PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Trends in anti-diabetes medication use among hospitalised patients with type 2 diabetes: a retrospective single-center cohort study.
AUTHORS	Meier, Nicole; Laager, Rahel; Gregoriano, Claudia; Schütz, Philipp; Mueller, Beat; Struja, Tristan; Kutz, Alexander

VERSION 1 – REVIEW

REVIEWER	Kiguba, Ronald Makerere University College of Health Sciences, Pharmacology and Therapeutics
REVIEW RETURNED	23-Feb-2024

GENERAL COMMENTS	Thank you for giving me the opportunity to review this study. I have a few comments to improve the study further: 1. Abstract conclusion: State that the trends in the use of individual drugs are consistent with policy-related changes and/or the introduction of newer drugs. What is the public health importance of the observed trends? 2. Introduction: It is recommended to end this section by stating the aim/objective rather than the objective even if they intrinsically represent the same message. 3. Methods (Data source and study design): The details on ethics seem to belong elsewhere in the manuscript rather than in this section. 4. Study population: Delete "....declined general informed consent..." due to redundancy. Patients who didn't consent are automatically excluded from the study. 5. Study population: Justify why dead patients were excluded from the study 6. Results (Baseline characteristics): Give clarity on whether the unit of analysis is a patient or an admission. If the latter is used, do bear in mind that a single patient can contribute more than one admission. This needs to be clear in the Methods and Results 7. Discussion: Discuss the impact of the COVID-19 pandemic on the data for the period 2019-2022 as used for this analysis

REVIEWER	Rendell, Marc Univ Nebraska
REVIEW RETURNED	19-Mar-2024

GENERAL COMMENTS	The authors recorded medication lists of patients with type 2 diabetes admitted to a local Cantonal hospital in Switzerland. They found a shift toward diabetes medications which carry benefits going beyond glucose control, namely SGLT2 inhibitors and GLP-1 agonists. This is clearcut.

	The problem here is that we are looking at one very limited observable in a large health system. The question is whether there has been a shift in use of antidiabetes medications in both outpatients and inpatients in the Canton and then in all of Switzerland. It is understood that the Swiss health care system does not maintain comprehensive data. In fact, Switzerland can be considered a data poor country when it comes to health care information. However, if the data on both outpatients and inpatients can be accessed, that should be the goal. The second problem is that the authors do not discuss the constraints on prescription medications which exist in Switzerland. Newer medications such as SGLT2 inhibitors and GLP-1 receptor agonists are restricted by costs in most countries, including the U.S.A. So the utilization of given agents is the product of desire to prescribe and the countervailing restrictions on the use of high cost drugs. We need to know the degree of those restrictions in Switzerland.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:

1. Abstract conclusion: State that the trends in the use of individual drugs are consistent with policy-related changes and/or the introduction of newer drugs. What is the public health importance of the observed trends?
REPLY: Thank you for your input, we changed the abstract`s conclusion accordingly and now refer on the public health importance too.
"This real-world data from 2019 to 2022 demonstrate a significant shift in anti-diabetes medications, with decreased use of sulfonylureas and increased prescriptions of SGLT-2 inhibitors, especially in patients with CVD or CKD. This trend aligns with international guidelines and indicates swift adaptation by healthcare providers, signaling a move towards more effective diabetes management.“
2. Introduction: It is recommended to end this section by stating the aim/objective rather than the objective even if they intrinsically represent the same message.
REPLY: Thank you for your input. As suggested, the last part of the introduction is now focusing on the aim/objective of our study only.
”As prescribing trends of anti-diabetes medications among hospitalized patients are widely lacking, the aim of this study was to assess the trends in use of different anti-diabetes medications in medical inpatients with T2D.We sought to determine whether these trends are aligning with the recommendations from international practice guidelines.”

3. Methods (Data source and study design): The details on ethics seem to belong elsewhere in the manuscript rather than in this section.
REPLY: Thank you. We agree and have addressed it accordingly.

4. Study population: Delete "....declined general informed consent..." due to redundancy. Patients who didn't consent are automatically excluded from the study.
REPLY: Thank you. We agree and have addressed it accordingly.

5. Study population: Justify why dead patients were excluded from the study
REPLY: Thank you for your input. Patients who died during hospitalization were excluded because any change in medication between admission and discharge (death) would be given by the death and not by the physician’s clinical judgement. As the “end-of-life” setting resembles a specific clinical setting, we preferred to rather exclude dying patients. This, however, would be an excellent study question for an additional analysis.
This specification has now been addressed in the methods part as follows:
“Exclusion criteria included any other type of diabetes and in-hospital death. The exclusion of in-

hospital deaths was implemented because the end-of-life setting represents a distinct clinical context in which any changes in medication between admission and death are driven by the circumstance of death rather than by the physician's clinical judgment."

6. Results (Baseline characteristics): Give clarity on whether the unit of analysis is a patient or an admission. If the latter is used, do bear in mind that a single patient can contribute more than one admission. This needs to be clear in the Methods and Results
REPLY: Thank you for your input and the opportunity to clarify. The unit of our analysis was the hospitalization. Consequently, a single patient could have contributed to more than one hospitalization. This has been now addressed more clearly in the methods` part (Statistical analysis). To avoid confusion, we are also using a consistent nomenclature by replacing "patients" to "hospitalisations".
"Baseline characteristics were tabulated for the overall cohort. The 4-year study period was segmented into 16 quarters (3-month time intervals, respectively) and hospitalisations were assigned to one of these intervals based on their calendar time of hospital admission. Hospitalisations could have contributed to more than one anti-diabetes medication if the inclusion criteria were met. Since the unit of analysis was any single hospitalization, one single patient could have contributed to more than one hospitalisation."

7. Discussion: Discuss the impact of the COVID-19 pandemic on the data for the period 2019-2022 as used for this analysis
REPLY: Thank you for your suggestion to discuss the potential impact of the COVID pandemic related to our results. Although any causal conclusions may not be possible, the following - more hypothetical - considerations are now discussed as follows:
"During the COVID-19 pandemic, affecting the first part of our study period, healthcare systems experienced significant disruptions, which likely influenced the trends in anti-diabetes medication management observed from 2019 to 2022. Although this analysis relies on data from hospitalizations only, the prioritization of medications that require less frequent monitoring, such as SGLT-2 inhibitors, might have been driven by the need to reduce patient exposure to COVID-19 and adapt to the rise of telehealth. Additionally, the increased risk of COVID-19 complications in individuals with diabetes may have prompted more aggressive management strategies, particularly favoring medications with cardiovascular and renal benefits. Changes in hospital admission patterns and disruptions in medication supply chains could also have contributed to the shifts in prescribing practices during the pandemic. Variations in patient access to healthcare due to economic reasons might be possible but unlikely to have relevantly influenced any prescribing trends in Switzerland."

Reviewer #2:

The authors recorded medication lists of patients with type 2 diabetes admitted to a local Cantonal hospital in Switzerland. They found a shift toward diabetes medications which carry benefits going beyond glucose control, namely SGLT2 inhibitors and GLP-1 agonists. This is clearcut.

The problem here is that we are looking at one very limited observable in a large health system. The question is whether there has been a shift in use of anti-diabetes medications in both outpatients and inpatients in the Canton and then in all of Switzerland. It is understood that the Swiss health care system does not maintain comprehensive data. In fact, Switzerland can be considered a data poor country when it comes to health care information. However, if the data on both outpatients and inpatients can be accessed, that should be the goal.
REPLY: Thank you for your review and your valuable input. The reviewers correctly point out the limitations due to the scarcity of comprehensive healthcare (outpatient-) data in Switzerland. While there is a unified national health data collection strategy for inpatient data, no similar strategy exists for outpatient data. Since there is no integration of outpatient data within existing inpatient data, thereby capturing a fuller picture of anti-diabetes medication use across different healthcare regions, this remains a major limitation of this study. Thus, given the current gaps in outpatient data, particularly in combination with critical clinical information, we are not able to sufficiently address your suggestions. These limitations have now been addressed more clearly in the discussion part as follows:
“This study also has limitations. First, external validity is constrained by its single-center cohort design. Second, the absence of clinical information and laboratory values, along with unknown reasons for (de-)prescribing, further limits the conclusion of this study. Thus, it remains unclear whether a medication was deprescribed following clinical guidelines among older people or in response to any adverse drug events. Third, our analysis was confined to in-hospital data, and therefore, does not extend to outpatients. However, based on existing evidence regarding the efficacy of SGLT-2i and GLP-1 RA, significant deviations from our findings appear unlikely. Fourth, even though our “incident cohort” included individuals who had not filled any anti-diabetes medication prescriptions at hospital admission, there remains a possibility that certain "incident users" may not have been initiating the anti-diabetes treatment of interest for the first time. Finally, given the origin of data, underreporting of ICD-10 based diagnoses due to coding issues must be considered.”

Nonetheless, as there are only few analyses focusing on prescribing trends among hospitalized patients, this study adds an important piece to the pharmacoepidemiology of anti-diabetes medications in our country.

The second problem is that the authors do not discuss the constraints on prescription medications which exist in Switzerland. Newer medications such as SGLT2 inhibitors and GLP-1 receptor agonists are restricted by costs in most countries, including the U.S.A. So the utilization of given agents is the product of desire to prescribe and the countervailing restrictions on the use of high cost drugs. We need to know the degree of those restrictions in Switzerland.
REPLY: In Switzerland, health insurance companies impose certain limitations that are determined by Swissmedic approvals and cost negotiations with manufacturers. SGLT-2 inhibitors are covered under the mandatory basic health insurance once lifestyle modifications alone do not achieve sufficient glycemic control. For GLP-1 receptor agonists, there is an additional requirement of a minimum BMI of 28 kg/m^2. These restrictions are in accordance with both international and national guidelines that specify when the use of these medications is appropriate. For patients who receive treatment consistent with these guidelines, cost-related restrictions are minimal due to the low co-payment of 10% for medications, applicable when no generic alternatives are available.
However, we agree that the availability of these newer medications can be impacted by disruptions in the medication supply chain. This issue has particularly affected GLP-1 receptor agonists, though it is less significant since most prescriptions for GLP-1 RA are in the outpatient setting. Therefore, we think that these disruptions should not have significantly impacted the prescribing patterns of anti-diabetes medications, nor the trends observed in our study.

We now address this issue in the discussion part as follows: “In Switzerland, health insurance limitations dictated by Swissmedic approvals and manufacturer cost negotiations affect medication access. SGLT-2i are covered by mandatory health insurance when lifestyle changes fail to control glycemia adequately. GLP-1 RA additionally require a minimum BMI of 28 kg/m^2 for coverage. These criteria align with international and national guidelines, ensuring minimal cost-related restrictions due to a 10% co-payment for non-generic medications. While supply chain disruptions have impacted the availability of newer medications, particularly GLP-1 RA, their effect is mitigated by their predominant prescription in the outpatient setting, suggesting minimal influence on the observed prescribing trends in our study. Therefore, we think that these disruptions should not have significantly

impacted the prescribing patterns of anti-diabetes medications, nor the trends observed in our study."

VERSION 2 – REVIEW

REVIEWER	Rendell, Marc Univ Nebraska
REVIEW RETURNED	14-May-2024

GENERAL COMMENTS	The authors have acknowledged that Switzerland lacks adequate tracking of ambulatory care. All the data they have is hospital based. That is not necessarily an overwhelming hurdle to publish their data. They must state this limitation at the outset of the article and then point out in conclusion that their findings only pertain to those patients who are sick enough to be hospitalized. That means these were patients whose underlying health conditions predisposed to treatment with SGLT2 inhibitors, such as patients with heart and/or renal failure or obese patients as relates to GLP1 receptor agonists. Therefore their data does not necessarily reflect penetration of use of these agents into the general type 2 diabetes population. They have also provided valuable data on reimbursement of the use of these agents in the Swiss heatlh system. A 10% copay is not onerous compared to the situation in the United States. They should make this point a feature in their paper.

VERSION 2 – AUTHOR RESPONSE

Reviewer #2:
The authors have acknowledged that Switzerland lacks adequate tracking of ambulatory care. All the data they have is hospital based. That is not necessarily an overwhelming hurdle to publish their data. They must state this limitation at the outset of the article and then point out in conclusion that their findings only pertain to those patients who are sick enough to be hospitalized. That means these were patients whose underlying health conditions predisposed to treatment with SGLT2 inhibitors, such as patients with heart and/or renal failure or obese patients as relates to GLP1 receptor agonists. Therefore their data does not necessarily reflect penetration of use of these agents into the general type 2 diabetes population.
REPLY: Thank you for your remark. We changed the "Strenghts and limitations" at the outset of the article accordingly: "Our analysis was confined to in-hospital data, and therefore, does not extend to outpatients."

Similarly, we also changed the abstract`s conclusion accordingly. "This real-world data from 2019 to 2022 demonstrate a significant shift in anti-diabetes medications within the in-hospital setting, with decreased use of sulfonylureas and increased prescriptions of SGLT-2 inhibitors, especially in hospitalisations with CVD or CKD."

We also point it out in the discussion section as follows: "Third, our analysis was confined to in-hospital data, and therefore, does not extend to outpatients. Consequently, our findings only pertain to patients who were sick enough to be hospitalized and whose underlying health conditions probably predisposed to the treatment with SGLT-2i, such as patients with heart and/or renal failure or obese patients as relates to GLP1-RA. However, based on existing evidence regarding the efficacy of SGLT-2i and GLP-1 RA, significant deviations from our findings appear unlikely."

Finally, we changed the conclusion section as follows. “Our real-world data show a relevant shift in the use of anti-diabetes medications from 2019 to 2022 in the in-hospital setting with a constant decrease in the use of sulfonylureas and a strong increase in prescription of SGLT-2i, particularly among hospitalisations with CVD or CKD.”

They have also provided valuable data on reimbursement of the use of these agents in the Swiss heatlh system. A 10% copay is not onerous compared to the situation in the United States. They should make this point a feature in their paper.
REPLY: Thank you for your input. We now address it in our discussion section accordingly: “This low co-payment is not onerous compared to other countries, such as the United States. This lower financial hurdle could lead to more frequent prescriptions of new and more expensive antidiabetic medications like SGLT-2i and GLP-1 RA in Switzerland compared to other countries with higher out-of-pocket costs.”