Preventive Cardiology Update

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Disclosures

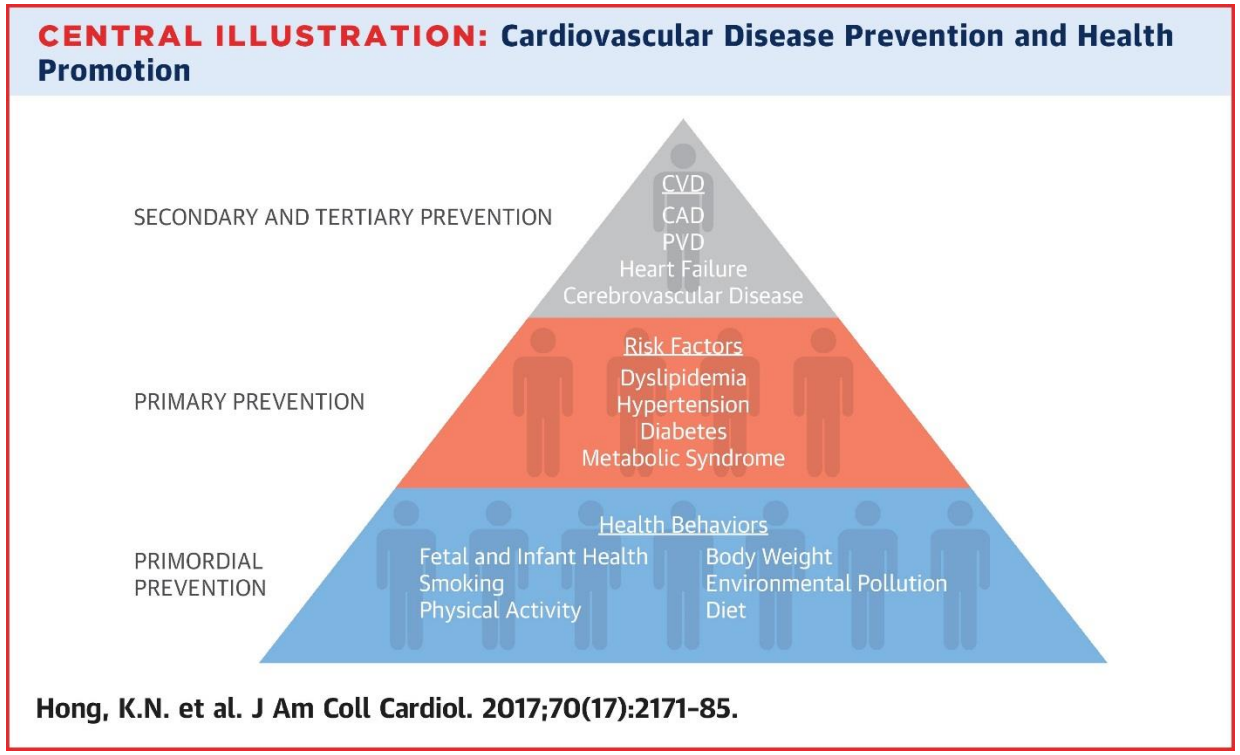
None

Outline

I. Review the role of **icosapent ethyl** in reducing the risk of cardiovascular events.
II. Summarize the recent evidence guiding recommendations for the use of **aspirin** for ***primary*** *prevention* of cardiovascular events.
III. Explore the role of **rivaroxaban** for ***secondary*** *prevention* of cardiovascular events.

Ather**S**clerotic **C**ardio**V**ascular **D**isease

- ASCVD
  - Coronary artery disease
  - Stroke
  - Peripheral arterial disease
  - *Heart failure*
- Epidemiology
  - Underlying cause of around one third of all deaths, 841,000 in 2016
  - Estimated annual cost $351.2 billion in 2014-2015
  - 14% of total health expenditures



Benjamin E, *et al*. Circ. 2019

Ideal Cardiovascular Health: Life's Simple 7

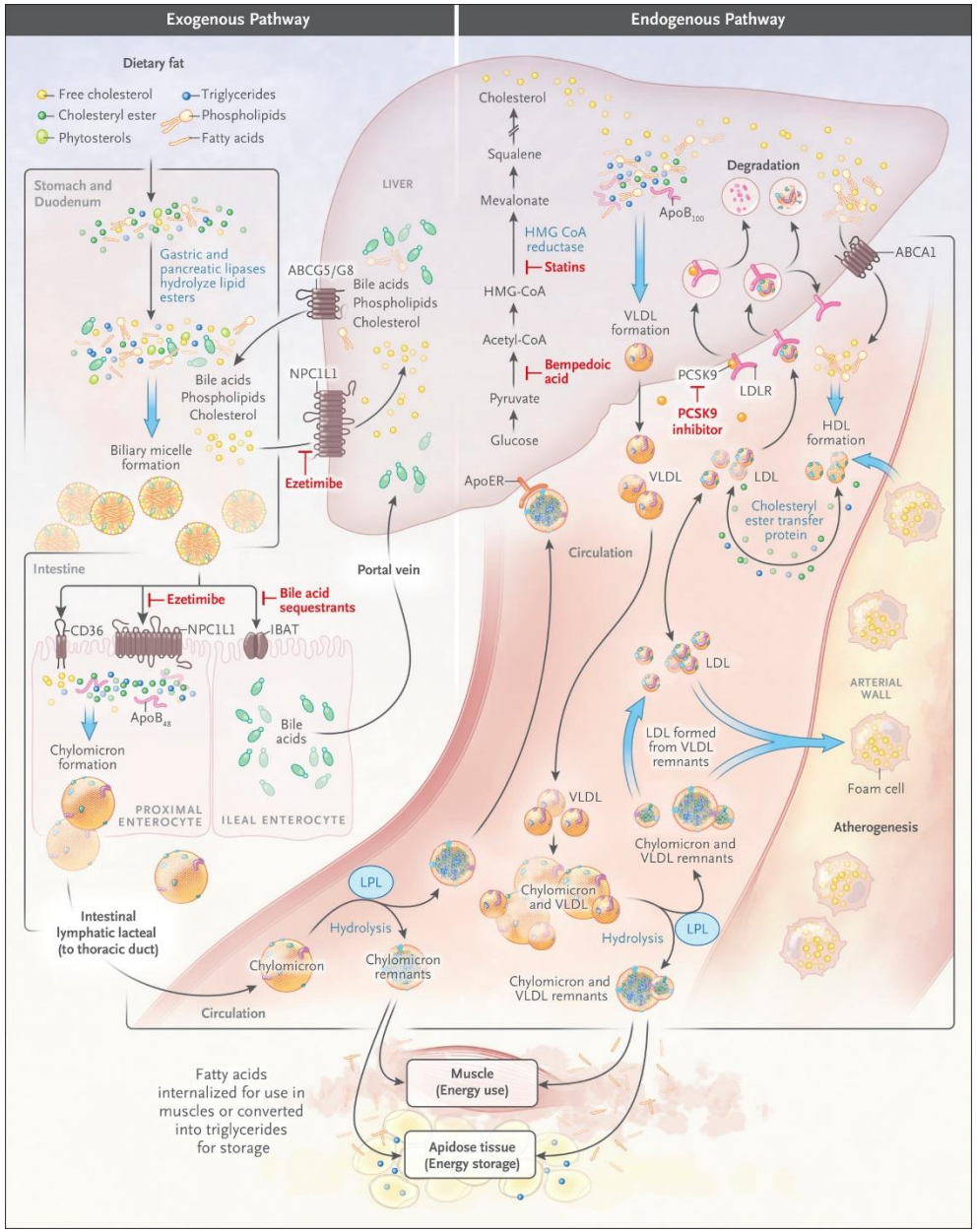
- Cigarette smoking
  - Never or quit > 12 months ago
- Healthy diet
  - 4-5 components, Mediterranean-type diet
- Body mass index
  - < 25 kg/m^2
- Total cholesterol
  - < 200 mg/dL (not treated)
- Physical activity
  - >= 150 min/week, moderate intensity
- Fasting blood glucose
  - < 100 mg/dL (not treated)
- Blood pressure
  - < 120 / < 80 mmHg (not treated)

HIGH STANDARD: 17% adults >= 5 metrics (diet < 1%)

https://www.heart.org/en/professional/workplace-health/lifes-simple-7

Fish Oil

- Long-chain n-3 (omega-3) polyunsaturated fatty acids
  - Eicosapentaenoic acid (EPA)
  - Docosahexaenoic acid (DHA)
- Reduce triglycerides
  - Decreased VLDL production in liver
  - Increased VLDL clearance from circulation
- Initial open-label trials encouraging (GISSI and JELIS), though meta-analyses (through 2017) showed no significant ASCVD reduction



Michos *et al*. N Eng J Med. 2019

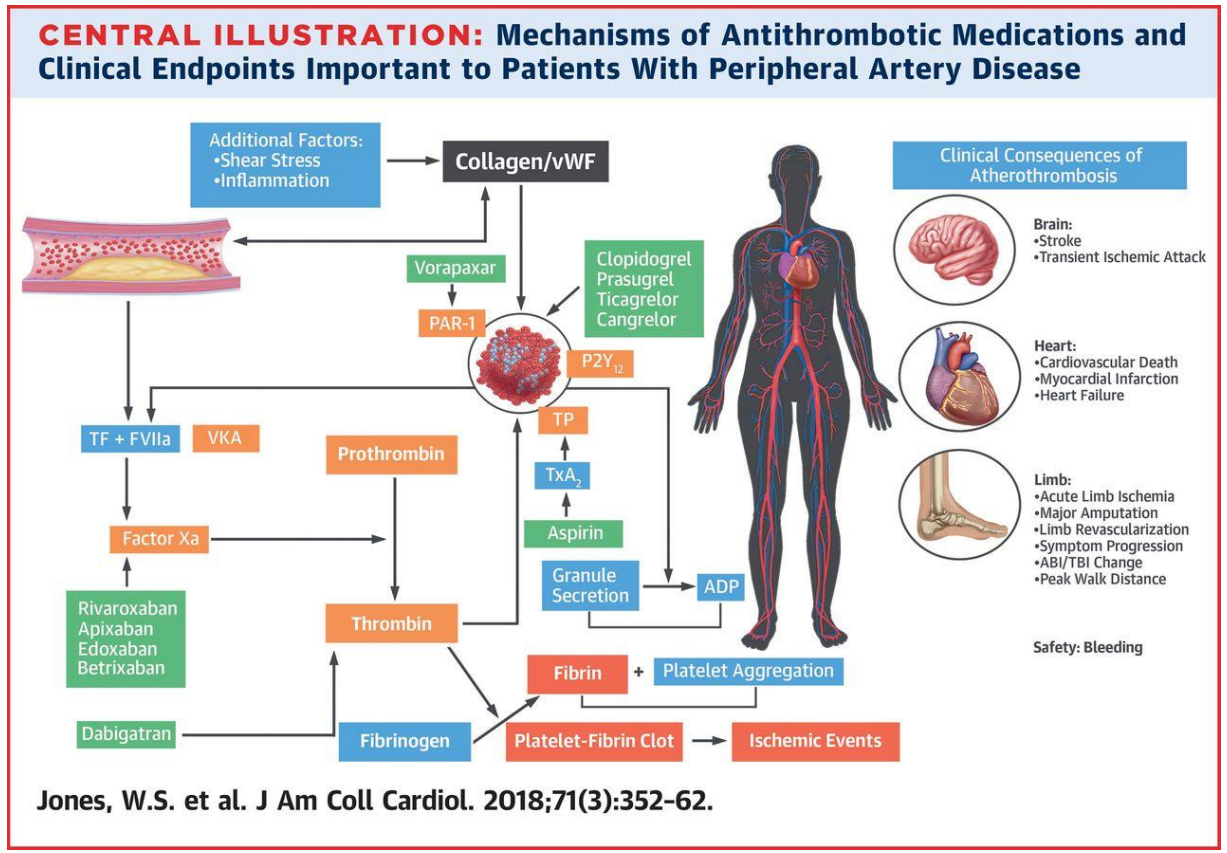
Icosapent Ethyl

- Proprietary and highly purified form of EPA
- REDUCE-IT
  - 45 yr+ with established CVD (71%) or 50 yr+ with DM + risk factor(s) (29%)
  - n 8,179, median f/u 4.9 yr
  - statin + icosapent ethyl (2 g BID) vs statin + placebo
  - TG 135-499 mg/dL, LDL 41-100 mg/dL
  - reduced CV death/MI/CVA/revasc/UA 17.2% vs 22% (ARR 5%, RRR 22%, NNT 20)
  - Increased hospitalization for Afib/flutter (3.1% vs 2.1%, p 0.004, NNH 100)
  - Serious bleeding (2.7% vs 2.1%, p 0.06)

- FDA approval, December 2019
  - Adjunctive therapy for cardiovascular event prevention
  - TG >= 150 mg/dL
  - Established CVD or DM + at least 2 risk factors
  - Distinct from severe TG (> 500 mg/dL)
- ASCVD reduction more than triglyceride reduction (20%) alone
  - Potential anti-inflammatory, antithrombotic, and membrane stabilizing effects possible
  - Does not lower or raise LDL
- Not generalizable to other fish oil preparations (OTC or Rx)

Bhatt DL *et al*. N Engl J Med. 2019

Coagulation and Antithrombotic Medications



- Antiplatelet
  - Aspirin
    - COX inhibitor
  - P2Y12 inhibitors
- Antithrombotic
  - VKA
  - NOAC
    - Rivaroxaban
      - Factor Xa inhibitor

Primary Prevention: Aspirin (100 mg daily)

- ASCEND
  - Diabetic adults (n 15,480, mean age 63 yr, 7.4 yr f/u)
  - Vascular events (MI, stroke, vascular death) reduced (8.5% vs 9.6%, ARR 1.1%, RRR 11%, NNT 90)
  - Major bleeding increased (4.1% vs 3.2%, ARI 0.9%, RRI 28%, NNH 111)
- ASPREE
  - Older adults >= 70 yr (n 19,114, median age 74 yr, 4.7 yr f/u)
  - Primary outcome (death, dementia, or persistent physical disability) no difference
  - Secondary outcome (fatal and nonfatal MI, stroke or CHF hospitalization) no difference
  - Major bleeding increased (3.8% vs 2.8%, ARI 1.0%, RRI 36%, NNH 100)
- ARRIVE
  - [Anticipated] Elevated risk adults (n 12,546, 5 yr f/u)
  - Primary (CV death, MI, UA, stroke, TIA) no difference (4.3% vs 4.5%)
  - GI bleed (mostly mild) increased (0.97% vs 0.46%, ARI 0.51%, RRI 111%, NNH 196)
- Risk factors for GI bleed:
  - Prior GI bleed or PUD, age > 70 yr, thrombocytopenia, coagulopathy, CKD, concurrent use of other medications that increase bleeding risk, *etc*

ASCEND. N Engl J Med. 2018
McNeil JJ *et al*. N Engl J Med. 2018
Gaziano *et al*. Lancet. 2018

Primary Prevention: Aspirin (75-100 mg daily)

Arnett et al.
2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

4.6. Aspirin Use

Recommendations for Aspirin Use Referenced studies that support recommendations are summarized in Online Data Supplements 17 and 18.		
COR	**LOE**	**Recommendations**
IIb	**A**	**1. Low-dose aspirin (75-100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk (S4.6-1–S4.6-8).**
III: Harm	**B-R**	**2. Low-dose aspirin (75-100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age (S4.6-9).**
III: Harm	**C-LD**	**3. Low-dose aspirin (75-100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding (S4.6-10).**

Prior guidelines recommended consideration of 10 yr ASCVD risk with threshold > =10%.

Secondary Prevention: Rivaroxaban

- COMPASS
  - Stable CAD or PAD or both (patients < 65 yr required to have both or 2 additional risk factors including past stroke)
  - n 27,395, mean f/u 23 mon (stopped for superiority)
  - rivaroxaban 2.5 mg BID + aspirin 100 mg daily vs aspirin 100 mg daily
  - reduced CV death/stroke/MI 4.1% vs 5.4% (ARR 1.3%, RRR 24%, NNT 77)
  - increased major bleeding 3.1% vs 1.9% (ARI 1.2%, RRI 63%, NNH 83)
  - also tested rivaroxaban 5 mg BID (no reduced MACE vs aspirin, but increased bleeding risk)

- FDA approval, October 2018
  - Cardiovascular event reduction
  - Along with low-dose aspirin
  - Chronic CAD or PAD
- Clinical application
  - Patient selection
  - DAPT vs rivaroxaban
    - MACE vs major bleeding similar
    - DAPT score helps to individualize
  - Time horizon, limited data

Eikelboom *et al*. N Engl J Med. 2017

Summary

- ASCVD is a leading cause of death and driver of health expenditures
- Prevention is the responsibility of all providers
- Life's simple 7:
  - Cigarette smoking, healthy diet, body mass index, total cholesterol, physical activity, fasting blood glucose, blood pressure
- Beyond lifestyle modification, focus on ASCVD risk calculation and statin therapy, if indicated

- Icosapent ethyl
  - Adjunct to statin for ASCVD risk reduction if TG > 150 mg/dL for patients with CAD or DM and additional risk factors
- Aspirin
  - More limited role in **primary prevention**
- Rivaroxaban
  - Low dose (2.5 mg BID) + low dose aspirin among patients with CAD and/or PAD reduces ASCVD risk at the expense of increased bleeding risk

Competency Question 1

1. Icosapent ethyl is FDA approved for cardiovascular risk reduction in the following patients:

    a) On maximally tolerated statin therapy
    b) With triglycerides 150 mg/dL or higher
    c) With established cardiovascular disease or diabetes mellitus and at least two additional risk factors for cardiovascular disease
    d) All of the above

Competency Question 2

2. Updated guideline statements for the use of low-dose aspirin (75-100 mg daily) for **primary prevention** of atherosclerotic cardiovascular disease (ASCVD) include:

    a) Aspirin might be considered among select adults 40 to 70 years old that are at higher ASCVD risk but not at increased risk of bleeding
    b) Aspirin should not be administered on a routine basis among adults older than 70 years old
    c) Aspirin should not be administered among adults of any age who are at increased risk of bleeding
    d) All of the above

Competency Question 3

3. Rivaroxaban is FDA approved for cardiovascular event risk reduction in the following patients:

    a) With chronic coronary or peripheral artery disease
    b) On low dose aspirin (75-100 mg daily)
    c) On dual antiplatelet therapy with aspirin and a P2Y12 inhibitor (such as clopidogrel, prasugrel, or ticagrelor)
    d) A and B only

Acknowledgements and Key References

- Joseph Poole
- Linda Groarke
- Conference Planning Committee

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1. Bhatt D et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med* 2019; 380:11-22.
2. Arnett DK et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease. *J Am Coll Cardiol* 2019; 74(10):e177-e232.
3. Eikelboom JW et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med* 2017; 377:1319-1330.

Questions?