Updates in Internal Medicine
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Disclosures

• I probably have a few biotechnology and pharmaceutical stocks in my mutual funds but I have no idea which ones they are.
• I wish I had more disclosures.
How were topics selected?

• Departure from established practice.
• Not covered elsewhere at this conference (i.e. lipids, geriatrics, hospital medicine, women’s health).
• Common problems/issues that general internists manage or co-manage.
Outline of Updates

1. DVT/PE new recommendations
2. SPRINT vs. JNC 8 recommendations
3. Spironolactone for resistant HTN
4. New medications for HFrEF recommended
5. PrEP on demand
6. Normal-weight central obesity worse than BMI-measured obesity
Guide to the Grading System

• The strength of the recommendation is categorized as strong (1/I) or weak/uncertain (2/II).

• The quality of evidence is categorized as high (Grade A), moderate (Grade B), or low (Grade C). The rating of the quality of evidence reflects the strengths and limitations of the body of evidence (type of study, bias, etc.).

• Grade D is recommended AGAINST while Grade E is “expert opinion.”
Chest DVT/PE Recommendations 2016
Chest DVT/PE recommendations 2016

• BIG NEWS?: In patients with low-risk PE with favorable home circumstances, HOME treatment or early discharge is recommended (Grade 2B).

• In patients with DVT of the leg or PE and no cancer, dabigatran, rivaroxaban, apixaban, or edoxaban (NOAC/DOAC) over warfarin is recommended for at least 3 months (Grade 2B).

• In cancer patients, LMWH should be first line therapy for at least 3 months (Grade 2C). Life-long anticoagulation is recommended (Grade 1B for low bleeding risk, Grade 2B for high risk).

--Chest. 2016 Feb;149(2):315-52
Chest DVT/PE recommendations 2016

• For those with a first-time “unprovoked” DVT/PE, with a low or moderate bleeding risk, life-long anticoagulation is recommended (Grade 2B).

• For those with high risk of bleeding, 3 months of therapy is still recommended (Grade 1B).

• In patients with a second “unprovoked” DVT, recommendations are similar to first time DVT/PE.

--Chest. 2016 Feb;149(2):315-52
Chest DVT/PE recommendations 2016

• In patients who have had an “unprovoked” DVT/PE, who stop anticoagulation, aspirin is recommended (Grade 2B). Dose? 100mg! Where can I buy Aspirin 100mg?

• For those with “provoked” DVT/PE (surgery, transient risk factor), 3 months of therapy is recommended over life-long anti-coagulation (Grade 2B).

• In patients who receive anticoagulation, an IVC filter is recommended AGAINST (Grade 1B).

--Chest. 2016 Feb;149(2):315-52
Practical Considerations

- Are we now supposed to give life-long coagulation to everyone in whom we do not have a proximate cause for DVT/PE (i.e. surgery, pregnancy, estrogen, >8 hr flight)?
- Men have 75% greater risk of recurrence.
- Those with positive D-dimer at one month have double the risk of those with negative D-dimer.
- Women with a negative D-dimer have the same risk of recurrent DVT/PE as those with provoked DVT/PE (15% at 5 years).

--Chest. 2016 Feb;149(2):315-52
How to dose the NOACs/DOACs in DVT/PE (not the same as afib!)

• Apixaban (Eliquis): 10mg bid for 7 days, then 5mg bid thereafter up to 3 months. 2.5 mg twice daily is used for extended therapy (Chest. 2016 Feb;149(2):315-52).

• Rivaroxaban (Xarelto): 15mg bid for 21 days, followed by 20mg qd thereafter.

• Dabigatran (Pradaxa): Need initial treatment with parenteral therapy 5 days. 150mg bid. Has reversal agent!

• Edoxaban (Savaysa): Need initial treatment with parenteral therapy 5-10 days. Weight based dosing.

JNC 8 vs. SPRINT

"I'm here about the details."
JNC 8 Review

• The JNC 8 issued its recommendations in 2014.
• It was a panel composed of generalists, cardiologists, nephrologists, geriatricians, and epidemiologists.
• Only RCTs with at least 2,000 participants were included. Only studies that had BP measurement as primary outcome were included.

JNC 8: Key Recommendations

For patients > 60 years-old:

- Initiate pharmacologic treatment to lower BP at SBP $\geq 150$ mm Hg or DBP $\geq 90$ mm Hg and treat to a goal SBP $< 150$ mm Hg and goal DBP $< 90$ mm Hg. (Grade A)
- “In 2 of the trials that provide evidence supporting an SBP goal lower than 150 mm Hg, the average treated SBP was 143 to 144 mm Hg. Many participants in those studies achieved an SBP lower than 140 mm Hg with treatment that was generally well tolerated. Two other trials suggest there was no benefit for an SBP goal lower than 140 mm Hg, but the confidence intervals around the effect sizes were wide and did not exclude the possibility of a clinically important benefit.”

For patients <60 years-old:

- In the general population <60 years, initiate pharmacologic treatment to lower BP at DBP ≥90 mm Hg and treat to a goal DBP <90 mm Hg. (Grade A) In the general population <60 years, initiate pharmacologic treatment to lower BP at SBP ≥140 mm Hg and treat to a goal SBP <140 mm Hg. (Grade E)
- In the population aged ≥18 years with chronic kidney disease (CKD), initiate pharmacologic treatment to lower BP at SBP ≥140 mm Hg or DBP ≥90 mm Hg and treat to goal SBP <140 mm Hg and goal DBP <90 mm Hg. (Grade E)
- In the population aged ≥18 years with diabetes, initiate pharmacologic treatment to lower BP at SBP ≥140 mm Hg or DBP ≥90 mm Hg and treat to a goal SBP <140 mm Hg and goal DBP <90 mm Hg. (Grade E)

SPRINT Overview

• Sprint 9,361 people with SBP of 130-180 mmHg. Over 2,000 of the original recruited group of 14,000 were excluded for being on too many meds or BP being out of range. 352 were excluded for orthostasis. 718 were excluded for not being at increased cardiac risk.

• Patients could be on any combination of antihypertensives (thiazides preferred first line agent, ARB donated by Takeda).

• Goal was to treat to a systolic blood pressure <120 mmHg in the treatment arm and <140 mmHg in the control arm.

SPRINT Design

• At higher risk of event: Pre-existing CAD (not stroke), CKD (eGFR 20-60), 10 yr risk of CAD of 15% or more by Framingham criteria, age 75 or older.
• Participants seen monthly for 3 months, then every 3 months.
• Participants were seated in a quiet room for 5 min, then an automatic BP monitor took 3 measurements without clinician in room (Brett, *J Watch*. 2016).

SPRINT Findings

• Composite Primary Outcome: MI, ACS not resulting in MI, CVA, decompensated CHF, or death from cardiac cause.

• Primary Outcome event occurred in 562 participants. 243 (1.65% per year) in intensive treatment group. 319 (2.19% per year) in standard treatment group. Absolute risk difference: 0.54% per year. Relative risk of death from cardiac causes was 43% less with intensive treatment.

SPRINT Findings

• If 1,000 people were treated to an SBP goal of <120mmHg, 16 would benefit (fewer MIs, CVAs, death), 22 would be harmed (syncope, AKI, electrolyte abnormalities) and 962 will be neither benefitted nor harmed.

• It took an average of about 3 medications to get to Sprint goal.

Practical Considerations

• Some patients may benefit from a lower blood pressure goal.
• Those at lower cardiovascular risk and those with diabetes may not benefit (were excluded from trial).
• How blood pressure is measured matters.
• SPRINT vs. JNC 8 provides space for shared decision making and taking patient preferences into account.
Spironolactone for resistant HTN
Spironolactone for resistant HTN

• My patient is on three BP agents already and BP is not controlled. What now? Secondary work up?
• Does sodium retention cause resistant HTN?
• Spironolactone vs. Bisoprolol vs. Doxazosin vs. Placebo in addition to patient’s usual meds.
• 335 patients who were meant to cycle through all 4 treatment regimens (220 actually did).
• BP measured using at-home devices.

Anti-hypertensives used

• Patients enrolled were already on an ACE-i or ARB, CCB, and thiazide diuretic.
• Alpha-blocker Doxazosin (reduce peripheral resistance)
• Beta 1-blocker Bisoprolol (inhibits release of renin, decreases cardiac output)
• Spironolactone (blocks the mineralocorticoid receptor).

Methods

• Patients studied were 18-79 years old in the UK.
• Dose of spironolactone was 25-50mg.
• BP was measured 3 times in the morning and 3 times in the evening at home for 4 days before study visit.
• BP measured in the office with automatic monitor and mean of last 2 measurements were taken.
• Target SBP was <135mmHg as measured on home monitor.

## Results

<table>
<thead>
<tr>
<th></th>
<th>Blood pressure (mm Hg)</th>
<th>Change from baseline (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>133.5 (132.3 to 134.8)</td>
<td>-14.4 (-15.6 to -13.1)</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>138.8 (137.6 to 140.1)</td>
<td>-9.1 (-10.3 to -7.8)</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>139.5 (138.2 to 140.8)</td>
<td>-8.4 (-9.7 to -7.1)</td>
</tr>
<tr>
<td>Placebo</td>
<td>143.7 (142.5 to 145.0)</td>
<td>-4.2 (-5.4 to -2.9)</td>
</tr>
<tr>
<td><strong>Mean differences</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone vs placebo</td>
<td>-10.2 (-11.7 to -8.74)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Spironolactone vs mean bisoprolol and doxazosin</td>
<td>-5.64 (-6.91 to -4.36)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Spironolactone vs doxazosin</td>
<td>-5.30 (-6.77 to -3.83)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Spironolactone vs bisoprolol</td>
<td>-5.98 (-7.45 to -4.51)</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are mean (95% CI). Sensitivity analysis using only the mean home systolic blood pressure at the final visit of each cycle (week 12).

*Table 3: Home systolic blood pressure at final visit of each cycle*

Interesting Findings

• Placebo effect was seen in clinic BP measurements but not at-home BP measurements.

• 2% of patients had hyperkalemia on spironolactone—defined as K >6 mmol/L.

• 58% of patients considered “resistant” hypertensives become controlled on spironolactone.

Practical Considerations

• The study included mostly white patients in the UK.
• Diabetics made up 14% of the trial participants.
• Patients with eGFR < 45 mL/min were excluded from the trial.
• Participants were only on each medication for 3 months (would more hormonal side effects, problems with renal function occur later?).
• Overall, spironolactone is probably worth a try in treatment resistant hypertensives without much renal impairment whose labs you are closely monitoring.
2016 ACC/AHA/HFSA Focused Update on New Pharmacologic Therapy for Heart Failure
Vasopeptidase inhibitors.

Suzanne Oparil, and Roland E. Schmieder Circ Res. 2015;116:1074-1095
Heart Failure Update 2016

• ACE or ARB should be utilized in HFrEF (Grade IA recommendation) “in conjunction with b-blockers and aldosterone antagonists in selected patients.”

• “Unlike ACE-i, ARBs do not inhibit kininase and are assoc with much lower incidence of cough and angioedema, although kininase inhibition by ACE-i may produce beneficial vasodilatory effects.”

• ARNI (Angiotenin Receptor/Neprilysin Inhibitor) is a reasonable alternative to ACE or ARB (Grade IB recommendation).

--Yancy CW et. al. J Am Coll Cardiol. 2016 May 17
Evidence for ARNI

- Patients were NYHA class II, III, or IV. EF 40% or less, changed to 35% or less one year into the trial.
- Control group was on enalapril.
- Target dose of valsartan/sacubitril in the trial was 97/103mg bid.
- In symptomatic patients, valsartan/sacubitril (Entresto) reduced the composite end point of CV death or HF hospitalization by 20% (relative risk).
- The overall mortality over the course of the trial (2009-2012) was 17.0% in the Entresto group and 19.8% in the Enalapril group (p<0.001).

Potential Concerns about ARNI

- Hypotension (was an issue with niseritide) in 14% of patients vs. 9.2% in control group (p<0.001).
- Angioedema occurred at nearly twice the rate in the Entresto group vs. control group (N=19 vs. N=10).
- NB: In earlier studies ACE-i + neprilysin inhibitor tripled rate of angioedema. Therefore, it is recommended that patients on an ACE-i undergo a washout period of 36 hours before Entresto is started. A history of angioedema is a contraindication to Entresto.

More about the HFrEF guidelines

• No recommendation was made in regard to NYHA IV patients likely because only small numbers were included in the original trial.

• Another new medication—Ivabradine was given a weak recommendation for use in HFrEF patients.

• Ivabradine is recommended for patients on maximal dose b-blockade who still have a heart rate>70. Slows conduction through the SA node. Authors noted that only 25% of patients in the trial were on optimal b-blockade hence the weak recommendation. B-blockers are certainly still first line and should be maximized.

--Yancy CW et. al. J Am Coll Cardiol. 2016 May 17
PrEP on Demand?
A brief history of PrEP

• In 2012, the CDC approved Truvada (tenofovir-emtricitabine) for pre-exposure prophylaxis of HIV in “high risk” individuals.

• Taken daily, Truvada decreases transmission of HIV by 90% through sexual contact and by 70% through needle use.

• Data for MSM is the strongest. Data in women is lacking and has been mixed.

Problems with daily PrEP

Covering the Cost of PrEP Care

Insured

Medication
- Bill insurance
- Apply for copay assistance from Gilead or PAF

Lab Test
- Bill insurance

Clinic Visits
- Bill insurance

Not insured
But may be eligible for Medicaid or ACA Plans

Apply

Household Income
500% FPL or less

Medication
- Gilead Medication Assistance Plan
- WA State Medication Assistance

Lab Test
- Care at CHC with sliding fee scale
- NY State PrEP Assistance Plan

Clinic Visits
- Care at CHC with sliding fee scale
- NY State PrEP Assistance Plan

Not eligible for Medicaid or ACA plans OR
Insurance denies claim

Household Income
more than 500% FPL

Medication
- Bill insurance
- Apply for copay assistance from Gilead or PAF

Lab Test
- Bill insurance

Clinic Visits
- Bill insurance

Abbreviations
ACA - Affordable Care Act
FPL - Federal Poverty Level
CHC - Community Health Center
PAF - Patient Advocate Foundation
Problems with daily PrEP

- http://www.floridahealth.gov
Problems with Daily PrEP

• Cost: Estimated at $1300/mo. (PBS Newshour)
• Adherence: In some studies, only 50% of participants had detectible drug levels when checked. In these studies PrEP had much lower than 90% efficacy. (Mayer, et al. J Int AIDS Soc. 2015)
• Side-effects: Decreased BMD, fat redistribution, lactic acidosis, hepatic steatosis, renal toxicity, pancreatitis (Gilead Pharmaceuticals)
• Fear of resistance: need HIV test prior to initiation of ppx and then q3 months.
PrEP on demand, coming soon?

- On-Demand Pre-Exposure Prophylaxis in Men at High-Risk for HIV-1 Infection
- 400 MSM studied.
- Followed for median of 9.3 months.
- 14 HIV infections occurred in the placebo group, 2 in ppx group.
- RRR of 86% (p=0.002)

PrEP on demand, coming soon?

• Regimen: 2 Truvada pills 2-24 hours prior to sex. Third pill 24 hours after the 1st dose. Fourth pill 24 hours after that. If many days of sex in a row, 1 pill daily and then 2 post-exposure pills after the last episode.

• Median of 15 pills used/month (range 11-21).

• Side effects were mainly GI, 15%. Also 1% had decrease in CrCl <60 mL/min.

Practical Considerations

• There was no increase in “risk-taking” behaviors in this PrEP study or in others.
• This is only one study and does not address women at all and also does not address what might occur with less frequent use of Truvada.
• HIV researcher/clinician: “Promising. It is not in the guidelines yet but we are into it.”
Normal Weight Central Obesity
Normal Weight Central Obesity

Apple Shaped Obesity

Pear Shaped Obesity

abdominal fat

subcutaneous fat

abdominal fat

subcutaneous fat
Can you be “fat and fit”?  

• Higher BMI has long been associated with higher total and CV mortality.  
• Recent data has challenged these findings.  
• Accuracy of BMI has been challenged.  
• Being normal weight doesn’t necessarily mean that one is “healthy.”
Methods

• NHANES III data from 1988-1994 used (more recent NHANES data did not collect hip measurements).
• 16,000 adults studied.
• BMI>18.5 and no cancer dx.
• Took the data and constructed risk models.
• BMI of 22 considered normal, BMI of 27.5 overweight, BMI of 33 representing obese.
• WHR 0.89=not obese and 1.0=obese for men and 0.8=not obese and 0.92=obese for women. (WHO defines central obesity as >0.90 for men and >0.85 for women)

Results

• Cox proportional hazards analysis showed WHR but not BMI associated with high mortality risk.
• Men with normal-weight central obesity had 2 fold higher mortality risk than an overweight or obese man who was not centrally obese.
• Women with normal weight central obesity had a 40% and 32% higher total mortality than an overweight or obese woman who was not centrally obese, respectively.

Practical Considerations

- You will need to buy a tape measure.
Questions?

• Thank you.
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