[Color index : Important | Notes | Extra]

Dyslipidemia and Risk Assessment of cardiovascular diseases

Objectives:

- Describe the pathogenesis and etiology of coronary artery disease
- Discuss the primary prevention of cardiovascular disease (CVD)
- List the CVD risk factors
- Compare various CVD risk assessment tools
- Provide a comprehensive management for patients with acute coronary syndrome (ACS)
- Define the goals of LDL, HDL and triglycerides to be achieved.
- Discuss the AHA/ACC 2013 guidelines for management of dyslipidemia
- Recognize the medications for high cholesterol e.g., statins and ezetimibe
- Recognize the medication for high triglyceride e.g. fibrates, nicotenic Acid and omega-3

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References : Slides , doctor's note ,ACC/AHA Prevention Guideline, 433 team

[Color index : Important | Notes | Extra]

Helpful videos: CAD

Dyslipidemia

Coronary artery disease

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 :

1. Not smoking
2. Being physically active
3. Having a normal blood pressure
4. Having a normal blood glucose level
5. Having a normal total cholesterol level
6. Being normal weight
7. Eating a healthy diet

Risk factors for CVD:

Modifiable		Non-modifiable
• Smoking	• High blood cholesterol	• Age
• High blood pressure	• Physical inactivity	• Gender
• Obesity	• Diabetes	• Family Hx of CAD

Emerging risk factors for CAD[1][2]

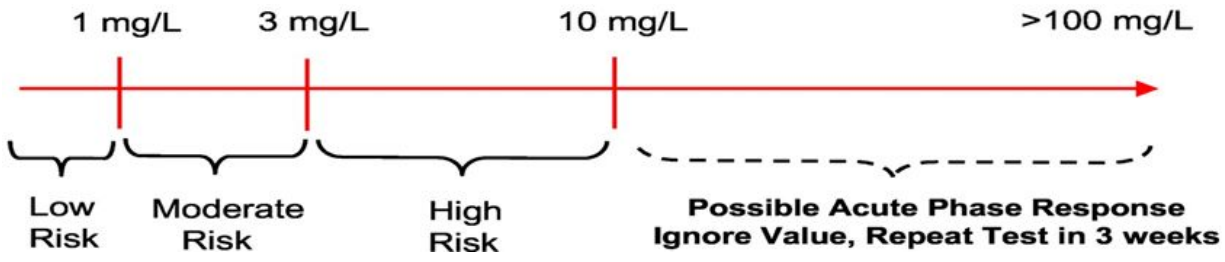
- Elevated high-sensitivity C-reactive protein *
- Coronary artery calcification
- Elevated lipoprotein (a)
- Homocysteine
- Fibrinogen

[1] According to ATP III

[2] one of them will upgrade the risk „اذا جاني مريض ومتردد اعالجه او لا مثلا الريسك ٦٪ اذا عنده وحدة من هذي ترفع الريسك وتخليني اعالج (5-7.5)م

* 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 patient with chest pain and C-reactive protein level is
Between 3 to 10 ⟶ indicate the patient is at high risk of develop an attack
If higher than 10 ⟶ indicate that the patient is having an acute attack

Framingham risk score (FRS)

- 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
❑ Systolic BP
❑ Total cholesterol levels
❑ Smoking Status
❑ HTN treatment
❑ HDL-C levels

Risk Factor		Risk Points				Points
		Men		Women		
Age						
30-34		0		0		
35-39		2		2		
40-44		5		4		
45-49		7		5		
50-54		8		7		
55-59		10		8		
60-64		11		9		
65-69		13		10		
70-74		14		11		
75+		15		12		
HDL-C (mmol/L)						
>1.6		-2		-2		
1.3-1.6		-1		-1		
1.2-1.3		0		0		
0.9-1.2		1		1		
<0.9		2		2		
Total Cholesterol						
<4.1		0		0		
4.1-5.2		1		1		
5.2-6.2		2		3		
6.2-7.2		3		4		
>7.2		4		5		
Systolic Blood Pressure (mmHg)		Not Treated	Treated	Not Treated	Treated	
<120		-2	0	-3	-1	
120-129		0	2	0	2	
130-139		1	3	1	3	
140-149		2	4	2	5	
150-159		2	4	4	6	
160+		3	5	5	7	
Diabetes	Yes	3		4		
	No	0		0		
Smoker	Yes	4		3		
	No	0		0		
Total Points						

Total Points	10-Year CVD Risk (%)*	
	Men	Women
-3 or less	<1	<1
-2	1.1	<1
-1	1.4	1.0
0	1.6	1.2
1	1.9	1.5
2	2.3	1.7
3	2.8	2.0
4	3.3	2.4
5	3.9	2.8
6	4.7	3.3
7	5.6	3.9
8	6.7	4.5
9	7.9	5.3
10	9.4	6.3
11	11.2	7.3
12	13.3	8.6
13	15.6	10.0
14	18.4	11.7
15	21.6	13.7
16	25.3	15.9
17	29.4	18.51
18	>30	21.5
19	>30	24.8
20	>30	27.5
21+	>30	>30

Click here to see it more clear

Classification of patients based on FRS:

Low risk	**< 10% CHD risk at 10 years**
Intermediate risk	**10-20% CHD risk at 10 years**
High risk	**> 20% CHD risk at 10 years**

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

Major CAD types

- Stable angina: due to atheroma[3]
- Acute coronary syndrome:
  - Unstable angina
  - Myocardial infarction (STEMI or NSTEMI)

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

[3] is a reversible accumulation of degenerative material in the inner layer of an artery wall.

Signs & finding of MI

Positive Signs	Negative 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 “S3”	Positional chest pain
Hypotension	

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

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*

* also reduce mortality

Dyslipidemia

- 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	Made by	Rich in	Function
Chylomicron	Endothelium of small intestines **Absorbed into:** lymph vessels, then into the blood	TGS	transport fats from the intestinal mucosa to the liver
VLDL	Liver from excess dietary carbohydrate and protein along with the Chylomicron remnant	TGs	Deliver TGs to body cells
LDL	Liver (VLDL once it has lost a lot of its TG's)	Cholesterol	Deliver cholesterol to all body cells
HDL	Liver and Small Intestine	-	Pick up cholesterol from body cells and take it back to the liver

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.*

Table 5 is old it is not important

AHA/ACC vs IAS

ACC/AHA 2013 "ATP IV"	International Atherosclerosis Society (IAS)
• Recommendations based on what has been shown to reduce risk in RCTs[4] • 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[5] risk and that lowering "atherogenic cholesterol" (LDL-C and 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

- The changes compared to ATP-III 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

- 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

[4] randomized control trials
[5] Atherosclortic cardiovascular disease

	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	4 specific 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

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/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 3-4 times per week

Four Major Statin Benefit Groups

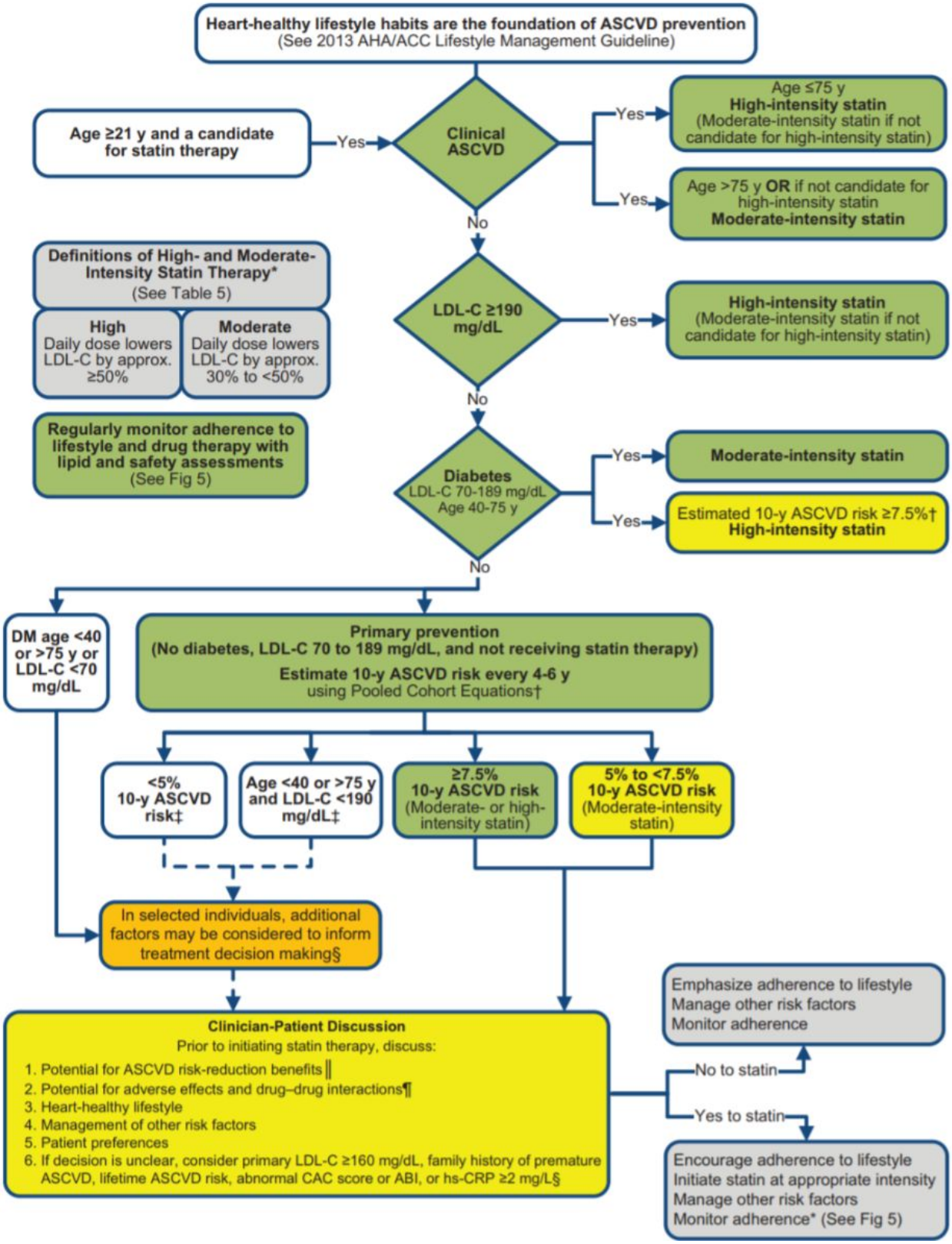
LDL for familial hypercholesteremia is less than 70 because they have 20 fold higher risk to develop CVD
also patients with ASCVD < 70
for diabetic with any risk factor < 70
★ only diabetic < 100
but even though they are high-risk patients so they should be on a statin even if LDL below 100 with no other risk factors
100 is the target to change the dose or add other medications

1. **Individuals with clinical ASCVD such as:**
    a. Acute coronary syndrome
    b. History of myocardial infarction
    c. Stable angina
    d. Transient ischemic attack
    e. Peripheral artery disease
2. **Individuals with LDL >190**
    a. These are patients with familial hyperlipidemia
    b. They deserve special consideration
    c. Often start with untreated LDL of 325-400 mg/dl
3. **Individuals with DM, 40-75 yo with LDL 70-189 and without clinical ASCVD**
    a. All have indication for statin
    b. Diabetics with > 7.5% 10 year risk get high intensity statin therapy
    c. Diabetics with < 7.5% 10 year risk of CAD get moderate intensity statin therapy
4. **Individuals <u>without</u> clinical ASCVD or DM with LDL 70-189 and estimated 10-year ASCVD risk >7.5%**
    a. Age 40-75 years that do not meet above criteria, but have a 10 year risk of >7.5 %
    b. 10 year and lifetime risk as determined by CV Risk Calculator. "pooled cohort risk assessment equation"

- **No recommendations on statin therapy for patients with**
    - NYHA class II-IV
    - ESRD on dialysis

Explanation: (summarize the algorithm in next page)

- **For the first group:** based on the guideline, if you have clinical ASCVD and <75 and don't have any history of intolerance to statin, you should be started on high intensity statin. On the other hand, if >75, or not a candidate for high intensity statin due to let's say intolerance to statins, you are a candidate for moderate-intensity statin
- **For the second group:** if your LDL is >190, you need to be started on high-intensity statin, unless you have contraindication to high dose àstart on moderate dose
- **For the third group:** individuals with diabetes with above mentioned group age, you need to calculate the 10 year ASCVD risk using a new equation/calculator called "pooled Cohort Equations" if the 10 year risk is greater than 7.5%, start them on high-intensity, otherwise, you can start them on moderate-intensity statin
- **For the last group:** you need to calculate patient's risk factor and start them on moderate-to-high intensity statin if their estimated 10-year ASCVD risk is >7.5%
- High intensity statin, it is mean the daily dose of statin that lowers the LDL by approximately >50%.
- Moderate intensity statin,it is mean the daily dose of statin that lowers the LDL by approximately 30-50%.


Heart-healthy lifestyle habits are the foundation of ASCVD prevention
(See 2013 AHA/ACC Lifestyle Management Guideline)
Age ≥21 y and a candidate for statin therapy
Yes
Clinical ASCVD
Yes
Age ≤75 y
High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)
Yes
Age >75 y OR if not candidate for high-intensity statin
Moderate-intensity statin
No
Definitions of High- and Moderate-Intensity Statin Therapy*
(See Table 5)
High
Daily dose lowers LDL-C by approx. ≥50%
Moderate
Daily dose lowers LDL-C by approx. 30% to <50%
LDL-C ≥190 mg/dL
Yes
High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)
No
Regularly monitor adherence to lifestyle and drug therapy with lipid and safety assessments
(See Fig 5)
Diabetes
LDL-C 70-189 mg/dL
Age 40-75 y
Yes
Moderate-intensity statin
Yes
Estimated 10-y ASCVD risk ≥7.5%†
High-intensity statin
No
DM age <40 or >75 y or LDL-C <70 mg/dL
Primary prevention
(No diabetes, LDL-C 70 to 189 mg/dL, and not receiving statin therapy)
Estimate 10-y ASCVD risk every 4-6 y
using Pooled Cohort Equations†
<5% 10-y ASCVD risk‡
Age <40 or >75 y and LDL-C <190 mg/dL‡
≥7.5% 10-y ASCVD risk
(Moderate- or high-intensity statin)
5% to <7.5% 10-y ASCVD risk
(Moderate-intensity statin)
In selected individuals, additional factors may be considered to inform treatment decision making§
Clinician-Patient Discussion
Prior to initiating statin therapy, discuss:
1. Potential for ASCVD risk-reduction benefits‖
2. Potential for adverse effects and drug–drug interactions¶
3. Heart-healthy lifestyle
4. Management of other risk factors
5. Patient preferences
6. If decision is unclear, consider primary LDL-C ≥160 mg/dL, family history of premature ASCVD, lifetime ASCVD risk, abnormal CAC score or ABI, or hs-CRP ≥2 mg/L§
No to statin
Emphasize adherence to lifestyle
Manage other risk factors
Monitor adherence
Yes to statin
Encourage adherence to lifestyle
Initiate statin at appropriate intensity
Manage other risk factors
Monitor adherence* (See Fig 5)

Statins dosing[6]

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 statins is Rosuvastatin ⟶ effect on LDL and HDL
- The worst statins is Simvastatin ⟶ drug-drug interaction "higher dose"

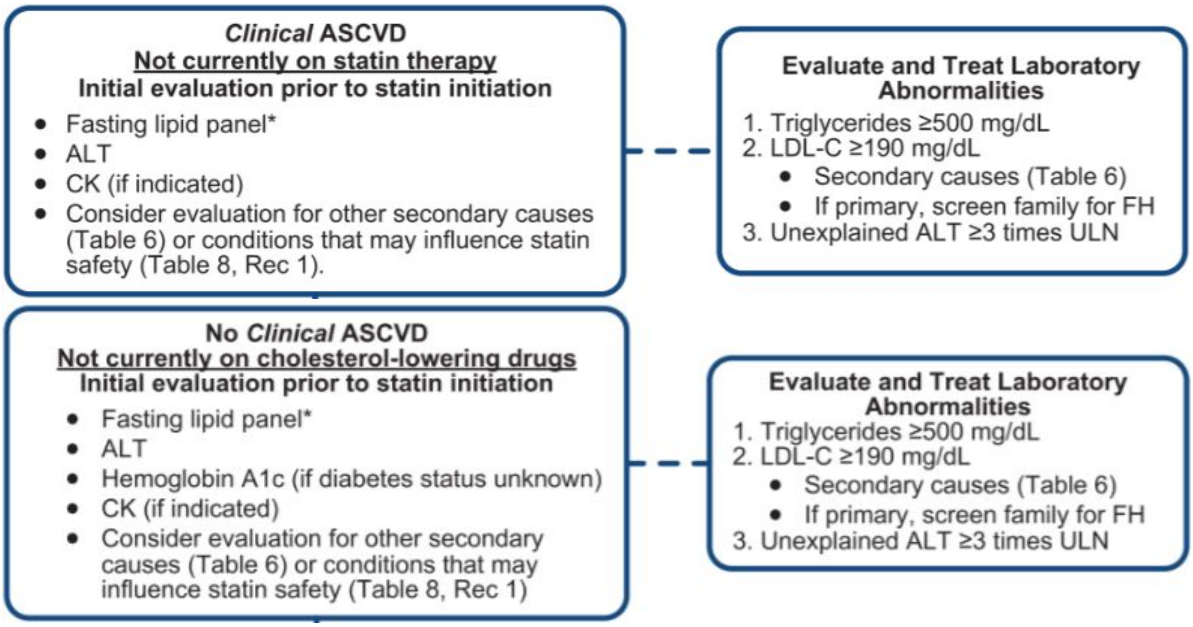
Clinical controversies

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

We may give them statins if any of additional risk assessment is positive

- Additional risk assessment may be necessary
  - High sensitivity C-reactive protein
  - Ankle-brachial index
  - Coronary artery scores
  - Family history of premature CHD
  - Elevated lifetime risk of ASCVD

these are tests you have to check it before initiate statin and the secondary causes in next table



TGs: More than 300 the concern is **CVD** - More than 500 the concern is **Pancreatitis**

[6] statin reduce CVD risk by 20-30% so the absolute reduction is about 3%

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*

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

Statins safety recommendations

- 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 80 mg, or increase the dose of simvastatin to 80mg (Grade B)

statin intolerance means when the patient can not tolerate 2 type of statins in the lowest dose

Management of side effects of statins

- Mild to moderate muscle symptoms
    - Discontinue statin until muscle symptoms resolve
    - Rechallenge with a lower dose
    - If symptoms resume, Discontinue statin and rechallenge 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
    - Reinforce lifestyle modifications
- Memory impairment
    - Consider other potential causes before stopping statin

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

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
  - TGs (>500)

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	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: • dysbetalipoproteinemia • TG >400 mg/dL Relative: • TG >200 mg/dL
Nicotinic acid	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	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:
  - Ezetimibe: reduce cholesterol absorption, the only proved drug to lower CVD risk with statin
  - Omega 3: reduce TGs
  - PCSK9 inhibitors: New + good but expensive and injectable
- One of the side effect of HMG CoA reductase inhibitors (statins) is myopathy
- Bile acid sequestrants is the least favorable class of drugs for TGs and HD
- To prevent flushing (side effect of nicotinic acid) we give NSAIDs before
- Fibric acids is best class of non-statins therapy, combined with statins has good outcomes (fenofibrate not gemfibrozil)

Summery

- 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

Studies conclusions

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

- **YES:** *Non-statin* lowering LDL-C with ezetimibe reduces cardiovascular events
- **YES:** Even Lower is Even Better (achieved mean LDL-C 53 vs. 70 mg/dL at 1 year)
- **YES:** Confirms ezetimibe safety profile

Reaffirms the LDL hypothesis, that reducing LDL-C prevents cardiovascular events

Results could be considered for future guidelines