Update in Outpatient Medicine
Medical Grand Rounds
ACP Scientific Session
November 3, 2017

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Disclosures

- Stock Holdings
  - Abbott Labs
  - Abbvie
  - Bristol Myers Squibb
  - GE
  - Proctor and Gamble
  - Walgreens
Topics

- Statin Intensity and Mortality in ASCVD
- Statins to prevent cardiovascular disease
- Hypertension
- Protecting against GI bleeding in the elderly
- Use of anticoagulants in atrial fibrillation
- Prostate cancer screening
- Treatment of hypothyroidism
- Intra-articular steroids for OA of knee

USPTF Recommendation Statement
Statin Use for the Primary Prevention of Cardiovascular Disease in Adults

- Systematic review 19 RCT’s enrolling 71,344 participants without prior CVD events

USPTF Recommendation Statement
Statin Use for the Primary Prevention of Cardiovascular Disease in Adults

- 14% RRR all cause mortality
- 31% RRR CV mortality
- 36% RRR AMI
- No increase in adverse events
  - Evidence on the association of statins and DM mixed
  - RCT’s do not conclusively support a major causative role for myalgia
  - No clear evidence of cognitive decline

USPTF Recommendation Statement
Statin Use for the Primary Prevention of Cardiovascular Disease in Adults

- Initiate low to moderate dose statins in adults aged 40-75 with no history of CVD and ≥ 1 CVD risk and ≥ 10% CVD event risk using ACC pooled risk calculator
  - CVD risks- dyslipidemia (LDL > 130 or HDL ≤ 40, HTN, DM, smoking
    - Grade B recommendation
- Statin use on patients above but 7.5-10% CVD risk Grade C recommendation
- Statin use for primary prevention age > 75 Grade I
Association Between Intensity of Statin Therapy and Mortality in ASCVD

- Retrospective cohort analysis 509,766 adults with ASCVD treated in the VA
- Mean follow up 492 days
- Adherence 81-83%
- Results consistent for older patients

JAMA Cardiol 2017;2(1):47-54
Association Between Intensity of Statin Therapy and Mortality in ASCVD

Adverse events associated with unblinded, but not blinded statin therapy- ASCOT-LLA

- 10,240 patients aged 40-79 with 3 or more risk factors for CVD but no history of MI or treatment for angina
  - Included patients with total cholesterol ≤ 6.5 mmol/L (approx, 250 mg/dl)
  - Included patients with previous CVA, PAD, LVH, DM
- Randomized to 10 mg atorvastatin vs. placebo
- Trial stopped for efficacy after median 3.3 years follow up. Patients then told of statin assignment and offered open label treatment
Blinded patients

Unblinded patients

Muscle related symptoms not present during blinded phase
Cannot extrapolate to higher doses or very elderly patients

Statin Intolerance and Risk of CV Events and All Cause Mortality

- Retrospective cohort study of all Medicare beneficiaries hospitalized for AMI 2007-13, continuously enrolled 1 year before and 1 year after index event (105,329 enrollees)
  - Excluded patients with statin or other lipid lowering therapy during look back period
  - Compared occurrence of MI, CHD event and all cause mortality between highly adherent (PDC ≥ 80%) and intolerant patients
  - 52.8% highly adherent, 1.65% met primary definition of statin intolerance, 10.7% met secondary definition of statin intolerance
**CENTRAL ILLUSTRATION Statin Intolerance Among Medicare Beneficiaries**

**Excess Risk From Statin Intolerance**

- High Adherence: 33.8%
- Statin Intolerance: 1.65%

**Reasons for Statin Intolerance**

- Green: Decreasing statin and initiating a new dose (17.1%)
- Orange: Switching from a statin to no statin (37.4%)
- Red: Having ICD-9 codes for multiorgan failure followed by statin down-situation or discontinuation (11.4%)
- Blue: Having ICD-9 codes for ambulatory patient adverse events followed by statin down-situation or discontinuation (1.2%)
- Light blue: Switching between 3 types of statins within one year after initiation (33.2%)

**FIGURE 1** Cumulative Incidence for Recurrent MI, CHD Events, and All-Cause Mortality for Beneficiaries With Statin Intolerance and High Adherence to High-Intensity Statins

Cumulative incidence for recurrent myocardial infarction and coronary heart disease events were adjusted for the competing risk of all-cause mortality. Abbreviations as in Figure 1.
Continued Statin Prescriptions After Adverse Reactions and Patient Outcomes

- Retrospective cohort study of 28,266 patients with a presumed adverse reaction to a statin
  - Prescribed 2000-2011
  - Continuation of statin determined through EMR review
  - Primary outcome MI, CVA, or death from any cause
  - 70.7% continued on a statin

Summary- Cholesterol Lowering

- USPTF endorses statin therapy for primary prevention in higher risk patients
- Statin intolerance is less frequent than believed and patients can frequently tolerate a rechallenge
  - Nocebo effect
- Patients who stop taking statins have worse outcomes, including higher mortality
- Substantial opportunity to increase prescribing and improve adherence, especially in patients with known ASCVD
Intensive vs. Standard BP Control and CV Outcomes in Adults ≥ 75 years old

- Subset of SPRINT trial
  - 2636 community dwelling patients ≥ 75 years old with SBP 130-180 mm Hg at high risk for CVD disease
  - Clinical or subclinical CVD other than CVA
  - CKD (excluding PCKD), eGFR 20-59 ml/min
  - Framingham 10 year risk ≥ 15%
  - Age ≥ 75
  - Excluded patients with DM, CVD, LEF or symptomatic CHF, ESRD, dementia, expected survival < 3 years, unintentional weight loss > 10%, SBP < 110 following standing 1 minute, poor adherence

JAMA 2016;315(24):2673-82

33% of intensive treated group was frail
NNT to prevent mortality or cardiac event = 60
NNH = 544
Systolic BP Reduction and Risk of CV Disease and Mortality

- Systematic review and network meta-analysis of 42 trials with 144,220 patients
- Pooled results of trials and analyzed results by 5 mm increments of SBP control from < 120 mm to ≥ 160 mm
- Analyzed with and without SPRINT
- Accounted for trial heterogeneity by adjusting for trial length and event rates in reference groups

Results consistent when excluding SPRINT Trial
Association of JNC-8 and SPRINT SBP Targets and Cognitive Decline - Healthy ABC Study

- Prospective community based study of 3075 well functioning, cognitively intact patients age 70-79 in Pittsburgh and Memphis
  - 42% African American; 52% female
  - Analysis based on 1657 patients treated for hypertension
  - Assessed cognition with the Digit Symbol Substitution Test and the Modified MMSE (100 point scale)

JAMA Neurol 2017; 74(10):1199-1205
Summary- Hypertension

- Treatment of hypertension straightforward but targets are complex
- Many patients can be treated with 2 prescriptions/3 drug
  - ACE or ARB/diuretic combination pill
  - Calcium channel blocker such as amlodipine
- If intensification needed consider spironolactone or other drug based on comorbidities
- Targets require individualization
  - High risk cardiac (SPRINT) <120/80
    - Exclude DM, previous CVA, CHF, standing SBP < 110, limited life expectancy
    - Include frail patients without other exclusions
    - May be of benefit in broader population

Age specific risks and outcomes of anti-platelet treatment after vascular events

- Prospective population cohort of 3166 patients with 1st TIA or MI treated with anti-platelet drugs in Oxfordshire UK
  - Excluded patients taking anti-coagulants
- Assessed for recurrent ischemia, bleeding events and disability (modified Rankin score) at 30 days, 6 months, year 1,5,10
- Assessed bleeding by reviewing administrative data from hospital admissions and transfusion records.
- Stratified events by age < 75, ≥ 75 and 5 year age bands

Lancet 2017; 390:490-99
Figure 1: Annual rates of bleeding events requiring medical attention
• PPI’s reduce UGI bleed 70-90% in patients on anti-platelet agents
• 40% of major bleeds are UGI
• Estimated NNT 23 to prevent major UGI bleed in patients on anti-platelet agents in patients > 75
• Estimated NNT 25 to prevent fatal or disabling UGI bleed in patients > 85
• Consider co-prescription of PPI with ASA and/or clopidogrel in patients > 75 in patients with vascular disease

Association of preceding anti-thrombotic treatment and severity if stroke in patients with AF
• Retrospective observational study of 94,474 patients with acute ischemic stroke and known AF admitted 10/12-3/15 at hospitals participating in Get With the Guidelines program.
• Outcomes NIHSS score and in hospital mortality
• >95% patients high risk CHA2DS2-VASc ≥ 2
  • 28.6% of untreated patients and 35.9% of patients only on anti-platelet therapy had prior CVA or TIA
• Most common documented reasons for lack of anti-coagulation were risk of bleeding and falls

JAMA 2017;317:1057-1067
Association of preceding anti-thrombotic treatment and severity if stroke in patients with AF

**Preceding anti-platelet therapy**

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Anti-plt</th>
<th>Warfarin INR ≤ 2</th>
<th>Warfarin INR ≥ 2</th>
<th>NOAC</th>
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<tr>
<td>Mod-severe CVA</td>
<td>27.1%</td>
<td>24.8%</td>
<td>25.8%</td>
<td>15.8%</td>
<td>17.5%</td>
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<td>In-hosp mortality</td>
<td>9.3%</td>
<td>8.1%</td>
<td>8.8%</td>
<td>6.4%</td>
<td>6.3%</td>
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</table>

Outcomes Associated With Resuming Warfarin Treatment After Hemorrhagic Stroke or Traumatic Intracranial Hemorrhage in Patients with Atrial Fibrillation

- Observational cohort study using data from Danish nationwide databases
- Identified patients with spontaneous intracranial hemorrhage or traumatic intracranial hemorrhage
- Median follow up 279 days

JAMA Intern Med 2017;177(4) 563-570
In patients with hemorrhagic stroke, resuming warfarin decreases the rate of recurrent stroke, but have an increased risk of recurrent intracranial hemorrhage.

Patients with traumatic ICH have fewer strokes and ICH with warfarin resumption.

**USPTF Draft Recommendation on Screening for Prostate Cancer**

- Draft recommendation changed from Grade D to Grade C
- Draft recommends clinicians inform men aged 55-69 about the potential benefits and harms of PSA screening
  - Grade D recommendation for men 70 and older
- Small potential benefit of reducing the chance of dying from prostate cancer
- Many men will experience potential harms including additional testing, overdiagnosis, overtreatment and complications
- Recommend shared decision making
Reconciling the Effects of Screening on Prostate Cancer Mortality in the ERSPC and PLCO Trials

- Examination of individual records ERSPC and PLCO
- Cox regression analysis of prostate cancer death adjusted for age and trial
- Performed extended analysis accounting for increased incidence due to screening, estimating mean lead times
- After adjustment, reductions in prostate cancer mortality was 25%-31% in ERSPC and 27-32% in PLCO
- Must weigh benefit vs. harms

Ann Intern Med doi:10.7326/M16-2586

- Metastasis freedom >97% at 10 years
- Surveillance failure at 10 years 10-12%
- Intervention freedom at 10 years 48.7%-52.3%
- Differences between low risk and selected intermediate/high risk patients not significant
Follow up of Prostatectomy vs. Observation for Early Prostate Cancer

- Long term follow up from the PIVOT Trial
  - Randomized 731 men with localized prostate cancer
    - PSA < 50, age < 75, Stage T1-T2NxM0, life expectancy > 10 years
- Outcomes
  - All cause mortality
  - Prostate cancer specific mortality
  - Disease progression
  - Definitive intervention
  - Health outcomes

NEJM 2017;377:132-42
Cumulative Incidence of Death Though 19.5 Years

<table>
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<th>RP</th>
<th>Observation</th>
<th>ARR</th>
<th>NNT</th>
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<tr>
<td><strong>All cause Mortality</strong></td>
<td>61.3%</td>
<td>66.8%</td>
<td>5.5% (NS)</td>
<td>18</td>
</tr>
<tr>
<td>&lt; 65</td>
<td>47.5%</td>
<td>59.5%</td>
<td>12% (NS)</td>
<td>8</td>
</tr>
<tr>
<td>&gt; 65</td>
<td>68.2%</td>
<td>70.8%</td>
<td>2.6% (NS)</td>
<td>38</td>
</tr>
<tr>
<td>PSA ≤ 10</td>
<td>58.5%</td>
<td>62.7%</td>
<td>3.8% (NS)</td>
<td>26</td>
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<tr>
<td>PSA &gt; 10</td>
<td>65.9%</td>
<td>74.4%</td>
<td>8.5% (NS)</td>
<td>12</td>
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<tr>
<td>Low risk</td>
<td>55.4%</td>
<td>56.1%</td>
<td>0.7% (NS)</td>
<td>143</td>
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<tr>
<td>Intermediate</td>
<td>59.7%</td>
<td>74.2%</td>
<td>14.5%</td>
<td>7</td>
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<tr>
<td>High Risk</td>
<td>71.4%</td>
<td>73.8%</td>
<td>2.3% (NS)</td>
<td>43</td>
</tr>
</tbody>
</table>

Differences for prostate specific mortality did not differ

Disease Progression, Treatment, Adverse Events

<table>
<thead>
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<th></th>
<th>RP</th>
<th>Observation</th>
<th>Absolute Difference</th>
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<tbody>
<tr>
<td><strong>Any progression</strong></td>
<td>40.9%</td>
<td>68.4%</td>
<td>27.5%</td>
</tr>
<tr>
<td><strong>Local Progression</strong></td>
<td>34.1%</td>
<td>61.9%</td>
<td>27.8%</td>
</tr>
<tr>
<td><strong>Regional Progression</strong></td>
<td>9.1%</td>
<td>14.2%</td>
<td>5.1%</td>
</tr>
<tr>
<td><strong>Systemic Progression</strong></td>
<td>10.2%</td>
<td>14.7%</td>
<td>4.5%</td>
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<tr>
<td><strong>Definitive treatment</strong></td>
<td>33.5%</td>
<td>59.7%</td>
<td>26.2%</td>
</tr>
<tr>
<td><strong>Erectile dysfunction</strong></td>
<td>14.6%</td>
<td>5.4%</td>
<td>9.1%</td>
</tr>
<tr>
<td><strong>Incontinence</strong></td>
<td>17.3%</td>
<td>4.4%</td>
<td>12.9%</td>
</tr>
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</table>
Intermediate Term Outcomes for Men with Very Low, Low, and Intermediate/High Prostate Cancer Managed by Active Surveillance

- Cohort study of 635 men with localized prostate cancer managed by active surveillance
- Active surveillance protocol
  - PSA every 6-12 months
  - DRE each visit
  - 12 core biopsy more than 1 year after diagnosis, every 1-3 years
  - Prostate mpMRI, urinary PCA3, genomic testing at discretion of urologist
- 18.4% cohort had intermediate/high risk disease
- Men with intermediate/high risk disease (Gleason score ≥ 7) had low volume disease and age > 70

Journal of Urology 2017;198:591-598
Prostate Cancer Screening and Treatment of Low Risk Prostate Cancer

- USPTF draft recommendation returns to shared decision making
- Long term follow up indicates observation or active surveillance is safe in patients with low risk disease
- Consider active surveillance in selected intermediate disease patients
  - Older men with low volume disease
- Active surveillance becoming standard of care in patients with very low risk disease regardless of age

Association of Thyroid Function with Life Expectancy With and Without Cardiovascular Disease

- Population based cohort study, 7785 participants with TSH and FT$_4$ levels within reference range
- Outcome measures – incident nonfatal CVD, CVA, CHF, overall mortality.
- Assessed life expectancy, years lived with and without CVD, by tertiles of TSH and FT$_4$

JAMA Intern Med. Doi:10.001/jamainternmed.2017.4836 Published online 9/18 2017
Patients with lower TSH and FT₄ levels had lower mortality

Patients with higher FT₄, 32% higher rates of CVD and 50% higher mortality

May have implications for patients on thyroid replacement

Thyroid Hormone Therapy for Older Persons with Subclinical Hypothyroidism

• 737 patients ≥ 65 years old with TSH 4.6-19.99 mIU/l and normal FT₄
• 60% of the screened population were excluded due to spontaneous reversion to normal TSH
• Randomized to 50 μg daily (25 μg if < 50 kg or CAD), dose titrated to TSH 0.4-4.59 mIU/l
• Outcomes ThyPRO and Tredness questionnaires
Hypothyroidism Summary

• Subclinical hypothyroidism in the elderly is common
• No evidence that treatment improves symptoms
• People with high normal FT₄ have higher mortality and greater incidence of developing CVD
• May have implications for targets thyroid replacement in patients with documented need for replacement
Effect of Intra-articular Triamcinolone vs. Saline in Knee Osteoarthritis

- 140 patients age ≥ 45 with knee OA and ultrasonic evidence of effusion synovitis
- Randomized to 40 mg triamcinolone injection vs. saline every 12 weeks for 2 years
  - Allowed to take acetaminophen as needed but held 2 days before each assessment
- Assessed every 3 months with WOMAC questionnaire and MRI yearly (to assess cartilage volume)

JAMA 2017;317:1967-1975
Effect of Intra-articular Triamcinolone vs. Saline in Knee Osteoarthritis

- Steroid injections do not have long term benefits to improve pain or function
- Steroid injections are associated with some erosion of articular cartilage

Questions?