Updates in Outpatient Medicine

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Aspirin for Primary Prevention
A 57-year-old woman is evaluated during a routine follow-up visit for diabetes mellitus. She also has hypertension, depression and hyperlipidemia. Medications are metformin, enalapril, chlorthalidone, and high-intensity rosuvastatin. She has no drug allergies.

On physical examination, blood pressure is 126/74 mm Hg. The remainder of the examination is unremarkable.

Her 10-year risk for atherosclerotic cardiovascular disease is 10.5% according to the Pooled Cohort Equations. She has been instructed in intensive lifestyle modifications.

Which of the following is most appropriate for primary prevention of ASCVD in this patient?

A. Add 81 mg aspirin
B. Change metformin to liraglutide
C. Add 325 mg aspirin
D. No further intervention
Aspirin “The Wonder Drug”

- Aspirin has unquestioned benefit for secondary prevention
- Aspirin's routine use for primary prevention, however, has been the subject of controversy because of questionable benefits and increased bleeding risk
Recommendations based on information from multiple systematic reviews (CV benefits, colorectal cancer benefits, and bleeding risks) and a decision analytic model that attempted to synthesize these different outcomes.

The differing recommendations by age reflected increasing bleeding risk with age and that multiple years of aspirin use were needed to observe the CRC benefits.

These recommendations predate the 3 large, recent trials of aspirin use for primary prevention and 2 meta analyses.
Previously, USPTF 2009 A level recommendation for use of aspirin use in adults 50-75 at increased CV risk

A Level- The USPSTF recommends the service. There is high certainty that the net benefit is substantial

In 2016, downgraded to B level recommendation for use of aspirin use in adults aged 50-59

- who have a 10% or greater 10-year CV risk
- are not at increased risk of bleeding
- have a life expectancy of at least 10 years
- and are willing to take low-dose aspirin for a minimum of 10 years

B Level- The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.
C level recommendation for adults 60-69 for shared medical decision making for those at increased CV risk

C level- The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.

The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults younger than 50 years and adults aged 70 years or older.
ARRIVE (Aspirin to Reduce Risk of Initial Vascular Events)

- Funded by Bayer
- Randomized over 12,000 patients with moderate CV risk to either 100 mg of coated aspirin or placebo
- Average of 5 years of follow-up
- No significant difference in CV events between 2 groups (aspirin 4.4% vs. placebo 4.5%, p=0.60)
- Aspirin was associated with an increased risk of GI bleeding (aspirin 0.97% vs. 0.46%, p=0.0007)
ASPREE (Aspirin in Reducing Events in the Elderly)

- Randomized over 19,000 patients aged 70 or older (65 or older among blacks and Hispanics) to either 100 mg of coated aspirin or placebo
- Mean follow-up 4.7 years
- Non-statistically significant reduction in CV events
- The rate of major hemorrhage was 8.6 events per 1000 person-years in the aspirin group and 6.2 events per 1000 person-years, in the placebo group (hazard ratio, 1.38; 95% CI, 1.18 to 1.62; P<0.001).
- Higher all-cause mortality was observed among apparently healthy older adults who received daily aspirin than among those who received placebo and was attributed primarily to cancer-related death
ASCEND (A Study of Cardiovascular Events in Diabetes)

- Randomized over 15,000 patients aged 40 and older with diabetes and no prior CVD to either 100 mg of coated aspirin or placebo
- Mean age 63
- Mean follow-up 7.4 years
- Serious vascular events occurred in a significantly lower percentage of participants in the aspirin group than in the placebo group (658 participants [8.5%] vs. 743 [9.6%]; rate ratio, 0.88; 95% confidence interval [CI], 0.79 to 0.97; P=0.01)
- Major bleeding events occurred in 314 participants (4.1%) in the aspirin group, as compared with 245 (3.2%) in the placebo group (rate ratio, 1.29; 95% CI, 1.09 to 1.52; P=0.003), with most of the excess being gastrointestinal bleeding and other extracranial bleeding
Recent Mata Analyses (included 3 recent trials)

- Association of Aspirin Use for Primary Prevention With Cardiovascular Events and Bleeding Events, A Systematic Review and Meta-analysis (Zhang et al)
  - meta-analysis of 13 trials with 164,225 participants without cardiovascular disease
  - The use of aspirin in individuals without cardiovascular disease was associated with a lower risk of cardiovascular events and an increased risk of major bleeding

- Aspirin for Primary Prevention of Cardiovascular Events (Abdelaziz et al)
  - A total of 15 randomized controlled trials including 165,502 participants were available for analysis
  - Aspirin for primary prevention reduces nonfatal ischemic events, but significantly increases nonfatal bleeding events
Conclusions form ARRIVE, ASPREE, and ASCEND and meta analyses

- Aspirin for primary prevention has at best moderate protective effects
- Aspirin has modest increased risk of adverse effects of increased bleeding
- The greatest potential benefit of aspirin would accrue in those at the highest CV risk who are not at increased risk of bleeding
2019 ACC/AHA Guideline on the Primary Prevention of CV Disease

- Aspirin should **not** be used in the routine primary prevention of ASCVD due to lack of net benefit.
- Low-dose aspirin might be considered for primary prevention of ASCVD in select higher ASCVD adults aged 40-70 years who are not at increased bleeding risk.
- Low-dose aspirin should not be administered on a routine basis for primary prevention of ASCVD among adults >70 years.
- Low-dose aspirin should not be administered for primary prevention among adults at any age who are at increased bleeding risk.
Why isn’t aspirin still a wonder drug

- We are doing better with other CV interventions
  - Smoking
  - Statin therapy
  - HTN control
- Decreases overall CV disease risk and reduces added benefit of aspirin
- Tips the balance of the CV benefit vs bleeding complications closer to one another
A 57-year-old woman is evaluated during a routine follow-up visit for diabetes mellitus. She also has hypertension, depression and hyperlipidemia. Medications are metformin, enalapril, chlorthalidone, and high-intensity rosuvastatin. She has no drug allergies. On physical examination, blood pressure is 126/74 mm Hg. The remainder of the examination is unremarkable. Her 10-year risk for atherosclerotic cardiovascular disease is 10.5% according to the Pooled Cohort Equations. She has been instructed in intensive lifestyle modifications. Which of the following is most appropriate for primary prevention of ASCVD in this patient?

A. Add 81 mg aspirin
B. Change metformin to liraglutide
C. Add 325 mg aspirin
D. No further intervention
Correct answer: A. **Add 81 mg of aspirin.** The USPSTF recommends initiating low-dose aspirin use for primary prevention of CVD and colorectal cancer in adults 50-59 who have a 10% or greater 10-year CVD risk, are not at increased risk of bleeding, have at least a 10-year life expectancy, and are willing to take low-dose aspirin for at least 10 years.

Reference:


Vaping and e-cigarettes
What is an e-cigarette?

- Entered market in 2003 in China and 2006 in the US and Europe
- A type of electronic nicotine delivery device consisting of a cartridge containing a liquid, an atomizer, and a battery
- Liquid includes nicotine, propylene glycol/glycerol, and flavorings
- User activates the atomizer by inhaling or pressing a button
- The atomizer heats and aerosolizes the liquid in the cartridge creating a vapor for inhalation
- Simulates smoking experience without combustion
- More recent versions feature rechargeable batteries, heating elements and refillable cartridges that deliver higher nicotine concentrations
Prevalence

- In U.S. adults, ever use increased from 3.3% to 8.5% from 2010 to 2013.
- Overall in 2016, 15.3% of adults had ever used e-cigarettes with 3.2% current use.
- The reported increase in e-cigarette use by high school students from 2011 to 2017 was greater than any other nicotine product.
- In 2018, 21% of high school students reported current use of e-cigarettes vs. 12% in 2017.
- Almost 5% of middle school students reported current use.
- Most adult and adolescent users already use conventional cigarettes.
- Rates of e-cigarette use are increasing among current and former smokers but not among never smokers.
Role in Smoking Cessation/Reduction

- Limited available evidence
- Many advertisements for e-cigarettes make claims that they are effective for smoking cessation
- Trial of 866 smokers using e-cigarettes vs NRT
  - Cigarette abstinence 18% for e-cigarettes vs 9.9% for NRT
  - Among those abstinent at one year, e-cigarette use was 80% among e-cigarette cohort vs. 9% in the NRT cohort
- Other smaller trials have not found e-cigarettes to be more effective than NRT in smoking cessation
- E-cigarettes have not received Food and Drug Administration approval as smoking cessation devices
Adverse health effects

- No exposure to tars, oxidant gases, and CO
- Most users get comparable nicotine levels to cigarette smokers
- Nicotine exposure increase heart rate and produces measurable levels of cotinine
- Nicotine is highly addictive substance
Adverse health effects

- Most experts believe e-cigarettes are safer than traditional cigarettes.
- However, chronic consequences of inhalation of e-cigarette vapor are unknown.
- Little is known about the effects of aerosolized propylene glycol or glycerol.
- Long term CV risks are unknown, but thought to be lower than traditional cigarettes.
- Limited data on respiratory function effects.
Outbreak of Lung Injury Associated with the Use of E-Cigarettes

- Recognized in summer 2019
- As of November 13, 2019, 2,172 cases of e-cigarette use associated lung injury (EVALI) have been reported to CDC from 49 states with 42 deaths
- All EVALI patients have reported a history of using e-cigarettes
  - THC is present in most of the samples tested by FDA to date, and most patients report a history of using THC-containing products (75-80%)
  - 30% have underlying asthma
- The latest findings suggest products containing THC, particularly those obtained off the street or from other informal sources are linked to most of the cases
Updated November 8, 2019, at 1:00 PM EST

Recent CDC laboratory testing of bronchoalveolar lavage fluid samples from 29 patients with EVALI submitted to CDC from 10 states found vitamin E acetate in all of the BAL fluid samples.

Vitamin E acetate is used as an additive (thickening agent) in the production of e-cigarette or vaping products.

This is the first time that we have detected a potential chemical of concern in biologic samples from patients with these lung injuries.

While it appears that vitamin E acetate is associated with EVALI, evidence is not yet sufficient to rule out contribution of other chemicals of concern to EVALI.
Youth and nonsmoker concerns

- Non-smokers are not using e-cigarettes to stop them from using traditional cigarettes so there is no mitigating harm reduction.
- E-cigarette adolescent ever users had a higher probability of initiating cigarette smoking compared to e-cigarette adolescent never users (31% vs. 8%).
- Respiratory symptoms seem to be greater among younger users.
Updated 2018 Cholesterol Guidelines
A 72-year-old man is evaluated during a wellness visit. He has no symptoms. Medical history is significant for hypertension and impaired fasting glucose. He has never smoked cigarettes. Medications are hydrochlorothiazide and metformin. On physical examination, blood pressure is 130/80 mm Hg; other vital signs are normal. BMI is 29. The remainder of the physical examination is normal.

Laboratory studies:
- Total Cholesterol: 271 mg/dl
- LDL Cholesterol: 155 mg/dl
- HDL Cholesterol: 50 mg/dl
- TG: 330 mg/dl

In addition to therapeutic lifestyle changes, which of the following is the most appropriate therapy for primary prevention of ASCVD in this patient?
A. Ezetimibe
B. Simvastatin
C. Rosuvastatin
D. No further intervention
What has changed?

- 2018 Guidelines for Treatment of Blood Cholesterol, published in *Circulation* by a joint task force of the American Heart Association and the American College of Cardiology
- The 2018 guidelines incorporate key updates in four specific categories from the previous 2013 edition
- Publication of three new RCTs that support the use of non-statin lipid-modifying therapy to reduce ASCVD events in high-risk patients
4 major statin benefit groups for whom the ASCVD risk reduction clearly outweighs the risk of adverse events

1) Clinical ASCVD
   a. High-intensity statin (≤75 yo)
   b. Moderate-intensity statin (>75 yo or not a candidate for high-intensity)

2) Primary elevations of LDL-C >190 mg/dL
   High-intensity statin (or moderate-intensity, if not a candidate for high-intensity)

3) Diabetes aged 40 to 75 years with LDL-C 70 to 189 mg/dL and without clinical ASCVD
   a. Moderate-intensity statin
   b. High-intensity statin (if 10-year ASCVD risk ≥ 7.5%)

4) Without clinical ASCVD or diabetes, aged 40-75 years, with LDL-C 70 to 189 mg/dL and estimated 10-year ASCVD risk >7.5%
   Moderate to high-intensity statin
A non-fasting plasma lipid profile can be obtained to estimate ASCVD risk and document baseline LDL-C in adults 20 years and older who are not on lipid-lowering therapy.

The updated guidelines reinforce the importance of healthy living, lifestyle modification, and prevention.

In addition to lifestyle interventions, statins continue to be the cornerstone of therapy for lipid management.

- High-intensity statin therapy lowers LDL-C levels by ≥50%.
- Moderate-intensity statin therapy lowers LDL-C levels by 30% to 49%.
- Low-intensity statin therapy lowers <30%.

More emphasis on thresholds and targets.

Highlights shared medical decision making.

Attempts to individualize recommendations.
Secondary Prevention

- In patients with clinical ASCVD, reduce LDL-C with high-intensity statin therapy or maximally tolerated statin therapy.
- In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL to consider addition of non-statins to statin therapy.
  - Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.
  - In very high-risk ASCVD patients, it is reasonable to add ezetimibe to maximally tolerated statin therapy when the LDL-C level remains ≥70 mg/dL.
  - In patients at very high risk whose LDL-C level remains ≥70 mg/dL on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable, although the long-term safety (>3 years) is uncertain and cost effectiveness is low at mid-2018 list prices.
2018 Guideline Primary Prevention

Key Point 1

- Patients ages 20-75 years and LDL-C ≥190 mg/dl, use high-intensity statin **without** risk assessment.
  - If the LDL-C level remains ≥100 mg/dL, adding ezetimibe is reasonable
  - If the LDL-C level on statin plus ezetimibe remains ≥100 mg/dL and the patient has multiple factors that increase subsequent risk of ASCVD events, a PCSK9 inhibitor may be considered
2018 Guideline Primary Prevention
Key Point 2

- Age 40-75 years and LDL-C ≥70 and <190 mg/dl without diabetes, use the risk estimator that best fits the patient and risk-enhancing factors to decide intensity of statin.

  - **Risk 5% to <7.5%** (borderline risk). Risk discussion: if risk-enhancing factors are present, discuss moderate-intensity statin and consider coronary CACs in select cases.

  - **Risk ≥7.5-20%** (intermediate risk). Risk discussion: use moderate-intensity statins and increase to high-intensity with risk enhancers.

  - **Risk ≥20%** (high risk). Risk discussion to initiate high-intensity statin to reduce LDL-C by ≥50%.

- Option of CACs to risk stratify if there is uncertainty about risk.
  - If CAC = 0, can avoid statins and repeat CAC in the future (5-10 years), the exceptions being high-risk conditions such as diabetes, family history of premature CHD, and smoking.
  - If CACs 1-100, it is reasonable to initiate moderate-intensity statin for persons ≥55 years.
  - If CAC >100 or 75th percentile or higher, use statin at any age.
Risk Enhancers

- Family history of premature ASCVD
- LDL-C 160–189 mg/dL or non-HDL-C 190–219 mg/dL
- Metabolic syndrome
- Chronic kidney disease (CKD)
- Chronic inflammatory conditions (e.g., rheumatoid arthritis, HIV)
- Premature menopause (before age 40 y) and pregnancy-associated conditions that increase later ASCVD risk (e.g., preeclampsia)
- High-risk race/ethnicities (e.g., South Asian ancestry)
<table>
<thead>
<tr>
<th>High intensity</th>
<th>Moderate intensity</th>
<th>Low intensity</th>
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<tbody>
<tr>
<td>Daily dosage lowers LDL-C by approximately ≥ 50% on average</td>
<td>Daily dosage lowers LDL-C by approximately 30% to 50% on average</td>
<td>Daily dosage lowers LDL-C by &lt; 30% average</td>
</tr>
<tr>
<td><strong>Atorvastatin (Lipitor), 40† to 80 mg</strong></td>
<td><strong>Atorvastatin, 10 (20) mg</strong></td>
<td><strong>Simvastatin, 10 mg</strong></td>
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<tr>
<td><strong>Rosuvastatin (Crestor), 20 (40) mg</strong></td>
<td><strong>Rosuvastatin, (5) 10 mg</strong></td>
<td><strong>Pravastatin, 10 to 20 mg</strong></td>
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<td><strong>Simvastatin (Zocor), 20 to 40 mg‡</strong></td>
<td><strong>Lovastatin, 20 mg</strong></td>
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<td></td>
<td><strong>Pravastatin (Pravachol), 40 (80) mg</strong></td>
<td><strong>Fluvastatin, 20 to 40 mg</strong></td>
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<td><strong>Lovastatin (Mevacor), 40 mg</strong></td>
<td><strong>Pitavastatin, 1 mg</strong></td>
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<td><strong>Fluvastatin XL (Lescol XL), 80 mg</strong></td>
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<td><strong>Fluvastatin, 40 mg twice daily</strong></td>
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<td></td>
<td><strong>Pitavastatin (Livalo), 2 to 4 mg</strong></td>
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**NOTE:** Specific statins and dosages noted in bold were evaluated in RCTs included in critical question 1, critical question 2, and the Cholesterol Treatment Trials 2010 meta-analysis included in critical question 3 (see full guideline for details). All of these RCTs demonstrated a reduction in major cardiovascular events. Statins and dosages listed in italics are approved by the U.S. Food and Drug Administration but were not tested in the RCTs reviewed.

LDL-C = low-density lipoprotein cholesterol; RCT = randomized controlled trial.

*—Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biologic basis for a less-than-average response.

†—Evidence from one RCT only: down-titration if unable to tolerate atorvastatin, 80 mg, in Incremental Decrease through Aggressive Lipid Lowering study.

‡—Although simvastatin, 80 mg, was evaluated in RCTs, initiation of simvastatin, 80 mg, or titration to 80 mg is not recommended by the U.S. Food and Drug Administration because of the increased risk of myopathy, including rhabdomyolysis.

2018 Guideline Primary Prevention
Key Point 3

- Diabetes and age 40-75 years, use moderate-intensity statin and risk estimate to consider high-intensity statins
- In those with multiple ASCVD risk factors, consider high-intensity statin with aim of lowering LDL-C by 50% or more.
- Risk-enhancers in diabetics include
  - ≥10 years for T2DM and 20 years for type 1 DM
  - ≥30 mcg albumin/mg creatinine
  - eGFR <60 ml/min/1.73 m²
  - Retinopathy
  - Neuropathy
  - ABI <0.9
2018 Guideline Primary Prevention
Key Point 4

- Age >75 years, clinical assessment and risk discussion
A 72-year-old man is evaluated during a wellness visit. He has no symptoms. Medical history is significant for hypertension and impaired fasting glucose. He has never smoked cigarettes. Medications are hydrochlorothiazide and metformin. On physical examination, blood pressure is 130/80 mm Hg; other vital signs are normal. BMI is 29. The remainder of the physical examination is normal.

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In addition to therapeutic lifestyle changes, which of the following is the most appropriate therapy for primary prevention of ASCVD in this patient?

A. Ezetimibe
B. Simvastatin
C. Rosuvastatin
D. No further intervention
Correct answer: B. Simvastatin. In patients aged 40 to 75 years with no atherosclerotic cardiovascular disease (ASCVD) or diabetes mellitus and with a 10-year ASCVD risk of 7.5% or higher accompanied by the presence of ASCVD risk enhancers, the American Heart Association and American College of Cardiology recommend moderate-intensity statin therapy for primary prevention of ASCVD.

Reference: