Prevention: The Future of Lipid-Lowering Therapies
The Physician's Perspective

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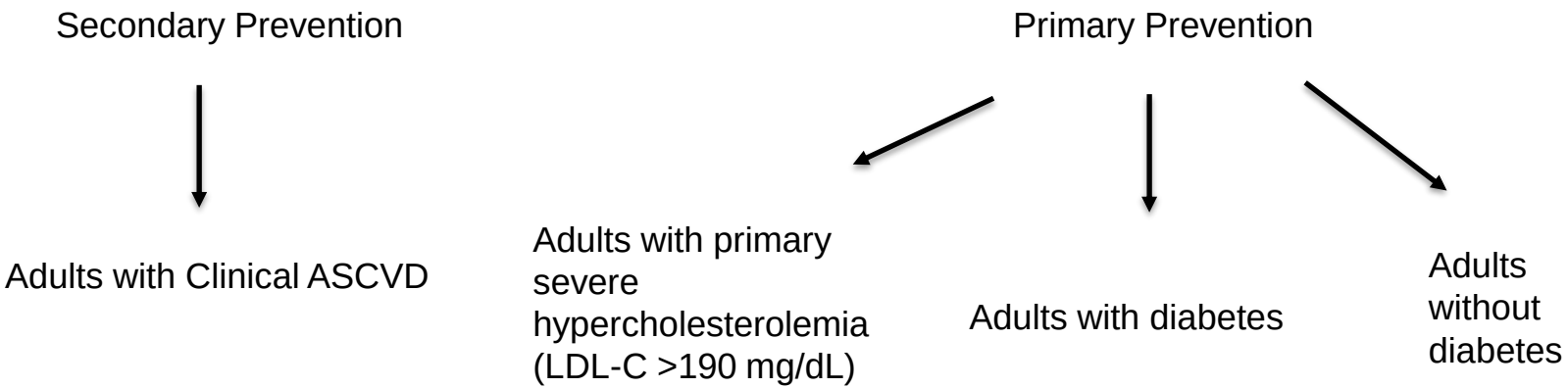
Disclosures

- Amgen, Speakers Bureau
- Novartis Advisory Board

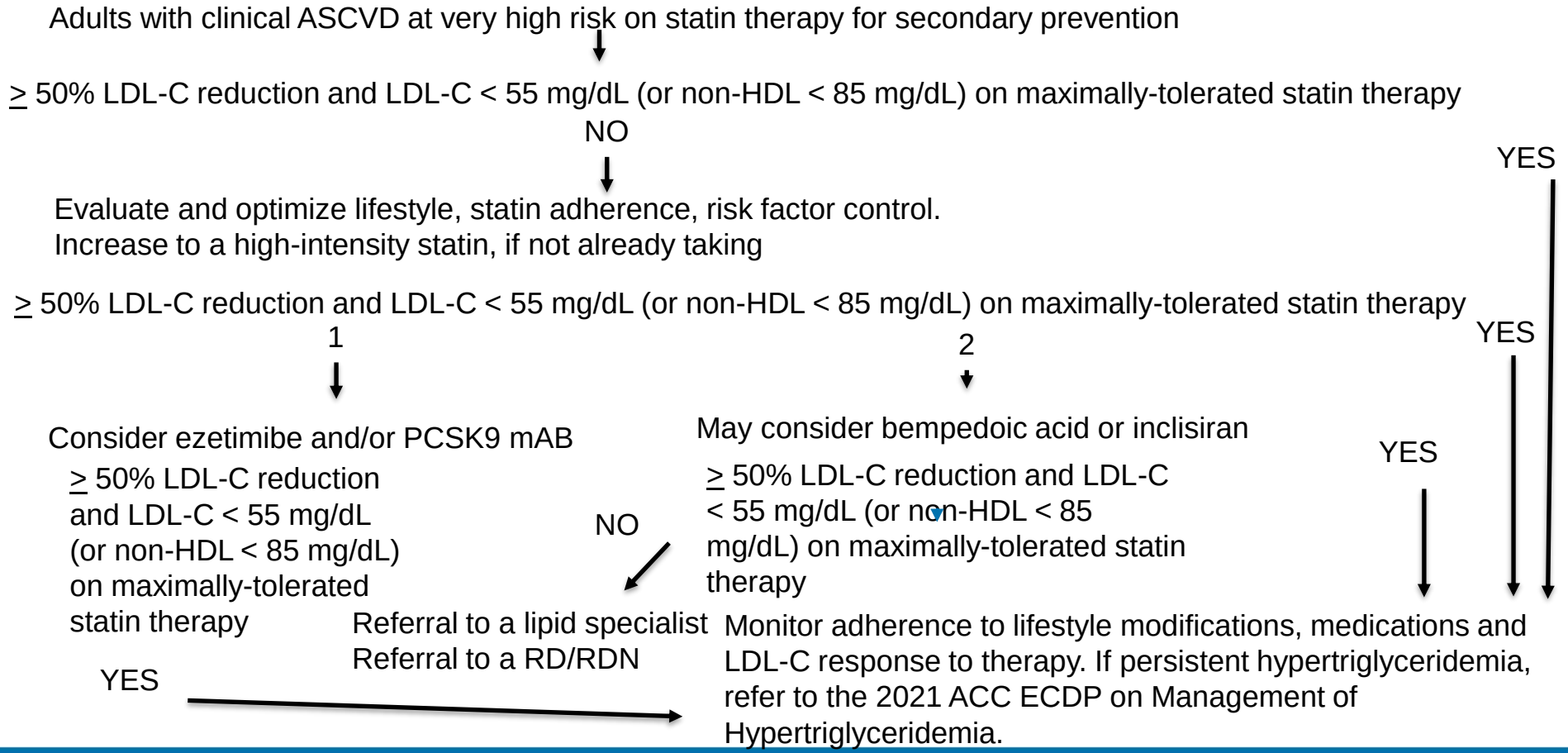
Recent Expert Consensus Decision Panel

- 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

Lloyd-Jones et al. JACC. 2022



Lloyd-Jones et al. JACC. 2022



Lloyd-Jones et al. JACC. 2022

Criteria for Defining Patients at Very High Risk of Future ASCVD events

Major ASCVD Events
Recent ACS (within the past 12 months)
History of MI (other than recent ACS event listed above)
History of ischemic stroke
Symptomatic PAD (h/o claudication with ABI < 0.85 or previous revascularization or amputation

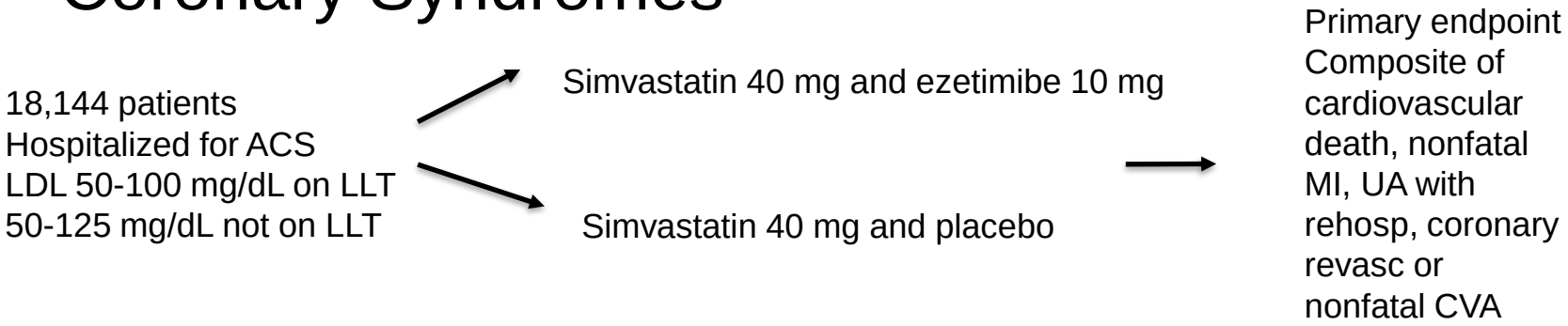
High-Risk Conditions
Age ≥ 65 years
Heterozygous familial hypercholesterolemia
History of prior CABG or PCI outside of the major ASCVD event
Diabetes
Hypertension
CKD (eGFR 15-59 mL/mn/1.73 m2)
Current smoking
Persistently elevated LDL-C (LDL-C ≥ 100 mg/dL) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

Multiple major events or 1 major event and multiple high-risk conditions

Grundy SM et al, 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol, *Journal of the American College of Cardiology* (2018), doi: https://doi.org/10.1016/j.jacc.2018.11.003.

IMPROVE-IT

- Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes



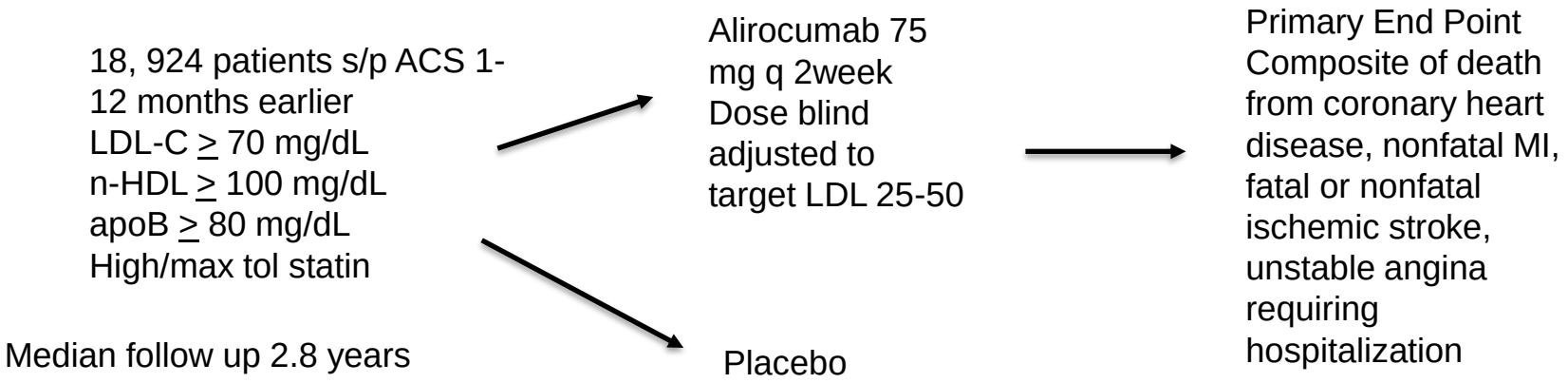
Median follow up 6 years

32.7 versus 34.7%

Cannon et al. N Engl J Med. 2015; 372. 2387

Odyssey Outcomes

- Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome

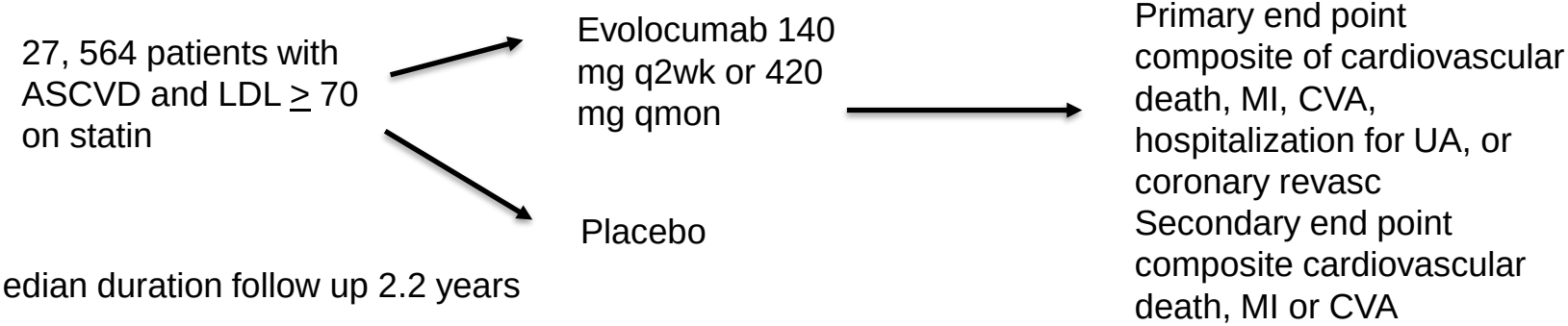


15% relative risk reduction in the primary end point

Schwartz et al. N Engl J Med. 2018; 379. 2097

Fourier

- Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease



LDL-C reduction in 59% (92 mg/dL vs 30 mg/dL)

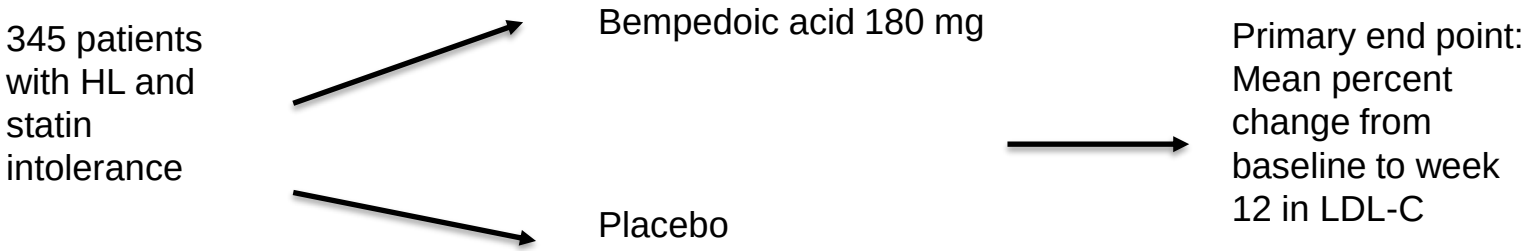
15% relative risk reduction in the primary end point

20% relative risk reduction in the secondary end point

Sabatine et al. N Eng J Med. 2017;376: 1713

CLEAR Serenity

- Efficacy and safety of bempedoic acid in patients with hypercholesterolemia and statin intolerance

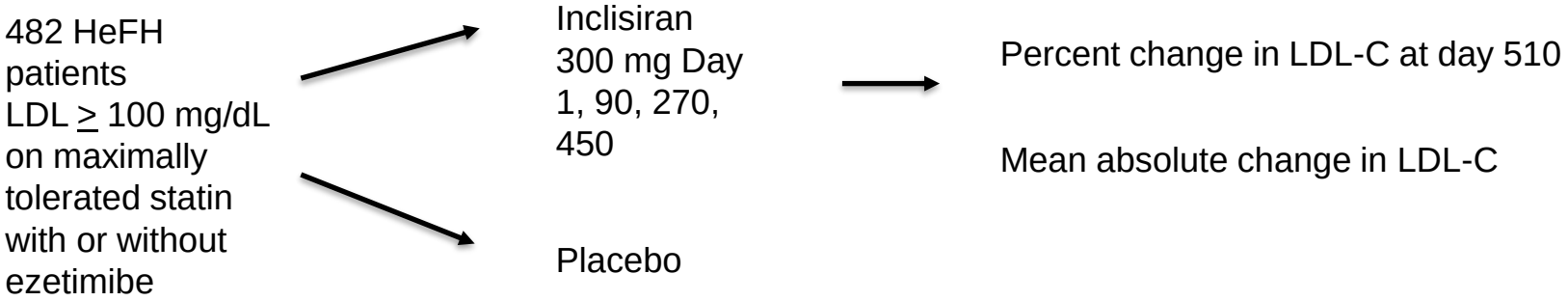


21% reduction in LDL-C

Laufs et al. J Am Heart Assoc. 2019;8

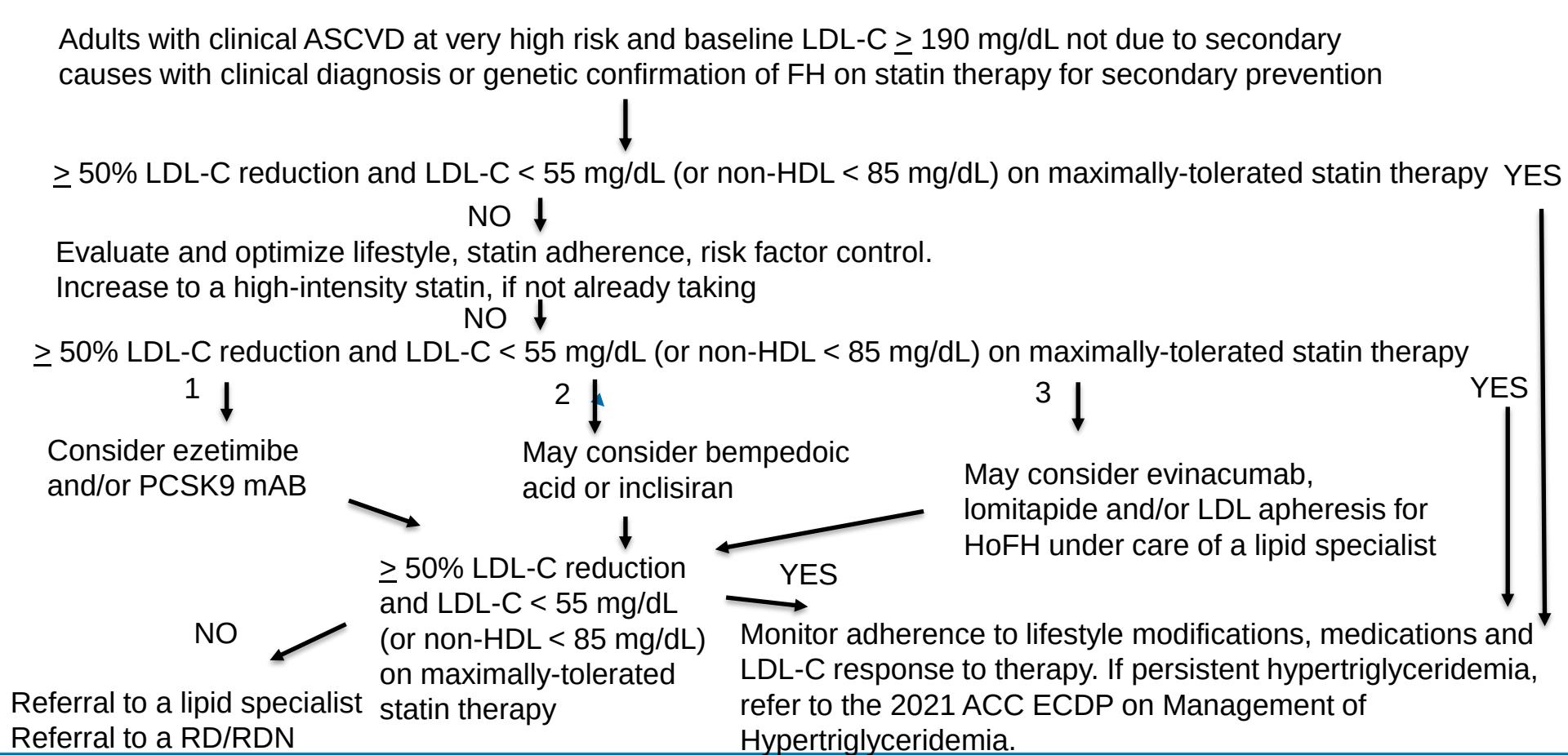
ORION-9

- Inclisiran for the Treatment of Heterozygous Familial Hypercholesterolemia



Percent change at day 510 was reduction in 39.7% in inclisiran, increase of 8.2% in placebo for a between group difference of -47.9%

Raal et al. N Engl J Med. 2020;382:1520



Lloyd-Jones et al. JACC. 2022

FH Diagnostic Categories		
ICD-10 Category	Clinical Criteria	With Genetic Testing Performed
Heterozygous FH	LDL-C ≥ 160 mg/dL for children and ≥ 190 mg/dL for adults and with 1 first-degree relative similarly affected or with premature CAD or with positive genetic testing for an LDL-C-raising gene defect (LDL receptor, apoB or PCSK9)	-Presence of 1 abnormal LDL-C--raising gene defect (LDL receptor, apoB or PCSK9) -Diagnosed as heterozygous FH if LDL-C-raising defect positive and LDL-C < 160 mg/dL -Occasionally, heterozygotes will have LDL-C > 400 mg/dL; they should be treated similarly to homozygotes -Presence of both abnormal LDL-C-raising gene defects (LDL receptor, apoB or PCSK9) and LDL-C-lowering gene variant(s) with LDL-C < 160 mg/dL

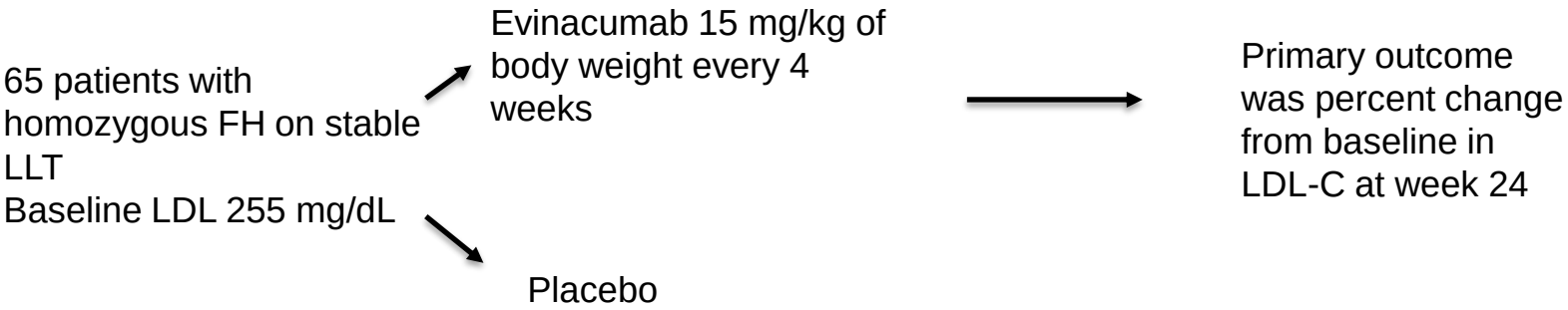
Gidding et al. Circulation. 2015;132:2167

FH Diagnostic Criteria Cont.		
Homozygous FH	-LDL-C > 400 mg/dL and 1 or both parents having clinically diagnosed FH, positive genetic testing for an LDL-C-raising gene defect (LDL receptor, apoB or PCSK9) or autosomal-recessive FH -If LDL-C > 560 or LDL-C > 400 mg/dL with aortic valve disease or xanthoma at < 20 years of age, homozygous FH highly likely	-Presence of 2 identical (true homozygous FH) or nonidentical (compound heterozygous FH) abnormal LDL-C-raising gene defects (LDL receptor, apoB or PCSK9); includes the rare autosomal-recessive type -Occasionally, homozygotes will have LDL-C <400 mg/dL
Family history of FH	LDL-C level no a criterion; presence of a first-degree relative with confirmed FH	Genetic testing not performed

Gidding et al. Circulation. 2015;132:2167

Evinacumab

- Evinacumab for Homozygous Familial Hypercholesterolemia



Relative reduction from baseline in LDL-C of 47.1%.

Raal et al. N Engl J Med. 2020; 383:711

Use of Lipoprotein(a) in clinical practice: A biomarker whose time has come. A scientific statement from the National Lipid Association

- Comprised of the LDL-like particle and apolipoprotein(a) [apo(a)] attached to apolipoprotein B (apoB) via a disulfide bridge
- Meta-analyses of prospective, population-based studies of high Lp(a) and large Mendelian and GWA studies demonstrate and confirm high risk of MI, ischemic stroke, aortic valve stenosis, coronary artery stenosis, heart failure, cardiovascular mortality and all-cause mortality.
- An Lp(a) level >50 mg/dL (>100 nmol/L) may be considered as a risk-enhancing factor favoring the initiation of statin therapy. This level corresponds to the 80th population percentile in populations which are predominantly Caucasian

Wilson et al. J of Clin Lipid. 2019: 13; 3: 374

Emerging Lp(a) Therapies

- Antisense oligonucleotide pelacarsen resulted in reduction of Lp(a) by 80% given 20 mg weekly and 72% given 60 mg every 4 weeks; 98% and 81% respectively achieved Lp(a) levels < 125 nmol/L[1]

- N-acetylgalactosamine (GalNAc)-conjugated siRNA olpasiran resulted in Lp(a) reductions of 71-97%[2]

1. Tsimikas et al. N Engl J Med 2020;382:244 2. Koren et al. Nat Med 2022;28:96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