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UPDATE IN HOSPITAL MEDICINE

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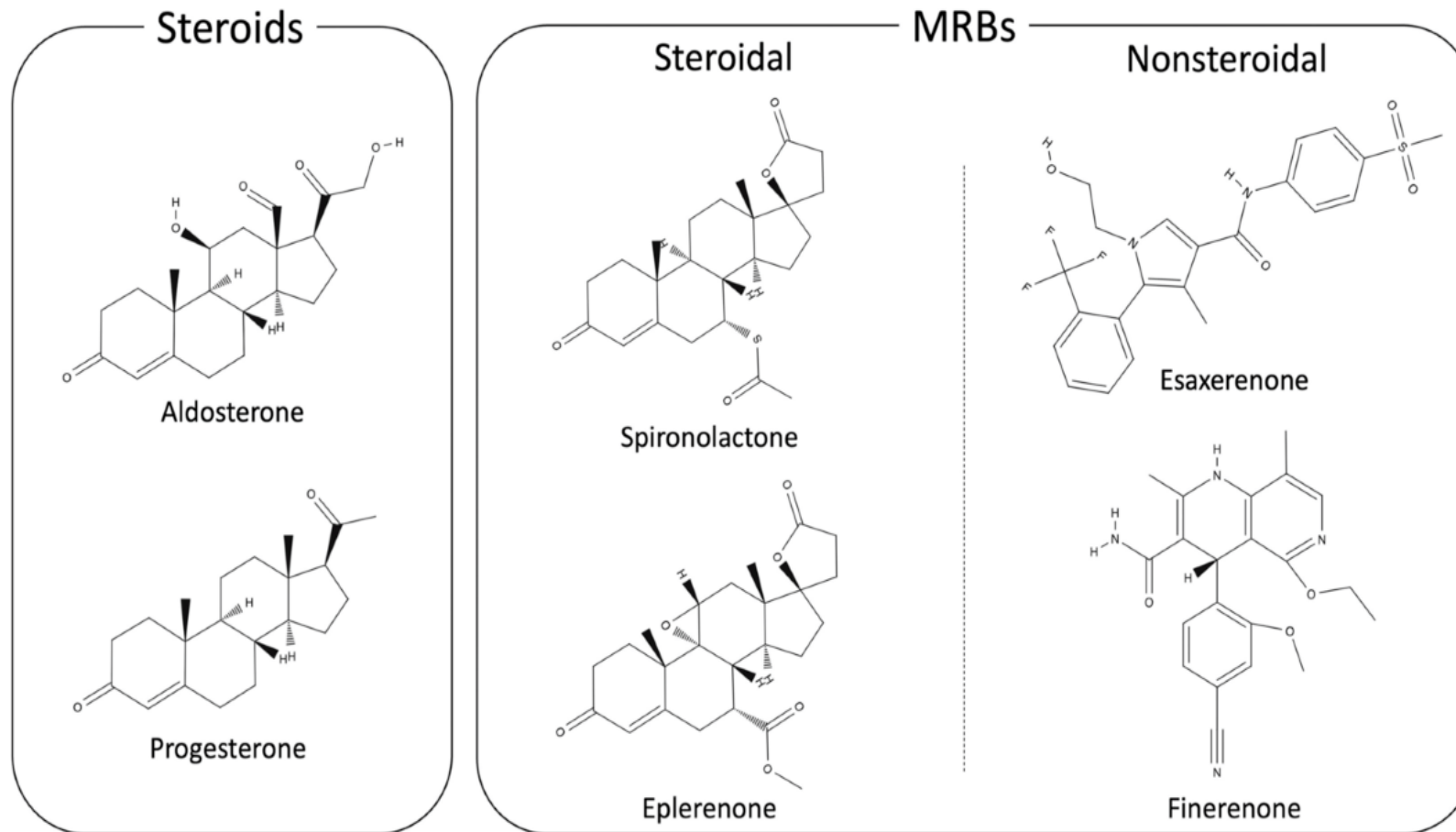
- I have no financial relationship with a commercial entity producing health-care related products and/or services

Objectives

- Review new data on non-steroidal mineralocorticoid antagonists and GLP-1 agonists in heart failure with preserved ejection fraction
- Review new data on antihypertensive use in the hospital setting
- Review data on paracentesis timing in patients admitted to the hospital with cirrhosis and ascites
- Review data on GLP-1 agonists and endoscopy timing
- Review data on “discharge before noon”
- Review new studies in preoperative assessment

Non-Steroidal Mineralocorticoid Receptor Antagonists in HFpEF

Finerenone: A Non-Steroidal Mineralocorticoid Receptor Antagonist



Steroidal MRAs such as spironolactone have major off-target side effects

- partial estrogen agonists (gynecomastia) and progesterone agonists (irregular menses)
- Interfere with testosterone synthesis and binding (decreased libido)

Not seen with non-steroidal MRAs such as finerenone
Finerenone (\$\$\$),
spironolactone (\$)

FINEARTS Trial: Finerenone in HFpEF

- Randomized double-blind trial, 6001 pts with heart failure and LVEF $\geq 40\%$, mean age 72 (>40 yr for enrolment); median follow-up 32 months
- Composite outcome better in finerenone group, driven by less CHF
- Hospitalization or urgent visit for CHF (rate ratio, 0.82; 95% CI, 0.71 to 0.94; $P=0.006$)
- Cardiovascular deaths and all-cause mortality similar in both arms
- Hyperkalemia: 14.3% vs 6.9% in placebo arm
- Similar to TOPCAT results (NEJM 2014): spironolactone reduced CHF hospitalizations, but not all-cause hospitalizations or cardiovascular mortality
 - Hyperkalemia: 18.7% spironolactone vs 9.1% placebo
 - 2.5% quit spironolactone due to gynecomastia

Finerenone May Decrease Incidence of Type 2 Diabetes

- Prespecified subset analysis of FINEARTS trial
- Compared with placebo, finerenone reduced new-onset diabetes by 24% (HR 0.76, 95% CI 0.59–0.97, $p=0.026$)
- Mechanism unclear, possibly related to higher levels of potassium and mineralocorticoid blockade
 - Hypokalemia decreases insulin secretion
 - High aldosterone associated with insulin resistance
- Spironolactone not been associated with reduced incidence of diabetes, perhaps due to off-target activity on corticosteroid receptor, which negates beneficial effects on K^+ levels and mineralocorticoids

Antihypertensives in the Hospital Setting

*A 75-year-old man is admitted with right lower lobe pneumonia. You receive Voaltes from his nurse every 30 minutes about his asymptomatic elevated BP. At what systolic BP threshold will treatment **NOT** increase his risk of acute kidney injury?

1. 140-159 mm Hg
2. 160-179 mm Hg
3. ≥ 180 mm Hg
4. None of the above

As-Needed Blood Pressure Medication is Associated with Acute Kidney Injury

- Retrospective cohort study in Veterans Affairs system
- 133,760 vets (96% male, mean age 71 yr) hospitalized ≥ 3 days on non-ICU medical or surgical floors for reasons not requiring acute BP lowering and who are already on scheduled BP medications
- Comparison: as-needed BP meds used vs no as-needed BP meds used for asymptomatic inpatients with at least one systolic BP > 140
- Propensity score-matched to reduce confounding by indication
- Most commonly used prn agents: beta-blockers, direct vasodilators
- Maximum premedication systolic BP higher in the as-needed BP medication group (180.1 mm Hg) vs the no as-needed BP medication group (169.6 mm Hg)

As-Needed Blood Pressure Medication: Outcomes

- Increased AKI risk in prn group (adjusted HR, 1.23; 95% CI, 1.18-1.29)
- Risk higher with IV antihypertensives
- IV-only prn antihypertensives vs no as-needed BP medication use associated with 64% increased risk of AKI (HR, 1.64; 95% CI, 1.48-1.81)
- Oral as-needed BP medication use vs none associated with smaller, but still significant, AKI risk (HR, 1.17; 95% CI, 1.11-1.24)
- As-needed BP meds associated with 2.11 times greater risk of a 25% systolic BP drop in one hour (HR, 2.11; 95% CI, 1.81-2.46)
- Composite outcome of death, stroke, MI increased in prn group (rate ratio 1.69; 95% CI, 1.49-1.92)

AKI Risk Highest When As-Needed Antihypertensives Used in Lower BP Ranges

- Association between as-needed BP medication use and AKI strongest when preindex maximum systolic BP only slightly elevated
- 140-159 mm Hg (HR, 1.31; 95% CI, 1.20-1.44)
- 160-179 mm Hg (HR, 1.19; 95% CI, 1.10-1.29)
- ≥ 180 mm Hg (HR, 1.10; 95% CI, 1.10-1.20)
- Risk similar with one-time vs recurring prns

Blood Pressure Intensification in Older Adults at Discharge

- 2019 UCSF study
- Retrospective propensity-matched cohort study
- 4056 older adults admitted to VA hospitals with noncardiac conditions (PNA, UTI, DVT); mean age 77 yrs, 98% male
- Exposure: Rx at hospital discharge for new or higher-dose antihypertensive
- 30-day risk of readmission (HR 1.23; 95% CI, 1.07-1.42) and serious adverse events (HR, 1.41; 95% CI, 1.06-1.88) higher with BP med intensification
- No improvement in BP control or reduction in CV events at one year

AHA Recommendations on Managing Hypertension in Acute Care Settings

- Avoid intravenous antihypertensives in the absence of hypertensive emergency
- The threshold to start or intensify antihypertensive medications in response to asymptomatic elevated inpatient BP should be high
- Elevated BP in the hospital without new or worsening target-organ damage may be best served by accurate remeasurement and attention to contributing circumstantial factors
- In the ED setting, for asymptomatic elevated BP or asymptomatic markedly elevated BP, evidence supports avoiding intensifying hypertension medications, with a preference toward restarting home medications and planning for close outpatient follow-up

Liver Disease

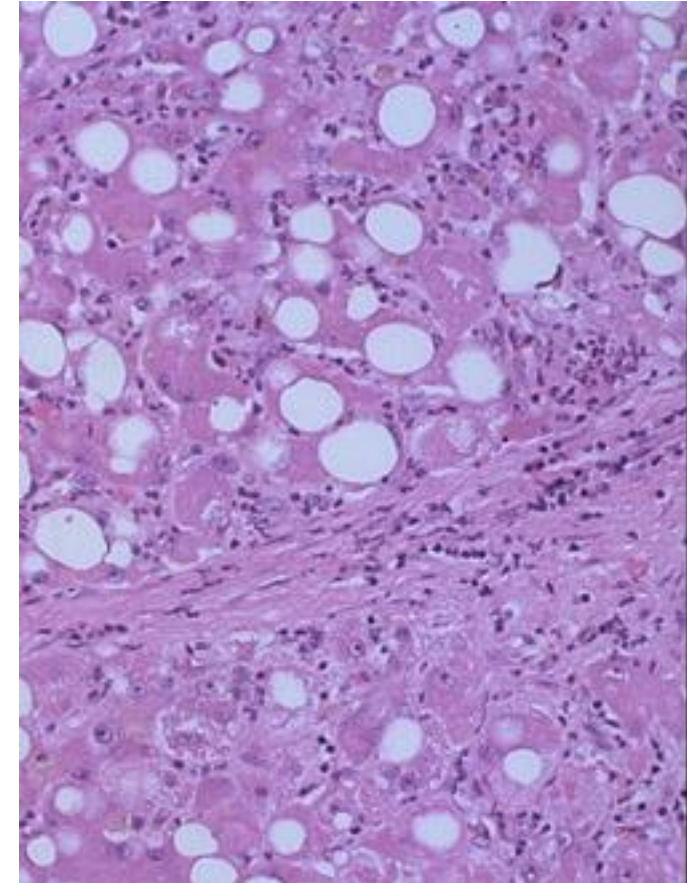
Early Paracentesis Associated with Lower Risk of Death in Cirrhosis with Ascites

- Systematic review/meta-analysis
- Paracentesis timing in patients hospitalized with cirrhosis and ascites (78,744 patients); 7 studies (all retrospective cohorts/inpatient databases)
- Early (within 12-24 hours of admission) vs delayed (>24 hours)
- In-hospital mortality:
 - within 24 hours of admission vs >24 hours: OR 0.67, 95% CI 0.45–0.98, $P = 0.04$
 - within 12 hours of admission vs >24 hours: OR 0.51, 95% CI 0.32–0.79, $P = 0.003$
- Also: lower rates of AKI, shorter LOS
- Presumed benefit: earlier antibiotics, earlier albumin
- Caveat: 95% of patients were from one study!

Alcoholic Hepatitis and Prednisolone: Background

- In patients with acute alcoholic hepatitis and Maddrey's discriminant function ≥ 32 , prednisolone 40 mg daily x 28 days is associated with a non-significant reduction in 28-day mortality compared to placebo, 14% vs 18% (OR 0.72; 95% CI, 0.52 to 1.01; $P=0.06$)
- No effect on 90-day or 1-year mortality
- Serious infections occurred in 13% of patients treated with prednisolone, vs 7% with placebo ($P=0.002$)

N Engl J Med 2015;372:1619



Standard or Tapered-Dose Prednisolone for Alcohol-Associated Hepatitis (STASH Trial)

- 254 patients with severe alcoholic hepatitis (MELD score ≥ 21 and/or DF ≥ 32)
- Open-label randomized trial of prednisolone 40 mg daily x 28 days vs prednisolone 40 mg daily, tapering by 10 mg/week (40/30/20/10, then off)
- Infection rate on day 90 was 33.1% in the fixed-dose group, compared with 19.7% in the tapered dose group; HR 0.57 (95% CI 0.35–0.94; $P = 0.03$)
- Mortality on day 90 was 16.5% in the fixed-dose group and 13.4% in the tapered-dose group ($P = 0.48$); HR 0.8; 95% CI 0.42–1.52

GLP-1 Agonists and Metformin

GLP-1 Agonists Reverse Fibrosis in Metabolic Dysfunction–Associated Steatohepatitis (MASLD)

- Randomized, double-blind, placebo-controlled trial of semaglutide 2.4 mg weekly in patients with MASLD (aka NASH) and stage 2 (moderate) or stage 3 fibrosis (advanced/early cirrhosis)
- Placebo group: standard care, lifestyle counselling
- Interim analysis of liver biopsy at week 72, compared to baseline
- Resolution of steatohepatitis without worsening of fibrosis
 - 62.9% semaglutide, 34.3% placebo, $P < 0.001$
- Decreased liver fibrosis without worsening of steatohepatitis
 - 36.8% semaglutide group, 22.4% placebo, $P < 0.001$
- Weight loss -10.5% with semaglutide, -2.0% with placebo ($P < 0.001$)

Semaglutide Reduces Heart Failure Events in Heart Failure with Preserved EF (HFpEF)

- Post-hoc pooled analysis of 3743 patients with heart failure with preserved ejection fraction (HFpEF) across 4 clinical trials of semaglutide; >80% had BMI of at least 30
- Semaglutide reduced the risk of the combined endpoint of cardiovascular death or heart failure events
 - 5.4% semaglutide vs 7.5% placebo
 - HR 0.69 (95% CI 0.53-0.89); p=0.0045
- Major effect of semaglutide was reduced risk of heart failure events
 - 2.8% vs 4.7%; HR 0.59 (0.41-0.82); p=0.0019
- No significant effect on cardiovascular death alone
 - 3.1% vs 3.7%; HR 0.82 (0.57-1.16); p=0.25

GLP-1–Receptor Agonists and Endoscopy

- GLP-1 agonists decrease gut motility
- Discordant society recommendations
 - Anesthesia: hold before endoscopy; GI: individualized approach
- EGD in 815 patients on GLP-1 agonists
- 70 (8.7%) had retained gastric contents on endoscopy; 65 of these (93%) had diabetes
- Only 1 (1.4%) required unplanned intubation; none had aspiration events
- Those in whom GLP-agonists were held were less likely to have retained contents (4.4% vs 12.7%, $P < 0.001$), but there were no significant differences in rates of intubation or aborted procedures
- Meta-analysis of colonoscopy prep in 10,833 patients
- 10.6% on GLP-1s had inadequate prep, vs 4.6% controls (OR 2.10, $P = 0.0003$)

Should Metformin Be Continued in Hospitalized Patients with Type 2 Diabetes?

- Observational cohort of 67,162 VA diabetic inpatients
- Equally split between those who continued metformin, and those who did not
- Within 90 days of hospital discharge, those who received metformin had lower risks of:
 - Hypoglycemia (1.5% vs 1.8%; OR 0.83, 95% CI 0.73–0.93; $p = 0.003$)
 - Readmission (29.4% vs 30.6%; OR 0.96, 95% CI 0.92–1.00; $p = 0.03$)
 - Mortality (6.4% vs 7.4%; OR 0.86, 95% CI 0.80–0.92; $p < 0.001$)
 - Insulin prescriptions at discharge (18.5% vs 20.3%; OR 0.89, 95% CI 0.84–0.95; $p < 0.001$)
- Consider continuing metformin in inpatients without sepsis, heart failure, advanced kidney disease, or other risk factors for lactic acidosis

General Hospital Medicine

*Which of the following statements are true about “discharge before noon”?

1. It decreases length of stay
2. It decreases ED boarding time
3. It is associated with higher job satisfaction among medical and nursing staff
4. None of the above

Discharge Before Noon

- After adjustment, discharge before noon was associated with an extra day in hospital in 38,365 discharges at UCSF Medical Center
 - Patients kept an extra day to buff numbers? (J Hosp Med 2016;11:859-861)
- Studies showing decreased ED boarding times with discharge before noon had confounders, such as increased staffing
- Studies that looked at discharge before noon in isolation did not show decreased ED boarding times
- Early morning discharges associated with disrupted workflow and decreased teaching time, with a possible contribution to burnout

Preoperative Evaluation

Should ACE Inhibitors and Angiotensin Receptor Blockers Be Stopped Before Non-Cardiac Surgery?

- Randomized controlled trial of perioperative continuation of ACE inhibitors and ARBs vs discontinuation 48 hours pre-op
- 2222 patients enrolled
- All-cause mortality and major postop complications 22% in the discontinuation group and 22% in the continuation group
- Hypotension during surgery occurred in 41% in the discontinuation group and 54% in the continuation group
- AKI 11% in both groups

Improved Outcomes with Early Surgery for Hip Fracture in Patients with Myocardial Injury

- HIP ATTACK: 2970 patients with low-energy-mechanism hip fracture, randomized to surgery within 6 hours of diagnosis vs standard care
- Subset of 322 patients with elevated troponins; mean age 82
- Median time to OR 6 hrs in accelerated group, 29 hours in standard group
- Patients with elevated troponin had lower mortality with accelerated surgery (10% vs 23%; HR = 0.43; 95% CI = 0.24 to 0.77)
- Lower mortality with accelerated surgery most marked with troponin >2.1 times upper limit of normal (6% vs 30%; HR = 0.17; 95% CI = 0.05-0.58)

Take-Home Messages 1

- Mineralocorticoid receptor antagonists, GLP-1 agonists, and SGLT2 inhibitors all reduce heart failure events in HFpEF
- Finerenone (non-steroidal MRA) prevents hospitalizations for heart failure with preserved EF, but without the hormonal side effects of spironolactone; it also may reduce the risk of incident diabetes
- The use of IV antihypertensives in patients not admitted to hospital with hypertensive urgency is associated with adverse outcomes
- Tapering doses of prednisolone in alcoholic hepatitis reduce infection rates, compared to standard doses; larger studies are needed to determine efficacy

Take-Home Messages 2

- In hospitalized patients with cirrhosis and ascites, early paracentesis (12-24 hrs) associated with lower mortality and AKI rates and a shorter length of stay
- GLP-1 agonists affect prep quality for endoscopy, but significant adverse events such as unplanned intubation are uncommon
- Continuing metformin in hospitalized patients without lactic acidosis may reduce adverse outcomes after hospital discharge
- Patients with hip fracture and elevated troponins have lower mortality with expeditious surgery