Endocrine (2019) 65:15–24
https://doi.org/10.1007/s12020-019-01931-y

META-ANALYSIS

Check for updates

Type 2 diabetes and risk of heart failure: a systematic review and meta-analysis from cardiovascular outcome trials

Dario Giugliano[1] · Maria Ida Maiorino[1] · Miriam Longo[2] · Giuseppe Bellastella[1] · Paolo Chiodini[2] · Katherine Esposito[3]

Received: 8 January 2019 / Accepted: 9 April 2019 / Published online: 26 April 2019

Abstract

Aim We performed a meta-analysis of randomized controlled trials (RCTs) that evaluated the effect of dipeptidyl peptidase-4 inhibitors (DPP-4i), glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and sodium glucose co-transporter-2 inhibitors (SGLT-2i) on heart failure (HF) risk in patients with type 2 diabetes (T2D).

Methods and results The electronic search was carried out until 10 November 2018. RCTs were included if they compared add-on therapy with any DPP-4i, GLP-1 RAs, or SGLT-2i with placebo, and included in the outcome hospitalization for HF, and other outcomes required for cardiovascular safety studies. Risk of HF was the primary outcome for this meta-analysis. We used a random-effect model to calculate hazard ratio (HR) and 95% CI. Twelve trials were identified, involving 120,765 patients. Compared with placebo, HF risk showed a non-significant 10% reduction with the newer anti-hyperglycemic drugs (HR = 0.90, 0.80–1.01); use of DPP-4i and GLP-1 RAs was associated with nonsignificant modifications of the HF risk (+5% and −9%, respectively), while the use of SGLT-2i was associated with a significant 31% reduction of the HF risk (HR = 0.69, 0.61–0.79, $P < 0.001$), with no heterogeneity ($I^2 = 0\%$, $P = 0.741$), suggesting a class effect. The meta-regression analysis of all 12 trials showed no association of reductions of hemoglobin A1C with HF risk.

Conclusion In T2D, SGLT-2i can reduce the risk of HF that is unrelated to improved glycemic control; DPP-4i and GLP-1 RAs behave as neutral.

Keywords Heart failure · MACE · Type 2 diabetes · DPP-4i · GLP-1 RAs · SGLT-2i

Introduction

The prevalence of type 2 diabetes (T2D) and heart failure (HF) continues to increase with the general aging of the population. Prevalence of HF is 2.5 times higher in individuals with diabetes than the general population, and up to 49% of patients with HF are estimated to have diabetes. Furthermore, patients with both T2D and HF have worse outcomes than patients with HF without diabetes [1]. Significant and clinically relevant decreases (−40.3% for ischemic heart disease and −29.2% for stroke) in major cardiovascular (CV) disease death have occurred in adults with and without diabetes from 1988 to 2015 in the US [2]; in contrast, HF did not show any significant change, but paradoxically showed an increase (+11%) in young adults.

Despite the growing number of therapeutic options, uncertainty surrounds the clinical benefits and risks of varying intensities of glucose control for patients with T2D. Tight glycemic control has an imperfect role to reduce the CV complications in patients with T2D. As far as HF is

These authors share last authorship: Paolo Chiodini, Katherine Esposito

Supplementary information The online version of this article (https://doi.org/10.1007/s12020-019-01931-y) contains supplementary material, which is available to authorized users.

✉ Dario Giugliano
dario.giugliano@unicampania.it

[1] Division of Endocrinology and Metabolic Diseases, Department of Advanced Medical and Surgical Sciences, Università della Campania L. Vanvitelli, Naples, Italy

[2] Medical Statistics Unit, Università della Campania L. Vanvitelli, Naples, Italy

[3] Diabetes Unit, Department of Advanced Medical and Surgical Sciences, Università della Campania L. Vanvitelli, Naples, Italy

concerned, the risk of HF after intensive glycemic control remains unchanged, with a residual risk as high as 100% [3].

Starting from 2005, three new classes of drugs were launched to treat diabetic hyperglycemia, particularly glucagon-like peptide-1 receptor agonists (GLP-1 RAs), dipeptidyl peptidase-4 inhibitors (DPP-4i), and sodium glucose co-transporter-2 inhibitors (SGLT-2i). In 2008, FDA required the proof of cardiovascular safety as a prerequisite for the approval of new glucose-lowering drugs [4], which led to dedicated cardiovascular outcome trials (CVOTs). All these trials had a similar design, consisting in the addition of the newer drug or placebo to a background of previous diabetes treatment and lipid and/or antihypertensive therapy. This has represented a unique opportunity to group and evaluate drugs belonging to the same class, in order to see whether their cardiovascular effects are generalizable.

Recognizing that 12 CVOTs have been completed, we planned a systematic review and meta-analysis of CVOTs that evaluated the effect of GLP-1 RAs, DPP-4i, and SGLT-2i on HF risk in patients with T2D. In particular, we sought to answer the following questions:

(1) What is the effect of these drugs on the risk of HF?
(2) Is the effect restricted to a particular drug class?
(3) Is there any difference among drugs belonging to the same class?
(4) What is their effect on other CV parameters, including MACE (major adverse cardiovascular events) and its components, and overall death?

Although recent meta-analyses had addressed similar topics (for some drugs or some CV outcomes only) [5, 6], to our knowledge this is the first one to analyze all CVOT trials so far published.

Methods

We conducted this systematic review and meta-analysis based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines [7]. The PRISMA checklist and the protocol are provided in Supplementary Data. Neither ethics approval nor patient consent was required for this analysis. The authors are experienced in meta-analyses [8–10].

Data sources and searches

Databases for search included PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and ClinicalTrials.gov (http://www.clinicaltrials.gov). The last search was performed on 10 November 2018. The search terms used were "dipeptidyl-peptidase inhibitor", "saxagliptin", "alogliptin", "sitagliptin", "linagliptin"; "glucagon-like peptide-1 receptor agonist", "exenatide", "lixisenatide", "liraglutide", "semaglutide", "dulaglutide", "albiglutide"; sodium-glucose co-transporter-2 inhibitor", "empagliflozin", "canagliflozin", "dapagliflozin"; "hospitalization for heart failure", "cardiovascular mortality", "myocardial infarction", "stroke", and "all-cause mortality". The search was filtered to include only randomized controlled trials (RCTs) or meta-analyses involving humans. Reference lists of prior reviews and meta-analyses were also manually searched to capture relevant RCTs that were not indexed by normal keywords.

Study selection

We included trials if they were RCTs performed in adults with T2D, compared add-on therapy with any DPP-4i, GLP-1RA, or SGLT-2i with placebo, and included in the outcome (either primary or secondary) hospitalization for HF, as well as other outcomes required by regulatory agencies for cardiovascular safety studies in diabetes (cardiovascular mortality, non-fatal myocardial infarction, or non-fatal stroke). We excluded trials if they were completed before the FDA guidance of 2008.

Data extraction and quality assessment

Two investigators (D.G. and M.I.M.) used a standardized tool to independently abstract all data, and disagreements were resolved by consensus. Results reported in trial publications (primary trial results and subsequent secondary publications), and their accompanying supplementary materials, were used as the primary source of information. Available additional sources, including, but not limited to, the US Food and Drug Administration, European Medicines Agency, and pharmaceutical company websites, were searched to capture any additional data. The relevance of studies was assessed with a hierarchical approach on the basis of title, abstract, and the full manuscript. After the initial screening of titles and abstracts, the studies included by both reviewers were compared, and disagreement was resolved by consensus.

We evaluated the risk of bias of the included RCTs according to the Cochrane Collaboration's tool for assessing the risk of bias [11]. The risks of bias were categorized as high, low, and unclear. Methodologic quality was also assessed by calculating the Jadad score [12] for each RCT. This quality scale includes points for randomization (1 point), tables of random numbers or computer-generated randomization (1 point), double-blind (1 point), placebo (1 point), and follow-up (numbers and reasons for withdrawal in each group: 1 point). We gave an additional point if the analysis was by intention to treat. We considered a score of >4 as good quality.

Data synthesis and analysis

The primary efficacy outcome for this meta-analysis was the effect of DPP-4i, GLP-1 RAs, and SGLT-2i on the risk of HF compared with placebo. Additional preplanned analyses were conducted on the incidence of MACE, its components (cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke), and all-cause mortality. Hazard ratios (HR) and 95% confidence intervals (95% CI) were collected for CV efficacy outcomes. Heterogeneity between studies was assessed by using the Q statistic and I^2, which is the proportion of total variance observed between the trials attributed to the differences between trials rather than to sampling error. $I^2 < 25\%$ was considered as low in heterogeneity, $I^2 > 75\%$ as high in heterogeneity, and a Q statistic P value of <0.10 was considered significant. In a conservative way, we calculated the summary estimates and 95% CIs for CV efficacy outcomes using a random effects model meta-analysis. Publication bias was assessed visually with funnel plots and with the Egger test [13]; a P value of <0.10 was considered significant. The trim-and-fill method was used to estimate the effect of publication bias, if any. To evaluate whether the impact of novel glucose-lowering medications on incident HF (primary efficacy outcome of this meta-analysis) and MACE (principal outcome in all trials) was associated with hemoglobin A1c (HbA1c) reduction, we performed metaregression analyses. Metaregression model estimates the amount of heterogeneity related to study characteristics; this model relates the treatment effect to study-level covariates, while assuming additivity of within-study and between-studies components of variance. Restricted maximum likelihood estimators were used to estimate model parameters. Permutation test (using 1000 re-allocations) was used for assessing the true statistical significance of an observed metaregression finding [14]. Data were analyzed using Stata 11.2 software (StataCorp LP, College Station, TX). All statistical tests were two sided, and P values of <0.05 were regarded as significant.

Results

Search results

Of 60 articles screened for eligibility, 12 trials [15–26] were eligible and included in the meta-analysis (Supplementary Fig. 1). Their characteristics are summarized in Table 1. The participants were all patients with T2D (>18 years old). All trials were multinational and sponsored by industry. The trials have been published between 2013 and 2018, with 3 studies published in 2018. All trials were of parallel-group, double-blind design, and their mean duration ranged from 1.5 to 4.2 years. The baseline HbA1c level ranged from 7.3% to 8.7%, but was almost identical between groups (drug vs placebo) within the same trial. The populations studied ranged in size from 3297 (SUSTAIN-6) to 17,160 (DECLARE) and were of similar age (range: 60–66 years).

Intervention and risk of bias

The trials evaluated 120,765 patients. The primary endpoint of this meta-analysis was hospital admission for HF, defined as new hospitalization and/or presentation to acute care facility due to congestive HF. In almost all trials, hospital admission for HF was reported as a secondary outcome, while three- (ten trials) or four-point (two trials) MACE were the primary outcome (Table 1). The following classes of antidiabetic medications were evaluated: DPP-4i (saxagliptin [15], alogliptin [16], sitagliptin [17], linagliptin [18]) in 43,522 participants; GLP-1 RAs (lixisenatide [19], liraglutide [20], semaglutide [21], once-weekly exenatide [22], albiglutide [23]) in 42,920 participants; SGLT-2i (empagliflozin [24], canagliflozin [25], dapagliflozin [26]) in 34,323 participants.

According to the Cochrane Collaboration's tool for assessing risk of bias, there was no major risk of bias in any study (Supplementary Fig. 2). All trials had a quality score >4, indicating high quality (Supplementary Table 1).

Outcomes

In pooled analysis of the 12 trials, the risk of hospitalization for HF showed a non-significant 10% reduction (HR = 0.90, 0.80–1.01, $P = 0.068$) with the newer antihyperglycemic drugs, as compared with placebo, with significant heterogeneity between trials ($I^2 = 69.2\%$, $P < 0.001$) (Fig. 1, Table 2). There was no evidence of publication bias (Egger test, $P = 0.644$). In additional analyses restricted to drug classes, use of DPP-4i and GLP-1 RAs was associated with nonsignificant modifications of the HF risk, and nonsignificant heterogeneity between studies. By contrast, use of SGLT-2i was associated with a highly significant ($P < 0.001$) 31% reduction of the HF risk, with no heterogeneity ($I^2 = 0\%$, $P = 0.741$) (Fig. 1, Table 2). The reduction of hospitalization for HF by SGLT-2i was significant in T2D patients with (HR = 0.67, 0.54–0.84, $P < 0.001$) or without (HR = 0.71, 0.60–0.83, $P < 0.001$) a history of HF at baseline; the HR for the composite of CV death or hospitalization for HF was also statistically significant in patients with (HR = 0.71, 0.61–0.84, $P = 0.001$) or without (HR = 0.78, 0.65–0.94, $P = 0.008$) a history of HF at baseline (Supplementary Fig. 3). The metaregression analysis of all 12 trials showed no association between reductions of HbA1c and HF risk ($P = 0.581$) (Fig. 2).

In the overall analysis, the risk of MACE was significantly reduced by 8% (HR = 0.92, 0.87–0.97, $P =$

Table 1 Characteristics of CVOTs included in the meta-analysis

Trial/year of publication	Study drug/mean follow up (years)	Participants (*n*)	Mean age (years)	Baseline A1C (%) (mmol/mol)	ΔA1C (%)	Type of prior CV disease	Principal outcome	HF outcome	Study funder
SAVOR-TIMI 53, 2013	Saxagliptin, 2.1	16,492	65	8.0 (64)	−0.27	History of CV disease (CHD, CVD, PVD) or multiple risk factors fo CV disease	Three-point MACE	Secondary	AstraZeneca & Bristol–Myers Squibb
EXAMINE, 2013	Alogliptin, 1.5	5380	61	8.0 (6.4)	−0.36	Acute coronary syndrome within the previous 15–90 days	Three-point MACE	Secondary	Takeda
TECOS, 2015	Sitagliptin, 2.8	14,671	66	7.3 (56)	−0.29	Established CV disease (CHD, CVD, PVD)	Four-point MACE	Secondary	Merck Sharp & Dohme
CARMELINA, 2018	Linagliptin, 2.2	6979	65.9	7.9 (63)	−0.36	History of CV disease (CHD, CVD, PVD) or multiple risk factors for CV disease	Three-point MACE	Secondary	Boehringer Ingelheim
ELIXA, 2015	Lixisenatide, 2.1	6068	60	7.7 (61)	−0.27	Acute coronary syndrome within the previous 180 days	Four-point MACE	Secondary	Sanofi
LEADER, 2016	Liraglutide, 3.8	9340	64.3	8.7 (72)	−0.40	CV or CK disease (≥50 years) or CV risk factors (≥60 years)	Three-point MACE	Secondary	Novo-Nordisk
SUSTAIN-6, 2016	Semaglutide, 3.1	3297	64.6	8.7 (72)	−0.86	CV or CK disease (≥50 years) or CV risk factors (≥60 years)	Three-point MACE	Secondary	Novo-Nordisk
EXSCEL, 2017	Exenatide OW, 3.2	14,752	62	8.0 (64)	−0.53	CHD, CVD, PVD 27% without previous CV events	Three-point MACE	Secondary	Amylin Pharmaceuticals
HARMONY, 2018	Albiglutide, 1.6	9463	64	8.7 (72)	−0.42	CV disease (CHD, CVD, PVD)	Three-point MACE	Secondary[a]	GlaxoSmithKline
EMPA-REG OUTCOME, 2015	Empagliflozin, 3.1	7021	63.2	8.1 (65)	−0.30	CV disease (CHD, CVD, PVD)	Three-point MACE	Secondary	Boehringer Ingelheim & Eli Lilly
CANVAS, 2017	Canagliflozin, 2.4	10,142	63.3	8.2 (66)	−0.58	Symptomatic CV disease (>30 years) or two or two or more CV risk factors (>50 years)	Three-point MACE	Secondary	Janssen
DECLARE, 2018	Dapagliflozin, 4.2	17,160	63.8	8.3 (67)	−0.42	CV disease (40%) and multiple risk factors for CV disease (60%)	Three-point MACE[b]	Coprimary composite with CV death	AstraZeneca

ΔA1c decrease from baseline, compared with placebo, *CV* cardiovascular, *CHD* coronary heart disease, *CVD* cerebrovascular disease, *PVD* peripheral vascular disease, *CK* chronic kidney disease

[a]Composite of death from CV causes and hospital admission for HF

[b]Cardiovascular death, myocardial infarction, or ischemic stroke

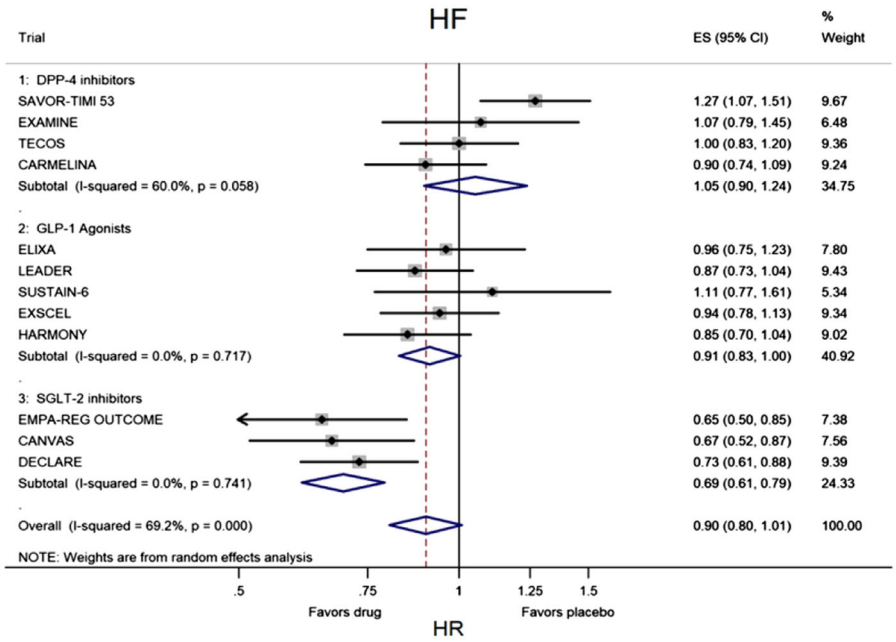

Fig. 1 Forest plots of meta-analysis for the primary endpoint, i.e., hospitalization for HF (heart failure). The results are expressed as hazard ratio (HR). ES effect size

0.001) with the use of DPP-4i, GLP-1 RAs, and SGLT-2i, as compared with placebo, with a significant degree of heterogeneity between trials ($I^2 = 45.8\%$, $P = 0.041$) (Fig. 3, Table 2). There was no evidence of publication bias (Egger test, $P = 0.210$). Compared with placebo, DPP-4i showed a neutral effect on MACE, while the use of both GLP-1 RAs and SGLT-2i was associated with significant reductions of MACE (12% and 11%, respectively), with significant heterogeneity for GLP-1 RAs ($I^2 = 58.8\%$, $P = 0.045$) and no heterogeneity for SGLT-2i ($I^2 = 0\%$, $P = 0.550$). The heterogeneity for GLP-1 RAs was reduced and became nonsignificant by excluding the ELIXA trial ($I^2 = 36.8\%$, $P = 0.191$) (Supplementary Fig. 4).

Overall, there was a significant ($P = 0.009$) 10% risk reduction in CV mortality associated with the use of newer drugs, as compared with placebo, with significant heterogeneity ($I^2 = 48.3\%$, $P = 0.031$) (Fig. 4, Table 2). There was no evidence of publication bias (Egger test, $P = 0.558$). The use of GLP-1 RAs was associated with a significant ($P = 0.004$) 12% risk reduction in CV mortality, with no heterogeneity ($I^2 = 0\%$, $P = 0.518$). Both DPP-4i and SGLT-2i were associated with no significant effect on CV mortality. The only two trials that showed a significant benefit on CV mortality were the LEADER (with liraglutide) and the EMPA-REG OUTCOME (with empagliflozin).

Overall, there was a significant ($P = 0.018$) 7% risk reduction of nonfatal MI associated with the use of newer drugs, as compared with placebo, with nonsignificant heterogeneity ($I^2 = 27.6\%$, $P = 0.174$) (Fig. 5, Table 2). There was no evidence of publication bias (Egger test, $P = 0.622$). The use of SGLT-2i was associated with a significant 12% risk reduction in nonfatal MI, with no heterogeneity ($I^2 = 0\%$, $P = 0.935$), although no single trial in this class produced a significant benefit on nonfatal MI.

Overall, there was a nonsignificant ($P = 0.203$) 5% risk reduction of nonfatal stroke associated with the use of newer drugs. Nonfatal stroke (Supplementary Fig. 5, Table 2) was significantly reduced by GLP-1 RAs (HR = 0.87, 0.77–0.99), with low heterogeneity ($I^2 = 6\%$, $P = 0.373$), although only the SUSTAIN-6 trial was associated with a significant benefit. There was no evidence of publication bias (Egger test, $P = 0.613$).

Overall, there was a significant ($P = 0.013$) 8% risk reduction in all-cause mortality associated with the use of newer drugs, as compared with placebo, with significant heterogeneity ($I^2 = 55.4\%$, $P = 0.010$) (Supplementary Fig. 6, Table 2). There was no evidence of publication bias (Egger test, $P = 0.793$). The use of GLP-1 RAs was associated with a significant 11% risk reduction in all-cause mortality, with no heterogeneity ($I^2 = 0\%$, $P = 0.663$); the reduction of all-cause mortality was also significant (17%) with the use of SGLT-2i, but heterogeneity between trials was high ($I^2 = 75.2\%$, $P = 0.018$). The use of DPP-4i was associated with a neutral effect on CV mortality, with low heterogeneity ($I^2 = 14.1\%$, $P = 0.322$).

Discussion

The results of 12 CVOTs trials so far published using DPP-4i, GLP-1 RAs, and SGLT-2i in 120,765 participants have provided the unique opportunity to evaluate their impact on the risk of HF in patients with T2DM, as individual trials

Table 2 Preplanned statistical analyses

Outcome	Trials (*n*)	Estimate (HR)	95% CI	*P* value	I^2 (%)	*P* value *Q* test
HF						
All	12	0.90	0.80–1.01	0.068	69.2	<0.001
DPP-4i	4	1.05	0.90–1.24	0.531	60.0	0.058
GLP-1 RAs	5	0.91	0.83–1.00	0.058	0	0.717
SGLT-2i	3	0.69	0.61–0.79	<0.001	0	0.741
MACE						
All	12	0.92	0.87–0.96	0.001	45.8	0.041
DPP-4i	4	0.99	0.94–1.05	0.798	0	0.948
GLP-1 RAs	5	0.88	0.80–0.96	0.005	58.8	0.045
SGLT-2i	3	0.89	0.83–0.96	0.001	0	0.550
CV mortality						
All	12	0.90	0.83–0.97	0.009	48.3	0.031
DPP-4i	4	0.98	0.89–1.08	0.655	2.6	0.379
GLP-1 RAs	5	0.88	0.80–0.96	0.004	0	0.518
SGLT-2i	3	0.81	0.63–1.05	0.116	79.9	0.007
Non-fatal MI						
All	12	0.93	0.87–0.99	0.018	27.6	0.174
DPP-4i	4	1.00	0.92–1.10	0.928	0	0.445
GLP-1 RAs	5	0.90	0.80–1.01	0.063	50.9	0.087
SGLT-2i	3	0.88	0.79–0.97	0.011	0	0.935
Non-fatal stroke						
All	12	0.95	0.88–1.03	0.203	8.6	0.361
DPP-4i	4	1.00	0.87–1.14	0.949	0	0.664
GLP-1 RAs	5	0.87	0.77–0.99	0.028	6.0	0.373
SGLT-2i	3	1.02	0.87–1.19	0.803	25.7	0.260
All-cause mortality						
All	12	0.92	0.86–0.98	0.013	55.4	0.010
DPP-4i	4	1.01	0.93–1.09	0.792	14.1	0.322
GLP-1 RAs	5	0.89	0.83–0.95	0.001	0	0.663
SGLT-2i	3	0.83	0.70–0.99	0.013	75.2	0.018

are frequently underpowered to evaluate a secondary outcome, as well as a single component of the primary outcome. In the pooled analysis of the 12 trials, we found a non-significant 10% reduction of HF risk in T2D patients treated with the newer anti-hyperglycemic drugs, without evidence of publication bias. However, the results of subgroup analyses show that the use of three different SGLT-2i (empagliflozin, canagliflozin, and dapagliflozin) was associated with a statistically significant 31% risk reduction in the HF outcome, with no heterogeneity, indicating that the effect was similar within the class. In particular, hospitalization for HF was reduced by 35% with empagliflozin, 33% with canagliflozin, and 27% with dapagliflozin. Neither DPP-4i nor GLP-1 RAs produced significant alteration of the HF risk, except for saxagliptin which was the only drug within the two classes associated with a significantly higher HF risk.

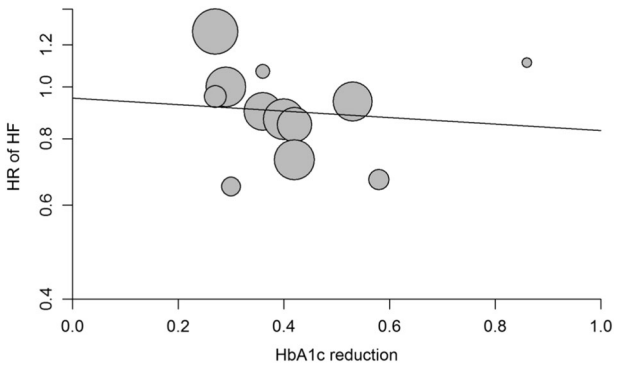

Fig. 2 Metaregression between reductions of HbA1c and hazard ratio for heart failure

The benefit of SGLT-2i on HF risk in T2D is a class effect. It is not associated with improved glycemic control, as the meta-regression analysis did not show any

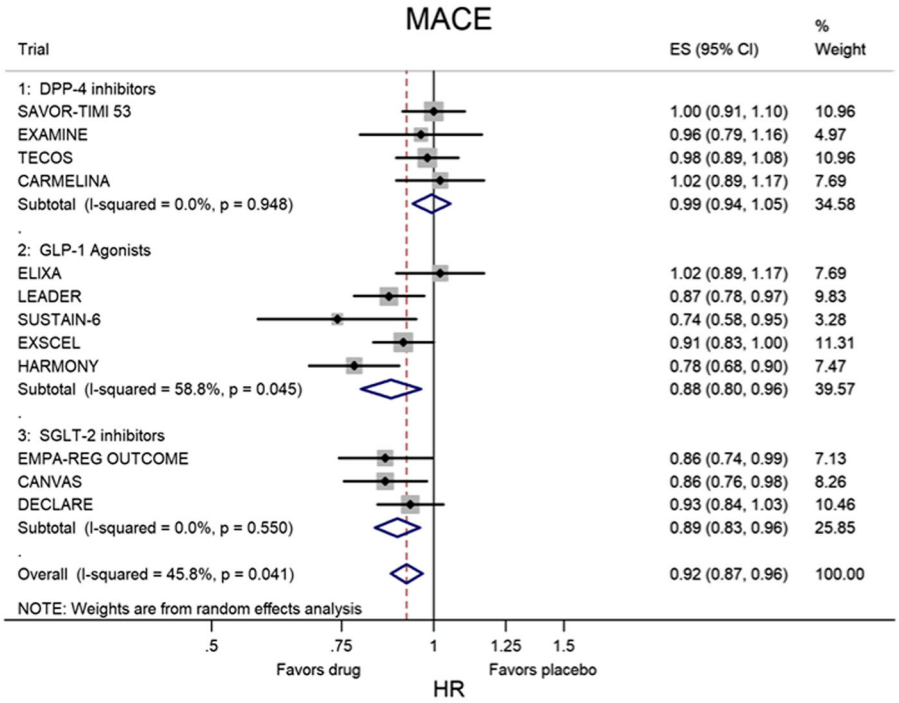

Fig. 3 Forest plots of meta-analysis for the risk of MACE. The results are expressed as hazard ratio (HR). ES effect size

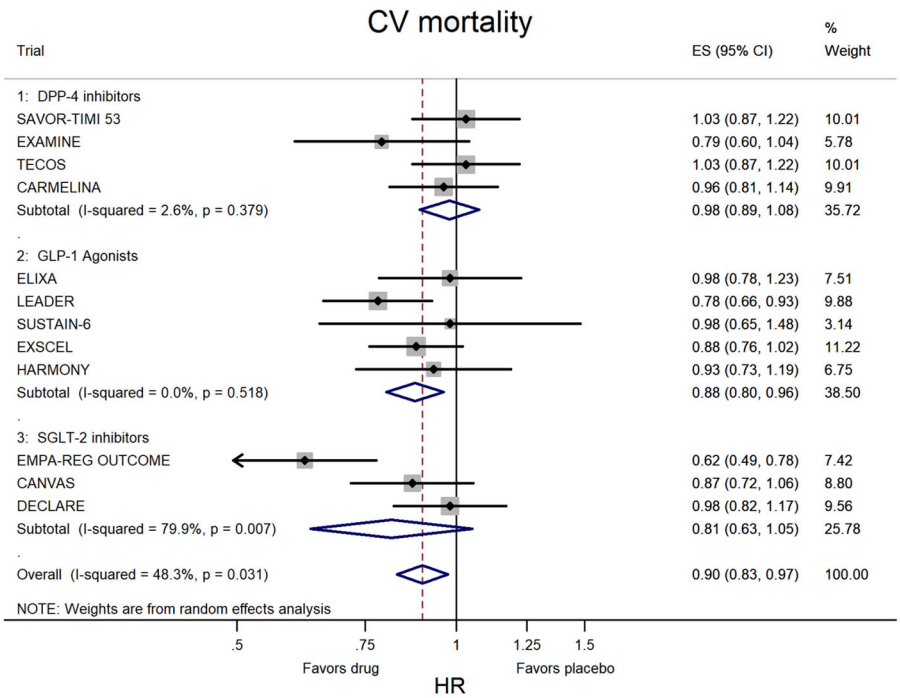

Fig. 4 Forest plots of meta-analysis for the risk of CV mortality. The results are expressed as hazard ratio (HR). ES effect size

association between reductions of A1C and HF risk in all trials. All this seems to call for nonglycemic effect as an explanation for the reduced HF risk with SGLT-2i. Lowering of blood pressure, decrease in intraglomerular pressure, reduction in albuminuria, and amelioration of volume overload are all plausible protective mechanisms of their benefit on HF and CV outlook; moreover, regulation of Na^+/H^+ exchange at the level of the heart and kidney and modulation of adipokine production may play a role as well [27].

The benefit on HF by SGLT-2i is clinically relevant and statistically significant in T2D patients with or without a prior history of HF [26, 28, 29]. Overall, there is a 34% and 30% HF risk reduction in T2D patients with or without a history of HF at baseline, respectively. However, only a limited number of participants in the three trials had a

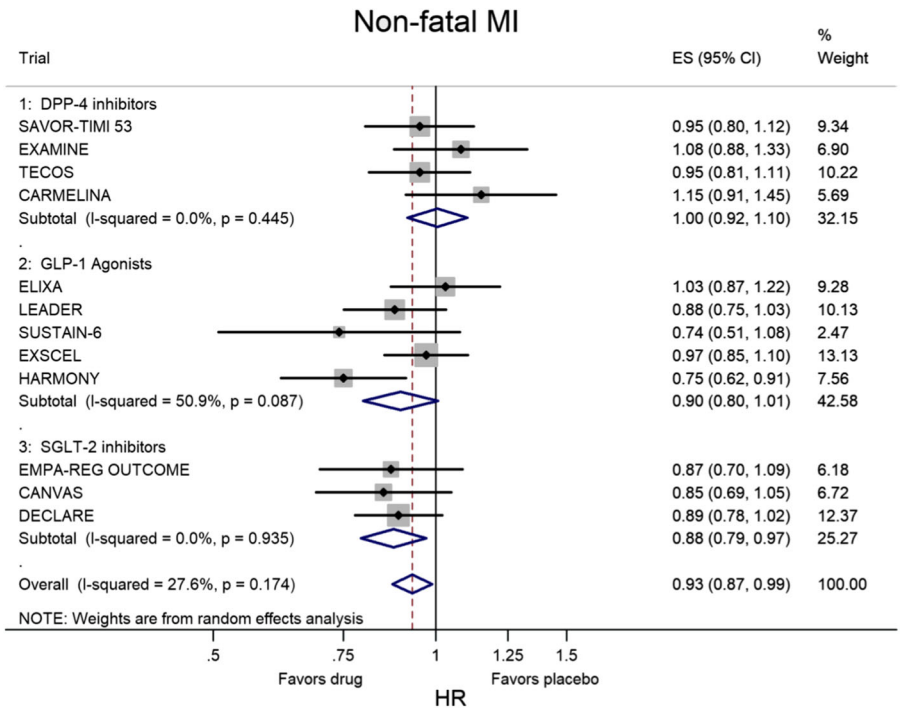

Fig. 5 Forest plots of meta-analysis for the risk of non-fatal IMI. The results are expressed as hazard ratio (HR). ES effect size

history of investigator-reported HF. For now, the new ADA/EASD consensus guidelines [30] suggest to consider a SGLT-2i with proven benefit when managing hyperglycemia in patients with T2D and clinical HF. Despite the inherent limitations linked to their retrospective nature, possibility of selection bias, residual cofounding, and relatively short follow-up, data derived from large international epidemiologic studies are a valuable addition to those generated by RCTs. One such study [31] collected real-world data from six countries and more than 300,000 patients, 87% of whom did not have a history of CV disease. Patients prescribed SGLT-2i had a 39% lower risk for HF hospitalization compared with other glucose-lowering drugs. Another study [32] collected data from 4 large US administrative claims databases, including 253,697 new users of SGLT-2i and 460,885 new users of non-SGLT-2i: new users of canagliflozin and new users of empagliflozin or dapagliflozin had a lower risk of HF (−18%, −38%, respectively) compared with new users of a DPP-4i or GLP-1 RAs, without any significant difference in the head-to-head comparison of SGLT-2i. The results of these large studies suggest the effectiveness of SGLT-2i on HF risk in a broader T2D patient population, that is more representative of those seen in primary care.

As a class, SGLT-2i was also associated with a significant 11% risk reduction for MACE (low heterogeneity), and a significant 17% reduction of all-cause mortality (high heterogeneity). Overall, there was a neutral impact of DPP-4i on all CV outcomes, whereas GLP-1 RAs showed a positive and significant impact on MACE, CV mortality, nonfatal stroke, and all-cause mortality. All 12 completed CVOTs succeeded in showing non-inferiority of the study drug to placebo for their primary composite MACE endpoint; even, 5 CVOTs (three with the GLP-1 RAs liraglutide, semaglutide, albiglutide, and two with the SGLT-2i empagliflozin and canagliflozin) have given evidence for superiority.

There is a great expectation about the possibility to translate the clinical benefits of SGLT-2i in the nondiabetic patient: dedicated outcome trials are ongoing, assessing empagliflozin (EMPEROR-Preserved [NCT03057951]) in patients with HF and preserved ejection fraction and dapagliflozin (Dapa-HF [NCT03036124]) in patients with chronic HF. Hopefully, such ongoing trials may tell us whether SGLT-2i will become a novel standard treatment in both diabetic and nondiabetic patients with chronic or acute HF.

The strengths of this meta-analysis are the inclusion of all CVTOs trials published until 10 November 2018, the very large number of participants, the use of a prespecified analyses, double-checking of data extraction, and the high quality of all trials, which minimizes the risk of bias, and more importantly, the absence of between-study heterogeneity, suggesting a class effect by SGLT-2i on HF risk. Our study has limitations as well. The first limitation is that HF was a secondary endpoint in all trials, except for DECLARE, with some differences in its definition: in fact, baseline HF prevalence, when reported, is poorly characterized, T2D patients with HF are poorly represented (<15% of the total enrolled sample), a minority of trials

report the rate of incident HF, whose definition is non-specific, and HF events are limited to HF hospitalization only. Despite all this, the SGLT-2i CVOT trials are all concordant in their outcome (i.e., significant reduction of the HF risk), with very close results (between 27% and 35% reduction). The second limitation relates to the use of aggregate data, which limits the ability to delve further into subgroups of interest. Another limitation relates to the duration of follow-up, which still spans 1.5–4.2 years. Moreover, the trials were generally conducted in patients who were considered to be at high or very high risk of CV events, which may limit their generalizability to those at lower risk. Finally, few data exist in literature about the effects of these newer drugs in the elderly diabetic patient who is at an increased risk for HF.

In conclusion, the findings of this meta-analysis suggest that SGLT-2i are useful in the prevention and treatment of HF in T2D patients. Future CV outcome trials of glucose-lowering therapies should enroll a proportion of patients with baseline HF similar to the prevalence of HF in the general population with T2D. However, it is likely that in the near future conducting trials of drugs against a placebo among such patients may no longer be ethical, as argued by FDA [33], also on the advice by recent guidelines [30] to use a medication with proven cardiovascular benefit in patients with T2D and established CV disease. In the meantime, the choice of a specific SGLT-2i for a T2D patient with HF should be based on additional benefit on CV risk, and individualized to each patient's needs, convenience, and tolerability.

Acknowledgements D.G. is the guarantor of this article.

Funding This research was supported in part by the "Associazione Salute con Stile", Naples, Italy.

Author contributions D.G., M.I.M., and M.L. conducted the literature search, data extraction, and data analysis. P.C. and D.G. did the statistical analyses. G.B. contributed to the data analysis and to writing the manuscript. K.E. and D.G. wrote, reviewed, and edited the manuscript. All the authors approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest D.G. received honoraria for speaking at meetings from Novartis, Sanofi-Aventis, Lilly, AstraZeneca, and Novo Nordisk. K.E. received honoraria for speaking at meetings from Novartis, Sanofi-Aventis, Lilly, AstraZeneca, Boehringer Ingelheim, and Novo Nordisk. M.I.M. received honoraria for speaking at meetings from Lilly and Novo Nordisk. The other authors declare that they have no conflict of interest.

References

1. P.M. Seferovi, M.C. Petrie, G.S. Filippatos, S.D. Anker, G. Rosano, J. Bauersachs, W.J. Paulus, M. Komajda, F. Cosentino, R.A. de Boer, D. Farmakis, W. Doehner, E. Lambrinou, Y. Lopatin, M.F. Piepoli, M.J. Theodorakis, H. Wiggers, Lekakis, A. Mebazaa, M.A. Mamas, C. Tschöpe, A.W. Hoes, J.P. Seferović, J. Logue, T. McDonagh, J.P. Riley, I. Milinković, M. Polovina, D.J. van Veldhuisen, M. Lainscak, A.P. Maggioni, F. Ruschitzka, J.J. V. McMurray, Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology. Eur. J. Heart Fail. **20**, 853–872 (2018)
2. Y.J. Cheng, G. Imperatore, L.S. Geiss, S.H. Saydah, A.L. Albright, M.K. Ali, E.W. Gregg, Trends and disparities in cardiovascular mortality among U.S. adults with and without self-reported diabetes mellitus, 1988–2015. Diabetes Care **41**, 2306–2315 (2018)
3. D. Giugliano, M.I. Maiorino, G. Bellastella, K. Esposito, Glycemic control in type 2 diabetes: from medication nonadherence to residual vascular risk. Endocrine **61**, 23–27 (2018)
4. Food and Drug Administration, *Guidance for Industry: Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes* (Food and Drug Administration, Silver Spring, Maryland, 2008). Available at: www.fda.gov/downloads/Drugs/Guidances/ucm071627.pdf
5. C.K. Kramer, C. Ye, S. Campbell, R. Retnakaran, Comparison of new glucose-lowering drugs on risk of heart failure in type 2 diabetes. A network meta-analysis. JACC Heart Fail. **6**, 823–830 (2018)
6. T.A. Zelniker, S.D. Wiviott, I. Raz, K. Im, E.L. Goodrich, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, R.H.M. Furtado, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, M.S. Sabatine,, SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet **393**(10166), 31–39 (2018)
7. M.I. Maiorino, P. Chiodini, G. Bellastella, L. Scappaticcio, M. Longo, K. Esposito, D. Giugliano, Free and fixed-ratio combinations of basal insulin and GLP-1 receptor agonists versus basal insulin intensification in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Diabetes Obes. Metab. **20**, 2309–2313 (2018)
8. M.I. Maiorino, P. Chiodini, G. Bellastella, A. Capuano, K. Esposito, D. Giugliano, Insulin and glucagon-like peptide 1 receptor agonist combination therapy in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Diabetes Care **40**, 614–624 (2017)
9. K. Esposito, P. Chiodini, A. Colao, A. Lenzi, D. Giugliano, Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. Diabetes Care **35**, 2402–2411 (2012)
10. A. Liberati, D.G. Altman, J. Tetzlaff, C. Mulrow, P.C. Gøtzsche, J.P. Ioannidis, M. Clarke, P.J. Devereaux, J. Kleijnen, D. Moher, The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann. Intern. Med. **151**, W65–W94 (2009)
11. J.P. Higgins, D.G. Altman, P.C. Gøtzsche, P. Jüni, D. Moher, A. D. Oxman, J. Savovic, K.F. Schulz, L. Weeks, J.A. Sterne; Cochrane Bias Methods Group; Cochrane Statistical Methods Group, The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Br. Med. J. **343**, d5928 (2011)
12. A.R. Jadad, R.A. Moore, D. Carroll, C. Jenkinson, D.J. Reynolds, D.J. Gavaghan, H.J. McQuay, Assessing the quality of reports of

randomized clinical trials: is blinding necessary? Control Clin. Trials **17**, 1–12 (1996)
13. M. Egger, G. Davey Smith, M. Schneider, C. Minder, Bias in meta-analysis detected by a simple, graphical test. Br. Med. J. **315**, 629–634 (1997)
14. J.P. Higgins, S.G. Thompson, Controlling the risk of spurious findings from metaregression. Stat. Med. **23**, 1663–1682 (2004)
15. B.M. Scirica, D.L. Bhatt, E. Braunwald, P.G. Steg, J. Davidson, B. Hirshberg, P. Ohman, R. Frederich, S.D. Wiviott, E.B. Hoffman, M.A. Cavender, J.A. Udell, N.R. Desai, O. Mosenzon, D.K. McGuire, K.K. Ray, L.A. Leiter, I. Raz; SAVOR-TIMI 53 Steering Committee and Investigators, Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N. Engl. J. Med. **369**, 1317–1326 (2013)
16. W.B. White, C.P. Cannon, S.R. Heller, S.E. Nissen, R.M. Bergenstal, G.L. Bakris, A.T. Perez, P.R. Fleck, C.R. Mehta, S. Kupfer, C. Wilson, W.C. Cushman, F. Zannad; EXAMINE Investigators, Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N. Engl. J. Med. **369**, 1327–1335 (2013)
17. J.B. Green, M.A. Bethel, P.W. Armstrong, J.B. Buse, S.S. Engel, J. Garg, R. Josse, K.D. Kaufman, J. Koglin, S. Korn, J.M. Lachin, D.K. McGuire, M.J. Pencina, E. Standl, P.P. Stein, S. Suryawanshi, F. Van de Werf, E.D. Peterson, R.R. Holman; TECOS Study Group, Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N. Engl. J. Med. **373**, 232–242 (2015)
18. J. Rosenstock, V. Perkovic, O.E. Johansen, M.E. Cooper, S.E. Kahn, N. Marx, J.H. Alexander, M. Pencina, R.D. Toto, C. Wanner, B. Zinman, H.J. Woerle, D. Baanstra, E. Pfarr, S. Schnaidt, T. Meinicke, J.T. George, M. von Eynatten, D.K. McGuire; CARMELINA Investigators, Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk. The CARMELINA randomized clinical trial. J. Am. Med. Assoc. **321**, 69–79 (2019)
19. M.A. Pfeffer, B. Claggett, R. Diaz, K. Dickstein, H.C. Gerstein, L. V. Køber, F.C. Lawson, L. Ping, X. Wei, E.F. Lewis, A.P. Maggioni, J.J. McMurray, J.L. Probstfield, M.C. Riddle, S.D. Solomon, J.C. Tardif; ELIXA Investigators, Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N. Engl. J. Med. **373**, 2247–2257 (2015)
20. S.P. Marso, G.H. Daniels, K. Brown-Frandsen, P. Kristensen, J.F. Mann, M.A. Nauck, S.E. Nissen, S. Pocock, N.R. Poulter, L.S. Ravn, W.M. Steinberg, M. Stockner, B. Zinman, R.M. Bergenstal, J.B. Buse; LEADER Steering Committee; LEADER Trial Investigators, Liraglutide and cardiovascular outcomes in type 2 diabetes. N. Engl. J. Med. **375**, 311–322 (2016)
21. S.P. Marso, S.C. Bain, A. Consoli, F.G. Eliaschewitz, E. Jódar, L. A. Leiter, I. Lingvay, J. Rosenstock, J. Seufert, M.L. Warren, V. Woo, O. Hansen, A.G. Holst, J. Pettersson, T. Vilsbøll; SUSTAIN-6 Investigators, Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N. Engl. J. Med. **375**, 1834–1844 (2016)
22. R.R. Holman, M.A. Bethel, R.J. Mentz, V.P. Thompson, Y. Lokhnygina, J.B. Buse, J.C. Chan, J. Choi, S.M. Gustavson, N. Iqbal, A.P. Maggioni, S.P. Marso, P. Öhman, N.J. Pagidipati, N. Poulter, A. Ramachandran, B. Zinman, A.F. Hernandez; EXSCEL Study Group, Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N. Engl. J. Med. **377**, 1228–1239 (2017)
23. A.F. Hernandez, J.B. Green, S. Janmohamed, R.B. D'Agostino Sr, C.B. Granger, N.P. Jones, L.A. Leiter, A.E. Rosenberg, K.N. Sigmon, M.C. Somerville, K.M. Thorpe, J.J.V. McMurray, S. Del Prato; Harmony Outcomes committees and investigators, Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet **392**, 1519–1529 (2018)
24. B. Zinman, C. Wanner, J.M. Lachin, D. Fitchett, E. Bluhmki, S. Hantel, M. Mattheus, T. Devins, O.E. Johansen, H.J. Woerle, U.C. Broedl, S.E. Inzucchi; EMPA-REG OUTCOME Investigators, Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N. Engl. J. Med. **373**, 2117–2128 (2015)
25. B. Neal, V. Perkovic, K.W. Mahaffey, D. de Zeeuw, G. Fulcher, N. Erondu, W. Shaw, G. Law, M. Desai, D.R. Matthews; CANVAS Program Collaborative Group, Canagliflozin and cardiovascular and renal events in type 2 diabetes. N. Engl. J. Med. **377**, 644–657 (2017)
26. S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, A.-M. Langkilde, M.S. Sabatine; DECLARE–TIMI 58 Investigators, Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N. Engl. J. Med. **380**, 347–357 (2019)
27. S. Verma, J.J.V. McMurray, SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia **61**, 2108–2117 (2018)
28. D. Fitchett, B. Zinman, C. Wanner, J.M. Lachin, S. Hantel, A. Salsali, O.E. Johansen, H.J. Woerle, U.C. Broedl, S.E. Inzucchi; EMPA-REG OUTCOME® Trial Investigators, Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. Eur. Heart J. **37**, 1526–1534 (2016)
29. K. Rådholm, G. Figtree, V. Perkovic, S.D. Solomon, K.W. Mahaffey, D. de Zeeuw, G. Fulcher, T.D. Barrett, W. Shaw, M. Desai, D.R. Matthews, B. Neal, Canagliflozin and heart failure in type 2 diabetes mellitus. Results from the CANVAS Program. Circulation **138**, 458–468 (2018)
30. M.J. Davies, D.A. D'Alessio, J. Fradkin, W.N. Kernan, C. Mathieu, G. Mingrone, P. Rossing, A. Tsapas, D.J. Wexler, J.B. Buse, Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia **61**, 2461–2498 (2018)
31. M. Kosiborod, M.A. Cavender, A.Z. Fu, A.Z. Fu, J.P. Wilding, K. Khunti, R.W. Holl, A. Norhammar, K.I. Birkeland, M.E. Jørgensen, M. Thuresson, N. Arya, J. Bodegård, N. Hammar, P. Fenici; CVD-REAL Investigators and Study Group, Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL study (comparative effectiveness of cardiovascular outcomes in new users of sodium-glucose cotransporter-2 inhibitors). Circulation **136**, 249–259 (2017)
32. P.B. Ryan, J.B. Buse, M.J. Schuemie, F. DeFalco, Z. Yuan, P.E. Stang, J.A. Berlin, N. Rosenthal, Comparative effectiveness of canagliflozin, SGLT2 inhibitors and non-SGLT2 inhibitors on the risk of hospitalization for heart failure and amputation in patients with type 2 diabetes mellitus: a real-world meta-analysis of 4 observational databases (OBSERVE-4D). Diabetes Obes. Metab. **20**, 2585–2597 (2018)
33. FDA Background Document, *Endocrinologic and Metabolic Drugs*. Advisory Committee Meeting October 24–25, 2018. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM623913.pdf. Accessed 25 Nov 2018