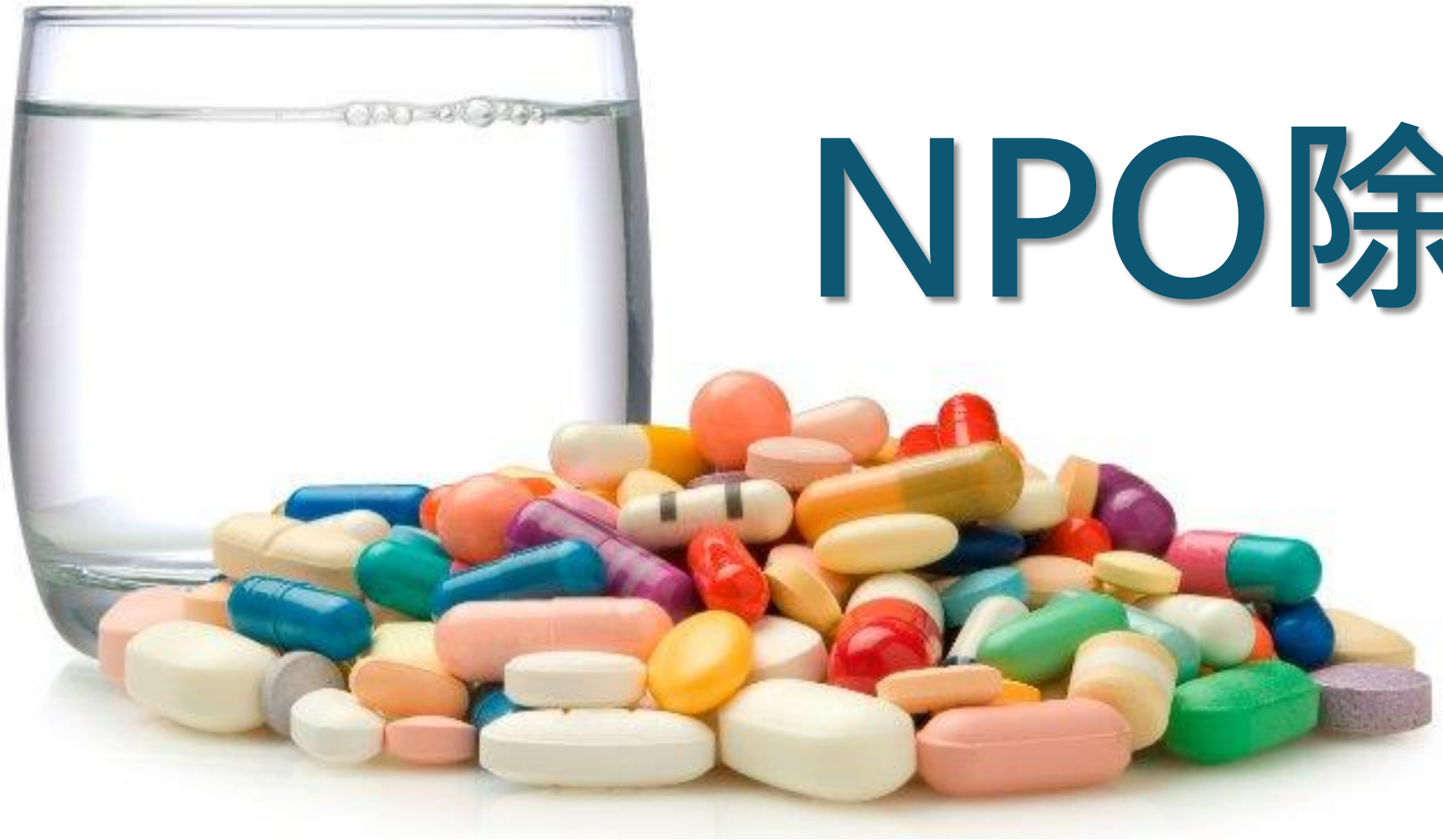
使用 ACEI / ARB 控制血壓的病人，術前準備需要停藥嗎？

PRESENTER: 萬芳醫院麻醉科R2符若萱

SUPERVISOR: DR.黃俊仁



NPO除藥

藥　理　別	代　表　藥　物
ARB 血管張力素受體抑制劑	Diovan®（Valsartan）、Olmetec®（Olmesartan）、Aprovel®（Irbesartan）、Cozzar®（Losartan）、
ACEI 血管張力素轉化酶抑制劑	Zestril®（Lisinopril）、Capoten®（Captopril）、Renitec®（Enalapril）、Monopril®（Fosinopril）
β blocker β 交感神經阻斷劑 α blocker α 交感神經阻斷劑	B blocker:Inderal®（Propranolol）、Tenormin®（Atenolol）、Concor®（Bisoprolol） α blocker:Minipress®（Prazosin）、Doxaben®（Doxazosin）
CCB 鈣離子通道阻斷劑	Norvasc®（Amlodipine）、Plendil®（Felodipine）、Adalat®（Nifedipine）
Diuretic 利尿劑	Natrilix®（Indapamide）、Lasix®（Furosemide） HCT®（Hydro-chlorothiazide）


Inderal?
Norvasc?
NPO除藥
Lasix?
Diovan?

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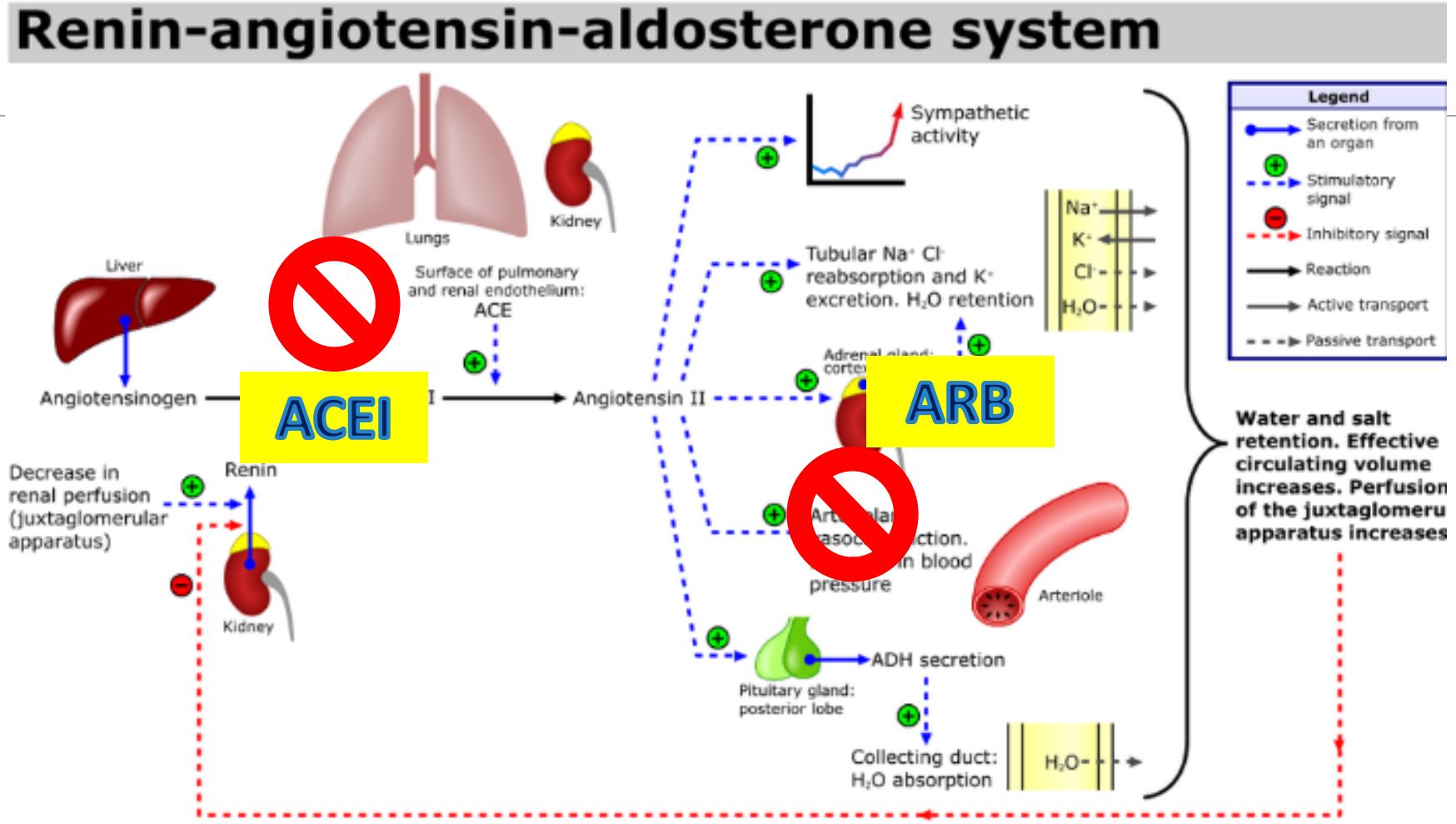
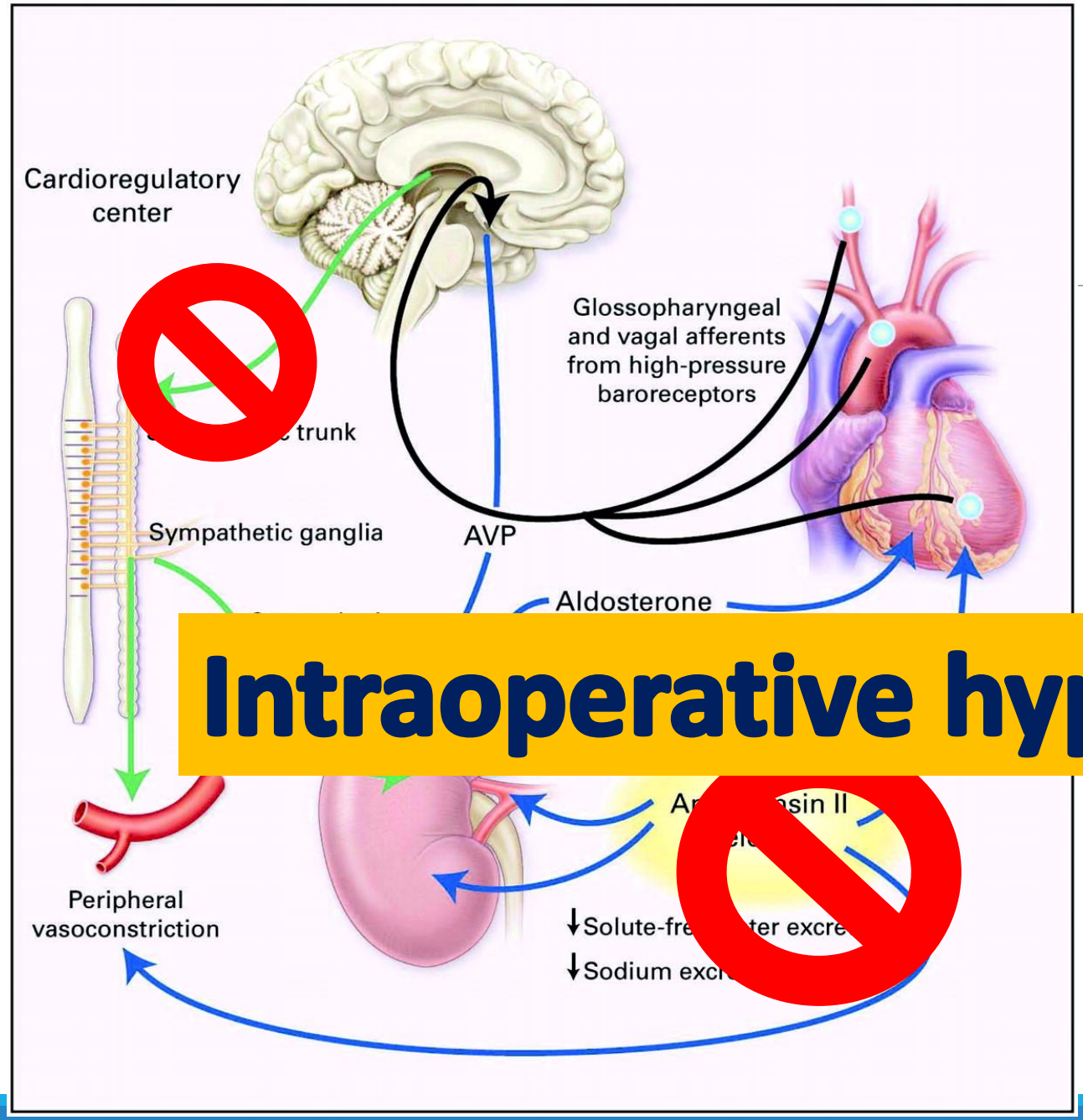
Diuretic 利尿劑	Natrilix®（Indapamide）、Lasix®（Furosemide）HCT®（Hydro-chlorothiazide）

Mechanism of Angiotensin Converting Enzyme Inhibitos (ACEI) and Angiotensin II Receptor Blocker (ARB)



Wikipedia



Intraoperative hypotension

Vasoconstriction:

1. Sympathetic activation
2. Angiotensin II (RAAS)
3. Vasopressin

N Engl J Med 341: 577–585, 1999

Intraoperative Hypotension

Relationship between Intraoperative Mean Arterial Pressure and Clinical Outcomes after Noncardiac Surgery: Toward an Empirical Definition of Hypotension - *Anesthesiology.* 2013 Sep;119(3):507-15.

- Intraoperative MAP less than 55 mmHg are associated with AKI and myocardial injury. MAP from less than 55 to 75 mmHg.

Association between Intraoperative Hypotension and Hypertension and 30-day Postoperative Mortality in Noncardiac Surgery. - *Anesthesiology.* 2015 Aug;123(2):307-19.

- Intraoperative hypotension, but not hypertension, is associated with increased 30-day operative mortality.

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Diuretic 利尿劑	Natrilix®（Indapamide）、Lasix®（Furosemide）HCT®（Hydro-chlorothiazide）

停藥/不停藥？

參考文獻

1. **ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery** - *J Nucl Cardiol*. 2015 Feb;22(1):162-215
2. **Perioperative angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers for preventing mortality and morbidity in adults (Review)** - *Cochrane Database Syst Rev*. 2016 Jan 27;(1)
3. **Withholding versus Continuing Angiotensin-converting Enzyme Inhibitors or Angiotensin II Receptor Blockers before Noncardiac Surgery** - *Anesthesiology.* 2017 Jan;126(1):16-27.

ACC/AHA Clinical Practice Guideline

2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

Developed in Collaboration With the American College of Surgeons, American Society of Anesthesiologists, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society of Vascular Medicine

J Nucl Cardiol. 2015 Feb;22(1):162-215

Table 6. Summary of Recommendations for Perioperative Therapy

Recommendations	COR	LOE	References
Coronary revascularization before noncardiac surgery			
Revascularization before noncardiac surgery is recommended when indicated by existing CPGs	I	C	25, 26
Coronary revascularization is not recommended before noncardiac surgery exclusively to reduce perioperative cardiac events	III: No Benefit	B	116
Timing of elective noncardiac surgery in patients with previous PCI			
Noncardiac surgery should be delayed after PCI	I	C: 14 d after balloon angioplasty	N/A
		B: 30 d after BMS implantation	231–233
Noncardiac surgery should optimally be delayed 365 d after DES implantation	I	B	234–237
A consensus decision as to the relative risks of discontinuation or continuation of antiplatelet therapy can be useful	IIa	C	N/A
Elective noncardiac surgery after DES implantation may be considered after 180 d	IIb*	B	234, 238
Elective noncardiac surgery should not be performed in patients in whom DAPT will need to be discontinued perioperatively within 30 d after BMS implantation or within 12 mo after DES implantation	III: Harm	B	231–237, 239
Elective noncardiac surgery should not be performed within 14 d of balloon angioplasty in patients in whom aspirin will need to be discontinued perioperatively	III: Harm	C	N/A

J Nucl Cardiol. 2015 Feb;22(1):162-215

Recommendations for Perioperative ACEI/ARB

Class IIa

1. Continuation of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) perioperatively is reasonable. [300-301](Level of Evidence: B)

2. If ACE inhibitors or ARBs are held before surgery, it is reasonable to restart as soon as clinically feasible postoperatively. (Level of Evidence: C)

J Nucl Cardiol. 2015 Feb;22(1):162-215

Angiotensin Converting Enzyme Inhibitors Are Not Associated with Respiratory Complications or Mortality After Noncardiac Surgery

Alparslan Turan, MD,* Jing You, MS,*† Ayako Shiba, MD,* Andrea Kurz, MD,* Leif Saager, MD,* and Daniel I. Sessler, MD*

Anesth Analg. 2012 Mar;114(3):552-60

Cleveland Clinic, Ohio. 2005 and 2009.

Retrospective cohort

79,228 patients → **9028 ACEI v.s. 9028 controls**

Non cardiac surgery under general anesthesia

Intraoperative ACE inhibitor users had more frequent transient intraoperative hypotension but no difference in other outcomes (30-day moratlity, in-hospital morbidity)

Anesth Analg. 2012 Mar;114(3):552-60

Angiotensin Converting Enzyme Inhibitors Are Not Associated with Respiratory Complications or Mortality After Noncardiac Surgery

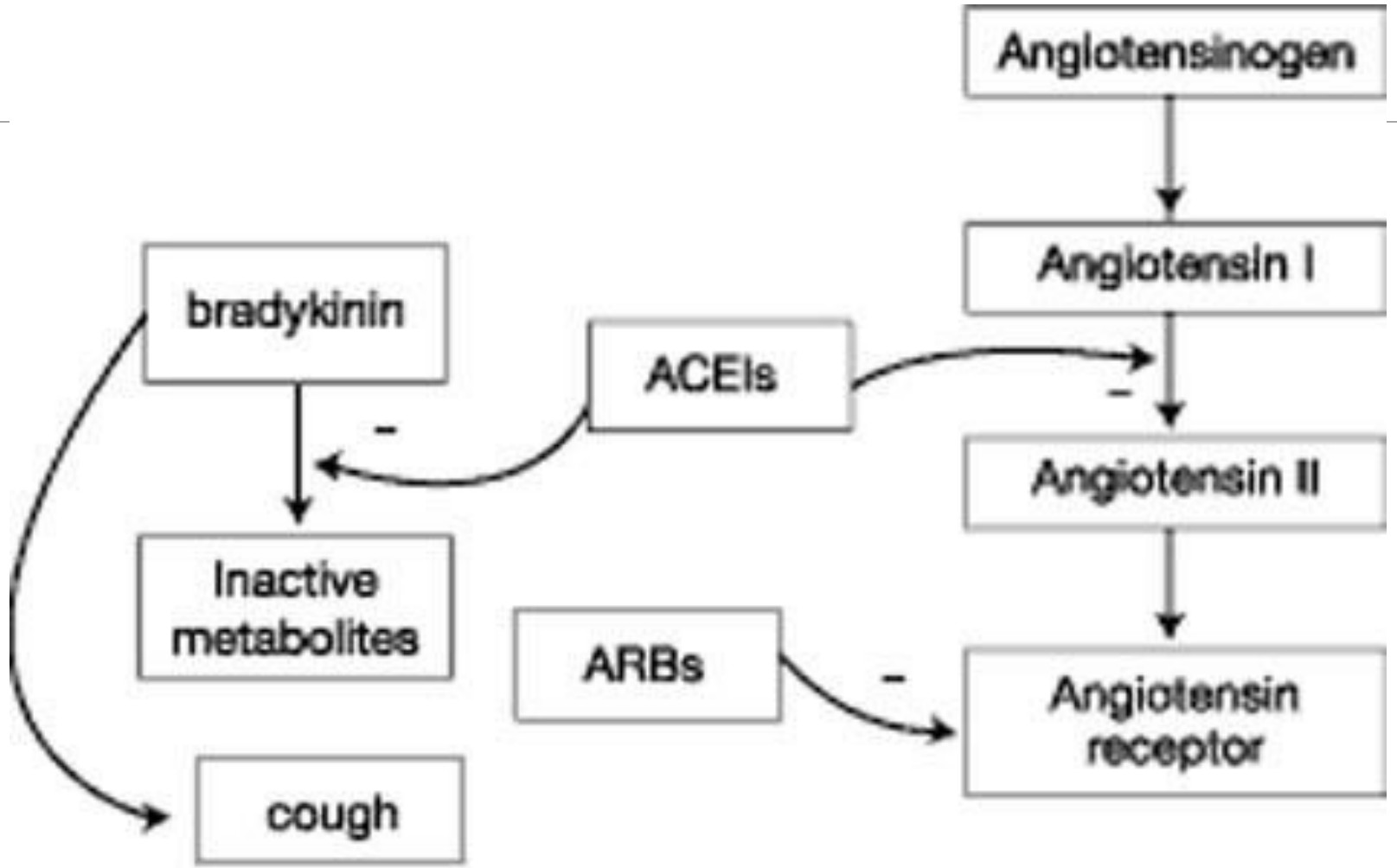
Alparslan Turan, MD,* Jing You, MS,*† Ayako Shiba, MD,* Andrea Kurz, MD,* Leif Saager, MD,* and Daniel I. Sessler, MD*

Group 1: patients taking ACEI chronically

Group 2: controls

Primary outcome: Respiratory complications

ACEI Induced Cough



K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease

Angiotensin Converting Enzyme Inhibitors Are Not Associated with Respiratory Complications or Mortality After Noncardiac Surgery

Alparslan Turan, MD,* Jing You, MS,*† Ayako Shiba, MD,* Andrea Kurz, MD,* Leif Saager, MD,* and Daniel I. Sessler, MD*

Group 1: patients taking ACEI chronically ←Withheld?

Group 2: controls

盲點1: ARBs in both groups

盲點2: ACEI routine: continue until the day before surgery, but not to take them the morning of surgery

Clinical consequences of withholding versus administering renin-angiotensin-aldosterone system antagonists in the preoperative period

Mayo Clinic College of Medicine, USA.

Meta-analysis

Non-emergency surgery

Using ACEI or ARB chronically

Withdrawing v.s. continuing angiotensin-converting enzyme inhibitors/ARB **up to the morning of surgery**

J Hosp Med. 2008 Jul;3(4):319-25.

Clinical consequences of withholding versus administering renin-angiotensin-aldosterone system antagonists in the preoperative period

Three RCTs (n=128 patients), 2 observational studies (n=306 patients)

ACEI/ARBs: more likely to develop hypotension requiring vasopressors at, or shortly after, induction of anaesthesia (RR 1.51, 95% CI 1.14 to 2.01; I^2=59%; five studies)

No change in important cardiovascular outcomes (ie, death, MI, stroke, kidney failure).

J Hosp Med. 2008 Jul;3(4):319-25.

Recommendations for Perioperative ACEI/ARB

Class IIa

1. Continuation of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) perioperatively is reasonable[200-301](Level of Evidence: B)

2. If ACE inhibitors or ARBs are held before surgery, it is reasonable to restart as soon as clinically feasible postoperatively. (Level of Evidence: C)

J Nucl Cardiol. 2015 Feb;22(1):162-215

Cochrane Database of Systematic Reviews

Perioperative angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers for preventing mortality and morbidity in adults

Review | Intervention

Zui Zou, Hong B Yuan, Bo Yang, Fengying Xu, Xiao Y Chen, Guan J Liu, Xue Y Shi

First published: 27 January 2016

Systematic review of Randomized controlled trials (RCTs)

Perioperative administration of ACEIs or ARBs v.s. placebo

Any type of surgery under general anaesthesia

Cochrane Database Syst Rev. 2016 Jan 27;(1)

Background

Cardiopulmonary bypass:

- RAS activation → disturbs balance of pro- and anti-inflammatory cytokines → modifies regional blood flow → morbidity
- Decreased effective renal plasma flow and glomerular filtration rate decreased

ACEI/ARBs: Reno-protective effect? Decrease myocardial ischaemia, perioperative mortality, and length of hospitalization?

Cochrane Database Syst Rev. 2016 Jan 27;(1)

Objectives

P: Adults (age ≥18 years), any type of surgery, general anesthesia

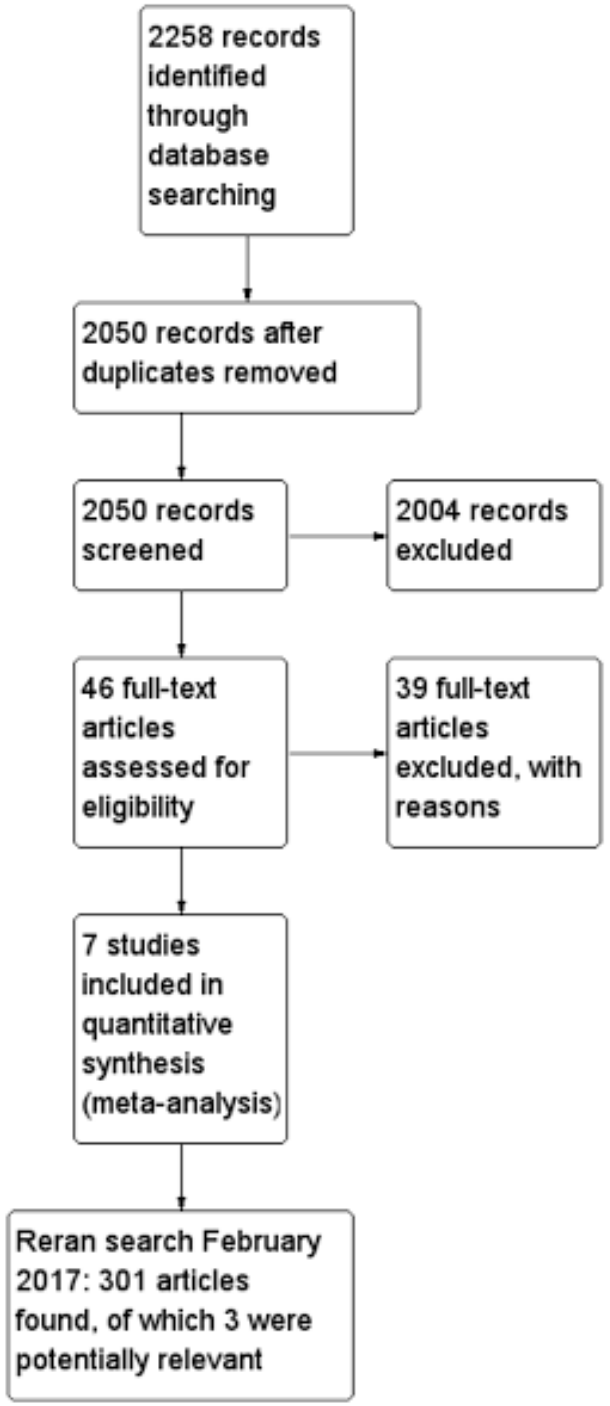
I: preoperative ACEIs or ARBs

C: Placebo

O: all-cause mortality, risk of acute myocardial infarction, risk of myocardial ischemia

Excluded studies in which participants underwent procedures that required local anaesthesia only, or participants who had already been on ACEIs or ARBs

Cochrane Database Syst Rev. 2016 Jan 27;(1)



Methods

Source: Cochrane, MEDLINE, EMBASE, contact of author
http://www.controlled-trials.com/
http://clinicaltrials.gov/

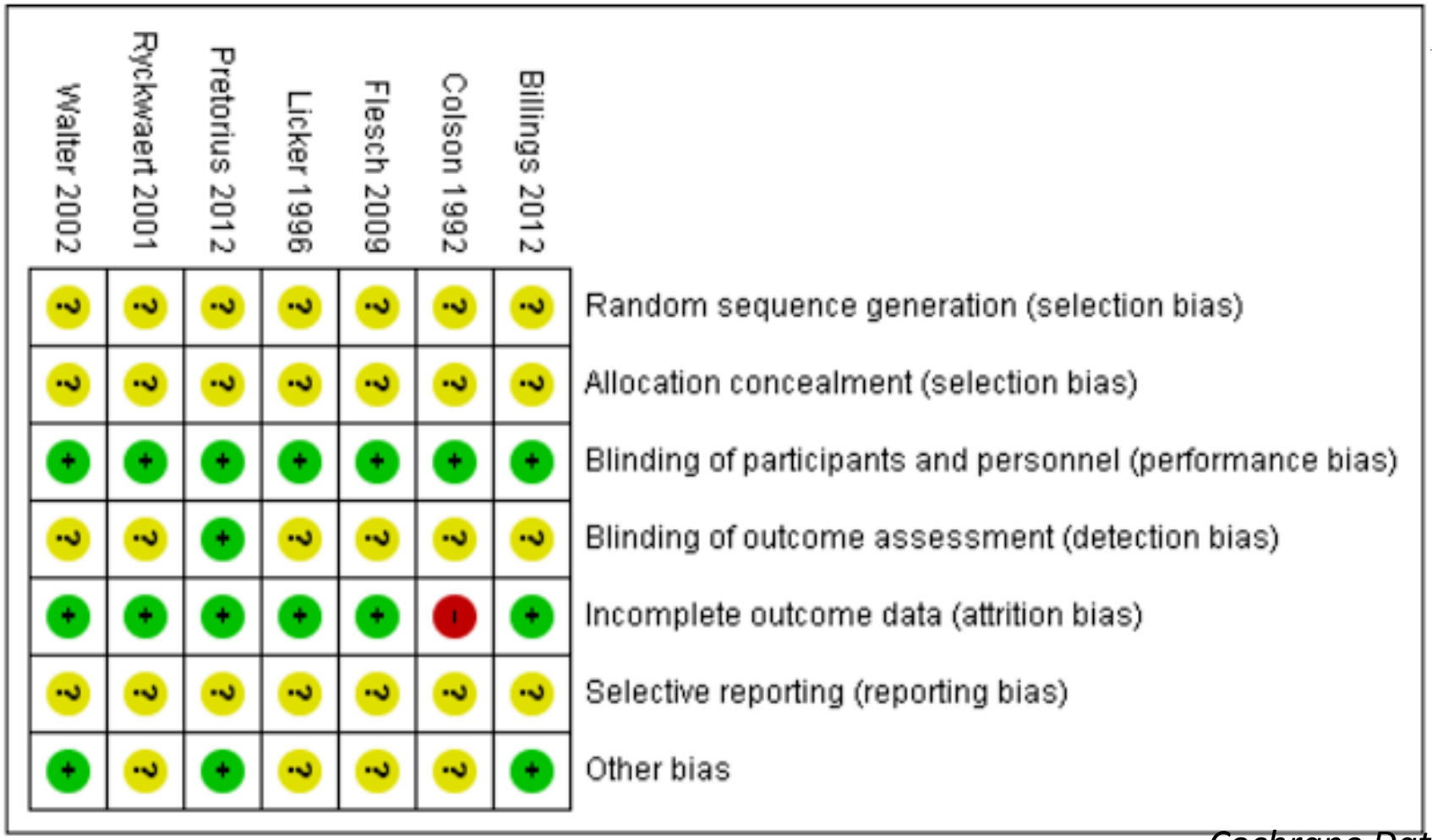
7 RCTs

N= 571 participants

2 trials: 36 participants undergoing non-cardiac vascular surgery
5 trials: 535 participants undergoing cardiac surgery

Cochrane Database Syst Rev. 2016 Jan 27;(1)

考科藍的誤差風險工具 (COCHRANE'S RISK OF BIAS TOOL)



Underpowered

Cochrane Database Syst Rev. 2016 Jan 27;(1)

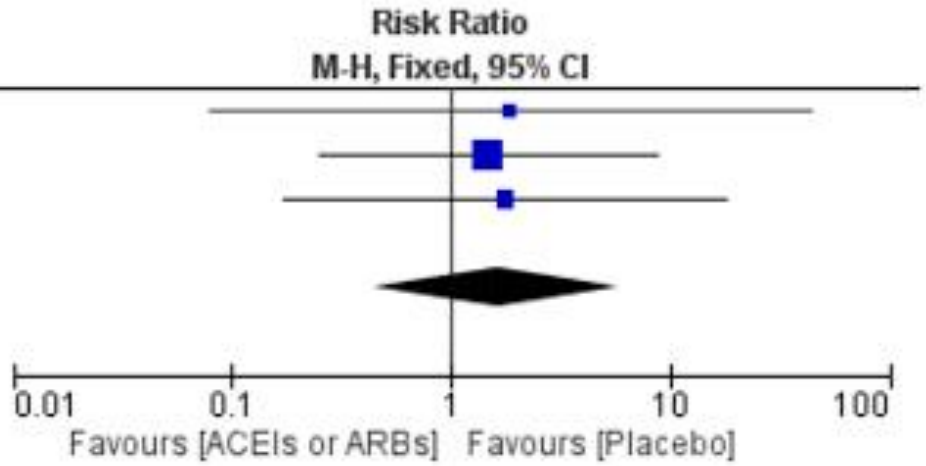
Results

Figure 4. Forest plot of comparison: 1 All-cause mortality, outcome: 1.1 All-cause mortality.

Study or Subgroup	ACEIs or ARBs Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Billings 2012	1	46	0	28	16.7%	1.85 [0.08, 43.94]
Pretorius 2012	3	151	2	147	54.6%	1.46 [0.25, 8.61]
Walter 2002	2	25	1	22	28.7%	1.76 [0.17, 18.11]
Total (95% CI)		**222**		**197**	**100.0%**	**1.61 [0.44, 5.85]**
Total events	6		3			

Heterogeneity: Chi² = 0.02, df = 2 (P = 0.99); I² = 0%

Test for overall effect: Z = 0.73 (P = 0.47)



Billings 2012: placebo vs ACEI/ARBs, 5-7 days before surgery, cardiac surgery

Pretorius 2012: placebo vs ACEI, 4-7 days before surgery, cardiac or vascular surgery

Walter 2002: placebo vs ACEI, 3-7 days before surgery, cardiac surgery

Cochrane Database Syst Rev. 2016 Jan 27;(1)

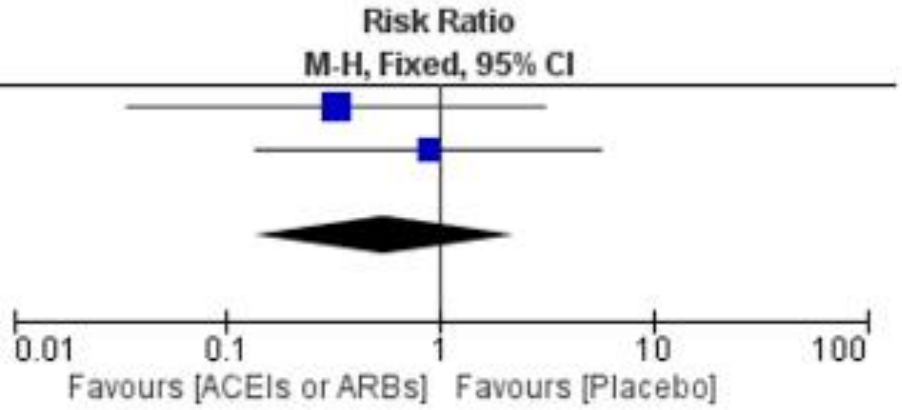
Results

Figure 5. Forest plot of comparison: 1 ACEIs or ARBs versus placebo, outcome: 1.2 ST-elevation or new Q wave in ECG test.

Study or Subgroup	ACEIs or ARBs Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Pretorius 2012	1	151	3	147	58.8%	0.32 [0.03, 3.08]
Walter 2002	2	25	2	22	41.2%	0.88 [0.14, 5.73]
Total (95% CI)		**176**		**169**	**100.0%**	**0.55 [0.14, 2.26]**
Total events	3		5			

Heterogeneity: Chi² = 0.45, df = 1 (P = 0.50); I² = 0%

Test for overall effect: Z = 0.83 (P = 0.41)



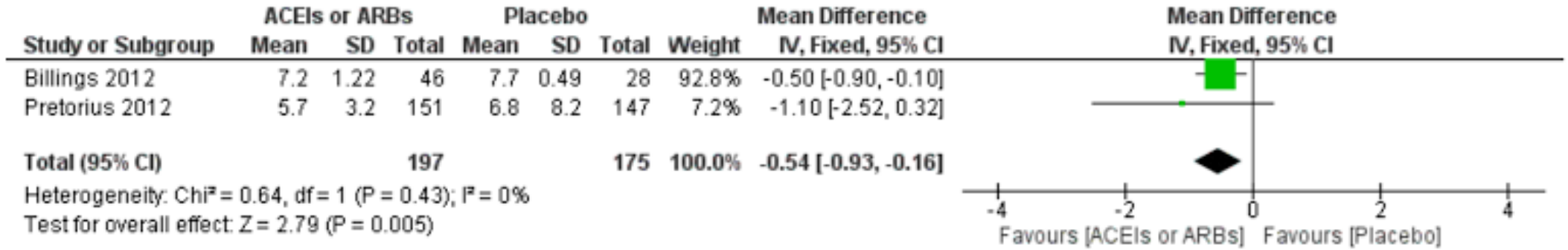
Pretorius 2012: placebo vs ACEI, 4-7 days before surgery, cardiac or vascular surgery

Walter 2002: placebo vs ACEI, 3-7 days before surgery, cardiac surgery

Cochrane Database Syst Rev. 2016 Jan 27;(1)

Results

Figure 8. Forest plot of comparison: 1 ACEIs or ARBs versus placebo, outcome: 1.5 Length of hospital stay.



Clinical backgrounds of participants varied

Cochrane Database Syst Rev. 2016 Jan 27;(1)

Table 1. Rate of hypotension

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
Rate of hypotension	1	298	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [0.86, 4.41]

Risk ratio < 1 favours angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor blockers group. Risk ratio > 1 favours control group.

Pretorius 2012

Table 2. Glomerular filtration rate

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
Glomerular filtration rate	1	16	Mean Difference (IV, Random, 95% CI)	-1.40 [-10.30, 7.50]

IV - inverse variance
IV: intravenous

Colson 1992

Cochrane Database Syst Rev. 2016 Jan 27;(1)

Conclusion

No evidence to support perioperative ACEIs or ARBs can prevent:

- Mortality
- Complications (hypotension, and cardiac surgery-related renal failure)
- Acute myocardial infarction

Cochrane Database Syst Rev. 2016 Jan 27;(1)

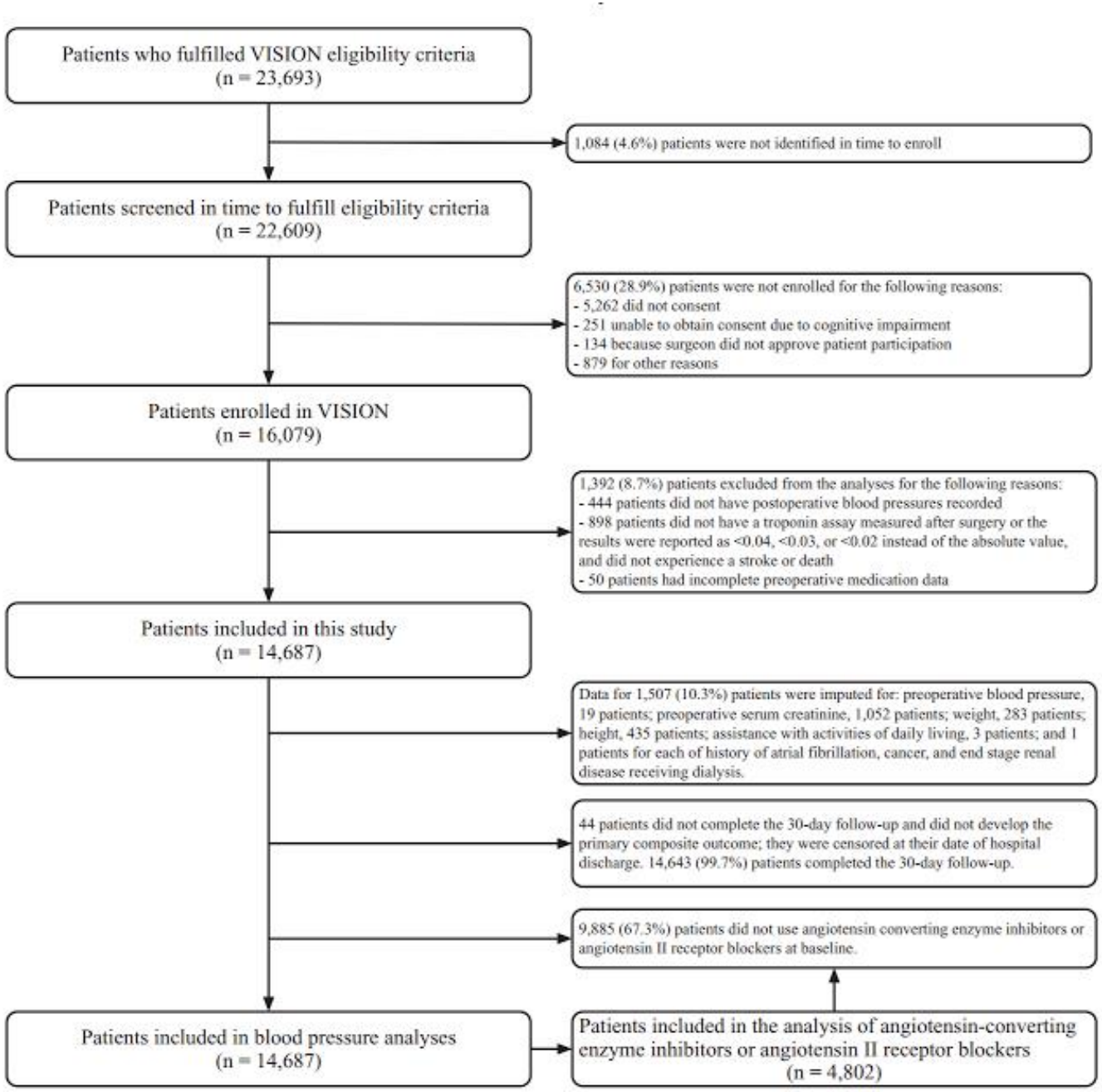
FREE

Perioperative Medicine | January 2017

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

Pavel S. Roshanov, M.D., M.Sc.; Bram Rochwerg, M.D., M.Sc.; Ameen Patel, M.D.; Omid Salehian, M.D., M.Sc.; Emmanuelle Duceppe, M.D.; et al

Anesthesiology. 2017 Jan;126(1):16-27.



Methods

VISION: Vascular events **I**n noncardiac **S**urgery pat**I**ents c**O**hort evaluatio**n**

International prospective cohort study

12 centers in 8 countries: (North and South America, Australia, Asia, and Europe)

- 14,687 patients included
- 4,802 patients included in ACEI/ARBs

Anesthesiology. 2017 Jan;126(1):16-27.

Methods

Baseline ACEI/ARB users:

- ACEI/ARB Continued before surgery: n= 3,557
- ACEI/ARB Withheld 24 hours before surgery: n= 1,245

Anesthesiology. 2017 Jan;126(1):16-27.

Table 1. Abridged Cohort Characteristics

Patient Characteristics	All Patients				Only Patients Who Took ACEI/ARB at Baseline			
	Overall	No Death or Primary Vascular Event	Death or Primary Vascular Event	*P* Value	ACEI/ARB at Baseline	ACEI/ARB Continued Preop.	ACEI/ARB Withheld Preop.	*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				Only Patients Who Took ACEI/ARB at Baseline			
	Overall	No Death or Primary Vascular Event	Death or Primary Vascular Event	*P* Value	ACEI/ARB at Baseline	ACEI/ARB Continued Preop.	ACEI/ARB Withheld Preop.	*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

Myocardial infarction in noncardiac surgery (MINS)

Measure troponin T to assess for myocardial injury 6 to 12h postoperatively and on the first 3 days after surgery

Only 15.8% of patients suffering MINS experience an ischemic symptom

Remaining 84.2% of events would likely go undetected without systematic postoperative troponin monitoring.

Routine monitoring of cardiac biomarkers in high-risk patients, both prior to and 48–72 h after major surgery, is recommended

Circulation 2012; 126:2020–35

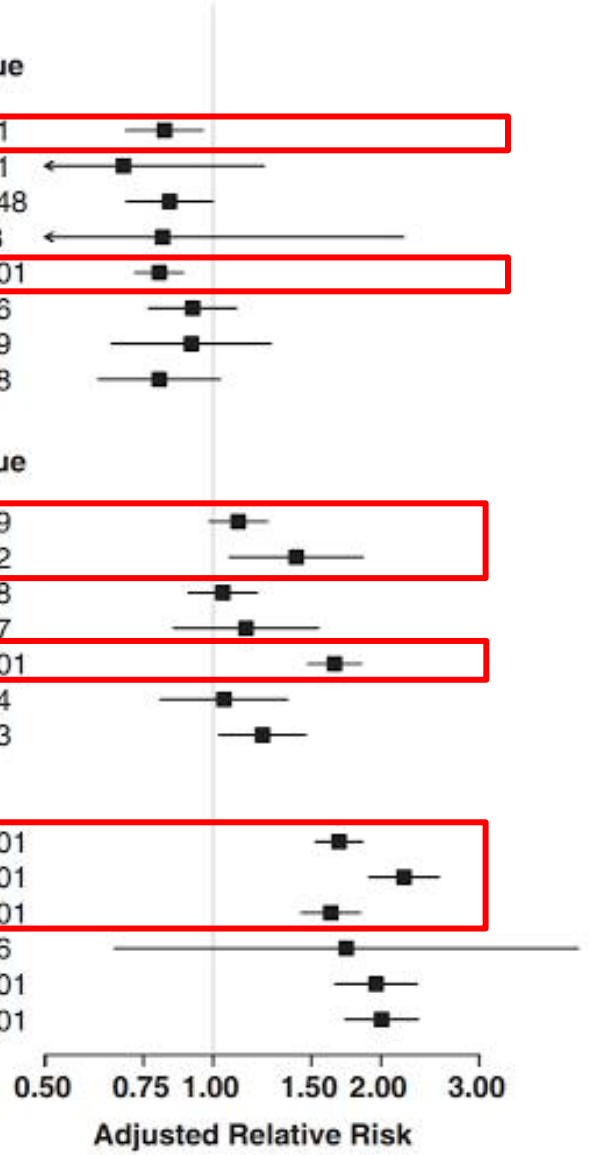
Anesthesiology. 2017 Jan;126(1):16-27.

A

Medication withheld	Outcome	Events in withheld *vs.* continued	aRR (95% CI), p–value
ACEI/ARBs	Death, MINS, or stroke	150/1245 (12.0%) *vs.* 459/3557 (12.9%)	0.82 (0.70–0.96), 0.01
	Death	25/1245 (2.0%) *vs.* 74/3557 (2.1%)	0.69 (0.39–1.24), 0.21
	MINS	132/1245 (10.6%) *vs.* 399/3541 (11.3%)	0.84 (0.70–0.998), 0.048
	Stroke	8/1245 (0.6%) *vs.* 26/3557 (0.7%)	0.81 (0.30–2.2), 0.68
	Intraop. hypotension	290/1245 (23.3%) *vs.* 1017/3557 (28.6%)	0.80 (0.73–0.88), <0.001
	Postop. hypotension	242/1245 (19.4%) *vs.* 719/3557 (20.2%)	0.92 (0.77–1.10), 0.36
	MI (Exploratory)	57/1245 (4.6%) *vs.* 148/3557 (4.2%)	0.91 (0.66–1.27), 0.59
	Death, MI, or stroke (Exploratory)	78/1245 (6.3%) *vs.* 221/3557 (6.2%)	0.81 (0.62–1.03), 0.08

B

Hypotension	Outcome	Events in exposed *vs.* unexposed	aRR (95% CI), p–value
Intraoperative	Death, MINS, or stroke	464/4162 (11.1%) *vs.* 945/10525 (9.0%)	1.11 (0.98–1.25), 0.09
	Death	133/4162 (3.2%) *vs.* 169/10525 (1.6%)	1.41 (1.07–1.86), 0.02
	MINS	353/4138 (8.5%) *vs.* 807/10496 (7.7%)	1.04 (0.90–1.20), 0.58
	Stroke	32/4162 (0.8%) *vs.* 58/10525 (0.6%)	1.14 (0.85–1.54), 0.37
	Postop. hypotension	1133/4162 (27.2%) *vs.* 1595/10525 (15.2%)	1.65 (1.48–1.84), <0.001
	MI (Exploratory)	137/4162 (3.3%) *vs.* 309/10525 (2.9%)	1.05 (0.80–1.35), 0.74
	Death, MI, or stroke (Exploratory)	273/4162 (6.6%) *vs.* 472/10525 (4.5%)	1.23 (1.03–1.47), 0.03
Postoperative	Death, MINS, or stroke	439/2728 (16.1%) *vs.* 970/11959 (8.1%)	1.68 (1.53–1.85), <0.001
	Death	125/2728 (4.6%) *vs.* 177/11959 (1.5%)	2.20 (1.90–2.54), <0.001
	MINS	346/2703 (12.8%) *vs.* 814/11931 (6.8%)	1.63 (1.44–1.84), <0.001
	Stroke	24/2728 (0.9%) *vs.* 66/11959 (0.6%)	1.73 (0.67–4.51), 0.26
	MI (Exploratory)	153/2728 (5.6%) *vs.* 293/11959 (2.5%)	1.96 (1.66–2.32), <0.001
	Death, MI, or stroke (Exploratory)	266/2728 (9.8%) *vs.* 479/11959 (4.0%)	2.01 (1.72–2.33), <0.001



Anesthesiology. 2017 Jan;126(1):16-27.

Confounding factors

Clinically significant **bleeding** during surgery:

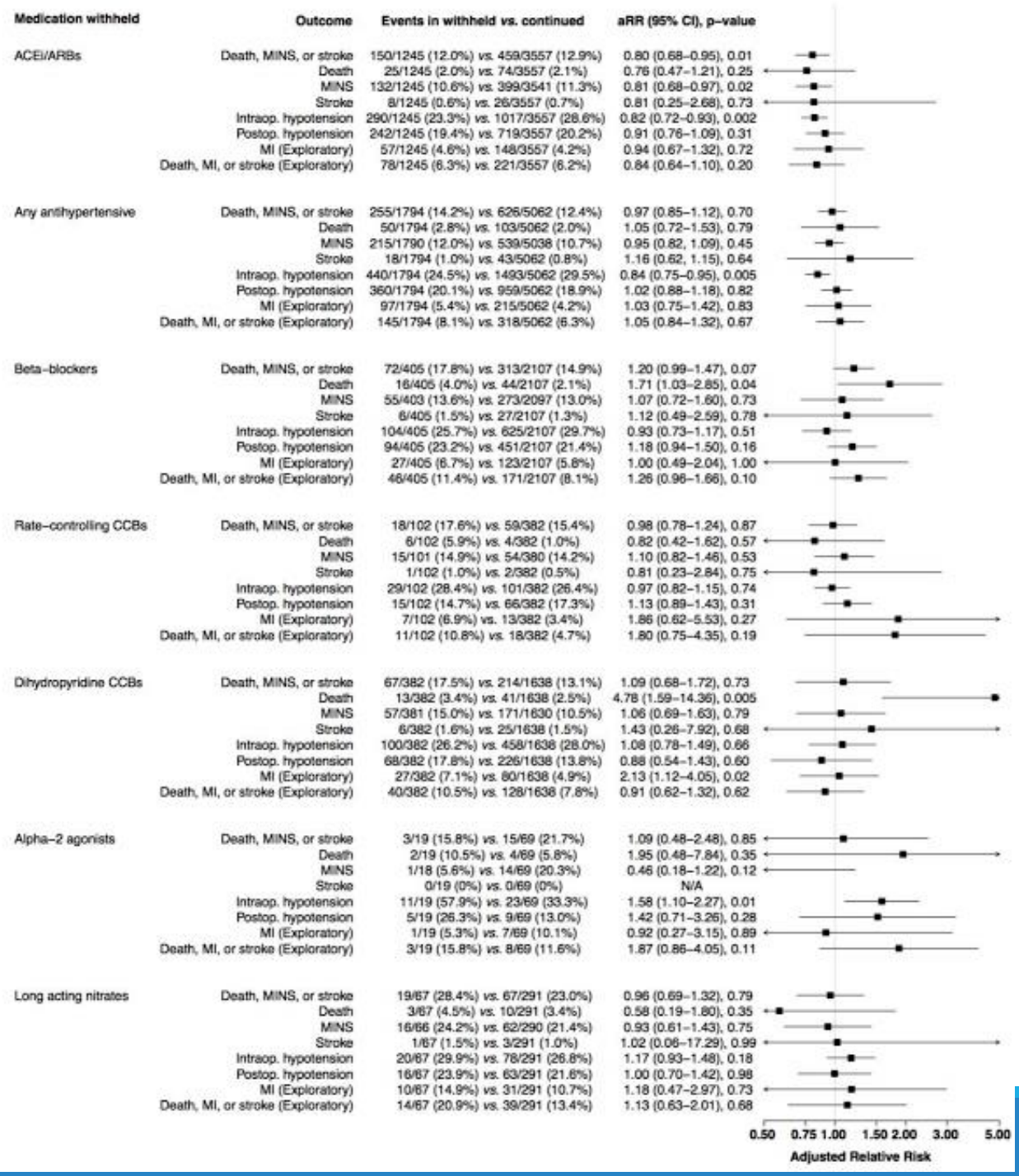
- 278 (5.8%) in baseline ACEI/ARB users
- Significantly associated with the composite of death and vascular events (aRR, 1.49; 95% CI, 1.13 to 1.97; P = 0.004)
- Not associated with withholding these medications (aRR, 0.94; 95% CI, 0.70 to 1.26; P = 0.69)

Significant **bleeding within 30 days of surgery**:

- In 955 (19.9%) ACEI/ARB users
- Significantly associated with the primary outcome (aRR, 2.05; 95% CI, 1.63 to 2.59; P < 0.001)
- Not associated with withholding these medications (aRR, 1.04; 95% CI, 0.92 to 1.18; P = 0.56)

Confounding Factors

Other antihypertensive medications



Medication withheld	Outcome	Events in withheld vs. continued	aRR (95% CI), p-value
ACEI/ARBs	Death, MINS, or stroke	150/1245 (12.0%) vs. 459/3557 (12.9%)	0.80 (0.68–0.95), 0.01
	Death	25/1245 (2.0%) vs. 74/3557 (2.1%)	0.76 (0.47–1.21), 0.25
	MINS	132/1245 (10.6%) vs. 399/3541 (11.3%)	0.81 (0.68–0.97), 0.02
	Stroke	8/1245 (0.6%) vs. 26/3557 (0.7%)	0.81 (0.25–2.68), 0.73
	Intraop. hypotension	290/1245 (23.3%) vs. 1017/3557 (28.6%)	0.82 (0.72–0.93), 0.002
	Postop. hypotension	242/1245 (19.4%) vs. 719/3557 (20.2%)	0.91 (0.76–1.09), 0.31
	MI (Exploratory)	57/1245 (4.6%) vs. 148/3557 (4.2%)	0.94 (0.67–1.32), 0.72
	Death, MI, or stroke (Exploratory)	78/1245 (6.3%) vs. 221/3557 (6.2%)	0.84 (0.64–1.10), 0.20
Any antihypertensive	Death, MINS, or stroke	255/1794 (14.2%) vs. 626/5062 (12.4%)	0.97 (0.85–1.12), 0.70
	Death	50/1794 (2.8%) vs. 103/5062 (2.0%)	1.05 (0.72–1.53), 0.79
	MINS	215/1790 (12.0%) vs. 539/5038 (10.7%)	0.95 (0.82, 1.09), 0.45
	Stroke	18/1794 (1.0%) vs. 43/5062 (0.8%)	1.16 (0.62, 1.15), 0.64
	Intraop. hypotension	440/1794 (24.5%) vs. 1493/5062 (29.5%)	0.84 (0.75–0.95), 0.005
	Postop. hypotension	360/1794 (20.1%) vs. 959/5062 (18.9%)	1.02 (0.88–1.18), 0.82
	MI (Exploratory)	97/1794 (5.4%) vs. 215/5062 (4.2%)	1.03 (0.75–1.42), 0.83
	Death, MI, or stroke (Exploratory)	145/1794 (8.1%) vs. 318/5062 (6.3%)	1.05 (0.84–1.32), 0.67
Beta-blockers	Death, MINS, or stroke	72/405 (17.8%) vs. 313/2107 (14.9%)	1.20 (0.99–1.47), 0.07
	Death	16/405 (4.0%) vs. 44/2107 (2.1%)	1.71 (1.03–2.85), 0.04
	MINS	55/403 (13.6%) vs. 273/2097 (13.0%)	1.07 (0.72–1.60), 0.73
	Stroke	6/405 (1.5%) vs. 27/2107 (1.3%)	1.12 (0.49–2.59), 0.78
	Intraop. hypotension	104/405 (25.7%) vs. 625/2107 (29.7%)	0.93 (0.73–1.17), 0.51
	Postop. hypotension	94/405 (23.2%) vs. 451/2107 (21.4%)	1.18 (0.94–1.50), 0.16
	MI (Exploratory)	27/405 (6.7%) vs. 123/2107 (5.8%)	1.00 (0.49–2.04), 1.00
	Death, MI, or stroke (Exploratory)	46/405 (11.4%) vs. 171/2107 (8.1%)	1.26 (0.96–1.66), 0.10
Rate-controlling CCBs	Death, MINS, or stroke	18/102 (17.6%) vs. 59/382 (15.4%)	0.98 (0.78–1.24), 0.87
	Death	6/102 (5.9%) vs. 4/382 (1.0%)	0.82 (0.42–1.62), 0.57
	MINS	15/101 (14.9%) vs. 54/380 (14.2%)	1.10 (0.82–1.46), 0.53
	Stroke	1/102 (1.0%) vs. 2/382 (0.5%)	0.81 (0.23–2.84), 0.75
	Intraop. hypotension	29/102 (28.4%) vs. 101/382 (26.4%)	0.97 (0.82–1.15), 0.74
	Postop. hypotension	15/102 (14.7%) vs. 66/382 (17.3%)	1.13 (0.89–1.43), 0.31
	MI (Exploratory)	7/102 (6.9%) vs. 13/382 (3.4%)	1.86 (0.62–5.53), 0.27
	Death, MI, or stroke (Exploratory)	11/102 (10.8%) vs. 18/382 (4.7%)	1.80 (0.75–4.35), 0.19
Dihydropyridine CCBs	Death, MINS, or stroke	67/382 (17.5%) vs. 214/1638 (13.1%)	1.09 (0.68–1.72), 0.73
	Death	13/382 (3.4%) vs. 41/1638 (2.5%)	4.78 (1.59–14.36), 0.005
	MINS	57/381 (15.0%) vs. 171/1630 (10.5%)	1.06 (0.69–1.63), 0.79
	Stroke	6/382 (1.6%) vs. 25/1638 (1.5%)	1.43 (0.26–7.92), 0.68
	Intraop. hypotension	100/382 (26.2%) vs. 458/1638 (28.0%)	1.08 (0.78–1.49), 0.66
	Postop. hypotension	68/382 (17.8%) vs. 226/1638 (13.8%)	0.88 (0.54–1.43), 0.60
	MI (Exploratory)	27/382 (7.1%) vs. 80/1638 (4.9%)	2.13 (1.12–4.05), 0.02
	Death, MI, or stroke (Exploratory)	40/382 (10.5%) vs. 128/1638 (7.8%)	0.91 (0.62–1.32), 0.62
Alpha-2 agonists	Death, MINS, or stroke	3/19 (15.8%) vs. 15/69 (21.7%)	1.09 (0.48–2.48), 0.85
	Death	2/19 (10.5%) vs. 4/69 (5.8%)	1.95 (0.48–7.84), 0.35
	MINS	1/18 (5.6%) vs. 14/69 (20.3%)	0.46 (0.18–1.22), 0.12
	Stroke	0/19 (0%) vs. 0/69 (0%)	N/A
	Intraop. hypotension	11/19 (57.9%) vs. 23/69 (33.3%)	1.58 (1.10–2.27), 0.01
	Postop. hypotension	5/19 (26.3%) vs. 9/69 (13.0%)	1.42 (0.71–3.26), 0.28
	MI (Exploratory)	1/19 (5.3%) vs. 7/69 (10.1%)	0.92 (0.27–3.15), 0.89
	Death, MI, or stroke (Exploratory)	3/19 (15.8%) vs. 8/69 (11.6%)	1.87 (0.86–4.05), 0.11
Long acting nitrates	Death, MINS, or stroke	19/67 (28.4%) vs. 67/291 (23.0%)	0.96 (0.69–1.32), 0.79
	Death	3/67 (4.5%) vs. 10/291 (3.4%)	0.58 (0.19–1.80), 0.35
	MINS	16/66 (24.2%) vs. 62/290 (21.4%)	0.93 (0.61–1.43), 0.75
	Stroke	1/67 (1.5%) vs. 3/291 (1.0%)	1.02 (0.06–17.29), 0.99
	Intraop. hypotension	20/67 (29.9%) vs. 78/291 (26.8%)	1.17 (0.93–1.48), 0.18
	Postop. hypotension	16/67 (23.9%) vs. 63/291 (21.6%)	1.00 (0.70–1.42), 0.98
	MI (Exploratory)	10/67 (14.9%) vs. 31/291 (10.7%)	1.18 (0.47–2.97), 0.73
	Death, MI, or stroke (Exploratory)	14/67 (20.9%) vs. 39/291 (13.4%)	1.13 (0.63–2.01), 0.68

Discussion

Could not study potentially relevant subgroups eg, heart failure, known cardiovascular disease

Crude dichotomous definition of hypotension (sBP < 90 mmHg) rather than actual values

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

Conclusion

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.

Clinicians should consider recommending that patients withhold ACEI/ARBs 24h before surgery.

Anesthesiology. 2017 Jan;126(1):16-27.

Appraisal:
CASP世代研究檢核表

(A)研究結果可信嗎?

1. 研究問題是否清楚且聚焦? Yes

P: All patients who undergo noncardiac surgery are eligible if they are > 45 years of age and receive a general or regional anesthetic

I: withhold ACEI/ARBs for 24 hours before surgery

C: continue ACEI/ARBs before surgery

O: Reduced death, MINS, stroke, perioperative hypotension in patients who withhold ACEI/ARBs

(A)研究結果可信嗎?

不明確

2.以可接受的方式招募受試者(世代)嗎?

所選擇的世代是否能代表特定的族群?

所選擇的世代有無特殊性?

Age>45 years

Brazil, Canada, China, Columbia, India, Malaysia, Spain: University and Non-University Hospitals

Overnight admission after surgery

所有應該收案的對象都已納入?

Age < 45 years

Outpatients

(A)研究結果可信嗎?

3.是否準確測量暴露的變項，以減少偏差?

Yes

研究者用主觀或客觀的測量?

該測量是否真實反應原來想要測量的變項 (測量是否 經過信效度驗證)?

所有受試者以相同的程序分派至不同暴露的組別

Participants answered a series of questions regarding their past medical, surgical, and social history.

Study personnel reviewed medical charts for additional history

(A)研究結果可信嗎?

4.結果測量是否精確以減少偏差? Yes

他們使用主觀或客觀的測量方式?

研究者用主觀或客觀的測量?

是否已建置可靠的系統以檢測所有的個案 (用於測量疾病的發生)?

不同組別的測量方式是否相似?

個案和/或結果的評估員是否盲化(有無盲化是否有影響)? → not mentioned

Measure cTnT to assess for myocardial injury 6 to 12h 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.

(A)研究結果可信嗎?

不明確

5. (a)研究者是否釐清所有重要的干擾因素?

Type of anesthetics, duration of ACEI/ARBs intake, dose

Yes

(b)研究者在研究設計和/或分析時是否考量干擾因素?

- Multivariable modified Poisson regression: 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).
- Cluster-robust variance estimator: potential center effects
- Sensitive analyses: significant intraoperative bleeding, significant bleeding within 30 days, association between holding versus continuing other antihypertensive agents and our primary outcome.

(A)研究結果可信嗎?

6. (a)研究對象的追蹤夠完整?

不明確

Timing of postoperative medication use was not captured with sufficient precision in VISION

(b)研究對象的追蹤時間夠久?

不明確

> 30 days ?

(B)研究結果為何?

7.研究的結果為何?

8.研究結果有多精準?

ACEI/ARB users who withheld their ACEI/ARBs in the 24h before surgery were less likely to suffer:

- Primary composite outcome of all-cause death, stroke, or myocardial injury (adjusted relative risk, 0.82; 95% CI, 0.70 to 0.96; P = 0.01)
- Intraoperative hypotension (adjusted relative risk, 0.80; 95% CI, 0.72 to 0.93; P < 0.001)

(B)研究結果為何?

9.你相信這個研究結果嗎?

Yes

n = 14,687; ACEI/ARBs n = 4,802

這是否可能是由於偏差、巧合或干擾因素造成的嗎?

是否研究設計和方法的缺陷足以造成不可信結果?

布拉德福德希爾準則(Bradford Hills criteria)(如：時間序列、劑量-效應關係、生物學合理性、一致性)

(C)研究結果對於當地病人有幫助嗎?

10.研究結果是否可以應用在本地族群? Yes

11.這個研究結果與其他現有的證據相符合? 不明確

Clinical consequences of withholding versus administering renin-angiotensin-aldosterone system antagonists in the preoperative period - *J Hosp Med.* 2008 Jul;3(4):319-25.

(C)研究結果對於當地病人有幫助嗎?

12.本研究在應用上的意義為何?

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.

Thank you!

使用 ACEI / ARB 控制血壓的病人，術前準備需要停藥嗎？

綠(同意):10人
黃(需討論):57人
紅(不同意):4人