GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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Optimizing Hormonal Therapy for Insomnia in Menopausal Women

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Different Regimens of Menopausal Hormone Therapy for Improving Sleep Quality: A Systematic Review and Meta-Analysis

Pan Z, Wen S, Qiao X, Yang M, Shen X, Xu L. Different regimens of menopausal hormone therapy for improving sleep quality: a systematic review and meta-analysis. *Menopause*. 2022;29(5):627-635. Published 2022 May 1. doi:10.1097/GME.0000000000001945

KEY TAKEAWAY: Hormone therapy (HT) improves self-reported sleep quality but does not improve sleep time, sleep latency, sleep efficiency, or arousal events.

STUDY DESIGN: Meta-analysis and systematic review of 15 randomized controlled trials (N=27,715)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: During menopause, women experience significant hormonal changes, including a decline in estrogen and progesterone levels. Along with vasomotor symptoms, such as hot flashes, insomnia is frequently reported and can greatly affect quality of life. While hormone replacement therapy is a standard treatment for menopausal symptoms, the optimal hormonal formulations for improving sleep quality remain unclear. This review analyzed the current literature to understand the association between HT and sleep disturbance.

PATIENTS: Menopausal and postmenopausal adult women with insomnia

INTERVENTION: Oral and transdermal estrogen and progesterone

CONTROL: Placebo treatment

PRIMARY OUTCOME: Sleep quality and sleep parameters
Secondary Outcome: Sleep quality comparing different formulations of estrogen, sleep quality with estrogen alone compared to estrogen and progesterone, sleep quality with estrogen comparing different formulations of progesterone

METHODS (BRIEF DESCRIPTION):

- Meta-analysis and systematic review of randomized controlled trials comparing hormone therapy (estrogen and/or progesterone) to placebo.
- Women ≥18 years old with menopause were included in the review.
- The included studies used a variety of hormone formulations and preparations.
- Estrogen formulations:
  - Oral conjugated equine estrogen 0.625 mg
  - Oral estrogen valerate 1–2 mg
  - Oral estradiol 2 mg
  - Transdermal estradiol 1 mg
  - Estrogel 2.5 mg
  - Transdermal estrogen 50 μg
  - Oral 17β-estradiol 0.5 mg
  - Transdermal 17β-estradiol 0.045–0.05 mg
- Progesterone formulations:
  - Oral micronized progesterone 10–200 mg
  - Oral medroxyprogesterone acetate 2.5–5 mg
  - Oral dydrogesterone 100 mg
  - Oral dienogest 3 mg
  - Transdermal levonorgestrel 0.015–0.040 mg
  - Oral trimegestone 0.13 mg
- Combined formulations:
  - Oral norethisterone 0.7 mg
  - Oral norethindrone acetate 0.5 mg
  - Oral tibolone 2.5 mg
- The primary outcome was a change in self-reported sleep quality questionnaire scores and objective improvement of sleep parameters using polysomnography to assess changes in sleep time, sleep latency, sleep efficiency, and arousal number.
  - Five trials used polysomnography.
  - 12 trials used a variety of subjective sleep questionnaires.

INTERVENTION (# IN THE GROUP): 14,058

COMPARISON (# IN THE GROUP): 13,657

FOLLOW-UP PERIOD: Four weeks to 48 months

RESULTS:

Primary Outcome –

- HT did not improve sleep time measured by polysomnography compared to placebo (3 trials, N=142; standardized mean difference [SMD] –0.14; 95% CI, –0.48 to 0.20; I^2=10%).
- HT did not improve sleep latency measured by polysomnography compared to placebo (3 trials, N=126; SMD –0.22; 95% CI, –0.57 to 0.13; I^2=0%).

- HT did not improve sleep efficiency measured by polysomnography compared to placebo (5 trials, N=187; SMD –0.09; 95% CI, –0.39 to 0.2; I^2=0%).
- HT did not improve sleep arousal measured by polysomnography compared to placebo (3 trials, N=126; SMD –0.07; 95% CI, –0.42 to 0.28; I^2=0%).
- HT improved self-reported sleep quality compared to placebo (12 trials, N=27,608; SMD –0.13; 95% CI, –0.18 to –0.08; I^2=41%).

Secondary Outcome –

- 17β-estradiol improved self-reported sleep quality compared to placebo (3 trials, N=577; SMD –0.24; 95% CI, –0.51 to –0.17; I^2=0%).
- Conjugated equine estrogen improved self-reported sleep quality compared to placebo (4 trials, N=26,653; SMD –0.10; 95% CI, –0.12 to –0.07; I^2=0%).
- Estrogen with progesterone improved self-reported sleep quality compared to placebo (6 trials, N=17,804; SMD –0.10; 95% CI, –0.13 to –0.07; I^2=0%).
- Estrogen with micronized progesterone improved self-reported sleep quality compared to placebo (2 trials, N=670; SMD –0.22; 95% CI, –0.37 to –0.06; I^2=0%).
- Estrogen and medroxyprogesterone acetate improved self-reported sleep quality compared to placebo (2 trials, N=17,079; SMD –0.10; 95% CI, –0.13 to –0.07; I^2=0%).
- Estrogen therapy alone, estradiol valerate, and estrogen with dienogest or norethisterone did not improve self-reported sleep quality compared to placebo.

LIMITATIONS:

- Moderate heterogeneity was present between the included studies.
- Significant variability of utilized sleep questionnaires between included studies.
- Included studies carry the risk of attrition and publication bias with some studies being funded by the pharmaceutical industry.
- No dose-response data for the use of 17β-estradiol or micronized progesterone was calculated.
- The included studies cannot differentiate between improved sleep quality due to indirect reduction of vasomotor symptoms and therefore improved insomnia.
- Unknown optimal duration of therapy for improvement of insomnia.

Levi Harris, DO, MPH
University of Missouri Bothwell Rural FMRP
Sedalia, MO

What's the Buzz? TENS Reduces Pain!

Efficacy and Safety of Transcutaneous Electrical Nerve Stimulation (TENS) for Acute and Chronic Pain in Adults: A Systematic Review and Meta-Analysis of 381 Studies (The Meta-TENS Study)

Johnson MI, Paley CA, Jones G, Mulvey MR, Wittkopf PG. Efficacy and safety of transcutaneous electrical nerve stimulation (TENS) for acute and chronic pain in adults: a systematic review and meta-analysis of 381 studies (the meta-TENS study). *BMJ Open*. 2022;12(2):e051073. Published 2022 Feb 10. doi:10.1136/bmjopen-2021-051073

KEY TAKEAWAY: Transcutaneous electrical nerve stimulation (TENS) units reduce acute and chronic pain during and immediately after treatment.

STUDY DESIGN: A systematic review and meta-analysis of 381 randomized controlled studies (RCTs) (N=24,532)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to low-certainty studies)

BRIEF BACKGROUND INFORMATION: Since their invention, there has been uncertainty regarding the efficacy of TENS units. Because of this, many providers have been historically hesitant to incorporate their use into their clinical practice or formal recommendations for patients. This meta-analysis is the first to pool data from pain irrespective of diagnosis, in a wide variety of regimens.

PATIENTS: Adults with acute or chronic pain

INTERVENTION: TEENS

CONTROL: Placebo, no treatment, standard care, high- vs low-frequency TENS

PRIMARY OUTCOME: Pain

METHODS (BRIEF DESCRIPTION):

- Adults ≥18 years old with any type of pain were included in the review.
- Studies used strong, non-painful TENS applied to, or close to, the site for pain relief.
- Any frequency or length of treatment, and self- or therapist administered.
- Authors compared TENs to placebo, no treatment, or standard care (which included exercise, physical therapy, or pharmacologic treatments).
- They also compared high vs low-frequency TENS.
- Patients reported pain prior to and during, or immediately after, treatment using standardized pain scores.
- They used standardized mean difference to report the effect size of pain reduction, with <0.40 being small, 0.40–0.69 being moderate, and ≥0.70 being large.

INTERVENTION (# IN THE GROUP):

- TENs vs placebo: 2,426 participants in 91 RCTs
- No treatment: 298 participants in 10 RCTs
- Standard care: 1,594 participants in 127 RCTs
- High-frequency TENS: 235 participants in 13 RCTs

COMPARISON (# IN THE GROUP):

- TENs vs placebo: 2,415 participants in 202 RCTs
- No treatment: 304 participants in 10 RCTs
- Standard care: 1,561 participants in 127 RCTs
- Low-frequency TENS: 233 participants in 13 RCTs

FOLLOW-UP PERIOD: Variable

RESULTS:

Primary Outcome –

- TENS reduced pain more than the following comparators:
  - Placebo (91 studies, n=4,841; standardized mean difference [SMD] –0.96; 95% CI, –1.1 to –0.78; I^2=88%)
  - No treatment (10 studiess, n=602; SMD –0.82; 95% CI, –1.2 to –0.46; I^2=76%)
  - Standard care (61 studies, n=3,155; SMD –0.72; 95% CI, –0.95 to –0.50; I^2=88%)
- High-frequency TENs did not reduce pain compared to low-frequency TENS (13 studies, n=468; SMD –0.19; 95% CI, –0.43 to 0.06; I^2=39%).
- TENS improved the following types of pain more than placebo:
  - Acute (57 studies, n=3,348; SMD –1.0; 95% CI, –1.2 to –0.79; I^2=89%)
  - Chronic (31 studies, n=1,417; SMD –0.87; 95% CI, –1.2 to –0.55; I^2=86%)
  - Post-operative (36 studies, n=1,788; SMD –0.92; 95% CI, –1.2 to –0.69; I^2=80%)
  - Procedural (10 studies, n=682; SMD –0.78; 95% CI, –1.4 to –0.31; I^2=88%)
  - Back (9 studies, n=364; SMD –0.69; 95% CI, –1.4 to –0.02; I^2=89%)

    - Labor (4 studies, n=397; SMD –1.3; 95% CI, –2.5 to –0.01; I^2=95%)
    - Fibromyalgia (3 studies, n=307; SMD –1.1; 95% CI, –2.1 to –0.07; I^2=91%)
- TENS did not improve headache-migraine pain compared to placebo (3 studies, n=230; SMD –1.2; 95% CI, –2.9 to 0.57; I^2=97%).

LIMITATIONS:

- Most trials included in the analysis were small, with <50 participants.
- The risk of bias was unclear in the majority of trials.
- There was significant heterogeneity observed across the trials.
- The funnel plot indicated the presence of publication bias.
- Adverse events were poorly reported in the included trials.

Justin Seymour, MD
Spokane FMRP
Spokane, WA

High Costs of Low Pressures: Should We Rethink Antihypertensive Therapy in the Elderly?

Antihypertensive Medication and Fracture Risk in Older Veterans Health Administration Nursing Home Residents

Dave CV, Li Y, Steinman MA, et al. Antihypertensive Medication and Fracture Risk in Older Veterans Health Administration Nursing Home Residents. *JAMA Intern Med*. 2024;184(6):661-669. doi:10.1001/jamainternmed.2024.0507

KEY TAKEAWAY: Antihypertensive medication initiation is associated with an increased risk of fracture in nursing home residents.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Falls and associated fractures cause significant morbidity and mortality in older adults, with long-term care residents being particularly vulnerable. Orthostatic hypotension is a common complication of antihypertensive medications, however, there is not much known about the correlation between blood pressure medication initiation and the risk of falls or fractures. Considering the potential risks of starting or intensifying anti-hypertensive medication is of high importance in primary care.

PATIENTS: Veterans Affairs (VA) nursing home residents >65 years old with hypertension (HTN)

INTERVENTION: Episode of initiating antihypertensive medication

CONTROL: Continuation of current regimen

PRIMARY OUTCOME: Nontraumatic fracture within 30 days

Secondary Outcome: Falls, syncope, traumatic brain injury (TBI), or other fractures requiring emergency department (ED) visit or hospitalization within 30 days

METHODS (BRIEF DESCRIPTION):

- VA nursing home residents (98% male) with HTN >65 years old, without end-stage renal disease, who were receiving a blood pressure lowering regimen for ≥4 weeks before the index date were included in the study.
- The unit of analysis was the treatment initiation episode, starting with an index date and lasting up to 30 days.
    - Patients who had an antihypertensive medication added on the index date were in the intervention group.
    - Treatment initiation episodes ended after discontinuing the antihypertensive medication, after the occurrence of an outcome event, or after the 30-day follow-up period or end of the study.
- Control episodes were created by evaluating each week of the nursing home stay as a potential control week using the same inclusion criteria as the intervention group.
    - Control episodes were patients who did not have an antihypertensive medication added as of the index date.
    - Control episodes ended after initiation of a new antihypertensive medication, occurrence of an outcome, 30-day follow-up period, or end of the study.
    - Due to the high number of controls, 1:4 propensity score matching was used.
- Individual patients could contribute multiple episodes to the intervention or the control groups.
- Nontraumatic fracture of the humerus, hip, pelvis, radius, or ulna within 30 days after the index date was assessed as the primary outcome.
- Falls, syncope, TBI, or other fractures requiring ED visits or hospitalizations within 30 days were assessed as the secondary outcomes.
- Incidence rates and adjusted hazard ratios were calculated using Cox proportional hazards regression models.
    - Adjustments were made for multiple factors, including demographics, indication for hypertensive medication use, cardiovascular conditions, cardiovascular medication, cognitive and physical function, and factors associated with falls and fractures.

INTERVENTION (# IN THE GROUP): 12,492

COMPARISON (# IN THE GROUP): 51,768

FOLLOW-UP PERIOD: 30 days

RESULTS:

Primary Outcome –

- The incidence of fracture was higher among the treatment initiation group than the control group (adjusted hazard ratio [aHR] 2.4; 95% CI, 1.4–4.1).

Secondary Outcome –

- Compared to the control group, initiation of an antihypertensive medication was associated with an increased risk of:
  - Falls requiring ED visit or hospitalization (HR 1.8; 95% CI, 1.5–2.1)
  - Syncope (HR 1.7; 95% CI, 1.3–2.2)
  - TBI or other fractures (HR 2.3; 95% CI, 1.4–3.7)

LIMITATIONS:

- The largest limitation was the observational study design, which cannot prove the causality of the association between anti-hypertensive initiation and the risk of fractures. There is likely some residual confounding.
- The data are from a mostly White male cohort, which limits generalizability.
- The study did not count medication dosage escalation in the intervention group, only newly added hypertensive medication.
- The study did not address the possible harms of not adding a blood pressure medication (suboptimal blood pressure control leading to adverse cardiovascular outcomes).

Sam Forrest, MD
Kaiser Permanente Washington FMRP
Seattle, WA

Noninvasive Nerve Stimulation Modules for the Relief of Temporomandibular Pain

Efficacy of Two Types of Noninvasive Nerve Stimulation in the Management of Myofascial Pain Caused by Temporomandibular Joint (TMJ) Disorders

Jha AK, Gupta S, Sinha A, et al. Efficacy of Two Types of Noninvasive Nerve Stimulation in the Management of Myofascial Pain Caused by Temporomandibular Joint (TMJ) Disorders. *Cureus*. 2023;15(7):e42584. Published 2023 Jul 27. doi:10.7759/cureus.42584

KEY TAKEAWAY: Microcurrent nerve stimulation (MENS) and transcutaneous electrical nerve stimulation (TENS) are effective at providing pain control and improving mouth opening after five days in adults with temporomandibular disorders (TMDs).

STUDY DESIGN: Randomized, single-blind, controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size and no control group)

BRIEF BACKGROUND INFORMATION: TMD affects 80% of the population. MENS therapy is a more recent therapeutic intervention than TENS. The study aimed to compare MENS to TENS therapy for the relief of masticatory muscle discomfort.

PATIENTS: Adults ≥18 years old

INTERVENTION: TENS and MENS

CONTROL: Baseline

PRIMARY OUTCOME: Pain and mouth-opening

METHODS (BRIEF DESCRIPTION):

- Adults from the Department of Oral Medicine and Radiology of the Institute with an official diagnosis of masticatory muscle pain and pain complaints for <3 weeks.
- Subjects were excluded if they were unwilling to participate, had an acute infection or precancerous lesions in the area, had implanted cardiac pacemakers or defibrillators, or were undergoing physiotherapy or using anti-inflammatory medications or analgesics.
- Patients were blinded and randomized to one of the following treatments:
  - TENS with a pulse width of 0.5 msec at 0–60 mA and 50 Hz frequency
  - MENS with 1000 A and 0.5 Hz frequency
- Pain was measured using a visual analog scale (VAS). Scores range from 0–5 or 5–10, with higher scores indicating worse pain.
- The mean differences reported for pain were reported as the number of points the pain improved by.

INTERVENTION (# IN THE GROUP):

- TENS: 60
- MENS: 60

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW-UP PERIOD: One month

RESULTS:

Primary Outcome –

- TENS did not improve mouth opening at day one compared to baseline (mean difference [MD] –0.60 mm; *P*=.09).
- TENS improved mouth opening at day five compared to baseline (MD –5.0 mm; *P*=.00).
- TENS improved mouth opening at one month compared to baseline (MD –5.3 mm; *P*=.00).
- MENS did not improve mouth opening at day one compared to baseline (MD –0.13 mm; *P*=1.0).
- MENS improved mouth opening at day five compared to baseline (MD –6.8 mm; *P*=.00).
- MENS improved mouth opening at one month compared to baseline (MD –7.2 mm; *P*=.00).
- TENS did not improve pain at day one compared to baseline (MD 0.2 mm; *P*=.25).
- TENS improved pain at day five compared to baseline (MD 4.5 mm; *P*=.00).
- TENS improved pain at one month compared to baseline (MD 4.7 mm; *P*=.00).
- MENS did not improve pain at day one compared to baseline (MD 0.60 mm; *P*=.02).
- MENS improved pain at day five compared to baseline (MD 5.1 mm; *P*=.00).
- MENS improved pain at one month compared to baseline (MD 5.1 mm; *P*=.00).

LIMITATIONS:

- There was a limited sample size with a brief observational time.
- The VAS was the only evaluation system for assessing pain.

- There was no control group.

Angela Awad, DO
Ocean University Medical Center
Brick, NJ

Is Reteplase Superior to Alteplase for Acute Ischemic Stroke?

Reteplasee versus Altepase for Acute Ischemic Stroke?
Li S, Gu HQ, Li H, et al. Reteplase versus Alteplase for Acute Ischemic Stroke. *N Engl J Med*. 2024;390(24):2264-2273. doi:10.1056/NEJMoa2400314

KEY TAKEAWAY: Among patients with ischemic stroke eligible for thrombolysis treatment within 4.5 hours of symptom onset, reteplase appears to improve functional outcomes compared to alteplase without increasing the risk of intracranial hemorrhage.

STUDY DESIGN: Multicenter, randomized, unblinded phase three trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to lack of blinding)

BRIEF BACKGROUND INFORMATION: As the quality of care for patients with acute ischemic stroke has improved internationally, intravenous (IV) thrombolysis treatment has increased. While alteplase is the internationally approved agent for reperfusion, additional effective and affordable agents are needed. This trial compared the efficacy and safety of reteplase, a novel recombinant plasminogen activator, with alteplase for acute stroke treatment.

PATIENTS: Adults with acute ischemic stroke

INTERVENTION: Reteplase

CONTROL: Alteplase

PRIMARY OUTCOME: Excellent function outcome and symptomatic intracranial hemorrhage within 36 hours
Secondary Outcome: Good functional outcome, early dramatic recovery, any intracranial hemorrhage and clinically relevant non-massive hemorrhage, death

METHODS (BRIEF DESCRIPTION):

- This open-label, noninferiority trial conducted at 62 sites in China included adults 18–80 years old with acute ischemic stroke presenting within 4.5 hours of symptom onset.
- Additional inclusion criteria were those who could receive thrombolysis, had excellent functional status prior to stroke onset, and had a disabling ischemic stroke.
    - Excellent functional status was defined using the modified Rankin score ≤1. Scores range from zero (no deficit) to six (death).
    - A disabling ischemic stroke was defined as a score of 4–25 on the National Institutes of Health Stroke Scale (NIHSS). Total scores range from zero (no neurologic deficit) to 42 (death).
- Those with prior or planned endovascular thrombectomy were excluded from the study.
- Participants had a median age of 63 years old, 71% were men, and the median NIHSS score was six.
- Eligible participants were randomized 1:1 to receive IV reteplase or IV alteplase.
    - Reteplase was administered as two 18 mg bolus doses separated by 30 minutes.
    - Alteplase 0.9 mg/kg dose was administered as a 10% bolus and the remaining infusion over 60 minutes.
- Functional outcomes were measured with an excellent or good modified Rankin scale score (scores of 0–1 or 0–2, respectively), with clinical assessments performed by neurologists with specialized training who were blinded to the group assignment.
- The primary efficacy outcome was an excellent functional outcome at 90 days (score 0–1 on the modified Rankin scale).
- Early dramatic recovery was defined as NIHSS score reduction by at least four points or a score of ≤1 point.
- The primary safety outcome of symptomatic intracranial hemorrhage was defined by the European Cooperative Acute Stroke Study III (ECASS III) as any extravascular blood within the intracranial space associated with an increase in NIHSS by ≥4 points.
- Clinically relevant nonmajor bleeding included hemorrhage requiring or prolonging hospitalization, or which resulted in laboratory testing, imaging, procedures, or necessitated a change in therapy, as defined by the International Society of Thrombosis and Hemostasis.
- Imaging studies were conducted if applicable, based on clinical assessment of the patient.

INTERVENTION (# IN THE GROUP): 707

COMPARISON (# IN THE GROUP): 705

FOLLOW-UP PERIOD: 90 days

RESULTS:

Primary Outcome –

- More patients in the reteplase group than the alteplase group achieved an excellent functional outcome (80% vs 70%, respectively; risk ratio [RR] 1.1; 95% CI, 1.1–1.2; *P*<.001 for noninferiority and *P*=.002 for superiority).
- The reteplase group and alteplase group did not differ in rates of symptomatic intracranial hemorrhage at 36 hours (2.4% vs 2.0%, respectively; RR 1.2; 95% CI, 0.54–2.8).

Secondary Outcome –

- More patients in the reteplase group compared to the alteplase group achieved a good functional outcome (85% vs 80%, respectively; RR 1.1; 95% CI, 1.0–1.1).
- Early dramatic recovery was higher in the reteplase group compared to the alteplase group at 24 hours (RR 1.2; 95% CI, 1.1–1.4) and seven days (RR 1.1; 95% CI, 1.0–1.2).
- The reteplase group and alteplase group did not differ in rates of any intracranial hemorrhage at 90 days (RR 1.6; 95% CI, 1.0–2.5).
- More patients in the reteplase group than the alteplase group had clinically relevant nonmassive hemorrhage (5.4% vs 2.4%, respectively; RR 2.2; 95% CI 1.0–4.8).
- At 90 days, death occurred in 30 patients treated with reteplase (4.3%) and 24 patients treated with alteplase (3.4%), a risk that was not statistically significant between the groups.

LIMITATIONS:

- Given the different dosing regimens, this trial used an open-label design, potentially introducing bias.
- Men were more represented than women, and participants were all Asian therefore limiting generalizability.
- Patients >80 years old or requiring endovascular thrombectomy were excluded, potentially resulting in a trial population with relatively younger age, a higher percentage of patients with excellent functional outcomes, and lower NIHSS scores.

Huilan Tang, MD
St Joseph's University Medical Center FMRP
Paterson, NJ

Small Plastics, Large Risks? Microplastics and Nanoplastics in Atheromas

Microplastics and Nanoplastics in Atheromas and Cardiovascular Events

Marfella R, Prattichizzo F, Sardu C, et al. Microplastics and Nanoplastics in Atheromas and Cardiovascular Events. *N Engl J Med*. 2024;390(10):900-910. doi:10.1056/NEJMoa2309822

KEY TAKEAWAY: Patients with evidence of microplastics and nanoplastics (MNP) in carotid plaques may have a higher risk of nonfatal myocardial infarction (MI), stroke, and death than patients without evidence of microplastics and nanoplastics in their carotid plaques.

STUDY DESIGN: Prospective, multicenter, observational study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: An emerging problem is the increasing prevalence of microplastics and nanoplastics in our environment. Recent preclinical studies have cited these small particles to be a potential cardiovascular risk factor, although direct evidence that extends to humans is lacking. This study investigated a composite measure of risk associated with microplastic and nanoplastic presence in carotid atheromas in patients who underwent carotid endarterectomy for asymptomatic carotid artery disease.

PATIENTS: Adults undergoing carotid endarterectomy

INTERVENTION: MNP-containing plaques

CONTROL: No MNP-containing plaques

PRIMARY OUTCOME: Nonfatal MI, stroke, or death of any cause

Secondary Outcome: Risk of the primary outcome based upon diabetes, hypertension, and total cholesterol

METHODS (BRIEF DESCRIPTION):

- The study was an observational study of patients 18–75 years old undergoing carotid endarterectomy at Hospital Cardarelli and the University of Salerno, Italy.
- Patients were deemed eligible if they had asymptomatic high-grade extracranial internal carotid artery stenosis (>70%), and were scheduled to undergo carotid endarterectomy.
- Patients were excluded if they had evidence of heart failure, vascular defects, malignant neoplasms, or if they had secondary causes of hypertension.
- Patients with MNP were younger (71 years old vs 73 years old), more likely to identify as male (77% vs 74%), with lower rates of diabetes (24% vs 30%) and hypertension (52% vs 65%) compared to patients without MNP.
- After undergoing endarterectomy, the atheroma samples were analyzed using pyrolysis-gas-chromatography and validated with electron microscopy and isotope analysis for 11 different MNPs
    - All researchers and analysts were blinded to the outcome data.
- Carotid plaque samples were divided into those in the presence of MNP and those that did not.
- The primary outcome was nonfatal MI, nonfatal stroke, or death, adjusted for differences in multiple baseline characteristics between the groups.
- The secondary outcomes were the risk of MI, nonfatal stroke, or death based on underlying risk factors of diabetes, hypertension, or total cholesterol.

INTERVENTION (# IN THE GROUP): 150

COMPARISON (# IN THE GROUP): 107

FOLLOW-UP PERIOD: 34 months

RESULTS:

Primary Outcome –

- Patients with MNP-containing atheromas were more likely to experience the primary composite outcome as compared to those without MNP-containing atheromas (20% vs 7.5%, respectively; adjusted hazard ratio [aHR] 4.5; 95% CI, 2.0–10)

Secondary Outcome –

- Patients with diabetes had an increased risk of death, nonfatal MI, and nonfatal stroke compared to those without diabetes (aHR 4.8; 95% CI, 2.4–9.6).
- Patients with hypertension had similar rates of death, nonfatal MI, and nonfatal stroke as compared to those without hypertension.
- Increasing levels of total cholesterol were not associated with an increased risk of death, nonfatal MI, and nonfatal stroke.

LIMITATIONS:

- Though preventative measures were taken, lab contamination cannot be ruled out.
- There was a lack of confounder analysis such as socioeconomic data and food and drinking water sources.
- Asymptomatic patients undergoing carotid endarterectomy may not be representative of the general population, and thus, findings are not generalizable to the United States.
- The ability to detect different types of plastics was limited- lower carbon isotopes (such as those in petroleum-containing plastics) were harder to differentiate from human tissues.
- The study was limited by only looking at carotid plaques MNPs may deposit differently in different locations.
- Patients with missed or lost follow-up were excluded from the analysis (15% excluded).

Dylan De Muth, MD
Alaska FMRP
Anchorage, AK