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ORIGINAL ARTICLE

Meta-analysed numbers needed to treat of novel antidiabetic drugs for cardiovascular outcomes

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Abstract

Aims Absolute treatment effects—i.e. numbers needed to treat (NNTs)—of novel antidiabetic drugs for cardiovascular outcomes have not been comprehensively evaluated. We aimed to perform a meta-analysis of digitalized individual patient outcomes to display and compare absolute treatment effects.

Methods and results Individual patient time-to-event information from Kaplan–Meier plots of *cardiovascular mortality (CM)* and/or *hospitalization for heart failure (HHF)* endpoints from cardiovascular outcome trials (CVOTs) evaluating dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and sodium glucose transporter 2 (SGLT2) inhibitors vs. placebo were digitalized using WebPlotDigitizer 4.2 and the R code of Guyot *et al.*; Weibull regression models were generated, validated, and used to estimate NNT for individual trials; random-effects meta-analysis generated Meta-NNT with 95% confidence intervals. Sixteen CVOTs reported time-to-event information (14 in primary diabetes and 2 in primary heart failure populations). Thirteen studies including 96 860 patients were meta-analysed for *CM*: At the median follow-up of 30 months, Meta-NNTs were 178 (64 to ∞ to −223) for DPP-4 inhibitors, 261 (158 to 745) for GLP-1 receptor agonists, and 118 (68 to 435) for SGLT2 inhibitors. Ten studies including 96 128 patients were meta-analysed for *HHF*: At the median follow-up of 29 months, estimated Meta-NNTs were −644 (229 to ∞ to −134) for DPP-4 inhibitors, 441 (184 to ∞ to −1100) for GLP-1 receptor agonists, and 126 (91 to 208) for SGLT2 inhibitors. SGLT2 inhibitors were especially effective for *HHF* in primary heart failure populations [Meta-NNT 25 (19 to 39)] vs. primary diabetes populations [Meta-NNT 233 (167 to 385)] at 16 months of follow-up.

Conclusions We found only modest treatment benefits of GLP-1 receptor agonists and SGLT2 inhibitors for *CM* and *HHF* in primary type 2 diabetes mellitus populations. In primary heart failure populations, SGLT2 inhibitor benefits were substantial and comparable in efficacy to established heart failure medication.

Keywords SGLT2 inhibitor; GLP-1 receptor agonist; Number needed to treat; Absolute treatment effect; Meta-analysis; Heart failure

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Introduction

Cardiovascular diseases (CVDs) and type 2 diabetes mellitus (T2DM) are among the leading causes of morbidity and mortality in Europe and worldwide.[1–3] Heart failure is a complex secondary syndrome to both and an emerging cardiovascular epidemic, whose incidence and healthcare-related cost continue to rise.[4,5]

Novel antidiabetic drugs, mainly dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor

agonists, and sodium glucose transporter 2 (SGLT2) inhibitors,[6] have shown benefits for both diabetes-related outcomes and cardiovascular endpoints in major cardiovascular outcome trials (CVOTs).[7] Current guidelines for the treatment of T2DM have issued respective recommendations,[8,9] especially for SGLT2 inhibitors and GLP-1 receptor agonists. Recently, updated European guidelines for the treatment of heart failure with reduced ejection fraction (HFrEF) now also recommend SGLT2 inhibitors, dapagliflozin and empagliflozin, as an integral part of pharmacotherapy[10] because of their benefits for cardiovascular and heart failure endpoints[11,12] —regardless of T2DM. Recent findings even show benefits of SGLT2 inhibitors in heart failure with preserved ejection fraction[13] —different from any other tested drug class before.

As the U.S. Food and Drug Administration requires trialists to show non-inferiority on the hazard ratio (HR) scale, CVOTs almost exclusively report relative effect estimates to describe treatment differences and meta-analyses of these studies thus resorted to analysis of relative effects.[14,15] Absolute effect sizes—e.g. numbers needed to treat (NNTs)—are difficult to find in trial reports, even though guidelines recommend their use.[16–18] This is unfortunate, as absolute effects rather than relative measures are key to judging drug efficacy, perform cost/benefit calculations from both medical and health-economics perspectives, and actually explain benefits to patients. Meta-analyses of CVOTs should offer the highest class of evidence on the subject but are difficult to perform for absolute effects due to lack of data in trial reports. However, there are validated methods[19–23] to digitalize time-to-event information from published reports.

We here report a meta-analysis of absolute treatment effects expressed as NNTs in the large CVOTs of DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors, focusing on the outcomes of cardiovascular mortality and hospitalization for heart failure.

Methods

Study selection and data extraction

All major randomized controlled CVOTs indicated in *fig. 1* of Cefalu *et al*.[6] with comparisons of SGLT2 inhibitors, GLP-1 receptor agonists, or DPP-4 inhibitors to placebo were eligible for inclusion. Full texts and online supplements of the CVOTs published until September 2020 were downloaded and searched for original Kaplan–Meier plots reporting time-to-event information for outcomes of *cardiovascular mortality* and *hospitalization for heart failure*. Outcomes of individual patients were digitalized from Kaplan–Meier plots using WebPlotDigitizer, Version 4.2,[19] and the R code of Guyot *et al*.[20] Both methods have been shown to be reliable and valid.[21–23] Additionally, original HRs with 95% confidence intervals (95% CIs) for both outcomes, as well as characteristics of the study and patients, were extracted from the original study reports. All data extractions were double checked; discrepancies were discussed and resolved in the group. CVOTs without placebo group or without reporting of Kaplan–Meier plots for either one of both relevant outcomes were excluded.

Weibull fits and absolute treatment effect estimates

Parametric Weibull regression models were fitted for all studies and both outcomes separately, in order to estimate survival functions that are needed to calculate NNTs. Weibull models are parametric proportional hazards models[24] and thus yield Weibull HRs for treatment effects, which can be compared with the original HRs. From the respective Weibull models, we estimated monthly probability differences (treatment − control) for being free of the event of interest from Month 1 to the respective maximal observation time of each individual trial. These probability differences were then inverted to arrive at estimates for the monthly NNT, which are thus necessarily time dependent.[25]

Numbers needed to treat notation

NNTs describe the number of patients that have to be treated for a certain time interval to prevent one additional outcome event in the treatment group: Positive NNT values indicate that the drug is beneficial compared with placebo (or *number needed to treat to benefit*); negative NNT values indicate placebo advantage (or *number needed to treat to harm*). Lower NNT values indicate more effective treatment, with the lowest possible value of NNT = 1 (or −1, respectively). A null effect of the treatment, corresponding to an HR of 1, is denoted by a value of infinity (∞) for the NNT. A 95% CI that does not include infinity (∞) [or −infinity (−∞), respectively] corresponds to a statistically significant absolute treatment effect (with a two-sided α probability of 5%).

Assessment of model validity

To assess the validity of the digitalized data, we compared HRs from the original papers to those from the Weibull models by calculating intra-class correlation coefficients. In addition, to assess the fit of the Weibull models graphically, we plotted Kaplan–Meier estimates from the digitalized data together with predicted survival curves from these models.

Meta-analysis

To summarize NNTs overall and in the three drug classes, we used random-effects inverse-variance meta-analysis. Meta-analyses were performed separately for monthly time points. A sensitivity analysis of SGLT2 inhibitors in studies with primary T2DM vs. primary HFrEF populations for the endpoint of *hospitalization for heart failure* was performed. All computations were performed on the probability difference scale and only for displaying results in figures and graphs transformed to the NNT scale. We used SAS (SAS Institute Inc., Cary, NC, USA), Version 9.4, for data management and analysis.

Results

Study selection

A total of 16 major CVOTs reported original time-to-event information for at least one of the two outcomes and were included in the analysis: four trials on DPP-4 inhibitors (CARMELINA, EXAMINE, SAVOR-TIMI 53, and TECOS[26–29]), six trials on GLP-1 receptor agonists (EXSCEL, HARMONY, LEADER, PIONEER 6, REWIND, and SUSTAIN 6[30–35]), and six trials on SGLT2 inhibitors (CANVAS, CREDENCE, DAPA-HF, EMPA-REG Outcome, EMPEROR-REDUCED, and VERTIS-CV[11,12,36–39]). The CAROLINA trial[40] was excluded for not having a placebo control; the results of FREEDOM-CVO and EMPEROR-PRESERVED[13] were not yet published in full text at the time of analysis. All endpoint definitions of individual trials are listed in Supporting Information, *Table* S1.

Study characteristics

An overview of all trials and a description of the study populations are given in *Table 1*: A total of 131 753 patients with time-to-event information were analysed; follow-up times in the studies ranged between 15.5 and 65.5 months for *cardiovascular mortality* and between 14.3 and 46.4 months for *hospitalization for heart failure*. The overall median follow-up time was 30.6 months for *cardiovascular mortality* and 29.2 months for *hospitalization for heart failure*. All trials featured high to very high cardiovascular risk patient populations.[41] They were conducted in patients with T2DM, with the exception of EMPEROR-REDUCED[12] and DAPA-HF,[11] which primarily included patients with heart failure, about half of them with diabetes mellitus.

Relative and absolute treatment effect estimates of individual trials

Thirteen studies with 4997 digitalized events from 96 860 observed patients gave information on *cardiovascular mortality* (*Table 2*). Ten studies with 4065 digitalized events from 96 128 observed patients reported data on *hospitalization for heart failure* (*Table 3*). For both outcomes, original study HRs, extracted HRs, and Weibull HRs with 95% CI are reported as relative effect measures. NNTs at 12, 24, 36, and 48 months are reported as absolute treatment effect estimates for individual trials (*Tables 2* and *3*). Additionally, monthly NNT point estimates with 95% CI for all three study drugs and both outcomes are graphically displayed in *Figure 1*.

Accuracy of data digitalization and Weibull model fits was assessed using scatterplots (Supporting Information, Figure S1) to compare the originally reported HRs to the Weibull HRs from digitalized data: Correspondence was excellent, with an intra-class correlation of 99.4% (95% CI: 98.7–100%) for *cardiovascular mortality* and 99.8% (99.5–100%) for *hospitalization for heart failure*. Supporting Information, *Figure* S2 depicts Kaplan–Meier estimates of both treatment groups based on the Weibull survival curves. Again, there is no relevant divergence that might compromise computation of NNTs.

Meta-analysis of absolute treatment effects

Results of the random-effects inverse-variance meta-analysis from monthly pooled survival data from the Weibull models for individual study drugs and for both outcomes are depicted in *Figure 2*: At the overall median follow-up time of 30 months for *cardiovascular mortality*, estimated Meta-NNTs were 178 (95% CI: 64 to ∞ to −223) for DPP-4 inhibitors, 261 (95% CI: 158 to 745) for GLP-1 receptor agonists, and 118 (95% CI: 68 to 435) for SGLT2 inhibitors. At the overall median follow-up time of 29 months for *hospitalization for heart failure*, estimated Meta-NNTs were −644 (95% CI: 229 to ∞ to −134) for DPP-4 inhibitors, 441 (95% CI: 184 to ∞ to −1100) for GLP-1 receptor agonists, and 126 (95% CI: 91 to 208) for SGLT2 inhibitors.

Accuracy of estimates (smallest 95% CI) was highest for GLP-1 receptor agonists regarding *cardiovascular mortality*, with Meta-NNTs of 351 (95% CI: 214 to 981; CI length 767), 205 (95% CI: 125 to 576; CI length 452), and 141 (95% CI: 86 to 389; CI length 302) after 24/36/48 months of follow-up. Regarding *hospitalization for heart failure*, most accurate estimates were found for SGLT2 inhibitors, with Meta-NNTs of 135 (95% CI: 101 to 205; CI length 105), 102 (95% CI: 73 to 167; CI length 94), and 76 (95% CI: 55 to 125; CI length 70) after 24/36/48 months of follow-up.

Table 1 Characteristics of included studies

Study	Journal and year	Study drug	Number of patients (*n*)	Median duration of follow-up (years)	Mean age (years)	Male sex (%)	Mean BMI (kg/m^2)
DPP-4 inhibitors							
CARMELINA[27]	JAMA 2018	Linagliptin	6991	2.2	65.9	62.9	31.4
EXAMINE[29]	NEJM 2013	Alogliptin	5380	1.5	61.0	67.8	28.7[a]
SAVOR-TIMI 53[28]	NEJM 2013	Saxagliptin	16 492	2.1	65.1	66.9	31.1
TECOS[26]	NEJM 2015	Sitagliptin	14 671	3.0	65.5	70.7	30.2
GLP-1 receptor agonists							
EXSCEL[32]	NEJM 2017	Exenatide	14 752	3.2	62.0	62.0	31.8
HARMONY[31]	Lancet 2018	Albiglutide	9463	1.6	64.2	69.4	32.3
LEADER[35]	NEJM 2016	Liraglutide	9340	3.8	64.3	64.2	32.5
PIONEER 6[33]	NEJM 2019	Semaglutide	3183	1.3	66.0	68.4	32.3
REWIND[30]	Lancet 2019	Dulaglutide	9901	5.4	66.2	53.7	32.3
SUSTAIN 6[34]	NEJM 2016	Semaglutide	3297	2.1	64.6	60.7	32.6
SGLT2 inhibitors							
CANVAS[37]	NEJM 2017	Canagliflozin	10 142	2.4	63.3	64.2	32.0
CREDENCE[38]	NEJM 2019	Canagliflozin	4401	2.6	63.0	66.1	31.3
DAPA-HF[11]	NEJM 2019	Dapagliflozin	4744	1.5	66.3	77.6	28.2
EMPA-REG[39]	NEJM 2015	Empagliflozin	7020	3.1	63.1	71.5	30.7
EMPEROR-REDUCED[12]	NEJM 2020	Empagliflozin	3730	1.3	66.8	76.0	27.9
VERTIS-CV[36]	NEJM 2020	Ertugliflozin	8246	3.0	64.4	70.0	31.9

BMI, body mass index; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, haemoglobin A1c; n.a., not available; SGLT2, sodium glucose transporter 2.
This table shows characteristics of randomized controlled trials included in the meta-analysis.
[a]Median instead of mean.

Table 1 (continued)

Study	T2DM (%)	Mean HbA1c (%)	Mean diabetes duration (years)	Atherosclerotic cardiovascular disease (%)	Heart failure (%)	Hypertension (%)	Current smoker (%)	Mean eGFR (mL/min/1.73 m^2)
DPP-4 inhibitors								
CARMELINA[27]	100	7.9	14.8	58.5	26.8	91.0	10.2	54.6
EXAMINE[29]	100	8.0	7.2[a]	100	27.9	83.1	13.6	71.1[a]
SAVOR-TIMI 53[28]	100	8.0	10.7	78.6	12.8	81.8	n.a.	72.6
TECOS[26]	100	7.2	11.6	74.0	18.0	n.a.	11.4	74.9
GLP-1 receptor agonists								
EXSCEL[32]	100	8.0	12.0	73.1	16.2	n.a.	11.7	76.3
HARMONY[31]	100	8.7	14.2	100	20.0	86.5	16.0	79.0
LEADER[35]	100	8.7	12.9	81.4	17.9	92.4	n.a.	n.a.

Table 1 (continued)

Study	T2DM (%)	Mean HbA1c (%)	Mean diabetes duration (years)	Atherosclerotic cardiovascular disease (%)	Heart failure (%)	Hypertension (%)	Current smoker (%)	Mean eGFR (mL/min/1.73 m^2)
PIONEER 6[33]	100	8.2	14.9	84.6	n.a.	95.3	10.9	74.2
REWIND[30]	100	7.4	10.6	31.5	8.6	93.2	14.2	75.0
SUSTAIN 6[34]	100	8.7	13.9	60.5	23.6	92.8	n.a.	n.a.
SGLT2 inhibitors								
CANVAS[37]	100	8.2	13.5	72.2	14.4	90.0	17.8	76.5
CREDENCE[38]	100	8.3	15.8	50.4	14.8	96.8	14.5	56.2
DAPA-HF[11]	41.8	6.5	n.a.	56.4	100	n.a.	n.a.	65.8
EMPA-REG[39]	100	8.1	n.a.	75.6	10.1	95.0	n.a.	74.1
EMPEROR-REDUCED[12]	49.8	n.a.	n.a.	51.7	100	72.3	n.a.	62.0
VERTIS-CV[36]	100	8.2	13.0	75.9	23.7	n.a.	n.a.	76.0

BMI, body mass index; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, haemoglobin A1c; n.a., not available; SGLT2, sodium glucose transporter 2.
This table shows characteristics of randomized controlled trials included in the meta-analysis.
[a]Median instead of mean.

Sensitivity analysis of sodium glucose transporter 2 inhibitors for *hospitalization for heart failure*

DAPA-HF[11] and EMPEROR-REDUCED[12] were conducted in primary HFrEF patient populations (*Table 1*). Their comparison to primary T2DM populations (*Figure 3*) showed remarkably higher efficacy of SGLT2 inhibitors for *hospitalization for heart failure* in HFrEF patients [Meta-NNT 25 (95% CI: 19 to 39) vs. Meta-NNT 233 (95% CI 167 to 385)] at 16 months of follow-up.

Discussion

In this meta-analysis of absolute treatment effects of novel antidiabetic drugs in all available trials and in HFrEF subpopulations, we found that (i) GLP-1 receptor agonists and SGLT2 inhibitors were both effective to reduce *cardiovascular mortality*; (ii) the most effective drug class to reduce *hospitalization for heart failure* was SGLT2 inhibitors, with the highest efficacy in patients with HFrEF compared with primary T2DM populations; and (iii) DPP-4 inhibitors were not effective to reduce either endpoint.

GLP-1 receptor agonists and SGLT2 inhibitors have received Class I recommendations in T2DM[8,9] and heart failure[10] guidelines for their potential to reduce CVD events and mortality; however, relevant CVOTs predominantly reported relative measures of effect (HRs, odds ratios, and risk ratios). Those normalize treatment effects to the baseline risk of the placebo population. Although this results in relatively stable results across the whole risk spectrum, results can also be misleading: A statistically highly significant relative risk reduction of 50% may turn out to be clinically irrelevant, if the baseline risk is very low for an event in the placebo group. The higher the baseline risk of a population, the more impact on absolute risk reduction can be expected from an intervention such as a study drug. Guidelines thus recommend reporting of both relative and absolute effect measures.[42] The latter are key for assessment of treatment efficacy, comparison to other drug classes, cost/benefit calculations, and explanation of benefits to patients.

All trials included in this analysis were rigorously designed and well-conducted international studies with low risk of bias.[14,15] All trials included high to very high cardiovascular risk patient populations with long-term T2DM and a high prevalence of atherosclerotic CVD and chronic kidney disease (*Table 1*); DAPA-HF and EMPEROR-REDUCED were conducted in populations with HFrEF, of whom 40–50% had diabetes mellitus. Treatment effects in this high baseline risk population were large—and meta-analysis of almost 100 000 patients for each endpoint thus provides robust absolute treatment effect estimates.

In contrast, however, no single trial of any of the three drug classes showed a particularly high level of efficacy on

Table 2 Effect estimates for the outcome of *cardiovascular mortality*

Study	Number of digitalized events (*n*)	Number of patients (*n*)	Event proportion (%)	Median duration of follow-up (years)	Original HR [95% CI]	Extracted HR [95% CI]	Weibull HR [95% CI]
DPP-4 inhibitors							
CARMELINA[27]	518	6991	7.4	2.2	0.96 [0.81 to 1.14]	0.96 [0.81 to 1.14]	0.96 [0.80 to 1.13]
EXAMINE[29]	237	5380	4.4	1.5	0.85 [0.66 to 1.10]	0.86 [0.66 to 1.11]	0.86 [0.64 to 1.08]
GLP-1 receptor agonists							
EXSCEL[32]	703	14 752	4.8	3.2	0.88 [0.76 to 1.02]	0.88 [0.76 to 1.02]	0.88 [0.75 to 1.01]
HARMONY[31]	252	9463	2.7	1.6	0.93 [0.73 to 1.19]	0.90 [0.70 to 1.15]	0.92 [0.69 to 1.15]
LEADER[35]	493	9340	5.3	3.8	0.78 [0.66 to 0.93]	0.77 [0.65 to 0.93]	0.78 [0.64 to 0.92]
PIONEER 6[33]	43	3183	1.4	1.3	0.49 [0.27 to 0.92]	0.48 [0.25 to 0.90]	0.47 [0.17 to 0.76]
REWIND[30]	657	9901	6.6	5.4	0.91 [0.78 to 1.06]	0.91 [0.78 to 1.06]	0.91 [0.77 to 1.05]
SUSTAIN 6[34]	70	3297	2.1	2.1	0.98 [0.65 to 1.48]	0.94 [0.59 to 1.51]	0.94 [0.50 to 1.38]
SGLT2 inhibitors							
CANVAS[37]	471	10 142	4.6	2.4	0.87 [0.72 to 1.06]	0.88 [0.73 to 1.06]	0.89 [0.73 to 1.06]
CREDENCE[38]	249	4401	5.7	2.6	0.78 [0.61 to 1.00]	0.77 [0.60 to 0.99]	0.77 [0.58 to 0.96]
DAPA-HF[11]	498	4744	10.5	1.5	0.82 [0.69 to 0.98]	0.82 [0.69 to 0.98]	0.82 [0.68 to 0.97]
EMPA-REG[39]	301	7020	4.3	3.1	0.62 [0.49 to 0.77]	0.60 [0.48 to 0.75]	0.60 [0.46 to 0.74]
VERTIS-CV[36]	505	8246	6.1	3.0	0.92 [0.77 to 1.11]	0.90 [0.75 to 1.09]	0.91 [0.74 to 1.07]

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium glucose transporter 2.
This table shows effect estimates of individual studies for the outcome of *cardiovascular mortality*; depicted are raw event rates, originally reported hazard ratios (HRs), extracted HR from Kaplan–Meier plots, HR as calculated from the Weibull model, and numbers needed to treat (NNTs) for 12, 24, 36, and 48 months; 95% confidence intervals (CIs) are in brackets.

Table 2 (continued)

Study	NNT [95% CI] 12 months	NNT [95% CI] 24 months	NNT [95% CI] 36 months	NNT [95% CI] 48 months
DPP-4 inhibitors				
CARMELINA[27]	995 [180 to ∞ to −282]	444 [80 to ∞ to −126]	282 [51 to ∞ to −80]	—
EXAMINE[29]	211 [80 to ∞ to −325]	123 [46 to ∞ to −190]	—	—
GLP-1 receptor agonists				
EXSCEL[32]	760 [349 to ∞ to −4279]	327 [151 to ∞ to −1886]	202 [93 to ∞ to −1168]	144 [66 to ∞ to −834]
HARMONY[31]	754 [192 to ∞ to −391]	358 [91 to ∞ to −186]	—	—
LEADER[35]	396 [230 to 1437]	173 [101 to 602]	107 [63 to 370]	77 [45 to 264]
PIONEER 6[33]	138 [76 to 774]	—	—	—
REWIND[30]	1662 [627 to ∞ to −2548]	634 [239 to ∞ to −980]	363 [137 to ∞ to −563]	246 [93 to ∞ to −382]
SUSTAIN 6[34]	1424 [159 to ∞ to −205]	—	—	—
SGLT2 inhibitors				
CANVAS[37]	806 [309 to −1318]	379 [145 to ∞ to −620]	246 [94 to ∞ to −401]	181 [69 to ∞ to −295]
CREDENCE[38]	262 [133 to 8805]	103 [53 to 2449]	61 [31 to 1395]	—
DAPA-HF[11]	82 [43 to 826]	39 [21 to 389]	—	—
EMPA-REG[39]	175 [116 to 353]	74 [50 to 143]	45 [30 to 86]	32 [22 to 61]
VERTIS-CV[36]	787 [272 to ∞ to −878]	338 [117 to ∞ to −379]	208 [72 to ∞ to −233]	149 [51 to ∞ to −167]

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium glucose transporter 2.
This table shows effect estimates of individual studies for the outcome of *cardiovascular mortality*; depicted are raw event rates, originally reported hazard ratios (HRs), extracted HR from Kaplan–Meier plots, HR as calculated from the Weibull model, and numbers needed to treat (NNTs) for 12, 24, 36, and 48 months; 95% confidence intervals (CIs) are in brackets.

cardiovascular mortality (*Table 2*): DPP-4 inhibitors did not show any effects; GLP-1 receptor agonists showed the lowest 4 year NNT of 77 in the LEADER trial; and SGLT2 inhibitors reached the best efficacy in DAPA-HF (24 month NNT of 39) and EMPA-REG (48 month NNT of 32). In comparison, the Meta-NNT across all trials at the median follow-up time was 261 for GLP-1 receptor agonists and 118 for SGLT2 inhibitors. These effects of all three drug classes on *cardiovascular mortality* do not seem very impressive when compared on an absolute scale: Metformin as the long-term standard of care in oral antidiabetic therapy has been estimated with a 10 year NNT of ~10–20 for major endpoints.[43] Typical heart failure medication (beta-blockers, angiotensin-converting enzyme inhibitors, mineralocorticoid receptor agonists, sacubitril/valsartan, etc.) showed estimated 5 year NNTs for all-cause mortality of ~8–24.[44,45] These data put GLP-1 receptor agonists and SGLT2 inhibitors in similar efficacy categories as PCSK9 inhibitors or statins for *cardiovascular mortality*.[46]

Table 3 Effect estimates for the outcome of *hospitalization for heart failure*

Study	Number of digitalized events (*n*)	Number of patients (*n*)	Event proportion (%)	Median duration of follow-up (years)	Original HR [95% CI]	Extracted HR [95% CI]
DPP-4 inhibitors						
CARMELINA[27]	431	6991	6.2	2.2	0.90 [0.74 to 1.08]	0.90 [0.74 to 1.08]
SAVOR-TIMI 53[28]	517	16 492	3.1	2.1	1.27 [1.07 to 1.51]	1.26 [1.06 to 1.50]
TECOS[26]	439	14 671	3.0	3.0	1.00 [0.83 to 1.20]	0.98 [0.81 to 1.18]
GLP-1 receptor agonists						
EXSCEL[32]	434	14 752	2.9	3.2	0.94 [0.78 to 1.13]	0.94 [0.78 to 1.14]
LEADER[35]	463	9340	5.0	3.8	0.87 [0.73 to 1.05]	0.87 [0.72 to 1.04]
SGLT2 inhibitors						
CANVAS[37]	243	10 142	2.4	2.4	0.67 [0.52 to 0.87]	0.68 [0.53 to 0.88]
DAPA-HF[11]	545	4744	11.5	1.5	0.70 [0.59 to 0.83]	0.71 [0.60 to 0.84]
EMPA-REG[39]	212	7020	3.0	3.1	0.65 [0.50 to 0.85]	0.63 [0.48 to 0.83]
EMPEROR-REDUCED[12]	552	3730	14.8	1.3	0.69 [0.59 to 0.81]	0.69 [0.59 to 0.82]
VERTIS-CV[36]	229	8246	2.8	3.0	0.70 [0.54 to 0.90]	0.68 [0.52 to 0.88]

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium glucose transporter 2.
This table shows effect estimates of individual studies for the outcome of *hospitalization for heart failure*; depicted are raw event rates, original study hazard ratios (HRs), extracted HR from Kaplan–Meier plots, HR as calculated from the Weibull models, and numbers needed to treat (NNTs) for 12, 24, 36, and 48 months; 95% confidence intervals (CIs) are in brackets.

Table 3 (continued)

Study	Weibull HR [95% CI]	NNT [95% CI] 12 months	NNT [95% CI] 24 months	NNT [95% CI] 36 months	NNT [95% CI] 48 months
DPP-4 inhibitors					
CARMELINA[27]	0.90 [0.73 to 1.07]	317 [116 to ∞ to −440]	168 [62 to ∞ to −233]	117 [43 to ∞ to −163]	—
SAVOR-TIMI 53[28]	1.25 [1.03 to 1.47]	−267 [−1178 to −150]	−144 [−629 to −81]	—	—
TECOS[26]	0.98 [0.80 to 1.16]	4463 [463 to ∞ to −584]	2257 [234 to ∞ to −296]	1522 [158 to ∞ to −199]	1154 [120 to ∞ to −151]
GLP-1 receptor agonists					
EXSCEL[32]	0.94 [0.76 to 1.12]	2190 [536 to ∞ to −1052]	983 [241 to ∞ to −473]	619 [152 to ∞ to −297]	447 [110 to ∞ to −215]
LEADER[35]	0.87 [0.71 to 1.03]	588 [257 to ∞ to −2006]	285 [125 to ∞ to −988]	188 [82 to ∞ to −654]	140 [61 to ∞ to −489]
SGLT2 inhibitors					
CANVAS[37]	0.67 [0.50 to 0.84]	374 [225 to 1101]	185 [112 to 530]	123 [74 to 351]	92 [56 to 264]
DAPA-HF[11]	0.71 [0.59 to 0.83]	38 [26 to 77]	21 [14 to 43]	—	—
EMPA-REG[39]	0.63 [0.46 to 0.81]	223 [135 to 648]	105 [64 to 291]	68 [42 to 186]	50 [31 to 137]
EMPEROR-REDUCED[12]	0.69 [0.58 to 0.81]	24 [16 to 44]	15 [10 to 27]	—	—
VERTIS-CV[36]	0.67 [0.50 to 0.85]	305 [178 to 1076]	150 [88 to 502]	99 [58 to 328]	74 [44 to 245]

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium glucose transporter 2.
This table shows effect estimates of individual studies for the outcome of *hospitalization for heart failure*; depicted are raw event rates, original study hazard ratios (HRs), extracted HR from Kaplan–Meier plots, HR as calculated from the Weibull models, and numbers needed to treat (NNTs) for 12, 24, 36, and 48 months; 95% confidence intervals (CIs) are in brackets.

Figure 1 Numbers needed to treat (NNTs) over study follow-up time for individual studies, for the outcome of (A) *cardiovascular mortality* and (B) *hospitalization for heart failure*. Blue: dipeptidyl peptidase-4 inhibitors, yellow: glucagon-like peptide-1 receptor agonists, red: sodium glucose transporter 2 inhibitors with their pointwise 95% confidence intervals. Estimates and confidence intervals are truncated from above at 100 000.

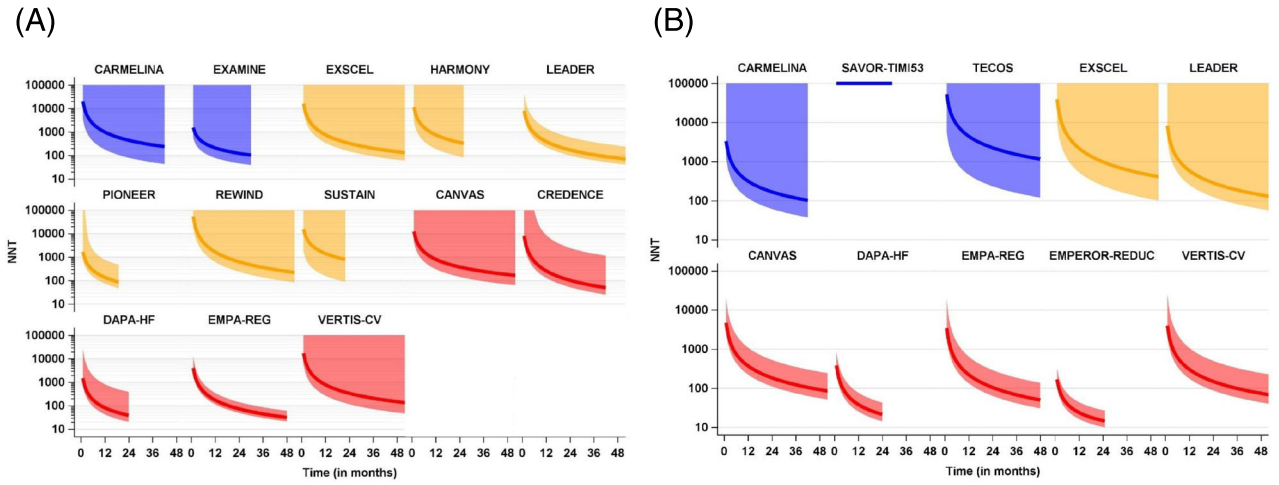
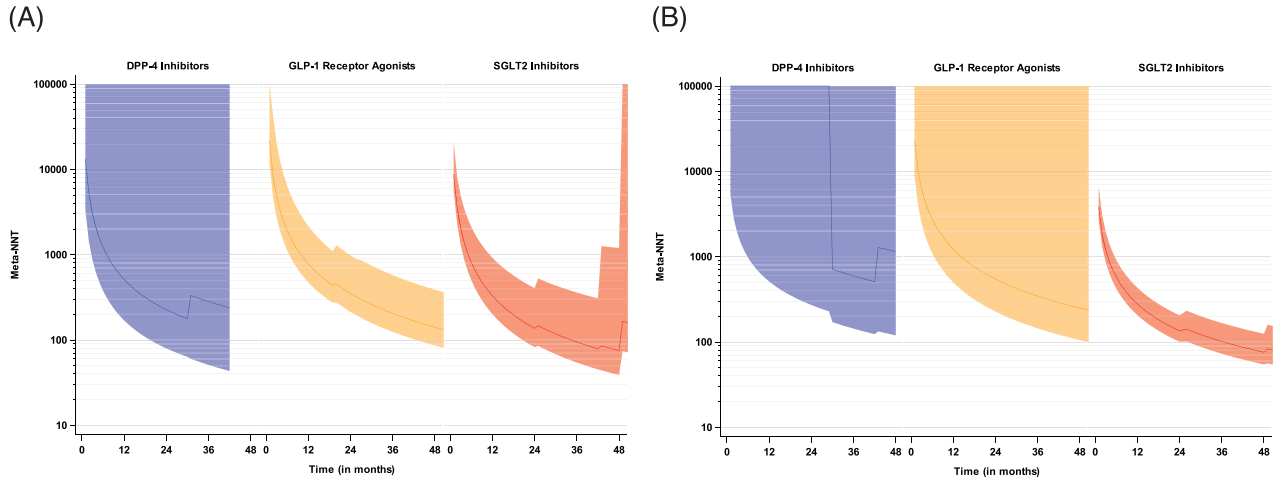
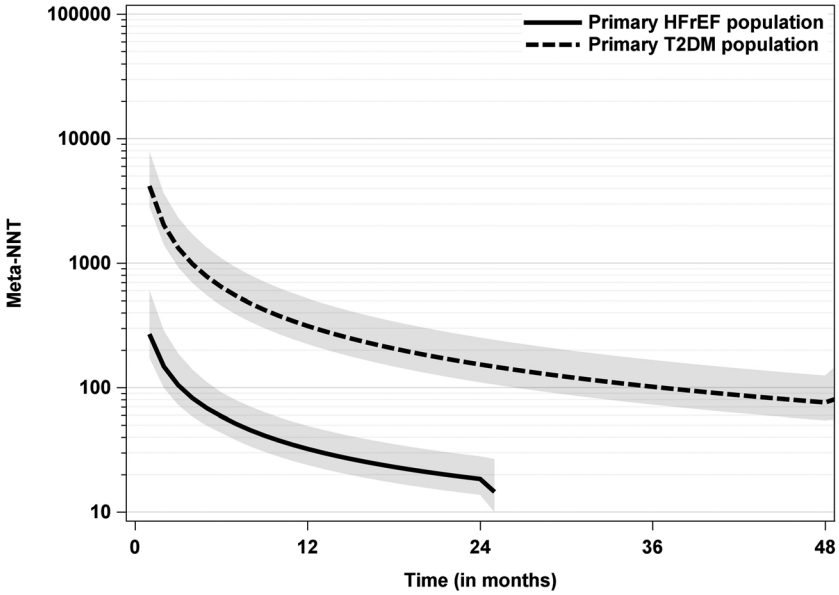


Figure 2 Random-effects inverse-variance meta-analysis of numbers needed to treat (Meta-NNT, with 95% confidence interval) over study follow-up time for the outcomes of (A) *cardiovascular mortality* and (B) *hospitalization for heart failure*. Data were pooled from all studies according to study drug. Estimates and confidence intervals are truncated from above at 100 000. DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium glucose transporter 2.



Regarding *hospitalization for heart failure*, GLP-1 receptor agonists and DPP-4 inhibitors showed no effects on this endpoint, either in single trials or in meta-analysis. SGLT2 inhibitors showed considerable effects (Meta-NNT at median follow-up of 126), which were especially large in the HFrEF trials DAPA-HF (24 month NNT of 21) and EMPEROR-REDUCED (24 month NNT of 15) and thus comparable with other established guideline-recommended heart failure medication.[44,45] This is a substantial difference between primary HFrEF populations and primary T2DM populations (*Figure 3*), even though population characteristics other than ejection fraction were similar (*Table 1*). SGLT2 inhibitors are thus very effective for the endpoint of *hospitalization for heart failure*, especially in HFrEF patient populations, with

Figure 3 Sensitivity analysis of numbers needed to treat (Meta-NNT, with 95% confidence interval) with sodium glucose transporter 2 inhibitors to reduce *hospitalization for heart failure*, stratified for studies with primary type 2 diabetes mellitus (T2DM) or primary heart failure with reduced ejection fraction (HFrEF) populations. Estimates and confidence intervals are truncated from above at 100 000.



smaller effects in non-HFrEF patients (*Figure* 3). This is confirmed by recent findings from EMPEROR-PRESERVED,[13] which found a 26 month NNT of ~31 for *hospitalization for heart failure* and of ~111 for *cardiovascular mortality*—again with 50% of the population also suffering from diabetes mellitus. Unfortunately, other trials in HFpEF are not yet available, which rendered further meta-analysis of HFpEF futile. Further research on the underlying mechanism for these surprisingly strong effects in heart failure is ongoing.[47] In addition, these results make SGLT2 inhibitors promising tools to reduce expenditures in heart failure care, where hospitalizations are the main driver of cost.[48]

Davies *et al*. previously performed an analysis of NNT for the class of GLP-1 receptor agonists,[49] however, not for the other two drug classes. Ludwig *et al*. reported NNTs for two drug classes[25] at median follow-up time points; however, they did not use original data but relied on formulas for summary data. Both groups used other software tools for data digitalization and different statistical models to arrive at NNT estimates as compared with our approach[25,49] —however with very similar results. Palmer *et al*. recently published a very large network meta-analysis[50] of GLP-1 receptor agonists and SGLT2 inhibitors including 764 trials with absolute treatment effect estimates, however did not use digitalization of time-to-event data, and thus offered no time-sensitive analysis. Hence, our work is the first to present absolute treatment effects in all three drug classes and offer time-sensitive meta-analysis of individual patient outcomes of *cardiovascular mortality* and *hospitalization for heart failure* in the large CVOTs.

Limitations

Trials were selected based on a common definition of CVOTs in diabetes mellitus[6]; however, there was no systematic literature review performed. Trial and population heterogeneity introduces unavoidable bias into this analysis, as in any other meta-analysis. This work relies on digitalized individual patient outcomes and fitted Weibull models rather than the original patient data, which renders analysis of endpoint associations with patient characteristics or other outcomes [e.g. haemoglobin A1c (HbA1c) and adverse events] impossible. However, this inherent main limitation is unavoidable, as no pooled primary data are available to perform such an analysis in a different way. To account for this and ensure validity of our methods, we performed sensitivity analyses on different levels and found that the full Weibull survival curves (from which the NNTs are directly derived) give excellent fits to the digitalized survival data; they additionally allow computation of HR and thus a comparison to the extracted data. The original studies used Cox models with proportional hazards assumptions, which—of course—might also be wrong.[51] And a parametric model additionally allows for directly estimating survival probabilities and NNTs.

As the full individual patient data were not available, it was impossible to adjust for the parallel competing risk of all-cause mortality. Although this would probably be less of a problem with the outcome of *cardiovascular mortality* (because most deaths in the CVOTs would be cardiovascular deaths), this might be an issue for *hospitalization for heart failure*: A patient who dies in the course of the trial is no lon-

ger at risk for this endpoint. We expect the risks for dying and *hospitalization for heart failure* to be positively correlated, and thus, we expect treatment effects rather being estimated as too small than overestimated.

Conclusions

In this meta-analysis of digitalized individual patient outcomes from CVOTs of novel antidiabetic drugs, we report absolute treatment benefits of GLP-1 receptor agonists and SGLT2 inhibitors on *cardiovascular mortality* and *hospitalization for heart failure*. Although the magnitude of effect of both drugs was rather small in primary T2DM populations, SGLT2 inhibitors showed high efficacy to prevent *hospitalization for heart failure* in patients with reduced ejection fraction, where they were comparable in effect to established heart failure medication.

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Conflicts of interest

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Individual Trial Endpoint Definitions.
Figure S1. Scatterplots to compare the hazard ratios (HRs) from the original publications (x-axis, with 95% CI) with the hazard ratios from the fitted Weibull model of the extracted data (y-axis, with 95% CI), both for outcomes of a) *Cardiovascular Mortality* and b) *Hospitalization for Heart Failure*.
Figure S2. Kaplan–Meier plots of the Weibull model fit from extracted data, for the placebo groups (red, with 95% CI) in comparison to the treatment groups (blue, with 95% CI), both for outcomes of a) *Cardiovascular Mortality* and b) *Hospitalization for Heart Failure*.

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