The Association between Baseline Insulin Treatment and Cardiovascular Events: A Meta-Analysis

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Khatib, Shao and Shi have nothing to disclose

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Abstract

We conducted a meta-analysis to compare major adverse cardiovascular events (MACE) in recent diabetes type 2 drugs cardiovascular outcome trials (CVOTs) in the subgroups that used insulin at baseline to the subgroups that did not.

English publications from 2010 to 2019 were searched in PubMed and Google Scholar. We searched published clinical trials for CVOTs with new drugs for type 2 diabetes and found 12 publications, of which 8 provided outcomes according to insulin use. We compared the event rate of the primary outcome in the group taking insulin with the one not taking insulin. Data was extracted by two investigators independently including: CVOT drug, publication year, sample size, duration of diabetes, mean hemoglobin A1c, mean age, number of patients in each treatment group.

We included 8 trials in the analysis: DECLARE, EMPAREG, EXSCEL, HARMONY, LEADER, SUSTAIN6, EXAMINE, and SAVOR-TIMI. The pooled relative risk was 1.52 (95% CI: 1.43~1.62) when comparing the treatment group with insulin at baseline with the treatment group of patients without insulin use.

In recent CVOTs, patients on Insulin regimen along with the new antidiabetic drug had higher RR of cardiovascular events than patients who used the new antidiabetic drug alone.

Keywords: type 2 diabetes, cardiovascular outcomes, trials
Introduction

In 2016, the statistics from the Centers for Disease Control and Prevention (CDC) showed that 23 million adults in the US were diagnosed with diabetes. Diabetes carries a two to three-fold increase in atherosclerotic disease in both men and women, including intermittent claudication, congestive heart disease and coronary artery disease. Multiple studies confirmed that patients with diabetes have higher mortality rates due to cardiovascular disease compared to patients that did not have diabetes.

In 2008, the Food and Drug Administration mandated that sponsors for new type 2 diabetes agents prove that therapy would not cause increased cardiovascular risk beyond a specified threshold based on findings of RECORD trial. There were 12 published cardiovascular outcome clinical trials (CVOTs) comparing the new drugs for type 2 diabetes to placebo from 2013. These trials included 3 sodium-glucose co-transporter 2 inhibitors (SGLT-2), 6 glucagon-like peptide-1 receptor agonists (GLP-1), and 3 dipeptidyl peptidase-4 inhibitors (DPP-4).

The CVOTs for SGLT-2 inhibitors and GLP-1 agonists showed that patients who were treated with these drugs had lower risk of cardiovascular events than patients treated with placebo, while CVOTs that had patients treated with DPP-4 inhibitors did not show cardiovascular benefit nor harm.

Most recent CVOTs focused on cardiovascular outcomes when patients were taking the drugs vs placebo or compared different diabetes drugs, it is unclear how the cardiovascular health is affected when patients’ regimen included insulin and other type 2 diabetes drugs. This is a very popular regimen and is often clinically used. Cosmi et al analyzed data to determine whether patients that used insulin had worse outcomes in heart failure patients, they concluded that insulin was associated with higher risks of death and hospitalizations in heart failure patients. Mendez et al did a cross sectional analysis of NHANES database to evaluate the relationship between insulin use and clinical outcomes including mortality, major cardiovascular outcome (MACE), and diabetic kidney disease. They
concluded that insulin use was associated with higher mortality, MACE and DKD in patients that had higher insulin resistance\textsuperscript{21}.

The CVOTs for the new type 2 diabetes drugs had good follow-up of subjects and adjudication of events, the trials included many patients taking insulin at baseline, which allowed us to examine the outcome when patients received the new diabetes agents along with insulin at baseline. As far as we know there has not been any previous analysis of CVOTs to examine the effect of insulin and diabetes drugs combination on cardiovascular events. This is a meta-analysis to assess the effect of combining the new diabetes type 2 agents with insulin on cardiovascular outcomes among diabetes population in the CVOTs.

**Materials and Methods**

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines\textsuperscript{22}.

**Data Sources and Searches**

PubMed and Google Scholar were used to search for the published clinical trials. Key words used in the search were “diabetes type 2”, “cardiovascular”, “outcome” and “trials”.

**Study Selection**

Eligible studies were included if they were trials of antidiabetics within insulin. In addition, the primary outcome of these trials should be a composite of major adverse cardiovascular events (MACE), such as cardiovascular death, myocardial infarction, or ischemic stroke. Trials were excluded if the primary outcome was not reported by insulin subgroups.

**Data Extraction**

After removing all duplicated articles, each of the potential titles and abstract was screened. Full texts of potentially relevant studies were then retrieved and assessed to determine eligibility for inclusion
according to established criteria detailed above (fig. 1). Data extraction for each study included CVOT drug, publication year, sample size, duration of diabetes, mean hemoglobin A1c, mean age, number of patients that were using insulin at baseline and were randomized to the drug, number of patients who were not using insulin at baseline and were randomized to the drug, number of patients who were using insulin at baseline and were randomized to the placebo, number of patients who were not using insulin at baseline and were randomized to the placebo, and number of primary outcome events in these subgroups. Any uncertainties or discrepancies between the two reviewers were resolved through consensus or consultation with another reviewer. Each study in this meta-analysis was assessed using Quality Assessment of Controlled Intervention Studies from the National Institute of Health which includes a series of criteria to rate quality. There was no attempt to contact authors during the study period.

Data Synthesis and Analysis

Studies only provided hazard ratios (HRs) for some comparison groups and there were no available data for us to calculate HRs for other interested comparison groups; therefore, we decided to calculate risk ratios (RRs) for all comparison groups based on number of cases and non-cases in each group provided in these studies for the consistency. We reported RRs for 4 comparison groups to compare the associations between new diabetes medicine treatment with or without insulin usage and cardiovascular events. Four group sets were listed as the following: new drug treatment without baseline insulin versus placebo without baseline insulin, new drug treatment with baseline insulin versus new drug treatment without baseline insulin, new drug treatment with baseline insulin versus placebo with baseline insulin, and placebo with baseline insulin versus placebo without baseline insulin. Heterogeneity was assessed using \( I^2 \) statistics, a value >50% was considered a measure of severe heterogeneity. Summary estimates of RRs and 95% CIs for the estimates were derived using the Dersimonian and Liard random effects model to account for the inter-study differences because this model is often used for meta-analysis of clinical studies. For the sensitivity analysis, we conducted the all analysis again excluding clinical trials of DPP-4 given they did not demonstrate cardiovascular benefit. The meta-analysis was performed using Stata 15.1 software package.
Publication bias was not assessed because the number of trials (<10) was inadequate to properly examine a funnel plot or to use more advanced regression-based assessments.  

Results  

We identified 12 cardiovascular outcome trials for Type 2 Diabetes drugs (table 1), however only 8 had all of the data required to perform our analysis (table 2). The CANVAS trial provided the number of cases but without number of patients in each subgroup, therefore, we could not get the RR and compare it with RRs from other trials. The TECOS trial did not provide the event number in the placebo group with baseline insulin. REWIND did not provide number of events in the insulin at baseline subgroup, and lastly, the ELIXA trial did not provide the number of primary outcome events in the group that was taking insulin at baseline.

For our analysis, we included 8 CVOTs for the Type 2 Diabetes drug therapy; 2 studies for sodium-glucose co-transporter 2 inhibitors (SGLT-2), 4 studies for glucagon-like peptide-1 receptor agonists (GLP-1), and 2 studies for dipeptidyl peptidase-4 inhibitors (DPP-4).

The EXAMINE and SAVOR-TIMI53 trials were removed for the sensitivity analysis, given that DPP-4 inhibitor drugs did not show cardiovascular benefit in their individual trials, so 6 CVOTs that consisted of 2 SGLT-2 inhibitors and 4 GLP-1 agonists were included.

The main meta-analysis results of four forest plots with RRs (95% CIs) for four group sets were showed in Figure 2. The first plot (a) compares the investigational drug with the placebo which was the primary objective of each of the individual trials. Plot (b) compares patients using the investigational drug with insulin at baseline with patients using the drug with no insulin at baseline. Plot (c) compares patients using insulin at baseline and the investigational drug with patients using insulin at baseline and placebo. Finally, plot (d) compares patients using insulin at baseline and placebo with patients not using insulin at baseline and also receiving placebo.
As shown in Figure 2. (a), the pooled RR of 0.85 (95% CI: 0.77–0.95) indicated that treatment with any new antidiabetic drugs but without insulin for type 2 diabetes was significantly associated with cardiovascular benefit compared with patients in the placebo group without insulin treatment at baseline. In patients who received insulin treatment at baseline, there was still a significant benefit in cardiovascular risk reduction with the study drug with a RR of 0.93 (95% CI: 0.88–0.98) as shown in Figure 2. (c). Adverse effects on cardiovascular outcomes were significantly associated with baseline insulin treatment in type 2 diabetes patients for both drug treatment groups (Figure 2. (b)) and placebo groups (Figure 2. (d)) with an RR of 1.52 (95% CI: 1.43–1.62) and 1.33 (95% CI: 1.16–1.52) respectively. The random effect model was applied in group (a) and group (d) separately because there was significant heterogeneity (I² >50%) for the association between diabetes treatment and risk of cardiovascular outcomes.

After excluding the 2 DPP-4 inhibitor studies, the associations of new treatment vs placebo were similar and statistically significant after the sensitivity analysis was done with a RR of 0.83 (95% CI: 0.72–0.96) as shown in Figure 3. (a). There was a statistically significant association shown in Figure 3. (c); patients who were treated with baseline insulin and the drug were less likely to experience cardiovascular events compared with those who just received baseline insulin and the placebo in trials with a RR of 0.89 (95% CI: 0.84–0.95). We found a statistically significant RR for cardiovascular events, 1.46 (95% CI: 1.35–1.57), when comparing patients received the drug treatment and baseline insulin with those received drug treatment alone (Figure 3. (b)). Comparing patients who received placebo treatment with insulin at baseline compared to placebo treatment only in Figure 3. (d), the RR is also statistically significant with 1.30 (95% CI: 1.09–1.56).

Discussion

This meta-analysis of CVOTs demonstrates that prior insulin treatment may attenuate the benefit seen with GLP-1 receptor agonists and SGLT-2 inhibitors when used in combination with insulin. Recent trials have shown that Canagliflozin, a SGLT-2 inhibitor, lowered the risk of cardiovascular events.
while Empagliflozin and Dapagliflozin had lower rates of cardiovascular outcomes and death\textsuperscript{10,11}. GLP-1 agonists trials showed that Lixisenatide and Exenatide did not have a significant difference in cardiovascular outcome when they were compared to placebo\textsuperscript{12,13}. Meanwhile, Albiglutide was shown to have cardiovascular benefit\textsuperscript{14}, while Semaglutide decreased the rates of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke\textsuperscript{15}. Another CVOT showed that the rate of first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke was lower in the group that took Liraglutide\textsuperscript{16}.

For those participants without baseline insulin, participants received the investigational drug treatment had lower risk of suffering from cardiovascular events. This result was expected given that most of these drugs provided cardiovascular benefit in their trials.

The cardiovascular events in the group that used insulin at baseline with the diabetes type 2 drugs had fewer events RR: 0.93 (95% CI 0.88-0.98) compared to the placebo group that used insulin at baseline. When the sensitivity analysis was done this result was still statistically significant RR: 0.89 (95% CI 0.84-0.95). There were fewer MACE outcomes in the groups that were treated with insulin at baseline with the drugs added, showing that the benefit of GLP-1 receptor agonists or SGLT-2 inhibitors remains evident in insulin treated patients, although the benefit is less than in patients who never received insulin. It is also important to note that not all GLP-1 RAs and SGLT2i have similar benefits.

Next, we compared cardiovascular outcomes in the group that used insulin with the investigational drugs vs the group that used the drugs without insulin at baseline, which was the primary objective of this meta-analysis. The group that used insulin and the drugs had more cardiovascular events than those that did not use insulin at baseline RR: 1.52 (95% CI 1.43-1.62). Results were consistent in the sensitivity analysis RR: 1.46 (95% CI 1.35-1.57). The results of comparing event rate in the group that used placebo with insulin versus the group that used placebo only was also consistent; it showed the group that used both insulin and placebo had more cardiovascular events RR: 1.33 (95% CI 1.16-
The result in the sensitivity analysis was still significant and compatible with a RR of 1.30 (95% CI 1.09-1.56).

The results above showed that patients using insulin had more cardiovascular events whether they used the new diabetes drugs or not. Our hypothesis for explaining the trend was that patients who were using insulin at baseline had diabetes for longer duration, probably had worse control and severer disease requiring insulin treatment, therefore, they were at higher risk for diabetes complications including cardiovascular disease.

Cosmi et al analyzed two datasets that included 24,012 heart failure patients, this data was obtained from four large randomized trials and an administrative database of 4 million patients. Patients that had diabetes and were treated with insulin had more severe heart failure than patients who were not taking insulin. Patients that were taking insulin had higher rates of mortality and heart failure hospitalizations. The survival was also lower in this group. The authors proposed the rationale behind the results was that insulin causes sodium and water retention, hypoglycemia was also more common which caused adrenergic activations, myocardial ischemia leading to lethal arrhythmia and causing a pro thrombotic state. However, the study was done in the highest risk patients and the results may not apply to a less severe disease state.

There was a cross sectional study done by Mendez et al and its purpose was to evaluate the insulin effect on clinical outcomes including mortality, MACE and diabetic kidney disease. They analyzed 3,124 diabetes patients using the NHANES database from 2001 to 2010 and these patients were segregated into high or low HOMA-IR groups. Results showed that there was a significant association between insulin use and increased mortality, MACE and diabetic kidney disease in the high HOMA-IR group but this relationship was not significant in low HOMA-IR group. Although the lack of randomization and interaction with insulin sensitivity makes the data less useful in clinical practice, this study suggested that insulin therapy may be less beneficial and potentially harmful for patients with high insulin resistance. Cardioprotective drugs might be deployed earlier to prevent the adverse effect of insulin resistance.
It is critical that we clarify we are not advising against the use of insulin. Multiple randomized controlled trials provided evidence that insulin is necessary to achieve glycemic control and is not associated with increased risk for cardiovascular events. A literature review of all randomized clinical trials (20) analyzing insulin against Diabetes type 2 drugs between 1950-2013 showed that insulin had no effect on all-cause mortality RR 0.99 (95% CI 0.92-1.06) or cardiovascular mortality RR 0.99 (95% CI 0.77-1.18).  

The strength of our meta-analysis lies in the large population of 82,904 patients included; of these, 37,352 used insulin at baseline while 45,552 did not. The trials were well conducted with robust adjudications of events. The weakness of our analysis is mostly due to the fact that we were unable to include all of the CVOTs, and inaccessibility to patient level data. We also attempted to stratify patients by insulin use duration and diabetes severity, however most of the studies did not provide the data needed. Some attempts were made to obtain patient level data however no data were obtained. We did not try to contact the authors directly for the missing data. The lack of patient level data was also limiting the adjustment for patients’ characteristics. Besides, most of these trials attempted to achieve glycemic equipoise between treatment group and placebo group by adding medication. We are unable to gauge the confounding effect of this post-randomization treatment on our results.

In conclusion, our meta-analysis has shown that in the recent CVOTs for Diabetes Type 2 Drugs, the use of these drugs (GLP-1 agonists and SGLT-2 inhibitors) led to reduction in cardiovascular events, this was seen whether patients were using insulin at baseline or were not. The cardiovascular benefit was significantly less though when patients were using insulin at baseline. We believe that as the disease progresses the benefit is attenuated, therefore it may be important to use these drugs early on in the disease before it progresses, and even in insulin treated patients, there is still a cardiovascular benefit gained when a GLP-1 or an SGLT-2 inhibitor is added to the treatment regimen. The need for insulin may serve as a surrogate marker of likelihood of lower benefit.
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Khatib did most of the database search, data collection, and writing of the manuscript.

Shao did the data analysis under Dr Lizheng’s supervision and wrote the methods and results sections.

Dr Fonseca is the guarantor.

Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.
References

1. BULLARD, K. M. et al. Prevalence of Diagnosed Diabetes in Adults by Diabetes Type - United States, 2016. MMWR Morb Mortal Wkly Rep, v. 67, n. 12, p. 359-361, Mar 2018. ISSN 1545-861X. Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/29596402 >.

2. KANNEL, W. B.; MCGEE, D. L. Diabetes and cardiovascular disease. The Framingham study. JAMA, v. 241, n. 19, p. 2035-8, May 1979. ISSN 0098-7484. Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/430798 >.

3. HAFFNER, S. M. et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med, v. 339, n. 4, p. 229-34, Jul 1998. ISSN 0028-4793. Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/9673301 >.

4. ABBOTT, R. D. et al. The impact of diabetes on survival following myocardial infarction in men vs women. The Framingham Study. JAMA, v. 260, n. 23, p. 3456-60, Dec 1988. ISSN 0098-7484. Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/2974889 >.

5. HERLITZ, J. et al. Prognosis in diabetics with chest pain or other symptoms suggestive of acute myocardial infarction. Cardiology, v. 80, n. 3-4, p. 237-45, 1992. ISSN 0008-6312. Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/1511471 >.

6. MIETTINEN, H. et al. Impact of diabetes on mortality after the first myocardial infarction. The FINMONICA Myocardial Infarction Register Study Group. Diabetes Care, v. 21, n. 1, p. 69-75, Jan 1998. ISSN 0149-5992. Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/9538972 >.

7. MCGUIRE, D. K. et al. FDA guidance on antihyperglycemic therapies for type 2 diabetes: One decade later. Diabetes Obes Metab, v. 21, n. 5, p. 1073-1078, May 2019. ISSN 1463-1326. Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/30690856 >.

8. HOLMAN, R. R.; SOURIJ, H.; CALIFF, R. M. Cardiovascular outcome trials of glucose-lowering drugs or strategies in type 2 diabetes. Lancet, v. 383, n. 9933, p. 2008-17, Jun 2014. ISSN 1474-547X. Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/24910232 >.

9. NEAL, B. et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med, v. 377, n. 7, p. 644-657, 08 2017. ISSN 1533-4406. Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/28605608 >.
ZINMAN, B. et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*, v. 373, n. 22, p. 2117-28, 11 2015. ISSN 1533-4406. Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/26378978>.

WIVIOTT, S. D. et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*, v. 380, n. 4, p. 347-357, 01 2019. ISSN 1533-4406. Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/30415602>.

PFEFFER, M. A. et al. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. *N Engl J Med*, v. 373, n. 23, p. 2247-57, Dec 2015. ISSN 1533-4406. Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/26630143>.

HOLMAN, R. R. et al. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*, v. 377, n. 13, p. 1228-1239, 09 2017. ISSN 1533-4406. Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/28910237>.

HERNANDEZ, A. F. et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet*, v. 392, n. 10157, p. 1519-1529, 10 2018. ISSN 1474-547X. Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/30291013>.

MARSO, S. P.; HOLST, A. G.; VILSBØLL, T. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*, v. 376, n. 9, p. 891-2, 03 2017. ISSN 1533-4406. Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/28249135>.

MARSO, S. P. et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*, v. 375, n. 4, p. 311-22, 07 2016. ISSN 1533-4406. Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/27295427>.

WHITE, W. B. et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med*, v. 369, n. 14, p. 1327-35, Oct 2013. ISSN 1533-4406. Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/23992602>.

SCIRICA, B. M. et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*, v. 369, n. 14, p. 1317-26, Oct 2013. ISSN 1533-4406. Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/23992601>.

GREEN, J. B. et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*, v. 373, n. 3, p. 232-42, Jul 2015. ISSN 1533-4406. Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/26052984>.

COSMI, F. et al. Treatment with insulin is associated with worse outcome in patients with chronic heart failure and diabetes. *Eur J Heart Fail*, v. 20, n. 5, p. 888-895, 05 2018. ISSN 1879-0844. Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/29488676>.
21 MENDEZ, C. E. et al. Insulin therapy in patients with type 2 diabetes and high insulin resistance is associated with increased risk of complications and mortality. *Postgrad Med*, p. 1-7, Jul 2019. ISSN 1941-9260. Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/31311382>.

22 MOHER, D. et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*, v. 4, p. 1, Jan 2015. ISSN 2046-4053. Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/25554246>.

23 HIGGINS, J. P. T.; GREEN, S. *Recommendations on testing for funnel plot asymmetry. Cochrane handbook for systematic reviews of interventions*; Chichester: The Cochrane Collaboration 2011.

24 ERPELDINGER, S. et al. Efficacy and safety of insulin in type 2 diabetes: meta-analysis of randomised controlled trials. *BMC Endocr Disord*, v. 16, n. 1, p. 39, Jul 2016. ISSN 1472-6823. Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/27391319>.

25 GERSTEIN, H. C. et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet*, v. 394, n. 10193, p. 121-130, 07 2019. ISSN 1474-547X. Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/31189511>.
Publications from 2010 to 2019 identified through PubMed and Google Scholar (n = 8,865)

Records after duplicates removed (n = 1681)

Records screened for title and abstract review (n = 12)

Records excluded (n = 0)

Full-text articles excluded (n = 4)

Trials that did not provide cardiovascular outcome by insulin use at baseline subgroups

Full-text articles assessed for eligibility (n = 12)

Studies included in meta-analysis (n = 8)

Figure 1. Literature review flow chart
Table (1) all the published CVOTs for new DM type 2 drugs

*Trials were excluded due to lack of data

| Trial          | Drug     | Mechanism of action   |
|----------------|----------|-----------------------|
| CANVAS\textsuperscript{9} | Canagliflozin | SGLT-2 inhibitor   |
| EMPAREG\textsuperscript{10} | Empagliflozin | SGLT-2 inhibitor   |
| DECLARE TIMI58\textsuperscript{11} | Dapagliflozin | SGLT-2 inhibitor   |
| ELIXA\textsuperscript{12} | Lixisenatide | GLP-1 receptor agonist |
| EXSCHEL\textsuperscript{13} | Exenatide | GLP-1 receptor agonist |
| HARMONY\textsuperscript{14} | Albiglutide | GLP-1 receptor agonist |
| SUSTAIN6\textsuperscript{15} | Semaglutide | GLP-1 receptor agonist |
| LEADER\textsuperscript{16} | Liraglutide | GLP-1 receptor agonist |
| EXAMINE\textsuperscript{17} | Alogliptin | DPP-4 inhibitor |
| SAVOR-TIMI53\textsuperscript{18} | Saxagliptin | DPP-4 inhibitor |
| TECOS\textsuperscript{19} | Sitagliptin | DPP-4 inhibitor |
| REWIND\textsuperscript{20} | Dalaglutide | GLP-1 receptor agonist |
Table (2) Characteristics of included studies

| Trial          | Drug       | Mean Age (yrs.) | Duration of diabetes (yrs.) | Number of patients | Mean HgbA1c (%) | No. of pts on insulin at baseline | No. of pts not on insulin at baseline |
|----------------|------------|-----------------|-----------------------------|--------------------|----------------|-----------------------------------|---------------------------------------|
| EMPAREG\textsuperscript{10} | Empagliflozin | 63              | 57% of pts >10 yrs.         | 7,028              | 8.1            | 3,387                            | 3,633                                 |
| DECLARE TIMI58\textsuperscript{11} | Dapagliflozin | 64              | 11                          | 17,160             | 8.3            | 7,013                            | 10,147                                |
| EXSCEL\textsuperscript{13} | Exenatide | 62              | 12                          | 14,752             | 8.0            | 6,836                            | 7,916                                 |
| HARMONY\textsuperscript{14} | Albiglutide | 64              | 14                          | 9,463              | 8.7            | 5,597                            | 3,866                                 |
| SUSTAIN6\textsuperscript{15} | Semaglutide | 65              | 14                          | 3,297              | 8.7            | 1,913                            | 1,384                                 |
| LEADER\textsuperscript{16} | Liraglutide | 64              | 13                          | 9,340              | 8.7            | 4,169                            | 5,171                                 |
| EXAMINE\textsuperscript{17} | Alogliptin | 61              | 7.2                         | 5,380              | 8.0            | 1,605                            | 3,775                                 |
| SAVOR-TIMI53\textsuperscript{18} | Saxagliptin | 65              | 10                          | 16,492             | 8.0            | 6,832                            | 9,660                                 |
| Total patients | -          | -               | -                           | -                  | -              | 37,352 (45%)                     | 45,552 (55%)                         |
(a). New treatment without insulin VS placebo without insulin

(b). New treatment with insulin VS new treatment

(c). New treatment with insulin VS insulin with placebo

(d). Insulin with placebo VS placebo

Figure 2. Results of meta-analysis
(a). New treatment VS placebo

(b). New treatment with insulin VS new treatment

(c). New treatment with insulin VS insulin with placebo

(d). Insulin with placebo VS placebo

Figure 3. Sensitivity analysis after excluding studies of DPP-4