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RESEARCH ARTICLE

SGLT2 Inhibitors are Blockbusters in Adults - But Not Studied in Children with Kidney Disease due to Industry Conflicts of Commercial Interest: A Call for Help To Regulators

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ABSTRACT

This article reviews the circumstances why and how the pharmaceutical industry is avoiding the pediatric investigation plans for their block-buster drugs in chronic kidney diseases. The "why" is easy to answer because it is just about economic reasons. Even Garfield the tomcat as a symbol of a multi-morbid domestic cat can be treated with a drug of the same substance group that has been approved for him, but children with kidney disease (and heart disease as well) are neglected. This is much to the disadvantage of sick children, who are thus deprived of the opportunity for evidence-based therapy. Just as in the time prior to the pediatric trial regulation, pediatricians remain in a legal gray zone of off-label use and expose themselves to the risk of lawsuits. The article is intended to start a discussion on how regulatory authorities could support the development of better treatment recommendations for children with kidney disease for drugs that are not promoted by the industry. This could be by working more closely with patient representatives and academia, by supporting the planning phase of investigator-initiated trials, or by scientific advice on cumulative real world and randomized controlled trial data on specific medications or substance groups.

Keywords: Dapagliflozin, Empagliflozin, Ramipril, SGLT2-inhibitors, ACE-inhibitors, pediatric investigation plan, chronic kidney disease, children, pediatrics, Alport syndrome, off-label use in children

Introduction

In summer 2023, the European Medicines Agency EMA approved empagliflozin as the second sodium glucose transporter 2 (SGLT2) inhibitor after dapagliflozin, for the treatment of chronic kidney disease. The approval in adults is paying off for the pharmaceutical industry: for the manufacturers, both drugs are blockbusters, with an estimated annual turnover of more than 10 billion euros. In medicine, SGLT2-inhibitors have evolved from diabetes drugs to game-changers in the treatment of heart failure and kidney disease. Due to the outstanding data, doctors are in a gold-rush mood for better treatment of adults. Does this also apply to sick children? After all, every drug before approval must also be tested on children in accordance with a pediatric investigation plan, which the regulatory authorities require early on in the development process. No, unfortunately, children with chronic kidney disease were deserted. This article explains the background of this neglect despite the high un-met medical need in children with kidney disease. It wants to encourage that - despite legal adversities and economic constraints - the regulatory authorities and other stakeholders can very well be the catalyst for pediatric investigation plans towards high evidence-based, better, and safer therapies together with industry and academia in one of our most vulnerable and neglected patient groups, children with chronic kidney diseases.

Main Text

Recently, a press release from the University Medical Center Göttingen announced the world's first pediatric randomized controlled trial (RCT) with the highest level of evidence with SGLT2-inhibitors in chronic kidney disease: DOUBLE PRO-TECT Alport.[1] This trial will decisively improve the evidence base for the benefits and risks of SGLT2 inhibitors in children with kidney disease from the end of 2023: the trial (Clinical Trial.gov Identifier NCT05944016) is funded by the German Research Foundation DFG (GR 1 852/7-1; Project No. 508779211). Alport syndrome was not picked by chance. It is a model for chronic kidney diseases that is ideally suited for translational therapy studies in children: it is the most common hereditary chronic kidney disease leading to end stage kidney failure early in life, accounting for 30-40% of proteinuric chronic kidney diseases in children and more than 10% of cases of end stage kidney failure in young adults.[2] In the US and Europe, more than 10,000 children are currently affected, most of them with a 100% risk of end stage kidney failure early in life. The disease affects genes coding for type IV collagen as major structural component of the glomerular basement membrane. Gene variants in Alport syndrome cause a mechanical deficit of the filtration unit, making the weaker and leaky glomerular basement membrane in patients with Alport syndrome to an ideal therapeutic target for SGLT2-ihibitors.[3] Due to a genetic switch in the GBM, Alport syndrome develops slowly after birth, opening a "window of opportunity" for early-on pre-emptive nephroprotective therapies. "Genotype-phenotype" correlation and "genotype-response to therapy (Angiotensin-converting enzyme (ACE)-inhibition) correlation" have been described in hundreds of patients with Alport syndrome worldwide.[4] A previous investigator-initiated randomized Placebo-controlled trial in children two years and older, EARLY PRO-TECT Alport,[5] registry data,[6] trial concepts discussed with the FDA,[7] a case series,[8] as well as a recent meta-analysis,4 cumulated high quality good clinical practice (ICH-GCP) conform clinical data from children with Alport syndrome and chronic kidney disease, a unique tool to plan the first Pediatric randomized controlled trial in chronic kidney disease with SGLT2-inhibitors.

The world's first pediatric randomized controlled trial, DOUBLE PRO-TECT Alport, is a proof of concept showing that – if a high unmet medical need meets academia - combined efforts of patient alliances and physicians can make things happen after a five-year planning phase: very positively, the idea for a Pediatric chronic kidney disease trial with SGLT2-inhibitors originates from industry. In 2017 and 2018, employees of Boehringer Ingelheim approached the International Alport Alliance with this idea, which led to the invention "Empagliflozin for use in treating Alport syndrome".[9] However, despite positive feedback from the Food and Drug Administration FDA on the study design in 2018, industries' Pediatric Investigation Plan (PIP) was not pursued further as of spring 2019. This unfortunate stop had no scientific reason, but economic causes triggered by fears of side effects in children that could damage big business in adults and by waivers granted by the regulatory bodies shortly before.[10,11] These waivers for Dapagliflozin and Empagliflozin not only allowed industry to stop their Pediatric Investigation Plan in children with chronic kidney disease in 2019. The waivers are also remarkable from a medical point of view in that they were scientifically outdated even then, worse still, they were simply wrong, in that the authorities wrote (citation page 2, Opinion of the Paediatric Committee on the granting of a product-specific waiver EMA/PDCO/529858/2018):[10] "The Paediatric Committee … recommends … to grant a product-specific waiver for all subsets of the

paediatric population and the above mentioned condition [chronic kidney disease] … , on the grounds that the specific medicinal product [Dapagliflozin] is likely to be unsafe in part or all of the paediatric population and … on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients." These waivers from 2018/2019 are still in place despite the 2022 marketing authorization for Dapagliflozin in children 10 years and older with type 2 diabetes.

As a consequence, with the very high unmet medical need in Pediatric chronic kidney disease as motivation, the trial-concept was submitted by academia to AstraZeneca and Boehringer Ingelheim (as manufacturers and patent holders of Dapagliflozin and Empagliflozin) as an investigator-initiated trial for consideration for industry-funding in 2019, 2020, 2021, and 2022. The last rejection of an industry grant for supply with study medication came in February 2023, leaving us with no choice but to plan the study completely independent from industry. Recently, the Investigator Initiated Trial (IIT) passed the highly competitive two-stage application process at the German Research Foundation DFG and got the final approval for public funding. Independence from industry enables the highest scientific quality, but it is a financial burden, because with a tight budget, the SGLT2-inhibitor and placebo now have to be bought from industry for up to 200,000 Euro. Money that is now missing for the travel costs of the children's parents to go to the trial centers. This seems to be an unfair situation, because industry would have invested a 20 times higher budget for such a trial. Thankfully, the German patient advocacy will try to cover parts of these costs and we hope for additional private donations to support international scientific collaboration on evidence synthesis.

After a five-year planning phase in a joint effort by industry, regulatory authorities, academia and patients – why do we still need a randomized controlled trial with SGLT2-inhibitors in children with chronic kidney disease in 2023?

There are three points that need to be considered: firstly, insufficient pre-clinical scientific data to translate data from old adults to children; secondly, risk to treat children with CKD without adequate scientific evidence; and thirdly, legal risk aspects of off-label therapy for pediatricians:

(1) Insufficient pre-clinical evidence for efficacy and safety to translate data from old adults to children

Two recent high quality pre-clinical studies,[12,13] raise concerns that in children with glomerular diseases SGLT2-inhibitors may not be - as solid and as foolproof - effective as in EMPA Kidney and DAPA-CKD patients who are 5 to 7 times their average age.[14,15] In vivo, empagliflozin monotherapy reduces albuminuria and prolongs the kidney survival of AS mice, however, unlike what has been observed in patients enrolled in DAPA-CKD or EMPA Kidney, the addition of empagliflozin to the standard of care (SOC) ramipril did not confer additional renoprotection, and overall, no difference across treatment groups was observed.[12] In another set of experiments, Ramipril monotherapy prolonged mean lifespan of Alport mice to 77.3±5.3 days with no additional benefit for dual ACE/SGLT2 inhibition, which prolonged mean lifespan to 80.3±11.0 days.[13] Of note, the Alport mouse model is fast progressive, so treatment effects in human patients with Alport syndrome should be better than in animal models. However, the pre-clinical trials make very clear that, if it comes to children with chronic kidney diseases, SGLT2-inhibitors will not cure glomerular diseases such as Alport syndrome and the therapy effects may be less in children than in the elders from DAPA-CKD and EMPA Kidney who had a higher BMI and had higher blood pressure and presumably more hyperfiltration. Together with young age of children with chronic kidney disease and the need for life-long solutions, early start of SGLT2-inhibition in children brings up long-term safety to the most important concern.

(2) risks of off-label approaches in children with kidney disease with SGLT2-inhibitors without adequate scientific evidence for safety and efficacy

In contradiction to the waivers of the authorities, of course there has been in 2018 and still is a huge unmet medical need for better add-on therapies of children with chronic kidney disease. Children with classical forms of Alport syndrome, for example, face a 100% risk of early end-stage kidney failure, which negatively effects their quality of life and life-expectancy. There are numerous very impressive patients' testimonies that there is a huge unmet medical need for therapies in children with chronic kidney disease (see homepage auf Alport Syndrome Foundation https://alportsyndrome.org/ , see Voice of Patients Report (FDA),[16] and video-portrait by the German ministry of Education and Research with English subtitles[17]). This therapeutic pressure leads to off-label use of SGLT2is in children without adequate evidence base, because data from patients in the retirement age cannot be extrapolated to children. The situation is similar to 10 years ago with the ACE-inhibitor Ramipril, which was evaluated in the randomized controlled trial EARLY PRO-TECT Alport:[5,6] if we don't start a randomized controlled trial with SGLT2-inhibition in children with chronic kidney disease now, we will

miss the once in a lifetime opportunity to create high level of evidence for early kidney protection by SGTL2 -Inhibitors in children on top of standard of care ACE-inhibitors. The children with chronic kidney disease face a life-time multimodal therapy and deserve this high level of evidence.

(3) legal risk aspects for pediatricians of SGLT2-inhibitor off-label therapy in children with kidney disease

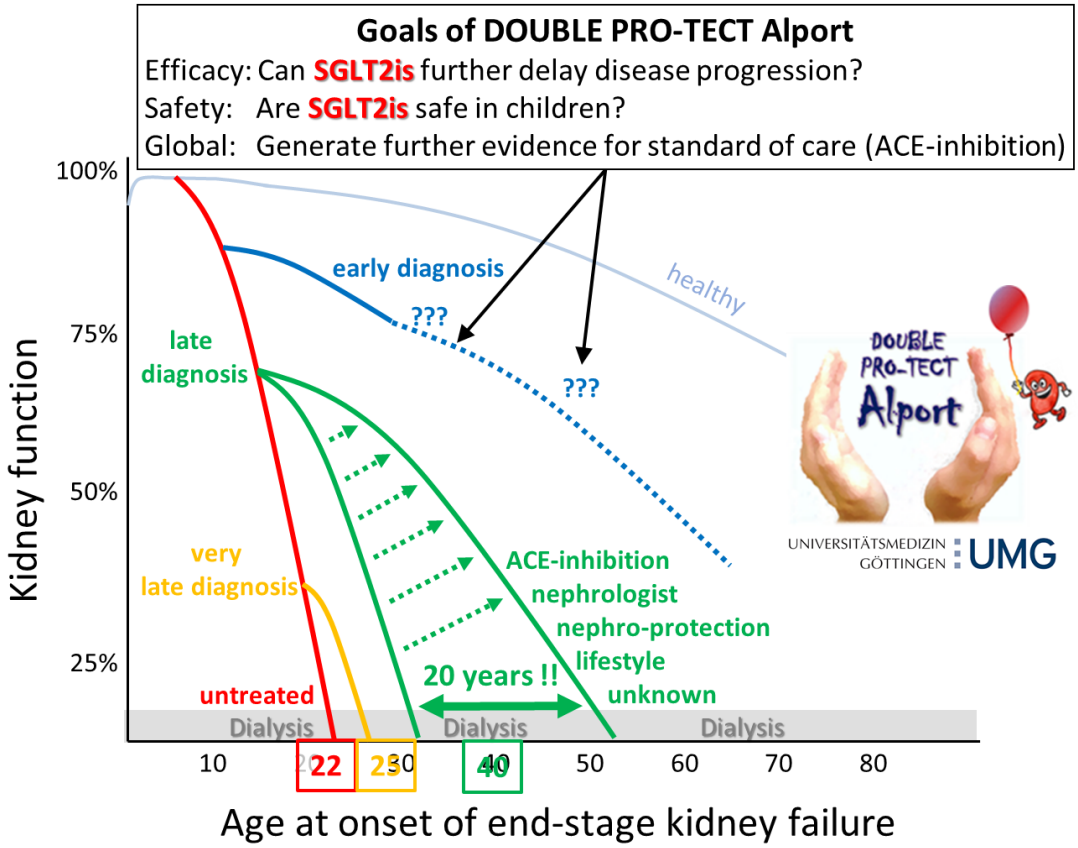
There are legal aspects of off-label use of SGLT2-inhibitors in children with chronic kidney disease, putting the pediatricians at risk of being convicted by the court: in Europe, the Pediatric Investigation Plan PIP waivers by the European Medicines Agency EMA from 2018 and 2019 are still in place and indicate that SGLT2-inhibitors might not be safe or effective, aggravating the legal problem of off-label use for the pediatrician.[10,11] If a severe side-effect occurs in a child with chronic kidney disease who is treated off-label with a SGLT2-inhibitor, the legal courts could interpret the European Medicines Agency EMA waiver as an unmistakable warning and convict the pediatrician of unsafe off-label use and thereby having neglected the risks of SGLT2-inhibitors in the child. Of course, the European Medicines Agency EMA does not want to lead pediatricians into an uncertain legal situation either - therefore the regulatory authorities European Medicines Agency EMA and the Food and Drug Administration FDA have a great interest in changing this unclear situation, but how?

As a consequence, the upcoming randomized controlled trial DOUBLE PRO-TECT Alport aims to generate this evidence for safety and efficacy of SGLT2-inhibitors: most participants will be children with an estimated glomerular filtration rate (eGFR) of about 100 ml/min/m^2 and an urine albumin to creatinine ration (UACR) of 300 mg/gCreatinine or higher. These children are still in an early stage of chronic kidney disease and much younger and healthier as the DAPA-CKD or EMPA-Kidney population (mean age about 63 years; mean eGFR about 40 ml/min/m^2),[14,15] however, the children with chronic kidney disease in DOUBLE PRO-TECT Alport face a 100% risk of early end-stage kidney failure. Patients will be randomized 2:1 to SGLT2-inhibitor versus Placebo on top of stable renin-angiotensin-system (RAS)-blockade, which is standard of care. Primary endpoint is change from baseline UACR at 48 weeks and key secondary endpoint is change from baseline eGFR at follow-up visit in week 52, which is 4 weeks off therapy. Early SGLT2-inhibitor therapy – if efficient and safe - buys the young patients time for additional therapies (NCT05448755, NCT05267262, and FIONA trial, NCT05196035).

DOUBLE PRO-TECT Alport will use Bayesian evidence synthesis and take advantage of patient alliances (Alport Syndrome Foundation, International Alport Alliance): data from more than 100 adults with Alport syndrome at start of SGLT2-inhibition have already been collected by the University Medical Center Goettingen (UMG). These real-world data will fuel the randomized controlled trial data from DOUBLE PRO-TECT Alport by borrowing real-world data for evidence synthesis, which is a powerful tool in small randomized controlled trial populations.[18] The full study protocol of DOUBLE PRO-TECT Alport will be published by end of 2023, academia from all over the world in Asia, Europe and America already raised their interest to adapt the trial protocol, hoping for additional funding sources for an international trial and to contribute to evidence synthesis.

Academia and patient representatives are the major driver for this trial, however, the goal of the investigator-initiated trial DOUBLE PRO-TECT Alport is to get industry and regulatory authorities back on board: Children with chronic kidney disease need the effort of industry - irrespective from economic interest as patents for SGLT2-inhibitors run out soon. Industry will make the difference if it comes to earlier diagnosis and therapy in children with chronic kidney disease. Sick children also need the regulatory authorities with their broad expertise and advice to industry – as the Food and Drug Administration FDA already agreed in 2018 to the study concept to the extent that it was possible for the industry, which made it possible for academia to implement it as investigator-initiated trial in 2023. DOUBLE PRO-TECT Alport is a proof of principle for academia-driven Pediatric randomized controlled trials in chronic kidney disease, however, experience shows that real world works even better with the expertise of industry and regulatory and, above all, we need all stakeholders on board for the dissemination of the results for the benefit of our vulnerable children with chronic kidney disease (figure 1).

Figure 1: Effect of early nephro-protective therapy in children with chronic kidney disease



Green: Effect of ACE-inhibition with a potential delay of end-stage kidney failure (median delay 18 years)[6]
Blue: Chances of early add-on therapy with SGLT2-inhibitor on top of ACE-inhibition with a potential further delay of end-stage kidney failure by life-time in some children with chronic kidney disease and many children with Alport syndrome and the co-incidence of less-severe missense variants. In the US, more than 70% of children with Alport syndrome have missense variants.
SGLT2is = sodium glucose transporter 2 inhibitors
ACE = Angiotensin converting enzyme

As a last point, this article would like to address a structural error in inexpensive repurposing therapies in children, which, due to a lack of industry interest, are not approved for children, but are nevertheless standard of care and seem to sink into the off-label area forever.

In Alport syndrome, the international therapy recommendations recommend ACE-inhibitors, especially Ramipril,[19] as a specific therapy for oligo-symptomatic small children from the age of 2 years, because observational studies in Europe and Asia show a clear therapeutic effect and a randomized controlled trial also shows the safety in small children, as was recently the case summarized in a meta-analysis.[4] From a scientific point of view, the evidence for the off-label use of ACE-inhibitors such as ramipril in children with Alport syndrome in terms of delaying dialysis and improving life expectancy is far better than the evidence for the - approved - enzyme replacement therapy in Fabry disease. Nevertheless, ACE-inhibitors such as ramipril are not approved, quite the opposite of enzyme replacement therapy for Fabry disease. The difference here lies in the industry's interest in approving the extremely expensive enzyme replacement therapy of around €250,000 a year therapy costs compared to barely €100 for ramipril. The industry is therefore not at all interested in the financial expense involved in approving ACE-inhibitors - in complete contrast to patients and doctors. It would be extremely helpful here if the European Medicines Agency EMA and the Food and Drug Administration FDA had a contact point for academic stakeholders, how the regulatory authorities assess the overall data situation of substance classes such as ACE-inhibitors and how this assessment can then be used publicly by medical societies worldwide for better, safer therapy recommendations. In our experience,

previous inquiries to the European Medicines Agency EMA (such as the champions program, a Proposal for a framework to support not-for-profit organisations and academia in drug repurposing)[20] have failed because the academic societies, academia and patient representatives have no commercial interest in self-marketing or labelling a specific ACE-inhibitor, but the substance group of ACE-inhibitors. If it comes to use of ACE-inhibitor in children with chronic kidney disease, we do not want to make a profit with a drug, but use it safely and effectively with the help of a Benefit-risk assessment by the European Medicines Agency EMA and the Food and Drug Administration FDA, which is absolutely possible due to the wide range of data for ACE-inhibitors in Alport syndrome.[2,4-7,12,13,19]

Now that ACE-inhibitors are and will remain standard of care anyway, why do we need advice by regulatory authorities?

An assessment by the European Medicines Agency EMA and the Food and Drug Administration FDA would be extremely helpful, because the regulatory authorities have global expertise and an overall view of the data situation that is outstanding worldwide. Again, Alport syndrome is the most common hereditary chronic kidney disease leading to end-stage kidney disease early in life, accounting for 30-40% of proteinuric chronic kidney disease cases in children and more than 10% of end-stage kidney failure cases in young adults.[2] In the US and Europe, more than 10,000 children are currently affected, most of them with a 100% risk of end stage kidney failure early in life. The assessment by the European Medicines Agency EMA and the Food and Drug Administration FDA would have a strong effect on the use of very inexpensive drugs for early and safe therapy for many children with chronic kidney disease and thus give this vulnerable group of patients easier access they deserve to the drugs - a big effect on the social systems worldwide through saved costs for kidney replacement therapies and an effect on quality of life and life expectancy that cannot be calculated with money (figure 1).

Conclusion

The Pediatric population with chronic kidney disease has been deserted from clinical trial programs for SGLT2-inhibitors, based on the immoral belief that there was no medical need to test SGLT2-inhibition in children. With unjustified, but legally valid waivers for the pediatric population in hands, SGLT2-manufacturers - for economic reasons - neglect their ethical responsibility for pediatric investigation plans. This deplorable situation, a throwback to the stone age prior the pediatric trial regulation,[21] has caused widespread frustration within the pediatric nephrology community. The SGLT2-inhibitor bexagliflozin was approved for animals by the Food and Drug Administration FDA a few months ago, Garfield the cat has his approved drug, but children with kidney disease don't. Approved for sick cats, but not for children.

This essay ends with the realization that this dilemma can very well be turned into a positive end to benefit sick children and their families with the joint forces of industry and regulatory authorities: industry makes billions in sales with its SGLT2-inhibitor blockbuster, one might need the long arm of the international law if necessary, so that the industry either complies with ethical principles or can buy its way out with money for academia to enable investigator-initiated trials. It does not feel right that the public sector, since our taxes ultimately finances research funding programs from the DFG or the NIH, fills this moral gap.

Conflicts of Interest Statement

OG is Initiator and Director of the European Alport registry (founded in 2006). He was or is in Advisory Boards for therapeutic development in nephrology for Reata Pharmaceuticals, Novartis, Roche, Boehringer Ingelheim, Retrophin, AstraZeneca, Ono Pharma, Bayer, Galapagos, and Novartis. He was Initiator and Coordinating Principal Investigator of the first randomized controlled trial in children with Alport syndrome, EARLY PRO-TECT Alport, and is Initiator and Coordinating Principal Investigator of the first Pediatric randomized controlled trial with SGLT2-inhibitor in children with chronic kidney disease, DOUBLE PRO-TECT Alport. OG is Medical Advisor for many Alport patient groups worldwide.

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Donation opportunities: An international research team is working together worldwide without financial support in order to improve the interpretation of the results of the randomized controlled trial as much as possible using the Bayesian evidence synthesis approach for drug safety and drug efficacy in children. You can support this international alliance with a donation for a research coordinator, UMG donation account of the University Medical Center Goettingen, IBAN: DE98 2605 0001 0000 0014 20; BIC: NOLADE21GOE; absolutely indicate „Purpose 1352720 – Gross Alport Syndrome".

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