Hold the ACEi and ARBs? What is the evidence?

Between Myth and Reality
Evidences and Doubts

The whole problem with the world is that fools and fanatics are always so certain of themselves, and wiser people so full of doubts.

-Bertrand Russell

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Disclosures

I did not receive any honoraria, don’t own any royalties, or gained other benefits for this presentation.

I do not hold significant “interest” that needs to be disclosed, related to the presentation.
Learning Objectives

1. Define physiology of blood pressure control by Angiotensin, identify current pharmacology strategies to control hypertension and compare anesthesiology preoperative guidelines.

2. Analyze the risk factors for intraoperative hypotension (IOH) and identify current mortality and morbidity related to IOH.

3. Discuss optimal perioperative clinical strategies based on evidence based medicine.
Renin-angiotensin-aldosterone system

Angiotensinogen → Angiotensin I → Angiotensin II

Liver

Lungs

Kidney

Surface of pulmonary and renal endothelium: ACE

Decrease in renal perfusion (juxtaglomerular apparatus)

Renin

Kidney

Sympathetic activity

Tubular Na⁺ Cl⁻ reabsorption and K⁺ excretion. H₂O retention

Adrenal gland: cortex

Aldosterone secretion

Arteriolar vasoconstriction. Increase in blood pressure

ADH secretion

Pituitary gland: posterior lobe

Collecting duct: H₂O absorption

Water and salt retention. Effective circulating volume increases. Perfusion of the juxtaglomerular apparatus increases.
ACE INHIBITORS AND ARB

Compelling Indications

- Systolic Heart Failure
- DM
- CKD with Proteinuria
- CAD

Monitoring

- 1-2 weeks after initiation or dose change for K & Cr
- Every 6 months on stable doses

Side Effects

- Dry Cough → Switch to ARB
- Angioedema: ARB likely okay, consider severity
- Hyperkalemia: supplements, diet, worsening renal fxn

Combining RAAS inhibitors is generally not recommended

- No added benefit CV or renal outcomes / Increased toxicity
- ACE or ARB + aldosterone antagonist is the exception

Avoid in Pregnancy
HYPOPERFUSION

Conditions Causing Hypoperfusion
- Hypotension
- Renal arterial disease
- Dehydration
- Congestive heart failure

ACE INHIBITOR TREATED

Afferent Arteriole (Decreased flow)
Effarent Arteriole (Constricted)
Afferent Arteriole (Decreased or normal flow)
Effarent Arteriole (Dilated)

Increased Serum Creatinine With RAAS Blockade

ACE inhibitor or ARB

↑ Afferent tone
↓ Flow
Luminal obstruction

↓ Effarent tone

ACE

GFR

ANATOMIC
Renal artery stenosis

FUNCTIONAL
- Effective arterial blood volume
- NSAIDs, calcineurin inhibitor
- Sepsis

Care with K⁺ retaining diuretics
Hypertension; low first dose (or prandopril)
Monitor K⁺, renal function
Chronic dry cough

ACE INHIBITORS: POTENTIAL SIDE EFFECTS

Opie 2012

via Bradykinin
Larynx

Adrenals
Aldo↓
Plasma K⁺↑

Acute BP↓
GFR falls

CHF

Delayed onset

Acute angioedema (rare)
ACEIs were found to prevent new onset DKD and death in normo-albuminuric people with diabetes, and could therefore be used in this population.
We found predominantly moderate quality evidence that all-cause mortality is similar when first-line RAS inhibitors are compared to other first-line antihypertensive agents.

- First-line thiazides caused less HF and stroke than first-line RAS inhibitors.

- Compared with first-line CCBs, first-line RAS inhibitors reduced HF but increased stroke. The magnitude of the reduction in HF exceeded the increase in stroke.
1. What are the current guidelines regarding ACEI/ARBs use in the perioperative period?
2. What are the dangers to using them during this period?
3. What do we know about these dangers?
4. Are the current “practice” guidelines appropriately addressing these matters? Is there enough evidence to justify them?

Clinical Questions and Dilemmas

- IOH (Intraoperative hypotension)
- AKI (Acute Kidney Injury)
- MINS (Myocardial Injury after Non cardiac Surgery)
- Others? (Stroke, IscOptNeu, “POCD/Delirium”)
**ACEIs or ARBs**

- Continuation of ACEIs or ARBs is reasonable perioperatively.
  
  **IIa, B**

- If ACEIs or ARBs are held before surgery, it is reasonable to restart it PO as soon as clinically feasible.
  
  **IIa, C**
We recommend withholding ACEI/ARB starting 24 hours before noncardiac surgery in patients treated chronically with an ACEI/ARB (Strong Recommendation; Low-Quality Evidence).

- Substantial increase in the risk of IOH associated with perioperative continuation of ACEI/ARB therapy.
- Because the risk of hypotension is greatest within 24 hours of surgery, physicians should consider restarting ACEI/ARB on day 2 after surgery in patients receiving chronic ACEI/ARB therapy, if the patient is hemodynamically stable.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Management of medications taken chronically and smoking before noncardiac surgery</td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td>Withhold at least 3 days before surgery and restart ASA when the risk of bleeding related to surgery has passed (ie, 8-10 days after major noncardiac surgery)</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>Continue the β-blocker during the perioperative period; however, if a patient’s systolic blood pressure is low before surgery, physicians should consider decreasing or holding the dose of the β-blocker before surgery</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>Withhold ACEI/ARB 24 hours before noncardiac surgery and restart ACEI/ARB on day 2 after surgery, if the patient is hemodynamically stable</td>
</tr>
<tr>
<td>Statin</td>
<td>Continue the statin during the perioperative period</td>
</tr>
<tr>
<td>Smoking</td>
<td>Discuss and facilitate smoking cessation (eg, nicotine replacement therapy), ideally starting ≥ 4 weeks before surgery</td>
</tr>
<tr>
<td>Initiation of new medications and coronary revascularization before noncardiac surgery</td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td>Do not initiate ASA for the prevention of perioperative cardiac events</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>Do not initiate a β-blocker within 24 hours before noncardiac surgery</td>
</tr>
<tr>
<td>α₁-Agonist</td>
<td>Do not initiate an α₁-agonist for the prevention of perioperative cardiovascular events</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>Do not initiate a calcium channel blocker for the prevention of perioperative cardiovascular events</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>Do not undertake preoperative prophylactic coronary revascularization for patients with stable coronary artery disease</td>
</tr>
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</table>

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; ASA, acetylsalicylic acid.

* This applies to patients age 45 years of age or older or 18-44 years of age with known significant cardiovascular disease (ie, history of coronary artery disease, cerebral vascular disease, peripheral vascular disease, congestive heart failure, or a severe obstructive intracardiac abnormality [eg, severe aortic stenosis, severe mitral stenosis, or severe hypertrophic obstructive cardiomyopathy]) undergoing noncardiac surgery requiring hospital admission.

* Except in patients with a recent coronary artery stent and patients undergoing carotid endarterectomy.

7.8 ACE Inhibitors and Angiotensin Receptor Antagonists

Observational studies have shown that patients on ACE inhibitors or angiotensin receptor blockers (ARBs) have more frequent transient intraoperative hypotension, but no difference in important outcomes such as death, myocardial infarction, stroke or renal failure [78, 79]. In the absence of protection, or hazard, the ACC/AHA guideline recommends to continue treatment with ACE inhibitors and ARBs perioperatively (IIa B). If they are withheld before surgery it is recommended to restart as soon as clinically feasible postoperatively (IIa C).

The ESC/ESA guideline recognises that perioperative use of ACE inhibitors or ARBs carries the risk of severe hypotension, especially following induction of anaesthesia. This adverse effect is less frequent when ACE inhibitors are discontinued the day before surgery, hence ACE inhibitors withdrawal should be considered 24 h before surgery when they are prescribed for hypertension, and resumed after surgery as soon as blood volume and arterial pressure are stable (IIa C). With ARBs hypotension occurs at least as much as with ACE inhibitors, and the response to vasopressors may be impaired.

In patients with stable left ventricular systolic dysfunction it appears reasonable to continue treatment with ACE inhibitors under close monitoring (IIa C). By contrast if LV dysfunction is discovered during the pre-operative evaluation in untreated patients in a stable condition, surgery should, if possible, be postponed, to allow for diagnosis of the underlying cause and the introduction of ACE inhibitors.

- Patients who withheld their ACEI/ARB in the 24 h before surgery were less likely to suffer of all-cause death, stroke, or myocardial injury after noncardiac surgery at 30 days compared to the ones who did not. 
  
  (150/1,245 [12.0%] vs. 459/3,557 [12.9%]; adjusted relative risk, 0.82; 95% CI, 0.70 to 0.96; P = 0.01); Adjusted relative risk, 0.80; 95% CI, 0.72 to 0.93; P < 0.001; respectively).

- The risk of PO hypotension was similar between the two groups.
  
  (adjusted relative risk, 0.92; 95% CI, 0.77 to 1.10; P = 0.36). Results were consistent across the range of preoperative blood pressures.

**A large randomized trial is needed to confirm this finding.**

**Recommendation: consider withholding ACEI/ARBs 24 h before surgery.**

**Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes.** Anesthesiology. 2014 Mar;120(3):564-78.

**Among adults undergoing noncardiac surgery, MINS is common and associated with substantial mortality.**
The VISION study, given its large sample size and complex multinational logistics, it was not designed to capture extensive physiologic data. Because of this, the hypotension variables were limited to a categorical response (yes/no) although the total duration of the episodes was captured. Unfortunately, neither medication use after surgery nor renal outcomes were systematically captured.

Although ACEI/ARB use was associated with intraoperative hypotension and was correlated with progressively longer total duration, it was not associated with the primary outcome. Postoperative hypotension was associated with the primary outcome but not with ACEI/ARB use.

An acute elevation of creatinine can be precipitated by hypovolemia, sepsis, hemodynamic instability due to new or worsening dysrhythmias, and so forth. Thus, it is tempting to speculate that patients with deteriorating renal function were given their ACEIs/ARBs inappropriately, leading to higher risk of adverse perioperative outcomes associated with either chronic preoperative or acute perioperative renal injury.
In patients with moderate renal insufficiency undergoing cardiac catheterization, withholding ACEI/ARB resulted in a non-significant reduction in contrast-induced AKI and a significant reduction in post-procedural rise of creatinine.

- Preoperative ACEI/ARB usage was associated with functional but not structural acute kidney injury.
- As AKI from ACEI/ARB in this setting is unclear.
Many different definitions of IOH were found and resulted in different IOH incidences.

Any episode of SBP < 80 mmHg was found in 41% of the patients, whereas 93% of the patients had at least one episode of SBP > 20% below baseline. Both definitions are frequently used in the literature.

There is no widely accepted definition of IOH.
MAP below absolute thresholds of 65 mmHg or relative thresholds of 20% were progressively related to both myocardial and kidney injury. They both had comparable ability to detect these outcomes.

At any given threshold, prolonged exposure was associated with increased odds.

Preoperative BP did not have important interactions with the outcomes studied at MAP < 65 mmHg

Anesthetic management can thus be based on IO pressures without regard to preoperative pressure.
• The MAP threshold where the risk for AKI or Myocardial injury increased was < 55 mmHg.

• Compared with never developing a MAP < 55 mmHg, those with a MAP < 55 mmHg for 1-5, 6-10, 11-20, and >20 min had graded increases in their risk of the two outcomes. (AKI: 1.18 [95% CI, 1.06-1.31], 1.19 [1.03-1.39], 1.32 [1.11-1.56], and 1.51 [1.24-1.84], respectively; myocardial injury 1.30 [1.06-1.5], 1.47 [1.13-1.93], 1.79 [1.33-2.39], and 1.82 [1.31-2.55], respectively).

Even short durations of an IO MAP < 55 mmHg are associated with AKI and myocardial injury.

Randomized trials are required to determine whether outcomes improve with interventions that maintain an IO MAP of at least 55 mmHg.
Clinically important hypotension was defined as SBP < 90 mmHg requiring treatment.

IO, the estimated average relative effect across MI and mortality per 10-min increase in hypotension duration was 1.08 (98.3% CI, 1.03, 1.12; P < 0.001).

For the remaining day of surgery, the OR per 10-min increase in hypotension duration was 1.03 (98.3% CI, 1.01, 1.05; P < 0.001).

The average relative effect OR in patients with hypotension during the subsequent 4 days of hospitalization was 2.83 (98.3% CI, 1.26, 6.35; P = 0.002).

Clinically important hypotension was significantly associated with a composite of MI and death during each of the perioperative periods.
• Depending on the definition, IOH occurred in 12-81% of the patients.

• 40% decrease from the pre-induction MAP with a cumulative duration > 30 min was associated with PO myocardial injury. (relative risk, 1.8; 99% CI, 1.2 to 2.6, P < 0.001).

• PO MI and death within 30 days occurred in 26 (6%) and 17 (4%) patients with IOH as defined by a < 60 mmHg, compared with 12 (3%; P = 0.08) and 15 (3%; P = 0.77) patients without IOH, respectively.

- Meta-analysis of 14 cohort studies that were heterogeneous in terms of definition of IOH.

- IOH alone was associated with increased risk of 30-day mortality, MACEs, especially myocardial injury, and AKI. (OR 1.29 [95% CI, 1.19-1.41]), (OR 1.59 [95% CI, 1.23-2.05]), (OR 1.67 [95% CI, 1.31-2.13]), (OR 1.39 [95% CI, 1.09-1.77]); respectively.

- Triple low (IOH coincident with low bispectral index and low MAC) also predicts increased risk of 30-day mortality (OR 1.32 [95% CI, 1.03-1.68]).
ACEIs/ARBs can be continued perioperatively if hemodynamically stable, good renal function and normal electrolytes.
Preoperative ACEI/ARB use was associated with marginally increased use of IV BP med for HTN but not for hypotension, and was not associated with increased MACE, stroke, or death.

The use of preoperative ACEI/ARB appears safe before CEA.
There was no statistically significant difference between the continued or withheld groups in:

- **Vasopressor or IV fluid administration** ((metaraminol use 3.5 [1.5-8.3] mg Vs. 3.5 [1.5-8.5] mg, P=0.67) (1000 ml [800-1500] ml Vs. 1000 [800-1500] ml, P=0.096) respectively).

- **Rates of PO AKI or AFib** ((13% vs 18%, P=0.25)(15% versus 18%, P=0.71) respectively).

No significant differences in measured outcomes between the continued or withheld ACEI/ARB groups were found.

**Problems:**
- Possibility of confounding
- Possibility of Insufficient sample size.

**Future prospective randomized clinical trials are required**

- Patients were classified into groups based upon the timing of PO resumption of an ACEIs (PO days 0 to 14 and 15 to 30).

- Nonresumption of an ACEI in PO days 0 to 14 was independently associated with increased 30-day mortality compared to the restart group. (hazard ratio: 3.44; 95% CI: 3.30-3.60; P < 0.001) Sensitivity analyses maintained this relationship.

Restarting of an ACE-I within PO day 0 to 14 is associated with a decreased 30-day mortality.
Conclusions

• ACEIs and ARBs are safe to use preoperatively.

• Withholding them for the IO period and restarting them as soon as clinically possible, might be the best course of action to prevent intra and postoperative hypotension and based on current evidences, HYPOTHETICALLY reduce adverse outcomes.

• Large scale randomized trials are still needed to find the right answer.
YOU SIT ON A
THRONÉ OF LIES