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

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ABSTRACT

Background: The effect on cardiovascular outcomes of withholding angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers in chronic users before noncardiac surgery is unknown.

Methods: In this international prospective cohort study, the authors analyzed data from 14,687 patients (including 4,802 angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker users) at least 45 yr old who had in-patient noncardiac surgery from 2007 to 2011. Using multivariable regression models, the authors studied the relationship between withholding angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers and a primary composite outcome of all-cause death, stroke, or myocardial injury after noncardiac surgery at 30 days, with intraoperative and postoperative clinically important hypotension as secondary outcomes.

Results: Compared to patients who continued their angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, the 1,245 (26%) angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker users who withheld their angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers in the 24 h before surgery were less likely to suffer the primary composite outcome of all-cause death, stroke, or myocardial injury (150/1,245 [12.0%] *vs.* 459/3,557 [12.9%]; adjusted relative risk, 0.82; 95% CI, 0.70 to 0.96; $P = 0.01$) and intraoperative hypotension (adjusted relative risk, 0.80; 95% CI, 0.72 to 0.93; $P < 0.001$). The risk of postoperative hypotension was similar between the two groups (adjusted relative risk, 0.92; 95% CI, 0.77 to 1.10; $P = 0.36$). Results were consistent across the range of preoperative blood pressures. The practice of withholding angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers was only modestly correlated with patient characteristics and the type and timing of surgery.

Conclusions: Withholding angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers before major noncardiac surgery was associated with a lower risk of death and postoperative vascular events. A large randomized trial is needed to confirm this finding. In the interim, clinicians should consider recommending that patients withhold angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers 24 h before surgery. **(ANESTHESIOLOGY 2017; 126:16-27)**

MORE than 200 million people have major noncardiac surgery worldwide each year.[1] Of those, millions die or suffer a major vascular complication during the perioperative period.[2,3] Perioperative hypotension has been associated with myocardial infarction (MI), stroke, and death.[2,4–6]

By blunting the effect of the sympathetic system on vascular tone, anesthesia may increase reliance on the renin–angiotensin and vasopressor systems to maintain blood pressure. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), which are commonly used in patients with a history of, or risk factors for,

What We Already Know about This Topic

- Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are commonly withheld before surgery for concern over intraoperative hypotension, but whether this affects clinical outcomes is unclear

What This Article Tells Us That Is New

- In a secondary analysis of 4,802 patients on these drugs in the Vascular events In noncardiac Surgery patIents cOhort evaluatioN prospective cohort study, those in whom the drugs were withheld in the 24 h before surgery were less likely to suffer a composite outcome of 30-day all-cause death, stroke, or myocardial injury (18% adjusted relative risk reduction)

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cardiovascular disease, block the physiologic renin–angiotensin response to hypotension.[7]

Current guidelines from the American College of Cardiology and American Heart Association recommend continuing ACEI/ARBs in the setting of noncardiac surgery; these recommendations are based on data from small randomized trials and observational studies with significant risk of bias.[8] By contrast, many anesthesia groups routinely withhold ACEI/ARBs on the day of surgery to avoid intraoperative hypotension.[9,10] Without strong evidence, the practice of withholding ACEI/ARBs on the day of surgery appears to depend largely on provider preference and local policy.

The primary objective of this study was to test the hypothesis that withholding ACEI/ARBs (compared to continuing them on the day of surgery) is associated with a lower risk of the 30-day composite outcome of all-cause death, myocardial injury after noncardiac surgery (MINS), and stroke. Secondary objectives included determining the relationship between withholding ACEI/ARBs and perioperative clinically important hypotension and the association between perioperative clinically important hypotension and the 30-day risk of the composite outcome of all-cause death, MINS, and stroke.

Materials and Methods

Cohort

We conducted analyses in a sample from the Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) study—a prospective international cohort study—that included 16,079 patients from 12 centers in eight countries (throughout North and South America, Australia, Asia, and Europe) recruited from August 2007 to January 2011 (ClinicalTrials.gov identifier: NCT00512109). The research ethics board at each site approved the protocol before patient recruitment.

Previous reports have described the VISION cohort study.[11–13] Briefly, participants at least 45 yr old undergoing noncardiac surgery who required an overnight hospital admission with general or regional anesthetic were screened sequentially, and if eligible and consenting, they answered a series of questions regarding their past medical, surgical, and social history. Study personnel reviewed medical charts for additional history.

Outcomes

Our primary outcome was a composite of 30-day all-cause death, MINS,[12] and stroke. These components were selected to fulfill the requirements for a valid composite outcome (*i.e.*, including mortality avoided competing risks, each component could influence clinical practice as they all impact 30-day mortality, and one would anticipate that they would be affected by ACEI/ARBs similarly).[14] MINS was defined as any peak non–high sensitivity cardiac troponin T (cTnT) value greater than or equal to 0.03 ng/ml resulting from myocardial ischemia (*i.e.*, without evidence of a nonischemic etiology) that occurred within the first 30 days after surgery.[12] Stroke was defined as a new focal neurologic deficit thought to be vascular in origin with signs and symptoms lasting more than 24 h.

Throughout each patient's hospital stay, research personnel performed clinical evaluations and reviewed medical records. We measured cTnT using the Roche fourth-generation Elecsys assay (Germany) to assess for myocardial injury 6 to 12 h postoperatively and on the first 3 days after surgery. Research staff obtained other information on death and stroke from in-hospital follow-up, review of medical records, and a follow-up telephone interview conducted with the patients or their caregivers 30 days after surgery. If the patient interview indicated the occurrence of an outcome, their primary care physicians were contacted to obtain further documentation. Physicians experienced in perioperative medicine adjudicated death, MINS, and stroke.

Secondary outcomes of interest included clinically important intraoperative and postoperative hypotension, defined *a priori* as systolic blood pressure (sBP) less than 90 mmHg for any duration for which an intervention was initiated (including initiation or intensification of intravenous fluids, use of vasopressors or inotropes, blood transfusion, or intraaortic balloon pump therapy) that occurred during surgery (intraoperative hypotension) and during postoperative days 0 to 3 (postoperative hypotension).

Definitions for all variables are available in Supplemental Digital Content 1, http://links.lww.com/ALN/B326, under Variable Definitions.

Analyses

We performed the analyses using Stata (version 13.1 MP; Stata Corp, USA). All hypothesis tests were two sided; $P < 0.05$ denoted statistical significance.

Primary Objective

Relationship between Withholding *versus* Continuing Preoperative ACEI/ARBs and the Composite of Death, MINS, or Stroke. Among patients who used ACEI/ARBs during

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the 7 days before surgery (*i.e.*, baseline users), we compared outcomes of patients who did not take ACEI/ARBs within 24 h before surgery to the outcomes of those who did. We used multivariable modified Poisson regression[15] to estimate relative risks adjusted for a large set of potential confounders (listed in table 1 and table S1 in Supplemental Digital Content 1, http://links.lww.com/ALN/B326), including patient characteristics, preoperative use of antihypertensive medications and antiplatelet agents or anticoagulants that may contribute to perioperative bleeding (use *vs.* no use 1 to 7 days before surgery), continuation, withholding, or new initiation of these medications on the day of surgery, and the type and the timing of surgery (elective *vs.* urgent or emergency surgery). We also accounted for potential center effects using a cluster-robust variance estimator[16] with study centers as clusters. We used restricted cubic spline functions to model continuous variables (preoperative sBP, age, body mass index, and estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration equation).[17] We did not study the effects of withholding ACEI/ARBs or other antihypertensive medications after surgery because the timing of postoperative medication use was not captured with sufficient precision in VISION.

Secondary Objectives

Effect of Preoperative sBP on the Relationship between Withholding of Preoperative ACEI/ARBs and the Composite of Death, MINS, or Stroke. We tested whether the relationship between withholding *versus* continuing ACEI/ARBs and the primary outcome was consistent across different levels of preoperative sBP. We used tests of interaction in a multivariable fractional polynomial approach with the algorithm outlined by Royston and Sauerbrei[18] to search for the optimal functional form of preoperative sBP that would significantly modify the effect of withholding ACEI/ARBs, where sBP was analyzed as a continuous variable.

Relationship between Clinically Important Hypotension and Withholding Preoperative ACEI/ARBs and Separately the Composite of Death, MINS, or Stroke. We undertook multivariable modified Poisson regression analyses as the primary objective to explore the relationship between clinically important intraoperative and, separately, postoperative hypotension and withholding *versus* continuing ACEI/ARBs in the 24 h before surgery.

In all patients (not limited to ACEI/ARB users), we undertook similar multivariable modified Poisson regression analyses to study the relationship between intraoperative and, separately, postoperative clinically important hypotension and the composite of death, MINS, and stroke.

Variation in Withholding Preoperative ACEI/ARBs. We estimated the proportion of variation in the practice of withholding or continuing ACEI/ARBs preoperatively that could be explained by study center, patient, and surgical factors. We first constructed a multivariable logistic regression model to predict the preoperative withholding of ACEI/ARBs with demographics, clinical factors, surgical factors, and the study center as independent variables. We next constructed a model that included only surgical factors and study center, and we compared it to the full model that also included demographics and clinical factors using a likelihood ratio test to determine whether clinical factors made a significant independent contribution to the explained variation. If the test was statistically significant, we estimated the independent contribution of clinical factors by subtracting the R^2 of the model without clinical factors (calculated using the method of McKelvey and Zavoina[19]) from the full model. We repeated the same process for surgical factors and study center. We took variation that could not be explained by these factors as reflecting provider preference.

Sensitivity Analyses

To test for residual confounding, we performed tracer analyses with significant intraoperative bleeding that resulted in intraoperative blood transfusion and significant bleeding within 30 days that required transfusion of blood products or reoperation. These common outcomes were associated with increased risk of our primary outcome but are unlikely to be influenced by withholding ACEI/ARBs. Failing to detect these associations would lend support for a causal nature to our primary results.[20,21]

We additionally looked for associations between withholding *versus* continuing other antihypertensive agents and our primary outcome. If withholding of several of these agents was associated with the primary outcome in the same direction as withholding of ACEI/ARBs, this may again suggest residual confounding.

We also conducted three *post hoc* sensitivity analyses in response to comments from peer reviewers. First, we repeated our main analyses using logistic regression in place of modified Poisson regression. Second, we repeated our main analyses based on the composite outcome of all-cause death, MI, and stroke at 30 days after surgery. Third, we examined the effect of progressively longer durations of intraoperative hypotension on the primary composite of death, MINS, or stroke at 30 days after surgery and performed a statistical test to assess for trend.

Approach to Missing Data

We excluded patients who did not have complete preoperative medication data or postoperative blood pressures recorded or (among those who did not die or experience a stroke) did not have a cTnT level measured or recorded correctly (*e.g.*, recorded as less than 0.04 ng/ml instead of exact value). We imputed all other missing data using single stochastic conditional imputation with predictive mean matching for continuous variables[22] and logistic regression for any other missing variables, both with fully conditional specification.[23] We included all variables and outcomes in the imputation model.

Table 1. Abridged Cohort Characteristics

Patient Characteristics	All Patients: Overall	All Patients: No Death or Primary Vascular Event	All Patients: Death or Primary Vascular Event	All Patients: *P* Value	Only Patients Who Took ACEI/ARB at Baseline: ACEI/ARB at Baseline	Only Patients Who Took ACEI/ARB at Baseline: ACEI/ARB Continued Preop.	Only Patients Who Took ACEI/ARB at Baseline: ACEI/ARB Withheld Preop.	Only Patients Who Took ACEI/ARB at Baseline: *P* Value
n	14,687	13,278	1,409	—	4,802	3,557	1,245	—
Demographics								
Age, y	64.8 (11.8)	64.0 (11.5)	71.9 (12.1)	< 0.001	68.8 (10.8)	68.8 (10.7)	69.0 (11.1)	0.54
Women, n (%)	7,570 (51.5)	6,948 (52.3)	622 (44.1)	< 0.001	2,398 (49.9)	1,804 (50.7)	594 (47.7)	0.07
Clinical characteristics								
Preop. systolic BP, mmHg	139.7 (23.7)	139.2 (23.3)	143.6 (26.8)	< 0.001	143.9 (24.0)	144.6 (24.5)	141.8 (22.5)	< 0.001
Preop. eGFR, $ml^{-1} \cdot min^{-1} \cdot 1.73\ m^{-2}$	79.0 (22.7)	80.9 (21.0)	60.7 (29.8)	< 0.001	72.5 (22.9)	72.7 (22.6)	71.9 (23.7)	0.28
Body mass index, kg/m^2	27.1 (6.0)	27.3 (6.0)	25.8 (5.9)	< 0.001	28.8 (6.3)	28.8 (6.3)	28.6 (6.0)	0.39
Requires assistance with ADLs, n (%)	822 (5.6)	573 (4.3)	249 (17.7)	< 0.001	315 (6.6)	222 (6.2)	93 (7.5)	0.13
History of COPD	1,233 (8.4)	1,021 (7.7)	212 (15.0)	< 0.001	510 (10.6)	375 (10.5)	135 (10.8)	0.77
History of CHF	681 (4.6)	487 (3.7)	194 (13.8)	< 0.001	405 (8.4)	297 (8.3)	108 (8.7)	0.72
History of CAD, n (%)								
No CAD	12,915 (87.9)	11,864 (89.4)	1,051 (74.6)	< 0.001	3,723 (77.5)	2,780 (78.2)	943 (75.7)	0.17
Not recent high risk	1,599 (10.9)	1,301 (9.8)	298 (21.1)		969 (20.2)	695 (19.5)	274 (22.0)	
Recent high risk CAD	173 (1.2)	113 (0.9)	60 (4.3)		110 (2.3)	82 (2.3)	28 (2.2)	
History of CVE, n (%)	1,066 (7.3)	819 (6.2)	247 (17.5)	< 0.001	528 (11.0)	399 (11.2)	129 (10.4)	0.41
History of PVD, n (%)	776 (5.3)	556 (4.2)	220 (15.6)	< 0.001	432 (9.0)	327 (9.2)	105 (8.4)	0.42
History of AF, n (%)	968 (6.6)	749 (5.6)	219 (15.5)	< 0.001	500 (10.4)	369 (10.4)	131 (10.5)	0.88
History of diabetes, n (%)								
No diabetes	11,827 (80.5)	10,859 (81.8)	968 (68.7)	< 0.001	3,147 (65.5)	2,315 (65.1)	832 (66.8)	0.37
No preop. insulin	1,505 (10.2)	1,339 (10.1)	166 (11.8)		872 (18.2)	662 (18.6)	210 (16.9)	
Preop. Insulin	1,355 (9.2)	1,080 (8.1)	275 (19.5)		783 (16.3)	580 (16.3)	203 (16.3)	
Active cancer, n (%)	3,904 (26.6)	3,521 (26.5)	383 (27.2)	0.59	1,194 (24.9)	906 (25.5)	288 (23.1)	0.10
Preoperative antihypertensive medications								
All preop. antihypertensives, n (%)								
Any taken at baseline	6,856 (46.7)	5,975 (45.0)	881 (62.5)	< 0.001	—	—	—	—
Any held on day of surgery	1,794 (26.2)	1,539 (25.8)	255 (28.9)	0.05	—	—	—	—
Any started on day of surgery	110 (1.4)	94 (1.3)	16 (3.0)	0.001	—	—	—	—
ACEI/ARB preop., n (%)								
Taken at baseline	4,802 (32.7)	4,193 (31.6)	609 (43.2)	< 0.001	—	—	—	—
Held on day of surgery	1,245 (25.9)	1,095 (26.1)	150 (24.6)	0.43	—	—	—	—
Started on day of surgery	82 (0.8)	70 (0.8)	12 (1.5)	0.03	—	—	—	—
β-blocker preop., n (%)								
Taken at baseline	2,512 (17.1)	2,127 (16.0)	385 (27.3)	< 0.001	1,316 (27.4)	985 (27.7)	331 (26.6)	0.45
Held on day of surgery	405 (16.1)	333 (15.7)	72 (18.7)	0.13	199 (15.1)	55 (5.6)	144 (43.5)	< 0.001
Started on day of surgery	38 (0.3)	31 (0.3)	7 (0.7)	0.03	19 (0.4)	10 (0.3)	9 (0.7)	0.04
Rate controlling CCB preop., n (%)								
Taken at baseline	484 (3.3)	407 (3.1)	77 (5.5)	< 0.001	253 (5.3)	194 (5.5)	59 (4.7)	0.33
Held on day of surgery	102 (21.1)	84 (20.6)	18 (23.4)	0.59	50 (19.8)	23 (11.9)	27 (45.8)	< 0.001
Started on day of surgery	5 (< 0.1)	3 (< 0.1)	2 (0.2)	0.02	4 (0.1)	4 (0.1)	0 (0.0)	0.23

(*Continued*)

Table 1. (*Continued*)

Patient Characteristics	All Patients: Overall	All Patients: No Death or Primary Vascular Event	All Patients: Death or Primary Vascular Event	All Patients: *P* Value	Only Patients Who Took ACEI/ARB at Baseline: ACEI/ARB at Baseline	Only Patients Who Took ACEI/ARB at Baseline: ACEI/ARB Continued Preop.	Only Patients Who Took ACEI/ARB at Baseline: ACEI/ARB Withheld Preop.	Only Patients Who Took ACEI/ARB at Baseline: *P* Value
Dihydropyridine CCB preop., n (%)								
Taken at baseline	2,020 (13.8)	1,739 (13.1)	281 (19.9)	< 0.001	1,096 (22.8)	803 (22.6)	293 (23.5)	0.49
Held on day of surgery	382 (18.9)	315 (18.1)	67 (23.8)	0.02	221 (20.2)	66 (8.2)	155 (52.9)	< 0.001
Started on day of surgery	70 (0.6)	56 (0.5)	14 (1.2)	0.001	30 (0.6)	20 (0.6)	10 (0.8)	0.34
α-2 agonist preop., n (%)								
Taken at baseline	88 (0.6)	70 (0.5)	18 (1.3)	< 0.001	39 (0.8)	32 (0.9)	7 (0.6)	0.25
Held on day of surgery	19 (22)	16 (23)	3 (17)	0.57	6 (15.4)	2 (6.3)	4 (57.1)	< 0.001
Started on day of surgery	12 (0.1)	12 (0.1)	0 (0.0)	0.26	6 (0.1)	5 (0.1)	1 (0.1)	0.60
Long-acting nitrate preop., n (%)								
Taken at baseline	358 (2.4)	272 (2.0)	86 (6.1)	< 0.001	202 (4.2)	152 (4.3)	50 (4.0)	0.70
Held on day of surgery	67 (18.7)	48 (17.6)	19 (22.1)	0.36	29 (14.4)	10 (6.6)	19 (38.0)	< 0.001
Started on day of surgery	11 (0.1)	7 (0.1)	4 (0.3)	0.002	5 (0.1)	3 (0.1)	2 (0.2)	0.47
Type of surgery, n (%)								
Major general surgery	2,975 (20.3)	2,644 (19.9)	331 (23.5)	0.001	831 (17.3)	585 (16.4)	246 (19.8)	0.01
Major thoracic surgery	364 (2.5)	324 (2.4)	40 (2.8)	0.36	102 (2.1)	84 (2.4)	18 (1.4)	0.05
Major urogenital surgery	1,813 (12.3)	1,680 (12.7)	133 (9.4)	<0.001	557 (11.6)	435 (12.2)	122 (9.8)	0.02
Major vascular surgery	479 (3.3)	376 (2.8)	103 (7.3)	< 0.001	270 (5.6)	212 (6.0)	58 (4.7)	0.09
Major neurosurgery	874 (6.0)	779 (5.9)	95 (6.7)	0.19	273 (5.7)	209 (5.9)	64 (5.1)	0.33
Major orthopedic surgery	2,968 (20.2)	2,564 (19.3)	404 (28.7)	< 0.001	1,268 (26.4)	930 (26.1)	338 (27.1)	0.49
Low-risk surgery	5,341 (36.4)	5,025 (37.8)	316 (22.4)	< 0.001	1,536 (32.0)	1,129 (31.7)	407 (32.7)	0.54
Urgent/emergent surgery	2,090 (14.2)	1,696 (12.8)	394 (28.0)	< 0.001	602 (12.5)	422 (11.9)	180 (14.5)	0.02
Primary outcome and components, n (%)								
Death, MINS, or stroke	1,409 (9.6)	—	—	—	609 (12.7)	459 (12.9)	150 (12.0)	0.43
Death from any cause	302 (2.1)	—	—	—	99 (2.1)	74 (2.1)	25 (2.0)	0.88
MINS	1,160 (7.9)	—	—	—	531 (11.1)	399 (11.3)	132 (10.6)	0.52
Stroke	90 (0.6)	—	—	—	34 (0.7)	26 (0.7)	8 (0.6)	0.75
Exploratory outcomes								
Death, MI, or stroke	745 (5.1)	27* (0.2)	718 (51.0)	< 0.001	299 (6.2)	221 (6.2)	78 (6.3)	0.95
MI	446 (3.0)	27* (0.2)	419 (29.7)	< 0.001	205 (4.3)	148 (4.2)	57 (4.6)	0.53
Hypotension								
Intraoperative hypotension	4,162 (28.3)	3,698 (27.9)	464 (32.9)	< 0.001	1,307 (27.2)	1,017 (28.6)	290 (23.3)	< 0.001
Postoperative hypotension	2,728 (18.6)	2,289 (17.2)	439 (31.2)	< 0.001	961 (20.0)	719 (20.2)	242 (19.4)	0.56

Denominators for medication proportions vary: for patients who took the medication at baseline (1 to 7 days before surgery), the denominator includes all patients; for patients who had their medication withheld on the day of surgery, the denominator includes only patients who were taking the medication at baseline; for patients who started the medication on the day of surgery, the denominator includes only patients who were not taking the medication at baseline. Column totals comprise the denominator for all other proportions. Continuous variables were kept continuous in all analyses. *P* values are two sided and based on Pearson chi-square tests for proportions and *t* tests for continuous variables. See table S1 in Supplemental Digital Content 1 (http://links.lww.com/ALN/B326) for additional details.

*27 patients who experienced MI were not captured by MINS. They qualified for MI based on the development of new pathologic Q waves on an electrocardiogram when troponin levels were not obtained or were obtained at times that could have missed the clinical event.

ACEI = angiotensin-converting enzyme inhibitor; ADL = activities of daily living; AF = atrial fibrillation; ARB = angiotensin II receptor blocker; BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CVE = cerebrovascular event; eGFR = estimated glomerular filtration rate; MI = myocardial infarction; MINS = myocardial injury after noncardiac surgery; preop. = preoperatively; PVD = peripheral vascular disease.

Results

We analyzed data from 14,687 (91.3%) of the 16,079 recruited patients (fig. 1) of whom 1,409 (9.6%) died or suffered a nonfatal stroke or MINS; MINS occurred in 1,160 patients (7.9%), stroke in 90 (0.6%), and death in 302 (2.1%). We imputed missing baseline characteristics (mostly serum creatinine, height, and weight) for 10.3% of the included patients. The prevalence of most baseline characteristics differed among patients who suffered an event compared to those who did not (table 1 and table S1 in Supplemental Digital Content 1, http://links.lww.com/ALN/B326). Table S2 (Supplemental Digital Content 1, http://links.lww.com/ALN/B326) shows that the 8.7% of patients who were omitted from the analysis for missing data were similar to those included.

Six thousand eight hundred fifty-six (46.7%) patients were taking an antihypertensive agent at baseline (*i.e.*, within 1 to 7 days before surgery); 4,120 (60.1%) used a single agent; 2,131 (31.1%) used two medications; and 605 (8.8%) used three or more. Four thousand eight hundred two patients took ACEI/ARBs at baseline; 2,275 of them (47.4%) were also using at least one other antihypertensive medication. Among all antihypertensive medication users, 1,794 (26.2%) had at least one of these medications withheld on the day of surgery (table 2). Typically only one antihypertensive agent was withheld (79.3% of patients), even in patients taking multiple agents at baseline. Patients with lower preoperative blood pressure were more likely to have their medications withheld on the day of surgery (table S3, Supplemental Digital Content 1, http://links.lww.com/ALN/B326).

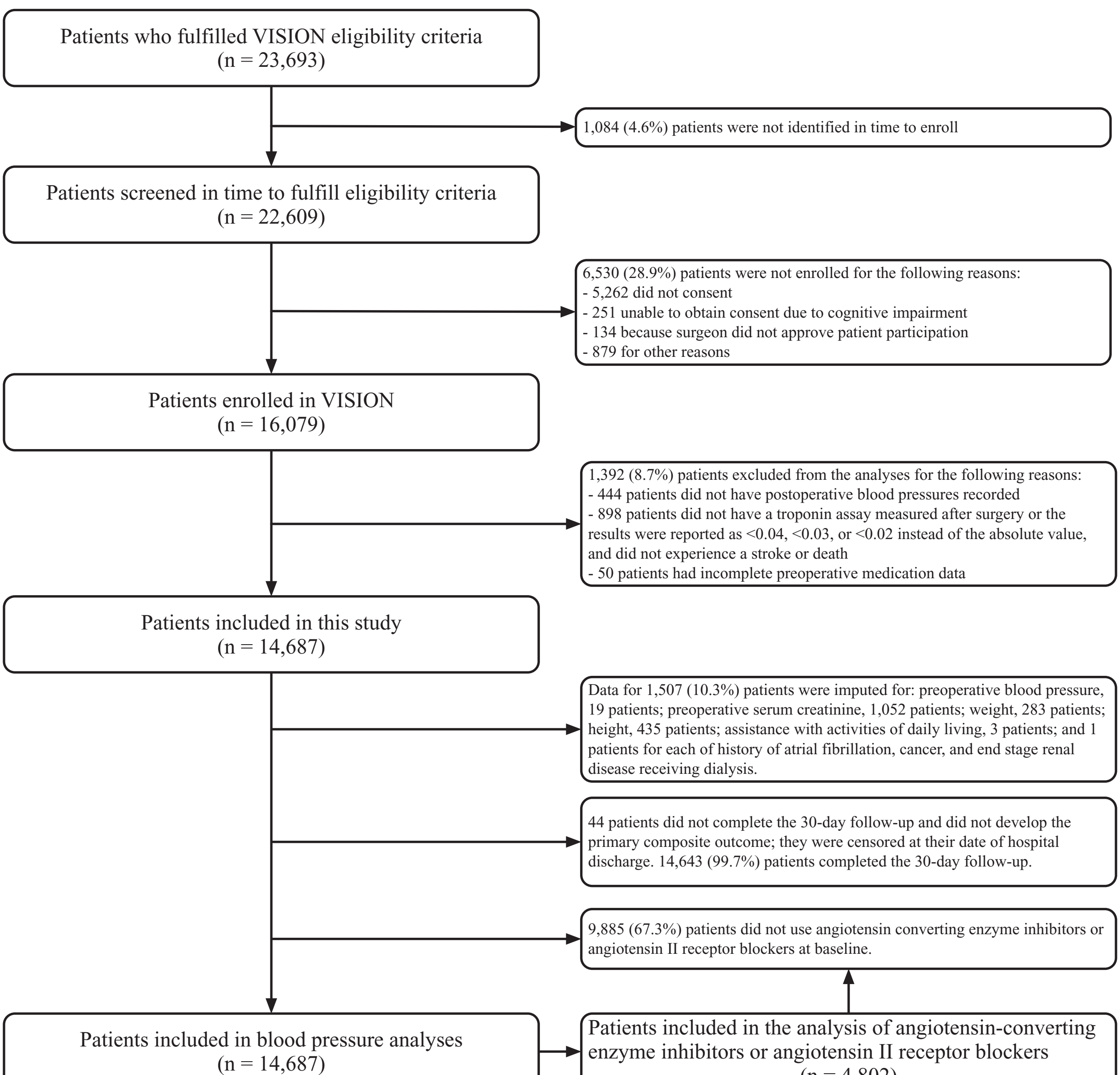

Fig. 1. Participant flowchart. VISION = Vascular events In noncardiac Surgery patIents cOhort evaluatioN.

Table 2. Number of Antihypertensive Medications That Patients Were Using at Baseline and the Number and Proportion Withheld on the Day of Surgery

No. of Antihypertensive Medications at Baseline	No. of Antihypertensive Medications Withheld on the Day of Surgery (% of Row Total) 0	1	2	3	4	Row Total (% of Total)
1	3,176 (77.1%)	944 (22.9%)				4,120 (60.1%)
2	1,507 (70.7%)	353 (16.6%)	271 (12.7%)			2,131 (31.1%)
3 or more	379 (62.6%)	125 (20.7%)	53 (8.8%)	42 (6.9%)	6 (1%)	605 (8.8%)
Column total (% of total)	5,062 (73.8%)	1,422 (20.7%)	324 (4.7%)	42 (0.6%)	6 (0.1%)	6,856

Results for the Primary Objective

Patients in whom ACEI/ARBs were withheld (n = 1,245; 25.9%) were largely similar to those in whom ACEI/ARBs were continued but were less likely to have very high preoperative blood pressure, less likely to undergo major urogenital surgery, and more likely to undergo major general and urgent or emergency surgery.

Among the 4,802 patients who took ACEI/ARBs at baseline, withholding ACEI/ARBs on the day of surgery was associated with an 18% reduction in the relative risk of the composite outcome of death, stroke, or MINS (adjusted relative risk [aRR], 0.82; 95% CI, 0.70 to 0.96; $P = 0.01$) with the results qualitatively consistent across the component outcomes (fig. 2).

Results for Secondary Objectives

The relationship between withholding ACEI/ARBs and the primary composite outcome was consistent across preoperative sBP readings; the P value for interaction was nonsignificant (*i.e.*, $P > 0.2$).

Withholding ACEI/ARBs was also associated with a 20% relative reduction in the risk of intraoperative hypotension (aRR, 0.80; 95% CI, 0.73 to 0.88; $P < 0.001$) but was not associated with postoperative hypotension (aRR, 0.92; 95% CI, 0.77 to 1.10; $P = 0.36$).

Among all patients (regardless of ACEI/ARB use), those who experienced clinically important hypotension during surgery (n = 4,162; 28.3%) were more likely to develop clinically important hypotension after surgery (aRR, 1.65; 95% CI, 1.48 to 1.84; $P < 0.001$). Adjusted for postoperative hypotension, intraoperative hypotension was not significantly associated with the composite outcome of death, MINS, or stroke within the 30 days after surgery (aRR, 1.11; 95% CI, 0.98 to 1.25; $P = 0.09$).

In total, 2,860 of 14,687 patients (19.5%) experienced at least one episode of clinically important postoperative hypotension; 2,728 (95.4%) of them experienced their first episode of postoperative hypotension by day 3 and the remainder between day 4 and discharge (fig. 3). Postoperative

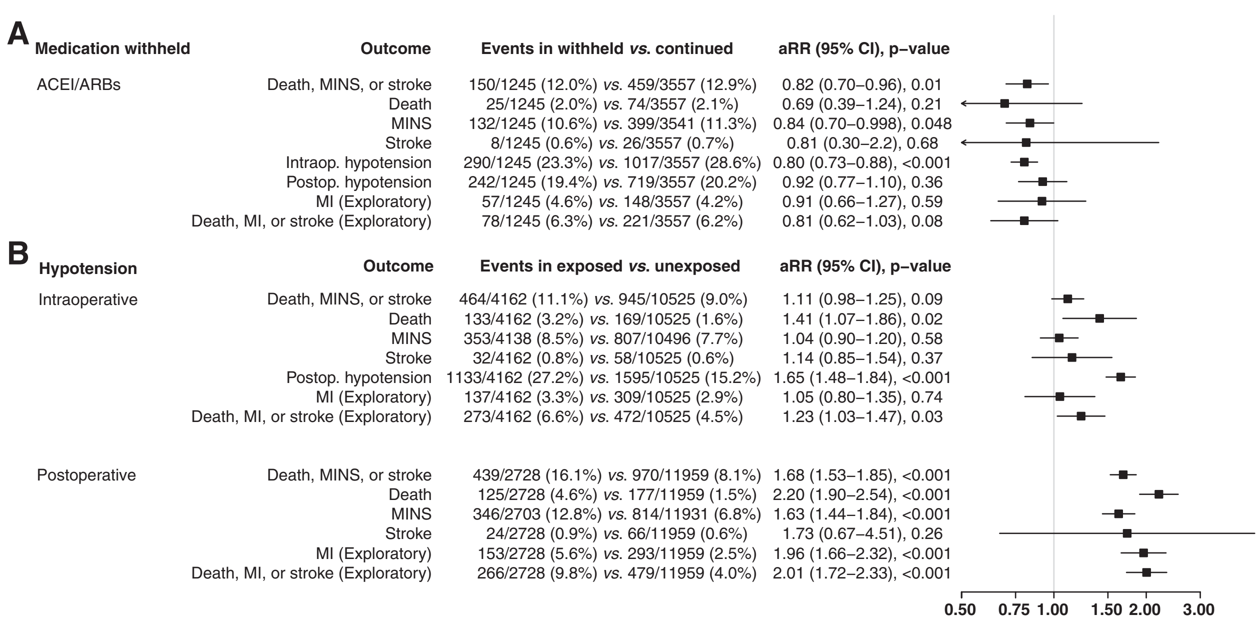

Fig. 2. (*A*) Adjusted association between withholding *versus* continuing preoperative angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) with postoperative 30-day death from any cause, myocardial injury after noncardiac surgery (MINS), or stroke, intraoperative and postoperative (day 0 to 3) hypotension, and the exploratory outcome myocardial infarction (MI) in 4,802 patients taking these medications at baseline. (*B*) Association between hypotension and postoperative death and vascular events in all 14,687 patients. aRR = adjusted relative risk.

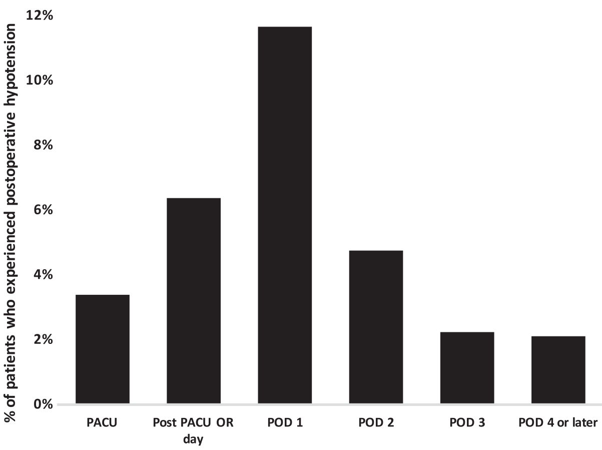

Fig. 3. Clinically significant hypotension in the postoperative period. In total, 2,860 of 14,687 patients (19.5%) experienced at least one episode of clinically significant hypotension after their surgery; 2,728 (95.4%) of those patients experienced a hypotensive episode by postoperative day (POD) 3. OR = operating room; PACU = postanesthesia care unit.

hypotension occurred in the postanesthesia care unit in 3.4% (n = 493) of patients; in the hours immediately after transfer out of the postanesthesia care unit in 6.3% (n = 931); and during the next day in 11.6% (n = 1,711). Patients who experienced clinically important hypotension by the third postoperative day (n = 2,728; 18.6%) were more likely to die or suffer a vascular event compared to their counterparts without postoperative hypotension (aRR, 1.68; 95% CI, 1.53 to 1.85; $P < 0.001$).

Only 6.62% of the propensity to withhold ACEI/ARBs on the day of surgery could be explained by available demographic and clinical information (explained 0.02%), surgical information (explained 0.6%), and center information (explained 6.0%). Figure S1 (Supplemental Digital Content 1, http://links.lww.com/ALN/B326) shows that the percentage of baseline ACEI/ARB users who had these medications withheld ranged from 9% to 44% across countries included in the study. Although these estimates are based on just 12 hospitals and relatively few patients, much variation likely reflects provider preference.

Sensitivity Analyses

Clinically significant bleeding during surgery occurred in 278 (5.8%) baseline ACEI/ARB users and was significantly associated with the composite of death and vascular events (aRR, 1.49; 95% CI, 1.13 to 1.97; $P = 0.004$) but not associated with withholding these medications (aRR, 0.94; 95% CI, 0.70 to 1.26; $P = 0.69$). Significant bleeding within 30 days of surgery occurred in 955 (19.9%) ACEI/ARB users and was significantly associated with the primary outcome (aRR, 2.05; 95% CI, 1.63 to 2.59; $P < 0.001$) but not associated with withholding these medications (aRR, 1.04; 95% CI, 0.92 to 1.18; $P = 0.56$). Withholding of other antihypertensive medications was not significantly associated with the primary outcome (fig. S2, Supplemental Digital Content 1, http://links.lww.com/ALN/B326), with wide CIs around the estimates. Both of these sensitivity analyses suggest that our primary results are specific to ACEI/ARBs and not explained by residual confounding.

A similar analysis suggested that some residual confounding affected the relationship between hypotension and the primary outcome, but the results remained qualitatively similar after adjusting for bleeding (Supplemental Digital Content 1, http://links.lww.com/ALN/B326, heading Sensitivity analysis for relationship between hypotension and the primary outcome).

The sensitivity analysis with logistic regression yielded results similar to our prespecified analyses (table S2, Supplemental Digital Content 1, http://links.lww.com/ALN/B326). The sensitivity analysis based on the composite outcome of death, MI, or stroke demonstrated similar results to the analyses based on the primary outcome. The association between withholding ACEI/ARB *versus* continuing these drugs before surgery and the composite outcome of death, MI, or stroke produced essentially the same point estimate of effect as seen with the primary composite outcome; however, the result in the sensitivity analysis was not statistically significant (aRR, 0.81; 95% CI, 0.62 to 1.03; $P = 0.08$). The sensitivity analysis had less power than the primary analysis because 205 (4.3%) baseline ACEI/ARB users suffered an MI, whereas 531 (11.1%) suffered MINS. The composite outcome of death, MI, or stroke was more likely to occur in patients who experienced intraoperative hypotension (aRR, 1.23; 95% CI, 1.03 to 1.47; $P = 0.03$) and postoperative hypotension (aRR, 2.01; 95% CI, 1.72 to 2.33; $P < 0.001$).

Figure S3 (Supplemental Digital Content 1, http://links.lww.com/ALN/B326) demonstrates a graded relationship between progressively longer durations of intraoperative hypotension and increasing risk of death, MINS, or stroke (*P* value for trend less than 0.001).

Discussion

One third of patients having major noncardiac surgery in this large prospective cohort study used ACEI/ARB on a regular basis. Of these patients, a quarter did not receive their ACEI/ARBs in the 24 h before surgery and had a lower adjusted risk of death or vascular events (aRR, 0.82; 95% CI, 0.70 to 0.96; $P = 0.01$) and of clinically important intraoperative hypotension (aRR, 0.80; 95% CI, 0.72 to 0.93; $P < 0.001$). The negligible association between clinical and surgical factors and the withholding of ACEI/ARBs suggests that clinician discretion, independent of patient characteristics, predominantly determined the decision to withhold.

Recent perioperative guidelines suggest continuing ACEI/ARBs before noncardiac surgery,[8] citing a meta-analysis and a retrospective cohort study. The meta-analysis included three small randomized trials (20 to 30 patients per arm) limited to cardiac and vascular surgery and two retrospective observational studies (n = 434 patients) undergoing nonemergency surgery.[24] The results suggested that patients given ACEI/ARBs before surgery were more likely to develop hypotension requiring a vasopressor during or shortly after induction of anesthesia (relative risk, 1.50; 95% CI, 1.15 to 1.96). The incidence of perioperative MI did not differ significantly in patients who continued or withheld ACEI/ARBs, but the CI was very wide and thus compatible with substantial benefit or harm (relative risk, 0.41; 95% CI, 0.07 to 2.53). A more recent meta-analysis arrived at similar conclusions.[25]

In a cohort analysis that matched 9,028 baseline ACEI users to 9,028 nonusers on a propensity score for baseline ACEI use, ACEI use was not associated with either 30-day mortality (odds ratio, 0.93; 95% CI, 0.73 to 1.19) or the composite of in-hospital morbidity and mortality (odds ratio, 1.06; 95% CI, 0.97 to 1.15).[26] The analysis had four limitations that we avoided in our analysis. First, patients who adhere to preventive medications (or placebo) have better health outcomes than those who have indications to take them but do not[27–29]—a "healthy user" bias that may counteract an increase in risk associated with taking ACEI. In contrast, we limited our comparisons to patients who were already taking these medications at baseline. Second, outcomes were collected as part of routine care, whereas VISION employed central adjudication of the primary outcomes and active surveillance for myocardial injury with serial cTnT measurements. Third, the study was conducted in a single center, while VISION was a multicenter, international study. Finally, we obtained information on whether medication was withheld directly from patients and medication records.

We found that hypotensive episodes were common in the hours and days after surgery. Postoperative hypotension was independently associated with a greater risk of death or vascular events. Intraoperative hypotension was also common but was not significantly associated with mortality and vascular events after adjustment for postoperative hypotension.

Our findings regarding postoperative hypotension parallel the results from the 10,010-patient PeriOperative ISchemic Evaluation (POISE)-2 trial. In POISE-2, 37.1% of patients in the placebo arm experienced clinically important hypotension; hypotension was associated with perioperative MI (hazard ratio, 1.37; 95% CI, 1.16 to 1.62).[30] The association between intraoperative hypotension and death or vascular events was not statistically significant in our analysis. Larger studies have reported an association between intraoperative hypotension, kidney and myocardial injury,[4] and mortality.[5] The difference from our findings may relate to these studies' use of lower thresholds to define intraoperative hypotension, our adjustment for postoperative hypotension, or insufficient power in our study.

Study Strengths

We used prospectively collected data from a representative sample of patients undergoing a broad range of surgeries in several countries, actively monitored and centrally adjudicated outcomes, ensured minimal loss-to-follow-up, had a comprehensive approach to missing data, adjusted for a wide range of potential confounders, and had no evidence of substantial residual confounding in sensitivity analyses. Our study is the first to assess the effect of preoperative ACEI/ARB management on the incidence of a cardiovascular outcome that includes MINS distinct from MI. Only 15.8% of patients suffering MINS experience an ischemic symptom, and the remaining 84.2% of events would likely go undetected without systematic postoperative troponin monitoring.[12] Accordingly, the third universal definition of MI consensus statement recommends monitoring perioperative troponin measurements in high-risk patients undergoing noncardiac surgery.[31] Among baseline ACEI/ARB users, 205 (4.3%) suffered an MI, whereas 531 (11.1%) suffered MINS. Given the almost identical point estimate of apparent effect in the sensitivity analysis, this lower incidence of MI is almost certainly the reason that the association between withholding ACEI/ARBs *versus* continuing these drugs before surgery and the composite outcome of death, MI, or stroke was not statistically significant (aRR, 0.81; 95% CI, 0.62 to 1.03; $P = 0.08$).

Study Limitations

Residual confounding is possible in any observational study. We adjusted for many variables and failed to detect substantial residual confounding in sensitivity analyses. Patients in whom ACEI/ARBs were withheld were generally similar to those in whom they were continued in unadjusted comparisons of baseline characteristics but notably appeared more likely to undergo urgent or emergency surgery. Urgent or emergency surgeries were those performed within 72 h of the acute event that led to surgery. Patients were admitted more than 24 h before many of these surgeries during which time clinicians could withhold their blood pressure medications. After adjusting for the type of surgery and patient characteristics and accounting for center effects, patients who underwent urgent or emergency surgery were not significantly more likely to have their ACEI/ARBs withheld than patients who underwent elective surgery ($P = 0.29$).

We excluded 8.7% of patients due to missing data on cTnT, postoperative blood pressure, or preoperative medication use. Included and excluded patients had similar baseline characteristics. We imputed missing data for baseline characteristics in 10.3% of included patients. Our findings regarding withholding *versus* continuing ACEI/ARBs were likely robust to this small amount of missing confounder data because clinical variables explained very little of the variation in this practice (*i.e.*, they were very weak confounders), and we made appropriate imputation efforts.

The need to control for many potential confounders and the correlation between them limited the statistical power of our analyses.[32] We could not reliably estimate the effects of withholding antihypertensive medications other than ACEI/ARBs and of starting medications not already used before the day of surgery or study potentially relevant subgroups such as patients with heart failure or known cardiovascular disease. Sample size may also have limited our statistical power to detect differential effects of withholding ACEI/ARBs at different levels of preoperative blood pressure. Regression results demonstrated wide CIs for outcomes with a limited number of events (*i.e.*, stroke and MI), but the direction of their point estimates was consistent with the composite outcome.

We relied on a crude dichotomous definition of hypotension (sBP less than 90 mmHg of any duration accompanied by intervention) rather than actual values. Our blood pressure threshold may have been too high, short durations of sBP slightly below 90 mmHg may not be prognostically significant, and the associations with death and vascular events may be driven by episodes with lower sBP or of a long duration. We relied on routine measurements commonly conducted at 4-h or longer intervals in the postoperative period and have likely missed some hypotensive episodes. Surveillance bias may have inflated the associations between postoperative hypotension and clinical outcomes because patients who develop complications are monitored more closely.

We could not evaluate renal outcomes in this subsample of VISION. Three randomized controlled trials totaling 64 patients studied renal outcomes of preoperative ACEI in cardiac and vascular surgery but detected no acute kidney injury events.[33] A prospective cohort study of 1,594 cardiac surgery patients found a graded increase in the risk of acute kidney injury across three groups of preoperative ACEI/ARB exposure (none, 31%; held, 34%; continued, 42%; *P* for trend 0.03).[34] The study suggested that, if anything, withholding of ACEI/ARBs is associated with a reduction in kidney injury.

We did not study the effects of withholding antihypertensive medications after surgery because the timing of postoperative medication use was not captured with sufficient precision in VISION.

Implications

We estimate that, if all patients who continue to take ACEI/ARBs on the day of surgery were to instead withhold them, 5.9% (95% CI, 1.2 to 10.1)—or over 500,000 patients per year—would avoid death, MINS, or stroke within 30 days of their operation. This estimate assumes that 100 million of the 200 million people who undergo major noncardiac surgery annually are at least 45 yr old,1,36 that 9.6% die or suffer an adverse perioperative vascular event, that our data accurately represents the international patient population and clinical practice, and that the relationship we observed is causal. Even if these assumptions are violated, our results have substantial global importance.

Conclusions

This international prospective cohort study suggests that withholding ACEI/ARBs on the day of a noncardiac surgery may reduce the risk of perioperative death, stroke, or myocardial injury in patients who take these medications chronically. A large randomized trial is needed to confirm this finding. In the interim, clinicians should consider recommending that patients withhold ACEI/ARBs 24 h before surgery.

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Competing Interests

Dr. Devereaux received grants from Roche-Diagnostics (Mannheim, Germany) and Abbott-Diagnostics (Abbott Park, Illinois). The other authors declare no competing interests.

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