GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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SPOTLIGHT: Are PCSK9 Modulators the Next Step in ASCVD Risk Mitigation?

Are PCSK9 Modulators the Next Step in ASCVD Risk Mitigation?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Meta-Analysis of Clinical Outcomes of PCSK9 Modulators in Patients with Established ASCVD

Talasaz AH, Ho AJ, Bhatty F, et al. Meta-analysis of clinical outcomes of PCSK9 modulators in patients with established ASCVD. *Pharmacotherapy*. 2021;41(12):1009-1023. doi:10.1002/phar.2635

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KEY TAKEAWAY: PCSK9 modulators, both antibody and siRNA, significantly reduce the risk of the most prevalent secondary cardiovascular (CV) outcomes, including myocardial infarction (MI), unstable angina requiring revascularization (UARR) and low-density lipoprotein (LDL), in patients with atherosclerotic cardiovascular disease (ASCVD). However, PCSK9 modulators have not been shown to decrease all-cause mortality, stroke, or CV death.

STUDY DESIGN: Meta-analysis of 8 randomized controlled trials (N=28,532)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Statins have made a significant and measurable reduction in primary and secondary ASCVD risk. However, for those who demonstrate intolerance or inadequate response to statins, PCSK9 modulators may offer an alternative for dyslipidemia management and ASCVD risk.

PATIENTS: Patients with established ASCVD

INTERVENTION: PCSK9 modulator

CONTROL: Placebo

PRIMARY OUTCOME: Risk of secondary CV events

Secondary Outcome: Safety outcomes

METHODS (BRIEF DESCRIPTION):

- Participants' mean age ranged from 50 to 75 years old, with 71% male in the U.S.
- Intervention was either alirocumab 75–150 mg every two weeks, evolocumab 140 mg every two weeks, or 420 mg every month, or inclisiran 284 mg on day one, day 90, then every six months.
- Both groups received high-intensity statin with or without ezetimibe.
- The risk of secondary CV outcomes was measured using reduction in all-cause mortality, CV death, stroke, MI, LDL, and UARR.
- Safety outcomes assessed for severe adverse events including new-onset type 2 diabetes mellitus (T2DM), neurocognitive disorders, myalgias, and injection site reactions.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: 1–2.8 years

RESULTS:

Primary Outcome –

- Compared to control, PCSK9 modulators significantly reduced:
  - MI (8 studies, N=54,002; odds ratio [OR] 0.74; 95% CI, 0.56–0.99)
  - UARR (8 studies, N=50,828; relative risk 0.84; 95% CI, 0.74–0.95)
  - LDL-C (7 studies, mean difference –51%; 95% CI, –61% to –41%)
- There were no significant differences in all-cause mortality, CV death, and stroke between the two groups.

Secondary Outcome –

- There were no significant differences in serious adverse events, including T2DM, neurocognitive disorders, and myalgias.
- Injection site reactions were significantly increased in the intervention group than in the control group (8 studies, N=53,933; OR 2.0; 95% CI, 1.4–2.9).

LIMITATIONS:

- Short durations of follow-up
- Trials included with and without known heterozygous familial hyperlipidemia, potentially resulting in significant heterogeneity.

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Do Exercise and Protein Improve Frailty in the Elderly?

Building Resilience and Reversing Frailty: A Randomised Controlled Trial of a Primary Care Intervention for Older Adults

Travers J, Romero-Ortuno R, Langan J, et al. Building resilience and reversing frailty: a randomised controlled trial of a primary care intervention for older adults. *Age Ageing.* 2023;52(2):afad012. doi:10.1093/ageing/afad012

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KEY TAKEAWAY: Increased physical activity and protein intake improves frailty status in older adults.

STUDY DESIGN: Multi-center, randomized, controlled, parallel-arm trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Frailty is associated with an increased mortality rate in older people. Primary care physicians can aid in the improvement of frailty in older individuals. There are effective interventions primary care physicians can provide older adults to improve frailty.

PATIENTS: Older adults with frailty

INTERVENTION: Exercise and protein consumption handouts

CONTROL: Usual care

PRIMARY OUTCOME: Frailty

Secondary Outcome: Muscle mass, bone mass, body fat, biological age, ease of intervention, change to overall health

METHODS (BRIEF DESCRIPTION):

- Individuals 65 years old or older presenting with a clinical frailty score of ≤5 were eligible to participate.
  - The clinical frailty scale measures higher levels of disability that require individuals to attain help with activities of daily living.
  - Those in nursing homes, end-of-life care, or with malignancy or CKD were excluded.
  - 17.7% of the intervention group and 16.9% of the control group were frail at baseline.
- Patients in the intervention group were provided a leaflet with a set of exercises to perform at home and a handout on post-workout protein consumption and a balanced diet.
- The control group continued usual care at their general provider.
- Frailty was measured by SHARE-FI prior to study and at three-months.
  - SHARE-FI is a gender-based frailty tool based on exhaustion, loss of appetite, handgrip strength, functional difficulties, and low physical activity.
- Muscle mass, bone mass, body fat, and biological age were recorded by Bioelectric Impedance Analysis (BIA).
- Ease of intervention and general health was self-reported on a five-point Likert scale.

INTERVENTION (# IN THE GROUP): 79

COMPARISON (# IN THE GROUP): 77

FOLLOW-UP PERIOD: Three months

RESULTS:

Primary Outcome –

- The intervention group was less likely to have frailty than the usual care group (OR 0.23; 95% CI, 0.07–0.72; NNT=8).

Secondary Outcome –

- The intervention improved grip strength more than usual care (adjusted difference 1.8 kg; 95% CI, 0.84–2.7).
- Muscle mass, bone mass, body fat, and biological age were not improved by the intervention.
- 66.2% of the intervention group reported the intervention was “easy” or “very easy” to undertake.
- No adverse events were noted.

LIMITATIONS:

- The possibility of selection and participant bias was present in this study. This was avoided by using eligibility criteria for every patient.
- The study did not explicitly state what directions were provided to the control group.

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Sound Advice: Consider Ultrasound-Guided Corticosteroid Injections for Achilles Tendinopathy

Effect of Ultrasonography-Guided Corticosteroid Injection vs Placebo Added to Exercise Therapy for Achilles Tendinopathy: A Randomized Clinical Trial

Johannsen F, Olesen JL, Øhlenschläger TF, et al. Effect of ultrasonography-guided corticosteroid injection vs placebo added to exercise therapy for Achilles tendinopathy: a randomized clinical trial. *JAMA Netw Open*. 2022 Jul 1;5(7):e2219661. doi: 10.1001/jamanetworkopen.2022.19661.

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KEY TAKEAWAY: Ultrasound-guided corticosteroid injection for chronic mid-substance Achilles tendinopathy (AT) in conjunction with exercise therapy significantly improves pain and function compared to placebo in conjunction with exercise therapy.

STUDY DESIGN: Double-blind randomized controlled trial (RCT)

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: AT is a common musculoskeletal complaint in primary care, often with a prolonged exercise-focused treatment plan that may take weeks to months to show improvements. Evidence previously supported exercise monotherapy. Some studies have shown short-term evidence for injectional monotherapy but limit investigation into corticosteroid injectional therapy in conjunction with exercise therapy outcomes.

PATIENTS: Adults with mid-substance AT

INTERVENTION: Ultrasound-guided corticosteroid injection

CONTROL: Ultrasound-guided placebo injection

PRIMARY OUTCOME: Pain and function at six months

Secondary Outcome: Pain and function at other time points, tendon thickness, doppler flow, morning pain, pain with activity

METHODS (BRIEF DESCRIPTION):

- Adults 18 to 65 years old (mean 46.5) with BMI <30 and no prior Achilles surgery or injection were included in the study from a university and a private practice clinic (60% of patients were male).
- Inclusion criteria:
  - Insidious onset of AT that was worsened by weight-bearing activities and was worse in the morning for >3 months.
  - Pain and swelling limited to 2–6 cm proximal to insertion.
  - Tendon thickness >7 mm on ultrasound or 20% larger than the contralateral side
- The treatment group received an injection of 1 mL methylprednisolone acetate (40 mg/mL) and 1 mL of lidocaine (10 mg/mL).
- The control group received 1 mL of lipid emulsion and 1 mL of lidocaine (10 mg/mL).
- Both groups completed exercise therapy three times per week.
- Follow-up occurred at 1, 2, 3, 6, 12, and 24 months. A repeat injection was offered at month 2 and 3 if any one of the following occurred:
  - Morning pain >20 mm on 100 mm visual analog scale (VAS; 0=no pain 100=worst pain)
  - Pain during activity >49 mm on VAS
  - Self-reported satisfaction <3 on a scale –5 to 5 (5=fully healed).
- Pain and function were measured via the Victorian Institute of Sport Assessment Achilles (VISA-A), which evaluated morning stiffness; pain with stretching, walking on flat ground, and with activities; and tolerance of activities (0–100; 0=complete incapacitation 100=no symptoms).
  - No known minimal clinically important difference for mid-substance AT but a change of 6 points was considered the minimal clinically important difference for insertional AT.
- Doppler flow was calculated with nonparametric Mann-Whitney *U* tests.

INTERVENTION (# IN THE GROUP): 48

COMPARISON (# IN THE GROUP): 52

FOLLOW-UP PERIOD: Two years

RESULTS:

Primary Outcome –

- The treatment group had a greater improvement in pain and function at six months compared to the placebo group (18 points greater improvement; 95% CI, 8.4–27).

Secondary Outcome –

- The treatment group had a greater improvement in pain and function at 1, 2, 3, and 24 months, but not at 12 months.

- The treatment group had lower doppler ultrasonography scores at 1, 2, 3, and 6 months, but not 12 or 24 months.
- The treatment group had greater morning pain improvement compared to placebo (16 points greater; 95% CI, 2.6–29).
- There was no difference in pain with activity between the groups.

LIMITATIONS:

- Use of VISA-A scoring method was disputed, due to the nature of self-administration.
- Clinical significance of tendon thickness and doppler scores were limited because their correlation to patient pain and function was not clearly delineated.

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

Which One Takes the Cake: Time-Restricted Eating vs Calorie-Restriction in NAFLD

Effects of Time-Restricted Eating on Nonalcoholic Fatty Liver Disease: The TREATY-FLD Randomized Clinical Trial

Wei X, Lin B, Huang Y, et al. Effects of Time-Restricted Eating on Nonalcoholic Fatty Liver Disease: The TREATY-FLD Randomized Clinical Trial. *JAMA Netw Open*. 2023;6(3):e233513. doi:10.1001/jamanetworkopen.2023.3513

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KEY TAKEAWAY: Time-restricted eating and daily calorie-restricted diets both equally improve NALFD.

STUDY DESIGN: Randomized, parallel-group, observer-blinded clinical trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: NAFLD is highly comorbid with diabetes, cardiovascular disease, and other metabolic disorders. Lifestyle modifications for weight loss have proven to improve these factors. Which diet works better is uncertain.

PATIENTS: Obese patients with NAFLD

INTERVENTION: Time-restricted eating

CONTROL: Calorie-restricted eating

PRIMARY OUTCOME: IHTG measures

Secondary Outcome: Body weight and fat, waist circumference, metabolic risk factors, liver stiffness

METHODS (BRIEF DESCRIPTION):

- 88 patients with obesity aged 18-75 (mean 32 y/o) and ultrasonography diagnosed NAFLD with intrahepatic triglyceride levels >5% were included.
  - Participants involved had a mean BMI of 32, with a range of 28 to 45.
- Participants were recruited from Nanfang Hospital in Guangzhou, China, and were randomly assigned to time-restricted eating or daily caloric restriction for 12 months.
- Participants were asked to weigh foods, keep a dietary log, take daily food pictures on a custom mobile app, and meet with nutritionists to strictly adhere to the program.
- They were instructed to continue with their physical activity routines in the trial.

INTERVENTION (# IN THE GROUP): 45

COMPARISON (# IN THE GROUP): 43

FOLLOW-UP PERIOD: 12 months

RESULTS:

Primary Outcome –

- There was no significant difference in intrahepatic triglyceride level content between the groups.
  - Six months: TRE 8.3% vs DCR 8.1% reductions (*P*>.05)
  - 12 months: TRE 6.9% vs DCR 7.9% reductions (*P*>.05)

Secondary Outcome –

- Secondary outcomes improved similarly between the groups.

LIMITATIONS:

- Intrahepatic triglyceride levels were determined through ultrasound compared to biopsies.
- Physical exercise was not controlled in the study.

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Is That Cup of Tea Affecting Your Risk for Gynecological Cancers?

Association Between Different Types of Tea Consumption and Risk of Gynecologic Cancer: A Meta-Analysis of Cohort Studies

Zheng F, Chen K, Zhong J, et al. Association between Different Types of Tea Consumption and Risk of Gynecologic Cancer: A Meta-Analysis of Cohort Studies. *Nutrients*. 2023;15(2):403. Published 2023 Jan 13. doi:10.3390/nu15020403

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KEY TAKEAWAY: There is no significant association between tea consumption and its effect on incidences and morbidity of gynecological cancers; however, black tea may decrease the risk of ovarian cancer.

STUDY DESIGN: Meta-analysis of 19 cohort studies (N=2,020,980)

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Gynecological cancers are common worldwide with ovarian cancer being the second most common cancer in women. Studies show that our dietary choices may affect the risk of cancer. Prior studies revealed conflicting results regarding the impact of tea consumption on gynecological cancers.

PATIENTS: Women

INTERVENTION: Tea consumption

CONTROL: No tea consumption

PRIMARY OUTCOME: Risk of gynecological cancers

METHODS (BRIEF DESCRIPTION):

- Nineteen prospective cohort studies during 1996 to 2019 were included.
  - Eleven studies associated tea consumption with ovarian cancers.
  - Ten studies reviewed the occurrence of endometrial cancers.
  - Three studies evaluated tea consumption and cervical cancer.
- Study participants were from the USA, Canada, China, Denmark, France, Germany, Greece, Italy, Japan, Netherlands, Norway, Singapore, Spain, Sweden, and the United Kingdom.
- There were 12,155 cases of gynecological cancers associated with tea intake.
  - 3,977 ovarian cancers
  - 6,946 endometrial cancers
  - 1,232 cervical cancers
- Tea consumption ranged between <1 cup/week to ≥ 5 cups/day.
- The types of teas consumed were herbal, non-herbal, black tea, green tea, or any tea.
- Six studies reviewed the correlation of black or green tea with gynecological cancer outcomes.
- Four studies classified herbal or non-herbal compared to nine studies that did not specify tea type with cancer outcome.
- Relative risks (RR) were determined using a fixed-effect or random effect for heterogeneous studies.
- A dose-response analysis was used to assess cups of tea on gynecological cancer outcomes.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: 7.5–26 years

RESULTS:

Primary Outcome –

- Tea consumption showed no significant risk on the majority of gynecological cancers (RR 1.0; 95% CI, 0.96–1.04).
- Black tea consumption showed a statistically significant decrease in the risk of ovarian cancer (pooled RR 0.67; 95% CI, 0.55–0.81).
- The dose-response relationship between the number of cups of tea per day with the risk for gynecological cancers was not significant.
- There was no association between tea consumption and cervical cancer.
- Consumption of green tea did not decrease the risk of endometrial or cervical cancers.

LIMITATIONS:

- Confounding variables such as coffee consumption and family history of cancer may have affected the accuracy of this analysis.
- Limited data studied the effects of green teas on ovarian cancer and any tea effects on vaginal cancer.
- Gynecological cancers were not classified by histology.

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Does Timing of Postpartum IUD Placement Increase the Risk of Certain Complications?

Complications After Interval Postpartum Intrauterine Device Insertion

Ramos-Rivera M, Averbach S, Selvaduray P, Gibson A, Ngo LL. Complications after interval postpartum intrauterine device insertion. *Am J Obstet Gynecol*. 2022;226(1):95.e1-95.e8. doi:10.1016/j.ajog.2021.08.028

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KEY TAKEAWAY: Uterine perforation after postpartum intrauterine device (IUD) insertion is greater when placed at four to eight weeks than at nine to 36 weeks.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: The timing of when to place the IUD in the postpartum period is still unclear. Previous studies have shown that IUD placement at different periods of time in the postpartum period can increase the risk of uterine perforation and IUD expulsion. This study aims to identify if there is a recommended timeline for IUD insertion to minimize complications.

PATIENTS: Postpartum patients

INTERVENTION: IUD placement 4–8 weeks postpartum

CONTROL: IUD placement 9–36 weeks postpartum

PRIMARY OUTCOME: IUD perforation and expulsion

METHODS (BRIEF DESCRIPTION):

- Data was collected from Kaiser Permanente Southern California electronic medical record (EMR) from 2010 to 2016.
- Inclusion Criteria: Women who were >18 years old following delivery of an infant >24 weeks gestation who had an IUD placed between 4- and 36 weeks postpartum, with a one-year follow-up post-IUD insertion.
- Outcomes evaluated through chart review included recording billing codes that pertained to the diagnosis of uterine perforation or IUD expulsion.
- Patient charts identified as having a complication were manually reviewed to confirm the outcome.
- Uterine perforation was defined as laparoscopic or image confirmed or provider suspected after sounding to a greater than expected depth at the time of IUD insertion.
- Uterine expulsion was defined as partial (defined as any part of the IUD noted in the cervix either visually on examination or on imaging) or complete.
- Data collected from the EMR included the number of weeks postpartum at the time of IUD placement, breastfeeding status, parity status, type of delivery (vaginal vs c-section), type of IUD, and provider type (attending, midlevel, or resident), along with demographic data that included age, BMI, race/ethnicity.
- Perforations and expulsions of postpartum IUDs were calculated at either the 4–8-week interval, to best capture the six-week postpartum visit or the 9–36 week interval.

INTERVENTION (# IN THE GROUP): 13,180

COMPARISON (# IN THE GROUP): 11,777

FOLLOW-UP PERIOD: One year

RESULTS:

Primary Outcome –

- Placement between four and eight weeks resulted in significantly more uterine perforations compared to placement between nine and 36 weeks (0.78% vs 0.46%; *P*=.001).
  - After controlling for race/ethnicity, breastfeeding status, IUD type, provider type, parity, most recent delivery type, and BMI, these findings persisted (adjusted odds ratio [aOR] 1.9; 95% CI, 1.3–2.9).
- Timing of IUD placement did not affect IUD expulsion rates (1.02 vs 1.2; *P*=.52).
- Perforation from an IUD plateaued around 22–23 weeks postpartum, based on a Kaplan-Meier survival curve.

LIMITATIONS:

- The study relied on EMR data gathering, which creates the possibility of bias, unmeasured confounding factors, missing data, or inaccurate provider coding or documentation.
- Expulsion rates were lower than expected in this study, which could have been impacted by coding variability, failure of patients to recognize or present for care after a complication, or seeking medical attention outside of the Kaiser Permanente system.

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Is More Always Better? HPV Testing vs Co-Testing

Evaluation of Co-Testing with Cytology and Human Papillomavirus Testing in Cervical Screening

Kleppe SA, Andersson H, Elfsrom KM, Dillner J. Evaluation of co-testing with cytology and human papillomavirus testing in cervical screening. *Prev Med*. 2023;166:107364.

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KEY TAKEAWAY: HPV screening alone is an accurate way to identify CIN2+ and cytology co-testing does not significantly improve the identification of CIN2+.

STUDY DESIGN: Retrospective cohort

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Cervical cancer screening was introduced in Sweden in the 1960s. Before 2015 women received cytology alone every three years between 23–49 and every five years from 50–60. Then in 2015, the National Board of Health and Welfare recommended HPV-based screening and for those women who were 41–42, cytology co-testing was also recommended. This transition and implementation were monitored by the Swedish National Cervical Screening Registry.

PATIENTS: Women in the Swedish National Cervical Screening Registry

INTERVENTION: HPV testing only

CONTROL: Cytology co-testing

PRIMARY OUTCOME: Concordance of HPV and cytology testing for CIN2+

METHODS (BRIEF DESCRIPTION):

- Women who had cytology co-testing within 14 days of their HPV test were identified.
  - Co-testing implementation as automatic, so 99.6% of all identified co-test samples were taken on the same day.
- Results were aggregated and the women were followed for six months to see if biopsies were taken.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): 10,643

FOLLOW-UP PERIOD: Six months

RESULTS:

Primary Outcome –

- Two out of 10,653 women with CIN2+ were HPV(-) and cytology (+).
- 189 with CIN2+ were HPV(+) and cytology (+).
- 6 women with CIN2+ were HPV (+) and cytology (-).

LIMITATIONS:

- 459 in the screening group with positive results in the co-test did not have biopsies taken.
- Limited generalizability due to only women in Sweden included.

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