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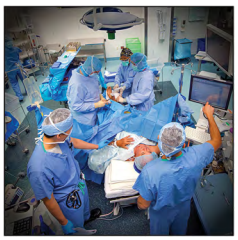
Intensive blood pressure control after endovascular thrombectomy for acute ischaemic stroke (ENCHANTED2/MT): A multicentre, open-label, blinded-endpoint, randomised controlled trial. Lancet 2022; 400:1585–96. PMID: 36341753.

Best practice for systolic blood management after acute ischemic stroke managed with endovascular thrombectomy is uncertain. This open-label, blinded-endpoint trial conducted at 44 tertiary hospitals in China randomized 821 adults (July 2020 to March 2022) with persistently elevated systolic blood pressure (140 mmHg or higher for more than 10 min) after reperfusion with endovascular thrombectomy for acute ischemic stroke due to intracranial large-vessel occlusion. Treatment arms were either more (systolic blood pressure target less than 120 mmHg) or less intensive treatment (target, 140 to 180 mmHg) from 1 h through 72 h. The primary outcome was functional recovery using the modified Rankin scale (range 0 [no symptoms] to 6 [death]) at 90 days. The trial was terminated early given safety concerns (initial target, 2,257 subjects). Subjects in the more intensive treatment group (407) were more likely to sustain poor functional outcome than those in the less intensive group (406), common odds ratio 1.37 [95% CI, 1.07 to 1.76]. Patients in this group also had higher risk of early neurologic deterioration (common odds ratio, 1.53 [95% CI, 1.18 to 1.97]) and major disability at 90 days (odds ratio, 2.07 [95% CI, 1.47 to 2.93]). No significant differences in symptomatic intracerebral hemorrhage were found between groups nor in serious adverse events, recurrent ischemic events, or mortality between groups. *(Article Selection: Martin J. London, M.D. Image: Adobe Stock.)*

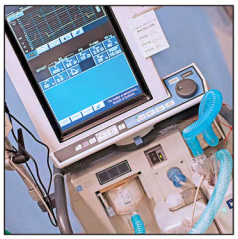
Take home message: This large, multicenter, randomized trial of more *versus* less intensive systolic blood pressure control over a 72-h period after endovascular thrombectomy induced reperfusion for acute large-vessel occlusion ischemic stroke was terminated early due to a higher incidence of poor functional outcomes with more intensive systolic blood pressure management.



Elective surgery system strengthening: Development, measurement, and validation of the surgical preparedness index across 1632 hospitals in 119 countries. Lancet 2022; 400:1607–17. PMID: 36328042.

The COVID-19 pandemic has had a detrimental impact on surgery and anesthesia services, particularly with regard to backlogs in elective surgery. To address the robustness of external stressors to surgical capability, The Lancet Commission on Global Surgery developed and validated a novel index, the surgical preparedness index, a measure of the worldwide fragility of planned surgical services. Initially, the index was developed through an international consensus process of 69 clinicians defining 23 prioritized core indicators (11 facilities and consumables, 2 staffing issues, 2 prioritization abilities, 8 systems parameters) with a score range from 23 (least prepared) to 115 (most prepared). This index was then assessed over a 2-month period in 2021 at 1,632 hospitals in 119 high-, middle-, and low-income countries (mean score for all sites was 84, and 89, 82, and 67 for high-, middle-, and low-income countries, respectively). To assess stability to stress (*e.g.*, COVID-19) the surgical volume before and after was calculated (surgical volume ratio). Overall, 75% of hospitals did not maintain their expected ratio, with the greatest reduction occurring in high- and middle-income centers. A linear mixed-effect regression model analysis demonstrated correlation of a 10-point increase in the index with a 4% increase in surgical volume ratio, independent of the income status. *(Article Selection: Beatrice Beck-Schimmer, M.D. Image: J. P. Rathmell.)*

Take home message: Based on assessment of four key domains of surgical preparedness, the newly developed surgical preparedness index can identify important areas for improvement in surgical and anesthesia care delivery associated with disruption of expected surgical volume in the face of external stressors.



Oxygen-saturation targets for critically ill adults receiving mechanical ventilation. N Engl J Med 2022; 387:1759–69. PMID: 36278971.

The optimal oxygen-saturation targets for critically ill adults requiring invasive mechanical ventilation are controversial. This study was a pragmatic, cluster-randomized, cluster-crossover trial at a single academic center (emergency department and medical intensive care unit) that randomized patients to a low (90%; range, 88 to 92%), intermediate (94%; range, 92 to 96%), or high saturation target (98%; range, 96 to 100%). Saturation was assessed by pulse oximetry. Other details of management were left to treating clinicians. Patients were enrolled over a 36-month period with exception of a 2-month pause during the COVID-19 pandemic. The primary outcome was the number of days alive and free of mechanical ventilation (ventilator-free days) through day 28. The secondary outcome was death by day 28. A total of 2,541 patients were analyzed (median ages, 57 to 59 yr; female, 45 to 47%; sepsis, 28 to 34%). There was no difference in the primary outcome between groups: low saturation (20 days; interquartile range, 0 to 25 days), intermediate saturation (21 days; interquartile range, 0 to 25 days), and high saturation (21 days; interquartile range, 0 to 26 days); $P = 0.81$. Likewise, there was no difference in in-hospital death by day 28 (35% *vs.* 34% *vs.* 33%). Adverse events (cardiac arrest, arrhythmia, myocardial infarction, stroke, and pneumothorax) were similar between groups. *(Article Selection: Martin J. London, M.D. Image: J. P. Rathmell.)*

Take home message: In a large, cluster-randomized, single-center trial, the use of a lower, intermediate, or higher oxygen saturation target during invasive mechanical ventilation did not influence the number of ventilator-free days at 28 days after randomization.

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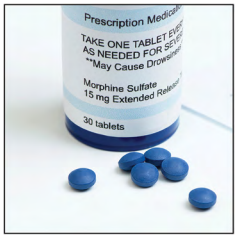
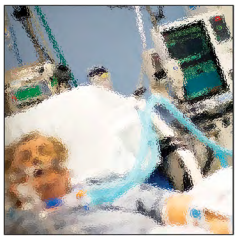


Effect of regular, low-dose, extended-release morphine on chronic breathlessness in chronic obstructive pulmonary disease: The BEAMS randomized clinical trial. JAMA 2022; 328:2022–32. PMID: 36413230.

Opioids are known to relieve symptoms of breathlessness; however their role in treating this symptom in patients with chronic obstructive pulmonary disease is uncertain. This multicenter (20 Australian centers), double-blind, placebo-controlled randomized clinical trial evaluated the impact of low-dose, extended-release oral morphine on chronic breathlessness in these patients with a modified Medical Research Council score of 3 to 4 after 1 week of treatment. Subjects were randomized 1:1:1 (8 mg/d, 16 mg/d, or placebo during week 1). At weeks 2 and 3, an additional 8 mg/d was added to the prior week's dose. The primary outcome was the change in the intensity of breathlessness using a numerical rating scale (0 [none] to 10 [worst or most intense]) comparing the mean baseline score to the mean score after week 1 of treatment *versus* the placebo group. Daily step count by actigraphy device was assessed at week 3. A total of 156 subjects were analyzed (median age, 72 yr; 48% female); 138 (88%) completed treatment at week 1. There was no significant difference in the primary outcome at week 1 between groups: 8 mg morphine *versus* placebo (mean breathlessness score difference, –0.3 [95% CI, –0.9 to 0.4]); 16 mg morphine *versus* placebo (mean difference, –0.3 [95% CI, –1.0 to 0.4]). No difference was noted in the daily step count assessment. *(Article Selection: Martin J. London, M.D. Image: Adobe Stock.)*

Take home message: In a randomized trial of ambulatory chronic obstructive lung disease patients with chronic severe breathlessness, low-dose, extended-release morphine at two doses did not significantly reduce intensity of breathlessness after 1 week of treatment.



Early active mobilization during mechanical ventilation in the ICU. N Engl J Med 2022; 387:1747–58. PMID: 36286256.

Early active mobilization of intensive care unit (ICU) patients requiring mechanical ventilation is postulated to enhance outcome. This international multicenter trial (49 hospitals, six countries) randomized 750 adult ICU patients undergoing mechanical ventilation to early mobilization (sedation minimization and daily physiotherapy) or usual care. The primary outcome was the number of days alive and out of the hospital at 180 days after randomization. Key secondary outcomes included mortality (180 days) and patient-reported outcome measures. The study cohorts were similar (mean age, 61 *vs.* 60 yr; female, 35% *vs.* 40%; unplanned admission, 82% *vs.* 84%; sepsis, 66% *vs.* 66%). The mean ± SD daily duration of mobilization was 21 ± 15 min *versus* 9 ± 9 min; intervention *versus* usual care (difference, 12 min/day; 95% CI, 10 to 14). There was no difference in the primary outcome between groups: median, 143 days (interquartile range, 21 to 161 days) *vs.* 145 days (interquartile range, 51 to 164 days); absolute difference, –2 days; 95% CI, –10 to 6 days; $P = 0.62$. Among secondary outcomes, neither death by day 180 (23% *vs.* 20%, odds ratio, 1.15; 95% CI, 0.81 to 1.65) nor patient-reported outcomes among survivors were different. Adverse events potentially due to mobilization were higher in reported in the early-mobilization group, 9% *vs.* 4% ($P = 0.005$). *(Article Selection: Martin J. London, M.D. Image: J. P. Rathmell.)*

Take home message: This international multicenter trial failed to detect an advantage to early mobilization in patients requiring mechanical ventilation on the number of days patients were alive and out of the hospital at 180 days relative to usual care. The intervention was associated with an increase in adverse events.

Electroacupuncture vs sham electroacupuncture in the treatment of postoperative ileus after laparoscopic surgery for colorectal cancer: A multicenter, randomized clinical trial. JAMA Surg 2023; 158:20–7. PMID: 36322060.

Despite widespread adoption of enhanced recovery after surgery protocols, postoperative ileus remains a problem with regard to adequate recovery after colorectal resection. The role of electroacupuncture in reducing ileus has not been studied. This multicenter (four Chinese tertiary centers) sham-controlled trial randomized adults undergoing primary laparoscopic resection of colorectal cancer with an enhanced recovery after surgery protocol to four sessions (30 min/day for 4 days after surgery) of electroacupuncture (five acupoints) or sham (four non-acupoints, no electrical stimulation). The primary outcome was the time to first defecation. Secondary outcomes included other patient-reported outcome measures, length of postoperative hospital stay, readmission rate within 30 days, and incidence of postoperative complications and adverse events. A total of 248 patients (mean age, 60 yr; 62% male) were analyzed. The primary outcome was significantly shorter in the treatment group (median [interquartile range] times to defecation 76 h [68 to 97 h) *vs.* 90 h [74 to 100 h]; mean difference, –8.8; 95% CI, –15.8 to –1.7; $P = 0.003$). Of the secondary outcomes, time to first flatus, tolerability of semiliquid diet, and solid food were significantly less as was prolonged ileus (risk ratio, 0.51; 95% CI, 0.27 to 0.95; $P = 0.03$). Other secondary outcomes were not different. There were no severe adverse events. *(Article Selection: Martin J. London, M.D. Image: Adobe Stock.)*

Take home message: In a multicenter trial of Chinese patients undergoing laparoscopic colon resection using enhanced recovery after surgery protocols, those receiving electroacupuncture for 4 days postoperatively had significantly shorter time to first defecation *versus* a sham procedure.

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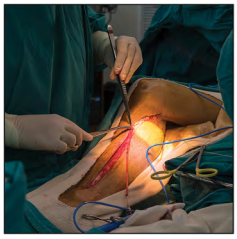


Surgery or endovascular therapy for chronic limb-threatening ischemia. N Engl J Med 2022; 387:2305–16. PMID: 36342173.

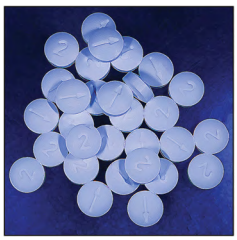
The relative roles of either endovascular therapy or surgical revascularization as initial therapies for chronic limb-threatening ischemia are not well delineated. This international, randomized trial of 1,830 patients with infrainguinal peripheral artery disease and limb ischemia studied two parallel cohorts: (1) patients with a single segment of great saphenous vein usable for surgery and (2) patients requiring an alternative bypass conduit. Within each cohort, patients were randomized (1:1) to surgical or endovascular treatment. The primary outcome was a composite of either a major adverse limb event (amputation above the ankle), a major limb reintervention (new bypass graft or graft revision, thrombectomy, or thrombolysis), or all-cause mortality. In cohort 1 (median follow-up, 2.7 yr), the primary outcome was significantly lower in the surgical group than in the endovascular group (43% *vs.* 57%; hazard ratio, 0.68; 95% CI, 0.59 to 0.79; $P < 0.001$). In cohort 2 (median follow-up, 1.6 yr), there was no significant difference (43% *vs.* 48%; hazard ratio, 0.79; 95% CI, 0.58 to 1.06; $P = 0.12$). There were no differences in the incidence of adverse events in any of the groups. *(Article Selection: Martin J. London, M.D. Image: Adobe Stock.)*

Take home message: In a large multicenter study of patients with infrainguinal peripheral artery disease and chronic limb-threatening ischemia, those with a great saphenous vein adequate for surgery had significantly less risk of a major adverse limb event or death relative to those undergoing endovascular therapy, while those without an adequate conduit did not.

Routine sterile glove and instrument change at the time of abdominal wound closure to prevent surgical site infection (ChEETAh): A pragmatic, cluster-randomised trial in seven low-income and middle-income countries. Lancet 2022; 400:1767–76. PMID: 36328045.

The effectiveness of changing gloves and instruments before wound closure in reducing postoperative abdominal surgical site infections is unclear. This multicenter, cluster-randomized trial in seven low- and middle-income African countries randomized clusters of patients undergoing abdominal surgery (consecutive adults and children undergoing elective or emergent abdominal surgery for a clean–contaminated, contaminated, or dirty operation) to standard practice (42 clusters) or intervention (change of gloves and instruments before wound closure for the entire scrub team [39 clusters]). The primary outcome was surgical site infection within 30 days after surgery using U.S. Centers for Disease Control and Prevention criteria and an intent-to-treat analysis. From June 2020 to April 2022, 81 clusters of 13,301 patients (7,157 routine *vs.* 6,144 intervention) were randomly assigned. Overall, 89% were adults, 46% underwent elective surgery, 61% underwent surgery that was clean–contaminated. Glove and instrument change occurred in 0.8% of standard practice *versus* 98.3% in the intervention group. The primary outcome was significantly lower in the intervention group (16% *vs.* 19%; adjusted risk ratio, 0.87; 95% CI, 0.79 to 0.95; $P = 0.0032$). Prespecified subgroup analyses did not show any evidence of heterogeneity of treatment effect. *(Article Selection: Martin J. London, M.D. Image: Adobe Stock.)*

Take home message: This multicenter, cluster-randomized trial in low- and middle-income African countries demonstrated significantly lower 30-day surgical site infection in patients undergoing abdominal surgery when scrub teams changed gloves and instruments before abdominal wound closure.



Buprenorphine versus methadone for opioid use disorder in pregnancy. N Engl J Med 2022; 387:2033–44. PMID: 36449419.

The impact of buprenorphine therapy for opioid use disorder during pregnancy relative to methadone has not been well established. This retrospective cohort study of Medicaid enrollees (2000 to 2018) evaluated maternal and neonatal outcomes between those receiving either drug during early pregnancy (up to gestational week 19), late pregnancy (from gestational week 20 through the day before delivery), and within 30 days before delivery. Of 2,548,372 successful pregnancies analyzed, 10,704 females were exposed to buprenorphine and 4,387 to methadone in early pregnancy, 11,272 were exposed to buprenorphine and 5,056 to methadone in late pregnancy, and 9,976 were exposed to buprenorphine and 4,597 to methadone in the 30 days before delivery. Neonatal abstinence syndrome was significantly lower in infants exposed to buprenorphine *versus* methadone, 52% *vs.* 69% (adjusted relative risk, 0.73; 95% CI, 0.71 to 0.75) in the 30 days before delivery. Preterm birth, 14% *versus* 25%, (adjusted relative risk, 0.58; 95% CI, 0.53 to 0.62); small size for gestational age, 12% *versus* 15% (adjusted relative risk, 0.72; 95% CI, 0.66 to 0.80); and low birth weight, 8% *versus* 15% (adjusted relative risk, 0.56; 95% CI, 0.50 to 0.63) were also lower. No significant differences were noted in the frequency of cesarean section, 34% *versus* 33% (adjusted relative risk, 1.02; 95% CI, 0.97 to 1.08) or severe maternal complications, 3.3% *versus* 3.5% (adjusted relative risk, 0.91; 95% CI, 0.74 to 1.13). *(Article Selection: Martin J. London, M.D. Image: J. P. Rathmell.)*

Take home message: Among females enrolled in Medicaid, buprenorphine use for opioid use disorder was associated with a lower risk of adverse neonatal outcomes compared to methadone, while no significant differences were noted in assessed adverse maternal outcomes.

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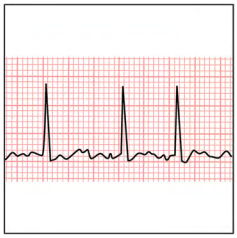
Association between preoperative hemodialysis timing and postoperative mortality in patients with end-stage kidney disease. JAMA 2022; 328:1837–48. PMID: 36326747.

There is a paucity of data on the timing of dialysis in patients with end-stage kidney disease before elective surgery. This retrospective cohort study analyzed the timing of dialysis with 90-day postoperative mortality in 1,147,846 surgical procedures (2011 to 2018) among 346,828 Medicare patients (median age, 65 yr) using the United States Renal Data System, a national registry of all patients treated with hemodialysis, linking records to Medicare claims. The distribution of timing intervals of dialysis to surgery was 65% 1-day, 25% 2-day, and 10% 3-day intervals. The primary outcome of all-cause 90-day postoperative mortality was 3.0% overall. Longer intervals between hemodialysis and surgery were significantly associated with higher risk: 2 days *versus* 1 day: absolute risk, 4.7% *versus* 4.2%; adjusted hazard ratio, 1.14 (95% CI, 1.10 to 1.18); 3 days *versus* 1 day: absolute risk, 5.2% *versus* 4.2%; adjusted hazard ratio, 1.25 (95% CI, 1.19 to 1.31); and 3 days *versus* 2 days: absolute risk, 5.2% *versus* 4.7%; adjusted hazard ratio, 1.09 (95% CI, 1.04 to 1.13). Hemodialysis on the same day as surgery was associated with a significantly lower hazard of mortality *versus* no same-day hemodialysis (absolute risk, 4.0% for same-day hemodialysis *vs.* 4.5% for no same-day hemodialysis; adjusted hazard ratio, 0.88 [95% CI, 0.84 to 0.91]). *(Article Selection: BobbieJean Sweitzer, M.D. Image: Adobe Stock.)*

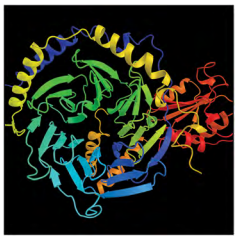
Take home message: Lengthier intervals between hemodialysis and elective surgery are significantly associated with higher postoperative mortality in Medicare patients with end-stage renal disease.



Transcriptomics-based network medicine approach identifies metformin as a repurposable drug for atrial fibrillation. Cell Rep Med 2022; 3:100749. PMID: 36223777.

The drug treatment of atrial fibrillation is only partially effective, and there is a need to develop new medications with alternative mechanisms of action. Use of network medicine methods could link drug targets, the human proteome, and disease modules, thus guiding repurposing of existing drugs. Transcriptomic data of human left atrium tissue obtained from 251 patients undergoing elective cardiac surgery was compared with drug-induced gene signatures from pluripotent cardiomyocytes. The results were then validated using a large-scale pharmacoepidemiologic dataset. There were 491 differentially expressed genes, coding for a number of atrial fibrillation–specific proteins and covering a wide range of cellular functions. Nine potential drug candidates that reversed dysregulated gene expression were identified from the network proximity of 2,891 drug targets (phenformin, metformin, furosemide, metacycline, rofecoxib, dantrolene, dapamide, alclometasone, and streptozocin). Five cohort propensity score comparisons (total n = 7720) were performed from a large Enterprise electronic data warehouse comparing metformin to the four commonly used antidiabetic oral agents (and their combination), finding that metformin was associated with a 52% reduced likelihood of atrial fibrillation (odds ratio, 0.48; 95% CI, 0.36 to 0.64; $P < 0.001$). *(Article Selection: Jamie Sleigh, M.D. Image: J. P. Rathmell.)*

Take home message: Metformin action on dysregulated gene networks associated with atrial fibrillation and pharmacoepidemiologic analyses suggest that it could potentially be used as a therapeutic agent.



State-selective modulation of heterotrimeric Gαs signaling with macrocyclic peptides. Cell 2022; 185:3950–65.e25. PMID: 36170854.

G-protein–coupled receptors are unique to eukaryotic cells and are important drug targets, with one-third of all Food and Drug Administration–approved drugs eliciting their biological effects through them. The ligand-activated seven-transmembrane domain receptors couple with G-proteins (heterotrimers) replacing GDP in G-protein's α subunit by GTP, which induces dissociation of the α subunit together with the bound GTP from the β and γ subunits, to further target intracellular functional proteins, particularly adenylyl cyclase as in the case of Gαs. The intrinsic GTPase activity of the α subunit forms GDP, resulting in the reconstitution of the heterotrimer and termination of signaling. To date, direct targeting of G-proteins, specifically their GDPase activity, was challenging. By screening a library of cyclic peptides, two macrocyclic peptides, GN13 and GD20, were found to specifically interact with Gαs. GN13 prevented the interaction of Gαs with adenylyl cyclase, reducing β2-adrenergic receptor-induced activation of adenylyl cyclase and the generation of its second messenger cAMP ("inhibition of the Gαs ON-state"). In contrast, GD20 specifically interacted with the GDP-bound inactive conformation of Gαs, preventing the dissociation of GDP. It also blocked the binding of Gαs to the Gβγ dimer, resulting in enhanced receptor-dependent Gβγ-signaling as evidenced by prolonged K+-channel activation ("blockage of the Gαs OFF-state with prolonged Gβγ activation"). *(Article Selection: Michael Zaugg, M.D., M.B.A. Image: Adobe Stock.)*

Take home message: Given the myriad physiologic cellular processes mediated by G-protein–coupled receptors, targeting specific G-proteins by macrocyclic peptides in a nucleotide state-selective manner to modulate intracellular signaling is a key step closer in the development of a highly promising entirely new class of drugs.

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