Topics

- Statin Intensity and Mortality in ASCVD
- Statins to prevent cardiovascular disease
- Hypertension
- Use of anticoagulants in atrial fibrillation
- Falls/Osteoporosis
- CRC Screening

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

Disclosures

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

Table 1. Statin Dosing and American College of Cardiology/American Heart Association Classification of Intensity*

<table>
<thead>
<tr>
<th>Statin</th>
<th>Low Intensity (LDL-C Lowering &lt;30%)</th>
<th>Moderate Intensity (LDL-C Lowering 30% to &lt;50%)</th>
<th>High Intensity (LDL-C Lowering ≥50%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>NA</td>
<td>10-20</td>
<td>40-80</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>20-40</td>
<td>Twice daily, 40</td>
<td>NA</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>20</td>
<td>40</td>
<td>NA</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>1</td>
<td>2-4</td>
<td>NA</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>10-20</td>
<td>40-80</td>
<td>NA</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>NA</td>
<td>5-10</td>
<td>20-40</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>10</td>
<td>20-40</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Table adapted from 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

Lancet published online 5/2/2017

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

JACC 2017;69 (11):1386-95
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
Assessing Cardiovascular Risk to Guide Hypertension Diagnosis and Treatment

- Evaluated data from nonpregnant adults aged 20-79 who participated in the NHANES survey (n = 14,142)
- Completed a mobile examination center visit
- SBP calculated by averaging up to 3 BP readings
- BP treatment status and medication type by self-report
- Possibly resistant hypertension defined as taking ≥3 meds with at least 1 being a diuretic

JAMA Cardiol 2016;1(8):864-871

Assessing Cardiovascular Risk to Guide Hypertension Diagnosis and Treatment

- 5.4% of US adults have an SBP ≥140 are taking BP meds and require intensification, 21.9% are already taking 3 or more meds with at least 1 diuretic and may have resistant hypertension
- 1.3% of US adults have SBP 120-139 and would have been SPRINT eligible, 27.2% may have treatment resistant hypertension
- These patients require careful assessment of adherence, barriers if nonadherent, or spironolactone if adherent and no contraindication
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

Disparities in Antihypertensive Medication Nonadherence Among Medicare Part D Beneficiaries-2014

- 70% of US adults aged ≥ 65 have HTN; 50% controlled
- Adherent patients have 45% higher rates of BP control and 38% decreased risk for a CV event
- Assessed patients have 45% higher rates of BP control and 38% decreased risk for a CV event
- Rates varied by drug class and # of meds
  - ARB<ACEI<CCB<BB<thiazide other diuretic
  - Adherence better with fixed dose meds

MMWR September 16, 2016: 65; 967-76
Nonadherence to Antihypertensive Treatment

- Consider in uncontrolled patients on 3 medication classes
- Strategies to promote adherence
  - Use fixed dose combinations (start on ACE/ARB + diuretic)
  - Oregon only used in 5.3% patients
  - Prescribe 90 day supply to reduce pharmacy trips
  - Synchronize refills
  - Promote technology aids to follow medication schedule

Oral Anticoagulant Therapy in Patients with Atrial Fibrillation
Insights from the NCDR PINNACLE Registry
429,417 patients with atrial fibrillation from 144 cardiology practices participating in the ACC-PINNACLE registry

- CHADS2
  - CHF
  - Hypertension
  - Age $\geq$ 75
  - Diabetes Mellitus
  - TIA or CVA (2 points)

- CHA2DS2-VASc
  - CHF
  - Hypertension
  - Age $\geq$ 65 (1 point)
  - $\geq$ 75 (2 points)
  - Diabetes mellitus
  - TIA or CVA (2 points)
  - CVD or PAD
  - Female Sex

Over 50% of PHP patients with stroke and known history of atrial fibrillation did not fill a prescription for an anticoagulant

JAMA Cardiology 2016;1(1):55-62

Stroke rates per year
- 0 points 0.2%
- 5 points 7.2%
- 1 point 0.6%
- 6 points 9.7%
- 2 points 2.2%
- 7 points 11.2%
- 3 points 3.3%
- 8 points 10.8%
- 4 points 4.8%
- 9 points 12.2%
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 anticoagulation were risk of bleeding and falls

**Clinical characteristics comprising the HAS-BLED Bleeding Risk Score**

<table>
<thead>
<tr>
<th>Letter</th>
<th>Clinical characteristic*</th>
<th>Points</th>
<th>HAS-BLED score (total points)</th>
<th>Bleeds per 100 patient-years*</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypertension (ie, uncontrolled blood pressure)</td>
<td>1</td>
<td>0</td>
<td>1.13</td>
</tr>
<tr>
<td>A</td>
<td>Abnormal renal and liver function (1 point each)</td>
<td>1 or 2</td>
<td>1</td>
<td>1.02</td>
</tr>
<tr>
<td>S</td>
<td>Stroke bleeding tendency or predisposition</td>
<td>1</td>
<td>1</td>
<td>1.88</td>
</tr>
<tr>
<td>B</td>
<td>Labile INRs (for patients taking warfarin)</td>
<td>1</td>
<td>3</td>
<td>3.74</td>
</tr>
<tr>
<td>L</td>
<td>Elderly (age greater than 65 years)</td>
<td>1</td>
<td>4</td>
<td>8.70</td>
</tr>
<tr>
<td>E</td>
<td>Drugs (concomitant aspirin or NSAIDs) or alcohol abuse (1 point each)</td>
<td>1</td>
<td>5 to 9</td>
<td>Insufficient data</td>
</tr>
</tbody>
</table>

None Anti-plt Warfarin INR ≤ 2 Warfarin INR ≥ 2 NOAC

**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>
</tr>
</thead>
<tbody>
<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>
</tr>
<tr>
<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>
</tr>
</tbody>
</table>
Relation between CHA2DS2-VASc scores and annual event rates of ischemic stroke and intracranial hemorrhage (ICH; left) and more widely defined thromboembolic events and bleedings (right) in relation to use of oral anticoagulation (OAC; n=159 013).

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

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

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

- Risk of stroke exceeds risk of bleeding in almost all patients with risk factors

Patient with atrial fibrillation and 5% risk of stroke/year would need to fall 300 times a year to have an equivalent risk of subdural hematoma

Arch Int Med 2003;163:1580-1586
Conclusions

- Use of anticoagulants to prevent thromboembolic events is low
- Benefits exceed risks in almost all patients
- Risks of bleeding often overestimated

Falls and Falls Injuries in Adults ≥ 65-United States 2014

- 2.8 million ED visits for fall related injuries, 800,000 hospitalizations, 27,000 deaths
- CDC analyzed data from the Behavioral Risk Factor Surveillance System Survey
  - 147,319 respondents
- 28.7% of older adults reported a fall
  - 37.5% of those who fell restricted activity at least 1 day or sought medical attention
- Only 58% of PHP members recall their provider asking about falls

Prevention of Falls in Older People Living in the Community

- Risk factors
  - Gait and Balance
  - Frailty
  - Co-morbidities
  - Polypharmacy
  - Visual impairment
  - CV causes i.e. syncope, orthostatic hypotension, cerebrovascular disease
  - DM

- Interventions
  - TUG test (abnormal >12 s)
  - Medication review
  - Exercise program such as Tai Chi
  - PT eval, especially if fear of falling or TUG test positive
  - Vitamin D 800 IU daily or test and supplement in patients with low levels
    - 17% reduction in falls
  - Calcium 1000-1200 mg daily
    - Evidence stronger in institutionalized people
Patterns of Prescription Drug Use Before and After a Fragility Fracture

- Retrospective cohort study using a 40% sample of FFS Medicare beneficiaries
- 168,133 patients who sustained a hip, wrist, or shoulder fracture
  - Community dwelling at time of fracture and for at least 30 days within 4 months of fracture
- 76% of patients were exposed to at least 1 non-opiate drug that increased fracture risk

JAMA IM 2016;176:1531-1538

<table>
<thead>
<tr>
<th>Proposed Mechanism of Increased Fracture Risk</th>
<th>Cohort Use Prior to Fracture, %</th>
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</thead>
<tbody>
<tr>
<td>Increased Risk of Falls</td>
<td></td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>2.8</td>
</tr>
<tr>
<td>Darbepoetin</td>
<td>1.2</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors*</td>
<td>10.8</td>
</tr>
<tr>
<td>Opioids</td>
<td>35.5</td>
</tr>
<tr>
<td>Selective serotonin receptor inhibitors*</td>
<td>26.4</td>
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<tr>
<td>Tricyclic antidepressants</td>
<td>4.8</td>
</tr>
<tr>
<td>Anti-Parkinson disease drugs</td>
<td>5.6</td>
</tr>
<tr>
<td>Central acting antihypertensives</td>
<td>3.9</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>8.6</td>
</tr>
<tr>
<td>Monoclonal anti-anginal agents</td>
<td>1.4</td>
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<tr>
<td>Thiazide diuretics</td>
<td>22.4</td>
</tr>
<tr>
<td>Thiazide-like diuretics</td>
<td>2.9</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Decreased Bone Density</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Glutaric acid thioureas*</td>
<td>7.9</td>
</tr>
<tr>
<td>Oral glucocorticoids*</td>
<td>9.8</td>
</tr>
<tr>
<td>Proton pump inhibitors*</td>
<td>25.6</td>
</tr>
<tr>
<td>lH2 receptor antagonists</td>
<td>5.6</td>
</tr>
<tr>
<td>Thiazide diuretics*</td>
<td>5.7</td>
</tr>
<tr>
<td>Amiloridines</td>
<td>9.3</td>
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<table>
<thead>
<tr>
<th>Unclear Primary Mechanism</th>
<th></th>
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<tbody>
<tr>
<td>Tricyclic antidepressants</td>
<td>5.2</td>
</tr>
<tr>
<td>Early-generation antipsychotics</td>
<td>1.8</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>21.0</td>
</tr>
</tbody>
</table>

| 29.4% completed 5 years of treatment with a medication possession ratio of ≥ 80% |

Risk of hip, subtrochanteric, and femoral shaft fractures among mid and long term uses of alendronate

- Danish national registry of 61,990 incident users of alendronate from 1996-2007
- Outcomes were incident fractures of the hip, subtrochanteric femur, and the femoral shaft
  - One case control study for hip fracture
  - One case control study for subtrochanteric and femoral shaft fracture
- 29.4% completed 5 years of treatment with a medication possession ratio of ≥ 80%
Fig 2 | Kaplan-Meier cumulative incidence plot of hip fracture and subtrochanteric and femoral shaft fracture (ST/FS) as function of time for all people treated with alendronate irrespective of adherence

Conclusions

- Benefits of long term bisphosphonates far exceed the risks
- Under treatment is common in high risk patients
- Over 50% of PHP patients with known osteoporosis and previous fracture who sustain a hip fracture are not treated with a bisphosphonate
Effectiveness of Screening Colonoscopy to Prevent CRC age 70-79

- Population based, prospective study 1,332,692 average risk FFS Medicare beneficiaries without colonoscopy within 5 years
  - Selected cohort who used other preventive services
  - Over 85% had Charlson co-morbidity score < 1
- Outcomes
  - 8 year incidence of CRC
  - Stage reported, but not mortality
  - 30 day adverse outcomes

Annals of Int Med 2017;166(1):18-26

<table>
<thead>
<tr>
<th></th>
<th>Age 70-74 Screened</th>
<th>Age 70-74 Unscreened</th>
<th>Age 75-79 Screened</th>
<th>Age 75-79 Unscreened</th>
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</thead>
<tbody>
<tr>
<td>8 year incidence CRC</td>
<td>2.19%</td>
<td>2.62%</td>
<td>2.84%</td>
<td>2.92%</td>
</tr>
<tr>
<td>Adverse events</td>
<td>5.6/10,000</td>
<td>10.3/10,000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adverse events: Arrhythmia > CHF > Syncope/hypotension > N/V
Bleeding requiring transfusion/perforation uncommon

Simulation model of CRC Screening in Previously Unscreened Elderly Patients

Ann Intern Med 2014;160:750-759
Marginal Benefit for More Frequent Surveillance of Low Risk Polyps

- Patients aged 70-74 have small reduction in CRC incidence and small risk of adverse events
- Patients aged 75 and older have no significant benefit in reducing CRC incidence and have small risk of adverse events
- Decisions for screening should consider results of past screening and presence of chronic illness
- Older patients with normal or low risk findings on colonoscopy (i.e. 1-2 polyps < 1 cm) should consider stopping surveillance or changing to stool based test (i.e. FIT)

Multitarget Stool DNA Testing for CRC Screening

- 12,776 patients age 50-84 at average risk for CRC enrolled at 90 sites
  - Excluded patients with previous colonoscopy within 9 years, + fecal blood in past 6 months.
- 9989 participants could be fully evaluated
  - 1168 did not undergo colonoscopy
  - 723 had insufficient stool or other sample issues
  - 304 had incomplete colonoscopy

Specificity for multitarget stool DNA further reduced in the elderly
Comparative Effectiveness and Cost Effectiveness of a Multi-target Stool DNA Test to Screen for Colonic Neoplasia

- Markov model to compare effectiveness of Multi-target DNA test vs. FIT vs. colonoscopy
  - Patients entered the model at age 50, screened from age 50-80 and followed until age 100
  - Assumed Medicare costs
    - FIT $19 per test
    - Multi-target stool DNA $496 per test
    - Added $153 per cycle to FIT for cost of program to ensure follow up

One time testing at age 70 MT-sDNA vs. FIT cost $27,884/QALY

Questions?