ACE Inhibitors and ARBs: Perioperative Management

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Division of Critical Care
Department of Anesthesiology
University of Michigan
Disclosures

None
Outline

• Background / history
• Mechanisms of BP maintenance and RAS antagonists
• Review of most current literature and guidelines
  • Perioperative ACEI/ARB management
  • Intraoperative BP goals
• Approaches to treatment
Hypertension

100 million!
## Blood Pressure Categories

<table>
<thead>
<tr>
<th>BLOOD PRESSURE CATEGORY</th>
<th>SYSTOLIC mm Hg (upper number)</th>
<th>DIASTOLIC mm Hg (lower number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NORMAL</td>
<td>LESS THAN 120 and LESS THAN 80</td>
<td></td>
</tr>
<tr>
<td>ELEVATED</td>
<td>120 – 129 and LESS THAN 80</td>
<td></td>
</tr>
<tr>
<td>HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 1</td>
<td>130 – 139 or 80 – 89</td>
<td></td>
</tr>
<tr>
<td>HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 2</td>
<td>140 OR HIGHER or 90 OR HIGHER</td>
<td></td>
</tr>
<tr>
<td>HYPERTENSIVE CRISIS (consult your doctor immediately)</td>
<td>HIGHER THAN 180 and/or HIGHER THAN 120</td>
<td></td>
</tr>
</tbody>
</table>
Hypertension

100 million!
Hypertension
100 million!

CAD
Stroke
Heart Failure
Diabetes

Sear JW. Anesth Analg. 2014; Bian B. et al. J Manag Care Pharm. 2010
<table>
<thead>
<tr>
<th>ACE Inhibitors</th>
<th>FDA Approval</th>
<th>Generic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>BMS BMS</td>
<td>04/06/81 10/12/84</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Merck Merck AstraZeneca</td>
<td>12/24/85 10/31/86 12/27/96</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Merck AstraZeneca</td>
<td>12/29/87 05/19/88 02/16/89 09/20/90</td>
</tr>
<tr>
<td>Ramipril</td>
<td>King</td>
<td>01/28/91</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>BMS BMS</td>
<td>05/16/91 11/30/94</td>
</tr>
<tr>
<td>Benazepril</td>
<td>Novartis Novartis</td>
<td>6/25/91 05/20/92 03/3/95</td>
</tr>
<tr>
<td>Quinapril</td>
<td>Pfizer Pfizer</td>
<td>11/19/91 12/28/99</td>
</tr>
<tr>
<td>Perindopril</td>
<td>Solvay</td>
<td>12/30/93</td>
</tr>
<tr>
<td>Moexipril</td>
<td>Schwarz Pharma Schwarz Pharma</td>
<td>4/19/95 06/27/97</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>Knoll Knoll</td>
<td>04/26/96 10/22/96</td>
</tr>
</tbody>
</table>

Bian B. et al. J Manag Care Pharm. 2010
<table>
<thead>
<tr>
<th>ARBs</th>
<th>FDA Approval</th>
<th>Generic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan</td>
<td>Cozaar Hyzaarb</td>
<td>Merck</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Merck</td>
</tr>
<tr>
<td></td>
<td>04/14/95 04/28/95</td>
<td></td>
</tr>
<tr>
<td>Valsartan</td>
<td>Diovan Diovan HCTb</td>
<td>Novartis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Novartis</td>
</tr>
<tr>
<td></td>
<td>12/23/96 03/06/98</td>
<td></td>
</tr>
<tr>
<td>Irbesartan</td>
<td>Avapro Avalideb</td>
<td>Sanofi-Aventis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sanofi-Aventis</td>
</tr>
<tr>
<td></td>
<td>09/30/97 09/30/97</td>
<td></td>
</tr>
<tr>
<td>Eprosartan</td>
<td>Teveten Teveten HCTb</td>
<td>Abbott</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abbott</td>
</tr>
<tr>
<td></td>
<td>12/22/97 11/01/01</td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>Atacand Atacand HCTb</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AstraZeneca</td>
</tr>
<tr>
<td></td>
<td>06/04/98 09/05/00</td>
<td></td>
</tr>
<tr>
<td>Telmisartan</td>
<td>Micardis Micardis HCTb</td>
<td>Boehringer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ingelheim</td>
</tr>
<tr>
<td></td>
<td>11/10/98 11/17/00</td>
<td></td>
</tr>
<tr>
<td>Olmesartan</td>
<td>Benicar Benicar HCTb</td>
<td>Sankyo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sankyo</td>
</tr>
<tr>
<td></td>
<td>04/25/02 06/05/03</td>
<td></td>
</tr>
<tr>
<td></td>
<td>09/26/07</td>
<td></td>
</tr>
</tbody>
</table>
ACEI and ARBs - benefits

Hypertension

Sear JW. Anesth Analg. 2014; Bian B. et al. J Manag Care Pharm. 2010
ACEI and ARBs - benefits

Hypertension

↓ ischemic events
- MI
- Stroke

Sear JW. Anesth Analg. 2014; Bian B. et al. J Manag Care Pharm. 2010
ACEI and ARBs - benefits

Hypertension

↑ cardiac function and survival
- Post-MI
- HFrEF

↓ ischemic events
- MI
- Stroke

Sear JW. Anesth Analg. 2014; Bian B. et al. J Manag Care Pharm. 2010
ACEI and ARBs - benefits

**Hypertension**
- ↓ ischemic events
  - MI
  - Stroke
- ↑ cardiac function and survival
  - Post-MI
  - HFrEF

**↓ CKD**
- DM
- Non-DM

Sear JW. Anesth Analg. 2014; Bian B. et al. J Manag Care Pharm. 2010
Spinal fusion surgery – deliberate hypotension
12 patients
Captopril given in preop
Observed impact on MAP and blood CN level
Captopril Reduces the Dose Requirement for Sodium Nitroprusside Induced Hypotension


<table>
<thead>
<tr>
<th>MAP</th>
<th>Awake</th>
<th>Anes</th>
<th>Surg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>70 ± 5</td>
<td>64 ± 4*</td>
<td>86 ± 5*†</td>
</tr>
<tr>
<td>Control</td>
<td>95 ± 5</td>
<td>80 ± 4</td>
<td>100 ± 4†</td>
</tr>
</tbody>
</table>

- ↓ MAP with Anesthesia
- ↓ SNP required by >50%
- Reduced cyanide level
Leading Article

ACE inhibitors and anaesthesia

I. McConachie and T.E.J. Healy

University of Manchester, Department of Anaesthesia, University Hospital of South Manchester, Withington, Manchester M20 8LR, UK.

Recently we have seen cases of severe, unexpected hypotension at induction of anaesthesia in well controlled hypertensive patients on monotherapy with captopril. This hypotension was persistent and only reversed by the infusion of large volumes of fluid. ACE inhibitors used to be reserved for patients with severe hypertension but are now prescribed increasingly by general practitioners for any patient with hypertension despite their not being recommended as first line treatment for hypertension.\(^1\) The increasing use of ACE inhibitors as monotherapy for hypertension may increase the incidence of such adverse anaesthetic occurrences.
Pioneers in Academic Anesthesiology:
Pitié-Salpêtrière Hospital, Paris, France

Including 13 Articles and 3 Editorials from or about
Work from Pitié-Salpêtrière Hospital
Influence of Chronic Angiotensin-converting Enzyme Inhibition on Anesthetic Induction

Pierre Coriat, M.D.,* Christine Richer, M.D.,† Tomais Douraki, M.D.,‡ Carlos Gomez, M.D.,§ Karl Hendricks, M.D.,‡ Jean-François Giudicelli, M.D.,∥ Pierre Viars, M.D.#
Influence of Chronic Angiotensin-converting Enzyme Inhibition on Anesthetic Induction

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Continue vs. hold ACEI

Effects on blood pressure

47 patients on ACEI chronically
Influence of Chronic Angiotensin-converting Enzyme Inhibition on Anesthetic Induction

Pierre Coriat, M.D., Christine Richer, M.D., Tomais Douraki, M.D., Carlos Gomez, M.D., Karl Hendricks, M.D., Jean-François Giudicelli, M.D., Pierre Viars, M.D.

Table 3. Heart Rate and Blood Pressure Values Measured before Induction, after Induction, at Intubation, and Lowest Recorded Value of These Parameters from after Induction up to 10 min after the Start of Mechanical Ventilation

<table>
<thead>
<tr>
<th>Group</th>
<th>Enalapril Continued</th>
<th>24h</th>
<th>Withdrawn</th>
<th>Continued</th>
<th>12h</th>
<th>Withdrawn</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>7</td>
<td>11</td>
<td></td>
<td>14</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preinduction</td>
<td>151 ± 29</td>
<td></td>
<td></td>
<td>156 ± 28</td>
<td></td>
<td>157 ± 28</td>
</tr>
<tr>
<td>Postinduction</td>
<td>84 ± 21</td>
<td></td>
<td></td>
<td>96 ± 22</td>
<td>108 ± 25</td>
<td></td>
</tr>
<tr>
<td>Intubation</td>
<td>120 ± 4</td>
<td></td>
<td></td>
<td>158 ± 40</td>
<td>162 ± 38</td>
<td></td>
</tr>
<tr>
<td>Lowest value</td>
<td>71 ± 10*</td>
<td></td>
<td></td>
<td>100 ± 15†</td>
<td>86 ± 11</td>
<td>101 ± 21†</td>
</tr>
<tr>
<td>Mean blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preinduction</td>
<td>105 ± 14</td>
<td></td>
<td>105 ± 14</td>
<td>105 ± 18</td>
<td></td>
<td>105 ± 18</td>
</tr>
<tr>
<td>Postinduction</td>
<td>69 ± 16</td>
<td></td>
<td>69 ± 16</td>
<td>73 ± 19</td>
<td></td>
<td>73 ± 15</td>
</tr>
<tr>
<td>Intubation</td>
<td>80 ± 14</td>
<td></td>
<td>109 ± 28</td>
<td>108 ± 28</td>
<td></td>
<td>105 ± 28</td>
</tr>
<tr>
<td>Lowest value</td>
<td>48 ± 8*</td>
<td></td>
<td>69 ± 15†</td>
<td>58 ± 9</td>
<td></td>
<td>69 ± 17†</td>
</tr>
</tbody>
</table>

SBP: Systolic blood pressure (mmHg)
MAP: Mean blood pressure (mmHg)
“Exaggerated hypotensive response to induction”

“Temporary withdrawal …attenuated the hypotensive response…”

“…help to provide stable blood pressure.”
The Hemodynamic Effects of Anesthetic Induction in Vascular Surgical Patients Chronically Treated with Angiotensin II Receptor Antagonists

Steven M. Brabant, MD, Michèle Bertrand, MD, Daniel Eyraud, MD, Pierre-Louis Darmon, MD, and Pierre Coriat, MD

Department of Anesthesiology, University Hospital Pitié-Salpêtrière, Paris, France

(Anesth Analg 1999;88:1388–92)

### Table 2. Hemodynamic Data until 30 Minutes After the Induction of Anesthesia

<table>
<thead>
<tr>
<th></th>
<th>ARA group (n = 12)</th>
<th>BB/CB group (n = 45)</th>
<th>ACEI group (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with hypotension</td>
<td>12*</td>
<td>27</td>
<td>18</td>
</tr>
<tr>
<td>Patients with refractory hypotension</td>
<td>4*</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative value</td>
<td>105 ± 12</td>
<td>98 ± 11</td>
<td>99 ± 13</td>
</tr>
<tr>
<td>Lowest value</td>
<td>54 ± 6†</td>
<td>66 ± 12</td>
<td>68 ± 10</td>
</tr>
<tr>
<td>Highest value</td>
<td>100 ± 16</td>
<td>89 ± 16</td>
<td>90 ± 11</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative value</td>
<td>66 ± 10</td>
<td>67 ± 9</td>
<td>65 ± 9</td>
</tr>
<tr>
<td>Lowest value</td>
<td>46 ± 5</td>
<td>54 ± 9</td>
<td>52 ± 7</td>
</tr>
<tr>
<td>Highest value</td>
<td>65 ± 11</td>
<td>68 ± 11</td>
<td>68 ± 12</td>
</tr>
</tbody>
</table>
ACEI and ARBs: Withhold?
Blood pressure maintenance
Blood pressure maintenance

RAS antagonists
RAS antagonists

Recent literature

Current guidelines

Treatment

Blood pressure maintenance
Maintenance of blood pressure
Maintenance of blood pressure

RAS
Renin-Angiotensin System
Maintenance of blood pressure

RAS
Renin-Angiotensin System

SNS
Sympathetic Nervous System
Maintenance of blood pressure

RAS
Renin-Angiotensin System

SNS
Sympathetic Nervous System

VS
Vasopressinergic System
Maintenance of blood pressure

RAS
Renin-Angiotensin System

SNS
Sympathetic Nervous System

VS
Vasopressinergic System
Renin-Angiotensin-Aldosterone System

- Renal hypoperfusion
- Hypotension
- Volume depletion
- Increased sympathetic activity

Liver

Angiotensinogen

Angiotensin I

ACE

Angiotensin II

Lung

Kidney

Angiotensin II

Kidney

Posterior pituitary

Vascular smooth muscle

Hypothalamus

Adrenal cortex

Constricts glomerular efferent arteriole and increases Na+/H+ exchanger activity

ADH secretion

Hypertension

Stimulates thirst

Aldosterone secretion
Renin-Angiotensin-Aldosterone System

- Renal hypoperfusion
- Hypotension
- Volume depletion
- Increased sympathetic activity

Liver → Angiotensinogen → Renin → Angiotensin I → ACE → Angiotensin II

- Kidney
- Posterior pituitary
- Vascular smooth muscle
- Hypothalamus
- Adrenal cortex

- Constricts glomerular efferent arteriole and increases Na+/H+ exchanger activity
- ADH secretion
- Hypertension
- Stimulates thirst
- Aldosterone secretion
Renin-Angiotensin-Aldosterone System

- Renal hypoperfusion
  - Hypotension
  - Volume depletion
  - Increased sympathetic activity
- Renal hypoperfusion
- Hypotension
- Volume depletion
- Increased sympathetic activity

Renin-Angiotensin-Aldosterone System

Liver ➔ Angiotensinogen ➔ Renin

ACE ➔ Angiotensin I ➔ Angiotensin II

Lung ➔

Kidney

- Kidney
  - Constricts glomerular efferent arteriole and increases Na+/H+ exchanger activity
- Posterior pituitary
  - ADH secretion
- Vascular smooth muscle
  - Hypertension
- Hypothalamus
  - Stimulates thirst
- Adrenal cortex
  - Aldosterone secretion
Renal hypoperfusion

- Hypotension
- Volume depletion
- Increased sympathetic activity

Angiotensin II – Type 1 receptor

- Kidney
  - Constricts glomerular efferent arteriole and increases Na+/H+ exchanger activity
- Posterior pituitary
  - ADH secretion
- Vascular smooth muscle
  - Hypertension
- Hypothalamus
  - Stimulates thirst
- Adrenal cortex
  - Aldosterone secretion
Renal hypoperfusion
  • Hypotension
  • Volume depletion
  • Increased sympathetic activity

Angiotensin II – Type 1 receptor
- Constricts glomerular efferent arteriole and increases Na+/H+ exchanger activity
- ADH secretion
- Hypertension
- Stimulates thirst
- Aldosterone secretion

Angiotensin II – Type 2 receptor
- ↓ Renin
- NO release
Maintenance of blood pressure

RAS
Renin-Angiotensin System

SNS
Sympathetic Nervous System

VS
Vasopressinergic System
↑ Catecholamines

↓ Vagal tone

RAS activation:

↑ Angiotensin II
↑ Catecholamines
↓ Vagal tone

RAS activation:
↑ Angiotensin II
- Sympathetic outflow
- Heart rate
- Vasoconstriction
Maintenance of blood pressure

RAS
Renin-Angiotensin System

SNS
Sympathetic Nervous System

VS
Vasopressinergic System
Hypothalamus

Posterior Pituitary

Vasopressin

VS
Vasopressinergic System

CNS
ACTH secretion
Gluconeogenesis
Anti-inflammatory

V3
Hypothalamus

Posterior Pituitary

Vasopressin

Hyperosmolarity

Decreased atrial receptor firing

Angiotensin II

Sympathetic stimulation

VS

Vasopressinergic System
Vasopressinergic System

- Hypothalamus
  - Angiotensin II
  - Sympathetic stimulation
  - Posterior Pituitary
  - Vasopressin
    - $V_1$ (Blood Vessels, Constriction)
    - Increased Systemic Vascular Resistance
    - Increased Arterial Pressure
    - $V_2$ (Kidneys, Fluid Reabsorption)
    - Increased Blood Volume
    - Endothelium: vWF, F8
    - $V_3$ (CNS)
      - ACTH secretion
      - Gluconeogenesis
      - Anti-inflammatory

Den Ouden, DT et al. Neth J Med. 2005
Arginine vasopressin ("ADH")

- Hyperosmolarity
- Decreased atrial receptor firing

**Hypothalamus**

- Posterior Pituitary

**Vasopressin**

- V1: Blood Vessels (Constriction) → Increased Systemic Vascular Resistance → Increased Arterial Pressure
- V2: Kidneys (Fluid Reabsorption) → Increased Blood Volume
- V3: CNS → ACTH secretion → Gluconeogenesis

**Sympathetic stimulation**

- Angiotensin II
Den Ouden, DT et al. Neth J Med. 2005

**Vasopressinergic System**

**VS**

- Vasopressinergic system (VS)

**Arginine vasopressin**

- "ADH"

**Vasopressin**

- **V1**
  - Blood Vessels (Constriction)
  - Increased Systemic Vascular Resistance
  - Increased Arterial Pressure

- **V2**
  - Kidneys (Fluid Reabsorption)
  - Increased Blood Volume
  - Endothelium: vWF, F8

- **V3**
  - CNS
  - ACTH secretion
  - Gluconeogenesis
  - Anti-inflammatory

**Hyperosmolarity**

- Hypothalamus

**Decreased atrial receptor firing**

- Hypothalamus

**Angiotensin II**

- Hypothalamus

**Sympathetic stimulation**

- Hypothalamus

**Desmopressin**

**Terlipressin**
Maintenance of blood pressure

- RAS (Renin-Angiotensin System)
- SNS (Sympathetic Nervous System)
- VS (Vasopressinergic System)
General Anesthesia

RAS
Renin-Angiotensin System

SNS
Sympathetic Nervous System

VS
Vasopressinergic System
General Anesthesia + ACEI/ARB

RAS
Renin-Angiotensin System

SNS
Sympathetic Nervous System

VS
Vasopressinergic System
Blood pressure maintenance

RAS antagonists

ACEI
ARB
Direct ant-Renin
Combo
ACE-Inhibitors (ACE-I)

- Angiotensinogen
- Angiotensin I
- Angiotensin II

- Bradykinin ↑
- Bradykinin

- Inactive peptide

- Endothelium-Derived Hyperpolarizing Factor
- Prostacyclin

- Nitric oxide ↑
- Fibrinolysis ↑
- Thrombocyte activity ↓

AT₁

AT₂

Messerli FH et al. J Am Coll Cardiol. 2018
BEWARE!

Aliskiren (FDA 2008):
   Tekturna
   Rasilez

half life: 24 - 40 h

Messerli FH et al. J Am Coll Cardiol. 2018
## Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Drug (ACE Inhibitor)</th>
<th>Clearance CL (L/h)</th>
<th>Drug (ARB)</th>
<th>Half-Life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benazeprilat</td>
<td>1.79</td>
<td>Losartan</td>
<td>2</td>
</tr>
<tr>
<td>Cilaaprilat</td>
<td>12.3</td>
<td>Valsartan</td>
<td>9</td>
</tr>
<tr>
<td>Fosinopril acid</td>
<td>2.34</td>
<td>Irbesartan</td>
<td>11–15</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>6.36 (renal)</td>
<td>Candesartan</td>
<td>3.5–4.0</td>
</tr>
<tr>
<td>Pentopril</td>
<td>12.78 (renal)</td>
<td>Telmisartan</td>
<td>24</td>
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<tr>
<td>Perindopril</td>
<td>9.36</td>
<td>Eprosartan</td>
<td>5–7</td>
</tr>
<tr>
<td>Ramiprilat</td>
<td>6.0 (renal)</td>
<td>Olmesartan</td>
<td>13 (approximately)</td>
</tr>
</tbody>
</table>
Recent literature

Current guidelines

Treatment
What is the evidence? 2000-2020

- Intraop hypotension
- Renal Failure
- Mortality
- Myocardial Infarction
- Stroke

ACEI / ARBs
Evidence

Retrospective analyses

Observational evidence / case studies
Evidence

Systematic reviews

Retrospective analyses

Observational evidence / case studies
Evidence

- Prospective clinical trials
- Systematic reviews
- Retrospective analyses
- Observational evidence / case studies
Evidence

- Small
- Heterogenous
- No comparator group
- Definitions

Inconsistent

- When stop
- Type of med
- Reason stop
- Outcomes measured

Prospective clinical trials

Systematic reviews

Retrospective analyses

Observational evidence / case studies
ACEI/ARB studies: variable definitions of hypotension

<table>
<thead>
<tr>
<th>Definitions</th>
<th>Requirement</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP &lt; 80 mmHg</td>
<td>&gt; 1 minute Post-induction Vasopressor used</td>
<td>Bertrand M. Anesth Analg. 2001 • ARB only • Vascular surgery</td>
</tr>
<tr>
<td>SBP &lt; 85 mmHg</td>
<td>&gt; 1 minute Post-induction and shortly thereafter</td>
<td>Coriat P. Anesthesiology. 1994 • ACEI only • Vascular surgery</td>
</tr>
<tr>
<td>SBP &lt; 85 mmHg</td>
<td>&gt; 1 minute 0-30 and 31-60 min</td>
<td>Comfere T. Anesth. Analg. 2005 • Elective surgery</td>
</tr>
<tr>
<td>SBP &lt; 90 mmHg</td>
<td>That prompted clinical intervention Any duration At any time</td>
<td>Roshanov P. Anesthesiology 2017 • Major NC surgery, including emergent</td>
</tr>
<tr>
<td>MAP &lt; 60 mm Hg</td>
<td>Any duration Post-induction Vasopressor used</td>
<td>Schirmer U. Anaesthesist. 2007 • ENT/ophthalmology</td>
</tr>
</tbody>
</table>
Two themes in literature
Two themes in literature

Chronic ACEI exposure vs Never ACEI exposure
Two themes in literature

Chronic ACEI exposure vs Never ACEI exposure

Withheld operative day
Two themes in literature

- Chronic ACEI exposure
  - Withheld operative day
- Never ACEI exposure

- University of Michigan
- Cleveland Clinic
Background:

- Retrospective, Propensity matched
- Non-cardiac surgery
- 12,000 pts (chronic ACEI/ARB held vs never ACEI/ARB)

Assessment:

- Intraoperative hypotension
- Perioperative MI and AKI
- ACEI / ARB
<table>
<thead>
<tr>
<th>Blood pressure parameters</th>
<th>Yes ACE-I (n = 3,759)</th>
<th>No ACE-I (n = 7,012)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;80 mmHg SBP epochs</td>
<td>1.4</td>
<td>1.3</td>
<td>NS</td>
</tr>
<tr>
<td>&lt;70 mmHg SBP epochs</td>
<td>0.41</td>
<td>0.40</td>
<td>NS</td>
</tr>
<tr>
<td>&lt;60 mmHg SBP epochs</td>
<td>0.12</td>
<td>0.11</td>
<td>NS</td>
</tr>
<tr>
<td>&lt;70 mmHg MAP epochs</td>
<td>3.9</td>
<td>3.9</td>
<td>NS</td>
</tr>
<tr>
<td>&lt;60 mmHg MAP epochs</td>
<td>1.3</td>
<td>1.2</td>
<td>NS</td>
</tr>
<tr>
<td>&lt;50 mmHg MAP epochs</td>
<td>0.24</td>
<td>0.21</td>
<td>NS</td>
</tr>
<tr>
<td>40% ↓ in SBP epochs</td>
<td>2.8</td>
<td>2.7</td>
<td>NS</td>
</tr>
<tr>
<td>50% ↓ in SBP epochs</td>
<td>0.75</td>
<td>0.70</td>
<td>NS</td>
</tr>
<tr>
<td>60% ↓ in SBP epochs</td>
<td>0.11</td>
<td>0.13</td>
<td>NS</td>
</tr>
<tr>
<td>40% ↓ in MAP epochs</td>
<td>1.4</td>
<td>1.2</td>
<td>NS</td>
</tr>
<tr>
<td>50% ↓ in MAP epochs</td>
<td>0.33</td>
<td>0.26</td>
<td>NS</td>
</tr>
<tr>
<td>60% ↓ in MAP epochs</td>
<td>0.05</td>
<td>0.04</td>
<td>NS</td>
</tr>
<tr>
<td>Vasopressor doses</td>
<td>4.5</td>
<td>4.2</td>
<td>0.04</td>
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<tr>
<td>Vasopressor infusion</td>
<td>157 (2.3%)</td>
<td>67 (1.8%)</td>
<td>NS</td>
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<tr>
<td>Length of surgery (h)</td>
<td>3.0</td>
<td>2.9</td>
<td>NS</td>
</tr>
<tr>
<td>PRBC units</td>
<td>0.20</td>
<td>0.21</td>
<td>NS</td>
</tr>
<tr>
<td>Blood pressure parameters</td>
<td>Yes ACE-I (n = 2,215)</td>
<td>No ACE-I (n = 1,664)</td>
<td>p Value</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-----------------------</td>
<td>----------------------</td>
<td>---------</td>
</tr>
<tr>
<td>&lt;80 mmHg SBP epochs</td>
<td>1.4</td>
<td>1.1</td>
<td>NS</td>
</tr>
<tr>
<td>&lt;70 mmHg SBP epochs</td>
<td>0.43</td>
<td>0.32</td>
<td>NS</td>
</tr>
<tr>
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</tr>
<tr>
<td>40% ↓ in SBP epochs</td>
<td>2.8</td>
<td>2.4</td>
<td>0.02</td>
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<tr>
<td>50% ↓ in SBP epochs</td>
<td>0.72</td>
<td>0.56</td>
<td>0.02</td>
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<td>60% ↓ in SBP epochs</td>
<td>0.11</td>
<td>0.10</td>
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<td>4.8</td>
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<td>Vasopressor infusion</td>
<td>31 (1.9%)</td>
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<td>3.1</td>
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<td>0.30</td>
<td>0.23</td>
<td>NS</td>
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</table>
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*

Background:

• Retrospective, Propensity matched
• Non-cardiac surgery
• 18,000 (9,000 ACEI users who withheld vs 9,000 non-ACEI)

Test:

• Intraoperative hypotension, vasoactive medications, IVF
• Perioperative mortality, MI and AKI
• ACEI only
**Table 6. Summary of Intraoperative Hemodynamic Characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>ACEI (n = 9028)</th>
<th>Non-ACEI (n = 9028)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasopressor use, yes, no. (%)</td>
<td>6049 (67)</td>
<td>5,925 (66)</td>
<td>0.051</td>
</tr>
<tr>
<td>Ephedrine, mg</td>
<td>0 [0, 10]</td>
<td>0 [0, 10]</td>
<td>0.42</td>
</tr>
<tr>
<td>Phenylephrine, mg</td>
<td>0 [0, 300]</td>
<td>0 [0, 200]</td>
<td>&lt;.001</td>
</tr>
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<td>Epinephrine, mg</td>
<td>0 [0, 0]</td>
<td>0 [0, 0]</td>
<td>0.86</td>
</tr>
<tr>
<td>Estimated blood loss, cc</td>
<td>100 [20, 300]</td>
<td>100 [25, 300]</td>
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</tr>
<tr>
<td>Crystalloid, L</td>
<td>3.1 [1.8, 4.4]</td>
<td>3.0 [1.8, 4.2]</td>
<td>0.08</td>
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</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>137 ± 22</td>
<td>136 ± 22</td>
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<tr>
<td>Average during surgery</td>
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<td></td>
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**Table 5. Incidence of Secondary Outcomes Within the Propensity-Matched Subset (n = 18,056)**

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<tr>
<th>Secondary outcome</th>
<th>Incidence (%)</th>
<th>ACEI (n = 9028)</th>
<th>Non-ACEI (n = 9028)</th>
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<td>30-day mortality*</td>
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<td>140 (1.6)</td>
<td>146 (1.7)</td>
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</tbody>
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Two themes in literature

- Chronic ACEI exposure vs. Never ACEI exposure
- Chronic ACEI exposure vs. Withheld operative day
Two themes in literature

- Chronic ACEI exposure (Withheld operative day)
- Never ACEI exposure

VS

- Chronic ACEI exposure
- Chronic ACEI exposure (Continued operative day)
Two themes in literature

- VISION study
- South Africa
Withholding versus Continuing Angiotensin-converting Enzyme Inhibitors or Angiotensin II Receptor Blockers before Noncardiac Surgery

Pavel S. Roshanov, M.D., M.Sc. (ANESTHESIOLOGY 2017; 126:16-27)

Study name: The “VISION” study
(Vascular events in noncardiac surgery patients cohort evaluation)

Background:
• International, prospective, cohort study
• Non-cardiac surgery

Size: Subgroup analysis of 4,802 on ACEI or ARBs

Test: Held ACEI/ARBs 24 hours before surgery

Outcome: 30 day mortality
Withholding versus Continuing Angiotensin-converting Enzyme Inhibitors or Angiotensin II Receptor Blockers before Noncardiac Surgery
Pavel S. Roshanov, M.D., M.Sc. (Anesthesiology 2017; 126:16-27)

- **Holding** ACEI / ARB 24hrs preop
  - ➔ less intraoperative hypotension
    - aRR 0.80 (0.73-0.88), p < 0.001
  - ➔ “holding is associated with lower risk of death”
    - composite outcome (mortality, MINS, stroke)
    - aRR 0.82 (0.70-0.96), p = 0.01
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### A. Medication withheld

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Events in withheld vs. continued</th>
<th>aRR (95% CI), p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, MINS, or stroke</td>
<td>150/1245 (12.0%) vs. 459/3557 (12.9%)</td>
<td>0.62 (0.70–0.96), 0.01</td>
</tr>
<tr>
<td>Death</td>
<td>25/1245 (2.0%) vs. 74/3557 (2.1%)</td>
<td>0.69 (0.39–1.24), 0.21</td>
</tr>
<tr>
<td>MINS</td>
<td>132/1245 (10.6%) vs. 399/3541 (11.3%)</td>
<td>0.84 (0.70–0.99), 0.048</td>
</tr>
<tr>
<td>Stroke</td>
<td>8/1245 (0.6%) vs. 26/3557 (0.7%)</td>
<td>0.81 (0.30–2.2), 0.68</td>
</tr>
<tr>
<td>Intraop. hypotension</td>
<td>290/1245 (23.3%) vs. 1017/3557 (26.6%)</td>
<td>0.60 (0.73–0.88), &lt;0.001</td>
</tr>
<tr>
<td>Postop. hypotension</td>
<td>242/1245 (19.4%) vs. 719/3557 (20.2%)</td>
<td>0.92 (0.77–1.10), 0.36</td>
</tr>
<tr>
<td>MI (Exploratory)</td>
<td>57/1245 (4.6%) vs. 148/3557 (4.2%)</td>
<td>0.91 (0.66–1.27), 0.59</td>
</tr>
<tr>
<td>Death, MI, or stroke (Exploratory)</td>
<td>78/1245 (6.3%) vs. 221/3557 (6.2%)</td>
<td>0.81 (0.62–1.03), 0.08</td>
</tr>
</tbody>
</table>

### B. Hypotension

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Events in exposed vs. unexposed</th>
<th>aRR (95% CI), p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, MINS, or stroke</td>
<td>464/4162 (11.1%) vs. 945/10525 (9.0%)</td>
<td>1.11 (0.98–1.25), 0.09</td>
</tr>
<tr>
<td>Death</td>
<td>133/4162 (3.2%) vs. 169/10525 (1.6%)</td>
<td>1.41 (1.07–1.86), 0.02</td>
</tr>
<tr>
<td>MINS</td>
<td>353/4138 (8.5%) vs. 807/10496 (7.7%)</td>
<td>1.04 (0.90–1.20), 0.58</td>
</tr>
<tr>
<td>Stroke</td>
<td>32/4162 (0.8%) vs. 58/10525 (0.6%)</td>
<td>1.14 (0.85–1.54), 0.37</td>
</tr>
<tr>
<td>Postop. hypotension</td>
<td>1133/4162 (27.2%) vs. 1595/10525 (15.2%)</td>
<td>1.65 (1.48–1.84), &lt;0.001</td>
</tr>
<tr>
<td>MI (Exploratory)</td>
<td>137/4162 (3.3%) vs. 309/10525 (2.9%)</td>
<td>1.05 (0.80–1.35), 0.74</td>
</tr>
<tr>
<td>Death, MI, or stroke (Exploratory)</td>
<td>273/4162 (6.6%) vs. 472/10525 (4.5%)</td>
<td>1.23 (1.03–1.47), 0.03</td>
</tr>
</tbody>
</table>

---

**Note:** Adjusted Relative Risk (aRR) with 95% Confidence Interval (CI) and p-value.
Background:
- 9 studies
  - 5 randomized clinical trials
  - 4 retrospective cohort studies

Size:
- 6,000 patients

Test:
- Continued vs held ACEI/ARBs 24 hours before surgery

Outcomes: intraop hypotension, major cardiovascular outcomes
A Systematic Review of Outcomes Associated With Withholding or Continuing Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers Before Noncardiac Surgery

Caryl Hollmann, MBChB, DA(SA), Nicole L. Fernandes, MBChB, DA(SA), and Bruce M. Biccard, MBChB, FCA, PhD

- **Holding ACEI / ARB preoperatively**
  - → **Less intraop hypotension**
  - OR 0.63; (0.47-0.85), p = 0.002

**Figure 4.** Intraoperative hypotension associated with withholding or continuing ACE-I or ARB therapy. ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; M–H, Mantel-Haenszel.
• Holding ACEI / ARB preoperatively
  • 0.002
  • \rightarrow \text{No association with mortality, MACE, stroke or AKI}

**Figure 2.** Mortality associated with withholding or continuing ACE-I or ARB therapy. Zero arm events not included. ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; M–H, Mantel-Haenszel.

**Figure 3.** Major adverse cardiac events associated with withholding or continuing ACE-I or ARB therapy. Zero arm events not included. ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; M–H, Mantel-Haenszel.
No clear association with adverse outcomes

ACEI/ARB $\rightarrow$ Intraoperative hypotension

Intraoperative hypotension $\neq$ Adverse outcomes?
Keep MAP > 55 mmHg
Cumulative BP

A. Postop Renal Injury

B. Postop Myocardial Injury

Relationship between Intraoperative Mean Arterial Pressure and Clinical Outcomes after Noncardiac Surgery…

Walsh et al. Anesthesiology 2013; 119:507-15
Keep MAP > 60 mmHg
Cumulative BP

A. Postop Renal Injury  B. Postop Myocardial Injury

Relationship between Intraoperative Mean Arterial Pressure and Clinical Outcomes after Noncardiac Surgery…

Walsh et al. Anesthesiology 2013; 119:507-15
Intraoperative Hypotension (MAP and Duration) and Postoperative Organ Injury: A Meta-analysis

<table>
<thead>
<tr>
<th>MAP</th>
<th>Mortality</th>
<th>AKI</th>
<th>MI</th>
<th>Stroke</th>
<th>Delirium</th>
<th>All</th>
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</thead>
<tbody>
<tr>
<td>80 mmHg</td>
<td>1.02</td>
<td>1.02</td>
<td>1.04</td>
<td>1.08</td>
<td>1.08</td>
<td>Low</td>
</tr>
<tr>
<td>70 mmHg</td>
<td>1.02</td>
<td>1.04</td>
<td>1.06</td>
<td>1.06</td>
<td>1.06</td>
<td>Low</td>
</tr>
<tr>
<td>60 mmHg</td>
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<td>1.06</td>
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</tr>
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Acute Kidney Injury Incidence versus Intraoperative Hypotension Nadir by Preoperative Risk Quartile

Mike Mathis, Robert Freundlich, et al. Anesthesiology, Nov 2019
“Avoid Hypotension” Individualize BP Management
And Cumulative “damage” so keep track
“Avoid Hypotension”  Individualize BP Management And Cumulative “damage” so keep track

Active Alerts
Cumulative time for MAP < 60 = 12 minutes.
New labs: Glucose.
Attending has not signed in.
Benefits to continuing ACEI/ARB

• Improved mortality to perioperative ACEI use in patients with reduced LV function.
  • Feringa et al. Semin Cardiothorac Vasc Anesth 2006

• Reduced post operative hypertension
  • Patients with poorly controlled preoperative blood pressure
    • Vasallo MC. J Cardiothorac Vasc Anesth. 2017
    • Pigott DW. Br J Anaesth. 1999

• Not restarting within 48hours post-operatively associated with increased morbidity/30d mortality
  • Lee SM et al. Anesthesiology. 2015
Guidelines (Non-cardiac surgery)

• 2014 ACC/AHA guidelines
  • Continuation is “reasonable”
  • If withheld, restart as “soon as feasible”
• 2017 Canadian Cardiovascular Society Guidelines
  • okay to hold 24 hours prior
  • Restart on post op day 2
• 2014 ESC/ESA Guidelines
  • Continue in stable patients with LV dysfunction / HF
  • Otherwise okay to hold 24 hours
• ASA - none
• UM – hold 24 hours prior to operative day (but don’t cancel case because of this....)
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  • Otherwise okay to hold 24 hours
• ASA - none
• UM – hold 24 hours prior to operative day (but don’t cancel case because of this....) \(\rightarrow\) JUST BE PREPARED TO TREAT BP!
Conventional Therapy

- Reduce anesthetic agent
- Volume expansion
- Vasoactive medications
  - Phenylephrine
  - Ephedrine
Vasopressin

• 0.5-1 unit bolus
• Infusions:
  - AVP: 0.03 unit/min
  - Terlipressin: 1-2mcg/kg/h
Treatment

- Conventional Therapy
- Vasopressin
  - Methylene Blue
  - Tertiary agents
    - AT2 Angiotensin II
Methylene Blue

- Interferes with NO – cGMP pathway, inhibiting the vasorelaxation effect on smooth muscle.
- Bolus dose of 1-2mg/kg over 10 – 20 minutes
- Followed by infusion of 0.25mg/kg/hr for 48-72 hours
Contraindications to MB

- SSRIs
- G6PD deficiency
MB contraindicated w/ SSRIs

- Methylene Blue is a potent monoamine oxidase (MAO) inhibitor.
- MB can produce serotonin toxicity in the perioperative period
MB contraindicated w/ SSRIs

- Methylene Blue is a potent monoamine oxidase (MAO) inhibitor.
- MB can produce serotonin toxicity in the perioperative period

- SSRIs
- SNRIs
- TCAs
- Tramadol
- Clomipramine
- Methamphetamines

MB contraindicated w/ G6PD deficiency

• Methylene Blue needs to be reduced
  • NADPH from Pentose Phosphate pathway
    • Requires G6PD enzyme
  • MB → Methylene Leucobluie
  • G6PD deficiency
    • MB promotes oxidative stress → methemoglobinemia, hemolysis

• The next slide is very busy, please don’t freak out.
Glycolysis

Pentose Phosphate pathway (hexose monophosphate shunt)

NADH and NADPH-dependent methemoglobin reduction

Methylene leucoblu

Cytochrome b5 reductase (95-99%) (aka methemoglobin reductase)
• Approved by FDA 12/21/2017
• Indication: increase blood pressure in distributive shock
• Mechanism of action: vasoconstriction and aldosterone release
• Half-life of less than one minute
• High-dose vasopressors: > 0.2 mcg/kg/min NE equivalent or greater
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Norepinephrine equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.1 μg/kg/min</td>
<td>0.1 μg/kg/min</td>
</tr>
<tr>
<td>Norepinephrine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.1 μg/kg/min</td>
<td>0.1 μg/kg/min</td>
</tr>
<tr>
<td>Dopamine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15 μg/kg/min</td>
<td>0.1 μg/kg/min</td>
</tr>
<tr>
<td>Phenylephrine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.0 μg/kg/min</td>
<td>0.1 μg/kg/min</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>0.04 U/min</td>
<td>0.1 μg/kg/min</td>
</tr>
</tbody>
</table>
AT2
Angiotensin II

Administration:

- Starting dose is 20 NANOgrams/kg/min
- Central access “recommended”
- Infusion only
- Compatible with norepinephrine, epinephrine, vasopressin, phenylephrine and dopamine
Titration (per FDA): https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209360s000lbl.pdf

- Titrate increments of 5-15 ng/kg/min every 5 minutes
- Max 80ng/kg/min within the first 3 hours
- Maintenance dose: 40 ng/kg/min
  - as low as 1.25 ng/kg/min may be used

- To allow downtitration of catecholamines
Adverse events to be aware of:

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>GIAPREZA N=163</th>
<th>Placebo N=158</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolic events&lt;sup&gt;a&lt;/sup&gt;</td>
<td>21 (12.9%)</td>
<td>8 (5.1%)</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>7 (4.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>16 (9.8%)</td>
<td>11 (7.0%)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>14 (8.6%)</td>
<td>9 (5.7%)</td>
</tr>
<tr>
<td>Fungal infection</td>
<td>10 (6.1%)</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Delirium</td>
<td>9 (5.5%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Acidosis</td>
<td>9 (5.5%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>7 (4.3%)</td>
<td>4 (2.5%)</td>
</tr>
<tr>
<td>Peripheral ischemia</td>
<td>7 (4.3%)</td>
<td>4 (2.5%)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Including arterial and venous thrombotic events

DVT prophylaxis should be considered
Hold or not hold?
Which patients?
How long?
High quality RTCs are needed
Impact of renin-angiotensin system inhibitors continuation versus discontinuation on outcome after major surgery: protocol of a multicenter randomized, controlled trial (STOP-or-NOT trial)

Matthieu Legrand\textsuperscript{1,2,3,4}, Emmanuel Futier\textsuperscript{5}, Marc Leone\textsuperscript{6}, Benjamin Deniau\textsuperscript{1,2,3}, Alexandre Mebazaa\textsuperscript{1,2,3,4}, Benoît Plaud\textsuperscript{1,2,3}, Pierre Coriat\textsuperscript{7}, Patrick Rossignol\textsuperscript{8,9}, Eric Vicaud\textsuperscript{9}, Etienne Gayat\textsuperscript{1,2,3,4} and for the STOP-OR-NOT study investigators

- ClinicalTrials.gov, NCT03374449. Registered on 11 December 2017.
- Prospective, RCT
- France, > 30 centers
- 2,222 patients planned
- Estimated completion date: 4/2021
Impact of renin-angiotensin system inhibitors continuation versus discontinuation on outcome after major surgery: protocol of a multicenter randomized, controlled trial (STOP-or-NOT trial)

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- Episodes of hypotension defined as MAP < 60
- Lowest and duration of hypotension recorded
  - Mortality
  - LOS
  - Vascular
  - Renal related
Conclusion

• Some patients may benefit from continuing ACEI/ARBs (and others will forget to hold)
• Preoperative planning
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  • Preoperative planning

• Don’t cancel the case!
  • Be prepared to treat
  • **Vasopressin** is likely the best choice
Conclusion

• Some patients may benefit from continuing ACEI/ARBs (and others will forget to hold)
  • Preoperative planning

• Don’t cancel the case!
  • Be prepared to treat
  • **Vasopressin** is likely the best choice

• At least MAP > 60 \(\rightarrow\) cumulative damage!
  • future decision support for individualized care
Thank you!