# Recent Trials in Perioperative Cardiology: A Summary

Written by Maria Vinall

Current themes in clinical trials include a movement toward large size, composite outcomes, and factorial designs. The studies reported in this session represent all 3 of these trends—most evidently, large study populations.

The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation Study [VISION; NCT00512109] was designed to evaluate the prognostic capabilities of troponin T and its role in monitoring patients after surgery. An additional goal was to establish diagnostic criteria for myocardial injury after noncardiac surgery (MINS) and evaluate predictors of 30-day outcomes.

The study is complete, having enrolled 40 000 patients aged ≥ 45 years who had noncardiac surgery requiring at least 1 overnight hospital stay. Troponin T was measured 6 to 12 hours post-surgery and on days 1, 2, and 3. A fourth-generation troponin T value ≥ 0.04 was considered abnormal. Patients were followed during hospitalization and at 30 days and 1 year.

Andrea M. Kurz, MD, Cleveland Clinic, Cleveland, Ohio, USA, presented data from the first 15 133 patients. Overall mortality was 1.9%, with 26.6% of deaths occurring at a median of 11 days after discharge; higher peak troponin concentrations were associated with higher 30-day mortality and reduced time to death.

The investigators have proposed the following definition of MINS: myocardial injury caused by ischemia that has prognostic relevance and occurs within 30 days of surgery. In these patients, a total troponin T level ≥ 0.03 that is of ischemic etiology is an independent predictor of 30-day mortality.

The investigators concluded that troponin T is an independent predictor of 30-day mortality and that postoperative myocardial injury is common, with most MINSs detected only by troponin screening. They recommend monitoring troponin concentrations on the first and second days after moderate- to high-risk surgery, with concentrations ≥ 0.03 prompting a cardiology consult.

The Perioperative Ischemic Evaluation-2 Trial [POISE-2; Devereaux PJ et al. *Am Heart J.* 2014] was a 2 × 2 factorial controlled phase 3 trial to assess the impact of low-dose clonidine vs placebo and low-dose aspirin vs placebo in patients having noncardiac surgery. The study included surgical inpatients aged ≥ 45 years with a history of vascular disease. Patients who had received bare-metal stents < 6 weeks before surgery or drug-eluting stents < 1 year before surgery were excluded, as were those who took aspirin within 72 hours before surgery.

Participants (n = 10 010) were randomized in a 1:1:1:1 ratio to receive clonidine plus aspirin, clonidine plus an aspirin placebo, a clonidine placebo plus aspirin, or a clonidine placebo plus an aspirin placebo. Clonidine (0.2 mg/d) was started just before surgery and continued until 72 hours after surgery. Aspirin (200 mg) was also started just before surgery but continued at 100 mg/d for 30 days in patients already taking aspirin (initiation cohort) or 7 days for aspirin-naïve patients (continuation cohort). The primary outcome was a death or nonfatal myocardial infarction (MI) at 30 days.

Philip Devereaux, MD, PhD, McMaster University, Hamilton, Ontario, Canada, discussed the recent results for patients randomized to aspirin vs placebo [Devereaux PJ et al. *N Engl J Med.* 2014]. There was no difference for aspirin compared with placebo on either the primary or secondary outcomes. There were no interactions with clonidine. Patients taking aspirin had a higher rate of acute kidney injury leading to dialysis when compared with those receiving placebo (HR, 1.75; 95% CI, 1.00 to 3.09; $P = .05$), as well as an increased incidence of major bleeding (HR, 1.23; 95% CI, 1.01 to 1.49; $P = .04$). The results were consistent in both the initiation and continuation groups.

Using multivariable regression analysis, the investigators determined that life-threatening/major bleeding preceding an MI independently predicted that a patient would proceed to an infarction. Among patients taking aspirin chronically, there was no increase in thrombotic events due to perioperative withholding of aspirin. The optimal time to restart aspirin appears

Peer-Reviewed Highlights From

**Anesthesiology 2014**

October 11–15, 2014
New Orleans, Louisiana

Table 1. Thirty-Day Results: Primary and Secondary Outcomes

| Outcome | Clonidine (n = 5009) | Placebo (n = 5001) | HR (95% CI) | *P* Value |
|---|---|---|---|---|
| Primary: death or MI | 367 (7.3) | 339 (6.8) | 1.08 (0.93 to 1.26) | .29 |
| Secondary: death, MI, or stroke | 380 (7.6) | 352 (7.0) | 1.08 (0.93 to 1.25) | .30 |

Data are presented as no. (%) unless otherwise indicated. MI, myocardial infarction.
Reproduced with permission from DI Sessler, MD.

to be 8 to 10 days after surgery, balancing the benefits against the risk of surgical bleeding.

Daniel I. Sessler, MD, Cleveland Clinic Foundation, Cleveland, Ohio, USA, presented the clonidine results from POISE-2 [Devereaux PJ et al. *N Engl J Med.* 2014]. There was no difference in either the primary or secondary outcome between clonidine and placebo (Table 1). There were no interactions with aspirin. Significantly more subjects in the clonidine group (n = 16) had a nonfatal cardiac arrest as compared with subjects treated with placebo (n = 5; HR, 3.20; 95% CI, 1.17 to 8.73; *P* = .02).

Clonidine was associated with significantly more clinically important hypotension (HR, 1.32; 95% CI, 1.24 to 1.40) and bradycardia (HR, 1.49; 95% CI, 1.32 to 1.69; both, *P* < .001). The incidence of stroke did not differ. Hypotension was a clinically important and significant predictor of MI (HR, 1.37; 95% CI, 1.16 to 1.62; *P* < .001).

Regarding both aspects of the POISE-2 trial, neither clonidine nor aspirin reduced postoperative MI or death. Clonidine significantly increased the risk of hypotension, while aspirin increased the risk of major bleeding—both of which are independent predictors of MIs. A safe and effective way of preventing postoperative MI remains to be determined.

The Nitrous Oxide Anesthesia and Cardiac Morbidity After Major Surgery: A Randomised Controlled Trial [ENIGMA-II; Myles PS et al. *Lancet.* 2014] tested the hypothesis that avoiding nitrous oxide ($N_2O$) in anesthesia during major surgery reduces the incidence of cardiac complications or death. The results were presented by Paul S. Myles, MB, BS, MPH, MD, Alfred Hospital, Melbourne, Australia.

ENIGMA-II was a multinational double-blind phase 4 trial including 7000 noncardiac patients having surgery lasting at least 2 hours. Participants were randomized in a 1:1 ratio to 70% $N_2O$ and 30% $O_2$ (n = 3543) or nitrogen and 30% $O_2$ (n = 3569). The primary end point was death and cardiovascular complications (MI, stroke, cardiac arrest, pulmonary embolism) 30 days after surgery. Secondary outcomes included MI, wound infection, nausea or vomiting, and hospital stay.

Subjects averaged 70 years old; 69% were American Society of Anesthesiologists status 3 or 4. The mean duration of anesthesia was 3.2 hours (range, 2.2 to 4.4). Among patients receiving $N_2O$, there was a significant reduction in the dose of the volatile anesthetic used as part of the general anesthetic regimen and a significant increase in the use of antiemetic prophylaxis (both *P* < .001). The 2 groups did not differ in the occurrence of the primary end point, which largely comprised MI in both groups (Table 2). Persistent nausea or vomiting was significantly (*P* < .001) more common in patients receiving $N_2O$ and persisted for 48 hours. There was no difference in recovery room stay or wound infections.

Dr Myles concluded that $N_2O$ is safe to use in most circumstances and its emetogenic properties can be controlled with antiemetic prophylaxis.

Table 2. Primary Outcomes

| Primary End Point | $N_2O$ (n = 3543) | No $N_2O$ (n = 3569) | RR (95% CI) | *P* Value |
|---|---|---|---|---|
| All | 283 (8.1) | 296 (8.4) | 0.96 (0.82 to 1.13) | .64 |
| Death | 42 (1.2) | 57 (1.6) | 0.74 (0.50 to 1.11) | .14 |
| Myocardial infarction | 215 (6.2) | 219 (6.2) | 0.99 (0.82 to 1.19) | .91 |
| Stroke | 26 (0.7) | 19 (0.6) | 1.38 (0.76 to 2.49) | .29 |
| Cardiac arrest | 15 (0.4) | 19 (0.5) | 0.80 (0.40 to 1.56) | .51 |
| Pulmonary embolism | 18 (0.5) | 22 (0.6) | 0.82 (0.44 to 1.53) | .54 |

Data are presented as no. (%) unless otherwise indicated. RR, relative risk.