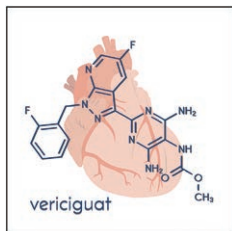


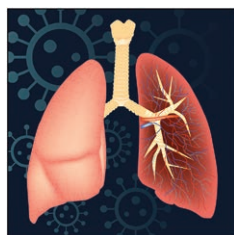
## Key Papers from the Most Recent Literature Relevant to Anesthesiologists



### Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2020; 382:1883–93. PMID: 32222134.

Vericiguat is a new oral soluble guanylate cyclase stimulator acting via a binding site independent of nitric oxide, sensitizing soluble guanylate cyclase to endogenous nitric oxide. A multinational, phase 3, randomized, double-blind, placebo-controlled trial enrolled 5,050 patients from 616 hospitals in 42 countries with heart failure with reduced ejection fraction (ejection fraction less than 45%; chronic heart failure New York Heart Association class II to IV) to treatment with vericiguat or placebo, along with guideline-based medical therapy. The primary outcome was a composite outcome of cardiovascular mortality or first hospitalization due to decompensated heart failure. Secondary outcomes were the components of the primary outcome, all-cause mortality, first and subsequent hospitalizations for decompensated heart failure, and a composite of all-cause mortality or first hospitalization due to decompensated heart failure. A total of 2,526 patients were randomized to receive vericiguat, of which 897 (35.5%) suffered a primary outcome event, compared to 972 of 2,524 (38.5%) in the placebo group (hazard ratio 0.90 [95% CI, 0.82 to 0.98],  $P = 0.02$ ). Regarding adverse events, 9.1% of patients treated with vericiguat had symptomatic hypotension and 4.0% had syncope, compared to 7.9% ( $P = 0.12$ ) and 3.5% ( $P = 0.30$ ) in the placebo group. (Article Selection: Beatrice Beck-Schimmer, M.D. Image: original image, Adobe Stock; image illustration, M. Lane-Fall.)

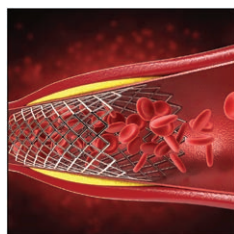
**Take home message:** Vericiguat along with guideline-based medical therapy significantly reduced the incidence of cardiovascular mortality or hospitalization for decompensated heart failure compared to placebo in patients with heart failure with reduced ejection fraction.



### Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med* 2020; 383:120–8. PMID: 32437596.

Autopsy findings of lungs from seven patients who died from COVID-19 were compared to lungs from seven patients who died from influenza A (H1N1)—associated acute respiratory distress syndrome and 10 age-matched, uninfected lungs. The histologic pattern of the lungs from COVID-19 patients showed distinctive vascular features including severe endothelial injury with intracellular SARS-CoV-2 virus, widespread vascular thrombosis with microangiopathy, occlusion of alveolar capillaries, and significant new vessel growth through intussusceptive angiogenesis. Microthrombi in alveolar capillaries were nine times as common in COVID-19 lungs compared to the influenza-infected lungs ( $P < 0.001$ ). COVID-19 lungs had only mild to marked interstitial edema while influenza lungs had florid interstitial edema and higher weights. There were significantly greater numbers of ACE2-positive cells in the lungs from COVID-19 and influenza patients compared to uninfected controls. ACE2-positive lymphocytes were not present in control lungs but were in the COVID-19 and influenza groups. SARS-CoV-2 virus within the endothelial cells suggests that direct viral effects and perivascular inflammation may contribute to endothelial injury. (Article Selection: BobbieJean Sweitzer, M.D., F.A.C.P. Image: original image, Adobe Stock; image illustration, M. Lane-Fall.)

**Take home message:** Vascular angiogenesis in the gas-exchange networks of COVID-19-infected lungs may uniquely impact ventilation and perfusion matching, potentially contributing to clinically observed hypoxemia.



### Rivaroxaban in peripheral artery disease after revascularization. *N Engl J Med* 2020; 382:1994–2004. PMID: 32222135.

Patients with peripheral arterial disease having lower-extremity revascularization, a group at high risk of vascular complications (particularly acute limb ischemia), were randomly assigned in a double-blind study ( $n = 6,564$ ) performed at 542 sites in 34 countries to receive rivaroxaban, a selective direct factor Xa inhibitor (2.5 mg twice daily) with aspirin (100 mg daily) or placebo with aspirin within 10 days of surgery. The primary outcome was a composite of acute limb ischemia, amputation for vascular causes, myocardial infarction, ischemic stroke, or cardiovascular death. The principal safety outcome was major bleeding defined by Thrombolysis in Myocardial Infarction (TIMI) classification. A secondary safety outcome was major bleeding by International Society on Thrombosis and Haemostasis (ISTH) criteria. Rivaroxaban plus aspirin was associated with significantly lower composite outcomes. The Kaplan–Meier estimates of the incidence at 3 yr were 17.3% and 19.9%, respectively (hazard ratio 0.85 [95% CI, 0.76 to 0.96];  $P = 0.009$ ). The incidence of major bleeding by TIMI criteria did not differ significantly between the groups. However, ISTH major bleeding was significantly higher with rivaroxaban and aspirin than with aspirin alone (hazard ratio 1.42 [95% CI, 1.10 to 1.84];  $P = 0.007$ ). (Article Selection: BobbieJean Sweitzer, M.D., F.A.C.P. Image: Adobe Stock.)

**Take home message:** For every 10,000 patients treated for 1 yr, rivaroxaban 2.5 mg twice daily plus aspirin will prevent 181 primary therapeutic outcome events at a cost of 29 safety outcome events.



### Association of functional, cognitive, and psychological measures with 1-year mortality in patients undergoing major surgery. *JAMA Surg* 2020; 155:412–8. PMID: 32159753.

Surgical risk assessment predominantly focuses on a patient's medical comorbidities. This study sought to link preoperative physical and cognitive functional status, as well as psychological well-being, to long-term postoperative mortality in adults aged 66 or older undergoing major surgery (abdominal aortic aneurysm repair, coronary artery bypass graft, or colectomy). Using the Health and Retirement Survey, an ongoing prospectively acquired cohort funded by the National Institute for Aging, the study authors conducted a retrospective analysis of 1,341 participants enrolled between 1992 and 2014, assessing factors associated with 1-yr postsurgical all-cause mortality by linking data to Medicare Claims. After covariate adjustment, mortality (17% of cohort) was associated with dependence in more than one activity of daily living (29% vs. 13%), more than one instrumental activity of daily living (21% vs. 14%), poor exercise tolerance (17% vs. 11%), dementia (21% vs. 12%), and depression (19% vs. 12%). An increased number of risk factors was associated with increased mortality (10% for zero risk factors, 27.8% for two risk factors). (Article Selection: Marilyn D. Michelow, M.D. Image: original image, Adobe Stock; image illustration, M. Lane-Fall.)

**Take home message:** Measures of physical, cognitive, and social function are associated with 1-yr postoperative mortality in older adults after major surgery and should be considered in the preoperative assessment for risk stratification and potential modification.



### Effects of gender bias and stereotypes in surgical training: A randomized clinical trial. *JAMA Surg* 2020; 155:552–60. PMID: 32432669.

Perception of pro-male bias and stigma consciousness may impact female surgical trainees' career engagement and performance on tests of technical skill. This two-phase study of 77 surgical trainees (49.4% women) was conducted at three academic centers. The first phase used surveys administered 5 to 6 months apart to assess career engagement, susceptibility to stereotype threat, and perception of pro-male bias. Residents were then randomized to read abstracts either claiming that women performed poorly compared with men on a test of surgical technical skill or that there was no sex difference in test performance (stereotype threat). Residents were then administered the Fundamentals of Laparoscopic Surgery simulation-based skills assessment. On the survey, men who perceived more pro-male bias had higher career engagement scores (interaction coefficient 1.02 [95% CI, 0.19 to 2.24];  $P = 0.04$ ), but there was no association between the two variables among women. On the skills test, there was no significant difference in assessment scores between men and women or between arms of the study overall. However, assessment scores were significantly lower in women who reported higher susceptibility to stereotype threat on the survey and were exposed to the stereotype threat abstract (coefficient  $-43.4$  [95% CI,  $-48.0$  to 38.9];  $P = 0.001$ ). (Article Selection: Marilyn D. Michelow, M.D. Image: Adobe Stock.)

**Take home message:** Perception of a male bias among male surgical residents may increase career engagement. However, stigma consciousness may negatively affect female surgical trainee skill performance.



### Physical therapy versus glucocorticoid injection for osteoarthritis of the knee. *N Engl J Med* 2020; 382:1420–9. PMID: 32268027.

Osteoarthritis is commonly treated with either physical therapy or intraarticular steroid injections. There are few comparative effectiveness studies available to help clinicians select one approach over the other. Investigators in the U.S. Military Health System performed a randomized trial involving 156 patients (mean  $\pm$  SD age,  $56.1 \pm 8.7$ ; female sex 48.1%), comparing 1-yr outcomes between patients assigned to intraarticular glucocorticoid injection (up to three injections in 1 yr) or a structured physical therapy program over the 12-month period. The primary outcome was the total score on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC); secondary outcomes focused on knee joint function. At 1 yr, both groups showed marked improvement in WOMAC scores; the glucocorticoid group improved from  $108.8 \pm 47.1$  to  $55.8 \pm 53.8$ , while the physical therapy group improved from  $107.1 \pm 42.4$  to  $37.0 \pm 30.7$ . The mean between-group difference of 18.8 points (95% CI, 5.0 to 32.6) favored physical therapy over joint injection. The secondary outcomes showed similar advantages for physical therapy. (Article Selection: J. David Clark, M.D., Ph.D. Image: Adobe Stock.)

**Take home message:** Patients undergoing a structured physical therapy program had less pain and functional disability at 1 yr relative to those receiving intraarticular glucocorticoid injection.

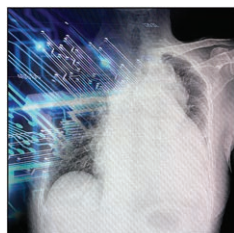


### Effect of surgery vs functional bracing on functional outcome among patients with closed displaced humeral shaft fractures: The FISH randomized clinical trial. *JAMA* 2020; 323:1792–801. PMID: 32396179.

Closed humeral shaft fractures commonly result from falls and motor vehicle accidents and are traditionally treated with functional bracing. However, surgery is becoming more common despite limited evidence of improved outcomes. At two Finnish hospital trauma centers, 82 patients (mean age 48.9 yr; 46% women) were randomized to receive bracing or open reduction and internal plate fixation. The Disabilities of Arm, Shoulder and Hand (DASH) score at 12 months was the primary outcome (0 = no disability, 100 = extreme; minimal clinically important difference = 10 points). At 12 months, the mean

DASH score for the surgery group was 8.9 (95% CI, 4.2 to 13.6) versus 12.0 (95% CI, 7.7 to 16.4) for the bracing group, between-group difference  $-3.1$  points (95% CI,  $-9.6$  to  $3.3$ ;  $P = 0.34$ ). Improvements in the DASH scores for both groups were clinically similar at intermediate timepoints during the year-long period of observation. However, 13 patients from the bracing group crossed over into the surgical arm, and there was a 25% rate of nonunion in the bracing group compared with no nonunions in the surgical group. (Article Selection: J. David Clark, M.D., Ph.D. Image: original image, Adobe Stock; image illustration, M. Lane-Fall.)

**Take home message:** Open reduction with internal fixation did not significantly improve functional outcome in patients with traumatic closed humeral fractures, although a high rate of crossover and nonunion tempers the results.

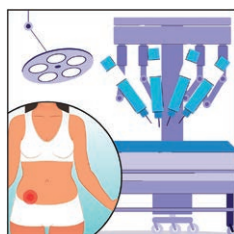


### A machine learning approach to management of heart failure populations. *JACC Heart Fail* 2020; 8:578–87. PMID: 32387064.

Heart failure is a prevalent chronic health condition associated with significant costs. With the development of value-based care models, efforts are needed to optimize its management at a population level. Such an approach requires an effective method to stratify patients in need of appropriate interventions. This study sought to generate a model for managing populations of heart failure patients using a large 20-yr retrospective dataset (Geisinger electronic health record). The authors applied machine learning models to 26,971 heart failure patients analyzing 276,819 clinical episodes to predict 1-yr all-cause mortality. Twenty-six clinical variables, 90 diagnostic codes, 41 electrocardiographic measurements, 44

echocardiographic measurements, and 8 evidence-based “care gaps” (flu vaccine, blood pressure less than 130/80 mmHg, A1c less than 8%, cardiac resynchronization therapy, and active medications) were included. Machine learning models achieved areas under the receiver-operating characteristic curve of 0.74 to 0.77, outperforming linear regression models. Prospectively applying models to the 13,238 currently living patients predicted 2,844 to die within a year and closing “care gaps” was predicted to save 231 of these lives. (Article Selection: David Faraoni, M.D., Ph.D., F.C.C.P., F.A.H.A. Image: original image, Adobe Stock; image illustration, M. Lane-Fall.)

**Take home message:** Prospective adoption of machine learning models may eventually improve care of patients with heart failure and their survival.



### Robotic inguinal vs transabdominal laparoscopic inguinal hernia repair: The RIVAL randomized clinical trial. *JAMA Surg* 2020; 155:380–7. PMID: 32186683.

Robotic inguinal hernia repair is an alternative to the traditional laparoscopic approach, but any clinical benefits remain unclear. The authors report a multicenter, single-blinded, randomized pilot study of 102 patients comparing standard laparoscopic transabdominal preperitoneal repair to robotic transabdominal preperitoneal repair (54 laparoscopic, 48 robotic at six sites). Primary outcomes included postoperative pain, health-related quality of life, mobility, wound morbidity, and cosmesis at 30 days after surgery. Secondary outcomes were defined as cost, surgeon ergonomics, and surgeon mental workload. No differences in preoperative, 1-week, or 30-day points between the groups in wound events, readmissions,

pain (visual analog scale) or quality of life were observed. Robotic hernia repair was associated with longer median operative times (75.5, interquartile range, 59.0 to 93.8 vs. 40.5, 29.2 to 63.8 min;  $P < 0.01$ ), higher median cost (\$3258, \$2568 to \$4118 vs. \$1421, \$1196 to \$1930;  $P < 0.01$ ) and higher mean surgeon mental frustration ( $32.7 \pm 23.5$  vs.  $20.1 \pm 19.2$ ;  $P = 0.004$ ), assessed by the NASA Task Load Index Scale. No differences in surgeon ergonomics were observed. (Article Selection: Beatrice Beck-Schimmer, M.D. Image: original image, Adobe Stock; image illustration, M. Lane-Fall.)

**Take home message:** Robotic hernia repair did not show any clinical benefit compared to traditional laparoscopic hernia repair, and was associated with higher costs, longer operating times, and increased surgeon frustration.



### Remdesivir for the treatment of Covid-19—Preliminary report. *N Engl J Med* 2020 May 22 [Epub ahead of print]. PMID: 32445440.

Efficacious therapeutic agents for COVID-19 have not been rigorously reported. This study reports preliminary results of 1,063 patients in the Adaptive COVID-19 Treatment Trial (80% North American), evaluating remdesivir, an inhibitor of viral RNA-dependent, RNA polymerase with known inhibitory activity against SARS-CoV and the Middle East respiratory syndrome, *versus* placebo in hospitalized adults with laboratory-confirmed COVID-19 and evidence of lower respiratory tract involvement (85% requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation). Patients were randomized to remdesivir (200 mg IV load the first day, 100 mg day up to 9 additional days) *versus* normal

saline placebo. The primary outcome was recovery (hospital discharge or hospitalization for infection control purposes). Remdesivir reduced median recovery time (11 days [95% CI, 9 to 12]) *versus* 15 days for placebo (95% CI, 13 to 19; rate ratio for recovery 1.32 [95% CI, 1.12 to 1.55];  $P < 0.001$ ). No differences in mortality by 14 days were observed (7.1% with remdesivir and 11.9% with placebo; hazard ratio, 0.70; 95% CI, 0.47 to 1.04). Serious adverse events occurred in 21.1% of the remdesivir group *versus* 27.0% of the placebo group. The trial was terminated early by the data safety monitoring board based on the primary outcome. (Article Selection: Martin J. London, M.D. Image: original image, Adobe Stock/Centers for Disease Control and Prevention; image illustration, M. Lane-Fall.)

**Take home message:** Intravenous remdesivir was superior to placebo in shortening time to recovery in hospitalized adults with COVID-19 with lower respiratory tract infection.



### Studies on the mechanism of general anesthesia. *Proc Natl Acad Sci USA* 2020; 117:13757–66. PMID: 32467161.

Volatile anesthetic drugs have a wide range of different chemical structures, and typically their potency has been related to their lipophilicity. Anesthetic activation of protein ion channel targets could result from direct binding to hydrophobic protein regions, or *via* nonspecific membrane binding to lipid rafts surrounding the protein channel. Using nanoscale microscopy on *in vitro* human cells and targeted mutations in *Drosophila* fruit flies (reduced anesthetic sensitivity), the authors demonstrate that chloroform and isoflurane activation of TWIK-related potassium channel-1 (TREK-1) currents is mediated by disrupting phospholipase D2 (PLD2) localization in lipid rafts, thus reducing production of phosphatidic acid, a signaling lipid necessary to open the channel. One mM chloroform and isoflurane increased raft area threefold ( $P < 0.0001$ ). The anesthetic activation of the TREK-1 potassium current was eliminated in cells with a catalytically inactive PLD2 mutant, and in a cell-free system. PLD2 was activated by diethyl ether, chloroform, isoflurane, and xenon, but not by ketamine and the nonimmobilizer F6. *Drosophila* mutants with an inactive PLD2 took longer to become anesthetized with chloroform (~600 vs. ~350 s,  $P < 0.0001$ ). (Article Selection: Jamie W. Sleight, M.D. Image: original image, Adobe Stock; image illustration, M. Lane-Fall.)

**Take home message:** Volatile anesthetics target membrane-based channels, disrupting lipid rafts. Levels of membrane phosphatidic acid appear to regulate anesthetic sensitivity *in vivo*.



### Graduated compression stockings as adjuvant to pharmaco-thromboprophylaxis in elective surgical patients (GAPS study): Randomised controlled trial. *BMJ* 2020; 369:m1309. PMID: 32404430.

Recommendations for the use of graduated compression stockings for prevention of postoperative venous thromboembolism (VTE) are based primarily on older literature. Their role in contemporary surgical practice is less certain. The authors conducted a prospective, randomized controlled, multicenter, noninferiority trial in 1,858 patients at moderate or high risk for VTE undergoing elective surgery in seven United Kingdom National Health Service hospitals comparing the incidence of lower limb deep vein thrombosis or pulmonary embolism in patients within 90 days of surgery (primarily upper or lower

gastrointestinal or obstetric/gynecological) receiving either low molecular weight heparin or low molecular weight heparin plus graduated compression stockings for the duration of their hospitalization. Patients underwent bilateral ultrasound evaluations of the lower extremities between 14 and 21 days postsurgery. The primary outcome occurred in 1.7% of patients treated with low molecular weight heparin alone *versus* 1.4% in the low molecular weight heparin plus graduated compression stockings (95% CI, -0.65% to 1.26%), indicating that low molecular weight heparin was not inferior to low molecular weight heparin plus graduated compression stockings in preventing these thromboembolic complications in this surgical population. (Article Selection: Charles W. Emala, Sr., M.D., M.S. Image: original image, Adobe Stock; image illustration, M. Lane-Fall.)

**Take home message:** The finding of noninferiority for low molecular weight heparin alone relative to low molecular weight heparin plus graduated compression stockings suggests the latter may not be necessary in most patients undergoing elective surgery.