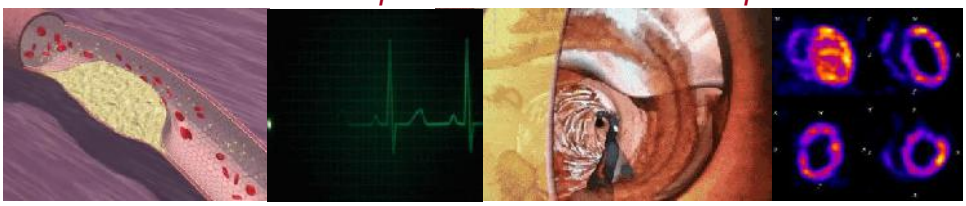
Management of Chronic Coronary Syndrome

Internal Medicine Comprehensive Review and Update 2022



David M. Dudzinski, MD, FACC, FAHA, FASE

Cardiology Division; Post-MI Clinic

Massachusetts General Hospital, Harvard Medical School

dmd@post.harvard.edu, @criticalecho

No disclosures; there may be discussion of off-label uses

1

What's New 2022?

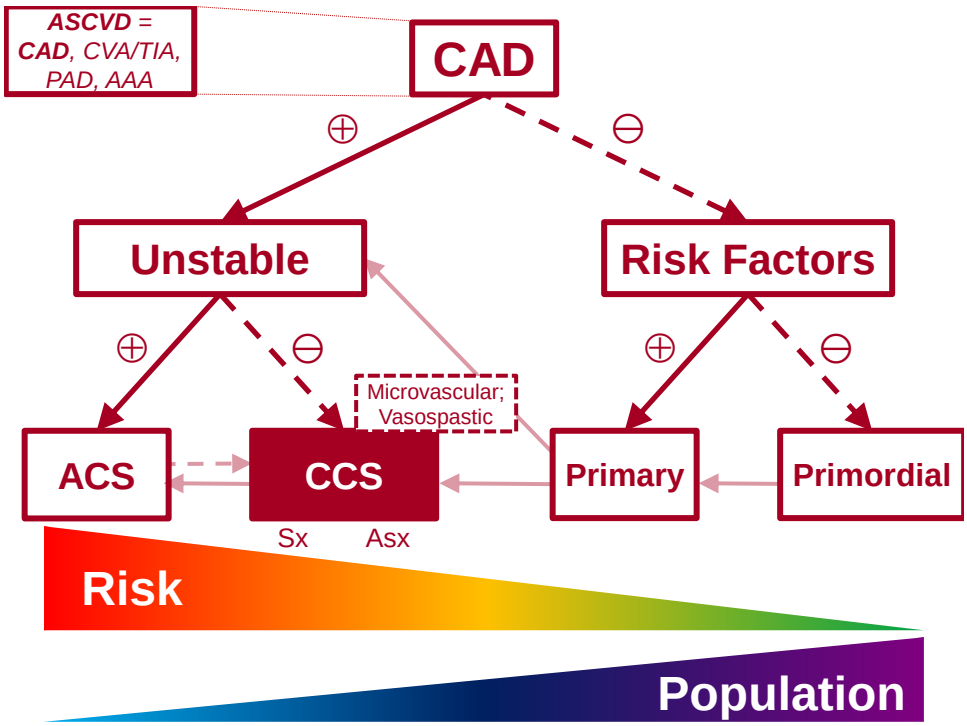
- ISCHEMIA substudies: ischemia severity, QOL
- CLARIFY
- SCAPIS (Swedish Cardiopulmonary Bioimage)
- Influenza after AMI
- MASTER-DAPT
- Inclirsan FDA approval December 2021
- IPE cost effectiveness studies
- LoDoCo2 landmarks substudy
- STEP

2

Select Abbreviations

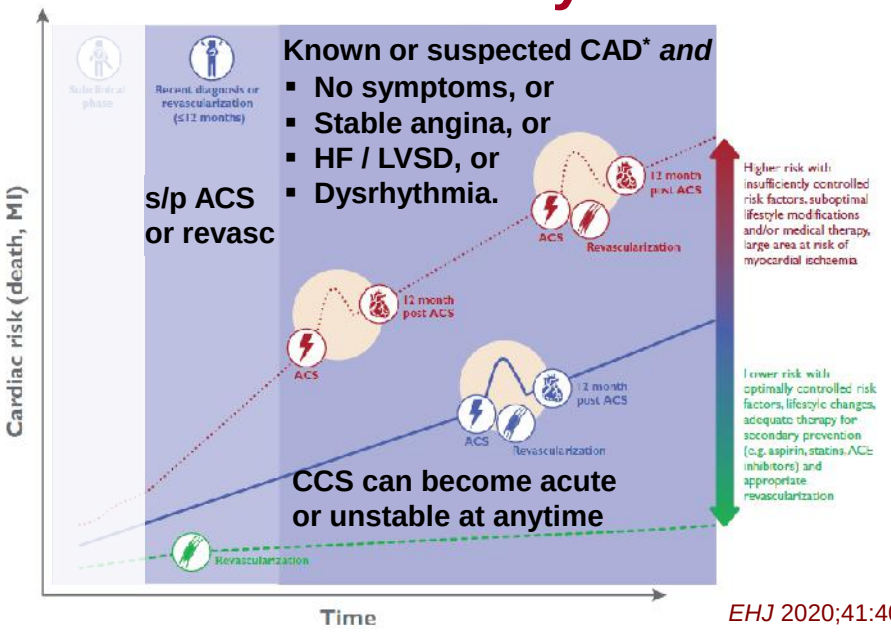
- ACM: All-cause mortality
- ACS: Acute coronary syndrome
- ADR: Adverse drug reactions
- ASCVD Atherosclerotic cardiovascular disease
- CABG: Coronary artery bypass grafting
- CCS: Chronic coronary syndrome or Canadian Cardiovascular Society
- CCTA: Cardiac CT angiogram
- CKD: Chronic kidney disease
- CON: Conservative strategy (ISCHEMIA)
- CSβB: Cardioselective β-blocker
- CV: Cardiovascular
- DAPT: Dual antiplatelet therapy
- DBRCT: Double-blinded randomized controlled trial
- DOAC: Direct oral anticoagulant
- DPI: Dual pathway inhibition
- ED: Erectile dysfunction
- EF: Ejection fraction
- EZE: Ezetimibe
- GLP: Glucagon-like peptide
- HeFH: Heterozygous familial hypercholesterolemia
- HFH: Heart failure hospitalization
- HR: Heart rate, or hazard ratio
- INV: Invasive strategy (ISCHEMIA)
- IST: In-stent thrombosis
- LLT: Lipid-lowering therapy
- LMCA: Left main coronary artery
- LVSD: Left ventricular systolic dysfunction
- mAb: Monoclonal antibody
- MACE: Major adverse cardiovascular events
- MB: Major bleeding
- MI: Myocardial infarction
- MVD: Multivessel (coronary) disease
- NM: Neuromuscular
- NS: Non-significant (statistical)
- NSβB: Non-selective β-blocker
- NSTE: Non-ST elevation
- NYHA: New York Heart Association
- oCAD: Obstructive CAD
- OMT: Optimal medical therapy
- PAD: Peripheral arterial disease
- PCI: Percutaneous coronary intervention
- PEP: Primary endpoint
- QALY: Quality-adjusted life-year
- RF: Risk factor
- SAPT: Single antiplatelet therapy
- SCA: Sudden cardiac arrest
- SDM: Shared decision-making
- SGLT: Sodium-glucose cotransporter
- STEMI: ST-segment elevation MI
- TAA: Thoracic aortic aneurysm
- TVR: Target vessel revascularization
- UA: Unstable angina
- UP: Unprotected (eg LMCA)
- VHD: Valvular heart disease
- VT: Ventricular tachycardia

3



4

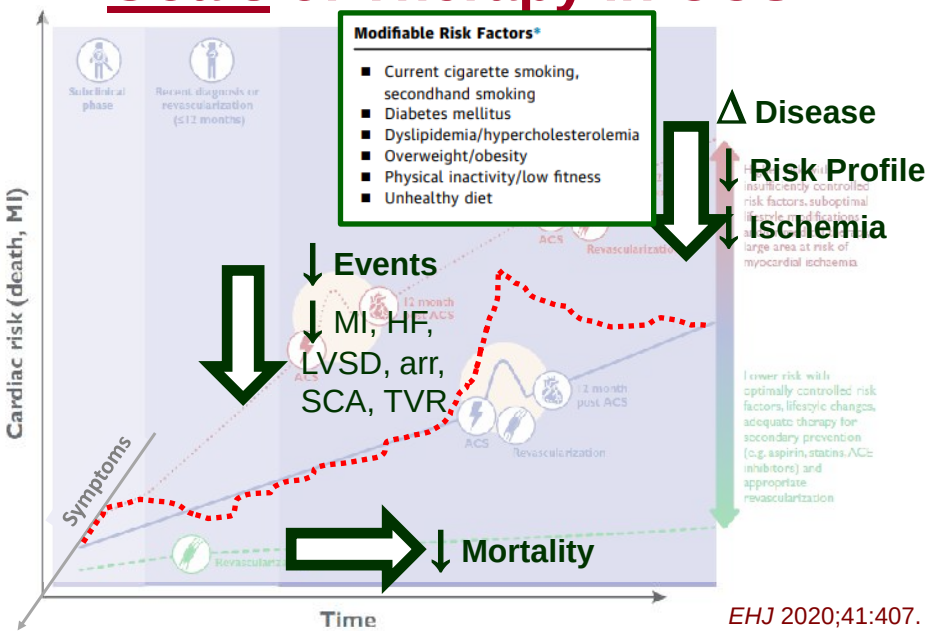
A Natural History of CCS



EHJ 2020;41:407.

5

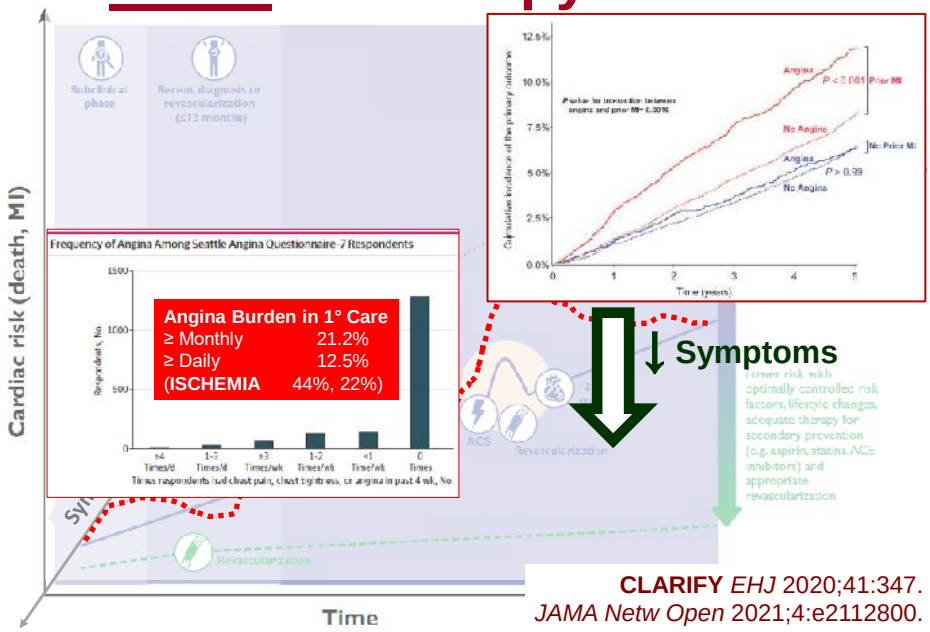
Goals of Therapy in CCS



EHJ 2020;41:407.

6

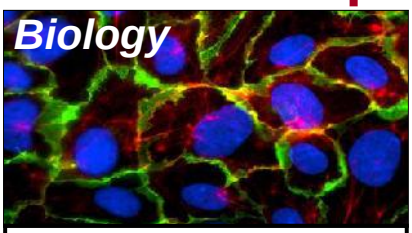
Goals of Therapy in CCS



CLARIFY *EHJ* 2020;41:347.
JAMA Netw Open 2021;4:e2112800.

7

CCS Therapeutic Overview



Disease Modification

- Non-pharmacologic
- Antithrombotic
- Anti-lipid and anti-glycemic
- Immunomodulation

Hemodynamics and Blood Supply:Demand

- BP and HR agents
- Anti-ischemic agents
- Revascularization
- Collateral coronary flow

8

Initial *Invasive* Therapy?

Sx \ Isch	None ←60%→	Mild	Mod	Severe
0 12%				
I 30%				
II 36%				
III 21%				
IV				

COURAGE
1999-2004
PCI did not ↓ death, MI, MACE on top of OMT

Criticisms:
- Low ischemia burden
- Angiography pre-randomization (bias)
- High crossover (32%)
- BMS only (2.7% DES)

Exclude:
- CCS IV angina
- "markedly positive" stress
- HF, shock, EF < 0.30, severe VHD
- Revascularization < 6 m
- Anatomy unfavorable for PCI

JACC 2007;50:1598 & 1604.
NEJM 2007;356:1503.

9

Initial *Invasive* Therapy?

ISCHEMIA

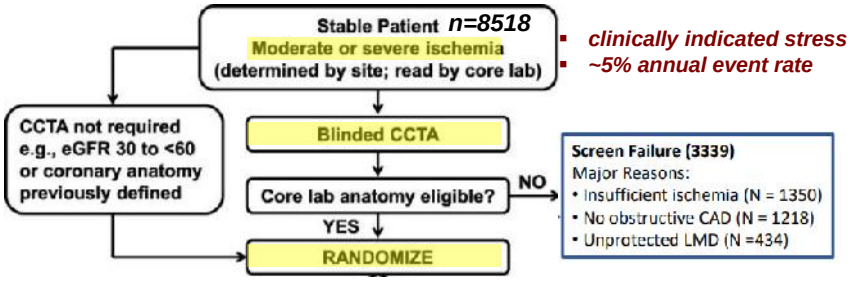
Sx \ Isch	None	Mild ←12%	Mod 33%	Severe 54%
0				
I				
II				
III				
IV				

COURAGE
ISCHEMIA

NEJM 2020;382:1395 & 1408.

10

ISCHEMIA



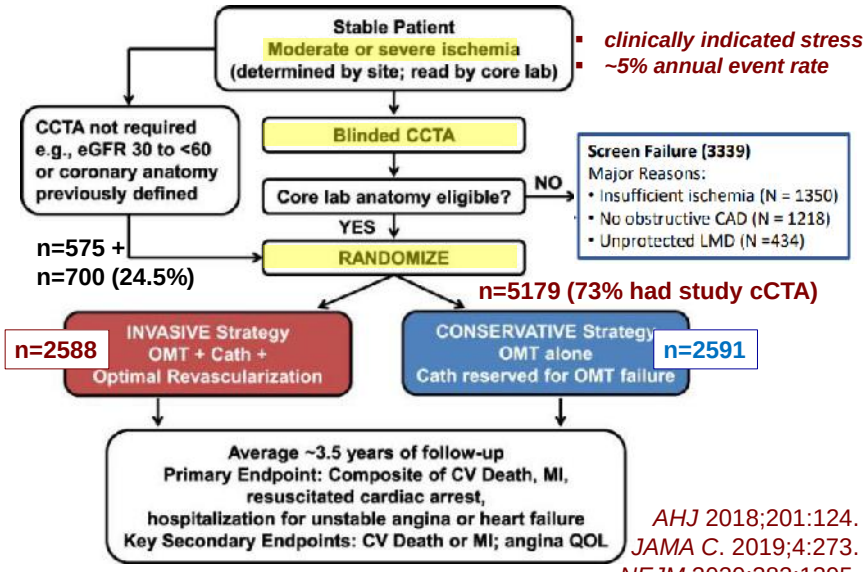
Exclude: recent CCS III; or CCS IV angina

- ACS <2m, PCI < 12m, CVA < 6m or ICH
- UPLMCA > 50% (eg cCTA)
- No CAD (all < 50%)
- Unsuitable anatomy (PCI/CABG)
- "Unacceptable angina" on OMT
- NYHA III/IV, EF < 0.35, severe VHD, VT
- eCrCl < 30 or ESRD on HD

AHJ 2018;201:124.
NEJM 2020;382:1395.

11

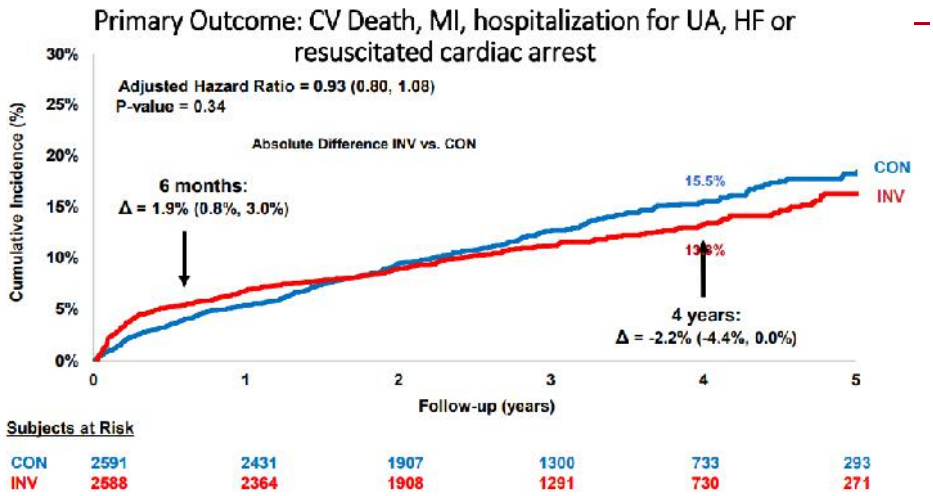
ISCHEMIA



AHJ 2018;201:124.
JAMA C. 2019;4:273.
NEJM 2020;382:1395.

12

ISCHEMIA: OMT for CCS



No trial in CCS shows PCI reduces death (or spontaneous MI)

NEJM 2020;382:1395. *Circulation* 2020;142:841.

13

ISCHEMIA Remarks

- Does **not** apply to **highly symptomatic**; HF, LVSD, VHD, LMCA, no oCAD.*
- Secondary outcomes
  - **No ↓ ACM or CV death**
  - No net ↓ MI but
  - ↓ "spontaneous MI" HR 0.67, p<0.01
  - ↓ UA hosp, HR 0.50, p=0.02
  - ↑ HFH, HR 2.23, p=<0.01
- ? benefit if HF + EF 0.35-0.45†
- *No Δ by ischemia severity or coronary anatomy*

- Limitations
  - Unblinded (no sham)
  - ? Low event rate: 6.5% death at 4 years
  - Limited followup (3.3 y): **ISCHEMIA-EXTEND**
  - Females = only 23%.¶ **CIAO-ISCHEMIA**
  - Completeness of revasc?
- **Is cCTA required to assess for LMCA in practice?**
  - 434/8518=**5.1%**
  - *SCAPIS: 0.1% overall but ♀6.6-♂9.2% if CAC >100***

**Trials* 2015;16:411

***Circulation* 2021;144:916. ¶*JAMA Cardiol* 2020;5:773.
†*Circulation* 2020;142:1725. *NEJM* 2020;382:1395 & 1408.

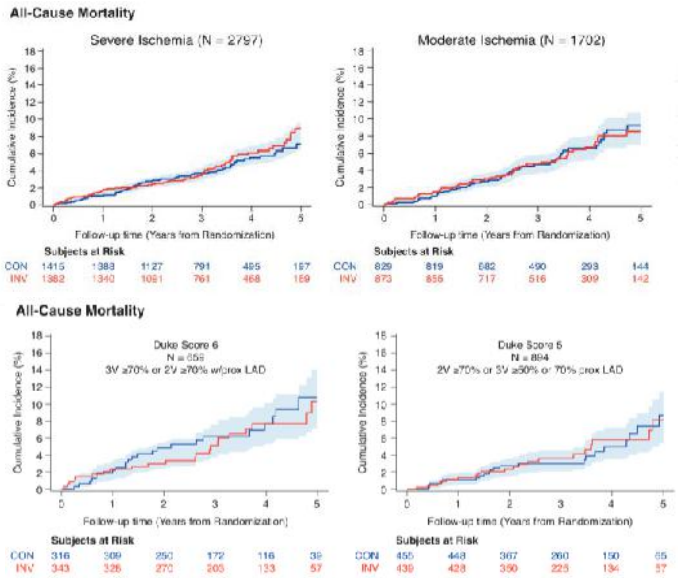
14

ISCHEMIA Outcomes by Severity

Ischemia severity not associated with outcome

CAD severity associated with outcome

Intervention:
↓ MI
no Δ ACM



Circ 2021;144:1024.

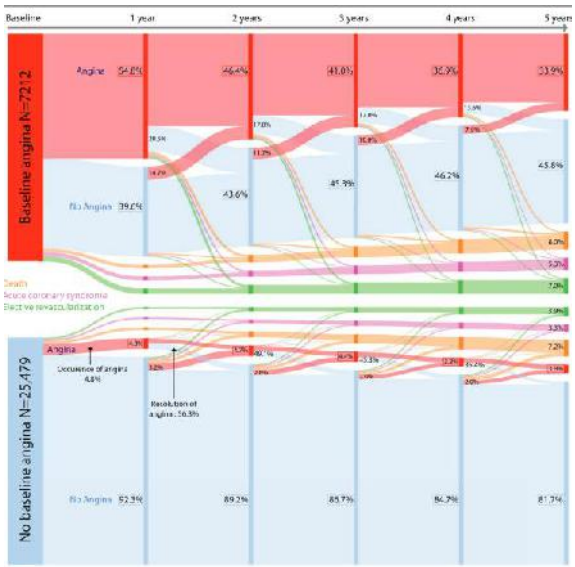
15

CLARIFY
Evolution of Angina in CCS

Angina in ¼

33k well-treated contemporary cohort

Resolves in 2/5 in one year



Circulation 2021;144:512.

16

Non-Pharmacologic Interventions (and Lifestyle)

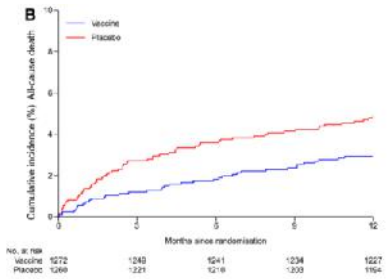
- Education
  - Cardiac rehab
- Nutrition
  - ↓saturated/trans fats
  - ↓ultraprocessed foods
  - ↓Na
  - ↑fruits/vegetable, fiber
- Exercise: >30 min mod aerobic activity 5-7d/wk
- Weight/BMI < 25
  - Waist circumference
- Smoking cessation
  - Avoid secondhand
- Moderate/↓ alcohol
- Mental Health
  - Stress and depression
- Respiratory
  - OSA
  - Avoid air pollution
  - Influenza vaccination
  - Pneumococcus
  - COVID-19 precautions

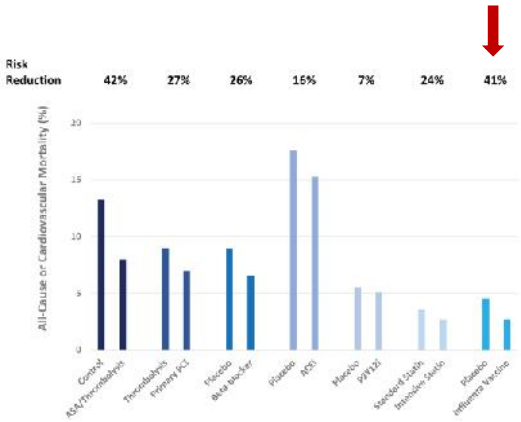
Address at every visit

JAMA Network Open 2022;5:e223849. *JAMA* 2021;325:1765. *JACC* 2021;77:1520. *EHJ* 2020;41:407. *Circ* 2019;140:e596.

17

Non-Pharmacologic Interventions (and Lifestyle)





- n=2571, N=30
- Vaccine v. placebo post-AMI
- ACM ARR 2.0%
- HR 0.59, p=0.01

Circulation 2021;144:1476 and 1485.

18

Antiplatelet Agents in CCS

- **SAPT: Low-dose aspirin (CCS: prior ACS, CAD, post-revascularization – PCI, CABG)**
  - **Chewable**, non-enteric coated (to avoid absorption issues)
  - Consider causes of "resistance": adherence, ↓ absorption (age, weight, PPI), NSAID, COX-1 polymorphisms
  - Clopidogrel if aspirin contraindicated or not tolerated
  - *Evolution of practice to $P2Y_{12}i$ rather than aspirin?*

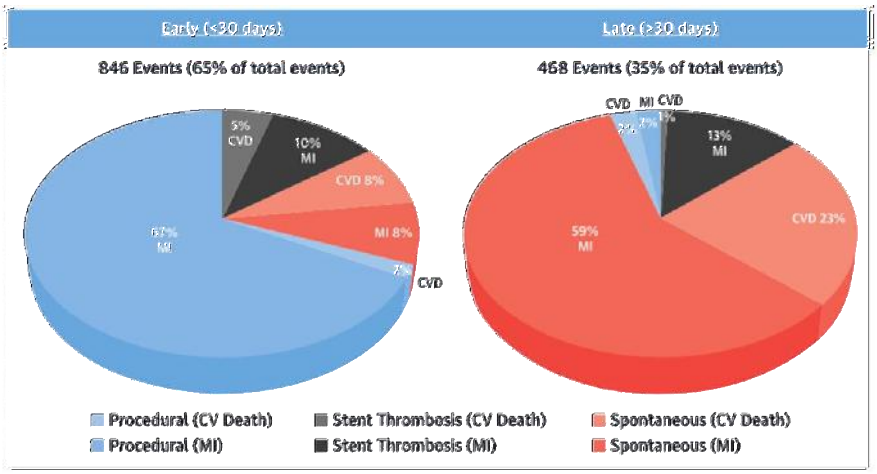
- Dual therapies (DAPT v. dual pathway inhibition DPI)
  - ?Consider dual therapy if high ischemic† > bleeding risk
    - *† MVD and either DM, recurrent MI, PAD, CKD III/IV*
  - **"Dual" = $P2Y_{12}i$ if tolerated 1y post-MI,** or **rivaroxaban 2.5 BID**
  - *(recommendations for patients without anticoagulation indication)*

ADAPTABLE *NEJM* 2021;384:1981. *EHJ* 2020;41:407.
JACC 2005;46:1258 and 2008;51:1829. *Circulation* 2013;127:377.

19

CCS Risks Over Time

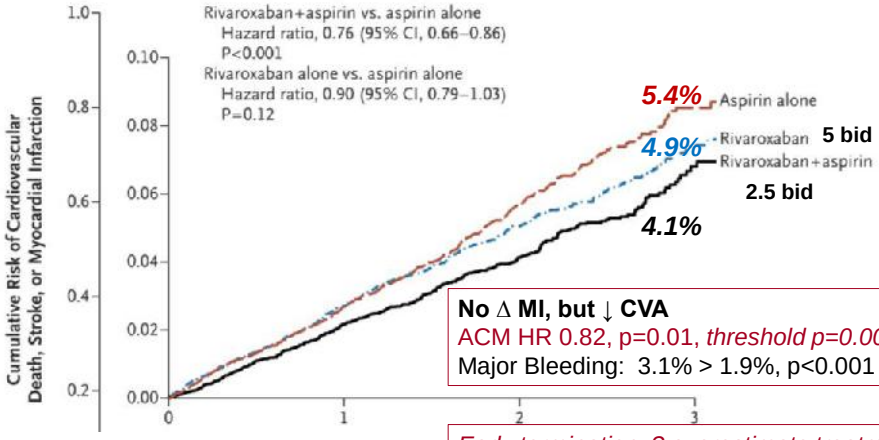
Timing and Etiology of MI and CV Death after PCI for ACS



JACC 2020;75:1095.

20

COMPASS
Low dose anti-Xa in stable ASCVD (CAD + >2 RF)



No Δ MI, but ↓ CVA
ACM HR 0.82, p=0.01, *threshold p=0.0025*
Major Bleeding: 3.1% > 1.9%, p<0.001

Early termination: ? overestimate treatment effect and ? underestimate harm

n=27395

COMPASS *NEJM* 2017;377:1319;
COMPASS-CAD *Lancet* 2018;391:205; **COMPASS-PCI** *Circulation* 2020;141:1141.

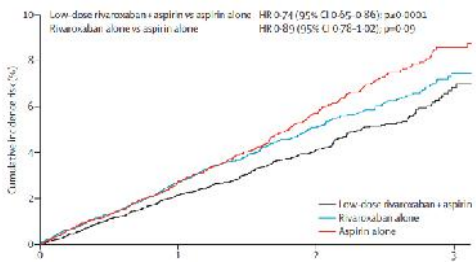
21

COMPASS
Low dose anti-Xa in stable ASCVD

- Similar curves for subgroups:

COMPASS-CAD

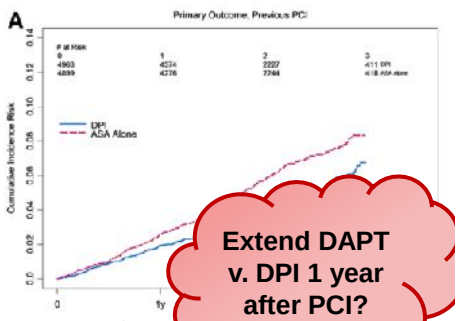
n=24824



PEP HR 0.74
No Δ MI
ACM HR 0.77

COMPASS PCI

n=9862, 5.4 year after PCI



Extend DAPT v. DPI 1 year after PCI?

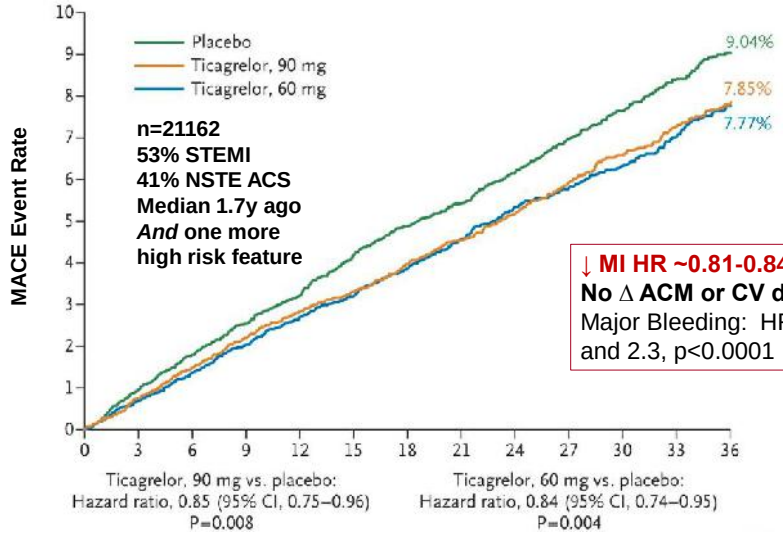
PEP HR 0.74
No Δ MI
ACM HR 0.73

COMPASS *NEJM* 2017;377:1319;
COMPASS-CAD *Lancet* 2018;391:205; **COMPASS-PCI** *Circulation* 2020;141:1141.

22

PEGASUS

Extended duration ticagrelor 1-3 year after MI

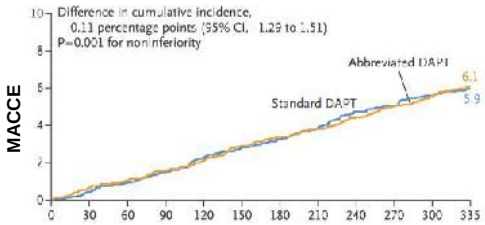


PEGASUS-TIMI 54 *NEJM* 2015;372:1791.

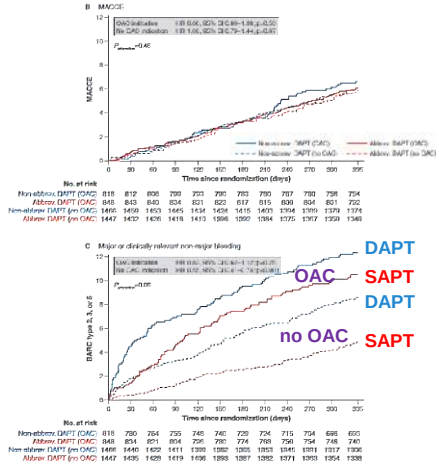
23

MASTER DAPT

- 1 m v. 3-6 m DAPT (median 193 days) after *biodegradable* stent
  - n=4434 high-bleed risk patients
  - ACS 60% or CCS 40%



- Subgroup assessing OAC indications



NEJM 2021;385:1643; *Circulation* 2021;144:1196.

24

"Triple Therapy" Trials

- Overall: DOAC (±↓ dose) + $P2Y_{12}$i vs. ASA + $P2Y_{12}$i + VKA
  - ↓ bleed without aspirin
  - ↑ MI (NS) without ASA, with stent-thrombus rates 0.7-1.4%
  - *But* not powered for death or thrombotic events
- **Balance small ischemic ↑ versus significant ↓ in bleed**

Trial	n	%PCI	%ACS	Medication Regimen			MACE	ST	MB
WOEST	567	100	27	--	Clop	VKA	11.1	**1.4**	**3.2**
				ASA	Clop	VKA	17.6	3.2	5.6
PIONEER AF PCI*	2124	100	52	--	Clop*	Riva 2.5BID	5.6	0.9	**1.9**
				ASA	Clop*	VKA	6.0	0.7	3.3
RE-DUAL PCI†	2725	100	51	--	Clop*	Dabi 150BID	7.9	0.9	**5.6**
				ASA	Clop*	VKA	8.3	0.9	8.4
AUGUSTUS*	4614	76	61	--	Clop*	Apix 2.5BID	6.5	1.9	**2.9**
				ASA	Clop*	Apix 2.5BID		1.0	5.6
				ASA	Clop*	VKA	7.3		

WOEST *Lancet* 2013;381:1107; **PIONEER-AF PCI** *NEJM* 2016;375:2424; **RE-DUAL PCI** *NEJM* 2017;3771513; *JACC* 2019;74:699; *EHJ* 2020;41:407; **AUGUSTUS** *NEJM* 2019;380:1509.

25

CCS Antithrombotic Schema

	Sinus Rhythm	AF or Other Indication for Anticoagulation
Post ACS (PCI or not)	**Aspirin** and **Ticagrelor or Prasugrel** > 6-12 months > 3-6 months if ↑ bleed risk ? Longer term PEGASUS TIMI	**Aspirin** (**1w-1m**: IST v. bleed risk) **+ DOAC** (± ↓ dose) > VKA (INR 2-2.5) **+ $P2Y_{12}$i** (6-12 months) ▪ Clopidogrel with VKA ▪ Prasugrel/ticagrelor with DOAC
CCS	**Aspirin** Consider rivaroxaban vs DAPT (post-MI, high risk without bleed, IIa per ESC)	DOAC > VKA (if able) SAPT: Aspirin <→ **$P2Y_{12}$i** or none¶
CCS s/p elective PCI	**Aspirin**, and **$P2Y_{12}$i > 3-6 months** ≤ 3 months if ↑ bleed risk ? Rivaroxaban (?>1y)	Growing consensus*† ▪ OAC (DOAC > VKA) and ▪ SAPT 6 to >12m post-PCI, based on individualized risk

**Circulation* 2018;138:527. *JACC* 2019;74:699 and ¶2021;77:629. *EHJ* 2020;41:407.
OAC-ALONE *Circulation* 2018;139:604. †**AFIRE** *NEJM* 2019;381:1103.

26

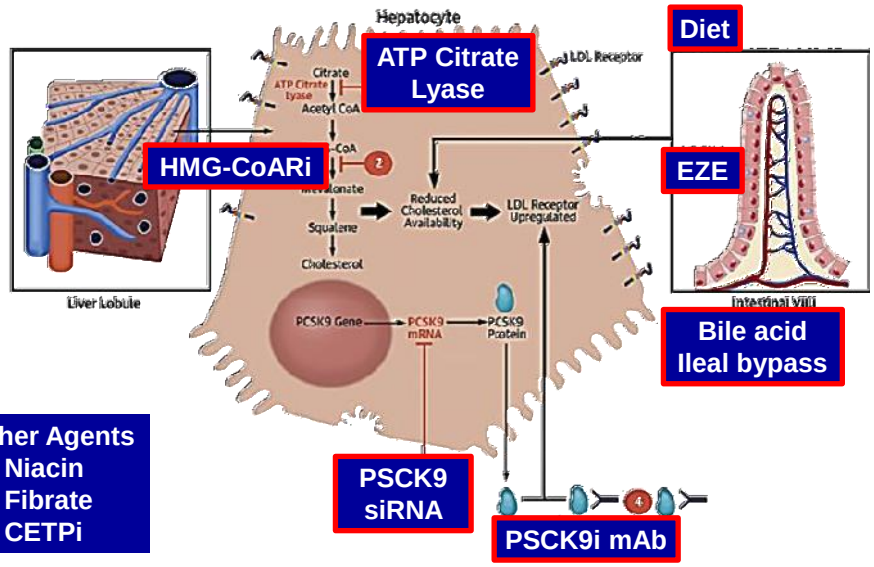
Individualizing Antiplatelets

Longer Duration *Ischemic/Thrombotic Risk*	Shorter Duration *Bleeding Risk*
▪ ACS (plaque rupture) ▪ RF: DM, CKD, smoking ▪ Extent of disease ▪ Prior revascularization(s) ▪ PCI Factors / Complexity – Number of stents, vessels – Bifurcation, long lesions – Thrombotic lesions – Stent location / extent of subtended territory	▪ Prior bleeding ▪ Other medications ▪ Age ▪ Anemia, thrombocytopenia ▪ CKD ▪ Malignancy ▪ ***Trends: shorter DAPT, ?away from ASA toward $P2Y_{12}$i monotherapy***

**Circulation* 2018;138:527. *JACC* 2019;74:699 and ¶2021;77:629. *EHJ* 2020;41:407.
OAC-ALONE *Circulation* 2018;139:604. †**AFIRE** *NEJM* 2019;381:1103.

27

Lipid Lowering Therapy



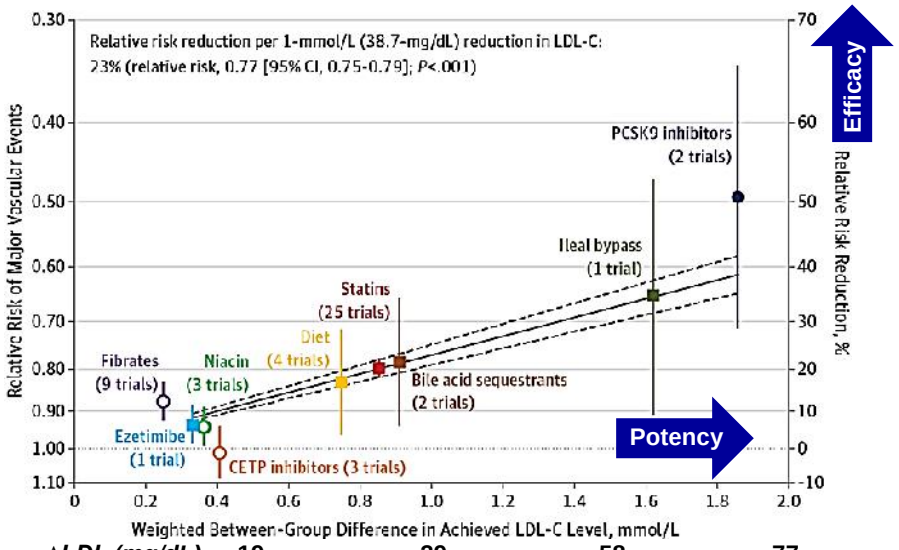
Other Agents
- **Niacin**
- **Fibrate**
- **CETPi**

JACC 2020;75:1945.

28

Relative Risk MACE versus ΔLDL

Effect agnostic of LLT class

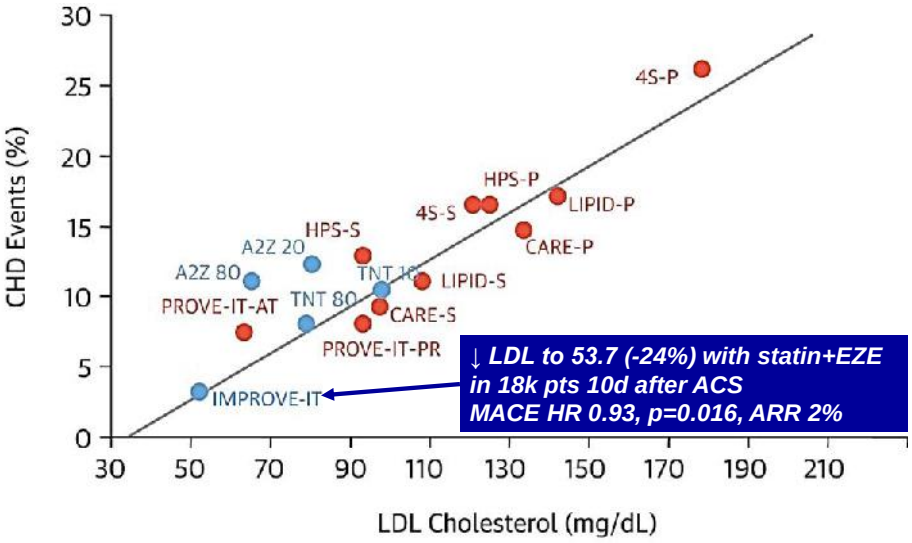


JAMA 2016;316:1289.

29

LDL Goal in CCS

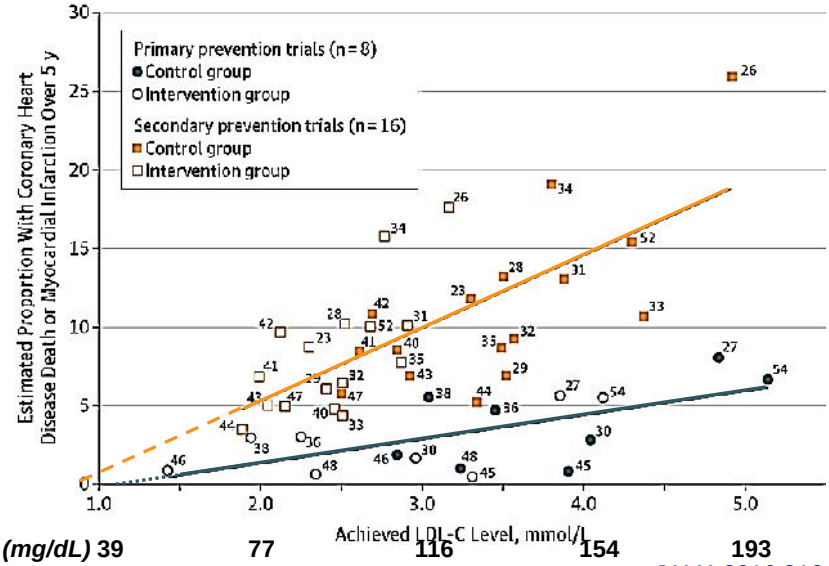
<50-70 mg/dL



IMPROVE-IT *NEJM* 2015;372:2387; *JACC* 2004;43:2142 and 2016;67:362.

30

Meta-Analysis: LDL in 1°/2° Trials <50-70 mg/dL



LDL (mg/dL) **39** **77** **116** **154** **193**

JAMA 2016;316:1289.

LDL: How Low is Too Low?

- Concern: cholesterol = membrane component, precursor for steroid hormones, bile acid, vitamin D, etc
- Mammal, infant, anthropological, heterozygous hypobetalipoproteinemia: LDL 30-70 mg/dl
- RCTs [LDL]
  - FOURIER (<25 in 2/5)
  - ODYSSEY (48)
  - IMPROVE-IT (30)

We don't believe as cardiologists that there is a "range" of normal LDL anymore. Lower is better.

Dr. Goldhaber 2020

"There's never been any evidence from any clinical trials showing a hazard of very low LDL cholesterol levels."

STEVEN NISSEN

JACC 2004;43:2142; *J Lipids* 2018;2018:8598054; *NEJM* 2017;377:633
JAMA Cardiol 2017;2:547 & 2018;3:823. *Circulation* 2018;139:e1082; *JACC* 2020;75:1945

I	Clinical ASCVD (age <75), high-intensity statin for 50% LDL reduction
IIa	For very high risk ASCVD: **LDL < 70**: statin→EZE→ PSCK9i

AHA/ACC ADA

Table 6 Atherosclerotic Cardiovascular Disease Risk Categories and LDL-C Goals

Risk category	Risk factors[a]/10-year risk[b]	LDL-C
Extreme risk	– Progressive ASCVD including unstable angina in patients after achieving an LDL-C <70 mg/dl – Established clinical cardiovascular disease in patients with DM, CKD 3/4, or HeFH – History of premature ASCVD (<55 male, <65 female)	<55 (mg/dL)
Very high risk	– Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease; 10-year risk >20% – Diabetes or CKD 3/4 with 1 or more risk factor(s) – HeFH	<70 (mg/dL)

AACE/ACE ESC

3.3.3 Statins and other lipid-lowering drugs

Dyslipidaemia should be managed according to lipid guidelines with pharmacological and lifestyle intervention.[155] Patients with established CAD are regarded as being at very high risk for cardiovascular events and statin treatment must be considered, irrespective of LDL-C levels. The goal of treatment is to lower LDL-C by at least 50% from baseline and to <1.4 mmol/l. (<55 mg/dL) although a lower target LDL-C of <1.0 mmol/l. (<40 mg/dL) may be considered in patients who have experienced a second vascular event within 2 years, not necessarily of the same type as the first event, whilst taking maximally tolerated statin-based therapy. When this level cannot be achieved, the addition of ezetimibe has been demonstrated to decrease cholesterol and cardiovascular events in post-ACS patients, and in those with diabetes,[316] with no further effect on mortality.[317]

Circulation 2018;139:e1082.
Diabetes Care 2020;43S1:S111.

Endocr Pract 2017;23:479.
EHJ 2020;41:111 and 407.

33

Very High-Risk for Future ASCVD Events*

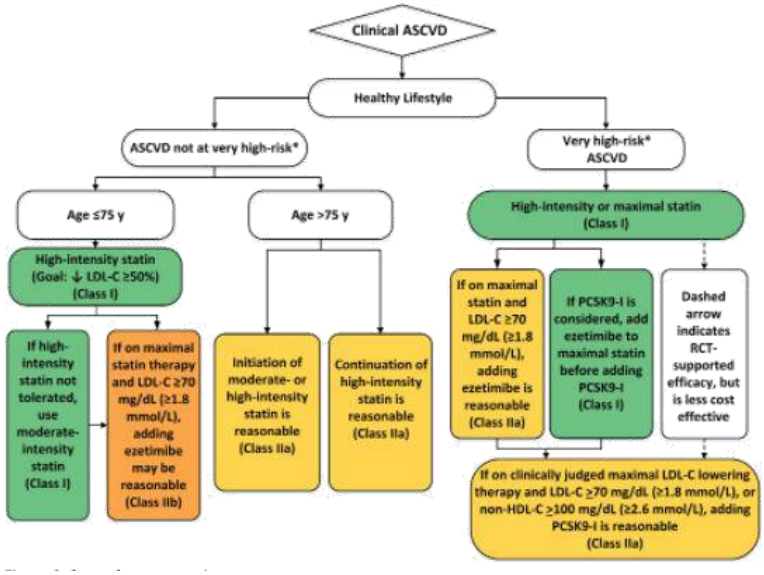
Table 4

Major ASCVD Events
Recent acute coronary syndrome (within the past 12 months)
History of myocardial infarction (other than recent acute coronary syndrome event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ankle brachial index <0.85, or previous revascularization or amputation)
High-Risk Conditions
Age ≥65 years
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or PCI outside of the major ASCVD event(s)
Diabetes Mellitus
Hypertension
Chronic kidney disease (eGFR 15-59 mL/min/1.73 m²)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL (≥2.6 mmol/L)) despite maximally tolerated statin therapy and ezetimibe
History of congestive heart failure

*Very High Risk includes a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions.

34

CCS: LLT / Statin Indications



JACC 2019;73:e285. *Circulation* 2019;140:e596.

35

Statin Regimens

High Intensity	Moderate Intensity	Low Intensity
Lowers LDL-C by ≥50%	Lowers LDL-C by 30%-49%	Lowers LDL-C by <30%
Atorvastatin (40 mg) 80 mg **Rosuvastatin 20 mg (40 mg)**	**Atorvastatin 10 mg** (20 mg) **Rosuvastatin** (5 mg) **10 mg** **Simvastatin 20-40 mg** **Pravastatin 40 mg** (80 mg) **Lovastatin 40 mg** (80 mg) Fluvastatin XL 80 mg **Fluvastatin 40 mg BID** Pitavastatin 1-4 mg	Simvastatin 10 mg **Pravastatin 10-20 mg** **Lovastatin 20 mg** Fluvastatin 20-40 mg

www.heart.org/cholesterol

36

PSCK9 Inhibition: mAb and siRNA

TABLE 3 Results From Placebo-Controlled Cardiovascular Outcome Trials of PCSK9 Inhibitor Treatment

Trial (Ref. #) (Intervention)	Randomized Patients, N	Description of Participants	Average Duration of Follow-Up	LDL-C Reduction (mg/dl) at 52 Weeks	Outcome	PCSK9 Inhibitor, n*	Placebo, n*	Result: HR (95% CI)
FOURIER (5) (evolocumab 140 mg every 2 weeks or 420 mg monthly)	27,564	CVD, elevated LDL-C	2.2 yrs	56	CVD death, MI, stroke, hospitalization for UA, or coronary revascularization†	1,344	1,563	0.85 (0.79–0.92)
					CVD death, MI, or stroke‡	816	1,013	0.80 (0.73–0.88)
ODYSSEY Outcomes (47) (alirocumab 75 mg every 2 weeks)	18,924	Recent ACS, elevated LDL-C, non-HDL-C or apo B	2.8 yrs	48	CHD death, nonfatal MI, ischemic stroke, or hospitalization for UA†	903	1,052	0.85 (0.78–0.93)
					Major CHD event‡	793	899	0.88 (0.80–0.96)
					Any CVD event‡	1,301	1,474	0.87 (0.81–0.94)
SPIRE-1 and SPIRE-2 (46) (bococizumab 150 mg every 2 weeks)	27,438	CVD or high risk	10 months	51	Nonfatal MI, nonfatal stroke, hospitalization for UA requiring urgent revascularization, or CVD death†	352	397	0.88 (0.76–1.02)

2°

↓59% to 30

↓61% to 48

- **Role**: added to maximal statin and EZE in very high risk ASCVD when LDL level remains > 70 mg/dL
- **ADR**: injection site reaction, URI, nasopharyngitis, muscle, GI
- **Cost-effectiveness**: ?
- ***PCSK9 intrahepatic siRNA**: ↓ LDL 50.7% (injection d1, d90, q6m) to day 510, on maximal statin *JACC* 2020;75:1945 and **ORION** *2021;77:1182.

FOURIER *NEJM* 2017;376:1713; **ODYSSEY OUTCOMES** *NEJM* 2018;379:2097.

37

Bempedoic Acid

- ATP-citrate lyase inhibitor: first step in synthesis of fatty acid (citrate → Acetyl CoA) = precedes HMG-CoA-R
- CLEAR WISDOM: n=779 ASCVD/HeFH added to maximal statin, 1°: ↓ LDL 17%/12 week
  - No mortality and morbidity data
  - Side effects: ↑ urate, gout, muscle spasm, tendon rupture, nasopharyngitis, UTI, LFTs
- CLEAR OUTCOMES: studying statin intolerant (n=13k)
  - CLEAR SERENITY: ↓ LDL -21%/12 week (n=345)
- FDA approved February 2020
  - Labeling: monitor urate and for signs of hyperuricemia
  - Do not combine with: > simvastatin 20, > pravastatin 40
  - ? 2nd-3rd line in statin intolerant (combine with EZE)

JACC 2020;75:1945. **CLEAR SERENITY** *JAHA* 2019;8:e011662; **CLEAR HARMONY** *NEJM* 2019;380;1022; **CLEAR WISDOM** *JAMA* 2019;322:1788.

38

Icosapent Ethyl

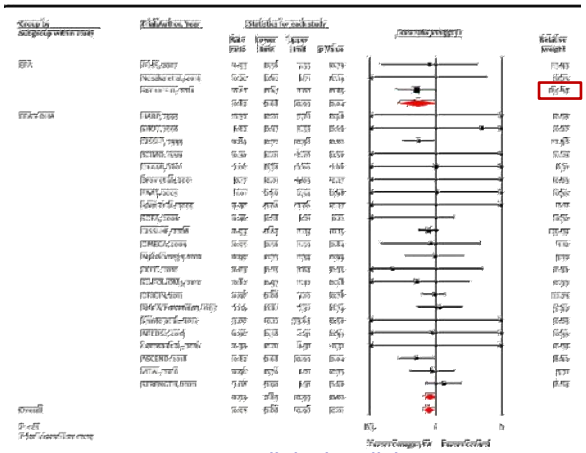
- ω-3: EPA (C20, 5n, ω-3) rather than DHA (C22, 6n, ω-3)
- REDUCE-IT: n=8179, TG 150-499, ASCVD or DM+1RF
  - 71% secondary prevention, 94% statin, 59% DM, TG 216, LDL 75
  - 2g BID dosing: ↓ TG -45 mg/dL, LDL -5 mg/dL at 1 year
  - ? Anti-inflammation mechanism
  - ↓ MACE 4.8%, and ↓ CV death, CVA, MI, revasc; *not* ACM
  - EVAPORATE: ↓ CT low-attenuation plaque volume (-17% v. +109%)
- ADR:
  - Atrial fibrillation HR 1.5, 1% absolute risk
  - arthralgia, edema, constipation, bleed
- FDA indications: adjunct to
  - Diet for TG > 500
  - **maximal statin in patient with TG > 150 and ASCVD, or DM and >2 risk factors to ↓ MACE (indication added 12/2019)**

REDUCE IT *NEJM* 2019;380:11; *JAMA Netw Open* 2022;5:e2148172.
EVAPORATE *EHJ* 2020;40:3925.

39

Omega-3 Fatty Acids: Evolving Story

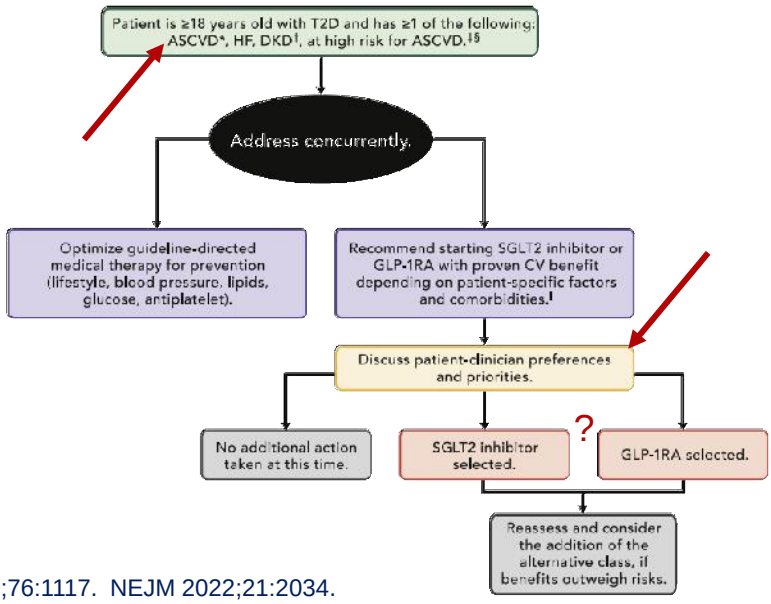
- Several subsequent negative RCT (13k+2.2k+1k)
  - Generally **EPA + DHA** formulations. Is *that* the difference? Placebo?
  - Meta-analysis:
  - *N=38*
  - *ACM shown*
  - *(similar NFMI)*



eClinicalMedicine 2021;38:100997.
STRENGTH *JAMA* 2020;324:2268 and 324:1855. *Circulation* 2021;143:528.

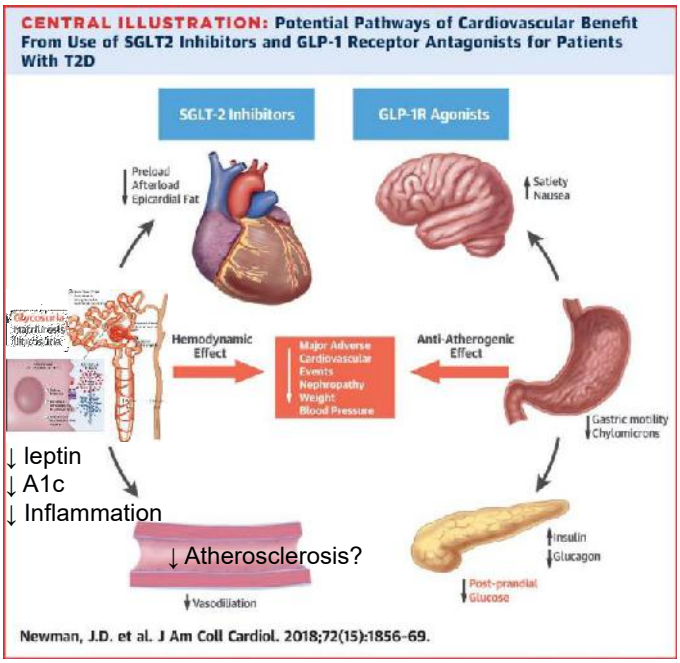
40

Which GLP-1RA or SGLT2i?



JACC 2020;76:1117. NEJM 2022;21:2034.

41

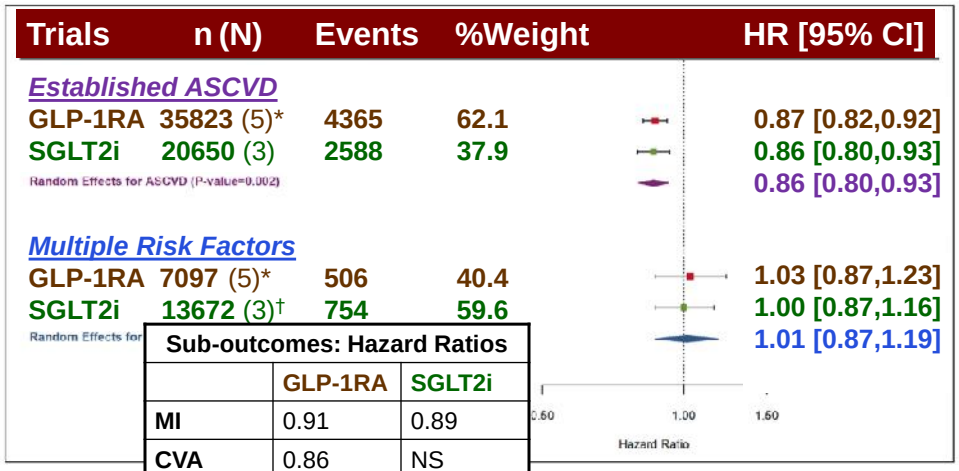


JACC 2018;72:1845 and 1856, and 2020;75:422 and 436 and 1956.

42

GLP-1RA and SGLT2i in ASCVD

Meta-analysis: composite MI, CVA, CV death



Sub-outcomes: Hazard Ratios		
	GLP-1RA	SGLT2i
MI	0.91	0.89
CVA	0.86	NS
HFH	NS	***0.69***
CV death	**0.88**	**0.84**

**REWIND not included (Lancet* 2019;394:121), †CREDENCE *not included (NEJM* 2019;380:2295)
Circulation 2019;139:2022.

43

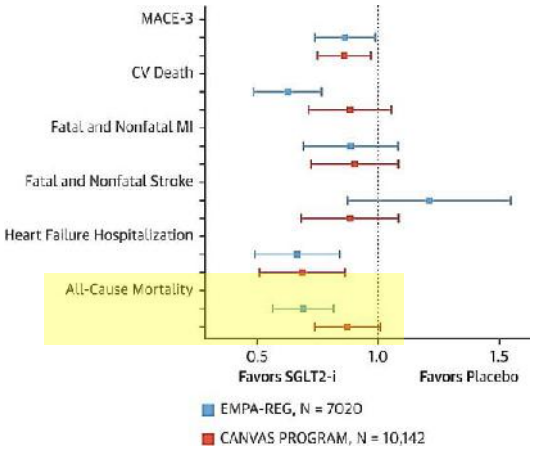
Which GLP-1RA or SGLT2i?

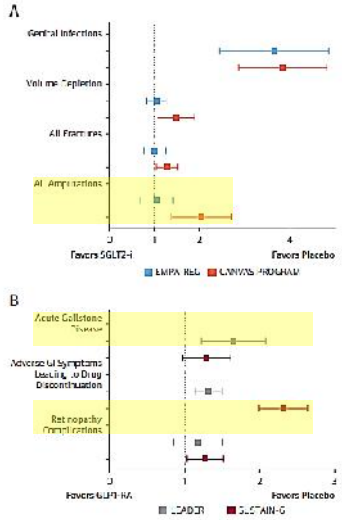
- Trials generally designed to test cardiovascular safety (FDA 2008; non-inferiority), but showed ASCVD efficacy benefit (superiority)
- Heterogenous profiles within classes
  - Different medication pharmacodynamics?
  - Different trial design and patients?
  - Or class effects?
- Questions: *First-line? Combination?*

Diabetes Care 2018;41:2669.
JACC 2018;72:1856 and 2020;75:1956 and 76:1117.

44

Which GLP-1RA or SGLT2i?





Liraglutide Semaglutide

Diabetes Care 2018;41:2669.
JACC 2018;72:1856.

45

Both ↓ MACE, independent of ΔA1c

SGLT2i	GLP-1RA
▪ ↓ **HF hospitalization** ▪ ↓ **multiple CKD endpoints** ▪ ~↓ weight	▪ ↓ macroalbuminuria ▪ ↓ **weight** ▪ ↓ **CVA** (*Dula, Sema SQ*)
▪ No hypoglycemia ▪ ? Euglycemic DKA ▪ ? ↑LDL ▪ Genitourinary infections ▪ Amputation/fracture (CAN)	▪ No hypoglycemia ▪ **GI side-effects (N/V/D/AP)** ▪ **? ↑ HR** ▪ ? **Gallstone**, ? Pancreatitis ▪ Thyroid cancer ▪ Proliferative retinopathy
▪ *EMPA*: ACM HR 0.68, p<0.001, MACE HR 0.86 – Not if **eGFR** < 45 (*EMPA*, *CAN*) or eGFR < 60 (*DAPA*; ↓ *CAN* dose)	▪ ↓ MACE *Lira*, *Dula*, *Sema SQ* ▪ ↓ ACM *Lira* (HR 0.85); *Sema **PO*** (HR 0.51, but no ↓MACE?)

ATVB 2018;38:2207. *Diabetes Care* 2018;41:2669.
JACC 2017;69:2646, 2018;72:1787,1845,1856, and 2020;75:435,1956 and 76:1117.

46

Immunomodulators and Anti-Inflammatory Agents

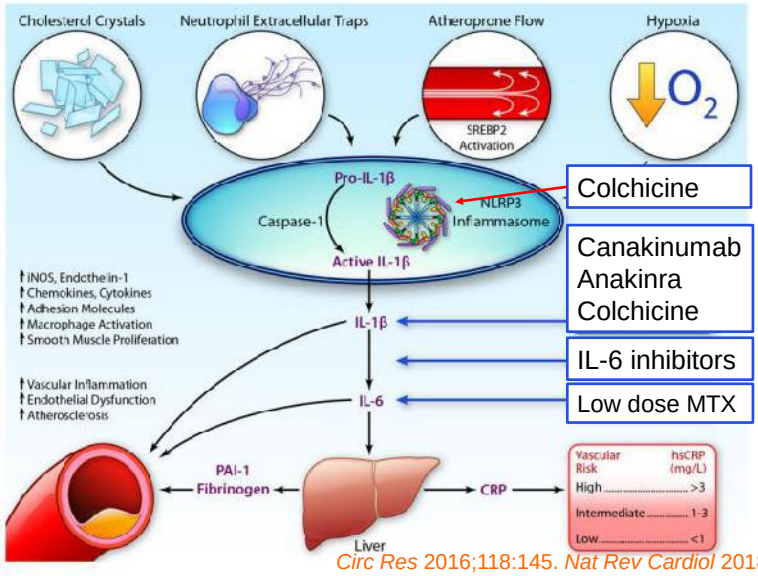
- Statins and RAAS agents may exert pleiotropic off-target effects:
  - **Anti-inflammation**, anti-fibrosis, anti-apoptosis, anti-oxidant, anti-thrombotic, etc
  - Multiple molecular pathways

- anti-Interleukin-1β mAb (Canakinumab)
- Methotrexate
- Colchicine

Circ Res 2017;120:229.
Pharmacol Rep 2008;60:514.

47

Mechanisms and Targets



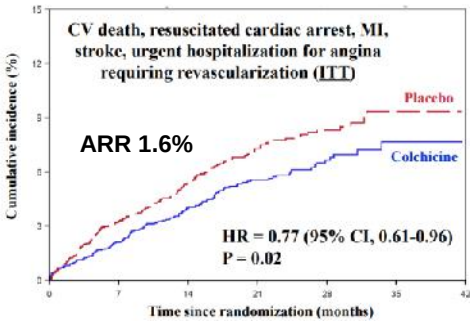
Circ Res 2016;118:145. *Nat Rev Cardiol* 2018;15:203.
Circulation 2020;141:787. *Clin Res* Cardiol 2021;epub. Eur *Cardiol* 2021;16:e20.

48

Colchicine

COLCOT

- DBRCT of 0.5 mg QD added to OMT
- n=4745: MI**<30d**
  - Average 13.5 from MI
  - 93% PCI; 98% DAPT, 95% LLT, 88% βB
  - Exclude HF, EF <0.35, IBD/diarrhea, NM, CKD, recent CVA, ↑CPK, liver, cancer, glucocorticoids
  - 19% women, 73% white



- **Time to initiation**
  - **<3 d: HR 0.52** (p 0.007)
  - 4% ARR (4.3% v. 8.3%)
  - 4-7 d or > 8d: NS

JACC 2013;61:404. *NEJM* 2019;381;2497. *EHJ* 2020;42:4092.

49

Colchicine

COLCOT

- DBRCT of 0.5 mg QD added to OMT
- n=4745: MI**<30d**
  - Average 13.5 from MI
  - 93% PCI; 98% DAPT, 95% LLT, 88% βB
  - Exclude HF, EF <0.35, IBD/diarrhea, NM, CKD, recent CVA, ↑CPK, liver, cancer, glucocorticoids
  - 19% women, 73% white

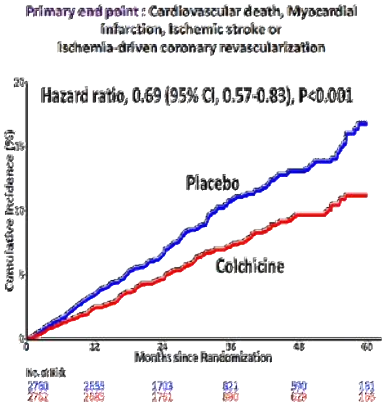
- Criticisms
  - **↓ CV death and MI *NS***
  - **Driven by CVA, angina**
  - 23m followup
  - 1/5 stop drug early
  - ? Stable CAD/CCS
  - Limited CRP data (no ↓)
  - Δ Dose in US practice
  - ↑ pneumonia (+0.5%)
- ↓ cost 47%; ↑ QALY

JACC 2013;61:404. *NEJM* 2019;381;2497. *EHJ* 2020;42:4092. *EHJQCCO* 2020;epub

50

Low Dose Colchicine in CAD (2)

- DBRCT of 0.5 mg QD in n=5522 with CCS ≥ 6 months (84% ACS)
  - 76%PCI/13%CABG
  - 90% antiplatelet, 97% LLT, 62% βB
  - Exclude severe HF, VHD, CKD
- 2.8% ARR
  - 6.8% v. 9.6%
  - Did ↓ MI (HR 0.70), ARR 1.2%



- **Concerns**
  - **15% female (1° result NS)**
  - **Non-CV death HR 1.51 (NS)**
  - **ACM HR 1.21 (NS)**

Circulation 2022;145:626. *NEJM* 2020;383:1838.

51

Trials: Inflammation Hypothesis

RCT	Population	n	Intervention	Result
SOLID-TIMI-52 **VISTA-16** **STABILITY**	ACS ACS **CCS**	13206 5145 15828	Darapladib (PLA2i) Varespladib Darapladib	No ↓ MACE No ↓ MACE; ↑ MI No ↓ MACE
LATITUDE-TIMI-60	ACS	3503	Losmapimod (p38 MAPK inhibitor)	No ↓ MACE at 12w
Colchicine-PCI	**Peri-PCI**	400	1.8 mg colchicine	↓ CRP and IL6, no ↓ 30d MACE
COPS	ACS	795	0.5 mg Colchicine BID 1m → QD 11m	***Excess non CV mortality*** (p=0.02)
CLEAR-SYNERGY	STEMI/PCI	~4000	2x2 colchicine and spironolactone	***~2025***

- Other neutral results: anti-TNF, leukotrienes, COX-2 inhibitors, steroids, adhesion molecules, IL-1R antagonist
- Other more targeted therapies? IL18 (NLRP3), IL6

JAMA 2014;311:252 and 312:1006 and 2016;315:1591. *Am Heart J* 2019;218:46.
NEJM 2014;370:1702. *Circulation* 2020;141:787 and 142;1890. *Circ Card Interv* 2020;13:008717.

52

Blood Supply > Demand

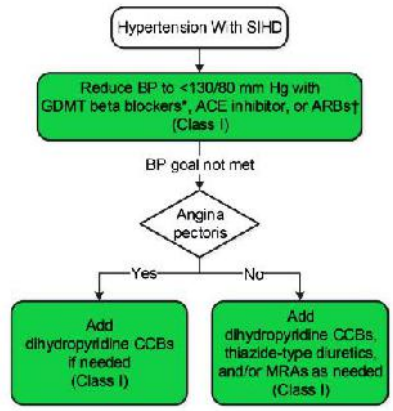
53

Hemodynamic (HR/BP) Agents

TABLE 23 BP Thresholds for and Goals of Pharmacological Therapy in Patients With Hypertension According to Clinical Conditions

Clinical Condition(s)	BP Threshold, mm Hg	BP Goal, mm Hg
General		
2° Clinical CVD or 10-year ASCVD risk ≥10%	≥130/80	<130/80 (I)
1° No clinical CVD and 10-year ASCVD risk <10%	≥140/90	<130/80 (IIa)
Older persons (≥65 years of age, noninstitutionalized, ambulatory, community-living adults)	≥130 (SBP)	<130 (SBP)
Specific comorbidities		
Diabetes mellitus = *ACEI > ARB*	≥130/80	<130/80
Chronic kidney disease = *ACEI > ARB*	≥130/80	<130/80
Chronic kidney disease after renal transplantation	≥130/80	<130/80
Heart failure	≥130/80	<130/80
2° Stable ischemic heart disease	≥130/80	<130/80
Secondary stroke prevention	≥140/90	<130/80
Peripheral artery disease	≥130/80	<130/80

FIGURE 5 Management of Hypertension in Patients With SIHD



*CS βB	NS βB
Metoprolol Carvedilol Bisoprolol Nebivolol	Nadolol Propranolol

EHJ 2020;41:407.
JACC 2018;71:e127.

54

STEP: BP Control in Elderly

SBP 110-130
versus 130-150

8.5k Chinese patients ages 60-80y, SBP 140-190.
No CVA.

ARB, CCB, HCTZ

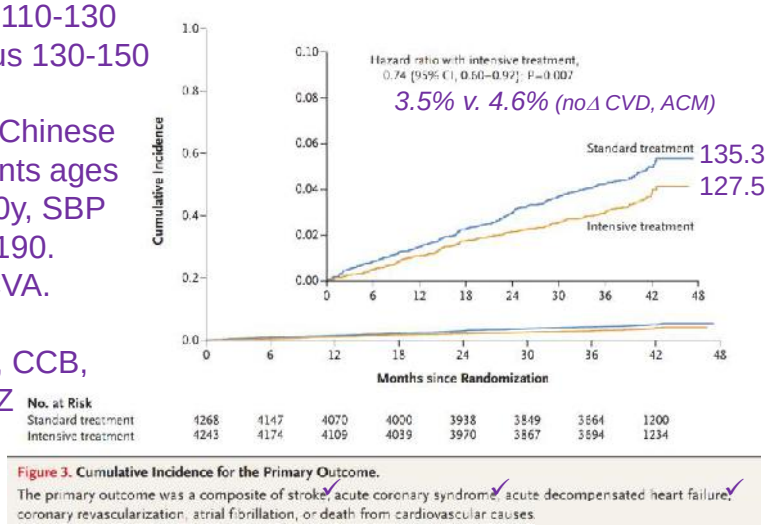


Figure 3. Cumulative Incidence for the Primary Outcome.
The primary outcome was a composite of stroke, acute coronary syndrome, acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes.

3.5% v. 4.6% (noΔ CVD, ACM)

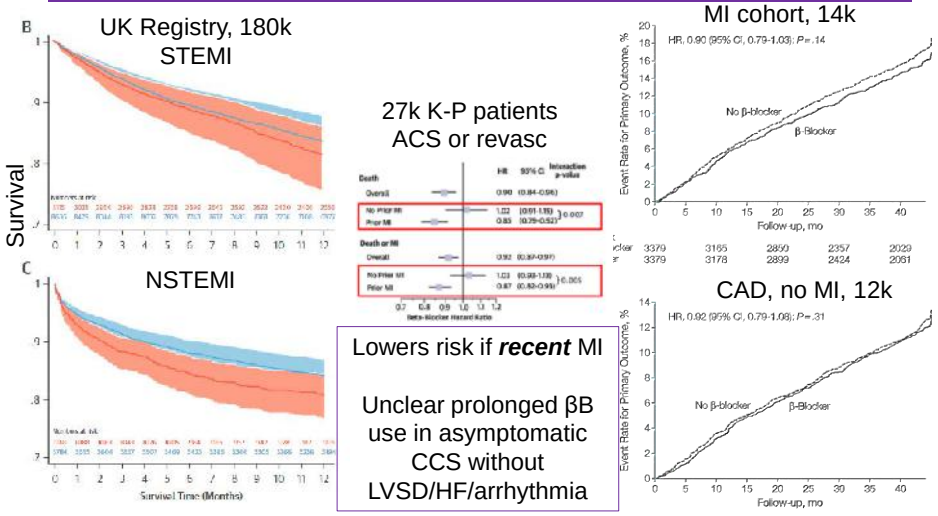
135.3 mmHg
127.5 mmHg

RR hypotension (<110/<50) 1.31

NEJM 2021;385:1268.

55

β-Antagonists in CCS



Lowers risk if ***recent*** MI

Unclear prolonged βB use in asymptomatic CCS without LVSD/HF/arrhythmia

BMJ 1999;318:1730; *Neth J Med* 2009;67:284; ***JAMA* 2012;308:1340**;
Circulation 2012;126:e354; ***JACC* 2014;64:257**; *JACC Interv* 2016;16:1639;
***JACC* 2017;69:2710** & 2019;672; *Circulation CVQO* 2019;12:e005103; *BMC Medicine* 2020;18:103.

56

β-Antagonists

CENTRAL ILLUSTRATION Effects of β-Blockers in Heart Failure and Coronary Artery Disease

Cardiac Disease	Effects of β-Blockers Based on RCTs	Recommendations
Post ACS	Immediate effect: • Reduces mortality (pre-reperfusion era data) • Reduces re-infarction • Can increase risk of heart failure and cardiogenic shock (mainly observed in patients at higher risk) Longer-term effect: • Reduces mortality (pre-reperfusion era data)	• Initiate post-ACS in patients without a low blood pressure or clinical evidence of decompensated heart failure • Start at low doses, and titrate gradually to avoid adverse effects • Continue treatment for up to 3 years (or permanently if heart failure with reduced ejection fraction) • Large contemporary RCTs in progress to study long-term effect in patients without left ventricular dysfunction
Stable CAD (without recent ACS, and with normal left ventricular function)	Insufficient data on major adverse cardiac outcomes	• Use for angina • No data to support routine use • Large RCTs needed

Meta-meta-analysis: N=98 meta-analyses, 1.6M patient-years

Population	Primary Outcome	Secondary
Coronary Artery Disease	*All-Cause Mortality*	*Incident Myocardial Infarction*
Acute coronary syndrome (trials after routine reperfusion)	↔	↑
Acute coronary syndrome (trials before routine reperfusion)	↔	↑
Non-acute ischaemic heart disease (trials after routine reperfusion)	↓↓↓	↓↓↓
Non-acute ischaemic heart disease (trials before routine reperfusion)	↑	↑

↓↓↓ = *low evidence*

BMC Medicine 2020;18:103; *EHJ* 2020;41:407.
JACC 2019;74:672; *JACC* 2018;71:e127.

57

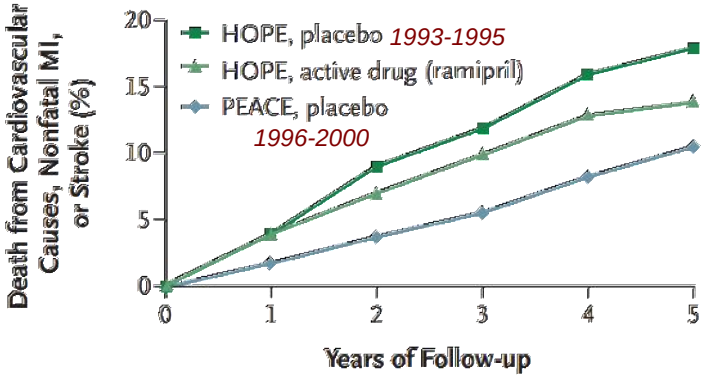
β-Antagonists

- Outcome benefit in CCS may be limited to
  - Post-MI: Long-term post STEMI (ESC 2019 class IIa)
  - ~3 years post-MI (AHA/ACC 2014 class I)
- Differences in cardioselectivity, lipophilicity, intrinsic sympathomimetic activity, vasodilation
- Impacts on exercise tolerance, fatigue, ED, mood, heart block, claudication, etc

BMJ 1999;318:1730; *Neth J Med* 2009;67:284; *JAMA* 2012;308:1340;
Circulation 2012;126:e354; *JACC* 2014;64:257; *JACC Interv* 2016;16:1639;
JACC 2017;69:2710 & 2019;672; *Circulation CVQO* 2019;12:e005103; *BMC Medicine* 2020;18:103.

58

RAAS Inhibitors

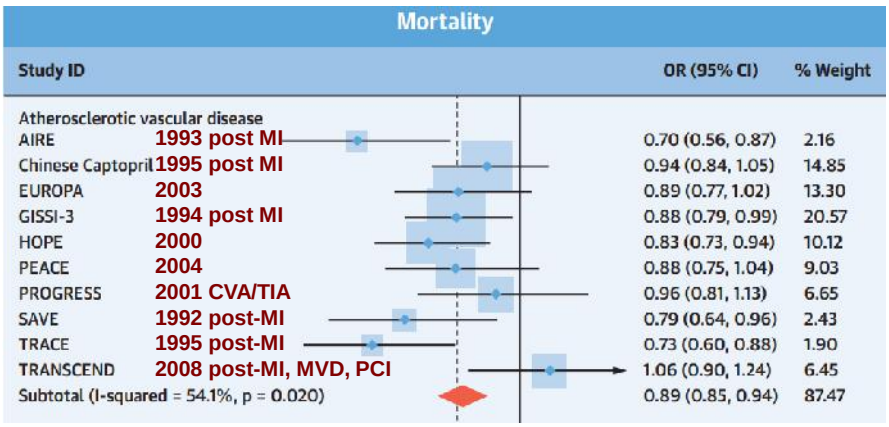


No benefit of ACEI in CCS with near-normal EF
(0.50 average, 15% = 0.40-0.50) on background of OMT (**90** v 76% ASA, **70** v 29% LLT, **60** v 39% βB)

NEJM 2004;351:2058.

59

Meta-analysis ACEI/ARB in CCS



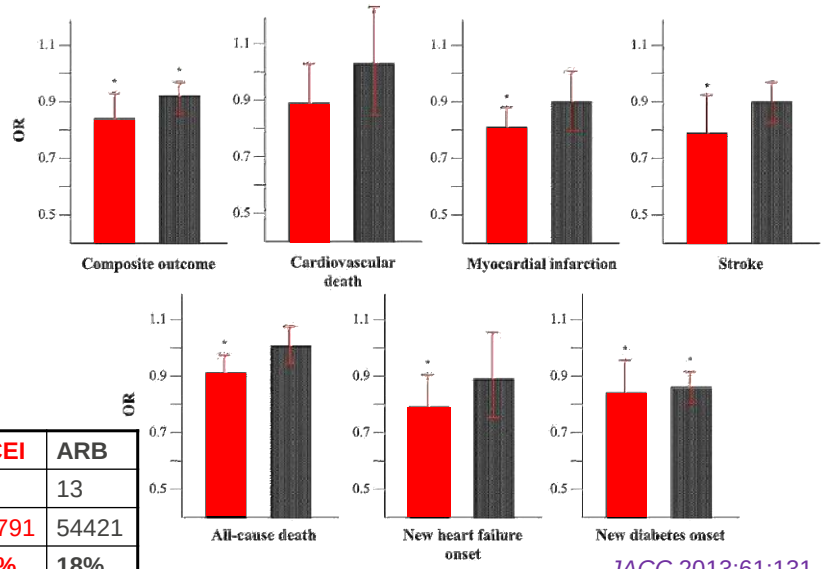
- ↓ mortality and MACE versus **placebo**, but not versus active cardioprotective medication control (and modern OMT?)
- AHA/ACC 2014 class IIa; ESC 2019 class IIa if "very high risk"

JACC 2019;74:683; *BMJ* 2017;356:j4; *EHJ* 2020;41:407.

60

Meta-analysis ACEI/ARB

non-HF with HTN, DM, CVA, CKD; overall 42% CAD



	ACEI	ARB
N	13	13
n	53791	54421
CAD	**66%**	**18%**

JACC 2013;61:131.

61

BP/HR and Anti-Anginal Agents

- **Uncertainties regarding role of βB and ACEI in CCS in disease modulation**
  - Clear role in neurohormonal modulation (Dr. Chris Newton-Cheh) in **LVSD** and **HFrEF**
  - βB: tachyarrhythmia, TAA
  - RAAS: HTN, TAA, DM, proteinuric CKD
- As ***anti-anginals***: individualize to patient
  - I: **βB** for initial therapy
  - I: **CCB** or **long-acting nitrate** if βB contraindicated or side effects or insufficient (*can consider combinations)
  - IIa: long-acting non-dihydropyridine (verapamil, diltiazem) rather than βB
  - IIa: Consider adjuncts
  - *Address: fever, anemia, thyroid, hypoxemia, VHD*

EHJ 2020;41:407.
JACC 2018;71:e127.

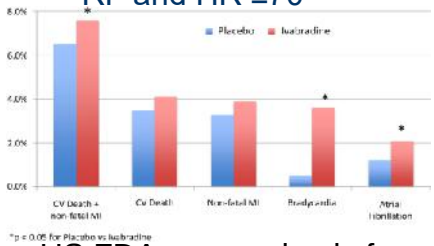
62

Adjunct Anti-Ischemic Agents

- **Ranolazine**
  - Pleiotropic mechanisms
  - Inhibits $I_{Na} \rightarrow \downarrow Ca^{+2}$
- Substitute for βB in CCS if βB causes side effects or ineffective or contraindicated
- Can combine with βB
  - caution: non-DHP CCB (CYP3A4)

JAHA 2016;5:e003196.

- **Ivabradine** SIGNIFY
  - Studied in CCS with class II angina + ≥ 1 RF and HR ≥70

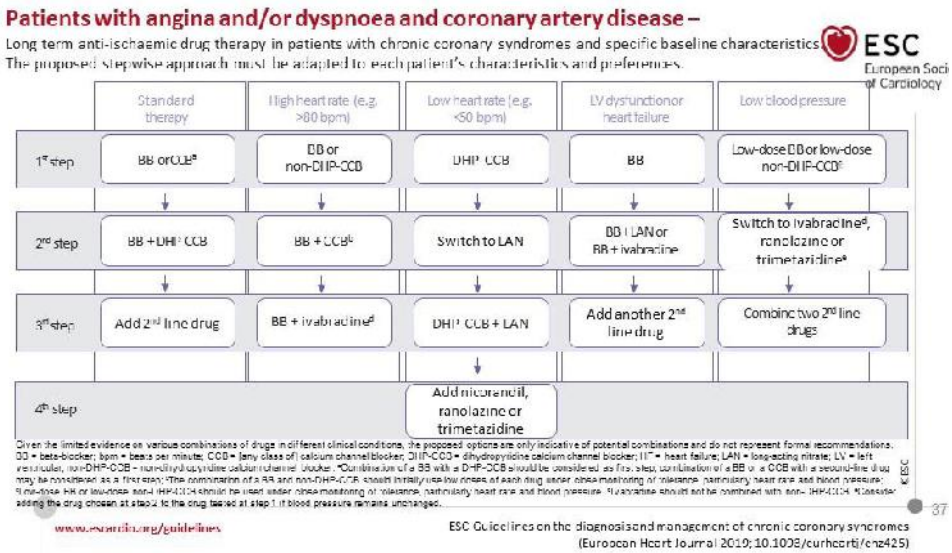


- US FDA approval only for HF, with HR > 70 despite βB

NEJM 2014;371:1091.
EHJ 2015;36:3297.

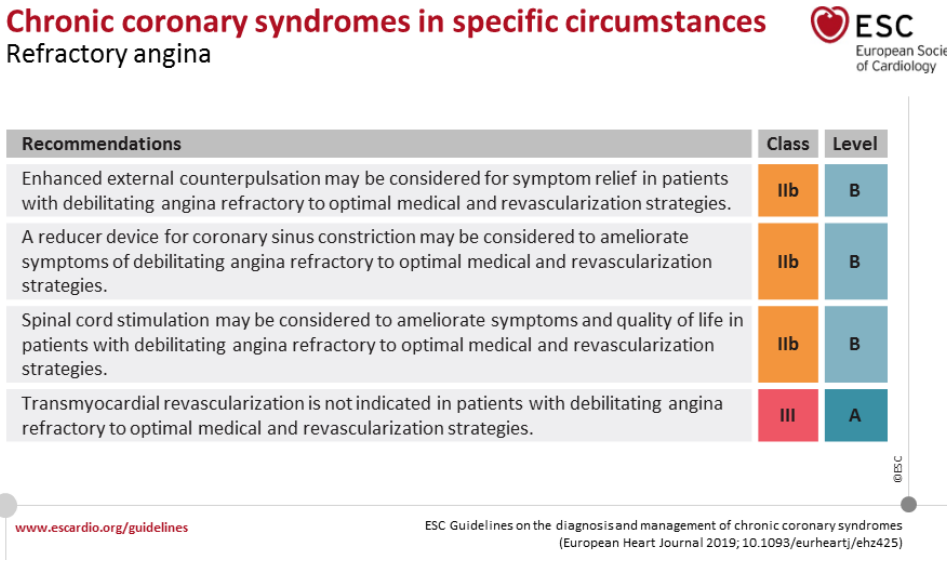
63

ESC Angina Rx Algorithm



64

ESC Angina Rx Algorithm



65

Nitrate: Mechanisms

- Reduce preload (heart volume)
- **Increase Coronary Collateral Flow**
- Dilate Normal and Diseased Coronary Arteries
- Reduce Coronary Artery Spasm
- Reduce afterload (SBP and σ)

Dr. Hutter.
JCI 1973;52:2836; *Circulation* 1982;66:689.

66

Nitrate: Dosing and Duration

Nitrate	Route	Dose Range	Duration	Dose Frequency
TNG	PO	0.3-0.4 mg	20 min	x3 prn
ISDN	PO	10-40 mg	4-5 hr	BID-TID*
ISMN	PO	10-20 mg	> 6 hr	BID
	PO/SR	60-240 mg	10-12 hr	QD-**BID**
Paste	TD	½" → 1"-2"	4-6 hr	QD-BID
Patch	TD	0.2-0.8mg/hr	24 hr	QD†

- SL TNG: should cause tingling sensation under tongue; heat and light sensitive tablet
- †TD patch: requires "patch-off" interval to ↓tolerance
- Avoid nitrates in: PDE5i; HOCM, severe AS

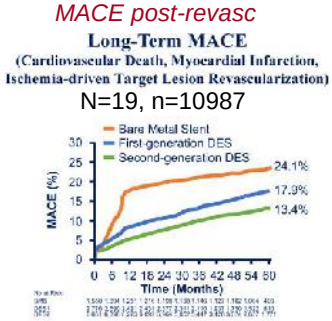
Dr. Hutter. EHJ 2020;41:407.

67

Collateral Coronary Flow

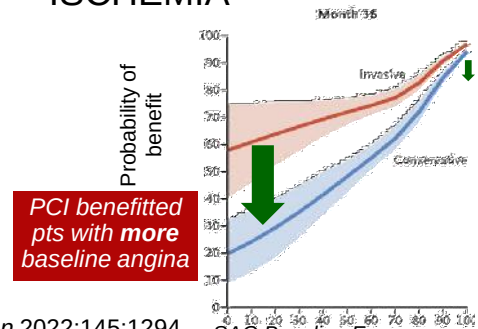
- Nitrates may promote collateral flow

CCS confers↑ risk for MACE post-revasc



Revascularization

- Indicated for
  - Survival benefit in: LMCA, 3VD, 2V with pLAD disease
  - **Symptoms refractory to OMT**
- ISCHEMIA



*PCI benefitted pts with **more** baseline angina*

SAQ Baseline Frequency (100=no angina)

ISCHEMIA *NEJM* 2020;382:1408. *Circulation* 2022;145:1294. *Circ Interv* 2020;13:e008565.

68

Therapies Without Clear Benefit

- HRT
- Vitamins B6, B12, C, E, and Folate
- Garlic, CoQ10
- Se, Cr

- ? Chelation (EDTA): TACT – HR 0.82 (0.69-0.99) for ↓ D / recurrent MI, CVA, angina hospitalization, revasc, but investigators concerned about 18% lost to followup which was 50% higher in placebo group
  - Risks: hypocalcemia, AKI
  - Listed as IIb (questionable)

TACT *JAMA* 2013;309:1241 & 1293.

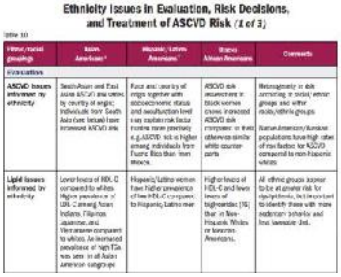
69

Individualizing Care

- Elderly Patients (*JACC* 2018;71:2015)
- Female Patients (*Lancet* 2020;396:P72): Dr. Wood
- Hispanic, Black, Asian Patients (*JACC* 2021;77:1480)
  - Goal: Ethically, culturally competent, individualized care
  - See eg ACC/AHA BP guidelines *JACC* 2018;71:e127 and blood cholesterol guideline *JACC* 2019;73:e285.

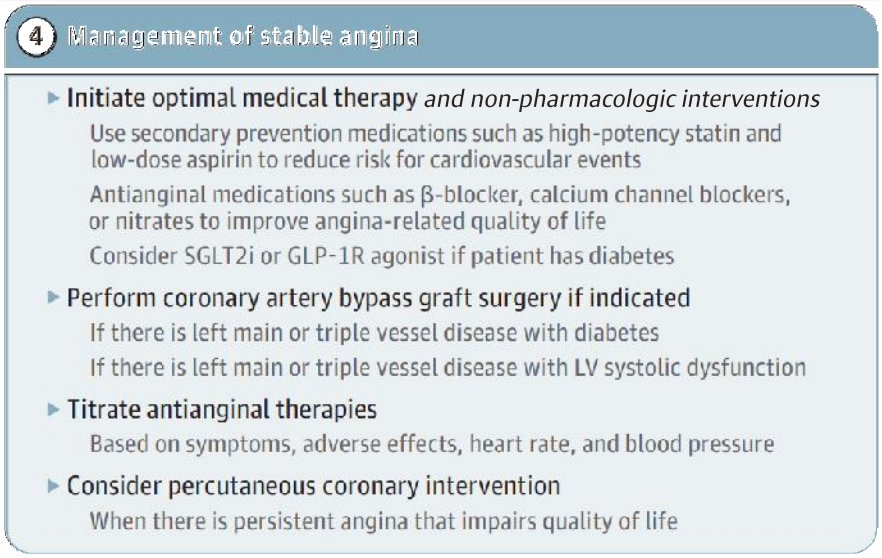
*Consider which patients have been **underrepresented** in trials*

- COVID-19:
  - ACS management impacts
  - CCS management overall similar
  - CCS/comorbidities=risk marker


Ethnicity Issues in Evaluation, Risk Decisions, and Treatment of ASCVD Risk (1 of 3)

70

Assess CCS/Angina; Identify Gaps; Alter Disease and Prevent Progression; SDM



JAMA 2021;325:1765.

71

Themes

- **ISCHEMIA**: medically manage CCS without severe angina, HF, LMCA; even if severe imaging ischemia
- Disease progression:
  - Non-pharmacologic
    - ✓ vaccination, rehab, etc
  - Antithrombotic
    - Tailor to ischemia/thrombosis risk
  - Anti-lipid and anti-glycemic
    - Maximal statin ± adjunct
    - ✓ A1c; use SGLT2i/GLP1-RA
  - Immunomodulation
    - Atherothrombosis role TBD
- Symptoms and Flow:
  - BP and HR agents
    - Individualized to patient
  - Anti-ischemic agents
- Select indications for
  - Revascularization

72