GEMs of the Week

Volume 1 Issue 1

GEMs
GOOD EVIDENCE MATTERS

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

A Slice of Bread Less a Day Keeps Celiac Away

Association of Gluten Intake During the First 5 Years of Life with Incidence of Celiac Disease Autoimmunity and Celiac Disease Among Children at Increased Risk

Andrén Aronsson C, Lee H, Hård af Segerstad EM, et al. Association of Gluten Intake During the First 5 Years of Life With Incidence of Celiac Disease Autoimmunity and Celiac Disease Among Children at Increased Risk. *JAMA*. 2019; 322(6):514–523.

KEY TAKEAWAY: Increased daily gluten consumption during the first 5 years of life significantly increases the incidence of celiac disease autoimmunity and celiac disease among predisposed children.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Gluten is a prevalent food antigen that can trigger inflammation of the gastrointestinal tract leading to celiac disease. Celiac disease typically presents in early childhood and is influenced by both genetic and environmental factors. Timing of gluten introduction in infants was not consistently associated with development of celiac disease in prior studies.
PATIENTS: Children with positive HLA antigens associated with T1DM and celiac disease.
INTERVENTION: Gluten intake from 3-day food diaries at defined intervals from 6 months to 5 years of age
CONTROL: N/A
OUTCOME: Celiac disease autoimmunity defined by two consecutive positive tissue transglutaminase autoantibodies (TTGA) (primary outcome), celiac disease defined by positive intestinal biopsy or persistently high TTGA (secondary outcome)

METHODS (BRIEF DESCRIPTION):

- A multinational birth cohort study at six clinical research centers in Finland, Germany, Sweden, and the United States (the Environmental Determinants of Diabetes in the Young [TEDDY] study) of 6605 children, with positive HLA antigens genotypes associated with T1DM and celiac disease, were followed from birth to 15 years of age at six clinical research centers.
- Gluten intake was estimated from 3-day food records at 6, 9, 12 months and then biannually until 5 years of age.
- TTGA were measured in serum samples at 2 years of age and then annually.
- Gastroenterology referrals were made at the clinical discretion of the primary physician, where biopsies could be made, but decision to do biopsy was not defined in the study protocol.

INTERVENTION (# IN THE GROUP): 6,605 in cohort
COMPARISON (# IN THE GROUP): N/A

FOLLOW UP PERIOD: Annual follow up from 5 years of age until 15 years of age

RESULTS:
PRIMARY OUTCOME:

- 1,216 children (18%) developed celiac disease autoimmunity and 447 (7%) developed celiac disease with peak incidence at two to three years old.
- Risk for celiac disease autoimmunity increased with every 1-gram/day increase in gluten consumption (Hazard Ratio [HR] 1.3, 95%CI, 1.2–1.4).
- Risk of celiac disease increased with every 1-gram/day increase in daily gluten consumption (HR 1.5; 95%CI, 1.4–1.7).

LIMITATIONS:

- Estimation of daily gluten intake was complicated by unknown gluten content between foods.
- Calculations were based on self-reported consumption data.

Amanda L. Dostaler, DO
University of Massachusetts Fitchburg Family Medicine Residency
Fitchburg, Massachusetts

Pressure is On: Updated evidence to guide selection of first-line antihypertensives

Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: a systematic, multinational, large-scale analysis

Suchard MA, Schuemie MJ, Krumholz HM, et al. Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: a systematic, multinational, large-scale analysis. *Lancet*. 2019; 394(10211):1816–1826.

KEY TAKEAWAY: Thiazide and thiazide-like diuretics are superior to angiotensin converting enzyme inhibitors in preventing cardiovascular events. Non-dihydropyridine calcium channel blockers are inferior to all other first-line agents in preventing CV events. No other between-class differences were found.

STUDY DESIGN: Retrospective comparative effectiveness and safety evaluation study

LEVEL OF EVIDENCE: Step 3

BRIEF BACKGROUND INFORMATION: Limited evidence exists to help guide clinicians to the most appropriate first-line antihypertensive agent. Previous studies lacked real-world outcomes and safety data comparing anti-hypertensive classes for initial therapy.

PATIENTS: Patients ages 10-69 with a diagnosis of hypertension who were new users of antihypertensive monotherapy across 9 observational databases in the United States, Japan, South Korea, and Germany.

INTERVENTION: Monotherapy treatment with one of five antihypertensive classes: Thiazide or thiazide-like diuretics (thiazides), angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), dihydropyridine calcium channel blockers (dCCB), or non-dihydropyridine calcium channel blockers (ndCCB)

CONTROL: Comparison for each class was made to the four other classes.

OUTCOME: Primary outcomes: acute MI, hospitalization for heart failure, and stroke.

Secondary outcomes: cardiovascular event, ischemic stroke, hemorrhagic stroke, heart failure, sudden cardiac death, and unstable angina. There were 46 safety outcomes.

METHODS (BRIEF DESCRIPTION): This study was a large-scale, comparative effectiveness and safety evaluation study using observational cohorts. Data was extracted from six claims systems and three electronic health records from July 1996 to March 2018. Patients included if they had a diagnosis of hypertension and were newly-initiated on one of the five studied anti-hypertensive classes. Patients were excluded who had events prior to initiation for each outcome. Each medication group was directly compared to the other four medication groups. Outcomes were measured by analysis of claims data and diagnosis codes. Hazard ratios between a medication class and its comparator were developed for each outcome.

INTERVENTION (# IN THE GROUP): Patients in each drug group (percent of total patients):

- ACEi – 2,378,000 (48%)
- Thiazides – 831,000 (17%)
- dCCB – 799,000 (16%)
- ARB – 752,000 (15%)
- ndCCB – 139,000 (3%)

COMPARISON (# IN THE GROUP): Same as intervention group, all groups served as both the intervention and the comparator in the multiple pairwise analyses.

FOLLOW UP PERIOD: Follow-up ranged from 217-3738 days. Twenty-five percent of patients had more than 5 years of follow-up.

RESULTS:

Significant Primary Outcomes:

Thiazides were superior to ACEi in preventing acute MI (HR 0.84; 95% CI, 0.75–0.95), hospitalization (HR 0.83; 95% CI, 0.74–0.95) and stroke (HR 0.83; 95% CI, 0.74–0.95. NNT=3 cardiovascular events avoided for every 1000 patients who initiate with a thiazide or thiazide-like diuretic instead of an ACE inhibitor)

Thiazides, ACEi, ARB, and dCCB classes were significantly better than ndCCB for:

- Acute MI (Thiazide vs ndCCB: HR 0.70; 95% CI, 0.59–0.84; ACEi vs ndCCB: HR 0.87; 95% CI, 0.77–1.00; ARB vs ndCCB: HR 0.78; 95% CI, 0.69–0.91; dCCB vs ndCCB: HR 0.84; 95% CI, 0.76–0.93)
- Hospitalization (Thiazide vs ndCCB: HR 0.70; 95% CI, 0.59–0.84; ACEi vs ndCCB: HR 0.87;95% CI, 0.77–1.00; ARB vs ndCCB: HR 0.78; 95% CI, 0.69–0.91 dCCB vs ndCCB: HR 0.84; 95% CI, 0.76–0.93)
- Stroke Thiazide vs ndCCB: HR 0.70; 95% CI, 0.59-0.84 ACEi vs ndCCB: HR 0.87; 95% CI, 0.77-1.00

ARB vs ndCCB: HR 0.78; 95% CI, 0.69-0.91; dCCB vs ndCCB: HR 0.84; 95% CI, 0.76-0.93
All other comparisons were not statistically significant among primary outcomes. Secondary outcomes followed similar trends as above.

Safety Outcomes:

Only comparative safety data for thiazides were presented in the main text. Thiazide diuretics resulted in more hypokalemia and hyponatremia when compared to other classes. ACE inhibitors and ARBs resulted in more cough and hyperkalemia. Sixteen additional safety outcomes occurred at a higher rate for ACE inhibitors versus thiazide diuretics, including all-cause mortality. Thiazides also resulted in less all-cause mortality compared to ndCCB and dCCB. ARBs resulted in less all-cause mortality compared to ACEi and ndCCB.

LIMITATIONS:

- Baseline blood pressures were not available for all databases.
- Baseline patient characteristics were not well-presented.

Janelle Wortman, PharmD
Providence St. Peter Family Medicine
Olympia, WA

Associations of Dietary Cholesterol or Egg Consumption with Incident Cardiovascular Disease and Mortality

Associations of Dietary Cholesterol or Egg Consumption with Incident Cardiovascular Disease and Mortality

Zhong VW, Horn LV, Cornelis MC, et al. Associations of Dietary Cholesterol or Egg Consumption With Incident Cardiovascular Disease and Mortality. *JAMA.* 2019; 321 (11):1081–1095.

KEY TAKEAWAY: Dietary cholesterol or egg consumption is significantly associated with an increased risk of cardiovascular disease (CVD) and all-cause mortality.

STUDY DESIGN: Pooled analysis of six observational prospective cohort studies in the United States.

LEVEL OF EVIDENCE: Step 2

BRIEF BACKGROUND INFORMATION: The association between dietary cholesterol intake or egg consumption and cardiovascular disease has remained obscure. Previous studies and recommendations from health agencies have failed to bring definitive clarification, and occasionally presented contradictory statements.
PATIENTS: 29,615 adults (pooled from 6 prospective cohort studies, median follow-up 17.5 years, from 1985-2016, mean age, 51.6 years at baseline, 44.9% male, 31.1% black).
INTERVENTION: None. Data compilation from observational prospective cohort studies.
CONTROL: None. Compared association of dietary cholesterol or egg intake and CVD and all-cause mortality.
OUTCOME: incident CVD (composite of fatal and nonfatal coronary heart disease, stroke, heart failure, and other CVD deaths) and all-cause mortality.

METHODS (BRIEF DESCRIPTION): Data pooled from six prospective cohort studies focused specifically on individuals' dietary intake. Data adjusted utilizing sequential statistical analysis for age, sex, race, education, smoking status, alcohol intake, use of hormone therapy, BMI, diabetes status, systolic blood pressure, use of anti-hypertensive medication, high-density lipoprotein (HDL) cholesterol, non-HDL cholesterol, and use of lipid-lowering medications. Individuals' self-reported data from each cohort homogenized to calculate cohort-stratified cause-specific hazard models.

INTERVENTION (# IN THE GROUP): 29,615
COMPARISON (# IN THE GROUP): N/A

FOLLOW UP PERIOD: One and two weeks (phone), four weeks (clinician), six weeks (questionnaire).

RESULTS:

- After median follow-up of 17.5 years, there were 5,400 incident CVD events (2,088 fatal and nonfatal CHD events, 1,302 fatal and nonfatal stroke events, 1,897 fatal and nonfatal heart failure events, and 113 other CVD deaths) and 6,132 all-cause deaths.
- For dietary cholesterol, each additional 300 mg intake above the current recommended guideline of a maximum of 300 mg/day resulted in an increased risk of incident CVD (adjusted hazard ratio (HR) 1.2; 95% CI, 1.11.2) and all-cause mortality (adjusted HR 1.2; 95% CI, 1.1-1.3).
- For egg consumption, each additional half egg consumed beyond the recommend half egg/day resulted in an increased risk of incident CVD (adjusted HR 1.1; 95% CI, 1.0-1.1) and all-cause mortality (adjusted HR 1.1; 95% CI, 1.0-1.1).
- The associations between egg consumption and incident CVD and all-cause mortality were no longer significant after adjusting for dietary cholesterol consumption (All 95% CI's include 1.0).

LIMITATIONS:

- Each cohort used different dietary assessment tools.
- US population only limits generalizability.
- Self-report data at risk of recall bias and only single measurement of dietary cholesterol/egg intake.
- Significant risk of residual confounding and ascertainment bias.
- Observational study cannot establish causality.

Jared Lambert, MD
University of Wyoming Family Medicine Residency Program
Casper, Wyoming

A Labor of Love, featuring OMT

Effect of Osteopathic Obstetrical Management on the Duration of Labor in the Inpatient Setting: A Prospective Study and Literature Review

Martingano D, Ho S, Rogoff S, Chang G, Aglialoro GC. Effect of Osteopathic Obstetrical Management on the Duration of Labor in the Inpatient Setting: A Prospective Study and Literature Review. *J Am Osteopath Assoc* 2019;119(6):371–378. doi: 10.7556/jaoa.2019.066.

KEY TAKEAWAY: In this prospective observational pilot study, patients who received intrapartum OMT experienced a shorter duration of labor (5.2hrs) than those who did not receive intrapartum OMT.

STUDY DESIGN: Prospective observational pilot study (N=100)

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Pregnancy can cause somatic dysfunction as well as increased pain and discomfort during labor. Additionally, vascular congestion caused by increased uterine size results in decreased vascular circulation, lymph flow, and constipation. Osteopathic manipulative treatment (OMT) may help resolve these issues, but prior studies have been conflicting.

PATIENTS: Pregnant women >34 weeks gestation, without preeclampsia, hypertension, or a scheduled cesarean delivery; mean age 28 years, mean gestational age 39 weeks; 48% nulliparous. All women had epidurals and used oxytocin at some point during labor.

INTERVENTION: Standardized OMT protocol once daily starting upon admission plus standardized obstetric care.

CONTROL: No OMT. Standardized obstetric care only.

OUTCOME:

- Primary outcome: total labor time
- Secondary outcomes: meconium-stained amniotic fluid, need for cesarean delivery due to failure to progress or lack of descent.

METHODS (BRIEF DESCRIPTION): Single site, pilot prospective observational study in New York City. Upon admission for labor, patients received standardized, 20 minute, OMT protocol plus standard care or standard care only. OMT protocol administered by same three osteopathic physicians. Patients excluded for contraindications to OMT such as acute abdomen, severe hypertension, or if scheduled for cesarean delivery. All obstetrical decisions made by single senior osteopathic obstetrician. Osteopaths managed the OMT patients, and allopaths managed the non-OMT patients. All patients received epidural anesthesia and intravenous oxytocin for labor augmentation.

INTERVENTION (# IN THE GROUP): 50
COMPARISON (# IN THE GROUP): 50

FOLLOW UP PERIOD: Through post-partum day 1 (no losses to follow-up).

RESULTS:

- The patients receiving the standardized OMT protocol experienced a shorter total labor duration compared to the control group 11.3 hrs (SD 6.6) (range 1.11-27 hrs) vs 16.5 hrs (SD 4.3) (range 1.0-58.8 hrs), respectively; *P*=.03).
- There were no significant differences in any of the secondary outcomes including total labor times between primiparous vs multiparous patients, meconium-stained amniotic fluid, and cesarean delivery (all *P*>.05).
- Adverse events from OMT not reported.

LIMITATIONS:

- Study underpowered for some outcomes.
- Single center study in urban center limits generalizability.
- Results likely limited to those with epidural anesthesia and augmentation with oxytocin.

Anne Wilson, DO
University of Wyoming
Casper, WY

OMT: effective therapy for low back pain

Recovery From Chronic Low Back Pain After Osteopathic Manipulative Treatment: A Randomized Controlled Trial

Licciardone JC, Gatchel RJ, Aryal S. Recovery From Chronic Low Back Pain After Osteopathic Manipulative Treatment: A Randomized Controlled Trial. *J Am Osteopath Assoc*. 2016; 116(3):144–155.

KEY TAKEAWAY: In patients with chronic low back pain, a trial of osteopathic manipulative treatment (OMT) before other more costly or invasive procedures may help reduce pain and hasten recovery.

STUDY DESIGN: Randomized double-blind, sham-controlled trial (n=455, 345 included in this analysis).

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Low back pain is one of the most common complaints. It is estimated that up to 84% of adults have low back pain at some point in their lives. There is little known about the recovery after OMT in patients with chronic low back pain.

PATIENTS: Adults aged 21-69 years with chronic low back pain of a least 3 months; median age 42, 65% women.

INTERVENTION: OMT.

CONTROL: Sham OMT.

OUTCOME:

- Primary outcome: recovery from OMT using a composite of the visual analog scale (VAS) and the Roland-Morris Disability Questionnaire (RMDQ) measured at 12 weeks.
- Secondary outcomes: multivariate and sensitivity analyses. Harms associated with OMT/sham OMT.

METHODS (BRIEF DESCRIPTION): 2x 2 factorial design. Patients and research staff blinded to assignment. OMT group received OMT at weeks 0, 1, 2, 3, 4, 6, and 8 with recovery assessed at week 12. Sham OMT group treated at the same intervals, but no actual OMT performed. Composite recovery outcome assessed with a 100-mm visual analog scale (VAS) for pain intensity and the Roland-Morris Disability Questionnaire (RMDQ). Recovery quantified as a VAS score of 10 mm or less and an RMDQ score of 2 or less at week 12. All analyses based on intention-to-treat.

INTERVENTION (# IN THE GROUP): 230
COMPARISON (# IN THE GROUP): 225

FOLLOW UP PERIOD: 12 weeks (8% lost to follow-up)

RESULTS:

- Median reduction on the VAS at 12 weeks was significantly greater in the OMT group vs sham OMT group (20mm vs 12mm, respectively; *P*=.002). There was no significant difference between groups on the RMDQ at 12 weeks (2 vs 2, respectively; *P*=.66).
- 34 patients in the OMT group (19%) met the dual recovery criteria vs 14 in the sham OMT group (8%)(relative risk (RR) 2.3; 95% CI, 1.3–4.2; NNT=9).
- After adjustment for confounding, the OMT group demonstrated greater odds for recovery compared to sham OMT group (odds ratio (OR) 2.9; 95% CI, 1.4–5.9).
- The 50-69-year-old patient subgroup demonstrated the most recovery with OMT (RR 7.5; 95% CI, 1.0–56.4; NNT=7)
- Patients without depression were more likely to recover with OMT compared to those with depression (RR 3.2; 95% CI, 1.6–6.5; NNT=6.5).

LIMITATIONS:

- Primary outcome analysis post-hoc.
- Study excluded 110 patients which could impact results.
- No recovery data beyond 12 weeks.
- Single site study; protocol performed by residents, fellows, and attendings.

Renae Marie Hepfner, DO
University of Wyoming
Casper, WY

OMT for Headaches

Osteopathy for Primary Headache Patients: A Systematic Review

Cerritelli F, Lacorte E, Ruffini N, Vanacore N. Osteopathy for primary headache patients: a systematic review. *Journal of Pain Research*. 2017; 10:601–611.

KEY TAKEAWAY: In adults with primary headaches, osteopathic manipulative therapy (OMT) reduces headache intensity and frequency, but the quality of evidence is low.

STUDY DESIGN: Systematic review of 5 RCTs (N=235); meta-analysis not performed.

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Headaches are common complaints and result in significant economic burden due to lost working days as well as costs of medication and healthcare visits. Current headache treatments are frequently inadequate. OMT is a nonpharmacological and noninvasive procedure that may decrease this burden. The impact of OMT on headaches is unclear.
PATIENTS: Adults (ages 18–65 years) with clinical diagnosis of headache, but excluding those with neurodegenerative, cardiovascular, respiratory, genetic, rheumatologic or psychiatric conditions.
INTERVENTION: OMT performed by an osteopath, modality and dosage were not considered.
CONTROL: Sham therapy, standard care, or no treatment.
OUTCOME: Primary outcome: mean difference (MD) in number of days with headache per month after at least 4 weeks of treatment. Secondary outcomes: safety, headache intensity, frequency and dose of medication use, any patient reported outcome measure, economic impact or cost reduction.

METHODS (BRIEF DESCRIPTION): Systematic literature review for RCTs by two authors independently through April 2016 including conference proceedings, and clinical trial registries. Excluded: descriptive studies, only compared different OMT modalities, or reported only physiological or laboratory results. No study was excluded from the review based on participant ages, gender or ethnicity. Quality assessed with the Jadad score and the Cochrane RoB tool. Heterogeneity assessed using the *I*2 test.

INTERVENTION (# IN THE GROUP): 101
COMPARISON (# IN THE GROUP): 134

FOLLOW UP PERIOD: Follow-up in the trials ranged from 9-20 months.

RESULTS:

- 4 out of 5 trials (n=213) reported outcomes of decreased headache frequency or days with migraines between treatment and control groups. One trial (n=22) did not report frequency as an outcome.
- 4 out of 5 trials (n=209) reported decreased headache intensity between OMT and control groups. One trial (n=26) did not report intensity as an outcome.
- Two trials (n=145) reported drug consumption as a study outcome and both reported a decrease in medication use between OMT and control groups.

Two trials (n=145) reported adverse events of which there were none. No comparison data provided; all $P<.05$.

LIMITATIONS:

- No differentiation between types of headaches.
- No differentiation between OMT modalities, dosing or timing.
- Overall quality of evidence low and high risk of bias.
- No meta-analysis due to high study heterogeneity.
- Published article did not include MD's or 95% CI's.

Zachary Pendleton, DO
University of Wyoming
Casper, WY

Renal Protection Effects of SGLT2 Inhibitors in Patients with Type 2 Diabetes

SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis
Neuen BL, Young T, Heerspink HJL, Neal B, Perkovic V, Billot L, Mahaffey KW, Charytan DM, Wheeler DC, Arnott C, Bompoint S, Levin A, Jardine MJ. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2019 Nov;7(11):845–854.

KEY TAKEAWAY: In type 2 diabetes, sodium-glucose co-transporter-2 (SGLT2) inhibitors reduce the risks of dialysis, transplantation, death due to kidney disease, and other kidney outcomes. The renoprotective effects are consistent at different baseline eGFR levels, various baseline urine albumin-to-creatinine ratios (UACR), and with or without renin-angiotensin system (RAS) blockade.

STUDY DESIGN: Systematic review and meta-analysis (4 studies, N=38723).

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: In patients with type 2 diabetes, the effect of SGLT2 inhibitors against kidney failure, dialysis, transplantation, or death are uncertain. Their impact on outcomes depending on eGRF level, degree of albuminuria, or RAS blockade are unknown.

PATIENTS: Patients with type 2 diabetes mellitus: mean age 63 years, 35% female.

INTERVENTION: SGLT2 inhibitor:

- Empagliflozin 10 mg and 25 mg daily.
- Canagliflozin 100 mg and 300 mg daily.
- Dapagliflozin 10 mg daily.

CONTROL: Placebo

OUTCOME: Primary outcomes: Composite of dialysis, kidney transplantation, or death due to kidney disease
Secondary outcomes: Composite kidney outcome by different baseline eGFR, levels of albuminuria, and RAS blockade use.

METHODS (BRIEF DESCRIPTION): Authors searched MEDLINE and other databases from inception to June 2019, English language publications only. RCTs involving cardiovascular or renal outcome trials of SGLT2 inhibitors versus placebo in patients with type 2 diabetes were included; trials including participants with type 1 diabetes or age<18 were excluded. Authors used the PRISMA guide for study conduct. Bias assessed using the Cochrane risk-of-bias tool. Random effects model used to generate relative risk with 95% CI's for primary outcomes and random-effects meta-regression for secondary outcomes. Heterogeneity assessed using the I2 statistic. Multiple sensitivity analyses performed on subgroup/secondary outcomes.

INTERVENTION (# IN THE GROUP): 21,266
COMPARISON (# IN THE GROUP): 17,457

FOLLOW UP PERIOD: 2.4–4.2 years

RESULTS:

Primary outcomes:

- In patients with type 2 diabetes, SGLT2 inhibitors compared to placebo significantly reduced:
  - Composite outcome of dialysis, transplantation, or death due to kidney disease (4 studies, n=38723; Relative Risk (RR) 0.67; 95% CI, 0.52–0.86).
  - Progression of end-stage kidney disease (4 studies, n=38723; RR 0.65; 95% CI, 0.53–0.81).
  - Progression of acute kidney injury (4 studies, n=38684; RR 0.75; 95% CI, 0.66–0.85).

Secondary outcomes:

- SGLT2 inhibitors demonstrated renoprotective benefits in all subgroups of eGFR and UACR, including eGFR lower than the approved level for SGLT2 inhibitors of 30 to < 45 mL/min per 1.73 m^2 (all $P<0.05$).
- SGLT2 inhibitors demonstrated additional significant benefit when taken together with RAS blockade (4 studies, n=37091; RR 0.58; 95% CI, 0.50–0.66) compared to no RAS blockade (3 studies, n=6572; RR 0.71; 95% CI, 0.49–1.02). No clinically significant difference in proportion of patients who had primary care versus secondary care consultation during 6 months of follow-up.

LIMITATIONS:

- All trials, aside from one were cardiovascular outcome trials not specifically powered for renal outcomes.
- Heterogeneity in baseline characteristics and inclusion criteria may affect reliability of results.

Quyen A. Nguyen, PharmD
Providence St. Peter Family Medicine
Olympia, WA

CV4 Technique for Treatment of Tension-Type Headaches

Compression of the Fourth Ventricle Using a Craniosacral Osteopathic Technique: A Systematic Review of the Clinical Evidence

Żurowska A, Malak R, Kołcz-Trzęsicka A, Samborski W, Paprocka-Borowicz M. Compression of the Fourth Ventricle Using a Craniosacral Osteopathic Technique: A Systematic Review of the Clinical Evidence. *Evidence-Based Complementary and Alternative Medicine*. 2017;2017:1–8.

KEY TAKEAWAY: Compression of the fourth ventricle (CV4) technique may be beneficial in individuals with tension-type headaches and chronic low back pain, but more research is needed.

STUDY DESIGN: Systematic Review of RCTs and Observational Studies (7 studies (5 RCTs, 2 observational, N=247)

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Osteopathic manipulative treatment (OMT) is a nonpharmacological treatment used by osteopathic physicians to treat musculoskeletal complaints. This systematic review analyzes an OMT technique known as CV4 to evaluate its clinical effectiveness and the evidence for its use.
PATIENTS: Patients receiving the CV4 technique for any reasons and evaluating its physiological effects.
INTERVENTION: CV4 only with no other OMT.
CONTROL: Patients not receiving the CV4 technique. Not all studies contained a control group.
OUTCOME: Any physiological parameter or clinical benefit including pain.

METHODS (BRIEF DESCRIPTION): Systematic literature review of multiple databases to August 2017 for human RCTs using CV4 technique only for any indication and evaluating physiological or any clinical outcome. English studies only. Quality assessed using Downs and Black checklist. Each article assessed by three reviewers independently. Of the 330 potential articles, 7 met inclusion for qualitative synthesis, 6 for meta-analysis.

INTERVENTION (# IN THE GROUP): Unable to determine from data provided.

COMPARISON (# IN THE GROUP): Unable to determine from data provided.

FOLLOW UP PERIOD: None (outcomes assessed immediately after CV4 performed).

RESULTS:

- No outcome data provided by authors for any of the included studies.
- One study (n=20, no control) demonstrated more rapid sleep onset with CV4.
- One study (n=60) demonstrated significant improvement of pain on a visual analog scale associated with tension-type headaches treated with CV4 compared to controls.
- In patients with chronic low back pain (n=81, no control), CV4 demonstrated improved modulates peak alpha frequency on EEG and promoted physical relaxation.
- In healthy adults (n=40), CV4 significantly decreased systolic and diastolic blood pressure, but not heart rate or catecholamine levels compared to controls.
- Adverse events from OMT not reported.

LIMITATIONS:

- Populations of most included studies consisted of healthy, asymptomatic adults.
- Small sample sizes and some studies lacked a control group.
- Meta-analysis not performed or data not provided.
- Minimal data provided by authors on included studies.

Trevor Irvine, DO
University of Wyoming
Casper, WY