Articles That Changed My Practice
(Primary Care edition)

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Question #1

- 52 yo comes in for 3 days of left lower quadrant abdominal pain. Tolerating oral intake. Exam: nontoxic, normal vitals, localized LLQ tenderness without peritoneal findings. CT abd/pelvis shows acute, uncomplicated diverticulitis.
- What treatment would you recommend?

A) Outpatient observation

B) Oral amoxicillin / clavulanate

C) Oral ciprofloxacin + metronidazole

D) ED referral for IV antibiotics + observation

E) Hospital admission

Uncomplicated acute diverticulitis

- Antibiotics had previously been considered the "unquestioned cornerstone of treatment"

- Newer evidence suggests diverticulitis may be more inflammatory than infectious

Gastroenterology 2015;149:1944-1949
Dis Colon Rectum 2020;63:728-747

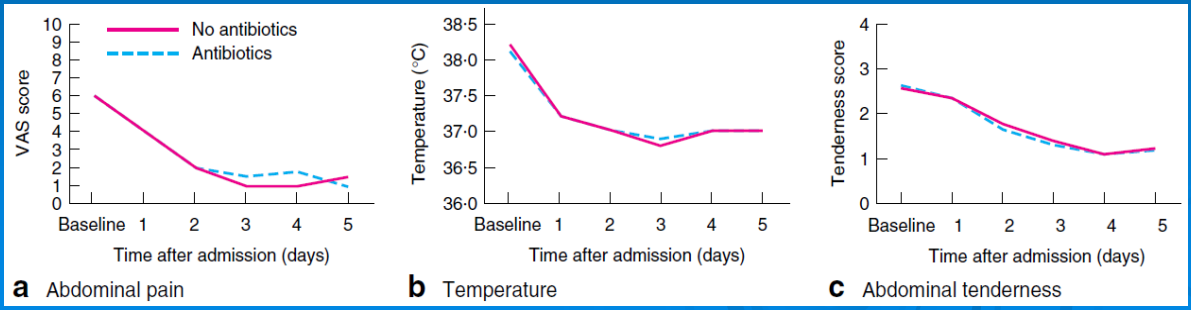
AVOD

- 623 people hospitalized w/ CT-verified, acute uncomplicated left-sided diverticulitis (Sweden/Iceland)
- (IV fluids + Antibiotics) vs. IVF alone

→ no difference in short-term complications, surgery, hospital length of stay

→ no difference in abd pain, bowel habits, recurrence, or above outcomes at 1 year

→ no difference in recurrence, complications, surgery, or colon CA at 11 years



Br J Surg 2012;99:532-9
Br J Surg 2019;106:1542-8

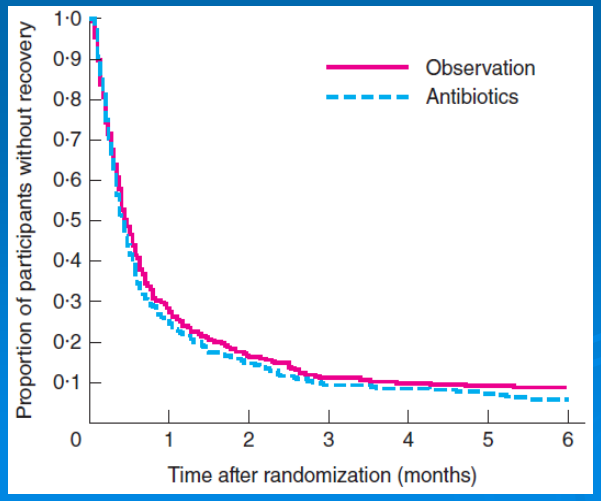
DIABLO

- 528 people w/ CT-proven, 1st-time, acute uncomplicated left-sided diverticulitis (Netherlands)
- IV Antibiotics (hospitalization) vs observational treatment

→ no difference in time to recovery

→ no difference in complicated / ongoing / recurrent dz, sigmoid resection, readmission, adverse events, mortality

→ no difference in recurrent/complicated diverticulitis at 24mos



Br J Surg 2017;104:52-61
Am J Gastroenterol 2018;113:1045-1052

STAND

- 180 people hospitalized w/ CT-proven acute uncomplicated diverticulitis (NZ)
  - Exclusions: 2+ SIRS criteria, immunosuppression, recent anti-inflammatories
  - IV or Oral Abx, vs placebo

→ No difference in hospital length of stay, readmission (7d or 30d), pain scores, need for procedural intervention

Clin Gastroenterol Hepatol 2021;19:503-510

Uncomplicated diverticulitis guidelines

- American Gastroenterological Association 2015, updated 2021:
  - Selective (not routine) use of antibiotics
  - Conditional recommendation, low quality of evidence
- National Institute for Health and Care Excellence 2019
  - Watchful waiting an option if systemically well and no comorbidities
  - Mod to very low quality evidence
- American Society of Colon and Rectal Surgeons 2020
  - Selected patients can be treated without antibiotics
  - Strong recommendation based on high-quality evidence (IA)
- American College of Physicians 2022
  - Manage most patients as outpatients
  - Select patients without antibiotics
  - Conditional, low-certainty

Gastroenterology 2015;149:1944-1949
Gastroenterology 2021;160:906-911
NICE guideline NG147. Nov 2019
Dis Colon Rectum 202;63:728-747
Ann Intern Med 2022;175:399-415

DINAMO-study

- 480 “OUTpatients” with mild acute diverticulitis
  - Initial presentation to the ED (Spain)
  - Exclusions included: 2+ SIRS, immunosuppression, DM w/ complications
  - Amox/clav + NSAIDs vs NSAIDs alone

  → No difference in hospitalizations, ED re-visits, pain

- Outpatient Amox/clav vs quinolone/metronidazole?
  - More Cdiff with quinolones, o/w similar outcomes

  → Amox/clav if using antibiotics

Answer: A

Ann Surg 2021;274:e435-e442
Ann Intern Med 2021. doi: 10.7326/M20-6315

Question #2

- 60yo w/ PMH DM2, PUD, history of pancreatitis and average home BP of 142/91 over the last 3 months despite intensive lifestyle modifications. Ualb/Cr ratio mildly elevated at 42mg/g. No current BP meds.
- Which of the following would you recommend for initial blood pressure treatment?

A) Amlodipine

B) Diltiazem

C) Hydrochlorothiazide

D) Lisinopril

E) Losartan

First-line Anti-HTsives

- 2017 ACC / AHA guideline:
  - Thiazide diuretics
  - Calcium-channel blockers
  - ACE inhibitors
  - ARBs

  Some condition specific guidance (e.g. gout, DM, CHF, etc.) but generally equally recommended

J Am Coll Cardiol 2018;71:e127-e248. doi: 10.1016/j.jacc.2017.11.006.

ACE inhibitors vs ARBs?

- Limited head-to-head data
  - Systematic reviews have included ≤4 RCTs, mostly w/ <500 pts, low event rates
  - AHRQ 2011: call for comparative effectiveness studies (but scant new evidence since then)
- Lisinopril = most commonly used anti-hypertensive worldwide

Hypertension 2021;78:591–603. DOI: 10.1161/HYPERTENSIONAHA.120.16667.)

ACE inhibitors vs ARBs

- LEGEND-HTN study
  - Global (US, Germany, South Korea) network of 8 large observational databases, 1996-2018
- Retrospective cohort design
  - Adjusted for tens of thousands baseline covariates
- Initial HTN treatment
  - ACEi: 80% lisinopril
  - ARB: losartan (45%), valsartan, olmesartan
- Primary outcomes: MI, HF, CVA, composite CV
- 51 secondary and safety outcomes:
  - E.g. Angioedema, cough, syncope, electrolyte abnormalities
  - Plus 76 “negative control” outcomes (check on false positives)

Hypertension 2021;78:591–603. DOI: 10.1161/HYPERTENSIONAHA.120.16667.)

ACE inhibitors vs ARBs

- **ACE inhibitors:** 2,297,881 pts | **ARB:** 673,938 pts
- No difference in MI, CHF, CVA, total CV events

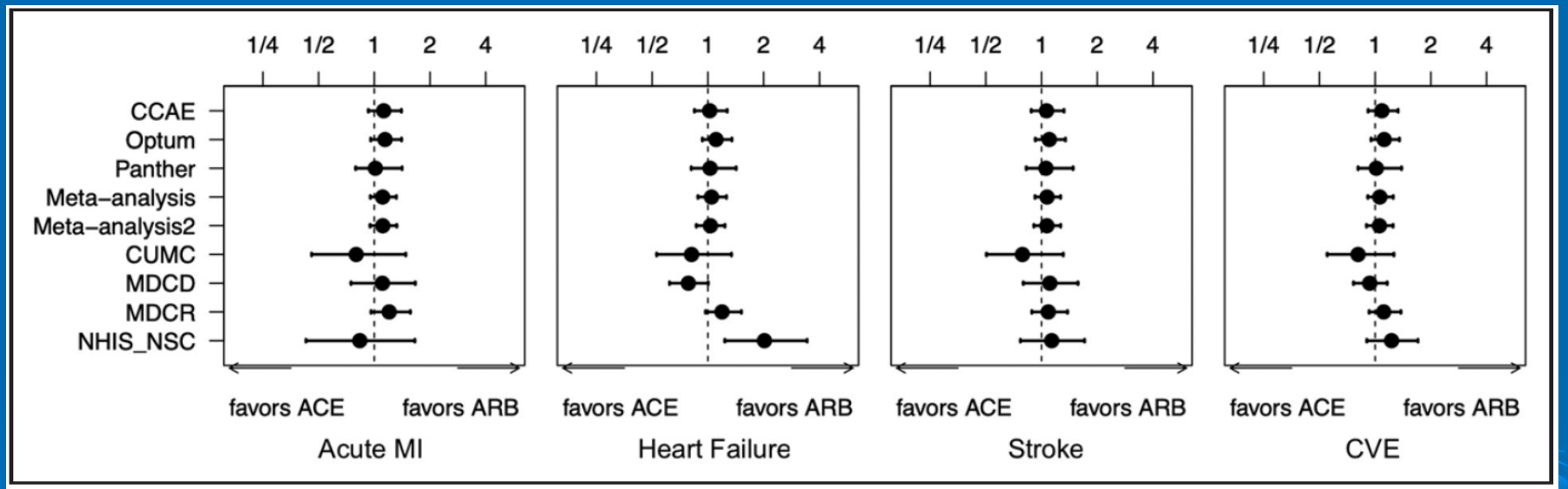


Figure 3. Risk of cardiovascular outcomes in ACE (angiotensin-converting enzyme) inhibitors vs angiotensin receptor blockers (ARBs) across all databases.

Hypertension 2021;78:591–603. DOI: 10.1161/HYPERTENSIONAHA.120.16667.)

ACE inhibitors vs ARBs

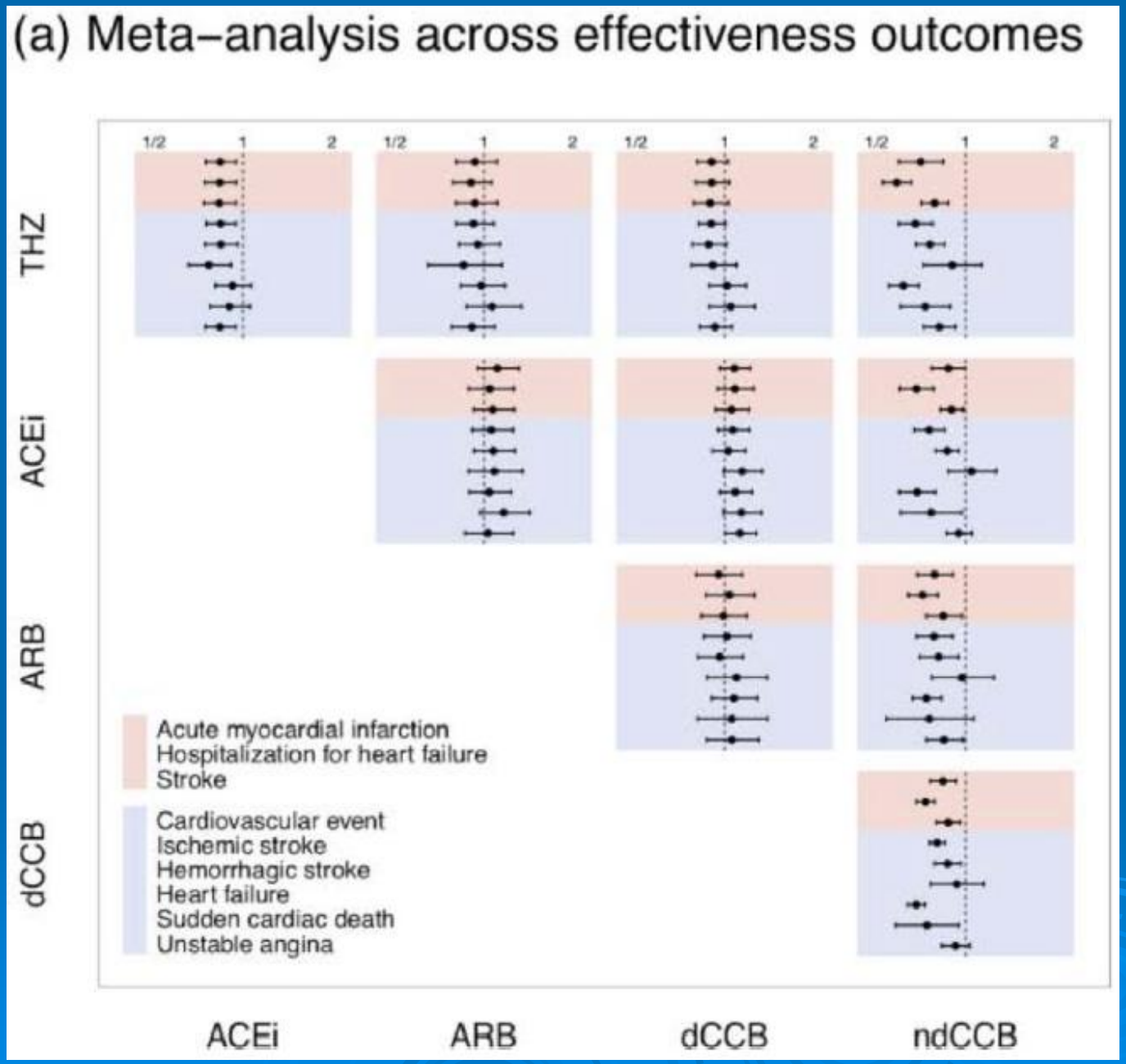
- But… ACE inhibitors had higher rates of:
  - Angioedema (HR 3.31)
  - Cough (HR 1.32)
  - Pancreatitis (HR 1.32)
  - GI bleeding (HR 1.18)
  - Abnormal weight loss (HR 1.18)
- ACEi: ↑bradykinin → cough, angioedema, ?pancreatitis (localized edema of pancreatic duct and pancreas)
- ?GI bleeding – little prior evidence on this

Hypertension 2021;78:591–603. DOI: 10.1161/HYPERTENSIONAHA.120.16667.)

Other LEGEND-HTN tidbits

- Frequency of use: ACEi 48%, Thiazide 17%, dCCB 16%, ARB 15%, ndCCB 3%
- Thiazide vs ACEi? Thiazides win:
  - ↓MI (HR 0.84), ↓HF hosp (HR: 0.83), ↓Stroke (HR 0.83)
  - Safer: e.g. ↓abd pain, diarrhea, GI bleed, hypoTN, neutropenia, thrombocytopenia, angioedema, cough, ARF, hyperK, etc.
  - Cochrane 2023 (first-line thiazides vs others):
    - Thiazides likely ↓CV events and withdrawals due to adverse effects (vs beta-blockers, CCBs, ACEi)

JAMA 2021;326:1244-45
Lancet 2019;394:1816-1826
Cochrane 2023, Issue 7. Art. No: CD008161



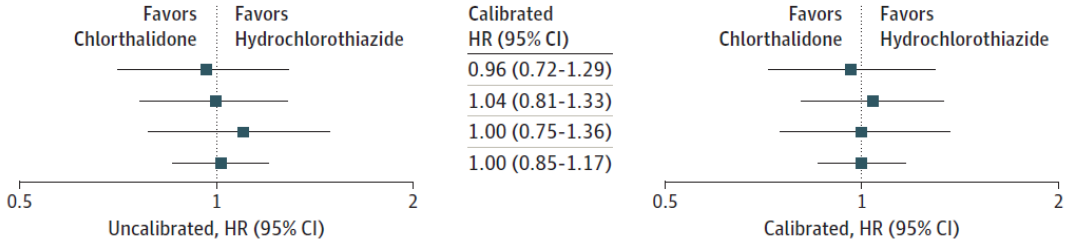
Lancet 2019;394:1816-1826

Other LEGEND-HTN tidbits

- Chlorthalidone vs HCTZ? HCTZ wins:
  - Composite CV outcome: HR 1.00 (0.85-1.17)
  - Chlorthalidone: ↑hypoK (HR 2.72), hypoNa (1.31), ARF (HR 1.37), CKD (HR 1.24), DM 2 (HR 1.21)

Figure 2. Homogeneity on Effectiveness

Source	Uncalibrated HR (95% CI)	Calibrated HR (95% CI)
CCAE	0.96 (0.70-1.29)	0.96 (0.72-1.29)
Optum	1.00 (0.76-1.28)	1.04 (0.81-1.33)
PanTher	1.10 (0.79-1.49)	1.00 (0.75-1.36)
Summary (I^2 <0.01)	1.01 (0.86-1.20)	1.00 (0.85-1.17)



Hazard ratios (HRs) and forest plot of the 3 databases and the meta-analysis for chlorthalidone vs hydrochlorothiazide on the composite cardiovascular disease outcome. The 3 databases showed excellent agreement. CCAE indicates Commercial Claims and Encounters Database.

- 2022 VA RCT: no change in CV events, more hypoK w/ chlorthalidone vs HCTZ

JAMA Int Med 2020;180:542-551
NEJM 2022;387:2401-10

Answer: E

Question #3

- 55yo w/ recent diagnosis of unprovoked DVT/PE, on apixaban for the past 3 months. Normal kidney function, no anemia, no history of major bleeding. Currently asymptomatic.
- What would you recommend regarding continued anticoagulation?

A) Discontinue anticoagulation at this time (3mos)

B) Continue for a total of 6mos, then stop

C) Continue for a total of 12mos, then stop

D) Continue for a total of 2 years, then stop

E) Continue anticoagulation indefinitely

VTE: Duration of anticoagulation

- 2021 ACCP guidelines:
  - Acute VTE: minimum 3 mos anticoagulation
  - VTE w/o transient risk factor (30% 5y recurrence)
    - Strongly recommend "extended-phase" anticoagulation
    - No predefined stop date (longest studies 2-4y)

    (Longer durations do not reduce recurrent VTE risk once anticoagulation is stopped -- Annals 2023)
    - Consider patient preference and risk for recurrent VTE or bleeding
  - Current tools for predicting recurrent VTE / bleeding risk are limited

Chest 2021;160:e545-e608

Ann Intern Med 2023. doi:10.7326/M22-3559

Risks/benefits of long-term anticoagulation

- 1st unprovoked VTE: Indefinite vs 3-6 mos treatment
  - Modeling study based on recent meta-analyses
  - Per 1000 hypothetical 55yo pts, lifelong anticoagulation:
    - 368 fewer recurrent VTE events (**14 fatal PE**)
    - 114 additional major bleeding events (**11 bleeding deaths and 30 ICH**)
    - Cost: CAD $16k / person, no change in QALYs
  - Possible benefit if:
    - Initial dx of PE
    - Very low bleeding risk (Age <65, no CKD, no prior bleeding, no antiplatelet, no anemia)
    - Reduced-dose DOAC used for extended-phase

Answer: ??

Ann Intern Med 2023. doi:10.7326/M22-3559

Question #4

- 72yo w/ HTN on losartan, amlodipine, spironolactone, and hydrochlorothiazide is scheduled for cholecystectomy.
- Which medication should be held on the morning of surgery?

A) Losartan

B) Amlodipine

C) Spironolactone

D) Hydrochlorothiazide

E) All of the above

F) None of the above

Question #5

- 62yo w/ Type 2 DM on insulin glargine, metformin, empagliflozin, glimepiride, and weekly injectable semaglutide is scheduled for sinus surgery.
- Which of the following medications should be held >1 day prior to surgery?

A) Insulin glargine

B) Metformin

C) Empagliflozin

D) Glimepiride

E) Semaglutide

Question #6

- 52yo w/ class 2 obesity scheduled for partial colectomy for recurrent diverticulitis.
- Which of the following weight-loss medications can be continued right up until the day prior to surgery?

A) Phentermine/topiramate

B) Orlistat

C) Semaglutide

D) Bupropion/naltrexone

E) Phentermine alone

Question #7

- 68yo scheduled for knee replacement. Currently on daily naproxen for disabling pain related to severe knee osteoarthritis. They were advised to stop their naproxen ahead of surgery.
- Of the following medications, which can be continued the longest leading up to surgery?

A) Celecoxib

B) Ibuprofen

C) Diclofenac

D) Naproxen

E) Piroxicam

Preoperative med management

- Lack of robust data on preop med management
- Society for Perioperative Assessment and Quality Improvement (SPAQI)

  - International, multidisciplinary society dedicated to the promotion of evidence-based perioperative medicine
  - Series of consensus statements to fill in gaps and resolve conflicting recommendations
  - Groups of experts in Anesthesiology, perioperative medicine, internal medicine, hospital medicine, relevant subspecialists

Mayo Clin Proc 2021;96:1325-1341

SPAQI consensus statements

8 statements on preoperative med management since 2021:

- Opioid and Nonopioid Analgesics:
https://www.mayoclinicproceedings.org/article/S0025-6196(20)30709-6/fulltext

- Dietary Supplements:
https://www.mayoclinicproceedings.org/article/S0025-6196(20)30920-4/fulltext

- Endocrine, Hormonal, and Urologic Meds:
https://www.mayoclinicproceedings.org/article/S0025-6196(20)31129-0/fulltext

- Gastrointestinal and Pulmonary Meds:
https://www.mayoclinicproceedings.org/article/S0025-6196(21)00633-9/fulltext

- Neurologic Meds:
https://www.mayoclinicproceedings.org/article/S0025-6196(21)00849-1/fulltext

- Psychiatric Meds:
https://www.mayoclinicproceedings.org/article/S0025-6196(21)00850-8/fulltext

- Rheumatologic and HIV Meds:
https://www.mayoclinicproceedings.org/article/S0025-6196(22)00261-0/fulltext

- Cardiovascular Meds:
https://www.mayoclinicproceedings.org/article/S0025-6196(22)00264-6/fulltext

SPAQI consensus statements

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- Gastrointestinal and Pulmonary Meds:
https://www.mayoclinicproceedings.org/article/S0025-6196(21)00633-9/fulltext

- Neurologic Meds:
https://www.mayoclinicproceedings.org

- Psychiatric Meds:
https://www.mayoclinicproceedings.org

- Rheumatologic and HIV Meds:
https://www.mayoclinicproceedings.org

- Cardiovascular Meds:
https://www.mayoclinicproceedings.org/article/S0025-6196(22)00264-6/fulltext

Hint: Google “SPAQI rheumatologic” or “SPAQI cardiovascular” to find

Hypertension meds

TABLE. Consensus Recommendations for the Preoperative Management of Cardiac Medications

Medication class	Medications	Continue/hold on the day of surgery	Additional considerations
α-Adrenoceptor blockers (α-blockers)	Doxazosin, phenoxybenzamine, prazosin, and terazosin	Continue	Ensure adequate hydration as postural hypotension may occur with prolonged fasting
Angiotensin-converting enzyme inhibitors	Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril, and ramipril	Hold	Consider continuing for low-risk, minimally invasive procedures with minimal sedation or local anesthesia
Angiotensin II receptor blockers	Azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan	Hold	Consider continuing for low-risk, minimally invasive procedures with minimal sedation or local anesthesia

- HOLD Loop diuretics, ACEi, ARBs, ARNIs (sacubitril/valsartan), Renin inhibitors (aliskerin) on the morning of surgery
- Other anti-HTsives (including non-loop diuretics) okay to continue

Answer: A

Mayo Clin Proc 2021;96:1325-1341

Diabetes meds

- Insulins:
  - NPH: ↓50% AM of surgery, consider ↓25% PM prior
  - Glargine/Detemir/Degludec: 60-80% PM prior or AM of (in those w/ DM2 and those prone to hypoglycemia)

- Non-insulin DM meds: continue day prior, hold AM of surgery, EXCEPT
  - SGLT-2: hold for 3d prior (4d for ertugliflozin)
  - Weekly GLP-1's: hold weekly dose within 7d prior *if* GI surgery or *if* concern for post-op nausea/vomiting/GI dysfunction

  (American Society of Anesthesiologists 2023: hold weekly GLP-1's for a week prior to *any* procedure)

Mayo Clin Proc 2021;96:1655-69

https://www.asahq.org/about-asa/newsroom/news-releases/2023/06/american-society-of-anesthesiologists-consensus-based-guidance-on-preoperative

Answer: C, maybe E

Weight loss meds (in GI statement)

- Phentermine: hold ≥4d prior
- Phentermine/topiramate: check pre-op bicarb, K, Cr, glc. Hold ≥4d prior (can give topiramate alone)
- Orlistat: hold on morning of surgery
- GLP-1 agonists: see Endo guideline
- Bupropion/Naltrexone: hold for 72h prior if opioids expected to be used perioperatively
  - Bupropion can be continued (including day of surgery) as per Psych guideline

Answer: B

Mayo Clin Proc 2021;96:3158-77

NSAIDs (in Rheum statement)

- NSAIDs (non-selective): hold for 7d prior to surgery
- Celecoxib: continue preoperatively, including day of surg
  - Should have minimal effect on bleeding
  - Increasingly used perioperatively for pain control
  - But periop literature for celecoxib is limited (check w/ surgeon)

- Different hold times could be considered based on NSAID half-life, e.g.:
  - Ibuprofen, diclofenac, indomethacin: could hold for 1 day
  - Naproxen, meloxicam: could hold for 4 days
  - Nabumetone: could hold for 6 days
  - Piroxicam: could hold for 10 days

Answer: A

Mayo Clin Proc 2022;97:1551-71

Take home points (p1/2)

- Acute, uncomplicated diverticulitis can be safely treated without antibiotics in selected outpatients
- First-line HTN treatment:
  - Consider ARBs over ACEi – ?similar effectiveness, safer?
  - Consider Thiazides over ACEi – ?more effective, safer?
  - HCTZ over chlorthalidone – similar effectiveness, safer
- Duration of anticoagulation for unprovoked VTE:
  - Minimum 3 months
  - Balance of risks/benefits for 3 mos vs long-term anticoagulation may be closer than previously thought

Take home points (p2/2)

- Google “SPAQI Cardiovascular” or “SPAQI Endocrine” to find preop med recs
  - Hold ACEi/ARB, loop diuretics AM of surgery
  - Hold SGLT2 inhibitors for 3+ days preop
  - Hold GLP1 agonists for GI surgery (or perhaps any surgery)
  - Celecoxib (and shorter-acting NSAIDs) can be given closer to surgery