Pediatric Drugs

Dapagliflozin and Empagliflozin in Paediatric Indications: a Systematic Review

--Manuscript Draft--

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Full Title:	Dapagliflozin and Empagliflozin in Paediatric Indications: a Systematic Review
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Abstract:	Introduction: In adults, sodium glucose type 2 transporter inhibitors have revolutionized the treatment of type 2 diabetes mellitus, heart failure and chronic kidney disease. Objective: We aimed to review information on compassionate use, clinical pharmacology, efficacy, and safety of dapagliflozin and empagliflozin in children. Methods: Systematic review of published clinical trials, case reports or observational studies in Medline, Excerpta Medica and Web of Science databases from inception to September 2023. For the two randomised-controlled trials on type 2 diabetes mellitus, we implemented a meta-analysis on the primary outcome (mean difference in HbA1c between intervention and placebo groups). Review Manager (RevMan), version 5.4.1 was used for this purpose. Results: Thirty-five articles (nine case reports, 10 case series, one prospective non-controlled trial, four controlled randomized trials, two surveys, six pharmacokinetic studies, and three pharmacovigilance studies) were selected in which 415 children were exposed to either dapagliflozin or empagliflozin: 189 diabetic patients (mean age 14.7±2.9 years), 32 children with glycogen storage disease type Ib (GSD Ib), G6PC3-deficiency or severe congenital neutropenia type 4 (8.5±5.1 years), 47 children with kidney disease or heart failure (11.2±6.1 years), 84 patients in pharmacokinetic studies (15.1±2.3 years) and 63 patients in toxicological series. The effect of dapagliflozin and empagliflozin in type 2 diabetes mellitus was demonstrated by HbA1c reduction in two randomized trials among a total of 177 adolescents, with a mean HbA1c difference of -0.82% (95%-CI -1.34 to -0.29) as compared to placebo (no heterogeneity, I2=0%). Dose ranged between 5-20 mg (mean 11.4±3.7) once daily for dapagliflozin and between 5-25 mg (mean 15.4±7.4) once daily for empagliflozin. Among the paediatric cases of GSD Ib, empagliflozin 0.1-1.3 mg/kg/d improved neutropenia, infections, and gastrointestinal health. Dapagliflozin (mean dose 6.9±5.2 mg once daily) was well-tolerated in children with chronic kidney disease and heart failure. Side effects were generally mild, the most frequent being hypoglycaemia in children with GSD Ib (33% of patients) or type 2 diabetes mellitus (14% of patients) on concomitant hypoglycaemic drugs. Diabetic ketoacidosis is rare in children. Conclusion: Early evidence suggests that dapagliflozin and empagliflozin are well tolerated in children. A clinical pharmacology rationale currently exists only for adolescents with diabetes mellitus. Prospero registration number: CRD42023438162.
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Author Comments:	On behalf of my co-authors, I submit the enclosed manuscript for consideration by Pediatric Drugs. Sodium glucose type 2 transporter inhibitors (SGLT2i) have revolutionized the treatment of type 2 diabetes mellitus, heart failure and chronic kidney disease in adults. There are hopes that similar results might be achievable also in children. Yet, only their use in type 2 diabetes mellitus adolescents has so far been properly investigated. In an effort to improve the understanding of the clinical pharmacology and potential benefit-risk profile of SGLT2-inhibitors in paediatric heart failure, chronic kidney disease and glycogen storage disease type Ib, we performed a systematic review of the experience with the use of dapagliflozin and empagliflozin in children. The results from this review will support the implementation of prospective protocols for the evaluation of efficacy and safety of these drugs in Paediatrics. We believe that this contribution might be of interest to the readership of Pediatric Drugs. Please do not hesitate to contact me, should you need any further information. Kind regards, Sebastiano A.G. Lava (December 26th, 2023)
Response to Reviewers:	Ref.: Manuscript PDDA-D-23-00211 entitled “Dapagliflozin and Empagliflozin in Paediatric Indications: a Systematic Review and Meta-Analysis” Dear Dr Caroline Herdson, dear Editors, many thanks for your email, the detailed peer review of our manuscript and for the opportunity to revise it and improve its quality. The interesting and constructive comments raised by the Reviewers and by the Editorial Office were carefully addressed, and ooint-by-point answers are provided below. We feel that the revised manuscript is of improved quality and we would like to thank the Reviewers and the Editorial office for their effort in helping us improving our submission. We really hope that it can now be accepted for publication in Pediatr Drugs. We look forward to hearing back from you. We would be glad to respond to any further questions and comments that you may have. Best regards, Sebastiano A.G. Lava (London, 12th February 2024) Point-by-point answers to the comments Reviewer #1 The author team reviewed the use of Dapagliflozin and Empagliflozin in children in at least 7 areas, including diabetes, glycogen storage diseases, G6P3-deficiency, heart failure, kidney disease, pharmacokinetics and pharmacovigilance. Out of 35 articles retrieved, meta-analysis could only be performed in two RCTs in diabetes. This reflects the sparseness of high-quality evidence on the effectiveness and safety of these two medications, and the cautionary tone we need to take in making conclusions based on currently available data. Because much of the work in this manuscript is descriptive summary of the articles gathered over a broad range of conditions, rather than meta-analysis of a focused population-intervention-outcome combination, the inclusion of the term "meta-analysis" in the title may be misleading. In fact, the work appears to be more like a scoping review barring the inclusion of the single meta-analysis of two

studies. I would thus, as a form of compromise, suggest that the authors remove the term "meta-analysis" in the title and retain the term "systematic review".

Thank you for your comments. We modified the title as requested. Furthermore, also taking into account the comments from Reviewer 2, we moderated the wordings regarding the meta-analysis throughout the manuscript.

Following are comments pertaining to each part of the work:

1. Abstract: Results, first line: it will be helpful to provide a breakdown on the types of study among the 35 articles retrieved.
Thank you. This information has been added to the revised abstract.

2. Abstract: Results: survey findings do not appear to add substantial weight on the evidence at this stage and do not need to be included in the abstract.
We agree, thank you for pointing this out. The pertaining sentence has been deleted from the Abstract.

3. Abstract: Results, meta-analysis results on the outcome of HbA1c: please add no of studies, no of cumulative participants, heterogeneity as indicated by I square alongside the pooled effect estimate.
Thank you. The requested information has been added to the revised Abstract.

4. Abstract: Conclusion- wording looks too strong for the quality of evidence available. Suggest: "Early evidence appear to suggest that dapagliflozin and empagliflozin are well tolerated in children".
Thank you. The conclusion has been modified and moderated.

5. Key points: point no 2 - the wording appears too definite as the findings are at best preliminary. The authors should put the findings in the context of early evidence that need to be verified by further robust studies.
Thank you. Key point #2 has been modified accordingly.

6. Introduction, paragraph 2: "we performed a systematic review of the experience with the use of dapagliflozin and empagliflozin in children". This appear to me a statement closest to the objective of the review. The wording is unclear, especially with the use of the word "experience", which to me suggest an evaluation of user and carer experience. The more appropriate term would be "effectiveness and safety".
Thank you. We deleted the word “experience” and modified the sentence into “we performed a systematic review of the use of dapagliflozin and empagliflozin in children”. (We did not use the words “effectiveness and safety” here to avoid a repetition with the subsequent sentence, and also to take into account the limitations of current evidence, as you correctly pointed out in your comment above.)

7. Methods, search strategy, paragraph 1: PRISMA is a guideline for reporting not conduct of systematic review. The statement should read "...and was reported according to the 2020 Preferred....".
Thank you. The wording has been corrected accordingly.

8. Methods, Eligibility criteria: please specify the types of study that would be accepted and excluded.
Thank you. This is now specified in the revised Methods section.

9. Methods, Analysis: the first paragraph appears to be a description of statistical analysis of individual primary studies, not meta-analysis. Analysis of primary studies is unusual in a systematic review and meta-analysis, unless there are some individual studies that were not analyzed appropriately. Were there any of such cases, if so, please state here clearly. Otherwise, this paragraph is probably not relevant in a systematic review and meta-analysis and need not be included.
Thank you for your comment. However, we kindly disagree. In a systematic review, an attempt is made to assess in a summative manner the results from individual studies. This paragraph does not relate to calculation within the single included studies, but to their summative analysis. Indeed, methods have been developed to combine study results, even when a meta-analysis is not possible. The first author has

published n>50 systematic reviews on several topics, especially on rare diseases and conditions, and, over the years, has collected an extensive experience with such approaches. In particular, the statistical approach described in this paragraph was used to integrate reported data on type 2 diabetes mellitus and GSD Ib (balancing the number of patients reported in each article), as well as comparing the weighted characteristics (age, weight, …) of individuals reported for the different indications. Therefore, we would like to keep this paragraph, that is important to transparently report the methods used in the systematic, summative assessment of the studies that did not qualify for a meta-analysis.

10. Methods, Analysis, paragraph 2. Here the authors described the methods of meta-analysis. Given that meta-analysis could only be performed on one condition and one outcome with 2 studies, how were the results of the other included studies synthesized? If they were synthesized narratively, which appears to be the case, the authors should put a statement here.
Thank you. Please also see answer to your comment #9. Studies that could not be included in the meta-analysis were summatively assessed according to the methods described in the paragraph discussed in comment #9. Addressing rare conditions with systematic reviews is a challenging task. Over approximately 15 years, the first author has collected a pretty extensive experience in dealing with these difficulties, perfectionating some skills with these tricky situations. Tables 1, 2, 3 and Figure 3 are examples of such a systematic (albeit not meta-analysis) and summative, combined assessment of several studies.

11. Findings, Diabetes Mellitus, paragraph 3: here the authors reported the only results of meta-analysis. Please include the number of studies and cumulative participant number, and I square value. If I square is high that indicates substantial heterogeneity, some efforts should be made to explore plausible explanation.
Thank you. This information has been added.

12. Findings, Glycogen storage disease, last paragraph: 15% of hypoglycaemia appears high. If this is part of the expected occurrence in the condition, please put the findings in context.
Thank you. Owing to comments from Reviewer #2 (asking to favor the presentation of summative results as provided in the Tables and Figures), we deleted this sentence from the body of the manuscript. Anyway, please also note that in the preceding paragraph we state that “The authors acknowledged that, hypoglycaemia and lactic acidosis being common occurrences in GSD Ib, it was impossible to determine whether empagliflozin contributed to these events.”.

13. Discussion: overall discussion can be shortened by around 20-30%, especially given that most findings are preliminary.
Thank you. In the revised manuscript, the Discussion (despite including new contents as requested by the 3 Reviewers and the Editor) is now n=330 words (>20%) shorter than the original Discussion.

14. Discussion: in the discussion about the effects of the medication in diabetes (paragraph 3), the authors should emphasize evidence from RCTs above others as RCTs offer higher-quality evidence.
Thank you. This has been added to the revised Discussion.

15. Conclusions: second sentence- in view of the mostly preliminary evidence, the tone of conclusion should be more circumspect, for example "seemingly" positive benefit-risk balance instead of simply "positive benefit-risk balance".
Thank you. We agree. The sentence has been modified as suggested.

16. I wish the authors the best in their revision.
Thank you very much. Thank you indeed for your constructive comments, that – we feel – have helped us in improving the quality of our presentation.

Reviewer #2
Abstract
17. The methods section only reports a systematic review and not the meta-analysis
Thank you. This is an important point. This information has now been added to the

Abstract.

18. Which software was used for conducting a systematic review and meta-analysis?
No specific software was used for the systematic review, apart from the statistical software (this information has now been added to the body of the manuscript). For the meta-analysis, Review Manager (RevMan), version 5.4.1 (The Cochrane Collaboration, 2020) was used (this information has now been added to the Abstract).

Introduction
19. More details can be mentioned about the drugs.
Any previous literature, work, or citations on this topic?
Some details on the mentioned drugs (including pertaining references) are now provided in the revised Introduction.

20. Why is there a need for a systematic literature review?
Thank you. This is indeed worth better stressing in the Introduction. As already stated in the original submission, data on dapagliflozin and empagliflozin use for younger children or children with indications different from type 2 diabetes mellitus is limited. Importantly, this issue has not been systematically addressed yet. This important statement has been added to the revised manuscript. Thank you again!

Methods
21. In section 2.4 - The scale used for rating and scoring was a validated scale. If yes, what was the name, and kindly cite it. If not, how was it developed?
Unfortunately, while there are validated methods to assess RCTs, cohort studies or case-control studies, there is no officially recommended scale to grade completeness or reporting in systematic reviews focusing on rare conditions, for which most literature is composed of case reports and small case series. The research group around the first author, over the last 20 years, has conducted numerous (n>50) systematic reviews on rare conditions. These reviews often ground on scanty available literature, mostly comprised of case reports, case series or uncontrolled investigations, for which traditional evidence assessment methods (like the Newcastle-Ottawa scale) are inappropriate. Over the years, and after the suggestions of some Reviewers and Editors while evaluating some of our previous works, we have developed a rating of “completeness of reporting” (which we used for the first time in 2018), which is flexible and can be applied also on such types of reports, and that we have been using a number of times (in approximately 20 systematic reviews), perfectionating it over the years. In the manuscript, as a methodological proof, we cite one recent example of its use (but, with a rapid search in my files, just over the last two years, I identified n=10 systematic reviews where we used this scale).

22. Why were other commonly used database such as PubMed, Embase, Scopus not considered?
We think this is just a confusion about synonyms, and we are very sorry about that. Actually, the literature search was performed in the National Library of Medicine (i.e. PubMed), Excerpta Medica (i.e. Embase) and Web of Science databases. In the revised manuscript, we provide the synonyms between brackets. We hope this makes it clearer to both the Reviewer and the Readership. Thank you for raising this point, which improves the clarity of our presentation.

Results
23. The type of studies included should be described in the methods section and the results section should report the numbers, for example: case reports (n=4), etc.
Thank you. This information has been added.

24. Not every study should be described here in the main text, most of the information should be presented succinctly in the table format.
Thank you. You are absolutely right, and we strongly agree with you. Several studies were already summarized in the Tables or Figures. We deleted the duplicate parts reporting (not that relevant) details on some single studies. Furthermore, while summarizing the results of some specific studies that were difficult or impossible to report in a summative way, we deleted some details and shortened the pertaining parts of the manuscript.

25. As per the rules, meta-analysis cannot be conducted on 2 studies. It does not hold any value. Please take out the meta-analysis and its mention from the manuscript.
Thank you. We understand your criticism, which we faced and discussed already among us while preparing the original submission. However, in an effort to combine and address the requests from the different Reviewers and the Editorial comments, we kept the meta-analysis. Nevertheless, taking into account your comment and the comments of Reviewer #1 and the Editorial Office, in the revised manuscript, we deleted the word “meta-analysis” from the title and we moderated the wordings regarding the meta-analysis throughout the manuscript. Also, please note that, according to the Cochrane Handbook for Systematic Reviews of Interventions, Version 6.4 (2023), Chapter 10: Analysing data and undertaking meta-analysis, “Meta-analysis is the statistical combination of results from two or more separate studies.” [https://training.cochrane.org/handbook/current/chapter-10].

26. Conduct GRADE analysis to show the importance of this study.
Thank you. A GRADE analysis has been performed and the manuscript amended (Methods and Results sections).

Discussion section
27. Very very long. It does not list just important pointers gained from the study but instead explains some more studies. Entire essence of discussion is lost.
Thank you. The Discussion has been shortened by >20% of its preceding length. The sentences referring to two new studies (one article, and one conference abstract) presented in the Discussion (but not included in the systematic review) have been deleted.

Reviewer #3

This review examines the use of SGLT2 inhibitors in young people with T2D, T1D, CKD, heart failure, and several rare disorders of glycogen metabolism. Only the diabetes studies were designed for prospective regulatory review. The paper is well-written and the statistical approaches appear logical to this reviewer who is not an expert statistician. Data, although limited, on use of these agents to treat CKD, heart failure, and rare disorders of glycogen metabolism are particularly important and the anecdotal available evidence is analyzed in an appropriate manner. I have one major and one minor concern.

Major:
28. The patients with diabetes included 138 T2D, and 48 T1D, followed in a small number of studies for 24-52 weeks. The authors state unequivocally in the abstract as well as other site, that "Diabetic ketoacidosis is exquisitely rare in children." The incidence of DKA requiring hospitalization in children with T1D treated with insulin is in the neighborhood of 5 episodes/100 patient years. It may be a bit higher in those on pumps. With only 48 children with DKA followed in a controlled clinical trial for 24-52 weeks, it is impossible to make this statement. The authors must temper their statement and perhaps call for larger studies. This may end up being a fantastic drug class but presently it comes with much theoretical risk of euglycemic ketoacidosis. There is not even a theoretical reason I can come up with that would make the risks less for children than for adults.
Thank you. You are making an important point, thank you for raising it to our attention. The word “exquisitely” has been deleted from the abstract. Furthermore, in the body of the manuscript we added that no cases have been reported “so far”, and, in the discussion/conclusion, we now acknowledge that, given the low number of children studied so far, the ability to detect rare side effects is limited.

Minor:
29. There are numerous abbreviations in the text which are never explained-- they should be spelled out and explained in the text or in a glossary:
Thank you. Abbreviations have been consistently explained (on their first occurrence) or substituted with full wording.

30. p 10 3.2.2 G6P3 deficiency-- might actually be good to at least briefly allude to the pathophysiology of these rare disorders

Thank you. In the revised Results section, we briefly added that G6PC3 deficiency is one of the potential causes of severe congenital neutropaenia type 4. Furthermore, in the revised Discussion, we now make clear that the pathophysiology explained for GSD Ib is the same also for G6PC3 deficiency (i.e. in both G6PC3-deficiency and GSD1b, 1,5-anhydroglucitol-6-phosphate accumulates in neutrophils, inhibiting hexokinases, therefore impairing energy generation and causing neutrophil malfunction and apoptosis).

31. p 16 last para of3.2.4 UGT1A9 ontogeny
Thank you. UGT1A9 has now been modified into “UDP-glucuronosyltransferase family 1 member 9 (UGT1A9)”. UGT 1A9 is an enzyme of the glucuronidation pathway, which transforms small lipophilic molecules into water-soluble metabolites.

32. p 20-- this reviewer does not understand the mention, line 6 of skin sodium-- is this intracellular, or related to sweat sodium?
Thank you. It has been a pretty recent discovery that “sodium can be stored on negatively charged glycosaminoglycans in the skin interstitium, where it becomes osmotically inactive”. Thus, the skin interstitium may function as a “fluid-buffering system able to store sodium without commensurate water retention” [Lava SA et al. Pediatr Nephrol. 2015; 30:1389–1396]. In the revised manuscript, we now try to make this a bit more clear (revised sentence: “sodium stored in the skin interstitium”) and cite a review, that might help the readership to have a better understanding of this exciting physiological process.

Editorial Office comments

33. * Please note the reviewer suggestion to remove 'meta-analysis' from the title.
Thank you. “Meta-analysis” has been deleted from the title.

34. * Literature search information – A full search strategy for at least one of the databases must be provided as ESM. To ensure transparency and replicability, we encourage authors to conform to PRISMA recommendations and report all search strategies used, the specific results from each database that was searched, and the date that each database was searched. This can be included in the Supplementary Information.
Thank you. This information is provided in the body of the manuscript (Section 2.1: “Searches were performed in the National Library of Medicine (PubMed®), Excerpta Medica (Embase®), and Web of Science databases to September 12th, 2023. Original reports with no date limits were considered. The search strategy used the terms (dapagliflozin OR empagliflozin) AND (childhood OR child OR paediatrics).”), respectively in Figure 1.

35. * Please spell out 'Pediatric Drugs' in the title page of the Supplementary Information.
This has been corrected.

36. * Please ensure that a running header of ≤ 100 characters is provided.
Thank you. The current running header is n=57 characters (spaces included) long.

37. * Abstract: Please restructure into Introduction, Objective, Methods, Results and Conclusion sections.
Thank you. The structure of the Abstract has been corrected, as requested.

38. * Please clarify if study authors were contacted for additional information. A list of such studies with information sought should be provided as ESM.
Thank you for this question. As part of our initial methodological strategy, we were planning to contact authors of the original reports when needed. However, while performing the analysis, this turned out not to be necessary, so that in the end we did not contact Authors of included reports. Taking into account this comment, we deleted the pertaining sentence in the Methods.

39. * Please clarify the process for duplicate identification.
There are two types of issues. Duplicate publications (i.e. the same article identified through two different databases) are identified simply by their coordinates (authors,

	title, journal, year, volume, pages, and codes like PMID or doi). Duplicate cases, or multiple reports (i.e. the same case published in two different articles) are more tricky to pick up. I am explaining the strategy we used to identify these cases while answering your next comment (“multiple reports”). 40. * Please clarify how you dealt with multiple reports. # Suspicion of multiple reports arises when a similar publication is characterized by some (or all) of following similarities: same author names, institution(s), setting (outpatient, inpatient, chronic therapy versus acute emergency, …), patient characteristics (age, sex, weight, height, diagnosis, duration of therapy, administered dose), measures of outcome used (i.e. “neutrophil count”), and outcome(s) reported (e.g. “normalization of absolute neutrophil count”, “remission of intestinal symptoms”, “improvement in oral ulcers”), respectively same values of specific baseline characteristics or outcomes (e.g. heart rate 124/min), date (e.g. series of 3 patients presented between 2012 and 2016), duration of follow-up [https://handbook-5-1.cochrane.org/chapter_7/7_2_2_identifying_multiple_reports_from_the_same_study.htm]. This is now briefly summarized in the Methods section of the revised manuscript.
Suggested Reviewers:	Gregorio P. Milani, MD MSc Associate Professor, Università degli Studi di Milano gregorio.milani@unimi.it Outstanding clinician, famous paediatrician with extensive academic tracking (n > 220 scientific articles), among others in fluid & electrolytes / diuretics, and nutrition. Editor of Eur J Pediatr. Advanced training in medical statistics, extensive experience in systematic reviews and meta-analysis.
	Mario G. Bianchetti, MD Professor & Former Dean, Università della Svizzera italiana mario.bianchetti@usi.ch Excellent clinician, renowned paediatric nephrologist with extensive academic tracking (n > 390 scientific articles), among others in fluid & electrolytes, arterial hypertension, paediatric clinical pharmacology of diuretics and anti-hypertensive drugs. Decades of experience in systematic reviews (author of n>60 systematic reviews).
	Maristella Santi, MD Consultant Endocrinologist & Diabetologist, University Hospital of Fribourg maristella.santi@gmail.com Recognized clinician, outstanding paediatric endocrinologist with good academic tracking, marked interest in management of diabetes mellitus in children.
	Damien Schaffner, MD Paediatric Cardiologist, Deutsches Herzzentrum Berlin - Charité damien.schaffner@bluewin.ch Excellent clinician, recognized paediatric cardiologist with academic experience, marked interest in cardiac intensive care and therapy advancements in paediatric cardiology including severe heart failure.
	Giacomo D Simonetti, MD Chair of Paediatrics, Paediatric Institute of Southern Switzerland, Ente Ospedaliero Cantonale giacomo.simonetti@eoc.ch Excellent clinician, internationally recognized paediatric nephrologist with extensive academic tracking (n > 240 scientific articles) in chronic kidney disease therapy, arterial hypertension, clinical pharmacology of anti-hypertensive drugs in children.
	Giuseppe Pontrelli, MD MSc PhD Head, Clinical trials quality team, Ospedale pediatrico Bambino Gesù giuseppe.pontrelli@obpg.net Recognized paediatrician and renowned researcher, with good academic tracking (n>70 peer-reviewed articles). Great experience in drug investigation in children and development and evaluation of therapeutic interventions in Paediatrics.

Manuscript entitled “Dapagliflozin and Empagliflozin in Paediatric Indications: a Systematic Review and Meta-Analysis”

Dear Editors,

On behalf of my co-authors, I submit the enclosed manuscript for consideration by *Pediatric Drugs*.

Sodium glucose type 2 transporter inhibitors (SGLT2i) have revolutionized the treatment of type 2 diabetes mellitus, heart failure and chronic kidney disease in adults. There are hopes that similar results might be achievable also in children. Yet, only their use in type 2 diabetes mellitus adolescents has so far been properly investigated.

In an effort to improve the understanding of the clinical pharmacology and potential benefit-risk profile of SGLT2-inhibitors in paediatric heart failure, chronic kidney disease and glycogen storage disease type Ib, we performed a systematic review of the experience with the use of dapagliflozin and empagliflozin in children. The results from this review will support the implementation of prospective protocols for the evaluation of efficacy and safety of these drugs in Paediatrics.

We believe that this contribution might be of interest to the readership of *Pediatric Drugs*.

Please do not hesitate to contact me, should you need any further information.

Kind regards,
Sebastiano A.G. Lava (December 26th, 2023)

Dapagliflozin and Empagliflozin in Paediatric Indications: a Systematic Review

Running header: Dapagliflozin and Empagliflozin in Paediatric Indications

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- Manuscript: n=6111 words
- Tables: n=3

- Figures: n=3
- Supplementary Tables: n=2
- Supplementary Figure: n=1
- References: n=69

Keywords: sodium glucose transporter type 2 inhibitors, dapagliflozin, empagliflozin, paediatric pharmacology, pharmacokinetics, diabetes mellitus, heart failure, chronic kidney disease, glycogen storage disease type Ib

Abstract

Introduction: In adults, sodium glucose type 2 transporter inhibitors have revolutionized the treatment of type 2 diabetes mellitus, heart failure and chronic kidney disease.

Objective: We aimed to review information on compassionate use, clinical pharmacology, efficacy, and safety of dapagliflozin and empagliflozin in children.

Methods: Systematic review of published clinical trials, case reports or observational studies in Medline, Excerpta Medica and Web of Science databases from inception to September 2023. For the two randomised-controlled trials on type 2 diabetes mellitus, we implemented a meta-analysis on the primary outcome (mean difference in HbA1c between intervention and placebo groups). Review Manager (RevMan), version 5.4.1 was used for this purpose.

Results: Thirty-five articles (nine case reports, 10 case series, one prospective non-controlled trial, four controlled randomized trials, two surveys, six pharmacokinetic studies, and three pharmacovigilance studies) were selected in which 415 children were exposed to either dapagliflozin or empagliflozin: 189 diabetic patients (mean age 14.7±2.9 years), 32 children with glycogen storage disease type Ib (GSD Ib), G6PC3-deficiency or severe congenital neutropenia type 4 (8.5±5.1 years), 47 children with kidney disease or heart failure (11.2±6.1 years), 84 patients in pharmacokinetic studies (15.1±2.3 years) and 63 patients in toxicological series.

The effect of dapagliflozin and empagliflozin in type 2 diabetes mellitus was demonstrated by HbA1c reduction in two randomized trials among a total of 177 adolescents, with a mean HbA1c difference of -0.82% (95%-CI -1.34 to -0.29) as compared to placebo (no heterogeneity, I^2=0%). Dose ranged between 5-20 mg (mean 11.4±3.7) once daily for dapagliflozin and between 5-25 mg (mean 15.4±7.4) once daily for empagliflozin. Among the paediatric cases of GSD Ib, empagliflozin 0.1-1.3 mg/kg/d improved neutropenia, infections, and gastrointestinal health. Dapagliflozin (mean dose 6.9±5.2 mg once daily) was well-tolerated in children with chronic kidney disease and heart failure.

Side effects were generally mild, the most frequent being hypoglycaemia in children with GSD Ib (33% of patients) or type 2 diabetes mellitus (14% of patients) on concomitant hypoglycaemic drugs. Diabetic ketoacidosis is rare in children.

Conclusion: Early evidence suggests that dapagliflozin and empagliflozin are well tolerated in children. A clinical pharmacology rationale currently exists only for adolescents with diabetes mellitus.

Prospero registration number: CRD42023438162.

Key points

- Dapagliflozin and empagliflozin have revolutionized the treatment of type 2 diabetes mellitus, heart failure and chronic kidney disease in adults.
- Early evidence suggests that these molecules are well tolerated in Paediatrics. They have been successfully used in children and adolescents with type 2 diabetes mellitus, heart failure, chronic kidney disease, and glycogen storage disease type Ib. Further robust studies will need to verify these findings.
- A dose rationale currently exists only for adolescents with diabetes mellitus.

1. Introduction

In the late 90's, sodium glucose cotransporter type 2 inhibitors (SGLT2-inhibitors) were developed as non-insulin-dependent antidiabetic drugs, and were eventually approved by the Food and Drug Administration and the European Medicines Agency between 2012 and 2017. Concerns about the cardiovascular safety of the antidiabetic rosiglitazone led these agencies to require specific cardiovascular analyses for any new antidiabetic drug. Surprisingly, these trials not only demonstrated cardiovascular safety, but also showed impressive cardioprotective effects [1], which were detected in adult heart failure patients with and without type 2 diabetes mellitus (T2DM) [2, 3]. Given 25-26% reduction in a composite outcome of worsening heart failure or cardiovascular death [2, 3], since 2021 they have been recommended as routine therapy for adults with heart failure with reduced ejection fraction [4]. Furthermore, they are efficacious [5-7] and advised also for adult patients with heart failure with preserved ejection fraction [8]. The mechanisms of cardiovascular protection are multiple and include among others: diuresis (with a differential role on intra- and extracellular body fluid compartments) reducing cardiac overload, suppression of sympathetic nervous system overdrive, metabolism shift towards ketone bodies positively impacting cardiac energetics, increased haemoglobin/haematocrit, modification of $Na^+/K^+/Ca^{2+}$ ionic homeostasis and uric acid metabolism, and modulation of the FGF-23 / klotho pathway [1,9-13].

Also, prespecified analyses examined the effects of empagliflozin [14-16], dapagliflozin [17] and canagliflozin [18-19] on kidney outcomes, and detected a risk reduction of renal composite outcomes in the range of 30-40% [17]. Mechanisms are far beyond a simple improvement in glycaemic control and reduction of hyperfiltration. Indeed, sustained natriuresis, reduction in plasma volume, sodium stored in the skin interstitium [20] and body weight appear to play a role. Furthermore, metabolism shift away from glucose oxidation in favour of ketone and fatty acid oxidation might be beneficial for both the kidneys and the myocardium, two avid energy consumers [14].

Despite their impressive efficacy and good safety profile in adults with T2DM, heart failure and chronic kidney disease, and having been approved for T2DM in adolescents 10-18 years of age, limited data are available on dapagliflozin and empagliflozin for younger children or children with indications different from T2DM, and this topic has hitherto not been systematically addressed. In an effort to improve the understanding of the clinical pharmacology and potential benefit-risk profile of SGLT2-inhibitors in paediatric heart failure,

chronic kidney disease and glycogen storage disease type Ib, we performed a systematic review of the use of dapagliflozin and empagliflozin in children. The results from this review will support the implementation of prospective protocols for the evaluation of efficacy and safety of both drugs in paediatric heart failure, chronic kidney disease and glycogen storage disease type Ib.

2. Methods

2.1. Search Strategy

The review was pre-registered on PROSPERO (CRD42023438162) and is reported according to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations [21]. Searches were performed in the National Library of Medicine (PubMed®), Excerpta Medica (Embase), and Web of Science databases to September 12th, 2023. Original reports with no date limits were considered. The search strategy used the terms (dapagliflozin OR empagliflozin) AND (childhood OR child OR paediatrics). References listed within bibliographies of the retrieved records and relevant articles known to the authors were also considered. Identified titles and abstracts were independently screened by two authors in an unblinded fashion. Full-text publications of candidate reports were reviewed in detail for eligibility. Uncertainties and disagreements were solved through discussion and consensus. Institutional Review Board approval was not required for this literature review.

2.2. Eligibility criteria

We included original articles and letters (randomized controlled trials, pharmacokinetic investigations, prospective and retrospective studies, case series and case reports, pharmacovigilance database interrogations, survey studies) reporting human subjects aged 18 years or less, who were treated with dapagliflozin or empagliflozin. Reports addressing the use of dapagliflozin or empagliflozin in both adults and children were retained if they specifically presented paediatric data, and only paediatric cases were included in the analysis. Additionally, children made known to pharmacoepidemiology and monitoring institutions having (accidentally) ingested either dapagliflozin or empagliflozin were also retained. Articles in languages other than English, French, German, Italian, Portuguese, or Spanish were excluded. Multiple reports were suspected when two (or more) publications were characterized

by some (or all) of the following similarities: same authors, institutions or setting; patient characteristics; assessed endpoints; reported outcomes; observation period dates and duration; duration of follow-up. Cases reported twice in the literature were analyzed only once.

2.3. Data Extraction

Data were collected according to a pre-defined checklist, including demographics, underlying condition, comedication, laboratory values, administered molecule and dose, duration of treatment and follow-up, and observed side effects (including among others hypoglycaemia, urinary tract infections, metabolic acidosis, and presence of ketones in blood).

2.4. Completeness of reporting and grading of evidence

The completeness of reporting was evaluated for clinical studies on T2DM, glycogen storage disease type Ib (GSD Ib), proteinuric kidney disease, heart failure, and pharmacokinetics, according to the following four components [22]: 1. description of population and design; 2. information on dosage and treatment duration; 3. information on assessed outcomes and clinical course; 4. data on monitored side effects. Each component was rated as 0, 1, 2, and the reporting quality was graded according to the sum of each item as excellent (8), good (6 to 7), acceptable (4 to 5) or poor (0 to 3). Pharmacovigilance and survey studies could not be assessed by these means and are described separately. Furthermore, for the sake of completeness, we also graded the evidence of included reports according to the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework [23].

2.5. Analysis

Categorical data are given as counts and were analysed using the Fisher exact test or Chi-square test, as appropriate. Continuous data are presented as median and interquartile range (IQR), respectively as mean and standard deviation, depending on the measures reported in the pertaining original publication. Where appropriate, results were summarised in an integrated manner based on the equations recommended by Wan and colleagues, which allow estimation of mean and standard deviation from median, absolute range and sample size [24]. Weighted means were then calculated and compared with Brown-Forsythe and Welch analysis of variance (ANOVA). Two-sided p-values of <0.05 were used as threshold for statistically significant differences. GraphPad Prism for Macintosh 10.0.3 (GraphPad Software, San Diego, California, United States) was used for statistical comparisons.

Even though data was limited to two randomised-controlled trials on type 2 diabetes mellitus, we implemented a meta-analysis on the primary outcome (mean difference in HbA1c between intervention and placebo groups). The risk of bias was assessed along five categories, as recommended by the Cochrane collaboration (selection bias, performance bias, detection bias, attrition bias and reporting bias). We opted for a random-effects model because this method does not assume that studies share a common effect size and helps to address unobserved heterogeneity. Statistical heterogeneity was assessed with the I^2-index (heterogeneity is considered unimportant when I^2 is less than 30-40%), and results are displayed using forest plots, including 95% confidence interval (95%-CI). Funnel plot and Egger test were not performed due to the limited number of studies. Review Manager (RevMan), version 5.4.1 (The Cochrane Collaboration, 2020) was used for the purpose of this meta-analysis.

3. Results

3.1. Search Results

The literature search process is summarised in Figure 1. For the final analysis, we retained 35 reports published since 2016 [25-59]: 5 from Asia (Israel, N=1; Japan, N=3; People's Republic of China, N=1), 20 from Europe (Belgium, N=1; Germany, N=5; Hungary, N=1; Italy, N=3; Poland, N=1; Rumania, N=1; Sweden, N=2; the Netherlands, N=3; United Kingdom, N=3) and 10 from America (Brazil, N=1; Chile, N=1; United States of America, N=8).

The selected articles described 189 diabetic patients [25-32], 32 children with glycogen storage disease type Ib [33-43], G6PC3-deficiency [44] or severe congenital neutropenia type 4 [45], 9 patients with proteinuric kidney disease [46], 38 patients with heart failure [47], 84 patients in pharmacokinetic studies [48-53] and 63 patients in toxicological series [54-57], for a total of 415 children. They were nine case reports [29-31, 35, 38-40, 45, 57], 10 case series [25, 33, 34, 36, 37, 41-44, 47], one prospective non-controlled trial [46], two controlled, randomized, cross-over trials [27, 28], two double-blinded, multiple group, randomized controlled trials [26, 32], two surveys [58, 59], five pharmacokinetic studies [48-52], one physiologically-based pharmacokinetic investigation [53], and three pharmacovigilance studies [54-56].

Reporting completeness was rated for 29 original studies addressing T2DM (n=8), GSD Ib (n=13), proteinuric kidney disease (n=1), heart failure (n=1) or reporting pharmacokinetics (n=6): it was poor in 4, acceptable in 8, and good in 17 articles. As per the GRADE classification, rated for the same studies apart from the physiologically-based pharmacokinetic modelling exercise [53] (for which GRADE is an inappropriate instrument), evidence quality was very low in 13, low in 6, moderate in 5 and high in 4 articles.

T2DM patients (and pharmacokinetic studies participants) were significantly ($p<0.0001$) older (14.7 ± 2.9 years) and had a higher weight (85.7 ± 29.5 kg) when compared to glycogen storage disease type Ib (8.5 ± 5.1 years, 28.9 ± 14.7 kg), chronic kidney disease or heart failure (11.2 ± 6.1 years, 41.9 ± 38.6 kg) (Table 1).

3.2. Findings

3.2.1. Diabetes mellitus

Eight articles reported on subjects having received either dapagliflozin (n=103) or empagliflozin (n=86) for diabetes mellitus (type 2, n=138; type 1, n=48; congenital insulin resistance, n=3). Their mean age was >15 years and mean weight >85 kg, while mean BMI was 32 kg/m^2 (Table 1). Additionally, one article, which we address in more detail in the section on safety and tolerability, reported on a 17 year-old adolescent girl, who developed a normoglycaemic ketosis while on dapagliflozin. Her blood glucose decreased from 9.7 at baseline to 8.9 mmol/L while on therapy.

The studies differed as per the reported outcomes: blood glucose (6 studies), HbA1c (7 studies), time within desired range (1 study), changes in insulin dose (combination therapy) (5 studies), reduction in co-medication (4 studies). Furthermore, blood glucose and HbA1c were not always reported at baseline and at study end. Side effects were mostly mild, the most frequent being hypoglycaemia detected on regular monitoring (14% of patients). Only in one study, this was severe in 3 patients [26]. Hypoglycaemia was mostly experienced by patients who were also on insulin [26]. Of note, genito-urinary infections were rare (<3%) and no metabolic acidosis or ketoacidosis was reported (Table 2).

Four publications addressed the use of dapagliflozin (n=2) or empagliflozin (n=2) in T2DM (Table 3), two being case reports [30, 31] and two randomized controlled trials [26, 32]. These two trials included a total of 177 adolescents (91 in the intervention, 86 in the placebo groups) and showed a significant effect of SGLT2 inhibition, as compared to placebo, in reducing HbA1c after 24-26 weeks of treatment (mean difference -0.82%, 95%-CI -1.34 to -

0.29). Risk of bias was low (Supplementary Figure 1) and no significant heterogeneity was detected (I^2=0%, Figure 2).

Two case reports described a 16 year-old female with Prader-Willi syndrome with a difficult-to-manage T2DM [30], who was successfully controlled with liraglutide and empagliflozin (25 mg q.d.), respectively a previously small-for-gestational-age 12 year-old boy treated with metformin and dapagliflozin (5 mg 1x/d) [31]. None of these patients experienced adverse events.

Two studies addressed the use of dapagliflozin for type 1 diabetes mellitus. In a phase 1 crossover trial among 33 patients 12 to 21 years of age, Biester and colleagues investigated dapagliflozin as add-on to insulin for 24h [27]. Dapagliflozin reduced both mean insulin dose over 24h (by 13.6%, p<0.0001) and insulin administered within 4h after a standardized liquid mixed meal (p=0.0402). While beta-hydroxybutyrate levels significantly increased (0.17±0.13 mmol/L versus 0.11±0.08 mmol/L, p<0.0001), they were never >1.0mmol/L. Adverse events were mild and infrequent, without significant differences between treatment and placebo arms.

In another, double-blind, placebo-controlled, crossover study, in which 15 adolescents aged 15.4±1.6 years and 15 young adults aged 18.7±0.8 years were included, the effect of high dose dapagliflozin (10 mg, 2 single doses over 24h) on full closed loop insulin patients was investigated [28]. Time within the desired glycaemic range (3.9 to 10mmol/L) was significantly increased in patients receiving dapagliflozin (68%), as compared to placebo (50%, p<0.001). Dapagliflozin also led to a significant reduction in the total insulin dose. No severe hypoglycaemia episode and no diabetic ketoacidosis were recorded.

Finally, two case reports [25, 29] accounted for three patients having received either dapagliflozin (n=1) or empagliflozin (n=2) for Rabson-Mendenhall syndrome, a form of severe congenital insulin resistance. In these patients, diabetes had been difficult to control with insulin and metformin, and SGLT2-inhibitors led to HbA1c improvement and insulin dose reduction. Despite some increase in beta-hydroxybutyrate, its levels remained within normal range [29], and no ketoacidosis occurred. Galderisi and colleagues noticed increased calcium and phosphate excretion on empagliflozin and an increased calcium excretion on dapagliflozin, without any change in plasma levels [25].

3.2.2. Glycogen storage disease type Ib

Eleven publications individually reported on 29 patients with glycogen storage disease type Ib, one article described a case of severe congenital neutropenia type 4, and another described the course of two patients with G6PC3-deficiency (one of the potential causes of severe congenital neutropenia type 4). The case of a 6-year-old patient [36, 37], as well as three other cases started on empagliflozin at 8, 12 and 15.5 years of age [34, 60], reported twice in the literature, were analyzed only once. Furthermore, an international questionnaire collected data on 32 adults and 80 children with glycogen storage disease type Ib, ranging in age from 0 to 38, median 10.5 years [58]. Recently, the same group published a survey among patients or parents, including both adult and paediatric patients, addressing patient-reported outcomes [59]. Authors admitted that a relevant (yet unspecified) proportion of respondents was depicted in both surveys [59].

Individual cases ranged from 11 months to 16 years, with median of 8.0 years at start of empagliflozin therapy, for a follow-up of 10 to 1050 days (median 393 days). There was some variability in both the starting (from 0.1 mg/kg to 0.6 mg/kg) and the final dose (from 0.1 mg/kg to 1.3 mg/kg), as well as in the posology (mainly given once daily, but also twice daily [33] or even 3 times weekly). There were two cases, in which the initial dose was reduced because of positive, satisfactory clinical course, with maintenance of response [44].

There was heterogeneity in the collected outcomes. Globally, patients showed improved neutrophil counts and function (despite reduction, n=6, or weaning, n=13, of granulocyte colony stimulating factor, G-CSF, injections), reduced infections, need for hospitalisations and antibiotic treatments, improved gastrointestinal symptoms and reduced stool frequency, improved appetite, absorption and growth, better oral health and reduced aphthous lesions, improved skin, and wound healing, resolved anaemia and iron deficiency (Figure 3). For example, in a series of eight patients, seven were on treatment for iron deficiency and all ceased iron supplementation upon empagliflozin treatment [33]. Similarly, in a patient previously dependent on erythrocyte concentrate transfusions, these could be stopped [37]. Improved metabolic control (urate [33, 34, 38, 40], triglycerides [34, 35, 38] and cholesterol reduction or normalization [35, 40]) have also been reported. Intermediate metabolism was positively impacted, with normalization of urate and pentose metabolism intermediates [40]. Of note, not only glucose control, but also glycaemic fluctuations improved [35-37], which was imputed to a better intestinal meal tolerance [35, 37].

The case of a 6 year-old boy, who started to eat by himself for the first time, is noteworthy [37]. One patient, in addition to recurrent aphthous stomatitis and a severe Crohn-like irritable bowel disease, suffered from difficult-to-control juvenile idiopathic arthritis. This remitted within 3 weeks of empagliflozin treatment [35].

Neutrophil function was assessed by oxidative burst, neutrophil chemotaxis and bactericidal assay [37], respectively by immunophenotyping neutrophil subsets, assessing the proportion of mature and activated neutrophils [42]. Furthermore, plasma 1,5-anhydroglucitol (1,5-AG) was assessed in 20 cases and in all but one case decreased [33, 35, 37, 38, 40, 41, 43, 44] (Figure 3). Clinical improvement often occurred before or independently from the neutrophil count response [37] or without (complete) absolute neutrophil count (ANC) normalisation [44], leading to the hypothesis that the improvement in neutrophil function may play a major role [37, 42]. Furthermore, the amplitude of neutrophil count fluctuations was reduced with empagliflozin, suggesting increased neutrophil lifetime [37].

Globally, empagliflozin in these children was safe. No serious adverse events, and in particular no ketoacidosis, were reported. Similarly, hypoglycaemia was generally recorded on continuous or routine monitoring, glycaemia was mostly similar [38] or even better controlled than before treatment [37], and was easily managed with dietary modifications [42]. There was only one case of severe hypoglycaemia, causing overnight seizures [33], and explained in the context of strict dietary control with low carbohydrate intake [33]. Genitourinary infections were rare (Table 2) [33]. An 11 year-old girl developed generalized arthralgias after dose increase to 12.5 mg b.i.d. (0.6 mg/kg/day), which disappeared after reducing the dose to 10 mg b.i.d. (0.48 mg/kg/day) [40].

Respondents of an international survey across 24 countries provided data on 112 glycogen storage disease type Ib patients (n=80, 71%, of whom were <18 years of age), with median treatment duration of 9.5 (range <1 to 27) months [58]. The median paediatric dose was 0.4 mg/kg/d (absolute range 0.1-0.9 mg/kg/day), administered as single daily dose in 48/112 (43%) and as two divided doses in the remaining patients. In both adults and children, there were beneficial effects on neutropenia frequency, oral and anogenital lesions, recurrent bacterial infections, presence and severity of irritable bowel disease, and anaemia prevalence. Out of the 89 patients on G-CSF prior to SGLT2-inhibitor therapy, 49 (55%) could stop it and 15 (17%) reduce its dose.

Empagliflozin was well tolerated, with 77 (69%) patients not showing any adverse event. The most common adverse event was hypoglycaemia. Different from the individually reported cases (Table 2), this was often severe (defined as <3.0mmol/L and symptomatic) and involved 20 out of 111 patients (18%). There were 6/111 (5.4%) cases of lactic acidosis (3 children, 3 adults). The authors acknowledged that, hypoglycaemia and lactic acidosis being

common occurrences in GSD Ib, it was impossible to determine whether empagliflozin contributed to these events. There were 3 fungal (n=3/109, 2.8%, 1 of which in a child) and 8 urinary tract (n=8/104, 7.7%, 5 of which in children) infections. A 23 year-old adult with gastroenteritis and dehydration developed ketoacidosis.

The patient and caregiver survey recently performed by the same authors in an effort to address patient-reported outcomes was answered by 73 participants, including adult and paediatric patients. Results mirrored the previous healthcare providers survey [58, 59]. Furthermore, positive effects included improved appetite, physical activity, well-being, sleep and overall quality of life, and reduced number of hospitalizations and sick-day leaves of both patients and caregivers.

3.2.3. Heart failure and proteinuric kidney disease

Newland and colleagues reported their retrospective, single-centre experience with dapagliflozin in 38 heart failure patients 4 months to 21 years, median 12.2 (interquartile range 6.2-17.5) years of age [47]. The median dapagliflozin dose was 0.16 (IQR 0.12-0.19) mg/kg/day and the length of follow-up 130 (IQR 76-332) days. A range of diagnoses was included, mainly dilated cardiomyopathy (68%) but also restrictive cardiomyopathy, single-ventricle physiology, patients on ventricular assist device or post heart transplant. A pre-/post-comparison (Supplementary Table 1), despite no difference in New York Heart Association (NYHA) heart failure stage, showed a small but significant decrease in brain natriuretic peptide (from 222 to 166 pg/mL, p=0.04). Overall, dapagliflozin was safe, with stable estimated glomerular filtration rate (eGFR), no symptomatic hypoglycaemia, dehydration, or ketoacidosis. There were, however, six (16%) patients with urinary tract infection.

In a prospective trial among 9 patients with proteinuric kidney disease, median age 10.1 (IQR 8.7-11.7) years of age, dapagliflozin 5 mg (patient ≤30 kg) or 10mg (patient >30 kg) was administered daily for 12 weeks [46]. Proteinuria decreased by 33% at 4 weeks and 23% at 12 weeks, while albumin was unchanged from baseline at 4 weeks and slightly increased at 12 weeks. Based on a parametric approach, data analysis showed that eGFR did not change at 4 weeks, but slightly decreased at 12 weeks (103.8 ± 28.2 versus 109.2 ± 32.0 mL/min/1.73m^2 at baseline, p<0.048). However, looking at the individually reported data and performing non-parametric statistics, median eGFR was minimally, but significantly (p=0.0156) higher at 12 weeks, 105.8 (IQR 79.3-121.1), as compared to baseline, 103.1 (IQR 68.1-127.6). No patient discontinued medication owing to an adverse event, but one case of asymptomatic bacteriuria was reported.

3.2.4. Pharmacokinetics

We identified 5 clinical pharmacology studies [48-52], in which the pharmacokinetics and pharmacodynamics of dapagliflozin or empagliflozin were evaluated, and one physiologically-based pharmacokinetic model on dapagliflozin [53].

For dapagliflozin, the volume of distribution (V_d) ranged between 130 and 468 L, whereas clearance (CL) showed small variation (20 - 24 L/h), with a half-life ($t_{1/2}$) between 10.3 and 14.1 h. Exposure was dose-proportional, with maximal concentration (C_{max}) between 25 and 118 ng/mL and an area under the concentration-time curve (AUC_{0-24}) between 101 and 517 ng·h/mL, and time to maximum concentration (t_{max}) ranging between 0.9 and 1.5 h. For empagliflozin, V_d ranged between 101 and 186 L, and CL between 10 and 17 L/h, with t_{max} varying between 1.3 and 1.8h. C_{max} ranged between 175 and 692 nmol/L, and AUC_{0-24} was estimated between 1110 and 4720 nmol·h/L (Supplementary Table 2).

Laffel and colleagues [51] investigated the dose-concentration and the concentration-effect (assessed as urinary glucose excretion over 24h and fasting plasma glucose) relationship of empaglifozin following single administration in 27 adolescents with T2DM. Participant age and weight were (mean and SD) 14.1±2.0 years and 96.6±23.5 kg, respectively. They were hyperfiltrating, with mean eGFR of 165.8±25.8 mL/min/1.73m^2. Pharmacokinetic analysis was non-compartmental. The pharmacodynamic part of the study showed an exposure-response relationship similar to the adult population, when adjusted for baseline covariates, namely mean daily glucose, sex, race, and body weight.

Tirucherai and colleagues administered single-dose dapagliflozin to 23 adolescents 11 to 17 year old with T2DM (mean weight 99.7±26.4kg, BMI 35.7±7.7kg/m^2), randomized to receive 2.5 mg (n=7), 5 mg (n=8) or 10 mg (n=8) [50]. Mean urinary glucose excretion over 24h increased in a dose-proportional manner.

Parkinson and colleagues integrated the data from the Tirucherai study and from two adult studies on dapagliflozin in T2DM [49]. They were interested in examining the relationship between exposure (measured as AUC) and response (measured as 24h urine glucose excretion). Data from 63 adults and 20 children (mean age 14.5 years, mean weight 99.7kg, mean BMI 35.7kg/m^2) were available. Pharmacokinetic characteristics were similar, with children showing a slightly lower exposure than adults. Baseline eGFR, fasting plasma glucose and sex were significant covariates of the pharmacodynamic sigmoidal E_{max} model in both

populations, while black ancestry was identified as a covariate only in the paediatric population. Authors concluded that the same dose as in adults could be used for a planned phase III adolescent study in type 2 diabetes mellitus [26].

Busse and colleagues integrated data from a study including paediatric [27] and adult patients receiving a 10 mg single dose of dapagliflozin [48]. Data from 33 adolescents / young adults, mean 16.1 (range 12-21) years old and 67.7 (range 50-89) kg body weight, and from 54 adults, were available for pharmacokinetic analysis, while 31 adolescents and 65 adults contributed to the pharmacodynamic data. It was found that a 2-compartment model with 1st order absorption and 3 transit compartments was required to describe the data, with body weight as significant covariate for exposure. After accounting for this covariate, AUC_{0-24} was similar in adolescents and adults. In the pharmacodynamic analysis, using 24h urinary glucose excretion as a marker of the effect, a sigmoidal E_{max} model described the data, with baseline eGFR and glycaemia being significant covariates. Interestingly, changes in body weight (which was significant covariate of exposure) only slightly modified 24h urinary glucose excretion. This may be consistent with the finding in the adult study, that similar 24h urinary glucose excretion values were detected in the 5 and 10 mg doses, suggesting that the exposure-response curve was at the plateau.

In a stepwise approach, Jo and colleagues built a physiologically-based pharmacokinetic model for dapagliflozin [53], based on data from healthy adults following single-doses between 5 and 100 mg, and multiple-doses of 10 mg daily. The model was subsequently adapted to explore drug disposition in adolescents 11-18 year old with T2DM, yielding predicted exposure range that corresponds to drug levels observed in adolescents following single-doses of 2.5 and 10 mg. Finally, UDP-glucuronosyltransferase family 1 member 9 (UGT1A9) ontogeny was incorporated into the model to predict dapagliflozin exposure (C_{max} and AUC) in children 12-18, 6-12, 2-6, 1.5-2, 1-1.5 years, 6-12, 3-6 and 1-3 months old. The accuracy of these predictions was not verified [53].

3.2.5. Safety and Pharmacovigilance

We identified four studies focusing on the safety profile of dapagliflozin or empagliflozin in children: a review from reports to 13 poison centres [54], two pharmacoepidemiologic database interrogations [55, 56] and a case report [57].

In total, 63 patients, 2 to 19 years old were described. Intriguingly, no hypoglycaemia was reported. There was one case of normoglycaemic ketonaemia, one case of acute pancreatitis and 12 paediatric patients in a pharmacovigilance database interrogation that detected safety signals with respect to ketoacidosis and urogenital infections. Out of 49 paediatric patients with exposures to SGLT2 inhibitors reported to regional poison centres, only two were symptomatic, and neither developed significant sequelae, even after an intake of 125 mg empagliflozin with suicidal intent.

Pereyra and colleagues reported a 17 year-old girl with type 1 diabetes mellitus on subcutaneous insulin pump, who had been on empagliflozin for 11 months with better glucose control, decreased glucose variability and HbA1c [57]. After approximately 1.5 days of reduced carbohydrate intake and reduced insulin boluses without increase in basal insulin, she developed metallic taste, thick saliva, mild malaise, nausea, vomiting and fainting. A normoglycaemic ketonaemia was detected, but blood gases were not checked. This was treated as a diabetic ketoacidosis, with rapid clinical improvement.

Two pharmacovigilance databases were interrogated to detect possible safety signals [55, 56]. In a disproportionality analysis performed on the WHO-managed VigiBase database investigating the possible association between SGLT2 inhibitors and acute pancreatitis, out of 600 analyzed reports, only one patient was between 12 and 17 years [55]. Unfortunately, no details of this specific case were provided. In an interrogation of the Japanese spontaneous adverse events reporting database, out of the 4322 reports on possible adverse drug reactions to the six SGLT2-inhibitors marketed in Japan, only 12 were in children (n=4 <10 years of age and n=8 in the age group 10-19 years) [56]. Data on the paediatric reports were not detailed.

In a retrospective review of exposures reported to 13 poison centres from 6 States in the USA, Schaeffer and colleagues identified 88 cases, with mean age 25 years (absolute range 1 to 75 years) [54]. Eighty of them (91%) did not develop any symptoms, six patients (7%) developed minor and two (2%), aged 43 and 65 years, moderate symptoms. Hypoglycaemia was not observed. Out of the 88 reported exposures, 42 were <6 years, four were 6-12 years and three were 13-19 years of age. Out of the six patients with minor symptoms, two were children. The first, aged two years, developed nausea and tachycardia after unintentional ingestion of 5 mg dapagliflozin. The second, a 15 year old subject, developed high blood pressure (135/92 mmHg) and urinary incontinence after intentional intake of 125 mg empagliflozin.

4. Discussion

In adults, SGLT2 inhibitors have revolutionised the therapy of type 2 diabetes mellitus, heart failure and chronic kidney disease [1-8, 15-19]. The present systematic review documents the use of dapagliflozin or empagliflozin in at least 415 children and adolescents, of which 67% are still off-label use at the time of writing of this systematic review (all were off-label at the time the pertaining articles were published). It complements a recent literature review identifying 5 articles describing the paediatric use of dapagliflozin [61].

It is worth highlighting that this analysis provides a summative assessment of age, weight, dose, and safety information on patients exposed to either dapagliflozin or empagliflozin. None of the clinical studies included have considered the underlying pharmacokinetic-pharmacodynamic relationships as basis for the dose rationale in secondary indications (i.e. different from diabetes mellitus in adolescents).

Most patients had a form of diabetes mellitus and were (or had previously been) on co-therapies, mainly insulin and/or metformin. Indeed, randomized controlled trials (therefore offering a higher level of evidence than case series or non-controlled investigations) on dapagliflozin or empagliflozin in children and adolescents for T2DM are available and showed some efficacy, although less impressive than in adults. This might have several explanations: from study-specific characteristics like sample size, patient selection, difficulties in patient recruitment and the coincident SARS-CoV-2 pandemic fostering more sedentary behaviour [32], to limited self-care and antidiabetic drug compliance among adolescents [26, 62], to a more “aggressive” disease phenotype in youth-onset T2DM, with early insulin resistance, a faster decline in β- cell function and insulin production, on the background of physiologic pubertal insulin resistance [32, 63].

Based on glucose control and insulin dose reduction, the use of SGLT2 inhibitors appeared efficacious in over 50 cases of children and adolescents with either type 1 diabetes mellitus or congenital insulin resistance. On the other hand, in adults, because of the increased risk of diabetic ketoacidosis in such patients (approximately 5% as compared to roughly 0.05% in T2DM) [14], type 1 diabetes mellitus was not granted an indication in the label, even though compassionate use is common. Interestingly, we found only one reported case of a 17 year-old adolescent girl with type 1 diabetes mellitus on subcutaneous insulin pump, who developed normoglycaemic ketonaemia and symptoms consistent with diabetic ketoacidosis while being on empagliflozin [57]. In both adults and children with type 1 diabetes mellitus, it is important

to deliver an appropriate insulin dose to suppress lipolysis and ketogenesis [57], regularly check not only glucose but also ketones, and to adapt total daily insulin dose to carbohydrate intake variations [64].

A consistent body of evidence has also been collected with the use of empagliflozin in GSD Ib, G6PC3-deficiency, and severe congenital neutropenia type 4. Despite the rarity of the conditions, we detected 32 individually described cases. Furthermore, a survey among hospitals found at least 80 paediatric patients treated for this condition. The efficacy of empagliflozin in this severe disorder of carbohydrate metabolism has been remarkable, with patients being able to reduce or stop G-CSF (a therapy needing repeated injections and implying relevant long-term risks, including myelodysplastic syndrome and myeloid leukaemia), reducing recurrent infections, improving oral and gastrointestinal health, reduction of blood losses and improvement of anaemia and iron status, as well as normalization of uric acid. There is a convincing pathophysiological rationale (shared for both GSD Ib and G6PC3-deficiency [44]): by inhibiting the renal reabsorption of glucose and causing glucosuria, SGLT2 inhibitors decrease renal 1,5-anhydroglucitol (1,5-AG) reabsorption, reducing its plasma concentration and that of its toxic analogue 1,5-anhydroglucitol-6-phosphate, which accumulates in neutrophils inhibiting hexokinases, hereby impairing energy generation and causing malfunction and apoptosis.

Given the limited experience, there was significant variation in total daily dose, dosing interval (q.d. or b.i.d.), as well as on the selected pharmacodynamic endpoints based on which doses are titrated (both absolute neutrophil count and serum 1,5-anhydroglucitol-6-phosphate have been used). Whilst an obvious step towards treatment personalization in these patients would be the assessment of pharmacokinetics and corresponding pharmacokinetic-pharmacodynamic relationships, there are currently no pharmacokinetic studies for this indication, neither in adults nor in children.

SGLT2 inhibition has been a breakthrough in the therapy of heart failure in adults [1-4]. One retrospective report of paediatric experience of dapagliflozin among 38 children and young adults (4 months to 21 years old) revealed a positive effect of heart failure therapy, including SGLT2 inhibition, when comparing changes from baseline after a median treatment time of approximately 4 months [47]. The use of concomitant therapies and standard of care, as well as the absence of a control group precluded any conclusion on efficacy, but this preliminary experience delivered promising results and supported tolerability of dapagliflozin also in this population.

Various publications have focused on the pathophysiological and clinical interest of using SGLT2 inhibitors in paediatric chronic kidney disease (with or without diabetes mellitus) [14, 65]. Most reports consistently indicate a risk reduction of renal composite outcomes in the range of 30-40% [14, 16, 18, 19]. In the current review, one small paediatric study was identified in which 9 patients with proteinuric kidney disease, median 10.1 years old, received dapagliflozin for 3 months [46]. A significant reduction in proteinuria was observed, while effects on eGFR were controversial. By contrast, meta-analysis results from adults showed that SGLT2 inhibitors protect from acute kidney injury [66]. Furthermore, similar to what has long been known for ACE inhibitors, the slight (and reversible) dip in eGFR seen shortly after SGLT2 inhibitors initiation appears to reflect a decrease in hyperfiltration, and can therefore be seen as an early marker of their middle- and long-term nephroprotective effect [67].

As mentioned previously, pharmacokinetic studies were performed exclusively in adolescents with type 1 or 2 diabetes mellitus. We did not find any pharmacokinetic data in GSD Ib, paediatric chronic kidney disease or paediatric heart failure. Similarly, the pharmacokinetics of these drugs has not been evaluated in younger children with type 1 or 2 diabetes mellitus. Unsurprisingly, lack of data on drug disposition and understanding of interindividual variability in systemic exposure may explain the wide range of doses tested in younger children [47] and in GSD Ib [33, 59].

Based on the selectivity of the mechanisms of the two compounds, it can be anticipated that their safety profile may be comparable across the different paediatric indications. Indeed, available paediatric data suggests that SGLT2 inhibitors have a good tolerability and safety profile across the dose range and treatment periods evaluated so far. The most frequent adverse event was hypoglycaemia, occurring in approximately 10-20% of patients. For obvious reasons, this figure was almost 40% in GSD Ib (which manifests itself among others with hypoglycaemia) but absent in children with heart failure or chronic kidney disease. In T2DM, it was mainly associated with co-medications predisposing to hypoglycaemia. Interestingly, different from adult studies, no diabetic ketoacidosis was reported in children so far. Only one case of a 17 year-old girl with type 1 diabetes mellitus on a subcutaneous insulin pump presented with normoglycemic ketosis and symptoms compatible with ketoacidosis. It is, however, important to note that the relatively low number of patients hitherto reported reduces the ability to detect rare occurrences. Genitourinary infections were rare. Current data therefore supports the notion of a reassuring safety profile in children, and confirms the

importance of regular meals, as well as a careful approach in type 1 diabetes mellitus. Database interrogation studies, including children inadvertently exposed to a single high-dose of SGLT2 inhibitors, confirmed a safe profile.

Given the limited clinical experience and number of patients exposed to long-term therapy, we acknowledge some of the limitations of this review. First, the quality of reporting was variable. Second, the type of information provided in the original publications was somehow inconsistent, so that a meta-analysis was possible only for the two randomized controlled trials on adolescents with T2DM. Finally, we focused exclusively on dapagliflozin and empagliflozin, since these are the SGLT2 inhibitors that are also indicated for heart failure and chronic kidney disease in adults. However, other gliflozins are licensed for chronic kidney disease (canagliflozin) and several are licensed (with national variations) for T2DM. Despite the same pharmacological mechanisms, our conclusions may not be generalized to other molecules.

5. Conclusions

In summary, sodium-glucose cotransporter type 2 inhibitors have delivered remarkable improvements in the therapy of diabetes mellitus, heart failure and chronic kidney disease in adults. The present review shows that dapagliflozin and empagliflozin have hitherto been used in >400 children, with a seemingly positive benefit-risk balance, despite the lack of more robust dose rationale based on the underlying concentration-effect relationships. Indeed, from a safety point of view, although we acknowledge the relatively low number of studied patients with the pertaining reduced ability to detect rare occurrences, and the need for future, larger safety studies, diabetic ketoacidosis, the most concerning side effect of SGLT2 inhibitors, was uncommon in children and associated with further, identifiable risk factors (like co-medication with insulin) [68]. Notably, good quality data support their use for T2DM in adolescents. Similarly, these drugs have shown impressive results in GSD Ib. Case series and retrospective reports also appear to support their use in heart failure and chronic kidney disease, but additional studies, including pharmacokinetic evaluation, are urgently needed. Evidence generation in paediatric patients will benefit from the use of modelling and extrapolation concepts, providing a robust pharmacological basis for use of SLGT2 inhibitors in these indications [69, 70].

Statements and declarations

Conflicts of interest

The authors have no competing interests to declare that are relevant to the content of this article.

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Data availability statement

The data presented in this study is available from the corresponding author upon reasonable request.

Ethics approval, Standard of reporting, Registration

This being a systematic review, an ethical approval was not required.
The 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations were followed.
This systematic review was pre-registered on PROSPERO, with number CRD42023438162.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

CODE AVAILABILITY

Not applicable.

AUTHOR CONTRIBUTIONS

Dr Lava conceived and designed the study. Dr Lava and Dr Laurence conducted the literature search and performed article selection, data extraction, and reporting quality assessment. Dr Lava performed data analysis, including statistical analysis and meta-analysis, and wrote the first draft of the manuscript. Mr Di Deo contributed to Tables' and Figures' preparation, and supervised statistical analysis. Professor Sekarski, Professor Burch and Professor Della Pasqua critically revised the draft of the manuscript. All authors approved the final version of the manuscript.

References

1. Braunwald E. Gliflozins in the Management of Cardiovascular Disease. N Engl J Med. 2022;386(21):2024-2034. https://doi.org/10.1056/NEJMra2115011
2. McMurray JJV, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019;381(21):1995-2008. https://doi.org/10.1056/NEJMoa1911303
3. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020;383(15):1413-1424. https://doi.org/10.1056/NEJMoa2022190
4. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2022;24(1):4-131.
5. Nassif ME, Windsor SL, Borlaug BA, Kitzman DW, Shah SJ, Tang F, et al. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. Nat Med. 2021;27(11):1954-1960. https://doi.org/10.1038/s41591-021-01536-x
6. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Bohm M, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021;385(16):1451-1461. https://doi.org/10.1056/NEJMoa2107038
7. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med. 2022;387(12):1089-1098. https://doi.org/10.1056/NEJMoa2206286
8. Desai AS, Lam CSP, McMurray JJV, Redfield MM. How to Manage Heart Failure With Preserved Ejection Fraction: Practical Guidance for Clinicians. JACC Heart Fail. 2023;11(6):619-636. https://doi.org/10.1016/j.jchf.2023.03.011
9. Zelniker TA, Braunwald E. Mechanisms of Cardiorenal Effects of Sodium-Glucose Cotransporter 2 Inhibitors: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;75(4):422-434. https://doi.org/10.1016/j.jacc.2019.11.031

10. Joshi SS, Singh T, Newby DE, Singh J. Sodium-glucose co-transporter 2 inhibitor therapy: mechanisms of action in heart failure. Heart. 2021;107(13):1032-8. https://doi.org/10.1136/heartjnl-2020-318060
11. Katsiki N, Rizzo M, Mikhailidis DP. Sodium-glucose co-transporter-2 (SGLT-2) inhibitors and uric acid: More good news! J Diabetes Complications. 2023;37(7):108510. https://doi.org/10.1016/j.jdiacomp.2023.108510
12. Mora-Fernández C, Pérez A, Mollar A, Palau P, Amiguet M, de la Espriella R, et al. Short-term changes in klotho and FGF23 in heart failure with reduced ejection fraction—a substudy of the DAPA-VO2 study. Frontiers in Cardiovascular Medicine. 2023;10. https://doi.org/10.3389/fcvm.2023.1242108
13. Helmlinger G, Sokolov V, Peskov K, Hallow KM, Kosinsky Y, Voronova V, et al. Quantitative Systems Pharmacology: An Exemplar Model-Building Workflow With Applications in Cardiovascular, Metabolic, and Oncology Drug Development. CPT Pharmacometrics Syst Pharmacol. 2019;8(6):380-395. https://doi.org/10.1002/psp4.12426
14. Kula AJ. Considerations and possibilities for sodium-glucose cotransporter 2 inhibitors in pediatric CKD. Pediatr Nephrol. 2022;37(10):2267-2276. https://doi.org/10.1007/s00467-022-05456-x
15. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015;373(22):2117-28. https://doi.org/10.1056/NEJMoa1504720
16. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. N Engl J Med. 2016;375(4):323-34. https://doi.org/10.1056/NEJMoa1515920
17. Heerspink HJL, Stefansson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020;383(15):1436-1446. https://doi.org/10.1056/NEJMoa2024816
18. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017;377(7):644-657. https://doi.org/10.1056/NEJMoa1611925
19. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019;380(24):2295-2306. https://doi.org/10.1056/NEJMoa1811744

20. Lava SA, Bianchetti MG, Simonetti GD. Salt intake in children and its consequences on blood pressure. Pediatr Nephrol. 2015;30(9):1389-1396. doi: 10.1007/s00467-014-2931-3.
21. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71
22. Piffer A, Bianchetti MG, Leoni-Foglia C, Simonetti GD, Milani GP, Lava SAG. Vaptans for oedematous and hyponatraemic disorders in childhood: A systematic literature review. Br J Clin Pharmacol. 2022;88(10):4474-4480. https://doi.org/10.1111/bcp.15367
23. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-394.
24. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135. https://doi.org/10.1186/1471-2288-14-135
25. Galderisi A, Tamborlane W, Taylor SI, Attia N, Moretti C, Barbetti F. SGLT2i Improves Glycemic Control in Patients With Congenital Severe Insulin Resistance. Pediatrics. 2022;150(1). https://doi.org/10.1542/peds.2021-055671
26. Tamborlane WV, Laffel LM, Shehadeh N, Isganaitis E, Van Name M, Ratnayake J, et al. Efficacy and safety of dapagliflozin in children and young adults with type 2 diabetes: a prospective, multicentre, randomised, parallel group, phase 3 study. Lancet Diabetes Endocrinol. 2022;10(5):341-350. https://doi.org/10.1016/S2213-8587(22)00052-3
27. Biester T, Aschemeier B, Fath M, Frey M, Scheerer MF, Kordonouri O, et al. Effects of dapagliflozin on insulin-requirement, glucose excretion and ss-hydroxybutyrate levels are not related to baseline HbA1c in youth with type 1 diabetes. Diabetes Obes Metab. 2017;19(11):1635-1639. https://doi.org/10.1111/dom.12975
28. Biester T, Muller I, von dem Berge T, Atlas E, Nimri R, Phillip M, et al. Add-on therapy with dapagliflozin under full closed loop control improves time in range in adolescents and young adults with type 1 diabetes: The DAPADream study. Diabetes Obes Metab. 2021;23(2):599-608. https://doi.org/10.1111/dom.14258
29. Dos Santos SS, Ramaldes LA, Gabbay MAL, Moises RCS, Dib SA. Use of a Sodium-Glucose Cotransporter 2 Inhibitor, Empagliflozin, in a Patient with Rabson-

Mendenhall Syndrome. Horm Res Paediatr. 2021;94(7-8):313-316. https://doi.org/10.1159/000519613

30. Candler T, McGregor D, Narayan K, Moudiotis C, Burren CP. Improvement in glycaemic parameters using SGLT-2 inhibitor and GLP-1 agonist in combination in an adolescent with diabetes mellitus and Prader-Willi syndrome: a case report. J Pediatr Endocrinol Metab. 2020;33(7):951-955. https://doi.org/10.1515/jpem-2019-0389
31. Kuwabara R, Urakami T, Yoshida K, Morioka I. Case of type 2 diabetes possibly caused by excessive accumulation of visceral fat in a child born small-for-gestational age. J Diabetes Investig. 2020;11(5):1366-1369. https://doi.org/10.1111/jdi.13246
32. Laffel LM, Danne T, Klingensmith GJ, Tamborlane WV, Willi S, Zeitler P, et al. Efficacy and safety of the SGLT2 inhibitor empagliflozin versus placebo and the DPP-4 inhibitor linagliptin versus placebo in young people with type 2 diabetes (DINAMO): a multicentre, randomised, double-blind, parallel group, phase 3 trial. Lancet Diabetes Endocrinol. 2023;11(3):169-181. https://doi.org/10.1016/S2213-8587(22)00387-4
33. Halligan RK, Dalton RN, Turner C, Lewis KA, Mundy HR. Understanding the role of SGLT2 inhibitors in glycogen storage disease type Ib: the experience of one UK centre. Orphanet J Rare Dis. 2022;17(1):195. https://doi.org/10.1186/s13023-022-02345-2
34. Kaczor M, Greczan M, Kierus K, Ehmke Vel Emczynska-Seliga E, Ciara E, Piatosa B, et al. Sodium-glucose cotransporter type 2 channel inhibitor: Breakthrough in the treatment of neutropenia in patients with glycogen storage disease type 1b? JIMD Rep. 2022;63(3):199-206. https://doi.org/10.1002/jmd2.12278
35. Rossi A, Miele E, Fecarotta S, Veiga-da-Cunha M, Martinelli M, Mollica C, et al. Crohn disease-like enterocolitis remission after empagliflozin treatment in a child with glycogen storage disease type Ib: a case report. Ital J Pediatr. 2021;47(1):149. https://doi.org/10.1186/s13052-021-01100-w
36. Peeks F, Hoogeveen IJ, Feldbrugge RL, Burghard R, de Boer F, Fokkert-Wilts MJ, et al. A retrospective in-depth analysis of continuous glucose monitoring datasets for patients with hepatic glycogen storage disease: Recommended outcome parameters for glucose management. J Inherit Metab Dis. 2021;44(5):1136-1150. https://doi.org/10.1002/jimd.12383
37. Wortmann SB, Van Hove JLK, Derks TGJ, Chevalier N, Knight V, Koller A, et al. Treating neutropenia and neutrophil dysfunction in glycogen storage disease type Ib with an SGLT2 inhibitor. Blood. 2020;136(9):1033-1043. https://doi.org/10.1182/blood.2019004465

38. Mikami M, Arai A, Mizumoto H. Empagliflozin ameliorated neutropenia in a girl with glycogen storage disease Ib. Pediatr Int. 2021;63(11):1394-1396. https://doi.org/10.1111/ped.14629
39. View from inside: Nina, Glycogen storage disease warrior. J Inherit Metab Dis. 2020;43(4):653-656. https://doi.org/10.1002/jimd.12246
40. Tallis E, Karsenty CL, Grimes AB, Karam LB, Elsea SH, Sutton VR, et al. Untargeted metabolomic profiling in a patient with glycogen storage disease Ib receiving empagliflozin treatment. JIMD Rep. 2022;63(4):309-315. https://doi.org/10.1002/jmd2.12304
41. Hexner-Erlichman Z, Veiga-da-Cunha M, Zehavi Y, Vadasz Z, Sabag AD, Tatour S, et al. Favorable outcome of empagliflozin treatment in two pediatric glycogen storage disease type 1b patients. Front Pediatr. 2022;10:1071464. https://doi.org/10.3389/fped.2022.1071464
42. Guerra F, Gasperini S, Bonanomi S, Crescitelli V, Pretese R, Da Dalt L, et al. Finding balance between mature and immature neutrophils: The effects of empagliflozin in GSD-Ib. EJHaem. 2023;4(2):551-554. https://doi.org/10.1002/jha2.649
43. Murko S, Peschka M, Tsiakas K, Schulz-Jurgensen S, Herden U, Santer R. Liver transplantation in glycogen storage disease type Ib: The role of SGLT2 inhibitors. Mol Genet Metab Rep. 2023;35:100977. https://doi.org/10.1016/j.ymgmr.2023.100977
44. Boulanger C, Stephenne X, Diederich J, Mounkoro P, Chevalier N, Ferster A, et al. Successful use of empagliflozin to treat neutropenia in two G6PC3-deficient children: Impact of a mutation in SGLT5. J Inherit Metab Dis. 2022;45(4):759-768. https://doi.org/10.1002/jimd.12509
45. Ledeczi Z, Pittner R, Krivan G, Kardon T, Legeza B. Empagliflozin restores neutropenia and neutrophil dysfunction in a young patient with severe congenital neutropenia type 4. J Allergy Clin Immunol Pract. 2023;11(1):344-346 e1. https://doi.org/10.1016/j.jaip.2022.10.019
46. Liu J, Cui J, Fang X, Chen J, Yan W, Shen Q, et al. Efficacy and Safety of Dapagliflozin in Children With Inherited Proteinuric Kidney Disease: A Pilot Study. Kidney Int Rep. 2022;7(3):638-641. https://doi.org/10.1016/j.ekir.2021.12.019
47. Newland DM, Law YM, Albers EL, Friedland-Little JM, Ahmed H, Kemna MS, et al. Early Clinical Experience with Dapagliflozin in Children with Heart Failure. Pediatr Cardiol. 2023;44(1):146-152. https://doi.org/10.1007/s00246-022-02983-0
48. Busse D, Tang W, Scheerer M, Danne T, Biester T, Sokolov V, et al. Comparison of pharmacokinetics and the exposure-response relationship of dapagliflozin between

adolescent/young adult and adult patients with type 1 diabetes mellitus. Br J Clin Pharmacol. 2019;85(8):1820-1828. https://doi.org/10.1111/bcp.13981

49. Parkinson J, Tang W, Johansson CC, Boulton DW, Hamren B. Comparison of the exposure-response relationship of dapagliflozin in adult and paediatric patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2016;18(7):685-92. https://doi.org/10.1111/dom.12647

50. Tirucherai GS, LaCreta F, Ismat FA, Tang W, Boulton DW. Pharmacokinetics and pharmacodynamics of dapagliflozin in children and adolescents with type 2 diabetes mellitus. Diabetes Obes Metab. 2016;18(7):678-84. https://doi.org/10.1111/dom.12638

51. Laffel LMB, Tamborlane WV, Yver A, Simons G, Wu J, Nock V, et al. Pharmacokinetic and pharmacodynamic profile of the sodium-glucose co-transporter-2 inhibitor empagliflozin in young people with Type 2 diabetes: a randomized trial. Diabet Med. 2018;35(8):1096-1104. https://doi.org/10.1111/dme.13629

52. Penland RC, Melin J, Boulton DW, Tang W. Evaluation of the Pharmacokinetics of Dapagliflozin in Patients With Chronic Kidney Disease With or Without Type 2 Diabetes Mellitus. J Clin Pharmacol. 2023;63(5):551-559. https://doi.org/10.1002/jcph.2196

53. Jo H, Pilla Reddy V, Parkinson J, Boulton DW, Tang W. Model-Informed Pediatric Dose Selection for Dapagliflozin by Incorporating Developmental Changes. CPT Pharmacometrics Syst Pharmacol. 2021;10(2):108-118. https://doi.org/10.1002/psp4.12577

54. Schaeffer SE, DesLauriers C, Spiller HA, Aleguas A, Baeza S, Ryan ML. Retrospective review of SGLT2 inhibitor exposures reported to 13 poison centers. Clin Toxicol (Phila). 2018;56(3):204-208. https://doi.org/10.1080/15563650.2017.1357824

55. Frent I, Bucsa C, Leucuta D, Farcas A, Mogosan C. An investigation on the association between sodium glucose co-transporter 2 inhibitors use and acute pancreatitis: A VigiBase study. Pharmacoepidemiol Drug Saf. 2021;30(10):1428-1440. https://doi.org/10.1002/pds.5313

56. Katsuhara Y, Ikeda S. Correlations Between SGLT-2 Inhibitors and Acute Renal Failure by Signal Detection Using FAERS: Stratified Analysis for Reporting Country and Concomitant Drugs. Clin Drug Investig. 2021;41(3):235-243. https://doi.org/10.1007/s40261-021-01006-9

57. Pereyra AM, Ramirez C, Roman R. [Euglycemic ketosis in an adolescent with type 1 diabetes on insulin and dapaglifozin: Case report]. Rev Chil Pediatr. 2017;88(3):404-410. https://doi.org/10.4067/S0370-41062017000300015
58. Grunert SC, Derks TGJ, Adrian K, Al-Thihli K, Ballhausen D, Bidiuk J, et al. Efficacy and safety of empagliflozin in glycogen storage disease type Ib: Data from an international questionnaire. Genet Med. 2022;24(8):1781-1788. https://doi.org/10.1016/j.gim.2022.04.001
59. Grunert SC, Venema A, LaFreniere J, Schneider B, Contreras E, Wortmann SB, et al. Patient-reported outcomes on empagliflozin treatment in glycogen storage disease type Ib: An international questionnaire study. JIMD Rep. 2023;64(3):252-258. https://doi.org/10.1002/jmd2.12364
60. Kaczor M, Wesół-Kucharska D, Greczan M, Kierus K, Kałużny Ł, Duś-Żuchowska M, et al. Clinical characteristics and long-term outcomes of patients with glycogen storage disease type 1b: a retrospective multi-center experience in Poland. Pediatr Endocrinol Diabetes Metab. 2022;28(3):207-212. doi: 10.5114/pedm.2022.116115.
61. Grube PM, Beckett RD. Clinical studies of dapagliflozin in pediatric patients: a rapid review. Ann Pediatr Endocrinol Metab. 2022;27(4):265-272. https://doi.org/10.6065/apem.2244166.083
62. Tommerdahl KL, Nelson RG, Bjornstad P. Dapagliflozin in young people with type 2 diabetes. Lancet Diabetes Endocrinol. 2022;10(5):303-304. https://doi.org/10.1016/S2213-8587(22)00075-4
63. Amiel SA, Sherwin RS, Simonson DC, Lauritano AA, Tamborlane WV. Impaired insulin action in puberty. A contributing factor to poor glycemic control in adolescents with diabetes. N Engl J Med. 1986;315(4):215-9. https://doi.org/10.1056/NEJM198607243150402
64. Danne T, Garg S, Peters AL, Buse JB, Mathieu C, Pettus JH, et al. International Consensus on Risk Management of Diabetic Ketoacidosis in Patients With Type 1 Diabetes Treated With Sodium-Glucose Cotransporter (SGLT) Inhibitors. Diabetes Care. 2019;42(6):1147-1154. https://doi.org/10.2337/dc18-2316
65. Cirillo L, Ravaglia F, Errichiello C, Anders HJ, Romagnani P, Becherucci F. Expectations in children with glomerular diseases from SGLT2 inhibitors. Pediatr Nephrol. 2022;37(12):2997-3008. https://doi.org/10.1007/s00467-022-05504-6
66. Zhao M, Sun S, Huang Z, Wang T, Tang H. Network Meta-Analysis of Novel Glucose-Lowering Drugs on Risk of Acute Kidney Injury. Clin J Am Soc Nephrol. 2020;16(1):70-78. https://doi.org/10.2215/CJN.11220720

67. Heerspink HJL, Cherney DZI. Clinical Implications of an Acute Dip in eGFR after SGLT2 Inhibitor Initiation. Clin J Am Soc Nephrol. 2021;16(8):1278-1280. https://doi.org/10.2215/CJN.02480221

68. Meoli M, Lava SAG, Bronz G, Goeggel-Simonetti B, Simonetti GD, Alberti I, et al. Eu- or hypoglycemic ketosis and ketoacidosis in children: a review. Pediatr Nephrol. 2023. https://doi.org/10.1007/s00467-023-06115-5

69. Bellanti F, Della Pasqua O. Modelling and simulation as research tools in paediatric drug development. Eur J Clin Pharmacol. 2011;67 Suppl 1(Suppl 1):75-86. https://doi.org/10.1007/s00228-010-0974-3

70. Harnisch L, Shepard T, Pons G, Della Pasqua O. Modeling and simulation as a tool to bridge efficacy and safety data in special populations. CPT Pharmacometrics Syst Pharmacol. 2013;2(2):e28. https://doi.org/10.1038/psp.2013.6

Figures – Legends

Figure 1

Dapagliflozin and empagliflozin in Paediatrics. Flowchart of the literature search.

Figure 2

Randomized controlled trials on dapagliflozin or empagliflozin use in adolescents with type 2 diabetes mellitus (T2DM). Forest plot depicting the mean difference in HbA1c change after 24 [14], respectively 26 [20] weeks of treatment with either dapagliflozin [14], empagliflozin [20] or placebo among a total of 177 adolescents with T2DM.

Figure 3

Dapagliflozin and empagliflozin use in 32 children and adolescents with glycogen storage disease type Ib (GSD Ib). Panel A depicts the number and proportion of patients reported to have improved in the listed clinical aspects. Panel B reports the absolute neutrophil counts at baseline as compared to last reported encounter in 29 patients with GSD Ib. Panel C shows the haemoglobin at baseline as compared to last reported encounter in 14 patients with GSD Ib. Box plots depict median (line within the box) and 25^{th} and 75^{th} percentiles (boundaries of the boxes), while the whiskers (error bars) represent the minimal and maximal reported values. *Abbreviations*: 1,5-AG = 1,5-anhydroglucitol, ANC = absolute neutrophil count, G-CSF = granulocyte colony stimulating factor, GIT = gastrointestinal tract, Hb = haemoglobin, WBC = white blood cells.

Supplementary Figure 1

Risk of bias of papers included in the meta-analysis of empagliflozin / dapagliflozin use in adolescents with T2DM. Risk of bias was assessed according to five categories as recommended by the Cochrane collaboration: selection bias (D1), performance bias (D2), detection bias (D3), attrition bias (D4) and reporting bias (D5).

Dapagliflozin and Empagliflozin in Paediatric Indications: a Systematic Review ~~and Meta-Analysis~~

Running ~~heading~~ header: Dapagliflozin and Empagliflozin in Paediatric Indications

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Abstract

~~**Aims**~~ **Introduction:** In adults, sodium glucose type 2 transporter inhibitors ~~(SGLT2i)~~ have revolutionized the treatment of type 2 diabetes mellitus ~~(T2DM)~~, heart failure and chronic kidney disease.

Objective: We aimed to review information on compassionate use, clinical pharmacology, efficacy, and safety of dapagliflozin and empagliflozin in children.

Methods: Systematic review of published clinical trials, case reports or observational studies in Medline, Excerpta Medica and Web of Science databases from inception to September 2023. For the two randomised-controlled trials on type 2 diabetes mellitus, we implemented a meta-analysis on the primary outcome (mean difference in HbA1c between intervention and placebo groups). Review Manager (RevMan), version 5.4.1 was used for this purpose.

Results: Thirty-five articles (nine case reports, 10 case series, one prospective non-controlled trial, four controlled randomized trials, two surveys, six pharmacokinetic studies, and three pharmacovigilance studies) were selected in which 415 children were exposed to either dapagliflozin or empagliflozin: 189 diabetic patients (mean age 14.7±2.9 years), 32 children with glycogen storage disease type Ib (GSD Ib), G6PC3-deficiency or severe congenital neutropenia type 4 (8.5±5.1 years), 47 children with kidney disease or heart failure (11.2±6.1 years), 84 patients in pharmacokinetic studies (15.1±2.3 years) and 63 patients in toxicological series. ~~Additionally, a survey of healthcare professionals identified 80 children with GSD Ib having received empagliflozin.~~

The effect of dapagliflozin and empagliflozin in ~~T2DM~~ type 2 diabetes mellitus was demonstrated by HbA1c reduction in two randomized trials among a total of 177 adolescents, with a mean HbA1c difference of -0.82% (95%-CI -1.34 to -0.29) as compared to placebo (no heterogeneity, I^2=0%). Dose ranged between 5-20 ~~mg~~ (mean 11.4±3.7) mg once daily for dapagliflozin and between 5-25 ~~mg~~ (mean 15.4±7.4) mg once daily for empagliflozin. Among the paediatric cases of GSD Ib, empagliflozin 0.1-1.3 mg/kg/d improved neutropenia, infections, and gastrointestinal health. Dapagliflozin (mean dose 6.9±5.2 mg once daily) was well-tolerated in children with chronic kidney disease and heart failure.

Side effects were generally mild, the most frequent being hypoglycaemia in children with GSD Ib (33% of patients) or ~~T2DM~~ type 2 diabetes mellitus (14% of patients) on concomitant hypoglycaemic drugs. Diabetic ketoacidosis is ~~exquisitely~~ rare in children.

Conclusion: Early evidence suggests that dapagliflozin and empagliflozin are well tolerated in children. A clinical pharmacology rationale currently exists only for adolescents with ~~T2DM~~ diabetes mellitus.

Prospero registration number: CRD42023438162.

Key points

- Dapagliflozin and empagliflozin have revolutionized the treatment of type 2 diabetes mellitus, heart failure and chronic kidney disease in adults.
- Early evidence suggests that these molecules are well tolerated in Paediatrics~~, and~~. They have been successfully used in children and adolescents with type 2 diabetes mellitus, heart failure, chronic kidney disease, and glycogen storage disease type Ib. Further robust studies will need to verify these findings.
- A dose rationale currently exists only for adolescents with ~~type 2~~ diabetes mellitus.

1. Introduction

In the late 90's, sodium glucose cotransporter type 2 inhibitors (SGLT2-inhibitors) were developed as non-insulin-dependent antidiabetic drugs, and were eventually approved by the Food and Drug Administration and the European Medicines Agency between 2012 and 2017. Concerns about the cardiovascular safety of the antidiabetic rosiglitazone led these agencies to require specific cardiovascular analyses for any new antidiabetic drug. Surprisingly, these trials not only demonstrated cardiovascular safety, but also showed impressive cardioprotective effects [1], which were detected in adult heart failure patients with and without type 2 diabetes mellitus (T2DM) [2, 3]. Given 25-26% reduction in a composite outcome of worsening heart failure or cardiovascular death [2, 3], since 2021 they have been recommended as routine therapy for adults with heart failure with reduced ejection fraction [4]. Furthermore, they are efficacious [5-7] and advised also for adult patients with heart failure with preserved ejection fraction [8]. The mechanisms of cardiovascular protection are multiple and include among others: diuresis (with a differential role on intra- and extracellular body fluid compartments) reducing cardiac overload, suppression of sympathetic nervous system overdrive, metabolism shift towards ketone bodies positively impacting cardiac energetics, increased haemoglobin/haematocrit, modification of $Na^+/K^+/Ca^{2+}$ ionic homeostasis and uric acid metabolism, and modulation of the FGF-23 / klotho pathway [1,9-13].

Also, prespecified analyses examined the effects of empagliflozin [14-16], dapagliflozin [17] and canagliflozin [18-19] on kidney outcomes, and detected a risk reduction of renal composite outcomes in the range of 30-40% [17]. Mechanisms are far beyond a simple improvement in glycaemic control and reduction of hyperfiltration. Indeed, sustained natriuresis, reduction in plasma volume, sodium stored in the skin interstitium [20] and body weight appear to play a role. Furthermore, metabolism shift away from glucose oxidation in favour of ketone and fatty acid oxidation might be beneficial for both the kidneys and the myocardium, two avid energy consumers [14].

Despite their impressive efficacy and good safety profile in adults with T2DM, heart failure and chronic kidney disease, and having been approved for T2DM in adolescents 10-18 years of age, limited data are available on dapagliflozin and empagliflozin for younger children or children with indications different from T2DM, and this topic has hitherto not been systematically addressed. In an effort to improve the understanding of the clinical pharmacology and potential benefit-risk profile of SGLT2-inhibitors in paediatric heart failure,

chronic kidney disease and glycogen storage disease type Ib, we performed a systematic review of ~~the experience with~~ the use of dapagliflozin and empagliflozin in children. The results from this review will support the implementation of prospective protocols for the evaluation of efficacy and safety of both drugs in paediatric heart failure, chronic kidney disease and glycogen storage disease type Ib.

2. Methods

2.1. Search Strategy

The review was pre-registered on PROSPERO (CRD42023438162) and ~~was conducted~~ is reported according to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations ~~[10]~~ [21]. Searches were performed in the National Library of Medicine (PubMed®), Excerpta Medica (Embase), and Web of Science databases to September 12th, 2023. Original reports with no date limits were considered. The search strategy ~~incorporated~~ used the terms (dapagliflozin OR empagliflozin) AND (childhood OR child OR paediatrics). References listed within bibliographies of the retrieved records and relevant articles known to the authors were also considered. Identified titles and abstracts were independently screened by two authors in an unblinded fashion. Full-text publications of candidate reports were reviewed in detail for eligibility. Uncertainties and disagreements were solved through discussion and consensus. Institutional Review Board approval was not required for this literature review.

2.2. Eligibility criteria

We included original articles and letters (randomized controlled trials, pharmacokinetic investigations, prospective and retrospective studies, case series and case reports, pharmacovigilance database interrogations, survey studies) reporting human subjects aged 18 years or less, who were treated with dapagliflozin or empagliflozin. Reports addressing the use of dapagliflozin or empagliflozin in both adults and children were retained if they specifically presented paediatric data, and only paediatric cases were included in the analysis. Additionally, children made known to pharmacoepidemiology and monitoring institutions having (accidentally) ingested either dapagliflozin or empagliflozin were also retained. Articles in languages other than English, French, German, Italian, Portuguese, or Spanish were

excluded. Multiple reports were suspected when two (or more) publications were characterized by some (or all) of the following similarities: same authors, institutions or setting; patient characteristics; assessed endpoints; reported outcomes; observation period dates and duration; duration of follow-up. Cases reported twice in the literature were analyzed only once.

2.3. Data Extraction

Data were collected according to a pre-defined checklist, including demographics, underlying condition, comedication, laboratory values, administered molecule and dose, duration of treatment and follow-up, and observed side effects (including among others hypoglycaemia, urinary tract infections, metabolic acidosis, and presence of ketones in blood). ~~When relevant data were incomplete, efforts were made to contact authors of the original reports.~~

2.4. Completeness of reporting and grading of evidence

The completeness of reporting was evaluated for clinical studies on T2DM, glycogen storage disease type Ib (GSD Ib), proteinuric kidney disease, heart failure, and pharmacokinetics, according to the following four components ~~[11]~~ [22]: 1. description of population and design; 2. information on dosage and treatment duration; 3. information on assessed outcomes and clinical course; 4. data on monitored side effects. Each component was rated as 0, 1, 2, and the reporting quality was graded according to the sum of each item as excellent (8), good (6 to 7), acceptable (4 to 5) or poor (0 to 3). Pharmacovigilance and survey studies could not be assessed by these means and are described separately. Furthermore, for the sake of completeness, we also graded the evidence of included reports according to the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework [23].

2.5. Analysis

Categorical data are given as counts and were analysed using the Fisher exact test or Chi-square test, as appropriate. Continuous data are presented as median and interquartile range (IQR), respectively as mean and standard deviation, depending on the measures reported in the pertaining original publication. Where appropriate, results were summarised in an integrated manner based on the equations recommended by Wan and colleagues, which allow estimation of mean and standard deviation from median, absolute range and sample size ~~[12]~~ [24]. Weighted means were then calculated and compared with Brown-Forsythe and Welch analysis of variance (ANOVA). Two-sided p-values of <0.05 were used as threshold for

statistically significant differences. GraphPad Prism for Macintosh 10.0.3 (GraphPad Software, San Diego, California, United States) was used for statistical comparisons.

Even though data was limited to two randomised-controlled trials on type 2 diabetes mellitus, we implemented a meta-analysis on the primary outcome (mean difference in HbA1c between intervention and placebo groups). The risk of bias was assessed along five categories, as recommended by the Cochrane collaboration (selection bias, performance bias, detection bias, attrition bias and reporting bias). We opted for a random-effects model because this method does not assume that studies share a common effect size and helps to address unobserved heterogeneity. Statistical heterogeneity was assessed with the I^2-index (heterogeneity is considered unimportant when I^2 is less than 30-40%), and results are displayed using forest plots, including 95% confidence interval (95%-CI). Funnel plot and Egger test were not performed due to the limited number of studies. Review Manager (RevMan), version 5.4.1 (The Cochrane Collaboration, 2020) was used for the purpose of this meta-analysis.

3. Results

3.1. Search Results

The literature search process is summarised in Figure 1. For the final analysis, we retained 35 reports published since 2016 ~~[13-47]~~ [25-59]: 5 from Asia (Israel, N=1; Japan, N=3; People's Republic of China, N=1), 20 from Europe (Belgium, N=1; Germany, N=5; Hungary, N=1; Italy, N=3; Poland, N=1; Rumania, N=1; Sweden, N=2; the Netherlands, N=3; United Kingdom, N=3) and 10 from America (Brazil, N=1; Chile, N=1; United States of America, N=8).

The selected articles described 189 diabetic patients ~~[13-20]~~ [25-32], 32 children with glycogen storage disease type Ib ~~[21-31]~~ [33-43], G6PC3-deficiency ~~[32]~~ [44] or severe congenital neutropenia type 4 ~~[33]~~ [45], 9 patients with proteinuric kidney disease ~~[34]~~ [46], 38 patients with heart failure ~~[35]~~ [47], 84 patients in pharmacokinetic studies ~~[36-41]~~ [48-53] and 63 patients in toxicological series ~~[42-45]~~ [54-57], for a total of 415 children. They were nine case reports [29-31, 35, 38-40, 45, 57], 10 case series [25, 33, 34, 36, 37, 41-44, 47], one prospective non-controlled trial [46], two controlled, randomized, cross-over trials [27, 28], two double-blinded, multiple group, randomized controlled trials [26, 32], two surveys [58, 59], five

pharmacokinetic studies [48-52], one physiologically-based pharmacokinetic investigation [53], and three pharmacovigilance studies [54-56].

Reporting completeness was rated for 29 original studies addressing T2DM (n=8), GSD Ib (n=13), proteinuric kidney disease (n=1), heart failure (n=1) or reporting pharmacokinetics (n=6): it was poor in 4, acceptable in 8, and good in 17 articles. As per the GRADE classification, rated for the same studies apart from the physiologically-based pharmacokinetic modelling exercise [53] (for which GRADE is an inappropriate instrument), evidence quality was very low in 13, low in 6, moderate in 5 and high in 4 articles.

T2DM patients (and pharmacokinetic studies participants) were significantly ($p<0.0001$) older (14.7 ± 2.9 years) and ~~therefore~~ had a higher weight (85.7 ± 29.5 kg) when compared to glycogen storage disease type Ib (8.5 ± 5.1 years, 28.9 ± 14.7 kg), chronic kidney disease or heart failure (11.2 ± 6.1 years, 41.9 ± 38.6 kg) (Table 1).

3.2. Findings

3.2.1. Diabetes mellitus

Eight articles reported on subjects having received either dapagliflozin (n=103) or empagliflozin (n=86) for diabetes mellitus (type 2, n=138; type 1, n=48; congenital insulin resistance, n=3). Their mean age was >15 years and mean weight >85 kg, while mean BMI was 32 kg/m^2 (Table 1). Additionally, one article, which we address in more detail in the section on safety and tolerability, reported on a 17 year-old adolescent girl, who developed a normoglycaemic ketosis while on dapagliflozin. Her blood glucose decreased from 9.7 at baseline to 8.9 mmol/L while on therapy.

The studies differed as per the reported outcomes: blood glucose (6 studies), HbA1c (7 studies), time within desired range (1 study), changes in insulin dose (combination therapy) (5 studies), reduction in co-medication (4 studies). Furthermore, blood glucose and HbA1c were not always reported at baseline and at study end. Side effects were mostly mild, the most frequent being hypoglycaemia detected on regular monitoring (14% of patients). Only in one study, this was severe in 3 patients ~~[14]~~ [26]. Hypoglycaemia was mostly experienced by patients who were also on insulin ~~[14]~~ [26]. Of note, genito-urinary infections were rare (<3%) and no metabolic acidosis or ketoacidosis was reported (Table 2).

Four publications addressed the use of dapagliflozin (n=2) or empagliflozin (n=2) in T2DM (Table 3), two being case reports ~~[18, 19]~~ [30, 31] and two randomized controlled trials

~~[14, 20]~~ [26, 32]. ~~The latter~~ These two trials included a total of 177 adolescents (91 in the intervention, 86 in the placebo groups) and showed a significant effect of SGLT2 inhibition, as compared to placebo, in reducing HbA1c after 24-26 weeks of treatment (mean difference -0.82%, 95%-CI -1.34 to -0.29). Risk of bias was low (Supplementary Figure 1) and no significant heterogeneity was detected (I^2=0%, Figure 2).

~~Specifically, in a multicentre, placebo-controlled, double-blind randomised phase 3 study, Tamborlane and colleagues evaluated dapagliflozin as an add-on therapy (to be added to either metformin, insulin or both) [14]. They compared dapagliflozin and placebo among 72 patients with T2DM. Fifty-three of them were 10 to 17 years old: 29 of those received dapagliflozin and 24 received placebo. The study was designed as a 24-week double-blind period, followed by a 28-week open-label extension in which all participants received dapagliflozin. The primary outcome was the difference in HbA1c between the two groups at 24 weeks, which was non-significant. However, a sensitivity analysis including the per-protocol population showed significant differences (-1.13%, 95%-CI -1.99 to -0.26, p=0.012). During the randomised phase, 11 patients (28%) experienced hypoglycaemia, while 13 participants were hypoglycaemic (10 of them were also receiving insulin) during the open-label extension. Three patients on dapagliflozin (and one on placebo) had severe hypoglycaemia, but nobody needed to stop treatment. No diabetic ketoacidosis was reported.~~

~~Recently, Laffel and colleagues used a single placebo group to investigate both empagliflozin and linagliptin in adolescents 10-17 years of age with T2DM previously treated with either insulin, metformin or both [20]. Participants randomised to empagliflozin were started on 10 mg once daily and, based on their HbA1c response, underwent a further randomisation into a 10 mg or 25 mg dose group at 14 weeks, with the HbA1c response assessed at 26 weeks. The HbA1c reduction in the empagliflozin group (-0.84%, 95%-CI -1.50 to -0.19, p=0.012) was significantly different from placebo. Empagliflozin was well-tolerated, the most frequent adverse event being hypoglycaemia (23% of participants versus 9% in the placebo group), which was never severe. No diabetic ketoacidosis was reported.~~

Two case reports described a 16 year-old female with Prader-Willi syndrome with a difficult-to-manage T2DM ~~[18]~~ [30], who was successfully controlled with liraglutide and empagliflozin (25 mg q.d.), respectively a previously small-for-gestational-age 12 year-old boy treated with metformin and dapagliflozin (5 mg 1x/d) ~~[19]~~ [31]. None of these patients experienced adverse events.

Two studies addressed the use of dapagliflozin for type 1 diabetes mellitus. In a phase 1 crossover trial among 33 patients 12 to 21 years of age, Biester and colleagues investigated dapagliflozin as add-on to insulin for 24h ~~[15]~~ [27]. Dapagliflozin reduced both mean insulin dose over 24h (by 13.6%, p<0.0001) and insulin administered within 4h after a standardized liquid mixed meal (p=0.0402). While beta-hydroxybutyrate levels significantly increased (0.17±0.13 mmol/L versus 0.11±0.08 mmol/L, p<0.0001), they were never >1.0mmol/L. Adverse events were mild and infrequent, without significant differences between treatment and placebo arms. ~~These investigators also performed a non-compartmental pharmacokinetic analysis, which is presented below in section 3.2.4.~~

In another, double-blind, placebo-controlled, crossover study, in which 15 adolescents aged 15.4±1.6 years and 15 young adults aged 18.7±0.8 years ~~old~~ were included, ~~Biester and colleagues investigated~~ the effect of high dose dapagliflozin (10 mg, 2 single doses over 24h) on full closed loop insulin patients was investigated ~~[16]~~ [28]. ~~The primary outcome was t~~Time within the desired glycaemic range (3.9 to 10mmol/L)~~, which~~ was significantly increased in patients receiving dapagliflozin (68%), as compared to placebo (50%, p<0.001). ~~This was confirmed in the subgroup analysis of adolescents (69%±7% versus 51%±12%, p<0.001).~~ Dapagliflozin also led to a significant reduction in the total insulin dose ~~(31±10 U/24h versus 40±13 U/24h, p=0.004)~~. No severe hypoglycaemia episode and no diabetic ketoacidosis were recorded.

Finally, two case reports ~~[13, 17]~~ [25, 29] accounted for three patients having received either dapagliflozin (n=1) or empagliflozin (n=2) for Rabson-Mendenhall syndrome, a form of severe congenital insulin resistance. In these patients, diabetes had been difficult to control with insulin and metformin, and SGLT2-inhibitors led to HbA1c improvement and insulin dose reduction. Despite some increase in beta-hydroxybutyrate, its levels remained within normal range ~~[17]~~ [29], and no ketoacidosis occurred. Galderisi and colleagues noticed increased calcium and phosphate excretion on empagliflozin and an increased calcium excretion on dapagliflozin, without any change in plasma levels ~~[13]~~ [25].

3.2.2. Glycogen storage disease type Ib

Eleven publications individually reported on 29 patients with glycogen storage disease type Ib, one article described a case of severe congenital neutropenia type 4, and another described the course of two patients with G6PC3-deficiency (one of the potential causes of severe congenital neutropenia type 4)~~, whilst another described a case of severe congenital~~

~~neutropenia type 4~~. The case of a 6-year-old patient ~~[24, 25]~~ [36, 37], as well as three other cases started on empagliflozin at 8, 12 and 15.5 years of age ~~[22]~~ [34, 60], reported twice in the literature, were analyzed only once. Furthermore, an international questionnaire collected data on 32 adults and 80 children with glycogen storage disease type Ib, ranging in age from 0 to 38, median 10.5 years ~~[46]~~ [58]. Recently, the same group published a survey among patients or parents, including both adult and paediatric patients, addressing patient-reported outcomes [59]. Authors admitted that a relevant (yet unspecified) proportion of respondents was depicted in both surveys ~~[47]~~ [59].

Individual cases ranged from 11 months to 16 years, with median of 8.0 years at start of empagliflozin therapy, for a follow-up of 10 to 1050 days (median 393 days). There was some variability in both the starting (from 0.1 mg/kg to 0.6 mg/kg) and the final dose (from 0.1 mg/kg to 1.3 mg/kg), as well as in the posology (mainly given once daily, but also twice daily ~~[21]~~ [33] or even 3 times weekly). There were two cases, in which the initial dose was reduced because of positive, satisfactory clinical course, with maintenance of response ~~[32]~~ [44].

There was heterogeneity in the collected outcomes. Globally, patients showed improved neutrophil counts and function (despite reduction, n=6, or weaning, n=13, of granulocyte colony stimulating factor, G-CSF, injections), reduced infections, need for hospitalisations and antibiotic treatments, improved gastrointestinal symptoms and reduced stool frequency, improved appetite, absorption and growth, better oral health and reduced aphthous lesions, improved skin, and wound healing, resolved anaemia and iron deficiency (Figure ~~2~~ 3). For example, in a series of eight patients, seven were on treatment for iron deficiency and all ceased iron supplementation upon empagliflozin treatment ~~[21]~~ [33]. Similarly, in a patient previously dependent on erythrocyte concentrate transfusions, these could be stopped ~~[25]~~ [37]. Improved metabolic control (urate ~~[21, 22, 26, 28]~~ [33, 34, 38, 40], triglycerides ~~[22, 23, 26]~~ [34, 35, 38] and cholesterol reduction or normalization ~~[23, 28]~~ [35, 40]) have also been reported. Intermediate metabolism was positively impacted, with normalization of urate and pentose metabolism intermediates ~~[28]~~ [40]. Of note, not only glucose control, but also glycaemic fluctuations improved ~~[23-25]~~ [35-37], which was imputed to a better intestinal meal tolerance ~~[23, 25]~~ [35, 37].

The case of a 6 year-old boy, who started to eat by himself for the first time, is noteworthy ~~[25]~~ [37]. One patient, in addition to recurrent aphthous stomatitis and a severe Crohn-like irritable bowel disease, suffered from difficult-to-control juvenile idiopathic arthritis. This remitted within 3 weeks of empagliflozin treatment ~~[23]~~ [35].

Neutrophil function was assessed by oxidative burst, neutrophil chemotaxis and bactericidal assay ~~[25]~~ [37], respectively by immunophenotyping neutrophil~~s~~ subsets, assessing the proportion of mature and activated neutrophils ~~[30]~~ [42]. Furthermore, plasma 1,5-anhydroglucitol (1,5-AG) was assessed in 20 cases and in all but one case decreased ~~[21, 23, 25, 26, 28, 29, 31, 32]~~ [33, 35, 37, 38, 40, 41, 43, 44] (Figure ~~2~~ 3). Clinical improvement often occurred before or independently from the neutrophil count response ~~[25]~~ [37] or without (complete) absolute neutrophil count (ANC) normalisation ~~[32]~~ [44], leading to the hypothesis that the improvement in neutrophil function may play a major role ~~[25, 30]~~ [37, 42]. Furthermore, the amplitude of neutrophil count fluctuations was reduced with empagliflozin, suggesting increased neutrophil lifetime ~~[25]~~ [37].

Globally, empagliflozin in these children was safe. No serious adverse events, and in particular no ketoacidosis, were reported. Similarly, hypoglycaemia was generally recorded on continuous or routine monitoring, glycaemia was mostly similar ~~[26]~~ [38] or even better controlled than before treatment ~~[25]~~ [37], and was easily managed with dietary modifications ~~[30]~~ [42]. There was only one case of severe hypoglycaemia, causing overnight seizures ~~[21]~~ [33], and explained in the context of strict dietary control with low carbohydrate intake ~~[21]~~ [33]. Genitourinary infections were rare (Table 2) ~~[21]~~ [33]. An 11 year-old girl developed generalized arthralgias after dose increase to 12.5 mg b.i.d. (0.6 mg/kg/day), which disappeared after reducing the dose to 10 mg b.i.d. (0.48 mg/kg/day) ~~[28]~~ [40].

Respondents of an international survey across 24 countries provided data on 112 glycogen storage disease type Ib patients (n=80, 71%, of whom were <18 years of age), with median treatment duration of 9.5 (range <1 to 27) months ~~[46]~~ [58]. The median paediatric dose was 0.4 mg/kg/d (absolute range 0.1-0.9 mg/kg/day), administered as single daily dose in 48/112 (43%) and as two divided doses in the remaining patients. In both adults and children, there were beneficial effects on neutropenia frequency ~~(decreased from 83% to 47% on empagliflozin, while frequency of severe neutropenia decreased from 29% to 10%)~~, oral and anogenital lesions ~~(from 68% to 13%)~~, recurrent bacterial infections ~~(from 54% to 8%)~~, presence ~~(from 60% to 22%)~~ and severity of irritable bowel disease, and anaemia prevalence ~~(from 73% to 30%)~~. Out of the 89 patients on G-CSF prior to SGLT2-inhibitor therapy, 49 (55%) could stop it and 15 (17%) reduce its dose.

Empagliflozin was well tolerated, with 77 (69%) patients not showing any adverse event. The most common adverse event was hypoglycaemia. Different from the individually reported cases (Table 2), this was often severe (defined as <3.0mmol/L and symptomatic) and

involved 20 out of 111 patients (18%). There were 6/111 (5.4%) cases of lactic acidosis (3 children, 3 adults). The authors acknowledged that, hypoglycaemia and lactic acidosis being common occurrences in GSD Ib, it was impossible to determine whether empagliflozin contributed to these events. There were 3 fungal (n=3/109, 2.8%, 1 of which in a child) and 8 urinary tract (n=8/104, 7.7%, 5 of which in children) infections. A 23 year-old adult with gastroenteritis and dehydration developed ketoacidosis.

The patient and caregiver survey recently performed by the same authors in an effort to address patient-reported outcomes was answered by 73 participants, including adult and paediatric patients. ~~Median age at empagliflozin treatment start was 10 (absolute range 0-48) years, treatment duration 9.5 (absolute range 0-27) months, and daily dose 0.36 (absolute range 0.05-1.9) mg/kg/day, mostly (66%) administered as two divided doses.~~ Results mirrored the previous healthcare providers survey ~~[46]~~ [58]~~, with improved neutropenia, oral and anogenital lesions, skin infections, gastrointestinal symptoms and anaemia in >80% of patients, as well as ability to either stop (49%) or reduce (42%) G-CSF~~ ~~[47]~~ [59]. Furthermore, positive effects included improved appetite, physical activity, well-being, sleep and overall quality of life, and reduced number of hospitalizations and sick-day leaves of both patients and caregivers~~. While seventy-five percent did not report any adverse effects, hypoglycaemia occurred in 15% of interviewees. One case of ketoacidosis was reported, but it was not stated whether this was in an adult or paediatric patient~~ ~~[47]~~ [59].

3.2.3. Heart failure and proteinuric kidney disease

Newland and colleagues reported their retrospective, single-centre experience with dapagliflozin in 38 heart failure patients 4 months to 21 years, median 12.2 (interquartile range 6.2-17.5) years of age ~~[35]~~ [47]. The median dapagliflozin dose was 0.16 (IQR 0.12-0.19) mg/kg/day and the length of follow-up 130 (IQR 76-332) days. A range of diagnoses was included, mainly dilated cardiomyopathy (68%) but also restrictive cardiomyopathy, single-ventricle physiology, patients on ventricular assist device or post heart transplant. A pre-/post-comparison (Supplementary Table 1), despite no difference in New York Heart Association (NYHA) heart failure stage, showed a small but significant decrease in brain natriuretic peptide (from 222 to 166 pg/mL, p=0.04). Overall, dapagliflozin was safe, with stable estimated glomerular filtration rate (eGFR) ~~(from a median of 118 to 100mL/min/1.73m^2, p=0.09)~~, no symptomatic hypoglycaemia, dehydration, or ketoacidosis. There were, however, six (16%) patients with urinary tract infection.

In a prospective trial among 9 patients with proteinuric kidney disease, median age 10.1 (IQR 8.7-11.7) years of age, dapagliflozin 5 mg (patient ≤30 kg) or 10mg (patient >30 kg) was administered daily for 12 weeks ~~[34]~~ [46]. Proteinuria decreased by 33% at 4 weeks and 23% at 12 weeks, while albumin was unchanged from baseline at 4 weeks and slightly increased at 12 weeks. Based on a parametric approach, data analysis showed that eGFR did not change at 4 weeks, but slightly decreased at 12 weeks (103.8 ± 28.2 versus 109.2 ± 32.0 mL/min/1.73m^2 at baseline, p<0.048). However, looking at the individually reported data and performing non-parametric statistics, median eGFR was minimally, but significantly (p=0.0156) higher at 12 weeks, 105.8 (IQR 79.3-121.1), as compared to baseline, 103.1 (IQR 68.1-127.6). No patient discontinued medication owing to an adverse event, but one case of asymptomatic bacteriuria was reported.

3.2.4. Pharmacokinetics

We identified 5 clinical pharmacology studies [48-52], in which the pharmacokinetics and pharmacodynamics of dapagliflozin or empagliflozin were evaluated, and one physiologically-based pharmacokinetic model on dapagliflozin [53].

For dapagliflozin, the volume of distribution (V_d) ranged between 130 and 468 L, whereas clearance (CL) showed small variation (20 - 24 L/h), with a half-life ($t_{1/2}$) between 10.3 and 14.1 h. Exposure was dose-proportional, with maximal concentration (C_{max}) between 25 and 118 ng/mL and an area under the concentration-time curve (AUC_{0-24}) between 101 and 517 ng·h/mL, and time to maximum concentration (t_{max}) ranging between 0.9 and 1.5 h. For empagliflozin, V_d ranged between 101 and 186 L, and CL between 10 and 17 L/h, with t_{max} varying between 1.3 and 1.8h. C_{max} ranged between 175 and 692 nmol/L, and AUC_{0-24} was estimated between 1110 and 4720 nmol·h/L (Supplementary Table 2).

Laffel and colleagues ~~[39]~~ [51] investigated the dose-concentration and the concentration-effect (assessed as urinary glucose excretion over 24h and fasting plasma glucose) relationship of empaglifozin following single administration ~~of doses of 5, 10 and 25 mg~~ in 27 adolescents with T2DM. Participant age and weight were (mean and SD) 14.1±2.0 years and 96.6±23.5 kg, respectively. They were hyperfiltrating, with mean eGFR of 165.8±25.8 mL/min/1.73m^2. ~~The pP~~harmacokinetic ~~study was based on frequent blood sampling and data were analysed using~~ analysis was non-compartmental ~~methods~~. The pharmacodynamic part of the study showed an exposure-response relationship similar to the adult population, when adjusted for baseline covariates, namely mean daily glucose, sex, race,

and body weight. ~~Seven participants (26%) reported at least one adverse event, but no one was serious or deemed clinically relevant.~~

Tirucherai and colleagues administered single-dose dapagliflozin to 23 adolescents 11 to 17 year~~s~~ old with T2DM (mean weight 99.7±26.4kg, BMI 35.7±7.7kg/m^2), randomized to receive 2.5 mg (n=7), 5 mg (n=8) or 10 mg (n=8) ~~[38]~~ [50]. ~~Absorption was pretty rapid (median t_{max} 0.88 to 1.5h), and exposure dose-proportional.~~ Mean urinary glucose excretion over 24h increased in a dose-proportional manner. ~~Similarly, fasting plasma glucose levels decreased in all dosing groups. Six patients (25%) experienced at least one adverse event, without any dose-dependent pattern, most were mild and none was considered to be clinically significant or related to the intake of dapagliflozin. There was no ketoacidosis.~~

Parkinson and colleagues integrated the data from the Tirucherai study and from two adult studies on dapagliflozin in T2DM~~, all investigating single-dose intake of 2.5, 5 and 10 mg [37]~~ [49]. They were interested in examining the relationship between exposure (measured as AUC) and response (measured as 24h urine glucose excretion). Data from 63 adults and 20 children (mean age 14.5 years, mean weight 99.7kg, mean BMI 35.7kg/m^2) were available. Pharmacokinetic characteristics were similar, with children showing a slightly lower exposure than adults. Baseline eGFR, fasting plasma glucose and sex were significant covariates of the pharmacodynamic sigmoidal E_{max} model in both populations, while black ancestry was identified as a covariate only in the paediatric population. ~~Model-predicted urinary glucose excretion in adolescents was higher than in adults, and authors postulated this may have been associated with the higher baseline eGFR in adolescents, consistent with the mechanism of action of SGLT2 inhibitors.~~ Authors concluded that the same dose as in adults could be used for a planned phase III adolescent study in type 2 diabetes mellitus ~~[14]~~ [26].

~~Penland evaluated the pharmacokinetics of dapagliflozin in chronic kidney disease (CKD, with and without diabetes mellitus), integrating data from 5 studies, one of which was the paediatric study by Tirucherai reported above. Despite providing insight in dapagliflozin pharmacokinetics in CKD, this study did not shed further light on age- and weight-dependent changes to dapagliflozin pharmacokinetics in children [40].~~

Busse and colleagues integrated data from a study including paediatric ~~[15]~~ [27] and adult patients receiving a 10 mg single dose of dapagliflozin ~~[36]~~ [48]. Data from 33 adolescents / young adults, mean 16.1 (range 12-21) years old and 67.7 (range 50-89) kg

body weight, and from 54 adults, were available for pharmacokinetic analysis, while 31 adolescents and 65 adults contributed to the pharmacodynamic data. It was found that a 2-compartment model with 1st order absorption and 3 transit compartments was required to describe the data, with body weight as significant covariate for exposure. After accounting for this covariate, AUC_{0-24} was similar in adolescents and adults. In the pharmacodynamic analysis, using 24h urinary glucose excretion as a marker of the effect, a sigmoidal E_{max} model described the data, with baseline eGFR and glycaemia being significant covariates. Interestingly, changes in body weight (which was significant covariate of exposure) only slightly modified 24h urinary glucose excretion. This may be consistent with the finding in the adult study, that similar 24h urinary glucose excretion values were detected in the 5 and 10 mg doses, suggesting that the exposure-response curve was at the plateau.

In a stepwise approach, Jo and colleagues built a physiologically-based pharmacokinetic model for dapagliflozin ~~[41]~~ [53], based on data from healthy adults following single-doses between 5 and 100 mg, and multiple-doses of 10 mg daily. The model was subsequently adapted to explore drug disposition in adolescents 11-18 year~~s~~ old with T2DM, yielding predicted exposure range that corresponds to drug levels observed in adolescents following single-doses of 2.5 and 10 mg. Finally, UDP-glucuronosyltransferase family 1 member 9 (UGT1A9) ontogeny was incorporated into the model to predict dapagliflozin exposure (C_{max} and AUC) in children 12-18, 6-12, 2-6, 1.5-2, 1-1.5 years, 6-12, 3-6 and 1-3 months old. The accuracy of these predictions was not verified ~~[41]~~ [53].

3.2.5. Safety and Pharmacovigilance

We identified four studies focusing on the safety profile of dapagliflozin or empagliflozin in children: a review from reports to 13 poison centres ~~[42]~~ [54], two pharmacoepidemiologic database interrogations ~~[43, 44]~~ [55, 56] and a case report ~~[45]~~ [57].

In total, 63 patients, 2 to 19 years old were described. Intriguingly, no hypoglycaemia was reported. There was one case of normoglycaemic ketonaemia, one case of acute pancreatitis and 12 paediatric patients in a pharmacovigilance database interrogation that detected safety signals with respect to ketoacidosis and urogenital infections. Out of 49 paediatric patients with exposures to SGLT2 inhibitors reported to regional poison centres, only two were symptomatic, and neither developed significant sequelae, even after an intake of 125 mg empagliflozin with suicidal intent.

Pereyra and colleagues reported a 17 year-old girl with type 1 diabetes mellitus on subcutaneous insulin pump, who had been on empagliflozin for 11 months with better glucose control, decreased glucose variability and HbA1c ~~[45]~~ [57]. After approximately 1.5 days of reduced carbohydrate intake and reduced insulin boluses without increase in basal insulin, she developed metallic taste, thick saliva, mild malaise, nausea, vomiting and fainting. A normoglycaemic ketonaemia was detected, but blood gases were not checked. This was treated as a diabetic ketoacidosis, with rapid clinical improvement.

Two pharmacovigilance databases were interrogated to detect possible safety signals ~~[43, 44]~~ [55, 56]. ~~First, i~~ In a disproportionality analysis performed on the WHO-managed VigiBase database~~, Frent and colleagues investigated~~ investigating the possible association between SGLT2 inhibitors and acute pancreatitis~~. O~~ , out of 600 analyzed reports, only one patient was between 12 and 17 years ~~[43]~~ [55]. Unfortunately, no details of this specific case were provided. ~~Second, Katsuhara and colleagues interrogated~~ In an interrogation of the Japanese spontaneous adverse events reporting database~~. O~~ , out of the 4322 reports on possible adverse drug reactions to the six SGLT2-inhibitors marketed in Japan, only 12 were in children (n=4 <10 years of age and n=8 in the age group 10-19 years) ~~[44]~~ [56]. Data on the paediatric reports were not detailed.

In a retrospective review of exposures reported to 13 poison centres from 6 States in the USA, Schaeffer and colleagues identified 88 cases, with mean age 25 years (absolute range 1 to 75 years) ~~[42]~~ [54]. Eighty of them (91%) did not develop any symptoms, six patients (7%) developed minor and two (2%), aged 43 and 65 years, moderate symptoms. Hypoglycaemia was not observed. Out of the 88 reported exposures, 42 were <6 years, four were 6-12 years and three were 13-19 years of age. Out of the six patients with minor symptoms, two were children. The first, aged two years, developed nausea and tachycardia after unintentional ingestion of 5 mg dapagliflozin. The second, a 15 year old subject, developed high blood pressure (135/92 mmHg) and urinary incontinence after intentional intake of 125 mg empagliflozin.

4. Discussion

In adults, SGLT2 inhibitors have revolutionised the therapy of ~~T2DM~~ type 2 diabetes mellitus, heart failure and chronic kidney disease ~~[1-3, 8, 9, 48]~~ [1-8, 15-19]. The present

systematic review documents the use of dapagliflozin or empagliflozin in at least 415 children and adolescents, of which 67% are still off-label use at the time of writing of this systematic review (all were off-label at the time the pertaining articles were published). It complements a recent literature review identifying 5 articles describing the paediatric use of dapagliflozin ~~[49]~~ [61].

It is worth highlighting that this analysis provides a summative assessment of age, weight, dose, and safety information on patients exposed to either dapagliflozin or empagliflozin. None of the clinical studies included have considered the underlying pharmacokinetic-pharmacodynamic relationships as basis for the dose rationale in secondary indications (i.e. different from diabetes mellitus in adolescents).

Most patients had a form of diabetes mellitus and were (or had previously been) on co-therapies, mainly insulin and/or metformin. Indeed, randomized controlled trials (therefore offering a higher level of evidence than case series or non-controlled investigations) on dapagliflozin or empagliflozin in children and adolescents for T2DM are available and showed some efficacy, although less impressive than in adults. This might have several explanations: from study-specific characteristics like sample size, patient selection, difficulties in patient recruitment and the coincident SARS-CoV-2 pandemic fostering more sedentary behaviour ~~[20]~~ [32], to limited self-care and antidiabetic drug compliance among adolescents ~~[14, 50]~~ [26, 62], to a more “aggressive” disease phenotype in youth-onset T2DM, with early insulin resistance, a faster decline in β- cell function and insulin production, on the background of physiologic pubertal insulin resistance ~~[20, 51]~~ [32, 63].

Based on glucose control and insulin dose reduction, the use of SGLT2 inhibitors appeared efficacious in over 50 cases of children and adolescents with either type 1 diabetes mellitus or congenital insulin resistance. On the other hand, in adults, because of the increased risk of diabetic ketoacidosis in such patients (approximately 5% as compared to roughly 0.05% in T2DM) ~~[4]~~ [14], type 1 diabetes mellitus was not granted an indication in the label, even though compassionate use is common. Interestingly, we found only one reported case of a 17 year-old adolescent girl with type 1 diabetes mellitus on subcutaneous insulin pump, who developed normoglycaemic ketonaemia and symptoms consistent with diabetic ketoacidosis while being on empagliflozin ~~[45]~~ [57]. In both adults and children with type 1 diabetes mellitus, it is important to deliver an appropriate insulin dose to suppress lipolysis and ketogenesis ~~[45]~~ [57], regularly check not only glucose but also ketones, and to adapt total daily insulin dose to carbohydrate intake variations ~~[52]~~ [64]. ~~Indeed, in a series focusing on overweight or obese type 1 diabetic young adults (therefore not included in this review), a 16 year-old girl developed diabetic ketoacidosis after voluntarily skipping insulin injections for 2 days [53].~~

A consistent body of evidence has also been collected with the use of empagliflozin in GSD Ib, G6PC3-deficiency, and severe congenital neutropenia type 4. Despite the rarity of the conditions, we detected 32 individually described cases. Furthermore, a survey among hospitals found at least 80 paediatric patients treated for this condition. The efficacy of empagliflozin in this severe disorder of carbohydrate metabolism has been remarkable, with patients being able to reduce or stop G-CSF (a therapy needing repeated injections and implying relevant long-term risks, including myelodysplastic syndrome and myeloid leukaemia), reducing recurrent infections, improving oral and gastrointestinal health, reduction of blood losses and improvement of anaemia and iron status, as well as normalization of uric acid. There is a convincing pathophysiological rationale (shared for both GSD Ib and G6PC3-deficiency [44]): by inhibiting the renal reabsorption of glucose and causing glucosuria, SGLT2 inhibitors decrease renal 1,5-anhydroglucitol (1,5-AG) reabsorption, reducing its plasma concentration and that of its toxic analogue 1,5-anhydroglucitol-6-phosphate, which accumulates in neutrophils inhibiting hexokinases, hereby impairing energy generation and causing malfunction and apoptosis.

Given the limited experience, there was significant variation in total daily dose, dosing interval (q.d. or b.i.d.), as well as on the selected pharmacodynamic endpoints based on which doses are titrated (both absolute neutrophil count and serum 1,5-anhydroglucitol-6-phosphate have been used). Whilst an obvious step towards treatment personalization in these patients would be the assessment of pharmacokinetics and corresponding pharmacokinetic-pharmacodynamic relationships, there are currently no pharmacokinetic studies~~, opportunistic blood sampling or therapeutic drug monitoring~~ for this indication, neither in adults nor in children.

~~Large randomised controlled trials in adults with heart failure delivered impressive results for both dapagliflozin and empagliflozin, with 25-26% reduction of a composite outcome of worsening heart failure or cardiovascular death [2, 3]. Interestingly, despite the otherwise disappointing results in the therapy of heart failure with preserved ejection fraction (HFpEF) [54], SGLT2 inhibitors are efficacious even in this condition [55-57] and are nowadays advised for adults with an established diagnosis of HFpEF [58]. The mechanisms of cardiovascular protection are multiple and include among others: diuresis (with a differential role on intra- and extracellular body fluid compartments) reducing cardiac overload, suppression of sympathetic nervous system overdrive, metabolism shift towards ketone bodies positively impacting cardiac energetics, increased haemoglobin/haematocrit, modification of $Na^+/K^+/Ca^{2+}$ ionic~~

homeostasis and uric acid metabolism, and modulation of the FGF-23 / klotho pathway [1, 59-63].

SGLT2 inhibition has been a breakthrough in the therapy of heart failure in adults [1-4]. One retrospective report of paediatric experience of dapagliflozin among 38 children and young adults (4 months to 21 years old) revealed a positive effect of heart failure therapy, including SGLT2 inhibition, when comparing changes from baseline after a median treatment time of approximately 4 months [35] [47]. The use of concomitant therapies and standard of care, as well as the absence of a control group precluded any conclusion on efficacy, but this preliminary experience delivered promising results and supported tolerability of dapagliflozin also in this population. On the other hand, a survey among 29 USA paediatric cardiology units (published as a conference abstract and therefore not included in this analysis) found that 18 (62%) of them had been using SGLT2 inhibitors in 185 children or adolescents with heart failure (median age 12.5, IQR 9.5-15 years) [64].

Various publications have focused on the pathophysiological and clinical interest of using SGLT2 inhibitors in paediatric chronic kidney disease (with or without diabetes mellitus) [4, 65] [14, 65]. Most reports consistently indicate a risk reduction of renal composite outcomes in the range of 30-40% [4, 6, 8, 9] [14, 16, 18, 19]. Mechanisms are far beyond a simple improvement in glycaemic control and reduction of hyperfiltration. Indeed, sustained natriuresis, reduction in plasma volume, skin sodium and body weight appear to play a role. Furthermore, metabolism shift away from glucose oxidation in favour of ketone and fatty acid oxidation might be beneficial for both the kidneys and the myocardium, two avid energy consumers [4]. In the current review, one small paediatric study was identified in which 9 patients with proteinuric kidney disease, median 10.1 years old, received dapagliflozin for 3 months [34] [46]. A significant reduction in proteinuria was observed, while effects on eGFR were controversial. By contrast, meta-analysis results from adults showed that SGLT2 inhibitors protect from acute kidney injury [66]. Furthermore, similar to what has long been known for ACE inhibitors, the slight (and reversible) dip in eGFR seen shortly after SGLT2 inhibitors initiation appears to reflect a decrease in hyperfiltration, and can therefore be seen as an early marker of their middle- and long-term nephroprotective effect [67].

As mentioned previously, pharmacokinetic studies were performed exclusively in adolescents with type 1 or 2 diabetes mellitus. We did not find any pharmacokinetic data in GSD Ib, paediatric chronic kidney disease or paediatric heart failure. Similarly, the pharmacokinetics of these drugs has not been evaluated in younger children with type 1 or 2

diabetes mellitus. ~~However, a sophisticated physiologically-based pharmacokinetic model was built for dapagliflozin. The model was deemed to be robust enough for prospective predictions in younger children, but authors warned that dose recommendations "should be verified and revised with" more clinical pharmacokinetic data [41].~~ Unsurprisingly, lack of data on drug disposition and understanding of interindividual variability in systemic exposure may explain the wide range of doses tested in younger children ~~[35]~~ [47] and in GSD Ib ~~[21, 47]~~ [33, 59].

Based on the selectivity of the mechanisms of the two compounds, it can be anticipated that their safety profile may be comparable across the different paediatric indications. ~~In fact~~ Indeed, available paediatric data suggests that SGLT2 inhibitors have a good tolerability and safety profile across the dose range and treatment periods evaluated so far. The most frequent adverse event was hypoglycaemia, occurring in approximately 10-20% of patients. For obvious reasons, this figure was almost 40% in GSD Ib (which manifests itself among others with hypoglycaemia) but absent in children with heart failure or chronic kidney disease. In T2DM, it was mainly associated with co-medications predisposing to hypoglycaemia. ~~Severe or symptomatic hypoglycaemia was rarely reported.~~ Interestingly, different from adult studies, no diabetic ketoacidosis was reported in children so far. Only one case of a 17 year-old girl with type 1 diabetes mellitus on a subcutaneous insulin pump presented with normoglycemic ketosis and symptoms compatible with ketoacidosis. It is, however, important to note that the relatively low number of patients hitherto reported reduces the ability to detect rare occurrences. ~~In a survey collecting data on 112 GSD Ib patients treated with empagliflozin (and in a patients and parents survey), one adult (0.9%) was reported to have developed ketoacidosis [46, 47].~~ Genitourinary infections were ~~globally~~ rare ~~(Table 2)~~. Current data therefore supports the notion of a reassuring safety profile in children, and confirms the importance of regular meals, as well as a careful approach in type 1 diabetes mellitus. Database interrogation studies, including children inadvertently exposed to a single high-dose of SGLT2 inhibitors, confirmed a safe profile.

Given the limited clinical experience and number of patients exposed to long-term therapy, we acknowledge some of the limitations of this review. First, the quality of reporting was variable. Second, the type of information provided in the original publications was somehow inconsistent, so that a meta-analysis was possible only for the two randomized controlled trials on adolescents with T2DM. Finally, we focused exclusively on dapagliflozin and empagliflozin, since these are the SGLT2 inhibitors that are also indicated for heart failure and chronic kidney disease in adults. However, other gliflozins are licensed for chronic kidney disease (canagliflozin) and several are licensed (with national variations) for T2DM. Despite

the same pharmacological mechanisms, our conclusions may not be generalized to other molecules.

5. Conclusions

In summary, sodium-glucose cotransporter type 2 inhibitors have delivered remarkable improvements in the therapy of diabetes mellitus, heart failure and chronic kidney disease in adults. The present review shows that dapagliflozin and empagliflozin have hitherto been used in >400 children, with a seemingly positive benefit-risk balance, despite the lack of more robust dose rationale based on the underlying concentration-effect relationships. Indeed, from a safety point of view, although we acknowledge the relatively low number of studied patients with the pertaining reduced ability to detect rare occurrences, and the need for future, larger safety studies, diabetic ketoacidosis, the most concerning side effect of SGLT2 inhibitors, was uncommon in children and associated with further, identifiable risk factors (like co-medication with insulin) [68]. Notably, good quality data support their use for T2DM in adolescents. Similarly, these drugs have shown impressive results in GSD Ib. Case series and retrospective reports also appear to support their use in heart failure and chronic kidney disease, but additional studies, including pharmacokinetic evaluation, are urgently needed. Evidence generation in paediatric patients will benefit from the use of modelling and extrapolation concepts, providing a robust pharmacological basis for use of SLGT2 inhibitors in these indications [69, 70].

Statements and declarations

Conflicts of interest

The authors have no competing interests to declare that are relevant to the content of this article.

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Data availability statement

The data presented in this study is available from the corresponding author upon reasonable request.

Ethics approval, Standard of reporting, Registration

This being a systematic review, an ethical approval was not required.
The 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations were followed.
This systematic review was pre-registered on PROSPERO, with number CRD42023438162.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Code availability

Not applicable.

Author Contributions

Dr Lava conceived and designed the study. Dr Lava and Dr Laurence conducted the literature search and performed article selection, data extraction, and reporting quality assessment. Dr Lava performed data analysis, including statistical analysis and meta-analysis, and wrote the first draft of the manuscript. Mr Di Deo contributed to Tables' and Figures' preparation, and supervised statistical analysis. Professor Sekarski, Professor Burch and Professor Della Pasqua critically revised the draft of the manuscript. All authors approved the final version of the manuscript.

References

1. Braunwald E. Gliflozins in the Management of Cardiovascular Disease. N Engl J Med. 2022;386(21):2024-2034. https://doi.org/10.1056/NEJMra2115011
2. McMurray JJV, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019;381(21):1995-2008. https://doi.org/10.1056/NEJMoa1911303
3. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020;383(15):1413-1424. https://doi.org/10.1056/NEJMoa2022190
4. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2022;24(1):4-131.
5. Nassif ME, Windsor SL, Borlaug BA, Kitzman DW, Shah SJ, Tang F, et al. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. Nat Med. 2021;27(11):1954-1960. https://doi.org/10.1038/s41591-021-01536-x
6. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Bohm M, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021;385(16):1451-1461. https://doi.org/10.1056/NEJMoa2107038
7. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med. 2022;387(12):1089-1098. https://doi.org/10.1056/NEJMoa2206286
8. Desai AS, Lam CSP, McMurray JJV, Redfield MM. How to Manage Heart Failure With Preserved Ejection Fraction: Practical Guidance for Clinicians. JACC Heart Fail. 2023;11(6):619-636. https://doi.org/10.1016/j.jchf.2023.03.011
9. Zelniker TA, Braunwald E. Mechanisms of Cardiorenal Effects of Sodium-Glucose Cotransporter 2 Inhibitors: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;75(4):422-434. https://doi.org/10.1016/j.jacc.2019.11.031

10. Joshi SS, Singh T, Newby DE, Singh J. Sodium-glucose co-transporter 2 inhibitor therapy: mechanisms of action in heart failure. Heart. 2021;107(13):1032-8. https://doi.org/10.1136/heartjnl-2020-318060
11. Katsiki N, Rizzo M, Mikhailidis DP. Sodium-glucose co-transporter-2 (SGLT-2) inhibitors and uric acid: More good news! J Diabetes Complications. 2023;37(7):108510. https://doi.org/10.1016/j.jdiacomp.2023.108510
12. Mora-Fernández C, Pérez A, Mollar A, Palau P, Amiguet M, de la Espriella R, et al. Short-term changes in klotho and FGF23 in heart failure with reduced ejection fraction—a substudy of the DAPA-VO2 study. Frontiers in Cardiovascular Medicine. 2023;10. https://doi.org/10.3389/fcvm.2023.1242108
13. Helmlinger G, Sokolov V, Peskov K, Hallow KM, Kosinsky Y, Voronova V, et al. Quantitative Systems Pharmacology: An Exemplar Model-Building Workflow With Applications in Cardiovascular, Metabolic, and Oncology Drug Development. CPT Pharmacometrics Syst Pharmacol. 2019;8(6):380-395. https://doi.org/10.1002/psp4.12426
14. Kula AJ. Considerations and possibilities for sodium-glucose cotransporter 2 inhibitors in pediatric CKD. Pediatr Nephrol. 2022;37(10):2267-2276. https://doi.org/10.1007/s00467-022-05456-x
15. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015;373(22):2117-28. https://doi.org/10.1056/NEJMoa1504720
16. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. N Engl J Med. 2016;375(4):323-34. https://doi.org/10.1056/NEJMoa1515920
17. Heerspink HJL, Stefansson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020;383(15):1436-1446. https://doi.org/10.1056/NEJMoa2024816
18. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017;377(7):644-657. https://doi.org/10.1056/NEJMoa1611925
19. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019;380(24):2295-2306. https://doi.org/10.1056/NEJMoa1811744

20. Lava SA, Bianchetti MG, Simonetti GD. Salt intake in children and its consequences on blood pressure. Pediatr Nephrol. 2015;30(9):1389-1396. doi: 10.1007/s00467-014-2931-3.

~~10.~~ 21. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71

~~11~~ 22. Piffer A, Bianchetti MG, Leoni-Foglia C, Simonetti GD, Milani GP, Lava SAG. Vaptans for oedematous and hyponatraemic disorders in childhood: A systematic literature review. Br J Clin Pharmacol. 2022;88(10):4474-4480. https://doi.org/10.1111/bcp.15367

23. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-394.

~~12~~ 24. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135. https://doi.org/10.1186/1471-2288-14-135

~~13~~ 25. Galderisi A, Tamborlane W, Taylor SI, Attia N, Moretti C, Barbetti F. SGLT2i Improves Glycemic Control in Patients With Congenital Severe Insulin Resistance. Pediatrics. 2022;150(1). https://doi.org/10.1542/peds.2021-055671

~~14~~ 26. Tamborlane WV, Laffel LM, Shehadeh N, Isganaitis E, Van Name M, Ratnayake J, et al. Efficacy and safety of dapagliflozin in children and young adults with type 2 diabetes: a prospective, multicentre, randomised, parallel group, phase 3 study. Lancet Diabetes Endocrinol. 2022;10(5):341-350. https://doi.org/10.1016/S2213-8587(22)00052-3

~~15~~ 27. Biester T, Aschemeier B, Fath M, Frey M, Scheerer MF, Kordonouri O, et al. Effects of dapagliflozin on insulin-requirement, glucose excretion and ss-hydroxybutyrate levels are not related to baseline HbA1c in youth with type 1 diabetes. Diabetes Obes Metab. 2017;19(11):1635-1639. https://doi.org/10.1111/dom.12975

~~16~~ 28. Biester T, Muller I, von dem Berge T, Atlas E, Nimri R, Phillip M, et al. Add-on therapy with dapagliflozin under full closed loop control improves time in range in adolescents and young adults with type 1 diabetes: The DAPADream study. Diabetes Obes Metab. 2021;23(2):599-608. https://doi.org/10.1111/dom.14258

~~17~~ 29. Dos Santos SS, Ramaldes LA, Gabbay MAL, Moises RCS, Dib SA. Use of a Sodium-Glucose Cotransporter 2 Inhibitor, Empagliflozin, in a Patient with Rabson-

Mendenhall Syndrome. Horm Res Paediatr. 2021;94(7-8):313-316. https://doi.org/10.1159/000519613

~~18~~ 30. Candler T, McGregor D, Narayan K, Moudiotis C, Burren CP. Improvement in glycaemic parameters using SGLT-2 inhibitor and GLP-1 agonist in combination in an adolescent with diabetes mellitus and Prader-Willi syndrome: a case report. J Pediatr Endocrinol Metab. 2020;33(7):951-955. https://doi.org/10.1515/jpem-2019-0389

~~19~~ 31. Kuwabara R, Urakami T, Yoshida K, Morioka I. Case of type 2 diabetes possibly caused by excessive accumulation of visceral fat in a child born small-for-gestational age. J Diabetes Investig. 2020;11(5):1366-1369. https://doi.org/10.1111/jdi.13246

~~20~~ 32. Laffel LM, Danne T, Klingensmith GJ, Tamborlane WV, Willi S, Zeitler P, et al. Efficacy and safety of the SGLT2 inhibitor empagliflozin versus placebo and the DPP-4 inhibitor linagliptin versus placebo in young people with type 2 diabetes (DINAMO): a multicentre, randomised, double-blind, parallel group, phase 3 trial. Lancet Diabetes Endocrinol. 2023;11(3):169-181. https://doi.org/10.1016/S2213-8587(22)00387-4

~~21~~ 33. Halligan RK, Dalton RN, Turner C, Lewis KA, Mundy HR. Understanding the role of SGLT2 inhibitors in glycogen storage disease type Ib: the experience of one UK centre. Orphanet J Rare Dis. 2022;17(1):195. https://doi.org/10.1186/s13023-022-02345-2

~~22~~ 34. Kaczor M, Greczan M, Kierus K, Ehmke Vel Emczynska-Seliga E, Ciara E, Piatosa B, et al. Sodium-glucose cotransporter type 2 channel inhibitor: Breakthrough in the treatment of neutropenia in patients with glycogen storage disease type 1b? JIMD Rep. 2022;63(3):199-206. https://doi.org/10.1002/jmd2.12278

~~23~~ 35. Rossi A, Miele E, Fecarotta S, Veiga-da-Cunha M, Martinelli M, Mollica C, et al. Crohn disease-like enterocolitis remission after empagliflozin treatment in a child with glycogen storage disease type Ib: a case report. Ital J Pediatr. 2021;47(1):149. https://doi.org/10.1186/s13052-021-01100-w

~~24~~ 36. Peeks F, Hoogeveen IJ, Feldbrugge RL, Burghard R, de Boer F, Fokkert-Wilts MJ, et al. A retrospective in-depth analysis of continuous glucose monitoring datasets for patients with hepatic glycogen storage disease: Recommended outcome parameters for glucose management. J Inherit Metab Dis. 2021;44(5):1136-1150. https://doi.org/10.1002/jimd.12383

~~25~~ 37. Wortmann SB, Van Hove JLK, Derks TGJ, Chevalier N, Knight V, Koller A, et al. Treating neutropenia and neutrophil dysfunction in glycogen storage disease type Ib with an SGLT2 inhibitor. Blood. 2020;136(9):1033-1043. https://doi.org/10.1182/blood.2019004465

~~26~~ 38. Mikami M, Arai A, Mizumoto H. Empagliflozin ameliorated neutropenia in a girl with glycogen storage disease Ib. Pediatr Int. 2021;63(11):1394-1396. https://doi.org/10.1111/ped.14629

~~27~~ 39. View from inside: Nina, Glycogen storage disease warrior. J Inherit Metab Dis. 2020;43(4):653-656. https://doi.org/10.1002/jimd.12246

~~28~~ 40. Tallis E, Karsenty CL, Grimes AB, Karam LB, Elsea SH, Sutton VR, et al. Untargeted metabolomic profiling in a patient with glycogen storage disease Ib receiving empagliflozin treatment. JIMD Rep. 2022;63(4):309-315. https://doi.org/10.1002/jmd2.12304

~~29~~ 41. Hexner-Erlichman Z, Veiga-da-Cunha M, Zehavi Y, Vadasz Z, Sabag AD, Tatour S, et al. Favorable outcome of empagliflozin treatment in two pediatric glycogen storage disease type 1b patients. Front Pediatr. 2022;10:1071464. https://doi.org/10.3389/fped.2022.1071464

~~30~~ 42. Guerra F, Gasperini S, Bonanomi S, Crescitelli V, Pretese R, Da Dalt L, et al. Finding balance between mature and immature neutrophils: The effects of empagliflozin in GSD-Ib. EJHaem. 2023;4(2):551-554. https://doi.org/10.1002/jha2.649

~~31~~ 43. Murko S, Peschka M, Tsiakas K, Schulz-Jurgensen S, Herden U, Santer R. Liver transplantation in glycogen storage disease type Ib: The role of SGLT2 inhibitors. Mol Genet Metab Rep. 2023;35:100977. https://doi.org/10.1016/j.ymgmr.2023.100977

~~32~~ 44. Boulanger C, Stephenne X, Diederich J, Mounkoro P, Chevalier N, Ferster A, et al. Successful use of empagliflozin to treat neutropenia in two G6PC3-deficient children: Impact of a mutation in SGLT5. J Inherit Metab Dis. 2022;45(4):759-768. https://doi.org/10.1002/jimd.12509

~~33~~ 45. Ledeczi Z, Pittner R, Krivan G, Kardon T, Legeza B. Empagliflozin restores neutropenia and neutrophil dysfunction in a young patient with severe congenital neutropenia type 4. J Allergy Clin Immunol Pract. 2023;11(1):344-346 e1. https://doi.org/10.1016/j.jaip.2022.10.019

~~34~~ 46. Liu J, Cui J, Fang X, Chen J, Yan W, Shen Q, et al. Efficacy and Safety of Dapagliflozin in Children With Inherited Proteinuric Kidney Disease: A Pilot Study. Kidney Int Rep. 2022;7(3):638-641. https://doi.org/10.1016/j.ekir.2021.12.019

~~35~~ 47. Newland DM, Law YM, Albers EL, Friedland-Little JM, Ahmed H, Kemna MS, et al. Early Clinical Experience with Dapagliflozin in Children with Heart Failure. Pediatr Cardiol. 2023;44(1):146-152. https://doi.org/10.1007/s00246-022-02983-0

~~36~~ 48. Busse D, Tang W, Scheerer M, Danne T, Biester T, Sokolov V, et al. Comparison of pharmacokinetics and the exposure-response relationship of dapagliflozin between

adolescent/young adult and adult patients with type 1 diabetes mellitus. Br J Clin Pharmacol. 2019;85(8):1820-1828. https://doi.org/10.1111/bcp.13981

~~37~~ 49. Parkinson J, Tang W, Johansson CC, Boulton DW, Hamren B. Comparison of the exposure-response relationship of dapagliflozin in adult and paediatric patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2016;18(7):685-92. https://doi.org/10.1111/dom.12647

~~38~~ 50. Tirucherai GS, LaCreta F, Ismat FA, Tang W, Boulton DW. Pharmacokinetics and pharmacodynamics of dapagliflozin in children and adolescents with type 2 diabetes mellitus. Diabetes Obes Metab. 2016;18(7):678-84. https://doi.org/10.1111/dom.12638

~~39~~ 51. Laffel LMB, Tamborlane WV, Yver A, Simons G, Wu J, Nock V, et al. Pharmacokinetic and pharmacodynamic profile of the sodium-glucose co-transporter-2 inhibitor empagliflozin in young people with Type 2 diabetes: a randomized trial. Diabet Med. 2018;35(8):1096-1104. https://doi.org/10.1111/dme.13629

~~40~~ 52. Penland RC, Melin J, Boulton DW, Tang W. Evaluation of the Pharmacokinetics of Dapagliflozin in Patients With Chronic Kidney Disease With or Without Type 2 Diabetes Mellitus. J Clin Pharmacol. 2023;63(5):551-559. https://doi.org/10.1002/jcph.2196

~~41~~ 53. Jo H, Pilla Reddy V, Parkinson J, Boulton DW, Tang W. Model-Informed Pediatric Dose Selection for Dapagliflozin by Incorporating Developmental Changes. CPT Pharmacometrics Syst Pharmacol. 2021;10(2):108-118. https://doi.org/10.1002/psp4.12577

~~42~~ 54. Schaeffer SE, DesLauriers C, Spiller HA, Aleguas A, Baeza S, Ryan ML. Retrospective review of SGLT2 inhibitor exposures reported to 13 poison centers. Clin Toxicol (Phila). 2018;56(3):204-208. https://doi.org/10.1080/15563650.2017.1357824

~~43~~ 55. Frent I, Bucsa C, Leucuta D, Farcas A, Mogosan C. An investigation on the association between sodium glucose co-transporter 2 inhibitors use and acute pancreatitis: A VigiBase study. Pharmacoepidemiol Drug Saf. 2021;30(10):1428-1440. https://doi.org/10.1002/pds.5313

~~44~~ 56. Katsuhara Y, Ikeda S. Correlations Between SGLT-2 Inhibitors and Acute Renal Failure by Signal Detection Using FAERS: Stratified Analysis for Reporting Country and Concomitant Drugs. Clin Drug Investig. 2021;41(3):235-243. https://doi.org/10.1007/s40261-021-01006-9

~~45~~ 57. Pereyra AM, Ramirez C, Roman R. [Euglycemic ketosis in an adolescent with type 1 diabetes on insulin and dapaglifozin: Case report]. Rev Chil Pediatr. 2017;88(3):404-410. https://doi.org/10.4067/S0370-41062017000300015

~~46~~ 58. Grunert SC, Derks TGJ, Adrian K, Al-Thihli K, Ballhausen D, Bidiuk J, et al. Efficacy and safety of empagliflozin in glycogen storage disease type Ib: Data from an international questionnaire. Genet Med. 2022;24(8):1781-1788. https://doi.org/10.1016/j.gim.2022.04.001

~~47~~ 59. Grunert SC, Venema A, LaFreniere J, Schneider B, Contreras E, Wortmann SB, et al. Patient-reported outcomes on empagliflozin treatment in glycogen storage disease type Ib: An international questionnaire study. JIMD Rep. 2023;64(3):252-258. https://doi.org/10.1002/jmd2.12364

~~48. Authors/Task Force M, McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2022;24(1):4-131. https://doi.org/10.1002/ejhf.2333~~

60. Kaczor M, Wesół-Kucharska D, Greczan M, Kierus K, Kałużny Ł, Duś-Żuchowska M, et al. Clinical characteristics and long-term outcomes of patients with glycogen storage disease type 1b: a retrospective multi-center experience in Poland. Pediatr Endocrinol Diabetes Metab. 2022;28(3):207-212. doi: 10.5114/pedm.2022.116115.

~~49~~ 61. Grube PM, Beckett RD. Clinical studies of dapagliflozin in pediatric patients: a rapid review. Ann Pediatr Endocrinol Metab. 2022;27(4):265-272. https://doi.org/10.6065/apem.2244166.083

~~50~~ 62. Tommerdahl KL, Nelson RG, Bjornstad P. Dapagliflozin in young people with type 2 diabetes. Lancet Diabetes Endocrinol. 2022;10(5):303-304. https://doi.org/10.1016/S2213-8587(22)00075-4

~~51~~ 63. Amiel SA, Sherwin RS, Simonson DC, Lauritano AA, Tamborlane WV. Impaired insulin action in puberty. A contributing factor to poor glycemic control in adolescents with diabetes. N Engl J Med. 1986;315(4):215-9. https://doi.org/10.1056/NEJM198607243150402

~~52~~ 64. Danne T, Garg S, Peters AL, Buse JB, Mathieu C, Pettus JH, et al. International Consensus on Risk Management of Diabetic Ketoacidosis in Patients With Type 1 Diabetes Treated With Sodium-Glucose Cotransporter (SGLT) Inhibitors. Diabetes Care. 2019;42(6):1147-1154. https://doi.org/10.2337/dc18-2316

53. Urakami T, Yoshida K, Suzuki J. Efficacy of Low-dose Dapagliflozin in Young People with Type 1 Diabetes. Intern Med. 2023;62(2):177-186. https://doi.org/10.2169/internalmedicine.9632-22

54. Teuber JP, Essandoh K, Hummel SL, Madamanchi NR, Brody MJ. NADPH Oxidases in Diastolic Dysfunction and Heart Failure with Preserved Ejection Fraction. Antioxidants (Basel). 2022;11(9). https://doi.org/10.3390/antiox11091822

55. Nassif ME, Windsor SL, Borlaug BA, Kitzman DW, Shah SJ, Tang F, et al. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. Nat Med. 2021;27(11):1954-1960. https://doi.org/10.1038/s41591-021-01536-x

56. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Bohm M, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021;385(16):1451-1461. https://doi.org/10.1056/NEJMoa2107038

57. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med. 2022;387(12):1089-1098. https://doi.org/10.1056/NEJMoa2206286

58. Desai AS, Lam CSP, McMurray JJV, Redfield MM. How to Manage Heart Failure With Preserved Ejection Fraction: Practical Guidance for Clinicians. JACC Heart Fail. 2023;11(6):619-636. https://doi.org/10.1016/j.jchf.2023.03.011

59. Zelniker TA, Braunwald E. Mechanisms of Cardiorenal Effects of Sodium-Glucose Cotransporter 2 Inhibitors: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;75(4):422-434. https://doi.org/10.1016/j.jacc.2019.11.031

60. Joshi SS, Singh T, Newby DE, Singh J. Sodium-glucose co-transporter 2 inhibitor therapy: mechanisms of action in heart failure. Heart. 2021;107(13):1032-8. https://doi.org/10.1136/heartjnl-2020-318060

61. Katsiki N, Rizzo M, Mikhailidis DP. Sodium-glucose co-transporter-2 (SGLT-2) inhibitors and uric acid: More good news! J Diabetes Complications. 2023;37(7):108510. https://doi.org/10.1016/j.jdiacomp.2023.108510

62. Mora-Fernández C, Pérez A, Mollar A, Palau P, Amiguet M, de la Espriella R, et al. Short-term changes in klotho and FGF23 in heart failure with reduced ejection fraction—a substudy of the DAPA-VO2 study. Frontiers in Cardiovascular Medicine. 2023;10. https://doi.org/10.3389/fcvm.2023.1242108

63. Helmlinger G, Sokolov V, Peskov K, Hallow KM, Kosinsky Y, Voronova V, et al. Quantitative Systems Pharmacology: An Exemplar Model-Building Workflow With Applications in Cardiovascular, Metabolic, and Oncology Drug Development. CPT

Pharmacometrics Syst Pharmacol. 2019;8(6):380-395. https://doi.org/10.1002/psp4.12426

64. Butts R, Nandi D, Hong B, Lorts A, Spinner J. (1115) SGLT2 Inhibitor Use in Pediatric Heart Failure. The Journal of Heart and Lung Transplantation. 2023;42(4, Supplement):S479. https://doi.org/https://doi.org/10.1016/j.healun.2023.02.1326

65. Cirillo L, Ravaglia F, Errichiello C, Anders HJ, Romagnani P, Becherucci F. Expectations in children with glomerular diseases from SGLT2 inhibitors. Pediatr Nephrol. 2022;37(12):2997-3008. https://doi.org/10.1007/s00467-022-05504-6

66. Zhao M, Sun S, Huang Z, Wang T, Tang H. Network Meta-Analysis of Novel Glucose-Lowering Drugs on Risk of Acute Kidney Injury. Clin J Am Soc Nephrol. 2020;16(1):70-78. https://doi.org/10.2215/CJN.11220720

67. Heerspink HJL, Cherney DZI. Clinical Implications of an Acute Dip in eGFR after SGLT2 Inhibitor Initiation. Clin J Am Soc Nephrol. 2021;16(8):1278-1280. https://doi.org/10.2215/CJN.02480221

68. Meoli M, Lava SAG, Bronz G, Goeggel-Simonetti B, Simonetti GD, Alberti I, et al. Eu- or hypoglycemic ketosis and ketoacidosis in children: a review. Pediatr Nephrol. 2023. https://doi.org/10.1007/s00467-023-06115-5

69. Bellanti F, Della Pasqua O. Modelling and simulation as research tools in paediatric drug development. Eur J Clin Pharmacol. 2011;67 Suppl 1(Suppl 1):75-86. https://doi.org/10.1007/s00228-010-0974-3

70. Harnisch L, Shepard T, Pons G, Della Pasqua O. Modeling and simulation as a tool to bridge efficacy and safety data in special populations. CPT Pharmacometrics Syst Pharmacol. 2013;2(2):e28. https://doi.org/10.1038/psp.2013.6

Figures – Legends

Figure 1

Dapagliflozin and empagliflozin in Paediatrics. Flowchart of the literature search.

Figure 2

Randomized controlled trials on dapagliflozin or empagliflozin use in adolescents with type 2 diabetes mellitus (T2DM). Forest plot depicting the mean difference in HbA1c change after 24 [14], respectively 26 [20] weeks of treatment with either dapagliflozin [14], empagliflozin [20] or placebo among a total of 177 adolescents with T2DM.

Figure 3

Dapagliflozin and empagliflozin use in 32 children and adolescents with glycogen storage disease type Ib (GSD Ib). Panel A depicts the number and proportion of patients reported to have improved in the listed clinical aspects. Panel B reports the absolute neutrophil counts at baseline as compared to last reported encounter in 29 patients with GSD Ib. Panel C shows the haemoglobin at baseline as compared to last reported encounter in 14 patients with GSD Ib. Box plots depict median (line within the box) and 25^{th} and 75^{th} percentiles (boundaries of the boxes), while the whiskers (error bars) represent the minimal and maximal reported values. *Abbreviations*: 1,5-AG = 1,5-anhydroglucitol, ANC = absolute neutrophil count, G-CSF = granulocyte colony stimulating factor, GIT = gastrointestinal tract, Hb = haemoglobin, WBC = white blood cells.

Supplementary Figure 1

Risk of bias of papers included in the meta-analysis of empagliflozin / dapagliflozin use in adolescents with T2DM. Risk of bias was assessed according to five categories as recommended by the Cochrane collaboration: selection bias (D1), performance bias (D2), detection bias (D3), attrition bias (D4) and reporting bias (D5).

Table 3: Data from n=8 paediatric studies on dapagliflozin (n=5 articles, n=103 patients) or empagliflozin (n=4 articles, n=86 patients) in diabetes mellitus (1 article reported 1 patient having received dapagliglozin and 1 patient having received empagliflozin [13]). Continuous data are provided as mean and standard deviation (SD), but when the number of data was limited also the absolute range is reported. Proportions are provided as absolute numbers and percentages.

	N=189	
Glucose initial [mmol/L] #	9.58	± 2.79
Glucose final [mmol/L]*	9.29	± 1.55
Delta Glucose* (relative change final relative to max.)	-17.2%	± 10.2 [absolute range -7 to -48%]
HbA1c initial §	8.07%	± 1.21
HbA1c final +	7.78%	± 0.65
Delta HbA1c+ (relative change final relative to max.)	-10.5%	± 6.4% [absolute range -51 to -9%]
Previous treatment(s) (y/n)	183:6	(97%)
SGLT2i used in combination with other drugs (y/n)	183:6	(97%)
SGLT2i used in combination with insulin (y/n) ♣	51:2	(96%)

CAVE: in Tamborlane et al. [14], outcomes were assessed as between-group difference at the end of week 24, where dapagliflozin-receiving participants were n=29; in Laffel et al. [20], primary outcome was assessed as between-group difference at week n=26, where participants receiving empagliflozin were n=52

* data available for n=5 studies, including n=102 patients

§ data available for n=8 studies, reporting data of n=157 patients

\+ data available for n=6 studies, including n=85 patients

♣ information not specifically reported for n=136 cases

Table 2 : Side effects experienced by children having received either dapagliglozin or empagliflozin.

	All	**Diabetes mellitus**	**GSD Ib and G6PC3-deficiency**	**Heart failure and CKD**
Number of patients (fapagliflozin / empagliflozin)	268	189 (103/86)	32 (0 / 32)	47 (47 / 0)
Metabolic acidosis	0	0	0	0
Hyperketonaemia	2 (0.75%)	2 (1.1%)	0	0
UTI	5 (1.9%)	3 (1.6%)	2 (6.3%)	0
Genital infection	4 (1.5%)	2 (1.1%)	1 (3.1%)	1 (2.1%)
Hypoglycemia *	38 (14%)	27 (14%)	11 (33%)	0
Symptomatic or severe hypoglycemia	5 (1.9%)	3 (1.6%)	2 (6.3%)	0
Acute kidney injury $^{\Delta}$	4 (1.5%)	0	0	4 (8.5%)

CKD: chronic kidney disease, GSD Ib: glycogen storage disease type Ib, PK: pharmacokinetics

* $p<0.0001$ across groups, diabetes mellitus versus GSD Ib $p=0.0099$, diabetes mellitus versus heart failure / CKD $p=0.0034$, GSD Ib versus heart failure / CKD $p<0.0001$

Δ $p<0.0001$ across groups

Table 1: Demographics and baseline characteristics of children and adolescents having received either dapagliflozin or empagliflozin. Proportions are presented as absolute number and percentage, continuous data as mean ± standard deviation.

	Diabetes mellitus	**GSD Ib and G6PC3-deficiency**	**Heart failure and CKD**	**PK studies**	**p-value**
Number of studies (dapagliflozin / empagliflozin)	8 (5/4)◊	14 (0/14)	2 (2/0)	4 (3/1)	NA
Number of patients (dapagliflozin / empagliflozin)	189 (103/86)	32 (0 / 32)	47 (47 / 0)	84 (57 / 27)	NA
Indication	- T1 DM, n=48 - T2 DM, n=138 - Congenital insulin resistance, n=3	- GSD Ib, n=29 - G6PC3-deficiency, n=2 - Congenital neutropenia type 4, n=1	- DCM, n=26 - Single ventricle, n=7 - Diastolic HF, n=4 - RCM, n=1 - Alport syndrome, n=5 - FSGS, n=1 - Dent syndrome, n=1 - "Proteinuria", n=2	- T1 DM, n=33 - T2 DM, n=51	NA
Age, years	14.7 ± 2.9	8.5 ± 5.1	11.2 ± 6.10	15.1 ± 2.3	<0.0001 *
Sex, females (%)	117 (62%)	18 (56%)	24 (51%)	52 (62%)	ns
Weight [kg]	85.7 ± 29.5	28.9 ± 14.7	41.9 ± 38.6	85.5 ± 25.5	<0.0001 Δ
Height [cm]	168 ± 10	-	137 ± 49 §	169 (SD n.r.)	-
BMI [kg/m^2]	32.0 ± 10.3	-	19.6 ± 7.0	27.6 ± 7.83	<0.0001 ✚
Dose dapagliflozin [mg]	11.4 ± 3.7, range 5-20mg	-	6.9 ± 5.2 mg	2.5, 5, 10mg	-
Dose empagliflozin	15.4 ± 7.4, range 5-25mg	0.44 ± 0.28 mg/kg range 0.1-1.3 mg/kg	-	5, 10, 25mg	-
Length of follow-up (months)	7.5 ± 4.8	12 ± 10	5.9 ± 5.2	single dose	ns

CKD: chronic kidney disease, DCM: dilated cardiomyopathy, GSD Ib: glycogen storage disease type Ib, HF: heart failure, PK: pharmacokinetics, RCM: restrictive cardiomyopathy, T1DM: type 1 diabetes mellitus, T2DM: type 2 diabetes mellitus, n.r.: not reported, NA: not applicable.

◊ One manuscript [25] reported one patient having received dapagliflozin and one patient having received empagliflozin.

§ data available only for the n=38 patients with heart failure

* Diabetes mellitus versus GSD Ib p=0.0006, diabetes mellitus versus heart failure / CKD p<0.0001, GSD Ib vs patients included in PK studies p<0.0001, heart failure / CKD versus patients included in PK studies p=0.0006, remaining multiple comparisons p=ns

Δ Diabetes mellitus versus GSD Ib p<0.0001, diabetes mellitus versus heart failure / CKD p<0.001, GSD Ib vs PK p=0.0003, heart failure / CKD versus PK p<0.0001, remaining multiple comparisons p=ns

✚ Diabetes mellitus versus heart failure / CKD p<0.0001, heart failure / CKD versus PK p<0.0001, diabetes mellitus versus PK p=0.0004.

Figure 1

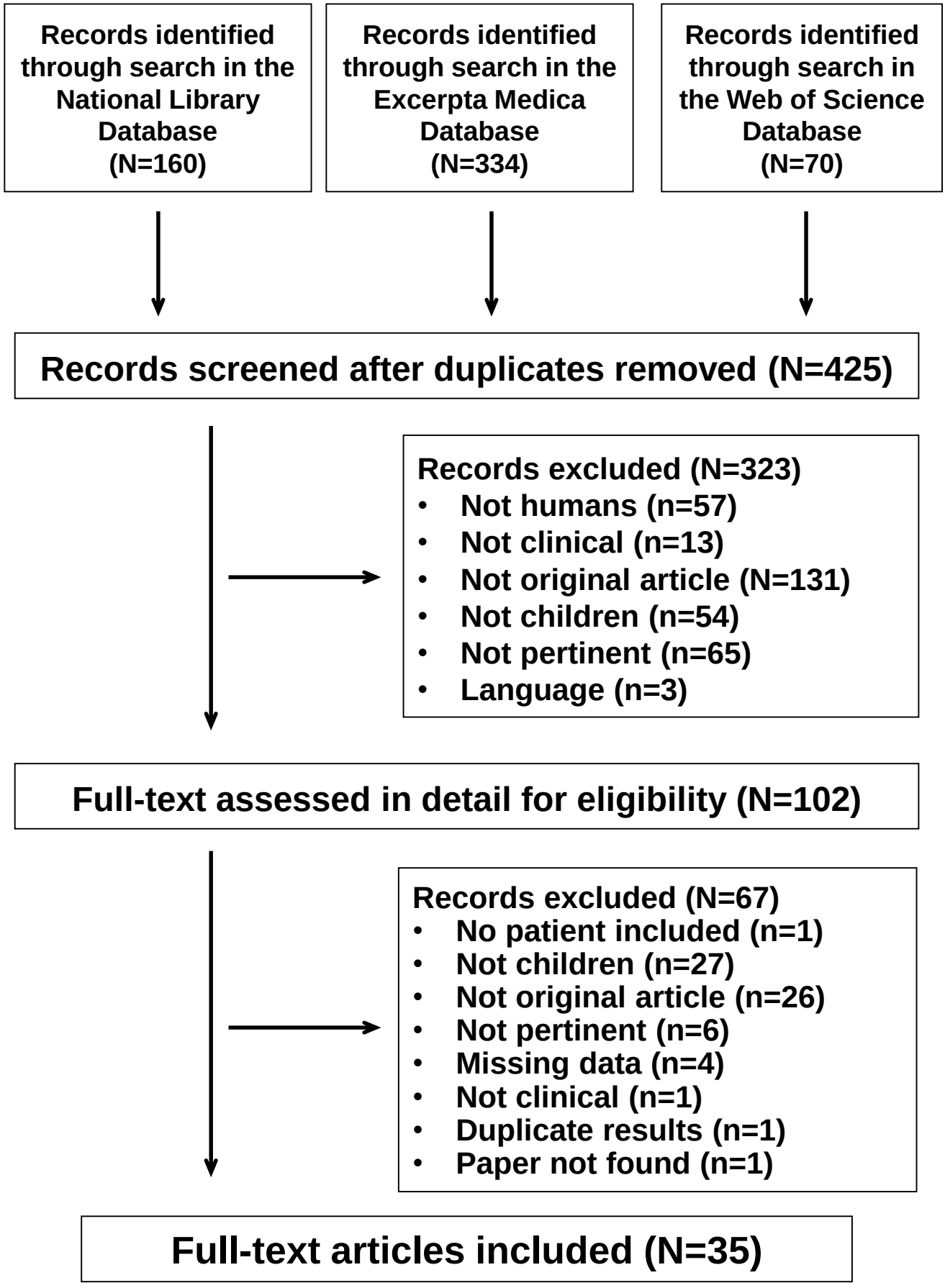


Figure 2

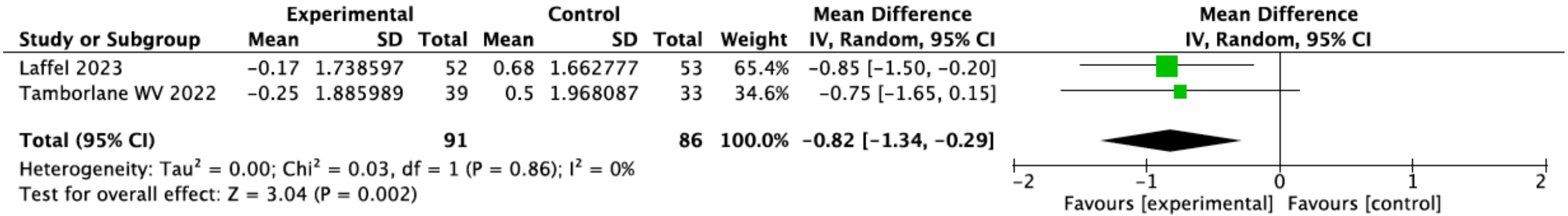
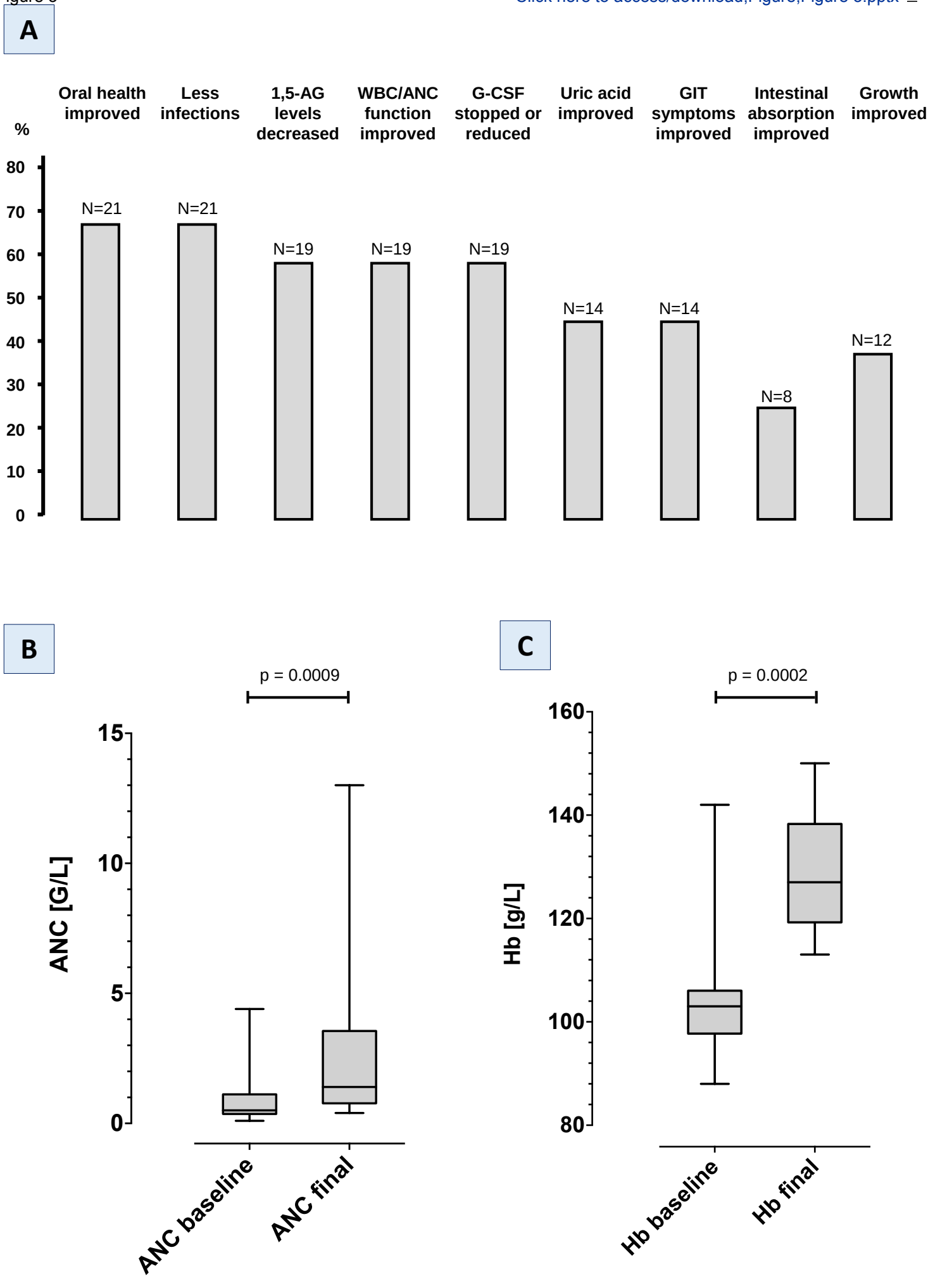


Figure 3

Click here to access/download;Figure;Figure 3.pptx



Ref.: Manuscript PDDA-D-23-00211 entitled "Dapagliflozin and Empagliflozin in Paediatric Indications: a Systematic Review and Meta-Analysis"

Dear Dr Caroline Herdson, dear Editors,

many thanks for your email, the detailed peer review of our manuscript and for the opportunity to revise it and improve its quality. The interesting and constructive comments raised by the Reviewers and by the Editorial Office were carefully addressed, and ooint-by-point answers are provided below.

We feel that the revised manuscript is of improved quality and we would like to thank the Reviewers and the Editorial office for their effort in helping us improving our submission. We really hope that it can now be accepted for publication in *Pediatr Drugs*.

We look forward to hearing back from you. We would be glad to respond to any further questions and comments that you may have.

Best regards,

Sebastiano A.G. Lava
(London, 12th February 2024)

Point-by-point answers to the comments

Reviewer #1

The author team reviewed the use of Dapagliflozin and Empagliflozin in children in at least 7 areas, including diabetes, glycogen storage diseases, G6P3-deficiency, heart failure, kidney disease, pharmacokinetics and pharmacovigilance. Out of 35 articles retrieved, meta-analysis could only be performed in two RCTs in diabetes. This reflects the sparseness of high-quality evidence on the effectiveness and safety of these two medications, and the cautionary tone we need to take in making conclusions based on currently available data. Because much of the work in this manuscript is descriptive summary of the articles gathered over a broad range of conditions, rather than meta-analysis of a focused population-intervention-outcome combination, the inclusion of the term "meta-analysis" in the title may be misleading. In fact, the work appears to be more like a scoping review barring the inclusion of the single meta-analysis of two studies. I would thus, as a form of compromise, suggest that the authors remove the term "meta-analysis" in the title and retain the term "systematic review".

Thank you for your comments. We modified the title as requested. Furthermore, also taking into account the comments from Reviewer 2, we moderated the wordings regarding the meta-analysis throughout the manuscript.

Following are comments pertaining to each part of the work:

1. Abstract: Results, first line: it will be helpful to provide a breakdown on the types of study among the 35 articles retrieved.
Thank you. This information has been added to the revised abstract.

2. Abstract: Results: survey findings do not appear to add substantial weight on the evidence at this stage and do not need to be included in the abstract.

We agree, thank you for pointing this out. The pertaining sentence has been deleted from the Abstract.

3. Abstract: Results, meta-analysis results on the outcome of HbA1c: please add no of studies, no of cumulative participants, heterogeneity as indicated by I square alongside the pooled effect estimate.
Thank you. The requested information has been added to the revised Abstract.

4. Abstract: Conclusion- wording looks too strong for the quality of evidence available. Suggest: "Early evidence appear to suggest that dapagliflozin and empagliflozin are well tolerated in children".
Thank you. The conclusion has been modified and moderated.

5. Key points: point no 2 - the wording appears too definite as the findings are at best preliminary. The authors should put the findings in the context of early evidence that need to be verified by further robust studies.
Thank you. Key point #2 has been modified accordingly.

6. Introduction, paragraph 2: "we performed a systematic review of the experience with the use of dapagliflozin and empagliflozin in children". This appear to me a statement closest to the objective of the review. The wording is unclear, especially with the use of the word "experience", which to me suggest an evaluation of user and carer experience. The more appropriate term would be "effectiveness and safety".
Thank you. We deleted the word “experience” and modified the sentence into “we performed a systematic review of the use of dapagliflozin and empagliflozin in children”. (We did not use the words “effectiveness and safety” here to avoid a repetition with the subsequent sentence, and also to take into account the limitations of current evidence, as you correctly pointed out in your comment above.)

7. Methods, search strategy, paragraph 1: PRISMA is a guideline for reporting not conduct of systematic review. The statement should read "...and was reported according to the 2020 Preferred....".
Thank you. The wording has been corrected accordingly.

8. Methods, Eligibility criteria: please specify the types of study that would be accepted and excluded.
Thank you. This is now specified in the revised Methods section.

9. Methods, Analysis: the first paragraph appears to be a description of statistical analysis of individual primary studies, not meta-analysis. Analysis of primary studies is unusual in a systematic review and meta-analysis, unless there are some individual studies that were not analyzed appropriately. Were there any of such cases, if so, please state here clearly. Otherwise, this paragraph is probably not relevant in a systematic review and meta-analysis and need not be included.
Thank you for your comment. However, we kindly disagree. In a systematic review, an attempt is made to assess in a summative manner the results from individual studies. This paragraph does not relate to calculation within the single included studies, but to their summative analysis. Indeed, methods have been developed to combine study results, even when a meta-analysis is not possible. The first author has published n>50 systematic reviews on several topics, especially on rare diseases and conditions, and, over the years, has collected an extensive experience with such approaches. In particular, the statistical approach described in this paragraph was used to integrate reported data

on type 2 diabetes mellitus and GSD Ib (balancing the number of patients reported in each article), as well as comparing the weighted characteristics (age, weight, …) of individuals reported for the different indications.
Therefore, we would like to keep this paragraph, that is important to transparently report the methods used in the systematic, summative assessment of the studies that did not qualify for a meta-analysis.

10. Methods, Analysis, paragraph 2. Here the authors described the methods of meta-analysis. Given that meta-analysis could only be performed on one condition and one outcome with 2 studies, how were the results of the other included studies synthesized? If they were synthesized narratively, which appears to be the case, the authors should put a statement here.
Thank you. Please also see answer to your comment #9. Studies that could not be included in the meta-analysis were summatively assessed according to the methods described in the paragraph discussed in comment #9. Addressing rare conditions with systematic reviews is a challenging task. Over approximately 15 years, the first author has collected a pretty extensive experience in dealing with these difficulties, perfectionating some skills with these tricky situations. Tables 1, 2, 3 and Figure 3 are examples of such a systematic (albeit not meta-analysis) and summative, combined assessment of several studies.

11. Findings, Diabetes Mellitus, paragraph 3: here the authors reported the only results of meta-analysis. Please include the number of studies and cumulative participant number, and I square value. If I square is high that indicates substantial heterogeneity, some efforts should be made to explore plausible explanation.
Thank you. This information has been added.

12. Findings, Glycogen storage disease, last paragraph: 15% of hypoglycaemia appears high. If this is part of the expected occurrence in the condition, please put the findings in context.
Thank you. Owing to comments from Reviewer #2 (asking to favor the presentation of summative results as provided in the Tables and Figures), we deleted this sentence from the body of the manuscript. Anyway, please also note that in the preceding paragraph we state that “The authors acknowledged that, hypoglycaemia and lactic acidosis being common occurrences in GSD Ib, it was impossible to determine whether empagliflozin contributed to these events.”.

13. Discussion: overall discussion can be shortened by around 20-30%, especially given that most findings are preliminary.
Thank you. In the revised manuscript, the Discussion (despite including new contents as requested by the 3 Reviewers and the Editor) is now n=330 words (>20%) shorter than the original Discussion.

14. Discussion: in the discussion about the effects of the medication in diabetes (paragraph 3), the authors should emphasize evidence from RCTs above others as RCTs offer higher-quality evidence.
Thank you. This has been added to the revised Discussion.

15. Conclusions: second sentence- in view of the mostly preliminary evidence, the tone of conclusion should be more circumspect, for example "seemingly" positive benefit-risk balance instead of simply "positive benefit-risk balance".
Thank you. We agree. The sentence has been modified as suggested.

16. I wish the authors the best in their revision.
Thank you very much. Thank you indeed for your constructive comments, that – we feel – have helped us in improving the quality of our presentation.

Reviewer #2

Abstract

17. The methods section only reports a systematic review and not the meta-analysis

Thank you. This is an important point. This information has now been added to the Abstract.

18. Which software was used for conducting a systematic review and meta-analysis?

No specific software was used for the systematic review, apart from the statistical software (this information has now been added to the body of the manuscript). For the meta-analysis, Review Manager (RevMan), version 5.4.1 (The Cochrane Collaboration, 2020) was used (this information has now been added to the Abstract).

Introduction

19. More details can be mentioned about the drugs.

Any previous literature, work, or citations on this topic?

Some details on the mentioned drugs (including pertaining references) are now provided in the revised Introduction.

20. Why is there a need for a systematic literature review?

Thank you. This is indeed worth better stressing in the Introduction. As already stated in the original submission, data on dapagliflozin and empagliflozin use for younger children or children with indications different from type 2 diabetes mellitus is limited. Importantly, this issue has not been systematically addressed yet. This important statement has been added to the revised manuscript. Thank you again!

Methods

21. In section 2.4 - The scale used for rating and scoring was a validated scale. If yes, what was the name, and kindly cite it. If not, how was it developed?

Unfortunately, while there are validated methods to assess RCTs, cohort studies or case-control studies, there is no officially recommended scale to grade completeness or reporting in systematic reviews focusing on rare conditions, for which most literature is composed of case reports and small case series. The research group around the first author, over the last 20 years, has conducted numerous (n>50) systematic reviews on rare conditions. These reviews often ground on scanty available literature, mostly comprised of case reports, case series or uncontrolled investigations, for which traditional evidence assessment methods (like the Newcastle-Ottawa scale) are inappropriate. Over the years, and after the suggestions of some Reviewers and Editors while evaluating some of our previous works, we have developed a rating of "completeness of reporting" (which we used for the first time in 2018), which is flexible and can be applied also on such types of reports, and that we have been using a number of times (in approximately 20 systematic reviews), perfectionating it over the years. In the manuscript, as a methodological proof, we cite one recent example of its use (but, with a rapid search in my files, just over the last two years, I identified n=10 systematic reviews where we used this scale).

22. Why were other commonly used database such as PubMed, Embase, Scopus not considered?

We think this is just a confusion about synonyms, and we are very sorry about that. Actually, the literature search was performed in the National Library of Medicine (i.e. PubMed), Excerpta Medica (i.e. Embase) and Web of Science databases. In the revised manuscript, we provide the synonyms between brackets. We hope this makes it clearer to both the Reviewer and the Readership. Thank you for raising this point, which improves the clarity of our presentation.

Results

23. The type of studies included should be described in the methods section and the results section should report the numbers, for example: case reports (n=4), etc.
Thank you. This information has been added.

24. Not every study should be described here in the main text, most of the information should be presented succinctly in the table format.
Thank you. You are absolutely right, and we strongly agree with you. Several studies were already summarized in the Tables or Figures. We deleted the duplicate parts reporting (not that relevant) details on some single studies. Furthermore, while summarizing the results of some specific studies that were difficult or impossible to report in a summative way, we deleted some details and shortened the pertaining parts of the manuscript.

25. As per the rules, meta-analysis cannot be conducted on 2 studies. It does not hold any value. Please take out the meta-analysis and its mention from the manuscript.
Thank you. We understand your criticism, which we faced and discussed already among us while preparing the original submission. However, in an effort to combine and address the requests from the different Reviewers and the Editorial comments, we kept the meta-analysis. Nevertheless, taking into account your comment and the comments of Reviewer #1 and the Editorial Office, in the revised manuscript, we deleted the word “meta-analysis” from the title and we moderated the wordings regarding the meta-analysis throughout the manuscript. Also, please note that, according to the Cochrane Handbook for Systematic Reviews of Interventions, Version 6.4 (2023), Chapter 10: Analysing data and undertaking meta-analysis, “Meta-analysis is the statistical combination of results from two or more separate studies.” *[https://training.cochrane.org/handbook/current/chapter-10]*.

26. Conduct GRADE analysis to show the importance of this study.
Thank you. A GRADE analysis has been performed and the manuscript amended (Methods and Results sections).

Discussion section
27. Very very long. It does not list just important pointers gained from the study but instead explains some more studies. Entire essence of discussion is lost.
Thank you. The Discussion has been shortened by >20% of its preceding length. The sentences referring to two new studies (one article, and one conference abstract) presented in the Discussion (but not included in the systematic review) have been deleted.

Reviewer #3

This review examines the use of SGLT2 inhibitors in young people with T2D, T1D, CKD, heart failure, and several rare disorders of glycogen metabolism. Only the diabetes studies were designed for prospective regulatory review. The paper is well-written and the statistical approaches appear logical to this reviewer who is not an expert statistician. Data, although limited, on use of these agents to treat CKD, heart failure, and rare disorders of glycogen metabolism are particularly important and the anecdotal available evidence is analyzed in an appropriate manner. I have one major and one minor concern.

Major:
28. The patients with diabetes included 138 T2D, and 48 T1D, followed in a small number of studies for 24-52 weeks. The authors state unequivocally in the abstract as well as other site, that "Diabetic ketoacidosis is exquisitely rare in children." The incidence of DKA requiring hospitalization in

children with T1D treated with insulin is in the neighborhood of 5 episodes/100 patient years. It may be a bit higher in those on pumps. With only 48 children with DKA followed in a controlled clinical trial for 24-52 weeks, it is impossible to make this statement. The authors must temper their statement and perhaps call for larger studies. This may end up being a fantastic drug class but presently it comes with much theoretical risk of euglycemic ketoacidosis. There is not even a theoretical reason I can come up with that would make the risks less for children than for adults.
Thank you. You are making an important point, thank you for raising it to our attention. The word "exquisitely" has been deleted from the abstract. Furthermore, in the body of the manuscript we added that no cases have been reported "so far", and, in the discussion/conclusion, we now acknowledge that, given the low number of children studied so far, the ability to detect rare side effects is limited.

Minor:
29. There are numerous abbreviations in the text which are never explained-- they should be spelled out and explained in the text or in a glossary:
Thank you. Abbreviations have been consistently explained (on their first occurrence) or substituted with full wording.

30. p 10 3.2.2 G6P3 deficiency-- might actually be good to at least briefly allude to the pathophysiology of these rare disorders
Thank you. In the revised Results section, we briefly added that G6PC3 deficiency is one of the potential causes of severe congenital neutropaenia type 4. Furthermore, in the revised Discussion, we now make clear that the pathophysiology explained for GSD Ib is the same also for G6PC3 deficiency (i.e. in both G6PC3-deficiency and GSD1b, 1,5-anhydroglucitol-6-phosphate accumulates in neutrophils, inhibiting hexokinases, therefore impairing energy generation and causing neutrophil malfunction and apoptosis).

31. p 16 last para of3.2.4 UGT1A9 ontogeny
Thank you. UGT1A9 has now been modified into "UDP-glucuronosyltransferase family 1 member 9 (UGT1A9)". UGT 1A9 is an enzyme of the glucuronidation pathway, which transforms small lipophilic molecules into water-soluble metabolites.

32. p 20-- this reviewer does not understand the mention, line 6 of skin sodium-- is this intracellular, or related to sweat sodium?
Thank you. It has been a pretty recent discovery that "sodium can be stored on negatively charged glycosaminoglycans in the skin interstitium, where it becomes osmotically inactive". Thus, the skin interstitium may function as a "fluid-buffering system able to store sodium without commensurate water retention" *[Lava SA et al. Pediatr Nephrol. 2015; 30:1389–1396]*. In the revised manuscript, we now try to make this a bit more clear (revised sentence: "sodium stored in the skin interstitium") and cite a review, that might help the readership to have a better understanding of this exciting physiological process.

Editorial Office comments

33. * Please note the reviewer suggestion to remove 'meta-analysis' from the title.
Thank you. "Meta-analysis" has been deleted from the title.

34. * Literature search information – A full search strategy for at least one of the databases must be provided as ESM. To ensure transparency and replicability, we encourage authors to conform to PRISMA recommendations and report all search strategies used, the specific results from each

database that was searched, and the date that each database was searched. This can be included in the Supplementary Information.
Thank you. This information is provided in the body of the manuscript (Section 2.1: “Searches were performed in the National Library of Medicine (PubMed®), Excerpta Medica (Embase®), and Web of Science databases to September 12th, 2023. Original reports with no date limits were considered. The search strategy used the terms (dapagliflozin OR empagliflozin) AND (childhood OR child OR paediatrics).”), respectively in Figure 1.

35. * Please spell out 'Pediatric Drugs' in the title page of the Supplementary Information.
This has been corrected.

36. * Please ensure that a running header of ≤ 100 characters is provided.
Thank you. The current running header is n=57 characters (spaces included) long.

37. * Abstract: Please restructure into Introduction, Objective, Methods, Results and Conclusion sections.
Thank you. The structure of the Abstract has been corrected, as requested.

38. * Please clarify if study authors were contacted for additional information. A list of such studies with information sought should be provided as ESM.
Thank you for this question. As part of our initial methodological strategy, we were planning to contact authors of the original reports when needed. However, while performing the analysis, this turned out not to be necessary, so that in the end we did not contact Authors of included reports. Taking into account this comment, we deleted the pertaining sentence in the Methods.

39. * Please clarify the process for duplicate identification.
There are two types of issues. Duplicate publications (i.e. the same article identified through two different databases) are identified simply by their coordinates (authors, title, journal, year, volume, pages, and codes like PMID or doi). Duplicate cases, or multiple reports (i.e. the same case published in two different articles) are more tricky to pick up. I am explaining the strategy we used to identify these cases while answering your next comment (“multiple reports”).

40. * Please clarify how you dealt with multiple reports.
Suspicion of multiple reports arises when a similar publication is characterized by some (or all) of following similarities: same author names, institution(s), setting (outpatient, inpatient, chronic therapy versus acute emergency, …), patient characteristics (age, sex, weight, height, diagnosis, duration of therapy, administered dose), measures of outcome used (i.e. “neutrophil count”), and outcome(s) reported (e.g. “normalization of absolute neutrophil count”, “remission of intestinal symptoms”, “improvement in oral ulcers”), respectively same values of specific baseline characteristics or outcomes (e.g. heart rate 124/min), date (e.g. series of 3 patients presented between 2012 and 2016), duration of follow-up *[https://handbook-5-1.cochrane.org/chapter_7/7_2_2_identifying_multiple_reports_from_the_same_study.htm]*.
This is now briefly summarized in the Methods section of the revised manuscript.