GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

Volume 1; Issue 2

What's in this week's issue?

Spotlight: Smoking after e-cigarette use in adolescents and young adults

Does e-cigarette use lead to cigarette smoking in adolescents and young adults?

Association between Initial Use of e-Cigarettes and Subsequent Cigarette Smoking Among Adolescents and Young Adults. A Systematic Review and Meta-analysis

Chadi N, Schroeder R, Jensen JW, Levy S. Association B between Electronic Cigarette Use and Marijuana Use Among Adolescents and Young Adults. *JAMA Pediatrics*. 2019; 173(10). doi:10.1001/jamapediatrics.2019.2574.

KEY TAKEAWAY: Adolescents and young adults with prior e-cigarette use are at greater risk to start smoking cigarettes or to have used cigarettes in the past 30 days.
STUDY DESIGN: Systematic review and meta-analysis
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Electronic cigarettes use is increasingly popular among adolescents and young adults. Many assume e-cigarettes are safer than cigarettes. Many utilize e-cigarettes for smoking cessation. Longitudinal studies suggest e-cigarette smoking is associated with subsequent cigarette smoking initiation. No systematic review/meta-analysis has been performed to date to quantify the risk of smoking initiation and current use in this population.
PATIENTS: Adolescents and young adults (14-30 years old) with no prior smoking history; 56% female
INTERVENTION: E-cigarette use
CONTROL: No E-cigarette use
OUTCOME: Cigarette smoking initiation for baseline e-cigarette ever users compared to never-users. 30-day cigarette smoking for past 30-day e-cigarette users compared to non-past 30-day users. Pooled probabilities for above adjusted for known demographic, psychosocial, and behavioral risk factors for smoking.

METHODS (BRIEF DESCRIPTION):
Comprehensive literature search of numerous databases and meeting abstracts through February 2017. Nine longitudinal studies (N=16,621) met inclusion criteria regarding association of subsequent cigarette use among e-cigarette users in adolescents and young adults. Study data extracted and assessed for quality and risk of bias. Adjusted pooled odds ratios calculated using a random-effects model. Sensitivity analysis and heterogeneity assessments performed.

INTERVENTION (# IN THE GROUP): 1174 e-cigarette users at baseline, never cigarette smokers; 119 past 30-day e-cigarette users at baseline
COMPARISON (# IN THE GROUP): 6994 never cigarette smokers at baseline; 1965 not past-30 day cigarette smokers at baseline

FOLLOW UP PERIOD: 6-18 months

RESULTS:

- Pooled probabilities for cigarette smoking initiation (7 studies, n=8168): 23.2% baseline ever e-cigarette users vs 7.2% baseline never users
- Pooled probabilities for past 30-day cigarette smoking at follow-up (2 studies, n=2084): 21.5% baseline past 30-day e-cigarette users vs. 4.6% baseline non–past 30-day e-cigarette users
- Ever e-cigarette use was significantly associated with subsequent cigarette smoking compared to never e-cigarette use (7 studies, n=8168; adjusted pooled odds ratio (OR) 3.5; 95% CI, 2.2–5.1)
- Past 30-day e-cigarette use was significantly associated with past 30-day cigarette smoking vs. non-past 30-day e-cigarette use (2 studies, n=2084; adjusted pooled odds ratio (OR) 4.2; 95% CI, 2.5–7.2)

LIMITATIONS:

- Moderate level of heterogeneity in the included studies I2=56%
- High rates of lost to follow-up in included studies, > 20%
- No information on types of e-cigarettes used
- Limited generalizability as US population only
- Follow-up too short to evaluate long-term cigarette use

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Xa or K … Which Keeps the Doctor Away?

Factor Xa inhibitors versus vitamin K antagonists for preventing cerebral or systemic embolism in patients with atrial fibrillation

Slot B, Berge E. Factor Xa inhibitors versus vitamin K antagonists for preventing cerebral or systemic embolism in patients with atrial fibrillation. *Cochrane Database of Systematic Reviews* 2018, Issue 3.

KEY TAKEAWAY: In patients with atrial fibrillation, treatment with factor Xa inhibitors significantly reduced the occurrence of stroke and other systemic embolic events compared to vitamin K antagonists, and also reduced major bleeding, intracranial hemorrhage, and all-cause mortality.

STUDY DESIGN: Systematic review and meta-analysis of randomized control trials (RCTs)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: The incidence and prevalence of atrial fibrillation, the most common arrhythmia in adults, is expected to continue to rise. Vitamin K antagonists, while effective, have been underutilized. Factor Xa inhibitors are promising both in terms of efficacy and their potential to increase the use of effective anticoagulation. It is important to compare the efficacy and safety of these two classes of medication.

PATIENTS: Adults with non-valvular atrial fibrillation; average age 65-75 years; 1/3rd women

INTERVENTION: Factor Xa inhibitors (apixaban, betrixaban, darexaban, edoxa-ban, idraparinux, idrabiotaparinux, or rivaroxaban. 90% of patients on either apixaban, edoxaban, or rivaroxaban)

CONTROL: Vitamin K antagonists (warfarin)

OUTCOME: Composite of all strokes (ischemic or hemorrhagic) and systemic embolic events
Secondary: Number of intracranial hemorrhages, all-cause deaths, and major bleeding

METHODS (BRIEF DESCRIPTION): Systematic review and meta-analysis of 13 RCTs including 67,688 adults with a diagnosis of atrial fibrillation (67,477 analyzed for the primary endpoint) comparing factor Xa inhibitors to vitamin K antagonists for at least 4 weeks. Authors independently searched multiple databases, extracted data, and assessed for bias. Weighted risk estimates calculated using odds ratios with fixed-effect and random-effect models (if high heterogeneity) for the primary and secondary outcomes. This was an update of the previous Cochrane Review on this topic published in 2013.

INTERVENTION (# IN THE GROUP): 37,746 analyzed for the primary endpoint

COMPARISON (# IN THE GROUP): 29,731 analyzed for the primary endpoint

FOLLOW UP PERIOD: 12 weeks – 2.8 years

RESULTS:

Primary outcomes:

- Factor Xa inhibitors significantly decreased the composite of all strokes (ischemic and hemorrhagic) and other systemic embolic events compared with vitamin K antagonists. (13 trials; N=67,477; OR 0.89; 95% CI, 0.82–0.97; NNT=304 [apixiban] and 376 [rivaroxaban])

Secondary outcomes:

- Factor Xa inhibitors significantly reduced the number of major bleeds compared with warfarin (13 trials; N=67,396; OR 0.78; 95% CI, 0.73–0.84; NNT 100)
- Factor Xa inhibitors significantly reduced the number of intracranial hemorrhages compared with warfarin (12 trials; N=66,259; OR 0.50, 95% CI, 0.42–0.59; NNT 167)
- Factor Xa inhibitors significantly reduced the risk of all-cause death compared with warfarin (10 studies; N=65,624; OR 0.89, 95% CI, 0.83–0.95; NNT 1000)

LIMITATIONS:

- Study compared 7 different factor Xa inhibitors which may limit applicability; however, 90% of the subjects received apixaban, edoxaban, or rivaroxaban.
- The absolute difference for the primary endpoint was small. High heterogeneity in secondary outcome data, but overall quality of data rated moderate to high.

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Early Versus Delayed Feeding in Patients with Acute Pancreatitis

Early versus delayed feeding in patients with acute pancreatitis. A systematic review.
Vaughn VM, Shuster D, Rogers MAM, et al. Early versus delayed feeding in patients with acute pancreatitis. A systematic review. *Ann Internal Med.* 2017; 166(12):883–892.

KEY TAKEAWAY: Mild/moderate pancreatitis patients receiving early enteral feeding experience reduced length of stay and no increase in mortality.
STUDY DESIGN: Systematic review of 11 RCTs; N=948.
LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: The decision to initiate early or delayed feeding in patients with acute pancreatitis remains controversial.
PATIENTS: Adults hospitalized with mild to severe acute pancreatitis
INTERVENTION: Early enteral feeding =< 48 hours
CONTROL: Delayed enteral feeding > 48 hours
OUTCOME: Length of hospital stay, mortality, readmission
Secondary outcomes: feeding intolerance, nausea, vomiting, recurrent abdominal pain, necrotizing pancreatitis

METHODS (BRIEF DESCRIPTION): Literature search included MEDLINE via OVID, EMBASE, the Cochrane library, CINAHL, and Web of Science from March 2015 to January 2017. Eleven RCTs (N=948) met inclusion criteria. Data extracted and assessed for risk of bias using the Cochrane Collaboration tool. Due to heterogeneity, meta-analysis was not performed.

INTERVENTION (# IN THE GROUP): Early enteral feeding; n=488
COMPARISON (# IN THE GROUP): Delayed enteral feeding; n=482

FOLLOW UP PERIOD: Variable (data not provided).

RESULTS:

Length of Stay

- In patients with mild/moderate pancreatitis early feeding was associated with decreased length of stay (4 trials, n=136; data not provided; all P< 0.05).
- In only 1 of 4 trials, early feeding was associated with a decreased length of stay for patients with severe pancreatitis (n=43; 1.3 vs. 4.5 days; P < 0.05).

Mortality

- No difference in mortality between groups in patients with mild/moderate pancreatitis (3 trials, n=407; Risk Difference (RD) 0; 95% CI, -10–10).
- No difference in mortality between groups with severe pancreatitis (2 trials, n=419; RD -7 to 4; 95% CI, -15–12).

Readmission

- Decreased risk of readmission in the early feeding group in patients with mild/moderate pancreatitis (2 trials, n=94; RD -5 to -3; 95% CI, -24–13).

Secondary outcomes:

- Feeding Intolerance
  - Less feeding intolerance associated with early feeding in patients with mild/moderate pancreatitis (2 trials, n=76; RD -44 to -25; 95% CI, -70 to -3).
  - No difference between groups in patients with severe pancreatitis (1 trial, n=214; RD 7; 95% CI, -6–21).
- Recurrent Abdominal pain
  - No difference in recurrent abdominal pain between groups in patients with mild/moderate pancreatitis (3 trials, n=166; RD -25 to 7; 95% CI, -57–28).
- Nausea and Vomiting
  - Early feeding associated with reduced nausea and vomiting (1 trial, n=35; RD -33; 95% CI, -56 to -11,).

LIMITATIONS:

1. Meta-analysis not performed due to heterogeneity.
2. Sample size of included studies small.
3. Some trials reported in abstract form only.
4. Benefit in patients with severe pancreatitis remains unclear.

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Buzz this! Catheter Ablation for Atrial Fibrillation in Heart Failure

Catheter Ablation for Atrial Fibrillation with Heart Failure

Marrouche NF, Brachmann J, Andresen D, et al. Catheter Ablation for Atrial Fibrillation with Heart Failure. *N Engl J Med* 2018; 378:417–27.

KEY TAKEAWAY: In patients with atrial fibrillation and symptomatic NYHA Class II-IV heart failure, catheter ablation was associated with a reduction in death from any cause or hospitalization for heart failure compared to medical therapy.

STUDY DESIGN: Multicenter, open-label, randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Patients with comorbid atrial fibrillation and heart failure experience higher morbidity and mortality compared to heart failure alone. The impact of treating these patients with catheter ablation as opposed to medical therapy remains unclear.

PATIENTS: Patients > 18 years (mean 64, 87% male) with paroxysmal or persistent atrial fibrillation, NYHA Class II-IV heart failure, LVEF 35% or less, with implantable defibrillator, with failure of anti-arrhythmic therapy, or unwilling to take medications, or unacceptable side effects

INTERVENTION: Catheter ablation

CONTROL: Medical therapy

OUTCOME: Composite of death from any cause or hospitalization for heart failure

METHODS (BRIEF DESCRIPTION): Patients randomly assigned 1:1 to catheter ablation or medical therapy. Run-in phase of 5 weeks. After ablation, patients received warfarin for 6 months. Medical therapy managed according to guidelines emphasizing rhythm control. Patients followed-up at regular intervals up to 60 months.

INTERVENTION (# IN THE GROUP): 179

COMPARISON (# IN THE GROUP): 184

FOLLOW UP PERIOD: Median follow-up: 37.8 months

RESULTS:

Primary outcome:

- Patients in the catheter ablation group experienced significantly fewer occurrences of the composite endpoint of death from any cause or hospitalization for heart failure compared to medical therapy (28.5% vs 44.6%; HR 0.62; 95% CI, 0.43–0.87; NNT=6).

Secondary outcomes:

- Rates for death from any cause was 24 (13.4%) vs. 46 (25%) for patients treated with catheter ablation and medical therapy, respectively (HR 0.53; 95% CI, 0.35–0.86; NNT=9).
- Heart failure hospitalizations rates were 37 (20.7%) vs 66 (35.9%) for patients treated with catheter ablation vs. medical therapy, respectively (HR 0.56; 95% CI, 0.37–0.83; NNT=7).
- Cardiovascular hospitalization rates were 64 (35.8%) vs. 89 (48.4%) for patients treated with catheter ablation vs medical therapy, respectively (HR 0.72; 95% CI, 0.52–0.99; NNT=8).
- Cardiovascular death rates between the two groups were 20 (11.2%) vs. 41 (22.3%) for catheter ablation and medical therapy, respectively (HR 0.49; 95% CI, 0.29–0.84; NNT=9).

LIMITATIONS:

- Unblinded, open-label design
- A greater number of patients in the ablation group crossed over to the medical treatment group.
- Industry funded and Biotronik assisted with data management and statistical analysis
- Highly selected population (5 week run-in period) limits generalizability
- Outcome difference may be driven by harms of medical therapy due to more complex medical regimens in that group

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Prenatal selective serotonin reuptake inhibitor (SSRI) exposure has an impact on fetal brain development, particularly in brain regions critical to emotional processing

Associations between Brain Structure and Connectivity in Infants and Exposure to Selective Serotonin Reuptake Inhibitors during Pregnancy

Lugo-Candelas C, Cha J, Hong S, et al. Associations Between Brain Structure and Connectivity in Infants and Exposure to Selective Serotonin Reuptake Inhibitors During Pregnancy. *JAMA Pediatrics*. 2018; 172(6):525–533.

KEY TAKEAWAY: Prenatal selective serotonin reuptake inhibitor (SSRI) exposure has an impact on fetal brain development, particularly in brain regions critical to emotional processing. It is not clear what clinicians should do about these data or what the outcomes mean for patients.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: SSRI use among pregnant women has increased over the past 30 years. There is limited and mixed literature on prenatal SSRI exposure in humans. Serotonin plays a vital role in neurodevelopment. Animal studies have shown that prenatal SSRI exposure may alter fetal brain development and subsequent functioning. Based on the results of prior animal studies, this study hypothesized that prenatal SSRI exposure alters grey matter morphology and white matter connectivity in the corticolimbic circuit.
PATIENTS: Infants
INTERVENTION: In utero exposure to selective serotonin reuptake inhibitors
CONTROL: Infants with no in utero SSRI exposure or in utero untreated maternal depression exposure
OUTCOME: Brain MRI analysis of infants' gray matter volume and white matter structural connectivity

METHODS (BRIEF DESCRIPTION):

- Participants: 204 pregnant women (aged 18-45) were recruited and completed a prenatal mood and medication assessment between 19 and 39 weeks' gestation. The participants were assigned to one of three groups: SSRI group, untreated maternal depression group, and healthy group. Group membership was determined based on the mother's depression scores on the Center for Epidemiological Studies Depression scale. Scores ≥16 were considered to be indicative of clinically significant depression.
- Imaging: 103 sleeping, nonsedated infants underwent MRI brain when they were approximately 3.43 (SD 1.50) weeks of age. 98 of these infants had usable MRI data, the other five infants were excluded due to imaging artifacts caused by excessive head motion.
- Imaging Analysis: 80 infants had usable T2-weighted scans and 91 infants had at least 1 usable diffusion-weighted imaging run.
- Statistical Analysis: Linear regression with permutation testing was used for both grey matter morphometry and white matter connectivity. Primary contrast maps were used to compare the SSRI group vs both the untreated maternal depression group and the healthy group.

INTERVENTION (# IN THE GROUP): 149
COMPARISON (# IN THE GROUP): 151

FOLLOW UP PERIOD: N/A

RESULTS:

- Voxel-based morphometry: Infants with in utero SSRI exposure had significant gray matter volume expansion in the right amygdala (Cohen d = 0.65; 95% CI, 0.06–1.23) and right insula (Cohen d = 0.86; 95% CI, 0.26–1.14) compared with both healthy controls and infants exposed to untreated maternal depression (P<.05; whole brain correction).
- Connectome-level analysis of white matter structural connectivity: Infants with in utero SSRI exposure had a significant increase in connectivity between the right amygdala and the right insula with a large effect size (Cohen d = 0.99; 95% CI, 0.40–1.57) compared with healthy controls and untreated maternal depression (P<.05; whole connectome correction)

LIMITATIONS:

- Lack of random assignment. Participants in this study were not randomly assigned to the SSRI or untreated maternal depression groups. This lack

of random assignment could have led to unmeasured sample differences.

- Sociodemographic confounding variables. The groups in this study differed sociodemographically (income, race/ethnicity, birth weight, maternal education). Although this study utilized statistical adjustment to account for these confounding variables, the study may have been able to avoid these variables with random assignment.
- Lack of longitudinal follow-up. In order to determine if developmental trajectories are affected, the behavioral correlates of this study's findings will need to be followed with longitudinal studies.
- Limited accuracy of diffusion probabilistic tractography. The accuracy of the fiber orientation estimates in diffusion probabilistic tractography may be limited by a small number of gradient directions (n = 11).

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Reducing anxiety over treating anxiety: Which drugs are most effective?

Pharmacological treatments for generalized anxiety disorder: a systematic review and network meta-analysis

Slee A, Nazareth I, Bondaronek P, Liu Y, Cheng Z, Freemantle N. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis [published correction appears in Lancet. 2019 Apr 27;393(10182):1698]. *Lancet*. 2019; 393(10173):768–777.

KEY TAKEAWAY: Duloxetine, pregabalin, venlafaxine and escitalopram and pregabalin reduce the symptoms of generalized anxiety disorder (GAD) and have low rates of discontinuation.

STUDY DESIGN: Systematic review and network meta-analysis

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Generalized anxiety disorder is a common medical condition with a lifetime prevalence of 5.7% and can lead to significant distress in daily functioning. There are many pharmacological treatments for GAD. While many placebo-controlled studies exist, there are few direct comparisons between each drug used for treatment of GAD.

PATIENTS: Patients with GAD

INTERVENTION: 22 separate pharmacological interventions for GAD

CONTROL: Placebo

OUTCOME: Change in anxiety as measured by HAM-A

METHODS (BRIEF DESCRIPTION): 89 trials were included. Criteria for inclusion were GAD diagnosed by DSM-IV, DSM-IVTR, DSM-V, ICD-10 or CCMD-3, randomized clinical trial status, comparison of at least two pharmacological treatments or placebo, and at least 10 patients in each comparison group.

All studies included change in Hamilton Anxiety Rating Scale as a primary or secondary endpoint. HAM-A is a 14-item scale, range is 0-56 with higher scores indications more anxiety. Median baseline HAM-A score for research subjects was 25. Principal summary measures were difference in change in anxiety (95% credible interval) and the odds ratio for discontinuation (95% credible interval) to assess for acceptability of the drug.

INTERVENTION (# IN THE GROUP): 25,441 patients across 89 trials

COMPARISON (# IN THE GROUP): Data not provided

FOLLOW UP PERIOD: 4-26 weeks (median duration 8 weeks)

RESULTS:

For most treatments, reduction in anxiety was greater than placebo and drug acceptability was similar to use of placebo.

- Duloxetine (MD -3.13, 95% CrI -4.13 to -2.13), Pregabalin (MD -2.79, 95% CrI -3.69 to -1.91), Venlafaxine (MD -2.69, 95% CrI -3.50 to -1.89) and Escitalopram (MD -2.45, 95% CrI -3.27 to -1.63) showed reduction in anxiety compared with placebo in large patient samples without significant discontinuation of the drug.
- Quetiapine (MD -3.60, 95% CrI -4.83 to -2.39) had the largest effect on anxiety reduction, however patients assigned to the quetiapine drug groups were more likely to discontinue the trial compared to patients in the placebo group (OR 1.44, 95% CrI 1.16 to 1.80).
- Paroxetine and Benzodiazepines are well-studied interventions, but patients assigned to these drugs showed higher rates of discontinuation.
    - Benzodiazapine: OR 1.43 (95% CrI 1.12–1.86)
    - Paroxetine: OR 1.24 (95% CrI 1.03–1.50)

Active drug comparisons were more likely to have significant findings when comparing an effective drug with an ineffective drug.

LIMITATIONS:

Absolute drop-out rates for each intervention were not included, this would have helped demonstrate the importance of the odds ratio in qualifying the acceptability of each drug. The article did not specify the minimum reduction in HAM-A score that results in clinically significant reduction in symptoms.

The study only compared pharmacological treatments and excluded non-pharmacological interventions.

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New Treatment Option for Sickle Cell Anemia

A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease

Vichinsky E, Hoppe CC, Ataga KI, et al. A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease. *N Engl J Med*. 2019 Aug 8; 381(6):509–519.

KEY TAKEAWAY: Voxelotor in sickle cell anemia increases hemoglobin and reduces hemolysis markers within two weeks of initiation.

STUDY DESIGN: Randomized, double-blind, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Sickle cell disease affects over 100,000 people in the U.S. and can shorten life span by 30 years. Hemoglobin S polymerizes into inflexible chains that stick in small capillaries and leads to vaso-occlusion, tissue ischemia, fatigue, and organ damage. Voxelotor binds to and stabilizes the oxygenated hemoglobin to extend red-cell half-life.

PATIENTS: Sickle cell diseased patients aged 12 to 65 years old with a hemoglobin level between 5.5 and 10.g g/dL and 1 to 10 vaso-occlusive crisis (VOC) episodes within the past year

INTERVENTION: Voxelotor 1500 mg or 900 mg by mouth once daily

CONTROL: Placebo tablet by mouth once daily

OUTCOME: Primary outcome was percentage of patients with a hemoglobin increase of one gram per deciliter or more from baseline at 24 weeks.

METHODS (BRIEF DESCRIPTION):

- Demographics of the participants at baseline included a median age of 24 for both voxelotor groups and age 28 for the placebo group; the majority of participants were of black race for all groups.
- Intervention: 1:1:1 random assignment to voxelotor 1500 mg, voxelotor 900 mg and placebo with treatment occurring up to 72 weeks. 24 weeks of treatment was adequate for statistical analysis, however participants treated through 72 weeks allowed them eligibility in an open-label phase 3 extension study assessing long term effects of voxelotor.
- Inclusion criteria continued: confirmed sickle cell disease, VOC defined as an acute painful crisis or acute chest syndrome with no explanation other than VOC and required analgesics as documented by a healthcare professional, if receiving hydroxyurea then stable use for 3 months prior to enrollment
- Exclusion: regularly scheduled red-cell transfusions, transfusion in the past 60 days or hospitalized for VOC in the past 14 days before enrollment; could be rescreened at the investigators' discretion
- Intention-to-treat analysis included all participants that underwent randomization; if a hemoglobin measurement was taken within 2 months after a red-cell transfusion, it was replaced with the last-observed value prior to transfusion.

INTERVENTION (# IN THE GROUP): 90 in voxelotor 1500 mg; 92 in voxelotor 900 mg

COMPARISON (# IN THE GROUP): 92

FOLLOW UP PERIOD:

- Screening period 28 to 35 days
- Treatment occurred up to 72 weeks
- End of trial visits for up to 4 weeks after the last dose of medication

RESULTS:

A greater percentage of voxelotor-treated patients had a 1mg/dl hemoglobin increase from baseline than placebo-treated patients at 24 weeks

- 1500 mg voxelotor group: 51% (95% CI, 41%–61%)
- 900 mg voxelotor group: 33% (95% CI, 23%–42%)
- Placebo group: 7% (95% CI, 1%–12%; NNT=3)

LIMITATIONS:

- Funded by Global Blood Therapeutics (involved in writing the manuscript for publication)
- Disease-oriented primary outcome (instead of vaso-occlusive crises, transfusions, mortality)

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Should a screening breast MRI be recommended?

Supplemental MRI Screening for Women with Extremely Dense Breast Tissue

Bakker MF, de Lange SV, Pijnappel RM, et al. Supplemental MRI Screening for Women with Extremely Dense Breast Tissue. *New England Journal of Medicine*. 2019; 381(22):2091–2102.

KEY TAKEAWAY: Women aged 50–75 with dense breast tissue identified on negative screening mammogram who were offered a screening MRI had lower interval breast cancer rates than women undergoing mammogram alone.

STUDY DESIGN: Multisite, randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: There is no consensus on recommendation for follow-up when dense breast tissue is identified on routine mammogram. This trial sought to determine whether supplemental MRI could improve early detection and reduce rates of interval breast cancer.

PATIENTS: Women 50–75 years old with extremely dense breast tissue identified on a negative screening mammogram

INTERVENTION: Optional supplemental screening breast MRI

CONTROL: Digital mammography screening every 2 years

OUTCOME: 2 year Interval breast cancer rate

METHODS (BRIEF DESCRIPTION):

- Women in the Dutch national screening program who had dense breast tissue and a negative screening mammogram were randomly assigned.
- The intervention group was offered a screening MRI, 59% accepted and underwent the MRI. If the MRI demonstrated a BI-RADS lesion rated 3–5 they were offered follow up screening (level 3) or biopsy (level 4–5).
- All participants were followed for 2 years for interval cancers and tumor characteristics. Interval cancers were defined as any breast cancer diagnosed within 24 months after initial mammogram screening.
- Intention to treat analysis and complier average causal effect (CACE) analysis of those who would have accepted the MRI screening if it had been offered was completed. Those randomized to the control group were not informed of their group assignment to reduce self-initiated MRI examination.

INTERVENTION (# IN THE GROUP): 8,061

COMPARISON (# IN THE GROUP): 32,312

FOLLOW UP PERIOD: 2 years

RESULTS:

Primary outcomes:

- The interval cancer rate was 2.5 per 1000 screenings lower in the MRI-Invitation group than the mammogram-only group (95% CI, 1.0–3.7, P<0.001).
- The interval cancer rate in only those that completed the MRI was lower by 4.2 per 1,000 screenings than mammography alone (95% CI, 2.0–6.4, p<.001). In the MRI invitation group an interval cancer was diagnosed in 20 women; four who received MRI screening or 0.8 per 1,000 screenings and 16 who declined MRI screening or 4.9 per 1,000. In the control group an interval cancer was diagnosed in 161 women or 5 per 1,000 screenings.

Secondary outcomes:

- The positive predictive value of a positive MRI result was 17.4% (95% CI 14.2–21.2). The false positive rate was 8% or 79.8 per 1000 screenings (95% CI 72.4–87.9) with a specificity of 92%.
- The MRI sensitivity was 95.2% (95% CI, 88.1–98.7)

LIMITATIONS:

- Interval cancer is a surrogate marker, not a patient-oriented outcome. The study was not able to address overall mortality or morbidity associated with breast cancer. Interval cancers may have been caught early enough to not have significant impact on morbidity and mortality.
- In the United States mammography is frequently recommended every 1 year whereas this study evaluated a 2 year screening schedule.

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