Antihypertensives, Antilipidemics and Antithrombotics. Oh My!

Updates in Pharmacotherapy for Secondary Prevention of ASCVD

Matthew Lillyblad, Matthew P. Lillyblad, PharmD, BCCCP, BCCP
Clinical Pharmacy Coordinator - Cardiology & Critical Care
Clinical Pharmacy Specialist - Advanced Heart Failure
Residency Program Director - PGY2 Cardiology Pharmacy
Residency Abbott Northwestern Hospital, part of Allina Health

American Heart Association.

Allina Health

ABBOTT NORTHWESTERN HOSPITAL

Antihypertensives, Antilipidemics, and Antithrombotics….Oh My!

Updates in Pharmacotherapy for Secondary Prevention of ASCVD

2021 American Heart Association MN Statewide Cardiovascular Summit

Matthew P. Lillyblad, PharmD, BCCCP, BCCP
Clinical Pharmacy Coordinator- Cardiology & Critical Care
Abbott Northwestern Hospital, part of Allina Health
Minneapolis, Minnesota

Disclosure

- The content of this presentation has been created by the presenter and does not necessarily reflect the views of Abbott Northwestern Hospital or Allina Health
- No current or recent financial relationships with pharmaceutical companies exist
- No potential conflicts of interest exist
- The use of medications outside of their FDA approved indication may be included in this presentation

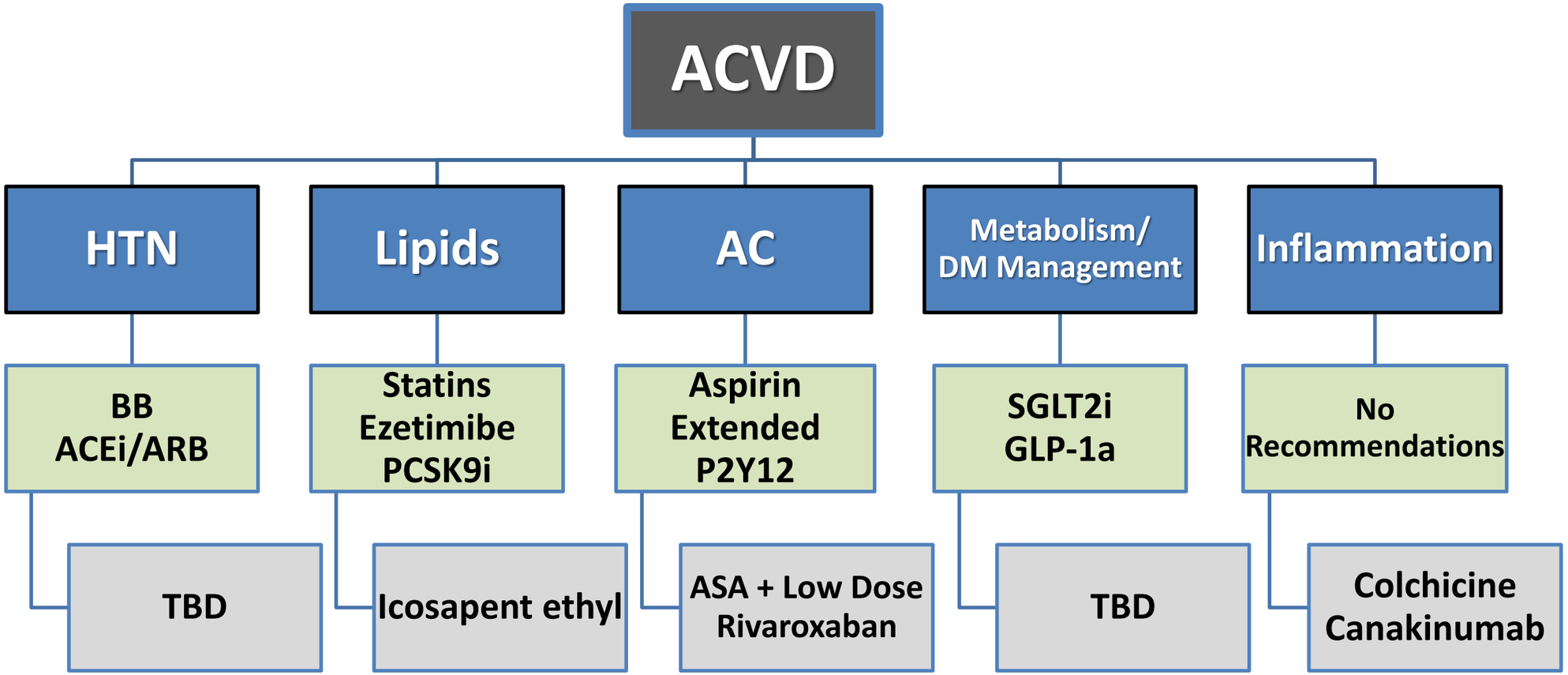
Objectives

- Describe evidence-based treatment strategies for antiplatelet and anticoagulant therapies in patients with ASCVD
- Describe evidence-based treatment strategies for hypercholesterolemia management in patients with ASCVD
- Describe evidence-based treatment strategies for blood pressure management in patients with ASCVD

Scope of this Presentation

- Secondary prevention of ASCVD
- Advances/treatment strategies that are evolving or not yet reflected in the most recent guidelines
- Focus for today:
  - Antithrombotic management → Dual pathway inhibition
  - Lipid Management → Icosapent ethyl
  - HTN → β-blocker treatment in stable CAD

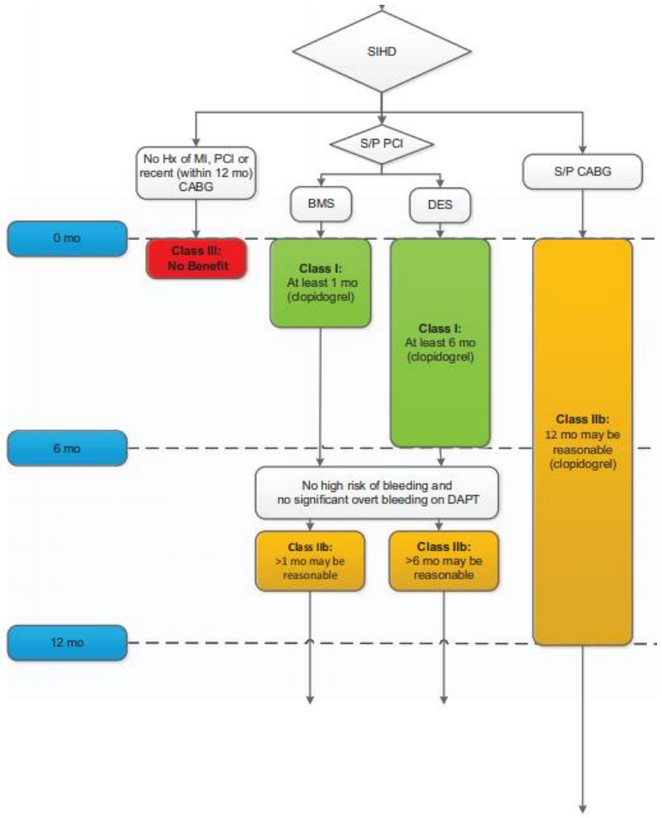
Secondary Prevention of ASCVD



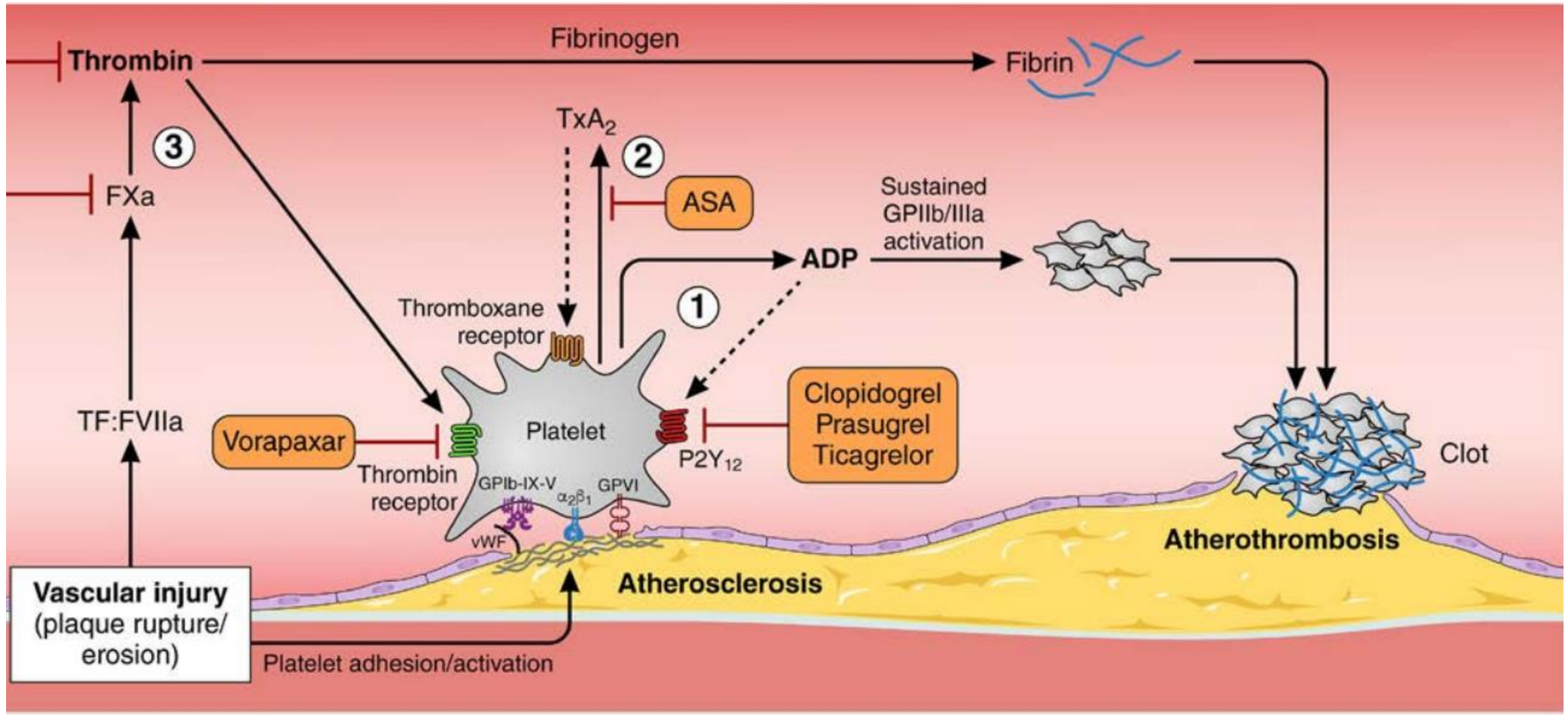
Dual Pathway Inhibition in CAD/PAD

Case: AR

- 60 yo female with ASCVD with 3 vessel disease s/p PIC 3 years ago and PAD (ABI 0.55)
- Pertinent PMH: HTN, HLD, DM II, CKD 3, smoker
- Current BP 122/69, HR 75
- Meds: Aspirin 81 mg daily, Clopidogrel 75 mg daily, rosuvastatin 40 mg, evolocumab 140 mg Q2 weeks, lisinopril 20 mg daily, dapaglifozin 10 mg daily, metformin 500 mg BID, nicotine replacement therapy
- AP is trying hard to quit smoking and is very concerned about her heart and vascular disease. Her friend with PAD just required an amputation

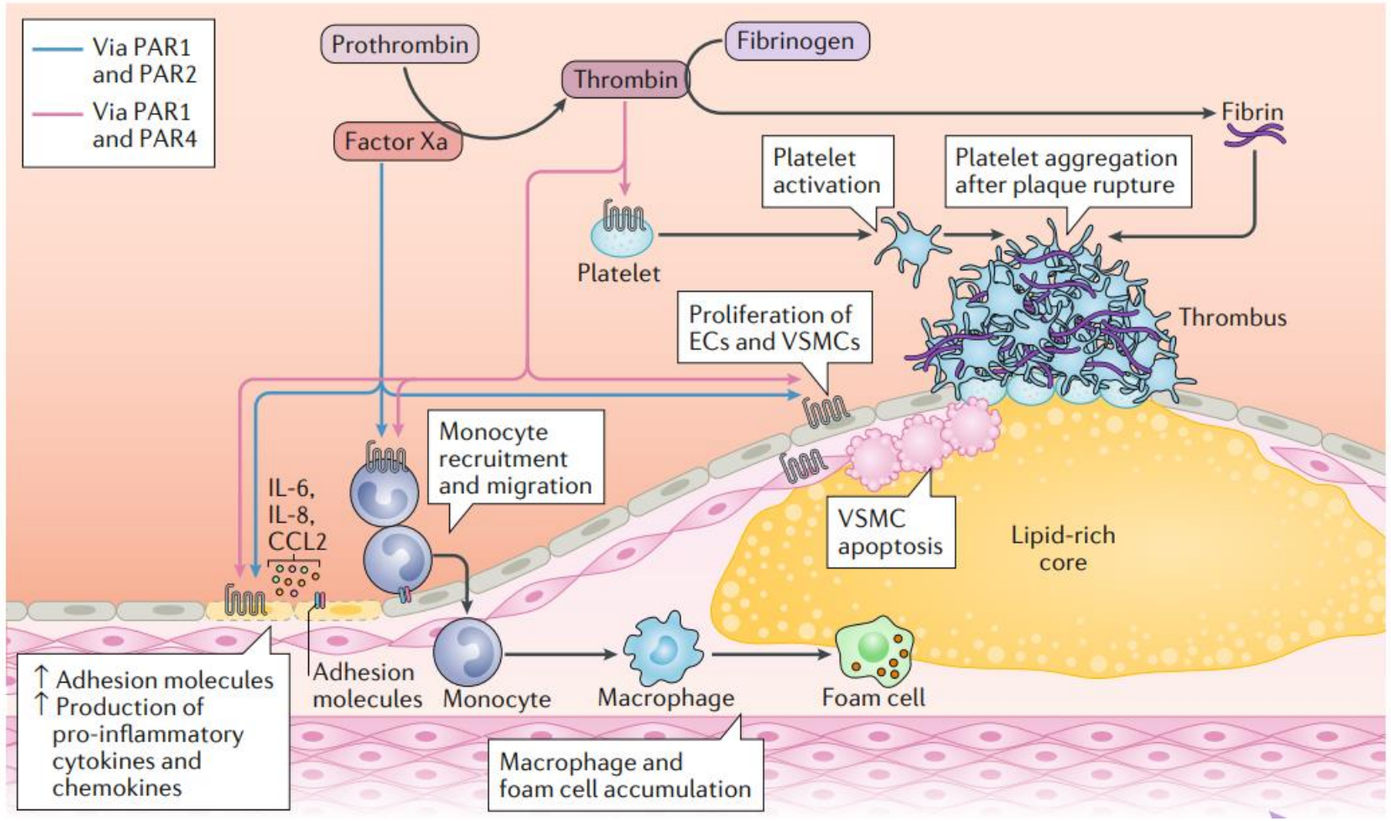


ASCVD and Thrombosis



Circulation. 2019;139:2170–2185.

Rationale for Dual Pathway Inhibition in ASCVD



Nat Rev Cardiol. 2020 Apr;17(4):242-257.

Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease (COMPASS Trial)

- **Population:** 27.395 patients over ~2 years (stopped early due to benefit)
  - <65 years old
  - 90.6% with CAD, 27.3% PAD
  - 62% previous MI and 4% previous stroke
  - Strong background GDMT
  - Run in phase
- **Intervention:** ASA 100 mg + rivaroxaban 2.5 mg BID vs. rivaroxaban 5 mg BID vs. ASA 100 mg
- **Primary end point:** CV death, stroke, or MI

COMPASS Benefits

CV death, Stroke, or MI
ASA + Riva 4.1% vs. ASA 5.4%, HR 0.76 (CI 0.66–0.86)

CV Death
ASA+R 1.7% vs. ASA 2.2%
HR 0.78 (0.64–0.96)

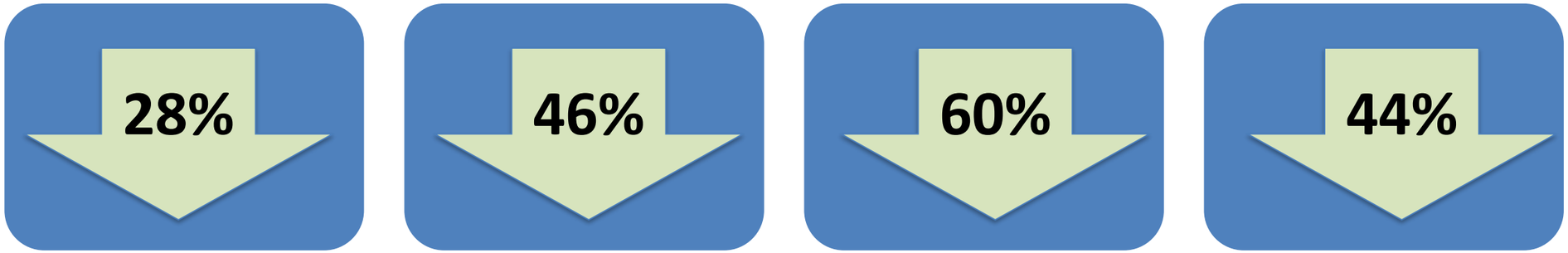
Any Stroke
ASA+R 0.9% vs. ASA 1.6%
HR 0.58 (0.44–0.76)

Any MI
ASA+R 1.9% vs. ASA 2.2%
HR 0.89 (0.75–1.05)

All-Cause Death
ASA+R 3.4% vs. ASA 4.1%
HR 0.82 (0.71–0.96)

CV = cardiovascular, MI = myocardial infarction

COMPASS PAD Analysis



MACE | **MALE** | **Amputations** | **Acute Limb Ischemia**

MACE = cardiovascular death, myocardial infarction, or stroke

MALE = major adverse limb events = acute or chronic limb ischemia over the course of the trial follow-up, including any additional major amputations due to a vascular event that was not included in acute or chronic limb ischemia

COMPASS Trial Safety

Outcome	Results
Study Defined Major Bleeding	3.1% vs. 1.9% HR 1.70 (CI 1.40–2.05)
ISTH Major Bleeding	2.3% vs. 1.3% HR 1.78 (CI 1.41–2.23)
Intracranial Hemorrhage	0.3% vs. 0.3% HR 1.16 (CI 0.67–2.00)
Fatal Bleeding	0.2% vs. 0.1% HR 1.49 (CI 0.67–3.33)

DPI vs. Extended DAPT for Stable CAD

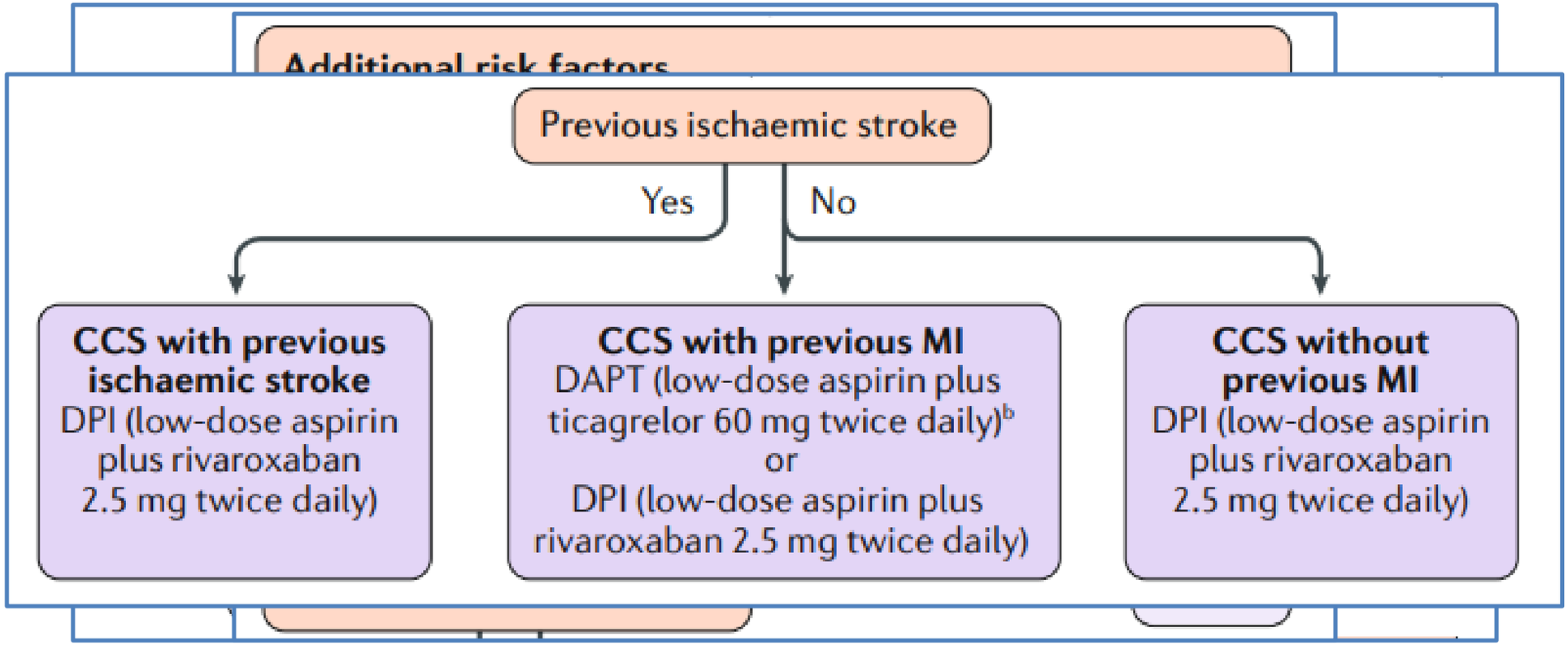
PEGASUS ↔Death, ↔CV Death, ↓MI, ↓Stroke

- MI in the last 1-3 years → ~80% PCI history
- Excluded previous stroke

COMPASS ↓Death, ↓CV Death, ↔MI, ↓Stroke

- ~60% previous MI
- ~60% PCI history → mean ~5 years prior to randomization
- ~25% PAD

DPI vs. DAPT in Secondary/Tertiary Prevention

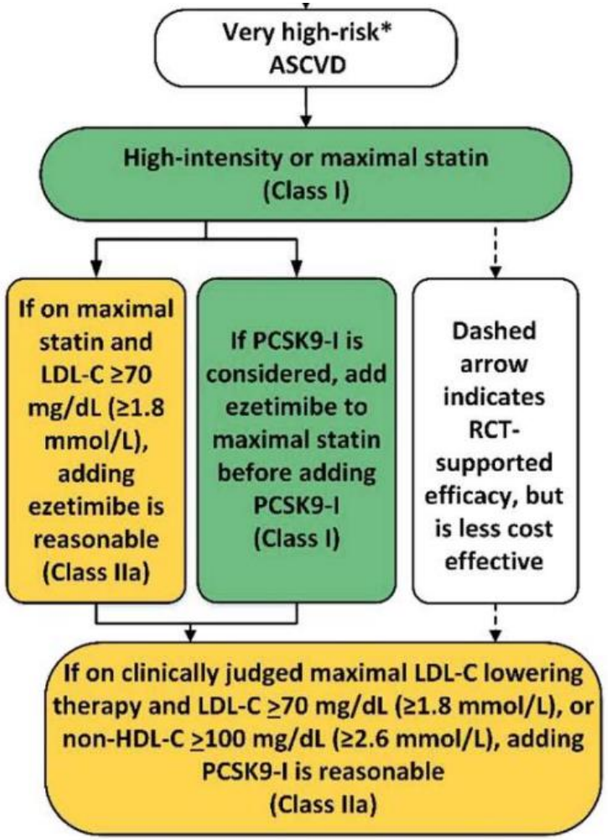


Nat Rev Cardiol. 2020 Apr;17(4):242-257.

Icosapent Ethyl for Dyslipidemia

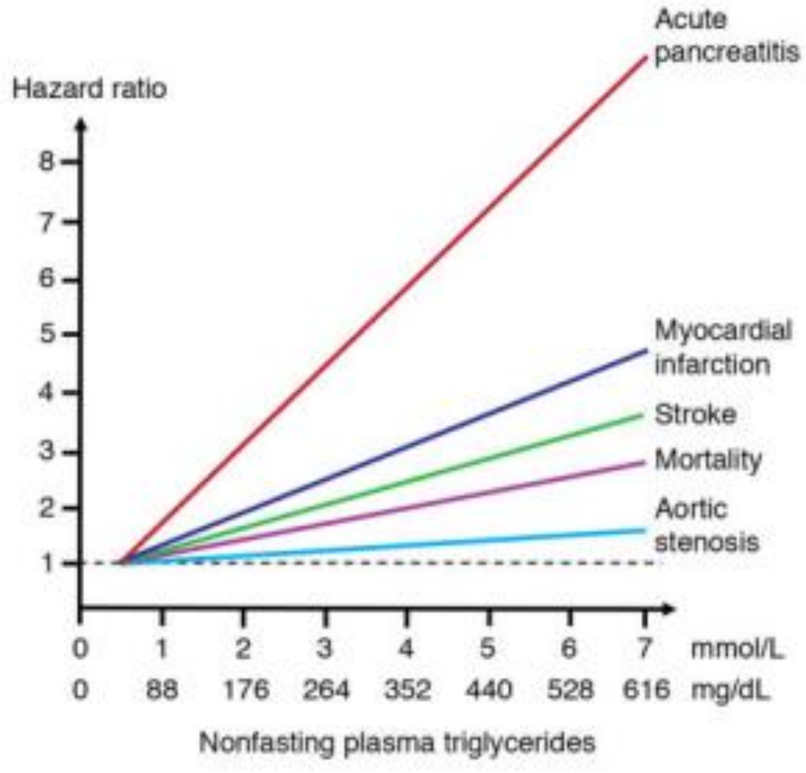
Case: IE

- 6o yo male with CAD s/p 3-vessel CABG 1 year ago
- Pertinent PMH: HFrEF, HTN, HLD, smoker, OSA
- BP: 115/75 mmHg, last EF 30%, NYHA II symptoms
- Fasting lipid panel: LDL-C 75 mg/dl; triglycerides 244 mg/dl; HDL-C 38 mg/dl; and non–HDL-C, 130 mg/dl
- Meds: ASA 81 mg, sacubitril/valsartan 49/51 mg BID, metoprolol succinate 100 mg daily, spironolactone 25 mg daily, rosuvastatin 40 mg daily, ezetimibe 10 mg daily
- IE has been compliant with lifestyle changes and diet to the best of his ability



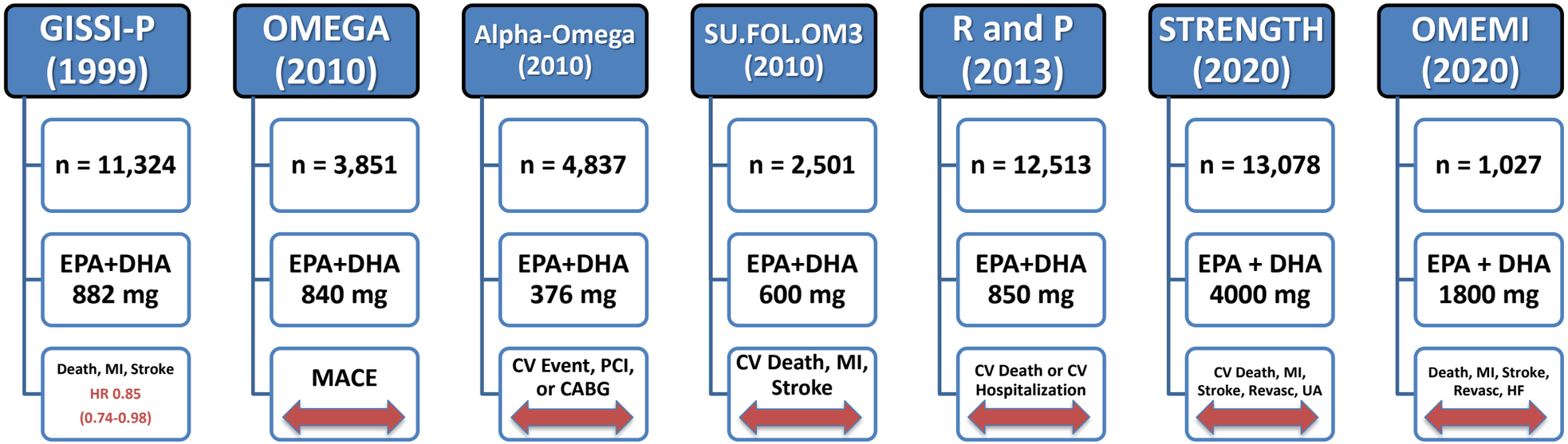
Triglycerides (TG), Omega-3 FA and ASCVD

- Prevalence TG ≥150 mg/dl was ~25%
- High TG → ↑ASCVD independent of LDL
- Standard treatment strategies specific to TG lack consistent risk reduction
  - AHA: TG ≥175 mg/dL = 'risk-enhancing factor''
    - Favors the initiation or intensification of statin therapy
- Interest from fatty-fish consumption and ASCVD risk
- Traditional omega-3 supplements = eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA)



Eur Heart J Suppl. 2020 Oct 6;22(Suppl J):J21-J33.

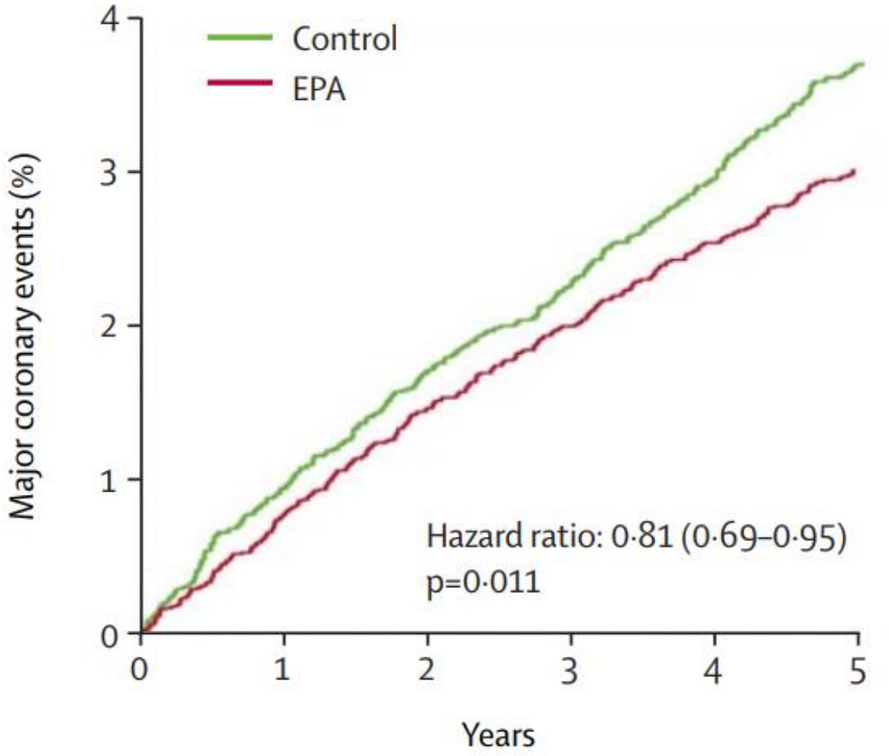
Secondary Prevention Trials with Mixed Omega-3s



CABG = coronary artery bypass grafting, CV = cardiovascular, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, MACE = major adverse cardiac events, MI = myocardial infarction, Revasc = revascularization

Glimmer of Hope for Omega-3 FA: JELIS Trial

- 18,645 Japanese patients with hypercholesterolemia
  - Total Cholesterol >250 mg/dL (mean 274)
  - LDL >170 mg/dL (mean 181)
  - Mean Triglycerides ~150 mg/dL
  - ~20% with ASCVD
- Randomly assigned to receive EPA 1.8 grams + statin vs. statin alone
- Primary endpoint = “major coronary event”
  - Sudden cardiac death, fatal and non-fatal MI, unstable angina pectoris, PCI, or CABG



Lancet 2007; 369: 1090–98

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia (REDUCE-IT Trial)

- **Population:** 8,179 patients over ~5 years
  - 70.7% with established ASCVD
  - All prescribed statins → >90% moderate/high intensity
  - Triglyceride level 135-499 mg/dL → median 216 mg/dL
  - LDL 41-100 mg/dL → median ~75 mg/dL
- **Intervention:** Icosapent ethyl (pure EPA) 2 grams twice daily vs. placebo
  - Treatment → Triglycerides ↓20%
- **Primary end point:** CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina

REDUCE-IT Outcomes

CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or UA
Icosapent ethyl (IE) 17.2% vs. Placebo (P) 22.0%, HR 0.75 (CI 0.68-0.83)
NNT = 21 over 5 years

CV Death
IE 4.3% vs. P 5.2%
HR 0.80 (CI 0.66-0.98)

All-Cause Death
IE 6.7% vs. P 7.6%
HR 0.8[illegible] (0.[illegible]-1.02)

Any Stroke
IE 2.4% vs. P 3.3%
HR 0.72 (CI 0.55-0.93)

Revascularization
IE 5.3% vs. P 7.8%
HR 0.65 (CI 0.55–0.78)

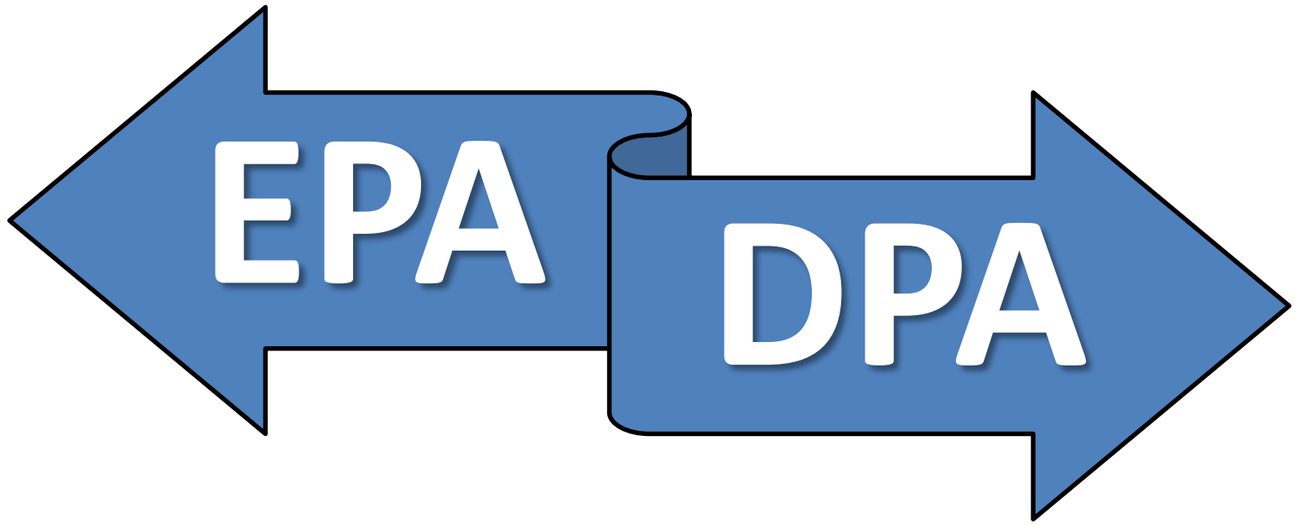
Any MI
IE 6.1% vs. P 8.7%
HR 0.69 (CI 0.58-0.81)

CV = cardiovascular, MI = myocardial infarction, UA = unstable angina

Clinical Outcomes with Dyslipidemia Treatments for ASCVD

Drug Class (Trial)	MI	Stroke	CV Death
Vitamin B3 Niacin (AIM-HIGH)	↔	↔	↔
PPAR alpha agonist Gemfibrozil (VA-HIT)*	↓ 23%	↔	↔
NPC1L1 protein inhibitor Ezetimibe (IMPROVE IT)	↓ 13%	↔	↔
PCSK9 Inhibitors Evolocumab (FOURIER)	↓ 27%	↓ 21%	↔
Pure EPA Icosapent (REDUCE-IT)	↓ 31%	↓ 28%	↓ 20%

How do we explain REDUCE-IT vs. Other Omega-3 Trials



vs. Dose?

- Stabilizes membrane structure
- Anti-oxidant
- Reduces inflammation
- Promotes vasodilation

- Destabilizes membrane structure
- Blunted anti-oxidant

Mineral Oil Placebo Controversy

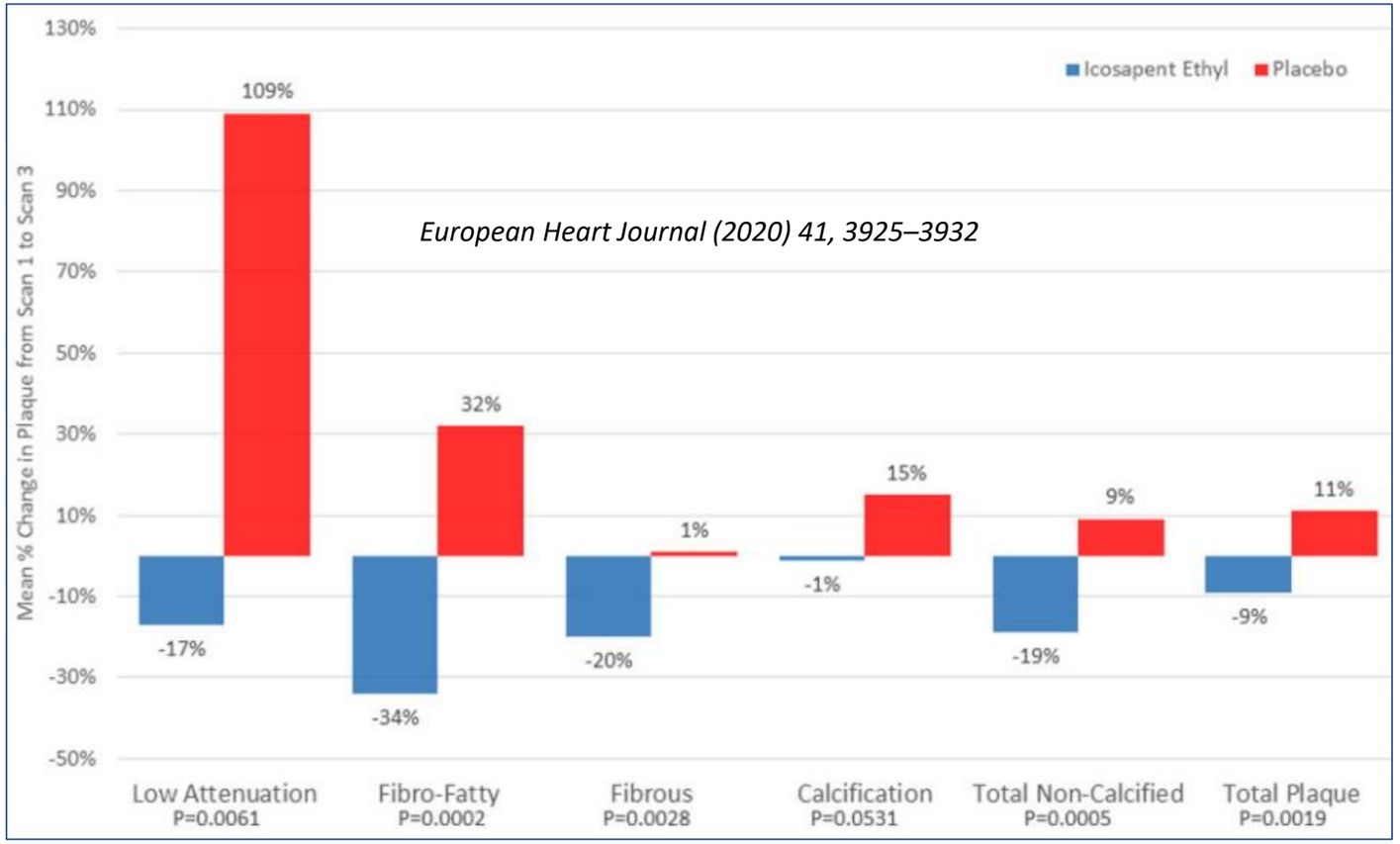
- Placebo in REDUCE-IT = mineral oil capsule
- Mineral oil negatively impacts ASCVD outcomes → exaggerating benefits?
- Placebo findings from REDUCT-IT
  - hsCRP 2.1 → 2.8mg/L in the mineral oil group
    - FDA advisory committee → little effect on the end points
  - ↑ LDL-C levels ~10 mg/dL
    - Need 40 mg/dL+ difference = 22-25% difference in outcomes
- DDI with statins theoretical
- Other trials in which mineral oil was used = variable effects on lipids and inflammation

Safety in REDUCE-IT

Diarrhea	• IE 9.0% vs. P 11.1% (p = 0.002)
Edema	• IE 6.5% vs. P 5.0% (p = 0.002)
Atrial Fibrillation	• IE 5.3% vs. P 3.9% (p = 0.003)
Serious Bleeding	• IE 2.7% vs. P 2.1% (p = 0.06)

IE = icosapent ethyl, P = placebo

Mechanisms of Benefit: EVAPORATE



European Heart Journal (2020) 41, 3925–3932

Considerations for Clinical Practice

Drug/Dose

- Icosapent only
- 2 grams twice daily with food

Patient Selection

- ASCVD (High vs. Very High AHA risk?)
- Max tolerated statin
- Controlled LDL ≤80 mg/dL
- Triglycerides ≥175 mg/dL
- Cost: AWP ~$400 per month

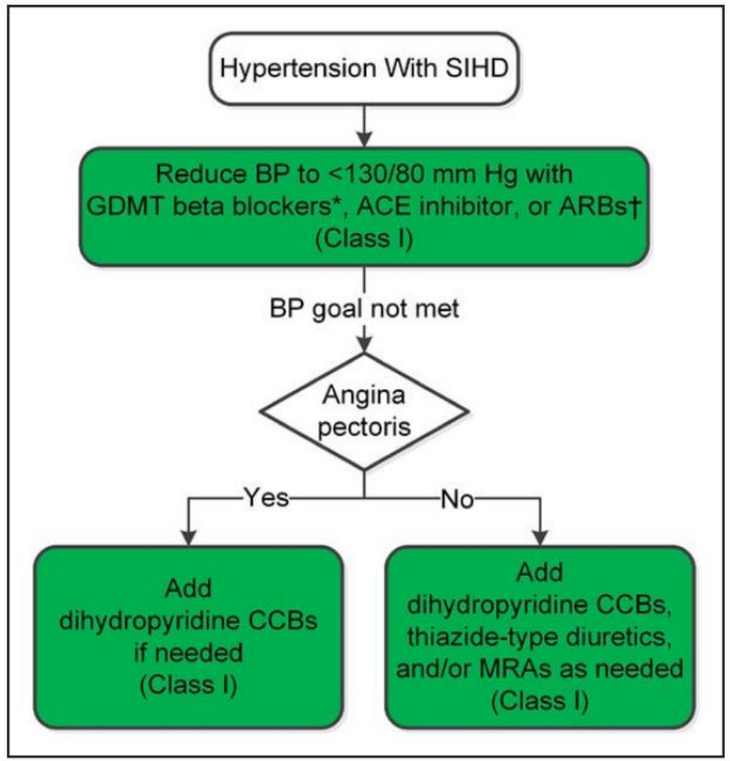
Monitoring

- No triglyceride target (↓~20% trial)
- Atrial fibrillation, bleeding, edema

B-Blockade for Stable CAD

Case: BB

- 64 yo male with a history of NSTEMI s/p PCI with 2 DES (LAD, RCA) 4 years ago
- Pertinent PMH: DMII, Stage 3 CKD, depression, OA
- Current BP 95/65 mmHg, HR 82, A1c = 6.8, EF 65% 1 year ago
- No angina or palpitations since his MI
- Feels “sluggish” but able to conduct normal daily activities
- Meds: ASA 81 mg, carvedilol 25 mg BID, metformin 1000 mg BID, atorvastatin 80 mg QD, sertraline 100 mg QD
- Recently discussed starting rivaroxaban 2.5 mg BID and empaglifozin 25 mg QD with his MD but only agreed to the empaglifozin because he “feels like he takes to many meds”



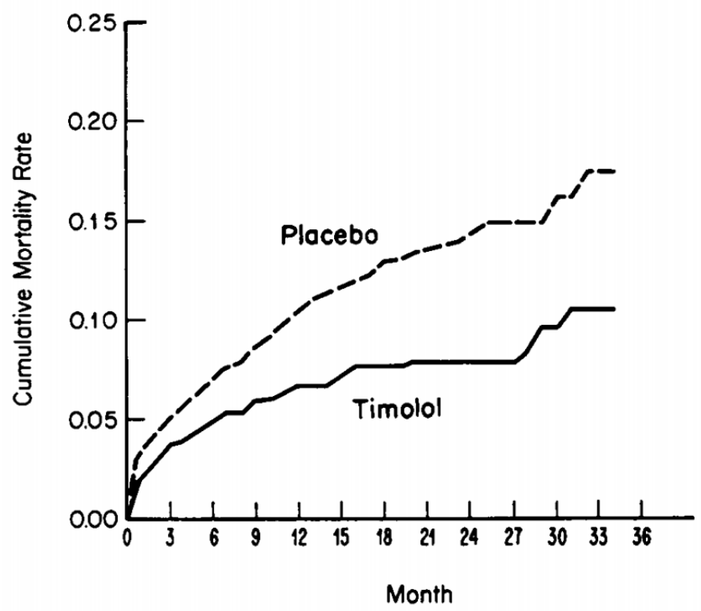
Hypertension. 2018;71:e13-e115.

β-Blockade and CAD

- Introduced in the 1960s as an effective treatment for angina
- Activation of the adrenergic system occurs in ACS →
  - Atrial and ventricular arrhythmias
  - Promotion of adverse ventricular remodeling, systolic dysfunction and HF
  - Reduced coronary perfusion
  - Increased O2 demand
- Subsequently studied in ACS and found to be beneficial acutely and chronically
- Beta-Blockers became a standard of care with ACS and chronically thereafter

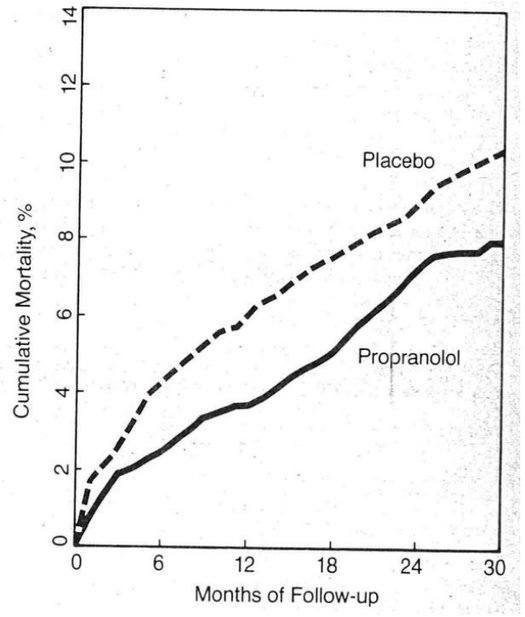
Landmark β-Blocker Trials

Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction.



N Engl J Med. **1981**;304:801–807.

The beta-blocker heart attack trial. beta-Blocker Heart Attack Study Group.



JAMA. **1981**;246:2073–2074.

ASCVD Standards of Care in Original BB Trials

Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction.

0% ASA
0% P2Y12 Antagonist
0% Statin
0% Ezetimibe
0% PCSK9 Inhibitor
0% ACEi
??% HTN Management
0% PCI
0% CABG
0% Fibrinolytics

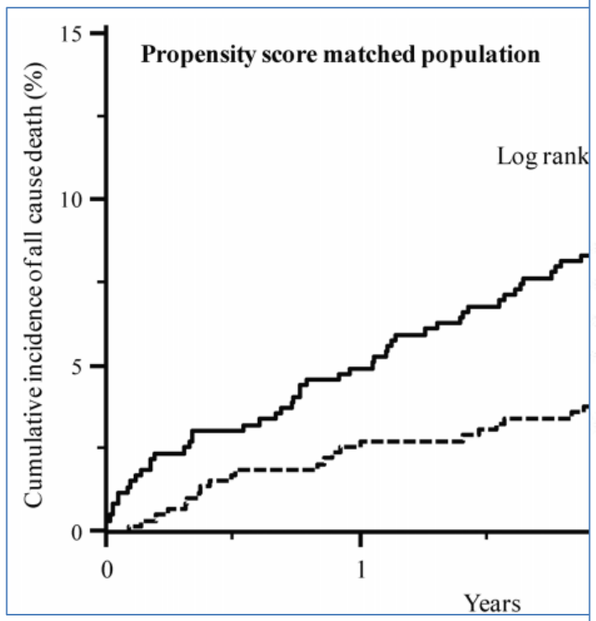
The beta-blocker heart attack trial. beta-Blocker Heart Attack Study Group.

??% ASA
0% P2Y12 Antagonist
0% Statin
0% Ezetimibe
0% PCSK9 Inhibitor
% ACEi
??% HTN Management
0% PCI
0% CABG
0% Fibrinolytics

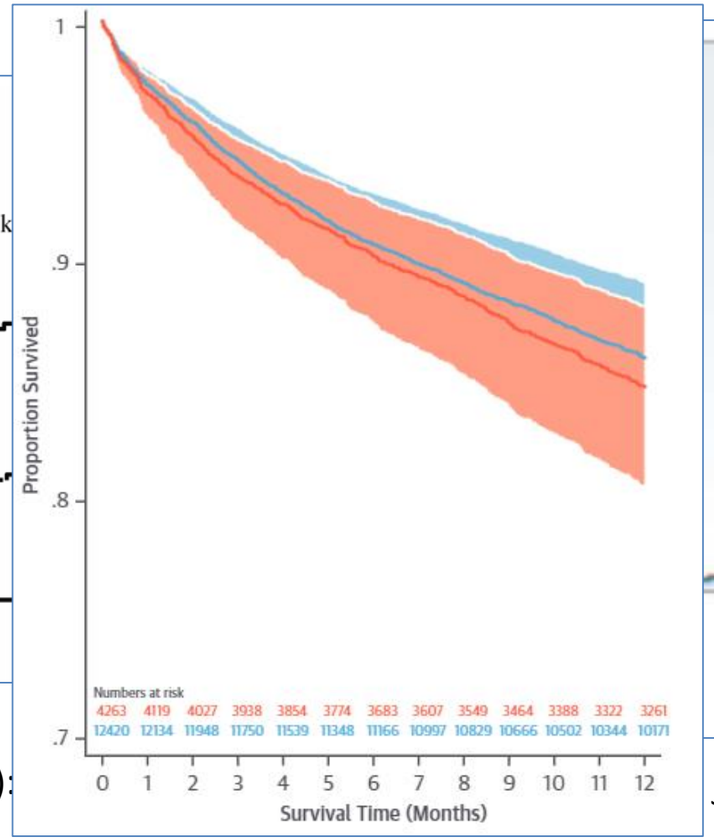
AHA Guideline Statements Regarding BB

Guide	Recommendation
2018 STEMI	• .....except those at low risk (normal/near-normal EF, successful reperfusion, absence of significant VT) and those with contraindications should receive beta-blocker therapy. Treatment should begin within a few days of the event, if not initiated acutely, and continue indefinitely. (Class I, LOE: A) • It is reasonable to prescribe to low-risk patients who have no contraindications (Class IIa, LOE: A)
2017 HTN	In adults who have had a MI or ACS, it is reasonable to continue GDMT beta blockers beyond 3 years as long-term therapy for hypertension. (Class IIa, LOE: B)
2014 NSTEMI	It is reasonable to continue beta-blocker therapy in patients with normal LV function with NSTE ACS (Class Iia, LOE: C)

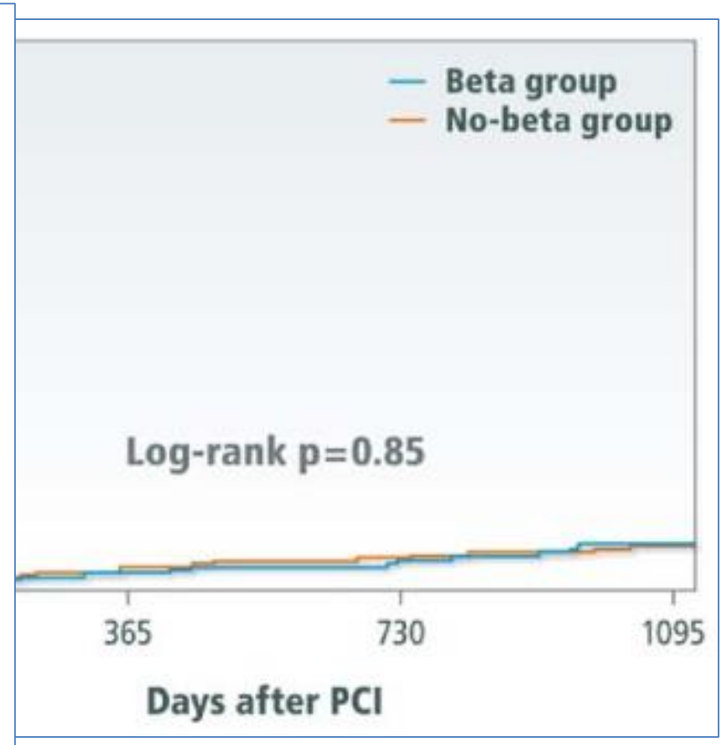
Contemporary Analyses of β-Blockers after AMI: 1-3 years



Heart. 2014 Mar;100(6):



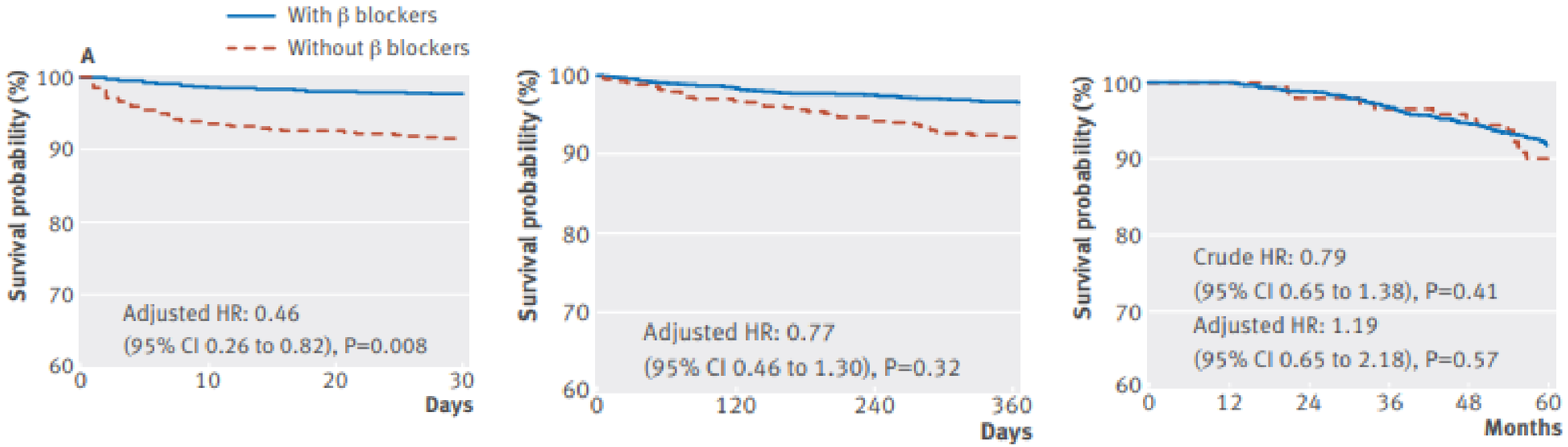
J Am Coll Cardiol 2017;69:2710–20.



J Cardiol 2010;106:1225–33.

Contemporary Analyses of β-Blockers after AMI: 30 days vs. 1 year vs. 5 years

- Multicenter prospective cohort study → French registry (FAST-MI) of STEMI/NSTEMI
- 2,679 consecutive patients with AMI without HF or left ventricular dysfunction
- 56% STEMI, 68% PCI or thrombolysis
- Underwent propensity score matching for each time point



BMJ. 2016 Sep 20;354:i4801.

More Studies on the Way

- Danish trial of beta-blocker treatment after myocardial infarction without reduced ejection fraction (DANBLOCK)
- Evaluation of Decreased Usage of Beta-blockers After Myocardial Infarction in the SWEDEHEART Registry (REDUCE-SWEDEHEART)
- Beta-blocker Treatment After acute Myocardial Infarction in revascularized patients without reduced left ventricular ejection fraction (BETAMI)

If there is no harm, why stop BB?

Polypharmacy with Established Benefits	BB Tolerability	Other Anti-HTN Meds
• ASA • P2Y12 inhibitors • Low dose OAC • Statin • Ezetimibe • PCSK9i • Icosapent • SGLT2i/GLP-1a • See other Anti-HTN	• Depression • Fatigue • Sexual dysfunction • Bradycardia/Heart Block • Caution in DM • Caution in pulmonary disease • Caution in PAD	• Outcomes benefit → ACEi/ARBs • Better HTN control → Thiazides, CCB, ACEi/ARBN

Candidacy for B-Blocker Discontinuation in ASCVD

Switch

- **>1-3 year(s) post-MI** AND BB-related ADEs OR
- Low BP impeding the use of GDMT for another indication
- CAD without ACS or angina
- "At risk" for CAD

Consider

- **>1-3 year(s) post-MI** AND
- Concerns with polypharmacy OR
- At risk for BB-related ADE

Continue

- EF ≤40%/recovered EF OR
- Angina OR
- Atrial or Ventricular Tachyarrhythmia

Conclusion

- ASCVD is prevalent and secondary/tertiary prevention is critical
- Following GDMT improves outcomes but the field continues to evolve
- Dual Pathway Inhibition (DPI) with aspirin and rivaroxaban 2.5 mg provides significant reduction in important ASCVD events in patients with stable CAD
- Icosapent ethyl is the first omega-3 FA treatment to provide significant reduction in ASCVD when add to statin therapy in patients with elevated triglycerides
- The role of chronic β-blocker treatment beyond 1-3 years post AMI is evolving and may provide an opportunity for de-prescribing in the field were medication keep getting added to standards of care