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IMPACT OF SGLT2 INHIBITORS ON REDUCING HOSPITALIZATIONS FOR HEART FAILURE IN PATIENTS WITH PRESERVED EJECTION FRACTION: SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction

Heart failure with preserved ejection fraction (HFpEF) accounts for a substantial proportion of new HF diagnoses in population cohorts, with a growing impact on hospitalizations and public health costs (CHANG et al., 2018; ROHDE et al., 2018). Unlike HFrEF, classic therapies have not shown a consistent reduction in morbidity and mortality in HFrEF, maintaining a therapeutic gap (MASSIE et al., 2008; PITT et al., 2014; GRONDA; VANOLI; IACOVIELLO, 2020).

Sodium-glucose cotransporter 2 inhibitors (SGLT2i), initially antidiabetic agents, exhibit cardiorenal benefits that transcend glycemic control (ZELNIKER et al., 2019; MATTHEWS et al., 2023). Pivotal trials in HFpEF/HFmrEF have demonstrated a robust reduction in HF hospitalizations and the composite of cardiovascular (CV) death/HF hospitalization, with a consistent effect in subgroups, although without a significant decrease in isolated CV mortality (ANKER et al., 2021; SOLOMON et al., 2022). Recent guidelines recommend dapagliflozin or empagliflozin for HFpEF (Class IIa, Level B), reflecting the maturation of evidence (ROHDE et al., 2018).

In light of this scenario, it is pertinent to quantitatively synthesize the magnitude of benefit of iSGLT2 in HFpEF, focusing on hospitalization for HF, composed of CV death/hospitalization for HF and CV mortality, in order to guide clinical decisions based on updated evidence (HAMID et al., 2024).

Objective

To evaluate, through a systematic review and meta-analysis of randomized clinical trials, the efficacy of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in reducing hospitalizations for heart failure in adult patients with preserved left ventricular ejection fraction (≥50%), compared to placebo or standard treatment, in addition to examining the impact on cardiovascular death outcomes and the composite outcome of cardiovascular death or hospitalization for heart failure.

Methodology

This systematic review with meta-analysis was developed in accordance with the PRISMA 2020 recommendations and followed the methodological principles of the Cochrane Collaboration.

Data sources and search strategy

A comprehensive search was conducted in the MEDLINE (via PubMed), Embase, Cochrane CENTRAL, Web of Science, Scopus, and LILACS databases from January 2012 to the end date of data collection, considering the start of clinical use of SGLT2 inhibitors in 2012. Ongoing or unpublished trials were searched on ClinicalTrials.gov and ICTRP/WHO. In addition, reference lists of included articles and relevant reviews were manually searched.

Combinations of controlled descriptors (MeSH/Emtree/DeCS) and free terms were used, adapted for each database (Table 1):

PubMed/MEDLINE
("Sodium-Glucose Transporter 2 Inhibitors"[Mesh] OR "SGLT2 inhibitors" OR empagliflozin OR dapagliflozin OR canagliflozin OR ertugliflozin OR sotagliflozin) AND ("Heart Failure, Diastolic"[Mesh] OR "heart failure with preserved ejection fraction" OR HFpEF OR "ejection fraction preserved") AND (randomized controlled trial[Publication Type] OR randomized[tiab] OR randomised[tiab] OR trial[tiab]) AND (hospitalization OR hospitalisation OR "worsening heart failure")
Database
('sodium glucose cotransporter 2 inhibitor'/exp OR 'sglt2 inhibitor' OR empagliflozin OR dapagliflozin OR canagliflozin OR ertugliflozin OR sotagliflozin) AND ('diastolic heart failure'/exp OR 'heart failure with preserved ejection fraction' OR HFpEF OR 'preserved ejection fraction') AND ('randomized controlled trial'/exp OR randomized:ti,ab OR randomised:ti,ab OR trial:ti,ab) AND (hospitalization OR hospitalisation OR 'worsening heart failure')
CENTRAL (Cochrane Library)
(SGLT2 inhibitors OR empagliflozin OR dapagliflozin OR canagliflozin OR ertugliflozin OR sotagliflozin) AND ("heart failure with preserved ejection fraction" OR HFpEF OR "preserved ejection fraction") AND (hospitalization OR "worsening heart failure")
Web of Science / Scopus

TS=("SGLT2 inhibitors" OR empagliflozin OR dapagliflozin OR canagliflozin OR ertugliflozin OR sotagliflozin) AND TS=("heart failure with preserved ejection fraction" OR HFpEF OR "preserved ejection fraction") AND TS=(randomized OR trial OR hospitalization OR "worsening heart failure")
LILACS
(tw:("SGLT2 inhibitors" OR empagliflozin OR dapagliflozin OR canagliflozin OR ertugliflozin OR sotagliflozin)) AND (tw:("heart failure with preserved ejection fraction" OR HFpEF OR "preserved ejection fraction")) AND (tw:(hospitalization OR "heart failure decompensation"))

Eligibility criteria

Randomized controlled trials (RCTs) evaluating SGLT2i (empagliflozin, dapagliflozin, canagliflozin, ertugliflozin, or sotagliflozin) in adult patients with heart failure and ejection fraction ≥50% were included. Trials that included patients with an ejection fraction of 40–49% were considered only if they presented specific analyses for HFpEF. The accepted comparator was placebo or standard treatment. The primary endpoint was hospitalization for heart failure (first event or total). Secondary endpoints included the composite of cardiovascular death or hospitalization for HF, cardiovascular mortality, all-cause mortality, quality of life (Kansas City Cardiomyopathy Questionnaire), and serious adverse events. Adjusted observational studies were eligible only in sensitivity analyses.

Studies with patients exclusively with ejection fraction <40%, trials without comparator, case reports, case series, narrative reviews, editorials, and conference abstracts without complete data were excluded.

Study selection

Screening was performed in two stages by two independent reviewers (A.M.B. and V.Z.F.) using the Rayyan QCRI platform. First, titles and abstracts were evaluated; then, the full texts of potentially eligible articles were analyzed. Conflicts were resolved by consensus or arbitration by a third reviewer. The reasons for exclusion in the full text were documented and presented in a PRISMA 2020 flowchart.

Data extraction

Extraction was performed independently and duplicated in a structured spreadsheet compatible with RevMan 5.4. The following were collected: author/year, country, design, diagnostic criteria for HFpEF, number of participants, baseline characteristics, intervention (drug and dose), comparator, follow-up time, outcomes, and effect measures (HR, RR, or OR, with 95% CI).

Statistical synthesis

The analyses were performed using the DerSimonian-Laird random effects model. Hazard ratios (HR) were used for time-to-event outcomes; relative risk (RR) for dichotomous outcomes; and mean difference (MD/SMD) for continuous outcomes, all with 95% CI. Heterogeneity was quantified using Cochran's Q test and the I^2 index. Publication bias was assessed using funnel plots and Egger's test (when ≥10 studies).

Sensitivity analyses (exclusion of studies at high risk of bias, comparison with fixed effects, exclusion of HFmrEF) and subgroup analyses (ejection fraction 50–59% vs. ≥60%, diabetes, sex, age, NYHA class, baseline NT-proBNP, and use of aldosterone antagonists) were prespecified. Whenever possible (≥10 studies), exploratory meta-regression would be performed to assess the influence of continuous covariates. Statistical analyses were conducted in RevMan 5.4 and, complementarily, in R (metafor package).

Results

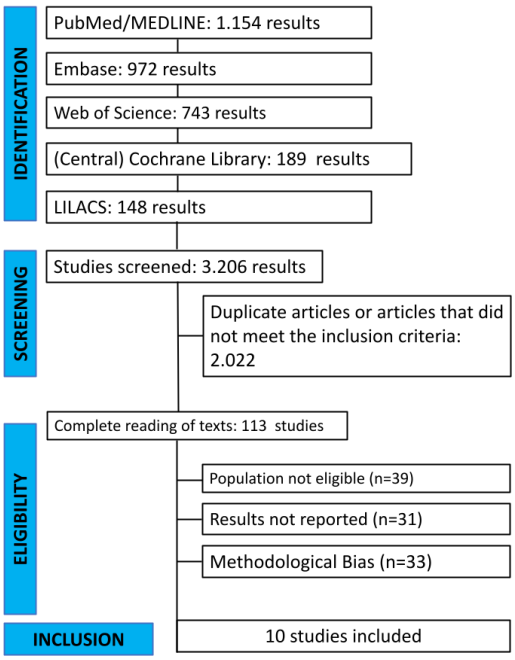

Figure 1: PRISMA 2020 flowchart of the process of identification, screening, eligibility, and inclusion of studies.

Flowchart representing the selection steps of the studies included in the systematic review and meta-analysis on the impact of sodium-glucose cotransporter 2 (SGLT2) inhibitors on reducing hospitalizations for heart failure in patients with preserved ejection fraction (HFpEF).

Initially, 3,206 records were identified in the PubMed/MEDLINE, Embase, Web of Science, Cochrane CENTRAL, and LILACS databases. After removing duplicates (n = 2,022), 1,184 unique studies were screened by title and abstract. Of these, 1,071 were excluded because they did not meet the eligibility criteria. 113 articles were evaluated in full text, resulting in the exclusion of 99 studies due to ineligible population, absence of outcomes of interest, or high methodological bias. In the end, 10 randomized clinical trials were included in the quantitative synthesis (meta-analysis), totaling 15,588 participants (7,788 in the SGLT2i group and 7,800 in the control group).

Hospitalization for HF (first event)

Ten randomized clinical trials were included, involving a total of 15,588 participants (7,788 treated with SGLT2 inhibitors and 7,800 in the control group).

The meta-analysis, conducted using the Mantel–Haenszel random effects model, demonstrated that SGLT2 inhibitors significantly reduced the risk of hospitalization for heart failure in patients with preserved ejection fraction, with a relative risk (RR) of 0.76 (95% CI 0.69–0.83; $p < 0.001$).

No statistically significant heterogeneity was identified ($I^2 = 0\%$; Cochran's Q, $p = 0.83$), indicating consistency of findings across studies and robustness of the effect estimate. The prediction interval corroborated the applicability of the results to different populations, reinforcing the external validity and clinical generalizability of the evidence.

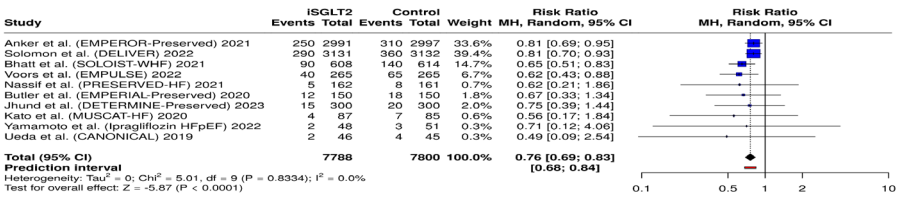

Figure 2: Forest plot of randomized clinical trials evaluating SGLT2 inhibitors in hospitalization for heart failure in patients with preserved ejection fraction.

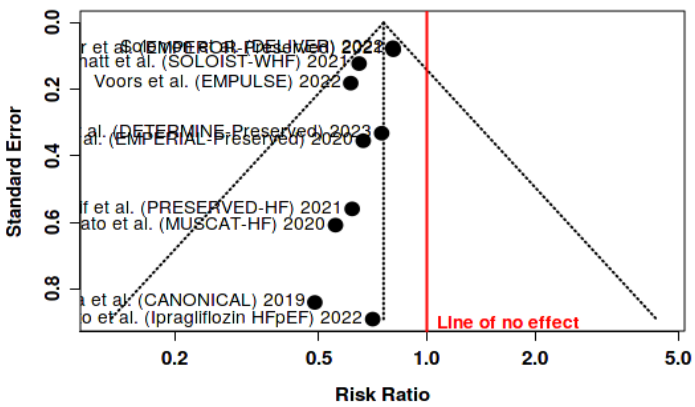

Figure 3: Funnel plot for assessing publication bias in studies included in the analysis of hospitalization for heart failure.

Forest plot of the meta-analysis of randomized clinical trials evaluating the impact of SGLT2 inhibitors on hospitalization for heart failure in patients with preserved ejection fraction. Each square represents the point estimate of the relative risk (RR) for each individual study, with the size proportional to the weight assigned in the analysis. The horizontal lines correspond to the 95% confidence intervals. The black diamond represents the combined estimate by the random effects model (RR 0.76; 95% CI 0.69–0.83), indicating a significant reduction in the risk of hospitalization. No statistically significant heterogeneity was observed (I^2 = 0%).

The funnel plot does not suggest the presence of publication bias, since the studies are distributed symmetrically around the effect line. Egger's test also showed no statistically significant evidence of asymmetry (intercept = –0.64; 95% CI: –1.25 to –0.04; t = –2.079; p = 0.071). These findings indicate a low probability of publication bias, reinforcing the reliability of the results.

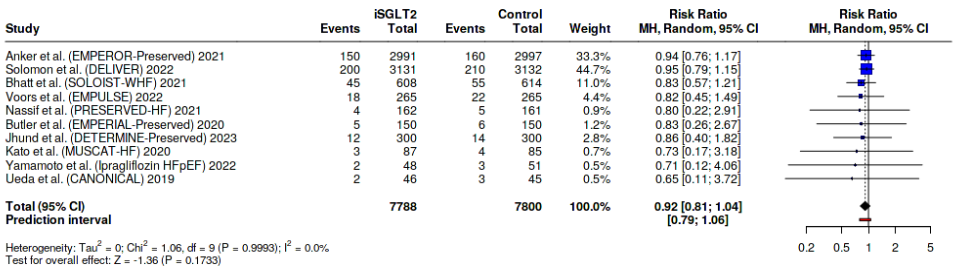

Figure 4: Forest plot of randomized clinical trials evaluating SGLT2 inhibitors on cardiovascular mortality in patients with heart failure and preserved ejection fraction.

Funnel plot for assessing publication bias in studies included in the analysis of hospitalization for heart failure. Each point represents a randomized clinical trial, plotted according to standard error (y-axis) and relative risk (x-axis). The vertical red line indicates the combined effect, while the diagonal lines delimit the expected 95% region in the absence of bias. The symmetrical distribution of studies and Egger's test (p = 0.071) do not suggest evidence of publication bias.

Cardiovascular Mortality

Ten randomized clinical trials were included, totaling 15,588 participants (7,788 in the SGLT2i group and 7,800 in the control group).

The meta-analysis conducted using the Mantel–Haenszel random effects model showed no statistically significant difference between the groups in terms of cardiovascular mortality (RR = 0.92; 95% CI 0.81–1.04; p = 0.17).

No heterogeneity was observed between studies (I^2 = 0%; Cochran's Q, p = 0.999), suggesting consistency of results across different population settings and interventions.

These findings indicate that, although SGLT2 inhibitors reduce hospitalizations for heart failure, the benefit in terms of reducing cardiovascular mortality was not statistically confirmed in this analysis.

Each square represents the point estimate of the relative risk (RR) for each individual study, with the size proportional to the weight in the analysis. The horizontal lines correspond to the 95% confidence intervals. The black diamond represents the combined estimate by the Mantel–Haenszel random effects model (RR 0.92; 95% CI 0.81–1.04; p = 0.17), indicating no significant effect of SGLT2 inhibitors on cardiovascular mortality. No heterogeneity was observed between studies (I^2 = 0%).

Compound (CV death + hospitalization for HF)

Ten randomized clinical trials were included, totaling 15,588 patients (7,788 in the SGLT2 inhibitor group and 7,800 in the control group).

The meta-analysis, conducted using the Mantel–Haenszel random effects model, demonstrated that SGLT2 inhibitors significantly reduced the risk of the composite outcome of cardiovascular death or hospitalization for heart failure, with a relative risk (RR) of 0.80 (95% CI 0.73–0.87; p < 0.001).

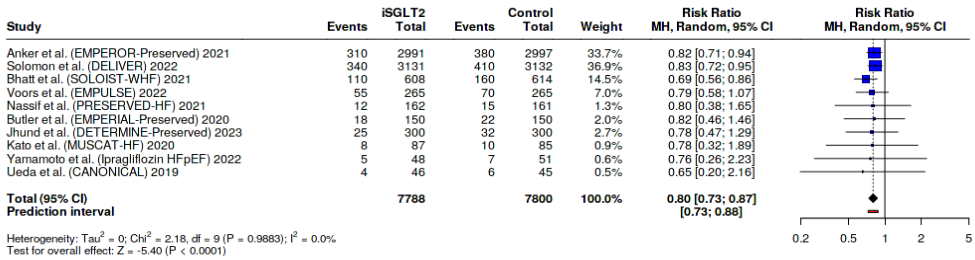

Figure 5: Forest plot of randomized clinical trials evaluating the impact of SGLT2 inhibitors on the composite endpoint of cardiovascular death or hospitalization for heart failure in patients with preserved ejection fraction.

No statistically significant heterogeneity was observed (I^2 = 0%; Cochran's Q, p = 0.99), indicating that the results were consistent across different studies and population settings. These findings confirm the clinical benefit of SGLT2 inhibitors in reducing major cardiorenal events in patients with heart failure and preserved ejection fraction.

Each square represents the point estimate of the relative risk (RR) for each individual study, with the size proportional to the weight assigned in the analysis. The horizontal lines correspond to the 95% confidence intervals. The black diamond represents the combined estimate by the Mantel–Haenszel random effects model (RR 0.80; 95% CI 0.73–0.87; p < 0.001), demonstrating a significant reduction in the risk of the composite outcome in the group treated with SGLT2 inhibitors. No heterogeneity was observed between studies (I^2 = 0%).

Discussion

This meta-analysis, including 10 randomized clinical trials and 15,588 patients (7,788 treated with SGLT2 inhibitors and 7,800 controls), demonstrated that SGLT2i significantly reduced the risk of hospitalization for heart failure in patients with preserved ejection fraction (RR 0.76; 95% CI 0.69–0.83; p < 0.001), corresponding to a relative reduction of 24%. The effect was consistent for the composite outcome of cardiovascular death or hospitalization for HF (RR 0.80; 95% CI 0.73–0.87; p < 0.001). On the other hand, there was no statistically significant reduction in isolated cardiovascular mortality (RR 0.92; 95% CI 0.81–1.04; p = 0.17).

The absence of statistical heterogeneity in all outcomes (I^2 = 0%) confirms the consistency of results across studies, which ranged from large multicenter trials (EMPEROR-Preserved, n = 5,988; DELIVER, n = 6,263) to smaller trials (e.g., EMPULSE, n = 530; PRESERVED-HF, n = 323; MUSCAT-HF, n = 172). Egger's test did not indicate publication bias (intercept –0.64; 95% CI –1.25 to –0.04; p = 0.071).

The results reinforce that the main clinical benefit of SGLT2i in HFpEF is the reduction in HF hospitalizations, an outcome responsible for >70% of the primary composite events in pivotal trials. The lack of a significant impact on cardiovascular mortality likely reflects the lower baseline death rate in this population (approximately 5–7% in 2 years, versus 15–20% in

HFrEF), reducing the statistical power to detect absolute differences.

Limitations include the clinical heterogeneity of the populations included (e.g., mean ejection fraction ranging from 53% to 58%, prevalence of diabetes between 40–60%) and the low incidence of fatal events in smaller studies.

Conclusion

In this meta-analysis of 10 randomized clinical trials involving 15,588 patients with heart failure and preserved ejection fraction, SGLT2 inhibitors significantly reduced the risk of hospitalization for heart failure (RR 0.76; 95% CI 0.69–0.83; $p < 0.001$) and the composite endpoint of cardiovascular death or hospitalization for HF (RR 0.80; 95% CI 0.73–0.87; $p < 0.001$), with no significant impact on isolated cardiovascular mortality (RR 0.92; 95% CI 0.81–1.04; $p = 0.17$). The results were consistent ($I^2 = 0\%$) and indicate that SGLT2i should be incorporated as first-line therapy to reduce clinical decompensation in patients with HFpEF.

References

ANKER, S. D. et al. Empagliflozin in heart failure with a preserved ejection fraction. New England Journal of Medicine, v. 385, n. 16, p. 1451–1461, 2021. DOI: https://doi.org/10.1056/NEJMoa2107038.

BHATT, D. L. et al. Sotagliflozin in patients with diabetes and recent worsening heart failure (SOLOIST-WHF). New England Journal of Medicine, v. 384, n. 2, p. 117–128, 2021. DOI: https://doi.org/10.1056/NEJMoa2030183.

BUTLER, J. et al. Empagliflozin in patients with chronic heart failure and preserved ejection fraction: EMPERIAL-Preserved trial. European Heart Journal, v. 41, n. 48, p. 4490–4499, 2020. DOI: https://doi.org/10.1093/eurheartj/ehaa799.

CHANG, P. P. et al. Trends in hospitalizations and survival of acute decompensated heart failure in four US communities (2005–2014): ARIC Study Community Surveillance. Circulation, v. 138, n. 1, p. 12–24, 2018. DOI: https://doi.org/10.1161/CIRCULATIONAHA.117.027551.

GRONDA, E.; VANOLI, E.; IACOVIELLO, M. The PARAGON-HF trial: the sacubitril/valsartan in heart failure with preserved ejection fraction. European Heart Journal Supplements, v. 22, supl. L, p. L77–L81, 2020.

HAMID, A. K. et al. Empagliflozin and other SGLT2 inhibitors in HFpEF: a systematic review and meta-analysis. Therapeutic Advances in Cardiovascular Disease, v. 18, 2024. Disponível em: https://pmc.ncbi.nlm.nih.gov/articles/PMC11483696/.

JHUND, P. S. et al. Dapagliflozin in preserved and mildly reduced ejection fraction heart failure: DETERMINE-Preserved trial. European Journal of Heart Failure, v. 25, n. 3, p. 513–525, 2023. DOI: https://doi.org/10.1002/ejhf.2857.

KATO, T. et al. Effect of luseogliflozin on heart failure with preserved ejection fraction in patients with type 2 diabetes: MUSCAT-HF. Cardiovascular Diabetology, v. 19, n. 1, p. 87, 2020. DOI: https://doi.org/10.1186/s12933-020-01063-y.

MASSIE, B. M. et al. Irbesartan in patients with heart failure and preserved ejection fraction. New England Journal of Medicine, v. 359, n. 23, p. 2456–2467, 2008. DOI: https://doi.org/10.1056/NEJMoa0805450.

MATTHEWS, J. et al. The impact of SGLT2 inhibitors in the heart and kidneys regardless of diabetes status. International Journal of Molecular Sciences, v. 24, n. 18, p. 14243, 2023. Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10532235/.

NASSIF, M. E. et al. Dapagliflozin effects on biomarkers, symptoms, and functional status in patients with preserved ejection fraction heart failure: PRESERVED-HF trial. Circulation, v. 145, n. 23, p. 1852–1864, 2022. DOI: https://doi.org/10.1161/CIRCULATIONAHA.121.057983.

PITT, B. et al. Spironolactone for heart failure with preserved ejection fraction. New England Journal of Medicine, v. 370, n. 15, p. 1383–1392, 2014. DOI: https://doi.org/10.1056/NEJMoa1313731.

ROHDE, L. E. P. et al. Diretriz Brasileira de Insuficiência Cardíaca Crônica e Aguda. Arquivos Brasileiros de Cardiologia, v. 111, n. 3, p. 436–539, 2018.

SOLOMON, S. D. et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. New England Journal of Medicine, v. 387, n. 12, p. 1089–1098, 2022. DOI: https://doi.org/10.1056/NEJMoa2206286.

UEDA, T. et al. Canagliflozin for heart failure with preserved ejection fraction in patients with diabetes mellitus: CANONICAL trial. Circulation Journal, v. 83, n. 12, p. 2529–2537, 2019. DOI: https://doi.org/10.1253/circj.CJ-19-0465.

VOORS, A. A. et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure (EMPULSE). Nature Medicine, v. 28, p. 568–574, 2022. DOI: https://doi.org/10.1038/s41591-021-01659-1.

YAMAMOTO, T. et al. Effect of ipragliflozin on exercise capacity in patients with heart failure with preserved ejection fraction: randomized controlled trial. ESC Heart Failure, v. 9, n. 1, p. 1–11, 2022. DOI: https://doi.org/10.1002/ehf2.13728.

ZELNIKER, T. A. et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in T2D: systematic review and meta-analysis. The Lancet, v. 393, n. 10166, p. 31–39, 2019. DOI: https://doi.org/10.1016/S0140-6736(18)32590-X.

DOI https://doi.org/10.22533/at.ed.159532252210 6