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Effect of discontinuing antihypertensives on perioperative hypotension in older patients before non-cardiac surgery: multicentre, randomised, double blind, controlled trial

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ABSTRACT

OBJECTIVE

To determine whether discontinuing versus continuing angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) on the morning of surgery reduces perioperative hypotension in older patients undergoing non-cardiac surgery.

DESIGN

Multicentre, randomised, double blind, placebo controlled trial.

SETTING

Five tertiary teaching hospitals in China, November 2020 to December 2023.

PARTICIPANTS

2036 older patients (60-80 years) using ACE inhibitors or ARBs for at least two weeks and scheduled for non-cardiac surgery under general anaesthesia.

INTERVENTIONS

Patients were randomised to receive their usual ACE inhibitor or ARB or a placebo in identical capsules on the morning of surgery.

MAIN OUTCOME MEASURES

The primary outcome was the incidence of perioperative hypotension (mean blood pressure ‹65 mm Hg or a ≥30% decrease from baseline requiring treatment). Secondary outcomes included duration of hypotension, requirement for a vasopressor, intraoperative fluid volume, postoperative hypotension, and 30 day complications (neurocognitive disorders, major cardiocerebral events) or mortality.

RESULTS

2012 patients (mean age 68.8 years; 54.4% male) completed the study: 1004 were included in the antihypertensive group and 1008 in the no antihypertensive group. The incidence of perioperative hypotension was lower in the no antihypertensive group (314/1008, 31.2%) versus antihypertensive group (457/1004, 45.5%): adjusted odds ratio 0.52 (95% confidence interval (CI) 0.43 to 0.63); absolute risk difference -14.4% (95% CI -18.5% to -10.1%); P<0.001. The duration of hypotension and requirement for a vasopressor were both reduced in the no antihypertensive group: adjusted mean difference -1.3 minutes (95% CI -1.8 to -0.8 minutes) and 28.5% *v* 41.1%; adjusted odds ratio 0.54 (95% CI 0.44 to 0.66). Intraoperative fluid volume, postoperative hypotension, 30 day complications, and mortality did not differ significantly between groups.

CONCLUSIONS

Discontinuing ACE inhibitors or ARBs on the morning of surgery in older patients with hypertension statistically significantly reduced perioperative hypotension and the requirement for vasopressors without increasing 30 day complications or mortality. This simple strategy provides high certainty evidence for preoperative drug management in this patient population.

TRIAL REGISTRATION

Chinese Clinical Trial Registry ChiCTR2000039376.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Perioperative hypotension is common in older patients with hypertension and is a modifiable risk factor for organ injury

Whether to discontinue or continue angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) before non-cardiac surgery remains inconclusive

Recent randomised trials showed inconsistent results, and current guidelines confer only weak recommendations (class 2b) for discontinuation of ACE inhibitors or ARBs to prevent intraoperative hypotension

WHAT THIS STUDY ADDS

In this randomised, double blind, placebo controlled trial, discontinuing ACE inhibitors or ARBs on the morning of surgery reduced perioperative hypotension and vasopressor requirement in older patients undergoing non-cardiac surgery

30 day complications or mortality did not increase

Introduction

An estimated one third of surgeries worldwide involve patients aged 60 years or older; in China, about 60% of such patients have hypertension.[1] In this population, hypotension during surgery is substantially associated with acute kidney injury, myocardial injury, and death.[2-6] Although hypotension is not the only cause of organ injury, maintaining haemodynamic stability remains a fundamental priority for perioperative care, especially avoiding sustained low blood pressure.[7-9]

Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are the preferred antihypertensives for organ protection.[10-12] Whether to stop antihypertensives before surgery is contentious: some studies have found an association between withholding treatment and intraoperative hypotension, whereas others have found no difference.[13-16] Two recent open label trials (SPACE (Stopping Perioperative ACE-inhibitors or angiotensin-II receptor blockers) and Stop-or-Not) that investigated

the discontinuation of treatment 48-72 hours before surgery showed neutral effects on major complications and conflicting results for hypotension, leaving optimal timing undefined.[17 18] The 2025 American Heart Association guidelines weakly recommend (class 2b) discontinuation of antihypertensives before surgery to prevent intraoperative hypotension in patients undergoing major surgery.[19] The prolonged withholding of ACE inhibitors or ARBs may, however, provoke rebound postoperative hypertension. Whether a same day omission strategy can achieve a favourable balance between reducing intraoperative hypotension and avoiding important rebound hypertension remains uncertain.

We conducted a multicentre randomised trial to determine the effects of discontinuing versus continuing ACE inhibitors or ARBs on the morning of surgery on the incidence of perioperative hypotension in older patients with hypertension undergoing non-cardiac surgery.

Methods

Trial design

This multicentre, randomised, double blind, placebo controlled trial was conducted at five tertiary university hospitals across four provinces in east and central China: First Affiliated Hospital of Soochow University (Jiangsu), Zhongshan Hospital Fudan University (Shanghai), Fudan University Shanghai Cancer Centre (Shanghai), The First Affiliated Hospital of Anhui Medical University (Anhui), and The First Affiliated Hospital of Zhengzhou University (Henan). The trial protocol has been previously published.[20] All patients provided written informed consent before recruitment.

Participants

We enrolled older patients (aged 60-80 years) with hypertension and American Society of Anesthesiologists (ASA) physical status II (mild systemic disease) or III (severe systemic disease but not incapacitating) using ACE inhibitors or ARBs for at least two weeks and scheduled for non-cardiac surgery under general anaesthesia. We excluded patients who required emergency surgery; had uncontrolled hypertension (systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg), existing hypotension (mean blood pressure ≤65 mm Hg), or currently used vasopressors; had severe comorbidities (acute coronary syndrome, heart failure, acute respiratory distress syndrome, respiratory failure, acute stroke, Child-Pugh ≥B, serum creatinine ≥200 µmol/L); and used ACE inhibitors or ARBs irregularly (evening or night-time only, intermittently or concomitantly).

Randomisation and blinding

A biostatistician independent of enrolment and data management performed randomisation using a central password protected system (https://www.91trial.com). Patients were allocated 1:1 using permuted blocks of 2 and 4, stratified by centre. On the day before surgery, an independent researcher accessed the random codes to assign patients to either continuation or discontinuation of ACE inhibitors or ARBs. The allocation details remained concealed from all other staff until enrolment was complete. Patients, surgeons, anaesthetists, postoperative care staff, data collectors, and statisticians were masked to patient assignment.

Interventions

Trained research staff visited the ward daily and provided a participant information sheet for patients to read, discuss with family, and ask questions. Written informed consent was obtained the evening before surgery. According to the random codes, an independent researcher (consultant anaesthetist) at each centre prescribed ACE inhibitors or ARBs to patients assigned to the antihypertensive group with drug type and dose identical to their usual prescription, or inactive placebo (starch and lactose) to patients assigned to the no antihypertensive group. ACE inhibitors, ARBs, and placebos were included in identical opaque size 0 capsules (supplementary figure S1) and supplied in indistinguishable sachets labelled only with the randomisation number.

The antihypertensives were scheduled to restart on the morning of postoperative day 1 at the preoperative dose. Treatment was delayed to postoperative day 2 or later if any of the following was present: mean blood pressure <65 mm Hg requiring treatment within the preceding 12 hours, vasopressor required, or acute kidney injury (criteria detailed in supplementary table S1); the site principal investigator confirmed the decision and reassessed patients daily thereafter.

Anaesthesia management

Baseline blood pressure was the mean of three cuff measurements taken from the upper arm before surgery. In theatre and recovery, cuff blood pressure was measured every three minutes; invasive arterial monitoring was used for major or high risk operations and for patients with multiple comorbidities.

Anaesthesia was induced with etomidate and maintained with propofol infusion (target bispectral index 40-60) or sevoflurane inhalation (target end tidal concentration of 0.8-1.3 minimum alveolar concentration) to achieve equivalent depth. Other anaesthetic management followed the published protocol.[20] To ensure consistency of data, all blood pressure readings were obtained from cuff blood pressure measurements and recorded continuously by an electronic information system. In cases of hypotension (mean blood pressure <65 mm Hg or ≥30% decrease from baseline) during surgery and in recovery, a standardised management was applied. Firstly, the measurement interval was shortened to one minute until blood pressure became stable. Secondly, hypovolaemia was corrected with fluid resuscitation using crystalloids, colloids, or blood products. Initial vasopressor treatment included ephedrine (5-10 mg) or phenylephrine (50-100 µg); if hypotension recurred despite repeated boluses, noradrenaline (norepinephrine) infusion 0.05-1

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μg/kg/min was administered. Hypertension was controlled with vasodilators (nitroglycerin, sodium nitroprusside) or beta blocker (esmolol). Bradycardia was primarily managed with anticholinergics (atropine, glycopyrronium), with epinephrine or isoprenaline administered to patients who did not respond to treatment. Supraventricular tachycardia was treated with verapamil, and ventricular tachycardia was managed with amiodarone, lidocaine, or cardioversion.

On the wards, cuff blood pressure was monitored every 30 minutes for the first six hours after surgery and then every two hours for up to 24 hours, after which it was monitored every six hours for three postoperative days or until hospital discharge. For patients admitted to the intensive care unit (ICU), invasive blood pressure was continuously monitored, and hypotension was treated at the clinicians' discretion and recorded in the electronic medical records.

Outcomes

Supplementary table S1 lists the definitions of all outcome measurements. The primary outcome was the incidence of perioperative hypotension, defined as a mean blood pressure of <65 mm Hg or a ≥30% decrease from baseline that required intravenous fluid or vasopressor, or both, administered during surgery or in recovery.

Secondary outcomes included duration of hypotension (cumulative time blood pressure was below the hypotension threshold),[2 21] vasopressor requirement, intraoperative fluid volume, hypotension within the first three postoperative days, and 30 day perioperative neurocognitive disorder (diagnosed by psychiatrists), major adverse cardiocerebral events (MACE; myocardial infarction, heart block, cardiac arrest, stroke, or coma), or mortality.

Exploratory outcomes included perioperative hypertension (mean blood pressure >110 mm Hg or ≥30% increase from baseline), tachycardia or bradycardia requiring treatment, intraoperative adverse events (allergic reaction, hypoxia, new onset arrhythmia, hyperthermia, hypothermia, oliguria, electrolyte and acid-base disorders, major bleeding, and cardiac arrest), Ramsay sedation and numerical rating scale pain scores at recovery discharge, postoperative nausea and vomiting within the first three postoperative days, time to extubation, admission to the ICU, and length of hospital stay.

Post hoc outcomes included lowest intraoperative mean blood pressure, maximum decrease in mean blood pressure from baseline (baseline-the lowest value), proportion of patients having prolonged hypotensive episodes (≥5, 10, and 15 minutes), and 30 day acute kidney injury (defined according to the Kidney Disease: Improving Global Outcomes guidelines).[22]

Sample size

The sample size was determined based on a large prospective cohort study, in which the incidence of intraoperative hypotension was 28.6% in patients continuing ACE inhibitors or ARBs.[13] To detect a 20% lower risk of the primary outcome of discontinuing versus continuing antihypertensives (from 28.6% to 22.9%) with a power of 80% and a significance level of 0.05, we determined that 916 patients would be required in each arm. Assuming a 10% dropout rate, we recruited 1018 patients in each arm.

Statistical analysis

Continuous variables are presented as means with standard deviations (SDs) or medians with interquartile ranges (IQRs) depending on distribution, whereas categorical variables are presented as numbers (percentages). Between group comparisons were summarised using odds ratios, risk ratios, absolute risk differences, and mean difference with the corresponding 95% confidence intervals (CIs). The intention-to-treat population comprised all randomised patients who provided informed consent and underwent surgery. The per protocol population was defined as patients who underwent randomisation and received interventions according to the study protocol. The primary outcome was analysed in both the intention-to-treat and the per protocol populations, whereas the secondary and exploratory outcomes were analysed by intention to treat only.

Main analyses were performed on an intention-to-treat basis using multivariable models adjusted for prespecified fixed effect covariates (age, body mass index, ASA classification, hypertension grade, preoperative myocardial infarction, atrial fibrillation, diabetes, anaemia, diuretics preoperatively, and centre). These factors were chosen for their known association with perioperative hypotension. Multivariable logistic regression was used to analyse perioperative hypotensive events, vasopressor requirement, hypotension within three postoperative days, and 30 day complications; as a sensitivity analysis for outcomes with sparse data, we also performed Firth's bias reduced logistic regression analysis. Hypotension duration and intraoperative fluid loading volume were analysed using multivariable linear regression. We compared the lowest intraoperative mean blood pressure between the two groups using multivariable linear regression, adjusting for baseline mean blood pressure.

For the primary outcome, we conducted prespecified subgroup analysis with logistic regression for age (60-70 *v* 71-80 years), hypertension grade (1 *v* 2),[23] diabetes status (yes *v* no), type of surgery (abdominal, thyroid or breast, urological, orthopaedic, other), duration of surgery (<120 *v* ≥120 minutes), and centre. We also examined patients' age and duration of surgery on a continuous scale for linear interactions and for non-linear interactions with restricted cubic splines.

All variables were captured through a mandatory field electronic system (www.91trial.com) with real time logic checks and central monitoring to ensure that every variable was entered before the case was locked. We carried out complete case analysis. For

Table 1 | Baseline and intraoperative characteristics of older adults (60-80 years) according to ACE inhibitor or ARB treatment on morning of non-cardiac surgery in intention-to-treat population. Values are number (percentage) unless stated otherwise

Characteristics	Antihypertensive group (n=1004)	No antihypertensive group (n=1008)
Mean (SD) age (years)	68.7 (5.3)	68.9 (5.2)
Male sex	550 (54.8)	545 (54.1)
Mean (SD) height (cm)	164.4 (7.8)	164.4 (7.7)
Mean (SD) weight (kg)	66.5 (11.0)	66.2 (10.1)
Mean (SD) body mass index	24.5 (3.3)	24.5 (3.1)
Current smoker	63 (6.3)	66 (6.5)
Alcohol use*	9 (0.9)	9 (0.9)
ASA classification:		
II	829 (82.6)	838 (83.1)
III	175 (17.4)	170 (16.9)
Hypertension grade:		
1	678 (67.5)	621 (61.6)
2	326 (32.5)	387 (38.4)
Median (IQR) duration of hypertension (months)	120 (60-204)	120 (60-216)
Median (IQR) baseline blood pressure (mm Hg):		
Systolic	150 (135-163)	150 (136-167)
Diastolic	80 (71-88)	80 (71-87)
Mean	102 (94-111)	103 (95-112)
Median (IQR) baseline heart rate (beats/min)	73 (66-80)	73 (66-82)
Other comorbidities:		
Coronary artery disease	105 (10.5)	113 (11.2)
Myocardial infarction	22 (2.2)	25 (2.5)
Arrhythmia	44 (4.4)	42 (4.2)
Atrial fibrillation	21 (2.1)	24 (2.4)
Peripheral vascular disease	15 (1.5)	17 (1.7)
Previous TIA or stroke	117 (11.7)	125 (12.4)
Diabetes	201 (20.0)	203 (20.1)
Chronic lung disease	20 (2.0)	13 (1.3)
Previous cancer	50 (5.0)	63 (6.3)
Hypoalbuminaemia	28 (2.8)	36 (3.6)
Anaemia	113 (11.3)	129 (12.8)
Other†	107 (10.7)	119 (11.8)
Preoperative drugs:		
ACE inhibitor only	78 (7.8)	75 (7.4)
ARB only	492 (49.0)	514 (51.0)
ACE inhibitor+others	62 (6.2)	60 (6.0)
ARB+others	372 (37.1)	359 (35.6)
Diuretics	108 (10.8)	136 (13.5)
Nitrates	13 (1.3)	17 (1.7)
Statins	61 (6.1)	59 (5.9)
Anticoagulants	40 (4.0)	54 (5.4)
Antiplatelets	130 (13.0)	141 (14.0)
Other‡	178 (17.7)	164 (16.3)
Study centres:		
Centre 1	206 (20.5)	208 (20.6)
Centre 2	215 (21.4)	221 (21.9)
Centre 3	203 (20.2)	202 (20.0)
Centre 4	176 (17.5)	174 (17.3)
Centre 5	204 (20.3)	203 (20.1)
Type of anaesthesia:		
General only	874 (87.1)	890 (88.3)
General with nerve block	130 (12.9)	118 (11.7)
Anaesthetics and analgesics (median (IQR)):		
Propofol (mg)	100 (30-188)	100 (30-180)
Etomidate (mg)	16 (14-18)	17 (14-18)
Sufentanil (µg)	35 (25-50)	35 (25-45)
Remifentanil (mg)	0.1 (0.0-0.9)	0.1 (0.0-0.8)
Sevoflurane (%)	1.5 (0.0-2.0)	2.0 (0.0-2.0)
Dexmedetomidine (µg)	20 (0-35)	20 (0-30)
Continuous blood pressure monitoring	503 (50.1)	511 (50.7)
Median (IQR) duration of surgery (min)	100 (65-152)	101 (67-150)
Surgery type:		
Hepatobiliary	90 (9.0)	95 (9.4)
Gastrointestinal	163 (16.2)	172 (17.1)
Urinary	218 (21.7)	230 (22.8)

(Continued)

Table 1 | (Continued)

Characteristics	Antihypertensive group (n=1004)	No antihypertensive group (n=1008)
Gynaecological	35 (3.5)	40 (4.0)
Thyroid	27 (2.7)	33 (3.3)
Breast	95 (9.5)	75 (7.4)
Orthopaedic	79 (7.9)	69 (6.9)
Spinal	38 (3.8)	63 (6.3)
Other	259 (25.8)	231 (22.9)
Blood transfusion	38 (3.8)	42 (4.2)
Median (IQR) blood loss (mL)	45 (20-100)	50 (20-100)
Median (IQR) urine output (mL)	250 (100-400)	200 (100-400)

ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; ASA=American Society of Anesthesiologists; IQR=interquartile range; SD=standard deviation; TIA=transient ischaemic attack.
*Weekly consumption equivalent to 150 mL of alcohol.
†Includes heart failure, hypercholesterolaemia, hypothyroidism, hyperthyroidism, rheumatoid arthritis, atrophic gastritis, hepatitis B virus infection, Parkinson's disease, and insomnia.
‡Includes antiarrhythmic drugs, antidiabetics, thyroxine, chemotherapy drugs, escitalopram, omeprazole, antidepressants, antiviral drugs, and traditional Chinese medicine.

the primary outcome, a two sided P<0.05 indicates a significant difference. For the secondary outcomes, we conducted multiple comparison corrections using the Benjamini-Hochberg approach to control for false discovery rate, with an adjusted P<0.05 indicating a significant difference. Statistical analyses were conducted using the SAS version 9.4 and R version 3.6.

Patient and public involvement

No patients or members of the public were involved in the design, conduct, or reporting of this study, primarily due to the lack of funding for patient and public involvement activities and limited experience in public engagement. We discussed the study with patients to gain their perspectives. After submission, we asked a member of the public to read the manuscript

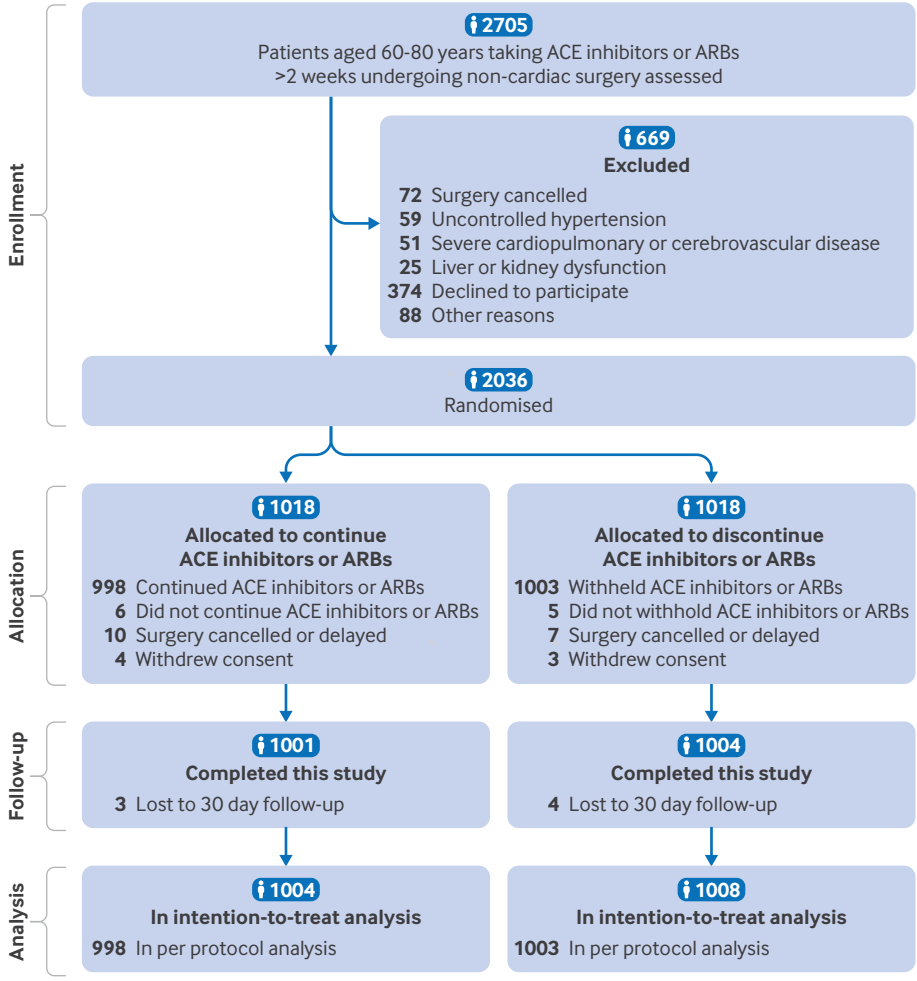


Fig 1 | Trial flow chart. ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker

to ensure that it was clear and comprehensible from a lay perspective.

Results

Recruitment and participant flow

Overall, 2705 patients were screened from November 2020 to December 2023 (fig 1). After excluding 669 patients, 2036 were randomised (1018 per group). Surgery was cancelled or delayed in 17 of those patients, and seven patients withdrew consent. The intention-to-treat analysis therefore included 2012 patients (1004 who continued an ACE inhibitor or ARB and 1008 who discontinued such treatment). After randomisation, 11 patients had protocol deviations: six in the antihypertensive group did not use an ACE inhibitor or ARB and five in the no antihypertensive group used an ACE inhibitor or ARB. Hence, the per protocol analysis included 998 patients in the antihypertensive group and 1003 patients in the no antihypertensive group. Overall, 2005/2012 (99.7%) patients were included in the complete case analysis; only seven were lost to 30 day follow-up, and no baseline or perioperative variables were missing.

Baseline and perioperative data

Baseline characteristics were well balanced between the two groups (table 1). Mean age was 68.7 years (54.8% men) in the antihypertensive group and 68.9 years (54.1% men) in the no antihypertensive group. The median duration of hypertension was 10 years in both groups. Most patients were categorised as having ASA physical status II and grade 1 hypertension. The median preoperative mean blood pressure was 102 mm Hg (IQR 94-111 mm Hg) in the antihypertensive group versus 103 (95-112) mm Hg in the no antihypertensive group. In total, 13.9% of participants in the antihypertensive group used ACE inhibitors with or without other drugs and 86.1% used ARBs. In the no antihypertensive group, 13.4% of participants used ACE inhibitors and 86.6% used ARBs. Supplementary table S2 lists the types of antihypertensives. The two groups were comparable for anaesthesia type and drugs, continuous blood pressure monitoring, surgical type and duration, blood transfusion, blood loss, and urine output (table 1).

Primary outcome

In the intention-to-treat analysis, perioperative hypotension occurred in 314/1008 (31.2%) patients in the no antihypertensive group versus 457/1004 (45.5%) in the antihypertensive group (odds ratio 0.54, (95% CI 0.45 to 0.65); absolute risk difference -14.4% (95% CI -18.5% to -10.1%); P<0.001) (table 2). Discontinuing ACE inhibitors or ARBs significantly reduced the odds of perioperative hypotension (0.52 (95% CI 0.43 to 0.63); P<0.001) in the multivariable analysis adjusted for baseline covariates and centre. Most hypotensive events were recorded during surgery. The per protocol analysis confirmed these findings.

Secondary outcomes

In the multivariable analysis, the no antihypertensive group had a shorter duration of hypotension during the perioperative period (mean difference -1.3 minutes (95% CI -1.9 to -0.8); false discovery rate adjusted P<0.001) and lower vasopressor requirement (adjusted odds ratio 0.54 (95% CI 0.44 to 0.66); false discovery rate adjusted P<0.001) (table 3). Supplementary table S3 lists the type and doses of vasopressors used. There

Table 2 | Primary outcome (perioperative hypotension) in older adults (60-80 years) according to ACE inhibitor or ARB treatment on morning of non-cardiac surgery. Values are number (percentage) unless stated otherwise

	Antihypertensive group*	No antihypertensive group†	Estimate (95% CI)	P value	Absolute risk difference (%)	P value	Adjusted estimate (95% CI)‡	P value
Perioperative hypotension: intention-to-treat analysis:								
Overall	457 (45.5)	314 (31.2)	OR 0.54 (0.45 to 0.65); RR 0.68 (0.61 to 0.77)	<0.001	-14.37 (-18.54 to -10.14)	<0.001	OR 0.52 (0.43 to 0.63); RR 0.69 (0.62 to 0.77)	<0.001
In surgery	448 (44.6)	307 (30.5)	OR 0.54 (0.45 to 0.65); RR 0.68 (0.61 to 0.77)	<0.001	-14.17 (-18.33 to -9.97)	<0.001	OR 0.52 (0.43 to 0.63); RR 0.69 (0.61 to 0.77)	<0.001
In recovery	46 (4.6)	25 (2.5)	OR 0.53 (0.32 to 0.86); RR 0.54 (0.34 to 0.87)	0.01	-2.10 (-3.79 to -0.50)	0.01	OR 0.53 (0.31 to 0.88); RR 0.56 (0.35 to 0.89)	0.02
Perioperative hypotension: per protocol analysis:								
Overall	455 (45.6)	313 (31.2)	OR 0.54 (0.45 to 0.65); RR 0.68 (0.61 to 0.77)	<0.001	-14.38 (-18.57 to -10.15)	<0.001	OR 0.52 (0.43 to 0.63); RR 0.68 (0.62 to 0.77)	<0.001
In surgery	446 (44.7)	306 (30.5)	OR 0.54 (0.45 to 0.65); RR 0.68 (0.61 to 0.77)	<0.001	-14.18 (-18.35 to -9.96)	<0.001	OR 0.52 (0.43 to 0.63); RR 0.69 (0.61 to 0.77)	<0.001
In recovery	46 (4.6)	25 (2.5)	OR 0.53 (0.32 to 0.86); RR 0.54 (0.33 to 0.87)	0.01	-2.12 (-3.82 to -0.51)	0.01	OR 0.53 (0.31 to 0.88); RR 0.56 (0.35 to 0.89)	0.02

ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; CI=confidence interval; OR=odds ratio; RR=risk ratio.
*1004 participants in intention-to-treat analysis and 998 in per protocol analysis.
†1008 participants in intention-to-treat analysis and 1003 in per protocol analysis.
‡Adjusted for age, body mass index, American Society of Anaesthesiologists classification, grade of hypertension, preoperative comorbidities (myocardial infarction, atrial fibrillation, diabetes, and anaemia), preoperative use of diuretics, and study centre.

Table 3 | Secondary outcomes in older adults (60-80 years) according to ACE inhibitor or ARB treatment on morning of non-cardiac surgery. Values are number (percentage) unless stated otherwise

Outcomes	Antihypertensive group	No antihypertensive group	Estimate (95% CI)	P value	FDR adjusted P value	Adjusted estimate (95% CI)*	P value	FDR adjusted P value
Mean (SD) duration of perioperative hypotension (min)	4.5 (6.2)	3.2 (5.8)	MD -1.3 (-1.9 to -0.8)	<0.001	<0.001	MD -1.3 (-1.8 to -0.8)	<0.001	<0.001
Vasopressor requirement	413 (41.1)	287 (28.5)	OR 0.57 (0.47 to 0.69)	<0.001	<0.001	OR 0.54 (0.44 to 0.66)	<0.001	<0.001
Median (IQR) intraoperative fluid (mL)	1000 (1000-1500)	1000 (963-1500)	MD -20 (-72 to 32)	0.46	0.64	MD -19 (-70 to 32)	0.47	0.66
Postoperative hypotension ≤3 days	9 (0.9)	5 (0.5)	OR 0.55 (0.17 to 1.60) OR 0.57; (0.19 to 1.61)†	0.29; 0.29†	0.50	OR 0.63 (0.19 to 1.86); OR 0.68 (0.22 to 1.89)†	0.42; 0.46†	0.66
30 day complications:	n=1001	n=1004						
PND	15 (1.5)	24 (2.4)	OR 1.61 (0.85 to 3.15); OR 1.59 (0.84 to 3.08)†	0.15; 0.15†	0.36	OR 1.57 (0.80 to 3.14); OR 1.53 (0.80 to 3.01)†	0.19; 0.20†	0.45
MACE	18 (1.8)	17 (1.7)	OR 0.94 (0.48 to 1.84); OR 0.94 (0.48 to 1.83)†	0.86; 0.86†	0.86	OR 0.86 (0.43 to 1.72); OR 0.86 (0.43 to 1.70)†	0.67; 0.66†	0.69
Mortality	2 (0.2)	3 (0.3)	OR 1.50 (0.25 to 11.37); OR 1.40 (0.27 to 8.39)†	0.66; 0.69†	0.77	OR 1.47 (0.22 to 11.97); OR 1.24 (0.24 to 7.26)†	0.69; 0.79†	0.69

ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; CI=confidence interval; FDR=false discovery rate; IQR=interquartile range; MACE=major adverse cardiocerebral events (myocardial infarction, heart block, cardiac arrest, stroke, and coma); MD=mean difference; OR=odds ratio; PND=perioperative neurocognitive disorders; SD=standard deviation.
*Adjusted for age, body mass index, American Society of Anesthesiologists classification, grade of hypertension, preoperative comorbidities (myocardial infarction, atrial fibrillation, diabetes, and anaemia), preoperative use of diuretics, and study centre.
†Firth's correction for the logistic regression analysis.

were no significant between group differences in intraoperative fluid volume, incidence of hypotension within three postoperative days, and 30 day complications (perioperative neurocognitive disorder and MACE) or mortality; the Firth's correction for the logistic regression analysis produced similar results.

Exploratory and post hoc outcomes

The incidence of hypertension during surgery and recovery was comparable between the two groups (table 4). Within the first three postoperative days, the incidence of hypertension was higher in the no antihypertensive group (15.2% *v* 7.9%; odds ratio 2.10 (95% CI 1.58 to

Table 4 | Exploratory and post hoc outcomes in older adults (60-80 years) according to ACE inhibitor or ARB treatment on morning of non-cardiac surgery. Values are number (percentage) unless stated otherwise

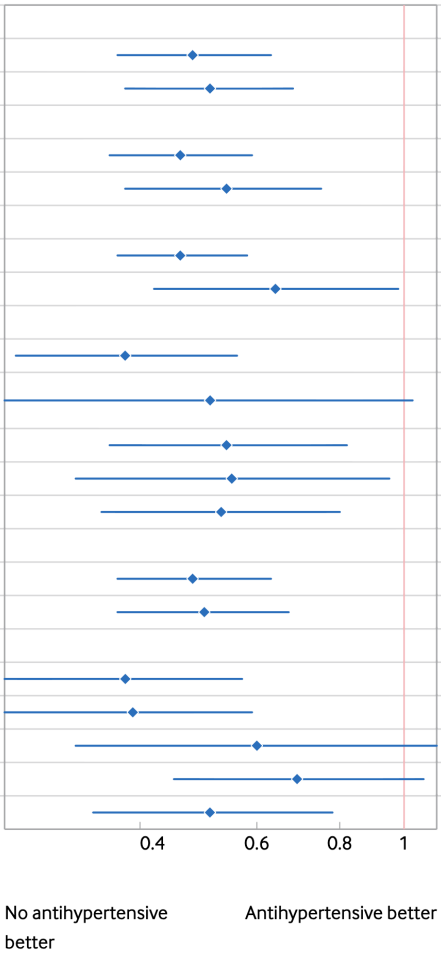
Outcomes	Antihypertensive group (n=1004)	No antihypertensive group (n=1008)	Estimate (95% CI)
Exploratory outcomes			
Hypertension:			
During surgery	110 (11.0)	127 (12.6)	OR 1.17 (0.89 to 1.54)
In recovery	76 (7.6)	89 (8.8)	OR 1.18 (0.86 to 1.63)
≤3 postoperative days	79 (7.9)	153 (15.2)	OR 2.10 (1.58 to 2.80)
Arrhythmias requiring treatment:			
Tachycardia	16 (1.6)	12 (1.2)	OR 0.74 (0.34 to 1.57)
Bradycardia	23 (2.3)	28 (2.8)	OR 1.22 (0.70 to 2.15)
Intraoperative adverse events*	207 (20.6)	224 (22.2)	OR 1.10 (0.89 to 1.36)
Median (IQR) scores at recovery discharge:			
Ramsay sedation scale	2 (2-2); n=986	2 (2-2); n=985	MD 0.0 (-0.0 to 0.0)
NRS for pain	1 (1-2); n=986	1 (1-3); n=985	MD 0.0 (-0.0 to 0.0)
PONV ≤3 postoperative days	243 (24.2)	260 (25.8)	OR 1.09 (0.89 to 1.33)
Median (IQR) time to extubation (min)	16 (11-22)	16 (12-22)	MD 0.0 (-0.0 to 0.0)
ICU admission	18 (1.8)	23 (2.3)	OR 1.28 (0.69 to 2.42)
Median (IQR) length of hospital stay (days)	8.0 (5.0-12.0)	8.0 (5.0-11.3)	MD -0.0 (-0.0 to 0.0)
Post hoc outcomes			
Median (IQR) lowest intraoperative MBP (mm Hg)	76 (66-85)	78 (69-87)	MD 1.8 (1.1 to 2.5)†
Median (IQR) maximum MBP decrease (mm Hg)	28 (18-36)	25.5 (17-34)	MD -2.0 (-3.0 to -1.0)
Perioperative hypotension:			
≥5 min	378 (37.7)	260 (25.8)	OR 0.58 (0.48 to 0.70)
≥10 min	256 (25.5)	178 (17.7)	OR 0.63 (0.51 to 0.78)
≥15 min	95 (9.5)	67 (6.7)	OR 0.68 (0.49 to 0.94)
30 day acute kidney injury	87 (8.7); n=1001	88 (8.8); n=1004	OR 1.00 (0.74 to 1.38)

ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; CI=confidence interval; ICU=intensive care unit; IQR=interquartile range; MBP=mean blood pressure; MD=mean difference; NRS=numerical rating scale; OR=odds ratio; PONV=postoperative nausea and vomiting; SD=standard deviation.
*Allergic reaction, hypoxia, new onset arrhythmia, hyperthermia, hypothermia, oliguria, electrolyte and acid base disorders, major bleeding, and cardiac arrest.
†Multivariable linear regression, adjusting for baseline mean blood pressure.

Perioperative hypotensive events

Incidence of perioperative hypotensive events in participants discontinuing or continuing antihypertensive (ACE inhibitor or ARB) on morning of surgery by prespecified subgroup

Subgroups	Antihypertensive group (No/Total No (%))	No antihypertensive group (No/Total No (%))	Adjusted odds ratio (95% CI)	P value	P for interaction
Age (years)					0.93
60-70	247/572 (43.2)	169/568 (29.8)	0.48 (0.37 to 0.63)*	<0.001	
71-80	210/432 (48.6)	145/440 (33.0)	0.51 (0.38 to 0.68)*	<0.001	
Hypertension grade					0.39
1	310/678 (45.7)	189/621 (30.4)	0.46 (0.36 to 0.59)*	<0.001	
2	147/326 (45.1)	125/387 (32.3)	0.54 (0.38 to 0.75)*	<0.001	
Diabetes					0.18
NO	359/803 (44.7)	236/805 (29.3)	0.46 (0.37 to 0.58)*	<0.001	
YES	98/201 (48.8)	78/203 (38.4)	0.64 (0.42 to 0.98)*	0.04	
Type of surgery					0.21
Abdominal	121/253 (47.8)	74/267 (27.7)	0.38 (0.26 to 0.56)*	<0.001	
Thyroid or breast	37/122 (30.3)	20/108 (18.5)	0.51 (0.25 to 1.03)†	0.06	
Urological	103/218 (47.2)	79/230 (34.3)	0.54 (0.36 to 0.82)*	0.004	
Orthopaedic	68/116 (58.6)	55/132 (41.7)	0.55 (0.32 to 0.95)*	0.03	
Others	128/295 (43.4)	86/271 (31.7)	0.53 (0.35 to 0.80)*	0.002	
Duration of surgery (min)					0.97
<120	239/587 (40.7)	166/589 (28.2)	0.48 (0.37 to 0.63)*	<0.001	
≥120	218/417 (52.3)	148/419 (35.3)	0.50 (0.37 to 0.67)*	<0.001	
Study centres					0.11
Centre 1	109/206 (52.9)	64/208 (30.8)	0.38 (0.25 to 0.57)*	<0.001	
Centre 2	88/215 (40.9)	50/221 (22.6)	0.39 (0.25 to 0.59)*	<0.001	
Centre 3	30/203 (14.8)	19/202 (9.4)	0.60 (0.32 to 1.12)‡	0.11	
Centre 4	92/176 (52.3)	77/174 (44.3)	0.69 (0.45 to 1.07)*	0.10	
Centre 5	138/204 (67.6)	104/203 (51.2)	0.51 (0.34 to 0.78)*	0.002	



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ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; ASA=American Society of Anesthesiologists; CI=confidence interval.

*Adjusted for age, body mass index, ASA classification, grade of hypertension, preoperative comorbidities (myocardial infarction, atrial fibrillation, diabetes, and anaemia), preoperative use of diuretics, and study centre.

†Adjusted for age, body mass index, ASA classification, grade of hypertension, preoperative comorbidities (atrial fibrillation, diabetes, and anaemia), preoperative use of diuretics, and study centre.

‡Adjusted for age, body mass index, grade of hypertension, preoperative comorbidities (atrial fibrillation and diabetes), and study centre.

Fig 2 | Incidence of perioperative hypotensive events in the prespecified subgroups. An interactive version of this graphic is available at https://public.flourish.studio/visualisation/30580937/

2.80)). These episodes were brief; 98% were managed with oral or enteral nifedipine or captopril, and only four patients who required ICU admission received intravenous nicardipine. All other exploratory outcomes did not differ between the two groups (table 4).

In the post hoc analyses, the median lowest intraoperative mean blood pressure was 76 (IQR 66-85) mm Hg in the antihypertensive group versus 78 (69-87) mm Hg in the no antihypertensive group (adjusted mean difference 1.8 (95% CI 1.1 to 2.5) mm

Hg; supplementary figure S2a). The median maximum decrease in mean blood pressure from baseline was 28 (IQR 18-36) mm Hg in the antihypertensive group versus 25.5 (17-34) mm Hg in the no antihypertensive group (median difference -2.0 (95% CI -3.0 to -1.0) mm Hg; supplementary figure S2b). Lower proportions of patients in the no antihypertensive group experienced hypotensive episodes lasting ≥5 minutes (25.8% *v* 37.7%; odds ratio 0.58 (95% CI 0.48 to 0.70)), ≥10 minutes (17.7% *v* 25.5%; 0.63 (95% CI 0.51 to 0.78)), and ≥15 minutes (6.7% *v* 9.5%; 0.68 (95% CI 0.49 to 0.94) (table 4)). Thirty day acute kidney injury rates were similar between the two groups.

Subgroup analysis

No statistically significant subgroup interactions were observed for age, hypertension grade, history of diabetes, type of surgery, duration of surgery, and study centres (fig 2). Within the subgroups, discontinuing antihypertensives was associated with a statistically significant decrease in hypotension during the perioperative period in all strata except thyroid or breast surgery and centres 3 and 4. In multivariable analysis, longer surgery duration was independently associated with overall higher risk of hypotension (main effect P<0.001, supplementary figure S3), whereas age showed no independent association (main effect P=0.10, supplementary figure S4). Neither age nor duration modified the treatment effect as there was no statistically significant linear or non-linear interaction between continuous age and group (P for interaction 0.98 and 0.09, respectively), or between continuous duration and group (P for interaction 0.49 and 0.95, respectively).

Discussion

This multicentre, randomised, double blind, placebo controlled trial compared the discontinuation of antihypertensive treatment (ACE inhibitors or ARBs) on the morning of surgery compared with continuing treatment in older patients aged 60-80 years with hypertension undergoing non-cardiac surgery. In the intention-to-treat analysis, the incidence of perioperative hypotension was lower in the no antihypertensive group, which was consistent with the per protocol analysis. This treatment effect did not differ by subgroup. In addition, the duration of hypotension was shorter in the no antihypertensive group and the need for vasopressors was reduced, without affecting 30 day complications or mortality. Within three days postoperatively, the incidence of hypotension was low in both groups, while the incidence of hypertension was higher in the no antihypertensive group.

Older patients with hypertension are prone to hypotension in the perioperative period, a modifiable risk factor for organ injury. Previous studies indicated that sustaining mean blood pressure <65 mm Hg for ≥13 minutes was associated with increased postoperative complications and mortality.[3 24] Interventional trials showed that maintaining optimal blood pressure reduced organ dysfunction after major non-cardiac surgery.[25 26] In our study, discontinuing antihypertensive treatment on the morning of surgery reduced the overall incidence of perioperative hypotension compared with continuing treatment (31.2% *v* 45.5%). Intraoperative blood loss and fluid loading volume were similar between the two groups, indicating that the excess hypotension was due to preoperative drugs and not to surgical bleeding or anaesthetic effects. Although we found no between group differences in 30 day perioperative neurocognitive disorder, MACE, acute kidney injury, or mortality, the reductions in prolonged hypotensive episodes lasting ≥10 minutes (17.7% *v* 25.5%) and ≥15 minutes (6.7% *v* 9.5%) provide a clinically plausible benefit, particularly for patients at high risk of organ injury.

The lowest intraoperative mean blood pressure was 1.8 mm Hg higher in the no antihypertensive group. This difference appears small at the individual level, but to put this finding into context three factors need to be considered. Firstly, the binary outcome was prespecified and clinically meaningful. It captures hypotension of clinical consequence that requires an intervention that is anaesthetist initiated, rather than a numerical difference in mm Hg. The 65 mm Hg threshold is supported by the class 1 recommendation in the 2024 American Heart Association and American College of Cardiology perioperative guideline,[27] marks the point where the risk of organ injury increases steeply,[3 28] and is widely used in contemporary trials.[29-34] Secondly, the lowest mean blood pressure is a post-treatment variable. Every hypotensive episode triggered protocolised rescue, so the observed difference reflects blood pressure after rescue treatment had been applied. By contrast, the binary outcome captures the critical moment when the anaesthetist administered intravenous fluid or vasopressors to treat hypotension. Thirdly, the continuous and binary findings are consistent. The no antihypertensive group had the higher lowest mean blood pressure values and smaller maximum decreases from baseline, aligning with the binary outcome and further supported by fewer patients experiencing prolonged hypotensive episodes (≥5, ≥10, and ≥15 minutes). Together, these considerations explain how a small population mean shift translates into a 14.4% absolute risk reduction in hypotension requiring intervention.

Comparison with previous work

Current evidence to determine whether ACE inhibitors or ARBs should be discontinued or continued before surgery has been inconsistent, especially in older patients aged 60-80 years. An observational study linked 24 hour omission to fewer intraoperative hypotensive episodes and lower composite rates of stroke, myocardial infarction, or death.[13] An early randomised trial also reported a lower incidence of hypotension after major non-cardiac surgery when ACE inhibitors or ARBs were withheld.[14] The findings of two recent multicentre trials in major non-cardiac surgery were, however, contradictory. One included

high risk patients and showed that discontinuation of ACE inhibitors or ARBs for two or three days before surgery did not affect myocardial injury (48.3% *v* 41.3%) or requirement for a vasopressor (9.3% *v* 8.4%) but increased postoperative hypertension (12.9% *v* 5.4%).[17] Another trial found that discontinuing ACE inhibitors or ARBs for 48 hours before surgery reduced intraoperative hypotension (41% *v* 54%) with identical major complications or mortality at four weeks (22% in both groups) and no excess severe hypertension (<1%).[18]

Recent meta-analyses of randomised trials also showed inconsistency. One meta-analysis pooled data from nine clinical trials and found that discontinuation of ACE inhibitors or ARBs was associated with a lower rate of intraoperative hypotension without affecting mortality, major complications, or postoperative hypertension.[35] Two further meta-analyses (seven and 14 trials, respectively) showed that discontinuation of ACE inhibitors or ARBs had no impact on major complications or mortality, but the incidence of intraoperative hypotension decreased and the risk of postoperative hypertension increased.[36 37] The certainty of evidence remains low because previous trials were open label and used heterogeneous washout periods. Our randomised double blind trial showed that discontinuation of ACE inhibitors or ARBs on the morning of surgery improved intraoperative blood pressure control, reduced prolonged hypotensive events, and reduced the requirement for a vasopressor.

Strengths and clinical implications of this study

Compared with previous studies, our trial has several specific strengths. Firstly, we enrolled adults aged ≥60 years who had used ACE inhibitors or ARBs for a median of 10 years; a group at high risk of perioperative hypotension. Secondly, 86.3% of patients were using ARBs (alone or in combination with other drugs), reflecting contemporary prescribing and contrasting with about 50% of patients using ACE inhibitors in previous studies.[17 18] Thirdly, identical placebos were used to mask patients and anaesthetists, eliminating potential bias that may have affected earlier open label trials. Finally, ACE inhibitors and ARBs were withheld only on the morning of surgery, a shorter discontinuation window than the 48-72 hours used in two large multicentre trials.[17 18] The 24 hour omission period offered a clinically useful balance between the risks of perioperative hypotension and rebound hypertension and aligns with the 2024 American Heart Association and American College of Cardiology recommendation in high risk non-cardiac surgery.[27]

This same day omission strategy produced an absolute reduction of 14% in perioperative hypotension and reduced prolonged episodes (≥5, ≥10, and ≥15 minutes). Postoperative hypertension increased by 7%, but these transient rises were easily managed and did not prolong hospital stay or increase complications. Consequently, discontinuing ACE inhibitors or ARBs before non-cardiac surgery should be considered whenever intraoperative hypotension is a concern, supporting the simple patient instruction to stop the morning dose on the day of surgery. Our findings provide high certainty evidence and will inform future international guidelines on perioperative management of these agents in older adults.

Limitations of this study

This trial has several limitations. Firstly, we included older patients with hypertension (>80% ASA classification II) undergoing predominantly short-to-moderate non-cardiac surgery (median 100 minutes) with few major comorbidities. These features may explain the low observed rate of perioperative hypotension and indicate that dedicated trials in higher risk patients or prolonged procedures are warranted. Secondly, the trial was designed without patient and public involvement; consequently, the primary endpoint focused on a haemodynamic measure rather than patient centred outcomes such as major complications and quality of life. Thirdly, follow-up was only up to 30 days after surgery, and therefore future studies with longer follow-up and effective monitoring of biomarkers are needed to assess long term organ function. Fourthly, the median hospital stay of eight days in our patients was consistent with previous Chinese cohorts but longer than that in the US or Europe, but this was largely due to differences in healthcare systems.[18 38 39] Finally, this trial was conducted at five Chinese centres. Although diet and lifestyle vary globally, the pathophysiology of hypertension and the pharmacodynamics of ACE inhibitors or ARBs are comparable across populations,[40 41] supporting the generalisability of our findings. Multinational validation is still needed.

Conclusions

In this multicentre, randomised, double blind trial, discontinuing ACE inhibitors or ARBs on the morning of surgery statistically significantly reduced perioperative hypotension and vasopressor requirement compared with continuing treatment, and with no increase in 30 day complications or mortality in older patients with hypertension. This simple strategy provides high certainty evidence supporting omission of the morning dose in this population.

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Contributors: FJ conceived the study and was involved in the study design, interpretation of findings, and critical revision of the manuscript; FJ is the guarantor and takes responsibility for the overall content of the manuscript. CM and DMA were involved in the study design, interpretation of findings, and critical revision of the manuscript. YYang conducted the study and the analyses, was involved in writing and revising the manuscript, had full access to all data, and takes responsibility for the integrity of the data. KP conducted the analyses, was involved in interpretation of the findings and revision of the manuscript and had full access to all data. JZhong coordinated and supervised the study and was involved in reviewing and editing the manuscript. JZhang, XL, and JYang coordinated and supervised the study and were involved in reviewing and editing the manuscript. LL, JG, PS, CC, YYu, JYuan, and YZ conducted the study and were involved in reviewing and editing the manuscript. HL critically revised the manuscript. All authors contributed to interpretation of the findings, reviewed and edited the manuscript, and approved the final version. During the revision of this manuscript, the authors used OpenAI's ChatGPT-5.2 (2025) and Kimi K2.5 (2026) to improve language and readability of the manuscript. The authors reviewed and edited the content as needed and take full responsibility for the content of the publication. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: This study was approved by the medical ethics committees of First Affiliated Hospital of Soochow University (2020-077-1), Fudan University Zhongshan Hospital (B2020-281), Fudan University Shanghai Cancer Centre (2102231-8), First Affiliated Hospital of Anhui Medical University (2021-07-60), and First Affiliated Hospital of Zhengzhou University (2020-KY-0325-003). The trial was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki.

Data sharing: The supplementary file includes the code used to analyse the data in the paper. The data underlying the findings in this paper are openly and publicly available and can be found in Mendeley Data (doi:10.17632/rcwrg97ns9.1). If you encounter problems accessing the data, please contact the corresponding author FJ.

Transparency: The corresponding author (FJ) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Dissemination to participants and related patient and public communities: The findings will be shared broadly through social media platforms to reach both academic and non-academic audiences. The results will be presented at national and international conferences to inform the wider medical community. We believe that the publication of this research will contribute valuable evidence that may support the development of clinical guidelines and inform relevant policy decisions. The findings will be shared and explained to relevant patient groups, ensuring that they can benefit from the insights of this research.

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Supplementary information: Additional material, including code used to analyse data in the study