Anesthesiology 2010; 113:962–7

Timothy J. Brennan, Ph.D., M.D., Editor

Perioperative Medicine

J. Lance Lichtor, M.D., and Joseph F. Antognini, M.D., Editors

Elective thoracic aortic aneurysm surgery: Better outcomes from high-volume centers. J Am Coll Surg 2010; 210:855–60.

Reductions in morbidity and mortality have been shown when complex surgeries are performed at high-volume *versus* low-volume centers. However, surgical volume-to-outcome relationships have not yet been examined for thoracic aortic aneurysms.

In this retrospective study, data were collected over a 3-yr period from the Virginia Cardiac Surgery Quality Initiative database, which includes 17 hospitals and 13 cardiac surgical practices—containing data on more than 99% of open-heart operations in Virginia. Investigators blinded to the case count at each center assessed perioperative mortality after thoracic aortic aneurysm repair at low-volume (less than 40 operations) *versus* high-volume centers (more than 80 operations). (See figure at the bottom of this page.)

Interpretation

Using a statewide database to examine outcomes after elective thoracic aortic aneurysm surgery, the authors found that mortality, renal failure, prolonged ventilator course, and hospital costs were all decreased at high-volume *versus* low-volume centers. Though supportive of results from similar studies, researchers' definitions of low and high volume were arbitrary.

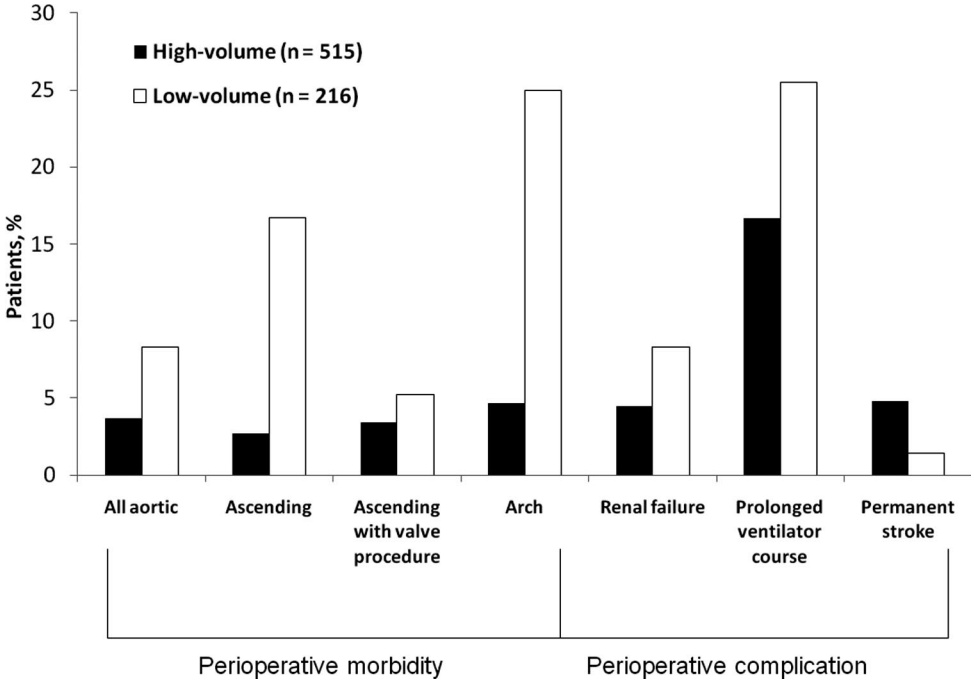
Everolimus-eluting *versus* paclitaxel-eluting stents in coronary artery disease. N Engl J Med 2010; 362:1663–74.

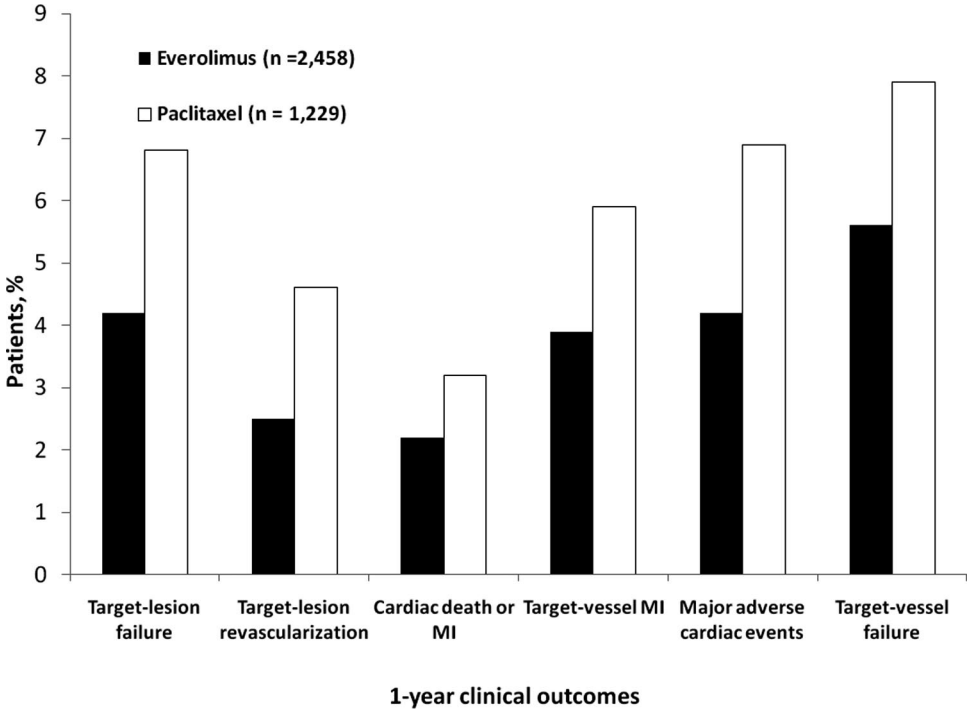
Second-generation drug-eluting coronary stents. N Engl J Med 2010; 362:1728–30.

Studies have demonstrated that drug-eluting stents have superior efficacy with reduced restenosis compared with bare-metal stents in patients undergoing percutaneous coronary intervention. However, despite numerous studies, the comparative safety and efficacy of drug-eluting stents with paclitaxel and everolimus remain unclear.

This prospective, multicenter, randomized, single-blind, active-treatment–controlled trial (SPIRIT IV) was conducted to compare everolimus-eluting stents with paclitaxel-eluting stents, without routine follow-up angiography in 3,687 patients at 66 U.S. sites.

At 1-yr follow-up (97.9% completion), everolimus-eluting stents were superior to paclitaxel-eluting stents on the





basis of incidence of target-lesion failure. (See figure at the top of this page.)

Interpretation

Second generation drug-eluting stents using everolimus instead of paclitaxel have better drug delivery, and stent structure is improved. In this multisite U.S. study of 3,687 patients, the composite target-lesion failure was decreased when everolimus was used for percutaneous coronary intervention. However, cardiac death rates were not different. Specifically, outcomes for diabetic patients did not demonstrate clinical benefit from everolimus *versus* paclitaxel. As the article's accompanying editorial indicates, more study is needed.

Apixaban *versus* enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): A randomized double-blind trial. Lancet 2010; 375:807–15.

For orthopedic patients, it is important to prevent clotting while minimizing risk of bleeding. Currently available agents (*e.g.*, warfarin, enoxaparin) are effective but require difficult dosing schedules or routes of administration. Previous studies have shown that apixaban, an orally active factor-Xa inhibitor, is useful in patients undergoing orthopedic surgery.

The current multicenter, randomized, double-blind, phase III trial (ADVANCE-2) compared the efficacy and safety of oral apixaban with a commonly used anticoagulant, enoxaparin, after elective total knee replacement. Patients undergoing elective unilateral or bilateral total knee replacement were randomized to receive oral apixaban, 25 mg, twice daily beginning 12–24 h after wound closure (n = 1,528) or subcutaneous enoxaparin, 40 mg, once daily beginning 12 h before surgery (n = 1,529). Patients were assessed daily for symptomatic deep vein thrombosis and pulmonary embolism, bleeding, and wound complications—as well as follow up at 30 and 60 days after the last dose of study drug.

The majority (72%) of patients were women aged approximately 67 yr. The mean duration of treatment was 12 days in both groups. The primary endpoint, a compilation of all-venous thromboembolism and all-cause death, was significantly decreased in the apixaban group compared with the enoxaparin group (15 *vs.* 24%; relative risk, 0.62; $P < 0.0001$). There were two fatal pulmonary embolisms in the apixaban group. Of the patients who entered the follow-up period, symptomatic deep vein thrombosis (2/1,458 and 1/1,469) and pulmonary embolism (3/1,458 and 1/1,469) were rare in both groups. Major or clinically relevant nonmajor bleeding were comparable in the two groups (4 *vs.* 5% in the apixaban and enoxaparin groups, respectively; $P = 0.09$).

Interpretation

Thromboprophylaxis is an important part of the postoperative care of orthopedic patients; however, physicians must balance the benefits of preventing blood clots with the risk of bleeding. Apixaban, an orally available inhibitor of factor Xa, provided superior prevention of deep venous thrombosis, pulmonary embolism, and death compared with enoxaparin, a low molecular weight heparin. Bleeding rates were similar between the two groups.

Characteristics	DREAM		EVAR 1	
	Endovascular (n = 178)	Open (n = 173)	Endovascular (n = 626)	Open (n = 626)
Age, yr	69.6	70.7	74.1	74.0
Median follow-up, yr	6.4		6.0	
Overall death, %	34	33	41	42
Aneurysm-related	NC	NC	5.7	6.3
Per 100-person years	NC	NC	7.5	7.7
Overall survival at 6 yr, %	68.9	69.9	54	54
Reintervention, %	6.4*	2.1*	27.7†	16.8†

* Reintervention calculated at least 4 yr after surgery ($P = 0.003$). † Reintervention calculated 6 yr after surgery ($P = 0.03$).
DREAM = Dutch Randomized Endovascular Aneurysm Repair; EVAR 1 = Endovascular Aneurysm Repair; NC = not calculated.

Long term outcome of open or endovascular repair of abdominal aortic aneurysm. N Engl J Med 2010; 362:1881–9.

Endovascular *versus* open repair of abdominal aortic aneurysm. N Engl J Med 2010; 362:1863–71.

Compared with open repair, endovascular repair may offer a perioperative survival benefit in patients with large abdominal aortic aneurysms. However, long-term follow-up studies are needed to determine whether beneficial effects of either surgery are sustained.

These two studies present long-term follow-up from the Dutch Randomized Endovascular Aneurysm Repair (DREAM) and the Endovascular Aneurysm Repair (EVAR 1) trials. Both were randomized, multicenter trials of adults with abdominal aortic aneurysms eligible for either open surgical repair or endovascular repair. (See table.)

Interpretation

These two long-term, multicenter, randomized controlled trials challenge the view that endovascular repair of abdominal aortic aneurysm is superior to open repair in terms of outcome. In both studies, survival rates were similar at 6 yr. In both studies, the number of secondary interventions was greater in the endovascular group.

Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med. 2010; 362: 959–69.

Oxygen toxicity in preterm infants may result in increased risk of death, retinopathy, and other conditions. However, previous studies have demonstrated conflicting results on the appropriate range of oxygen saturation to minimize retinopathy without increasing adverse outcomes.

A randomized trial, SUPPORT (Surfactant, Positive Pressure, and Oxygenation Randomized Trial), with a 2×2 factorial design was conducted to compare target ranges of oxygen saturation of 85–89% (n = 654) or 91–95% (n = 662) among infants who were born between 24 weeks, 0 days and 27 weeks, 6 days of gestation. The primary outcome was a composite of severe retinopathy of prematurity (defined as the presence of threshold retinopathy, the need for surgical ophthalmologic intervention, or the use of bevacizumab), death before discharge from the hospital, or both. All infants were also randomly assigned to continuous positive airway pressure or intubation and surfactant.

Comparable rates of severe retinopathy or death were found in the lower and higher oxygen-saturation groups (28.3 and 32.1%, respectively). No significant interaction was found between oxygen saturation levels and ventilation intervention either. Although severe retinopathy occurred less often in the lower oxygen group (8.6 *vs.* 17.9%; relative risk, 0.52; $P < 0.001$), death before discharge occurred more frequently (19.9 *vs.* 16.2%; relative risk, 1.27; $P = 0.04$). Rates of other adverse events were similar between the two groups.

Interpretation

Retinopathy has been a long-standing problem in the care of premature newborns. Anesthesiologists and neonatologists have tried to minimize this complication by using decreased oxygen partial pressures. However, this study suggests that lower oxygenation is associated with increased mortality.

Effect of bar-code technology on the safety of medication administration. N Engl J Med 2010; 362:1698–707.

More than 25% of medication-use adverse events may be preventable. Implementation of health care information technology, such as computerized physician-order entry and bar-code medication verification, has demonstrated reductions in the incidence of serious medication errors.

To evaluate the effect of an electronic medication administration (eMAR) system on the incidence of medication errors, a prospective, before-and-after quasi-experimental study was conducted. The rate of errors was calculated over a 9-month period before and after the implantation of the bar-code eMAR in a single 735-bed tertiary academic medical center that administered 5.9 million doses of medication in the study period. Two clinicians reviewed the errors to determine their potential to

harm patients and classified those that could be harmful as potential adverse drug events.

Of 14,041 medication administrations and 3,082 order transcriptions reviewed, approximately 30, 52, and 17% were observed in medical, surgical, and intensive care units, respectively. There was a 41.4% relative reduction in nontiming errors in units that used the bar-code eMAR ($P < 0.001$). The most common types of errors in units that did *versus* those that did not use the system included errors in oral *versus* nasogastric tube administration (4.4% *vs.* 3.6%), administration documentation (2.9 *vs.* 0.6%), dose (2.0 *vs.* 1.1%), and wrong medication (1.0 *vs.* 0.4%). Errors occurred more frequently in surgical and intensive care units compared with medical units. There was a 50.8% relative reduction in the rate of potential adverse drug events (other than those associated with timing errors) in units that used the bar-code eMAR ($P < 0.001$). The rate of timing errors in medication administration was reduced by 27.3% ($P < 0.001$). Transcription errors occurred at a rate of 6.1% on units that did not use the bar-code eMAR but were completely eliminated on units that did use it.

Interpretation

Patient safety is receiving increased attention by patients, healthcare workers, and the public in general. Medication errors remain a vexing problem that requires innovative solutions. This report shows that a bar-coding system, matching the prescribed drug with the correct patient and administered drug, reduces medication errors. Such a system is likely to be used in many (if not all) operating rooms in the future.

Critical Care Medicine

Jean Mantz, M.D., Ph.D., Editor

Rates of major depressive disorder and clinical outcomes following traumatic brain injury. JAMA 2010;303:1938–45.

Major depressive disorder (MDD) is one of the most common disabilities associated with traumatic brain injury (TBI). However, the rates, predictors, and outcomes for patients with MDD after TBI are unknown.

As part of a recruitment phase for a clinical trial, this study prospectively investigated the rate of MDD during the first year after TBI, as well as predictors and outcomes for MDD. Adult-oriented patients (N = 559) admitted to a level I trauma center with mild to severe TBI were consecutively enrolled and followed *via* phone call 1–6, 8, 10, and 12 months after injury.

Fifty-three percent of patients met MDD criteria at least once during the first year after TBI, and the rate was highest during the first month. Age, sex, cocaine intoxication, lifetime alcohol dependence, and a preinjury history of mental disorders (*e.g.*, depression, posttraumatic stress disorder) were closely associated with MDD. Patients with MDD were more likely to report comorbid anxiety disorders (60 *vs.* 7%; risk ratio, 8.77), only 44% of whom received antidepressants or counseling. A lower quality of life at 1 yr was reported in patients with MDD compared with the nondepressed group.

Interpretation

This cohort study identifies MDD as an unexpectedly frequent consequence of TBI. MDD is a predictor of poorer quality of life postinjury. Efforts should be aimed at better detecting and treating MDD in patients with TBI.

The effect of multidisciplinary care teams on intensive care unit mortality. Arch Intern Med 2010; 170:369–76.

Multidisciplinary care teams including physicians, nurses, respiratory therapists, and clinical pharmacists may improve outcomes for medically complex critically ill patients. However, few studies have demonstrated sufficient data to recommend this approach for wide adoption.

This multicenter study using hospital-level organizational surveys and patient-level outcome data was conducted to determine the independent effect of multidisciplinary care teams on mortality of a retrospective cohort of critically ill patients (N = 107,324).

Hospitals had either low-intensity physician staffing and no multidisciplinary care (48.2%), low-intensity physician staffing with multidisciplinary care (32.1%), or high-intensity physician staffing with multidisciplinary care (19.6%). Overall 30-day mortality was 18.3%. After adjusting for patient and hospital characteristics, multidisciplinary care was associated with significant reductions in the odds of death (odds ratio [OR], 0.84). This result held true after stratification by intensivist physician staffing. The OR was 0.78 in intensive care units with no multidisciplinary care compared with an OR of 0.88 in intensive care units with low-intensity physician staffing and multidisciplinary care teams. The results were also consistent in subgroups including patients with sepsis, patients requiring invasive mechanical ventilation, and patients in the highest quartile of severity of illness.

Interpretation

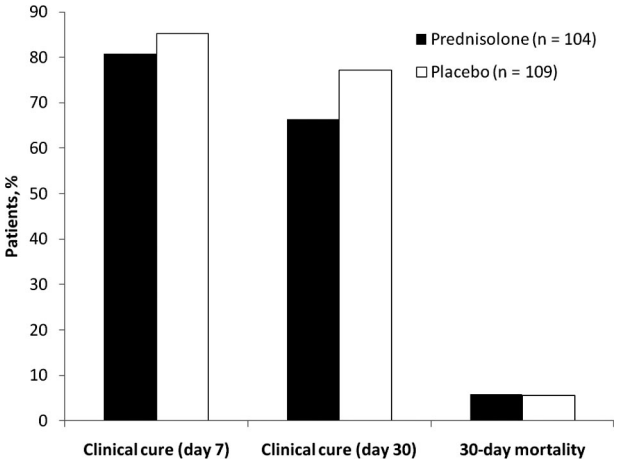
This retrospective study supports the view that creating a multidisciplinary care team in the intensive care unit, perhaps even without high intensity physician staffing, may reduce mortality in critically ill patients. The basis for this improved outcome by multidisciplinary care teams needs to be tested prospectively.

Efficacy of corticosteroids in community acquired pneumonia. A randomized double-blind clinical trial. Am J Resp Crit Care Med 2010; 181:975–82.

Studies on the efficacy of corticosteroids in patients with sepsis and septic shock have demonstrated conflicting results. Similarly, the effects in patients with community-acquired pneumonia (CAP) are still unclear.

To assess the efficacy of corticosteroids in CAP, adjunctive prednisolone was administered to patients hospitalized with CAP in this randomized, placebo-controlled trial. Patients received antibiotics and either placebo or prednisolone, 40 mg, for 7 days. Pneumonia Severity Index and CURB-65 (Confusion, serum Urea nitrogen, Respiratory rate, Blood pressure, and age more than 64) were used to measure illness severity.

Of 213 patients enrolled, 25.4% of patients had a CURB-65 score greater than 2, and 43.7% of patients were in Pneumonia Severity Index class IV–V. No clinical outcome difference was observed between groups at day 7 or 30. Length of stay was approximately 10 days in both groups. Late failure and recurrence of signs and symptoms 72 h after admittance, was more common in the prednisolone group than in the placebo group (19.2 *vs.* 6.4%; $P = 0.04$). Adverse events were few and not different between the two groups.



Interpretation

This study indicates that prednisolone (40 mg daily for 1 week) does not improve outcomes for patients hospitalized with CAP. It may contribute to late failure in patients with nonsevere CAP. Therefore, prednisolone should not be routinely recommended for treatment with antibiotics for CAP.

Pain Medicine

Timothy J. Brennan, Ph.D., M.D., Editor

A gain-of-function mutation in TRPA1 causes familial episodic pain syndrome. Neuron 2010; 66:671–80.

Mutations in ion channels, such as the cation transient receptor potential (TRP) channels, have been implicated in numerous disorders including pain. TRPA1, expressed on primary afferent nociceptors, is gated by cold temperatures and may be mechanosensitive. However, a correlation between heritable pain-sensation disorders and TRPA1 has not yet been described.

Whole-genome scanning was conducted on individual family members (13 affected, 10 unaffected) with familial episodic pain syndrome and 287 potential genes were identified using haplotype analysis. Linkage and haplotype analysis mapped this phenotype to a 25-centiMorgan region on chromosome 8q12–8q13. In familial episodic pain syndrome–affected individuals, a point mutation (N855S) in the S4 transmembrane segment of TRPA1 was identified. Tactile detection thresholds, vibration detection thresholds, and cold/heat or pressure-pain detection thresholds were similar in affected and unaffected relatives. The mutant channel showed a normal pharmacologic profile but altered biophysical properties, with a 5-fold increase in inward current on activation at normal resting potentials.

Interpretation

The TRPA1 receptor is a key sensory receptor for environmental irritants and painful stimuli. This study indicates that TRPA1 function is altered in heritable pain syndrome and that variance of the TRPA1 receptor can alter pain perception in humans.

Adenosine A1 receptors mediate local antinociceptive effects of acupuncture. Nat Neurosci 2010; 13:883–8.

The mechanistic basis for the analgesic effects of acupuncture is not well understood. Currently, it is believed that the release of endogenous opioid peptides is a primary mechanism; however, this theory does not account for the local pain-relieving effects of acupuncture.

This *in vitro* mouse study investigated whether adenosine is involved in the antinociceptive effects of acupuncture. Samples of interstitial fluid were collected to measure adenosine and adenosine nucleotides before, during, and after acupuncture in mouse models of inflammatory and neuropathic pain.

Compared with baseline, 30 min of acupuncture increased extracellular concentrations of adenosine (by 24-fold). Adenosine monophosphate, adenosine diphosphate, and adenosine triphosphate also increased. While extracellular adenosine triphosphate concentrations returned to baseline after the session, adenosines, adenosine monophosphate, and adenosine diphosphate remained significantly increased for up to 60 min. In the inflammatory pain model, acupuncture significantly increased touch threshold and threshold to thermal pain ($P < 0.01$). In a neuropathic pain model, acupuncture significantly reduced mechanical allodynia ($P < 0.01$). Both effects returned to baseline within 24 h. Furthermore, administration of deoxycoformycin increased the accumulation of extracellular adenosine by 3.7-fold in mice receiving acupuncture, and significantly prolonged its analgesic effects.

Interpretation

Clinical trials in acupuncture have shown limited and variable efficacy in several pain states. This study demonstrates that the analgesic effects of acupuncture are in part mediated by adenosine and its receptors in animals. This study suggests that enhancing adenosine receptor function may improve the analgesic effects of acupuncture in humans.

Cerebral processing of pain in school-aged children with neonatal nociceptive input: An exploratory fMRI study. PAIN 2010; 150:257–67.

Nociceptive circuits respond strongly to injury and may develop activity-related plasticity, especially at birth and in preterm infants. These early insults may result in long-term alterations in pain processing.

The long-term effects of painful procedures on preterm and full-term children in the neonatal intensive care unit (NICU) were assessed using functional magnetic resonance imaging and pain testing. This study compared the cerebral pain response in school-aged children and adolescents (aged 11–16 yr), chosen retrospectively with experience in a NICU after preterm (≤31 weeks gestational age, N = 9) or full-term birth (≥37 weeks gestational age, N = 9), to full-term control children without early hospitalization (N = 9).

Children in both NICU groups had a greater increase in pain intensity in response to tonic heat stimuli and control children showed greater habituation across trials. Preterm but not the full-term NICU children exhibited significant activation in a number of brain regions (thalamus, anterior cingulate cortex, cerebellum, basal ganglia, and periaqueductal gray) that were not significantly activated in control children in response to pain stimuli. Significantly higher activation was observed in former NICU preterm infants than controls in primary somatosensory cortex, anterior cingulate cortex, and insula.

Interpretation

This study demonstrates that preterm neonates who were subject to medical procedures have increased responses to painful stimuli as children. This suggests that procedures in preterm infants may be a predisposing factor for increased pain sensitivity. The clinical significance of these enhanced responses remains to be determined.