Annals of Internal Medicine ORIGINAL RESEARCH

Effects of a Hypotension-Avoidance Versus a Hypertension-Avoidance Strategy on Neurocognitive Outcomes After Noncardiac Surgery

Maura Marcucci, MD; Matthew T.V. Chan, MBBS; Thomas W. Painter, MBChB; Sergey Efremov, MD; Hector J. Aguado, PhD, MBBS; Sergey V. Astrakov, MD; Ydo V. Kleinlugtenbelt, MD; Ameen Patel, MD; Juan P. Cata, MD; Mohammed Amir, MBBS; Mikhail Kirov, MD; Kate Leslie, MD; Emmanuelle Duceppe, MD; Flavia K. Borges, MD; Miriam de Nadal, MD; Vikas Tandon, MD; Giovanni Landoni, MD; Valery V. Likhvantsev, MD; Vladimir Lomivorotov, MD; Daniel I. Sessler, MD; María José Martínez-Zapata, MD; Denis Xavier, MD; Edith Fleischmann, MD; Chew Yin Wang, MBChB; Christian S. Meyhoff, MD; Maria Wittmann, MD; David Torres, MD; David Highton, MBChB; Michael Jacka, MD; Vishwanath B., MD; Kelly Zarnke, MD; Ravinder Singh Sidhu, MSc; Giorgio Oriani, MD; Sabry Ayad, MD; Steven Minear, MD; Tristan E. Weaver, MD; Kurt Ruetzler, MD; Claudia Brusasco, PhD; Joel L. Parlow, MD; Elizabeth Maxwell, MBChB; Scott Miller, MD; Marko Mrkobrada, MD; Keyur Suresh Chandra Bhatt, MD; Prashant Rahate, MD; Ana Kowark, MD; Giuseppe De Blasio, MD; Sandra N. Ofori, MBBS; David Conen, MD; Sadeesh Srinathan, MD; Wojciech Szczeklik, MD; Raja Jayaram, MD; Richard K. Ellerkmann, MD; Mona Momeni, MD; Ingrid Copland; Jessica Vincent, MSc; Kumar Balasubramanian, MSc; Zhuoru Li, MSc; Michael Ke Wang, MD; Deyang Li, MSc; Michael H. McGillion, PhD; Andrea Kurz, MD; Mukul Sharma, MD; Timothy G. Short, MD; and P.J. Devereaux, MD; on behalf of the cogPOISE-3 Trial Investigators and Study Groups*

Background: Perioperative hemodynamic abnormalities have been associated with neurocognitive outcomes after noncardiac surgery.

Objective: To compare the effects of perioperative hypotension-avoidance versus hypertension-avoidance strategies on delirium and 1-year cognitive decline after noncardiac surgery.

Design: Randomized controlled trial. (ClinicalTrials.gov: NCT03505723)

Setting: 54 centers, 19 countries.

Participants: 2603 high-vascular-risk patients undergoing noncardiac surgery, receiving 1 or more chronic antihypertensive medications (mean age, 70 years).

Intervention: In the hypotension-avoidance strategy, the intraoperative mean arterial pressure (MAP) target was 80 mm Hg or greater; before and for 2 days after surgery, renin–angiotensin–aldosterone system inhibitors were withheld, and other chronic antihypertensive medications were administered for systolic blood pressures of 130 mm Hg or greater following an algorithm. In the hypertension-avoidance strategy, the intraoperative MAP target was 60 mm Hg or greater; all chronic antihypertensive medications were continued perioperatively.

Measurements: Delirium on postoperative day 1 to 3 (primary outcome); decline of 2 points or more at the Montreal Cognitive Assessment (MoCA) 1 year after surgery compared with baseline (secondary outcome).

Results: 95 of 1310 patients (7.3%) in the hypotension-avoidance and 90 of 1293 patients (7.0%) in the hypertension-avoidance group had delirium (relative risk [RR], 1.04 [95% CI, 0.79 to 1.38]). Among 701 patients who completed 1-year MoCA (full or telephone version), 129 of 347 (37.2%) in the hypotension-avoidance and 117 of 354 (33.1%) in the hypertension-avoidance group had a decline of 2 or more points (RR, 1.13 [CI, 0.92 to 1.38]). Nineteen percent in the hypotension-avoidance and 27% in the hypertension-avoidance strategy had hypotension requiring an intervention (RR, 0.63 [CI, 0.52 to 0.76]), mostly intraoperatively; only 5%, in both groups, had hypotension postoperatively.

Limitation: The COVID-19 pandemic challenged site participation in the substudy; although large, the sample size was lower than expected.

Conclusion: There was no evidence of a difference in neurocognitive outcomes between the hypotension-avoidance and hypertension-avoidance strategies.

Primary Funding Source: Canadian Institutes of Health Research, Canada; National Health and Medical Research Council, Australia; Research Grant Council, Hong Kong SAR, China.

Ann Intern Med. 2025;178:000-000. doi:10.7326/ANNALS-24-02841
For author, article, and disclosure information, see end of text.
This article was published at Annals.org on 3 June 2025.
* For members of the cogPOISE-3 Trial Investigators and Study Groups, see the Appendix (available at Annals.org).

Among the public, "brain damage" and "permanent cognitive changes" are the most feared complications of surgery and anesthesia, even more than death (1, 2). Up to 20% of older patients undergoing noncardiac surgery develop postoperative delirium (3). Among other major postoperative complications, delirium is the strongest predictor of institutionalization, hospital readmission, and resource utilization (4, 5). Postoperative delirium is associated with long-term cognitive impairment and incident dementia (6–9). Even in absence of delirium, up to 30% of older patients undergoing major

See also:

Editorial comment

Web-Only
Supplement

J_ID: AIM ART NO: ANNALS-24-02841 Date: 21-May-25 Page: 2 Total Pages: 15 ini:

noncardiac surgery have substantial cognitive changes 1 year after surgery (10, 11).

Hypotension is common during and after noncardiac surgery (12–14). It is biologically plausible that acute systemic blood pressure abnormalities, and in particular hypotension, may lead to delirium by impairing cerebral perfusion, especially in people with altered cerebral autoregulation such as patients who are older, have vascular disease, or take antihypertensive therapy (15–18). Observational studies have indeed suggested that both perioperative hypotension and hypertension may increase the risk for postoperative delirium or cognitive dysfunction (19–24).

A few small randomized controlled trials (RCTs) have evaluated the effects on neurocognitive outcomes after noncardiac surgery of higher or personalized, versus lower or standard, intraoperative blood pressure targets (25–31). They had contrasting results, with some showing an association between higher targets and lower incidence or severity of delirium and some showing no evidence of a difference between groups. No RCT evaluated the effect on neurocognition of the perioperative continuation or discontinuation of antihypertensive medications (32).

We undertook the cogPOISE-3 trial, a substudy of the POISE-3 (PeriOperative ISchemic Evaluation) trial (33), to evaluate the hypothesis that, in patients undergoing noncardiac surgery and chronically using antihypertensive therapy, 2 blood pressure management strategies—differing in intraoperative blood pressure target and management of chronic antihypertensive medication—would differ on their effects on postoperative neurocognitive outcomes, with a hypotension-avoidance strategy being superior to a hypertension-avoidance strategy.

METHODS

Design, Setting, and Ethics

The POISE-3 trial was an international RCT in which patients undergoing noncardiac surgery, with or at risk for vascular disease, were randomly assigned to receive intraoperative tranexamic acid or placebo (34); according to a partial factorial design, patients taking 1 or more antihypertensive medications were also eligible for randomization to a perioperative hypotension-avoidance strategy or a hypertension-avoidance strategy. The main POISE-3 blood pressure management trial showed no evidence of a difference between the 2 strategies for their effect on the primary composite outcome of major vascular complications 30 days after randomization (33).

The cogPOISE-3 substudy was a 1:1 randomization superiority trial, comparing the effects of the 2 blood pressure management strategies on postoperative delirium (primary objective) and on cognitive decline 1 year after surgery (secondary objective). For the primary objective, at centers that agreed to participate in cogPOISE-3, local ethics boards approved an amended POISE-3 protocol that included delirium as an outcome. Thereafter, every POISE-3 participant at a cogPOISE-3 participating center was included in the delirium assessment. Additional separate consent was required for inclusion in the baseline and 1-year cognitive assessment.

The cogPOISE-3 protocol and statistical analysis plan are available at Annals.org.

Recruitment started in June 2018 in the main trial and in October 2019 in cogPOISE-3. Recruitment continued until July 2021.

Study Population

The eligibility criteria for the cogPOISE-3 trial (delirium component) reflected those of the main POISE-3 blood pressure management trial (**Supplement Methods 1** in the **Supplement**, available at Annals.org). In brief, participants were aged 45 years or older, undergoing noncardiac surgery requiring at least 1 overnight stay, with a history of vascular disease or multiple vascular risk factors, and receiving 1 or more antihypertensive medications for 30 days or more in the 6 weeks preceding randomization. Only patients without a history of dementia (as reported by the patient's caregivers or medical chart) were eligible for the cognitive assessment component.

Randomization and Blinding

Randomization followed the same central web-based randomization process as in the main trial, stratified by center and using random block sizes, with an additional randomization stratum based on whether participants consented to the cognitive assessment. Patients, health care providers, and study personnel were aware of the group allocation.

Procedures

Study personnel instructed participants not to take their antihypertensive medications the night before and the morning of surgery, and to bring these medications to the hospital. For patients randomly assigned to the hypotension-avoidance strategy, anesthesiologists were to target an intraoperative mean arterial pressure (MAP) of 80 mm Hg or greater from the time of anesthetic induction until the end of surgery, using means (for example, fluids, vasopressors) at their discretion. On the day of surgery and during the first 2 days after surgery, patients were not to receive any angiotensin-converting enzyme inhibitor (ACEI), angiotensin-receptor blocker (ARB), or direct renin inhibitor. The rest of the patient's chronic antihypertensive medications were managed in a stepwise manner based on an algorithm (**Supplement Methods 2**) that continued β-blockers for systolic blood pressures (SBPs) of 130 mm Hg or greater, and other antihypertensive classes only for SBPs of 160 mm Hg or greater. For patients randomly assigned to the hypertension-avoidance strategy, intraoperatively, anesthesiologists were to target a MAP of 60 mm Hg or greater. Patients

ID: banen Time: 17:48 I Path: //mumnasprod/home$/banen$/CP-ACPJ250220

J_ID: AIM ART NO: ANNALS-24-02841 Date: 21-May-25 Page: 3 Total Pages: 15 ini:

were to receive all of their antihypertensive medications on the morning of surgery and restart them immediately after surgery.

Trained study personnel screened participants twice daily, once ante meridiem and once post meridiem, from postoperative day 1 until postoperative day 3, discharge, or delirium diagnosis, whichever came first, using the 3-Minute Diagnostic Interview for the Confusion Assessment Method (3D-CAM) (35). We used CAM-ICU when patients were in intensive care units or postanesthesia care units (36). Research personnel could report CAM assessments performed by local health care personnel when available.

Trained study personnel administered the Montreal Cognitive Assessment (MoCA) (37) and the Digit Symbol Substitution Test (DSST) (38) at baseline and 1 year after surgery, following procedures successfully implemented in the international NeuroVISION cohort study (10) (**Supplement Methods 3**).

To increase feasibility during the COVID-19 pandemic, we allowed the 1-year cognitive assessment to occur either in person or remotely, and up to 18 months after randomization. Remotely, research personnel could administer either the full MoCA (scored from 0 to 30) via videoconference or its adapted shorter version via telephone (that is, blind MoCA, which is missing the drawing-based items and is scored from 0 to 22 [https://mocacognition.com]).

Outcomes

The primary outcome was in-hospital delirium during the first 3 postoperative days. Delirium was considered present when at least 1 of the CAM assessments met the diagnostic criteria.

The secondary delirium outcomes included severity of delirium among those with delirium and scoring 2 points or more on the CAM-severity scale, regardless of meeting the criteria for delirium. Severity was measured only in patients who had at least 1 3D-CAM assessment available and uploaded on the central database, using the algorithm described by Vasunilashorn and colleagues (39) (**Supplement Methods 4**). Scoring 2 points or more on the CAM-based severity scale has been associated with an increased risk for adverse clinical outcomes, regardless of meeting the CAM features required for a diagnosis of delirium (39, 40).

The secondary 1-year cognitive outcomes included a decline of 2 or more points at the MoCA compared with baseline, change in the MoCA score compared with baseline, and change in the DSST score compared with baseline.

To enhance the interpretation of the main POISE-3 results, we had added, post hoc, an outcome called "clinically significant hypotension," defined as an SBP less than 90 mm Hg requiring an intervention occurring from randomization to day 4 after surgery or discharge (33). We analyzed this outcome also in the cogPOISE-3 subpopulation.

Statistical Analysis

The cogPOISE-3 statistical analysis plan was finalized before any analysis was undertaken. We assumed that 4500 POISE-3 participants would participate in cogPOISE-3, with 1350 participating in the cognitive component. We assumed that 7.5% to 10% of patients in the control group would experience delirium and 25% to 30% of patients would have a MoCA decline of 2 points or more at 1 year. With these assumptions, the expected sample size would have provided at least 80% power (with a 2-tailed α error of 0.05) to show a 25% to 30% relative risk (RR) reduction in delirium, and a similar reduction on the 2-point or more MoCA decline at 1 year, with the hypotension-avoidance strategy compared with the hypertension-avoidance strategy (**Supplement Methods 5**).

We analyzed patients according to the group to which they were assigned. Only patients with at least 1 CAM assessment were included in the delirium analyses. For the primary outcome analysis, we compared the proportion of patients with delirium in the hypotension-avoidance strategy group with that in the hypertension-avoidance strategy group using a generalized linear model for binary outcomes, stratified by randomization status in the tranexamic acid trial and inclusion in the cognitive assessment; we performed a Cochran–Mantel–Haenszel test to test for heterogeneity among strata. We reported the RR, absolute differences, and corresponding 95% CIs. Because death or discharge within the first 3 days after surgery could compete with CAM assessment and delirium detection, we performed sensitivity time-to-event analyses that accounted for these competing risks, with the treatment effect expressed as a hazard ratio (HR) and corresponding 95% CI. For the analysis on delirium severity, we calculated the median (IQR) of the highest severity scores in patients with delirium in the 2 study groups and compared them using quantile regression. For the proportion of patients with 2 or more points of CAM-severity score, we performed the same analysis as for the primary outcome.

Supplement Methods 6 reports details for the prespecified subgroup analyses. Each subgroup effect was assessed in logistic regression models with delirium as the dependent variable and including the treatment-by-subgroup interaction term. Based on the knowledge of nonoptimal adherence with the 2 strategies as calculated for the main trial (33), we analyzed whether the effect on delirium was modified by the adherence with the assigned strategies. **Supplement Methods 7** provides the adherence definitions.

For the analyses on 1-year MoCA outcomes, we included every patient who had a 1-year MoCA, regardless of the method (in person or remote), version (full vs. blind MoCA), and the actual time for the follow-up (whether 1 year, or extended time). As prespecified in the statistical analysis plan, we made this decision before running any outcome analyses, after verifying that method, version, and timing of 1-year MoCA

ID: banen Time: 17:48 I Path: //mumnasprod/home$/banen$/CP-ACPJ250220

J_ID: AIM ART NO: ANNALS-24-02841 Date: 21-May-25 Page: 4 Total Pages: 15 ini:

were distributed evenly between groups (**Supplement Table 1**). To compare the proportion of patients with a decline of 2 or more points in their 1-year MoCA score, we performed a χ^2 test and reported the RR, absolute difference, and corresponding 95% CIs. As sensitivity analysis, we repeated the analyses after imputing missing 1-year MoCA data (including missing MoCAs and missing items at the blind MoCA), according to an evidence-informed data imputation technique (**Supplement Methods 8**). The effect of the intervention on continuous MoCA and DSST scores at 1 year, accounting for baseline scores, was assessed in linear regression analyses with the MoCA or DSST score at 1 year as the dependent variable and the variable for the study group and the baseline MoCA or DSST score as independent variables (41).

Statistical analyses were performed using SAS software, version 9.4 (SAS Institute).

Role of the Funding Source

The funders had no role in the study design, conduct, analyses, or manuscript preparation.

RESULTS

Patient Characteristics

Since cogPOISE-3 activation, the 54 centers (19 countries) that agreed to participate in the substudy randomly assigned 2834 patients; of them, 2603 (1310 assigned to the hypotension-avoidance and 1293 to the hypertension-avoidance strategy) completed at least 1 CAM assessment and were included in the primary delirium analysis (**Figure 1**). **Table 1** describes the preoperative patient characteristics and the type of surgery and anesthesia for the 2603 patients included in the primary analysis.

F1 T1

Adherence to the Assigned Strategies and Perioperative Hemodynamics

Intraoperatively, patients in the hypotension-avoidance strategy spent a median of 27 more minutes with MAP of 80 mm Hg or greater than patients in the hypertension-avoidance strategy (**Supplement Table 2**). The average adherence with the administration of chronic antihypertensive medications according to the assigned strategies, before and after surgery, ranged between 63.7% and 77.1% (**Supplement Table 3**). This translated into fewer patients receiving an ACEI/ARB in the hypotension-avoidance strategy group (3.4% on the day of surgery, 4.1% on day 1 after surgery, and 4.2% on day 2 after surgery), compared with patients in the hypertension-avoidance strategy group (45.6% on the day of surgery, 51% on day 1 after surgery, and 53.5% on day 2 after surgery). This also translated into fewer patients receiving 1 or more antihypertensive medications in the hypotension-avoidance group (33.7% on the day of surgery, 34.7% on day 1 and day 2 after surgery), compared with patients in the hypertension-avoidance strategy group (76.0% on the day of surgery, 85.3% on day 1 after surgery, and 87.1% on day 2 after surgery) (**Supplement Table 4**).

Fewer patients in the hypotension-avoidance group than in the hypertension-avoidance group experienced clinically significant hypotension according to our definition, from randomization to postoperative day 4 (243 patients [19%] vs. 344 patients [27%]; RR, 0.70 [95% CI, 0.60 to 0.81]). Most of these events (90%) occurred intraoperatively, and the difference in the incidence of clinically significant hypotension was limited to the time of surgery (**Supplement Table 5**). On average, there were small (1.0 to 1.6 mm Hg or beats per minute) to no between-group differences in blood pressure and heart rate at discrete postrandomization times outside of the operating room (**Supplement Tables 6** and **7**).

Delirium Outcomes

Delirium occurred in 95 patients (7.3%) in the hypotension-avoidance and in 90 patients (7.0%) in the hypertension-avoidance group (RR, 1.04 [CI, 0.79 to 1.38]; difference, 0.3% [CI, −1.7% to 2.3%]; $P = 0.77$) (**Table 2**). The primary outcome analyses did not change when accounting for discharge or death as competing risks (**Table 2** and **Supplement Table 8**). At least 1 3D-CAM–severity score was available for 2374 patients (91%). Among patients with delirium, the median severity score was 4.0 (IQR, 3.0 to 5.0) in both groups (median difference, 0 [IQR, −0.78 to 0.79]; $P > 0.99$). Among all patients, 17.7% versus 18.0% scored 2 or more points at 3D-CAM severity (RR, 1.00 [CI, 0.96 to 1.04]; $P = 0.86$) (**Table 2**).

T2

There was no evidence of a difference in the effect of the hypotension-avoidance versus the hypertension-avoidance strategy on delirium occurrence according to patient age; whether patients were receiving chronic ACEI/ARB therapy or not, and chronic β-blocker therapy or not; whether they were receiving 1 or more chronic antihypertensive medications; according to preoperative SBP, estimated glomerular filtration rate, and N-terminal pro-B-type natriuretic peptide values; and whether patients were enrolled in the cognitive evaluation or not (**Supplement Figures 1** to **3**).

There was no statistically significant interaction between the average center-level adherence and the difference in delirium between the 2 strategies (**Figure 2**). There was a statistically significant interaction between the patient-level adherence with the intraoperative strategy and the difference in delirium (**Supplement Figure 4**); however, the interaction was not in the direction of a treatment effect, or greater treatment effect, among patients managed with greater adherence to the assigned strategy.

F2

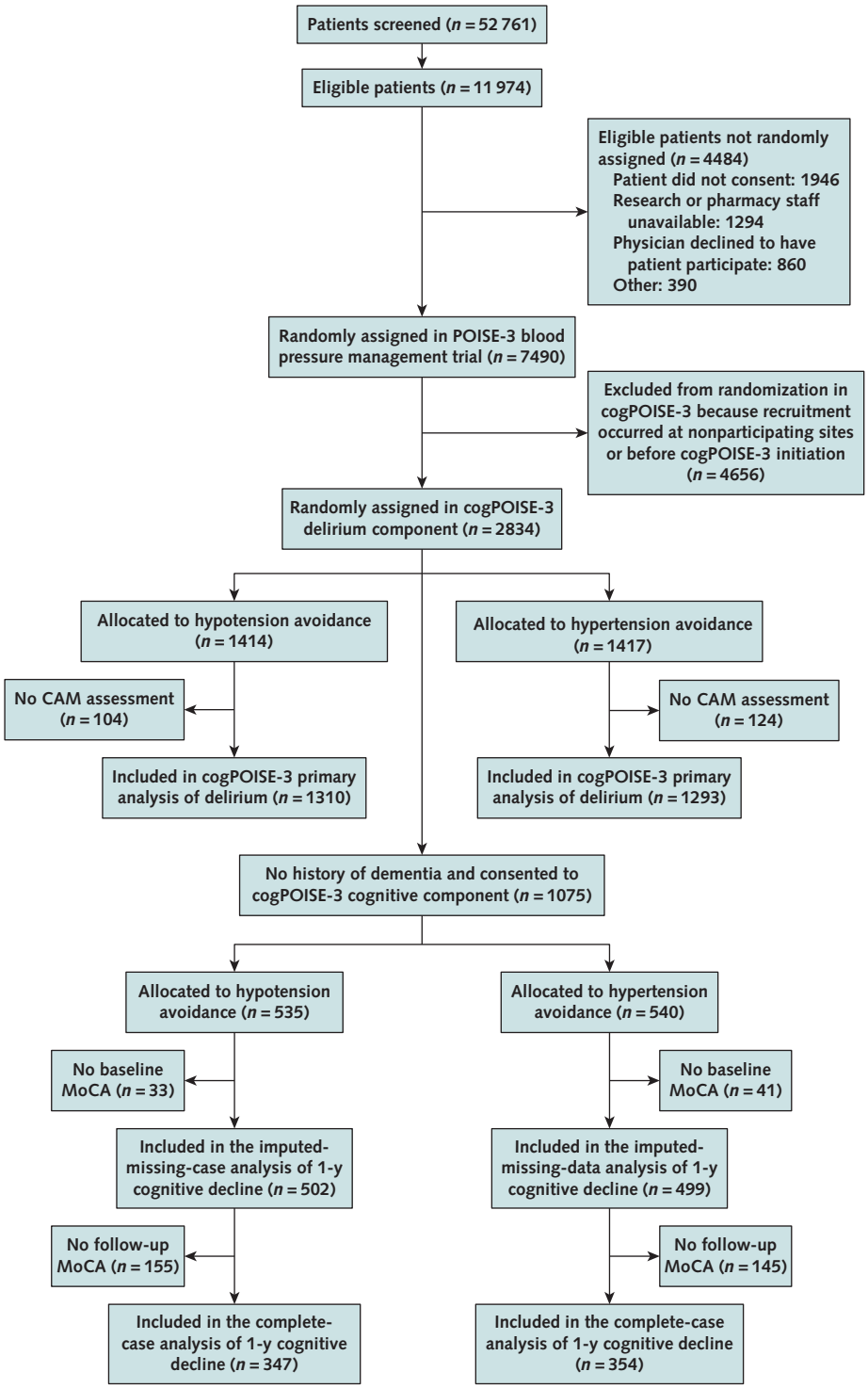
One-Year Cognitive Outcomes

Among the 1075 patients who were enrolled in the 1-year cognitive evaluation (44 centers, 18 countries), 1001 (502 in the hypotension-avoidance and 499 in the hypertension-avoidance strategy group) had a preoperative MoCA done; 701 (347 in the

ID: banen Time: 17:48 I Path: //mumnasprod/home$/banen$/CP-ACPJ250220

J_ID: AIM ART NO: ANNALS-24-02841 Date: 21-May-25 Page: 5 Total Pages: 15 ini:

Figure 1. Patient flow diagram.



CAM = Confusion Assessment Method; cogPOISE-3 = a substudy of the POISE-3 trial; MoCA = Montreal Cognitive Assessment; POISE-3 = the PeriOperative ISchemic Evaluation trial.

ID: banen Time: 17:48 I Path: //mumnasprod/home$/banen$/CP-ACPJ250220

J_ID: AIM ART NO: ANNALS-24-02841 Date: 21-May-25 Page: 6 Total Pages: 15 ini:

Table 1. Preoperative Patient Characteristics and Intraoperative Measures

Characteristic	Hypotension-Avoidance Strategy (*n* = 1310)	Hypertension-Avoidance Strategy (*n* = 1293)
Mean age (SD), *y*	70.3 (9.7)	70.1 (9.6)
Age category, *n (%)*		
<65 y	334 (25)	359 (28)
65–75 y	545 (42)	553 (43)
>75 y	431 (33)	381 (29)
Sex, *n (%)*		
Male	640 (49)	643 (50)
Female	670 (51)	650 (50)
Eligibility criteria met,* *n (%)*		
Preoperative NT-proBNP ≥200 ng/L	265 (20)	258 (20)
History of coronary artery disease	377 (29)	377 (29)
History of peripheral artery disease	139 (11)	143 (11)
History of stroke	104 (8)	101 (8)
Undergoing major vascular surgery	92 (7)	104 (8)
Risk criteria†		
Undergoing major surgery‡	1048 (80)	1031 (80)
History of congestive heart failure	266 (20)	269 (21)
History of transient ischemic attack	56 (4)	55 (4)
Diabetes requiring medication	459 (35)	430 (33)
Age ≥70 y	745 (57)	726 (56)
History of hypertension	1284 (98)	1269 (98)
Preoperative serum creatinine >175 μmol/L (>2.0 mg/dL)	15 (1)	17 (1)
History of smoking within 2 y before surgery	251 (19)	248 (19)
Undergoing emergent/urgent surgery	245 (19)	215 (17)
Other medical history, *n (%)*		
History of atrial fibrillation	146 (11)	126 (10)
Active cancer	364 (28)	370 (29)
History of dementia	27 (2)	21 (2)
Mean preoperative creatinine (SD)		
μmol/L	86.6 (27.5)	87.0 (30.7)
mg/dL	0.98 (0.31)	0.98 (0.35)
Mean preoperative MoCA score (SD)§	24.8 (4.2)	24.1 (4.3)
Mean preoperative DSST score (SD)‖	39.2 (16.7)	38.2 (16.4)
Chronic antihypertensive medications		
Mean number per patient (SD)	2 (1)	2 (1)
Patients on ≥3 medications, *n (%)*	385 (29)	345 (27)
Type of chronic antihypertensive medication, *n (%)*		
ACEI or ARB	938 (72)	909 (70)
β-blocker	619 (47)	597 (46)
Dihydropyridine CCB	456 (35)	431 (33)
Thiazide or thiazide-like diuretic	300 (23)	287 (22)
Rate-controlling CCB	35 (3)	26 (2)
Loop diuretic	111 (8)	104 (8)
Aldosterone antagonist	21 (2)	17 (1)
Other potassium-sparing diuretic	36 (3)	29 (2)
α-blocker	96 (7)	96 (7)
Hydralazine	9 (1)	7 (<1)
Long-acting nitrate	19 (1)	26 (2)
Other vasodilator (for example, minoxidil)	1 (<1)	2 (<1)
α2-Adrenergic agonist	17 (1)	14 (1)
Direct renin inhibitor	1 (<1)	1 (<1)
Mean preoperative systolic blood pressure (SD), mm Hg¶	138.1 (19.5)	138.3 (19.8)
Mean preoperative diastolic blood pressure (SD), mm Hg¶	78.1 (10.8)	78.3 (11.1)
Mean preoperative heart rate (SD), beats per min¶	74.5 (11.6)	74.3 (11.7)
Surgery performed, *n (%)*	1310 (100)	1292 (>99)
General	501 (38)	525 (41)
Orthopedic	418 (32)	367 (28)
Vascular	136 (10)	135 (10)
Urological	132 (10)	141 (11)
Gynecological	22 (2)	24 (2)
Thoracic	39 (3)	28 (2)
Spinal	59 (5)	67 (5)
Plastic	3 (<1)	4 (<1)
Low-risk surgery	0 (0)	1 (<1)
Median duration of surgery (IQR), *min*	127.5 (84–202)	126.0 (80–215)
Type of intraoperative anesthesia, *n (%)*		
General, alone or combined with other type of anesthesia	1103 (84)	1117 (86)
Nerve block, alone or combined with other type of anesthesia	133 (10)	103 (8)
Only sedation or local	258 (20)	225 (18)
Volatile agent	386 (30)	407 (32)

Continued on next column

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; CCB = calcium-channel blocker; DSST = Digit Symbol Substitution Test; MoCA = Montreal Cognitive Assessment; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

* Patients were eligible for enrollment in the study if they met 1 or more of the eligibility criteria.

† Meeting this eligibility criterion involved meeting at least 3 of the 9 risk criteria listed here.

‡ Major surgery was defined as intraperitoneal, intrathoracic, retroperitoneal, or major orthopedic surgery.

§ Provided for the 701 patients (347 in the hypotension-avoidance strategy group and 354 in the hypertension-avoidance strategy group) who were enrolled in the cognitive component of cogPOISE-3 and completed both a baseline and a follow-up MoCA.

‖ Provided for the 514 patients (254 in the hypotension-avoidance strategy group and 260 in the hypertension-avoidance strategy group) who were enrolled in the cognitive component of cogPOISE-3 and completed both a baseline and a follow-up DSST.

¶ First measured on the morning of surgery, before induction, and before the administration of any antihypertensive medication.

hypotension-avoidance, and 354 in the hypertension-avoidance strategy group) also had a follow-up MoCA done and were included in the primary MoCA analysis (**Figure 1**; **Supplement Tables 9** and **10**). A 2 or more MoCA point decrease at follow-up compared with baseline occurred in 129 patients (37.2%) in the hypotension-avoidance and 117 (33.1%) in the hypertension-avoidance group (RR, 1.20 [CI, 0.88 to 1.64]; difference, 4.1% [CI, −2.9% to 11.2%]; $P = 0.25$) (**Table 3**), among T3 patients who had a 1-year MoCA done (any method/version), and in 158 (31.5%) and in 140 (28.1%), respectively (RR, 1.12 [CI, 0.93 to 1.36]; difference, 3.4% [CI, −2.2% to 9.1%]; $P = 0.24$), when missing follow-up data were imputed. We found no evidence of a difference

ID: banen Time: 17:48 I Path: //mumnasprod/home$/banen$/CP-ACPJ250220

Table 2. Delirium Outcomes

Outcomes	Hypotension-Avoidance Strategy, *n/N (%)*	Hypertension-Avoidance Strategy, *n/N (%)*	RR or HR or Median Difference (95% CI or IQR)	*P* Value
Primary outcome: delirium				
Primary analysis	95/1310 (7.3)	90/1293 (7.0)	1.04 (0.79 to 1.38)*	0.77
Sensitivity analyses				
Delirium with discharge as competing outcome†	95/1310 (7.3)	90/1293 (7.0)	1.05 (0.79 to 1.39)‡	0.75
Delirium with death as competing outcome§	95/1310 (7.3)	90/1293 (7.0)	1.05 (0.79 to 1.39)‡	0.75
Secondary outcomes: 3D-CAM severity score				
Median severity score among patients with delirium (IQR)‖	4.0 (3.0 to 5)	4.0 (3.0 to 5)	0 (−0.78 to 0.78)¶	>0.99
≥2 severity score in the overall population	212/1198 (17.7)	211/1174 (18.0)	1.00 (0.96 to 1.04)	0.86

3D-CAM = 3-Minute Diagnostic Interview for Confusion Assessment Method; HR = hazard ratio; RR = relative risk.
* Relative risk is reported.
† The median length of stay was 3.9 days (IQR, 2.2 to 6.2 days) in the hypotension-avoidance group and 4.0 days (IQR, 2.2 to 6.3 days) in the hypertension-avoidance group, among those who had at least 1 CAM assessment and were included in the primary outcome analyses. The median length of stay was 3.2 days (IQR, 1.1 to 7.0 days) in the hypotension-avoidance group and 3.1 days (IQR, 1.3 to 6.1 days) in the hypertension-avoidance group, among the 231 patients who were enrolled in cogPOISE-3 but did not undergo any CAM assessment and could not be included in the primary outcome analyses.
‡ Hazard ratio.
§ Two patients in the hypotension-avoidance group and 1 in the hypertension-avoidance group died after randomization into cogPOISE-3 and within postoperative day 3 before any CAM assessment could be done. These patients are not included in the current delirium analyses. Among the 2603 patients included because they had at least 1 CAM assessment performed, 2 patients in the hypotension-avoidance group and none in the hypertension-avoidance group died before postoperative day 3; death was the reason for missing assessment for 3 of the due CAM assessments (**Supplement Table 8**).
‖ Severity scoring based on availability of a full 3D-CAM assessment was available for 158 patients with delirium (79 in the hypotension-avoidance and 79 in the hypertension-avoidance group).
¶ Median difference.

between groups for the 1-year cognitive outcome according to any other definition (**Table 3**).

Discussion

Among 2603 high-vascular-risk adult patients having major noncardiac surgery (mean age, 70 years), our study found no evidence of a difference in their effects on postoperative delirium frequency and severity between 2 perioperative blood pressure strategies that differed in the intraoperative MAP targets and perioperative management of patients' antihypertensive medications. Among the subset of 1001 patients undergoing prospective cognitive evaluation, after imputing follow-up scores based on the reasons for missing data, a similar proportion in the 2 groups had cognitive decline 1 year after surgery according to our study definition.

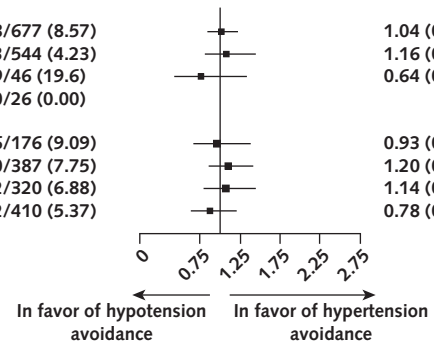
Five RCTs in noncardiac surgery compared higher versus lower intraoperative blood pressure targets for their effects on neurocognitive outcomes (29, 30, 42–44). Two found no evidence of outcome differences between the 2 randomization groups (42, 43); 3 found that patients randomly assigned to higher blood pressure targets had a lower incidence or severity of delirium (29, 30, 44). All of these RCTs were single center, with the largest including 322 patients (29, 30, 42–44). A recent trial (single center, 328 patients) compared personalized blood pressure management (that is, maintaining intraoperative MAP above preoperative MAP from automated 24-hour blood pressure monitoring) with routine blood pressure management (that is, maintaining MAP >65 mm Hg) (31). They found no difference in their composite primary outcome of delayed neurocognitive recovery or delirium between postoperative days 3 and 7 (31). All of these trials evaluated strategies that focused on intraoperative blood pressure management, and cognitive dysfunction was evaluated at 3 to 4 months after surgery at the latest (42, 43). The cogPOISE-3 study is the largest trial addressing this question by comparing 2 comprehensive perioperative blood pressure management strategies and looking at cognitive effects 1 year after surgery. To our knowledge, with 2603 patients included in the delirium analyses and 701 patients (1001 after missing data imputation) included in the long-term analyses, cogPOISE-3 is the largest existing trial evaluating interventions targeting neurocognitive outcomes after noncardiac surgery.

The results of the cogPOISE-3 trial add to the results of the main POISE-3 trial to provide robust evidence—coming from a multicenter, large RCT—for the lack of difference in clinically important outcomes between the 2 studied strategies. We explored 2 possible explanations for why our initial hypothesis proved wrong. The first possible explanation is that our hypothesis was in fact true, but we could not prove it because of the suboptimal adherence with the assigned strategies. However, as in the main trial, we found no subgroup or dose-response effect based on the degree of adherence, measured either at the

J_ID: AIM ART NO: ANNALS-24-02841 Date: 21-May-25 Page: 8 Total Pages: 15 ini:

Figure 2. Treatment effect on delirium by center-average percentage adherence with the study blood pressure management strategies.

	Total Events/ Total (%)	Hypotension Events/Total (%)	Hypertension Events/Total (%)	RR (95% CI)	*P* Value for Interaction
Intraoperative adherence					
<60.0	119/1364 (8.72)	61/687 (8.88)	58/677 (8.57)	1.04 (0.73–1.46)	0.87
≥60.0 and <70.0	50/1092 (4.58)	27/548 (4.93)	23/544 (4.23)	1.16 (0.68–2.01)	
≥70.0 and <80.0	15/94 (16.0)	6/48 (12.5)	9/46 (19.6)	0.64 (0.25–1.65)	
≥80.0	1/53 (1.89)	1/27 (3.70)	0/26 (0.00)		
Pre/postoperative adherence					
<60.0	32/365 (8.77)	16/189 (8.47)	16/176 (9.09)	0.93 (0.48–1.81)	0.64
≥60.0 and <70.0	67/784 (8.55)	37/397 (9.32)	30/387 (7.75)	1.20 (0.76–1.91)	
≥70.0 and <80.0	47/638 (7.37)	25/318 (7.86)	22/320 (6.88)	1.14 (0.66–1.98)	
≥80.0	39/816 (4.78)	17/406 (4.19)	22/410 (5.37)	0.78 (0.43–1.44)	



Center-average percentage adherence intraoperatively (Intraoperative Adherence) was calculated as the average percentage adherence to the intraoperative mean arterial pressure target in either strategy, across all participants randomly assigned in that center. Center-average adherence preoperatively and postoperatively (Pre-/Postoperative Adherence) was calculated as the average of the daily mean percentage adherence to the preoperative and postoperative phases of the assigned strategy of administration of antihypertensive medications, across all participants randomly assigned in that center. RR = relative risk.

center or patient level, which suggests that this is not the explanation. In contrast, the most plausible explanation is that our hypothesis was truly wrong because our assumption that the 2 strategies would differ in their impact on perioperative hemodynamics was wrong. We indeed demonstrated only small average blood pressure differences between the 2 strategies and an 8% difference only in the frequency of clinically significant hypotension occurring intraoperatively. These intraoperative hypotensive events were likely soon detected and counteracted and, as such, did not impact clinical outcomes. Further research is needed to identify other strategies that could positively affect hemodynamics more substantially and beyond the highly monitored operating room, and thus possibly result in improved neurocognitive outcomes.

Similarly to what was found in the international NeuroVISION cohort, cogPOISE-3 confirmed that around 30% of older adult patients undergoing noncardiac surgery have cognitive decline 1 year after noncardiac surgery based on a 2 or more point decrease in MoCA scores and when using an information-based imputation approach to missing follow-ups (10). A decrease of 2 or more points on a MoCA score has been associated with cognitive decline based on formal neuropsychological testing (45, 46). Studies have shown a decline of 1.4 to 2.2 points on the MoCA score for *every additional 10 years of age* in community-dwelling people aged 65 years or older (47, 48). In the COMPASS trial, among 1654 patients with a mean age of 71 years with established cardiovascular disease at baseline, a 2 or more point MoCA decline occurred in 28% of patients *for 2 years* (49). Although large confirmatory prospective studies including a nonsurgical comparator are needed, our findings support the hypothesis that the frequency and rate of the cognitive changes in the first year after noncardiac surgery are not what one would expect based on normal aging or baseline vascular disease.

Table 3. Cognitive Outcomes at 1 Year After Randomization

Analyses	Hypotension-Avoidance Strategy, *n/N (%)*	Hypertension-Avoidance Strategy, *n/N (%)*	RR or Mean Difference (95% CI)	*P* Value
Primary analysis				
≥2 MoCA point decrease at 1 y compared with baseline*	129/347 (37.2)	117/354 (33.1)	1.13 (0.92 to 1.38)	0.25
Secondary, sensitivity, and post hoc analyses				
≥2 MoCA point decrease at 1 y compared with baseline (imputation of missing data)	158/502 (31.5)	140/499 (28.1)	1.12 (0.93 to 1.36)	0.24
Mean MoCA at 1 y adjusted for baseline (SD)*†	24.9 (0.2)	25.1 (0.2)	−0.14 (−0.65 to 0.37)	0.58
Mean DSST at 1 y adjusted for baseline (SD)†‡	38.7 (0.6)	38.5 (0.6)	0.3 (−1.5 to 2.0)	0.78

DSST = Digit Symbol Substitution Test; MoCA = Montreal Cognitive Assessment; RR = relative risk.
* The analysis includes 701 patients with a baseline and 1-year MoCA, regardless of the method, version, and timing of MoCA performed at 1 year.
† From linear regression adjusted for baseline MoCA or DSST score.
‡ The analysis included 514 patients with a baseline and 1-year DSST.

ID: banen Time: 17:48 I Path: //mumnasprod/home$/banen$/CP-ACPJ250220

Our study has limitations. Due to the COVID-19 pandemic, fewer POISE-3 centers than planned could eventually participate in cogPOISE-3, and we had a smaller sample size than expected. On average, we included an older surgical population, but we did not restrict the inclusion in cogPOISE-3 only to the oldest POISE-3 participants, which could in part explain the incidence of delirium being on the lower end of the expected range. However, results were consistent across different outcome definitions and age subgroups. The pandemic also posed challenges to the completion of the cognitive follow-up and likely contributed to the 30% of missing 1-year MoCA data. However, the main complete-case analysis, and the sensitivity analysis using imputation of missing 1-year data based on the reasons for missing data, provided consistent results. Moreover, the trial proved the feasibility of remote cognitive assessments in this patient population internationally. Lack of blinding was another limitation; however, if investigators or outcome assessors were biased toward 1 group, this did not result in detection of a treatment effect. Other limitations include missing CAM assessments—even if with no different frequency between the 2 groups and still ensuring morning and afternoon coverage—and the inability to characterize any baseline or 1-year cognitive deficit as a "neurocognitive disorder": that would have required a standardized multidimensional assessment that was deemed difficult to implement in this large pragmatic trial (50).

In conclusion, among patients having inpatient noncardiac surgery, our findings do not support targeting an intraoperative MAP of 80 mm Hg or greater, compared with a MAP of 60 mm Hg or greater, and perioperatively withholding ACEI/ARBs and continuing other chronic antihypertensive medications following an algorithm, compared with continuing all chronic antihypertensive medications, to improve postoperative neurocognitive outcomes.

and From Population Health Research Institute, Hamilton, Ontario, Canada; Clinical Epidemiology and Research Centre, Humanitas University & IRCCS Humanitas Research Hospital, Milan, Italy; and Department of Health Research Methods, McMaster University, Hamilton, Ontario, Canada (M.M.); The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China (M.T.V.C.); Acute Care Medicine, The University of Adelaide, Adelaide, South Australia, Australia (T.W.P.); Saint Petersburg State University Hospital, Saint Petersburg, Russia (S.E.); Trauma & Orthopaedic Surgery Department, Hospital Clínico Universitario de Valladolid, Valladolid, Spain (H.J.A.); Department of Anesthesiology, Novosibirsk State University, Novosibirsk, Russia (S.V.A.); Department of Orthopedic and Trauma Surgery, Deventer Ziekenhuis, Deventer, the Netherlands (Y.V.K.); Department of Medicine, McMaster University, Hamilton, Ontario, Canada (A.P., V.T., D.L.); MD Anderson Cancer Center, Houston, Texas (J.P.C.); Department of Surgery, Shifa International Hospital and Shifa Tameer-e-Millat University, Islamabad, Pakistan (M.A.); Department of Anesthesiology and Intensive Care Medicine, Northern State Medical University, Arkhangelsk, Russia (M.K.); Department of Critical Care Medicine, Melbourne Medical School, University of Melbourne, Melbourne, Victoria, Australia (K.L.); Population Health Research Institute, Hamilton, Ontario, Canada; and Department of Medicine, Centre Hospitalier de l'Universite de Montreal, Montreal, Quebec, Canada (E.D.); Population Health Research Institute, Hamilton, Ontario; Department of Health Research Methods, McMaster University, Hamilton, Ontario; and Department of Medicine, McMaster University, Hamilton, Ontario, Canada (F.K.B., D.C.); Department of Anesthesiology and Intensive Care, Hospital Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain (M.d.N.); Department of Anesthesiology and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan; and Vita-Salute San Raffaele University, Milan, Italy (G.L.); V. Negovsky Reanimatology Research Institute FRCC RR, Moscow, Russia (V.V.L.); Department of Anesthesiology and Intensive Care, E. Meshalkin National Medical Research Centre, Novosibirsk, Russia; and Department of Anesthesiology and Perioperative Medicine, Penn State College of Medicine, Penn State Milton S. Hershey Medical Center, Hershey, Pennsylvania (V.L.); Center for Outcomes Research and Department of Anesthesiology, UTHealth, Houston, Texas (D.I.S.); Iberoamerican Cochrane Centre, Public Health and Clinical Epidemiology Service, Institut de Recerca Sant Pau, CIBERESP, Barcelona, Spain (M.J.M.-Z.); St. John's Medical College, Bangalore, India (D.X.); Department of Anaesthesia, Intensive Care Medicine and Pain Medicine, Medical University of Vienna, Vienna, Austria (E.F.); Department of Anesthesiology, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia (C.Y.W.); Department of Anaesthesia and Intensive Care, Copenhagen University Hospital–Bispebjerg and Frederiksberg, Copenhagen, Denmark (C.S.M.); Department of Anesthesiology and Intensive Care Medicine, University Hospital Bonn, Bonn, Germany (M.W.); Departamento de Epidemiología y Estudios en Salud, Universidad de Los Andes, Santiago, Chile (D.T.); Princess Alexandra Hospital, Woolloongabba, Queensland, Australia (D.H.); Anesthesiology and Critical Care, University of Alberta, Edmonton, Alberta, Canada (M.J.); Nanjappa Hospital, Karnataka, India (V.B.); University of Calgary, Calgary, Alberta, Canada (K.Z.); Sidhu Hospital Doraha Ludhiana, Ludhiana, India (R.S.S.); IRCCS Galeazzi Sant'Ambrogio (OGSA), Site Istituto San Siro, Milan, Italy (G.O.); Outcome Research Consortium, Department of Anesthesiology, Cleveland Clinic, Cleveland, Ohio (S.A.); Cleveland Clinic Florida, Weston, Florida (S.M.); The Ohio State University Wexner Medical Center, Columbus, Ohio (T.E.W.); Department of Anesthesiology and Intensive Care Medicine, Ordensklinikum Linz, Linz, Austria (K.R.); Anaesthesia and Intensive Care Medicine, Galliera Hospital, Genova, Italy (C.B.); Department of Anesthesiology and Perioperative Medicine, Queen's University and Kingston Health Sciences Centre, Kingston, Ontario, Canada (J.L.P., T.G.S.); Department of Anaesthesia, Auckland City Hospital, Auckland, New Zealand (E.M.); Wake Forest School of Medicine, Winston Salem, North Carolina (S.M.); Department of Medicine, Western University, London, Ontario, Canada (M.M.); Surat Institution, Surat, India (K.S.C.B.); Rahate Surgical Hospital, Nagpur, India (P.R.); Department of Anesthesiology and Intensive Care Medicine, University Hospital Bonn, Bonn, Germany; and University Hospital

RWTH Aachen, Aachen, Germany (A.K.); IRCCS Galeazzi Orthopedic Institute, Milan, Italy (G.D.B.); Population Health Research Institute, Hamilton, Ontario; and Department of Medicine, McMaster University, Hamilton, Ontario, Canada (S.N.O., M.K.W., M.S.); Section of Thoracic Surgery, Department of Surgery, University of Manitoba, Winnipeg, Manitoba, Canada (S.S.); Centre for Intensive Care and Perioperative Medicine, Jagiellonian University Medical College, Krakow, Poland (W.S.); Department of Anaesthetics, Clinical Neurosciences, University of Oxford, Oxford University Hospitals NHS Trust, Oxford, United Kingdom (R.J.); Department of Anesthesiology, Klinikum Dortmund, University Witten-Herdecke, Dortmund, Germany (R.K.E.); Cliniques Universitaires Saint-Luc, Brussels, Belgium (M.M.); Population Health Research Institute, Hamilton, Ontario, Canada (I.C., J.V., K.B., Z.L.); Population Health Research Institute, Hamilton, Ontario; and School of Nursing, McMaster University, Hamilton, Ontario, Canada (M.H.M.); Outcome Research Consortium, Department of Anesthesiology, Cleveland Clinic, Cleveland, Ohio; and Department of General Anesthesiology, Emergency and Intensive Care Medicine, Medical University of Graz, Graz, Austria (A.K.); and Population Health Research Institute, Hamilton, Ontario: and Department of Health Research Methods, McMaster University, Hamilton, Ontario, Canada (P.J.D.).

Note: All authors had full access to data, provided approval for the final submitted version to be published, and agreed to be accountable for all aspects of the work and take responsibility for the decision to submit for publication.

Acknowledgment: The authors acknowledge the role of the ANZCA Clinical Trials Network for conducting the study across Australia and New Zealand.

Financial Support: The cogPOISE-3 substudy was possible thanks to the following research grants that supported the main POISE-3: Canadian Institutes of Health Research Foundation Grant FDN-143302 (Dr. Devereaux), Canada; National Health and Medical Research Council (NHMRC), Funding Schemes, NHMRC Project Grant 1162362 (Dr. Leslie), Australia; and General Research Fund 14104419 (Dr. Chan), Research Grant Council, Hong Kong SAR, China. POISE-3 also received financial support from the Population Health Research Institute and the Hamilton Health Science Research Institute, Hamilton, Ontario, Canada, and an investigator-initiated study grant from Roche Diagnostics International (Dr. Devereaux). Dr. Marcucci also received a separate research grant from the Canadian Institutes of Health Research to support the cogPOISE-3 substudy (Project Grant PJT-165830).

Disclosures: Disclosure forms are available with the article online.

Data Sharing Statement: The Population Health Research Institute (PHRI) is the sponsor of this trial. The PHRI believes the dissemination of clinical research results is vital and sharing of data is important. PHRI prioritizes access to data analyses to researchers who have worked on the trial for a substantial duration, have played substantial roles, and have participated in raising the funds to conduct the trial. PHRI balances the length of the research study, and the intellectual and financial investments that made it possible with the need to allow wider access to the data collected. Data will be disclosed only upon request and approval of the proposed use of the data by a Review Committee. Data will be available to the journal for evaluation of reported analyses. Data requests from other non-POISE-3 investigators will not be considered until 5 years after the closeout of the trial.

Corresponding Author: Maura Marcucci, Clinical Epidemiology and Research Centre, Humanitas University & IRCCS Humanitas Research Hospital, Via Rita Levi Montalcini, 4–20072 Pieve Emanuele, Milan, Italy; Population Health Research Institute, Hamilton, ON, Canada; and Department of Health Research Methods, McMaster University, Hamilton, ON, Canada; e-mail, maura.marcucci@hunimed.eu.

Author contributions are available at Annals.org.

References

1. **Matthey P, Finucane BT, Finegan BA.** The attitude of the general public towards preoperative assessment and risks associated with general anesthesia. Can J Anaesth. 2001;48:333-339. [PMID: 11339773] doi:10.1007/BF03014959
2. **Rowley P, Boncyk C, Gaskell A, et al.** What do people expect of general anaesthesia? Br J Anaesth. 2017;118:486-488. [PMID: 28403409] doi:10.1093/bja/aex040
3. **Silva AR, Regueira P, Albuquerque E, et al.** Estimates of geriatric delirium frequency in noncardiac surgeries and its evaluation across the years: a systematic review and meta-analysis. J Am Med Dir Assoc. 2021;22:613-620.e9. [PMID: 33011097] doi:10.1016/j.jamda.2020.08.017
4. **Witlox J, Eurelings LS, de Jonghe JF, et al.** Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. JAMA. 2010;304:443-451. [PMID: 20664045] doi:10.1001/jama.2010.1013
5. **Gleason LJ, Schmitt EM, Kosar CM, et al.** Effect of delirium and other major complications on outcomes after elective surgery in older adults. JAMA Surg. 2015;150:1134-1140. [PMID: 26352694] doi:10.1001/jamasurg.2015.2606
6. **Goldberg TE, Chen C, Wang Y, et al.** Association of delirium with long-term cognitive decline: a meta-analysis. JAMA Neurol. 2020;77:1373-1381. [PMID: 32658246] doi:10.1001/jamaneurol.2020.2273
7. **Lee SJ, Jung SH, Lee SU, et al.** Postoperative delirium after hip surgery is a potential risk factor for incident dementia: a systematic review and meta-analysis of prospective studies. Arch Gerontol Geriatr. 2020;87:103977. [PMID: 31751902] doi:10.1016/j.archger.2019.103977
8. **Huang H, Li H, Zhang X, et al.** Association of postoperative delirium with cognitive outcomes: a meta-analysis. J Clin Anesth. 2021;75:110496. [PMID: 34482263] doi:10.1016/j.jclinane.2021.110496
9. **Fong TG, Davis D, Growdon ME, et al.** The interface between delirium and dementia in elderly adults. Lancet Neurol. 2015;14:823-832. [PMID: 26139023] doi:10.1016/S1474-4422(15)00101-5
10. **NeuroVISION Investigators.** Perioperative covert stroke in patients undergoing non-cardiac surgery (NeuroVISION): a prospective cohort study. Lancet. 2019;394:1022-1029. [PMID: 31422895] doi:10.1016/S0140-6736(19)31795-7
11. **Suwanabol PA, Li Y, Abrahamse P, et al.** Functional and cognitive decline among older adults after high-risk surgery. Ann Surg. 2022;275:e132-e139. [PMID: 32404660] doi:10.1097/SLA.0000000000003950
12. **Roshanov PS, Rochwerg B, Patel A, et al.** Withholding versus continuing angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers before noncardiac surgery: an analysis of the Vascular events In noncardiac Surgery patIents cOhort evaluatioN prospective cohort. Anesthesiology. 2017;126:16-27. [PMID: 27775997] doi:10.1097/ALN.0000000000001404

13. **Devereaux PJ, Sessler DI, Leslie K, et al; POISE-2 Investigators.** Clonidine in patients undergoing noncardiac surgery. N Engl J Med. 2014;370:1504-1513. [PMID: 24679061] doi:10.1056/NEJMoa1401106
14. **Turan A, Chang C, Cohen B, et al.** Incidence, severity, and detection of blood pressure perturbations after abdominal surgery: a prospective blinded observational study. Anesthesiology. 2019;130:550-559. [PMID: 30875354] doi:10.1097/ALN.0000000000002626
15. **Xing C-Y, Tarumi T, Meijers RL, et al.** Arterial pressure, heart rate, and cerebral hemodynamics across the adult life span. Hypertension. 2017;69:712-720. [PMID: 28193707] doi:10.1161/HYPERTENSIONAHA.116.08986
16. **Strandgaard S.** Autoregulation of cerebral blood flow in hypertensive patients. The modifying influence of prolonged antihypertensive treatment on the tolerance to acute, drug-induced hypotension. Circulation. 1976;53:720-727. [PMID: 815061] doi:10.1161/01.cir.53.4.720
17. **Immink RV, van den Born BJ, van Montfrans GA, et al.** Impaired cerebral autoregulation in patients with malignant hypertension. Circulation. 2004;110:2241-2245. [PMID: 15466625] doi:10.1161/01.CIR.0000144472.08647.40
18. **Rudolph JL, Jones RN, Rasmussen LS, et al.** Independent vascular and cognitive risk factors for postoperative delirium. Am J Med. 2007;120:807-813. [PMID: 17765051] doi:10.1016/j.amjmed.2007.02.026
19. **Wesselink EM, Kappen TH, Torn HM, et al.** Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. Br J Anaesth. 2018;121:706-721. [PMID: 30236233] doi:10.1016/j.bja.2018.04.036
20. **Yang L, Sun DF, Han J, et al.** Effects of intraoperative hemodynamics on incidence of postoperative delirium in elderly patients: a retrospective study. Med Sci Monit. 2016;22:1093-1100. [PMID: 27038856] doi:10.12659/msm.895520
21. **Scholz AF, Oldroyd C, McCarthy K, et al.** Systematic review and meta-analysis of risk factors for postoperative delirium among older patients undergoing gastrointestinal surgery. Br J Surg. 2016;103:e21-e28. [PMID: 26676760] doi:10.1002/bjs.10062
22. **Maheshwari K, Ahuja S, Khanna AK, et al.** Association between perioperative hypotension and delirium in postoperative critically ill patients: a retrospective cohort analysis. Anesth Analg. 2020;130:636-643. [PMID: 31725024] doi:10.1213/ANE.0000000000004517
23. **Gregory A, Stapelfeldt WH, Khanna AK, et al.** Intraoperative hypotension is associated with adverse clinical outcomes after noncardiac surgery. Anesth Analg. 2021;132:1654-1665. [PMID: 33177322] doi:10.1213/ANE.0000000000005250
24. **Wachtendorf LJ, Azimaraghi O, Santer P, et al.** Association between intraoperative arterial hypotension and postoperative delirium after noncardiac surgery: a retrospective multicenter cohort study. Anesth Analg. 2022;134:822-833. [PMID: 34517389] doi:10.1213/ANE.0000000000005739
25. **Feng X, Hu J, Hua F, et al.** The correlation of intraoperative hypotension and postoperative cognitive impairment: a meta-analysis of randomized controlled trials. BMC Anesthesiol. 2020;20:193. [PMID: 32758153] doi:10.1186/s12871-020-01097-5
26. **van Zuylen ML, Gribnau A, Admiraal M, et al.** The role of intraoperative hypotension on the development of postoperative cognitive dysfunction: a systematic review. J Clin Anesth. 2021;72:110310. [PMID: 33932723] doi:10.1016/j.jclinane.2021.110310
27. **Cai J, Tang M, Wu H, et al.** Association of intraoperative hypotension and severe postoperative complications during non-cardiac surgery in adult patients: a systematic review and meta-analysis. Heliyon. 2023;9:e15997. [PMID: 37223701] doi:10.1016/j.heliyon.2023.e15997
28. **D'Amico F, Fominskiy EV, Turi S, et al.** Intraoperative hypotension and postoperative outcomes: a meta-analysis of randomised trials. Br J Anaesth. 2023;131:823-831. [PMID: 37739903] doi:10.1016/j.bja.2023.08.026
29. **Xu X, Hu X, Wu Y, et al.** Effects of different BP management strategies on postoperative delirium in elderly patients undergoing hip replacement: a single center randomized controlled trial. J Clin Anesth. 2020;62:109730. [PMID: 31982847] doi:10.1016/j.jclinane.2020.109730
30. **Zhang Y, Zhang Y, Zhou Z, et al.** Higher intraoperative mean arterial blood pressure does not reduce postoperative delirium in elderly patients following gastrointestinal surgery: a prospective randomized controlled trial. PLoS One. 2022;17:e0278827. [PMID: 36548296] doi:10.1371/journal.pone.0278827
31. **Nicklas JY, Bergholz A, Däke F, et al.** Personalised blood pressure management during major noncardiac surgery and postoperative neurocognitive disorders: a randomised trial. BJA Open. 2024;11:100294. [PMID: 39050403] doi:10.1016/j.bjao.2024.100294
32. **Kassie GM, Nguyen TA, Kalisch Ellett LM, et al.** Preoperative medication use and postoperative delirium: a systematic review. BMC Geriatr. 2017;17:298. [PMID: 29284416] doi:10.1186/s12877-017-0695-x
33. **Marcucci M, Painter TW, Conen D, et al; POISE-3 Trial Investigators and Study Groups.** Hypotension-avoidance versus hypertension-avoidance strategies in noncardiac surgery: an international randomized controlled trial. Ann Intern Med. 2023;176:605-614. [PMID: 37094336] doi:10.7326/M22-3157
34. **Devereaux PJ, Marcucci M, Painter TW, et al; POISE-3 Investigators.** Tranexamic acid in patients undergoing noncardiac surgery. N Engl J Med. 2022;386:1986-1997. [PMID: 35363452] doi:10.1056/NEJMoa2201171
35. **Marcantonio ER, Ngo LH, O'Connor M, et al.** 3D-CAM: derivation and validation of a 3-minute diagnostic interview for CAM-defined delirium: a cross-sectional diagnostic test study. Ann Intern Med. 2014;161:554-561. [PMID: 25329203] doi:10.7326/M14-0865
36. **Ely EW, Inouye SK, Bernard GR, et al.** Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA. 2001;286:2703-2710. [PMID: 11730446] doi:10.1001/jama.286.21.2703
37. **Nasreddine ZS, Phillips NA, Bédirian V, et al.** The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53:695-699. [PMID: 15817019] doi:10.1111/j.1532-5415.2005.53221.x
38. **Wechsler D.** Adult Intelligence Scale-Revised. Psychological Corporation; 1981.
39. **Vasunilashorn SM, Guess J, Ngo L, et al.** Derivation and validation of a severity scoring method for the 3-minute diagnostic interview for confusion assessment method-defined delirium. J Am Geriatr Soc. 2016;64:1684-1689. [PMID: 27374833] doi:10.1111/jgs.14234
40. **Inouye SK, Kosar CM, Tommet D, et al.** The CAM-S: development and validation of a new scoring system for delirium severity in 2 cohorts. Ann Intern Med. 2014;160:526-533. [PMID: 24733193] doi:10.7326/M13-1927
41. **Vickers AJ, Altman DG.** Statistics notes: analysing controlled trials with baseline and follow up measurements. BMJ. 2001;323:1123-1124. [PMID: 11701584] doi:10.1136/bmj.323.7321.1123
42. **Langer T, Santini A, Zadek F, et al.** Intraoperative hypotension is not associated with postoperative cognitive dysfunction in elderly patients undergoing general anesthesia for surgery: results of a randomized controlled pilot trial. J Clin Anesth. 2019;52:111-118. [PMID: 30243062] doi:10.1016/j.jclinane.2018.09.021
43. **Williams-Russo P, Sharrock NE, Mattis S, et al.** Randomized trial of hypotensive epidural anesthesia in older adults. Anesthesiology. 1999;91:926-935. [PMID: 10519494] doi:10.1097/00000542-199910000-00011
44. **Hu A-M, Qiu Y, Zhang P, et al.** Higher versus lower mean arterial pressure target management in older patients having non-cardiothoracic surgery: a prospective randomized controlled trial. J Clin Anesth. 2021;69:110150. [PMID: 33418429] doi:10.1016/j.jclinane.2020.110150
45. **Krishnan K, Rossetti H, Hynan LS, et al.** Changes in Montreal Cognitive Assessment scores over time. Assessment. 2017;24:772-777. [PMID: 27318033] doi:10.1177/1073191116654217

46. **Tan HH, Xu J, Teoh HL, et al.** Decline in changing Montreal Cognitive Assessment (MoCA) scores is associated with post-stroke cognitive decline determined by a formal neuropsychological evaluation. PLoS One. 2017;12:e0173291. [PMID: 28346532] doi:10.1371/journal.pone.0173291

47. **Rossetti HC, Lacritz LH, Cullum CM, et al.** Normative data for the Montreal Cognitive Assessment (MoCA) in a population-based sample. Neurology. 2011;77:1272-1275. [PMID: 21917776] doi:10.1212/WNL.0b013e318230208a

48. **Santangelo G, Siciliano M, Pedone R, et al.** Normative data for the Montreal Cognitive Assessment in an Italian population sample. Neurol Sci. 2015;36:585-591. [PMID: 25380622] doi:10.1007/s10072-014-1995-y

49. **Sharma M, Hart RG, Smith EE, et al.** Rivaroxaban for prevention of covert brain infarcts and cognitive decline: the COMPASS MRI substudy. Stroke. 2020;51:2901-2909. [PMID: 32951537] doi:10.1161/STROKEAHA.120.029762

50. **Evered L, Silbert B, Knopman DS, et al; Nomenclature Consensus Working Group.** Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-20181. J Alzheimers Dis. 2018;66:1-10. [PMID: 30347621] doi:10.3233/JAD-189004

Author Contributions: Conception and design: M. Marcucci, M. T.V. Chan, T.W. Painter, A. Patel, K. Leslie, E. Duceppe, F.K. Borges, G. Landoni, D.I. Sessler, S. Ayad, M. Mrkobrada, D. Conen, W. Szczeklik, J. Vincent, A. Kurz, M. Sharma.

Analysis and interpretation of the data: M. Marcucci, M.T.V. Chan, Y.V. Kleinlugtenbelt, M. Kirov, K. Leslie, F.K. Borges, D.I. Sessler, C.Y. Wang, C.S. Meyhoff, D. Torres, S. Ayad, K. Ruetzler, M. Mrkobrada, K.S.C. Bhatt, A. Kowark, S.N. Ofori, D. Conen, R. Jayaram, R.K. Ellerkmann, K. Balasubramanian, Z. Li, T.G. Short.

Drafting of the article: M. Marcucci, J.P. Cata, M. Amir, M. Kirov, D.I. Sessler, D. Highton, G. Oriani, S. Ayad, T.E. Weaver, K. Ruetzler, C. Brusasco, W. Szczeklik, R. Jayaram, M.K. Wang, M. Sharma.

Critical revision of the article for important intellectual content: M. Marcucci, M.T.V. Chan, S. Efremov, H.J. Aguado, Y.V. Kleinlugtenbelt, A. Patel, M. Amir, K. Leslie, E. Duceppe, F.K. Borges, G. Landoni, D.I. Sessler, M.J. Martinez-Zapata, D. Xavier, E. Fleischmann, C.Y. Wang, C.S. Meyhoff, K. Zarnke, S. Ayad, T.E. Weaver, K. Ruetzler, C. Brusasco, E. Maxwell, A. Kowark, S.N. Ofori, D. Conen, W. Szczeklik, R. Jayaram, R.K. Ellerkmann, M.K. Wang, A. Kurz, P.J. Devereaux.

Final approval of the article: M. Marcucci, M.T.V. Chan, T.W. Painter, S. Efremov, H.J. Aguado, S.V. Astrakov, Y.V. Kleinlugtenbelt, A. Patel, J.P. Cata, M. Amir, M. Kirov, K. Leslie, E. Duceppe, F.K. Borges, M. de Nadal, V. Tandon, G. Landoni, V.V. Likhvantsev, V. Lomivorotov, D.I. Sessler, M.J. Martinez-Zapata, D. Xavier, E. Fleischmann, C.Y. Wang, C.S. Meyhoff, M. Wittmann, D. Torres, D. Highton, M. Jacka, V.B., K. Zarnke, R.S. Sidhu, G. Oriani, S. Ayad, S. Minear, T.E. Weaver, K. Ruetzler, C. Brusasco, J.L. Parlow, E. Maxwell, S. Miller, M. Mrkobrada, K.S.C. Bhatt, P. Rahate, A. Kowark, G. De Blasio, S.N. Ofori, D. Conen, S. Srinathan, W. Szczeklik, R. Jayaram, R.K. Ellerkmann, M. Momeni, I. Copland, J. Vincent, K. Balasubramanian, Z. Li, M.K. Wang, D. Li, M.H. McGillion, A. Kurz, M. Sharma, T.G. Short, P.J. Devereaux.

Provision of study materials or patients: M. Marcucci, M.T.V. Chan, H.J. Aguado, S.V. Astrakov, Y.V. Kleinlugtenbelt, A. Patel, J.P. Cata, M. Amir, M. Kirov, E. Duceppe, G. Landoni, D. Xavier, C.Y. Wang, C.S. Meyhoff, M. Jacka, V.B., K. Zarnke, G. Oriani, S. Ayad, S. Minear, K. Ruetzler, J.L. Parlow, S. Miller, A. Kowark, S. Srinathan, R.K. Ellerkmann, A. Kurz, T.G. Short.

Statistical expertise: M. Mrkobrada, K. Balasubramanian.

Obtaining of funding: M. Marcucci, M.T.V. Chan, K. Leslie, E. Duceppe, G. Landoni, M. Mrkobrada, T.G. Short.

Administrative, technical, or logistic support: A. Patel, F.K. Borges, V.B., S. Minear, T.E. Weaver, I. Copland, J. Vincent, D. Li, A. Kurz.

Collection and assembly of data: M.T.V. Chan, T.W. Painter, S. Efremov, H.J. Aguado, S.V. Astrakov, Y.V. Kleinlugtenbelt, A. Patel, M. Amir, M. Kirov, K. Leslie, E. Duceppe, M. de Nadal, V. Tandon, G. Landoni, V.V. Likhvantsev, V. Lomivorotov, D.I. Sessler, M.J. Martinez-Zapata, E. Fleischmann, C.S. Meyhoff, M. Wittmann, D. Torres, D. Highton, M. Jacka, V.B., K. Zarnke, R. S. Sidhu, G. Oriani, S. Ayad, S. Minear, T.E. Weaver, K. Ruetzler, C. Brusasco, J.L. Parlow, E. Maxwell, M. Mrkobrada, P. Rahate, G. De Blasio, S.N. Ofori, D. Conen, W. Szczeklik, R.K. Ellerkmann, I. Copland, K. Balasubramanian, A. Kurz, T.G. Short.

Appendix: Members of the cogPOISE-3 Trial Investigators and Study Groups

STUDY GROUPS

Operations Committee

P.J. Devereaux (Chair), Shrikant I. Bangdiwala, Flavia K. Borges, David Conen, Ingrid Copland, Gordon Guyatt, Maura Marcucci, Daniel I. Sessler, Jessica Vincent.

International Operations Committee

P.J. Devereaux (Chair), Shrikant I. Bangdiwala, Bruce Biccard, Flavia K. Borges, Matthew T.V. Chan, David Conen, Ingrid Copland, John Eikelboom, Gordon Guyatt, Kate Leslie, Vladimir Lomivorotov, Christian S. Meyhoff, Maura Marcucci, Thomas Painter, Joel Parlow, Toby Richards, Daniel I. Sessler, Wojciech Szczeklik, Vikas Tandon, Jessica Vincent, Denis Xavier.

Steering Committee

P.J. Devereaux (Chair), Pascal Alfonsi, Mohammed Amir, Shrikant I. Bangdiwala, Bruce M. Biccard, Flavia K. Borges, Matthew T.V. Chan, David Conen, Ingrid Copland, Emmanuelle Duceppe, John Eikelboom, Edith Fleischmann, Peter Gross, Gordon Guyatt, Raja Jayaram, Ydo V. Kleinlugtenbelt, Andrea Kurz, Giovanni Landoni, Kate Leslie, Vladimir Lomivorotov, Maria José Martinez Zapata, Yannick Lemanach, Michael McGillion, Christian S. Meyhoff, Maura Marcucci, Thomas Painter, Joel Parlow, Carisi Polanczyk, Toby Richards, Pavel Roshanov, Denis Schmartz, Daniel I. Sessler, Tim Short, Sadeesh Srinathan, Wojciech Szczeklik, Vikas Tandon, David Torres, Jessica Vincent, Chew Yin Wang, Dale Williams, Maria Wittmann, Denis Xavier, Salim Yusuf.

Data and Safety Monitoring Board (DSMB)

Ian Roberts (Chair), Dean Fergusson, Pierre Foëx, Finlay McAlister.

Project Office Staff

Ingrid Copland, Sara Di Diodato, Rosemary Howe, Hannah MacDonald, Louise Mastrangelo, Clare McGall, Natalie Mercuri, Sarah Molnar, David Stillo, Trisha Southall, Jennifer Swanson, Makayla Tosh, Jessica Vincent.

Study Statisticians and Programmers

Kumar Balasubramanian, Shrikant I. Bangdiwala, Eric Deng, Li Zhuoru, Tamara Marsden, Mark Molec, Olga Shestakovska, Robin Zhao.

National Leaders

Mohammed Amir (Pakistan), Matthew T.V. Chan (Hong Kong SAR, China), P.J. Devereaux (Canada), Edith Fleischmann (Austria), Raja Jayaram (United Kingdom), Ydo Kleinlugtenbelt (Netherlands), Giovanni Landoni (Italy), Vladimir Lomivorotov (Russia), Maria José Martinez Zapata (Spain), Christian S. Meyhoff (Denmark), Thomas Painter (Australia and New Zealand), Denis Schmartz (Belgium), Daniel I. Sessler (United States), Wojciech Szczeklik (Poland), David Torres (Chile), Chew Yin Wang (Malaysia), Maria Wittmann (Germany), Denis Xavier (India).

Participating Centres

COUNTRY/*Centre* (NUMBER OF PATIENTS RECRUITED Delirium/cognitive)

AUSTRALIA (103/32) – *National Coordination Office (Royal Adelaide Hospital):* Gillian Ormond; *Royal Adelaide Hospital (45/6*): Thomas Painter, Louise de Prinse, Sam Lumb, Simon Macklin, Christine S. Charlton, Johanna Somfleth, Carolyn M. Wood; *Princess Alexandra Hospital Southside Clinical Unit, University of Queensland (54/25*): David Highton, Palvannan Sivalingam, Allison Kearney, Sabrina Oishi, Victoria Forrester, Edward Pilling, Sibi Mathew-Kurian, Joanne Cummins, Juanita Muller; *Flinders Medical Centre (3/1*): Jason P. Koerber, Vanessa J. Scotland; *Royal Melbourne Hospital (1/0*): Kate Leslie, Vi Ha.

AUSTRIA (34/32) – *Medical University of Vienna (34/32*): Barbara Kabon, Christian Reiterer, Alexander Taschner, Nikolas Adamowitsch, Oliver Zotti.

BELGIUM (2/1) – *Cliniques Universitaires Saint Luc; Université Catholique de Louvain (2/1*): Mona Momeni, Audrey Dieu.

CANADA (433/160) – *Juravinski Hospital (100/24*): Kelly Lawrence, Krysten Gregus, Ahraaz Wyne, Amna Ahmed, Shariq Haider, Shervin Zandi, Amitabha Chakroborty, Dale Williams, Samir Raza, Philip Joseph; *Hamilton General Hospital (85/37*): Tomas VanHelder, Susan O'Leary, John Harlock, Mohamed Panju, Kajenny Srivaratharajan, Betty Chui, Ryan Proc, Lisa Trombetta, Ted Rapanos, Shirley Pettit; *St. Joseph's Healthcare (73/29*): Vikas Tandon, Harsha Shanthanna, John Neary, Katie Connolly, Muammar Abdulrahman, Spencer Wikkerink, Faraaz Quraishi, Rahima Nenshi; *Kingston Health Sciences Centre (57/0*): Joel L. Parlow, Deborah A. Dumerton, Jason Erb, Jessica Shelley, Elorm Vowotor, Reegan Todd, Emile Peponoulas; *Centre Hospitalier de l'Université de Montréal (5/1*): Nikola Joly, Francois-Martin Carrier; *University of Alberta Hospital (55/20*): Michael Jacka, Michelle Graham, James Greene, Derek Dillane, David Bigam, Ella McMurtry, Michael Zaugg, Jason Foerster, David Williams; *University of Calgary (37/37*): Kelly B. Zarnke, Linet Kiplagat, Shannon M. Ruzycki, Evan Minty, Prism S. Schneider, Melinda Davis, Rahim Kachra, Michael Bosch; *University of Manitoba (5/5*): Biniam Kidane, Duane Funk, Lawrence Tan; *University of Western Ontario (16/7*): Marko Mrkobrada, George K. Dresser, Jaclyn A. Ernst, Luc Dubois, Stephanie N. Handsor.

CHILE (15/0) – *Clínica Santa Maria (15/0*): David Torres, Maite Fuentes, Javiera Vasquez, Valentina Paz.

CHINA (228/226) – *The Chinese University of Hong Kong (228/226*): Matthew T.V. Chan, William KK Wu, Gavin M. Joynt, Lin Zhang, Gordon YS. Choi, Wai Tat Wong, Linda ML. Lai, Chi-Fai Ng, Philip WY. Chiu, James YW. Lau, Malcolm Underwood, Beaker Fung, Eva Lee, Ka Yan Hui, Chee Sam Chan, Winnie Wing Sam Chan.

DENMARK (45/1) – *Copenhagen University Hospital - Bispebjerg and Frederiksberg (45/1*): Christian S. Meyhoff, Marlene Søgaard, Ossian Gundel, Diana B. Jensen, Anne Sofie Jensen.

GERMANY (24/21) – *Department of Anesthesiology, Klinikum Dortmund, University Witten-Herdecke (2/2*): Nicholas Kiefer, Holger Pohl, Mihiri U. Amarasekara; *University Hospital Bonn (11/8*): Mark Coburn, Claudia Neumann, Markus Velten, Gregor Massoth, Alma Puskarevic*; Medical Faculty University Hospital RWTH Aachen (11/11*): Rolf Rossaint, Sebastian Ziemann, Linda Grüßer, Julia Wallqvist, Pascal Kowark, Christian Bach.

INDIA (127/88) – *National Coordination Office (St. John's Medical College and Research Institute, Bangalore)*: Mangala Rao, Freeda Xavier, Susan Maria Subbin; *SIDS Hospital & Research Centre (21/3):* Dhaval Mangukiya, Jignesh Patel, Daxa Kachhadiya, Sanjay Thumar, Viral Parekh; *Nanjappa Hospital (40/37*): Vishwanath B., Sachin.D.N.B, Veena Gopal, Shivaraj. D. M., Ajay S., Veena T.S.; *Sidhu Hospital, Doraha (33/33*): Ravinder Singh Sidhu, Gursaran Kaur Sidhu, Naveen Laiker, Abhitej Singh Sidhu; *ACE Hospital and Research Center (1/1*): Suresh B. Patankar, Suparn K. Khaladkar, Gururaj A. Padsalgi; *Rahate Surgical Hospital (12/12*): Prashant Vitthalrao Rahate*; Sengupta Hospital & Research Institute (2/0*): Shantanu P. Sengupta, Kunda Mungulmare; *Government Medical College, Trivandrum (10/1*): Prem Haridas Menon, Rajeev Damodaran Nair Sarojini Amma; *Government TD Medical College (6/1*): Alen Sigamani, Manesh Stephen; *Rabindranath Tagore International Institute of Cardiac Sciences (2/0*): Rahul Guhabiswas.

ITALY (199/25) – *IRCCS San Raffaele Scientific Institute (45/25*): Stefano Turi, Cristina Nakhnoukh, Francesco G. Nisi, Gabriele Valsecchi, Rosalba Lembo, Francesco De Donato, Gaetano Lombardi, Barbara Ferrara; *Instituto Clinico San Siro (78/0*): Giorgio Oriani, Tancredi Guerrerio, Cesare Donarini, Marisa Iacurti, Georges Ghanem; *Galliera Hospital (60/0*): Claudia Brusasco, Giulia Orefice, Francesco Corradi, Michela Gandini, Michela Rosa, Silvia Di Maio; *IRCCS Galeazzi Orthopedic Institute (16/0*): Luigi Zagra, Paolo Perazzo, Chiara Colombo, Federica Marra.

MALAYSIA (38/16) – *Universiti Malaya (38/16*): Chew Yin Wang, Chao Chia Cheong, Tyng Yan Ng, Ri Qi Yeow, Yang Qun Choy, Xue Lin Chan, Choo Kian Gan, Nor Ashikin Md Sari.

NETHERLANDS (94/31) – *Deventer Hospital (94/31*): Ydo V. Kleinlugtenbelt, Ellie B.M. Landman, Jan-Hein M. G. Cobben, Bas Staffhorst, Roel Mes, Hannie Elskamp-Meijerman, Monique Voskamp-Wierik te, Rochel Dijkgraaf, Kim M. Welberg, Judith J. Postmus.

NEW ZEALAND (18/18) – *Auckland City Hospital (18/18*): Vikrant Singh, Douglas Campbell, Davina McAllister, Sarah Dandy, Leanda Ritchie, Kevin Wang.

PAKISTAN (66/61) – *Shifa International Hospital (66/61*): Tehreem Zahid, Sumeyya Azam, Ahmed Sohail, Yumna Hassan, Sibgha Aimon, Muhammad Uneeb, Maaz Ahmed Yusufi, Zia Nazir, Sundus Ayub Awan, Faisal Aziz Sandeela, Wara Qazi.

POLAND (14/4) – *Szpital Zakonu Bonifratrów w Krakowie (10/0*): Maciej Chwala, Anna Władarczyk; *University Hospital Zielona Góra (4/4*): Bartosz Kudlin¨ski, Jarosław Zawisza, Magdalena Wirtek.

RUSSIA (828/151) – *Saint Petersburg State University Hospital (515/27*): Sergey Efremov, Alexey Y. Kulikov, Mikhail A. Alexeev, Konstantin S. Trukhin, Andrey A. Cherednichenko, Irina A. Andrianova, Svetlana S. Mikhailova, Andrey A. Sorokin, Elizaveta A. Leonova, Oleg V. Kuleshov, Alexander A. Safronov, Svetlana

L. Nepomnyaschaya, Anna S. Kotova, Maxim S. Stoliarov, Dmitry V. Shmatov, Dmitry D. Shkarupa, Elena A. Shirshova; *Novosibirsk State University (152/67*): Sergey Astrakov, Elena L. Neporada, Konstantin N. Kungurtsev, Vyacheslav V. Zhukov, Ilya G. Werner, Igor Yu. Chudnovets; *E. Meshalkin National Medical Research Center (32/8*): Andrey A. Karpenko, Samandar M. Ismoilov, Mikhail N. Deryagin, Liudmila V. Lomivorotova, Alexander M. Cherniavskiy, Gleb B. Moroz, Roman V. Osinsky; *Northern State Medical University/City Hospital #1 of Arkhangelsk (71/43*): Mikhail Kirov, Vsevolod V. Kuzkov, Ayyaz Hussain, Alexey A. Smetkin, Darja V. Carionova, Yana Y. Ilyina, Dmitrii A. Volkov, Evgenia V. Fot, Maria M. Sokolova, Maria V. Veshnyakova, Evgenia B. Lochekhina; *Moscow Regional Clinical and Research Institute, MONIKI (58/6)*: Valery V. Likhvantsev, Alexey M. Ovezov, Levan B. Berikashvili, Oleg N. Gerasimenko.

SPAIN (257/102) – *Hospital Clínico Universitario de Valladolid (162/100*): David C. Noriega; Gonzalo Martinez-Municio, Adela Pereda-Manso, Elvira Mateos-Álvarez, Silvia Santiago-Maniega, María Bragado-González, Juan Berrocal-Cuadrado, Rodrigo Poves-Álvarez, Ángel Fernández-Collantes, Gema Rodríguez-Cerón, Blanca De Prada-Martín, Rocío López Herrero, Mercedes Hernando Verdugo; *Hospital Universitari Vall d'Hebron (95/2*): Esther Cano, Maddalena Pasini, Patricia Galan, Alejandro Madrid, Elena Camio, Marcos de Miguel, Ivette Chocron, Susana González, Dina Butron, Gemma Vidal, Maria T. Ferrer.

UNITED KINGDOM (2/1) – *West Middlesex University Hospital (Chelsea and Westminister Foundation Trust) (2/1*): Surendini Thayaparan.

USA (307/115) – *Cleveland Clinic (Main Campus (51/8*), *Fairview Campus (74/0*),: Kurt Ruetzler, Sabry Ayad, Tatyana Kopyeva, Jacek B. Cywinski, Allen Keebler, Stacy Ritzman, Sandra B. Machado, Mariel R. Manlapaz, Alparslan Turan, Daniel I. Sessler, Elyad Ekrami, Mauro Bravo, Ruben Agudelo-Jimenez, Azfar Niazi, Andrew Volio, Daniel D. Kim, Jorge Araujo-Duran; *MD Anderson Cancer Center (77/77*): Gabriel E. Mena, January Tsai, Shital Vachhani, Teresa Moon-Calderon, Piotr Kwater, Timothy Jackson, Javier Lasala, Dilip Thakar, Crystal Wright, Ifeyinwa Ifeanyi, Elena Potylchanski; *Cleveland Clinic Florida (31/19)*: Camila Teixeira, Syed Nasim, Edward Noguera, Mario Pimentel, Snehal Raut, Sameep Baral, Jeff Jacobs, Steven Minear; *The Ohio State University Wexner Medical Center (52/9*): Sergio D. Bergese, Alberto A. Uribe, Michael Essandoh, Juan Fiorda-Diaz, Johnny McKeown, Olufunke Dada, Marco Echeverria-Villalobos, Caitlin Hatten, Jaume Borell-Vega; *Wake Forest School of Medicine (22/2*): Scott Alan Miller, Bruce Cusson, Lynne Harris.