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Cardiovascular risk and lifetime benefit from preventive treatment in type 2 diabetes: A post hoc analysis of the CAPTURE study

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Abstract

Aim: To assess the potential gain in the number of life-years free of a (recurrent) cardiovascular disease (CVD) event with optimal cardiovascular risk management (CVRM) and initiation of glucose-lowering agents with proven cardiovascular benefit in people with type 2 diabetes (T2D).

Materials and Methods: 9,416 individuals with T2D from the CAPTURE study, a non-interventional, cross-sectional, multinational study, were included. The diabetes lifetime-perspective prediction model was used for calculating individual 10-year and lifetime CVD risk. The distribution of preventive medication use was assessed according to predicted CVD risk and stratified for history of CVD. For the estimation of absolute individual benefit from lifelong preventive treatment, including optimal CVRM and the addition of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose co-transporter-2 inhibitors (SGLT-2is), the model was combined with treatment effects from current evidence.

Results: GLP-1 RA or SGLT-2i use did not greatly differ between patients with and without CVD history, while use of blood pressure-lowering medication, statins and aspirin was more frequent in patients with CVD. Mean (standard deviation [SD]) lifetime benefit from optimal CVRM was 3.9 (3.0) and 1.3 (1.9) years in patients with and without established CVD, respectively. Further addition of a GLP-1 RA and an SGLT-2i in patients with CVD gave an added mean (SD) lifetime benefit of 1.2 (0.6) years.

Conclusions: Life-years gained free of (recurrent) CVD by optimal CVRM and the addition of a GLP-1 RA or aSGLT-2i is dependent on baseline CVD status. These results aid individualizing prevention and promote shared decision-making in patients with T2D.

KEYWORDS
antidiabetic drug, cardiovascular disease, GLP-1, SGLT2 inhibitor, type 2 diabetes

1 | INTRODUCTION

The prevalence of type 2 diabetes (T2D) is rapidly increasing worldwide and the current global prevalence is 9%.[1] Furthermore, patients with T2D have a 2-fold excess risk of cardiovascular disease (CVD), independent of other risk factors, compared with people without T2D.[2] CVD is the main cause of disability and death in patients with T2D, and is also associated with reduced health-related quality of life and increased healthcare costs.[3] Assessing risk and preventing CVD in patients with T2D are therefore highly important.

Available glucose-lowering agents (GLAs) with proven cardiovascular (CV) benefits include glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose co-transporter-2 inhibitors (SGLT-2is).[4,5] The results of several randomized controlled trials indicate that these treatments provide specific benefits for patients with a history of CVD, above and beyond glycaemic control.[6,7] Therefore, current guidelines advocate their use in high-risk patients,[8-11] although implementation of these therapies remains limited.[12,13] Guidelines recommend regular cardiovascular risk management (CVRM) as the first-line treatment strategy: the effects of lipid-lowering,[14,15] glucose-lowering[16] and blood pressure-lowering medications,[17,18] aspirin use (in secondary prevention)[19] and smoking cessation,[20] are all highly significant in CVD risk reduction, and their use is monitored.

There is a wide distribution in terms of individual benefit from optimal CVRM and preventive treatment in patients with T2D, based on risk factor burden, baseline risk and duration of treatment. The diabetes lifetime-perspective prediction (DIAL) model predicts CVD risk in patients with T2D while adjusting for non-CVD mortality as a competing risk.[21] Furthermore, the model allows incorporation of treatment effects (hazard ratios [HRs] from trials or meta-analyses) to assess the number of life-years gained without a (recurrent) CVD event with the initiation of preventive medication strategies. The individual CVD risk and benefit from preventive treatment initiation can be discussed in clinical practice, and enhances shared decision-making between the patient and clinician.

CAPTURE was a non-interventional, cross-sectional study that collected demographic and clinical characteristics for 9823 adults with T2D across 13 countries worldwide in 2019,[13] aiming to estimate CVD risk distribution and assess treatment patterns. The aim of this post hoc analysis of data from CAPTURE was to estimate the potential gain in the number of life-years free of a (recurrent) CVD event with CVRM and initiation of GLAs with proven CV benefits.

2 | MATERIALS AND METHODS

2.1 | Study population

All patients included in the CAPTURE cohort attended a single, routine clinical visit in a primary or specialist care setting. Because of the functionality of the DIAL model, regions were defined solely based on geography and did not account for inter-regional differences, for example in healthcare systems. Regions were defined as Latin America (Argentina, Brazil and Mexico), Western Europe (Italy and France), Eastern Europe (Turkey, the Czech Republic and Hungary), Australia, East Asia (China and Japan) and the Middle East (Saudi Arabia and Israel). Baseline characteristics were described as mean ± standard deviation (SD) for continuous variables, median (interquartile range [IQR]) for skewed variables and count (percentage) for categorical variables.

Missing data in the cohort were imputed using single imputation by predicted mean matching (aregImpute algorithm in R, Hmisc package, version 4.5-0). Imputation was performed with stratification according to region. The proportion of patients with missing data was: 0% for sex, age, region, history of CVD and medication use; 0.1% for diabetes duration; 2% for systolic blood pressure and body mass index; 7% for HbA1c level; 22% for non-high-density lipoprotein (HDL)-cholesterol level; 19% for estimated glomerular filtration rate (eGFR); 1% for smoking status; and 34% for albuminuria. Non-imputed baseline data, including numbers of missing values, are provided in Table S1.

The DIAL model is suitable for CVD risk prediction for patients with T2D aged 30-85 years who have an eGFR above 30 ml/min/1.73m^2. Therefore, CAPTURE participants younger than 30 years and older than 85 years were excluded (n = 169), as were those with an eGFR below 30 ml/min/1.73m^2 (n = 250), including 12 patients in both categories. Exclusion was performed after imputation of missing data. This resulted in a cohort for CVD risk prediction of 9416 patients with T2D, 2901 with a history of CVD and 6515 without a history of CVD (Figure S1).

2.2 | DIAL model for estimating CVD risk and treatment benefit

The DIAL model has previously been described in detail,[21] and is available via an online interactive calculator (www.u-prevent.com). Individual 10-year and lifetime CVD risks were calculated using previously validated life-table methods.[22] The model was combined with HRs from meta-analyses on the effect of tGLP-1 RAs and SGLT-2is, respectively, on CV outcomes,[4,5] to estimate individual absolute benefit from treatment in terms of gain in life-years free of (recurrent) CVD event.

2.3 | Definition of individual optimal preventive treatment

Individuals were stratified into risk groups (moderate, high or very high CVD risk) according to the 2021 European Society of Cardiology (ESC) CVD prevention guidelines (Table S2).[10] Optimal treatment was likewise assessed in line with these guidelines. The main analyses were based on CVRM according to step 2 of the ESC guidelines' two-step approach. Figure S2 shows life-years gained free of (recurrent) CVD with optimal CVRM according to step 1 and step 2, stratified for history of CVD. Lifetime benefit was calculated individually for all patients using the scenario that those who were currently smoking would stop, and that all patients would reach their respective risk

group targets for low-density lipoprotein (LDL)-cholesterol level, HbA1c concentration and systolic blood pressure. It was also assumed that treatment with aspirin, GLP-1 RA and/or SGLT-2i was initiated, if appropriate, following the aforementioned guidelines. GLP-1 RA and SGLT-2i therapy was therefore assigned to all patients classified as being at very high CVD risk. Definitions of targets are provided in Table S3.

2.4 | Prediction of individual CVD risk and lifetime benefit from preventive treatment

Patient-level data from the CAPTURE study (age, sex, body mass index, smoking status, HbA1c level, history of CVD, duration of T2D, non-HDL-cholesterol level, insulin use, eGFR, albuminuria and region) were used for predicting individual CVD risk using the DIAL model. In line with the original DIAL model, Eastern Europe was set as a high-risk region and the remaining regions were defined as low-risk regions.

Predicted risk was calculated taking current antiplatelet medication, GLP-1 RA and SGLT-2i use into consideration using HRs from current best available evidence.[4,5,19] Current treatment with lipid-lowering and antihypertensive medication was assumed to act by reducing non-HDL-cholesterol level and systolic blood pressure, respectively, both of which were included as predictors in the DIAL model. Treatment effects of GLP-1 RAs (HR of 0.85 in patients with CVD and 1.00 in those without CVD)[4] and SGLT-2is (HR of 0.89 in patients with CVD and 1.00 in those without CVD),[5] as well as HRs for reduction of blood pressure, HbA1c level and LDL-cholesterol level, aspirin treatment and smoking cessation, were combined with the DIAL model to estimate individual lifetime benefit free of (recurrent) CVD with initiation of preventive treatment.[23] HRs were based on three-component major adverse CV events (including myocardial infarction, stroke and CV death) as outcome. Table S4 provides a full list of HRs for treatment effects.

2.5 | Distribution of predicted CVD risk, current use of preventive medication and lifetime benefit

Distributions of predicted 10-year and lifetime risk of a (recurrent) CVD event were stratified according to history of CVD. A high CVD risk was defined as a 10-year risk of CVD of more than 10%[10] and a lifetime risk of CVD as greater than 50%. Distributions of the use of preventive GLAs with proven CV benefit (GLP-1 RAs and SGLT-2is) were stratified by history of CVD and according to deciles of predicted lifetime CVD risk. Distributions of the use of CVRM medications (antihypertensive medication, statins and aspirin) were assessed in the same way.

Distributions of numbers of life-years gained without a (recurrent) CVD event with optimal CVRM and the addition of GLP-1 RA and SGLT-2i were stratified by history of CVD and assessed according to deciles of predicted lifetime risk. All analyses were performed with R-statistical programming (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria).

2.6 | Sensitivity analyses

Given that there was a substantial amount of missing data, we performed all the analyses as a complete case analysis. Baseline tables for

TABLE 1 Baseline characteristics of the CAPTURE study population included in this analysis (N = 9416)

Characteristic	History of CVD (n = 2901)	No history of CVD (n = 6515)
Demographics and medical history		
Age, y	67 ± 9	61 ± 11
Sex, men	1831 (63)	3303 (51)
Diabetes duration, y, median (IQR)	13 (7-20)	10 (5-16)
Smoking, current	428 (15)	888 (14)
Nephropathy	800 (28)	1081 (17)
Retinopathy	697 (24)	1028 (16)
Neuropathy	874 (30)	1243 (19)
Cardiovascular medication use		
Blood pressure-lowering medication	2240 (77)	3498 (54)
Lipid-lowering medication	1947 (67)	2845 (44)
Antiplatelet medication	1790 (62)	1309 (20)
Glucose-lowering agent use		
Metformin	2163 (75)	5208 (80)
Insulin	1323 (46)	2208 (34)
DPP-4i	802 (28)	2015 (31)
Sulphonylurea	642 (22)	1525 (23)
SGLT-2i	517 (18)	1062 (16)
GLP-1 RA	281 (10)	715 (11)
Clinical characteristics and laboratory values		
Systolic blood pressure, mmHg	132 ± 17	132 ± 15
Diastolic blood pressure, mmHg	76 ± 11	78 ± 10
Body mass index, kg/m^2	30 ± 6	30 ± 6
eGFR, ml/min/1.73m^2, median (IQR)	76 (59-90)	84 (68-96)
Microalbuminuria	870 (30)	1432 (22)
Macroalbuminuria	237 (8)	370 (6)
HbA1c, mmol/mol	62 ± 17	60 ± 18
HbA1c, %, mean	7.8	7.6
Cholesterol, mmol/L	4.2 ± 1.2	4.6 ± 1.1
HDL-cholesterol, mmol/L	1.2 ± 0.3	1.2 ± 0.3
LDL-cholesterol, mmol/L	2.3 ± 0.9	2.6 ± 0.9
Non-HDL-cholesterol, mmol/L	2.4 ± 1.0	2.6 ± 1.2
Predicted risks		
Mean 10-y risk of CVD, %	40.1	4.9
Mean lifetime risk of CVD, %	65.0	10.2

Note: Data are presented as n (%) or mean ± SD unless otherwise stated.
Abbreviations: CVD, cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; SD, standard deviation; SGLT-2i, sodium-glucose co-transporter-2 inhibitor.

patients with and without CVD were also stratified by lifetime CVD risk decile. Furthermore, the use of GLP-1 RA and SGLT-2i was assessed according to geographical region and stratified according to history of CVD. Gain in the number of life-years free of (recurrent) CVD with optimal CVRM and the addition of a GLP-1 RA and an SGLT-2i according to age was also evaluated. Lastly, the current ESC guidelines recommend considering a GLP-1 RA or SGLT-2i in patients with T2D without established CVD but at high risk of CVD.[10] Therefore, we assessed the lifetime benefit of adding a GLP-1 RA and an SGLT-2i to current treatment in patients without CVD, using the overall HR from the meta-analyses (HR for GLP-1 RAs of 0.86[4] and HR for SGLT-2is of 0.90[5]) for patients at high CVD risk.

3 | RESULTS

3.1 | Study population

Baseline characteristics stratified according to history of CVD are shown in Table 1. The cohort comprised 2901 patients with CVD (31%) and 6515 patients without CVD (69%). Generally, compared with patients without CVD, those with CVD were older, were more often male, had a longer duration of T2D, and more often had microvascular complications of T2D. Furthermore, patients with CVD more often used CV preventive medication and insulin.

3.2 | Distribution of CVD risk

Distributions of 10-year and lifetime CVD risk stratified according to history of CVD are shown in Figure 1. There was a wide distribution of both 10-year and lifetime risk, with a higher risk in patients with a history of CVD than in those without CVD. Two peaks were observed in patients with CVD: one at ~30% 10-year and 65% lifetime CVD risk, and one at ~95% 10-year and 98% lifetime CVD risk. Patients with T2D and a history of CVD with lower predicted risks were generally older, had lower risk factor levels and had a higher frequency of preventive CV medication use. The majority of patients with T2D and a history of CVD at very high predicted CVD risk belonged to a high-risk region. Among patients with a history of CVD, 96% had a 10-year risk of recurrent CVD of more than 10%, and 80% had a lifetime risk of recurrent CVD of more than 50%. In patients without a history of

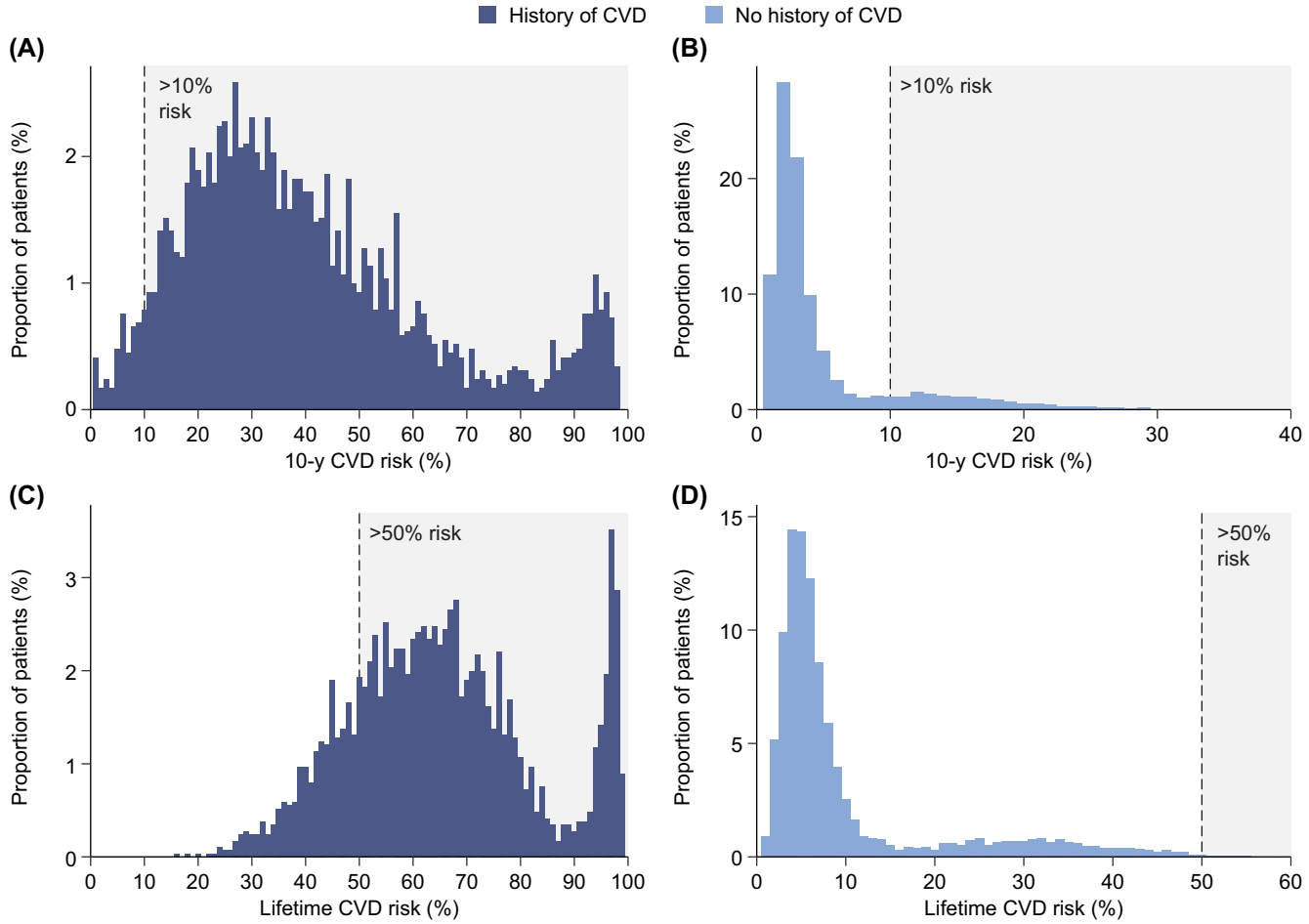

FIGURE 1 Predicted 10-year CVD risk for patients, A, With CVD, and B, Without CVD, and predicted lifetime CVD risk for patients, C, With CVD, and D, Without CVD in the CAPTURE study. CVD, cardiovascular disease

CVD, 14% had a 10-year risk of a first CV event of more than 10%, and only 0.4% had a lifetime risk of a first CV event of more than 50%.

3.3 | Distribution of preventive CVD treatment

The distribution of preventive medication use stratified by history of CVD and according to decile of predicted lifetime CVD risk is shown in Figure 2. Larger proportions of patients with CVD were using blood pressure-lowering medication, statins and aspirin than those of patients without CVD (Figure 2A,B). Among patients with and without CVD, those with a higher predicted lifetime CVD risk generally had lower statin and aspirin use. Patients with CVD and at higher predicted CVD risk had higher use of antihypertensive medication. GLP-1 RA use (10% in patients with CVD and 11% in patients without CVD) was lower than SGLT-2i use (18% in patients with CVD and 16% in patients without CVD). Overall, the proportion of patients with T2D using a GLP-1 RA or an SGLT-2i did not greatly differ between patients with and without a history of CVD (Figure 2C,D). In patients with a history of CVD, there was a trend for both GLP-1 RA and SGLT-2i use to be lower in individuals with a higher predicted CVD risk. In patients without CVD, no clear pattern according to risk decile was observed.

3.4 | Distribution of lifetime benefit from preventive treatment

The distribution of the number of life-years gained without (recurrent) CVD with optimal CVRM and addition of a GLP-1 RA and an SGLT-2i is shown in Figure 3. In patients with CVD, mean (SD) number of life-years gained without recurrent CVD was 0.9 (0.5) years (Figure 3A) with the addition of a GLP-1 RA and 0.6 (0.4) years with the addition of an SGLT-2i (Figure 3B). The lifetime benefit from optimal CVRM was higher in patients with CVD (overall mean [SD] lifetime benefit gained 3.9 [3.0] years) (Figure 3C) than in those without CVD (overall mean [SD] lifetime benefit gained 1.3 [1.9] years) (Figure 3D). In

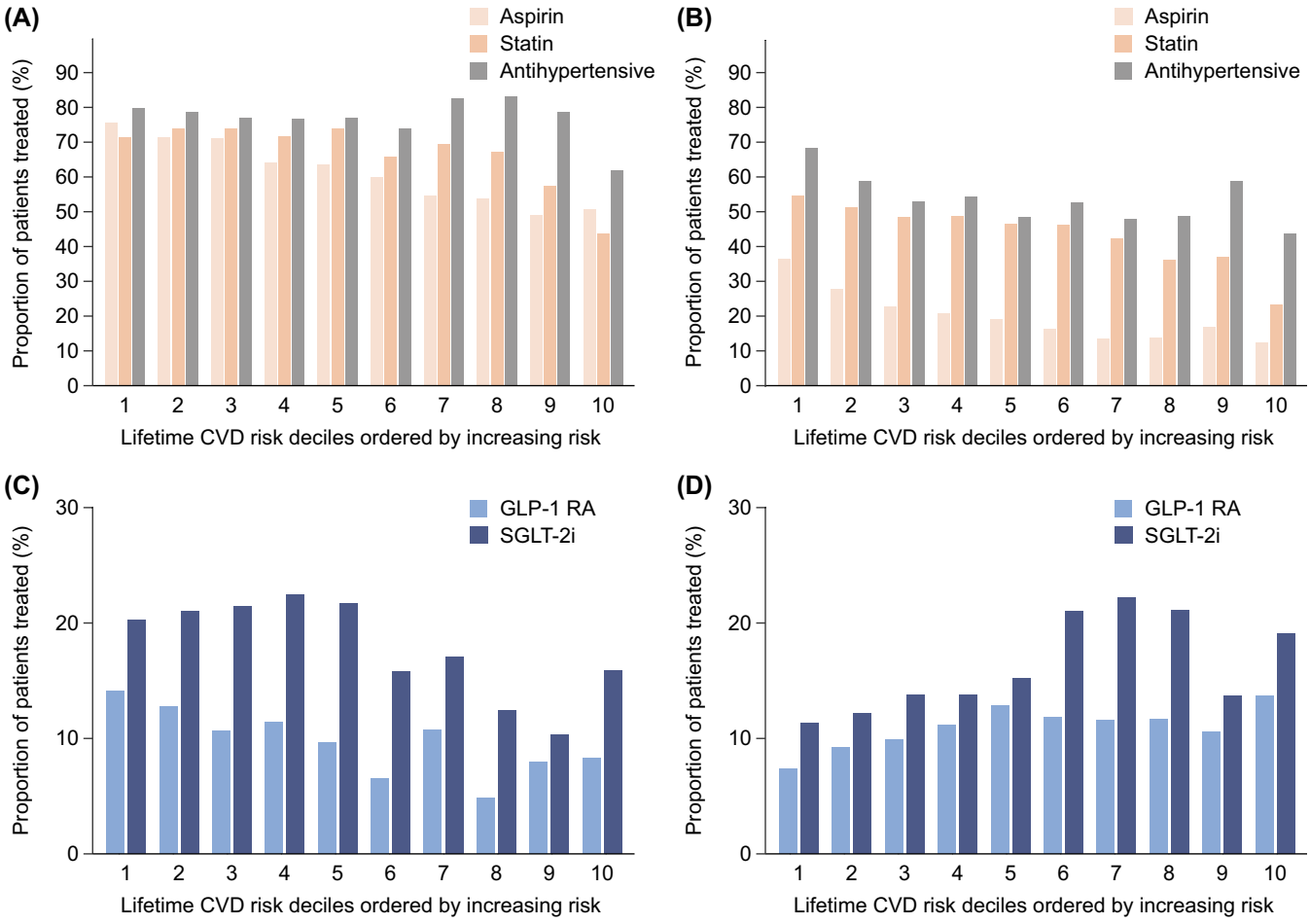

FIGURE 2 Distribution of current preventive medication use according to predicted lifetime CVD risk stratified by history of CVD. CVRM in patients, A, With CVD, and B, Without CVD. GLA treatment in patients, C, With CVD and, D, Without CVD. CVD, cardiovascular disease; CVRM, cardiovascular risk management; GLA, glucose-lowering agent; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium-glucose co-transporter-2 inhibitor

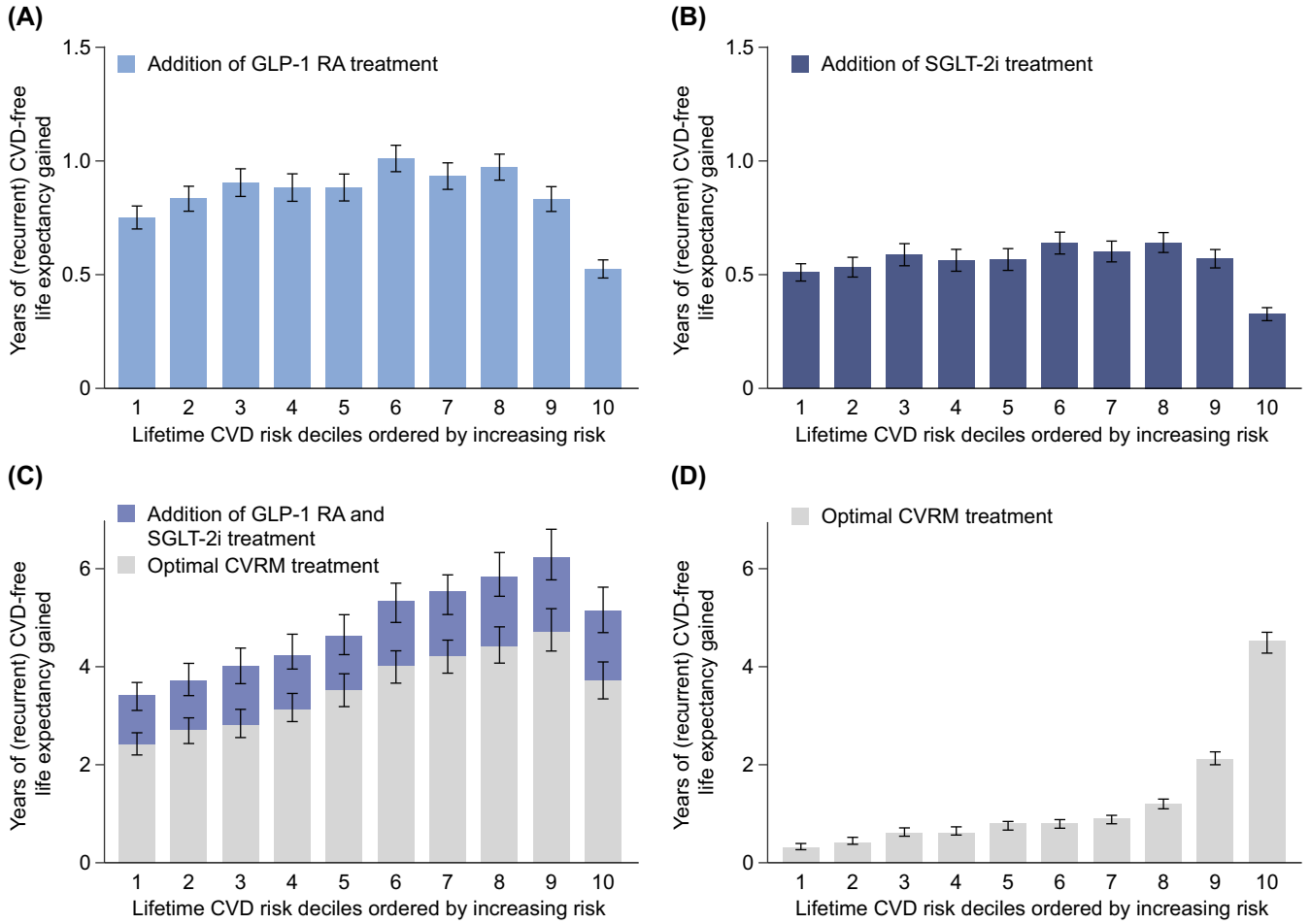

FIGURE 3 Distribution of the number of predicted life-years gained without (recurrent) CVD with the addition of, A, GLP-1 RA, and B, SGLT-2i treatment in patients with CVD, and with optimal CVRM, in patients, A, B and C, With CVD, and D, Without CVD. Optimal CVRM includes smoking cessation (if the patient was a smoker), reaching specified target goals for LDL-cholesterol level, HbA1c level and systolic blood pressure, and initiation of aspirin treatment if appropriate. C also shows the number of predicted life-years gained without (recurrent) CVD with the addition of aSGLT-2is and GLP-1 RAs to CVRM. Error bars represent 95% confidence intervals. CVD, cardiovascular disease; CVRM, cardiovascular risk management; GLP-1 RA, glucagon-like peptide-1 receptor agonist; LDL, low-density lipoprotein; SGLT-2i, sodium-glucose co-transporter-2 inhibitor

patients with CVD, higher predicted CVD risk was associated with greater lifetime benefit from optimal CVRM, except for in the highest lifetime CVD risk decile. In patients with CVD, addition of both a GLP-1 RA and an SGLT-2i to optimal CVRM led to an overall mean (SD) gain in the number of life-years free of a (recurrent) CVD event of 1.2 (0.6) years, which increased with rising lifetime CVD risk.

3.5 | Sensitivity analyses

When performing the analyses as a complete case analysis (n = 3532), the results did not change substantially (data not shown). Baseline tables stratified by history of CVD and lifetime CVD risk decile are shown in Tables S5 and S6. There was a wide distribution in the use of GLP-1 RAs and SGLT-2is according to geographical region (Figure S3). Younger age at treatment initiation was associated with a larger gain in number of life-years free of (recurrent) CVD with optimal treatment and further addition of a GLP-1 RA and an SGLT-2i (Figure S4). Lastly, when assessing the lifetime benefit of adding a GLP-1 RA and an SGLT-2i to current treatment in patients without CVD but at high CVD risk, a higher predicted CVD risk was associated with more benefit from treatment (Figure S5).

4 | DISCUSSION

This post hoc analysis of the CAPTURE data showed a wide distribution of predicted CVD risk in patients with and without a history of CVD. The use of preventive medication varied across lifetime CVD risk deciles. Antihypertensive medication, statins and aspirin use was much more common in patients with CVD; however, no clear difference in GLP-1 RA and SGLT-2i use was seen between patients with and without CVD. When adding a GLP-1 RA and a SGLT-2i to current treatment, a wide distribution of gain in the number of life-years

without a (recurrent) CVD event was observed. The benefit of adding these GLAs to optimal CVRM was considerably smaller. Higher lifetime benefits of preventive treatment were seen in patients with T2D with a higher predicted CVD risk, and younger patients had a higher lifetime benefit from preventive treatment.

The use of prediction models in the field of CV medicine is increasing.[24] Well-performing models allow individualized predictions and tailored risk management based on a series of easily obtainable clinical values and patient characteristics. Translating CVD risk into lifetime CVD risk and life-years free of CVD with and without initiation of specific treatments is clear and relatable for patients, and may promote shared decision-making. Patients with T2D are often the primary managers of their condition, and such discussion may aid adherence to treatment or lifestyle changes, provided that the treating physician tailors communication to the individual.

Several CVD prediction models have been developed for patients with T2D[25,26]; however, we chose the DIAL model because it is contemporary and also allows assessment of absolute risk reduction and gain in life-years without (recurrent) CVD with preventive treatment. Furthermore, the model accounts for non-CV mortality as a competing risk and allows for longer prediction time spans (including lifetime predictions). The model was derived and externally validated in large, contemporary population-based T2D cohorts from various regions, making it applicable to general T2D populations in routine clinical settings in various countries and regions.

We observed two peaks in the distribution of predicted risk of recurrent CVD in patients with CVD. Patients with T2D and a history of CVD with lower predicted risks were generally older, and thus possibly causing a healthy survivor effect. Furthermore, as would be expected, risk factor levels were lower and there was a higher frequency of preventive CV medication use in these patients. The second peak could be attributed to the fact that the majority of patients with T2D and a history of CVD at very high predicted CVD risk belonged to a high-risk region, as was seen in the predicted risk stratified baseline table.

Prescriptions of aspirin and statins appeared to be less frequent in patients with an increasing predicted lifetime risk of CVD. These patients at the highest risk of CVD are probable to have this high risk because of poor CVRM. GLP-1 RAs and SGLT-2is provide significant CVD risk reduction independent of glucose lowering. Meta-analyses in patients with T2D and a history of CVD have found a 15% lower risk of major CVD outcomes with a GLP-1 RA[4] and a 11% lower risk with an SGLT-2i,[5] compared with placebo. In the present study, there was a trend for patients with CVD at higher predicted CVD risk to have a lower frequency of both GLP-1 RA and SGLT-2i use. Only a small proportion of patients with CVD in the CAPTURE cohort used these therapies, and no substantial difference was seen between patients with and without CVD, even though these GLAs are recommended for patients with CVD in current guidelines.[10,11] The present study did not consider other reasons contributing to the low GLP-1 RA and SGLT-2i use, including lack of reimbursement from healthcare providers or contraindications in high-risk patients. Furthermore, the CAPTURE data were collected in 2019, and rates of GLP-1 RA and SGLT-2i use may have changed since then. We applied the CV treatment effects of GLP-1 RAs and SGLT-2is only to patients with established CVD, because a significant effect was observed only in this patient group in the meta-analyses.[4,5] It should be acknowledged that these preventive GLAs will probably also be effective in patients with CVD risk factors only, rather than established CVD, and interaction with established CVD in the meta-analyses was non-significant for both GLP-1 RAs and SGLT-2is.[4,5] Current guidelines recommend considering GLP-1 RAs and SGLT-2is in patients with T2D without established CVD but at a high risk of CVD[10]; however, because there is still limited evidence that this effect is significant in patients with CVD risk factors only, we chose not to incorporate this in our main analyses.

CVRM remains the primary focus in reducing CVD risk in patients with T2D, including smoking cessation, lowering of lipid levels, blood pressure and blood glucose concentrations, aspirin use and lifestyle interventions[11]; however, the level of evidence for the efficacy of these interventions differs. Optimal CVRM is difficult to achieve in a large percentage of patients with T2D,[27] and these patients will benefit from GLP-1 RAs or SGLT-2is in terms of years gained free of (recurrent) CVD. In the present study, we combined HRs for several preventive treatments according to the best available current evidence, to show the absolute benefit an individual patient may gain from treatment, both with optimal CVRM and with the addition of GLP-1 RAs and SGLT-2is. We observed a wide distribution of the gain in (recurrent) CVD-free life expectancy. Patients with established CVD at higher CVD risk gained more life-years free of (recurrent) CVD, except for those in the highest decile, most probably because of lower overall life expectancy in this group of patients and lower lifelong benefit from treatment. We previously used the DIAL model to show the benefit of adding semaglutide treatment for high-risk patients, which also showed a wide distribution in the number of life-years gained without (recurrent) CVD and a greater gain in patients with T2D at higher CVD risk.[28] Furthermore, this approach has been used in other populations, including apparently healthy people[29] and patients with vascular disease.[30] By using an external cohort of patients with T2D spanning various regions and including preventive treatment, we have expanded on these previous studies.

The cohort with T2D included patients from various regions, making our results applicable worldwide. However, the original CAPTURE study involved a selected population, with inclusion of patients from both specialist care and general practice, which might not represent the general T2D population in each specific country; the use of preventive medication is probable to be higher than that in the general population with T2D. This may also lead to a degree of selection bias, and participants in the CAPTURE study may have been at higher CVD risk than the general population of patients with T2D. Furthermore, because of the functionality of the DIAL model, the geographical regions were based solely on country location and did not represent inter-regional differences in healthcare systems. Also, because the DIAL model only allows for prediction of CVD as the outcome, no assessment could be performed regarding the risk of chronic kidney disease and hospitalization for heart failure, which are also highly relevant outcomes in people with T2D. With the data on people with

T2D currently available, it is not feasible to validate the DIAL model for longer than 10-year time-span predictions, because this would require a cohort with a lifetime follow-up. The DIAL model has shown reasonable discrimination and calibration for 10-year risk of CVD in different populations[21,28]; however, as data on populations with T2D accrue, the model will benefit from longer time-span validations. Substantial amounts of data were missing for some predictors, which might have affected the results; however, imputation was used to reduce the risk of bias and a complete case analysis was also performed, which did not alter the results substantially. Furthermore, because data were collected cross-sectionally and no follow-up was available, we were unable to geographically recalibrate the model to the current cohort. Recalibration according to the geographical regions from the original DIAL model was therefore used. HRs of preventive treatment are constant, so patients were assumed to experience the same clinical benefit for the remainder of their life expectancy.

In conclusion, we found a wide distribution of lifetime CVD risk in patients with T2D from the CAPTURE study. There was also a wide distribution in benefit from preventive treatment, in terms of both optimal CVRM and the addition of GLP-1 RAs and SGLT-2is. Translating CVD risk into lifetime risk and expressing the benefit of preventive treatment as gain in (recurrent) CVD-free life expectancy aids in individualizing prevention in patients with T2D and shared decision-making in the clinical setting.

AUTHOR CONTRIBUTIONS

All the authors contributed to the study design. OM represented the investigators of the original CAPTURE study and advised on the post hoc analysis for this study. HBØ and JW analysed the data. HBØ drafted the manuscript. All the authors contributed to data interpretation, critically reviewed and revised the manuscript, and approved the final version. JW is the guarantor of this work.

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CONFLICT OF INTEREST

HBØ, FM, FLJV and JW have nothing to disclose. VH is a volunteer patient advocate with type 2 diabetes for Diabetes Ireland. EMH and JBH are employees of Novo Nordisk A/S. GY is an employee of Novo Nordisk International Operations. OM has participated in advisory boards and/or speaker's bureaux for AstraZeneca, Boehringer Ingelheim, BOL Pharma, Eli Lilly, Janssen, MSD, Novo Nordisk and Sanofi; via Hadassah Hebrew University Hospital, she has received research grant support from AstraZeneca and Novo Nordisk.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14887.

DATA AVAILABILITY STATEMENT

The data sets used and/or analysed during the current study are available from the corresponding author on reasonable request.

ETHICAL APPROVAL

Approval by an ethics committee was not required for this study because only de-identified secondary data were used.

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SUPPORTING INFORMATION

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

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