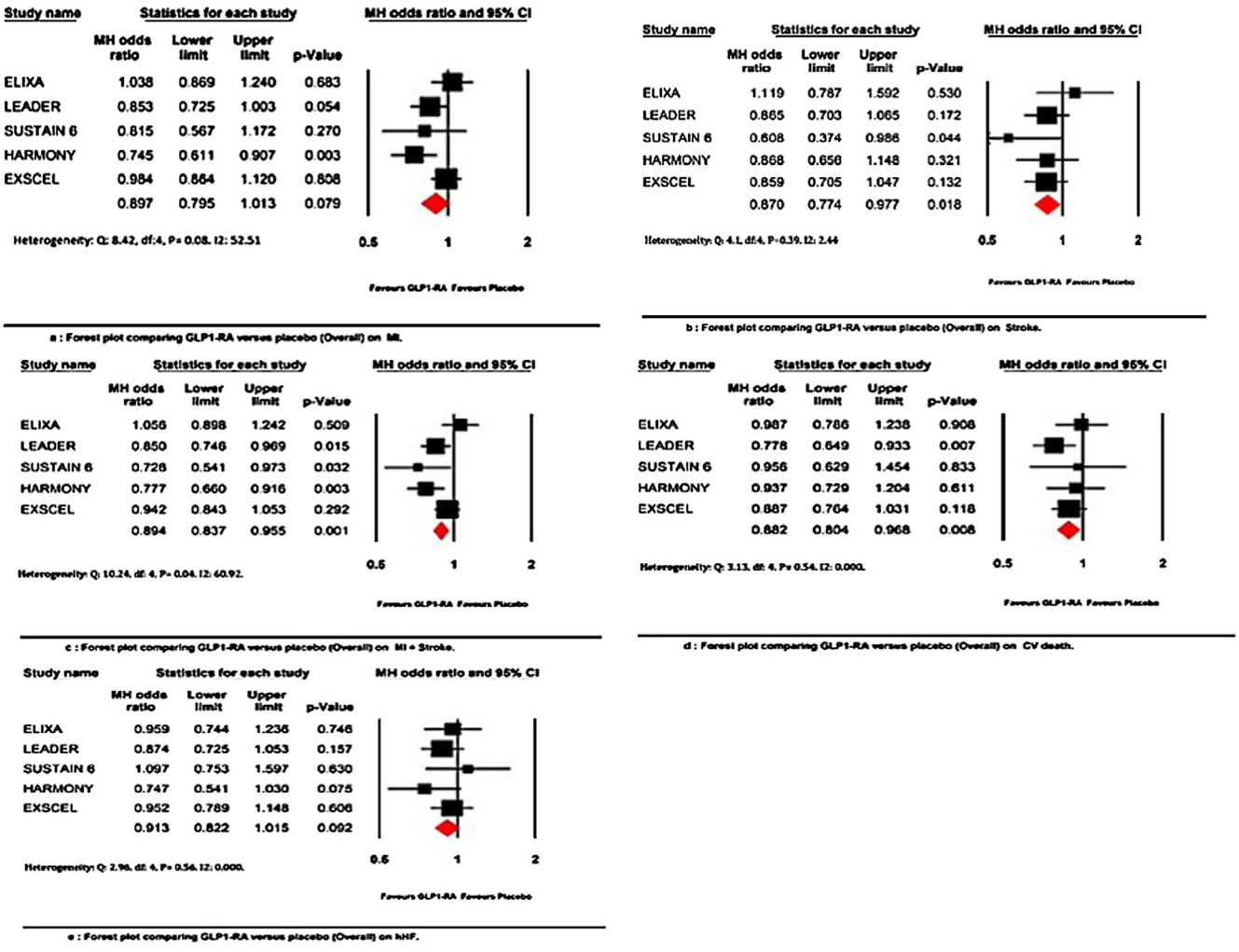

Fig. 1 – GLP1-RA (Overall) Vs. Placebo on CV outcomes. (a) MI; (b) Stroke; (c) MI + stroke; (d) CV Death; (e) hHF. ELIXA: Lixisenatide. LEADER: Liraglutide. SUSTAIN 6: Semaglutide. HARMONY: Albiglutide. EXSCEL: Exenatide LAR.

2.2. Data analysis

Data was analyzed from the 13 trials which satisfied the inclusion criteria with additional inputs from the supplementary materials, and critical inputs by the regulatory authorities (FDA & EMA). Meta-analysis was performed using Comprehensive Meta-analysis software version 3, Biostat Inc., Englewood, NJ, United States. Mantel-Haenszel (MH) odds ratio (OR) with 95% confidence interval was used to assess the impact of the treatment on the selected cardiovascular outcomes compared to standard of care. Effect size – MH OR (both individual studies as well as the final effect size) was calculated using fixed or random effect model depending on heterogeneity and study characteristics. Heterogeneity was assessed using the Cochrane Q and Higgin's I^2 test. Effect size bias was assessed by funnel plots, with the precision (1/SE) plotted against the effect size. Individual study bias was assessed using the Cochrane collaboration tool (Supplementary appendix 2).

3. Results

3.1. Trial characteristics

13 RCTs were identified for analysis. We divided the trials into 3 distinct groups (DPP-4i:5 trials, SGLT-2i:3 trials and GLP-1RA:5 trials). The meta-analysis was performed separately in these 3 distinct groups and an indirect comparison was planned since no head-to-head comparison with cardiovascular outcomes as a primary end point is available as of now.

The baseline characteristics are detailed in Table 1.

3.2. Cardiovascular outcomes data

3.2.1. GLP1-RA

The analysis of GLP1-RA was done by dividing the 5 trials into two groups (one excluding the short-acting GLP1-RA-Lixisenatide).

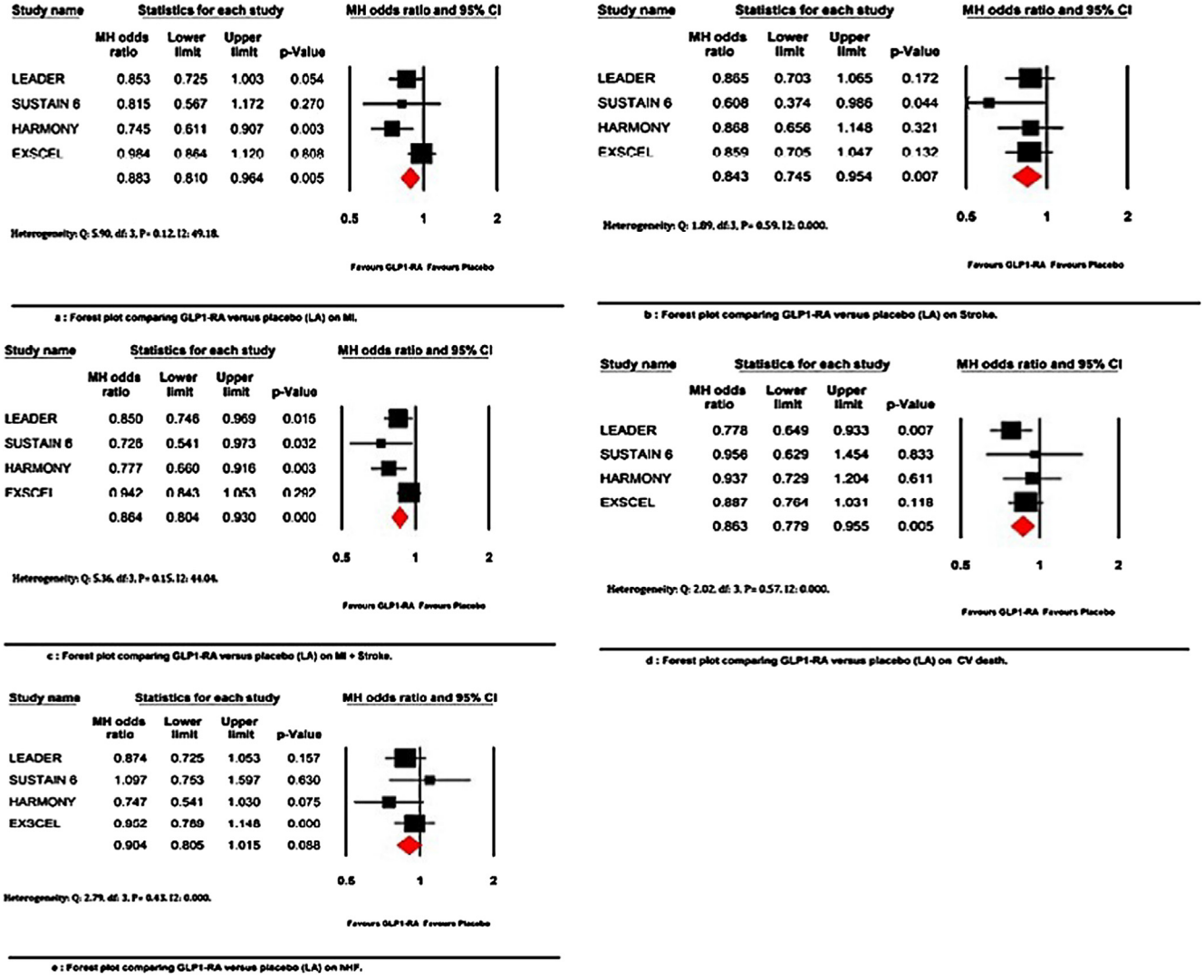

Fig. 2 – GLP1-RA (LA) Vs. Placebo on CV outcomes. (a) MI; (b) Stroke; (c) MI + stroke; (d) CV Death; (e) hHF. LEADER: Liraglutide. SUSTAIN 6: Semaglutide. HARMONY: Albiglutide. EXSCEL: Exenatide LAR.

Summary of 5 trials: The pooled analysis of all the 5 available CVOTs with GLP1-RA resulted in a statistically non-significant 11% reduction in MI (OR: 0.89; P = 0.08; 95%CI: 0.71–1.01). However, there was a statistically significant 13% reduction in stroke (P = 0.02; 95%CI: 0.77–0.98), 11% reduction in the combined end points of MI & stroke (P = 0.001; 95% CI: 0.84–0.96) and a significant 12% reduction in CV death (P = 0.01; 95% CI: 0.80–0.97). The impact of GLP1-RA inhibitors on hHF was neutral (OR: 0.91; P = 0.09; 95% CI: 0.82–1.02) [Fig. 1].

Summary of 4 trials (excluding small-acting GLP1-RA-lixisenatide): The pooled analysis of the 4 long-acting GLP1-RA resulted in a 12% statistically significant reduction in MI (P = 0.01; 95%CI: 0.81–0.96), a 16% statistically significant reduction in stroke (P = 0.007; 95% CI: 0.75–0.95), a 14% statistically significant reduction in the combined end point of MI & Stroke (P < 0.001; 95% CI: 0.80–0.93), and a 14% statistically significant reduction in CV mortality (P = 0.01; 95% CI: 0.78–0.96). The impact of GLP1-RA inhibitors on hHF was neutral (OR: 0.90; P = 0.09; 95% CI: 0.81–1.02) [Fig. 2].

3.2.2. *DPP-4i*

The analysis of DPP-4i was also divided into two groups (with and without the omarigliptin data). One of the reasons for doing so was incorporate all the CVOT outcomes data available and also to do a separate analysis excluding omarigliptin as the study was truncated early resulting in very few events with the possibility of skewing the data [16].

Summary of 5 trials: The pooled analysis of all the 5 available CVOTs with DPP-4i resulted in a neutral effect on MI (OR:0.99; P = 0.98; 95%CI: 0.91–1.09), stroke (OR: 0.99; P = 0.83; 95%CI: 0.87–1.12), the combined end points of MI & Stroke (OR: 0.99; P = 0.89; 95% CI: 0.92–1.07), and CV death (OR: 0.99; P = 0.90; 95% CI:0.91–1.09) [Fig. 3].

Summary of 4 trials (excluding Omarigliptin): The pooled analysis of the 4 DPP-4i (excluding truncated omarigliptin CVOT) resulted in a neutral effect on MI (OR: 1.01; P = 0.88; 95%CI: 0.92–1.10), stroke (OR: 0.99; P = 0.88; 95% CI: 0.87–1.13), the combined end points of MI & Stroke (OR: 1.00; P = 0.97; 95% CI: 0.93–1.08), and CV death (OR: 0.99; P = 0.87; 95% CI: 0.91–1.09) [Fig. 4].

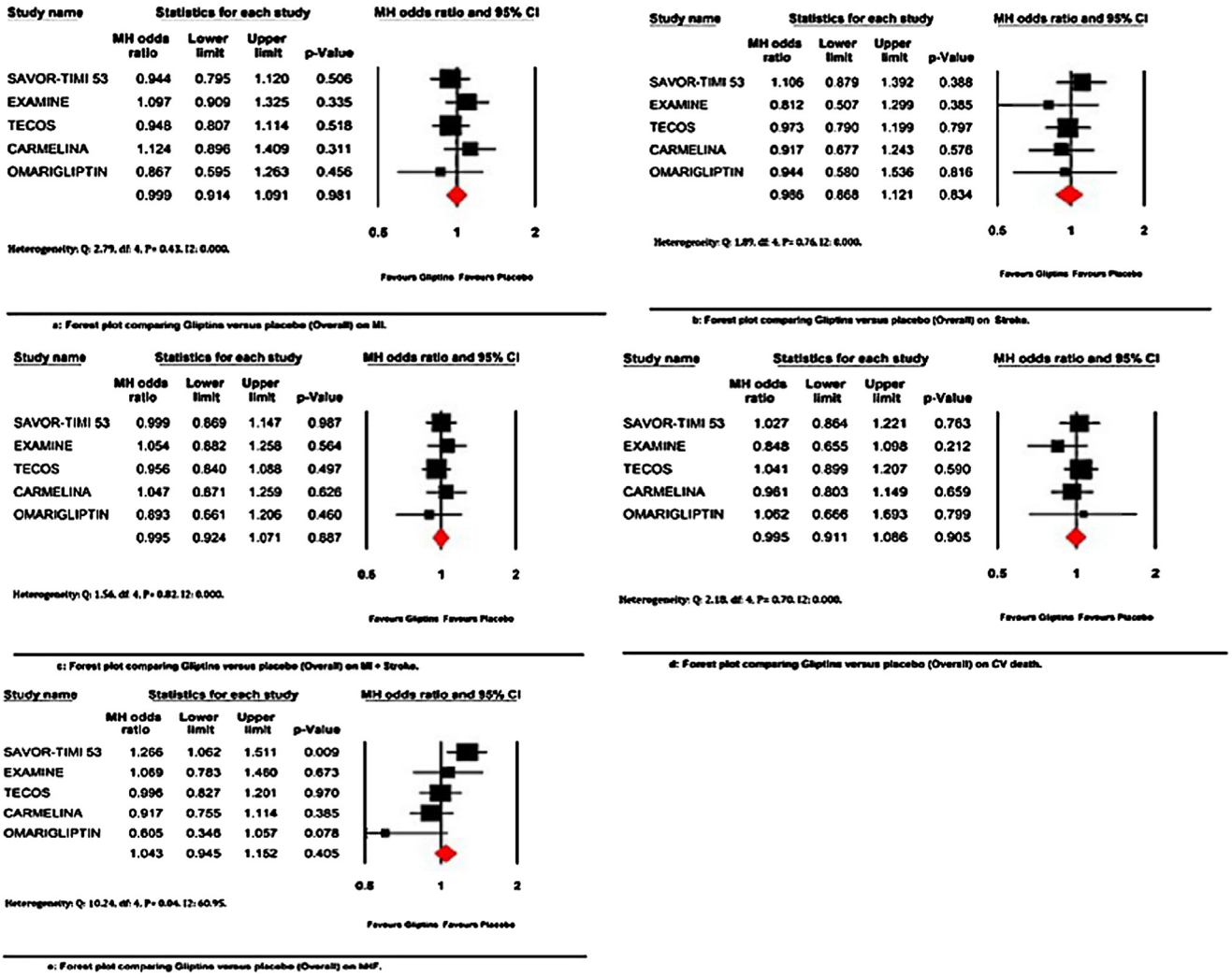

Fig. 3 – Gliptins (Overall) Vs. Placebo on CV outcomes. (a) MI; (b) Stroke; (c) MI + stroke; (d) CV Death; (e) hHF. SAVOR-TIMI 53: Saxagliptin. EXAMINE: Alogliptin. TECOS: Sitagliptin. CARMELINA: Linagliptin. OMARIGLIPTIN: Omarigliptin.

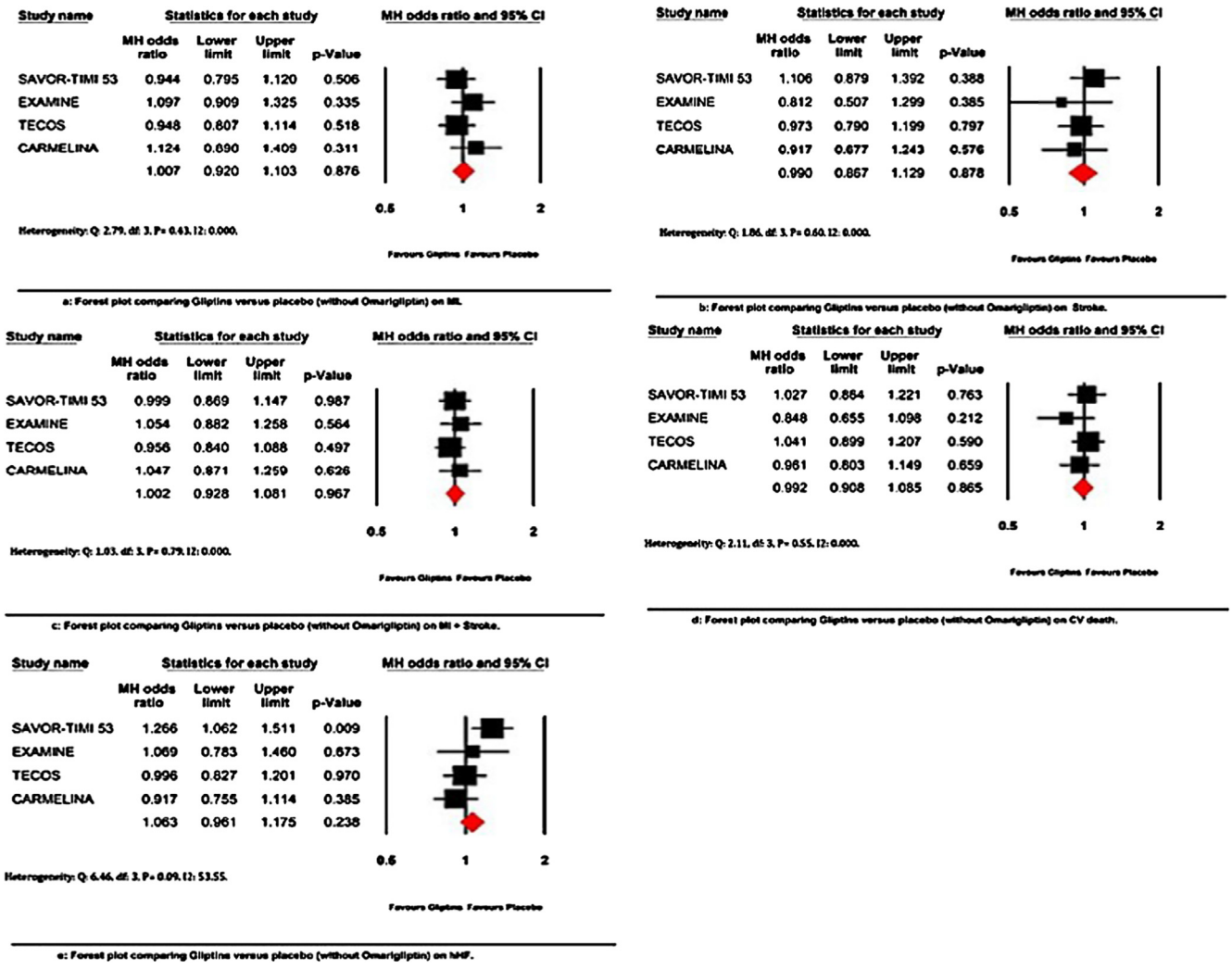

Fig. 4 – Gliptins (without Omarigliptin) Vs. Placebo on CV outcomes. (a) MI; (b) Stroke; (c) MI + stroke; (d) CV Death; (e) hHF. SAVOR-TIMI 53: Saxagliptin. EXAMINE: Alogliptin. TECOS: Sitagliptin. CARMELINA: Linagliptin.

Meta-analysis of hHF comparing gliptins versus placebo (including omarigliptin data):

- The risk ratio (OR) was 1.04; 95% CI: 0.95–1.15 which was statistically non-significant (P = 0.41) [Fig. 3].

Meta-analysis of hHF comparing gliptins versus placebo (excluding omarigliptin data):

- The risk ratio (OR) was 1.06; 95% CI: 0.96–1.18 which was statistically non-significant (P = 0.24) [Fig. 4].

3.2.3. *SGLT2-i*

The pooled analysis of all the 3 available CVOTs with SGLT2-i resulted in a neutral effect on MI (OR:0.91; P = 0.08; 95%CI: 0.83–1.01), stroke (OR: 1.05; P = 0.34; 95%CI: 0.93–1.20), the combined end points of MI & Stroke (OR: 0.96; P = 0.37; 95% CI: 0.89–1.05) and CV death (OR: 0.87; P = 0.41; 95% CI: 0.63–1.21). There was statistically significant 28% reduction in hospitalization for heart failure (P < 0.001; 95%CI: 0.64–0.82) [Fig. 5].

4. Discussion

This meta analyses of CVOTs of the newer anti diabetic agents is in all likelihood the first such, looking at all drugs and analyzing the individual aspects of the cardiovascular events. It is novel that in addition to the end points usually studied in CVOTs, (MI or stroke), a totality of all MI & stroke inclusive of fatal and non-fatal events have been analyzed.

Global burden of disease estimates that the largest number of deaths from non-communicable diseases is due to cardiovascular disease. A staggering 85.1% of these deaths are cause by a combination of MI and stroke [17]. No CVOT nor meta-analysis has looked at this obviously pertinent endpoint previously. This is the first study to look at this composite adding further novelty to the data.

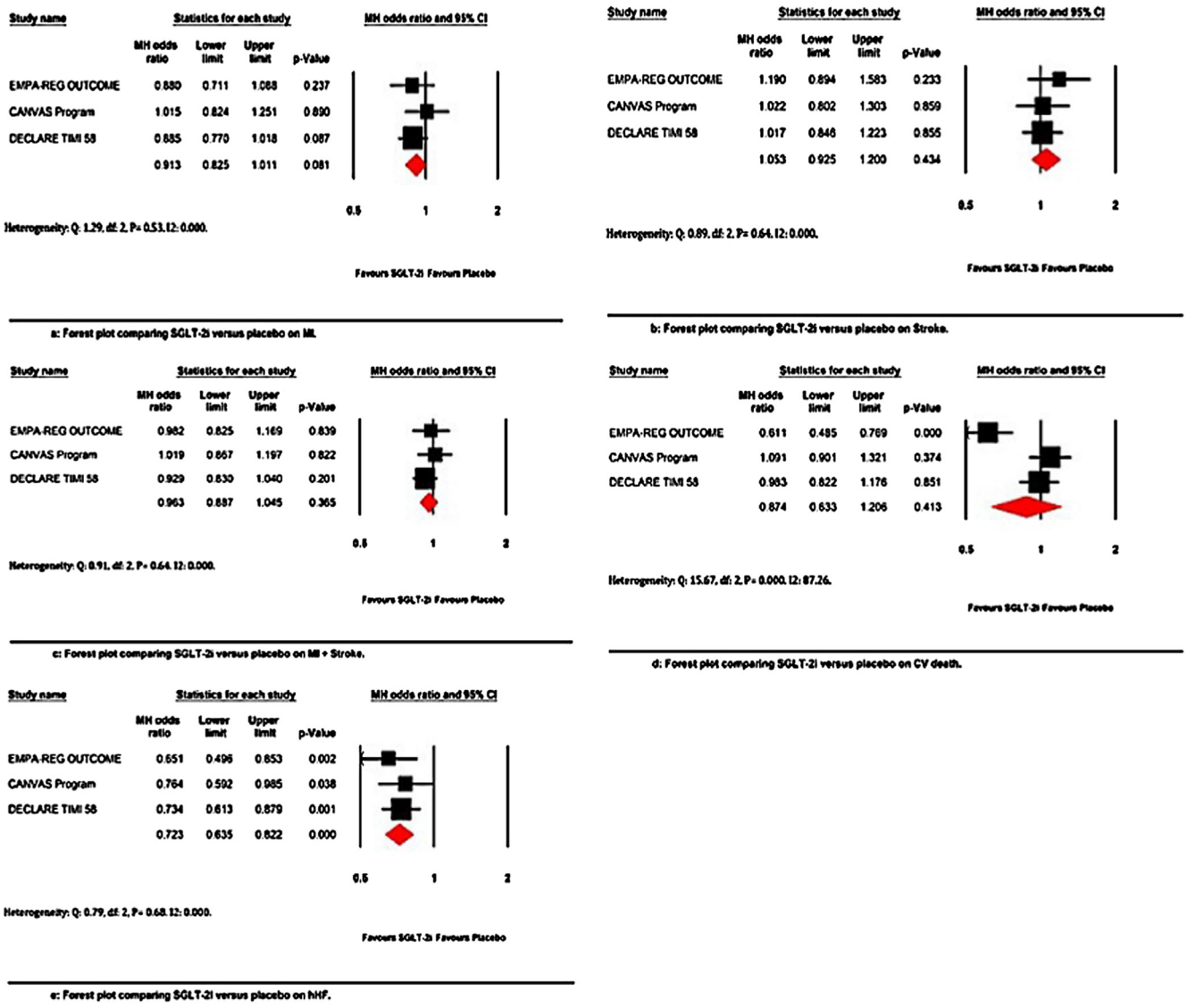

Fig. 5 – SGLT-2i Vs. Placebo on CV outcomes. (a) MI; (b) Stroke; (c) MI + stroke; (d) CV Death; (e) hHF. EMPA-REG OUTCOME: Empagliflozin. CANVAS Program: Canagliflozin. DECLARE TIMI 58: Dapagliflozin.

All this expands the information base of the already known results of these trials in confirming and clarifying the effects of each of these groups of drugs.

Animal studies and small clinical studies have highlighted that GLP1-RA reduce inflammation in the vascular endothelium thereby improving endothelial function, in addition to causing vasodilatation, improving plaque stability, blood flow and reducing platelet aggregation [18]. There has been 5 CVOTs with the GLP1-RA; 4 of them with the long acting (LEADER [Liraglutide], SUSTAIN 6[Semaglutide], EXSCEL [Exenatide LAR] and HARMONY [Albiglutide]) and 1 with the short acting (ELIXA [Lixisenatide]); 3 with the GLP1 backbone (Liraglutide, Semaglutide & Albiglutide) and 2 with the exendin backbone (Exenatide LAR, Lixisenatide). This meta-analysis confirms that GLP1-RA reduce atherosclerotic cardiovascular disease with a statistically significant reduction in a total of stroke and MI. In fact, if the ELIXA trial (excluding short acting GLP1-RA) is not included, GLP1 -RA demonstrates a significant reduction in CV death, MI and stroke and a combination of the latter two. Moreover, it could be speculated that GLP1 RA descending from the GLP1 -RA backbone provide huge protection from ASCVD, contrasting with those descended from the Exendin backbone. There is however no benefit shown in hHF with GLP1-RA. This is in keeping with all other previous literature and reiterates the stand taken by various august bodies like the American Diabetes Association that GLP1-RA should be the second line therapy after metformin in patients with established atherosclerotic vascular disease [19].

There has been 5 CVOTs with DPP-4i – SAVOR TIMI (Saxagliptin), EXAMINE (Alogliptin), TECOS (Sitagliptin), CARMELINA (Linagliptin), Omarigliptin CVOT. In keeping with the findings of these trials the meta-analyses reaffirm that DPP-4i are cardiovascular neutral inasmuch that they cause no harm in patients with AtheroSclerotic CardioVascular Disease (ASCVD), whether it be CV death, MI or Stroke. Inclusive of

Omarigliptin (a DPP-4i not available in clinical practice), DPP-4i are also completely safe in hHF (RR 1.013 CI 0.857–1.197 P = 0.879), a much-debated area. This is most reassuring for gliptins as a group as it lays to rest the stigma that has been attached to the group following the FDA branding in 2017, with the exception of saxagliptin which seems to have demonstrated a molecule-specific increased risk of hHF as demonstrated by the SAVOR-TIMI 53 trial and the data examined from the FAERS database.

The 3 CVOTs with SGLT2-i clearly express a statistically significant reduction in hHF (RR 0.728, 95% CI: 0.64–0.83). However, there is no benefit with SGLT2-i in CV death, all MI, all stroke. This would be in keeping with previously published studies which seem to indicate that SGLT2-i confer benefit to T2D patients with AtheroSclerotic CardioVascular Disease (ASCVD) primarily by inducing fluid loss and thereby reducing after load and because of this mode of action they largely have no effect on atherosclerotic events. However, this meta-analysis contrasts with a recently published meta-analysis which indicated that there was some benefit in reduction of ASCVD in patients with established cardiovascular disease from SGLT-2i [20].

There were a few limitations with this meta-analysis. The selection criteria were extremely restrictive and could have led to exclusion of numerous observational and randomized trials. However, we performed this meta-analysis by including studies which satisfied the FDA/EAMA recommended criteria of the minimum number of events and 1.5 years follow up. Although large population based observational studies can give important information about the real-life application of the drug in question along with a very good idea about its safety, RCTs are still considered the "gold standard" method of testing a hypothesis. We also appreciate that there were differences in the baseline, inclusion criteria and definitions of end points in all these different studies but the differences were small and subtle. Finally, we did not assess the composite primary end point (MACE) or the adverse effects of the individual agents. In order of keep the end-points analysis more focused and clinically relevant we chose to include the objective, individual CV end points instead of a composite. As far as the safety end-points were concerned, in view of the numerous meta-analysis on this topic published already, we chose to opt out of evaluating them and instead concentrated on those objective, individual end-points responsible for additional label change for the products.

The main strength of this meta-analysis was the large population & events studied. The inclusion of hard objective end-points as part of the analysis plan was another strength of this study.

This report supports the position of ADA/EASD algorithm which places GLP1-RA and SGLT2-i inhibitors as second line therapy for T2D patients with ASCVD [21]. However our meta-analysis clearly depicts that GLP1RA would be at the heart of treatment for patients with atherosclerotic disease like MI, Stroke, while SGLT2-i would be more suitable for preventing hospitalization for heart failure.

With elegant data supporting the metabolic benefits of SGLT2-i and GLP1-RA combination therapy, it would probably be most opportune to treat T2D patients with a combination of both these drugs.

5. Conclusion

This meta-analysis confirms that DPP-4i are neutral as a group in all aspects of cardiovascular disease. SGLT2-i show a definite benefit in reduction of hospitalization for heart failure but are largely neutral otherwise. GLP1-RA as a class reduce risk of atherosclerotic vascular disease showing a significant reduction in myocardial infarction and stroke and a combination of both. The ideal treatment regimen in T2D with established CVD would therefore be a combination of GLP1-RA and SGLT2-i on a background of Metformin therapy to address the entire cardiovascular composite.

Contributors

BS contributed to conceptualizing and formulating the study design. Both BS &SG performed the literature search and performed the meta-analysis along with constructing the figures and tables. BS analyzed the data and prepared the manuscript. The final write-up and editing was done by BS.

Conflict of interest & funding

None to declare.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.02.014.

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