IHD, Dyslipidemia, and CVD risk assessment

This file was made 1st by Med433 Team
Then, Revised and Updated by Med434 Team

References :
Doctor's slides and notes
AHA , ACC

Anything started by The Green color ,from med434

Before starting :

How to convert mg/dl into mmol?
For LDL and HDL :
Mg/dl **divided by 40**
EX. 140 mg/dl / 40 = 3.5 mmol

For TGs :
Mg/dl **divided by 90**

Objectives

- Cardiovascular disease
- Dyslipidemia and Introduction to new guidelines on lipid management
- Comparison with ATP III guidelines
- Current statin treatment recommendations
- Criticism to AHA/ACC
- Treat to target vs fire and forget

(1CAD

Pathogenesis:

CAD is the narrowing of the coronary artery, decreasing the blood supply to the heart, leading to ischemia of the heart muscle cells.

Etiology:

CAD is mostly due to Atherosclerosis.

Atherosclerosis and thrombosis are the most important pathogenic mechanisms.

Primary prevention of CVD

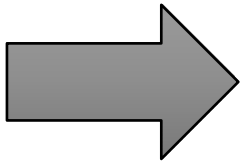
The achievement and maintenance of good health is being emphasized in programs from The American Heart Association that promote seven ideal cardiovascular health metrics, including:

- Not smoking
- Being physically active
- Having a normal blood pressure
- Having a normal blood glucose level
- Having a normal total cholesterol level
- Being normal weight
- Eating a healthy diet

CAD risk factors

Modifiable	Non--Modifiable
• Cigarette and tobacco smoke • High blood cholesterol • High blood pressure • Physical inactivity • Obesity • Diabetes	• Age • Gender • Family history of CVD

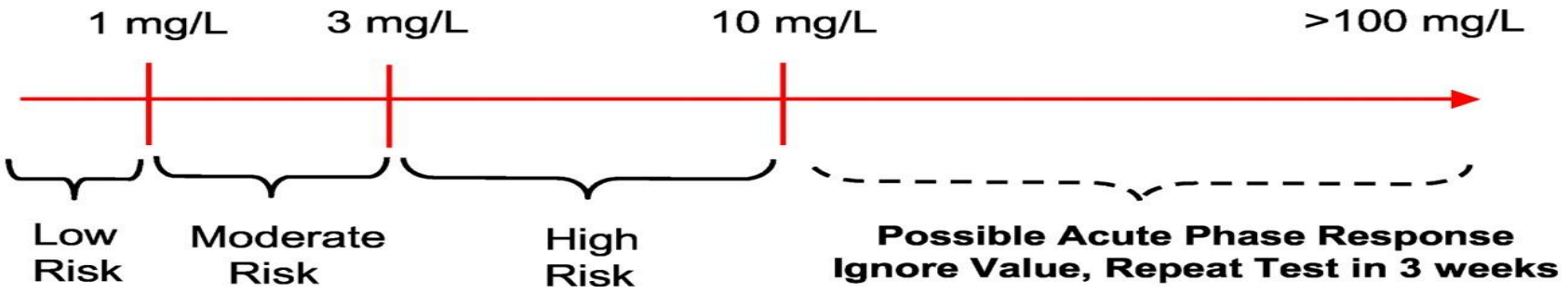
Emerging risk factors for CAD



. Emerging Risk Factors According to ATP 2Table *2004III Final Report Update*
.1Elevated high--sensitivity C--reactive protein
.2Coronary artery calcification
.3Elevated lipoprotein (a(
.4Homocysteine
.5Fibrinogin

C-reactive protein

A person's baseline level of inflammation, as assessed by the plasma concentration of CRP, predicts the long-term risk of a first myocardial infarction.



In pt with chest pain and C reactive protein level is

Between 3 to 10 : →→that indicate the pt is at high risk of develop an attack

If higher than 10 →→that indicate that the pt is having an acute attack

The Framingham risk score

- Scoring system used to calculate a pt's risk of coronary events.
- The Framingham Heart Study first introduced the term risk factor to medical literature.
- The following risk factors are used to assess cumulative risk:

Age Smoking Status

Systolic BP HTN treatment

Total cholesterol levels HDL-C levels

Calculating 10-Year Risk in Women

(Age (years	34-20	69-65	64-60	59-55	54-50	49-45	44-40	39-35	74-70	79-75
Points	7-	12	10	8	6	3	0	3-	16	14

Points

Age 39–20	Total Cholesterol	Age 49-40	Age 59-50	Age 69-60	Age 79-70
0	mg/dL)) 160>	0	0	0	0
4	199–160	3	2	1	1
8	239–200	6	4	2	1
11	279-240	8	5	3	2
13	280 ≤	10	7	4	2

HDL CHOLESTEROL	
mg/dL)) 60 ≤	1-
59–50	0
49–40	1
40 >	2

	Age -20	Age 49-40	Age 59-50	Age 69-60	Age 79-70
0	Nonsmoker	0	0	0	0
9	Smoker	7	4	2	1

Systolic BP	Untx"ed	Tx"ed
<120	0	0
129–120	3	1
139–130	4	4
149–140	5	3
160 ≤	6	4

25≤	24	23	2221	20	19	18	17	16	1514	13	12	11	109	9<	Points total:
30≤	27	2217	14	11	8	6	5	4	3	2	2	1	1	1	1year Risk (%) < 10

Tx"ed =TreatedUntx"ed = Untreated

NCEP/Framingham Estimate of 10-Year Coronary Heart Disease Risk in Men

Age (y):	20-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
Points:	-9	-4	0	3	6	8	10	11	12	13

Points

Total Cholesterol	Age 20-39y	Age 40-49y	Age 50-59y	Age 60-69y	Age 70-79y
<160 (mg/dl)	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
≥280	11	8	5	3	1

HDL Cholesterol	Points
≥60 (mg/dl)	-1
50-59	0
40-49	1
<40	2

Points

	Age 20-39y	Age 40-49y	Age 50-59y	Age 60-69y	Age 70-79y
Nonsmoker:	0	0	0	0	0
Smoker	8	5	3	1	1

Points

Systolic BP	Untx'ed	Tx'ed
<120 mmHg	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

Points Total:	<0	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	>17
10-Year Risk (%):	<1	1	1	1	1	1	2	2	3	4	5	6	8	10	12	16	20	25	≥30

Untx'ed = Untreated Tx'ed = Treated y = Years

Cases in which you don't need FRS؟

Patients who already have a high risk due to other diseases

We don't need FRS if:

- Stroke or TIA
- Bypass surgery or balloon angioplasty
- Type 2 diabetes
- Kidney disease
- Abdominal aortic aneurysm
- Familial hypercholesterolemia
- Peripheral artery disease
- Carotid artery disease

They already have HIGH RISK to develop CHD

. Classification of Patients based on The Framingham Risk Score3Table	
Low risk	< %10coronary heart disease risk at 10 years
Intermediate risk	20%–10risk of coronary event at 10 years
High risk	> %20risk of coronary event at 10 years

Major CAD types

❖❖Stable Angina; due to atheroma

❖❖acute Coronary Syndrome:

Unstable Angina

Myocardial Infarction (STEMI OR NSTEMI(

	STEMI	NSTEMI	Unstable angina
ST	↑	N↓–	N↓–
Troponin I,T	2 ↑ weeks	↑	Normal
CK–MB	3 ↑ days	↑	Normal

Myocardial infarction

Signs & findings

(200(N=63 –1256: 280; 1998. Findings Indicating Myocardial Infarction According to JAMA 4Table	
Negative Signs	Positive Signs
ST–segment elevation	Normal ECG
New Q–wave	Pleuritic, sharp or stabbing chest pain
Chest pain radiating to both the right and left arm simultaneously	Pain reproduced on palpation
Added heart sound “S”3	Positional chest pain
Hypotension	

Treatment of Acute Coronary Syndrome

- Aspirin (proven to prevent recurrent infarction and decreases mortality(
- Clopidogrel
- β–blockers
- ACE inhibitors & ARBs (should be used if there is intolerance of ACE inhibitors(
- Nitroglycerin
- Heparin
- Statins

Care following MI

- Risk factor modification.
- Cessation of smoking.
- Control blood sugar and blood pressure.
- Physical Rehabilitation and exercise
- Long–term medications:

Aspirin , Clopidogrel , β–blockers ,ACE inhibitors ,Aldosterone blockers, Statins

(2Dyslipidemia

- A disorder of lipoprotein metabolism, including lipoprotein overproduction or deficiency.
- May be manifested by elevation of the total cholesterol , (LDL) and the triglyceride concentrations, and a decrease in the (HDL) concentration in the blood.

Types	Chylomicron	VLDL	LDL	HDL
Made by:	small intestines in the fed stat **The ratio of TGs to Cholesterol here is 10:1**	the liver from excess dietary carbohydrate and protein along with the Chylomicron remnant	The Liver "VLDL once it has lost a lot of its TG's"	The Liver and Small Intestine
Absorbed into	the lymph vessels, then into the blood	**The ratio of TGs to Cholesterol here is 5:1**		
Rich in	TGs	TGs	Cholesterol	
Function	transport fats from the intestinal mucosa to the liver	Deliver TGs to body cells	Deliver cholesterol to all body cells	Pick up cholesterol from body cells and take it back to the liver

Apo 48 : means lipoprotein came from intestine
Apo100 : means came from Liver

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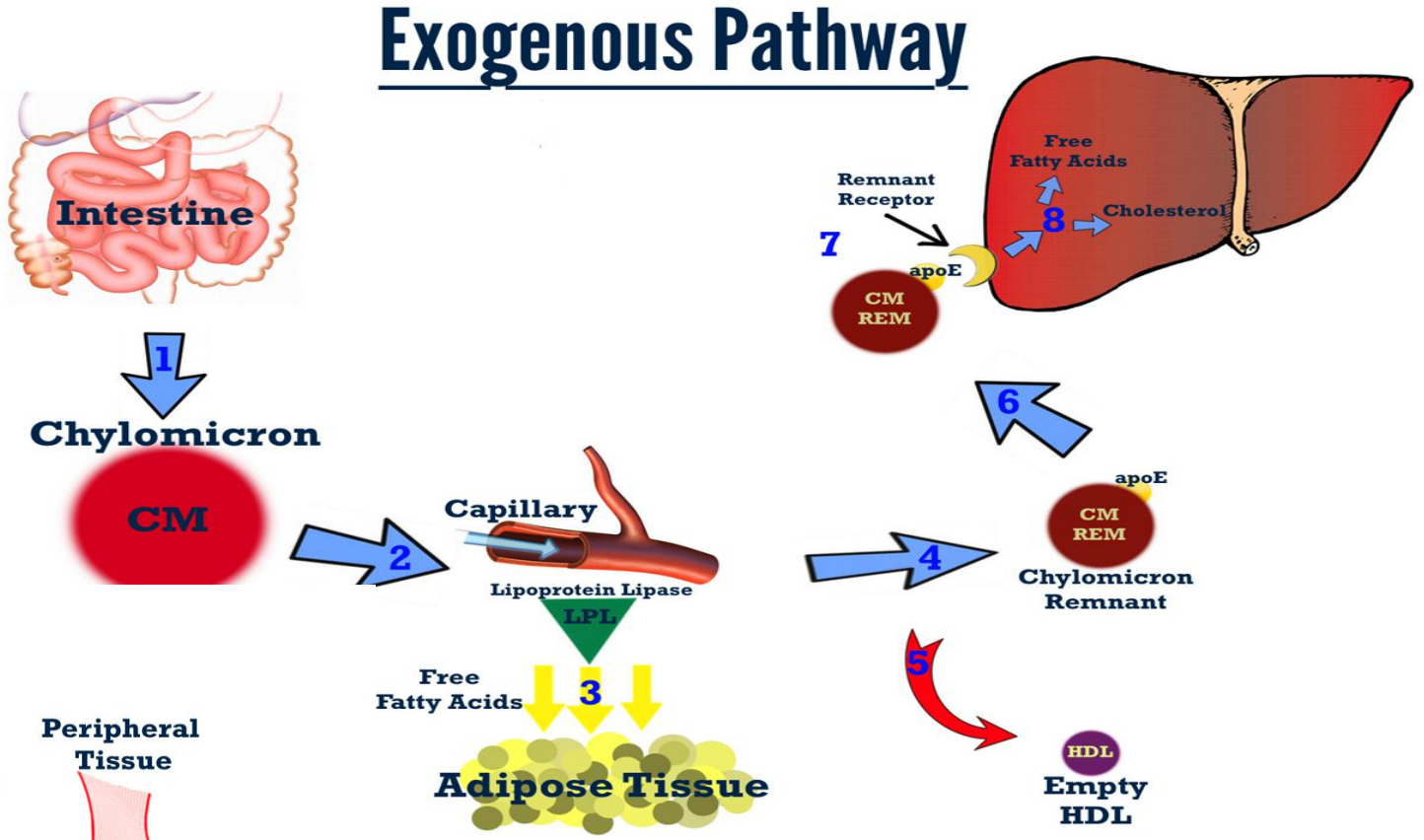
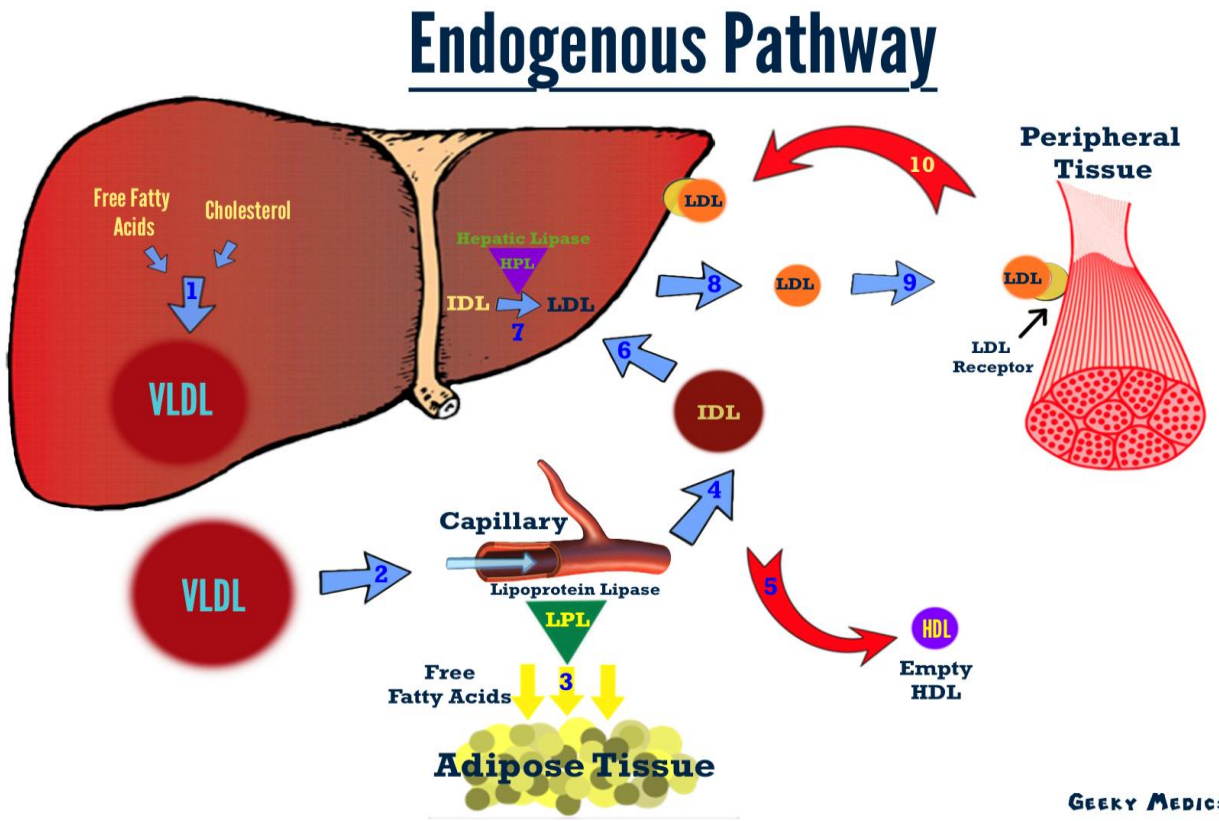
Lipid metabolism : Exogenous >>

Chylomicron go to the peripheral tissue > under the effect of **LPL** > loss TGs " free fatty acids" > converted into **chylo. Remnant** > and go to the Liver .





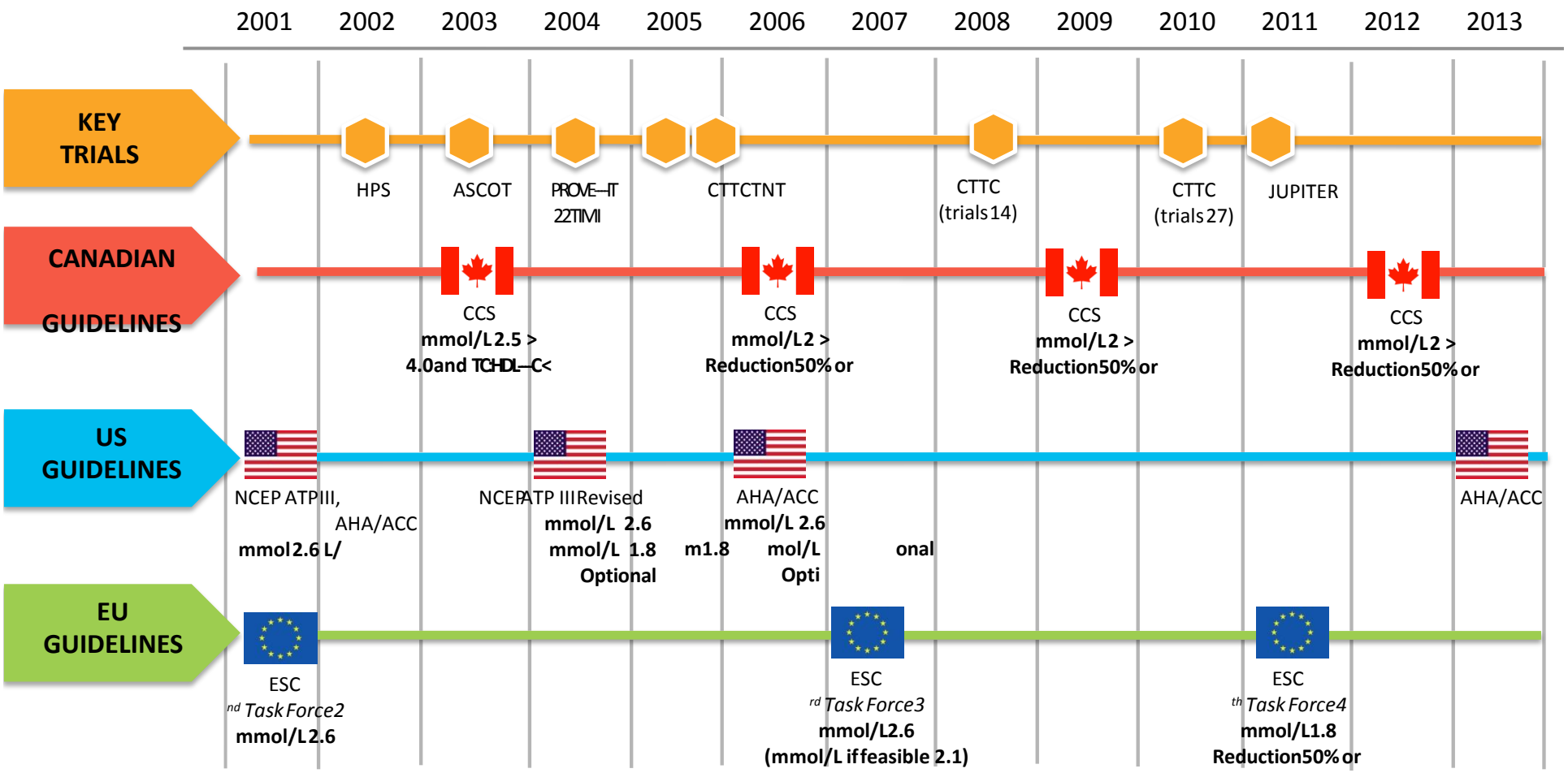
<< Endogenous :

VLDL go to peripheral tissue > under the effect of **LPL** > loss TGs > converted into **IDL** and go to the Liver .

Lipoprotein lipase enzyme LPL:

It works on Chylomicron and VLDL because they have ApoC2 Receptor , **so a deficiency in LPL OR ApoC2 can lead to increase TGs .**

Changes in Lipid Guidelines and Cholesterol Targets



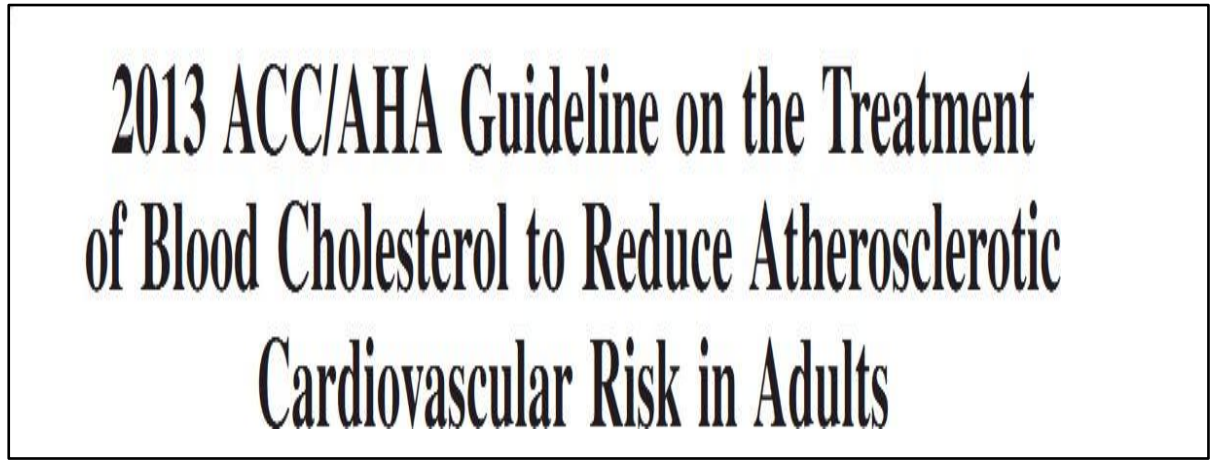
AHA/ACC vs IAS

ACC/AHA 2013“ it also called ATP IIII”	(International Atherosclerosis Society (IAS
• ACC/AHA (evolved from ATP IV/NHLBI efforts.(• Recommendations based on what has been shown to reduce risk in RCTs. • Many areas left to clinical judgment where RCT data were not available or limited. **Fire and forget**	• Apo B--containing lipoproteins is causally associated with ASCVD risk and that lowering “atherogenic cholesterol” (LDL–Cand non–HDL–C) will reduce risk. **Treat to target**

AHA/ACC

Use Critical Questions (CQs) to create the evidence search from which the guideline is developed

1. Cholesterol Panel: 3 CQs
2. Risk Assessment Work Group: 2 CQs
3. Lifestyle Management Work Group: 3 CQs



What has changed compared to ATP3 guideline?

- **No specific LDL cholesterol target**
- Initiate either **moderate--intensity** or **high--intensity statin** therapy for patients who fall into the four categories
- Measure lipids during follow--ups **to assess adherence** to treatment, **not to achieve a specific LDL target**

	ATP-III	AHA/ACC
Basis for recommendations	Expert opinion based on pathophysiology, observational, & RCT data	Evidence--based recommendations based on RCTs and systematic reviews
Risk stratification	CHD equivalents, risk factors, 10–year risk of MI	4specific risk groups based on benefits in clinical trials
Risk calculation	Framingham risk score	Pooled cohort equation
Goals of therapy	LDL & non–HDL levels ((stratified by risk	Statin intensity ((% LDL reduction
Role for monitoring	Fasting lipid panel to assess achievement of goal	Fasting lipid panel to assess adherence/therapeutic response
Role of non–statin agents	Encouraged use if needed to achieve LDL or non–HDL goal	Discourages use in most patients because of lack of evidence on improving outcomes

Table 2. ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dL)

LDL Cholesterol	
<100	Optimal
100-129	Near optimal/above optimal
130-159	Borderline high
160-189	High
≥190	Very high
Total Cholesterol	
<200	Desirable
200-239	Borderline high
≥240	High
HDL Cholesterol	
<40	Low
≥60	High

Table 5: LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories.

Risk Category	LDL Goal	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)	LDL Level at Which to Consider Drug Therapy
CHD or CHD Risk Equivalents (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL: drug optional)*
2+ Risk Factors (10-year risk ≤20%)	<130 mg/dL	≥130 mg/dL	10-year risk 10-20%: ≥130 mg/dL 10-year risk <10%: ≥160 mg/dL
0-1 Risk Factor†	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

* *Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.*

† *Almost all people with 0-1 risk factor have a 10-year risk <10%, thus 10-year risk assessment in people with 0-1 risk factor is not necessary.*

The scope of new the guidelines

- Focus on treatment of blood cholesterol to reduce ASCVD risk in adults.
- Emphasize **adherence to a heart healthy lifestyle as** foundation of ASCVD risk reduction.
- Identify individuals most likely to benefit from cholesterol--lowering therapy **“4 statin benefit groups“**
- Identify safety issues.

ACC/AHA -Why Not Continue to Treat to Target?

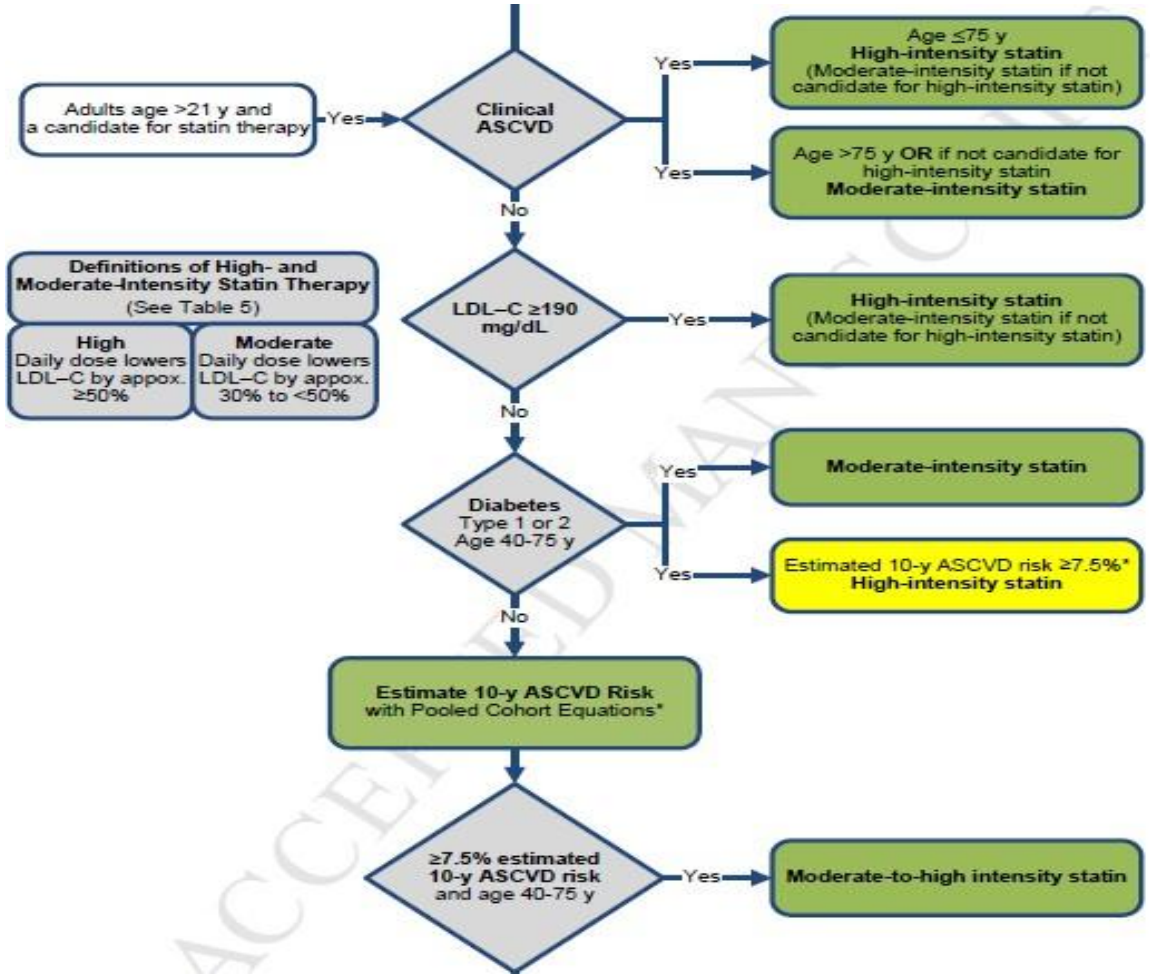
Major difficulties:

- Current RCT data do not indicate what the target should be
- Unknown magnitude of additional ASCVD risk reduction with one target compared to another
- Unknown rate of additional adverse effects from multidrug therapy used to achieve a specific goal

Therefore, unknown net benefit from treat–to–target

4Major Statin Benefit Groups

1. Individuals with clinical ASCVD
2. Individuals with LDL >190
3. Individuals with DM, 40–75yo with LDL 70–189and without clinical ASCVD
4. Individuals without clinical ASCVD or DM with LDL 70–189and estimated 10–year ASCVD risk >7.5%



Don’t Forget Healthy Lifestyle

- Healthy diet
- Regular exercise
- No Smoking
- Maintain healthy weight

2013ACC/AHA/NHLBI Guideline on Lifestyle for CVD Prevention

- Mediterranean or DASH–type diet
- Restrict consumption of saturated fats, trans fats, sweets, sugar--sweetened beverages, and sodium.
- Physical activity of moderate to vigorous intensity lasting 40 minutes per session 3–4times per week

Dosing Statins

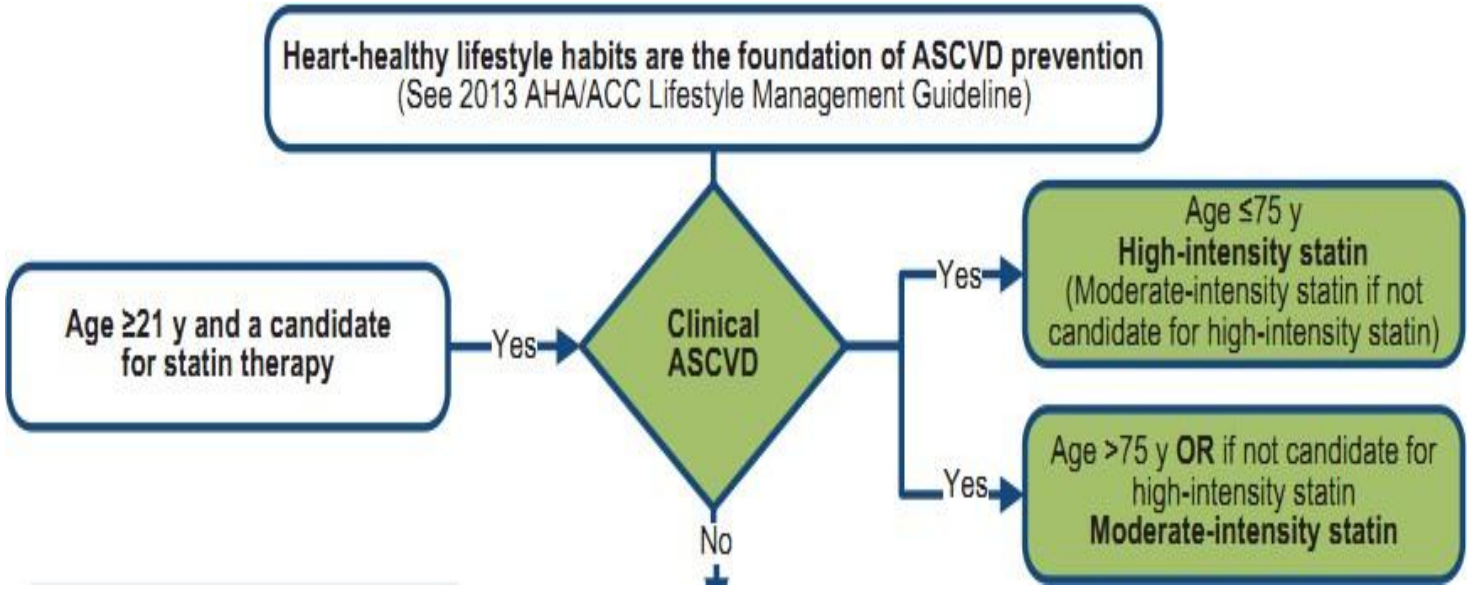
Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)*

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C on average, by approximately ≥50%	Daily dose lowers LDL–C on average, by approximately 30% to <50%	Daily dose lowers LDL–C on average, by <30%
Atorvastatin (40†)–80 mg **Rosuvastatin 20 *(40)* mg**	**Atorvastatin 10 *(20)* mg** **Rosuvastatin (5) 10 mg** **Simvastatin 20–40 mg‡** **Pravastatin 40 *(80)* mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 40 mg bid** *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* **Pravastatin 10–20 mg** **Lovastatin 20 mg** *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

The strongest statin is Rosuvastatin "effect on both LDL and HDL".

The worst statin in drug-drug interaction is Simvastatin " especially at higher dose".

.1 Patients with clinical ASCVD

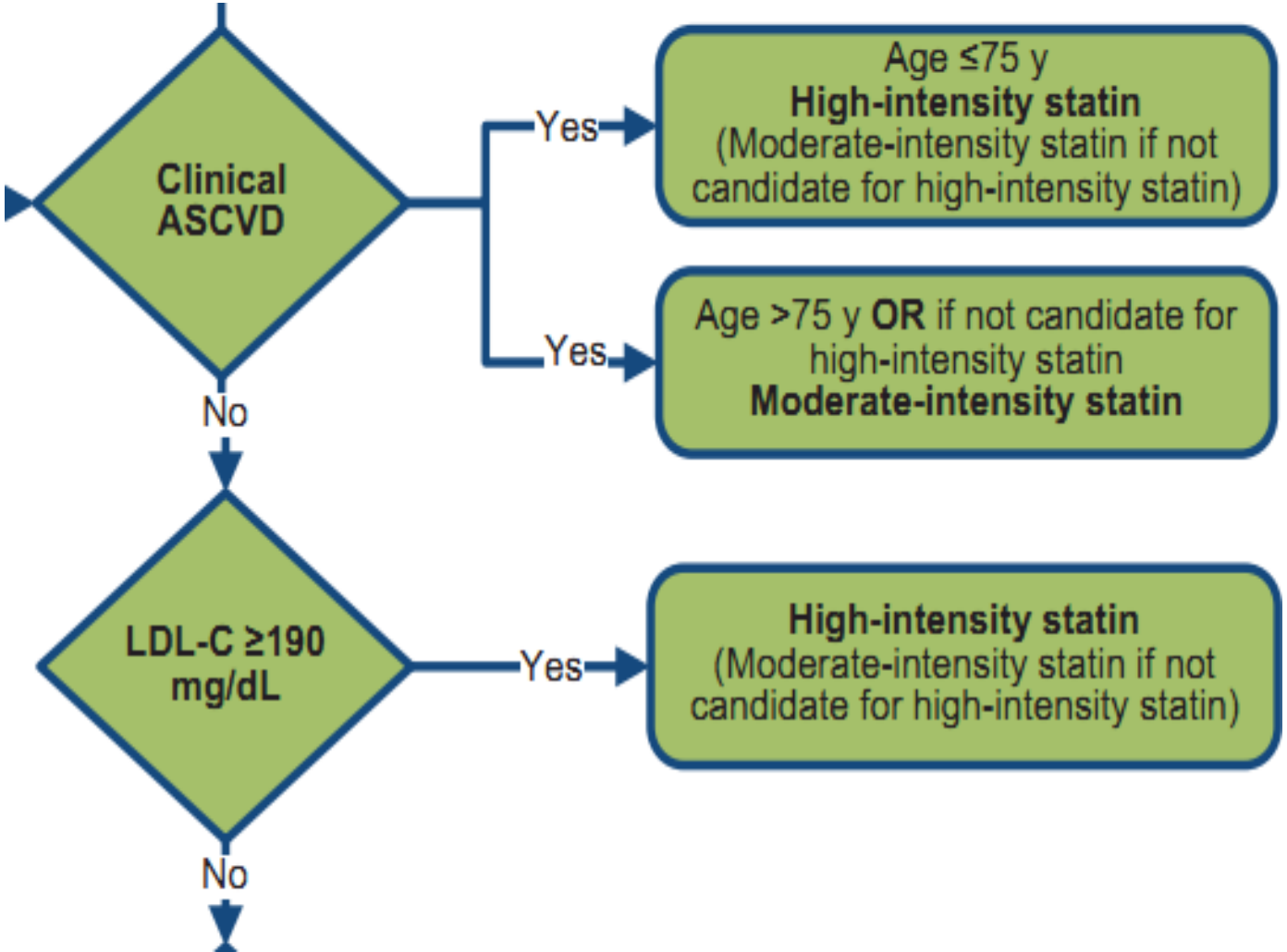


ASCVD = Atherosclerotic Cardiovascular Disease

- Acute coronary syndrome
- History of MI
- Stable angina
- Stroke
- TIA
- PAD

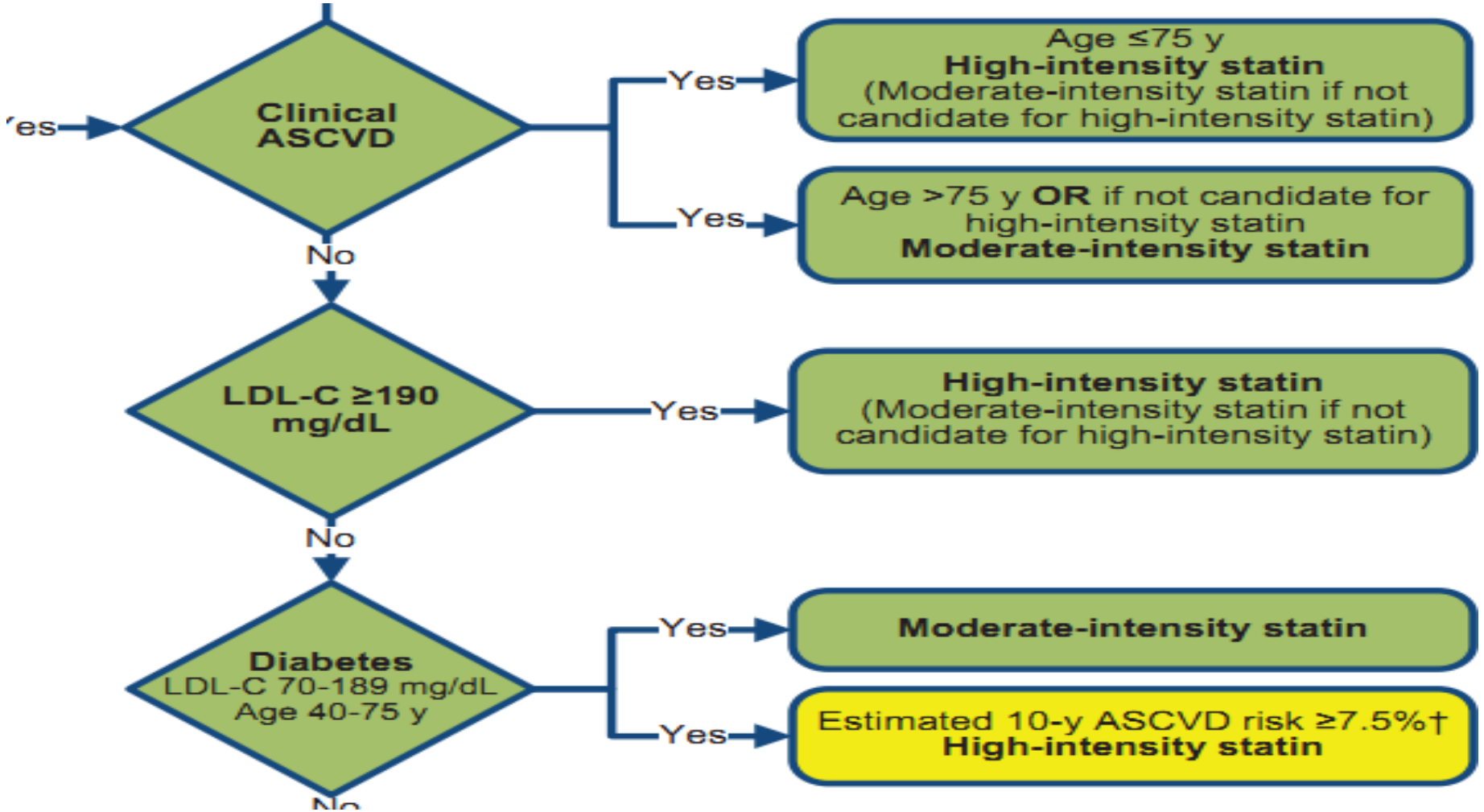
.2Patient with LDL greater than 190 mg/dl

- These are patients with familial hyperlipidemia
- They deserve special consideration
- Often start with untreated LDL of 325–400 mg/dl



.3 Patients with DM, age 40–75 years

- All have indication for statin
- Diabetics with > 7.5% 10 year risk get high intensity statin therapy
- Diabetics with < 7.5% 10 year risk of CAD get moderate intensity statin therapy

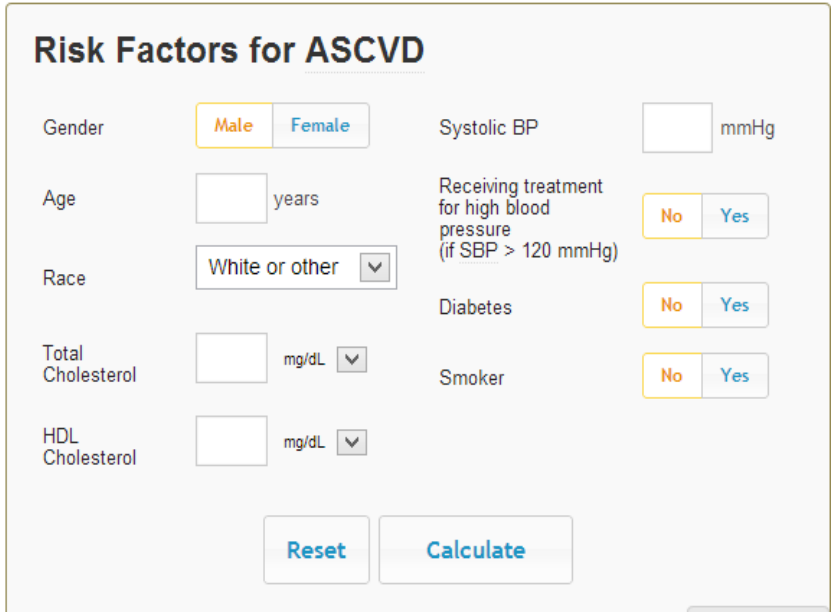


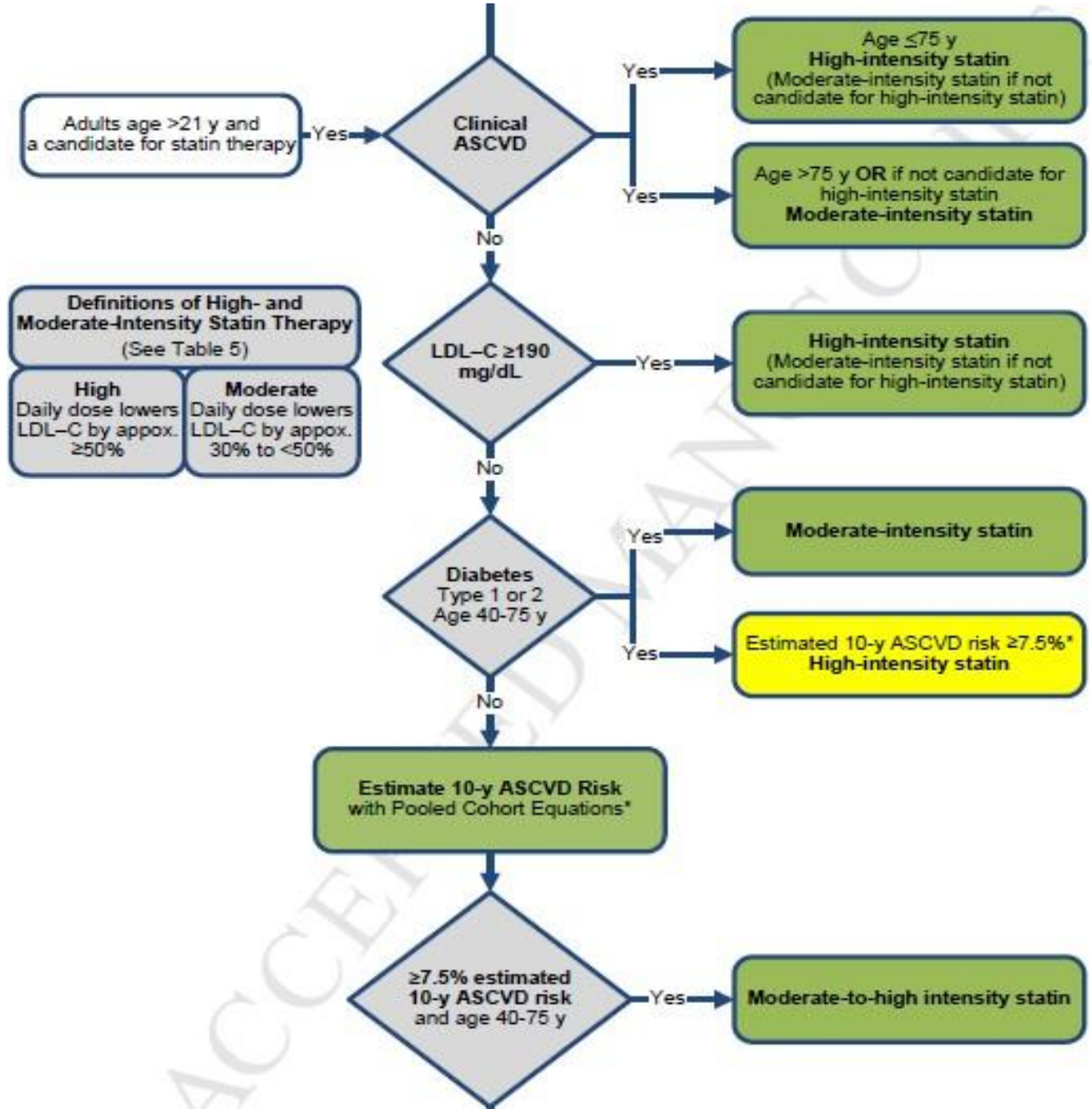
.4 Age 40–75 years that do not meet above criteria, but have a 10 year risk of >% 7.5

- 10 year and lifetime risk as determined by CV Risk Calculator.
- Specifically designed for this trial.
- Downloadable on AHA or ACC site.

Pooled Cohort Risk Assessment Equations

Predicts 10-year risk for a first atherosclerotic cardiovascular disease (ASCVD) event





Clinical controversies

❖❖Management of other patient groups

- Age <40 or >75 years without clinical ASCVD
- -10year risk of 5%-7.5%
- LDL ≥160mg/dl or other primary hyperlipidemias

❖❖Additional risk assessment may be necessary

1) High sensitivity C-reactive protein
2) Ankle-brachial index
3) Coronary artery scores
4) Family history of premature CHD
5) Elevated lifetime risk of ASCVD

Ex. A patient with no ASCVD , NO DM , Age 55 and LDL of 120 mg/dl
but the 10 Y R is between 5 – 7.5 " NOT > 7.5"!

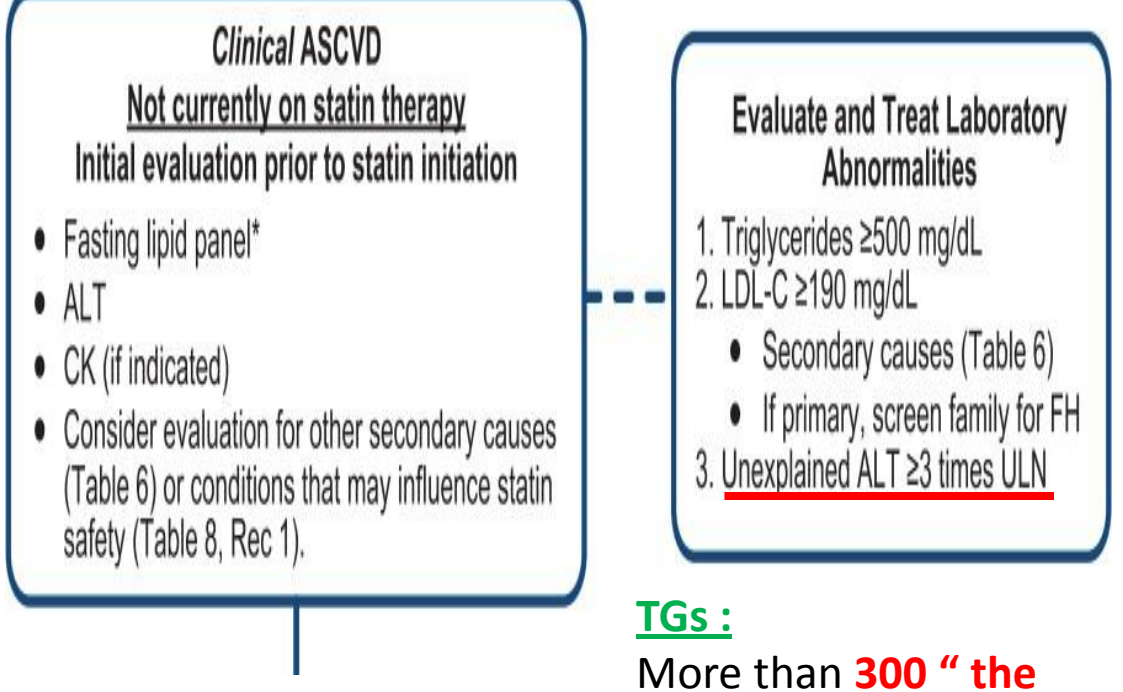
Q/ Will you give him statin ?
<< We **may** give him if any of additional risk assessment methods is positive .

If 10 Y R is lower than 5 ?
Usually NO

No recommendations on statin therapy for patients with:

I. NYHA class II–IV

II. ESRD on dialysis



TGs :

More than **300 " the concern is CVD"**

More than **500 " the concern is Pancreatitis"**

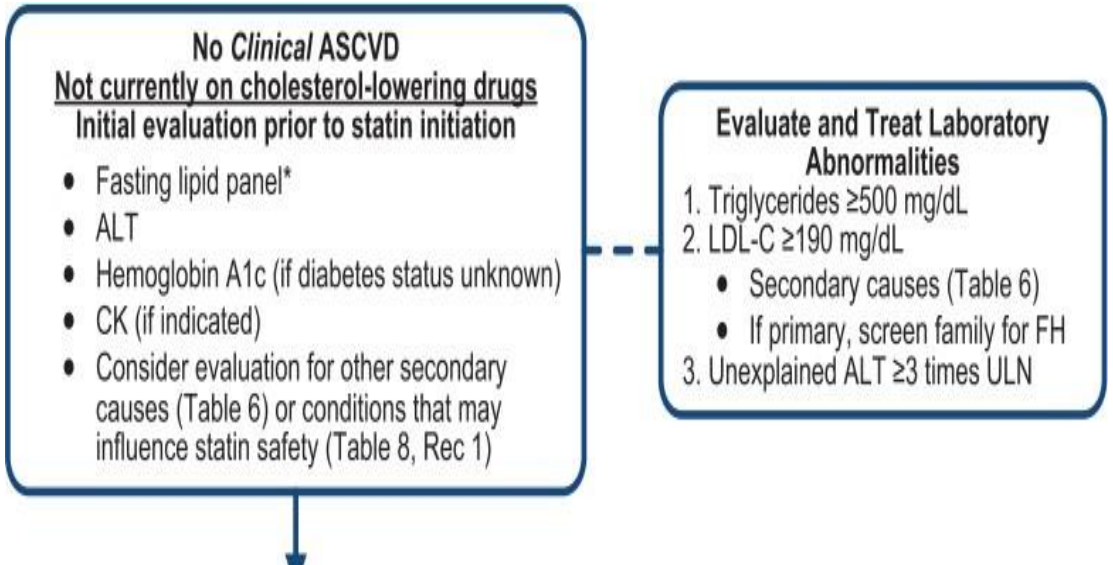


Table 6.

Secondary Causes of Hyperlipidemia Most Commonly Encountered in Clinical Practice

Secondary Cause	Elevated LDL-C	Elevated Triglycerides
Diet	Saturated or *trans* fats, weight gain, anorexia nervosa	Weight gain, very-low-fat diets, high intake of refined carbohydrates, excessive alcohol intake
Drugs	Diuretics, cyclosporine, glucocorticoids, amiodarone	Oral estrogens, glucocorticoids, bile acid sequestrants, protease inhibitors, retinoic acid, anabolic steroids, sirolimus, raloxifene, tamoxifen, beta blockers (not carvedilol), thiazides
Diseases	Biliary obstruction, nephrotic syndrome	Nephrotic syndrome, chronic renal failure, lipodystrophies
Disorders and altered states of metabolism	Hypothyroidism, obesity, pregnancy*	Diabetes (poorly controlled), hypothyroidism, obesity; pregnancy*

Drug Class	Agents and Daily Doses	Lipid/Lipoprotein Effects		Side Effects	Contraindications
HMG CoA reductase inhibitors (statins)	Lovastatin (20-80 mg) Pravastatin (20-40 mg) Simvastatin (20-80 mg) Fluvastatin (20-80 mg) Atorvastatin (10-80 mg) Cerivastatin (0.4-0.8 mg)	LDL HDL TG	↓18-55% ↑5-15% ↓7-30%	Myopathy Increased liver enzymes	Absolute: • Active or chronic liver disease Relative: • Concomitant use of certain drugs*
Bile acid sequestrants **This is the least favorable class of drugs for TGs and HDL**	Cholestyramine (4-16 g) Colestipol (5-20 g) Colesevelam (2.6-3.8 g)	LDL HDL TG	↓15-30% ↑3-5% No change or increase	Gastrointestinal distress Constipation Decreased absorption of other drugs	Absolute: • dysbeta-lipoproteinemia • TG >400 mg/dL Relative: • TG >200 mg/dL
Nicotinic acid **Nicotinic acid :** to prevent flushing we give NSAID " Aspirin" before.	Immediate release (crystalline) nicotinic acid (1.5-3 gm), extended release nicotinic acid (Niaspan®) (1-2 g), sustained release nicotinic acid (1-2 g)	LDL HDL TG	↓5-25% ↑15-35% ↓20-50%	Flushing Hyperglycemia Hyperuricemia (or gout) Upper GI distress Hepatotoxicity	Absolute: • Chronic liver disease • Severe gout Relative: • Diabetes • Hyperuricemia • Peptic ulcer disease
Fibric acids **Feno. Is the best**	Gemfibrozil (600 mg BID) Fenofibrate (200 mg) Clofibrate (1000 mg BID)	LDL *(may be increased in patients with high TG)* HDL TG	↓5-20% ↑10-20% ↓20-50%	Dyspepsia Gallstones Myopathy	Absolute: • Severe renal disease • Severe hepatic disease

Others:

Ezitimab: reduce chol. Absorbion

Omega3: reduce TGs

PCSK9 inhibitors: New + good but expensive and injectable

Combine statin with fibric acid > it is better to choice fenofibrate .not gemfibrozil

2013AHA/ACC Cholesterol Guidelines

AHA/ACC 2013 :
In general , statin reduce only 20-30% of the CVD risk so,
The doctor should **discuses with the patient** before starting statin therapy and inform him about the **absolute effect of the statin on risk reduction**
EX. Patient has a risk of 10% , if he used statin the risk will reduced into 8-7% .which means the absolute reduction in the risk in this patient is 2-3% only

Monitoring of statins:

Baseline ALT prior to initiation

- Consider baseline CK in patients at risk for muscle disorders
- Routine ALT or CK levels not recommended unless symptomatic

Baseline fasting lipid panel

- 4-12 weeks to assess therapeutic response and every 3-12 months if clinically warranted
- Reinforce adherence if response is less than expected
- Dose may be decreased if 2 consecutive LDL <40

That is because the cholesterol is important in cell development and growth , if LDL goes **lower than 40** it might lead to **a Hemorrhagic stroke .**

STATIN Safety recommendations

Conditions that could predispose pts to statin **side effect**:

- Impaired renal or hepatic function
- History of previous statin intolerance or muscle disorder
- Age >75
- History of hemorrhagic stroke

Consider use of lower-intensity statin if any of these characteristics are present

- Select the appropriate dose.
- Keep potential Side effects and drug–drug interaction In mind (grade A.(
- If high or moderate intensity statin not tolerated, use the maximum tolerated dose instead.
- It may be harmful to initiate simvastatin 80mg, or increase the dose of simvastatin to 80mg (Grade B.(

Management of adverse effects

Mild to moderate muscle symptoms

- D/C statin until muscle symptoms resolve
- Re--challenge with a lower dose
- If symptoms resume, D/C statin and re--challenge with lower dose of different statin
- Gradually titrate to target dose
- If symptoms don't resolve after 2 months, assume it is not statin--related and resume original statin

New onset diabetes **In1 of 250 patient only ,Statin interferes with glucose metabolism**

- Reinforce lifestyle modifications

Memory impairment

- Consider other potential causes before stopping statin

Non--statin therapies

Non statin therapies, alone or in combination with statins, do not provide acceptable risk reduction benefits compared to adverse effects.

These include:

- Zetia
- Fibrates
- Fish oil
- Niacin

For the most part, these should be avoided with few exceptions.

The role of non--statin agents

Limited evidence to support use of non-statin agents

Consider use of non-statin agents in the following situations:

- In addition to statins in high-risk patients with less than anticipated response:
  - Clinical ASCVD and age<75
  - Baseline LDL>190
  - Age 40-75 years with diabetes
- Completely statin-intolerant
- TG (>(500

Pooled Cohort Equations: Criticism

Estimates of 12 million to 45 million additional candidates for statin therapy based on CV risk estimates

- Pencina* et al. estimated 87.4% of men and 53.6% of women ages 60–75 would now be eligible for statins

Validation attempts have yielded conflicting results:

- %150–%75 when applied to data from the Women's Health Study and the Physician's Health Study
- Muntner‡ et al. reported good results in actual vs. predicted 5–year risks in a contemporary cohort of the REGARDS study

Observed and expected events for different scores were compared in MESA after a 10.2–year follow–up

Table 2. Predicted and Observed Events for Each Risk Score

Risk Score	Predicted Events, *n* (%)	Observed Events, *n* (%)	Signed Absolute Difference	Discordance, %*	c-Statistic	Discrimination Slope
Total (*n* = 4227)						
FRS-CHD†	397.6 (9.41)	263 (6.22)	3.18	51	0.68	0.05
FRS-CVD‡	561.3 (13.28)	448 (10.60)	2.68	25	0.71	0.09
ATPIII-FRS-CHD§	288.7 (6.83)	134 (3.17)	3.66	115	0.71	0.06
RRS‖	314.0 (7.43)	323 (7.64)	−0.21	−3	0.72	0.07
AHA-ACC-ASCVD¶	387.2 (9.16)	218 (5.16)	4.00	78	0.71	0.06
Men (*n* = 1961)						
FRS-CHD†	251.1 (12.80)	164 (8.36)	4.44	53	0.69	0.05
FRS-CVD‡	358.7 (18.29)	261 (13.31)	4.98	37	0.71	0.09
ATPIII-FRS-CHD§	218.6 (11.15)	86 (4.39)	6.76	154	0.71	0.05
RRS‖	213.5 (10.89)	196 (9.99)	0.89	9	0.70	0.06
AHA-ACC-ASCVD¶	232.1 (11.84)	125 (6.37)	5.46	86	0.71	0.06
Women (*n* = 2266)						
FRS-CHD†	146.5 (6.47)	99 (4.37)	2.10	48	0.60	0.01
FRS-CVD‡	202.6 (8.94)	187 (8.25)	0.69	8	0.70	0.05
ATPIII-FRS-CHD§	70.2 (3.10)	48 (2.12)	0.98	46	0.67	0.02
RRS‖	100.5 (4.44)	127 (5.60)	−1.17	−21	0.72	0.05
AHA-ACC-ASCVD¶	155.1 (6.84)	93 (4.10)	2.74	67	0.70	0.05

Treat to target vs Fire and forget

?Is There a Need for a Dramatic Change in Approach to ASCVD Prevention

IMPROVE-IT

IMProved Reduction of Outcomes: Vytorin Efficacy International Trial

A Multicenter, Double-Blind, Randomized Study to Establish the Clinical Benefit and Safety of Vytorin (Ezetimibe/Simvastatin Tablet) vs Simvastatin Monotherapy in High-Risk Subjects Presenting With Acute Coronary Syndrome

Study Design

IMPROVE-IT

Patients stabilized post ACS ≤ 10 days:
LDL-C 50–125*mg/dL (or 50–100**mg/dL if prior lipid-lowering Rx)

*3.2mM
**2.6mM

N=18,144

Standard Medical & Interventional Therapy

Simvastatin 40 mg

Uptitrated to Simva 80 mg if LDL-C > 79 (adapted per FDA label 2011)

Ezetimibe / Simvastatin 10 / 40 mg

Follow-up Visit Day 30, every 4 months

90% power to detect ~9% difference

Duration: Minimum 2 ½-year follow-up **(at least 5250 events)**

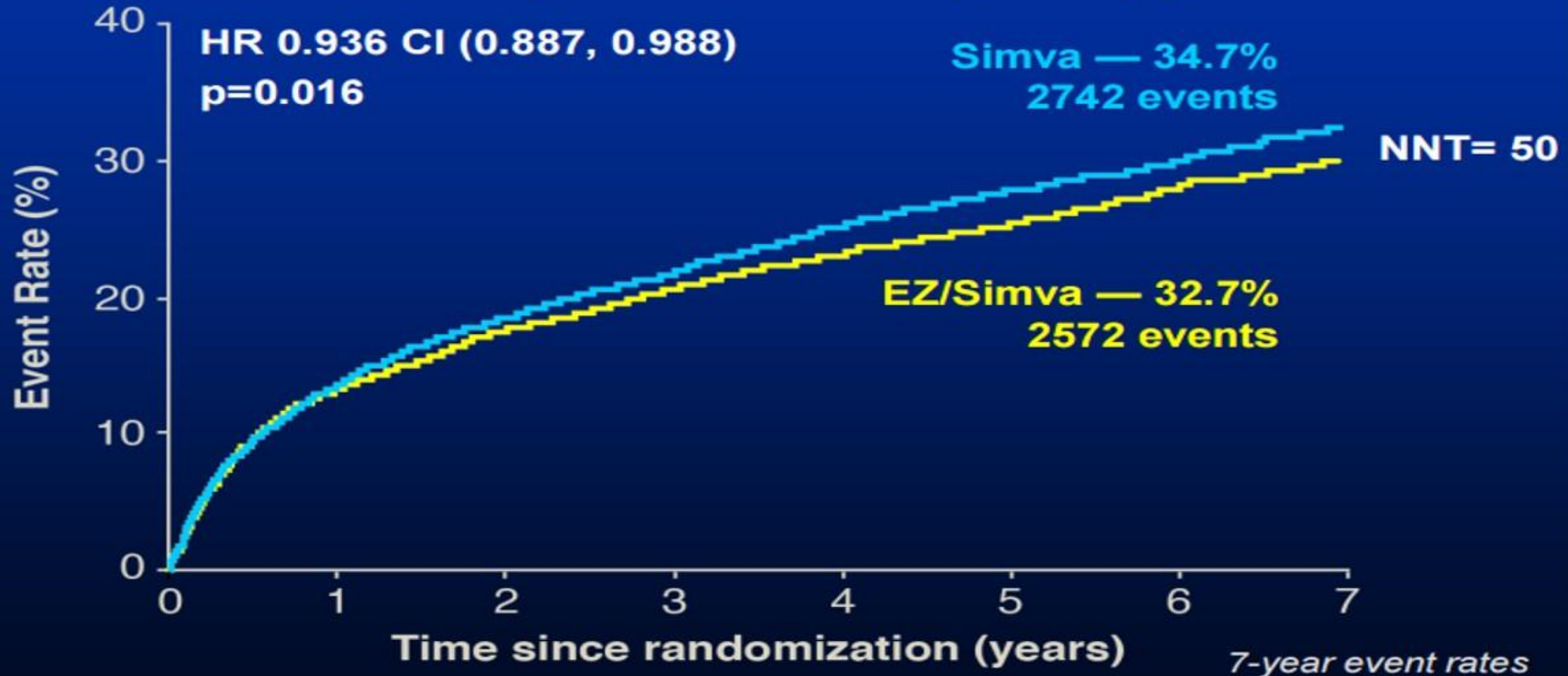
Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12

Primary Endpoint — ITT

IMPROVE-IT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke



7-year event rates

Conclusions

IMPROVE IT: First trial demonstrating incremental clinical benefit when adding a non–statin agent (ezetimibe) to statin therapy:

- **YES:** Non–statin lowering LDL–Cwith ezetimibe reduces cardiovascular events
- **YES:** Even Lower is Even Better (achieved mean LDL–C53 vs. 70 mg/dL at 1 year)
- **YES:** Confirms ezetimibe safety profile

Reaffirms the LDL hypothesis, that reducing LDL–Cprevents cardiovascular events

Results could be considered for future guidelines

The Future of Guidelines

- LDL-Creduction
- Incorporate IMPROVE-ITdata
- Incorporate early PCSK9 trials
- Thedata continues to support LDL-C targets and “lower is better.”

Summary

- Fire and forget approach
- Know the 4 high risk groups
- Use medications proven to reduce risk, ie statins
- Encourage healthy lifestyle
- Don’t forget patient preference

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