REVIEW ARTICLE

Effect of SGLT-2 inhibitors on cardiac autonomic function in type 2 diabetes mellitus: a meta-analysis of randomized controlled trials

Dimitrios Patoulias[1] · Alexandra Katsimardou[1] · Nikolaos Fragakis[2] · Christodoulos Papadopoulos[2] · Michael Doumas[1]

Abstract

Background Cardiac autonomic neuropathy (CAN) is a common complication of type 2 diabetes mellitus (T2DM). We sought to determine whether sodium-glucose co-transporter-2 (SGLT-2) inhibitors affect indices of CAN in patients with T2DM.

Methods We searched for parallel group or cross-over randomized controlled trials (RCTs) enrolling adult subjects with T2DM, assigned to a SGLT-2 inhibitor versus placebo or active comparator and addressing their effect on CAN. PubMed, Cochrane Library and gray literature sources were searched. We set as primary efficacy outcome the change in the low-frequency-to-high-frequency (LF/HF) ratio. We set as secondary efficacy outcomes: first, the change in the standard deviation of all 5 min mean normal RR intervals and second, the change in the square root of the mean of the sum of the squares of differences between adjacent RR intervals (r-MSSD). Protocol has not been registered at a publicly available repository.

Results We pooled data from four RCTs in a total of 247 subjects with T2DM. SGLT-2 inhibitor treatment did not have a significant effect on LF/HF ratio (MD = − 0.11, 95% CI − 0.35 to 0.12, $I^2 = 0\%$, $p = 0.36$). SGLT-2 inhibitor treatment did not have a significant impact either on SDNN (MD = − 2.83, 95% CI − 7.41 to 1.75, $I^2 = 31\%$, $p = 0.23$), or on r-MSSD (MD = − 0.14, 95% CI − 3.52 to 3.25, $I^2 = 46\%$, $p = 0.94$). Overall risk of bias was graded as low across the selected RCTs.

Conclusion SGLT-2 inhibitor treatment in patients with T2DM does not seem to provide any significant beneficial effect on CAN indices.

Keywords SGLT-2 inhibitor · Type 2 diabetes mellitus · Cardiac autonym neuropathy · Cardiovascular disease · Prognosis

Dimitrios Patoulias and Alexandra Katsimardou have contributed equally.

✉ Dimitrios Patoulias
   dipatoulias@gmail.com

1   Second Propedeutic Department of Internal Medicine, Aristotle University of Thessaloniki, General Hospital "Hippokration", Konstantinoupoleos 49, 54642 Thessaloníki, Greece

2   Third Department of Cardiology, Aristotle University of Thessaloniki, General Hospital "Hippokration", Thessaloníki, Greece

Introduction

Cardiac autonomic neuropathy (CAN) is a rather common complication of type 2 diabetes mellitus (T2DM), which is expected to rise, due to the growing epidemic of diabetes worldwide [1]. Recent studies have suggested that CAN is associated with coronary microvascular dysfunction [2] and progressive loss of kidney function in patients with T2DM [3]. In a recently published post hoc analysis of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, it was demonstrated that among subjects with T2DM, but without heart failure (HF) at baseline, CAN was highly predictive of the future risk incident HF [4]. Overall, CAN represents a prognostic risk marker for cardiovascular disease among patients with T2DM, also associated with an increased risk for all-cause mortality [5].

Besides the prognostic role of CAN in cardiovascular disease among individuals with T2DM, it has also been

associated with a higher recurrence rate of vaso-vagal syncope (VVS) among those patients compared to normoglycemic controls [6]. A recently published, prospective, multicenter study showed that patients with T2DM have higher heart rate variability (HRV) dysfunction compared to normoglycemic controls, and these alterations, associated with CAN, are highly predictive of VVS [6].

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors have been shown to provide outstanding cardiovascular and renal benefits in patients with T2DM during recent years [7]. In addition, they are recommended for patients with HF with reduced left ventricular ejection fraction (HFrEF), regardless of T2DM status at baseline, while, recent data also recommend their use in patients with HF, regardless of left ventricular ejection fraction, as they decrease the risk for recurrent hospitalization for HF decompensation and cardiovascular mortality [8, 9]. It has been hypothesized that amelioration of CAN by SGLT-2 inhibitors might partially account for their beneficial effects in patients with HF [10]. However, high-level evidence is relatively limited. Therefore, we sought to determine whether SGLT-2 inhibitors affect CAN indices, in patients with T2DM, pooling data from relevant published randomized controlled trials (RCTs).

Methods

This systematic review and meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines [11].

We searched for parallel group or cross-over RCTs enrolling adult subjects with T2DM, assigned to a SGLT-2 inhibitor versus placebo or active comparator, addressing their effect on CAN indices. We excluded trials enrolling subjects with type 1 diabetes mellitus (T1DM).

We used the following search strategy implemented on 24th May 2022 both in the PubMed and Cochrane Library databases: ((((((((((((SGLT2 inhibitor) OR (empagliflozin)) OR (dapagliflozin)) OR (canagliflozin)) OR (ertugliflozin)) OR (sotagliflozin)) OR (ipragliflozin)) OR (luseogliflozin)) OR (tofogliflozin)) OR (bexagliflozin)) OR (licogliflozin)) AND (((sympathetic nervous system activity) OR (heart rate variability)) OR (SDNN))). We searched the clinicaltrials. gov registry, as well. We did not impose any filter regarding sample size, study setting or publication language.

We set as primary efficacy outcome the change in the low-frequency-to-high-frequency (LF/HF) ratio, observed with SGLT-2 inhibitor treatment compared to control. We set as secondary efficacy outcomes: first, the change in the standard deviation of all 5-min mean normal RR intervals (SDANN) and second, the change in the square root of the mean of the sum of the squares of differences between adjacent RR intervals (r-MSSD).

After deduplication, two independent reviewers (D.P., C.P.) screened all records at title and abstract level and then assessed the full text of eligible records. Any disagreements between reviewers were resolved by consultation of a third senior reviewer (M.D.).

Three independent reviewers (D.P., N.F. and C.P.) extracted the data from the eligible reports. Extracted information were first author, year of study conduction, study setting, study sample size, country of origin, type of administered SGLT-2 inhibitor, type of control (placebo or active comparator), methods for the assessment of cardiac autonomic function, follow-up duration, mean age of participants, male-to-female ratio, major co-morbidities, baseline pharmacotherapy of interest and method for the assessment of CAN.

Differences were calculated with the use of mean difference (MD), with standard error (SE), after implementation of the inverse variance (IV) random effects formula. In those studies not reporting SE, we calculated SE from sample size and standard deviation (SD).

Statistical heterogeneity among studies was assessed by using I^2 statistics [2]. I^2 ranging between 0 and 40% is considered as low, I^2 ranging between 50 and 90% may represent substantial heterogeneity and I^2 ranging between 75 and 100% may be indicative of considerable heterogeneity [12]. All analyses were performed at the 0.05 significance level, with the RevMan 5.3. software [13].

Two independent reviewers (D.P. and C.P.) 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 [14]. Discrepancies between reviewers were solved by discussion, consensus or arbitration by a third senior reviewer (M.D.).

Results

We pooled data from four RCTs in a total of 247 subjects with T2DM [15–18]. Three trials were parallel-group [15–17], while the remaining one was cross-over [18]. Two trials assessed the effect of dapagliflozin on CAN [15, 18], while two trials evaluated the corresponding effect of empagliflozin [16, 17]. Study selection process is depicted in Fig. 1. A detailed description of participants' baseline characteristics of interest is summarized in supplementary table 1.

Regarding the primary efficacy outcome, SGLT-2 inhibitor treatment did not have a significant effect on LF/HF ratio in patients with T2DM (MD = − 0.11, 95% CI − 0.35 to 0.12, $I^2 = 0\%$, $p = 0.36$), as shown in Fig. 2. Concerning the secondary efficacy outcomes, SGLT-2 inhibitor treatment did not have a significant impact either on SDNN (MD = − 2.83, 95% CI − 7.41 to 1.75, $I^2 = 31\%$, $p = 0.23$),
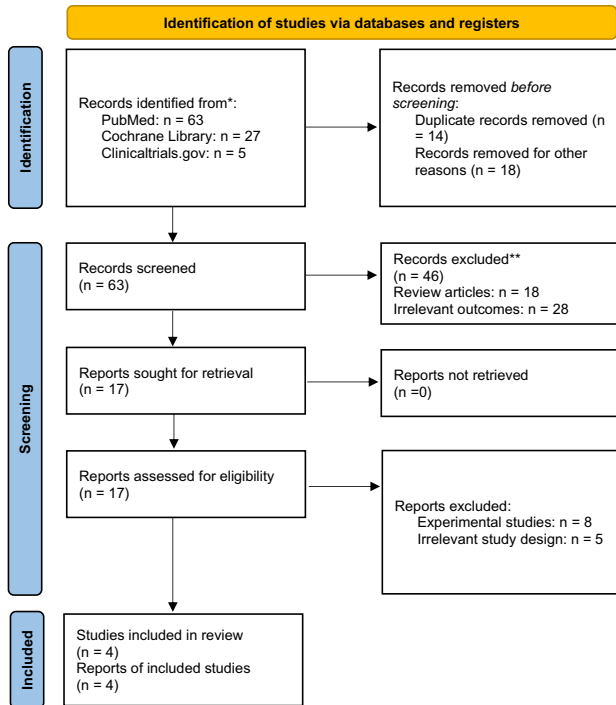
Fig. 1 Flow diagram depicting the study selection process. *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools

or on r-MSSD (MD $= -0.14$, 95% CI -3.52 to 3.25, $I^2 = 46\%$, $p = 0.94$), as shown in Figs. 3 and 4, respectively. Low statistical heterogeneity was documented for the assessed comparisons. Overall risk of bias is considered as low across the selected RCTs (supplementary Table 2).

Restriction of the analyses to those RCTs enrolling patients with T2DM and concomitant coronary artery disease [16, 17] did not reveal any statistically significant effect on the assessed electrocardiographic indices of CAN.

A sensitivity analysis excluding the only cross-over RCT performed by Ang et al. [18] did not have a significant impact on the generated results: SGLT-2 inhibitors did not have a significant effect on LF/HF ratio ($p = 0.23$, $I^2 = 0\%$), on SDNN ($p = 0.24$, $I^2 = 52\%$) and on r-MSSD ($p = 0.82$, $I^2 = 57\%$).

Alternate pooling methods (random-effects versus fixed-effects) did not have a significant effect on the generated results, as shown in supplementary Table 3.

Lack of access to individual patients' data did not permit us to perform subgroup analyses according to history of major co-morbidities, or background treatment of interest (such as beta-blockers).
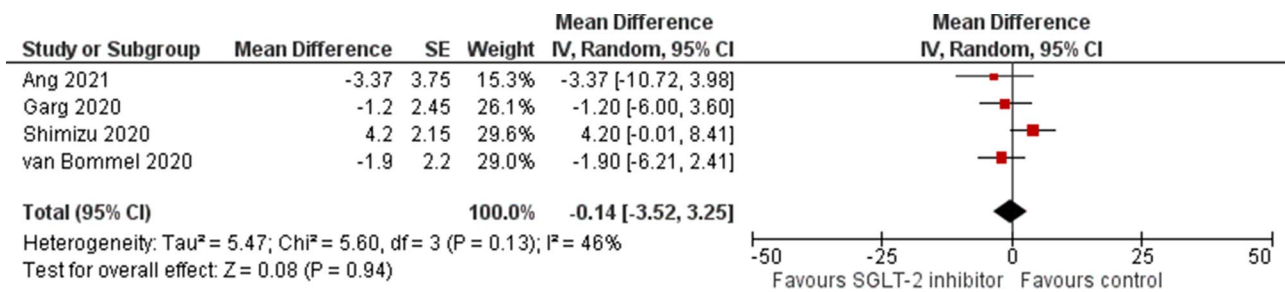
Finally, visual assessment of the corresponding funnel plot did not document any asymmetry, indicative of absence of significant publication bias (Supplementary Fig. 1). According to Cochrane Guidelines, no formal statistical testing (for example, Egger's test) was performed, due to the fact that there were less than 10 eligible RCTs.
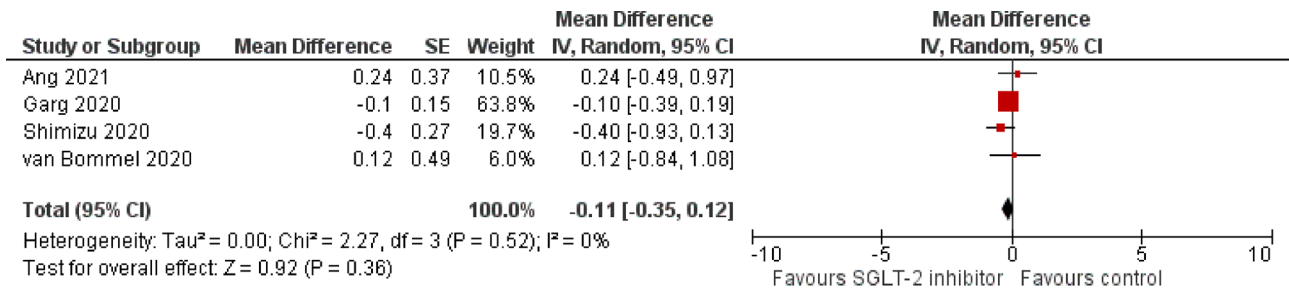

Fig. 2 Effect of SGLT-2 inhibitors compared to control on LF/HF ratio in patients with type 2 diabetes mellitus
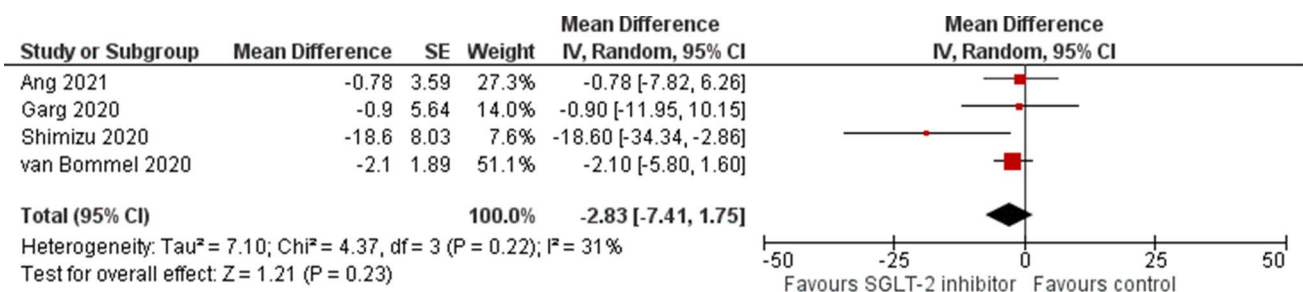
Fig. 3 Effect of SGLT-2 inhibitors compared to control on SDNN in patients with type 2 diabetes mellitus

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
Ang 2021	-3.37	3.75	15.3%	-3.37 [-10.72, 3.98]	
Garg 2020	-1.2	2.45	26.1%	-1.20 [-6.00, 3.60]	
Shimizu 2020	4.2	2.15	29.6%	4.20 [-0.01, 8.41]	
van Bommel 2020	-1.9	2.2	29.0%	-1.90 [-6.21, 2.41]	
Total (95% CI)			100.0%	-0.14 [-3.52, 3.25]	

Heterogeneity: Tau² = 5.47; Chi² = 5.60, df = 3 (P = 0.13); I² = 46%
Test for overall effect: Z = 0.08 (P = 0.94)

Fig. 4 Effect of SGLT-2 inhibitors compared to control on r-MSSD in patients with type 2 diabetes mellitus
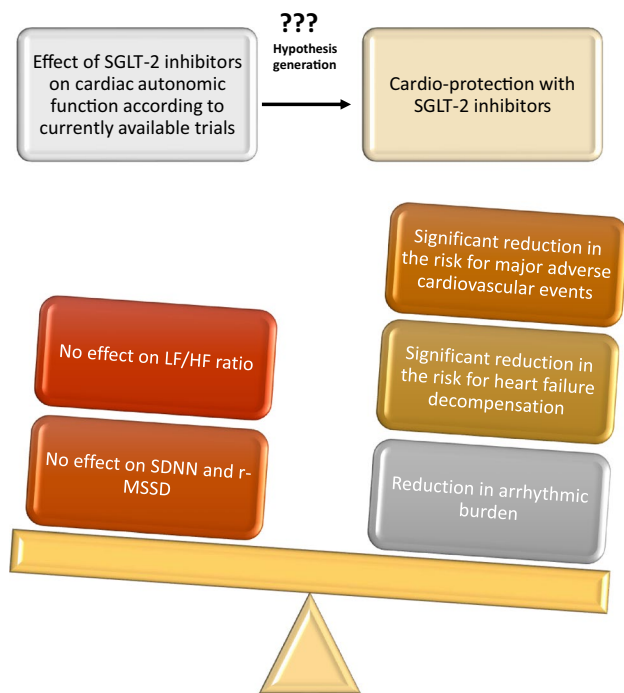
Fig. 5 Graphical abstract illustrating main results of the present meta-analysis

Discussion

Herein, we present the first relevant meta-analysis in the literature so far, suggesting that SGLT-2 inhibitor treatment in patients with T2DM, with or without cardiovascular co-morbidities, does not exert any significant effect on CAN indices (Fig. 5).

A former meta-analysis of observational studies in a total of 2932 participants, with half of them having background T2DM, showed that T2DM is significantly associated with CAN, with lower SDNN, r-MSSD and LF/HF ratio values been observed in patients with T2DM compared to healthy controls [19]. Besides glycemic control, age, male gender and blood pressure were identified as significant determinants of impaired HRV among the enrolled participants with T2DM [19].

It has also been confirmed that cardiac autonomic dysfunction is observed in patients with T2DM regardless of level of glycemic control, although worse glycemic control was associated with more impaired CAN [20]. As shown in two recently published studies, young-onset T2DM in adolescents and young adults is also associated with significant cardiac autonomic dysfunction, closely related to poor glycemic control, while it is also indicative of a worse overall cardiovascular risk profile [21, 22]. Therefore, CAN might also be predictive of the presence of asymptomatic coronary artery lesions, and thus of coronary artery disease [23], besides its predictive role in cardiovascular disease in patients with T2DM [5]. Therefore, prevention or amelioration of CAN would be ideal for those patients. Finally, the presence of CAN is responsible for an increased risk for mortality with an estimated relative risk of 3.65, based on the results of a meta-analysis of 15 studies [24].

Of course, it has to be admitted that diagnosis of CAN is challenging and multi-disciplinary. Besides assessment of HRV, ^{123}I-labeled metaiodobenzylguanidine (MIBG) cardiac scintigraphy has also been utilized for the assessment of CAN in clinical practice. Former studies, more than two decades ago, found that patients with insulin-dependent diabetes mellitus had a reduced global myocardial uptake of ^{123}I-MIBG, even in the absence of electrocardiographic indications of CAN [25]. More recent studies have also documented the role of ^{123}I-MIBG scintigraphy for the diagnosis of CAN in other settings [26, 27], however, highlighting the crucial and independent role of hyperglycemia on cardiac sympathetic denervation, which is associated with worse prognosis, strongly correlated with surrogate endpoints, such as heart failure incidence and all-cause death [26].

Current guidelines highlight the absence of any treatment capable of reversing established CAN, with treatment options being focused on ameliorating symptoms [28]. Therefore, early preclinical data suggesting that SGLT-2 inhibitors could modify the course of CAN were welcomed. For instance, SGLT-2 inhibitors improved dipping and the circadian rhythm of sympathetic nervous activity in rat

models of obesity and metabolic syndrome, while in another study with standard chow- and high-fat-fed rats, dapagliflozin attenuated the sympathetic nervous system response to glucose load [29–31]. In addition, a recently published prospective study, after propensity score matching, assessing 324 patients with well-controlled T2DM and VVS, documented that SGLT-2 inhibitor users, compared to non-users, had significantly lower incidence rates of CAN, assessed by electrocardiographic Holter analysis, while they experienced a significantly lower recurrence rate of VVS after 1-year, with SGLT-2 inhibitor treatment being an independent predictor of reduced risk of VVS recurrence by 45% [32].

Several mechanisms have been suggested for the cardioprotective effects of SGLT-2 inhibitors in clinical practice [33]. Most of them might also be associated with an improvement in CAN, as demonstrated in previously published experimental studies [34, 35]. T2DM is associated with low-grade, chronic inflammation [36], while, some cytokines, such as the pro-inflammatory interleukin-1β, might also be associated with T2DM pathogenesis. Sympathetic nervous system over-activation is also documented in individuals with T2DM, which has been shown to be associated with age and insulin resistance, irrespective of co-morbidities, such as obesity, hypertension, or metabolic syndrome [37, 38]. Over-inflammation and over-activation of sympathetic nervous system are directly implicated into pathogenesis of CAN and are therefore promising treatment targets [39].

SGLT-2 inhibitors have been shown to significantly ameliorate inflammatory burden in patients with T2DM and coronary artery disease treated with coronary artery bypass grafting (CABG), an effect associated with significant improvement in surrogate clinical endpoints, including cardiovascular outcomes and all-cause death, underlining the prominent role of inflammation in cardiovascular disease among patients with T2DM and the value of SGLT-2 inhibitor treatment [40]. In another prospective, observational study enrolling subjects with T2DM and acute myocardial infarction, it was shown that previous SGLT-2 inhibitor users compared to non-users experienced a significantly decreased inflammatory response, associated with smaller infarct size, regardless of age and level of glycemic control at baseline [41]. These results provide novel insights into the anti-inflammatory effects of SGLT-2 inhibitors and the clinical implications of such effects, since they are associated with improved cardiovascular outcomes.

However, evidence retrieved from our meta-analysis does not support an otherwise reasonable hypothesis of a beneficial effect of SGLT-2 inhibitors on CAN indices, as we have shown that SGLT-2 inhibitors do not provide any improvement in electrocardiographic parameters of CAN. Of course, our results are preliminary and should be interpreted with caution since this is the first meta-analysis of the relevant

RCTs. In addition, our results are in contrast with the results of a recently published observational study, which supported a beneficial role of SGLT-2 inhibitor treatment on CAN indices and their protective role against VVS recurrence among patients with T2DM [32].

The use of b-blockers was high in the two studies that included patients with established cardiovascular disease [16, 17]. This might have influenced the results of the interventions, as b-blockers are able to modify sympatho-vagal balance through vagal activation, possibly eliminating any benefits that could possibly otherwise be evident with the use of SGLT-2 inhibitors [42].

Of note, we should also clarify that cardiovascular autonomic reflex tests (CARTs), namely, heart rate variations during deep breathing, Valsalva maneuver, and lying-to-standing (heart rate tests) as indices of parasympathetic function, along with the orthostatic hypotension, the blood pressure response to a Valsalva maneuver and sustained isometric muscular strain as indices of sympathetic function, remain the mainstay for the assessment of CAN in clinical practice [43]. CARTs are safe, easy to perform, sensitive, specific, reproducible, while they allow CAN staging from early to advanced involvement, as documented by the CAN Subcommittee of the Toronto Consensus Panel on Diabetic Neuropathy [43]. The present meta-analysis pooled data from trials primarily assessing HRV, while only Ang and colleagues performed CARTs [18]. Thus, this can be considered as a main limitation of our meta-analysis.

We consider as additional limitations of our meta-analysis the limited number of relevant RCTs, the small sample size of the eligible trials, and the lack of access to individual participants' information, which would permit us to perform subgroup analyses of interest. As shown in supplementary table 1, enrolled subjects across the eligible RCTs had different levels of glycemic control, were mostly overweight or obese, had differential usage rates of cardiac acting drug classes other than b-blockers, while, availability of data concerning prior cardiovascular disease, CAN, cardio-respiratory fitness, or other co-morbidities of interest, is scarce and limited, restricting the generation of definite conclusions and the applicability of generated results into clinical practice. All these factors could have influenced CAN variables and thus limit the robustness of our results, in the absence of relevant sub-group analyses.

Importantly, inadequate glycemic control, as stated previously, and central obesity have been shown to be independent predictors of CAN development among subjects with T2DM or metabolic syndrome [44–46]. Three out of four trials included in our meta-analysis enrolled adults with insufficient glycemic control, overweight or obese, while only one trial, that performed by Shimizu and colleagues [16], recruited adult subjects with T2DM and almost within normal range body mass index and glycated hemoglobin levels.

This might partially explain the non-significant results of our meta-analysis, whereas a former observational study by Sardu et al. [32], which enrolled subjects with almost optimal glycemic control and low relative frequency rates of obesity, documented a significant effect of long-term administration of SGLT-2 inhibitors on the risk for VVS recurrence.

Moreover, the duration of electrocardiographic recordings differed among the included studies. Eligible RCTs utilized only empagliflozin or dapagliflozin, while, currently, there are no available trials utilizing other SGLT-2 inhibitors with established cardio-protective effects, such as canagliflozin, sotagliflozin or ertugliflozin. In addition, we did not register prospectively our protocol at a publicly available repository. Finally, there is a number of limitations in the assessment of CAN with the use of Holter monitoring that should not be overlooked, mainly the absence of standardized reference values [47]. It would be interesting if future trials also assessed the effect of SGLT-2 inhibitors on head-up tilt test, which may be positive in patients with CAN [48], and of course to assess the effect of SGLT-2 inhibitors on heart denervation, as assessed with ^{123}I-MIBG scintigraphy.

Conclusion

SGLT-2 inhibitor treatment in patients with T2DM does not seem to provide any significant beneficial effect on CAN indices. Further, larger RCTs are required to provide definitive answers on this sound scientific question.

Declarations

Conflict of interest None declared.

Ethical standard statement Not required for this type of manuscript.

Human and animal rights disclosure No experiment involving humans or animals was performed.

Informed consent Not required.

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