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META-ANALYSIS

# Cardiovascular efficacy and safety of dipeptidyl peptidase-4 inhibitors: A meta-analysis of cardiovascular outcome trials

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**Author contributions:** Patoulias DI and Doumas M conceived and designed the study; Patoulias DI, Boulmpou A and Teperikidis E collected and analyzed data; Patoulias DI, Boulmpou A and Siskos F performed study quality and risk of bias assessment; Patoulias DI, Boulnpou A, Katsimardou A and Papadopoulos CE wrote the first draft of the study; Doumas M and Vassilikos V critically revised the final draft.

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## Abstract

### *BACKGROUND*

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a generally safe and well tolerated antidiabetic drug class with proven efficacy in type 2 diabetes mellitus (T2DM). Recently, a series of large, randomized controlled trials (RCTs) addressing cardiovascular outcomes with DPP-4 inhibitors have been published.

### *AIM*

To pool data from the aforementioned trials concerning the impact of DPP-4 inhibitors on surrogate cardiovascular efficacy outcomes and on major cardiac arrhythmias.

### *METHODS*

We searched PubMed and grey literature sources for all published RCTs assessing cardiovascular outcomes with DPP-4 inhibitors compared to placebo until October 2020. We extracted data concerning the following "hard" efficacy outcomes: fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, hospitalization for heart failure, hospitalization for unstable angina, hospitalization for coronary revascularization and cardiovascular death. We also extracted data regarding the risk for major cardiac arrhythmias, such as atrial fibrillation, atrial flutter, ventricular fibrillation and ventricular tachycardia.

### *RESULTS*

We pooled data from 6 trials in a total of 52520 patients with T2DM assigned either to DPP-4 inhibitor or placebo. DPP-4 inhibitors compared to placebo led to

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a non-significant increase in the risk for fatal and non-fatal myocardial infarction [risk ratio (RR) = 1.02, 95%CI: 0.94-1.11, $I^2$ = 0%], hospitalization for heart failure (RR = 1.09, 95%CI: 0.92-1.29, $I^2$ = 65%) and cardiovascular death (RR = 1.02, 95%CI: 0.93-1.11, $I^2$ = 0%). DPP-4 inhibitors resulted in a non-significant decrease in the risk for fatal and non-fatal stroke (RR = 0.96, 95%CI: 0.85-1.08, $I^2$ = 0%) and coronary revascularization (RR = 0.99, 95%CI: 0.90-1.09, $I^2$ = 0%), Finally, DPP-4 inhibitors demonstrated a neutral effect on the risk for hospitalization due to unstable angina (RR = 1.00, 95%CI: 0.85-1.18, $I^2$ = 0%). As far as cardiac arrhythmias are concerned, DPP-4 inhibitors did not significantly affect the risk for atrial fibrillation (RR = 0.95, 95%CI: 0.78-1.17, $I^2$ = 0%), while they were associated with a significant increase in the risk for atrial flutter, equal to 52% (RR = 1.52, 95%CI: 1.03-2.24, $I^2$ = 0%). DPP-4 inhibitors did not have a significant impact on the risk for any of the rest assessed cardiac arrhythmias.

*CONCLUSION*

DPP-4 inhibitors do not seem to confer any significant cardiovascular benefit for patients with T2DM, while they do not seem to be associated with a significant risk for any major cardiac arrhythmias, except for atrial flutter. Therefore, this drug class should not be the treatment of choice for patients with established cardiovascular disease or multiple risk factors, except for those cases when newer antidiabetics (glucagon-like peptide-1 receptor agonists and sodium-glucose co-transporter-2 inhibitors) are not tolerated, contraindicated or not affordable for the patient.

**Key Words:** Dipeptidyl peptidase-4 inhibitors; Cardiovascular outcomes; Atrial fibrillation; Atrial flutter; Type 2 diabetes mellitus



**Core Tip:** The antidiabetic efficacy of dipeptidyl peptidase-4 (DPP-4) inhibitors has already been proven in recently published large randomized controlled trials. The purpose of the present meta-analysis was to clarify the impact of antidiabetic therapy with DPP-4 inhibitors on surrogate cardiovascular outcomes, and to elucidate the effect of these drugs on major cardiac arrhythmias. According to our analysis, this drug class does not significantly affect the risk for any of the addressed cardiovascular outcomes; however, it increases the risk for atrial flutter compared to placebo.

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## INTRODUCTION

It is well-established that type 2 diabetes mellitus (T2DM) represents an independent risk factor for the development of cardiovascular disease, which accounts for half of deaths among diabetic patients[1]. Patients with T2DM experience higher incidence of vascular interventions compared to high-risk patients without T2DM or cardiovascular disease at baseline, underscoring the necessity for targeted therapeutic interventions[2]. In addition, development of cardiovascular complications among patients with T2DM boosts medical costs, leading to an unbearable economic burden [3]. Besides major adverse cardiovascular events, patients with T2DM experience an increased risk of heart rhythm disorders, nevertheless the exact mechanisms of arrhythmogenesis in the context of T2DM are still under investigation[4].

Dipeptidyl peptidase-4 (DPP-4) inhibitors constitute a safe treatment option with adequate glycemic efficacy in T2DM. However, their cardiovascular efficacy has been

doubted over recent years, after the publication of relevant cardiovascular outcome trials. Previous meta-analyses failed to show any cardiovascular benefit with their use in patients with T2DM[5-7]. Since then, additional randomized controlled trials addressing "hard" cardiovascular outcomes with DPP-4 inhibitors have been published. Therefore, we sought to update and extend these meta-analyses, by incorporating all relevant data from published cardiovascular outcome trials until October 2020. In addition, we planned to assess the effect of DPP-4 inhibitors on major cardiac arrhythmias, since there are no relevant studies published in the literature so far.

## MATERIALS AND METHODS

Our meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We searched PubMed database and grey literature sources form inception to October 2020, in order to identify relevant cardiovascular outcome trials assessing the cardiovascular efficacy and safety of DPP-4 inhibitors in patients with T2DM. Our inclusion criteria were: (1) Randomized controlled trials; (2) Enrollment of patients with T2DM; (3) Enrollment of adult patients; and (4) Assessment of at least one cardiovascular outcome of interest. Our exclusion criteria were: (1) Observational studies; (2) Studies enrolling patients with type 1 diabetes mellitus; and (3) Studies enrolling children or adolescents.

We utilized the following search terms: "DPP-4 inhibitor", "dipeptidyl peptidase-4 inhibitor", "vildagliptin", "sitagliptin", "alogliptin", "linagliptin", "saxagliptin", "omarigliptin", "tenegliptin", "evogliptin", "gliptin", "cardiovascular outcome", "cardiac arrhythmia", "atrial fibrillation" combined with the use of Boolean operators "AND" and "OR". We used both free-text words and MeSH terms. We did not imply any filter regarding study setting, study sample, language or publication date. Unfortunately, we did not registered prospectively our protocol in a publicly available repository.

After de-duplication and assessment of eligible studies at title and abstract level for potential inclusion, two independent reviewers (D.P. and E.T.) extracted the data from the eligible reports, by using a pilot tested, data extraction form. We assessed the following cardiovascular efficacy outcomes: fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, hospitalization for heart failure, hospitalization for unstable angina, hospitalization for coronary revascularization and cardiovascular death. We also assessed the risk for the following cardiac arrhythmias with DPP-4 inhibitor treatment compared to placebo or active comparator: atrial fibrillation, atrial flutter, atrial tachycardia, ventricular fibrillation, ventricular tachycardia, ventricular extrasystoles, supraventricular tachycardia, sinus node dysfunction, second degree atrioventricular block, complete atrioventricular block.

As we assessed only dichotomous variables, differences were calculated with the use of risk ratio (RR), with 95% confidence interval (CI), after implementation of the Mantel-Haenszel random effects formula. Statistical heterogeneity among studies was assessed by using $I^2$ statistics. Heterogeneity was considered to be low if $I^2$ was between 0% and 25%, moderate if $I^2$ was between 25% and 50%, or high if $I^2$ was greater than 75%[8]. All analyses were performed at the 0.05 significance level, while they were undertaken with RevMan 5.3 software.

Two independent reviewers (D.P. and A.B.) assessed the quality of the included RCTs, by using the Revised Cochrane risk of bias tool for randomized trials (RoB 2.0) for the primary efficacy outcome[9]. Discrepancies between reviewers were solved by discussion, consensus or arbitration by a third senior reviewer (V.V.).

## RESULTS

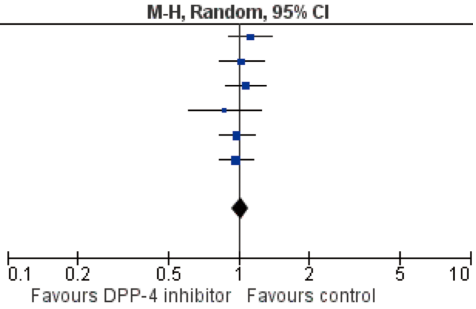
We finally pooled data from six trials in a total of 52520 patients[10-15]. Overall risk of bias was considered as low across all selected trials.

DPP-4 inhibitor treatment did not significantly affect any of the prespecified cardiovascular efficacy outcomes. More specifically, DPP-4 inhibitors compared to control led to a non-significant increase in the risk for fatal and non-fatal myocardial infarction (RR = 1.02, 95%CI: 0.94-1.11, $I^2$ = 0%), hospitalization for heart failure (RR = 1.09, 95%CI: 0.92-1.29, $I^2$ = 65%) and cardiovascular death (RR = 1.02, 95%CI: 0.93-1.11, $I^2$ = 0%), as shown in Figures 1A, 1C and 1F. In addition, DPP-4 inhibitors produced a non-significant decrease in the risk for fatal and non-fatal stroke (RR = 0.96, 95%CI:

**A**

| Study or Subgroup | DPP-4 inhibitor Events | Total | Control Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| CARMELINA | 165 | 3494 | 146 | 3485 | 14.8% | 1.13 [0.91, 1.40] |
| CAROLINA | 153 | 3023 | 148 | 3010 | 14.5% | 1.03 [0.83, 1.28] |
| EXAMINE | 187 | 2701 | 173 | 2679 | 17.6% | 1.07 [0.88, 1.31] |
| NCT01703208 | 52 | 2092 | 60 | 2100 | 5.2% | 0.87 [0.60, 1.25] |
| SAVOR-TIMI 53 | 234 | 8240 | 236 | 8173 | 22.1% | 0.98 [0.82, 1.18] |
| TECOS | 269 | 7257 | 276 | 7266 | 25.8% | 0.98 [0.83, 1.15] |
| **Total (95% CI)** | | **26807** | | **26713** | **100.0%** | **1.02 [0.94, 1.11]** |
| Total events | 1060 | | 1039 | | | |

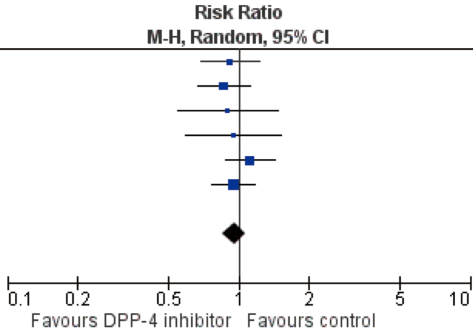
Heterogeneity: Tau² = 0.00; Chi² = 2.21, df = 5 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.39 (P = 0.69)




**B**

| Study or Subgroup | DPP-4 inhibitor Events | Total | Control Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| CARMELINA | 81 | 3494 | 88 | 3485 | 15.4% | 0.92 [0.68, 1.24] |
| CAROLINA | 104 | 3023 | 120 | 3010 | 20.7% | 0.86 [0.67, 1.12] |
| EXAMINE | 29 | 2701 | 32 | 2679 | 5.5% | 0.90 [0.55, 1.48] |
| NCT01703208 | 32 | 2092 | 34 | 2100 | 6.0% | 0.94 [0.59, 1.53] |
| SAVOR-TIMI 53 | 135 | 8240 | 120 | 8173 | 23.0% | 1.12 [0.87, 1.42] |
| TECOS | 157 | 7257 | 165 | 7266 | 29.4% | 0.95 [0.77, 1.18] |
| **Total (95% CI)** | | **26807** | | **26713** | **100.0%** | **0.96 [0.85, 1.08]** |
| Total events | 538 | | 559 | | | |

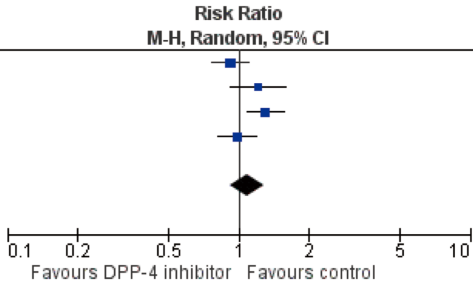
Heterogeneity: Tau² = 0.00; Chi² = 2.28, df = 5 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.70 (P = 0.48)




**C**

| Study or Subgroup | DPP-4 inhibitor Events | Total | Control Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| CARMELINA | 209 | 3494 | 226 | 3485 | 27.1% | 0.92 [0.77, 1.11] |
| CAROLINA | 112 | 3023 | 92 | 3010 | 19.8% | 1.21 [0.92, 1.59] |
| SAVOR-TIMI 53 | 256 | 8240 | 194 | 8173 | 26.9% | 1.31 [1.09, 1.57] |
| TECOS | 200 | 7257 | 202 | 7266 | 26.2% | 0.99 [0.82, 1.20] |
| **Total (95% CI)** | | **22014** | | **21934** | **100.0%** | **1.09 [0.92, 1.29]** |
| Total events | 777 | | 714 | | | |

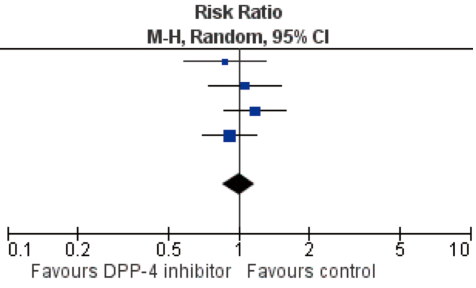
Heterogeneity: Tau² = 0.02; Chi² = 8.53, df = 3 (P = 0.04); I² = 65%
Test for overall effect: Z = 0.99 (P = 0.32)




**D**

| Study or Subgroup | DPP-4 inhibitor Events | Total | Control Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| CARMELINA | 42 | 3494 | 48 | 3485 | 15.3% | 0.87 [0.58, 1.32] |
| CAROLINA | 60 | 3023 | 56 | 3010 | 19.9% | 1.07 [0.74, 1.53] |
| SAVOR-TIMI 53 | 89 | 8240 | 75 | 8173 | 27.7% | 1.18 [0.87, 1.60] |
| TECOS | 104 | 7257 | 114 | 7266 | 37.2% | 0.91 [0.70, 1.19] |
| **Total (95% CI)** | | **22014** | | **21934** | **100.0%** | **1.00 [0.85, 1.18]** |
| Total events | 295 | | 293 | | | |

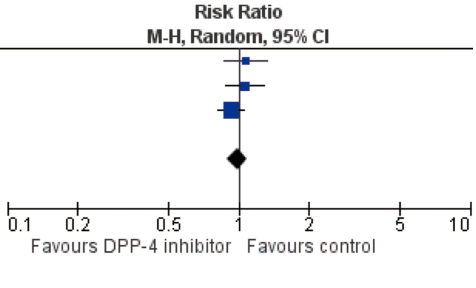
Heterogeneity: Tau² = 0.00; Chi² = 2.09, df = 3 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.04 (P = 0.97)




**E**

| Study or Subgroup | DPP-4 inhibitor Events | Total | Control Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| CARMELINA | 160 | 3494 | 149 | 3485 | 20.2% | 1.07 [0.86, 1.33] |
| CAROLINA | 202 | 3023 | 189 | 3010 | 26.1% | 1.06 [0.88, 1.29] |
| SAVOR-TIMI 53 | 395 | 8240 | 422 | 8173 | 53.7% | 0.93 [0.81, 1.06] |
| **Total (95% CI)** | | **14757** | | **14668** | **100.0%** | **0.99 [0.90, 1.09]** |
| Total events | 757 | | 760 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 1.93, df = 2 (P = 0.38); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)



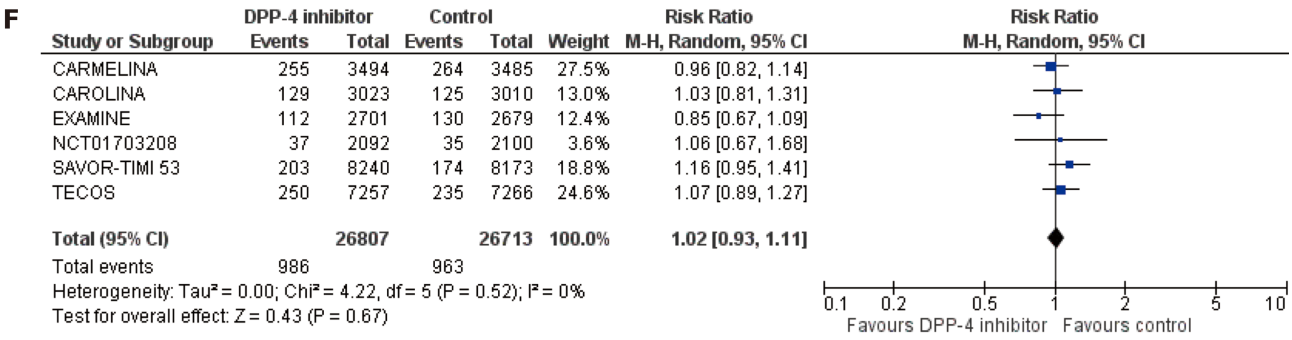



**Figure 1 Effect of dipeptidyl peptidase-4 inhibitor treatment compared to control on the risk.** A: Fatal and non-fatal myocardial infarction; B: Fatal and non-fatal stroke; C: Hospitalization for heart failure; D: Hospitalization due to unstable angina; E: Hospitalization for coronary revascularization; F: Cardiovascular mortality.

0.85-1.08, $I^2$ = 0%) and coronary revascularization (RR = 0.99, 95%CI: 0.90-1.09, $I^2$ = 0%), as depicted in Figures 1B and 1E. Finally, DPP-4 inhibitors demonstrated a neutral effect on the risk for hospitalization due to unstable angina (RR = 1.00, 95%CI: 0.85-1.18, $I^2$ = 0%), as shown in Figure 1D.

Regarding the risk for major cardiac arrhythmias, DPP-4 inhibitor treatment did not significantly affect the risk for atrial fibrillation (RR = 0.95, 95%CI: 0.78-1.17, $I^2$ = 0%), as shown in Supplementary Figure 1A. Of note, DPP-4 inhibitors were associated with a significant increase in the risk for atrial flutter, equal to 52% (RR = 1.52, 95%CI: 1.03-2.24, $I^2$ = 0%), as shown in Supplementary Figure 1B. Finally, DPP-4 inhibitors did not have a significant impact on the risk for any of the rest assessed major cardiac arrhythmias, as depicted in Supplementary Figures 1C-J.

## DISCUSSION

To our knowledge, this is the first meta-analysis of recently published, large, placebo-controlled cardiovascular outcome trials broadly assessing the cardiovascular efficacy and safety of DPP-4 inhibitors in T2DM. Our meta-analysis demonstrates a rather neutral effect of DPP-4 inhibitors on the risk for myocardial infarction, hospitalization for heart failure, stroke, urgent coronary revascularization and cardiovascular death; in parallel, we highlighted the absence of a significant effect of DPP-4 inhibitors on different types of cardiac arrhythmias, except for atrial flutter, for which corresponding risk increased by 52% compared to placebo. Our results are in accordance with previous meta-analyses in the field[6,16]; nevertheless, the impact of DPP-4 inhibitors on the arrhythmic burden across patients with T2DM has not been previously evaluated.

To date, a series of previous reports have indicated some cardioprotective effects of antidiabetic treatment with DPP-4 inhibitors; these generally safe and well-tolerated regimens have been associated with a significant reduction in blood pressure and with a rather low risk for hypoglycemia compared to other categories of antidiabetic drugs, while they do not increase body weight[17,18]. It has also been shown that they reduce arterial stiffness, whereas no significant effect on endothelial function was documented[19]. Additionally, in animal models, DPP-4 inhibitors have been shown to stabilize cardiac electrophysiology by decreasing the total number of premature ventricular contractions and demonstrating an antiapoptotic effect, significantly reducing the infarct size in experimental myocardial ischemia[20,21]. However, the above cardioprotective effects were not clearly translated into clinically significant results in relevant cardiovascular outcome trials and in our meta-analysis, as well.

Of particular interest is the finding of our analysis that DPP-4 inhibitors are associated with a significant increase in the risk for atrial flutter. Underlying pathophysiologic mechanisms remain largely unknown, since there are no relevant published data. However, it is well-established that diabetes mellitus increases the odds for atrial flutter development, almost by two times, as derived from epidemiological data two decades before[22]. In addition, it is known that atrial flutter at baseline is strongly associated with a significant increase in the 10-year risk for myocardial infarction, stroke, heart failure and all-cause death among affected subjects, constituting this arrhythmia as a prognostic marker of future adverse

cardiovascular outcomes[23]. Therefore, the observation that DPP-4 inhibitors actually increase the risk for atrial flutter is of utmost importance that may influence decision-making concerning high-risk patients, such as those suffering from T2DM.

The importance of documenting a neutral effect on a surrogate, prespecified endpoint for a drug class is as important as demonstrating a positive or negative effect, since knowledge about the risk to benefit profile of each different class plays a crucial role in decision-making process in daily clinical routine[24]. Furthermore, considering CVOTs demonstrating significant cardiovascular and renal benefits of other classes of glucose-lowering agents, namely sodium glucose cotransporter-2 inhibitors and glucagon-peptide-1 receptor agonists[25,26], in patients with T2DM, it is important that all such information is incorporated into the clinical guidelines, which have already incorporated these results in their latest recommendations[27,28].

## CONCLUSION

In conclusion, DPP-4 inhibitors do not confer any significant cardiovascular benefit for patients with T2DM. In addition, they are not associated with a significant risk for any major cardiac arrhythmias, except for atrial flutter. However, this drug class should not be the treatment of choice for patients with established cardiovascular disease or multiple risk factors, except for those cases when newer antidiabetics (glucagon-like peptide-1 receptor agonists and sodium-glucose co-transporter-2 inhibitors) are not tolerated, contraindicated or not affordable for the patient.

## ARTICLE HIGHLIGHTS

### *Research background*

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a safe and efficacious treatment option in type 2 diabetes mellitus (T2DM).

### *Research motivation*

Recently, several large, cardiovascular-outcome, randomized controlled trials (RCTs) with DPP-4 inhibitors in patients with T2DM have been published, raising some doubts on the cardiovascular efficacy and safety of this drug class.

### *Research objectives*

Herein the authors provide the most updated and broad relevant meta-analysis by pooling data of interest from the available cardiovascular-outcome RCTs, addressing the cardiovascular efficacy and safety of this drug class.

### *Research methods*

The authors searched PubMed and grey literature sources for all published RCTs assessing cardiovascular outcomes with DPP-4 inhibitors compared to placebo until October 2020.

### *Research results*

Overall, DPP-4 inhibitors seem to have a neutral effect on most surrogate cardiovascular outcome endpoints, such as cardiovascular death, myocardial infarction, stroke, hospitalization for heart failure decompensation, hospitalization for unstable angina or coronary revascularization.

### *Research conclusions*

DPP-4 inhibitors do not provide any clear cardiovascular benefit in patients with T2DM.

Notably, DPP-4 inhibitors are not associated with a significant effect on the risk for major cardiac arrhythmias, except for atrial flutter, increasing the risk by 52% compared to placebo.

### *Research perspectives*

DPP-4 inhibitors do not provide any clear cardiovascular benefit in patients with T2DM.

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