SGLT2-inhibitors modulate the Cardiac Autonomic Neuropathy and reduce the vaso-vagal syncope recurrence in patients with type 2 diabetes mellitus: the SCAN study

Celestino Sardu (drsarducele@gmail.com)
University of Campania “Luigi Vanvitelli”
Massimo Massetti
Catholic University of the Sacred Heart
Pietro Rambaldi
University of Campania “Luigi Vanvitelli”
Gianluca Gatta
University of Campania “Luigi Vanvitelli”
Salvatore Cappabianca
University of Campania “Luigi Vanvitelli”
Ferdinando Carlo Sasso
University of Campania “Luigi Vanvitelli”
Matteo Santamaria
Catholic University of the Sacred Heart
Mario Volpicelli
“S. Maria della Pietà Hospital”
Valentino Ducceschi
“Vecchio Pellegrini Hospital”
Giuseppe Signoriello
University of Campania “Luigi Vanvitelli”
Giuseppe Paolisso
University of Campania “Luigi Vanvitelli”
Raffaele Marfella
University of Campania “Luigi Vanvitelli”

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Abstract

Background: In patients with type 2 diabetes mellitus (T2DM) the vaso-vagal syncope (VVS) recurrence could be due to the alteration of autonomic system function, evaluated by heart rate variability (HRV), and by 123I-metaiodobenzylguanidine (123I-mIBG) myocardial scintigraphy indexes: Heart to Mediastinum ratio (H/M_{late}), and Washout rate (WR). The SGLT2-I could modulate/reduce autonomic dysfunction in T2DM patients with VVS. This effect could reduce the VVS recurrence in T2DM patients.

Methods: In a prospective multicenter study, we studied a population of 607 T2DM patients affected by VVS, as SGLT2-I-users (n 161) vs. Non-SGLT2-I users (n 446). Thus, in SGLT2-I-users vs. Non-SGLT2-I users, we investigated the HRV and 123I-MIBG modifications and VVS recurrence at 12 months of follow-up.

Results: At baseline, and follow-up end Non-SGLT2-I users vs. SGLT2-I-users over-expressed the inflammatory markers and norepinephrine, with worse glucose homeostasis and significant difference of HRV parameters, H/M_{late}, and the WR ($p<0.05$). Non-SGLT2-I users vs. SGLT2-I-users had higher recurrence of all causes VVS, and of vasodepressor, and mixed VVS ($p<0.05$). The Cox regression analysis showed that the H/M_{late} (0.710, CI 95% [0.481-0.985]; p 0.024), and SGLT2-I (0.550, CI 95% [0.324-0.934]; p 0.027) predicted all VVS recurrence.

Conclusions: Non-SGLT2-I users vs. SGLT2-I-users had alterations of the autonomic nervous system, with a higher rate of VVS recurrence at 1 year of follow-up. The indexes of cardiac denervation predicted the VVS recurrence, while the SGLT2-I reduced the risk of VVS recurrence.

Clinical trial registration number: NCT03717207.

Introduction

Vasovagal syncope (VVS) is caused by a transient loss of consciousness due to transient global hypo-perfusion, with a rapid onset, short duration, and complete spontaneous recovery (**1**). The VVS could recur until 35% of the cases, leading to adverse quality of life and worse prognosis (**2**). Notably, the VVS recurrence is higher in patients with type 2 diabetes mellitus (T2DM), and T2DM is an independent predictor of VVS recurrence (**3**). Intriguingly, the T2DM patients with VVS have a significant autonomic nervous system dysfunction with excessive vagal tone and sympathetic tone withdrawal (**3**). This could cause significant alterations of the heart rate (HR) with resting tachycardia, exercise intolerance, abnormal blood pressure regulation, and orthostatic hypotension (**4**). The excessive vagal tone could be evaluated by ECG Holter monitoring, via measurements of heart rate variability (HRV) parameters, as the low frequency (LF), the high frequency (HF), and the LF to HF ratio (LF/HFr), (**5**). The sympathetic system over-activity, and the cardiac autonomic dysfunction (CAN) in patients with VVS, could be evaluated by values of serum norepinephrine, and by 123I-metaiodobenzylguanidine (123I-mIBG) myocardial scintigraphy (**6, 7**). On the other hand, it should be pointed out that there are no conclusive data about the

evaluation of CAN by the analysis of HRV and of cardiac MIBG scintigraphy indexes in T2DM patients with VVS, and that less is known about the effects of anti-diabetic therapies on CAN, and their prognostic implications in T2DM patients with VVS. Concerning this, sodium-glucose transporter inhibitors (SGLT2-I) are drugs with direct effects on the glucose-control, which reduce cardiovascular outcomes in T2DM patients (**8**). Intriguingly, SGLT2-I could exert cardiovascular protective effects also via the modulation of sympathetic nerve activity which is an independent effect of glucose-control efficacy (**9**). Therefore, we might hypothesize that the SGLT2-I might significantly modulate the CAN in T2DM with VVS, leading to the reduction of VVS recurrence in T2DM under SGLT2-I (SGLT2-I users) as compared to T2DM patients without SGLT2-I therapy (Non-SGLT2-I users). On the other hand, the chronic use of SGLT2-I to reduce VVS recurrence in T2DM has never been investigated before, and it represents the novelty of the current study. Moreover, here we aimed to evaluate the CAN by HRV parameters and cardiac MIBG scintigraphy indexes at baseline and at 1 year of follow-up, and the rate of VVS recurrence in SGLT2-I users vs. Non-SGLT2-I users' T2DM patients at 1 year of follow up.

Methods

In a prospective multicenter study conducted at University of Campania "Luigi Vanvitelli", Naples, at "S. Maria della Pietà Hospital", Naples, at "Vecchio Pellegrini Hospital", Naples, at "Catholic University of the Sacred Heart", Rome, Italy, at Catholic University of Sacred Heart, Campobasso, and at Gemelli Molise, Campobasso, Italy, we investigated from June 2018 to March 2021 a population of 4794 consecutive patients who had reported at least two syncopal episodes of unknown origin during the previous 6 months, and who had a recurrence of syncope during Head-Up Tilt Test (HUT). We defined the VVS as a transient loss of consciousness whose cause was not determined by the following series of examinations performed in affected patients: clinical history, clinical examination (auscultation, carotid sinus massage, blood pressure measurement in supine, and upright position), electrocardiogram (ECG), chest X-ray, echocardiography, 24 h Holter ambulatory monitoring, late potentials, and a complete neurological examination (head imaging and electroencephalograms), according to last international guidelines (**10**). However, all enrolled patients performed a HUT. These patients were in stable sinus rate before performing the HUT, and they performed a 24 hours ECG Holter to assess sinus rhythm, HR, HRV, and the MIBG myocardial scintigraphy before receiving a HUT. Thus, we included only T2DM patients (n 607) from the study populations, according to diagnostic criteria for T2DM (**10**). **Figure 1**. The study complies with the Declaration of Helsinki, and the locally appointed Ethics Committee approved the research protocol (n 06062.18), and informed consent was obtained from all the subjects. The study population respected the following inclusion/exclusion criteria.

Inclusion criteria: eligible adults' patients with T2DM (≥18 years of age); previous VVS event; indication to receive a HUT; indication to practice cardiac MIBG scintigraphy; patients without previous cardiovascular disease; patients with an estimated glomerular filtration rate (eGFR) of at least 30 ml per minute per 1.73 m2 of body-surface area.

Exclusion criteria: patients with diagnosis of type 1 diabetes, neuropathy, heart failure and coronary heart disease or depression of left ventricle ejection fraction (LVEF < 55%); patients with severe anemia, thyroid dysfunction, concomitant treatment with anticholinergic agents, adrenergic antagonists, and vaso-constrictive agents that can affect the results of autonomic function test; patients with uncontrolled blood pressure (blood pressure ≥ 140/90 mmHg on two occasions 2 weeks apart).

Patients' monitoring.

The enrolled patients were regularly followed by clinical visits 10 days, and at 3^{th}, 6^{th} and 12^{th} months after clinical discharge by the treating physician. These patients had a diagnosis of VVS in accordance to the HUT result (**1**). All the patients gave their written informed to participate in the study. Clinical evaluations included physical examination, vital signs, and review of adverse events. We performed fasting blood (at least 12 hours from last meal) for glycemia, lipid profile (total cholesterol (TC), triglycerides, HDL-C, and LDL-C) at every visit. Syncope recurrence and other clinical events were collected during patients' interviews, visits, and hospital discharge schedules. The diagnosis of T2DM was made according to international recommendations, by plasma glucose values as fasting plasma glucose level ≥ 7.0 mmol/L (126 mg/dL), plasma glucose ≥ 11.1 mmol/L (200 mg/dL) either while fasting or not fasting, glycated hemoglobin ≥ 48 mmol/mol, and by the known clinical history of diabetes and by the current use of anti-diabetic medications (**11**). In the T2DM patients we defined SGLT2-I users as those receiving a SGLT2-I therapy for at least 6 months without discontinuation. We defined the rest of the T2DM patients as Non-SGLT2-I users. All the T2DM patients enrolled in the study had a glycated hemoglobin level of at least 7.0% and no more than 9.0%. The SGLT2-I users received either 10 mg or 25 mg of empagliflozin once daily, and/or canaglifozin 100 mg daily (mean duration of SGLT2-I therapy 16±4.8 months).

Cardiovascular autonomic neuropathy evaluation

We evaluated the autonomic function of study population by classical Ewing cardiovascular autonomic function tests, heart and pulse rate variability (**3**). The test was performed in the morning (08:00–10:30) in a room with quiet ambiance and temperature of 19–22 °C, in fasting condition from midnight and refraining from smoking and caffeine-containing beverages for almost 12 hours before the evaluations. Two experienced physicians blinded to study protocol evaluated the cardiovascular autonomic reflex function tests as parasympathetic and sympathetic tests (**3**, **4**, **5**). The parasympathetic tests evaluated the HR response during deep breathing, the Valsalva maneuver, and quick standing (**3**, **4**, **5**). The sympathetic tests evaluated the blood pressure response during the sustained handgrip test and quick standing (**3**, **4**, **5**). We evaluated the deep breathing test to determine the maximum and minimum R–R intervals during each breathing cycle during six deep breaths in 1 min (**3**). However, we expressed the R–R intervals during inspiration and expiration as the R–R inspiration/R–R expiration ratio (**3**). Again, we evaluated the Valsalva maneuver as a forced expiration in a manometer against 40 mmHg for 15 s, and the Valsalva ratio as division of longest R–R interval by shortest R–R interval (**3**). Moreover, during the quick standing test, we measured the HR response after standing from the R–R intervals calculation at 15

and 30 beats after standing and reported as the ratio of the longest vs. the shortest R–R interval (**3**). Thus, we calculated the sympathetic component of the standing test by the values of the systolic blood pressure response 2 min after standing (**3**). Finally, we evaluated the diastolic blood pressure response during the sustained handgrip by a dynamometer to establish a maximum developed force, followed by a handgrip squeeze of 30% of the maximum force for 5 min (**3**). Furthermore, we defined Cardiovascular autonomic neuropathy (CAN) as the composite CAN index including the HR ratio <1.30 plus Valsalva ratio <1.5 or a decrease of >10 mm Hg in diastolic blood pressure (DBP) upon standing (CAN+) (**3**).

Head-Up Tilt Test (HUT)

In the overall study population, and selectively in SGLT2-I-users vs. Non-SGLT2-I users, we performed the HUT in the morning in a quiet room with lights slightly dimmed after overnight fasting (**1-3**). Using a motorized tilt table with foot support, we had a first 5-minute supine control phase, and then we moved the patients to the 60°upright position for a maximum duration of 45minutes or until syncope developed (**1-3**). However, at 20 minutes, we administered to the patients 400 mg of nitroglycerin spray sublingually (**1-3**). To date, at the time of syncope, we immediately tilted back the patients to the horizontal position (**1-3**). We defined the syncope as an abrupt, transient loss of consciousness and a loss of postural tone associated with bradycardia, hypotension, or both (**1-3**). Therefore, we classified the VVS into three groups according to HUT response during the onset of syncope: i) vasodepressor VVS by evidence of a decrease in systolic blood pressure to <60 mmHg without decrease in HR during symptoms; ii) cardioinhibitory by evidence of an abrupt decrease in HR by ≥20% without any antecedent decrease in systolic blood pressure; iii) mixed response by evidence of a concurrent decrease in systolic blood pressure to <60 mmHg and a decrease in HR by ≥20% compared with averages 4 min before the onset of symptoms (**1-3**).

MIBG scintigraphy

At hospital admission for the VVS clinical event, and before performing the HUT, the authors practiced the 123I-MIBG myocardial scintigraphy. We used a standardized protocol at the time of hospitalization and at 1 year of follow-up (**6**). The 123I-MIBG myocardial scintigraphy was performed in VVS patients to assess the cardiac sympathetic nerve activity (**7**). Moreover, we used the 123I-MIBG, a norepinephrine analogous, to calculate the late heart-to-mediastinum ratio (H/M_{late}) and washout rate (WR). Thus, we evaluated the H/M_{late} as index of global neuronal function due to norepinephrine uptake and the WR as index of sympathetic tone. We withheld the drugs interfering with 123I-MIBG uptake, and thyroid uptake of unbound 123I was blocked with 500 mg of potassium perchlorate given orally 30 min before 123I-MIBG injection (**6**, **7**). We injected intravenously at rest, the dose ranging from 148 MBq to 370 MBq of 123I-MIBG. Then, we acquired both planar and SPECT images at 15 min after injection (early) and 4 h after injection (delayed, by the use of a dual-head gamma camera - ECAM Siemens, Erlangen, Germany) equipped with a low-energy, high-resolution collimator. A 20% window was usually centered over the 159-keV photopeak of 123I for imaging. Anterior planar images of the chest for global assessment of cardiac innervation were acquired using a 256x256 matrix. Thereafter, we acquired the SPECT images for the

regional evaluation, using a 64x64 matrix over 180˚, from the right anterior oblique position to the left posterior diagonal position. Thus, we performed the quantitative evaluations with a standard protocol from this imaging (**6**). Moreover, we evaluated at baseline and at 1 year of follow-up the H/M_{late} and WR in the study cohorts.

The formula to calculate WR was: $WR_{BKG\ corrected} = \frac{(He-Me) - [(Hl-Ml) \times 1.21]}{(He-Me)}$

The BKG is background; H is heart mean counts per pixel; M is mediastinum mean counts per pixel; "e" is early; "l" is late; and 1.21 is the correction factor for 123I decay at 3 h and 45 min (**6**, **7**).

Study endpoints.

The study endpoints were: 1) the evaluation of the HRV parameters in SGLT2-I-users vs. Non-SGLT2-I users at baseline and at 1 year of follow-up; 2) the evaluation of cardiac 123I-MIBG indexes in SGLT2-I-users vs. Non-SGLT2-I users at baseline and at 1 year of follow-up; 3) the rate of VVS recurrence after HUT diagnosis in SGLT2-I-users vs. Non-SGLT2-I users at 1 year of follow-up.

Statistical analysis

We made the descriptive statistical analysis by the correct measurements on the collected data. However, before the HUT we divided the VVS patients in SGLT2-I-users vs. Non-SGLT2-I users. Then, at follow-up after HUT, and during follow-up visits and controls, we divided patients with VVS recurrence vs. patients without VVS recurrence. Thus, as appropriate, we tested the study variables by parametric and non-parametric tests. The normality of the distribution was tested with the Kolmogorov-Smirnov test. We compared the categorical variables by chi-square or Fisher exact test where appropriate. The statistical significance was set at $p < 0.05$ (two-sided tests), and for multiple testing, we used a statistical significance of $p < 0.01$. The Kaplan curves were made at 1 year of follow-up to show the cumulative risk to have VVS recurrence (all causes, mixed, cardio-inhibitory, and vasodepressor VVS recurrence). The Log Rank test evaluated the comparison between SGLT2-I users and Non-SGLT2-I users regarding the cumulative risk of VVS recurrence (all causes, mixed, cardio-inhibitory, and vasodepressor) VVS recurrence) at 1 year of follow-up. We made the multivariate Cox multivariate regression analysis to predict all causes of VVS recurrence at 1 year of follow-up in the study population. Among all risk factors and all clinical and angiographic parameters evaluated (age, smoking, resting HR, systolic and diastolic blood pressure, etc.), only the variables presenting a $p \leq 0.25$ at univariate analysis were included in the model, and we used Hazard Ratios (HR) with 95% confidence intervals was calculated. We performed the statistical analysis using the SPSS software package for Windows 17.0 (SPSS Inc., Chicago, Illinois).

Results

In the current study, we included 607 T2DM patients with VVS, divided into 161 SGLT2-I-users vs. 446 Non-SGLT2-I users.

At baseline, we noted a significant difference regards inflammatory markers (white blood cells, C reactive protein (CRP) values, fasting glucose, glycated hemoglobin (Hb1Ac), and norepinephrine blood values comparing SGLT2-I-users vs. Non-SGLT2-I users ($p<0.05$). **Table 1**. Regarding the Autonomic dysfunction tests, the SGLT2-I-users vs. Non-SGLT2-I users showed significantly lower HR values, deep breathing/HR, Valsalva maneuver, lying to standing, and HF ($p<0.05$). **Table 1**. Conversely, the SGLT2-I-users vs. Non-SGLT2-I users showed significantly highest values of ECG Holter parameters, lower values of norepinephrine ($p<0.05$), and higher values (indexes) of myocardial denervation by MIBG cardiac scintigraphy as the Heart to Mediastinum ratio, and the washout rate ($p<0.05$). **Table 1, figure 1**.

At 1 year of follow-up, the SGLT2-I-users vs. Non-SGLT2-I users had significantly lower values of the mean values of fasting glucose, Hb1Ac, CRP, norepinephrine, and resting HR ($p<0.05$). **Table 2**. The SGLT2-I-users vs. Non-SGLT2-I users evidenced highest values of the investigated ECG Holter parameters ($p<0.05$). **Table 2, figure 2**. The SGLT2-I-users vs. Non-SGLT2-I users had significantly higher values of the Heart to Mediastinum ratio and lower values of the washout rate ($p<0.05$). **Table 2, figure 2**.

Finally, comparing SGLT2-I-users vs. Non-SGLT2-I users, we find a higher rate of the total number of VVS recurrence events, vasodepressor, and mixed type of VVS recurrence at 1-year follow-up ($p<0.05$). We did not find a significant difference of cardio-inhibitory VVS recurrence events at 1 year of follow-up in the study cohorts ($p>0.05$). **Table 2**.

We conducted a sub-group analysis only in the cohorts of SGLT2-I-users vs. Non-SGLT2-I users with the VVS recurrence at 1 year of follow-up, via the investigation of the indexes of sympathetic tone dysfunction, by HR, HRV and 123I-MIBG parameters. However, we evaluated these parameters in the cohorts of SGLT2-I-users vs. Non-SGLT2-I users with all causes of syncope (A), vaso-depressor syncope (B), cardio-inhibitory syncope (C), and mixed syncope recurrence (D) at 1 year of follow-up. Furthermore, we analyzed the data of CAN at 1 year of follow-up vs. baseline condition selectively in the SGLT2-I users and in the Non-SGLT2-I users. We reported these study results in the **supplementary files**.

The Cox regression analysis evaluated the risk factors to predict all causes of VVS recurrence at 1 year of follow-up in the study population. **Table 3**. To date, Heart to Mediastinum rate (0.710, CI 95% [0.481-0.985]; p 0.024), and SGLT2-I therapy (0.550, CI 95% [0.324-0.934]; p 0.027) predicted all causes of syncope recurrence. **Table 3**.

Finally, the Kaplan curves showed the cumulative risk to have all causes of syncope (A), vaso-depressor syncope (B), cardio-inhibitory syncope (C), and mixed syncope (D) recurrence in SGLT2-I-users vs. Non-SGLT2-I users at 1 year of follow-up. **Figure 3**.

Discussion

The principal findings of the current study are that the SGLT2-I could modulate autonomic system and reduce the VVS recurrence in T2DM patients at 1 year of follow-up. Notably, Non-SGLT2-I users vs. SGLT2-I users had over-inflammation, worse glycemic control, higher blood values of catecholamines, and more severe dysfunction of autonomic system at baseline and at follow-up end. Finally, the Non-SGLT2-I users vs. SGLT2-I users showed a higher recurrence rate of all causes of VVS and of mixed and vasodepressor VVS at 1 year of follow-up. In our study, the SGLT2-I users' patients differed regards those receiving 10 mg vs. 25 mg daily of empagliflozin, and a third group receiving canaglifozin 100 mg daily. On the other hand, the two-dose groups for empaglifozin, and the group under canaglifozin had a similar hazard ratio for cardiovascular outcomes. Thus, we might confirm the cardio-protective effects of the SGLT2-I, via the reduction of the volume overload and the blood pressure (**13**), with anti-inflammatory properties, and the modulation of the autonomic system (**14**). In our study, the SGLT2-I users vs. Non-SGLT2-I users had a significant down-regulation of inflammatory markers, norepinephrine serum values, and HR ($p<0.05$) at the follow-up end. Intriguingly, we observed significantly lower values of HR comparing the SGLT2-I users vs. Non-SGLT2-I users' patients with all causes of VVS, and for any type of VVS ($p<0.05$), at the exception of the cardio-inhibitory VVS ($p>0.05$). See **supplementary files**. This could be due to an excessive vagal tone with severe bradycardia, and asystole in the patients with cardio-inhibitory VVS recurrence (**1, 3, 10**). However, these mechanisms could lead to increased cardio-inhibitory VVS recurrence at follow-up end (**3**). In this setting, the cardiac 123I-MIBG could evaluate the cardiac denervation and the over-sympathetic tone in T2DM patients (**6**) and patients with VVS recurrence (**7, 15, 16**). Intriguingly, in our investigation, the SGLT2-I-users vs. Non-SGLT2-I users showed at baseline and at follow-up end the highest values of $H/M_{late.}$ The H/M_{late} is an index of cardiac denervation and a marker of autonomic system dysfunction in VVS patients (**15, 16**). At the clinical level, the SGLT2-I-users vs. Non-SGLT2-I users had a lower rate of VVS recurrence at the follow-up end. Thus, we might speculate that the SGLT2 pathways might be implied in the regulation of the sympathetic nervous system in patients with VVS. Indeed, the over-activation of the sympathetic system causes the up-regulation of SGLT2 pathways, while on the contrary, the SGLT2-I (block of SGLT2 pathways) mediate inhibitory effects on the sympathetic system (**17, 18**). In this context, the H/M_{late} is an index of cardiac sympathetic innervation and adrenergic nervous system integrity and function (**19**). However, the highest values of H/M_{late} ratio might evidence the integrity and best function of the autonomic system in SGLT2-I users vs. Non-SGLT2-I users' patients with VVS. In fact, we found that the highest values of H/M_{late} could lead to the lowest risk of having VVS recurrence at follow-up end. On the other hand, the SGLT2-I therapy could inversely and independently predict the risk of having VVS recurrence at follow-up. Indeed, we reported that the SGLT2-I therapy could reduce about the $\simeq$ 45% risk to have all causes of VVS recurrence. Therefore, the SGLT2-I might positively regulate/ameliorate the autonomic dysfunction in the patients with all causes of VVS, and with the mixed and vasodepressor VVS. This could consequently result in a lower rate of VVS recurrence in the SGLT2-I-users vs. Non-SGLT2-I users at 1 year of follow-up. In this context, the empagliflozin (SGLT2-I) at a 10-mg dosage significantly improved the HRV via modifying the HF, LF, and LF/HFr parameters (**16**). Intriguingly, from a previous study the LF/HFr is an independent predictor of VVS recurrence in T2DM patients (**3**). Therefore, we might speculate that the SGLT2-I might reduce the VVS recurrence in T2DM patients by the modulation of LF/HFr. In addition, the SGLT2-I cause ameliorative effects on the cardiac autonomic

denervation by a significant improvement of cardiac 123I-MIBG indexes (**16**). Furthermore, the lowest values of LF, HF, LF/HRr, and the significant difference in H/M_{late} and WR, which are indexes of integrity and function of the myocardial pre-synaptic nerve endings (**7**), might evidence a more severe CAN in Non-SGLT2-I users vs. SGLT2-I-users' patients with VVS. Thus, the SGLT2-I therapy might cause a significant modification of vasovagal tone (HRV indexes) and of the cardiac sympathetic dysfunction (123I-MIBG parameters) in T2DM patients with VVS. Conversely, this ameliorative effect on the autonomic dysfunction and cardiac denervation might significantly reduce VVS recurrence in the SGLT2-I users vs. Non-SGLT2-I users at 1 year of follow-up. Moreover, the SGLT2-I might lead to the amelioration of glucose homeostasis, hemodynamic, and CAN in T2DM patients with VVS. On the contrary, a worse glycemic control increased the predicted risk of having mixed VVS recurrence at follow-up end, as previously demonstrated in T2DM patients (**3**). Moreover, the best control of glycemia, blood pressure, and hemodynamic could reduce the VVS recurrence in T2DM patients with VVS (**1, 3**). Thus, the SGLT2-I might represent a relevant treatment to significantly ameliorate the glucose homeostasis, the hemodynamic, and the sympathetic system dysfunction in the T2DM patients with VVS. Intriguingly, we would report that the significant difference in the cumulative risk to have VVS recurrence (all causes, mixed and vaso-depressor syncope) played by SGLT-I was seen from the 5^{th} month of observation. **Figure 3**. Notably, who would remark to observe this ameliorative effect in patients (SGLT2-I users) which were chronically treated with empagliflozin, and canaglifozin. Indeed, the SGLT2-I users received the SGLT2-I for at least the previous 6 months before the study observation. However, the significant reduction of the cumulative risk to have VVS recurrence (all causes, mixed and vaso-depressor syncope) played by SGLT-I could be due to the chronic effect played by this class of anti-diabetic agents on the systemic and cardiac sympathetic axis.

Study limitations

The current study evidenced few limitations. Firstly, we collected the data of VVS recurrence by hospital discharge schedules, visits of follow-up, and interrogation of patients' diaries. However, by revising the collected data, we categorized the patients with vs. those without VVS recurrence. The duration of follow-up could affect long-term clinical outcomes. In addition, we did not implant internal loop recorders for continuous monitoring of syncope recurrence, and this could be limiting in the analysis of arrhythmic events in patients with VVS recurrence. Again, we did not investigate the effects of SGLT2-I at the molecular and cellular level in patients with VVS recurrence (**20**). Thus, we cannot report conclusive data about the cardio-protective and anti-inflammatory effects played by SGLT2-I (**21, 22**) in the patients with VVS recurrence. Again, in the current study we measured the plasma norepinephrine for the evaluation of systemic sympathetic activity. This could be limiting, and evidence intra-subject variability, but it is a valid and reproducible index of sympathetic activity, and used to evaluate the cardiac denervation by MIBG (**6**). Finally, the dimension of the study population could limit the importance of study results, and it cannot draw any definitive conclusion on the possible correlation between SGLT2-I therapy and VVS recurrence findings. Therefore, this remains a point to be demonstrated by an appropriately designed study

conducted on a higher number of VVS patients with T2DM diagnosis under the SGLT2-I vs. other classes of hypoglycemic drugs.

Conclusion

In T2DM patients with VVS recurrence, Non-SGLT2-I users vs. SGLT2-I users have hyper vagal tone and more severe CAN, by highest values of norepinephrine, and decreased heart uptake of norepinephrine (H/M_{late}). On the contrary, the SLGT2i-users vs. non-SLGT2i users evidence an increase in the WR at the follow-up end, via the amelioration of CAN. This effect might cause the reduction of all causes of VVS, and of mixed and vasodepressor VVS recurrence in SGLT2-I-users vs. Non-SGLT2-I users at follow-up end. Thus, SGLT2-I might have positive implications in the treatment of VVS recurrence in T2DM patients.

Abbreviations

123I-mIBG: 123I-metaiodobenzylguanidine;

CAN: cardiac autonomic dysfunction;

CRP: C reactive protein;

DBP: diastolic blood pressure;

ECG: electrocardiogram;

eGFR: glomerular filtration rate

HR: heart rate;

HRV: heart rate variability;

HF: high frequency;

LF/HFr: LF to HF ratio;

$H/M_{late:}$ late heart-to-mediastinum ratio;

Hb1Ac: glycated haemoglobin.

HR: Hazard Ratios;

HUT: Head-Up Tilt Test;

LF: low frequency;

LVEF: left ventricle ejection fraction;

SGLT2-I: sodium-glucose transporter inhibitors;

T2DM: type 2 diabetes mellitus:

VVS: Vasovagal syncope;

WR: washout rate;

Declarations

Ethics approval and consent to participate: the study complies with the Declaration of Helsinki, and the locally appointed Ethics Committee approved the research protocol (n 06062.18), and informed consent was obtained from all the participants.

Consent for publication: authors give full consent for publication.

Availability of data and materials: the study data are available on demand.

Competing interests: none to declare.

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Tables

Table 1. Characteristics of the study population at baseline.

STUDY VARIABLES AT BASELINE	Study population (n 607)	SGLT2-I users (n 161)	Non-SGLT2-I users (n 446)	P
CLINICAL CHARACTERISTICS				
Age, median IQR (years)	59 (37-74)	61 (41-74)	57(34-73)	0.200
Gender (male %)	315 (51.9)	81 (50.3)	234 (52.5)	0.681
Smokers	93 (15.3)	19 (11.8)	74 (16.6)	0.241
BMI > 30 kg/m2	50 (8.2)	12 (7.4)	38 (8.5)	0.121
Dyslipidemia (%)	215 (35.4)	53 (32.9)	162 (36.3)	0.516
Hypothyroidism (%)	70 (11.5)	18 (11.2)	52 (11.7)	0.174
Systolic BP (mmHg)	125±18	123±17	126±19	0.134
Diastolic BP (mmHg)	73±9	72±9	74±8	0.431
Systemic Hypertension	358 (59.0)	92 (57.1)	266 (59.6)	0.214
Prodromes (%)	320 (52.7)	84 (52.2)	236 (52.9)	0.718
Episodes/year (n)	2.3±1.9	2.5±1.2	2.2±1.5	0.128
LABORATORY DATA				
White blood cells, median IQR $x10^3$	9.3 (8.2-10.4)	9.4 (8.2-10.4)	8.9 (6.5-9.4)	0.024*
Platelets, $x10^3$	240.15±76.18	204.16±74.21	269.45±78.15	0.882
C reactive protein, mg	3.84±0.43	2.71±0.22	5.43±0.37	0.001*
Fasting glucose, median IQR (mmol)	6.64±2.12	6.0±1.86	7.11±2.17	0.001*
HB1Ac (%)	6.5 (5.4-7.0)	6.0 (5.5-6.6)	6.7 (5.4-7.0)	0.001*
Norepinephrine, median IQR (pg/ml)	1840.10 (1440.5-2210.20)	1465.12 (1217.52-1620.18)	1890.21 (1630.09-2250.15)	0.001*
AUTONOMIC DYSFUNCTION TESTs:				
Resting heart rate (bpm)	71±14	65±10	72±14	0.001*
Deep breathing; HR (ratio)	1.25±0.11	1.23±0.12	1.29±0.09	0.001*

Valsalva maneuver (ratio)	1.14±0.05	1.12±0.15	1.19±0.15	0.001*
Lying to standing (30:15 ratio)	1.08±0.16	1.02±0.11	1.23±0.61	0.001*
Postural BP changes (mmHg)	9.1±2.4	9.2±3.1	8.9±2.5	0.227
Sustained handgrip test (mmHg)	15.1±3.4	15.2±3.0	15.0±4.0	0.972
LF, normalized units	83.33±4.93	84.36±5.11	82.95±4.81	0.002*
HF, normalized units	18.37±1.43	18.11±1.55	18.49±1.38	0.001*
LF/HF ratio	4.57±0.48	4.68±0.44	4.52±0.49	0.001*
ECG Holter parameters				
Mean NN	820.78±68.57	832.95±56.89	802.71±68.52	0.001*
SDNN	181.18±32.14	186,60±31.96	173.67±30.93	0.008*
SDANN	174.13±37.47	176.06±39.23	166.25±38.39	0.011*
SD	86.42±17.40	89.88±16.72	81.62±17.38	0.001*
RMSSD	67.98±16.42	72.30±15.87	62.03±15.32	0.001*
pNN50	24.78±8.57	26.01±9.03	22.95±8.12	0.001*
123I-MIBG myocardial scintigraphy parameters				
Heart to Mediastinum ratio	2.08±0.55	2.38±0.45	1.89±0.54	0.001*
Washout rate (%)	43.44±9.36	48.72±7.39	41.49±9.26	0.001*
ECHOCARDIOGRAPHIC PARAMETERS				
IVS (mm)	10.6±1.4	10.6±1.4	10.7±1.4	0.527
LVEDv (ml/m^2)	50.6±11.5	50.2±11.8	51.1±11.2	0.223
LVESv (ml/m^2)	19.4±5.7	19.1±5.6	19.7±5.9	0.307
LVEF (%)	59±6	58±6	60±5	0.453
LAV (ml/m^2)	26.2±2.8	26.1±2.6	26.3±2.8	0.571

CARDIOVASCULAR MEDICATIONS				
Beta-blockers (%)	166 (27.3)	42 (26.1)	124 (27.8)	0.201
Calcium blockers (%)	103 (17.0)	27 (16.8)	76 (17.0)	0.547
ACE inhibitors (%)	257 (42.3)	67 (41.6)	190 (42.6)	0.625
ARS blockers (%)	84 (13.8)	22 (13.7)	62 (13.9)	0.518
Loop diuretics (%)	110 (18.1)	24 (14.9)	86 (19.3)	0.218
Thiazides diuretics (%)	130 (21.4)	30 (18.6)	100 (22.4)	0.367
Statins (%)	250 (41.2)	66 (41.0)	184 (41.2)	0.423
Class 1 antiarrhythmic drugs (%)	62 (10.2)	16 (9.9)	46 (10.3)	0.825
Class 3 antiarrhythmic drugs (%)	18 (3.0)	4 (2.5)	14 (3.1)	0.362
Digitalis (%)	47 (7.7)	11 (6.9)	36 (8.1)	0.410
Anti platelets (%)	188 (31.0)	52 (32.3)	136 (30.5)	0.707
Anticoagulants (%)	54 (8.9)	10 (6.2)	44 (9.9)	0.201
Hypoglycemic drugs				
Metformin	313 (51.6)	81 (50.3)	232 (52.0)	0.275
Sulfonylureas	72 (11.9)	18 (11.2)	54 (12.1)	0.484
Glinides	27 (4.4)	7 (4.3)	20 (4.5)	0.194
Glitazones	30 (4.9)	8 (5)	22 (4.9)	0.202
Incretins	79 (13.0)	21 (13.0)	58 (13.0)	0.821
Insulin therapy	122 (20.1)	32 (19.9)	90 (20.2)	0.262

Table 2. Characteristics of study population at 12 months of follow-up.

STUDY VARIABLES AT 12th MONTH	Study population (n 607)	SGLT2-I users (n 161)	Non-SGLT2-I users (n 446)	P
CLINICAL CHARACTERISTICS				
Smokers	94 (15.5)	24 (14.9)	70 (15.7)	0.887
BMI > 30 kg/m2	50 (8.2)	12 (7.5)	38 (8.5)	0.850
Dyslipidemia (%)	212 (34.9)	52 (32.3)	160 (35.9)	0.514
Hypothyroidism (%)	62 (9.4)	10 (6.2)	52 (11.7)	0.078
Systolic BP (mmHg)	121±17	120±16	122±17	0.136
Diastolic BP (mmHg)	74±8	73±9	76±8	0.061
Systemic Hypertension	339 (55.8)	81 (50.3)	258 (57.8)	0.148
Resting heart rate	77±12	72±12	79±11	0.001*
LABORATORY DATA				
White blood cells, median IQR $x10^3$	9.1 (8.0-10.2)	9.3 (8.2-10.0)	8.8 (6.6-9.5)	0.024*
Platelets, $x10^3$	224.23±76.78	250.26±78.05	210.20±74.15	0.621
C reactive protein, mg	2.25±0.19	1.56±0.17	2.47±0.20	0.001*
Fasting glucose, (mmol)	6.27±0.47	6.0±0.41	6.38±0.52	0.001*
HB1Ac (%)	6.3±0.88	6.1±0.81	6.4±0.93	0.001*
Norepinephrine, median IQR (pg/ml)	1622.28 (1225.39-2032.14)	1265.12 (1017.52-1414.36)	1972.41 (1702.40-2323.24)	0.001*
123I-MIBG myocardial scintigraphy parameters				
Heart to Mediastinum ratio	2.23±0.51	2.53±0.34	2.05±0.52	0.001*
Washout rate (%)	35.42±8.76	32.79±6.15	36.38±9.31	0.031*
ECG Holter parameters				
Mean NN	798.93±69.04	805.06±70.51	781.97±61.90	0.010*
SDNN	180.04±31.32	184,12±30.63	166.12±25.82	0.001*
SDANN	170.94±36.10	173.27±35.16	160.92±36.03	0.001*
SD	84.98±17.07	87.32±16.34	80.51±16.89	0.001*

RMSSD	65.77±16.91	68.84±16.08	57.25±16.30	0.001*
pNN50	23.51±8.34	24.85±8.74	20.32±6.50	0.001*
LF, normalized units	84.90±4.79	87.15±4.57	84.09±4.61	0.001*
HF, normalized units	16.65±1.15	15.97±1.62	16.91±0.79	0.032*
LF/HF ratio	5.13±0.51	5.52±0.66	4.98±0.32	0.001*
SYNCOPE RECURRENCE EVENTS (%)				
Total number of events	240	40	200	0.001*
Mixed (%)	133 (55.4)	26 (65.0)	107 (53.5)	0.039*
Cardio-inhibitory (%)	25 (10.4)	4 (10.0)	21 (10.5)	0.224
Vasodepressor (%)	82 (34.2)	10 (25.0)	72 (36.0)	0.004*
CARDIOVASCULAR MEDICATIONS				
Beta-blockers (%)	156 (25.7)	36 (22.4)	120 (26.9)	0.201
Calcium blockers (%)	78 (12.8)	20 (12.4)	58 (13.0)	0.606
ACE inhibitors (%)	238 (39.3)	60 (37.3)	178 (39.9)	0.341
ARS blockers (%)	80 (13.2)	20 (12.4)	60 (13.4)	0.499
Loop diuretics (%)	101 (16.6)	19 (11.8)	82 (18.4)	0.258
Tiazides diuretics (%)	129 (22.2)	29 (18.0)	100 (22.4)	0.309
Statins (%)	208 (34.3)	56 (34.8)	152 (34.1)	0.389
Class 1 antiarrhythmic drugs (%)	62 (10.2)	16 (9.9)	46 (10.3)	0.825
Class 3 antiarrhythmic drugs (%)	18 (3.0)	4 (2.5)	14 (3.1)	0.362
Digitalis (%)	47 (7.7)	11 (6.9)	36 (8.1)	0.410
Anti platelets (%)	188 (31.0)	52 (32.3)	136 (30.5)	0.707
Anticoagulants (%)	54 (8.9)	10 (6.2)	44 (9.9)	0.201
Hypoglycemic drugs:				
Metformin	317 (52.2)	85 (52.8)	239 (53.6)	0.568
Sulfonylureas	72 (11.9)	18 (11.2)	54 (12.1)	0.484
Glinides	27 (4.4)	7 (4.3)	20 (4.5)	0.194

Glitazones	30 (4.9)	8 (5)	22 (4.9)	0.202
Incretins	84 (13.8)	24 (14.9)	65 (14.6)	0.342
Insulin therapy	127 (20.9)	35 (21.7)	96 (21.5)	0.318

Table 3. Cox multiple regression analysis for all causes syncope, mixed syncope, cardioinhibitory syncope and vasodepressor syncope recurrence at 1 year of follow-up. The study population was of 607 patients.

ALL CAUSES OF VASOVAGAL SYNCOPE RECURRENCE	Multivariate analysis HR (95% CI)	P value
Age	0.763 [0.125-1.018]	0.135
Smoking	1.271 [0.839-1.927]	0.258
BMI	1.024 [0.506-2.070]	0.158
Prodromes	0.992 [0.944-1.043]	0.075
Hypertension	0.751 [0.471-1.198]	0.229
Systolic blood pressure	0.999 [0.950-1.050]	0.960
Glycemia	0.934 [0.677-1.289]	0.677
CRP	1.043 [0.747-1.455]	0.805
Noradrenaline	1.001 [0.998-1.003]	0.618
LVEF	1.005 [0.973-1.038]	0.749
Heart rate	1.007 [0.993-1.021]	0.323
LF/HF ratio	0.708 [0.458-1.096]	0.122
Heart to Mediastinum rate	0.710 [0.481-0.985]	0.024*
Washout rate	0.994 [0.972-1.016]	0.568
Beta blockers	1.007 [0.607-1.670]	0.980
SGLT2-I	0.550 [0.324-0.934]	0.027*

Figures

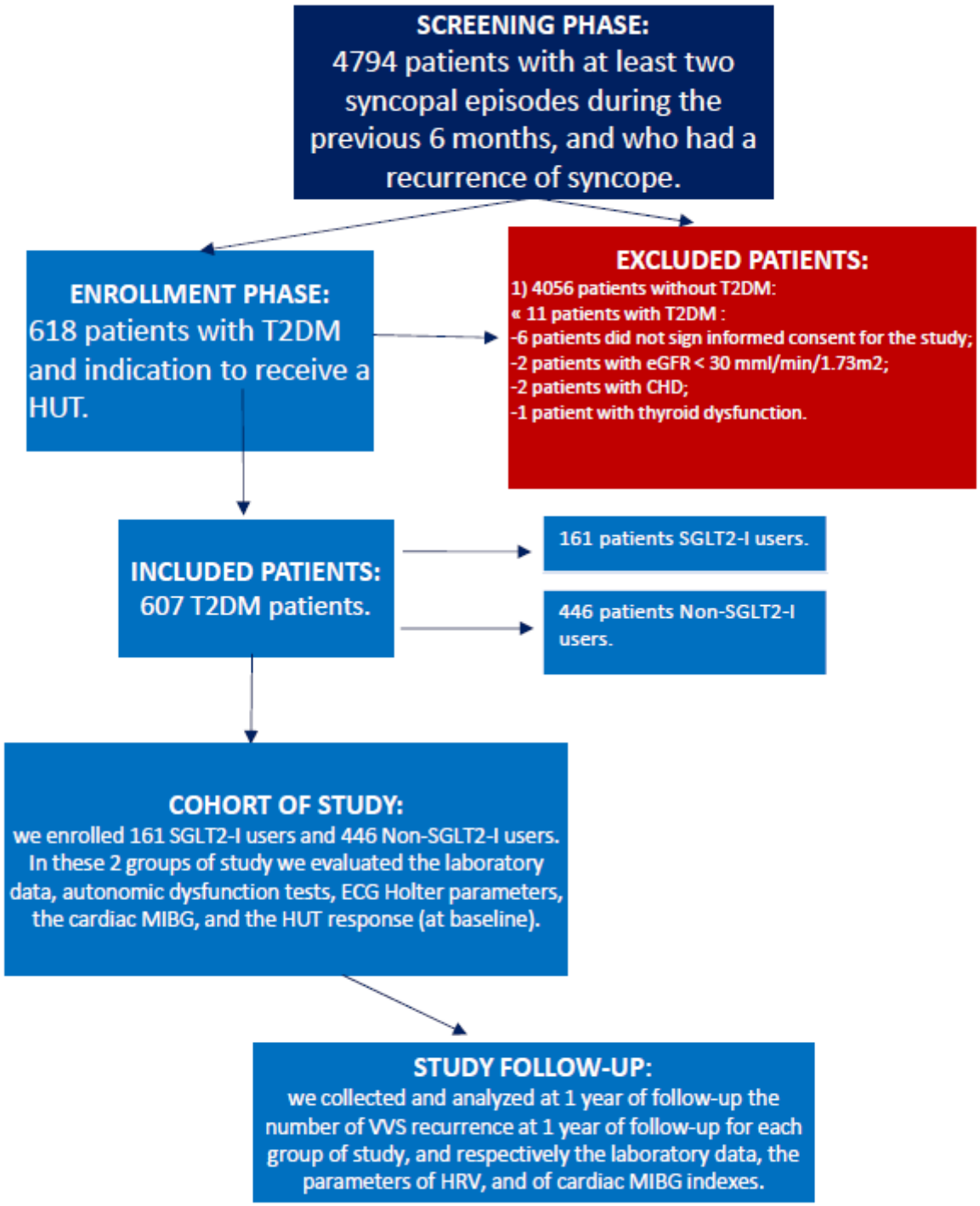

Figure 1

Study flow chart. CHD: coronary heart disease; eGFR: estimated glomerular filtration rate; HUT: Head-Up Tilt test; MIBG: metaiodobenzylguanidine; SGLT2-I: Sodium-Glucose Transporter 2 inhibitor; T2DM: type 2 diabetes mellitus; VVS: vaso-vagal syncope.

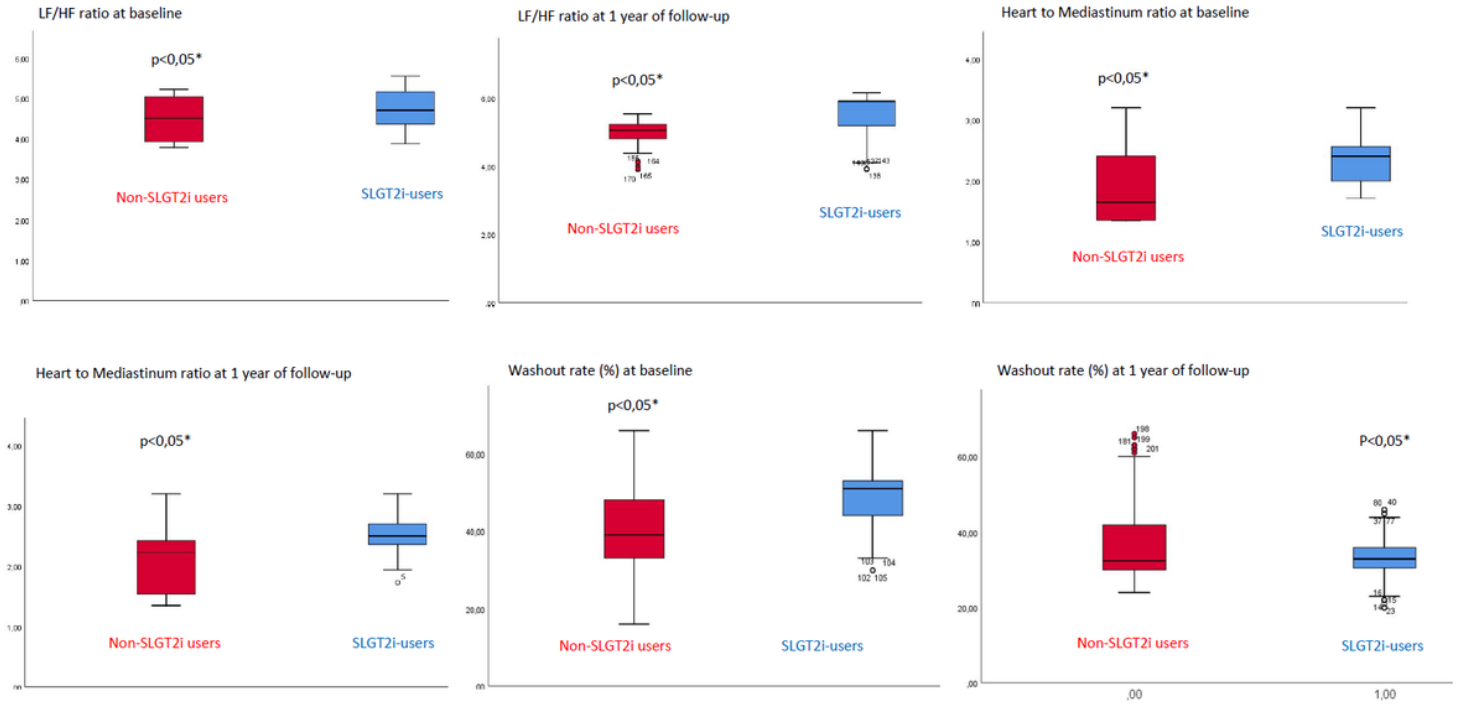

Figure 2

LF/HF ratio, Heart to Mediastinum ratio, and Washout rate (%) at baseline and at 1 year of follow-up in SGLT2-I users (blu color) vs. Non-SGLT2-I users (red color). LF: low frequency; HF: high frequency; SGLT2-i: sodium-glucose transporter 2 inhibitors. *is for statistical significant (p <0.05).

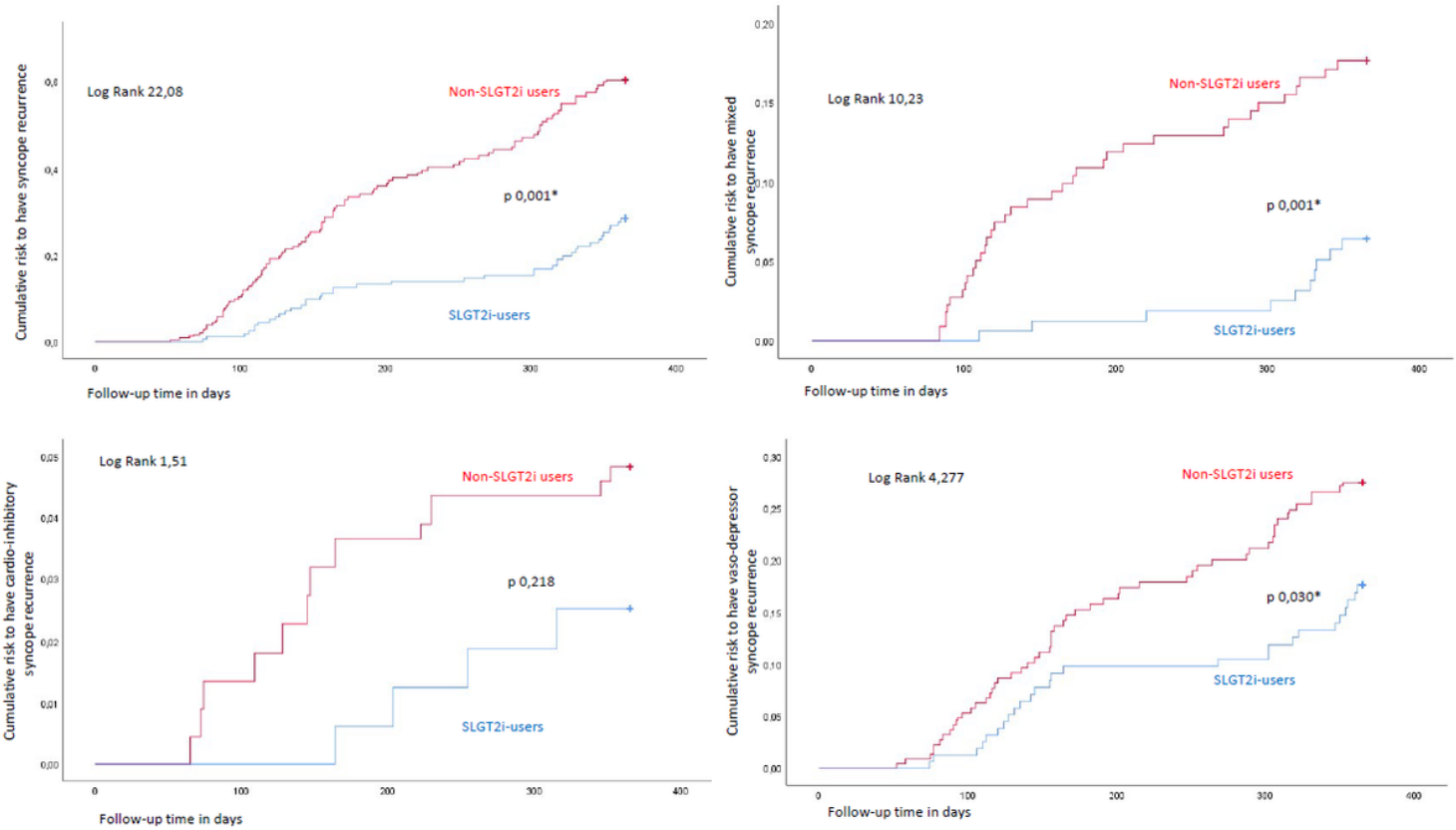

Figure 3

Kaplan curve for syncope recurrence (upper on the left), mixed syncope recurrence (upper right), cardio-inhibitory syncope recurrence (lower left), and vaso-depressor syncope recurrence (lower right) at 1 year of follow-up comparing SGLT2-I users (blu color) vs. Non-SGLT2-I users (red color). SGLT2-i: sodium-glucose transporter 2 inhibitors. *is for statistical significant ($p < 0.05$).

Supplementary Files

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