Dapagliflozin vs non-SGLT-2i treatment is associated with lower healthcare costs in type 2 diabetes patients similar to participants in the DECLARE-TIMI 58 trial: A nationwide observational study

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Abstract
Aims: To investigate how the cardiovascular (CV) risk benefits of dapagliflozin translate into healthcare costs compared with other non-sodium–glucose cotransporter-2 inhibitor glucose-lowering drugs (oGLDs) in a real-world population with type 2 diabetes (T2D) that is similar to the population of the DECLARE-TIMI 58 trial.

Methods: Patients initiating dapagliflozin or oGLDs between 2013 and 2016 in Swedish nationwide healthcare registries were included if they fulfilled inclusion and exclusion criteria of the DECLARE-TIMI 58 trial (DECLARE-like population). Propensity scores for the likelihood of dapagliflozin initiation were calculated, followed by 1:3 matching with initiators of oGLDs. Per-patient cumulative costs for hospital healthcare (in- and outpatient) and for drugs were calculated from new initiation until end of follow-up.

Results: A total of 24,828 patients initiated a new GLD; 6207 initiated dapagliflozin and 18,621 initiated an oGLD. After matching based on 96 clinical and healthcare cost variables, groups were balanced at baseline. Mean cumulative 30-month healthcare cost per patient was similar in the dapagliflozin and oGLD groups ($11,807 and $11,906, respectively; difference, −$99; 95% CI, −$629, $483; P = 0.644). Initiation of dapagliflozin rather than an oGLD was associated with significantly lower hospital costs (−$658; 95% CI, −$1169, −$108; P = 0.024) and significantly higher drug costs ($559; 95% CI, $471, $648; P < 0.001). Hospital cost difference was related mainly to fewer CV- and T2D-associated complications with use of dapagliflozin compared with use of an oGLD (−$363; 95% CI, −$665, −$61; P = 0.008).

Conclusion: In a nationwide, real-world, DECLARE-like population, dapagliflozin was associated with lower hospital costs compared with an oGLD, mainly as a result of reduced rates of CV- and T2D-associated complications.

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1 | INTRODUCTION

There is currently an epidemic of type 2 diabetes (T2D), and its increasing prevalence has resulted in a rapid increase in related healthcare costs over the last decade. In Sweden, healthcare costs for diabetes doubled, from €835 million to €1684 billion between 2006 and 2014, mainly driven by costs associated with hospital care for cardiovascular (CV) complications, in particular heart failure. Recent clinical trials have demonstrated that some newer glucose-lowering drugs (GLDs) have a beneficial effect on CV outcomes in patients with T2D, and these paradigm-changing effects could have the potential to reduce healthcare costs.

Dapagliflozin is a sodium–glucose cotransporter-2 inhibitor (SGLT-2i) that has been shown to be safe and to effectively reduce CV disease in both high- and low-CV-risk patients in clinical trial and real-world settings. In addition, dapagliflozin is increasingly prescribed worldwide and has been observed to be effective in reducing blood glucose levels in various clinical settings.

The DECLARE-TIMI 58 trial (ClinicalTrials.gov NCT01730534) was the largest CV outcomes trial (CVOT) concerning an SGLT-2i to date (dapagliflozin, n = 17,160) and applied broad eligibility criteria, resulting in a study population with established CV disease or with multiple CV risk factors. In this trial, use of dapagliflozin reduced the risk of CV death or heart failure compared with placebo (4.9% and 5.8%, respectively; hazard ratio [HR], 0.53; 95% CI, 0.43, 0.66), as well as reducing kidney disease progression (1.5% and 2.8%, respectively; HR, 0.53; 95% CI, 0.43, 0.66) in patients with or without established CV disease. Subsequent to the DECLARE-TIMI 58 trial, several observational studies have been conducted to investigate the use of dapagliflozin in a real-world clinical setting and its potential impact on CV outcomes. Firstly, a multinational study of more than 800,000 patients reported that the broad eligibility criteria of the DECLARE-TIMI 58 trial were applicable to 59% of the Swedish population with T2D. This representativeness was two- to four-fold greater than that of other SGLT-2i CVOTs. Secondly, assessment of the external validity of the results of the DECLARE-TIMI 58 trial demonstrated that the beneficial CV effects of dapagliflozin could be translated into a real-world population with T2D. Differences in CV mortality benefits have been shown between CVOTs and observational studies, and this may be explained by differences in the frailty of the patients included. This is supported by post hoc analyses of the DECLARE-TIMI 58 trial (Figure S1). While the safety, clinical benefits, representativeness and external validity of the DECLARE-TIMI 58 trial have been evaluated, the way in which the observed beneficial effects of dapagliflozin might impact healthcare costs is not known.

The aim of the present analysis was to compare the hospital healthcare costs of using dapagliflozin and those of using other glucose-lowering drugs (oGLDs) in a nationwide, real-world DECLARE-like population based on the main eligibility criteria of the DECLARE-TIMI 58 trial.

2 | MATERIALS AND METHODS

This nationwide, observational study is part of the D360 Nordic program, a large-scale epidemiological investigation that aims to obtain full-coverage understanding of T2D and its treatment. This program utilizes the unique features of the mandatory healthcare registries and corresponding healthcare systems in Sweden to identify all patients with T2D with filled prescriptions for a glucose-lowering drug (GLD) (Appendix, Section S1).

2.1 | Data sources

Sweden has a comprehensive, nationwide public healthcare system. All citizens have a unique personal identification number (person-ID), which is mandatory for all administrative purposes (including any contact with the healthcare system and drug dispensaries), thus providing a complete medical history from a population perspective. This study included data from the Swedish Prescribed Drug Register, the Cause of Death Register and the National Patient Register covering all hospitalizations with discharge diagnoses and all out-patient hospital visits (Appendix, Section S1). Individual patient-level data from the national registers were linked using the person-ID. The linked anonymized database was managed separately by Statisticon AB, Uppsala, Sweden. The study was approved by the Stockholm regional ethics committee (registration number 2013/2206–31).

2.2 | Study population

All incident new-user episodes of filled prescriptions for either dapagliflozin or a non-SGLT-2i GLD (oGLD) in Sweden between 2013 and 2016, in patients with T2D who were at least 18 years of age were eligible for inclusion in the analysis. Patients with type 1 diabetes, gestational diabetes, polycystic ovarian syndrome or cancer (current or prior history) were excluded (Appendix, Section 2). The DECLARE-like study population for evaluation was defined by the main inclusion and exclusion criteria of the DECLARE-TIMI 58 trial (≥40 years of age with established CV disease, or with multiple risk factors: men ≥55 and women ≥60 years with hypertension or dyslipidaemia); adoption from these trial criteria to registry data is shown in the online Appendix, Section S3.

The new-user date (index date) was defined as the date of the initial filled prescription for dapagliflozin or oGLD, and, for participants to be considered a new user, this date had to be preceded by a 12-month period without any filled prescription for the same drug class. This definition allowed for several possible new-user dates for a patient within the observation period, both within drug class and between classes, which eliminates the risk of immortal time bias while maximizing the number of observations.

2.3 | Baseline data

Patient characteristics included age at the date of index drug initiation, sex, index year and year of first registered GLD dispense
Year of first registered GLD dispense was used in the propensity score as a proxy for duration of T2D and index year was used to ensure that the treatments of interest were initiated at the same point in time. Comorbidities were searched for in all available data prior to and including the index date, with the exception of severe hypoglycaemia, which was included only if it occurred within the 12 months prior to index date, and cancer, which was included only if it occurred within five years prior to index date (detailed definitions are given in Table S5b). Prior medications were defined as any drugs dispensed within the 12 months prior to, and including, the index date (detailed definitions are given in Table S5c).

### 2.4 Healthcare cost outcomes

Healthcare costs for inpatient and outpatient hospital care were estimated using Diagnosis Related Groups (DRGs). The DRG-price level for 2016 (1 US$ [US dollar] = 8.56 SEK [Swedish Krona]) was applied throughout the study. Drug costs were based on the actual costs of dispensing at the pharmacy and were adjusted for inflation to the general price level for 2016 using the Consumer Price Index (CPI). Baseline costs were defined as mean per-patient costs for both the three and 12 months preceding initiation of dapagliflozin or an oGLD.

Cumulative healthcare cost per patient was calculated for incremental three-month intervals up to 30 months (ie, cost for 0–3 months, 0–6 months, etc., up to 0–30 months). For patients with a shorter follow-up period than the end of the time interval of interest, the observed cost was divided by the fraction of time the patient contributed, to get the expected cost for the full time period of interest, and then weighted according to the relative time in study up to the time point of interest, in order to avoid influence of extreme values. As an example, if a patient was followed for exactly 13-months, the patient would contribute with the actual cost for all time intervals up to 12 months. For the 0 to 15-month interval, the cost was then estimated as \(\frac{12}{15} \times \text{cost}\). For the remaining time intervals, the cost was estimated using the same approach, but modifying the denominator to include the time interval of interest.

In the calculation of average cost, individual cost estimates were weighted according to relative time-in-study up to the interval of interest. Thus, for all time points up to 12 months in the current example the weight was 1. For the 0 to 15-month interval, the patient contributed with exposure time during 13/15 (~87%) months and, therefore, had the weight of 0.87 for the estimation of mean cost at 15 months. For the 0 to 18-month interval, the weight would be 0.72, and so on, up to 30 months when the weight would be 0.43. As the aim of the study was to evaluate actual cost, and patients who die have no healthcare-related cost after the date of death, only the cost until death was calculated for patients who died during the study, and the weight was 1 for all subsequent time points. The justification for this simplistic imputation of costs is that all censoring occurs at the end of follow-up and is therefore completely uninformative. As a result, the cost after censoring is expected to be the same as before censoring.

### 2.5 Statistical analysis

Baseline characteristics are presented as mean and standard deviation for continuous variables, and as absolute and relative frequencies for categorical variables. In order to compare baseline characteristics between groups, standardized differences were calculated for all baseline variables. A difference of more than 10% was considered a non-negligible group imbalance, based on current standards.

A propensity score for each new user of dapagliflozin was calculated using a logistic regression model with patient characteristics, age, time since dispense of first GLD, three- and 12-month healthcare costs prior to index date, comorbidities, coronary revascularization, frailty, all separate classes of GLDs, dispense of CV disease preventive drugs and drugs associated with treatment of heart failure, and date of both index drug and first-line initiation as independent variables (Appendix, Section S4). Use of healthcare cost at both three- and 12-months in the propensity score ensured a balance of both the short-term (three-month) and long-term (12-month) costs between patients. For detailed information concerning variables included in the propensity score see Tables S5a-c. To maximize the number of eligible patients receiving dapagliflozin, while at the same time avoiding immortal time bias, all new user episodes (new drugs) are included prior to matching. One patient might, therefore, contribute with more than one index for different drugs and different time points. Propensity scores were then used to match each incident user of dapagliflozin with incident users of an oGLD (1:3 match; caliper of 0.2) using the Match function in the R package Matching. Confidence intervals (CIs) and \(P\) values for cost estimations and differences between groups were constructed using 500 bootstrap iterations. To explore the impact of patients with early censoring, a sensitivity analysis was performed which included only episodes with an index date during 2013 and 2014 (ie, with a minimum of 24 months of follow-up). All analyses were conducted using R statistical software (R version 3.5.0).

### 3 RESULTS

Initially, 287,180 new-user episodes of any GLD were identified. After matching, 24,828 episodes (6207 dapagliflozin and 18,621 oGLD) remained for analysis (Figure 1). Both groups were well balanced at baseline (Table 1 and Table S7), with a mean age of 66 years, 33% having CV disease, and with similar mean three- and 12-month healthcare costs prior to index ($987 and $3863, respectively).

#### 3.1 Hospital healthcare costs

At baseline, the three-month hospital healthcare costs per patient were well balanced between the dapagliflozin and oGLD groups ($729 and $705, respectively) (Table 2). Hospital healthcare cost was...
already significantly lower for patients treated with dapagliflozin compared with that for those treated with an oGLD at 12 months, and this difference further increased towards 30 months (−$658 (95% CI, −$1169, −$108; P = 0.024) (Figure 1 and Table 2). Diabetes- and CV-related hospital healthcare costs accounted for the highest proportion of the difference (−$363; 95% CI, −$665, −$61; P = 0.008); heart failure (−$102; 95% CI, −$184, −$16; P = 0.024), myocardial infarction (−$85; 95% CI, −$173, $1; P = 0.052) and kidney disease (−$78; 95% CI, −$170, $50; P = 0.156) were the most prominent contributors to the difference (Table 2). There was no difference in healthcare costs related to stroke between patients receiving dapagliflozin and those receiving an oGLD. Other diseases accounted for −$295 (95% CI, −$660, $81; P = 0.120) of the difference in costs between the groups.

3.2 | Drug costs

At baseline, GLD costs per-patient were well-balanced between the dapagliflozin and oGLD groups (Table 1). Drug cost was higher for the dapagliflozin group during the entire 30-month follow-up period (Table 2 and Figure 2). The difference in drug cost was largely driven by GLDs ($597; 95% CI, $527, $673; P < 0.001), with little contribution from other drugs, including those used for CV prevention. The majority of the difference could be explained by dapagliflozin cost, but balanced >50% by less use of other costly glucose lowering drugs compared to the oGLD group; lower average per-patient costs for dipeptidyl peptidase-4 inhibitors (DPP-4i) (−$167; 95% CI, −$183, −$149; P < 0.001), glucagon-like peptide-1 receptor agonists (GLP-1RA) (−$387; 95% CI, −$435, −$339; P < 0.001) and insulin (−$130; 95% CI, −$176, −$82; P < 0.001).

3.3 | Total healthcare costs

Total mean cumulative healthcare cost per patient, based on costs of hospital healthcare and drugs, was similar in the dapagliflozin group and the oGLD group during the full observation period and at 30 months (−$99; 95% CI, −$629, $483; P = 0.644) (Figure 2 and Table 2). In the sensitivity analysis, which included only patients with at least 24 months of follow-up, the number of new-user episodes was reduced from 24 828 to 8880 (2220 dapagliflozin; 6660 oGLD). In this analysis, nearly identical results for total mean cumulative healthcare costs were observed (Figure S2).

4 | DISCUSSION

In this nationwide, observational, real-world study, a novel approach was used to evaluate the estimated total healthcare costs for patients with T2D who initiated treatment with either dapagliflozin or a non-SGLT-2i oGLD in a population with a patient profile similar to that of the DECLARE-TIMI 58 trial. This DECLARE-like population, defined by applying the main eligibility criteria from the DECLARE-TIMI 58 trial to a real-world population, has been described previously.

In the DECLARE-like population, initiation of dapagliflozin was associated with significantly lower hospital healthcare costs compared with initiation of oGLDs. This lower cost was driven mainly by lower costs for CV and diabetes care, and these are related to the clinical benefits with dapagliflozin reported in previous studies, including beneficial effects on CV outcomes in clinical trials and observational studies. These lower hospital healthcare costs for patients initiating dapagliflozin are of importance because approximately 30% of hospital healthcare costs are related to CV-related diseases. Although the lower hospital healthcare costs were balanced by the cost of dapagliflozin treatment, there was less need for other costly GLDs (eg, GLP-1RAs, DPP-4is or insulin) in the dapagliflozin group compared with the oGLD group, resulting in a more than 50% compensation for the higher cost of dapagliflozin.

A smaller study using US data (n = 5444) that compared healthcare costs related to initiation of either dapagliflozin or sitagliptin reported similar findings, despite using a different methodology and using data from a country with a different healthcare
| TABLE 1 | Baseline characteristics of new users of dapagliflozin vs other glucose-lowering drugs (oGLD), propensity score matched 1:3 |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| | Dapagliflozin N = 6207 | oGLD N = 18 621 | Standardized difference (%)<sup>a</sup> |
| Age, years (SD) | 66.1 (7.5) | 66.2 (8.0) | 0.4 |
| Sex, female, n (%) | 2077 (33.5%) | 6287 (33.8%) | 0.5 |
| Years since first glucose-lowering drug (SD) | 7.3 (3.1) | 7.4 (3.0) | 3.2 |
| **Healthcare cost** | | | |
| Total healthcare cost last 12 months | 3922.5 (7541.5) | 3843.2 (7719.7) | 1.0 |
| Hospital care cost | 2805.9 (7336.2) | 2763.8 (7552.4) | 0.6 |
| Glucose-lowering drug cost | 732.6 (784.6) | 698.7 (812.9) | 4.2 |
| Other drugs cost | 383.9 (425.9) | 380.7 (488.8) | 0.7 |
| Total healthcare cost last 3 months | 1013.1 (3483.6) | 978.8 (2405.1) | 1.2 |
| Hospital care cost | 728.7 (3450.2) | 705.1 (2367.0) | 0.8 |
| Glucose-lowering drug cost | 185.8 (228.4) | 176.0 (236.0) | 4.2 |
| Other drugs cost | 99.0 (126.9) | 97.7 (160.8) | 0.9 |
| **Cardiovascular disease** | | | |
| Cardiovascular disease | 2035 (32.8%) | 6289 (33.8%) | 1.7 |
| Myocardial infarction | 793 (12.8%) | 2366 (12.7%) | 0.2 |
| Unstable angina | 397 (6.4%) | 1172 (6.3%) | 0.3 |
| Angina pectoris | 962 (15.5%) | 2840 (15.3%) | 0.6 |
| Heart failure | 504 (8.1%) | 1496 (8.0%) | 0.3 |
| Atrial fibrillation | 607 (9.8%) | 1802 (9.7%) | 0.3 |
| Stroke | 615 (9.9%) | 1918 (10.3%) | 1.1 |
| Peripheral artery disease | 355 (5.7%) | 1099 (5.9%) | 0.6 |
| Chronic kidney disease | 71 (1.1%) | 224 (1.2%) | 0.4 |
| **Microvascular complications** | | | |
| Microvascular complications | 2276 (36.7%) | 6894 (37.0%) | 0.6 |
| Severe hypoglycemia | 31 (0.5%) | 105 (0.6%) | 0.7 |
| Lower limb amputations | 25 (0.4%) | 81 (0.4%) | 0.4 |
| **Glucose-lowering drugs** | | | |
| Metformin | 4898 (78.9%) | 15 009 (80.6%) | 3.5 |
| Sulphonylurea | 1494 (24.1%) | 4653 (25.0%) | 1.7 |
| DPP-4i | 1628 (26.2%) | 4812 (25.8%) | 0.7 |
| GLP-1RA | 1003 (16.2%) | 2784 (15.0%) | 2.7 |
| Meglitinides | 314 (5.1%) | 965 (5.2%) | 0.5 |
| Thiazolidinediones | 149 (2.4%) | 436 (2.3%) | 0.3 |
| Acarbose | 45 (0.7%) | 144 (0.8%) | 0.5 |
| Insulin | 2611 (42.1%) | 7795 (41.9%) | 0.3 |
| Short-acting | 1011 (16.3%) | 2970 (15.9%) | 0.8 |
| Intermediate-acting | 1182 (19.0%) | 3548 (19.1%) | 0.0 |
| Premixed insulin | 709 (11.4%) | 2127 (11.4%) | 0.0 |
| Long-acting | 1011 (16.3%) | 2980 (16.0%) | 0.6 |
| **CV risk treatment** | | | N/A |
| Low-dose aspirin | 6207 (100.0%) | 18 621 (100.0%) | |
| Statins | 2683 (43.2%) | 8000 (43.0%) | 0.4 |
| Antihypertensives | 4770 (76.8%) | 14 397 (77.3%) | 0.9 |
| ACE inhibitors | 5627 (90.7%) | 16 901 (90.8%) | 0.3 |
| ARB | 2564 (41.3%) | 7718 (41.4%) | 0.2 |
| ARB | 2712 (43.7%) | 8135 (43.7%) | 0.0 |
| Dihydropyridines | 2444 (39.4%) | 7308 (39.2%) | 0.2 |
| Thiazides | 552 (8.9%) | 1637 (8.8%) | 0.3 |
| Beta blockers | 3198 (51.5%) | 9533 (51.2%) | 0.5 |

(Continues)
TABLE 1 (Continued)

| Drug Class                     | Dapagliflozin N = 6207 | oGLD N = 18 621 | Standardized difference (%)a |
|--------------------------------|------------------------|-----------------|-----------------------------|
| Loop diuretics                 | 1070 (17.2%)           | 3228 (17.3%)    | 0.2                         |
| Aldosterone antagonists        | 427 (6.9%)             | 1260 (6.8%)     | 0.4                         |
| Warfarin                       | 436 (7.0%)             | 1336 (7.2%)     | 0.5                         |
| Receptor P2Y12 antagonists     | 424 (6.8%)             | 1279 (6.9%)     | 0.1                         |

All numbers in parenthesis are percentage if not stated otherwise.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CV, cardiovascular; DPP-4i, dipeptidyl-peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide-1 receptor agonists; oGLD, other glucose lowering drugs; SD, standard deviation; SGLT-2i, Sodium-glucose-cotransporter-2-inhibitors.

aStandardized difference of >10% is considered to represent a non-negligible group imbalance.

infrastructure (eg., more than three-fold healthcare costs and insurance-based healthcare than in the present study). They also concluded that the lower hospital healthcare cost associated with dapagliflozin treatment was offset by the higher drug costs. The present study evaluated a larger, well-matched population (based on 96 clinical and cost variables at baseline, using propensity score matching) with a longer duration of follow-up, thus providing important additional detailed insights beyond those from the US study.

The present study is based on the cumulative healthcare costs reported to authorities by healthcare providers for reimbursement purposes, that is, DRG costs for hospital visits and the historic costs of drugs dispensed by the pharmacy. This analysis was based on historic data and on the cost of drugs and procedures, and no updated costs to reflect modern pricing have been used. Consequently, total healthcare cost savings could be different if updated with a lower drug cost. In addition, the costs to hospitals for specific procedures might vary over time, but this is unlikely to vary as much as drug costs. Moreover, the variation in costs for specific procedures would impact both groups and have little impact on between-group differences in hospital healthcare costs. However, as all costs in this study are historic, the difference in hospital and drug costs could be considered conservative estimates.

Unlike cost-effectiveness analyses, the analysis reported here does not include a measure of the outcomes, for example, Quality Adjusted Life Years (QALYs). However, as previously shown in a DECLARE-like population, treatment with dapagliflozin has beneficial CV effects compared with treatment with oGLDs, and this would lead to a QALY benefit. When considered along with this QALY benefit, the cost neutrality between dapagliflozin and oGLDs observed in this study indicates that dapagliflozin is cost-effective compared with oGLDs.

| Drug Class                     | Baseline costs (US$) | 12-month costs (US$) | 30-month costs (US$) |
|--------------------------------|----------------------|----------------------|----------------------|
|                                | Dapa                 | oGLD                 | Dapa                 | oGLD                 | Diff. 95%CI | p-value  |
| Total healthcare cost          | 1014                 | 979                  | 4968                 | 5054                 | –86 –351 to 224 | .500     |
| Hospital costs                 | 729                  | 705                  | 3136                 | 3456                 | –321 –587 to 19 | .028     |
| CV and diabetes                | 374                  | 378                  | 1410                 | 1569                 | –160 –303 to 2  | .048     |
| Heart failure                  | 29                   | 27                   | 101                  | 142                  | –40 –82 to 1   | .064     |
| Myocardial infarction          | 32                   | 29                   | 100                  | 153                  | –53 –107 to 4  | .036     |
| Stroke                         | 49                   | 38                   | 121                  | 113                  | 8 –34 to 55    | .772     |
| Kidney                         | 6                    | 20                   | 55                   | 86                   | –31 –76 to 32  | .260     |
| Other                          | 355                  | 327                  | 1726                 | 1887                 | –161 –333 to 61| .148     |
| Drugs costs                    | 285                  | 274                  | 1832                 | 1597                 | 235 202 to 272 | <.001    |
| Glucose-lowering drugs         | 186                  | 176                  | 1422                 | 1161                 | 262 233 to 289 | <.001    |
| Dapagliflozin                  | 0                    | 0                    | 648                  | 19                   | 629 621 to 639 | <.001    |
| DPP-4i                         | 29                   | 29                   | 103                  | 194                  | –91 –98 to 84  | <.001    |
| GLP-1RA                        | 48                   | 45                   | 201                  | 422                  | –221 –241 to 203| <.001    |
| Insulin                        | 87                   | 85                   | 372                  | 434                  | –62 –79 to 44  | <.001    |
| Other GLD                      | 22                   | 17                   | 99                   | 91                   | 7 3 to 12     | <.001    |
| Other drugs                    | 99                   | 98                   | 410                  | 437                  | –27 –40 to 12  | <.001    |

Abbreviations: CV, cardiovascular; dapa, dapagliflozin; DPP-4i, dipeptidyl-peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonists; oGLD, other glucose-lowering drugs; SGLT-2i, sodium glucose-cotransporter-2-inhibitor.
4.1 | Strengths of the study

This was a population-based, nationwide, real-world observational study that provides a high external validity and a large enough population to enable propensity-score matched analyses; few patients initiating dapagliflozin were lost (n = 379; 6%) during the matching process (Figure 1). The national register used, from an established and complete public healthcare system, included records of full coverage for hospitalizations, for filled drug prescriptions and for cause of death. In addition, cardiovascular diagnoses have been validated in the Swedish hospital care registry, showing high validity.40

4.2 | Limitations of the study

There are a number of important limitations to the current analysis. Because of the observational nature of the present study, causal relationships cannot be fully investigated as the presence of confounding factors such as selection bias or lack of available variables, impacting the CV risk at baseline, cannot be fully excluded. The close matching on a large number of essential variables ensures that some confounding factors were controlled for, but even propensity score matching does not eliminate all potential confounding, for example, residual confounding by indication. Furthermore, the present work provides no information concerning laboratory measurements, lifestyle parameters, primary healthcare data, socioeconomic data or duration of diabetes (where a proxy for time since diagnosis was used, matching for age at index date, time since first registered GLD treatment and classes of GLD at baseline).

The results of the current analysis are representative only of patients in a DECLARE-like population in Sweden and, therefore, cannot be extended to all patients with T2D in other countries. In addition, we had no information concerning emigration, which would mean that we will underestimate the cost for those who emigrated during follow-up. It has been suggested that primary analyses should be performed in single databases and discussed in the context of cross-national comparisons.41 We would, therefore, encourage multinational analyses similar to the DECLARE-like study presented here to be performed using healthcare registry data from across the world.17,32

As this was a cost study, the effects of mortality have not been fully accounted for. As a result of this, the lower mortality rate associated with initiation of dapagliflozin rather than an oGLD11 will have increased the healthcare costs for dapagliflozin as more patients remained alive, while the individual clinical benefit for each patient remaining alive is not accounted for.

Finally, information on primary healthcare costs, indirect costs, including sick leave, and other costs associated with CV disease and T2D were not captured. It is estimated that primary healthcare costs and indirect costs for T2D patients account for approximately 25%2 and 35%42 of total healthcare-related cost, respectively. Assuming that hospital and primary healthcare resources are positively correlated, the present study may have underestimated the cost differences.

In summary, several important limitations might have contributed to an underestimation of the favourable healthcare cost associated with dapagliflozin compared with an oGLD.

In conclusion, in this nationwide, observational study, initiation of dapagliflozin was associated with significantly lower hospital healthcare costs compared with initiation of oGLDs, mainly driven by lower costs for CV- and T2D-related care. These lower hospital healthcare costs were balanced by higher drug costs for dapagliflozin. However, a lower use of other costly GLDs was observed in patients initiating dapagliflozin. These results indicate that dapagliflozin, having well documented clinical benefits, can be prescribed to patients with T2D without increasing the total cost of healthcare. The observational nature of the study did not allow full exploration of causal relationships, because of the risk of confounding, and further studies are encouraged.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors participated in the research design. M. T. performed data management and statistical analyses after discussion with all authors. All authors participated in data interpretation and in writing the manuscript. All authors took final responsibility in the decision to submit for publication. All authors are guarantors of the manuscript.

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REFERENCES

1. IDF Diabetes Atlas Eighth Edition 2017. International Diabetes Federation. Available at http://www.idf.org/diabetesatlas. Published 2017. Accessed April 1, 2019.
2. Nathanson D, Sabale U, Eriksson JW, et al. Healthcare cost development in a type 2 diabetes patient population on glucose-lowering drug treatment: a Nationwide observational study 2006–2014. Pharmacoecon Open. 2018:2:393-402.
3. Norhammar A, Bodegard J, Nystrom T, Thuresson M, Eriksson JW, Nathanson D. Incidence, prevalence and mortality of type 2 diabetes requiring glucose-lowering treatment, and associated risks of cardiovascular complications: a nationwide study in Sweden, 2006-2013. Diabetologia. 2016;59:1692-1701.
4. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016:375:1834-1844.
5. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016:375:311-322.
6. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017:377:644-657.
7. Wiviott SD, Raz I, Bonaca MP, et al; DECLARE–TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380:347-357.
8. Zelniker TA, Wiviott SD, Raz I, et al. 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. 2019;393:31-39.
9. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117-2128.
10. Birkeland KI, Jorgensen ME, Carstensen B, et al. Cardiovascular mortality and morbidity in patients with type 2 diabetes following initiation of sodium-glucose co-transporter-2 inhibitors versus other glucose-lowering drugs (CVD-REAL Nordic): a multinational observational analysis. Lancet Diabetes Endocrinol. 2017;5:709-717.
11. Norhammar A, Bodegard J, Nystrom T, Thuresson M, Nathanson D, Eriksson JW. Dapagliflozin and cardiovascular mortality and disease outcomes in a population with type 2 diabetes similar to that of the DECLARE-TIMI 58 trial: a nationwide observational study. Diabetes Obes Metab. 2019;21:1136-1145.
12. Persson F, Nystrom T, Jorgensen ME, et al. Dapagliflozin is associated with lower risk of cardiovascular events and all-cause mortality in people with type 2 diabetes (CVD-REAL Nordic) when compared with dipeptidyl peptidase-4 inhibitor therapy: a multinational observational study. Diabetes Obes Metab. 2018;20:344-351.
13. Eriksson JW, Norhammar A, Bodegard J, et al. Dapagliflozin is associated with lower risk of hospitalization for kidney disease, heart failure and all-cause death compared to DPP-4i: CVD-REAL Nordic. 53rd EASD Annual Meeting, 11–15 September 2017, Lisbon, Portugal, 2017. https://www.easd.org/virtualmeeting/home.html#resources/dapagliflozin-compared-to-dpp4i-treatment-is-associated-with-lower-risk-of-kidney-disease-heart-failure-and-all-cause-death-cvd-real-nordic. Accessed April 1, 2019.
14. Furtado RHM, Bonaca MP, Raz I, et al. Dapagliflozin and cardiovascular outcomes in patients with type 2 diabetes and prior myocardial infarction: a sub-analysis from DECLARE TIMI-58 trial. Circulation. 2019;139:2516-2527.
15. Kato ET, Silverman MG, Mosenzon O, et al. Effect of Dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. Circulation. 2019;139:2528-2536.
16. Verma S, McMurray JCV. The serendipitous story of SGLT2 inhibitors in heart failure: new insights from DECLARE-TIMI 58. Circulation. 2019;139:2537-2541.
17. Kosiборода M, Lam CSP, Kohsaka S, et al. Cardiovascular events associated with SGLT-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL 2 study. J Am Coll Cardiol. 2018;71:2628-2639.
18. Bailey CJ, Gross JL, Pieters A, Bastien A, List JF. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. Lancet. 2010;375:2223-2233.
19. Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycaemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes Care. 2010;33:2217-2224.
20. Henry RR, Murray AV, Marmolejo MH, Hennicken D, Ptaszynska A, Kato ET, Silverman MG, Mosenzon O, et al. Effect of Dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. Circulation. 2019;139:2528-2536.
21. Verma S, McMurray JCV. The serendipitous story of SGLT2 inhibitors in heart failure: new insights from DECLARE-TIMI 58. Circulation. 2019;139:2537-2541.
22. Henry RR, Murray AV, Marmolejo MH, Hennicken D, Ptaszynska A, Kato ET, Silverman MG, Mosenzon O, et al. Effect of Dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. Circulation. 2019;139:2528-2536.
23. Lie JB, Gross JL, Pieters A, Bastien A, List JF. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. Lancet. 2010;375:2223-2233.
24. Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycaemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes Care. 2010;33:2217-2224.
25. Henry RR, Murray AV, Marmolejo MH, Hennicken D, Ptaszynska A, List JF. Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomised controlled trial. Int J Clin Pract. 2012;66:446-456.
26. List JF, Woo V, Morales E, Tang W, Fiedorek FT. Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. Diabetes Care. 2009;32:650-657.
27. Mathieu C, Ranetti AE, Li D, et al. Randomized, double-blind, phase 3 trial of triple therapy with Dapagliflozin add-on to Saxagliptin plus metformin in type 2 diabetes. Diabetes Care. 2015;38:2009-2017.
28. Nauk MA, Del Prato S, Meier JJ, et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week,
24. Rosenstock J, Vico M, Wei L, Salsali A, List JF. Effects of dapagliflozin, an SGLT2 inhibitor, on HbA1C, body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. Diabetes Care. 2012;35:1473-1478.

25. Strojek K, Yoon KH, Hruba V, Elze M, Langkilde AM, Parikh S. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. Diabetes Obes Metab. 2011;13:928-938.

26. Wilding JP, Norwood P, T’joen C, Bastien A, List JF, Fiedorek FT. A study of dapagliflozin in patients with type 2 diabetes receiving high doses of insulin plus insulin sensitizers: applicability of a novel insulin-independent treatment. Diabetes Care. 2009;32:1656-1662.

27. Wilding JP, Woo V, Soler NG, et al. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. Ann Intern Med. 2012;156:405-415.

28. Wiviott SD, Raz I, Bonaca MP, et al. The design and rationale for the Dapagliflozin effect on cardiovascular events (DECLARE)-TIMI 58 trial. Am Heart J. 2018;200:83-89.

29. Birkeland KI, Bodegard J, Norhammar A, et al. How representative of a general type 2 diabetes population are patients included in cardiovascular outcome trials with SGLT2 inhibitors? A large European observational study. Diabetes Obes Metab. 2018;20:1:e00036. https://doi.org/10.1111/dob.13612.

30. Persson F, Bodegard J, Lahtela JT, et al. Different patterns of second-line treatment in type 2 diabetes after metformin monotherapy in Denmark, Finland, Norway and Sweden (D360 Nordic): a multinational observational study. Endocrinol Diabetes Metab. 2018;2:e00036.

31. Lindh A, Persson F, Sobocki P, Bodegard J, Lindarck N. Nordic longitudinal data from electronic medical records and full population national registers: unique opportunities for new insights in benefit of diabetes patients. Value Health. 2015;18:A726.

32. Kosiborod M, Cavender MA, Fu AZ, et al. 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. 2017;136:249-259.

33. Eriksson JW, Bodegard J, Nathanson D, Thuresson M, Nystrom T, Norhammar A. Sulphonylurea compared to DPP-4 inhibitors in combination with metformin carries increased risk of severe hypoglycaemia, cardiovascular events, and all-cause mortality. Diabetes Res Clin Pract. 2016;117:39-47.

34. Nyström T, Bodegard J, Nathanson D, Thuresson M, Norhammar A, Eriksson JW. Second line initiation of insulin compared with DPP-4 inhibitors after metformin monotherapy is associated with increased risk of all-cause mortality, cardiovascular events, and severe hypoglycaemia. Diabetes Res Clin Pract. 2017;123:199-208.

35. Normand ST, Landrum MB, Guadagnoli E, et al. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. J Clin Epidemiol. 2001;54:387-398.

36. Sekhon J. Multivariate and propensity score matching software with automated balance optimization. J Stat Softw. 2011;42:1-52.

37. R: A Language and Environment for Statistical Computing [Computer Program]. Vienna, Austria: R Foundation for Statistical Computing; 2015. http://www.R-project.org/. Accessed April 1, 2019.

38. Parker ED, Wittbrodt ET, McPheeters JT, Frias JP. Comparison of healthcare resource utilization and costs in patients with type 2 diabetes initiating dapagliflozin versus sitagliptin. Diabetes Obes Metab. 2019;21:227-233.

39. Socialstyrelsen. Weight Lists for NordDRG. The National Board of Health and Welfare. Available at https://www.socialstyrelsen.se/klassificeringochkoder/norddrg/vikter. Published 2019. Accessed April 23, 2019.

40. Ludvigsson JF, Andersson E, Ekborn A, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.

41. Raschi E, Poluzzi E, Fadini GP, Marchesini G, De Ponti F. Observational research on sodium glucose co-transporter-2 inhibitors: a real breakthrough? Diabetes Obes Metab. 2018;20:2711-2723.

42. Bommer C, Heesemann E, Sagalova V, et al. The global economic burden of diabetes in adults aged 20-79 years: a cost-of-illness study. Lancet Diabetes Endocrinol. 2017;5:423-430.

SUPPORTING INFORMATION

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

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