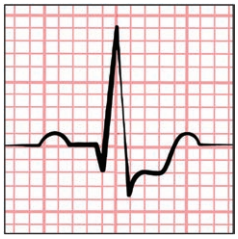
SCIENCE, MEDICINE, AND THE ANESTHESIOLOGIST
ANESTHESIOLOGY
Martin J. London, M.D., Editor
Key Papers from the Most Recent Literature Relevant to Anesthesiologists



Angiography after out-of-hospital cardiac arrest without ST-segment elevation. N Engl J Med 2021; 385:2544–53. PMID: 34459570.

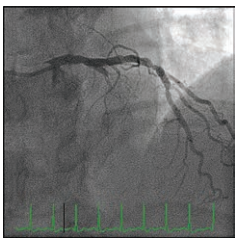
Mortality after out-of-hospital cardiac arrest is high, even with high-quality resuscitation. Up to 60% of these events are attributable to acute coronary syndrome, which is associated with ST-segment elevation and may be responsive to early coronary angiography. However, the benefits of early angiography among patients without ST-segment elevation is unclear. This open-label trial randomized out-of-hospital cardiac arrest patients (greater than 30 yr old) without ST-segment elevation to immediate angiography *versus* selectively delayed angiography. Revascularization was available to all patients for significant occlusion of at least one coronary artery. The primary outcome was 30-day all-cause mortality. From November 2016 to September 2019, 554 patients (median age 70 yr; 30% female; 38% with pre-existing coronary disease) at 31 sites in Germany and Denmark were studied. In the immediate group (n = 265), 96% of patients underwent angiography after a median 2.9 h, and of these 37% required revascularization. In the delayed group (n = 265), 62% underwent angiography after a median 47 h and of these 43% required revascularization. At 30 days, 54% of the immediate angiography group and 46% of the delayed-angiography group had died. In time-to-event analyses there was no difference in the primary outcome between groups (hazard ratio 1.28; 95% CI, 1.00 to 1.63; $P = 0.06$). *(Article Selection: Martin J. London, M.D. Image: J. P. Rathmell.)*

Take home message: In adult patients sustaining out-of-hospital cardiac arrest without evidence of ST-elevation, immediate coronary angiography was not associated with greater 30-day survival compared to a selective delayed approach.

Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): A randomised, controlled, open-label, platform trial. Lancet 2022; 399:143–51. PMID: 34800427.

Patients hospitalized with COVID-19 have an increased risk of thrombotic events. The role of antithrombotic effects of aspirin in treatment are uncertain. This randomized, controlled, open-label, platform trial (RECOVERY) conducted at 177 hospitals in the United Kingdom compared several treatments to usual care in hospitalized COVID-19 patients. In this phase, patients were randomized to 150 mg aspirin once per day until discharge or usual standard of care using unstratified randomization. Of the entire cohort, 97% had heparin-based thromboprophylaxis. The primary outcome was 28-day mortality using intention-to-treat analyses. Between November 2020 and March 2021, 7,351 patients were randomly allocated to receive aspirin and 7,541 patients to receive usual care alone. No difference in the primary outcome was observed (17% *vs.* 17%; rate ratio 0.96; 95% CI, 0.89 to 1.04; $P = 0.35$), including all prespecified subgroups of patients. There was no significant difference in the proportion meeting the composite endpoint of invasive mechanical ventilation or death (21% *vs.* 22%; risk ratio 0.96; 95% CI, 0.90 to 1.03; $P = 0.23$). Aspirin use was associated with fewer thrombotic events (4.6% *vs.* 5.3%; absolute reduction 0.6%; standard error 0.4%) and greater major bleeding events (1.6% *vs.* 1.0%; absolute increase 0.6%; standard error 0.2%). *(Article Selection: Martin J. London, M.D. Image: J. P. Rathmell.)*

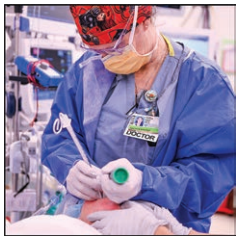
Take home message: In patients hospitalized with COVID-19, aspirin was not associated with lesser 28-day mortality or in the risk of progressing to invasive mechanical ventilation or death but was associated with lesser thrombotic events and greater bleeding events.



2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022; 145:e4–e17. PMID: 34882436.

This executive summary presents top 10 items from the complete 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization, which provides an extensive literature update and officially retires three previous guidelines (2011 percutaneous coronary intervention [PCI], 2011 coronary artery bypass graft [CABG], and 2015 PCI in ST-segment–elevation myocardial infarction [STEMI] guideline), including sections on revascularization in three other guidelines (2013 STEMI, 2014 non–STEMI, and 2012 stable ischemic heart disease). The guideline indicates the strength of recommendations and level of evidence for CABG or PCI to treat ischemic heart disease with a patient-centric approach. A multidisciplinary heart team approach is recommended for patients being evaluated for coronary revascularization when optimal strategy is uncertain. Revascularization decisions are based on disease complexity and technical treatment feasibility. Level 1 (strong) recommendations include CABG to treat significant left main stenosis and staged PCI of a significant noninfarct artery stenosis in selected hemodynamically stable patients with STEMI and multivessel disease after successful primary PCI. Calculation of surgical risk with the Society of Thoracic Surgeons score is recommended. Recommendations are also made regarding use of radial artery grafting, duration of dual antiplatelet therapy after PCI, and optimal management for diabetics with three-vessel disease. *(Article Selection: BobbieJean Sweitzer, M.D. Image: J. P. Rathmell.)*

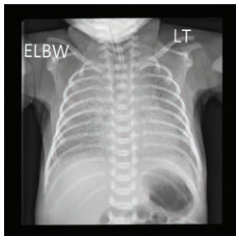
Take home message: Earlier PCI and CABG surgery guidelines have been updated with new evidence to guide clinicians in caring for patients undergoing coronary revascularization.



Effect of use of a bougie vs endotracheal tube with stylet on successful intubation on the first attempt among critically ill patients undergoing tracheal intubation: A randomized clinical trial. JAMA 2021; 326:2488–97. PMID: 34879143.

Twenty percent of emergency intubations in critically ill patients fail on a first attempt, putting the patients at risk for severe hypoxemia. This multicenter randomized controlled trial compared the effect of using bougie technique *versus* endotracheal tube with stylet in critically ill patients undergoing emergency tracheal intubation in 15 U.S. emergency departments/intensive care units. The primary outcome was defined as successful first-attempt intubation, secondary endpoints as incidence of severe hypoxemia (lowest oxygen saturation less than 80%) and procedural complications. Of 1,102 patients randomized (41% women, median age 58 yr), 80% in the bougie *versus* 83% in the stylet group were successfully intubated on the first attempt (absolute risk difference –2.6 percentage points [95% CI, –7.3 to 2.2]; $P = 0.27$). Severe hypoxemia was noted in 11% *versus* 9% of patients, respectively (absolute risk difference, 2.2 percentage points [95% CI, –1.6 to 6.0]). There was no difference in procedural complications such as esophageal intubation, oral or glottic injury, or pneumothorax. *(Article Selection: Beatrice Beck-Schimmer, M.D. Image: J. P. Rathmell.)*

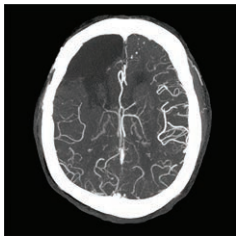
Take home message: In this multicenter trial, the incidence of successful intubation and complications was comparable using either a bougie or stylet assisted approach in randomized patients requiring emergency intubation.



Effect of minimally invasive surfactant therapy vs sham treatment on death or bronchopulmonary dysplasia in preterm infants with respiratory distress syndrome: The OPTIMIST-A randomized clinical trial. JAMA 2021; 326:2478–87. PMID: 34902013.

Efforts have been made to reduce the need for endotracheal intubation and instead support newly born preterm with continuous positive airway pressure (CPAP). Exogenous surfactant is usually limited to infants requiring a relatively high fraction of inspired oxygen (0.4 to 0.6). This prospective randomized placebo-controlled study sought to determine the effect of minimally invasive surfactant (200 mg/kg of poractant alfa administered as a one-time dose intratracheally with direct laryngoscopy *via* a thin catheter) in preterm infants with respiratory distress syndrome supported with a CPAP level of 5 to 8 cmH_2O and requiring inspired oxygen therapy at a fraction greater than or equal to 0.30 *versus* no surfactant. The primary outcome was the composite of death and/or physiological bronchopulmonary dysplasia assessed at 36 weeks' postmenstrual age. Among the 485 infants randomized, the primary outcome was not different between groups (44% surfactant group *vs.* 50% sham control; $P = 0.10$); neither was mortality before 36 weeks' postmenstrual age (10% *vs.* 8% respectively; $P = 0.51$). However, the incidence of bronchopulmonary dysplasia in survivors to 36 weeks' postmenstrual age was significantly lower in the surfactant group (37%) compared to the sham control group (45%), $P = 0.03$. *(Article Selection: David Faraoni, M.D., Ph.D. Image: J. P. Rathmell.)*

Take home message: In preterm infants with respiratory distress syndrome supported with continuous positive airway pressure, minimally invasive surfactant therapy did not significantly lower the incidence of mortality or bronchopulmonary dysplasia at 36 weeks' postmenstrual age.



Intravenous thrombolysis after first-ever ischemic stroke and reduced incident dementia rate. Stroke 2021 Dec 30 [Epub ahead of print]. PMID: 34965738.

The risk of dementia doubles after first-time cerebrovascular accident or stroke, highlighting the potential importance of high-quality stroke care. Intravenous thrombolysis is associated with improved functional outcomes after ischemic stroke when administered within a 4.5-h window; however, its effect on the risk of dementia is unknown. This pragmatic retrospective cohort study included patients presenting with first-ever ischemic stroke and no previous history of dementia from July 2003 to March 2013 using the province-wide, population-based Ontario Stroke Registry (n = 7,072; 46% female; mean age 71 yr). The primary outcome was incident dementia 1 yr after stroke and secondary outcomes included incident dementia at 5 yr and at last available follow-up. Using weighted Cox regression, thrombolysis was associated with a 24% lower rate of incident dementia at 1 yr (hazard ratio 0.76; 95% CI, 0.58 to 0.97) and this remained significant at 5 yr (hazard ratio 0.79; 95% CI, 0.66 to 0.91) and all available follow-up (median 6.3 yr; hazard ratio 0.79; 95% CI, 0.68 to 0.89). *(Article Selection: Meghan Prin, M.D. Image: J. P. Rathmell.)*

Take home message: Intravenous thrombolysis for first-ever stroke is associated with a 24% lower rate of incident dementia 1 yr poststroke, persisting for at least 5 yr. Dementia may be an important clinical target in future studies of stroke care.

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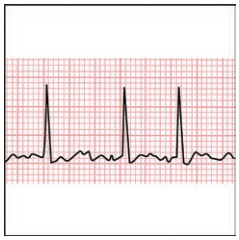
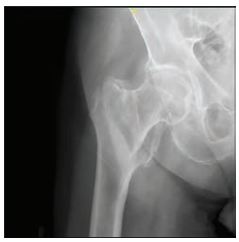


4-year outcomes after left atrial appendage closure versus nonwarfarin oral anticoagulation for atrial fibrillation. J Am Coll Cardiol 2022; 79:1–14. PMID: 34748929.

Left atrial appendage closure is a nonpharmacologic therapy increasingly used to prevent embolic complications in patients with atrial fibrillation. This noninferiority randomized trial at 10 centers in the Czech Republic (PRAGUE-17) compared atrial appendage closure to nonwarfarin direct oral anticoagulants in 402 patients with nonvalvular atrial fibrillation on a primary composite outcome (embolic events, cardiovascular death, clinically relevant bleeding, and procedure- or device-associated complications). The primary analysis noted no differences at a median of 20 months. At a median follow-up of 3.5 yr (interquartile range, 2.6 to 4.3; 1,354 patient-years), atrial appendage closure was noninferior to direct oral anticoagulation for the primary endpoint by modified intention-to-treat (subdistribution hazard ratio 0.81; 95% CI, 0.56 to 1.18; $P = 0.27$; P for noninferiority = 0.006). For the components of the composite endpoint, the corresponding subdistribution hazard ratios were 0.68 (95% CI, 0.39 to1.20; $P = 0.19$) for cardiovascular death, 1.14 (95% CI, 0.56 to 2.30; $P = 0.72$) for stroke/transient ischemic attack, 0.75 (95% CI, 0.44 to 1.27; $P = 0.28$) for clinically relevant bleeding, and 0.55 (95% CI, 0.31 to 0.97; $P = 0.039$) for nonprocedural clinically relevant bleeding. *(Article Selection: David Faraoni, M.D., Ph.D. Image: J. P. Rathmell.)*

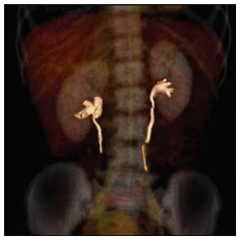
Take home message: In this long-term follow-up report of the PRAGUE-17 trial, atrial appendage closure remained noninferior to nonwarfarin direct oral anticoagulation for preventing major cardiovascular, neurological, or bleeding events in patients with nonvalvular atrial fibrillation.



Effect of regional vs general anesthesia on incidence of postoperative delirium in older patients undergoing hip fracture surgery: The RAGA randomized trial. JAMA 2022; 327:50–8. PMID: 34928310.

Dementia occurs frequently postoperatively in older patients sustaining hip fracture requiring surgical repair. The role of regional *versus* general anesthesia in its occurrence is uncertain. This clinical trial included 950 patients at nine Chinese hospitals, aged 65 yr and older, with or without pre-existing dementia, and a hip fracture requiring surgical repair (2014 to 2018). Patients were randomized to either regional (spinal, epidural, or a combination with no sedation; n = 476) or general anesthesia (intravenous, inhalational, or a combination; n = 474). The primary outcome was incidence of delirium within 7 postoperative days. The Delirium Rating Scale-Revised-98 was used to assess severity (range, 0 [none] to 39 [highest severity]). Among 950 randomized patients (mean age, 77 yr; 27% male), 941 were analyzed. The primary outcome was not different between groups: 6% regional anesthesia *vs.* 5% general anesthesia (unadjusted risk difference, 1.1%; 95% CI, –1.7 to 3.8%; $P = 0.48$). The mean severity score of delirium was 23 *versus* 24, respectively (unadjusted difference, –1.1; 95% CI, –4.6 to 3.1). There were no differences in the occurrence of a single episode of delirium (3% *vs.* 2%), the occurrence of hypoactive delirium (38% *vs.* 21%), median worst pain scores (0 *vs.* 0), median length of stay (7 *vs.* 7 days) or 30-day mortality (1.7% *vs.* 0.9%). *(Article Selection: Martin J. London, M.D. Image: J. P. Rathmell.)*

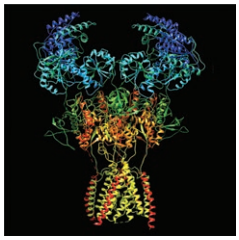
Take home message: In this multicenter randomized trial, the incidence of postoperative delirium after regional anesthesia without sedation compared to general anesthesia was not significantly different in older patients undergoing hip fracture repair.



Role of renal sympathetic nerve activity in volatile anesthesia's effect on renal excretory function. Function 2021; 6:zqab042. https://doi.org/10.1093/function/zqab042

In patients undergoing anesthesia and surgery, oliguria is common, but the underlying causes are not well elucidated. Understanding the mechanisms of oliguria during anesthesia and surgery could prevent acute kidney injury. The study tested the hypothesis that reduced urine output and reduced renal excretory function during surgery is due to increased renal sympathetic nerve activity. In a clinical study, renal function was measured before and during hypospadias surgeries in eight male pediatric patients (caudal block/sevoflurane). Reduced urinary flow (–65%), urinary sodium excretion (–49%), and increased plasma renin concentrations were observed, consistent with elevated renal sympathetic nerve activity, with no increase in plasma arginine vasopressin. As renal sympathetic nerve activity cannot be measured directly in humans, a study was conducted in sheep in the conscious state and under sevoflurane anesthesia. As with pediatric surgical patients, sevoflurane reduced urinary output (–52%) and urinary sodium excretion (–85%) and increased renal sympathetic nerve activity (burst frequency +105%, burst incidence +51%) compared to the conscious state. Surgical renal denervation normalized renal blood flow, urine output, and sodium excretion, consistent with the hypothesis that intact renal nerves are responsible for sevoflurane-mediated oliguria. *(Article Selection: Michael Zaugg, M.D. Image: J. P. Rathmell.)*

Take home message: Oliguria during sevoflurane anesthesia results from increased renal sympathetic nerve activity rather than from elevated plasma vasopressin or hypotension, explaining why simple fluid resuscitation during anesthesia may be ineffective in maintaining urine output.



Structures of the σ_2 receptor enable docking for bioactive ligand discovery. Nature 2021; 600:759–64. PMID: 34880501.

The σ2 receptor is a subtype of the mammalian σ membrane protein resident in the endoplasmic reticulum that regulates the sterol transporter NPC1. Although ubiquitously present, it is highly expressed in proliferating cells, tumors, and the central nervous system, and has been linked to cancer, pain, Alzheimers, and psychiatric disease. This study determined the molecular structure of this receptor in detail, in association with ligands roluperidone, PB28, and cholesterol. It consists of four transmembrane helices. Ordered water molecules form an essential part of the binding pocket that is required for successful ligand docking. Computer simulation (*in silico*) of the docking of 490,000,000 putative ligand molecules established 31 with a high affinity (less than 50 nM). Two potent σ2 selective ligands (Z4857158944 and Z1665845742), and one nonselective ligand (Z4446724338) were tested in a spared-nerve injury mouse model of neuropathic pain. The nonselective ligand (Z4446724338) completely reversed mechanical allodynia to preinjury levels. The effects peaked at 24 h after injection. These compounds did not have any effect on a panel of 19 other pain-related molecular targets, including μ-opioid receptors. *(Article Selection: Jamie Sleigh, M.D. Image: Cartoon of NMDA receptor, C22H31NO2, CC BY-SA 4.0,* via *Wikimedia Commons.)*

Take home message: This study demonstrates the utility of using structure-based screening of ultra-large ligand libraries to identify potentially useful *in vivo* probes for potential drug development in pain research.

Comparing Veterans Affairs and private sector perioperative outcomes after noncardiac surgery. JAMA Surg 2021 Dec 29 [Epub ahead of print]. PMID: 34964818.

Congress has recently increased the ability of veterans to receive non–Veterans Affairs (VA) surgical care. However, recent data comparing quality of non-VA *versus* VA care are lacking. Using Veterans Affairs Surgical Quality Improvement Program (VASQIP) and American College of Surgeons National Surgical Quality Improvement Program (NSQIP) data (calendar years 2015 to 2018), this study compared 30-day mortality following noncardiac surgery (primary outcome) and failure to rescue (postoperative death after a complication, secondary outcome) of VA hospitals *versus* private-sector hospitals. A total of 3,910,752 operations (3,174,274 from NSQIP and 736,477 from VASQIP) were analyzed (VASQIP 92% male *vs.* 47% in NSQIP; VASQIP 60% frail or very frail *vs.* 21% in NSQIP). Unadjusted NSQIP rates of 30-day mortality, complications, and failure to rescue were 0.8%, 9.5%, and 4.7%, *versus* 1.1%, 17.1%, and 6.7% in VASQIP (all differences $P < 0.001$). After adjustment, VA care was associated with an approximately 40% lower risk of perioperative death (adjusted relative risk, 0.59 [95% CI, 0.47 to 0.75]; $P < .001$). VA care was also associated with a lower risk of failure to rescue (adjusted relative risk, 0.55 [95% CI, 0.44 to 0.68]). An unmeasured confounder would require a relative risk of 2.78 [95% CI, 2.04 to 3.68] to obviate the main finding. *(Article Selection: Martin J. London, M.D. Image: Adobe Stock.)*

Take home message: VA surgical care is associated with lower perioperative mortality and lower failure to rescue despite higher-risk characteristics compared to nonveteran patients at non-VA hospitals.

Analgesic potential of terpenes derived from *Cannabis sativa*. Pharmacol Rev 2021; 73:98–126. PMID: 34663685.

Although Δ^9-tetrahydrocannabinol and cannabidiol are the two most researched constituents of *Cannabis sativa*, the leaves and flowers contain nearly 500 other chemical compounds. Roughly 150 of these are terpenes, and these compounds are receiving renewed attention as potential analgesics. This comprehensive review discusses the antinociceptive and anti-inflammatory effects of several terpene compounds, including limonene, linalool, geraniol, and others. Some of these (*e.g.*, linalool) have undergone extensive preclinical testing, most notably in models of nerve injury and inflammation, yet none have had a definitive target identified, although ion channels, G-protein coupled receptors, and the NMDA receptor are potential targets. Toxicities were rarely observed in preclinical testing. Complicating efforts, terpenes display an "entourage" effect whereby the overall effect of a mix of these chemicals is greater than or even different from what would be predicted from the effects of individual compounds. Small clinical studies suggest terpene-containing essential oils may lessen pain during migraine headaches, labor, and postsurgery, although properly controlling for the strong odors of these compounds has proven difficult. Overall, promising early data will need to be supported by robust clinical testing before these compounds can be used therapeutically. *(Article Selection: J. David Clark, M.D., Ph.D. Image: Adobe Stock.)*

Take home message: Terpene compounds present in *Cannabis sativa* hold promise for potential analgesic applications, although robust clinical testing has yet to be performed.

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