The past four decades have seen remarkable progress in establishing best perioperative practices. One of the challenges in improving perioperative care, however, is rooted in the interplay of the myriad interdependent, often opposing, mechanisms that contribute to perioperative myocardial infarction — excess bleeding, dramatic fluid shifts, unrelenting tachycardia, myocardial stress with fixed coronary obstruction, profound hypotension or hypertension, coronary plaque rupture, and coronary spasm. Strategies that mitigate one mechanism may lead to another. Devereaux et al. now report on two such strategies in the perioperative use of aspirin and the perioperative use of clonidine in patients undergoing noncardiac surgery. The authors report the results of the Perioperative Ischemic Evaluation 2 (POISE-2) trial, which was designed to evaluate separately the efficacy and safety of low-dose clonidine versus placebo and low-dose aspirin versus placebo in 10,010 patients with, or at risk for, atherosclerotic disease. Both in patients who had not been taking aspirin before the study and in those who were already on an aspirin regimen (the latter referred to as the continuation stratum), aspirin had no significant effect on the composite primary end point of death or nonfatal myocardial infarction at 30 days. Major bleeding was more common in the aspirin group than in the placebo group (4.6% vs. 3.7%; hazard ratio, 1.23; 95% confidence interval [CI], 1.01 to 1.49; P=0.04). Overall, it is likely that aspirin prevented some perioperative myocardial infarctions through thrombus inhibition, but this may have been at the expense of bleeding and other myocardial infarctions induced by a mismatch between the supply of and demand for oxygen. It would be important to investigate the temporal relationship between major bleeding and myocardial infarction. Importantly, among 4382 patients in the continuation stratum, there was no “rebound” increase in thrombotic events due to temporary perioperative interruption of aspirin. All the findings applied regardless of whether patients had a history of vascular disease or no history of vascular disease.

On balance, the authors provide cogent evidence against the use of aspirin perioperatively in patients with and those without preexisting vascular disease. Nonetheless, important questions linger. Although a substantial proportion of patients in the POISE-2 trial had some form of vascular disease, only 4.3% of the patients in the aspirin group had undergone prior coronary stenting. The safety of aspirin withdrawal in those who have previously undergone percutaneous coronary interventions may not be established by the POISE-2 trial. Furthermore, the authors excluded patients who had received a bare-metal or drug-eluting coronary stent less than 6 weeks and less than 1 year, respectively, before surgery. Perioperative aspirin may prevent myocardial infarction and stent thrombosis in patients with recent percutaneous coronary interventions and should not be withdrawn prematurely.

The use of low-dose clonidine, which blunts sympathetic outflow, would seem to be a beneficial addition to the armamentarium of the perioperative clinician. In the POISE-2 trial, however, clonidine did not significantly reduce the risk of the primary outcome and, as compared with placebo, was associated with higher rates of clinically important hypotension (47.6% vs. 37.1%; hazard ratio, 1.32; 95% CI, 1.24 to 1.40; P<0.001) and nonfatal cardiac arrest (0.3% vs. 0.1%; hazard ratio, 3.20; 95% CI, 1.17 to 8.73; P=0.02). Given these harms and the neutral effect on the primary outcome, clonidine should be avoided perioperatively. The prevalence of clinically important hypotension in both the clonidine group and the placebo group, however, bears scrutiny and could reflect the intensity of monitoring in the POISE-2 trial. Although one could even question the relevance of the results of the aspirin study in a trial in which so many patients had clinically important hypotension (which was an independent predictor of subsequent myocardial infarction), the authors report that there was no significant effect of clonidine on the results of the comparison of aspirin with placebo. Furthermore, the effect of metoprolol succinate in the POISE trial in reducing the risk of myocardial
infarction is contradictory to the deleterious effect of clonidine in the POISE-2 trial. Although the blunting of sympathetic outflow produced by clonidine may be fundamentally different from that produced by beta-blockers, the results of the POISE and POISE-2 trials taken together offer credibility to a calculated strategy of decreasing heart rate while avoiding perioperative hypotension.

The perioperative medicine community welcomes the results of the POISE-2 trial, while realizing that there are still many areas of uncertainty, including best practice in those who have undergone any percutaneous coronary intervention. It is not surprising that medical therapies directed at favorably modifying one mechanism causing perioperative myocardial infarction have the potential to increase risk through augmentation of a different pathway. Aspirin may reduce coronary thrombosis at the expense of excess bleeding; clonidine may reduce hypertensive swings only to be countered by clinically important hypotension. As observed by Chinese philosophers, the whole is made up of the yin and yang — complementary, interdependent, and conceptually opposing entities that comprise a whole. Future progress in perioperative medicine may depend on the implementation of strategies that successfully address one pathophysiological mechanism of perioperative myocardial infarction without being limited by another.

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

From the Department of Medicine, Samuel and Jean A. Frankel Cardiovascular Center, University of Michigan Health System and Medical School, Ann Arbor.

This article was published on March 31, 2014, at NEJM.org.


DOI: 10.1056/NEJMMe1402976
Copyright © 2014 Massachusetts Medical Society.