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SGLT2s: The Heart's New Power Couple

Effect of SGLT2 Inhibitors on Heart Failure Outcomes and Cardiovascular Death Across the Cardiometabolic Disease Spectrum: A Systematic Review and Meta-Analysis

Usman MS, Bhatt DL, Hameed I, et al. Effect of SGLT2 inhibitors on heart failure outcomes and cardiovascular death across the cardiometabolic disease spectrum: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2024;12(7):447-461. doi:10.1016/S2213-8587(24)00102-5

KEY TAKEAWAY: Sodium-glucose cotransporter-2 inhibitors (SGLT2is) reduce first and total hospitalizations for heart failure (HF), cardiovascular death, and all-cause mortality in patients with HF, type 2 diabetes mellitus (T2DM), chronic kidney disease (CKD), or atherosclerotic disease (ASCVD).

STUDY DESIGN: Systematic review and meta-analysis of 15 randomized controlled trials (N=100,952)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: SGLT2is were originally developed to treat T2DM by blocking the SGLT2 protein in the kidneys to lower blood glucose levels. Further trials revealed unexpected benefits on composite cardiovascular outcomes. This meta-analysis assessed the impact of SGLT2is on specific cardiovascular outcomes.

PATIENTS: Adult patients with HF, T2DM, CKD, or ASCVD

INTERVENTION: SGLT2is

CONTROL: Placebo

PRIMARY OUTCOME: HF hospitalization and mortality

METHODS (BRIEF DESCRIPTION):

- Trials included in this meta-analysis were primary or secondary analyses of double-blind trials that randomized >1,000 patients, comparing the effects of an SGLT2i and matching placebo on HF hospitalization, cardiovascular death, and all-cause mortality.
- The study population were 34% women with a mean age of 66 years old.
- Patients had one or more of the following diagnoses:
  - HF: Both reduced and preserved ejection fraction
  - T2DM
  - CKD defined by an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2 or a urinary albumin to creatinine ratio >30 mg/g
  - ASCVD of the coronary, cerebrovascular, or peripheral arterial systems, including acute myocardial infarction (MI) and stroke
- The severity of the above disease states were not specified.
- SGLT2i medications included canagliflozin, empagliflozin, dapagliflozin, ertugliflozin, and sotagliflozin (dosages not specified).
- Matching placebo served as control.
- Data on HF hospitalization, cardiovascular death, and all-cause mortality was stratified by disease state (HF, T2DM, CKD, ASCVD) and by demographics (age, sex, body mass index, eGFR, race, region).
- Hazard ratios for time-to-event outcomes were quantified using a random effects model.
- The rate ratio was reported for total HF hospitalizations in patients on SGLT2i compared to those on placebo, with a rate ratio of <1 suggesting a protective effect of SGLT2i and a ratio >1 suggesting a harmful effect.

INTERVENTION (# IN THE GROUP): 53,764

COMPARISON (# IN THE GROUP): 47,188

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- SGLT2is reduced the risk of first HF hospitalization in the following patient subgroups:
  - HF (hazard ratio [HR] 0.71; 95% CI, 0.67–0.77)
  - T2DM (HR 0.72; 95% CI, 0.67–0.77)
  - CKD (HR 0.68; 95% CI, 0.61–0.77)
  - ASCVD (HR 0.72; 95% CI, 0.66–0.79)
- SGLT2is reduced the risk of total HF hospitalization in the following patient subgroups:
  - HF (rate ratio [RR] 0.71; 95% CI, 0.66-–0.76)
  - T2DM (RR 0.68; 95% CI, 0.61–0.75)
  - CKD (RR 0.69; 95% CI, 0.61–0.78)
  - ASCVD (RR 0.72; 95% CI, 0.65–0.81)
- SGLT2is reduced the risk of cardiovascular death in the following patient subgroups:
  - HF (HR 0.86; 95% CI, 0.79–0.93)
  - T2DM (HR 0.85; 95% CI, 0.79–0.91)

    - CKD (HR 0.89; 95% CI, 0.82–0.96)
    - ASCVD (HR 0.87; 95% CI, 0.78–0.97)
- SGLT2is reduced all-cause mortality in the following patient subgroups:
    - HF (HR 0.90; 95% CI, 0.85–0.96)
    - T2DM (HR 0.87; 95% CI, 0.81–0.94)
    - CKD (HR 0.88; 95% CI, 0.81–0.96)
    - ASCVD (HR 0.86; 95% CI, 0.77–0.95)

LIMITATIONS:

- The inclusion of mostly patients from Western countries with adequate access to care and exclusion of patients with controlled comorbidities likely contributed to selection bias.
- There was publication bias in that positive results were more likely to be published and could have overestimated SGLT2i benefits.
- There were varying definitions of disease (CKD definition), disease severity (controlled vs uncontrolled T2DM), and standards of care.
- The study reviewed SGLT2is as a class as opposed to individual medications with specified dosages.
- Some of the trials had short follow-up with unclear long-term effects of SGLT2is.

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Kidney You Not: Donation Doesn't Spike BP, But GFR Dips

Hypertension and Kidney Function After Living Kidney Donation

Garg AX, Arnold JB, Cuerden MS, et al. Hypertension and Kidney Function After Living Kidney Donation. *JAMA*. 2024;332(4):287-299. doi:10.1001/jama.2024.8523

KEY TAKEAWAY: Kidney donation does not increase the risk of hypertension (HTN), or albuminuria compared to non-donation but increases the risk of developing reduced kidney function. After donation, the annual decline in estimated glomerular filtration rate (eGFR) is slower in donors than in nondonors.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Living donor kidney transplantation is considered the most effective option for patients with end-stage renal disease, significantly enhancing their quality of life. This study aimed to identify the risk of developing HTN, kidney impairment as measured by eGFR, and albuminuria in kidney donors.

PATIENTS: Normotensive adults

INTERVENTION: Living kidney donors

CONTROL: Living non-donors

PRIMARY OUTCOME: HTN, annualized change in eGFR, albuminuria

Secondary Outcome: Mortality, kidney failure, major cardiovascular events, health-related quality of life, depression, anxiety

METHODS (BRIEF DESCRIPTION):

- The prospective cohort study included patients from 17 transplant centers in Canada and Australia between 2004–2014.
- The participants were 66% female and 88% White, with an average age of 47 years old, BMI <30, and a mean eGFR of 100.
- Various strategies, such as reminders and follow-up calls, were employed to maximize sample retention.
- The study involved participants who had donated a kidney, concentrating on their post-donation HTN and kidney function as the intervention group.
- The study compared these donors to a matched non-donor group to assess differences in HTN and kidney function over time.
- The following were measured as the primary outcomes:
  - HTN was measured and defined as a systolic blood pressure (SBP) ≥140 mmHg and a diastolic BP (DBP) ≥90 mmHg.
  - Kidney function was assessed using the annualized eGFR at one, two, and four years from baseline.
  - A low eGFR was defined as an eGFR <60 mL/min/1.73m² and <45 mL/min/1.73m² at any follow up visit.
  - Albuminuria was evaluated by measuring urine albumin/creatinine levels (albumin to creatinine ratio ≥3 mg/mmol) to detect an increase in albumin excretion.
- The following were measured as the secondary outcomes:
  - Mortality, kidney failure, and major cardiovascular events including myocardial infarction (MI) or stroke, were evaluated using annual surveys and medical records.
    - These outcomes were reviewed and analyzed both individually and as a composite by a physician who was unaware of the donation status.
  - Health-related quality of life was assessed using the Short Form Health Survey (SF-36). Scores range from 0–100, where higher scores indicate better health and quality of life.
  - The Beck Depression Inventory was used to assess symptoms of depression, while the Beck Anxiety Inventory evaluated anxiety symptoms. On both inventories, higher scores reflect more severe symptomatology.
- A weighted statistical analysis was completed to adjust for baseline differences between kidney donors and non-donors, ensuring a more accurate comparison.

INTERVENTION (# IN THE GROUP): 924

COMPARISON (# IN THE GROUP): 928

FOLLOW-UP PERIOD: Median 7.3 years

RESULTS:

Primary Outcome –

- Kidney donors did not have an increased risk of HTN compared to nondonors (hazard ratio [HR] 1.1; 95% CI, 0.75–1.7).
- Kidney donors with an eGFR of <60 mL/min/1.73m² had an increased risk of reduced kidney function compared to nondonors (HR 12; 95% CI, 7.3–20).
- Kidney donors with an eGFR of <45 mL/min/1.73m² had an increased risk of reduced kidney function compared to nondonors (HR 12; 95% CI, 1.8–78).
- Kidney donors did not have an increased risk of albuminuria compared to nondonors (HR 1.5; 95% CI, 0.97–2.2).

Secondary Outcome –

- Kidney donors did not have an increased risk of death, kidney failure, and major cardiovascular events compared to nondonors.
- There was no statistical comparison completed for depression, anxiety, and quality of life for kidney donors compared to nondonors.

LIMITATIONS:

- The onset of HTN in kidney donors may not be directly linked to nephrectomy or the act of donation but could instead stem from other lifestyle-related risk factors over time.
- Key factors, such as a family history of kidney disease or prior transplantation among donors, were not included in the analysis and may have affected the outcomes.
- The overrepresentation of White participants within the donor group reduces the relevance of the findings to more ethnically diverse populations.
- Extending the follow-up period could have offered more detailed insights into the long-term effects and risks related to kidney donation.
- Donors reported certain health concerns, like tinnitus, more frequently, which may introduce reporting bias, as these issues are unlikely to have a direct connection to nephrectomy.

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Head-to-Head for Neck Pain: BEMER vs OMT

Effect of Osteopathic Manipulative Treatment and Bio-Electro-Magnetic Energy Regulation (BEMER) Therapy on Generalized Musculoskeletal Neck Pain in Adults

Palmer GM, Dominick N, Kane M, et al. Effect of osteopathic manipulative treatment and Bio-Electro-Magnetic Energy Regulation (BEMER) therapy on generalized musculoskeletal neck pain in adults. *J Osteopath Med*. 2023;124(4):153-161. Published 2023 Dec 1. doi:10.1515/jom-2023-0128

KEY TAKEAWAY: Bio-Electro-Magnetic Energy Regulation (BEMER) therapy may reduce neck disability compared to osteopathic manipulative treatment (OMT), OMT + BEMER, and sham treatment.

STUDY DESIGN: Randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size and lack of blinding)

BRIEF BACKGROUND INFORMATION: Neck pain is the fourth leading cause of disability worldwide with a prevalence of 10–20% of the population. BEMER uses pulse electromagnetic fields to improve tissue microcirculation, while OMT is a hands-on technique. The combination was previously promising for improvement in back pain but has not been studied for neck pain. This study aimed to compare the individual and combined effects of BEMER and OMT on measures of neck pain and disability.

PATIENTS: Adults with neck pain

INTERVENTION: BEMER and OMT+BEMER

CONTROL: OMT and sham treatments

PRIMARY OUTCOME: Neck pain and disability

METHODS (BRIEF DESCRIPTION):

- The authors conducted a single-blind randomized controlled trial at the Lake Erie College of Osteopathic Medicine in Lake Erie, Pennsylvania.
- Adults with ≥2 weeks of nonspecific neck pain were recruited via email invitation from among the faculty, students, and staff of the medical college.
- Patients were excluded if they were pregnant, had prior physical or manual therapy, symptoms or exam findings of cervical radiculopathy, body mass index (BMI) >30, and other medical conditions.
- Participants had an average age of 25 years old and 73% of participants identified as female.
- Subjects were randomized into one of four groups and were not informed of the other treatment arms:
  - BEMER (5 treatments per week)
  - OMT + BEMER (same frequency for each treatment)
  - OMT (3 treatments per week)
  - Control (light touch and sham BEMER treatment)
- All participants received standardized osteopathic structural examinations and diagnoses of somatic dysfunction during each treatment session.
- A standardized OMT sequence was used for those in OMT or OMT + BEMER groups addressing areas of dysfunction.
- BEMER treatment intensity setting was increased each week.
- Surveys were collected from subjects before and immediately after completing the three-week intervention.
- Neck pain was assessed using the Visual Analog Scale (VAS). Score range from 0–100 mm, with higher scores indicating worse pain.
- Functionality was using the:
  - Neck Disability Index (NDI): Scores range from 0–50, with higher scores indicating more limitations.

INTERVENTION (# IN THE GROUP):

- BREMER: 10
- OMT + BREMER: 10

COMPARISON (# IN THE GROUP):

- OMT: 10
- Control: 8

FOLLOW-UP PERIOD: Length of time

RESULTS:

Primary Outcome –

- BEMER alone improved functionality compared to other treatments:
  - BEMER vs OMT + BEMER (–9.8 vs –4.0, respectively; *P*<.01)
  - BEMER vs OMT (–9.8 vs –1.8, respectively; *P*<.001)
  - BEMER vs control (–9.8 vs –2.8, respectively; *P*<.005)

- There were no statistically significant difference in neck pain between any of the treatment groups compared to control (results presented via figure).

LIMITATIONS:

- The assessment of blinding to treatment arm on study participants was not discussed.
- OMT was performed by multiple practitioners on the same participant, which may have created inconsistent effects.
- OMT was performed by second year medical students and therefore may have been less effective than OMT by experienced practitioners.
- The subject population was relatively young, healthy, and predominantly female, limiting generalizability.
- The study size was small.
- The treatment duration was three weeks, where OMT may have better efficacy over longer treatment periods.
- BEMER was performed more frequently per week vs OMT, and with increasing intensity each week, which may have favored BEMER.

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Low Volume, High Stakes: The CES You Didn't See Coming

Post-Void Bladder Ultrasound in Suspected Cauda Equina Syndrome-Data from Medicolegal Cases and Relevance to Magnetic Resonance Imaging Scanning

Todd N, Dangas K, Lavy C. Post-void bladder ultrasound in suspected cauda equina syndrome-data from medicolegal cases and relevance to magnetic resonance imaging scanning. *Int Orthop*. 2022;46(6):1375-1380. doi:10.1007/s00264-022-05341-0

KEY TAKEAWAY: A post-void residual volume (PVR) of <200 mL does not definitively rule out cauda equina syndrome (CES).

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 4 (downgraded due to a lack of statistical analysis)

BRIEF BACKGROUND INFORMATION: Early diagnosis and surgical correction of CES is critical, as CES may be associated with permanent neurological damage and long-term, severe medical comorbidities and disability if not diagnosed and treated early. There are "red flag" symptoms indicative of CES, however, presentation of CES may be variable and there is no current consensus on testing that can reliably predict the presence of cauda equina compression on magnetic resonance images (MRIs). Previous studies have proposed that bladder ultrasound scans of PVR <200 mL in patients without clinical signs of CES accurately predict the probability of an MRI negative for CES. The authors of the present study contend this conclusion as CES symptomatology is variable and clinical assessments are operator dependent, thus the purpose of the present study is to retrospectively evaluate the utility of PVR ultrasounds in patients with CES.

PATIENTS: Adults with suspected CES

INTERVENTION: PVR scan <200 mL

CONTROL: PVR scan >200 mL

PRIMARY OUTCOME: CES presence

Secondary Outcome: Utilization of MRI, surgical correction within 24 hours

METHODS (BRIEF DESCRIPTION):

- 50 medicolegal cases involving patients litigating in relation to CES were retrospectively reviewed.
- CES cases without reported PVR (24), reported PVR >200 mL (12) and uncertain diagnoses (1) were excluded from the study.
- 13 CES cases with reported PVR <200 mL was identified and patient characteristics, symptomatology, and clinical course timeline were recorded to determine the number of confirmed cases of CES with PVR <200 mL.
- Demographics of the patient population included four males and nine females with a mean age 41 years old.
- The primary outcome assessed the presence of CES via a positive MRI scan with evidence of CES which was defined as a large lumbosacral disc prolapse occupying most of the canal cross-sectional are sufficient to compress the cauda equina.
- The secondary outcomes assessed MRI utilization and surgical correction of CES within 24 hours

INTERVENTION (# IN THE GROUP): 13

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Not applicable

RESULTS:

Primary Outcome –

- Clinicians identified CES in 13 patients who had a PVR <200 mL (statistical analysis was not completed).

Secondary Outcome –

- All 13 patients underwent MRI within 24 hours of PVR assessment (statistical analysis was not completed).
- 11 of the 13 patients received surgical decompression within 24 hours of MRI (statistical analysis was not completed).

LIMITATIONS:

- The conclusion from the paper may be considered conjectural or deductive and without significant results due to the absence of statistical analysis.
- A limited number of cases were audited.
- Symptomatology of each individual case was variable and cannot be compared to previous research.
- Generalizability of the study to the general population is decreased due to the case population being predominantly female.

- Only cases with confirmed CES were analyzed. There is no comparison to cases with similar presentations that were not CES cases.
- No comparison in outcomes (time to MRI, time to surgical correction) between cases where PVR <200 mL and PVR >200 mL.

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The opinions and assertions contained herein are those of the author and are not to be construed as official or as reflecting the views of the US Army Medical Department, the Army at large, or the Department of Defense.

Fish Oil Flex: Help for Your Joints, Not Your Jumps

Omega-3 Fatty Acid Supplementation on Post-Exercise Inflammation, Muscle Damage, Oxidative Response, and Sports Performance in Physically Health Adults: A Systematic Review of Randomized Controlled Trials

Fernández-Lázaro D, Arribalzaga S, Gutiérrez-Abejón E, Azarbayjani MA, Mielgo-Ayuso J, Roche E. Omega-3 Fatty Acid Supplementation on Post-Exercise Inflammation, Muscle Damage, Oxidative Response, and Sports Performance in Physically Healthy Adults-A Systematic Review of Randomized Controlled Trials. *Nutrients*. 2024;16(13):2044. Published 2024 Jun 27. doi:10.3390/nu16132044

KEY TAKEAWAY: Supplementation with omega-3 fatty acids (FA) presents conflicting data related to a decrease in inflammatory markers and circulating muscle biomarkers. Supplementation with omega-3 FA is associated with short-term improvement in some measures of athletic performance.

STUDY DESIGN: Systematic review and meta-analysis of 13 prospective randomized controlled trials (RCTs) (N=478)

LEVEL OF EVIDENCE: STEP 3 (downgraded due to lack of statistical analysis and no meta-analysis)

BRIEF BACKGROUND INFORMATION: People engaging in athletic endeavors often employ supplements to aid in recovery and improve performance. In both trained and untrained athletes, decreased inflammation is associated with decreased rates of injury. This study assessed the efficacy of omega-3 FAs in reducing muscle soreness and biological inflammation markers.

PATIENTS: Adults 18–69 years old without pre-existing medical conditions and with various activity levels

INTERVENTION: Omega-3 FA supplementation

CONTROL: Placebo

PRIMARY OUTCOME: Inflammatory markers, muscle damage, and sports performance

METHODS (BRIEF DESCRIPTION):

- A literature search and study selection were conducted by a search of Web of Science (WOS), Scopus, and MEDLINE libraries. Studies were included if they met the following criteria:
  - Included participants who are either recreationally trained or untrained athletes (professional athletes excluded)
  - Athlete physical activity ranged from untrained athletes (<3 hours per week of physical activity), physically active (>3 hours per week of physical activity), and amateur athletes (cyclists and endurance runners)
  - Supplementation with omega-3 FA was studied
  - Participants reported no additional supplement use besides omega-3 FA
  - Quantifiable markers of inflammation, muscle breakdown, or athletic performance were measured
  - Studies were included which had a designation as “excellent quality” or “good quality” according to the PEDro Scale.
- Total omega-3 FA supplementation was recorded and reported as an average per day.
- The primary outcomes of the study were inflammatory laboratory markers pre- and post-exercise, muscle damage, and sports performance.
  - The inflammatory markers followed were interleukin-6 (main exercise related interleukin), tumor necrosis factor-alpha (acute phase reactant), and C-reactive protein (CRP).
    - Some studies also looked at IL-18, IL-2, IL-8, and IL-10.
  - Muscle damage was assessed using serum lactate dehydrogenase (LDH) and creatinine kinase (CK) levels, as well as a 0–10 pain score measurement of delayed onset muscle soreness, with a score of zero being no pain.
  - Sports performance was measured using a comparison of maximal voluntary isometric contractions (MVIC), vertical jump height, one repetition maximum (1RM) of various exercises, and range of motion (ROM).

INTERVENTION (# IN THE GROUP): 272

COMPARISON (# IN THE GROUP): 148

FOLLOW-UP PERIOD: Varied (1–6 weeks)

RESULTS:

Primary Outcome –

- Omega-3 FA supplementation decreased circulating levels of interluekin-6, tumor necrosis factor-alpha and LDH compared to placebo (no statistical analysis completed).
- Omega-3 FA supplementation did not decrease CRP or CK compared to the placebo (no statistical analysis completed).
- Omega-3 FA supplementation did not improve MVIC compared to placebo (no statistical analysis completed).
- Omega-3 FA supplementation improved vertical jump performance and 1RM for squat and bench press compared to placebo (no statistical analysis completed).
- Omega-3 FA supplementation improved elbow/knee joint ROM for 1–3 days after exercise without a long-term effect (no statistical analysis completed).

LIMITATIONS:

- The articles summarized RCTs without additional secondary analysis
- The studies included in the analysis had a relatively small sample size.
- Various levels of training in the study participants led to heterogeneity amongst controls and sample groups.
- Men were presented in the studies at an outsized proportion compared to women.
- The RCTs possessed a lack of homogeneity in the dose, route of administration, and timing of supplementation between studies.

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The views expressed herein are those of the author and do not necessarily reflect the official policy of the Department of the Air Force, Defense Health Agency, Department of Defense, or the U.S. Government