Take 3 – Practical Practice Pointers© October 8, 2018 Edition

Aspirin for Primary Prevention, Acute COPD, E-Cigarettes and Youth

From the Literature and a Colleague

1) Aspirin for Primary Disease Prevention

In 2016, the US Preventive Services Task Force (USPSTF) released their updated recommendations of the use of aspirin for primary heart disease prevention and colorectal cancer (CRC) prevention. Remember that ***primary prevention*** means preventing disease BEFORE it starts. The recommendation included the following:

Recommended initiating low-dose aspirin (≤100 mg/day) use for the primary prevention of CVD and CRC in adults aged 50 to 59 **(B recommendation)** who have:

- a 10% or greater 10-year CVD risk (using the ACC/AHA risk calculator),
- are not at increased risk for bleeding,
- have a life expectancy of at least 10 years, and
- are willing to take low-dose aspirin daily for at least 10 years

Recommended that the decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60 to 69 who have a 10% or greater 10-year CVD risk should be an individual one. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin **(C recommendation)**. Those most likely to benefit are those who:

- are not at increased risk for bleeding,
- have a life expectancy of at least 10 years, and
- are willing to take low-dose aspirin daily for at least 10 years.

The current evidence was deemed insufficient for adults < 50 and ≥ 70.

Remember that the outcomes included both reduction in cardiovascular events as well as CRC mortality and accounted for the risks of bleeding.

Now, along comes three additional large, well-done aspirin trials (all using 100 mg doses) for primary prevention of ASCVD, summarized here briefly:

ARRIVE - >12,000 patients with 5 year f/u. Men >54 with >1 ASCVD risk factor, women > 59 with >2 ASCVD risk factors. (10-20% calculated ASCVD risk, excluding diabetes). 5 years follow up.

- No difference in combined rate of MI and stroke.
- Small (0.5%), but significant increase in GI bleeding

ASCEND - >15,000 middle aged or older patients with diabetes (vascular risk calculated as low-moderate for most) with 7.4 year follow up.

- Serious vascular events reduced by 1% (statistically significant)
- Major bleeding events increased by 1% (statistically significant)
- No differences in cancer incidence or outcome (though short f/u for this)

ASPREE - >19,000 healthy elderly (broad range of ASCVD risk, including DM) with 4.7 year follow up.

- All cause mortality significantly higher in aspirin group, mostly due to cancer
- No difference in ASCVD outcomes (fatal CHD, MI, stroke, CHF hospitalization)

- Major hemorrhage significantly increased with aspirin
- Disability-free survival (no death, dementia or physical disability) was equal

Guest Commentary from John Epling, MD (the opinions expressed here are only John's and not those of the USPSTF): Overall, aspirin doesn't seem to work as well in these populations as was previously thought. Any benefit found was offset by the risk of bleeding, and there were serious concerns about using aspirin in the unselected healthy elderly. Of note, both the ARRIVE and ASPREE trial authors noted that the expected rate of cardiovascular disease events was significantly lower (by half in each study) than predicted by their risk calculations (which varied). They surmised that this is likely due to overall declining rates of ASCVD and better control of CV risk factors in recent years. Remember that aspirin still has a solid indication if someone is diagnosed with ASCVD.

It is clear that the benefit of aspirin is limited by is effect on bleeding risk and by age. At this point, it seems prudent to reserve aspirin for your highest cardiovascular disease risk patients, only if their risk of bleeding is low, and only after a good discussion of the risks (bleeding) and benefits (for both ASCVD and colorectal cancer).

My Comment:
My thanks to John for his significant contribution to this Pointer and for his critical thinking expertise. A good reminder that a "baby" aspirin (an unfortunate term) is NOT harmless. This provides an opportunity to review your treatment plan with patients who are presently taking aspirin. Remember as well that the American Diabetes Association (ADA) 2018 standards of care recommend aspirin for primary prevention when 10 year cardiovascular risk is > 10% (ADA Grade C) and to consider with 10-year risk between 5%-10% (ADA Grade E). The ASPREE trial would call that recommendation into question as well. It will be interesting to see how the ADA responds (as well as the USPSTF!).

References:

- Bibbens-Domingo, K, et al. Aspirin Use for the Primary Prevention of Cadiovascular Disease and Colorectal Cancer: USPSTF Recommendation Statement. *Ann Intern Med.* 2016;164(12):836-845. Guideline
- McNeil JJ et al. Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly. *N Engl J Med*. September 2018. Link
- Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. *New England Journal of Medicine*. 2018;0(0):null. Link
- Gaziano JM et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. *The Lancet*. 2018;392(10152):1036-1046. Link

From the Guidelines and Follow-up and Question from Colleague

2) Management of Acute COPD Exacerbations

Question: Thank you for the summary of COPD management last week, but I didn't see anything about the acute management of COPD. Has anything changed with this?

Answer: In 2017, a guideline on the treatment of acute COPD exacerbations was published by a Joint Task Force of "COPD experts" from Europe and the US

representing the European Respiratory Society and the American Thoracic Society. The Task Force defined a COPD exacerbation as "episodes of increasing respiratory symptoms, particularly dyspnea, cough and sputum production, and increased sputum purulence. COPD exacerbations have a negative impact on the quality of life of patients with COPD, accelerate disease progression, and can result in hospital admissions and death."

Recommendations included (Strength of Recommendation/Quality of Evidence):

- For ambulatory patients with an exacerbation of COPD, we suggest a short course (≤14 days) of oral corticosteroids (Conditional/Very Low)
- For ambulatory patients with an exacerbation of COPD, we suggest the administration of antibiotics (Conditional/Moderate)
- For patients who are hospitalized with a COPD exacerbation, we suggest the administration of oral corticosteroids rather than intravenous corticosteroids if gastrointestinal access and function are intact (Conditional/Low)
- For patients who are hospitalized with a COPD exacerbation, we suggest the initiation of pulmonary rehabilitation within 3 weeks after hospital discharge (Conditional/Very Low), but not during hospitalization (Conditional/Very Low)

My Comment:
At Carilion Clinic, we have a "COPD Rescue Pack" order on our EHR for acute COPD exacerbations that includes a short course of oral antibiotics (either Amoxicillin 500 bid for 5 days or Azithromycin 500 qd for 3 days) and prednisone 40 mg qd for 7 days. I do worry that "exacerbations" are overdiagnosed and therefore antibiotics and oral steroids are overused in these patients, but unfortunately with lack of better markers of a bacterial exacerbation, this becomes a "clinical judgement" call and my observation is that most of us error on the side of intervention.

Reference:
Wedzicha JA, et al. Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J 2017; 49: 1600791. Link

From the Literature and the FDA – And a Warning to All Parents

3) The Epidemic Use of E-Cigarettes Among Adolescents

Adolescents' use of electronic cigarettes initially took the public health community by surprise. In 2011, less than 2% of U.S. high school students reported having used e-cigarettes in the previous month. But by 2015, the percentage had jumped to 16% and ensuing public education campaigns and policies helped bring the prevalence of past-month e-cigarette use among U.S. high school students down to 11% in 2016.

A recent evolution in technology and marketing threatens this progress. A new product class called "pod mods" — small, rechargeable devices that aerosolize liquid solutions containing nicotine, flavoring, and other contents encapsulated in cartridges— is rapidly gaining users, most alarmingly among adolescents. Use of Juul, a popular pod mod brand, is anecdotally rampant among young people and recent data indicate it had captured 50% of the total e-cigarette market.

Pod mods can deliver high levels of nicotine with few of the deterrents that are inherent in other tobacco products. Juul's website indicates that one pod delivers the amount of nicotine equivalent to approximately 20 combustible cigarettes. A unique combination of salt-based nicotine and other additives allows pod mods to deliver an addictive dose of nicotine without an aversive user experience or other tobacco-related side-effect.

Pod mods are easy to conceal from authority figures, closely resembling computer USB drives. Because of this, teen use of pod mods on school grounds, including use during class time, is reportedly widespread. And they are easy to use. Many e-cigarette devices require purchase of solutions from independent manufacturers, manual refilling, and user calibration. With most pod mods, consumers merely open their starter kit package, slide a flavor pod into the device, and start vaping.

E-cigarettes are not without risks. Their aerosol can include metals, volatile organic compounds, and flavoring additives, which may be harmful when inhaled.

The FDA has begun to take action. On April 24, 2018, the agency initiated nationwide undercover operations to identify and intervene with retailers that sell e-cigarettes to minors and implemented restrictions against third-party resale of Juuls on eBay.

On September 12, the FDA sent letters to five e-cigarette manufacturers whose products collectively represent more than 97 percent of the current market for e-cigs — JUUL, Vuse, MarkTen, blu e-cigs, and Logic, placing them on notice. The FDA gave these companies 60 days to come up with robust plans as to how they'll convincingly address the widespread use of their products by minors.

My Comment:
Sigh … As sad as this is, it should not be shocking to anyone. Here we have a commonly used, easily accessible, aggressively advertised/promoted, and highly addictive substance that continues to have very little regulation. I hope our negligence does not come back to haunt us. I fear it already is. Be sure to be asking your patients not only about their smoking history, but also their vaping history. Vaping is not considered "smoking."

References:

- Barrington-Trimis JL et al. Adolescents' Use of "Pod Mod" E-Cigarettes — Urgent Concerns. N Engl J Med September 18, 2018; 379:1099-1102. Article
- FDA Statement from FDA Commissioner Scott Gottlieb, M.D., on new steps to address epidemic of youth e-cigarette use. September 12, 2018. Link

Feel free to forward Take 3 to your colleagues. Glad to add them to the distribution list.

Mark

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