Advances in Lipid Management

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Prevention of Cardiovascular Disease

- Essence of prevention is lifestyle-related.
- Diet high in fruits and vegetables, and lifestyle with aerobic exercise
- INTERHEART STUDY

INTERHEART

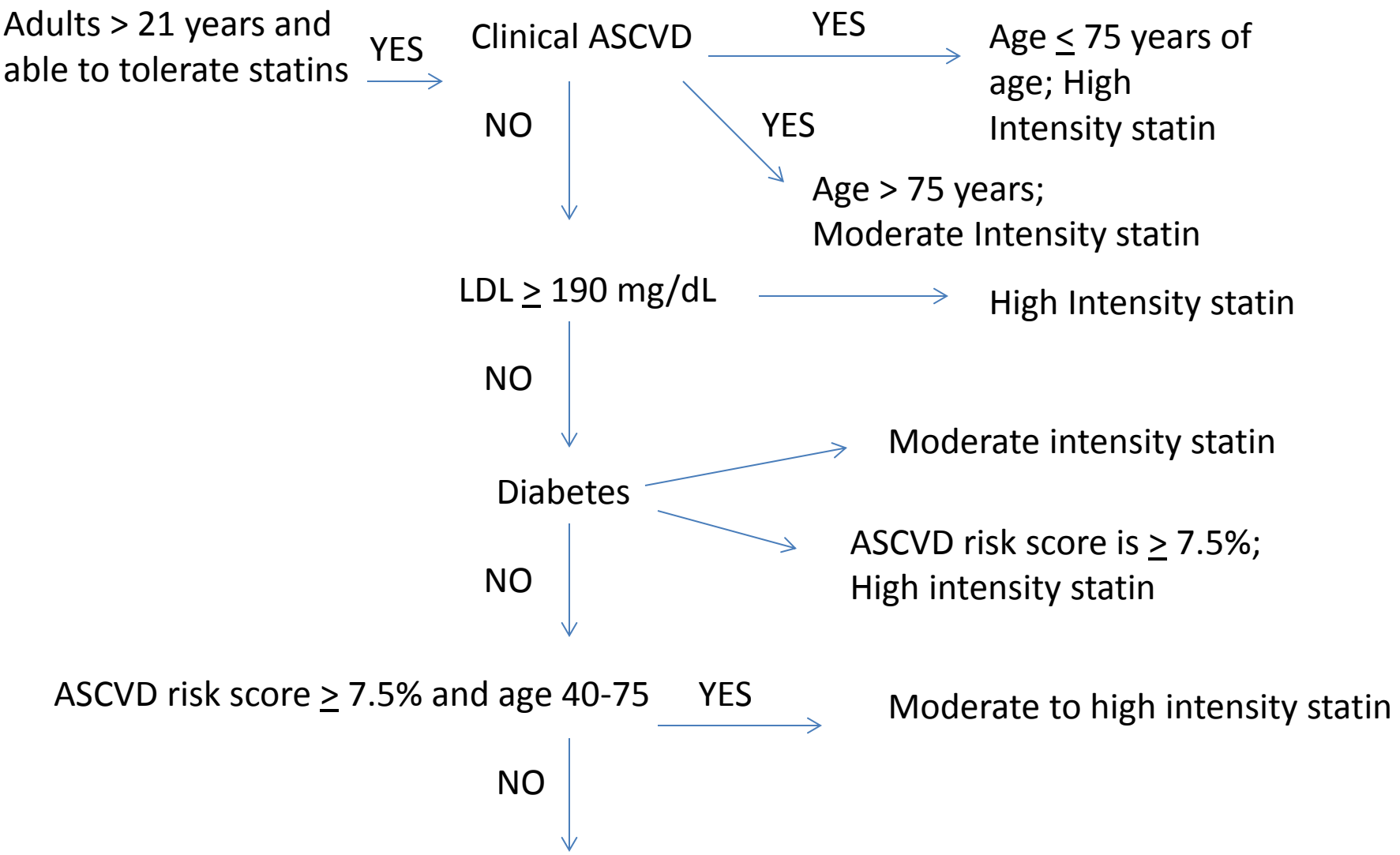
- Nine risk factors accounted for 90% of the risk of heart disease internationally
  - Smoking
  - Hypertension
  - Diabetes
  - Waist/hip ratio
  - Lack of daily consumption of fruits and vegetables
  - Physical activity
  - Lack of consumption of alcohol
  - Dyslipidemia
  - Psychosocial factors

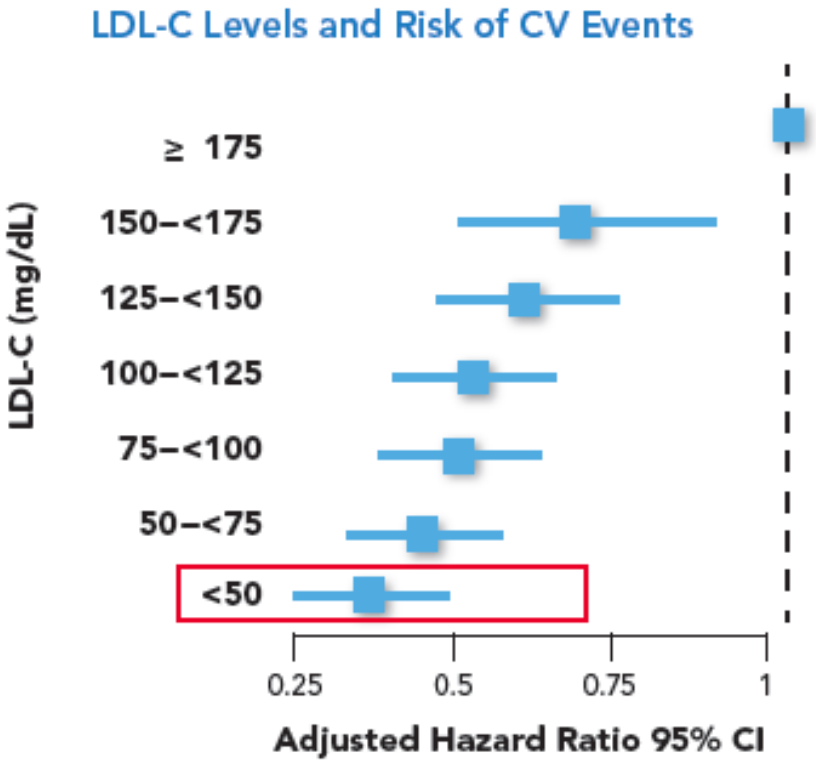
Yusef Lancet. 2004;364:937-952

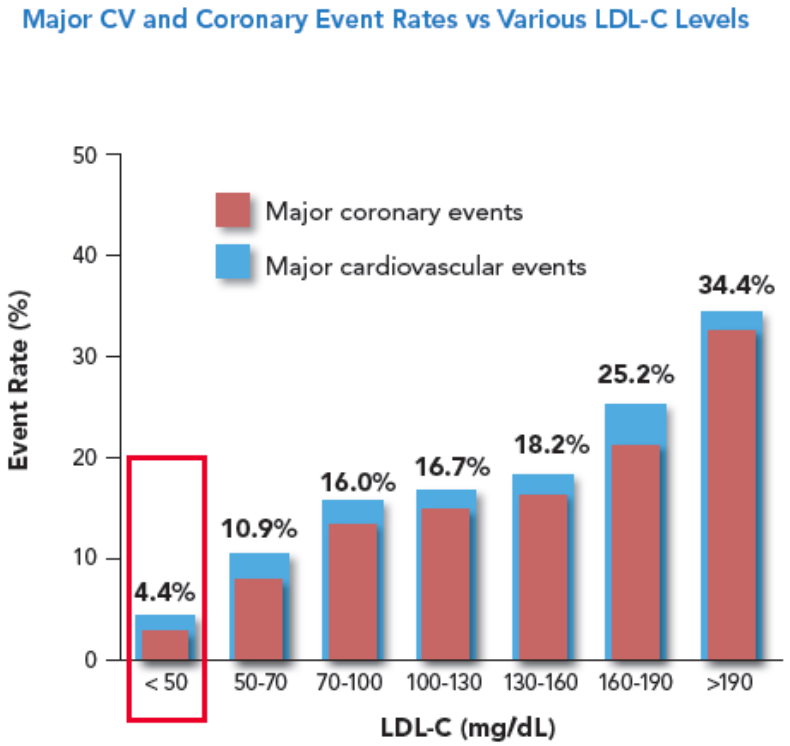
Dyslipidemia

- Dyslipidemia is a major modifiable risk factor for CVD

ASCVD Risk Benefit Groups





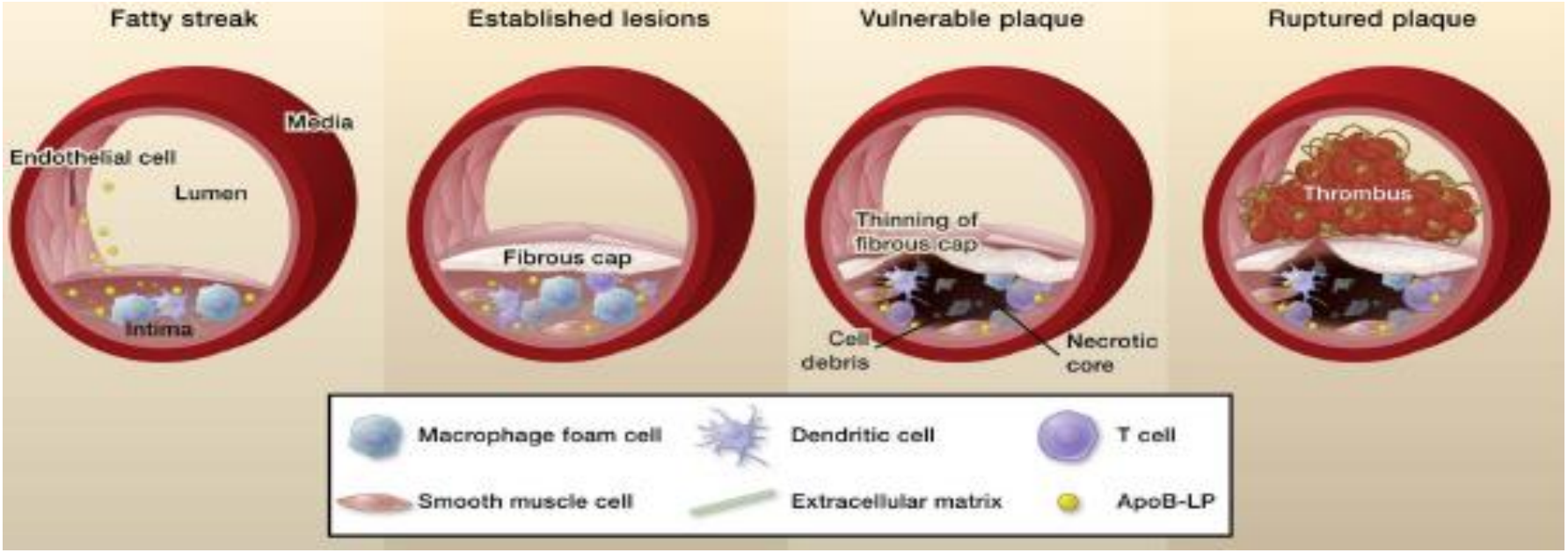


J Am Coll Cardiol 2014;64:485–94)

How Does Dyslipidemia Cause Coronary Artery Disease?

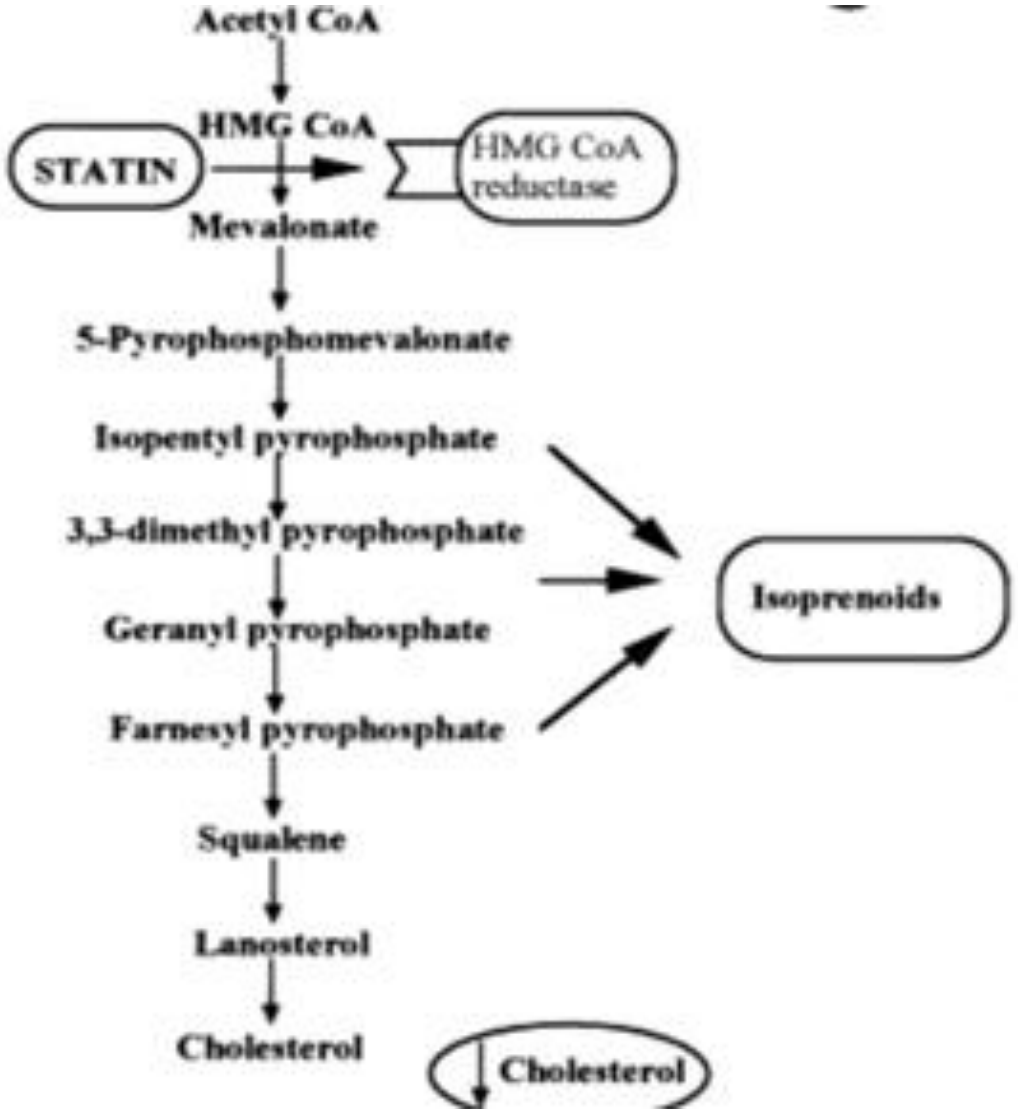
- Complex interplay between lipids and the endothelium of the vasculature

Progression of Atherothrombotic Vascular Events



Moore KJ, Tobas I, Cell April 29 2011; 145(3):341-355

How do statins work?



J Am Coll Cardiol. 2000;35(1):1-10. doi:10.1016/S0735-1097(99)00525-2

- Statins reduce MI and CVD mortality by 25-40% in the secondary prevention population and MI/CVA risk by similar numbers in the primary prevention population
- Statins should NOT be used in pregnancy and lactation

Statin intolerance

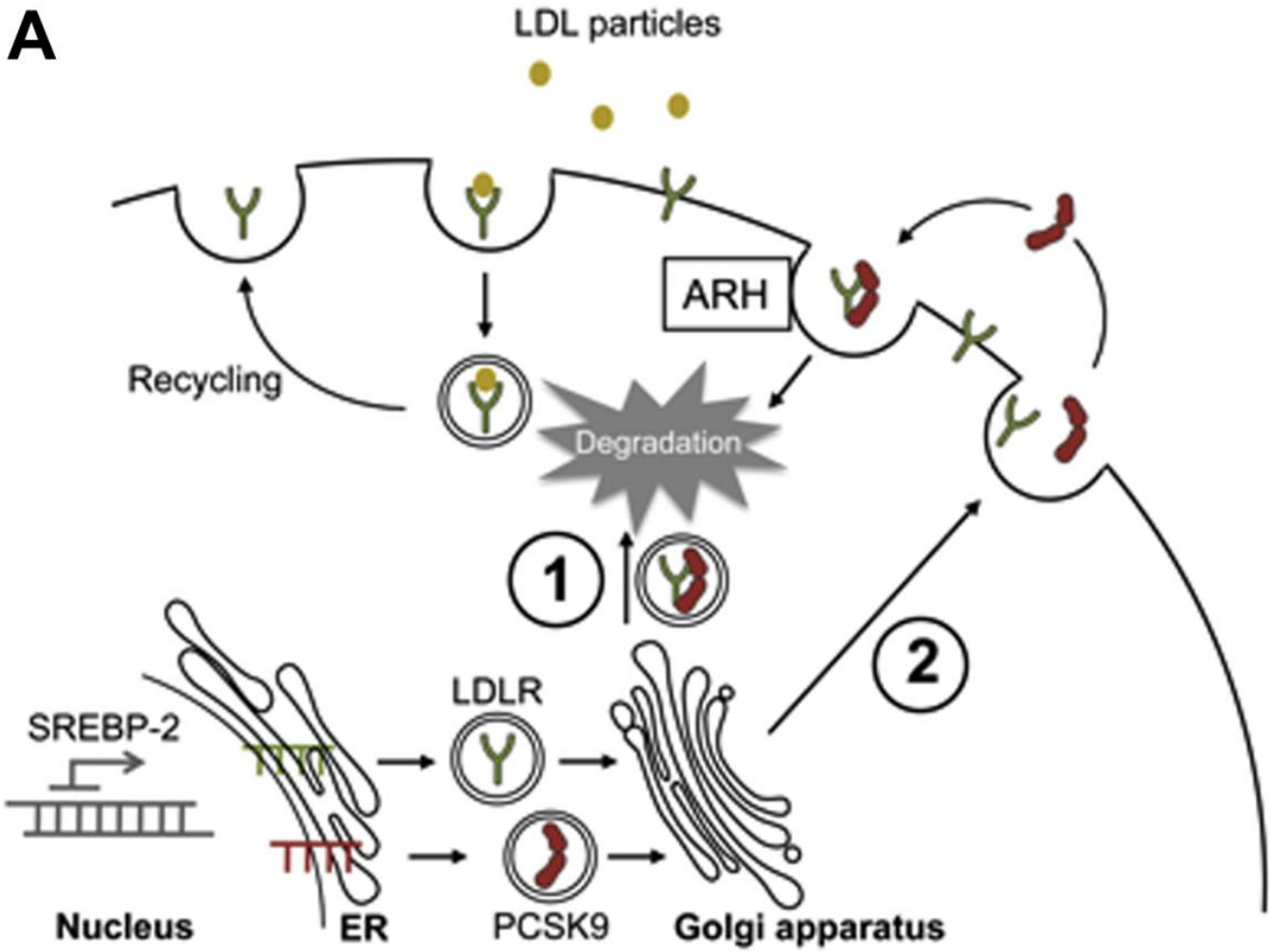
- Statin intolerance is a clinical syndrome characterized by:
- •The inability to tolerate at least 2 statins: one statin at the lowest starting daily dose AND another statin at any daily dose,
- •due to either objectionable symptoms (real or perceived) or abnormal lab determinations
- •which are temporally related to statin treatment and reversible upon statin discontinuation, but reproducible by re-challenge

- •with other known determinants being excluded*
- *such as hypothyroidism, interacting drugs, concurrent illnesses, significant changes in physical activity or exercise, or underlying muscle disease

Guyton JR et al. J Clin Lipid 2014 8: S72-S81

PCSK9 inhibitors

- Two major companies- Amgen and Sanofi/Regeneron



J Am Coll Cardiol. 2013;62(16):1401-1408. doi:10.1016/j.jacc.2013.07.056

Dramatic Reductions in LDL

- They lower LDL cholesterol by dramatic levels, down 50% to 70% reductions of LDL cholesterol, and this effect lasts for 2 to 4 weeks of treatment.
- Ongoing Phase III clinical trials
- Outcome trial in progress

Familial Hypercholesterolemias (FH)

- Group of genetic conditions resulting in severe elevations of blood cholesterol levels
- FH is among the most commonly occurring genetic metabolic disorders
- The heterozygous form occurs in approximately 1 in 330-500 people in many populations (estimated current US prevalence is 620,000)
- Homozygous form is quite rare, occurring in approximately 1/1 million individuals

- Total cholesterol in heterozygous FH patients (genetic defect inherited from one parent) are typically in the range of 300 to 550 mg/dL (but sometimes lower)
- In homozygous FH (genetic defects inherited from both parents), range from 650 to 1000 mg/dL
- Hypercholesterolemia is present from childhood, leading to early development of coronary heart disease
- The risk of premature coronary heart disease is elevated about 20-fold in untreated FH patients
- FH is underdiagnosed and undertreated

- Suspect FH when fasting LDL in adults > 20 years is $\geq$ 190 (mg/dL) or non-HDL $\geq$ 220 mg/dL
- In those < 20 years, suspect FH when LDL-C $\geq$ 160 mg/dL or non-HDL $\geq$ 190 mg/dL

Treatment of FH

- Individuals with FH have a very high lifetime risk of coronary heart disease and are at very high risk of premature coronary heart disease
- Early treatment is highly beneficial. Long-term drug therapy of patients with FH can substantially reduce or remove the excess lifetime risk of coronary heart disease due to the genetic disorder and can lower coronary heart disease event rates in FH patients to levels similar of those in the general population

- FH requires lifelong treatment and regular follow up
- Both children and adults with LDL-C ≥190 mg/dL (or non-HDL ≥ 220 mg/dL) after lifestyle changes will require drug therapy.
- For adult FH patients (≥ 20 years of age), drug treatment to achieve an LDL-C reduction of ≥ 50% should be initiated.
- Statins should be the initial treatment for all adults with FH

- For adult FH patients, initial treatment is the use of moderate to high doses of high potency statins (rosuvastatin, atorvastatin). Low potency statins are generally inadequate for FH patients
- For patients who cannot use a statin, most will require combination therapy (ezetimibe, niacin, bile acid sequestrants)
- Intensify drug treatment in higher risk patients (diabetes, current smoking, clinically evident coronary heart disease, a FH of early coronary heart disease, high lipoprotein (a)).

Homozygous FH

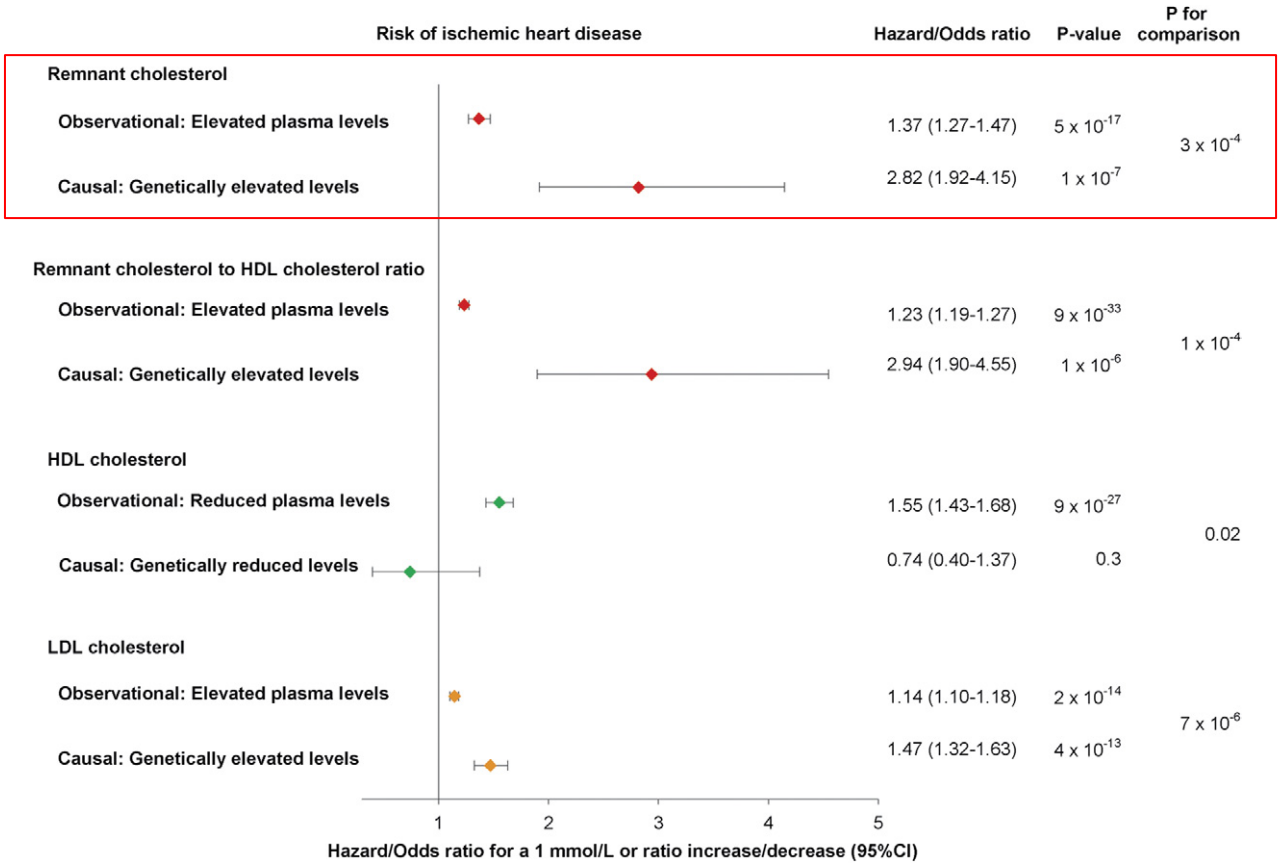
- Lomitapide (oral microsomal triglyceride transfer protein inhibitor) approved for the treatment of patients with homozygous FH. MTP plays a role in the assembly and secretion of triglyceride-rich apolipoprotein B-containing lipoproteins
- Mipomersen is a second-generation antisense oligonucleotide that inhibits production of apolipoprotein B. Given as a weekly injection, it lowers LDL-C levels in humans and is approved for use in patients with homozygous FH

LDL-Apheresis

- LDL-apheresis is a US FDA-approved medical therapy for FH patients who are not at their LDL-C treatment goal or who have ongoing symptomatic disease
- LDL apheresis is done weekly or biweekly and lowers LDL-C levels by up to 80% acutely and 30% chronically.

Residual risk

New Data Demonstrating that VLDL-c (remnant cholesterol) is associated with a two-fold greater risk than LDL-c



Varbo et al. Journal of the American College of Cardiology 2013

Management of High TG

- Limited data on who to treat
- Mild to moderate hyperTG (150-500, even up to 1000), main indication for therapy is reduction of CVD risk
  - Lifestyle
  - Statins – not most effective at lowering TG, most effective agents at lowering CVD risk
  - No trial of statins has looked specifically at patients with normal LDL and elevated TG.

Reduce TG, reduce CVD risk?

- Uncertain whether pharmacologic therapy targeted at reducing TG levels will reduce CVD risk.
- Several trials raise the possibility that pharmacologic treatment targeting TG will provide benefit
  - Helsinki Heart Study, CVD risk was highest in the cohort with a TG > 201 and an LDL/HDL > 5.0; a benefit from gemfibrozil was confined to this high risk group[1]

1. Manninen Circulation. 1992;85(1):37.

- VA-HIT- assessed efficacy of gemfibrozil in patients with low HDL (<40), relatively low LDL (<140) and TG levels <300. Gemfibrozil raised HDL by 6%, lowered TG by 31%, and had no significant effect on LDL. At five years, there was an absolute risk reduction of 4.4% in nonfatal MI or death from coronary cause, more than could be explained by the increase in HDL[1]
- ACCORD Lipid – fenofibrate showed no overall benefit when added to a statin in patients with DM2, but did improve outcomes in a subset of patients with both elevated TG (>204) and low HDL[2]
- Similar suggestions of benefit in such subgroups in the FIELD trial [3] and the Bezafibrate Infarction Prevention trial[4]

1. Rubins HB, N Engl J Med. 1999;341(6):410.
2. ACCORD Study Group, N Engl J Med. 2010;362(17):1563.
3. Keech A Lancet. 2005;366(9500):1849
4. Bezafibrate Infarction Prevention (BIP) study Circulation. 2000;102(1):21.

Do patients with elevated TG at baseline benefit from pharmocologic monotherapy?

- In statin trials, subgoups with high TG had higher risk in 4S, the CARE trial, WOSCOPS, AFCAPS-TEXCAPS and TNT and to have greater CVD risk reduction with lipid therapy in 4S and CARE.
- But CVD risk reduction similar across TG levels in LIPID, HPS and WOSCOPS and actually worse in patients with metabolic syndrome in the Anglo-Scandinavian Cardiac Outcome Trial.
- Thus, in patients with hyperTG, statin therapy may be beneficial in the setting of an LDL level that merits treatment.

Triglycerides and Cardiovascular Disease:
A Scientific Statement from the American Heart Association; Circulation 2011

- Statins benefit regardless of TG level, however fibrates more commonly show more benefit in those with high TG
- These high CVD risk subgroups benefited in Helsinki Heart Study, Bezafibrate trial and FIELD. In VA-HIT, fibrates reduced CVD risk across all categories of baseline TG
- The ACCORD trial (negative overall in the addition of fibrate to statin) did show benefit in the subgroup with elevated TG > 204 and low HDL
- Therefore, the aggregate data suggest that statin or fibrate may be beneficial in patients with high TG levels, low HDL or both

Is a high TG level in individuals receiving pharmacologic monotherapy associated with increased CVD risk?

- In LIPID, each 89 mg decrease in TG in on treatment patients with pravastatin significantly decreased CVD risk by 11%
- In PROVE-IT TIMI 22, achieving TG < 150 was associated with a 27% decrease in CVD risk
- Post hoc analysis of combined data from IDEAL and TNT, CVD risk was 30% higher when ontreatment TG> 150 and 63% higher in patients in the top quintile of high TG than those in the lowest
- However, after adjusting for HDL, ratio of apoB/apoA1, baseline glucose, BMI, HTN, T2DM and smoking eliminated the association.
- **Thus high risk statin treated patients who continue to have elevated TG levels display an increased risk for CVD but these patients also have other metabolic abnormalities and adjustment for measures of these associated abnormalities such as non-HDL and apoB decreases the predictive effect of TG.**

Do patients with elevated TG levels while undergoing statin therapy receive additional CVD risk reduction by the addition of a second drug that targets TG or TRL?

- Subgroup analysis in the JELIS trial which patients received EPA vs placebo on top of a statin, indicated those with TG > 150 had high CVD risk and those combination therapy with a statin plus EPA in this high risk subgroup reduced CVD risk by 53% compared with statin monotherapy. This was despite the fact that the dose of EPA was 1.8 g/d which translated into minimal TG reduction (5% between groups)
- Therefore the benefit in JELIS was not a TG mediated effect

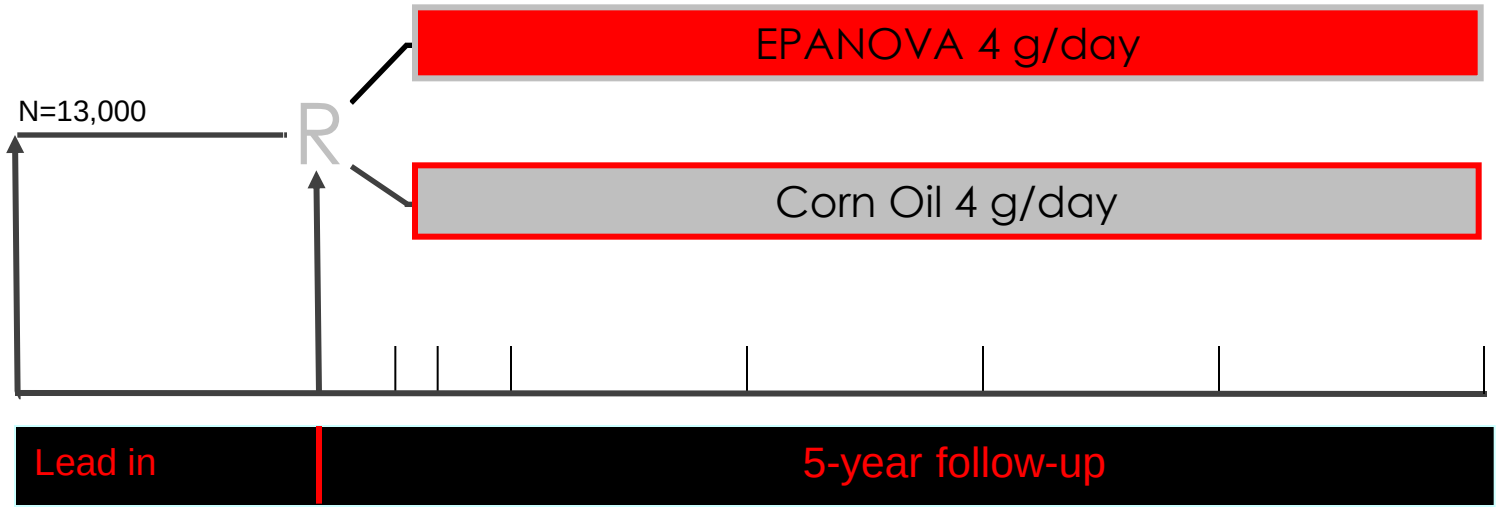
- Trials that used statin plus niacin combination therapy have shown a reduction in coronary arteriographic progression and regression as well as a reduction in CIMT
- Reduction in CVD outcomes were observed in several of these studies although the event rates were low, a statin placebo group was not used and the studies were not powered nor prespecified to address CVD outcomes
- Limited data on the addition of a second drug to a statin; ACCORD did not show an overall benefit to the addition of a fibrate to a statin, although there was benefit in a subgroup of high TG, low HDL
- Stage set for AIM-HIGH and HPS2-THRIVE

No Trials Done To Lower TG

- There are no prospective trials results proving that decreasing TG prevents atherosclerosis or improves outcomes.
- No trial requiring hyper-TG as part of the entry criteria and specifically addressing whether a TG-decrease intervention compared to placebo reduces CV events. All we have to date are post-hoc subset analyses of CV outcomes trials that did not require elevated TG at baseline.
- **There has never been a statin trial that addressed whether reduction of TG provided additional benefit**

A Long-Term Outcomes Study to Assess STatin Residual risk reduction with EpaNova in hiGh cardiovascular risk patienTs with Hypertriglyceridemia (STRENGTH)

Patients with TG 200-500 mg/dL and HDL-c < 40mg/dl at high risk for CVD.



Impact of Running

- 55, 137 adults in the Cooper Clinic in Texas
- Participants followed for 15 years
- Running was assessed by physical activity questionnaire
- Interestingly, runners had lower all-cause and CVD mortality (30% and 45% lower risk) with a 3-year life expectancy benefit.
- In addition, even running at slower speeds , at lower "doses," defined as < 51 minutes, < 6 miles, 1 to 2 times, < 6 miles/hour, was associated with significant and similar benefit.
- Persistent runners over an average of 5.9 years had the most significant mortality benefit with 29% and 50% lower risk of all-cause and CVD mortality.

Lee, Pate et al. 2014

Impact of a healthy lifestyle

- Healthy lifestyle is associated with decreased risk for incident coronary heart disease in young women followed from 1991 to 2011 in the Nurse's Health Study.
- 88,940 women were followed from 1991 to 2011.
- Six factors were considered to define optimal lifestyle (no smoking, healthy diet, 2.5 hours a week physical activity, < 7 hours/ week television watching, healthy BMI and moderate alcohol intake).
- Women who engaged in all 6 healthy lifestyle choices had a 92% lower risk for coronary heart disease and a 66% lower risk for a clinical cardiovascular risk factor (diabetes, hypertension or hypercholesterolemia).

(Chomistek, Chiuve et al. 2015

Hot off the press!

Wonkblog

The U.S. government is poised to withdraw longstanding warnings about cholesterol

819

Dietary Guidelines Advisory Committee

By Peter Whoriskey February 10 Follow @PeterWhoriskey

Conclusions

- 90% of MI's globally can be explained by nine risk factors
- LDL is causally linked to CVD
- PCSK9 inhibitors
- Familial hypercholesterolemia
- Statins
- 2013 ACC/AHA guidelines
- Residual risk- elevated non-HDL, high TG
- Lifestyle or medications for residual risk?

Severe hypertriglyceridemia

- TG > 1000
- TG carried in chylomicrons and large VLDL- statins less effective at reduction
- Fibrates and/or fish oil preferable
- Higher risk patients with CVD and very high TG→statin and fibrate or fish oil
- Lower risk patients with very high TG→evidence is less clear; combination therapy versus statin alone

AIM-HIGH

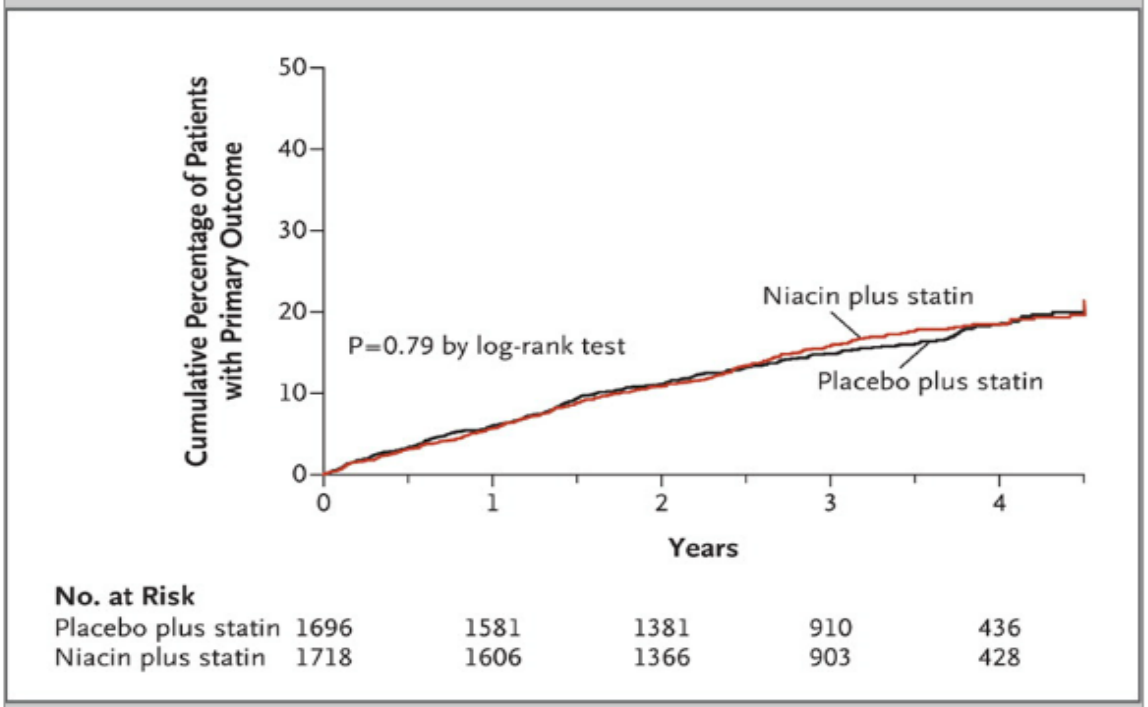
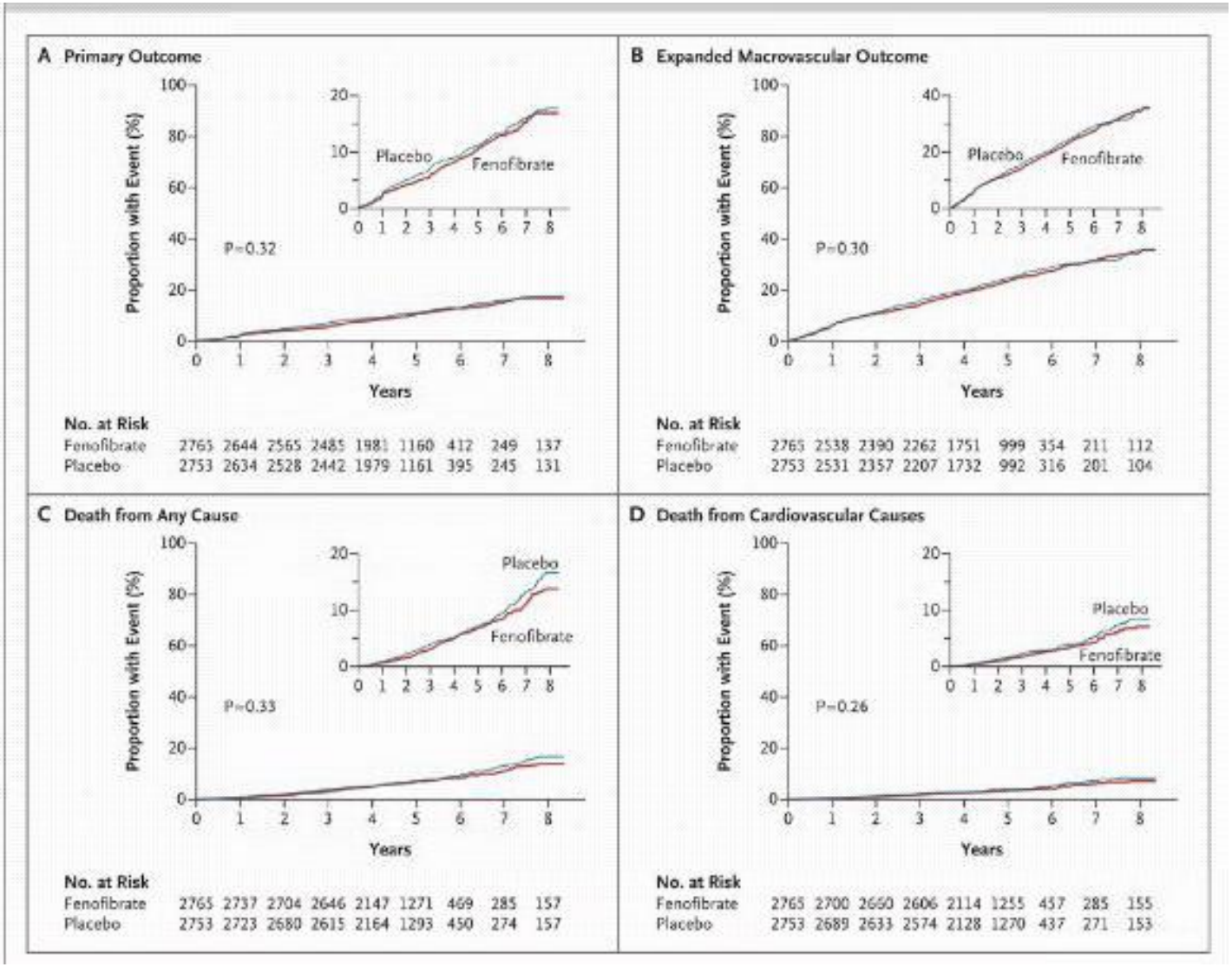


Figure 1. Kaplan–Meier Curve for the Primary End Point.

AIM-HIGH Investigators, NEJM 2011 Dec 15; 365(24):2255-67

ACCORD- LIPID



The ACCORD Study Group N Engl J Med 2010; 362:1563-1574

The NEW ENGLAND JOURNAL of MEDICINE

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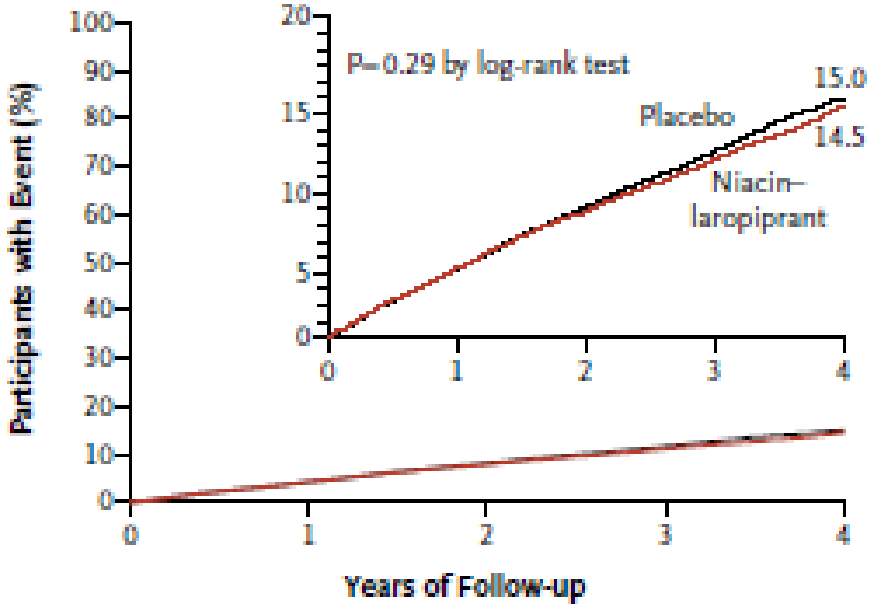
HPS2-THRIVE



No. at Risk					
Niacin–laropiprant	12,838	12,232	11,517	7672	4978
Placebo	12,835	12,247	11,523	7643	5036
Benefit per 1000 participants assigned to niacin–laropiprant		0±3	3±3	5±5	5±7

The HPS2-THRIVE Collaborative Group **N Engl J Med 2014;371:203-12.**

Outcome Data on Non-statins

Drug	Results
Cholestyramine	• Effective in primary prevention (Lipid Research Clinics 1984) and secondary prevention in men (Watts 1992)
Colestipol	• Significantly reduces cardiovascular events compared to placebo (Insull 2006)
Ezetimibe	• No cardiac outcomes data and ezetimibe did not cause regression of carotid intima-media thickness (surrogate marker) when added to a statin (Kastelein 2008, Taylor 2009)

Fenofibrate	• In type 2 diabetics, did not reduce primary outcome of fatal MI or CHD mortality. Improved secondary outcomes of non-fatal MI and coronary revascularization, a reduction in albuminuria, reduced laser treatments for retinopathy (FIELD 2005) • Added on to statin, did not lower risk of non-fatal MI, non-fatal stroke, or CV death, more than statin alone in patients with type 2 diabetes at high risk for CV disease. May be a subgroup (high TG, low HDL) that benefits (ACCORD 2010)
Gemfibrozil	• Effective in primary prevention in men (Helsinki Heart Study 1987) and in secondary prevention in men with low HDL (VA-HIT 1999)

Niacin	• Effective in secondary prevention (Coronary Drug Project 1975) • Niacin and simvastatin decreased atherosclerosis, coronary death, MI, stroke, or revascularization (HATS 2001) • Added on to statin, niacin decreased CIMT (ARBITER-2 2004, ARBITER-6 HALTS 2009) • In patients with stable CVD and LDL < 70, no benefit to addition of niacin to statin therapy (AIM-HIGH 2011) • In patients with DM, CVD, PAD, the addition of niacin + laropiprant + statin vs statin did not reduce MI or CV death and increased side effects (HPS2-THRIVE)
Omega-3 fatty acids	• Effective in secondary prevention (GISSI-Prevenzione 2002); however, recent meta-analysis did not show that omega-3 fatty acids reduce cardiovascular events or mortality (Rizos 2012)

What do the guidelines say in managing hyperTG

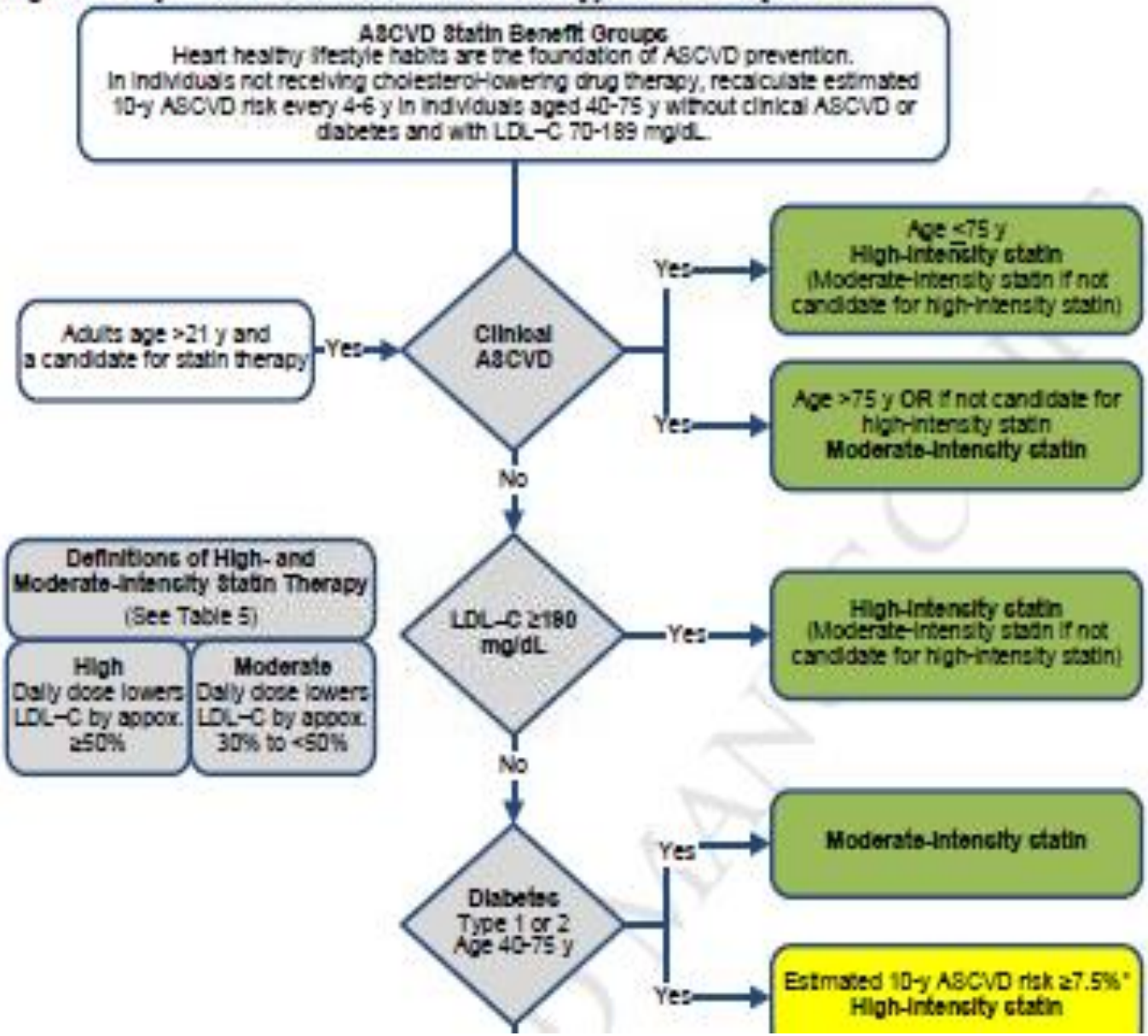
ATP III

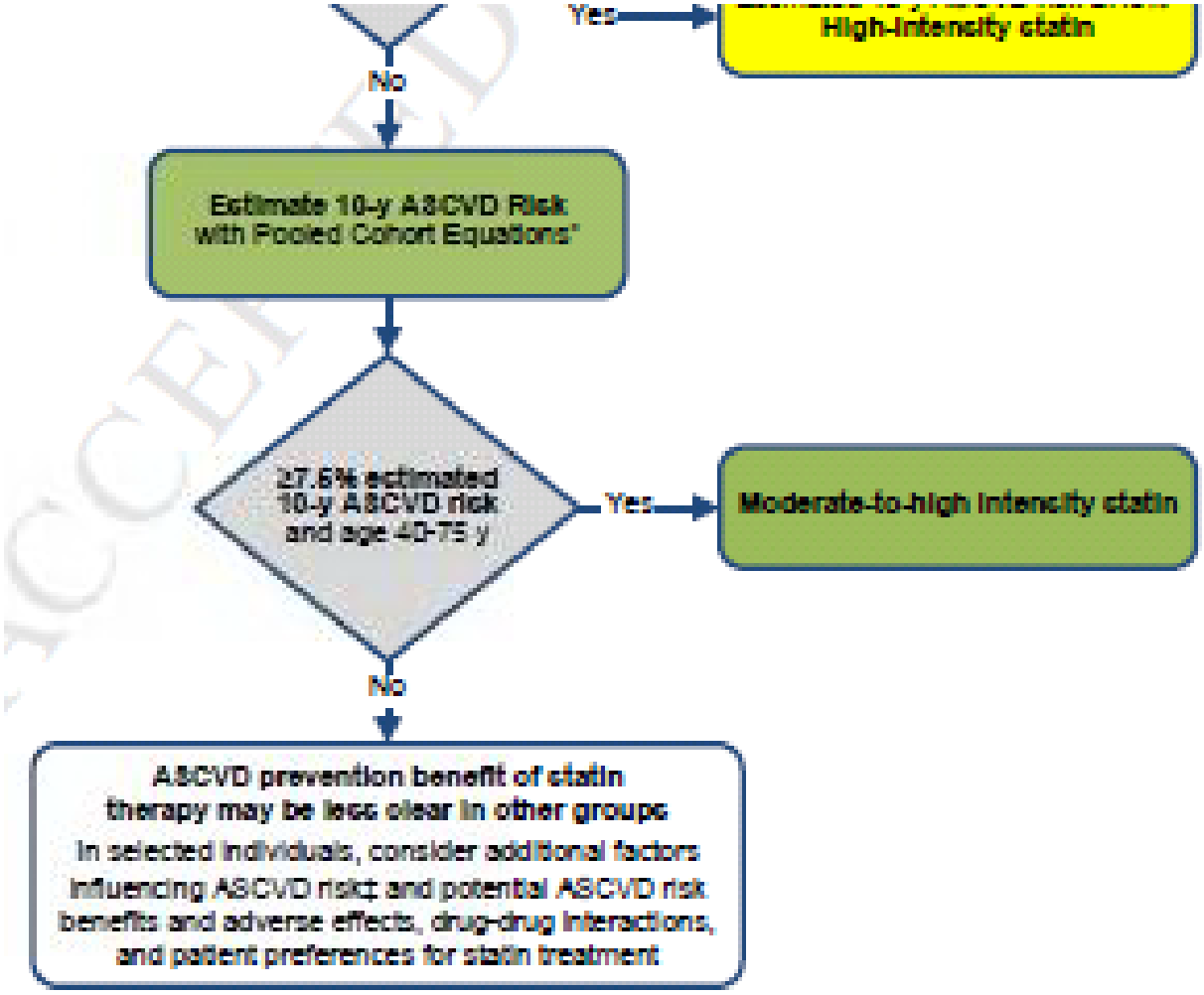
- TG > 500- risk for pancreatitis; primary problem to address.
- Elevated triglycerides are an independent risk factor for CVD.
- Reflects atherogenic potential of triglyceride rich lipoproteins; i.e. VLDL
- Therefore the sum of LDL and VLDL (non-HDL) is a secondary goal of treatment.
- Goal non-HDL is 30 mg/dL higher than LDL goal.
- Management: Diet, weight loss, drug therapy (statins or addition of nicotinic acid or fibrate).

NCEP ATP III

2013 ACC/AHA Blood Cholesterol Guidelines

Figure 2. Major recommendations for statin therapy for ASCVD prevention




Yes
High-intensity statin
No
Estimate 10-y ASCVD Risk
with Pooled Cohort Equations*
≥7.5% estimated
10-y ASCVD risk
and age 40-75 y
Yes
Moderate-to-high intensity statin
No
ASCVD prevention benefit of statin
therapy may be less clear in other groups
In selected individuals, consider additional factors
influencing ASCVD risk‡ and potential ASCVD risk
benefits and adverse effects, drug-drug interactions,
and patient preferences for statin treatment

NLA Lipid Guidelines- Draft

- A drug targeting triglyceride reduction should be considered for first-line therapy in those with triglycerides ≥500 mg/dL.
  - Triglyceride lowering drug therapies include fibrates, high-dose omega-3 fatty acids and nicotinic acid
  - A statin may be a reasonable first-line agent if the triglyceride concentration is ≥500 mg/dL but <1000 mg/dL, if no history of pancreatitis
- When used, drug therapy should be adequate to attain levels of atherogenic cholesterol (non-HDL-C and LDL-C) that are *below* the goal cut points.

European Guidelines 2012

- Primary goal will be to achieve the LDL target based on the total CV risk
- As compared with the overwhelming evidence for the benefits of LDL reduction, the evidence on the benefits of lowering elevated TG levels is modest.
- Lifestyle improves TG. Weight reduction, regular physical activity, can reduce TG by 20-30%, mandatory for all patients with obesity, metabolic syndrome, DM2
- Although the CVD risk is increased if fasting TG are > 150 , the use of drugs to lower TG should only be considered in subjects with **TG > 200** who cannot lower them by lifestyle measures and if the subject is at high total CV risk
- The available pharmacologic interventions include statins, fibrates, nicotinic acid, and n-3 PUFAs.
- As statins have significant effects on mortality as well as most CVD outcome parameters, these drugs are the first choice to reduce both total CVD risk and moderately elevated TG levels

Nonpharmacologic therapy

- Weight loss in obese patients
- Aerobic exercise
- Avoidance of concentrated sugars
- Avoidance of medications that raise TG
- Strict glycemic control in diabetics

Dietary management of high TG

- Mild to moderate high TG
  - Chylomicrons originate from dietary fat; VLDL from TG from the liver
  - Usually chylomicrons deliver their TG load to periphery quickly and moderate TG elevation from high VLDL
  - VLDL from lypolysis (augmented by obesity, diabetes, insulin resistance) and de novo synthesis of fatty acids and TG in the liver from **carbohydrates**
  - Focus of diet should be reduction in total intake and reduction in carbohydrates; also moderate exercise

- Moderate to severe high TG (TG above 500 or 1000), clearance of chylomicrons slow, such that chylomicrons are still present from last night's meal
- **Crucial to restrict dietary fat**
- Diet aimed at weight loss should be avoided in patients with severe high TG, because when weight loss diet ends and refeeding begins, patients likely to develop very high TG and resultant risk of pancreatitis.

Table 2: Lipid-Lowering Therapies

Medication	Mechanism of Action	Cholesterol effects	Side effects
HMG-CoA reductase inhibitors	Inhibit HMG-CoA reductase	↓ LDL 30-63% ↑ HDL 5% ↓ TG 20-40%	Hepatic dysfunction Myopathy
Bile acid resins	Interrupt enterohepatic circulation, increasing bile acid production, which increases LDL clearance, and decreases plasma LDL levels	↓ LDL 28% ↑ HDL 4-5% Can ↑ TG	Constipation Diarrhea Gas Impairment of fat soluble vitamins
Ezetimibe	Cholesterol absorption inhibitor	↓ LDL 18% ↑ HDL 1% ↓ TG 2%	
Fibrates	Activate PPAR-alpha 1) increases LPL activity, thereby increasing TG catabolism in VLDL and chylomicrons) 2) Increases HDL 3) Decreased VLDL 4) Decrease Apo CIII	↓ TG 20-70% ↑ or ↓ LDL (in hypertriglyceridemic patients, can ↑ LDL)	GI upset Can interact with statins to ↑ risk of rhabdomyolysis
Niacin	1) Decrease free fatty acid mobilization, leading to a decrease in VLDL 2) Decrease Apo B production 3) Increase HDL	↓ LDL up to 40% ↓ TG 20-25% ↑ HDL 25-50%	Flushing Hepatotoxicity
Omega-3 Fatty acids		↓ TG ↑ LDL in hypertriglyceridemic patients	

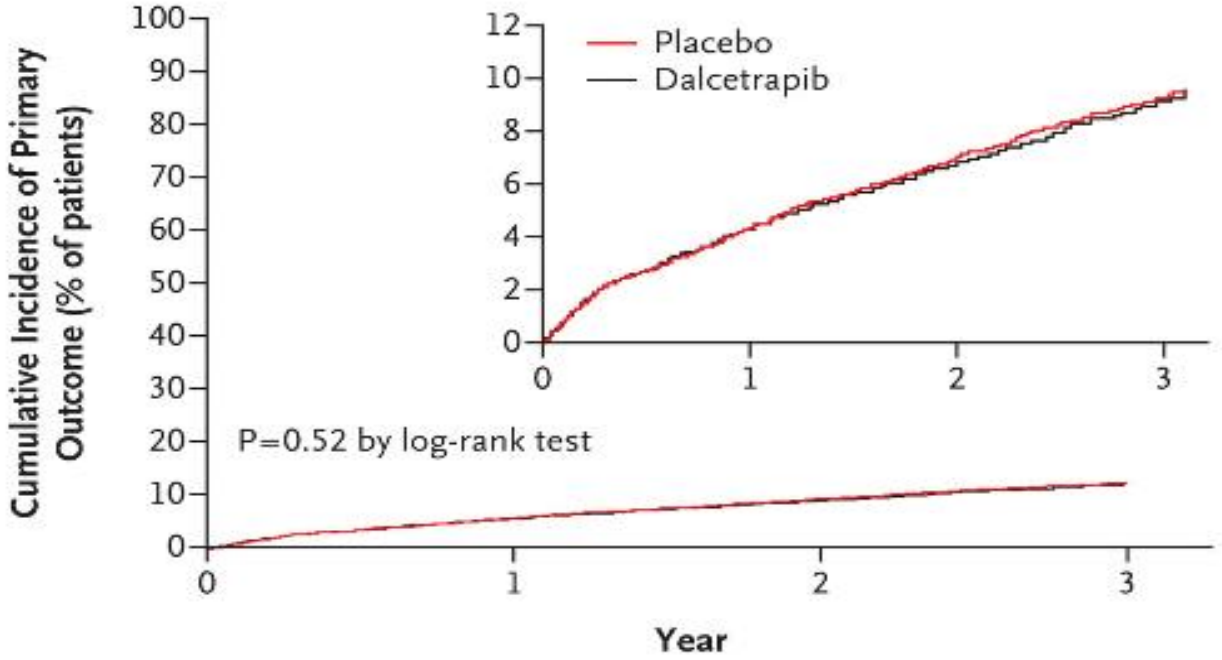
Effect of Lipid-Lowering Therapies on Triglyceride Reduction

Drug	% Triglyceride Reduction
Fibrates	30-50
Immediate-release niacin	20-50
Omega-3	20-50
Extended-release niacin	10-30
Statins	10-30
Ezetimibe	5-10

HDL

- Ideal levels of HDL higher in women than men (50 vs. 40)
- Low HDL related to the presence of CVD
- Causal relationship between low HDL and CVD not established
- It has not been proven that raising HDL is of benefit in reducing CVD risk
- Assaying the cholesterol content of HDL (HDL-C) may fail to adequately measure its protective effects.

dal-OUTCOMES



No. at Risk				
Placebo	7933	7386	6551	1743
Dalcetrapib	7938	7372	6495	1736

Schwartz GG et al; for dal-OUTCOMES Investigators. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *NEJM*. 2012;367:2089-2099.