UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
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# INSIGHTS ON SAFETY AND EFFICACY OF SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS: PERSPECTIVES ON CARDIOVASCULAR, RENAL, AND CANCER OUTCOMES

# EFICÁCIA E SEGURANÇA DOS INIBIDORES DO COTRANSPORTADOR 2 DE SÓDIO-GLICOSE: PERSPECTIVAS SOBRE DESFECHOS CARDIOVASCULARES, RENAIS E DE CÂNCER

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Tese apresentada ao Programa de Pós-Graduação em Ciências Médicas: Endocrinologia da Faculdade de Medicina da Universidade Federal do Rio Grande do Sul como requisito parcial para a obtenção do título de doutor em Endocrinologia.

Orientador: Prof. Dr. Fernando Gerchman
Coorientadora: Profa. Dra. Verônica Colpani

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## RESUMO

Os Inibidores do Transportador 2 de Sódio-Glicose (SGLT2) são fármacos hipoglicemiantes eficazes, tendo demonstrado reduzir desfechos cardiovasculares e renais não apenas em populações com diabetes tipo 2, mas também em populações com doença renal crônica ou insuficiência cardíaca, sem diabetes. No entanto, ainda há incerteza se esses benefícios são consistentes ao longo do espectro de risco de doença renal, especificamente entre os grupos de risco da relação albumina/creatinina urinária (UACR) e da classificação de risco da *Kidney Disease: Improving Global Outcomes* (KDIGO), que combina taxa de filtração glomerular estimada e UACR para estabelecer prognóstico. Além disso, considerando a expansão das indicações terapêuticas desses agentes e a sua ampla utilização na prática clínica, é de extrema importância estabelecer a segurança desses fármacos. Neste contexto, subsistem também incertezas relativamente aos potenciais efeitos dos inibidores do SGLT2 no risco de incidência de câncer e no risco de morte por câncer. No presente trabalho, por meio da realização de revisões sistemáticas e metanálises, avaliamos essas questões. Nossos resultados indicam que o efeito dos inibidores do SGLT2 em eventos cardiovasculares maiores parece ser diferente entre os grupos de risco KDIGO e UACR, com maiores reduções de risco relativo e absoluto na extremidade superior do espectro de risco. Da mesma forma, foi observada uma interação entre grupos de risco de UACR e desfechos compostos de insuficiência cardíaca e cardiorrenais que incluíram morte cardiovascular. Para outros desfechos cardiovasculares e renais, não foi observada interação entre os grupos de risco KDIGO e UACR, embora tenham sido observadas maiores reduções de risco absoluto em grupos com maior risco medido por esses marcadores. Referente ao risco de câncer, o tratamento com inibidores do SGLT2 não aumentou o risco global de incidência de câncer ou de mortalidade por câncer. Da mesma forma, não foi observada diferença entre indivíduos tratados com inibidores de SGLT2 e aqueles tratados com intervenções de controle na incidência de câncer sítio-específico. Os resultados do Trial Sequential Analysis indicaram que o atual tamanho de informação tem poder adequado para tirar conclusões para a população e desfechos neoplásicos estudados, e é improvável que novos estudos mudem estes resultados. Em resumo, a classificação KDIGO e os grupos UACR anteciparam os efeitos absolutos dos inibidores do SGLT2 nos desfechos cardiovasculares e renais, demonstrando também maiores reduções de risco relativo em grupos de maior risco para alguns desfechos cardiovasculares e cardiorrenais compostos, fornecendo informações úteis para a tomada de decisões clínicas. Além disso, nossos resultados não indicam risco aumentado de câncer com inibidores de SGLT2, fornecendo dados de segurança tranquilizadores sobre o uso desses agentes.



Palavras-chave: Inibidores do Transportador 2 de Sódio-Glicose; Doenças Cardiovasculares; Insuficiência Renal Crônica; Neoplasias; Metanálise.

## ABSTRACT

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are effective glucose-lowering agents, having been shown to reduce cardiovascular and renal outcomes not only in populations with type 2 diabetes, but also in populations with chronic kidney disease or heart failure, without diabetes. There is remaining uncertainty, however, if these benefits are consistent throughout the spectrum of kidney disease risk, specifically across risk groups of urinary albumin-to-creatinine ratio (UACR) and the Kidney Disease: Improving Global Outcomes (KDIGO) risk classification of chronic kidney disease, which combines estimated glomerular filtration rate and UACR to establish prognosis. Additionally, considering the expansion of therapeutic indications of these agents and their widespread use in clinical practice, it is of utmost importance to establish safety. In this context, there are also remaining uncertainties regarding the potential effects of SGLT2 inhibitors on the risk of incident cancer and the risk of death from malignancy. In the present work, through the conduction of systematic reviews and meta-analyses, we have assessed these questions. Our findings indicate that the effect of SGLT2 inhibitors on major adverse cardiovascular events seems to be different across KDIGO and UACR risk groups, with greater relative and absolute risk reductions in the higher end of the risk spectrum. Similarly, an interaction was observed between UACR risk groups and composite heart failure and cardiorenal outcomes which included cardiovascular death. For other cardiovascular and renal outcomes, no interaction was observed between KDIGO and UACR risk groups, although larger absolute risk reductions were observed in groups with a greater risk measured by these markers. Regarding the risk of malignancies, treatment with SGLT2 inhibitors did not increase the risk of overall incident cancer or cancer mortality. Similarly, no difference was observed between subjects treated with SGLT2 inhibitors and those treated with control interventions in incident site-specific cancers. Findings from Trial Sequential Analysis indicated that the current information size is sufficiently powered to draw conclusions for the population and cancer outcomes studied, and newer studies are unlikely to change these findings. In summary, the KDIGO classification and UACR groups anticipated the absolute effects of SGLT2 inhibitors on cardiovascular and renal outcomes, also demonstrating greater relative risk reductions in higher-risk groups for some composite cardiovascular and cardiorenal outcomes, providing useful information for clinical decision-making. In addition, our findings indicate no increased risk of cancer outcomes with SGLT2 inhibitors, providing reassuring safety data on the use of these agents.



Keywords: Sodium-Glucose Transporter 2 Inhibitors; Cardiovascular Diseases; Renal Insufficiency, Chronic; Neoplasms; Meta-analysis.

## LIST OF ABBREVIATIONS

| | |
|---|---|
| ASCVD | atherosclerotic cardiovascular disease |
| BMI | body mass index |
| CaMKII | calcium/calmodulin dependent kinase |
| CENTRAL | Cochrane Central Register of Controlled Trials |
| CI | confidence interval |
| CKD | chronic kidney disease |
| DOI | Digital Object Identifier |
| eGFR | estimated glomerular filtration rate |
| ESKD | end-stage kidney disease |
| FDA | Food and Drug Administration |
| GRADE | Grading of Recommendations, Assessment, Development and Evaluations |
| HR | hazard ratio |
| KDIGO | Kidney Disease: Improving Global Outcomes |
| MACE | major adverse cardiovascular events |
| MD | mean difference |
| NHE1 | sodium-hydrogen exchanger 1 |
| NHE3 | sodium-hydrogen exchanger 3 |
| NNH | number needed to harm |
| NNT | number needed to treat |
| NYHA | New York Heart Association |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |

| | |
|---|---|
| RCTs | randomized controlled trials |
| RD | risk difference |
| RoB 2 | Revised Cochrane risk-of-bias tool for randomized trials |
| Robvis | Risk-of-bias VISualization |
| RR | relative risk |
| SE | standard error |
| SGLT2 | Sodium-glucose cotransporter-2 |
| TSA | Trial Sequential Analysis |
| UACR | urinary albumin-to-creatinine ratio |
| WR | win ratio |

**SUMMARY**

# 2 JUSTIFICATION

Since there are remaining uncertainties between the consistency of SGLT2 inhibitors effect on cardiorenal outcomes across the spectrum of kidney disease, and the relationship between SGLT2 inhibitors and cancer remains unclear, this work aims to generate new evidence and provide answers to these questions.

# 3 OBJECTIVES

## 3.1 GENERAL OBJECTIVE

To evaluate the effect of SGLT2 inhibitors across the spectrum of kidney disease and their relationship with cancer outcomes.

## 3.2 SPECIFIC OBJECTIVES

- To evaluate the effect of SGLT2 inhibitors on cardiovascular outcomes and mortality across UACR levels and KDIGO classes.
- To evaluate the effect of SGLT2 inhibitors on renal outcomes across UACR levels and KDIGO classes.
- To evaluate the effect of SGLT2 inhibitors on cancer incidence and mortality.

# 4 ARTICLES

This thesis follows the format proposed by the Post-Graduate Program in Medical Sciences: Endocrinology, being presented in the form of a brief introduction, followed by three articles about the thesis theme.

**ARTICLE 1: "**SGLT2 inhibitors, cardiovascular outcomes, and mortality across the spectrum of kidney disease: a systematic review and meta-analysis"

**ARTICLE 2:** "SGLT2 inhibitors and renal outcomes across the spectrum of kidney disease: a systematic review and meta-analysis"

**ARTICLE 3:** "Sodium-glucose cotransporter-2 inhibitors and cancer outcomes: A systematic review and meta-analysis of randomized controlled trials"

**ARTICLE 1**

# SGLT2 INHIBITORS, CARDIOVASCULAR OUTCOMES, AND MORTALITY ACROSS THE SPECTRUM OF KIDNEY DISEASE

## A SYSTEMATIC REVIEW AND META-ANALYSIS

Bernardo Frison Spiazzi, Giovana Fagundes Piccoli, Laura Fink Wayerbacher, João Pedro Neves Lubianca, Bruno Guimarães Scalco, Mariana Hollmann Scheffler, Bruna Lorence Fraga, Verônica Colpani, Fernando Gerchman

2024

*Article submitted to JAMA Cardiology*

**ARTICLE 2**

# SGLT2 INHIBITORS AND RENAL OUTCOMES ACROSS THE SPECTRUM OF KIDNEY DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Bernardo Frison Spiazzi, Giovana Fagundes Piccoli, Laura Fink Wayerbacher, João Pedro Neves Lubianca, Bruno Guimarães Scalco, Mariana Hollmann Scheffler, Bruna Lorence Fraga, Verônica Colpani, Fernando Gerchman

2024

*Article submitted to the Journal of the American Society of Nephrology*

**ARTICLE 3**

# SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS AND CANCER OUTCOMES: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Bernardo F. Spiazzi, Rafaella A. Naibo, Laura F. Wayerbacher, Giovana F. Piccoli, Laura P. Farenzena, Thizá M. Londero, Gabriella R. da Natividade, Maira Zoldan, Nathália A.H. Degobi, Matheus Niches, Gilberto Lopes, Edward J. Boyko, Kristina M. Utzschneider, Verônica Colpani, Fernando Gerchman

2023

*Article published in Diabetes Research and Clinical Practice*

# 5 FINAL CONSIDERATIONS

The present work adds to the current literature on SGLT2 inhibitors exploring if the effects of these agents in preventing cardiovascular, renal, and mortality outcomes are consistent across the spectrum of kidney disease. Our findings show that the current combined data from high-quality large randomized placebo-controlled trials show an overall protective effect of SGLT2 inhibitors on cardiovascular, renal, and mortality outcomes, and that using the KDIGO classification and UACR groups anticipated the magnitude of the absolute effects expected. Moreover, in composite outcomes including cardiovascular death, larger relative reductions were observed in high-risk groups. Our findings also show that these agents prevent clinically meaningful renal outcomes in subjects at low risk for kidney disease, although the evidence is derived strongly from subjects with type 2 diabetes. These findings overall have applicability in clinical practice to help select patients who could benefit the most from treatment with SGLT2 inhibitors.

Furthermore, we have explored the relationship between SGLT2 inhibitors and cancer outcomes in adult populations using data only from randomized trials. The prior uncertainties regarding the risk of malignancies have chased this class of agents since their development program, and our findings provide reassuring data that these agents do not exert an effect on cancer outcomes for the adult populations that have been studied so far.

In summary, SGLT2 inhibitors prevent cardiovascular, renal, and mortality outcomes in populations with type 2 diabetes at high risk for or established cardiovascular disease, chronic kidney disease, and heart failure. KDIGO and UACR risk groups have shown great potential to anticipate the magnitude of beneficial effects of therapy, and the prior concerns regarding the risk of malignancies is not supported by the current body of evidence.

## 6. ADDITIONAL PUBLISHED ARTICLES IN THE DOCTORAL PERIOD


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