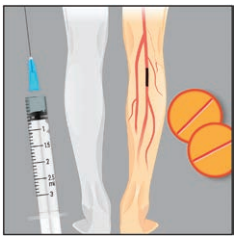
SCIENCE, MEDICINE, AND THE ANESTHESIOLOGIST

ANESTHESIOLOGY

Martin J. London, M.D., Editor

Key Papers from the Most Recent Literature Relevant to Anesthesiologists



Rivaroxaban or enoxaparin in nonmajor orthopedic surgery. N Engl J Med 2020; 382:1916–25. PMID: 32223113.

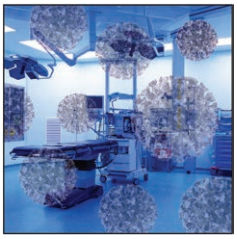
The therapeutic effect of anticoagulant thromboprophylaxis after major hip or knee replacement and hip fracture is well established. Its role in a variety of nonmajor lower limb procedures is controversial. This randomized, double-blind, noninferiority trial of 3,604 patients operated on at 200 sites in 10 countries evaluated the therapeutic effect of either rivaroxaban or enoxaparin (intended duration of therapy at least 2 weeks postoperatively based on investigator assessment of venous thromboembolic risk). The primary effect outcomes were major venous thromboembolism (symptomatic distal or proximal deep vein thrombosis, pulmonary embolism, or venous thromboembolism–related death during treatment or asymptomatic proximal deep vein thrombosis at the end of treatment). Safety outcomes included major bleeding (fatal, critical, or clinically overt bleeding or bleeding at the surgical site leading to intervention) and nonmajor clinically relevant bleeding. A total of 1,809 patients received rivaroxaban, and 1,795 patients received enoxaparin. The primary outcome occurred in 4 (0.2%) of the rivaroxaban group and in 18 (1.1%) of the enoxaparin group (risk ratio 0.25; 95% CI, 0.09 to 0.75; $P < 0.001$ for noninferiority; $P = 0.01$ for superiority). There were no significant differences in either of the safety outcomes (1.1% *vs.* 1.0% and 0.6% *vs.* 0.7%, respectively). *(Article Selection: Martin J. London, M.D. Image: M. Lane-Fall.)*

Take home message: Rivaroxaban was more effective and as safe as enoxaparin in the prevention of venous thromboembolic events after nonmajor orthopedic surgery of the lower limbs.

A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. N Engl J Med 2020; 383:517–25. PMID: 32492293.

Hydroxychloroquine has shown *in vitro* antiviral activity against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The authors investigated its use as postexposure prophylaxis in a randomized, double-blind, placebo-controlled trial of adults within 4 days of exposure to another person (household or occupational) with confirmed COVID-19 in the United States and Canada using recruitment *via* social or traditional media platforms. Study participants were classified as either having high risk exposure, without face mask or eye shield, or moderate risk exposure, with face mask but without eye shield. The primary outcome was the incidence of COVID-19 confirmed by the laboratory or development of COVID-19-related symptoms within 14 days. A total of 821 participants were studied; 414 randomized to hydroxychloroquine (1400 total mg first day, 600 mg for 4 days), 407 to placebo. Healthcare workers accounted for the majority of participants (66.4%); and 87.6% were high risk exposures. No difference in incidence of confirmed or probable COVID-19 was found between treated (11.8%) and placebo (14.3%) groups (absolute risk difference –2.4%; 95% CI, –7.0 to 2.2; $P = 0.35$). There was only one hospitalization in either group and no deaths. No serious adverse reactions were reported, but treated patients had more side effects (40.1%) than placebo (16.8%), primarily gastrointestinal. *(Article Selection: Beatrice Beck-Schimmer, M.D. Image: Adobe Stock. Illustration: M. Lane-Fall.)*

Take home message: Hydroxychloroquine did not prevent the occurrence of COVID-19 after exposure to subjects with confirmed COVID-19 and was associated with more side effects than placebo.



Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: An international cohort study. Lancet 2020; 396:27–38. PMID: 32479829.

Surgical patients with SARS-CoV-2 infection, either preoperatively or in the early postoperative period, are likely to be at increased risk of postoperative pulmonary complications and mortality. This multicenter, observational study from 235 hospitals in 24 countries early in the pandemic (January 1, 2020, to March 30, 2020), analyzed outcomes from 1,128 patients, of whom 280 (24.8%) had elective surgery and 835 (74.0%) had emergency surgery. Patients had a clinical or laboratory diagnosis of SARS-CoV-2 from 7 days before to 30 days after a surgical operation. Only 294 (26.1%) had a preoperative laboratory-confirmed infection, although laboratory confirmation was not available at all hospitals. Overall 30-day mortality was 23.8%, but of those who developed pulmonary complications (n = 577, 51.2%), mortality was 38%, accounting for 81.7% of all deaths. Mortality was significantly associated with: male *versus* female sex (odds ratio 1.75; 95% CI, 1.28 to 2.40); older than 70 yr *versus* younger than 70 yr of age (odds ratio 2.3; 95% CI, 1.65 to 3.22); American Society of Anesthesiologists grade III to V *versus* grades I to II (odds ratio 1.55; 95% CI, 1.01 to 2.39); emergency *versus* elective surgery (odds ratio 1.67; 95% CI, 1.06 to 2.63); and major *versus* minor surgery (odds ratio 1.52; 95% CI, 1.01 to 2.31). *(Article Selection: Jamie W. Sleigh, M.D. Image: Adobe Stock. Illustration: M. Lane-Fall.)*

Take home message: If possible, surgery should be deferred in patients at risk of having a perioperative SARS-CoV-2 infection, particularly older males, as half may develop pulmonary complications, and of those, more than one third may die.

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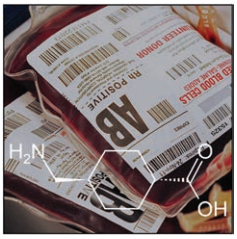
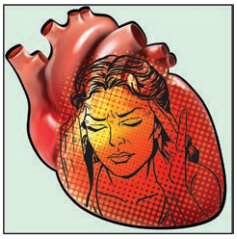


Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): An international randomised, double-blind, placebo-controlled trial. Lancet 2020; 395:1927–36. PMID: 32563378.

Tranexamic acid is now widely used in trauma and postpartum hemorrhage to reduce bleeding-associated mortality. Although a systematic review suggests therapeutic effect in upper gastrointestinal bleeding, study sample sizes have been small and safety data inconclusive. The investigators performed a large randomized, placebo-controlled trial of tranexamic acid in 12,009 subjects at 164 hospitals in 15 countries with significant (based on hemodynamics, transfusion risk, acute nature) upper or lower gastrointestinal bleeding. Treated patients received a loading dose of 1 g tranexamic acid followed by a maintenance dose of 3 g for 24 h *versus* placebo. A total of 5,994 patients (49.9%) received tranexamic acid and 6,015 (50.1%) placebo. The primary outcome, death due to bleeding within 5 days of randomization, occurred in 222 (4%) of treated subjects *versus* 226 (4%) of the placebo group (risk ratio 0.99; 95% CI, 0.82 to 1.18). Arterial thromboembolic events were similar between the tranexamic acid and placebo groups (42 [0.7%] *vs.* 46 [0.8%]; risk ratio 0.92; 95% CI, 0.60 to 1.39). Venous thromboembolic events were higher in the tranexamic acid group (48 [0.8%] *vs.* 26 [0.4%]; risk ratio 1.85; 95% CI, 1.15 to 2.98), as was the incidence of seizures (38 [0.6%] *vs.* 22 [0.4%]; risk ratio 1.73; 95% CI, 1.03 to 2.93). *(Article Selection: David Faraoni, M.D., Ph.D. Image: J. P. Rathmell.)*

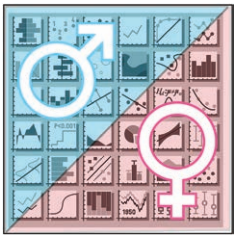
***Take home message*:** Tranexamic acid does not reduce death from significant upper or lower gastrointestinal bleeding and is associated with an increased risk of venous thromboembolic events and seizures.



Association of migraine with aura and other risk factors with incident cardiovascular disease in women. JAMA 2020; 323:2281–9. PMID: 32515815.

Previous cohort analyses of migraine headache consistently report significant associations with cardiovascular disease, particularly migraine with aura. The contribution of aura relative to other vascular risk factors is controversial. Using data from the Women's Health Study, a randomized trial of aspirin and vitamin E on primary prevention of cardiovascular disease and cancer in 27,858 female health professionals older than 45 yr of age, the investigators compared adjusted incidence rates of the primary outcome, cardiovascular disease (stroke, myocardial infarction, cardiovascular disease–related death) between four groups (self-reported migraine with aura, migraine without aura, no migraine, major vascular risk factors only). The adjusted incidence rate of cardiovascular disease was 3.36 per 1000 person-years in those reporting migraine with aura and 2.11 per 1000 person-years for those with migraine without aura or no migraine ($P < 0.001$). The incidence rate for women with migraine with aura was significantly higher than the adjusted incidence rate among women with obesity (2.29; 95%CI, 2.02 to 2.56), hypertriglyceridemia (2.67; 95%CI, 2.38 to 2.95), or low high-density lipoprotein cholesterol (2.63; 95%CI, 2.33 to 2.94), but was not significantly different from the rates among those with elevated systolic blood pressure (3.78; 95%CI, 2.76 to 4.81), high total cholesterol (2.85; 95%CI, 2.38 to 3.32), or family history of myocardial infarction (2.71; 95%CI, 2.38 to 3.05). Incidence rates among women with diabetes (5.76; 95% CI, 4.68 to 6.84) or who currently smoked (4.29; 95%CI, 3.79 to 4.79) were significantly higher than those with migraine with aura. *(Article Selection: BobbieJean Sweitzer, M.D. Image: M. Lane-Fall.)*

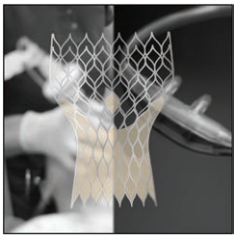
***Take home message*:** Self-reported migraine with aura in females was associated with increased cardiovascular disease incidence rates compared with those without aura or without migraine and the contribution varies depending on the presence of certain major vascular risk factors.



A 10-year follow-up study of sex inclusion in the biological sciences. eLife 2020; 9:e56344. PMID: 32513386.

Male subjects have traditionally been overrepresented in biomedical research, although funding agencies such as the National Institutes of Health now require investigators to consider sex as a biological variable. To assess changes in the inclusion of both sexes in biological research, the authors conducted a bibliometric analysis of nine biological science disciplines (general biology, immunology, neuroscience, physiology, pharmacology, reproduction, endocrinology, behavioral physiology, and behavior) for articles published in 34 journals in 2019. Results were compared to those from a similar study published in 2009. An overall increase in the inclusion of both sexes occurred over time (49% of 356 studies *vs.* 28% of 232, $P < 0.0001$). The 2009 to 2019 increases were particularly large in the fields of neuroscience (29% *vs.* 63%, $P < 0.0001$) and immunology (16% *vs.* 46%, $P < 0.0001$). Despite the increase, for eight of the nine disciplines there was no change in the proportion of studies that reported results analyzed by sex. The author's decisions not to include both sexes or to provide sex-specific results were generally not explained, and when explanations were given, they were often faulty. *(Article Selection: J. David Clark, M.D., Ph.D. Image: M. Lane-Fall.)*

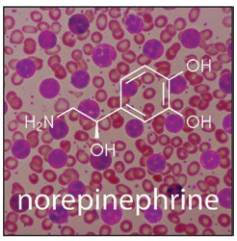
***Take home message*:** Inclusion of both sexes in a broad range of biological studies is increasing, but analysis of results by sex is still lacking.



Conscious sedation versus general anesthesia for transcatheter aortic valve replacement: Variation in practice and outcomes. JACC Cardiovasc Interv 2020; 13:1277–87. PMID: 32499018.

The use of conscious sedation for transcatheter aortic valve replacement *via* the transfemoral approach has steadily increased in the United States. Using the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy registry, the authors evaluated variation in use of conscious sedation in a large group of hospitals over time and tested its safety and effectiveness relative to general anesthesia using instrumental variable analysis with site-level preference for conscious sedation as the instrumental variable. This approach categorizes patients into treatment groups independent of patients' characteristics (so-called marginal populations based on hospital preferences). Of 120,080 patients at 559 sites in the registry who underwent transfemoral transcatheter aortic valve replacement between January 2016 and March 2019, use of conscious sedation increased from 33 to 64%. Twenty-six percent of sites used it in more than 80% of cases while 13% did not use it at all. It was associated with decreases in in-hospital mortality (adjusted risk difference 0.2%, $P < 0.010$) and 30-day mortality (adjusted risk difference 0.5%, $P < 0.001$), shorter length of hospital stay (adjusted risk difference 0.8 days, $P < 0.001$), and more frequent discharge to home (adjusted risk difference 2.8%, $P < 0.001$) compared with general anesthesia. *(Article Selection: Martin J. London, M.D. Image: Adobe Stock. Illustration: M. Lane-Fall.)*

Take home message: Conscious sedation is widely used for transcatheter aortic valve replacement and is associated with improved outcomes, although the magnitude of benefit is less than in earlier initial studies.



Norepinephrine dysregulates the immune response and compromises host defense during sepsis. Am J Respir Crit Care Med 2020 June 10 [Epub ahead of print]. PMID: 32520577.

Norepinephrine is the vasopressor recommended for treatment of septic shock. *In vitro, in vivo*, and clinical modalities were used to investigate relations between norepinephrine or vasopressin and the immune response to sepsis. *In vitro*, norepinephrine dose-dependently attenuated proinflammatory cytokines such as tumor necrosis factor-α and interferon γ-induced protein-10, increased anti-inflammatory interleukin-10 expression, while vasopressin had no effect. These effects were mediated via the ß-2 adrenoceptor and were reversed when blood was pre-exposed to a selective ß-2 antagonist. In murine models of sepsis, norepinephrine, but not vasopressin, led to a dose-dependent significant reduction in the expression of tumor necrosis factor α and interferon γ-induced protein-10, and an increase in interleukin-10 production. In humans challenged with lipopolysaccharide to induce a sepsis-like response, norepinephrine, but not vasopressin, increased concentration of interleukin-10 and decreased concentration of interferon γ-induced protein-10. In patients with septic shock, the authors compared tumor necrosis factor α/interleukin-10 ratios in patients on norepinephrine infusions who were or were not chronically taking ß-blocking agents. The ratio was significantly higher in patients taking ß-blockers, suggesting that ß-blockers counteract some of the anti-inflammatory effects of norepinephrine. *(Article Selection: Marilyn D. Michelow, M.D. Image: Adobe Stock. Illustration: M. Lane-Fall.)*

Take home message: Norepinephrine decreases the production of proinflammatory cytokines and increases the production of the anti-inflammatory cytokine interleukin-10, leading to an overall anti-inflammatory balance mediated through the ß-2 adrenoceptor and attenuated by the use of ß-blocking agents.

Associations between career satisfaction, personal life factors, and work-life integration practices among US surgeons by gender. JAMA Surg 2020; 155:742–50. PMID: 32579211.

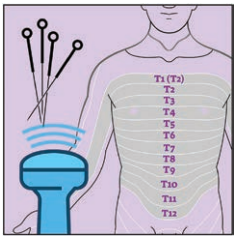
Physician burnout is a significant problem in medicine and surgery. This cross-sectional survey study of U.S. surgeons queried surgeon's career satisfaction on a 5-point Likert scale using multivariable proportional odds models to examine the association of personal and professional life factors with career satisfaction stratified by sex. The authors conducted a subanalysis of 31 questions from an online survey sent to 25,748 members of the American College of Surgeons. Data from 3,807 respondents, 83% male and 17% female, were analyzed. Eighty-two percent of males responded that they were satisfied with their careers *versus* 77% of females. Fewer females (33%) than males (41%) felt that their work schedule allowed sufficient time for family life. In sex-stratified analyses there were few differences between sexes in factors associated with career satisfaction. For both sexes, reporting insufficient time for family life was correlated with lower career satisfaction (male: odds ratio 0.66, 95% CI, 0.49 to 0.90, $P = 0.009$; female: odds ratio 0.49, 95% CI, 0.30 to 0.81, $P = 0.006$). For both sexes, collegial support of work-life balance was significantly associated with higher career satisfaction ($P < 0.001$). *(Article Selection: Marilyn D. Michelow, M.D. Image: Adobe Stock. Illustration: M. Lane-Fall.)*

Take home message: Female surgeons may have lower career satisfaction compared with their male colleagues. Sufficient time with family and collegial support for work-life balance appear to be important factors for career satisfaction in surgeons of either sex.

Morphine alters respiratory control but not other key obstructive sleep apnoea phenotypes: A randomised trial. Eur Respir J 2020; 55:1901344. PMID: 32165399.

Opioid-induced respiratory depression during sleep is of particular concern in patients with obstructive sleep apnea (OSA). However, it is unknown which of four pathophysiologic features of OSA (upper airway collapsibility, pharyngeal muscle responsiveness, respiratory arousal threshold, or ventilatory chemoreflex control [loop gain]) are affected by morphine during non-rapid-eye-movement sleep. The authors performed a double-blind, randomized, crossover study in 21 males (mean ± SD, age 51 ± 10 yr) with OSA administering 40 mg of morphine sulfate extended release or placebo before two sleep studies 1 week apart. Brief reductions in therapeutic continuous positive airway pressure were applied during non-rapid-eye-movement sleep to induce airflow limitation and carbon dioxide was delivered to measure hypercapnic responses. Compared to placebo, morphine did not change upper airway collapsibility (pharyngeal critical closure pressure [Pcrit]; –0.1 ± 2.4 *vs.* –0.4 ± 2.2 cm H_2O; $P = 0.58$), genioglossus muscle responsiveness (–2.2 microvolt/cm H_2O; 95% CI, –0.87 to –5.4; $P = 0.22$) or arousal threshold (–16.7 ± 6.8 *vs.* –15.4 ± 6.0 cm H_2O; $P = 0.04$). However, morphine reduced loop gain (–10.1 ± 2.6 *vs.* –4.4 ± 2.1; $P = 0.04$) and hypercapnic ventilatory response (7.3 ± 1.2 *vs.* 6.1 ± 1.5 l/min; $P = 0.006$). *(Article Selection: Charles W. Emala, Sr., M.D., M.S. Image: Adobe Stock. Illustration: M. Lane-Fall.)*

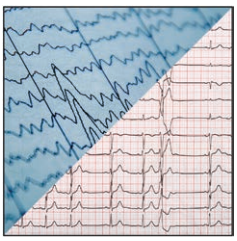
***Take home message*:** Parenteral morphine does not indiscriminately affect all pathophysiologic mechanisms of OSA during non-rapid-eye-movement sleep but does impair ventilatory control due to blunted chemosensitivity.



Effectiveness of intramuscular electrical stimulation on postsurgical nociceptive pain for patients undergoing open pancreaticoduodenectomy: A randomized clinical trial. J Am Coll Surg 2020; 231:339–50. PMID: 32623088.

Somatic abdominal pain is associated with functional limitation after open abdominal surgery. Intramuscular electrical stimulation has been utilized in chronic pain states and may have postoperative utility. This double-blind, randomized controlled, single-center trial evaluated "needle electrical twitch obtaining intramuscular stimulation" as an adjunct for postoperative pain control in 38 patients undergoing pylorus-sparing pancreaticoduodenectomy with general anesthesia. The intervention group (n = 18) received a single session of 14 ultrasound-guided stimulations in the transverse abdominis muscle after completion of surgery, while still anesthetized. The primary outcome was the visual analog score at postoperative day 3 (mean ± SD, intervention 3.2 ± 1.5 *vs.* nonintervention 4.0 ± 1.6; $P = 0.04$). Pain score, peak cough flow, and gait speed were also measured from the day before surgery to 2 weeks after hospital discharge. The improvement in peak cough flow from the second postoperative day to hospital discharge was greater (25.3% ± 12.9 *vs.* 17.1% ± 9.67; $P = 0.02$) and gait speed improved faster (93.3% ± 13.9 *vs.* 84.6% ± 16.0; $P < 0.01$) in the intervention group than in the control group. No postoperative pulmonary complications were noted in either group. *(Article Selection: Meghan E. Prin, M.D., M.S. Image: M. Lane-Fall.)*

***Take home message*:** A single session of intramuscular electrical stimulation in the transverse abdominus muscle after completion of surgery may be a useful adjunct in patients after open abdominal surgery.



Sensitivity of continuous electroencephalography to detect ictal activity after cardiac arrest. JAMA Netw Open 2020; 3:e203751. PMID: 32343353.

Twenty-five to fifty percent of patients hospitalized after cardiac arrest in a comatose state develop electroencephalographic (EEG) evidence of ictal activity, a feature portending worse clinical outcome for which treatment is recommended. However, the optimal method for detection remains controversial. This observational study compared the sensitivity of continuous EEG monitoring to intermittent EEG monitoring for the detection of epileptiform activity in 759 postcardiac arrest (primarily out of hospital) patients at two tertiary academic medical centers monitored for at least 24 h postarrest. Intermittent monitoring consisted of a 40-min EEG recorded in daylight hours. Fifty-four percent of the patients showed epileptiform patterns, but only 3.4% were deemed to be "treatable" seizures, defined as seizures likely to cause secondary brain injury. Intermittent monitoring had a sensitivity of 66% (95% CI, 62 to 69%) for epileptiform patterns, but only 7% (95% CI, 4 to 12%) for treatable seizures whereas up to 51 h of continuous monitoring was required to achieve sensitivity of 95%. However, its incorporation into logistic regression models predicting outcome yielded similar information to continuous monitoring. *(Article Selection: Jamie W. Sleigh, M.D. Image: Adobe Stock. Illustration: M. Lane-Fall.)*

***Take home message*:** Although relatively insensitive to the detection of epileptiform activity after cardiac arrest, intermittent monitoring yields similar information for multimodality prediction of patient status at hospital discharge.