GOOD EVIDENCE MATTERS

GEMs of the Week

SPOTLIGHT: No Safe Puff

Teens Who Vape Match Smokers' Nicotine

Don't Ignore The Cancer Clues

Bleeding Events in Anticoagulated Atrial Fibrillation

Not Just For Comfort

Epidurals and Maternal Morbidity

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Don’t Ignore the Cancer Clues: Bleeding Events in Anticoagulated Atrial Fibrillation

Bleeding and New Malignancy Diagnoses After Anticoagulation for Atrial Fibrillation: A Population-Based Cohort Study

Grewal K, Wang X, Austin PC, et al. Bleeding and New Malignancy Diagnoses After Anticoagulation for Atrial Fibrillation: A Population-Based Cohort Study. *Circulation*. 2025;151(11):773-782. doi:10.1161/CIRCULATIONAHA.124.070865

KEY TAKEAWAY: Bleeding after the initiation of anticoagulation for patients with atrial fibrillation (AF) is associated with a new malignancy diagnosis.

STUDY DESIGN: Population-based cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Anticoagulation for the primary prevention of ischemic strokes in patients with AF has been associated with an increased risk of bleeding. Furthermore, newly diagnosed AF has been associated with a higher incidence of cancer diagnoses. This study aimed to evaluate the relationship between bleeding in patients initiated on anticoagulation and the unmasking of an underlying malignancy.

PATIENTS: Patients >66 years old with AF

INTERVENTION: Presence of bleeding after initiation on anticoagulation

CONTROL: Absence of bleeding after initiation on anticoagulation

PRIMARY OUTCOME: Incident malignancy

Secondary Outcome: Site of origin of malignancy, stage of diagnosis

METHODS (BRIEF DESCRIPTION):

- The study included patients >66 years old who received direct oral anticoagulants (DOAC) or vitamin K antagonists following an AF diagnosis.
- Patient population mean age was 77 years old, with 52% of the population being male.
- Of the patient population, 69% were prescribed a DOAC and 31% were prescribed warfarin.
- Exclusion criteria included patients age <66 years old or >105 years old, patients with missing key data, patients on chronic dialysis, valvular heart disease, previous cancer diagnoses, history of venous thromboembolism, or a previous bleeding diagnosis in the past five years.
- All participants were initiated on either a direct oral antagonist or vitamin K antagonist at an AF approved dose for stroke prevention
- The outcomes measured the following:
  - Presence of bleeding within two years of anticoagulation initiation
  - Site of documented bleeding by any incidence of cancer within two years of anticoagulation initiation and the site of diagnosed malignancy.
- The primary and secondary outcomes were assessed by using hazard regression models.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Two years

RESULTS:

Primary Outcome –

- Bleeding after anticoagulation initiation increased incidence of cancer diagnosis (hazard ratio [HR] 4.0; 95% CI, 3.8–4.3).

Secondary Outcome –

- The strongest associations between bleeding and cancer diagnosis were seen in gastrointestinal (HR 15; 95% CI, 13–7.7), genitourinary (HR 12; 95% CI, 10–14), and respiratory (HR 10; 95% CI, 8.1–13) sites.
- Nasopharyngeal (HR 1.5; 95% CI, 1.2–2.0) and intracranial (HR 1.8; 95% CI, 1.4–2.2) bleeds were weakly associated with a site-specific cancer diagnosis.
- There was no association between breast cancer and bleeding.
- There was a lower presence of stage four diagnoses in patients whose cancer was diagnosed after bleeding compared to patients whose cancer was diagnosed in the absence of bleeding.
- After excluding breast cancer, which showed no association with bleeding, cancers diagnosed after bleeding were stage four compared to cancers diagnosed in the absence of bleeding (28% vs 34%, respectively; $P<.001$)

LIMITATIONS:

- This study was limited by its observational design, preventing it from determining causality and limiting its associations given confounding variables.

- Anticoagulation persistence was <100% which provides a bias towards the null hypothesis, as patients who were not appropriately anticoagulated may have harbored cancer diagnoses that were alternatively diagnosed.
- This study did not account for patients that were taking single or dual antiplatelet therapy in addition to anticoagulants, which could impact the incidence of bleeding.
- Of the 5,800 patients diagnosed with malignancy, 52% had staging data. The association between earlier staging and bleeding should be considered hypothesis-generating given this large subset of missing data.

Kobe Young, MD
SSM Health St. Louis University FMR
St. Louis, MO

Not Just for Comfort: Epidurals and Maternal Morbidity

Epidural Analgesia During Labor and Severe Maternal Morbidity: Population Based Study

Kearns RJ, Kyzayeva A, Halliday LOE, Lawlor DA, Shaw M, Nelson SM. Epidural analgesia during labor and severe maternal morbidity: population based study. *BMJ*. 2024;385:e077190. Published 2024 May 22. doi:10.1136/bmj-2023-077190

KEY TAKEAWAY: Administration of epidural analgesia reduces the risk of severe maternal morbidity (SSM) during labor.

STUDY DESIGN: Population based cohort analysis

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Maternal morbidity is on the rise, likely due to increased complexity among child-bearing patients stemming from characteristics such as advanced age and metabolic risk factors. Epidural analgesia is often recommended to pregnant women at high risk of SMM due to beneficial physiological effects and resultant access to quick anesthesia in the case of emergency. Previous studies have attempted to characterize the impact of epidural analgesia in reducing events affecting maternal morbidity, but these studies were limited in the range of factors considered and the duration of postpartum follow-up. This study aimed to measure whether epidural analgesia reduces SMM, with special attention to individuals with medical indications and who are delivering preterm.

PATIENTS: Women in labor

INTERVENTION: Administration of epidural analgesia

CONTROL: Absence of epidural analgesia

PRIMARY OUTCOME: SMM

Secondary Outcome: SMM + critical care admission, respiratory morbidity

METHODS (BRIEF DESCRIPTION):

- The study included Scottish women in labor between 24+0 and 42+6 weeks gestation. The birthing years spanned from 2007–2019.
- Researchers excluded individuals with elective cesarean section births.
- The study defined preterm births as <37 weeks gestation. Medical indications for analgesia included several conditions such as body mass index (BMI) >40, pre-eclampsia, multiple gestation pregnancy, or severe cardiorespiratory diseases such as congestive heart failure and asthma, among others.
- The median maternal age was 29, and 93% of participants were White, 4.4% were Asian, and 1.5% were Black.
- Researchers looked at individuals who received lumbar epidural analgesia compared to those who did not. They did not specify the dosing or timing of the administration.
- Researchers defined individuals as experiencing SMM if they met one or more of the 21 SMM criteria defined by the US Centers for Disease Control and Prevention (CDC) within 42 days postpartum.
- Researchers adapted this definition for postpartum hemorrhage, including it as a condition only if an associated critical care admission occurred.

INTERVENTION (# IN THE GROUP): 125,024

COMPARISON (# IN THE GROUP): 442,192

FOLLOW-UP PERIOD: Birth until 42 days postpartum

RESULTS:

Primary Outcome –

- Epidural analgesia reduced in SMM compared to no epidural analgesia (adjusted relative risk [aRR] 0.65; 95% CI, 0.50–0.85).
- Epidural analgesia for individuals with medical indications is associated with a reduction in SMM compared to no epidural analgesia (aRR 0.50; 95% CI, 0.34–0.72).
- Epidural analgesia for those with preterm deliveries is associated with a reduction in SMM compared to no epidural analgesia (aRR 0.53, 95% CI, 0.37–0.76)

Secondary Outcome –

- Epidural analgesia during labor reduced SMM + critical care admission compared with no epidural analgesia (aRR 0.46; 95% CI, 0.20–0.73).
- Epidural analgesia reduced SMM + critical care admission with medical indications compared with no epidural analgesia (aRR 0.32, 95% CI 0.17–0.59).
- Epidural analgesia reduced SMM + critical care admission in those who deliver preterm compared with no epidural analgesia (aRR 0.33; 95% CI, 0.17–0.63).

LIMITATIONS:

- This study did not look at outcomes with pre-planned caesarean sections, as these individuals were not in active labor.
- The lack of diversity in patient demographics limits the generalizability of the data.
- Researchers did not have data on patient preferences regarding discussions with providers about receiving an epidural for their delivery plan. This may or may not influence the number of individuals receiving epidurals.

Natasha Ignatowski, MD
SSM Health St. Louis University FMR
St. Louis, MO

No Safe Puff: Teens Who Vape Match Smokers' Nicotine

Nicotine Exposure from Smoking Tobacco and Vaping Among Adolescents

Hammond D, Reid JL, Goniewicz ML, et al. Nicotine Exposure From Smoking Tobacco and Vaping Among Adolescents. *JAMA Netw Open*. 2025;8(3):e2462544. Published 2025 Mar 3. doi:10.1001/jamanetworkopen.2024.62544

KEY TAKEAWAY: Adolescents who vape only have equal nicotine concentrations in their urine compared to adolescents who smoke only tobacco.

STUDY DESIGN: Observational cross-sectional study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Recent reviews have found that vaping results in less nicotine exposure than smoking tobacco, but different forms of e-cigarettes have different amounts of nicotine present. Most studies have consisted of only adults who previously smoked tobacco and haven't explored nicotine exposure in adolescents. This study aimed to compare the nicotine levels of adolescents who vape only, smoke only, smoke and vape, and those who don't smoke.

PATIENTS: Adolescents 16–19 years old

INTERVENTION: Only vaping, smoking only e-cigarettes, both vaping and smoking

CONTROL: Those who did not vape e-cigarettes, smoke cigarettes, or smoke cannabis

PRIMARY OUTCOME: Concentration of nicotine metabolites in urine

Secondary Outcome: Concentration of nicotine metabolites in urine between e-cigarettes with no nicotine salts and with nicotine salts

METHODS (BRIEF DESCRIPTION):

- Adolescents 16–19 years old in Canada, England, and the United States who had previously participated in the International Tobacco Control (ITC) Policy Evaluation Project Youth Tobacco and Vaping Surveys were invited to participate in a project extension.
- Parental consent was obtained for participants under the age of 18 years old.
- Participants included 129 adolescents from Canada, 131 from England, and 104 from the United States. Participants were 56% female and 44% male.
- Participants completed a first morning urine collection kit and a questionnaire and returned samples and questionnaires by courier between September 2019 and January 2022.
- Participants were separated into the following categories:
  - Vape only group: Vaped only e-cigarettes in the past week
  - Smoke only group: Smoked only cigarettes in the past week
  - Dual use group: Vaped and smoked in the past week
  - No use group (comparison group): No use of vaping, smoking tobacco, and smoking cannabis in the past week
- Patients who vaped were further separated into the following categories:
  - Those whose vape and used nicotine salt
  - Those whose vape and did not use nicotine salt
  - Those who did not know if their vape used nicotine salt
- Nicotine was measured using cotinine (in ng/mg,) trans-3'-hydroxycotinine (3OH-cotinine) (in ng/mg), and total nicotine equivalents (TNE-2) (in nmol/mg) concentrations in urine samples.
- Calculations were adjusted for creatinine concentration, age, sex, country, and past-week cannabis, and concentrations were compared using geometric means.

INTERVENTION (# IN THE GROUP):

- Vape only: 73
- Smoke only: 68
- Both vaping and smoking: 77

COMPARISON (# IN THE GROUP): 146

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- Vaping only had higher levels of cotinine, 3OH-cotinine, and TNE-2 compared to no use.
  - Cotinine (β 3.08; 95% CI, 2.5–3.7)
  - 3OH-cotinine (β 2.4; 95% CI, 1.9–2.9)
  - TNE-2 (β 2.6; 95% CI, 2.1–3.1)
- Smoking only had higher levels of cotinine, 3OH-cotinine, and TNE-2 compared to no use.

    - Cotinine (β 3.3; 95% CI, 2.6–3.9)
    - 3OH-cotinine (β 2.5; 95% CI, 2.0–3.0)
    - TNE-2 (β 2.7; 95% CI, 2.1–3.2)
- Dual use group had higher levels of cotinine, 3OH-cotinine, and TNE-2 compared to no use.
    - Cotinine (β 3.5; 95% CI, 2.9–4.2)
    - 3OH-cotinine (β 2.8; 95% CI, 2.3–3.3)
    - TNE-2 (β 3.0; 95% CI, 2.4–3.5)
- There was no significant difference between the vape only and smoke only groups in cotinine, 3OH-cotinine, and TNE-2.
- Cotinine (β –0.17; 95% CI, –0.87 to 0.53)
- 3OH-cotinine (β –0.1; 95% CI, –0.69 to 0.49)
- TNE-2 (β –0.07; 95% CI, –0.67 to 0.54)

Secondary Outcome –

- Nicotine salt group had higher 3OH-cotinine and TNE-2 compared to the no nicotine salt group
    - 3OH-cotinine (β 1.5; 95% CI, 0.30–2.8)
    - TNE-2 (β 1.4; 95% CI, 0.16–2.6)
- There was no difference in levels of cotinine for the nicotine salt group compared to the no nicotine salt group.
- Nicotine salt group had higher concentrations of cotinine, 3OH-cotinine, and TNE-2 compared to the group that didn't know if their vape uses nicotine salt group.
    - Cotinine (β 2.4; 95% CI, 0.74–4.0)
    - 3OH-cotinine (β 1.7; 95% CI, 0.24–3.2)
    - TNE-2 (β 1.9; 95% CI, 0.49–3.4)
- There was no difference between the no nicotine salt vape group and those who did not know if vape had nicotine salt in concentrations of cotinine, 3OH-cotinine, and TNE-2.

LIMITATIONS:

- Participants self-reported their smoking or vaping behaviors, likely introducing recall bias.
- This study measured only nicotine metabolites from those who smoked or vaped in the previous week and did not address those with second-hand exposure or who smoked or vaped longer than a week prior.
- Many participants who vaped did not know the nicotine concentrations or whether their vapes contained nicotine salts.
- Nicotine metabolite measurements in the urine may not serve as an accurate surrogate marker for patient-oriented outcomes such as addictive behaviors or health impacts from nicotine concentration.

Matthew Dreyer, MD, MBA
SSM Health St. Louis University FMRP
St. Louis, MO