Haritha R. Alla, MD, F.A.C.C, RPVI

Primary and Secondary Prevention of Coronary Artery Disease

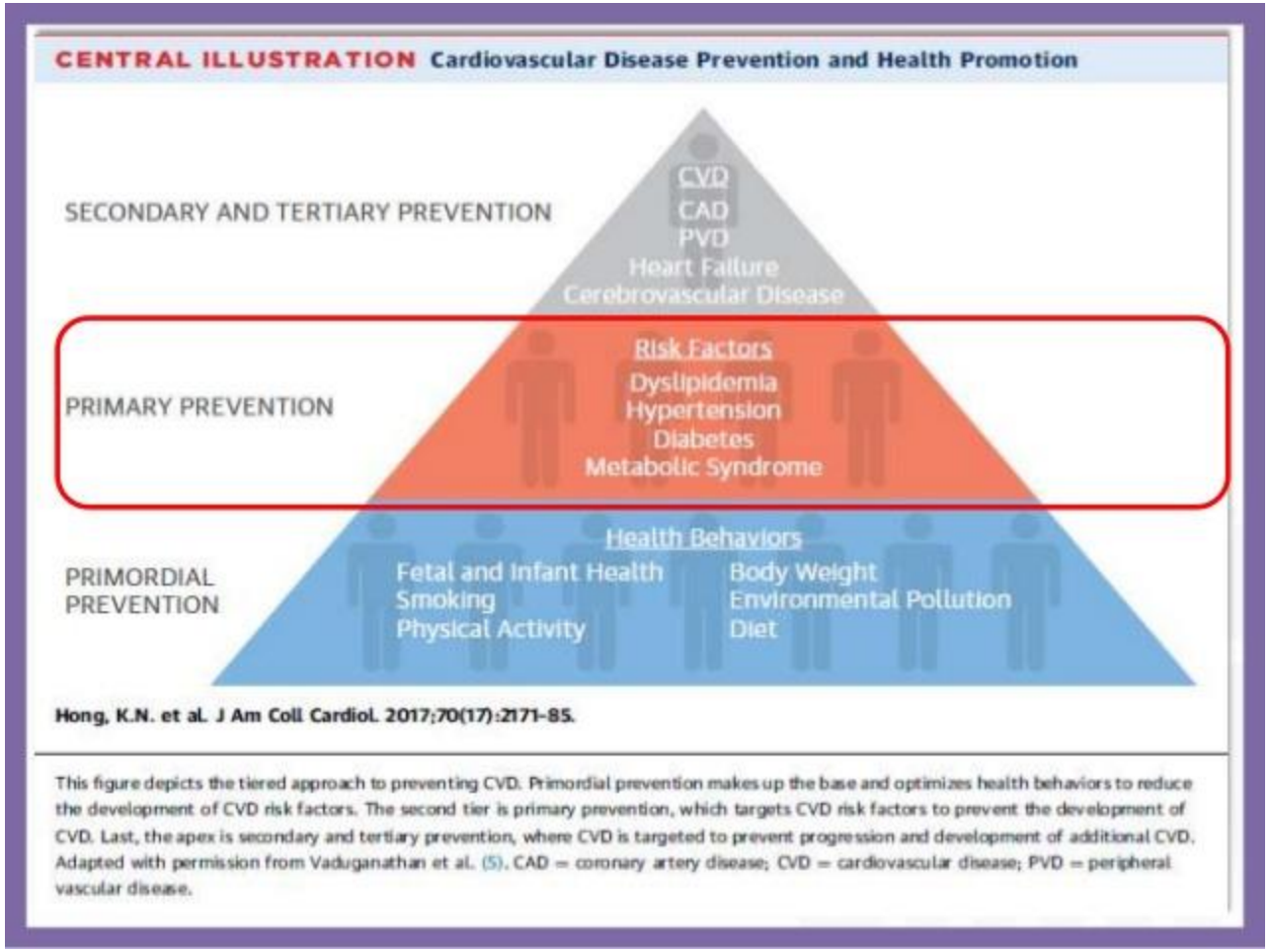

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Table 3. Risk-Enhancing Factors for Clinician-Patient Risk Discussion

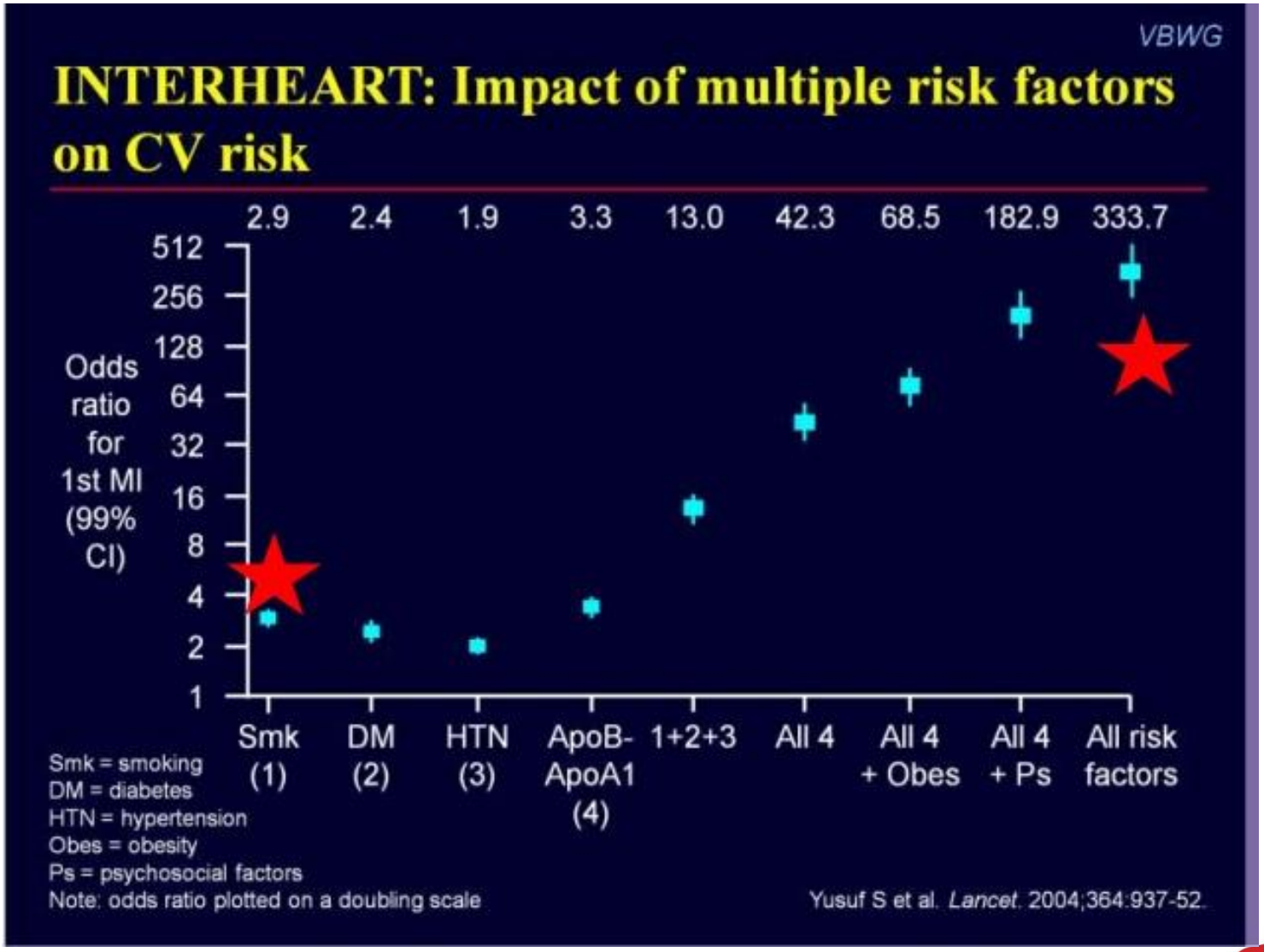
Risk-Enhancing Factors
• **Family history of premature ASCVD** (males, age <55 y; females, age <65 y) • **Primary hypercholesterolemia** (LDL-C 160–189 mg/dL [4.1–4.8 mmol/L]; non–HDL-C 190–219 mg/dL [4.9–5.6 mmol/L])* • **Metabolic syndrome** (increased waist circumference [by ethnically appropriate cutpoints], elevated triglycerides [>150 mg/dL, nonfasting], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 mg/dL in women] are factors; a tally of 3 makes the diagnosis) • **Chronic kidney disease** (eGFR 15–59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation) • **Chronic inflammatory conditions,** such as psoriasis, RA, lupus, or HIV/AIDS

ABI indicates ankle-brachial index; AIDS, acquired immunodeficiency syndrome; apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); and RA, rheumatoid arthritis.

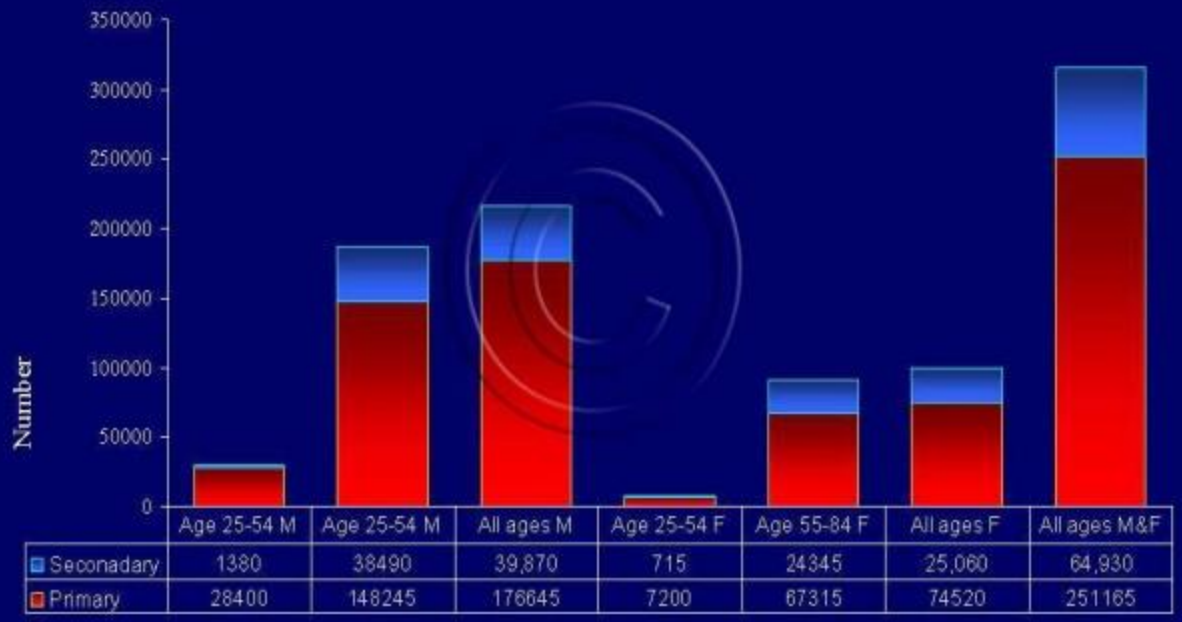
Table 3. Risk-Enhancing Factors for Clinician-Patient Risk Discussion (cont'd)

Risk-Enhancing Factors
• **History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk, such as preeclampsia** • **High-risk race/ethnicity** (e.g., South Asian ancestry) • **Lipids/biomarkers**: associated with increased ASCVD risk • Persistently elevated,* primary hypertriglyceridemia (≥175 mg/dL, nonfasting); • If measured: ▪ **Elevated high-sensitivity C-reactive protein** (≥2.0 mg/L) ▪ **Elevated Lp(a):** A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor, especially at higher levels of Lp(a). ▪ **Elevated apoB** (≥130 mg/dL): A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk-enhancing factor ▪ **ABI** (<0.9)

*Optimally, 3 determinations.


VBWG
INTERHEART: Impact of multiple risk factors on CV risk
2.9
2.4
1.9
3.3
13.0
42.3
68.5
182.9
333.7
512
256
128
64
32
16
8
4
2
1
Odds ratio for 1st MI (99% CI)
Smk (1)
DM (2)
HTN (3)
ApoB-ApoA1 (4)
1+2+3
All 4
All 4 + Obes
All 4 + Ps
All risk factors
Smk = smoking
DM = diabetes
HTN = hypertension
Obes = obesity
Ps = psychosocial factors
Note: odds ratio plotted on a doubling scale
Yusuf S et al. Lancet. 2004;364:937-52.

Age and Gender Difference in Deaths Prevented as a Result of Primary and Secondary prevention (1980-2000)



	Age 25-54 M	Age 25-54 M	All ages M	Age 25-54 F	Age 55-84 F	All ages F	All ages M&F
Seconadary	1380	38490	39,870	715	24345	25,060	64,930
Primary	28400	148245	176645	7200	67315	74520	251165

Young et al Am J Prev Medicine 2010

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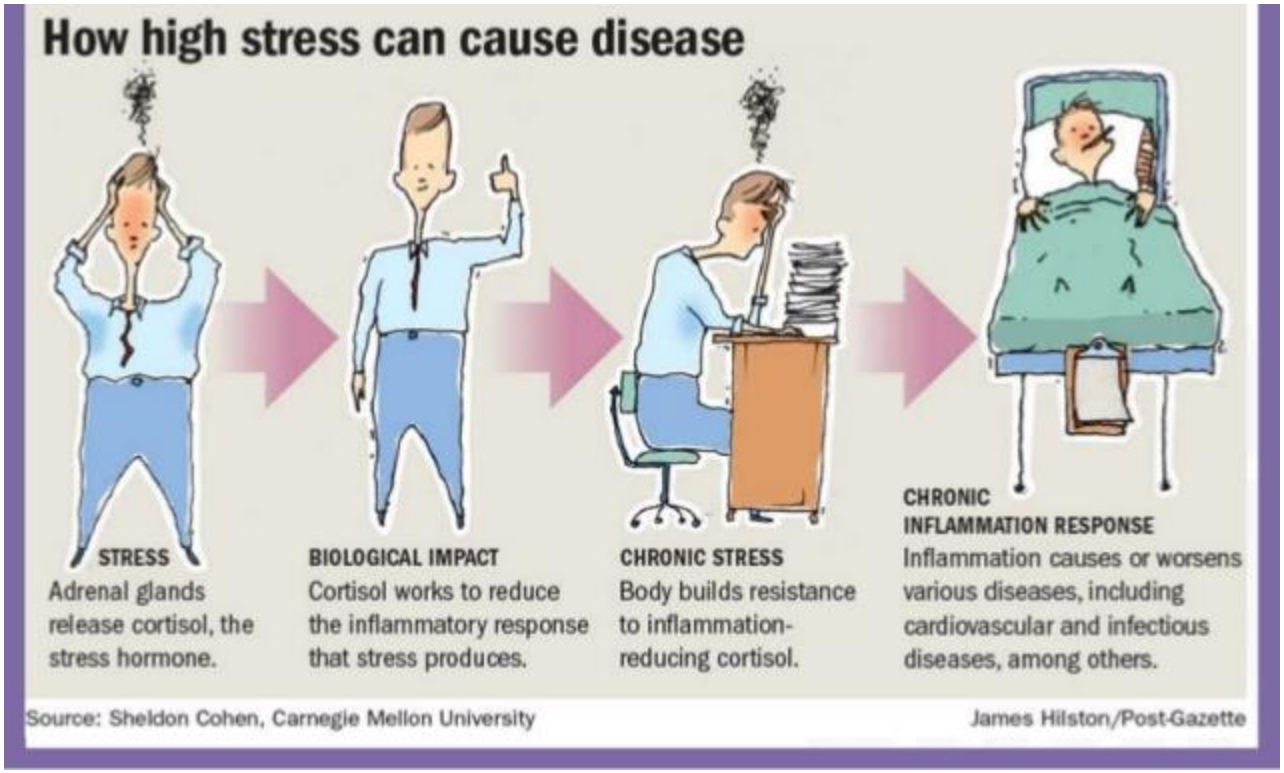
RISK FACTORS FOR HEART DISEASE

Non Modifiable Risk factors	Modifiable Risk factors	Novel Factors
AGE	SMOKING	C REACTIVE PROTEIN
GENDER	HYPERLIPIDEMIA	FIBRINOGEN
ETHNICITY	HYPERTENSION	CORONARY ARTERY CALCIFICATION
FAMILY HISTORY	DIABETES	HOMOCYSTEINE
PREVIOUS CARDIOVASCULAR EVENT	OBESITY	LIPOPROTEIN A
	PHYSICAL INACTIVITY	SMALL DENSE LDL
		RENAL DISEASE
	APOB / APOA1 RATIO	HIV


Abdominal obesity: a major risk factor for diabetes and cardiovascular disease
Endothelial dysfunction
Atherogenic dyslipidemia
Hypertension
Inflammatory profile
Insulin resistance
Pro-thrombotic state



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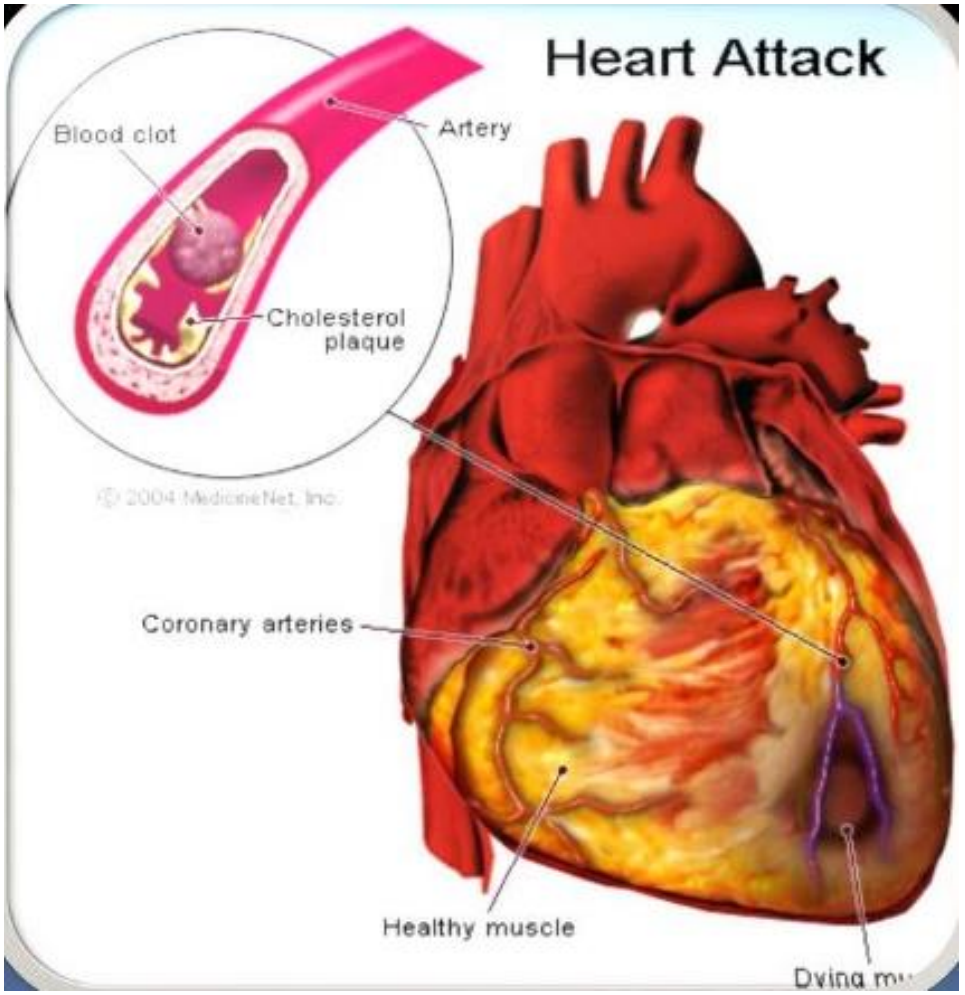

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Fig. 2. Treatment of T2DM for Primary Prevention of CVD

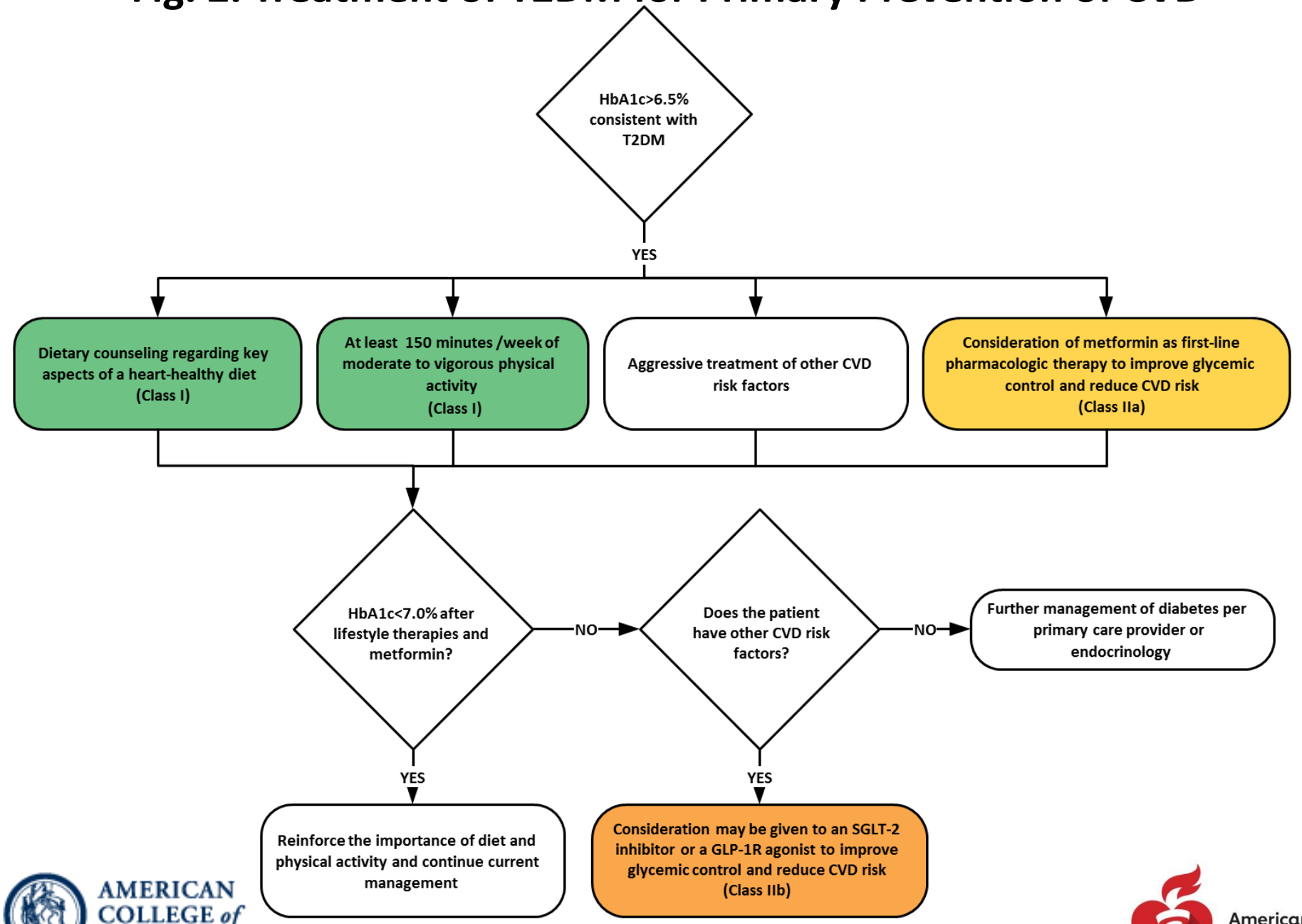

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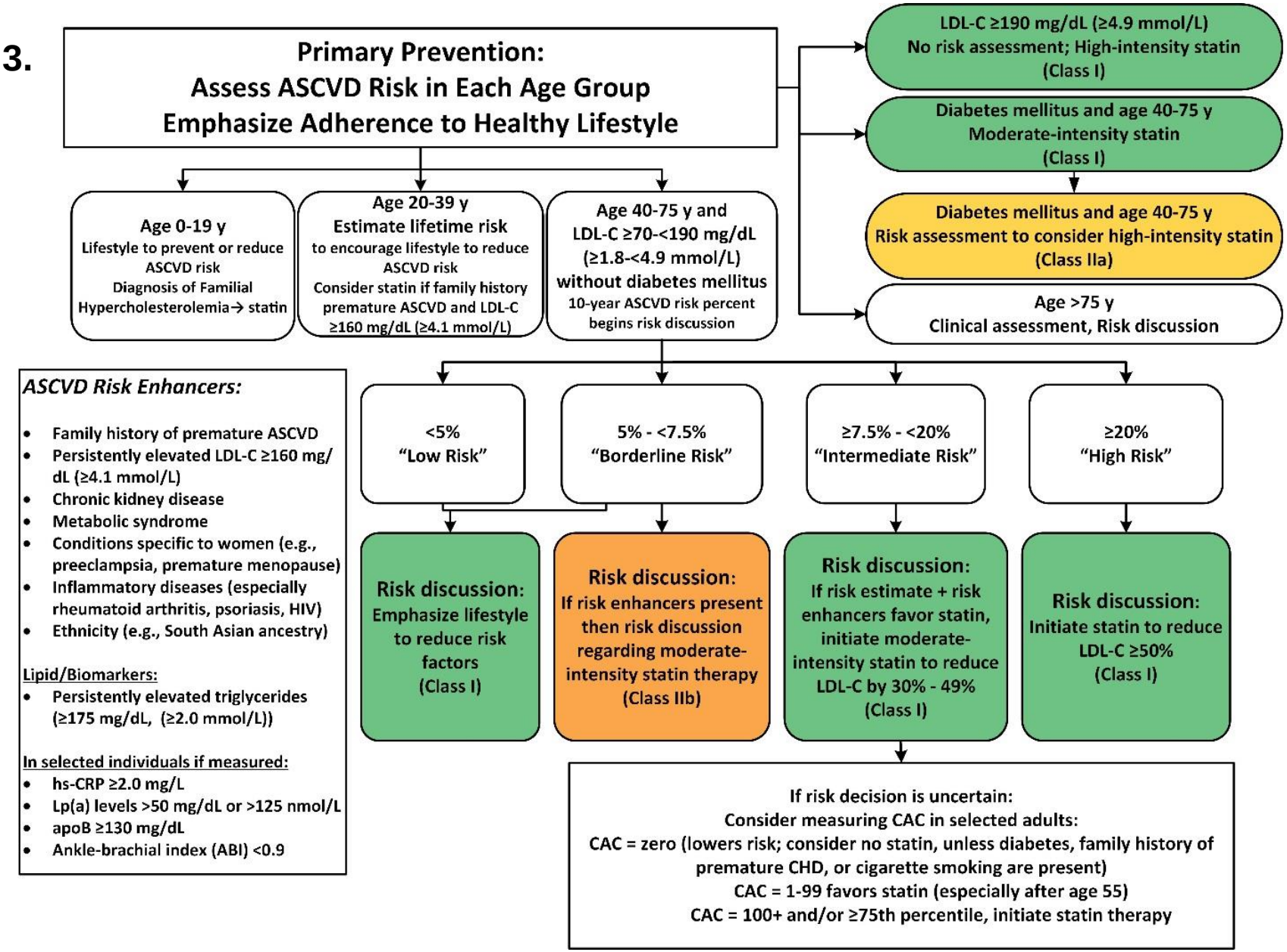
Fig. 3.



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Adults with High Blood Pressure or Hypertension

Recommendations for Adults with High Blood Pressure or Hypertension		
COR	**LOE**	**Recommendations**
I	**A**	**1. In adults with elevated blood pressure (BP) or hypertension, including those requiring antihypertensive medications nonpharmacological interventions are recommended to reduce BP. These include:** • **weight loss,** • **a heart-healthy dietary pattern,** • **sodium reduction,** • **dietary potassium supplementation,** • **increased physical activity with a structured exercise program; and** • **limited alcohol.**

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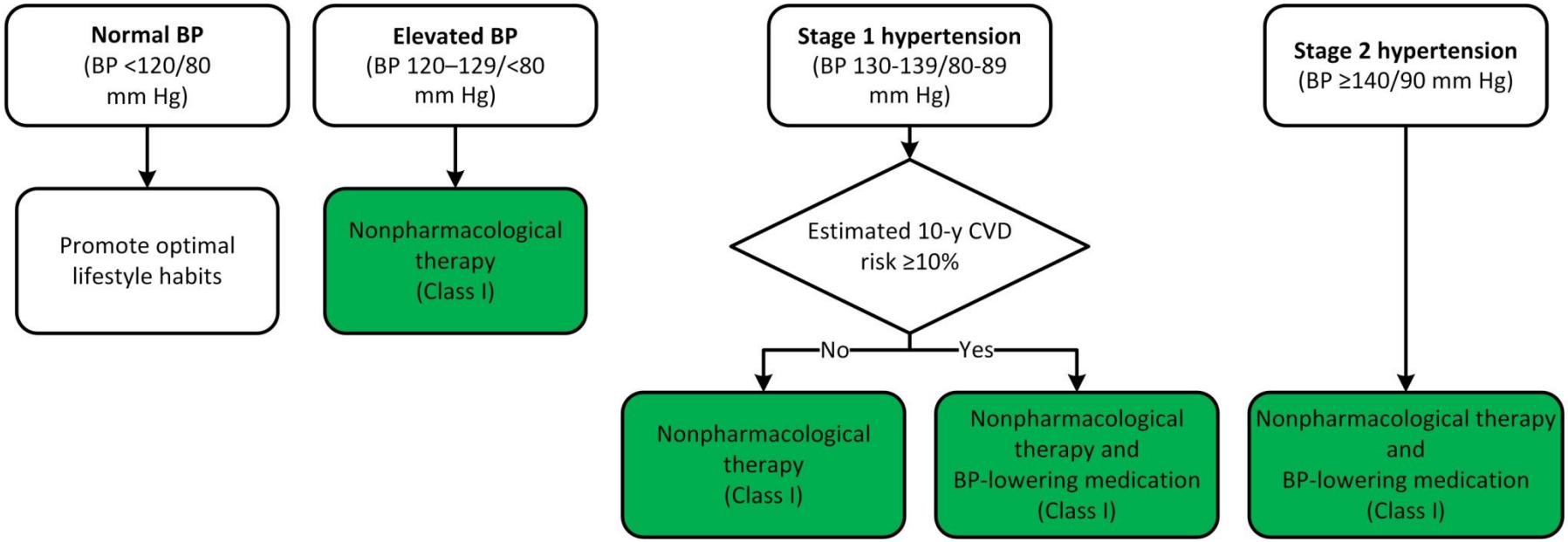
Figure 4. BP Thresholds and Recommendations for Treatment



BP indicates blood pressure; and CVD, cardiovascular disease.

- Genesis of atherosclerosis is prolonged, multifactorial process
- Horus study 10 years back used CT to investigate arterial calcification in mummies as marker of atherosclerosis
- Wann & Colleagues studied 4 mummies of Inuit hunter-gatherer people (lived about 500 years ago, consumed a marine diet rich in omega-3-FA). 2 men and a woman who died by age 25 had calcified atheroma.
- Previous study showed that the CV death in this population was low, hypothesizing it was due to diet rich in Omega-3-FA
- Speculation is that exposure to particulate matter from smoky indoor fires may have played a role in atherosclerosis in this population with otherwise healthy lifestyle
- Autopsy study of young soldiers dying from trauma in Korean and Vietnam wars had extensive subclinical atherosclerosis (they might have developed clinical CVD decades later if they lived)

Intermittent Fasting

- Fasting for 14 hours with eating window of 10 hours
- Patients with metabolic synd., prediabetes, HTN, overweight
- There was lowering of LDL, Hemoglobin A1C, BP, weight
- Fasting → depletes glucose → body mobilizes energy from fat leading to lipolysis → weight loss
- Fasting → low grade ketosis → lipolysis
- Flexibility, improvement in sleep quality, energy and endurance levels improved, felt better, long term adherence, aligning eating pattern with circadian rhythm

- Despite significant medical advances, CVD remains as leading cause of morbidity and mortality world wide
- Statins ⬇ LDL by 20 to 60%, which corresponds to 30% reduction in CVD events
- Despite the success of statins and other CV therapies, significant residual risk remains
- In addition to treating standard risk factors, elevated TG have been relooked as therapeutic target
- Several studies implicated elevated TG as an independent association with CVD risk
- Older trials of Omega-3-FA suggested possible benefit. AHA recommended treatment as reasonable for secondary prevention of CHD and SCD in those with prevalent CAD. However, Omega-3-FA utilizing mixed DHA/EPA products and dosages of one gram or less per day failed to show CV benefit

JELIS Study

- 18, 645 Japanese pts (20% with CHD)
- Total chol > 243, predominantly on low intensity statin
- EPA 1.8 g daily ➡ 19% RR in major CHD events at five years (2.8% vs 3.5%)
- Due to perceived biases (all Japanese pts, low intensity statin regimen, and open label design) these results had minimal clinical value

CHERRY Trial

- 193 post PCI Japanese pts
- Randomized to Pitavastatin + EPA 1.8 g daily vs. Pitavastatin monotherapy
- 6-8 month follow up
- Greater coronary plaque regression (81% vs 61% p=0.002)

3rd Trial

- 241 Japanese pts with ACS
- Randomized to Pitavastatin 2 mg + EPA 1.8 g daily vs. without EPA
- 58% risk reduction in CV death, non fatal MI, non fatal stroke and revascularization, 78% risk reduction in CV death in one year

REDUCE - IT

- Icosopent Ethyl (Vascepa) a purified ethyl ester of EPA
- 2g twice daily vs. mineral oil placebo on background of statin therapy in pts with CVD or diabetes + one additional risk factor
- LDL 41-100 mg/dl and TG 135-499 mg/dl
- 8179 pts (about 70% with established CVD, 30% for primary prevention)
- A striking reduction in first occurrence of primary endpoint (17.2% vs 22% decrease in CV death, MI, coronary revascularization, USA, stroke). All individual points were sig reduced
- 30% reduction in total (initial and recurrent) events related to primary endpoint on post ad-hoc analysis
- This magnitude of benefit is on par with statins, PCSK9 inhibitor.

- However, improvements in lipoprotein, inflammation parameters and even SCD did not predict the full range of benefit displayed, implying there are other factors involved
- Small increase in Afib/flutter and trend towards increased bleeding
- In Nov 2019, FDA unanimously voted CV risk reduction to label
- A month later, FDA approved Icosopent ethyl as a adjunctive therapy to reduce risk of CV events among adults with elevated TG of at least 150 mg
- Reduce – It demonstrated significant benefit of EPA to statin over statin monotherapy
- FDA month before approved: for CV risk reduction among adults already taking statin with TG level of 150 mg/dl or higher who have either established CAD or diabetes and two or more additional risk factors for CVD based on 25% risk reduction of events)
- Age, smoking, HTN, low HDL, elevated CRP, BMI > 25 kg/m^2, renal dysfunction, retinopathy, albuminuria, ABI < 0.9

- STRENGTH trial
- EPA + DHA
- Stopped early due to futility

- Non fasting lipids are about 50 mg/dl higher

LCD (low carb diet) and LFD (low fat diet)

- Diet recall study of 37,233 pts 1999-2014
- Avg age 50 yrs, 53% women
- No sig dif in LCD or LFD. Unhealthy or healthy components
- 20 percentile increase in unhealthy LCD linked with relative, total mortality ⬆ by 7%, 11% in cancer death. For LFD, ⬆ 6% , after adjusting to family history, DM, cancer, CHD
- 20 percentile increase in healthy LCD score relative, total mortality fell by 9% and 10% decrease in cancer deaths. For LFD, 15% relative decrease in cancer mortality and 11% relative drop in total mortality
- It is the type and quality of the fat and carbohydrates that matters for health
- LCD: high in plant protein, , Unsaturated fats, unprocessed carbs like whole grains, fruit, legumes, vegetables
- Low quality carbs (refined and added sugar) provide limited nutrition, has high glycemic load, ⬆ inflamtion, insulin resistance, dislipidemia)

Testosterone

- 1% topical gel
- > 65 yrs
- Double blind placebo control testosterone cardiovascular trial
- LV mass indexed to BSA showed signigicant increase in testosterone group

Aspirin Use

Recommendations for Aspirin Use		
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.**
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.**
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.**

- The most important way to prevent atherosclerotic vascular disease, heart failure, and atrial fibrillation is to promote a healthy lifestyle throughout life.
- Aspirin
- Statin
- PCSK9 inhibitors
- Icosopent Etyl
- ACE inhibitors
- Beta blockers
- Anti platlete agents
- Nitrates
- Cardiac rehab

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