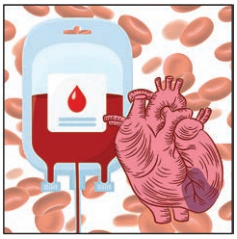
SCIENCE, MEDICINE, AND THE ANESTHESIOLOGIST

ANESTHESIOLOGY

Martin J. London, M.D., Editor

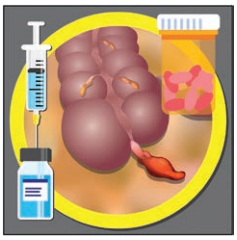
Key Papers from the Most Recent Literature Relevant to Anesthesiologists



Effect of a restrictive vs liberal blood transfusion strategy on major cardiovascular events among patients with acute myocardial infarction and anemia: The REALITY randomized clinical trial. JAMA 2021; 325:552–60. PMID: 33560322.

Optimal transfusion strategies for patients with acute myocardial infarction with anemia during hospitalization remain controversial. At 35 hospitals (France and Spain) the authors conducted a noninferiority, 1:1 randomized trial of 668 patients (2016 to 2019) with hemoglobin concentrations between 7 and 10 g/dl at any time during their admission, employing restrictive (transfusion at hemoglobin less than or equal to 8 g/dl) or liberal (transfusion at hemoglobin less than or equal to 10 g/dl) transfusion strategies. The primary clinical outcome was major adverse cardiovascular events (composite of all-cause death, stroke, recurrent myocardial infarction, or emergency revascularization) at 30 days. Noninferiority was defined by the upper boundary of the one-sided 97.5% CI for the relative risk of the primary outcome (less than 1.25). Of the 666 patients completing 30-day follow-up (median age, 77 yr [interquartile range, 69 to 84 yr]; 281 [42%] women), there were 342 in the restrictive group (36% transfused; 342 total units) and 324 in the liberal group (100% transfused; 758 total units). At 30 days, major adverse cardiovascular events occurred in 11% (95% CI, 7.5 to 14.6%) in the restrictive group and in 14% (95% CI, 10.0 to 17.9%) in the liberal group (difference, −3% [95% CI, −8.4 to 2.4%]). The relative risk of the primary outcome was 0.79 (one-sided 97.5% CI, 0.00 to 1.19), meeting the prespecified noninferiority criterion. *(Article Selection: Martin J. London, M.D. Image: M. Lane-Fall/Adobe Stock.)*

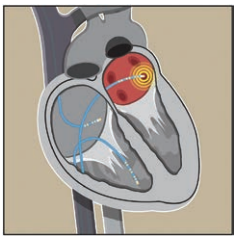
Take home message: In patients with acute myocardial infarction and anemia, a restrictive transfusion strategy resulted in a noninferior rate of major adverse cardiovascular events after 30 days, although the confidence interval included potential for clinically important harm.



Effect of oral moxifloxacin vs intravenous ertapenem plus oral levofloxacin for treatment of uncomplicated acute appendicitis: The APPAC II randomized clinical trial. JAMA 2021; 325:353–62. PMID: 33427870.

Antibiotic therapy in patients with appendicitis has been shown to be a safe alternative to surgery, although evidence-based antibiotic regimens remain controversial. The Appendicitis Acuta (APPAC) II multicenter, open-label, noninferiority randomized clinical trial (9 Finnish hospitals; 2017 to 2018) randomized 599 patients (ages 18 to 60 yr) with computed tomography–confirmed uncomplicated acute appendicitis to oral monotherapy (n = 295; oral moxifloxacin 400 mg/day for 7 days) *versus* intravenous followed by oral antibiotics (n = 288; intravenous ertapenem 1 g/day for 2 days followed by oral levofloxacin 500 mg/day and metronidazole 500 mg 3 times/day for 5 days). The primary outcomes were treatment success (greater than or equal to 65%; discharge from hospital without surgery and no recurrent appendicitis during 1-yr follow-up) and noninferiority of oral therapy, with a margin of 6% for difference. Of the randomized patients (age mean ± SD, 36 ± 12 yr; 263 [44%] women), 581 completed 1-yr follow-up with a treatment success rate of 70% (one-sided 95% CI, 65.8% to infinity) for oral antibiotics and 74% (one-sided 95% CI, 69.5% to infinity) for intravenous followed by oral antibiotics. The difference was −3.6% (one-sided 95% CI, −9.7% to infinity; $P = 0.26$ for noninferiority), with the confidence limit exceeding the noninferiority margin. *(Article Selection: Martin J. London, M.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: In adults with uncomplicated acute appendicitis, treatment with 7 days of oral moxifloxacin compared to 2 days of intravenous ertapenem followed by 5 days of levofloxacin and metronidazole had treatment success rates greater than 65% for either, but failed to demonstrate noninferiority.



Cryoablation or drug therapy for initial treatment of atrial fibrillation. N Engl J Med 2021; 384:305–15. PMID: 33197159.

In an aging population atrial fibrillation is the most common arrhythmia. This open-label, prospective trial randomized 303 patients (mean ages, 58 to 60 yr) with symptomatic paroxysmal atrial fibrillation (without daily use of a class I or III antiarrhythmic agent) at 18 Canadian centers to either cryothermy balloon catheter pulmonary vein ablation or antiarrhythmic drug therapy (flecanide, propafenone, sotalol, dronedarone, or amiodarone varying by local practice) for initial rhythm control. General anesthesia was used in 70% of cryoablation procedures. Patients were monitored for 12 months with an implantable cardiac monitoring device to detect tachyarrhythmias. The primary outcome was first recurrence of atrial fibrillation, atrial tachycardia, or flutter 3 to 12 months after initial treatment. Secondary outcomes were absence of symptomatic arrhythmias, atrial fibrillation burden, and quality of life ratings. Atrial tachyarrhythmias recurred in 43% of the ablation group and in 68% of the antiarrhythmic group (hazard ratio, 0.48; 95% CI, 0.35 to 0.66; $P < 0.001$). Symptomatic atrial tachyarrhythmias recurred in 11% of ablation patients and in 26% of antiarrhythmic drug patients (hazard ratio, 0.39; 95% CI, 0.22 to 0.68). Serious adverse events occurred in 5 patients (3%) undergoing ablation and in 6 patients (4%) receiving antiarrhythmics. *(Article Selection: BobbieJean Sweitzer, M.D. Image: M. Lane-Fall/Adobe Stock.)*

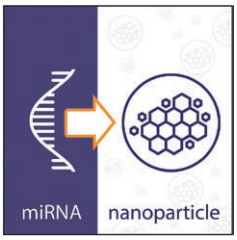
Take home message: In patients receiving initial treatment for symptomatic, paroxysmal atrial fibrillation, catheter cryoballoon ablation resulted in a significantly lower rate of atrial fibrillation recurrence at 1 yr compared to antiarrhythmic drug therapy.

DOI: 10.1097/ALN.0000000000003787

Better understanding the disparity associated with black race in heart transplant outcomes: A national registry analysis. Circ Heart Fail 2021; 14:e006107. PMID: 33525893.

Previous registry data have confirmed a higher risk of mortality of Black heart transplant recipients relative to White recipients. Age-related subgroup analyses are lacking. The authors retrospectively analyzed 22,997 adult heart transplant recipients (2005 to 2017) using the Scientific Registry of Transplant Recipients database (all transplants in the United States) using Cox regression adjusting for multiple factors, including socioeconomic status (education and insurance), human leukocyte antigen and panel reactive antigen status, and immunosuppressive regimens at discharge. Black recipients ages 18 to 30 yr (n = 514) had 2.05-fold (95% CI, 1.67 to 2.51) higher risk of mortality relative to comparable non-Black recipients (n = 1,274; $P < 0.001$, interaction $P < 0.001$); this risk was significant only in the first year post-transplant (adjusted hazard ratio, 2.30; 95% CI, 1.60 to 3.31; $P < 0.001$; subsequent years: adjusted hazard ratio, 0.84; 95% CI, 0.54 to 1.29; $P = 0.4$). In the first year, causes of mortality were similar between Black and White recipients (cardiovascular 30% *vs.* 25%; graft failure 28% *vs.* 23%). An attenuated association was observed in older recipients; ages 31 to 40, 1.53-fold greater risk (95% CI, 1.25 to 1.89; $P < 0.001$); 41 to 60 yr, 1.20-fold greater risk (95% CI, 1.09 to 1.33; $P < 0.001$). Between ages 61 to 80 yr, no association was noted (adjusted hazard ratio, 1.12; 95% CI, 0.97 to 1.29; $P = 0.1$). *(Article Selection: Martin J. London, M.D. Image: M. Lane-Fall/Adobe Stock.)*

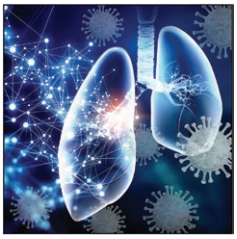
Take home message: Young Black recipients have a higher risk of mortality than non-Black recipients in the first year after heart transplant, suggesting further research is needed on socioeconomic barriers to care, as well as immunosuppressive regimens and treatment adherence.



Nanoparticle delivery of microRNA-146a regulates mechanotransduction in lung macrophages and mitigates injury during mechanical ventilation. Nat Commun 2021; 12:289. PMID: 33436554.

Mechanical ventilation induces lung injury by physical forces, which activate proinflammatory signaling. Previous findings suggest that microRNA, small noncoding RNAs, are upregulated in lung tissue in response to mechanical stress and that specifically miR-146a may downregulate proinflammatory signaling (IL-6, IL-8, TRAF6). However, the cellular origin of miR-146a and its therapeutic potential in reducing inflammation and ventilator-induced lung injury remain elusive. Using an *in vitro* model with human alveolar macrophages exposed to oscillatory pressure and *in vivo* mouse models including genetically modified miR-146a knockout mice subjected to high tidal volume ventilation (12 ml/kg), it was possible to demonstrate that mechanical stress increases expression of miR-146a predominantly in alveolar macrophages, but that this modest increase in expression is insufficient to dampen ventilator-induced lung injury. Intratracheal application of miR-146a administered as nanoparticles before injurious mechanical ventilation increased miR-146a to supraphysiologic levels (10- to 100-fold in the whole lung), resulting in reduced lung inflammation and stiffness, preserved alveolar capillary barrier function, and improved tissue oxygenation. *(Article Selection: Michael Zaugg, M.D., M.B.A. Image: M. Lane-Fall/Adobe Stock.)*

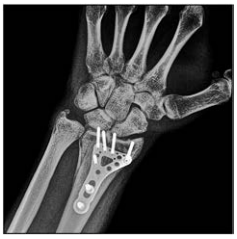
Take home message: Boosting the expression of endogenous miR-146a by nanoparticle-based intratracheal delivery of exogenous miR-146a to alveolar macrophages mitigates ventilator-induced lung injury in mice.



The impact of ventilation–perfusion inequality in COVID-19: A computational model. J Appl Physiol 2021; 130:865–76. PMID: 33439790.

COVID-19 patients are often disproportionally more hypoxemic than would be expected from the amount of consolidation seen on chest imaging. This pattern is similar to patients with pulmonary emboli from venous thrombi (*e.g.*, deep vein thrombosis). The authors studied five severely ill COVID-19 patients ($Pao_2/Fio_2 = 91 \pm 19$ mmHg), all of whom later died. The pure shunt fraction was equated with the fraction of nonaerated lung tissue estimated from quantitative computed tomography scans (0.33 ± 0.05). Pulmonary ventilation and perfusion were modeled and fitted to cardiac output, hemoglobin concentration, and inspired and arterial blood gases for four patients. The computational model showed the distribution of the patients' ventilation/perfusion ratios had high variance ($\log SD = 1.66 \pm 0.14$) and were bimodal, with very low ventilation/perfusion ratios (0.06 ± 0.02) driven by very high lung perfusion. *(Article Selection: Jamie W. Sleigh, M.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: This computational model suggests potential importance of microthrombi and severe vessel tone dysregulation in the pathogenesis of hypoxemia in COVID-19 adult respiratory distress syndrome.



Surgical plating vs closed reduction for fractures in the distal radius in older patients: A randomized clinical trial. JAMA Surg 2021; 156:229–37. PMID: 33439250.

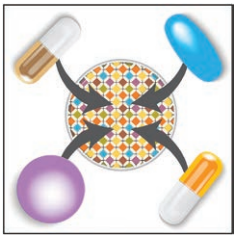
Distal radius fractures represent a common fracture type in the elderly, but it remains unclear if surgical treatment is better than nonsurgical treatment. The authors report a multicenter randomized trial (19 centers, Australia/New Zealand, the Combined Randomised and Observational Study of Surgery for Fractures in the Distal Radius in the Elderly [CROSSFIRE] study group) and parallel observational study, comparing surgery (open reduction and internal fixation using a volar-locking plate) to closed reduction with cast immobilization. The primary outcome was the Patient-Rated Wrist Evaluation score at 12 months follow-up. Between December 1, 2016 and December 31, 2018, 166 patients age 60 yr and older were enrolled, of which 81 underwent surgery and 85 closed reduction. One hundred thirty-four patients who refused randomization were included in the parallel observational cohort, 32 of whom had surgery and 102 closed reduction. There was no difference in the primary outcome at 12 months with a mean score 20 ± 21 for surgery and 22 ± 24 for closed reduction (mean difference, 1.7; 95% CI, –5.4 to 8.8). No differences in total complications, quality of life, wrist pain, or symptoms at 3 and 12 months were observed, but surgery was associated with more patient-reported treatment success (relative risk, 1.26; 95% CI, 1.07 to 1.48; $P = 0.005$) and greater use of postoperative physical therapy (relative risk, 1.32; 95% CI, 1.04 to 1.69; $P = 0.02$). *(Article Selection: Beatrice Beck-Schimmer, M.D. Image: Adobe Stock.)*

Take home message: In patients older than 60 yr, surgery using volar-locking plates showed no clinical benefit compared to closed reduction and cast immobilization at 12 months follow-up.

Global variation in postoperative mortality and complications after cancer surgery: A multicentre, prospective cohort study in 82 countries. Lancet 2021; 397:387–97. PMID: 33485461.

Surgery is a common treatment modality for patients diagnosed with cancer, but there are few data comparing postoperative outcomes between countries of different major income strata. This multicenter prospective cohort study included 15,958 patients undergoing surgery for breast (53%), colorectal (39%), or gastric (8%) cancer requiring general or neuraxial anesthesia between April 2018 and January 2019 (84 countries, 437 hospitals, 28-day enrollment periods): 57% high income, 17% upper middle income, and 26% low/middle income. The primary outcome was mortality or major complications (Clavien Dindo grades III, IV, or V) within 30 postoperative days. Three-level models accounting for patient and disease factors nested within hospitals and country of treatment were used to adjust outcomes. Mortality was higher for gastric cancer in low-income and middle-income countries (adjusted odds ratio, 3.72; 95% CI, 1.70 to 8.16) and for colorectal cancer in both low-income and middle-income countries (adjusted odds ratio, 4.59; 95% CI, 2.39 to 8.80) and upper-middle-income countries (adjusted odds ratio, 2.06; 95% CI, 1.11 to 3.83). There was no difference in mortality for breast cancer. The proportion of major postoperative complications was similar between income groups, but mortality after complications (failure to rescue) was significantly higher in low- and middle-income countries and upper-middle-income countries (adjusted odds ratios, 6.15 [95% CI, 3.26 to 11.59] and 3.89 [95% CI, 2.08 to 7.29], respectively) relative to high-income countries. *(Article Selection: Beatrice Beck-Schimmer, M.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: Thirty-day postoperative mortality after surgery for globally prevalent cancers is up to four times higher in resource-limited settings, despite patients experiencing similar major complication rates.



Polypill with or without aspirin in persons without cardiovascular disease. N Engl J Med 2021; 384:216–28. PMID: 33186492.

The polypill was proposed in 2003 after a modeling analysis suggested that fixed-dose combination therapy in persons with atherosclerotic cardiovascular disease and in all others 55 yr of age and older could reduce cardiovascular disease burden by 80% or more. The International Polycap Study 3 randomly assigned 5,713 participants in 86 centers in nine countries without known cardiovascular disease but with an elevated INTERHEART Risk Score (a previously validated global cardiovascular risk score) to receive a polypill (simvastatin 40 mg, atenolol 100 mg, hydrochlorothiazide 25 mg, and ramipril 10 mg) or placebo daily, aspirin (75 mg) or placebo daily, and vitamin D (60,000 IU) or placebo monthly. Outcomes were compared using a 2-by-2-by-2 factorial design (polypill *vs.* placebo, aspirin *vs.* placebo, and polypill plus aspirin *vs.* double placebo). The primary outcome was major adverse cardiac events. After a mean follow-up of 4.6 yr, the polypill plus aspirin led to fewer cardiac events (4.1% *vs.* 5.8%; hazard ratio, 0.69; 95% CI, 0.50 to 0.97). Low-density lipoprotein cholesterol concentration and systolic blood pressure were lower (19 mg/dl; 5.8 mmHg) with the polypill. However, the frequency of hypotension or dizziness was higher in treated patients. *(Article Selection: BobbieJean Sweitzer, M.D. Image: M. Lane-Fall/Adobe Stock.)*

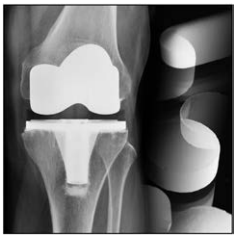
Take home message: Among adults at intermediate cardiovascular risk, a polypill containing a statin and three antihypertensives, along with aspirin daily, led to a lower rate of major adverse cardiac events relative to placebo.

DOI: 10.1097/ALN.0000000000003787

Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): A randomised, controlled, open-label, platform trial. Lancet 2021; 397:605–12. PMID: 33545096.

Azithromycin has been proposed as a treatment for COVID-19 given its immunomodulatory actions. In a randomized, controlled, open-label, adaptive platform trial (Randomised Evaluation of COVID-19 Therapy [RECOVERY]) at 176 hospitals in the United Kingdom used to evaluate potential therapies (dexamethasone, hydroxychloroquine, lopinavir-ritonavir), the safety and clinical benefit of azithromycin monotherapy (usual standard of care alone or usual standard of care plus azithromycin 500 mg once per day by mouth or intravenously for 10 days or until discharge) was evaluated in hospitalized COVID-19 patients. The primary outcome was 28-day all-cause mortality. A total of 16,442 patients were enrolled in the RECOVERY trial; 7,763 in the azithromycin study (33% azithromycin, 67% usual care alone; mean age 65 ± 16 yr, 38% female). No significant differences were noted in the primary outcome (22% *vs.* 22%; rate ratio, 0.97 [95% CI, 0.87 to 1.07]; $P = 0.50$), duration of hospital stay (median 10 days [interquartile range, 5 to greater than 28] *vs.* 11 days [interquartile range, 5 to greater than 28]) or the proportion of patients discharged from hospital alive within 28 days (rate ratio, 1.04 [95% CI, 0.98 to 1.10]; $P = 0.19$). Among nonintubated patients, no significant difference was seen in a composite endpoint of invasive mechanical ventilation or death (risk ratio, 0.95 [95% CI, 0.87 to 1.03]; $P = 0.24$). *(Article Selection: Martin J. London, M.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: In patients hospitalized with COVID-19, routine azithromycin therapy did not improve survival or other prespecified clinical outcomes.



Tapentadol vs oxycodone for postoperative pain treatment the first 7 days after total knee arthroplasty: A randomized clinical trial. Pain 2021; 162:396–404. PMID: 32773594.

Controlling acute perioperative pain is integral to early hospital discharge and ambulation after arthroplasty surgery. Although opioids are usually effective, they have numerous side effects (*e.g.*, sedation, nausea, constipation) and safety concerns (*e.g.*, respiratory depression). Tapentadol, an analgesic that acts at the μ-opioid and α-2-adrenergic receptors, is a potential therapy for postoperative pain that has not previously been compared to pure μ-opioids. This single-center (Norway) randomized, controlled, double-blinded study evaluated the daily administration of tapentadol extended-release (50 mg twice per day for 7 days) *versus* oxycodone controlled-release (10 mg twice per day for 7 days) *versus* placebo in 134 patients undergoing total knee arthroplasty with spinal anesthesia with intra-articular local infiltration and multimodal medications. The primary outcome was pain on mobilization self-assessed daily on a numeric rating scale (0 to 10) over the first 7 postoperative days. The primary outcome, reported as cumulative pain scores (area under the curve), was 528 ± 268 (interquartile range, 357 to 665) for placebo, 427 ± 204 (interquartile range, 304 to 544) for tapentadol extended-release, and 508 ± 244 (interquartile range, 292 to 687) for oxycodone controlled-release ($P = 0.12$). No significant effect was found in the secondary outcomes except for the incidence of constipation, which was lower in the tapentadol group ($P = 0.02$). *(Article Selection: Meghan Prin, M.D., M.S. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: The use of tapentadol did not result in less pain on mobilization in the first 7 days after total knee arthroplasty compared to oxycodone or placebo, although it did decrease the incidence of constipation.

Bupropion and naltrexone in methamphetamine use disorder. N Engl J Med 2021; 384:140–53. PMID: 33497547.

Methamphetamine use disorder is rising in the United States. In addition to being a cause of overdose deaths, this use disorder may lead to other medical, psychologic, and social comorbidities. Available treatments are poorly effective. The authors randomized 403 participants with moderate to severe methamphetamine use disorder to injectable sustained-release naltrexone (380 mg every 3 weeks) plus oral extended-release bupropion (450 mg per day) *versus* placebo. An innovative sequential trial design was employed; after 6 weeks of placebo, nonresponders in stage 1 were re-randomized to active or placebo treatment for an additional 6 weeks in stage 2. Urine samples were obtained twice weekly. The primary outcome response was defined as at least 3 of 4 negative urine samples during the final week of each stage of the trial. The weighted average response across the two stages was 13.6% with naltrexone–bupropion *versus* 2.5% with placebo ($P < 0.001$). Secondary endpoints including drug craving, social functioning, and Patient Health Questionnaire-9 scores also favored active treatment. Serious adverse events were similar between groups. *(Article Selection: J. David Clark, M.D., Ph.D. Image: M. Lane-Fall/Adobe Stock.)*

Take home message: Although the overall response rate to treatment was low, combination naltrexone–bupropion had a better therapeutic effect than placebo.