Bleeding Outcomes after Noncardiac Surgery — Are We POISEd to Do Better?

Jeffrey S. Berger, M.D.

The number of adults who undergo major noncardiac surgery is increasing worldwide,[1] including older patients with more coexisting conditions and increased risks of bleeding and thrombotic events.[2] Although perioperative bleeding is an important complication that leads to excess morbidity and mortality,[3] few therapies have been studied to prevent it.

Tranexamic acid is a lysine analogue that competes with lysine residues on fibrin for the binding of plasminogen, inhibiting the interaction of plasmin with fibrin and thereby preventing the dissolution of fibrin clot. Tranexamic acid has been shown to reduce the risk of death from bleeding in randomized trials involving patients with traumatic[4] or postpartum[5] hemorrhage, but the net benefit in noncardiac surgery is less certain. Although rapid hemostasis decreases the incidence of surgical bleeding complications, the mechanism of action of tranexamic acid may also increase the risk of vascular thrombosis. So, the balance of its benefit (reduced bleeding) and risk (thrombotic events) in noncardiac surgery requires clarification.

In this issue of the *Journal*, Devereaux et al.[6] report the results of the Perioperative Ischemic Evaluation–3 (POISE-3) trial, in which 9535 patients who were at increased cardiovascular risk and who were scheduled to undergo noncardiac surgery were randomly assigned to receive tranexamic acid (1-g intravenous bolus) or placebo at the start and end of surgery. At 30 days, the incidence of the composite bleeding outcome (life-threatening bleeding, major bleeding, or bleeding into a critical organ) was 24% lower with tranexamic acid than with placebo (9.1% vs. 11.7%; absolute difference, –2.6 percentage points; 95% confidence interval [CI], –3.8 to –1.4). The primary safety outcome was a composite of myocardial injury after noncardiac surgery, nonhemorrhagic stroke, peripheral arterial thrombosis, and symptomatic proximal venous thromboembolism (composite cardiovascular outcome). To establish the noninferiority of tranexamic acid with respect to the composite cardiovascular outcome, the upper boundary of the one-sided 97.5% confidence interval for the hazard ratio had to be below 1.125. In the POISE-3 trial, noninferiority was not met; a composite cardiovascular outcome event occurred in 14.2% of the patients in the tranexamic acid group and in 13.9% of those in the placebo group (hazard ratio, 1.02; 95% CI, 0.92 to 1.14; upper boundary of the one-sided 97.5% CI, 1.14; absolute difference, 0.3 percentage points; 95% CI, –1.1 to 1.7).

Careful consideration of these important results is crucial. First, the clear benefit in reducing the risk of a composite bleeding outcome event (a 2.6-percentage-point absolute difference and a number needed to treat of 38 patients) appears to have been driven by the incidence of major bleeding (7.6% in the tranexamic acid group and 10.4% in the placebo group); the incidence of life-threatening bleeding (1.6% and 1.7%, respectively) and of bleeding into a critical organ (0.3% and 0.4%, respectively) was infrequent and similar in the two groups. The definitions used are important. In the previous POISE-2 trial investigating aspirin in noncardiac surgery,[7] a stringent definition of major bleeding was used as the primary safety outcome, which occurred in 3.8% of the patients in the placebo group. In the POISE-3 trial, a composite bleeding outcome event occurred in 11.7% of the patients in the placebo group. This difference is noteworthy because therapeutic decisions are frequently made on the basis of absolute differences and the number needed to treat.

Second, the failure to show noninferiority for the primary safety outcome despite nearly identical incidences of the composite cardiovascular outcome in the two trial groups may be attributable to the commendably stringent noninferiority margin selected. Moving forward, how do we weigh the benefits and risks of tranexamic acid use among patients undergoing noncardiac surgery? Although no clear conclusions may be drawn about the individual components of the composite cardiovascular outcome, the 95% confidence interval of the hazard ratio is consistent with an increase in risk of up to 14%. The net benefit in patients at very high risk for cardio-

vascular events (e.g., those with previous coronary stenting) requires further investigation.

Third, because a meta-analysis showed an increased risk of seizure among patients receiving more than 2 g per day of tranexamic acid,[8] the POISE-3 investigators excluded patients with a previous seizure. Although infrequent, seizure occurred in 10 patients (0.2%) in the tranexamic acid group and in 3 (0.1%) in the placebo group (hazard ratio, 3.35; 95% CI, 0.92 to 12.20). Thus, even at this low dose of tranexamic acid, the risk of seizure may need to be considered as a part of the risk–benefit equation.

Overall, the POISE-3 trial is a major step forward in noncardiac surgery because it addresses a fundamental issue facing patients and surgeons — excess perioperative bleeding. Tranexamic acid is effective at decreasing the incidence and severity of bleeding events among patients undergoing noncardiac surgery. Although the trial was unable to prove noninferiority for the composite cardiovascular outcome, the between-group difference was small. Like all preventive therapies, benefits must be balanced against risks. The net clinical benefit of tranexamic acid should be patient-specific — that is, it is worthwhile for those at increased risk for bleeding outcomes but deleterious for those at increased risk for adverse cardiovascular events.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From the New York University Grossman School of Medicine, New York.

1. Smilowitz NR, Berger JS. Perioperative cardiovascular risk assessment and management for noncardiac surgery: a review. JAMA 2020;324:279-90.
2. Smilowitz NR, Gupta N, Guo Y, Beckman JA, Bangalore S, Berger JS. Trends in cardiovascular risk factor and disease prevalence in patients undergoing non-cardiac surgery. Heart 2018;104:1180-6.
3. Smilowitz NR, Oberweis BS, Nukala S, et al. Association between anemia, bleeding, and transfusion with long-term mortality following noncardiac surgery. Am J Med 2016;129(3):315-323.e2.
4. CRASH-3 trial collaborators. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. Lancet 2019;394:1713-23.
5. WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet 2017;389:2105-16.
6. Devereaux PJ, Marcucci M, Painter TW, et al. Tranexamic acid in patients undergoing noncardiac surgery. N Engl J Med 2022;386:1986-97.
7. Devereaux PJ, Mrkobrada M, Sessler DI, et al. Aspirin in patients undergoing noncardiac surgery. N Engl J Med 2014;370:1494-503.
8. Murao S, Nakata H, Roberts I, Yamakawa K. Effect of tranexamic acid on thrombotic events and seizures in bleeding patients: a systematic review and meta-analysis. Crit Care 2021;25:380.

DOI: 10.1056/NEJMe2204599