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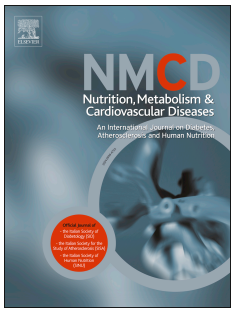

Adverse events with sodium-glucose co-transporter-2 inhibitors: a global analysis of international spontaneous reporting systems

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Adverse events with sodium-glucose co-transporter-2 inhibitors: a global analysis of international spontaneous reporting systems

Running title: Adverse events with SGLT2 inhibitors

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Abstract (250)

Background and Aims. We assessed post-marketing safety of sodium-glucose co-transporter-2 inhibitors (SGLT2-Is) by analyzing adverse events (AEs) reported in international pharmacovigilance databases.

Methods and Results. Eudravigilance, WHO-Vigibase (as of Feb 25, 2017) and the FDA Adverse Event Reporting System (FAERS, from 2004 to 2016 second quarter) were queried to extract AEs recording SGLT2-Is as suspect. Disproportionality analyses (case/non-case method) were performed in FAERS by calculating the reporting odds ratios (RORs) from System Organ Classes (SOCs) to Preferred Terms (PTs) (precise clinical entities). Potential signals were defined by statistically-significant ROR (lower limit of the 95% confidence interval - LL95%CI - >1) undetected by literature analysis (as of December 2016).

Results. SGLT2-Is were recorded in 7,972, 19,775, 11,137 reports (Eudravigilance, WHO-Vigibase and FAERS, respectively); in FAERS statistically significant ROR emerged for the following SOCs: “infections and infestations” (N=2,162; LL95%CI=3.25), “metabolism and nutrition disorders” (2,278; 1.36), “renal and urinary disorders” (1,665; 2.31), “reproductive system and breast disorders” (471; 4.85), “skin and subcutaneous tissue disorders” (1,136; 1.52). Skin toxicity emerged as potential signal (e.g., rash, photosensitivity, urticaria as PTs), both for SGLT2-Is as a class and as individual drugs. Severe adverse skin events (81 reports, 7% of the skin cases) mainly occurred in females aged 18-65 using SGLT2-Is as single antidiabetic regimen.

Conclusion. Among antidiabetics, SGLT2-Is are associated with higher reporting of infections, metabolism, renal and reproductive AEs, corroborating clinical trial evidence. Their large reporting patterns and the unexpected signal of skin toxicity justify active vigilance by clinicians and “real-time” monitoring by pharmacovigilance experts.

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Keywords: *gliflozins, sodium-glucose co-transporter-2 inhibitors, spontaneous reporting system, pharmacovigilance, disproportionality, skin toxicity*

Introduction

Pharmacological management of type 2 diabetes is entering a challenging era. Several classes of novel antidiabetic agents entered the market in the past decade: they have been tested not only for their ability to improve glycemic control, but also to demonstrate beneficial or at least neutral effects on cardiovascular (CV) outcomes [1].

Sodium-glucose co-transporter-2 inhibitors (SGLT2-Is), namely dapagliflozin, canagliflozin and empagliflozin are the latest glucose-lowering agents available, approved on the basis of their cardio-metabolic properties. In particular, clinically significant effect in reducing CV mortality was observed with empagliflozin (EMPA-REG OUTCOME trial) and canagliflozin (CANVAS program), although the putative mechanism is far to be elucidated [2].

However, the safety profile of SGLT2-Is is not fully characterized; while common adverse events (AEs) such urinary/genital tract infections (UTIs and GTIs, respectively) emerged from pre-approval phase, rare AEs such as ketoacidosis may escape detection in randomized clinical trials (RCTs) and case reports/series described in the literature are unlikely to reflect the entire safety spectrum [3]. Considering that clinical use is expected to increase exponentially along the years, monitoring of post-marketing AEs is a key aspect.

Spontaneous reporting systems (SRSs), owing to the large number of AEs, are essential to timely capture unpredictable and rare AEs, especially for recently-approved drugs, and represent a useful approach to monitor the safety of antidiabetic agents in unselected real-world patients with comorbidities and poly-pharmacotherapy *via* disproportionality approach [4-8]. In the present

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study, we queried international SRSs, namely the FDA Adverse Event Reporting System (FAERS), WHO-Vigibase and Eudravigilance to characterize the reporting pattern of SGLT2-Is and assess whether safety signals exist. Multiple SRSs offer a global perspective to map the entire spectrum of AEs across databases and verify whether differences exist in reporting pattern, while maintaining the individual peculiarities of each SRS.

Methods

Data sources and relevant peculiarities

The three SRSs differ as regards accessibility, data availability, catchment area, terminologies and coding systems to record AEs and drugs (**Appendix 1**). While it is important to exploit different databases to capture the largest population available, these databases cannot be simply aggregated due to the existence of redundancy (i.e., duplicate reports across SRSs). The key difference regards the possibility to download raw data and perform *ad hoc* disproportionality analyses, which is allowed only in FAERS (see below).

VigiBase (http://www.vigiaccess.org/) collects worldwide safety reports from health care professionals, pharmaceutical companies and patients); Eudravigilance is the European database of suspected AEs (www.adrreport.eu) collecting reports for authorized medicines in the European Economic Area, also including non-centrally-approved medicines; FAERS (https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugeffects/ucm082193.htm) is the FDA repository of AEs and medication errors spontaneously submitted by healthcare professionals, patients and manufacturers, gathering worldwide reports (including European reports potentially related to serious events and other non-US non-European data). In all databases, AEs are coded through the standardized Medical Dictionary for Regulatory Activities (MedDRA) terminology.

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Study design

The study was conceived as descriptive analysis (demographic information such as age and sex, and relevant frequencies of AEs) followed by comprehensive disproportionality approach. First, public released versions of Vigibase, Eudravigilance and FAERS [from the first quarter (Q1) of 2004 through Q2 of 2016] were used to create an overall case listing of AEs reported with the use of SGLT2-Is. These databases were queried using relevant active substances of approved SGLT2-Is, namely empagliflozin, dapagliflozin and canagliflozin (effective date of search in Vigibase and Eudravigilance: Feb 25, 2017).

Second, after gathering this overall picture, FAERS was mined to perform disproportionality analysis, as it allows customized statistical analyses after files are downloaded and processed for data quality, as previously described [9]. In summary, multistep automated strategies were applied to remove duplicates (i.e., reports with overlaps in 3 out of 4 key fields, namely event date, age, gender and Reporter Country), standardize drug names into active substances with relevant Anatomical Therapeutic Chemical (ATC) codes, and codify AEs through MedDRA terminology (version 19).

In order to control for major reporting bias and confounders, patients with diabetes were identified by restricting the analysis to spontaneous reports in which at least one antidiabetic agent was recorded (ATC code: A10), the so-called analysis by therapeutic area [10, 11], without considering recorded therapeutic indications because the extent of missing information (33% of total records).

Finally, we performed a *case/non-case* study, which can be viewed as a case-control analysis [12]. Cases were represented by AEs in which SGLT2-Is were mentioned by the reporter as suspect (“Primary Suspect” or “Secondary Suspect”); non-cases were all other AEs induced by other antidiabetic drugs. As a measure of disproportionality, the reporting odds ratio (ROR) with relevant 95% confidence interval (95%CI) was calculated [12]. ROR is a recognized

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pharmacovigilance approach to identify whether a given AE is reported more frequently than expected with a given drug; we considered statistically significant those cases with the lower limit of the 95%CI of the ROR >1, and at least five cases of interest reported (to reduce the likelihood of false positives). To this aim, PostgreSQL software version 9.5 was used.

A structured literature evaluation was undertaken to assess the novelty of the association (unexpectedness) (**Appendix 2**). The gathered evidence (MEDLINE search as of December 2016) was graded based on the strength (highest for systematic review; lowest for case report) and robustness (consistency of the data within the same piece of evidence in relation to the number of published studies): convincing clinical evidence was defined when AEs emerged from the majority of RCTs, including systematic reviews, with biological plausibility (i.e., the drug may directly or indirectly cause the clinical event via different postulated mechanisms). A potential signal was defined by drugs with disproportionality without convincing clinical evidence from the literature.

Disproportionality analyses in FAERS

Disproportionality approach was performed across the 5 levels of MedDRA hierarchy, which is multi-axial and helps to bring together similar medical conditions. AEs are codified at the Preferred Term (PT) level, which specifically identifies signs/symptoms of a given clinical entity (e.g., ketoacidosis); a given PT can be assigned to one or more High-Level Term [HLT], High-Level Group Term [HLGT] and System Organ Class (SOC) levels. Those SOCs emerging with disproportionality were further explored by analyzing relevant HLGTs, HLTs subordinated to HLGTs resulting in disproportionality and PTs subordinated to the HLTs resulting in disproportionality ("top-down" approach).

Different PTs can be also combined to define a specific clinical syndrome through an algorithmic approach known as Standardized MedDRA Query (SMQ). We defined *a priori* that only SMQs for severe events had to be used (i.e., a low-probability event with a high drug-

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attributable risk). It is anticipated here that only the SOC "skin and subcutaneous tissue disorders" emerged as potential safety signal. Therefore, relevant SMQ was "*Severe cutaneous adverse reactions*", including erythema multiforme, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Drug reaction with eosinophilia and systemic syndrome and acute generalized exanthematous pustolosis. The ROR was finally adjusted (Mantel-Haenszel correction) for co-reported drugs known to be strongly associated with severe skin toxicity [13-17] (**Appendix 3**).

Results

Descriptive analysis

Overall, Vigibase ranked first in terms of crude number of total reports submitted for SGLT2-Is, peaking 11,555 for canagliflozin. With the exception of dapagliflozin in Vigibase, the majority of reports recorded in FAERS and Eudravigilance were submitted by non-European Countries, especially Americas (**Table 1**). The reported Country was US in 83,5%, 94,6% and 85,2% of dapagliflozin, canagliflozin and empagliflozin reports, respectively. Most of reports occurred in patients aged 18-64, without a clear sex preponderance. For dapagliflozin all databases reported the highest percentage in this interval, ranging from 42,5 % to 50,6%. Similar data emerged for canagliflozin and empagliflozin.

"Infections and infestations", "renal and urinary disorders", "metabolism and nutrition disorders", "investigations", "general disorders and administration site conditions" and "gastrointestinal disorders" were the most frequently reported SOCs in all databases (**Appendix 4**). "Metabolism and nutrition disorders" was the SOC with the highest number of reports for all SGLT2-Is: it ranges from 19,4% to 41,9% for dapagliflozin, 20.7% to 40.1% for canagliflozin and 19,3% to 50,4% for empagliflozin. Other two relevant SOCs that reflect data from RCTs are "infections and infestations" and "renal and urinary disorders", with similar percentages. The former ranges from 18,2% to 25,1% for dapagliflozin, 19,9% to 22,9% for canagliflozin and 17,0%

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to 21,3% for empagliflozin. The latter varies between 13,0% (Vigibase-empagliflozin) and 21,2% (Eudravigilance-canagliflozin).

In FAERS, over the 13-year period, 8.238.509 raw reports were processed for drug codification and duplicate removal; 6.739.817 reports were retained, of which 345.498 included at least one antidiabetic drug. The distribution of reports across the various pharmacological classes is presented in **Appendix 5**. Overall, 11.828 reports were extracted with SGLT2-Is, of which 11.137 were finally retained (SGLT2-Is recorded as suspect).

Disproportionality analyses in FAERS

Considering SGLT2-Is as a class, statistically-significant ROR emerged in four SOCs: “infections and infestations” (N=2,162; ROR=3.41; 95%CI=3.25-3.58), “metabolism and nutrition disorders” (2,278; 1.43; 1.36-1.50), “renal and urinary disorders” (1,665; 2.44; 2.31-2.58), “reproductive system and breast disorders” (471; 5.36; 4.85-5.93), “skin and subcutaneous tissue disorders” (1,136; 1.62; 1.52-1.73) (**Figure 1**).

As regards active substances (**Table 2**), disproportionalities emerged for canagliflozin in the following SOCs: “infections and infestations” (ROR=3.51; 95%CI=3.31-3.73), “metabolism and nutrition disorders” (1.45; 1.37-1.53), ”renal and urinary disorders” (2.50; 2.35-2.67), ”reproductive system and breast disorders” (5.60; 4.98-6.30), ”skin and subcutaneous tissue disorders” (1.57; 1.45-1.70), ”social circumstances” (1.43; 1.18-1.74). Similar results emerged for dapagliflozin: ”infections and infestations” (3.15; 2.84-3.50), ”metabolism and nutrition disorders” (1.40; 1.27-1.55), ”renal and urinary disorders” (2.35; 2.09-2.63), ”reproductive system and breast disorders” (5.11; 4.17-6.27), ”skin and subcutaneous tissue disorders” (1.71; 1.50-1.94). An additional SDR was also detected for ”congenital, familial and genetic disorders” (2.16; 1.43-3.27). Data collected for empagliflozin showed a similar reporting pattern: statistically significant ROR for ”infections and infestations” (3.36; 2.93-3.86), ”metabolism and nutrition disorders” (1.38; 1.20-1.58), ”renal

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and urinary infections" (2.27; 1.94-2.66), "reproductive system and breast disorders" (4.42; 3.29-5.95), "skin and subcutaneous tissue disorders" (1.75; 1.47-2.08).

A synopsis of the literature appraisal is also provided in **Table 2**. The vast majority of RCTs are concordant in highlighting GTIs and UTIs as the most frequently reported AEs, likely depending on the mechanism of drug action. Accordingly, all SGLT2-Is emerged with disproportionalities for the SOC "infection and infestation". Results from RTCs showed also a high incidence of polyuria and glycosuria, which are strictly related to the osmotic diuresis induced by SGLT2-Is as well as vulvovaginitis, balanitis and prosthatitis. As expected, disproportionality analysis found statistically-significant RORs for the SOCs "renal and urinary disorders" and "reproductive system and breast disorders", for all SGLT2-Is.

Further analysis conducted at PT level revealed a high ROR for "fungal infection" (N= 838; ROR=25.62; 95%CI=22.24–29.50), "genital infection fungal" (135; 29.63; 14.52–60.48) and "vulvovaginal mycotic infection" (116; 23.45; 16.31–33.72). In addition, PTs included in HLT "female reproductive tract infection" such as "vulvovaginitis" and "vaginal infections" has significant ROR: the former has a ROR=25.87 (95%CI=5.67–118.11); the latter has a ROR=17.78 (95%CI=10.79–29.30). Moreover, within the SOC "metabolism and nutrition disorders", some relevant PTs emerged with high ROR: "diabetic ketoacidosis" (N=875; ROR=10.49; 95% CI=9.66-11.39), "ketoacidosis" (163;6.42; 5.40-7.64) and "dehydration" (3.96; 3.59-4.38). The full list of PTs with relevant disproportionality for gliflozins as a class as well as for individual agents is provided in **Appendix 6**.

Disproportionality for "Skin and subcutaneous tissue disorders" was unexpected because cutaneous events were not described in RCTs. We found statistically-significant RORs for 12 PTs, including: "rash" (N=317; ROR=2.97; 95%CI=2.64–3.33), "pruritus" (161, 1.65; 1.41-1.94), "urticaria" (130, 1.87; 1.56-2.24), "rash generalized" (64; 2.87; 2.22-3.72), "photosensitivity reaction" (10; 2.35; 1.23–4.48). The application of the SMQ "*Severe cutaneous adverse reactions*

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(SCAR)" retrieved a total of 81 cases, although no significant disproportionality emerged for SGLT2-Is as a class (ROR=0.90; 95%CI=0.72-1.12) or as active substances: canagliflozin (N=55; ROR=1.13; 95%CI=0.87-1.48), dapagliflozin (19; 1.18; 0.75–1.86) and empaglifozin (7; 0.81; 0.39–1.71). The adjustment did not result in ROR changes because only in 2 cases of SCAR submitted for canagliflozin concomitant drugs known to cause severe skin toxicity were recorded. Adverse skin events were severe in 7% of the cases and mainly occurred in females aged 18-65 with type 2 diabetes using SGLT2-I as single antidiabetic regimen (**Table 3**).

Discussion

SGLT2-Is entered the market of antidiabetic agents with promising data, including low risk of hypoglycemia and benefit on several CV outcomes, largely in keeping with a class effect. However, only a few post-marketing data are available on their overall safety profile, with sporadic case reports/series on specific safety issues (e.g., ketoacidosis).

We provide the largest comprehensive analysis of post-marketing AEs attributed to SGLT2-Is collected by major international pharmacovigilance databases. Two main findings emerged: a) although SGLT2-Is have been on the market for only 3 years, they account for ~3% of total antidiabetic reports in FAERS (collected in nearly 13-year period), with similar reporting patterns across international SRSs; b) disproportionality analysis in FAERS showed a higher reporting of infections, metabolism, skin, renal and reproductive AEs. While most of these events already emerged from pre-approval RCTs, the occurrence of skin toxicity is unexpected.

The remarkable reporting pattern is largely ascribable to predicable AEs, but warrants further discussion in conjunction with their steadily increasing utilization. According to the US prescriptions (2,009,505 outpatients prescriptions in 2015-Q4, based on the IMS data provided in the annual report issued by the Institute for Safe Medication Practices) [18] and our data, we estimated a raw reporting rate (i.e. the ratio between the number of US reports and dispensed prescriptions over the same time period) of 84 x 100,000 prescriptions, meaning that every 1,000

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treated patients nearly one AE is reported (**Appendix 7**). Although the actual incidence cannot be inferred from SRSs, this high reporting strengthens the importance to continue additional monitoring by clinicians, regulators and researchers.

The potential signal of skin toxicity was driven by cases of urticaria, pruritus, photosensitivity and various rashes reported with all SGLT2-Is. These skin manifestations, albeit unspecific, can easily be distinguished from typical dermatological manifestations occurring in patients with diabetes (e.g., acanthosis nigricans related to underlying diabetogenic mechanisms) and are likely to be hypersensitivity-like events rather than infection-related symptoms. A sensitivity analysis removing AEs by antidiabetics where "pruritus" was recorded did not affect disproportionality of relevant SOC (N=1.073; ROR=1.59; 95%CI=1.49-1.70).Other forms of skin events attributable to GTIs (and classified within SOC "reproductive system and breast disorders") were also reported: pruritus genital (38 cases), genital rash (36), genital pan (11), genital burning sensation (8), genital erythema (7), pelvic pain (7), all reaching statistical significance (**Appendix 6**). Notably, only for canagliflozin the terms rash and urticaria are mentioned as AEs in section 4.8 of the summary of product characteristics, thus suggesting that an update is warranted for other agents. Only one case report is published in the literature on generalized severe pruritus in patients treated with canagliflozin [19].

The exact mechanistic basis of the drug-induced cutaneous diseases is not fully understood, although hypersensitivity *via* immune-mediated mechanisms is likely to occur; in particular there is substantial evidence that most idiosyncratic events (such as those skin-related) are caused by chemically reactive species [20], and drugs containing an aromatic ring in their chemical structure were strongly associated with drug reactions with eosinophilia and systemic syndrome [16]. We hypothesized that the presence of aromatic rings together with the generation of acyl glucuronide metabolites may result in severe idiosyncratic skin toxicities [21].

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Signals of infection, metabolism and urinary/renal reproductive events derived in this analysis were largely in agreement with data obtained from pre-approval RCTs and also strengthened the notion that prescribers should be aware of these common safety issues and should monitor patients to avoid clinical worsening [3, 22, 23], as recognized in the latest version of the guideline of the American College of Physician [24]. Notably, we found a striking correspondence between expected clinical events (e.g., ketoacidosis) and specific PTs with disproportionality, thus underlining the predictive capacity of SRSs to detect truly positive events.

As regards the risks of breast cancer and bone fractures (imbalances in event occurrence, as compared to placebo from pre-approval RCTs, with inconclusive evidence so far [25, 26]) our data do not highlight potential safety issues: no significant RORs were found either for the SOCs "injury, poisoning and procedural complications" (comprising bone fractures) or for "neoplasms benign, malignant and unspecified (including cysts and polyps)".

We acknowledge inherent limitations of our study, in particular the exploratory nature of SRSs and relevant hypothesis-generating results, with lack of certainty on the true risk in clinical practice and incidence rate. Moreover, we cannot exclude the so-called channeling bias (i.e., the possibility that drugs may be differently prescribed in relation to the severity of disease). In fact, clinical information such as diabetes severity and duration is lacking, thus making a direct comparison among SGLT2-Is inappropriate. We also recognized that residual confounders may exist, including the role of concomitant medications. Finally, signals might theoretically be missed due to the adopted disproportionality approach (i.e., the exclusion of AEs where SGLT2-Is are reported as concomitant, and the top-down analysis of those SOCs resulting in statistical significance), although the impact of these issues is likely to be negligible.

Notwithstanding these limitations, our analysis has important strengths: it gained insight into the global reporting pattern of these novel antidiabetic medicines in an unselected population with diabetes, based on the largest publicly available SRSs, an approach only rarely performed in drug

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safety study. These studies offer a unique opportunity to monitor and re-assess in a quick and inexpensive manner the risk-benefit profile of drugs, which may be distorted in pre-approval RCTs mainly focused on composite efficacy endpoints [27]. Major confounders were accounted for, by restricting the analyses within the antidiabetic therapeutic area. Stimulated reporting following safety warnings and the Weber effect (i.e., a peak in reporting early after approval), traditionally claimed as reporting biases, are unlikely to occur according to recent studies performed on FAERS [28, 29], as confirmed by relatively low proportion of ketoacidosis reports (9% of total reports) .

From a research perspective, upon suspicion, we call clinicians to timely and accurately report drug-related events. Recently, a standardized case report form was proposed to facilitate comparisons and maintain data quality on Stevens Johnson Syndrome/Toxic Epidermal Necrolysis [30]. This will help standardize data collection and support proper causality assessment of adverse skin reactions. In our analysis, we found key information (e.g., dechallenge) only in a minority of reports.

In conclusion, the remarkable reporting pattern of SGLT2-Is over less than 3 years on the market and unpredictable cutaneous AEs justify the need of 1) maintaining active vigilance by clinicians and regulators; 2) performing a periodic “real-time” monitoring of reporting pattern by pharmacovigilance experts. In the meantime, diabetologists, dermatologists and pharmacologists should cooperate to fully characterize clinical data of patients experiencing skin toxicity in order to assess actual drug-related risk.

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Contribution statement E.P., E.R. and G.M. conceived the study. E.P. and E.R. designed the study and provided guidance on data analysis. E.R. and M.P. drafted the first version of the manuscript. E.F. collected and analyzed data. E.P. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors provided substantial contribution to data interpretation and their discussion. They critically revised the content and approved the final version of the manuscript.

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Appendices.

Appendix 1. Overview of the three international spontaneous reporting systems: differences and similarities.

Appendix 2. Synopsis of literature evaluation.

Appendix 3. Details on the approach used to identify drugs with known skin toxicity and calculate adjusted disproportionality analysis.

Appendix 4. Distribution of reports according to relevant system organ class (SOC). See methods for details. In parentheses relevant percentage is provided (out of total reports).

Appendix 5. Flowchart describing data-mining approach to process raw FAERS data and allocate reports of interest according to therapeutic class (antidiabetics).

* number of cases where at least one antidiabetic drug is recorded. Please note that one report may contain more than one antidiabetic drugs.

Appendix 6. Disproportionality analyses (SGLT2-Is, canagliflozin, dapagliflozin, empaglifozin) across MedDRA hierarchy for all System Organ Classes (SOCs). See methods for details. Highlighted in yellow=statistically significant disproportionality.

Appendix 7. Reporting rates for SGLT2-Is (2015-Q4). Prescription data were obtained from the Institute For Safe Medication Practice - QuarterWatch [annual report issue – June 2016] (http://www.ismp.org/QuarterWatch/pdfs/2015Q4.pdf).

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Figure Legend.

Figure 1. Suspected adverse events reported for SGLT2-Is as compared to other antidiabetic drugs (ROR with 95%CI), at the System Organ Class level (MedDRA terminology). See methods for details.

Figure 2. Disproportionality across MedDRA hierarchy for "Skin and subcutaneous tissue disorders", considering the entire class of SGLT2-Is. See methods for details.

Dotted lines indicate non-statistically significant disproportionality.

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ACCEPTED MANUSCRIPT

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Table 1. Demographic data. In parentheses relevant percentage is provided (out of total reports).

				DAPAGLIFLOZIN			***CANAGLIFLOZIN***			***EMPAGLIFLOZIN***		
				Vigibase	***EV[a]***	***FAERS***	***Vigibase***	***EV[a]***	***FAERS***	***Vigibase***	***EV[a]***	***FAERS***
Total reports				***5,752***	***2,496***	***2,450***	***11,555***	***4,688***	***7,389***	***2,468***	***788***	***1,309***
Geographical distribution	EU			2025 (35.2)	954 (38.2)	275 (11.2)	521 (4.5)	296 (6.3)	104 (1.4)	632 (25.6)	313 (39.7)	96 (7.3)
	NON- EU	AFRICA		1 (0.0)	1542 (61.8)	2 (0.1)	/	4392 (93.7)	1 (0.0)	/	475 (60.3)	/
		AMERICAS	USA	2717 (47.2)		2045 (83.5)	10828 (93.7)		6993 (94.6)	1532 (62.1)		1115 (85.2)
			Other			84 (3.4)			226 (3.1)			24 (1.8)
		ASIA		855 (14.9)		21 (0.9)	178 (1.5)		17 (0.2)	269 (10.9)		20 (1.5)
		OCEANIA		154 (2.7)		5 (0.2)	28 (0.2)		10 (0.1)	35 (1.4)		6 (0.5)
	UNK					18 (0.73)			38 (0.51)			48 (3.67)
Age group distribution	0-17			7 (0.1)	7 (0.3)	5 (0.2)	11 (0.1)	3 (0.1)	9 (0.1)	5 (0.2)	1 (0.1)	4 (0.3)
	18-64			2515 (43.7)	1264 (50.6)	1041 (42.5)	3566 (30.9)	2124 (45.3)	2726 (36.9)	969 (39.3)	412 (52.3)	531 (40.6)
	> 65			1144 (19.9)	634 (25.4)	403 (16.5)	1609 (13.9)	1013 (21.6)	1031 (14.00)	487 (19.7)	203 (25.8)	177 (13.5)
	UKW			2086 (36.3)	591 (23.7)	1001 (40.9)	6369 (55.1)	1548 (33.0)	3623 (49.0)	1007 (40.8)	172 (21.8)	597 (45.6)
Patient sex distribution	F			2857 (49.7)	1209 (48.4)	1142 (46.6)	5525 (47.8)	2299 (49.0)	3637 (49.2)	1187 (48.1)	366 (46.5)	653 (49.9)
	M			2515 (43.7)	1205 (48.3)	1117 (45.6)	4499 (38.9)	2184 (46.6)	3041 (41.2)	1056 (42.8)	402 (51.0)	553 (42.3)
	UKW			380 (6.6)	82 (3.3)	191 (7.8)	1531 (13.3)	205 (4.4)	711 (9.6)	225 (9.1)	20 (2.5)	103 (7.9)

[a] For Eudravigilance, EU means European Economic Area. EU: Europe; EV: Eudravigilance; F: females; M: males; UKW: unknown (missing data).

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Table 2. Exploratory disproportionality analysis in FAERS and relevant literature evaluation. In bold=statistically significant disproportionality. See methods for details.

	CANAGLIFLOZIN		***DAPAGLIFLOZIN***		***EMPAGLIFLOZIN***	
System Organ Class (SOC)	***ROR (95%CI)***	***Literature***	***ROR (95%CI)***	***Literature***	***ROR (95%CI)***	***Literature***
Blood and lymphatic system disorders	0.27 (0.19-0.37)	++ Haemoconcentration	0.64 (0.44-0.93)	++ Haemoconcentration	0.21 (0.09-0.49)	++ Haemoconcentration
Cardiac disorders	0.10 (0.09-0.12)		0.13 (0.11-0.17)		0.09 (0.06-0.13)	
Congenital, familial and genetic disorders	0.25 (0.12-0.5)		**2.16 (1.43-3.27)**			
Ear and labyrinth disorders	0.67 (0.49-0.90)		0.47 (0.25-0.87)			
Endocrine disorders	0.30 (0.17-0.55)		0.42 (0.17-1.01)			
Eye disorders	0.39 (0.34-0.46)		0.40 (0.31-0.52)		0.34 (0.23-0.50)	
Gastrointestinal disorders	0.81 (0.76-0.86)		0.90 (0.81-1.00)		0.99 (0.86-1.14)	
General disorders and administration site conditions	0.74 (0.70-0.78)		0.76 (0.69-0.84)		0.51 (0.44-0.59)	
Hepatobiliary disorders	0.32 (0.25-0.41)		0.41 (0.28-0.60)		0.2 (0.09-0.42)	
Immune system disorders	1.02 (0.84-1.24)		1.26 (0.93-1.71)		0.50 (0.26-0.96)	
Infections and infestations	**3.51 (3.31-3.73)**	+++ UTIs, GTIs	**3.15 (2.84-3.50)**	+++ UTIs, GTIs	**3.36 (2.93-3.86)**	+++ UTIs, GTIs
Injury, poisoning and procedural complications	0.84 (0.79-0.90)	+/- Bone fractures and decreased bone mineral density	0.54 (0.47-0.61)		0.23 (0.18-0.30)	
Investigations	0.86 (0.82-0.91)		0.8 (0.73-0.87)		0.67 (0.59-0.76)	
Metabolism and nutrition disorders	**1.45 (1.37-1.53)**	++ eDKA, hyperphosphatemia, hypermagnesiemia,	**1.40 (1.27-1.55)**	++ eDKA, hyperphosphatemia, hypermagnesiemia,	**1.38 (1.20-1.58)**	++ eDKA, hyperphosphatemia, hypermagnesiemia,

		hypovolaemia, hypoglycaemia, increase in LDL		hypovolaemia, hypoglycaemia, increase in LDL		hypovolaemia, hypoglycaemia, increase in LDL
Musculoskeletal and connective tissue disorders	1.02 (0.93-1.12)		1.05 (0.89-1.24)		0.96 (0.76-1.21)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0.16 (0.13-0.20)	+/- Breast cancer, bladder cancer	0.56 (0.44-0.70)	+/- Breast cancer, bladder cancer	0.13 (0.06-0.24)	
Nervous system disorders	0.63 (0.59-0.68)		0.60 (0.53-0.68)		0.64 (0.54-0.75)	
Pregnancy, puerperium and perinatal conditions						
Product issues	0.26 (0.20-0.34)		0.35 (0.23-0.52)			
Psychiatric disorders	0.71 (0.64-0.79)		0.62 (0.50-0.75)		0.45 (0.33-0.62)	
Renal and urinary disorders	**2.50 (2.35-2.67)**	+++ Polyuria, Glycosuria	**2.35* (2.09-2.63)**	+++ Polyuria, Glycosuria	**2.27 (1.94-2.66)**	+++ Polyuria, Glycosuria
Reproductive system and breast disorders	**5.60 (4.98-6.30)**	+++ vulvovaginitis, balanitis, prosthetitis	5.11* (4.17-6.27)	+++ vulvovaginitis, balanitis, prosthetitis	**4.42 (3.29-5.95)**	+++ vulvovaginitis, balanitis, prosthetitis
Respiratory, thoracic and mediastinal disorders	0.43 (0.37-0.49)		0.82 (0.69-0.97)		0.47 (0.35-0.63)	
Skin and subcutaneous tissue disorders	**1.57 (1.45-1.70)**		**1.71 (1.50-1.94)**		**1.75 (1.47-2.08)**	
Social circumstances	**1.43 (1.18-1.74)**		0.45 (0.25-0.81)			
Surgical and medical procedures	0.23 (0.19-0.28)		0.14 (0.09-0.21)		0.10 (0.05-0.21)	
Vascular disorders	0.62 (0.54-0.70)		0.73 (0.59-0.89)		0.53 (0.38-0.73)	

eDKA: euglycemic diabetic ketoacidosis; UTIs: urinary tract infections; GTIs: genital tract infections.

+++ = Adverse Events (AEs) emerging from the majority of randomized controlled trials (RCTs), including systematic reviews, with biological plausibility (i.e., the drug may directly or indirectly cause the clinical event via different postulated mechanisms).

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++ = AEs emerging from RCTs and case reports/series leading to safety warnings by Regulatory Agencies, with potential biological plausibility (i.e., the drug may cause the clinical event via increased patients' susceptibility or drug interactions).

+ = AEs emerging only from case reports/series, with potential biological plausibility (i.e., the drug may cause the clinical event via increased patients' susceptibility or drug interactions).

+/- = AEs emerging from a minority of RCTs, with further analyses revealing the inconsistency/inability/uncertainty to assign causality to a given drugs.

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Table 3. Demographic data on adverse skin events with SGLT2-Is in FAERS. in parenthesis, relevant percentage is presented.

	canagliflozin		dapagliflozin		empagliflozin	
	Tot. skin events	**Severe skin events**	**Tot. skin events**	**Severe skin events**	**Tot. skin events**	**Severe skin events**
Sex						
F	428 (58.4)	39 (70.9)	143 (54.6%)	12 (63.2)	85 (59.4%)	4 (57.1%)
M	270 (36.8)	15 (27.3)	111 (42.4%)	7 (36.8)	48 (33.6%)	3 (42.9)
Missing	35 (4.8)	1 (1.8)	8 (3.1%)	0	10 (7%)	0
Age						
<18	1 (0.1)	0	0	0	0	0
18-65	303 (41)	21 (38.2)	125 (47.7%)	11 (56.9)	70 (49%)	6 (85.7)
>65	115 (16)	11 (20)	43 (16.4%)	5 (26.3)	18 (12.6%)	0
missing	314 (43)	23 (41.8)	94 (35.9)	3 (15.8)	55 (38.5)	1 (14.3)
Reporter country						
Europe	9 (1.2)	0	16 (6.1%)	3 (15.8)	8 (5.6%)	2 (28.6)
USA	693 (94.5)	52 (94.6)	244 (93.1%)	15 (79)	126 (88.1%)	4 (57.1)
Other	29 (4)	3 (5.5)	2 (0.8%)	1 (5.3)	7 (4.9%)	1 (14.3)
missing	2 (0.3)	0	0	0	2 (1.4%)	0
Outcome						
Death	1 (0.1)	0	1 (0.4%)	0	1 (0.7%)	0
Disability	3 (0.4)	1 (1.8)	6 (2.3%)	0	0	0
Hospitalization	37 (5)	3 (5.5)	17 (6.5%)	0	7 (4.9%)	3 (42.9)
Life-threatening	11 (1.5)	1 (1.8)	3 (1.1%)	0	4 (2.8%)	0
Other event	197 (26.9)	32 (58.2)	36 (13.7%)	6 (31.6)	14 (9.8%)	2 (28.6)
Requiring intervention	0	0	0	0	0	0
Not stated	484 (66)	18 (32.7)	199 (76%)	13 (68.4)	117 (81.8%)	2 (28.6)
Indication of use						
T1D	4 (0.5)		3 (1.1%)		0	0
T2D	385 (51.7)	31 (53.4)	152 (56.1%)	10 (50)	77 (50%)	7 (100)
LADA	0		0	0	0	0
Unspecified diabetes	149 (20)	12 (20.7)	25 (9.2%)	3 (15)	25 (16.2%)	0
Other DM-related indication	26 (3.5)	1 (1.7)	13 (4.8%)	1 (5)	6 (3.9%)	0
Obesity/Diet	4 (0.5)	0	0	0	1 (0.6%)	0
Unknown	164 (22)	10 (17.2)	12 (4.4%)	3 (15)	34 (22.1%)	0
Off-label use	3 (0.4)	3 (5.2)	2 (0.7%)	0	0	0
Not stated	9 (1.2)	1 (1.7)	64 (23.6%)	3 (15)	11 (7.1%)	0
Antidiabetic regimen						
Monotherapy	308 (42)	22 (40)	104 (39.7%)	8 (42.1)	74 (51.7%)	3 (42.9)
Dual therapy	108 (14.7)	12 (21.8)	27 (10.3%)	2 (10.5)	16 (11.2%)	1 (14.3)
Triple therapy	76 (10.4)	2 (3.6)	33 (12.6)	2 (10.5)	12 (8.4%)	1 (14.3)
Multiple (≥4 drugs)	241 (32.9)	19 (34.5)	98 (37.4%)	7 (36.8)	41 (28.7%)	2 (28.6)
Total	***733***	***55***	***262***	***19***	***143***	***7***

T1D: type 1 diabetes; T2D: type 2 diabetes; LADA: latent autoimmune diabetes in adults.

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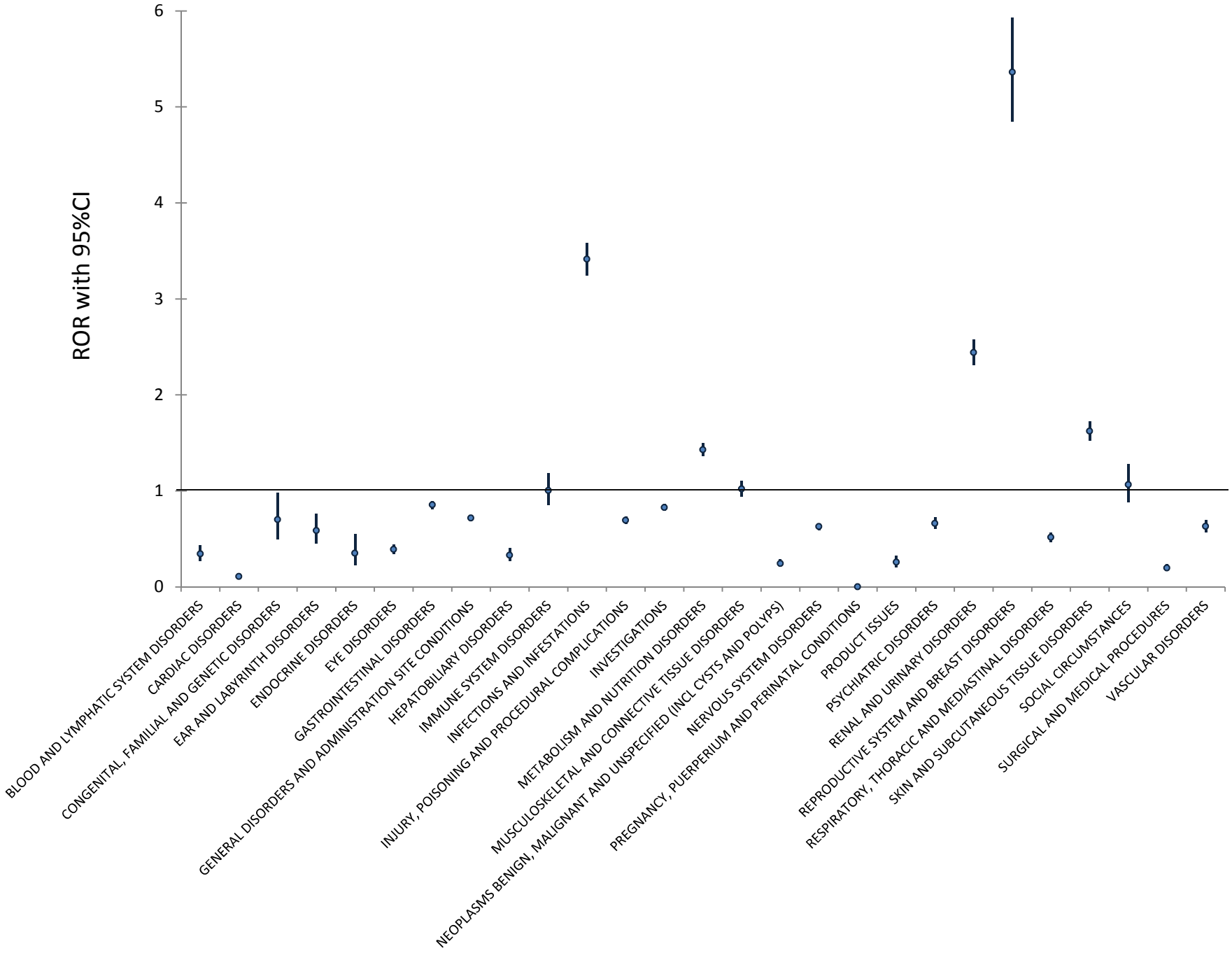

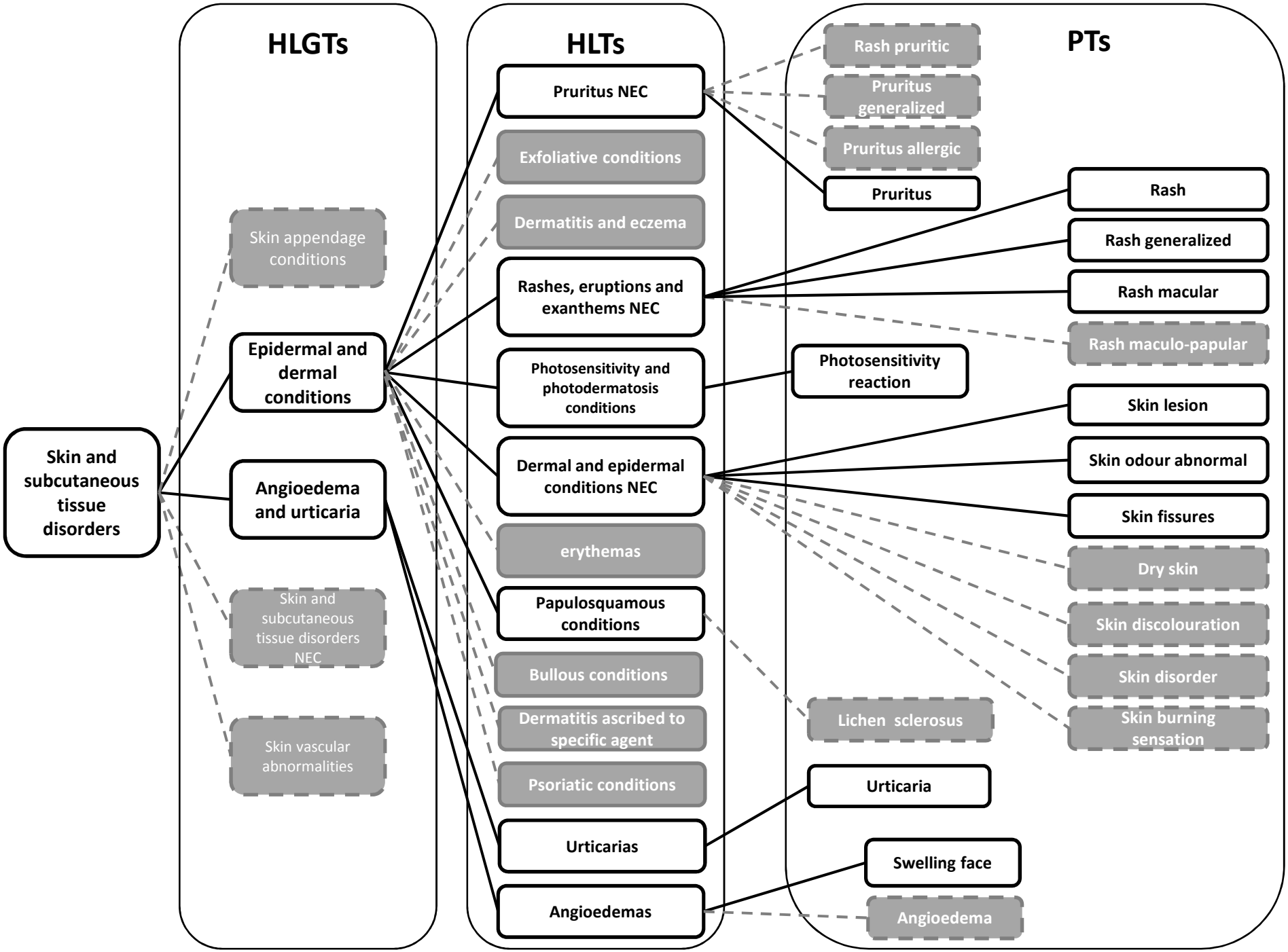
HLGTs
HLTs
PTs
Skin and subcutaneous tissue disorders
Skin appendage conditions
Epidermal and dermal conditions
Angioedema and urticaria
Skin and subcutaneous tissue disorders NEC
Skin vascular abnormalities
Pruritus NEC
Exfoliative conditions
Dermatitis and eczema
Rashes, eruptions and exanthems NEC
Photosensitivity and photodermatosis conditions
Dermal and epidermal conditions NEC
erythemas
Papulosquamous conditions
Bullous conditions
Dermatitis ascribed to specific agent
Psoriatic conditions
Urticarias
Angioedemas
Rash pruritic
Pruritus generalized
Pruritus allergic
Pruritus
Photosensitivity reaction
Lichen sclerosus
Urticaria
Swelling face
Angioedema
Rash
Rash generalized
Rash macular
Rash maculo-papular
Skin lesion
Skin odour abnormal
Skin fissures
Dry skin
Skin discolouration
Skin disorder
Skin burning sensation

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Highlights

- Multi-database pharmacovigilance analysis was performed to assess post-marketing safety of SGLT2-Is
- The majority of adverse events were predictable from pre-approval clinical evidence
- The unexpected signal of skin toxicity warrants active monitoring in the real-world
- Large analytical safety studies are needed for risk quantification

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