

Research Article

A Comparative Effectiveness Protocol of SGLT-2 Inhibitors Versus DPP-2 Inhibitors in Type-2-diabetes in Jordan

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Abstract

Worldwide approximately 463 million people (9.3%) have type 2 diabetes mellitus. The disease is progressive and is linked to dire complications including cardiovascular disease, chronic kidney disease, retinopathy, nephropathy, not to mention increased mortality. Mitigating such risk, complications and improving health outcomes remains a priority management of diabetes. SGLT-2 inhibitors are newer and more costly class of drugs used for type 2 diabetes, however, their comparative effectiveness research against alternative drug classes has been insufficiently conducted, in particular amongst varied study populations. This retrospective observational cohort study protocol aimed to estimate the effectiveness of SGLT2-inhibitors using hospital administrative database. A cohort of adult patient with type-2 diabetes and prescription use of SGLT-2 inhibitors and a separate adult cohort with type 2-diabetes prescribed DPP4-inhibitors will be included from King Abdullah University Hospital (KAUH) database. Patients will be followed up from index-date and clinical outcomes of interest will include safety measures (diabetic ketoacidosis, severe hypoglycemia, lower limb amputation, bone fracture) and efficacy measures (cardiovascular events, renal disease, cardiovascular related mortality). Propensity score matching will be adopted to manage bias due to confounding in the comparative analysis of outcomes between SGLT2 (intervention group) versus DPP4-i (comparator group). Multivariable Cox-proportional hazard regression analysis will be used to estimate the independent association between SGLT2i and the time-to event of outcomes compared to DPP4i. This study of comparative analysis of SGLT2 versus DPP4-i will provide evidence that can enable the possibility of mitigating medication related adverse effects.

Keywords

Diabetes, DPP4-4i, SGLT-2i, Comparative-effectiveness

1. Introduction

Type two diabetes mellitus (T2DM) is a progressive disease with an insidious onset. The condition is presented by hyperglycemia, which is a result of dysfunction in insulin secretion,

insulin resistance or both. Chronic hyperglycemia, resulting from the disease, culminates into microvascular and macrovascular complications, which also encompasses retinopathy,

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nephropathy, neuropathy (microvascular), coronary heart disease, peripheral vascular disease and cerebrovascular disease (macrovascular) [1]. Globally, the incident and prevalence rate of T2DM is increasing rapidly; T2DM is the second highest prevalent disease worldwide [2]. In the Middle East and North Africa, approximately 54.8 million (12.8%) people are diagnosed with T2DM. In Jordan, the prevalence of T2DM has dramatically heightened and become a major public health concern, between 1994 and 2017 the T2DM prevalence went from 9% to 30% [3]. In Jordan, T2DM has been reported to be an epidemic with significant financial impacts.

Cardiovascular diseases are significant impediment in patients with type-2 diabetes mellitus [4]. Approximately, a third of type-2 diabetes patients experience cardiovascular-related events, including atherosclerosis, coronary heart disease, angina, myocardial infarction and stroke. Furthermore, 20% of T2DM deaths are attributed to CV complications [5]. The impact of high CV prevalence among T2DM is not limited to health outcomes, but it also results in a significant financial burden on healthcare systems worldwide [6]. In their systematic review, Einarson et al. discovered that in relation to type-2 diabetes patients void of cardiovascular diseases, once they developed cardiovascular events, this resulted in 112% rise in healthcare costs, with evidently stroke being the leading contributing event to the cost [6]. It is estimated that up to 50% of T2DM treatment cost results from hospitalisation, drug, and healthcare related to cardiovascular events. There are several pharmacological agents used to manage and control T2DM including sodium-glucose cotransporter-2 (SGLT-2) inhibitors, which were introduced in 2012 [7]. Internationally accessible SGLT-2 inhibitors include canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. Sodium-glucose co-transporter-2 inhibitors (SGLT-2i) are usually utilized as a second-line management for type-2 diabetes and, in addition to their glucose-lowering impact, SGLT-2i have the added valuable effect on weight, blood-pressure and lipid-levels [7, 8].

Observational studies have found that, in comparison to other antidiabetic agents, SGLT-2 inhibitor was able to cause a higher reduction in CV events and mortality among T2DM patients [9-13]. The administration of dapagliflozin or any sodium-glucose co-transporter-2 inhibitors has been linked to a 40-5% reduction in the event of all-cause mortality and a 30-40% reduction in the risk of heart-failure. Additionally, the utilization of dapagliflozin or any SGLT-2 inhibitor has found to lower the risk of 3-point MACE [9-12]. Dapagliflozin or any SGLT-2 inhibitor impact on the possibility of MI, stroke, and CV mortality has been steady, suggesting reduced risks.

In few of CV outcome studies, empagliflozin and canagliflozin were found to lower the events of unfavorable CV incidents among T2DM patients [8-11]. Both agents minimized the events of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke (these are part of a combined outcome termed as 3-point major cardiovascular events or MACE) by 14%. Moreover, empagliflozin lowered the probability of Myocardial infarction by 13% and the risk of all-cause deaths

and hospitalisation by 32-38%. Lastly, initial results from a research conducted in the United States of America observed that empagliflozin was linked to a 49% reduction in heart-failure events [13, 14]. However, of the emerging evidence from these studies has been inconsistent in establishing significant associations [10, 12]. Moreover, the patients that took part in these trials had cardiovascular morbidities and therefore the results may not be generalizable to the wider T2DM patients' population including those with no CV risk. Additionally, investigating empagliflozin clinical outcomes was carried out in studies where less than 10% of the population used empagliflozin or any SGLT-2 inhibitor. Thus, the observations may not be generalizable to empagliflozin medication takers. To our best awareness, insufficient studies have investigated outcomes (beneficial or otherwise) linked with the use of empagliflozin in real-world setting in many Middle-Eastern countries, and more acutely in Jordan. Given the fact that, in Jordan, T2DM is highly prevalent, and that empagliflozin is relatively new to the Jordanian market. There is a need to assess clinical outcomes of empagliflozin in real-life clinical settings. This non-interventional observational study aims to assess the clinical effectiveness and safety of empagliflozin or other SGLT2i as a compared with Inhibitors of dipeptidyl peptidase 4 (DPP4i). The study also aims to examine the extent of healthcare resource utilization of empagliflozin or any SGLT2i prescribed patients versus DPP4i prescribed patients. The results of this study could inform clinical decision-making, especially that SGLT2i are costly and highly priced. The main outcome of interest includes heart-failure, stroke, myocardial infarction and cardiovascular related mortality. Secondary outcomes of interest include end-stage renal failure, bone fracture, diabetic ketoacidosis, severe hypoglycemia, urinary tract infections or genitourinary infections and lower limb amputation.

2. Method

2.1. Study Design

A longitudinal retrospective observational cohort study will be planned, using patient-level electronic information. The outcomes will be studied for all the eligible included patients. This study will be carried out in King Abdullah University Hospital (KAUH) the largest hospital in the northern region of Jordan. The hospital is an educational hospital, and it serves approximately a million-population residing in Irbid, Mafraq, Ajloun and Jerash.

2.2. Study Population

Eligible patients for this study, are those who have a first eligible prescription (index-date) of empagliflozin, SGLT2 inhibitor or DPP-4 inhibitor between 1st of January 2012 and 31st of December 2021, and who were previously naïve. Patients should have been diagnosed with T2DM before the index-date,

and be of 18-years of age. Patients with type-1-diabetes, gestational diabetes, secondary diabetes and/or end-stage renal disease (ESRD) up to twelve- months preceding the index date, and a diagnosis of neoplasm up to five years pre-index will be excluded. All patients who have less than twelve months of computerized data pre-and-post index date will be excluded to ensure sufficient data for follow up. Electronic medical records will be accessed to retrieve data related to eligible patients' demographics, clinical characteristics including medication prescriptions, biometric measures and study outcomes of interest will be examined. In particular, diagnostic information in the computerized healthcare register is encoded using the International Statistical Classification of Diseases and Related Health Problems 10th Revision, ICD-10, whereas pharmaceutically related section of data has details on date of medical prescribing/dispensing, and also the ATC class of the medicine.

2.3. Intervention

The intervention (exposure) is defined as the initiation of empagliflozin and any SGLT2i, including fixed dose combination medicines with an SGLT-2 inhibitors and other medicines other than DPP-4 inhibitors. The follow up will set to occur from baseline of first-time-use of the therapy and ended at the earliest date of the following events:

- 1) The first occurrence of the study outcomes of interests
- 2) Patient death (if this occurred prior to study end date)
- 3) Patient end of continuous registration in the hospital database
- 4) Last date of prescription collection or date of drug discontinuation (i.e., no further medicine prescription within 90-days after the last day's supply).
- 5) End of the study - 31st December 2021.
- 6) Switching from SGLT-2 inhibitor (exposure-medicines) to DPP-4 inhibitors (control-medicine). This will also include the switching within the two drug classes, e.g., from being initiated on empagliflozin to being switched to dapagliflozin; or initiated on sitagliptin and switched to linagliptin. The addition of other glucose-lowering medications such as metformin or insulin will not determine the censoring of the follow up.

A grace phase of 100% of the duration of the latest supply will be incorporated in the utilization period to account for uncertainty linked to actual drug use trend. Overlapping supplies and grace periods will be combined as exposure periods.

2.4. Comparative Cohort Group

DPP4-i (Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin, Alogliptin) will be used as the comparators of clinical outcomes in the analysis due to the medicine class being utilized in the management of the same disease phase as SGLT2i in type-2-diabetes. Furthermore, most DPP4-i has lower risk of

cardiovascular outcomes and thus would form a viable comparator of reference medicine group. Fixed-dose grouped medicines with a DPP-4 inhibitor and another medicine other than a SGLT-2 inhibitor (main exposure) will be involved.

2.5. Clinical Outcomes

The study endpoint will be time to the first outcomes as examined from patients' medical records during follow up. All clinical outcomes related to safety (diabetic ketoacidosis, severe hypoglycemia, lower limb amputation, bone fracture) and efficacy measures (cardiovascular events, renal disease, cardiovascular related mortality) are of interest in this study. A secondary outcome will be a comparison of healthcare resource utilization between the study cohorts prescribed SGLT2i versus DPP4i.

2.6. Sample Size Calculation

The sample size was computed to identify a 20% or 30% reduce in the outcome rate (hazard ratio (HR) 0.8 or 0.7) with 80% power and 5% alpha level. Varying expected outcome event rates (0.5-3% per patient-year) are obtainable assuming that each patient will continue to have either two years, one year or six months of follow-up time. In an average of two-years follow-up sample size required would be 6,000-35,000, in the case of one-year average follow-up; 12,000-71,000 sample size would be needed and, lastly in the case of six months follow up; 24,000-142,000 sample would be needed, with an outcome rate, power and alpha-level as described earlier [15].

3. Statistical Analysis Plan

Descriptive analysis will be carried out, and demographic and clinical data will be presented as mean \pm standard deviation (Sd), median (interquartile ranges), numbers and percentages. Relevant statistical tests will be used to compare subgroups depending on type of data. For categorical data, group comparisons will be performed by Pearson chi-squared test.

For continuous data, Student's t-test will be considered after having checked for assumptions, alternatively Wilcoxon-Mann-Whitney will be used.

Propensity score matching will be used to reduce confounding in the comparative analysis of outcomes between SGLT2 (intervention group) versus DPP4-i (comparator group). Pairwise propensity score model between *a*) empagliflozin sub-cohort and DPP-4i sub-cohorts and *b*) any SGLT2 sub-cohort and DPP4-i sub-cohort, will be estimated using logistic regression including all outlined covariates. A one-to-one matching will be used using the nearest neighbor algorithm, and calipers of width of 0.2. If there are multiple potential matches available with DPP-4i prescribed patients, then comparator patients will be sorted (ascending) by absolute difference in the logit of the propensity score; the comparator on the

top of the list will be selected. In case of a tie, the choice will be made randomly.

Standardized difference will be used to examine balancing of covariates matching procedure. A standardized difference of a covariate of less than 0.1 between treatment groups in this study indicates a negligible difference in the mean or prevalence of the covariate. If larger standardized differences than 0.1 for some covariates exist after matching, they will be used in post-matching adjustments.

Multivariable Cox-proportional hazard regression analysis will be used to estimate the independent association between SGLT2i and the time-to event of outcomes compared to DPP4i after adjusting for propensity matched confounders. Statistical significance was accepted at $p < 0.05$. Propensity score matching will be done in a 1:1 ratio using the nearest neighbor algorithm, using calipers of width of 0.2.

A number of sensitivity analyses will be performed, stratified by patients with and without the following conditions:

- 1) Pre-existing congestive heart failure (CHF) in the 12 months prior to the index date
- 2) History of CV disease in the 12 months prior to the index date
- 3) History of CV disease or CHF event requiring recent hospitalization (during the last 60 days prior to index date).

Two additional subgroups analyses will also be performed on the basis of metformin use:

- 1) Subgroup 1: Use of metformin at or in the twelve months prior to the index date
- 2) Subgroup 2: Use of metformin only (no other glucose-lowering drugs) at or in the twelve months prior to the index date.

Lastly additional subgroup analysis will be conducted on the basis of empagliflozin initiation:

- 1) Subgroup 1: those starting with 10mg
- 2) Subgroup 2: those starting with 25mg

4. Discussion

A meta-analysis of a number of placebo-controlled trials had shown that a significant reduction in the risk of major adverse cardiac events (MACEs) occurred for SGLT2i prescribed patients with T2DM [16]. This effect has been suggested to be due to the impact of SGLT2i on reducing body weight, protective effect on the myocardium and their plausible reduction of the overload of intracellular sodium [17, 18]. Although randomized trials are the gold standard for assessing efficacy of a treatment, observational studies complement trial results by providing real-world treatment effectiveness. Thus, the study will add evidence base information on the efficacy and safety of SGLT2i in T2DM patients in clinical practice through the collection and analysis of retrospective electronic healthcare data, and clarify whether there are patient-related factors related to treatment effectiveness. Moreover, the choice of study design was based on the European Network of

Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study design frameworks for evaluating treatment interventions [19]. Findings from this study will complement the results of the EMPA-REG OUTCOME randomized clinical trial and will provide further insights on the use of empagliflozin and other SGLT-2 inhibitors in routine care in patients with T2DM in Jordanian population. The chosen methodology is applied to reduce confounding by indication, ensure reproducibility and maximize generalizability to the T2DM population in Jordan (which in turn aids in safe and effective market access).

5. Ethics and Dissemination

The study will be reviewed and ethical approval will be sought by the Institutional Review Board (IRB) of King Abdullah University Hospital (KAUH). Once the study is approved, access to data for the list of patients who were prescribed SGLT2 or DPP4i during study period will be obtained. The results of this study will be disseminated through conference proceedings and published in peer-reviewed journals.

Abbreviations

HbA1c	Hemoglobin A1C
BMI	Body Mass Index
HR	Hazard Ratio
T2DM	Type-2-diabetes Mellitus
CV	Cardiovascular
SGLT-2i	Sodium-glucose Transporter-2-inhibitors
MACE	Major Adverse Cardiovascular Events
mg	Milligram
MI	Myocardial Infraction
CHF	Congestive Heart Failure
DPP4-i	Dipeptidyl Peptidase 4 Inhibitors
Sd	Standard Deviation
KAUH	King Abdullah University Hospital
ESRD	End-stage Renal Disease
ICD-10	International Statistical Classification of Disease
ENCePP	The European Network of Centres for Pharmacoepidemiology & Pharmacovigilance
EMPA-REG	Empagliflozin

Author Contributions

Muna Adan: Conceptualization, Validation, Manuscript writing, Review and editing

Hodan Hersi: Conceptualization, Validation

Ayan Hag: Manuscript writing, Review and editing

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Conflicts of Interest

The authors declare no conflicts of interest.

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