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|  | Clinical Study Report Synopsis |
|  | Drug Substance | Dapagliflozin |
|  | Study Code | D1690R00015 |
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| **Patient characteristics and cardiovascular and mortality outcomes in patients with high cardiovascular risk and type 2 diabetes mellitus initiating treatment with sodium-glucose co-transporter-2 inhibitors and other antidiabetic medications** |
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| Study dates: | First subject enrolled: 30 Nov 2017Last subject last visit: 31 Dec 2019 |
| Phase of development: | Therapeutic use (IV) |
| International Co-ordinating Investigator:  |  |
| Sponsor’s Responsible Medical Officer: |  |
|  |  |
| This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.  |
| This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object. |

Study centre(s)

Number of centres, countries: 17

Publications

1. Kidney outcomes associated with use of SGLT2 inhibitors in real-world clinical practice (CVD-REAL 3): a multinational observational cohort study. Heerspink, HJL, Karasik A, Thuresson M, Melzer-Cohen C, Chodick G, Khunti K. [*Lancet Diabetes & Endocrinology.* 2019;8:27-35. Doi : https://doi.org/10.1016/S2213-8587(19)30384-5.](file:///%5C%5Cspringernature.com%5CLondon%5CPharma%5CClients%5CAstraZeneca-DAPA%5CLIVE%20Projects%5CAd%20Hoc%20Projects%5CASZGBDP102348_DAPA%20bibliography%20and%20email%5CApril%5CLancet%20Diabetes%20%26%20Endocrinology.%202019%3B8%3A27-35.%20Doi%C2%A0%3A%20https%3A%5Cdoi.org%5C10.1016%5CS2213-8587%2819%2930384-5.)

2. Rates of myocardial infarction and stroke in patients initiating treatment with SGLT2-inhibitors versus other glucose-lowering agents in real-world clinical practice: Results from the CVD-REAL study. Kosiborod M, Birkeland KI, Cavender MA, Fu AZ, Wilding JP, Khunti K, Holl RW, Norhammar A, Jørgensen ME, Wittbrodt ET, Thuresson M, Bodegård J, Hammar N, Fenici P; CVD-REAL Investigators and Study Group. [*Diabetes Obes Metab.* 2018 Aug;20(8):1983-1987. doi: 10.1111/dom.13299. Epub 2018 Apr 17.](https://www.ncbi.nlm.nih.gov/pubmed/?term=Rates+of+myocardial+infarction+and+stroke+in+patients+initiating+treatment+with+SGLT2-inhibitors+versus+other+glucose-lowering+agents+in+real-world+clinical+practice%3A+Results+from+the+CVD-REAL+study.)

3. Lower cardiovascular risk associated with SGLT-2i in more than 400,000 patients: The CVD-REAL 2 study. Kosiborod M, Lam CSP, Kohsaka S, Kim DJ, Karasik A, Shaw J, Tangri N, Goh SY, Thuresson M, Chen H, Surmont F, Hammar N, Fenici P; CVD-REAL Investigators and Study Group. [*J Am Coll Cardiol*. 2018 Mar 7; 71 (23). pii: S0735-1097(18)33528-9. doi: 10.1016/j.jacc.2018.03.009. [Epub ahead of print]](https://www.ncbi.nlm.nih.gov/pubmed/?term=10.1016%2Fj.jacc.2018.03.009)*.*

4. 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. Persson F, Nyström T, Jørgensen ME, Carstensen B, Gulseth HL, Thuresson M, Fenici P, Nathanson D, Eriksson JW, Norhammar A, Bodegard J, Birkeland KI. [*Diabetes Obes Metab*. 2018 Feb;20(2):344-351. doi: 10.1111/dom.13077.](https://www.ncbi.nlm.nih.gov/pubmed/28771923)

5. 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. Birkeland KI, Jørgensen ME, Carstensen B, Persson F, Gulseth HL, Thuresson M, Fenici P, Nathanson D, Nyström T, Eriksson JW, Bodegård J, Norhammar A. [*Lancet Diabetes Endocrinol*. 2017 Sep;5(9):709-717. doi: 10.1016/S2213-8587(17)30258-9.](https://www.ncbi.nlm.nih.gov/pubmed/28781064)

6. Lower risk of heart failure and death in patients initiated on SGLT-2 inhibitors versus other glucose-lowering drugs: The CVD-REAL Study. Kosiborod M, Cavender MA, Fu AZ, Wilding JP, Khunti K, Holl RW, Norhammar A, Birkeland KI, Jørgensen M, Thuresson M, Arya N, Bodegård J, Hammar N, Fenici P; CVD-REAL Investigators and Study Group. *Circulation*. 2017;136:249–259.

7. Risk of cardiovascular events and death associated with initiation of SGLT2 inhibitors compared with DPP-4 inhibitors: an analysis from the CVD-REAL 2 multinational cohort study. Kohsaka S, Lam CSP, Kim DJ, Cavender MA, Norhammar A, Jørgensen ME, Birkeland KI, Holl RW, Franch-Nadal J, Tangri N, Shaw JE, Ilomäki J, Karasik A, Goh SY, Chiang CE, Thuresson M, Chen H, Wittbrodt E, Bodegård J, Surmont F, Fenici P, Kosiborod M, for the CVD-REAL 2 Investigators and Study Group. *Lancet Diab Endocrinol.* 2020;8(7):606-615.

8. Sodium-glucose cotransporter 2 inhibitors compared with other glucose-lowering drugs in Japan: Subanalyses of the CVD-REAL 2 Study. Kohsaka S, Takeda M, Bodegård J, Thuresson M, Kosiborod M, Yajima T, Wittbrodt E, Fenici P. *J Diabetes Investig*. 2020.doi: 10.1111/jdi.13321. [Epub ahead of print].

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

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| --- | --- | --- | --- |
| Primary | Descriptive | To describe the characteristics, including cardiovascular medications and morbidity, of patients with T2DM initiating use of SGLT-2i and DPP-4i, SU, GLP-1 RA and other standard of care treatments as well as a group of matched comparators, respectively in clinical practice to identify baseline variables that are different between the treatment groups. | Patient characteristics, including cardiovascular medications and morbidity |
| Primary | Descriptive | To describe the characteristics, including cardiovascular medications and morbidity, of patients with T2DM at high baseline risk for CV outcomes initiating use of SGLT-2i and DPP-4i, SU, GLP-1 RA and other standard of care treatments as well as a group of matched comparators, respectively, in clinical practice to identify baseline variables that are different between the treatment groups | Patient characteristics, including cardiovascular medications and morbidity |
| Primary | Descriptive | To describe the distribution of characteristics of patients, including cardiovascular medications and morbidity, by different diabetes medications in the group of other standard of care treatments and matched comparators. | Distribution of characteristics of patients, including cardiovascular medications and morbidity |
| Primary | Descriptive | To describe which diabetes medications patient initiating SGLT-2i used when initiating SGLT-2i use.  | Specific diabetes medications  |
| Primary | Descriptive | To describe the incidence of hospitalisation for CV events (including heart failure) and the mortality rate for both all-causes death and for CV related death, respectively, among patients with T2DM who initiate treatment with SGLT-2i and DPP-4i, SU, GLP-1 RA and other standard of care treatments as well as the group of matched comparators by baseline risk for CV outcomes. | Incidence of hospitalisation for CV events (including heart failure) and the mortality rate for both all-causes death and for CV related death, |
| Primary | Descriptive | To calculate the propensity scores for the groups (new users of SGLT-2i and DPP-4i, SU, GLP-1 RA and other standard of care treatments and the group of matched comparators respectively) and evaluate the possibilities for matching comparators. | Propensity scores |
| Primary | Comparative | To compare the risk for hospitalization for specific CV events (including heart failure) and mortality, both all-cause mortality and CV related mortality between patients with T2DM treated with SGLT-2 inhibitors as a class or a specific SGLT-2i substance versus an active comparison group. | Risk for hospitalization for specific CV events (including heart failure) and mortality, both all-cause mortality and CV related mortality |
| Secondary | Descriptive | To describe the proportion of patients switching to another diabetic medication class during follow up and the time from index date to the switch in new users of SGLT-2i and DPP-4i, SU, GLP-1 RA and other standard of care treatments as well as matched comparators, respectively.  | The proportion of patients switching to another diabetic medication class during follow up and the time from index date to the switch |
| Secondary | Descriptive | To describe the characteristics of patients with T2DM initiating use of SGLT-2i and DPP-4i, SU, GLP-1 RA and other standard of care treatments as well as a group of matched comparators, for patients with concomitant use of metformin to identify baseline variables that are different between the treatment groups | Patient characteristics for those with T2DM initiating use of SGLT-2i and DPP-4i, SU, GLP-1 RA and other standard of care treatments as well as a group of matched comparators |
| Secondary | Descriptive | To calculate the propensity scores for the groups (new users of SGLT-2i and DPP-4i, SU, GLP-1 RA and other standard of care treatments and the group of matched comparators respectively) with concomitant use of metformin and evaluate the possibilities for matching comparators | Propensity scores for the groups (new users of SGLT-2i and DPP-4i, SU, GLP-1 RA and other standard of care treatments and the group of matched comparators respectively) |
| Exploratory | Descriptive | To describe subpopulation by incremental CV risk profiles (comorbidities) at baseline and their evolution over the follow-up period | Baseline CV comorbidities and over the follow-up period |
| Exploratory | Descriptive | To describe over the follow up period any addition or change in the treatments, including within class changes, and rate of different combinations use | Addition and changes in treatments over the follow-up period |

Study design

This was a cohort study of patients with T2DM who are new users of SGLT-2 inhibitors and DPP-4i, SU, GLP-1RA and other standard of care treatments, respectively, in Sweden, United Kingdom and United States. In addition a group consisting of new users of different diabetic medications matched by index day and baseline characteristics were included.

The study period ranged from launch of the first SGLT-2i in each of the countries (November 2012 for Nordics and UK, March 2013 for US) and end at latest available data in each data source (during 2015 for UK and US databases and 2014 for Sweden). Dapagliflozin was the first SGLT-2i granted marketing approval by the European Commission (EC) for the treatment of T2DM in Europe in November 2012. The US Food and Drug Administration (FDA) approved canagliflozin as the first SGLT-2i for treatment of T2DM in March 2013, followed by dapagliflozin in January 2014 and empagliflozin in August 2014.

A new user of SGLT-2i, DPP-4i, SU or GLP-1 RA is defined as an individual receiving a prescription or filling a prescription of the mentioned diabetes medication classes with no issued/dispensed prescriptions of that medicine class during the preceding year. New users of the mixed group of other standard of care treatments as well as mixed group of matched comparators were defined as those receiving a prescription or filling a prescription of a specific drug with no issued/dispensed prescriptions of that drug during the preceding year. Those initiating metformin monotherapy use were not included in these groups.

The date of the first issued /filled prescription of the investigated medication classes (index medication group) during the study period was denoted the index date. Patients were followed from index date (inclusive) to the earliest of end of use of the index medication group, migration/leaving the practice/leaving the database, last date of data collection, death date or date of outcome. The availability of some of this information differs between databases and a definition for each database will be described.

Baseline characteristics including demographic and clinical characteristics were captured for patients in the year before the index date. Insulin use before index date was assessed during three months preceding the index date.

Target subject population and sample size

New users were defined as an individual with T2DM either receiving or filling a prescription of a SGLT-2i or DPP-4i, SU, GLP-1 RA and other standard of care treatments during the study period. Individuals with a previous issued/filled prescription of that medicine class during the preceding year (i.e. 365 before the index date) were not regarded as new users. The date of the first issued /filled prescription of the included medication classes during the study period was denoted the index date. The group consisting of other standard of care treatments was a mixture of diabetes medications initiated which was likely to have different compositions in different countries and depending on whether the patient was on oral diabetes medication only or on oral diabetes medication and insulin. This group included all diabetes medicines, allowing combinations and monotherapy use with the exception of metformin monotherapy and use of SGLT-2i. The class SGLT-2i included dapagliflozin, canagliflozin and empagliflozin. The group including comparators matched on baseline characteristics was matched on a 1:10 ratio with 10 matched comparators for each SGLT-2i user. These were matched on age at index date, gender, previous MI, previous stroke, previous heart failure, and use of CV-/glucose lowering drug treatment (e.g. ACE inhibitors or ARBs, high ceiling (LOOP) diuretics, diuretics, aldosterone antagonists, beta-blockers, SU, DPP-4i, and GLP-1 agonists) before the index date. In order to assess differences in patient characteristics by those on oral diabetes medication and those with insulin add-on, stratification was done by insulin use at index date described as in the exposure variable section.

High baseline CV risk was defined as a diagnosis of MI, unstable angina, stroke, evidence of multi-vessel coronary artery disease, evidence of single-vessel coronary artery disease, or occlusive peripheral artery disease before the index date. Other CV risk factors included obesity, dyslipidemia, hypertension, end stage renal disease and low socioeconomic status.

Since dapagliflozin and SGLT-2i are relatively recently introduced the population sizes were limited. Thus the main assessment of eligibility and comparability was conducted on medication class level to ensure a large enough population. Current numbers of SGLT-2i users are described below, dapagliflozin accounts for 80-100% of the patients on SGLT-2i in included European databases and 25-40% in the included US databases.

The current number of SGLT users and dapagliflozin users in each of the databases.

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| --- | --- | --- | --- | --- | --- |
|  | CPRD | THIN | Humedica | MarketScan | Sweden  |
| SGLT-2i users | 6684 | 4381 | 38,928 | 58,925 | ~3,000 |
| Dapagliflozin  | 5281 | 3790\* | 9,565 | 24,211 | ~3,000 |
| Updated to | 15/08/15\*\*\* | ~01/06/ 15  | 31/03/15 | 31/12/14 | 2014 |

\*a more recent count for dapagliflozin in THIN revealed: ~4,400 patients from data updated approx Sep/2015 \*\* Not available \*\*\* 15/6/15 (dapa)

Duration of treatment

Participants were followed from the index date until end of use of the index treatment or migration/leaving the practice/leaving the database, last date of data collection, death date (Sweden, UK) or date of outcome.

Statistical methods

Baseline characteristics were analysed using descriptive statistics. Categorical variables were described by frequencies and percentages, and mean ± standard deviation (SD) were used for continuous variables. The overall mean across all databases was a summary estimate of country-specific means, weighted according to the number of patients in each database. The proportion of exposure time contributed by individual agents was summarized both overall and by country.

A non-parsimonious propensity score for initiating SGLT-2i was developed separately for each country. All available variables in each country that could affect treatment assignment or outcomes were included in the propensity score (baseline comorbidity information was not available for Australia, although extensive medication data were available). Based on propensity scores, episodes of patients initiating SGLT-2i were matched 1:1 with episodes of initiating oGLD. The adequacy of matching was assessed by evaluating post-match standardized differences in patient characteristics. A non-negligible imbalance was considered if a >10% standardized difference occurred between the two groups post-match.

The incidence rate (IR) for each outcome was assessed by treatment group as the number of events divided by the total number of person-years at risk. The time to first event was compared between groups using Cox proportional hazards models, presented as hazard ratios (HR; 95%CI) for each outcome separately by country. The primary analysis used an intent-to-treat (ITT) approach where patients were followed from the start of index treatment until either occurrence of the first outcome event or the censoring date (whichever came first), regardless of whether index treatment was discontinued. The HRs for each endpoint from each individual country were then pooled for an overall weighted summary, using random-effects models with inverse variance weighting for each country.

Analyses for each outcome were also stratified according to the presence of prior CVD (defined as history of myocardial infarction, unstable angina, heart failure, atrial fibrillation, stroke, percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]); patient age and sex; history of heart failure, chronic kidney disease (CKD), or cancer; baseline use of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs), β-blockers, high ceiling diuretics, aldosterone antagonists, insulin, sulphonylureas, and statins.

Sensitivity analyses were performed in order to evaluate the stability of the findings: data for the primary analysis were additionally adjusted for multiple covariates (age, gender, frailty [defined as at least one hospitalization of at least three consecutive days during the year prior to index], history of heart failure, history of myocardial infarction, atrial fibrillation history, hypertension [if available], obesity/BMI [if available], duration of diabetes [if available], and use of ACEi or ARBs, β-blockers, Ca2+-channel blockers, statins, loop diuretics and thiazide diuretics); analyses were repeated using an on-treatment approach (follow-up censored at index treatment discontinuation).

Subject population

Patients with T2D were identified using standard diagnosis codes, except in Australia where this was based on physician or nurse educator clinical diagnosis of T2D. All episodes of new initiation of either SGLT-2i or other glucose-lowering drugs (oGLD) were selected within the country-specific date range for availability of SGLT-2i (Range: December 1, 2012 [Denmark] to May 1, 2016 [Taiwan]). Treatment initiation episodes were defined as written/dispensed prescription (as initial or add-on therapy) for any SGLT-2i or oGLD, including fixed-dose combinations, without any use of the same therapy during the preceding 12 months. Additional inclusion criteria were: age ≥18 years on the index date (defined as the prescription date for new initiation of an SGLT-2i or oGLD) and availability of historic data for more than 1-year in the database before the index date. Patients with type 1 or gestational diabetes were excluded. Patients were followed from the index date until migration/leaving the practice/database, last date of data collection, outcome date, or censoring date (Range: December 31, 2014 [Australia] to November 30, 2017 [Singapore]).

Summary of efficacy results

**Study population**

A total of 9,631,497 patients who newly initiated either SGLT-2i or oGLD treatment during the study period was identified; 477,894 (5.0%) were new users of SGLT-2i and 9,153,603 (95.0%) were new users of oGLD. Prior to propensity score matching, the patients who initiated SGLT-2i were younger, had slightly less prevalent heart failure, stroke and CKD at baseline and greater use of statins, ACEis and low-ceiling diuretics. Patients initiated on SGLT-2i were also more likely to be receiving other glucose-lowering drugs at baseline.

Following propensity score matching, there were 440,599 new initiators of SGLT-2i and 440,599 new initiators of oGLDs and the baseline characteristics were well-balanced. In both groups, the mean age was 58 years, 44% were women, and 31% had established CVD; 65% of patients received statins, 69% antihypertensive medications, and 76% metformin. Dapagliflozin contributed 60% of total exposure time, followed by canagliflozin (20%) and empagliflozin (14%), with other SGLT-2i providing smaller contributions. The DPP-4i class contributed to 25% of the oGLD exposure time, followed by insulin (18%), SUs (18%), metformin (13%) and TZDs (11%); other classes (GLP-1 RA, acarbose and metiglinides) contributed <10% each and made up the remainder.

For the countries included in this study, the proportion of new initiations that were SGLT-2i increased consistently over time; in North America, the proportion increased until 2015, with a slight decrease thereafter. When all countries included in this analysis were considered together, the proportion of new SGLT-2i initiation increased from around 3% of all new initiations in 2013, to about 15% in 2017.

**Outcomes**

The mean follow-up time for the primary ITT analysis was 396 days for SGLT-2i and 406 days for oGLDs initiations.

During 914,208 patient-years of follow-up there were 9121 events of HHF (3913 in the SGLT-2i group and 5208 in the oGLD group). Initiation of SGLT-2i was associated with a lower risk of HHF (ITT-unadjusted pooled HR: 0.66, 95%CI: 0.58–0.75; p<0.001). While there was heterogeneity, there were consistent associations between use of SGLT-2i and lower risk of heart failure in all of the 13 countries.

During 968,452 patient-years of follow-up, there were 10,252 events of all-cause death (3712 in the SGLT-2i group and 6540 in the oGLD group). Initiation of SGLT-2i was associated with a lower risk of all-cause death (ITT-unadjusted pooled HR: 0.52, 95%CI: 0.45–0.60; p<0.001). While there was heterogeneity, there were consistent associations between use of SGLT-2i and lower risk of all-cause death in all of the 13 countries.

For the composite outcome of HHF or all-cause death, there were 17,207 events (6932 in the SGLT-2i group and 10275 in the oGLD group) over 898,869 patient-years of follow-up. Initiation of SGLT-2i was associated with a lower risk of the composite of HHF or all-cause death (ITT-unadjusted pooled HR: 0.60, 95%CI: 0.53–0.68; p<0.001). While there was heterogeneity, there were consistent associations between use of SGLT-2i and lower risk of HHF or all-cause death in all of the 13 countries.

For myocardial infarction, there were 4880 events (2203 in the SGLT-2i group and 2677 in the oGLD group) over 916,305 patient-years of follow-up: initiation of SGLT-2i was associated with a lower risk of myocardial infarction (ITT-unadjusted pooled HR: 0.85, 95%CI: 0.78–0.92; p<0.001).

For stroke, there were 9111 events (3981 in the SGLT-2i group and 5130 in the oGLD group) over 913,571 patient-years of follow-up: initiation of SGLT-2i was associated with a lower risk of stroke (ITT-unadjusted pooled HR: 0.78, 95%CI: 0.72–0.85; p<0.001). There was no evidence of treatment heterogeneity across countries for the outcomes of myocardial infarction or stroke (p for interaction >0.07).

**Subgroup and sensitivity analyses**

Analyses of data stratified by baseline characteristics continued to favour SGLT-2i vs oGLD for the outcomes of HHF, all-cause death, composite of HHF or all-cause death, myocardial infarction and stroke across all subgroups, with very few significant interactions. Findings similar to the primary analyses were seen upon multivariable adjustment and in the on-treatment analyses.

Conclusion

The initiation of SGLT-2i as compared with other glucose-lowering drugs in routine clinical practice is associated with decreased risk of heart failure, all-cause death, myocardial infarction and stroke. The results of this large comparative effectiveness study with a broader, globally diverse population complement and extend the findings of completed randomized controlled trials.