Lecture 30

Editing file

MED438
KING SAUD UNIVERSITY

Ischemic Heart Diseases & Dyslipidemia

Objectives:

- ★ CVD risk factors and assessment tools.
- ★ Cardiovascular diseases.
- ★ Dyslipidemia and introduction to new guidelines on lipid management.

Color index:

Original text Important Doctor's notes Golden notes Extra

Introduction

Primary Prevention Of CVD

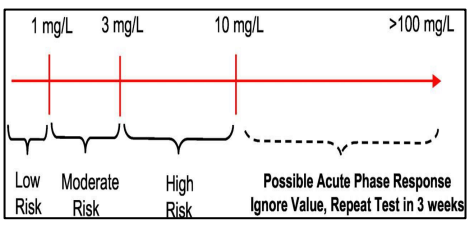
- The achievement and maintenance of good health is being emphasized in programs from The American Heart Association that promote seven ideal cardiovascular health metrics.
- **Including:**
  - Not smoking, being physically active, having a normal blood pressure, having a normal blood glucose, having a normal total cholesterol, being normal in weight & eating healthy diet.

CVD Risk Factors:

- Cardiovascular diseases (CVD) is a general term for conditions affecting the heart or blood vessels. Types:
  - Coronary heart diseases (angina, ACS or HF).
  - Strokes or TIAs.
  - Peripheral artery disease(chronic limb ischemia, etc).
  - Aortic disease(Abdominal aortic aneurysms,etc).
- Because each CVD risk assessment may target or build the assessment for the prevention of one or all the types of CVD. (You should know which one you want to prevent and what's the best tool for it)
- Calculated cardiovascular risk means the probability of having cardiovascular disease/IHD in 10 years. Thus know the benefit of starting preventive treatment (Statin).
- There risk factors constitute CVD risk assessment.

CVD Risk Factors		
Modifiable	**Non-Modifiable**	**Emerging risk factors**
1) Diabete. (Worst) **2)** Smoking Cigarette and tobacco. **3)** High Blood pressure. (Most common) **4)** High Blood Cholesterol. **5)** Obesity. **6)** Physical inactivity.	**1)** Age. **2)** Gender. **3)** Family history of CVD (Significant if premature death: ○ Male <55y ○ Female <65y)	**1)** Elevated high-sensitivity C-reactive protein. **2)** Coronary artery calcification. **3)** Elevated lipoprotein A (Highly Atherogenic) **4)** Homocysteine. **5)** Fibrinogen.

C-Reactive Protein



- A person's baseline level of inflammation as assessed by the plasma concentration of CRP.
- **It predicts the long-term risk of a first MI.**
- If a patient with chest pain and CRP level is:
  - Between 3 to 10: that indicate the patient is at high risk of developing an attack.
  - Above 10: that indicate that the patient is having an acute attack.

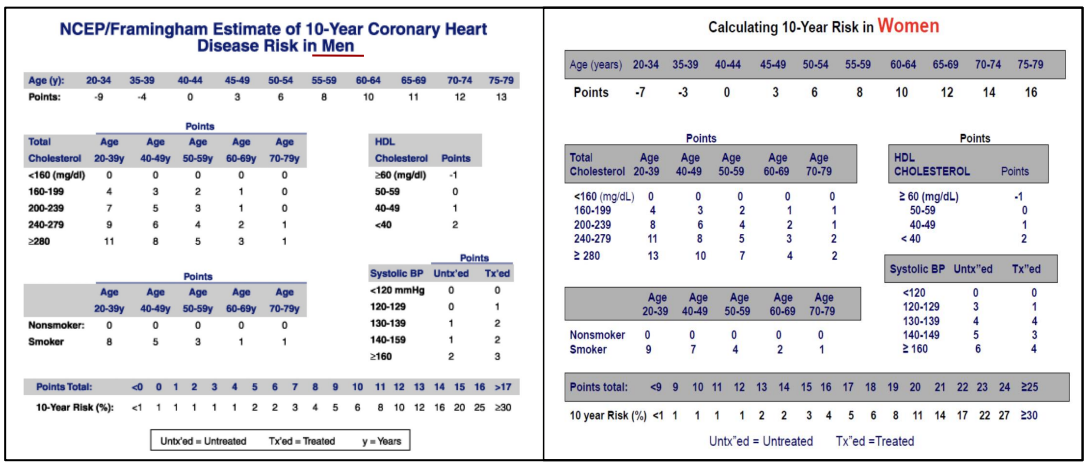
Coronary Artery Calcification

- High calcium score is an evidence of inflammation and an indication to start statin therapy.

CVD Risk Assessment

1- The Framingham Risk Score (FRS) OSCE:

- 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 (Variables) are used to assess cumulative risk:
  - Age
  - Systolic BP
  - Total cholesterol levels
  - Smoking Status
  - HTN treatment (Treated or not)
  - HDL-C levels
  - The more the variables, the higher the validity of the tool.
- **Cases in which you do not 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.**
  - They are in high risk, you don't need for risk assessment. Start managing them directly as secondary prevention.



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

Calculating 10-Year Risk in Women

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

Points

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

Points

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

	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

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

Points total:	<9	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	≥25
10 year Risk (%)	<1	1	1	1	1	2	2	3	4	5	6	8	11	14	17	22	27	≥30

Untx"ed = Untreated Tx"ed =Treated

Classification Of Patients Based On FRS	
Low Risk	<10% coronary heart disease risk at 10 years.
Moderate Risk	10-20% risk of coronary event at 10 years.
High Risk	>20% risk of coronary event at 10 years.

Example: 57y male non-smoker with the following parameters: Total cholesterol: 260, HDL: 45, BP: 135 (untreated). Calculate Framingham risk score?

- 57y → 8
- Non-smoker → 0
- Total cholesterol → 4
- HDL→1
- SYS BP→1
- Total points: 14 → 10y risk (16%).

Other CVD Assessment Tool

2- Pooled Cohort Risk Assessment Equations

- Established in 2013.
- It has some level of overestimation.
- Similar to Framingham but they added diabetes as a risk factor.
- Predicts 10-years risk for a first atherosclerosis cardiovascular disease (ASCVD) event.
- Estimates of 12 million to 45 million additional candidates for statin therapy based on CV risk estimate.
    - 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:
    - 75%-150% 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.
- The issue with these risk assessment modalities that they cannot fit or to be applied in different areas or regions (generalization). Because each community has specific characters and features beside ethnic or genetic background. That's why, we urgently need a Saudi CVD risk assessment that put ethnic and genetic background into consideration.
- Framingham risk score is an old CVD risk assessment that has been validated in many communities. **It's considered the best to use in our community.**
- **Notes:**
    - Reynolds risk score (RRS) involves CRP and premature cardiovascular disease with least underestimation.
    - Predicted outcome(s) must be well known in the assessment.
        - Ex. decrease risk of stroke.
    - **Formal assessment involves the tools, while informal assessment involves traditional history (for those below 40 years), it's called periodic cardiovascular assessment and should be repeated in 4+6 years.**

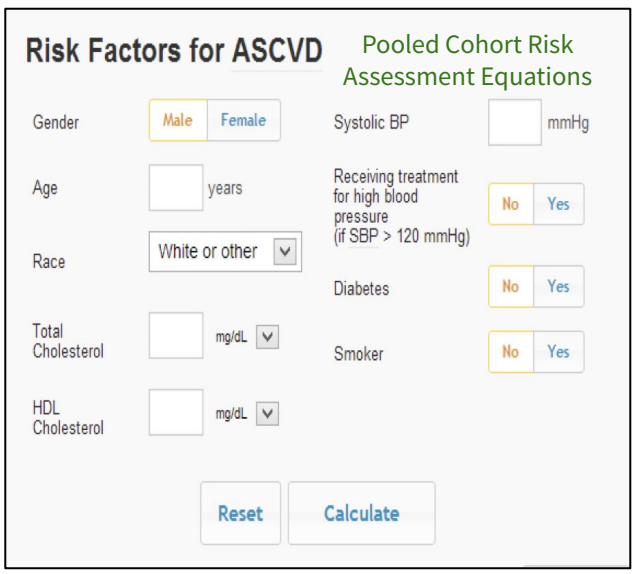


Table 2. Predicted and Observed Events for Each Risk Score

Risk Score	Predicted Events, *n* (%)	Observed Events, *n* (%)	Signed Absolute Difference	Discordance, %* Overestimation	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

Observed and expected events for different scores were compared in MESA after 10.2 years follow up:

Coronary Artery Disease (CAD)

- **Pathogenesis:**
  - CAD is the narrowing of the coronary artery, decreasing the blood supply to the heart, leading to ischemia of the heart muscle cells.
  - Theories suggest that atherosclerosis process starts at earlier age.
- **Etiology:**
  - CAD is mostly due to Atherosclerosis.
  - Atherosclerosis and thrombosis are the most important pathogenic mechanisms.
- **Major CAD types:**
  - Stable Angina; due to atheroma.
  - Acute Coronary Syndrome (ACS):
    - Unstable Angina.
    - Myocardial Infarction. (STEMI OR NSTEMI)
- Approach to chest pain suggestive of ACS:
  1. History and physical examination.
  2. ECG.
  3. Cardiac markers (Troponin and Creatine Kinase-MB).

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

Not every ST-elevation is MI. There are lots of differential diagnoses (14 or more). Ex. Hypotension, pulmonary embolism, pleural effusion, cerebral hemorrhage, pericarditis, bleeding or hyperkalemia

Signs & Findings Of Myocardial Infarction

Positive signs	Negative signs
ST-segment elevation	Normal ECG
New Q wave	Pleuritic, sharp or stabbing chest pain
Chest pain radiating to both arms simultaneously	Pain reproduced on palpation
Added heart sound “S3”	Positional chest pain
hypotension	

Treatment Of Coronary Artery Syndrome

1. Aspirin:
    - Proven to prevent recurrent infarction and decreases mortality.
2. Clopidogrel.
3. β- blockers.
4. ACE inhibitors & ARBs (should be used if there is intolerance of ACE inhibitors)
5. Nitroglycerin.
6. Heparin.
7. Statins.

What Are The Drugs That Are Proven To Reduce Mortality?

1. Aspirin.
2. B-blockers.
3. ACE inhibitors.
4. 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.

Dyslipidemia

Dyslipidemia Definition

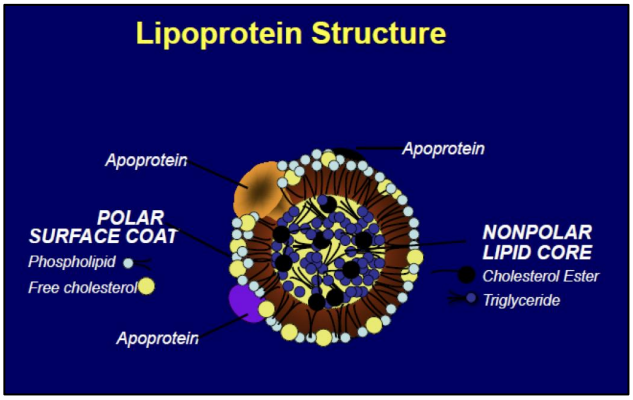
- A disorder of lipoprotein metabolism, including lipoprotein overproduction or deficiency.
  - Over production of lipoprotein (LDL, TGS, Total cholesterols)
  - Deficiency of HDL (or clearance / Metabolism)
- May be manifested by elevation of the total cholesterol, (LDL) and the triglyceride concentrations, and a decrease in the (HDL) concentration in the blood.

Types Of Lipids

Types	Chylomicron	VLDL	LDL	HDL
Made by	Small **intestines** in the fed stat.	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.	-	-	-
Rich in	TGs (Exogenous)	TGs (Endogenous)	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
• There is an inverse relationship between TAG and HDL.				

Types Of Lipids

- ApoProtien -100 in LDL
  - Stabilize LDL structure.
  - Act as receptors.
- Why we mentioned this, because in some causes of dyslipidemia are genetic that affect these structures.



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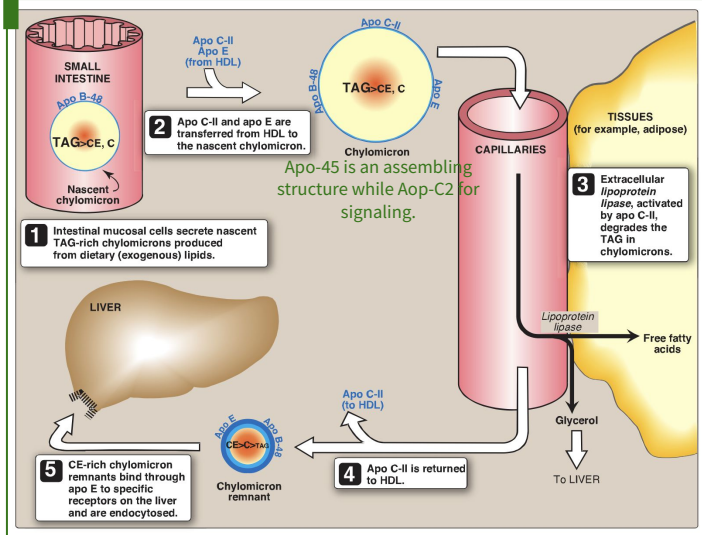


Figure 18.16
Metabolism of chylomicrons. Apo B-48, apo C-II, and apo E are apolipoproteins found as specific components of plasma lipoproteins. The lipoprotein particles are not drawn to scale (see Figure 18.13 for details of their size and density). TAG = triacylglycerol; C = cholesterol; CE = cholesteryl ester; HDL = high-density lipoprotein particle.

5. Regulation of lipoprotein lipase activity: *LPL* is synthesized by

2

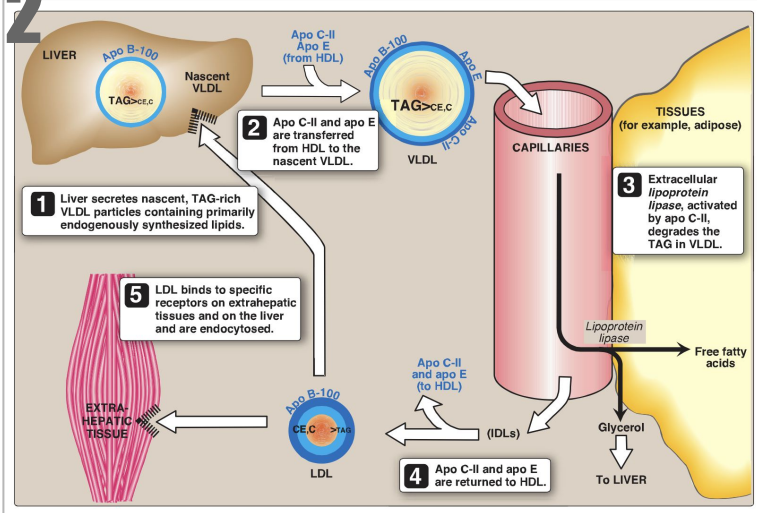


Figure 18.17
Metabolism of very-low-density lipoprotein (VLDL) and low-density lipoprotein (LDL). Apo B-100, apo C-II, and apo E are apolipoproteins found as specific components of plasma lipoprotein particles. The lipoproteins are not drawn to scale (see Figure 18.13 for details of their size and density). TAG = triacylglycerol; HDL = high-density lipoprotein particle; IDLs = intermediate-density lipoprotein particles; C = cholesterol; CE = cholesteryl ester.

3

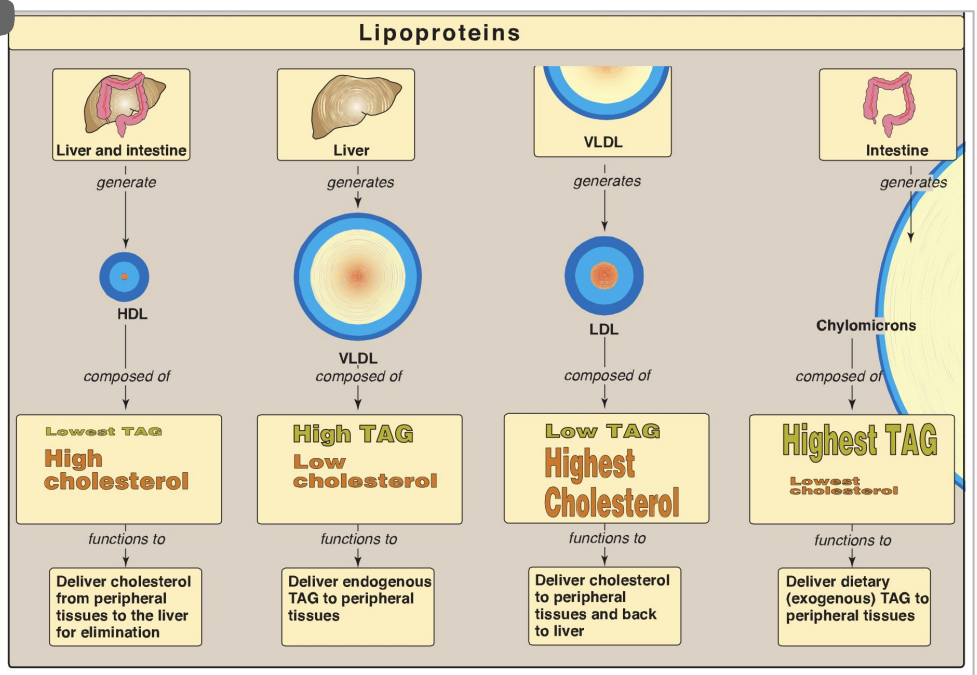
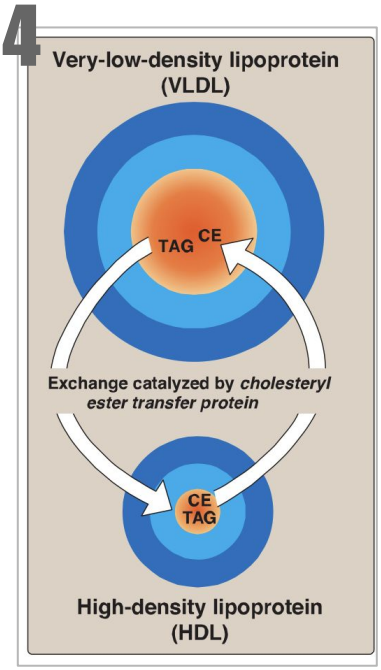


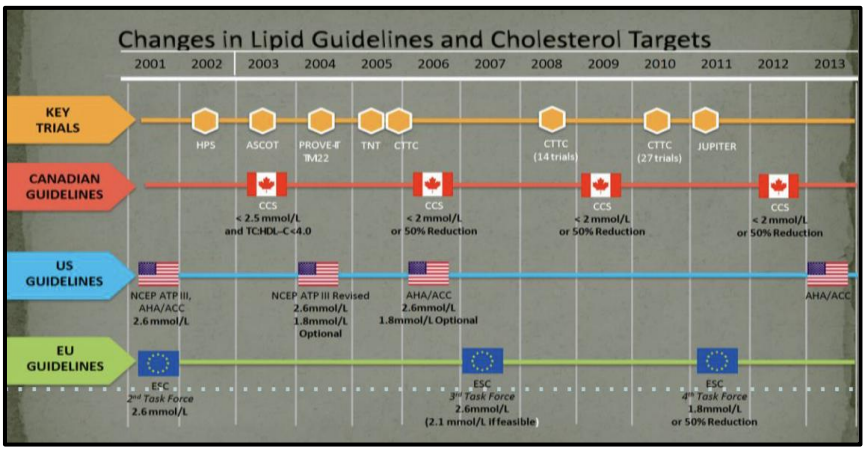
Figure 18.29
Concept map for cholesterol and the lipoproteins. HMG CoA = hydroxymethylglutaryl coenzyme A; SREBP = sterol regulatory element–binding protein; HDL = high-density lipoprotein; VLDL = very-low-density lipoprotein; LDL = low-density lipoprotein; TAG = triacylglycerol; NADP(H) = nicotinamide adenine dinucleotide phosphate.

4



Dyslipidemia Management

- Different guidelines with different recommendations.
- Recommendations are based on clinical trials and updated frequently.
- Dyslipidemia management
- Before starting the management we need to understand where are the previous guidelines.
- It's divided into 3 stages.
- Before 2013:
  - Where was a specific target to manage dyslipidemia (ex. patient with LDL 350 we start the treatment or step it up if it was resistance Tx until reaching a specific target ex. LDL 90). This approach is called **Treat to Target approach.**
- From 2013-2018:
  - Where the American Heart Association (AHA) and the American College of Cardiology (ACC) Developed a new controversial guideline without a target ! and only specified 4 groups (called statin benefit groups) of patients to give statin without even mentoring lipid levels. Then it was reviewed In 2018, which is the most important one right now. This approach is called **Fire and Forget approach.**
- After 2018.

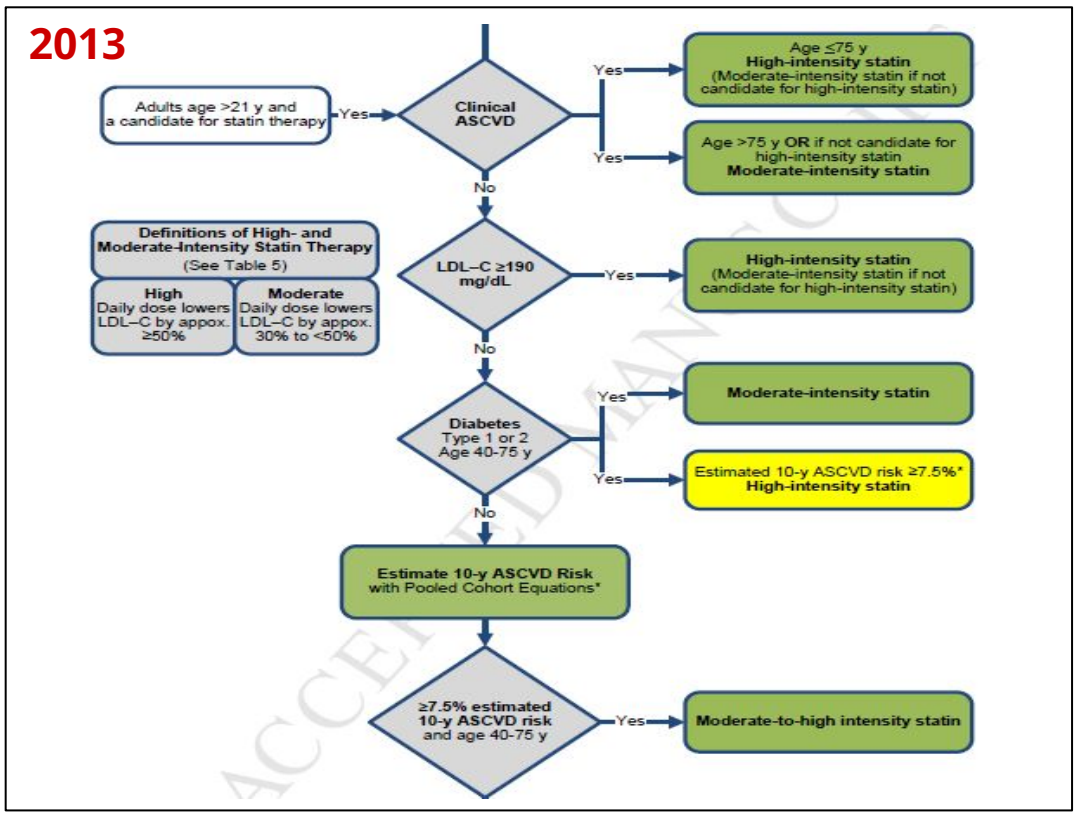


These guidelines recommended a 'target' for cholesterol. Until 2013, when American Heart Association (AHA) recommended that no 'target' for cholesterol (since is not proven that 2 is better than 2.5). They developed guidelines based on risks ASCVD and statin benefit prove.

AHA/ACC Vs IAS

AHA/ACC Vs IAS:

AHA/ACC 2013	IAS (International atherosclerosis society)
• ACC/AHA (elevated 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 approach.** • Even if it's within normal, start managing as required (Choosing the intensity of statin depends on each case). • No specific target.	• Apo B-containing lipoproteins is causally associated with ASCVD risk and what lowering "atherogenic Cholesterol" (LDL-S and non-HDL-C) will reduce risk. • **Treat to Target approach.**



- This guideline was developed in 2013. But we have an updated version of the guideline in **2018** where questions would come from. Although, it's better to know the base or components of this guideline, so it would make it easier for you to understand 2018 guideline.
- ASCVD, or atherosclerotic cardiovascular disease, is caused by plaque buildup in arterial walls and refers to the following conditions:
  - Coronary heart disease (CHD), such as myocardial infarction, angina, and coronary artery stenosis
  - Cerebrovascular disease, such as transient ischemic attack, ischemic stroke, and carotid artery stenosis
  - Peripheral artery disease, such as claudication.
  - Aortic atherosclerotic disease, such as abdominal aortic aneurysm and descending thoracic aneurysm.

ATP III classification

Statin Dosing

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***

Rule of six(6): Atorvastatin:
- 10mg = 38% reduction of LDL
- 20mg = 44% reduction of LDL
- 40mg = 50% reduction of LDL
- With doubling the dose reduction increase By 6%

ATP III Classification Of:

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.*

- Cholesterol is essential for multiple physiological functions in our body. So, you cannot lower cholesterol to zero! Need to maintain it within normal range.
- If cholesterol levels below 40= lower dose of statin.
- If it's still persistent below 40= stop statin.
- To convert Cholesterol from mmol/L to mg/dl multiply by. 38.5 **(~40)** while for TGs multiply by 88.5 **(~90).**
- Statin is the only group of anti-hyperlipidemic drugs that is proven to reduce mortality.
- Other important effects of statin other than LDL reduction:
  - Anti-inflammatory.
  - Anti-platelets.

Etiology Of Dyslipidemia

- **Primary Causes:**
  - Primary causes are **single or multiple gene mutations** that result in either overproduction or defective clearance of TG and LDL cholesterol, or in underproduction or excessive clearance of HDL.
  - You must Identify what is exactly abnormal ex. TCA, LDL or HDL etc…
  - Examples:
    - Familial hypertriglyceridemia.
    - Familial hypercholesterolemia.
    - Familial combined hyperlipidemia.
    - Polygenic hypercholesterolemia.
  - In familial dyslipidemia always start high intensity statin.
- **Secondary Causes:**
  - **Contribute to most cases of dyslipidemia in adults.**
  - The most important secondary cause in developed countries is a **sedentary lifestyle with excessive dietary intake** of saturated fat, cholesterol and trans fats.
  - **Examples:**
    - Diabetes mellitus.
    - Alcohol overuse.
    - Chronic kidney disease.
    - Hypothyroidism.
    - Primary biliary cirrhosis.
    - Other cholestatic liver disease.
    - Drugs (such as: thiazides, Beta-blocker, retinoids (Especially TCA → Acute pancreatitis), highly active antiretroviral agents, estrogen and progestins and glucocorticoids.) and Smoking.

Affected lipids	Conditions
↑ Total cholesterol and LDL-C	• Hypothyroidism • Nephrosis • Dysgammaglobulinemia (systemic lupus erythematosus, multiple myeloma) • Progestin or anabolic steroid treatment • Cholostatic diseases of the liver due to abnormal lipoproteins, as in primary biliary cirrhosis • Protease inhibitors for treatment of HIV infection
↑ Triglycerides and VLDL-C	• Chronic renal failure • T2DM • Obesity • Excessive alcohol intake • Hypothyroidism • Antihypertensive medications (thiazide diuretics and b-adrenergic blocking agents) • Corticosteroid therapy (or severe stress that increases endogenous corticosteroids) • Orally administered estrogens, oral contraceptives, pregnancy • Protease inhibitors for treatment of HIV infection

  - You should do **mandatory workups** for all patients with dyslipidemia to rule out secondary causes:
    - LFTs (Liver disease).
    - RFTs (Nephrotic syndrome).
    - TSH; When TSH > 10 it usually causes dyslipidemia.
    - Pregnancy test.
    - FPG and A1C.

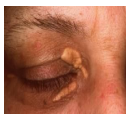
Secondary Causes of Hyperlipidemia Most Commonly Encountered in Clinical Practice

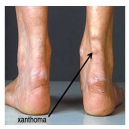
Secondary Cause	Elevated LDL-C	Elevated Triglycerides
Diet	Saturated or *trans* fats, weight gain, anorexia nervosa	Weight gain, very-low-fat diets, high intake of refined carbohydrates, excessive alcohol intake Saturated fat = elevate LDL Carbohydrates = elevate TGs
Drugs	Diuretics, cyclosporine, glucocorticoids, 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*

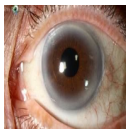
Signs & Symptoms

Signs & Symptoms:

- Dyslipidemia itself usually is **asymptomatic** but can lead to symptomatic vascular disease including:
  - Peripheral arterial diseases.
  - Coronary artery disease.
- The first presentation migh be a heart attack.
- High levels of TGs (>1000 mg/dl [11.3 mmol/l]) can cause acute pancreatitis.
- High levels of LDL can cause:
  - Eyelid xanthelasmas or Xanthomata (skin).
  - Arcus corneae. Especially in familial hypercholesterolemia.
  - Tendinous xanthoma commonly at the Achilles,
    Elbow and knee tendons as well as over the metacarpophalangeal joints.
  - In blood vessels it is called atheroma.







Measurements Of LDL-C & Non HDL-C:

2018
AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA
Guideline on the Management of Blood Cholesterol

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

Recommendations for Measurements of LDL-C and Non–HDL-C

Referenced studies that support recommendations are summarized in Online Data Supplement 1.

COR	LOE	Recommendations
I	B-NR	1. In adults who are 20 years of age or older and not on lipid-lowering therapy, measurement of either a fasting or a nonfasting plasma lipid profile is effective in estimating ASCVD risk and documenting baseline LDL-C (S2.2-1–S2.2-6).
I	B-NR	2. In adults who are 20 years of age or older and in whom an initial nonfasting lipid profile reveals a triglycerides level of 400 mg/dL (≥4.5 mmol/L) or higher, a repeat lipid profile in the fasting state should be performed for assessment of fasting triglyceride levels and baseline LDL-C (S2.2-1–S2.2-4).
IIa	C-LD	4. In adults who are 20 years of age or older and without a personal history of ASCVD but with a family history of premature ASCVD or genetic hyperlipidemia, measurement of a fasting plasma lipid profile is reasonable as part of an initial evaluation to aid in the understanding and identification of familial lipid disorders.

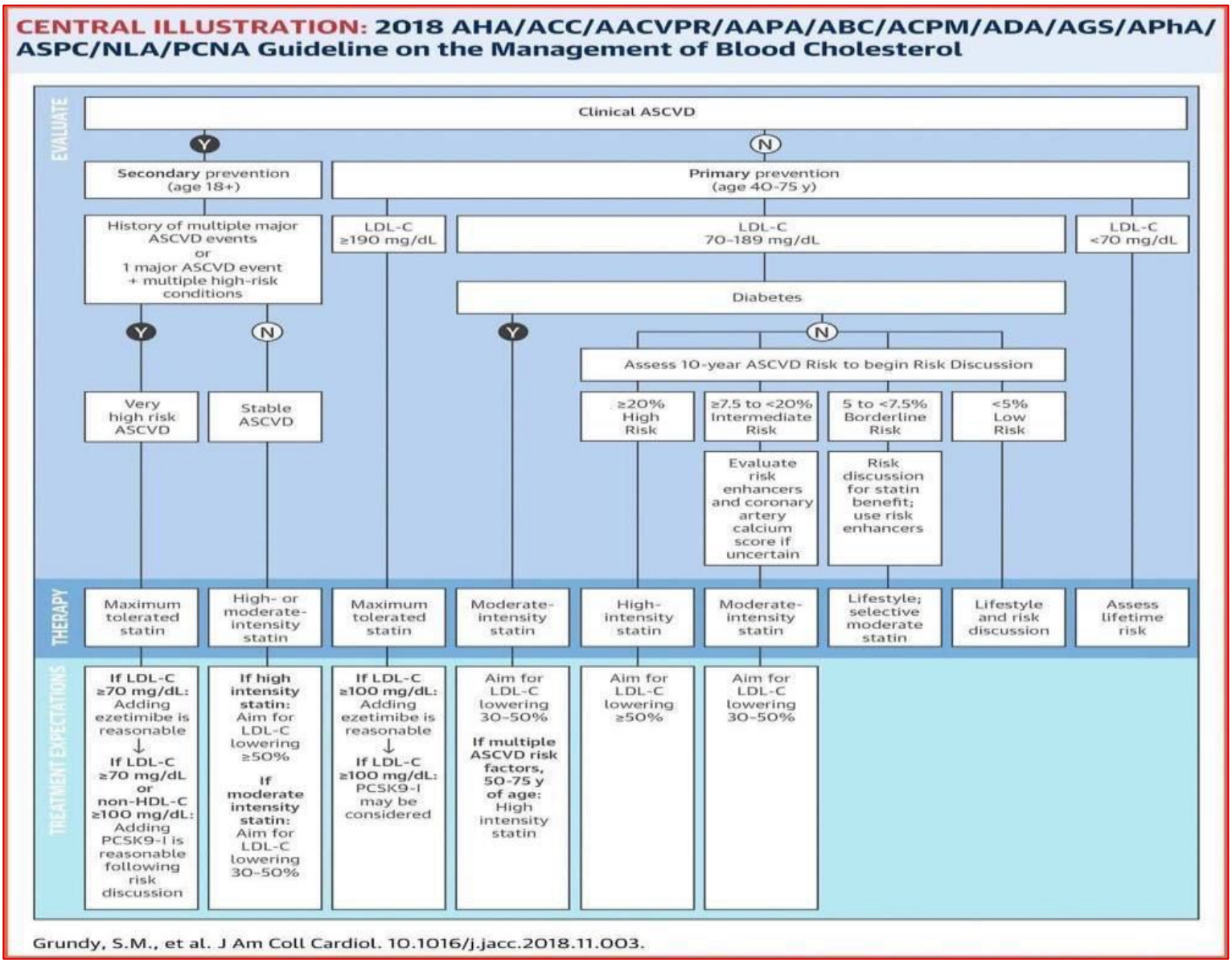
Frequent question in the practice, should I be fasting or not?

- To assess **ASCVD risk**, **no need for fasting.**
- For follow-up of **LDL**, **no need for fasting.**

What is the **lipoprotein** that's affected by **nonfasting**? **Triglycerides**, so we advise patients to fast for at least 10-12h.

2018 Guideline

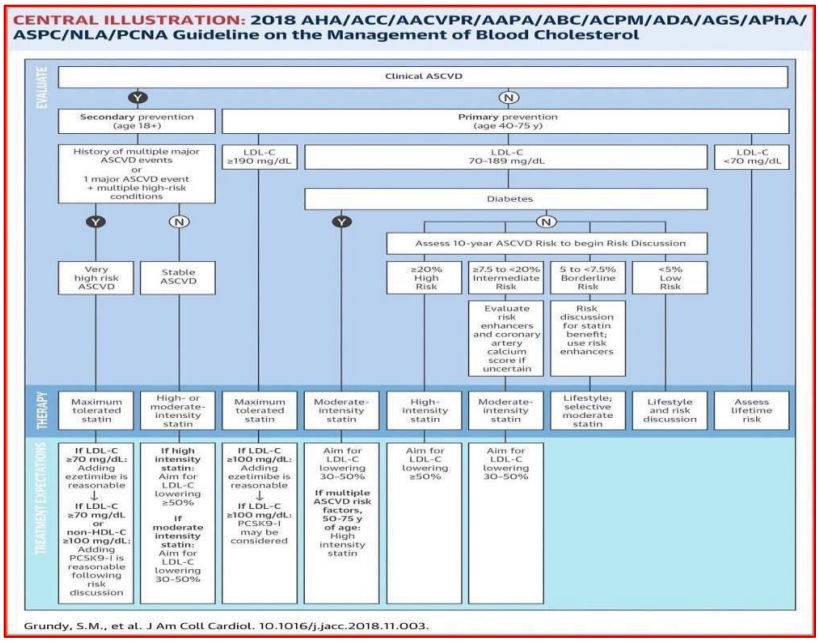
Full Explanation In The Next Page



Grundy, S.M., et al. J Am Coll Cardiol. 10.1016/j.jacc.2018.11.003.

Refill your coffee cup :)

2018 Guideline



- Similar to previous guidelines (2013) but with slight changes.
- Simply, we can generally divide it into 4 groups, AKA statin benefit groups:
- **1st Group: Clinical ASCVD ↓**
  - Clinical ASCVD = Patients with ACS, stroke, TIA, AAA etc..
  - So, we divide them to two groups based on:
    1. History of **Multiple** major ASCVD events.
    2. Or **one** Major ASCVD event **with Multiple** high risk factors.
       - First Group (A) **"very high risk"** who fit previous criteria (1 or 2):
         - Tx: Requires maximum tolerated statin (high intensity statin) with LDL target <70.
         - After 3 months, If it's still above 70, add Ezetimibe.
         - If it's still even above 70, add PCSK9-I. They are proven to decrease cholesterol and cardiovascular risk.
       - Second Group (B) who does not fit criteria (both 1&2) ;such as a patient with history of ACS only with only one risk high risk factor (age > 65)
         - Treat with high intensity statin.
- **2nd Group: LDL ≥ 190 (≥4.9 mmol/L) with LDL target <100 ↓**
  - Tx: High intensity statin. After 3 months, If it's still above 100, add Ezetimibe. If it's still even above 100, add PCSK9-I."Similar to very high risk group"
- **3rd Group: Diabetic patient**
  1. **40-75 years old:**
     - Tx: Moderate intensity statin "no need to calculate ASCVD risk"
  2. But if the patient is **50-75y** with **multiple high risk factors** (smoking,HTN or etc):
     - High intensity statin.
- **4th Group:** If the patient (40-75y) **doesn't have** clinical ASCVD, DM and LDL level within (70-189) "none of the above groups"
  - We divide them based on 10y risk estimation% of ASCVD to three groups:
    1. ASCVD Risk is >20%
       - Tx: High intensity statin.
    2. ASCVD Risk is 7.5-20%
       - Tx: moderate intensity statin" need to be discussed with the patient".
    3. ASCVD Risk is <7.5
       - Tx: Lifestyle modification, but consider multiple risk enhancer so you can start statin.

2018 Guideline

1st Group Secondary Prevention in Patients with Clinical ASCVD:

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 m^2)
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.

2nd Group Severe Hypercholesterolemia LDL ≥ 190 (≥4.9 mmol/L) with LDL Target <100

3rd Group Diabetes Mellitus in Adults:

Diabetes-specific Risk Enhancers That Are Independent of Other Risk Factors in Diabetes

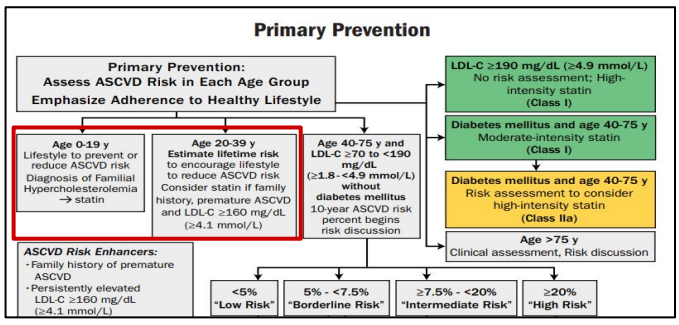
Table 5

- Long duration (≥10 years for type 2 diabetes or ≥ 20 years for type 1 diabetes)
- Albuminuria ≥30 mcg albumin/mg creatinine
- eGFR <60 ml/min/1.73 m^2
- Retinopathy
- Neuropathy
- ABI <0.9

- **Diabetic** patient below **40y** with multiple of the following **factors, statins** can benefit them.
  - Tx: Moderate intensity statin
- Statin can cause very mild increase in HbA1c, so in case of pre-diabetes, it can increase risk for development of DM by 9%.
- Pregnant women are given cholestyramine.

4th Group Primary Prevention Over The Life Span:

- Statins lower CVD events by 20-30%
- So, if a patient has ASCVD risk of 20%, and the doctor has just initiated statin. What will be his ASCVD risk for the next 10y?
  - 14% (30% of 20=6, so 20-6=14)
- (20-30%) this is known as relative risk reduction. We got 6% reduction (this is the absolute risk reduction)



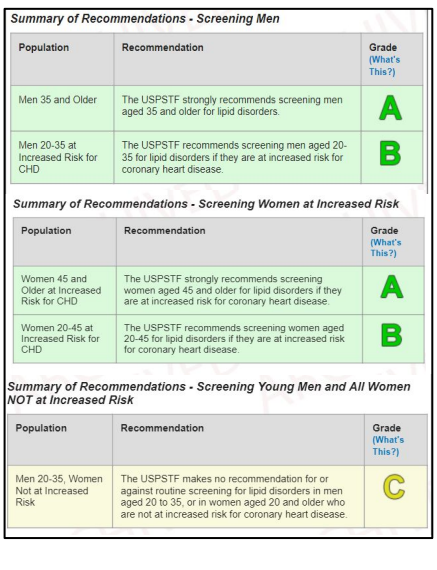
Risk Enhancing & Screening

Risk-Enhancing Factors For Clinician-Patient Risk Discussion

- **Family history of premature ASCVD;** (males <55 years; females <65 years).
- **Primary hypercholesterolemia;** (LDL- 160-189 mg/dL (4.1- 4.8 mmol/L); non-HDL-C 190-219 mg/dL (4.9-5.6 mmol/L).
- **Metabolic syndrome;** (increased waist circumference, elevated TG (>175 mg/dL, elevated BP, elevated glucose, low HDL-C (<40 mg/dL in men, <50 mg/dL in women) are factors; tally of 3 makes the diagnosis).
- **Chronic kidney disease;** (eGFR 15- 59 ml/min per 1.73 m? with or without albuminuria; not treated with dialysis or kidney transplantation).
- **Chronic inflammatory conditions;** such as psoriasis, rheumatoid arthritis (RA) or human immunodeficiency virus (HIV)/ acquired immunodeficiency syndrome (AIDS).
- **History of premature menopause (before age 40) and history of pregnancy-associated conditions that increase later ASCVD risk such as pre-eclampsia.**
- **High-risk ethnicities;** (e.g. South Asian ancestry)
- **Lipid/Biomarkers:** Associated with increased ASCVD risk:
    - Persistently* elevated, primary hypertriglyceridemia (≥175 mg/dl);
    - If measured:
        - **High-sensitivity C-reactive protein** - (≥2.0 mg/L)
        - **Elevated lipoprotein (a):** A relative indication for its measurement is family history of premature ASCVD.
            - An Lp(a) ≥ 50 mg/dL or 2125 mol/L constitutes a risk enhancing factor especially at higher levels of Lp(a).
        - **Elevated apo B 2130 mg/dL:** A relative indication for its measurement would be triglyceride ≥ 200 mg/dL.
            - A level ≥ 130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk enhancing factor.
        - **ABI <0.9.**

USPSTF Screening for Lipid Disorders in Adults:

- **Male**:
    - Anyone above 35y.
    - 20-35y with multiple risk factors .
- **Female**:
    - Anyone above 45y.
    - 20-45y with multiple risk factors.



Summary of Recommendations - Screening Men

Population	Recommendation	Grade (What's This?)
Men 35 and Older	The USPSTF strongly recommends screening men aged 35 and older for lipid disorders.	A
Men 20-35 at Increased Risk for CHD	The USPSTF recommends screening men aged 20-35 for lipid disorders if they are at increased risk for coronary heart disease.	B

Summary of Recommendations - Screening Women at Increased Risk

Population	Recommendation	Grade (What's This?)
Women 45 and Older at Increased Risk for CHD	The USPSTF strongly recommends screening women aged 45 and older for lipid disorders if they are at increased risk for coronary heart disease.	A
Women 20-45 at Increased Risk for CHD	The USPSTF recommends screening women aged 20-45 for lipid disorders if they are at increased risk for coronary heart disease.	B

Summary of Recommendations - Screening Young Men and All Women NOT at Increased Risk

Population	Recommendation	Grade (What's This?)
Men 20-35, Women Not at Increased Risk	The USPSTF makes no recommendation for or against routine screening for lipid disorders in men aged 20 to 35, or in women aged 20 and older who are not at increased risk for coronary heart disease.	C

Medical Therapy & Adjustment

1- Lifestyle Modification:

A- Physical activity

- R48. A reasonable and feasible approach to fitness therapy (i.e., exercise programs that include at least 30 minutes of moderate intensity physical activity [consuming 4-7 kcal/min] 4 to 6 times weekly, with an expenditure of at least 200 kcal/day) is recommended; suggested activities include brisk walking, riding a stationary bike, water aerobics, cleaning/scrubbing, mowing the lawn, and sporting activities (Grade A; BEL 1).
- R49. Daily physical activity goals can be met in a single session or in multiple sessions throughout the course of aday (10 minutes minimum per session); for some individuals, breaking activity up throughout the day may help improve adherence with physical activity programs (Grade A; BEL 1).
- R50. In addition to aerobic activity, muscle strengthening activity is recommended at least 2 days a week (GradeA; BEL 1)

B- Medical nutrition therapy

- R51. For adults, a reduced calorie diet consisting of fruits and vegetables (combined ≥5 servings/day), grains(primarily whole grains), fish, and lean meats is recommended (Grade A; BEL 1).
- R52. For adults, the intake of saturated fats, trans fats, and cholesterol should be limited, while LDL C lowering macronutrient intake should include plant stanols/sterols (~2 g/ day) and soluble fiber (10 25 g/day) (Grade A;BEL 1)
- R53. Primary preventive nutrition consisting of healthy lifestyle habits is recommended in all healthy children(Grade A; BEL .

C- Smoking cessation

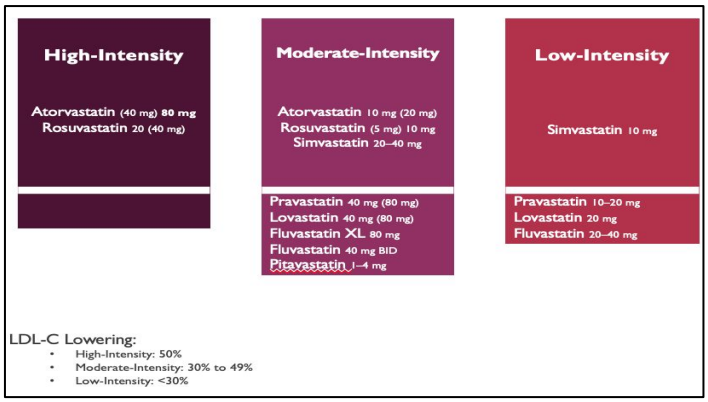
- R54. Tobacco cessation should be strongly encouraged and facilitated (Grade A; BEL 2 ; upgraded due to potential benefit).

2- Pharmacologic Thereby:

- Statins (Atorvastatin)
  - High-intensity statin has as well an immunomodulatory effect.
  - Statin can cause very mild increase in HbA1c, so in case of pre-diabetes, it can increase risk for development of DM by 9%.
- Cholesterol absorption inhibitors (Ezetimibe): Reduce intestinal absorption of cholesterol by inhibiting facilitator enzyme for cholesterol absorption (mainly cholesterol). Thus, you would affect exogenous pathway of cholesterol which only represent 20-25% at most.
- PCSK9 inhibitors (Alirocumab): PCSK9-I is involved in the degradation of low-density lipoprotein (LDL) receptors in the liver. Thus, blocking the activity of PCSK9-I will reduces the degradation of LDL receptors and increases the clearance of LDL cholesterol. PCSK9 inhibitors are injectable and expensive drugs.
- Fibrates.
- Omega 3 fish oil.
- Niacin.
- Bile acid sequestrants.
- MTP inhibitor.
- Antisense apo B oligonucleotide.
- Combination therapies.

2- Pharmacologic Thereby Cont..

- The highest reduction of **LDL** is achieved by **statins**
- **Bile acid sequestrants work mostly on LDL.**
- The highest reduction of **TGs** is achieved by **fibrates** followed by **nicotinic** acid.
  - **Start Tx with fibrate if TCA >500**
- The highest elevation of **HDL** is achieved **nicotinic acid**
- **Rule of 6: if you increase(Double) the dose of high-intensity statin the reduction of LDL increases by 6%.**



Agent	Usual recommended starting daily dosage	Dosage range	Method of administration
Cholesterol absorption inhibitors			
Ezetimibe	10 mg	10 mg	Oral
Combination therapies (single-pill)			
Ezetimibe/simvastatin	10/20 mg	10/10 to 10/80 mg	Oral

Agent	Usual recommended starting daily dosage	Dosage range	Method of administration
PCSK9 inhibitors			
Alirocumab	75 mg every 2 weeks	75-150 mg every 2 weeks	SQ
Evolocumab	140 mg every 2 weeks or 420 mg once monthly	Not applicable	SQ

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: • dysbeta-lipoproteinemia • 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

Statins Side Effects

Statin-Associated Side Effects	Frequency	Predisposing factors
Statin-associated muscle symptoms (SAMS)		
Myalgias (CK Normal)	Infrequent (1% to 5%) in RCTs; frequent (5% to 10%) in observational studies and clinical setting	Age, female sex, low body mass index, high-risk medications (CYP3A4 inhibitors, OATP1B1 inhibitors), comorbidities (HIV, renal, liver, thyroid, preexisting myopathy), Asian ancestry, excess alcohol, high levels of physical activity, and trauma
Myositis/myopathy (CK > ULN) with concerning symptoms or objective weakness	Rare	-
Rhabdomyolysis (CK >10 × ULN + renal injury)	Rare	-
Statin associated autoimmune myopathy (HMGCR antibodies, incomplete resolution)	Rare	-
New onset diabetes mellitus	Depends on population; more frequent if diabetes mellitus risk factors are present, such as body mass index ≥30, fasting blood sugar ≥100 mg/dL; metabolic syndrome, or A1c ≥6%.	Diabetes mellitus risk factors/metabolic syndrome High intensity statin therapy
Liver		
Transaminase elevation 3× ULN Stop medication if LFTs is elevated 3 times of normal.	Infrequent	-
Hepatic failure	Rare	-
CNS		
Memory/cognition	Rare/unclear	-
Cancer	No definite association	-

- **Other side effects (Unclear/unfounded frequency):** Renal function, Cataracts, Tendon rupture, Hemorrhagic stroke, Interstitial lung disease, Low testosterone.
- Proximal myopathy:
  - If the patient complains of muscle pain(myalgia), Creatine Kinase(CK) measurement is required:
    - If CK within normal = reassure patient.
    - If CK below 10times = you can continue medication but with observation.
    - If CK is above 10times= discontinue medication.
- To confirm that the cause is due to statin do challenge rechallenge test where you stop then give statin after 2 weeks if sme symptoms then its b/c of statin & you have to stop it.
  - Sometimes, there is a concurrent disease that causes myopathy such hypothyroidism,vit D deficiency or etc. so, you need to rule them out.
  - Also, we can stop the medication for a while, then check with the patient if the symptoms disappear. This can helps in diagnosis.
  - Statin intolerance happens when the patient has used 2 or more types of statins but with no response.

Management of adverse effects

Management Of Statins ADRS:

- **Mild to moderate muscle spasm:**
  - D/C statins until muscle spasm resolve.
  - Re-challenge a lower dose, if the symptoms resume, D/C statins 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:**
  - Reinforce lifestyle modification.
- **Memory impairment:**
  - Consider other potential causes before stopping statin.

Non-Statin Therapies:

- Non-statin therapies alone or in combination with statin do not provide acceptable risk reduction benefits compared to adverse effect.
- The Non-statin agents include:
  - Zetia.
  - Fibrates.
  - Fish oil.
  - Niacin.

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

Follow-Up:

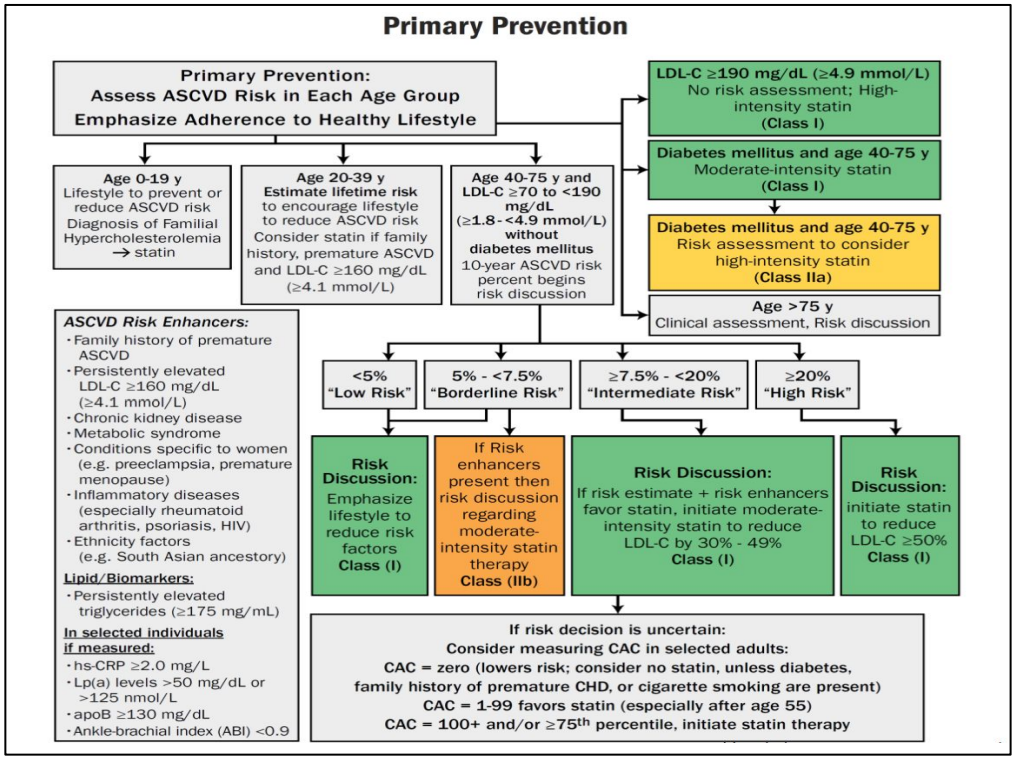
- Assess adherence and percentage response to LDL-C lowering medication and lifestyle changes with repeating lipid measurement **4-12 weeks** after statin initiation or dose adjustment.
- Repeat every **3-12 months** as needed.
- After starting management with statin or other modalities including Lifestyle modification, when to follow-up patient?
- 4-12 week (usually every 3m) because statin can show its effect after 1 month. And usually lipid profile changes within 1-3 months.

Extra

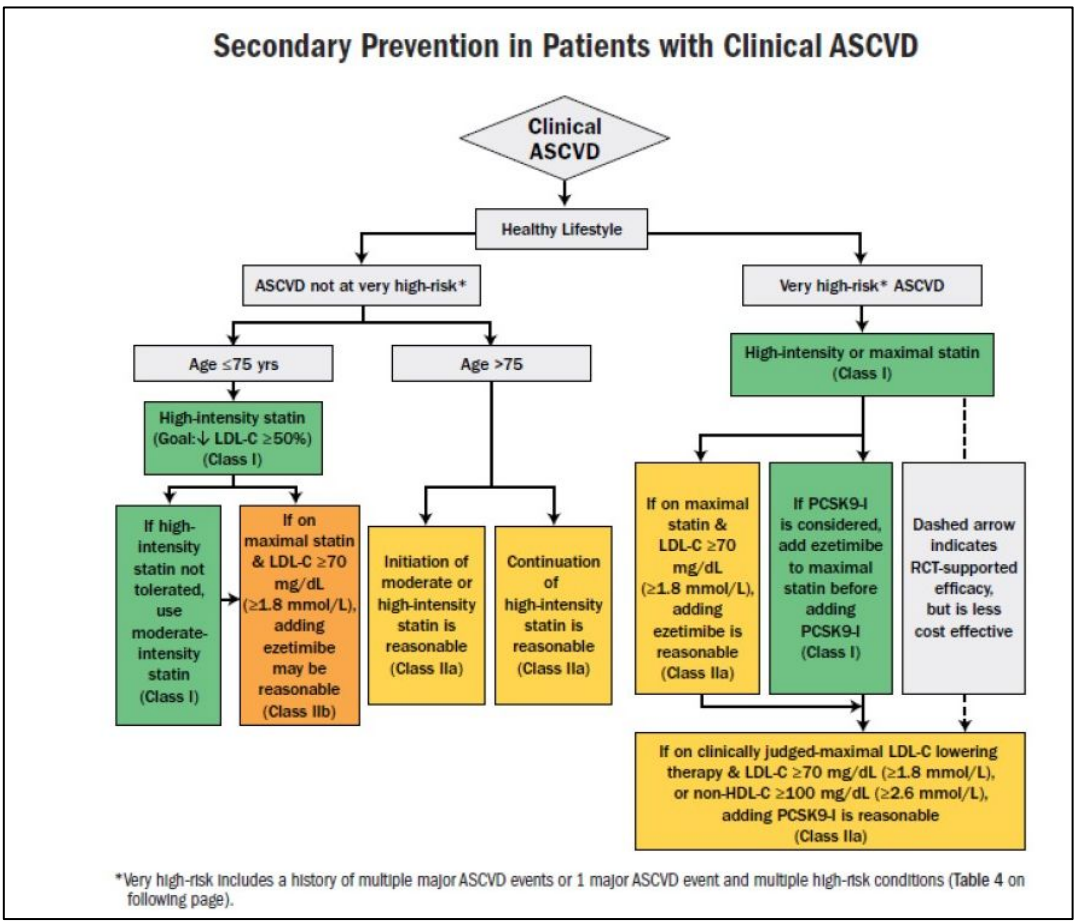
- The incidence of muscle symptoms in patients taking statins has ranged from 5% to 18% in large studies and are reported to be severe in 0.1%. Because statins are one of the most commonly prescribed medications worldwide, these percentages represent a significant number of affected patients.
- Treatment depends on the patient's symptoms and CPK levels. If the CPK is less than five times normal, reassurance will suffice. If CPK levels are between 5 and 10 times normal and the patient is asymptomatic or able to tolerate the symptoms, then the statin can still be continued. However, if the symptoms are intolerable, then the statin should be discontinued until the CPK normalizes. If CPK more than 10 times normal, the statin should be discontinued until levels return to normal. In these cases, once the CPK is again normal, either the same statin can be reintroduced at a lower dosage or on alternate-day dosing, or a different type of statin such as fluvastatin or pravastatin (which have been associated with a lower incidence of myalgias due to their pharmacologic properties) can be tried.

Prevention

Primary ACVSD Prevention:

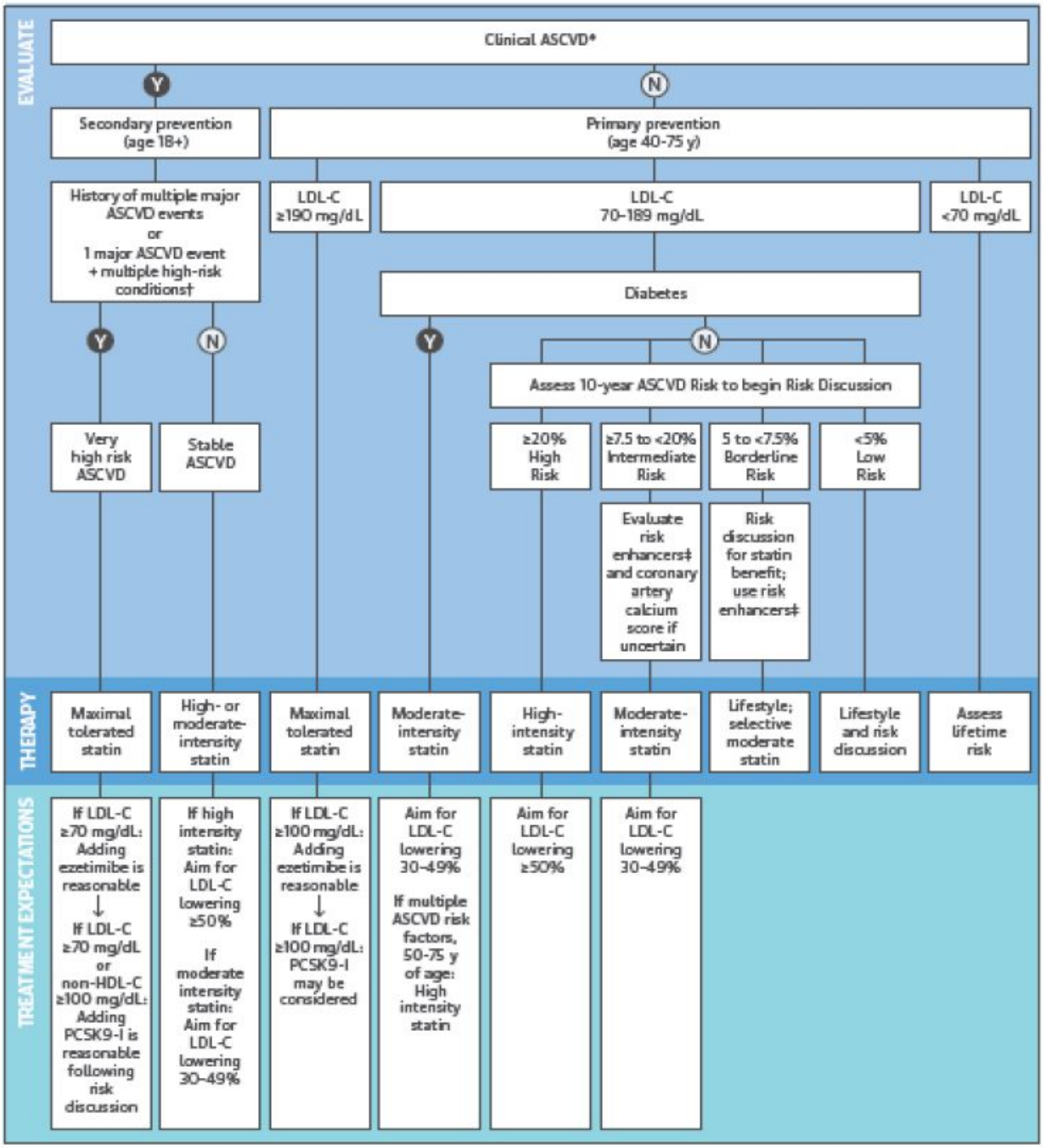


Secondary ACVSD Prevention:



Overview of Primary and Secondary ASCVD Prevention

This tool provides a broad overview of the 2018 Cholesterol Guideline.
Please refer to the full guideline document for specific recommendations.



* Clinical ASCVD consists of acute coronary syndromes, those with history of myocardial infarction, stable or unstable angina or coronary other arterial revascularization, stroke, TIA, or peripheral artery disease including aortic aneurysm, all of atherosclerotic origin.

† Major ASCVD events: Recent ACS, history of MI, history of ischemic stroke, symptomatic PAD; High-Risk Conditions: ≥65 y of age, heterozygous FH, hx of HF, prior CABG or PCI, DM, HTN, CKD, current smoking, persistently elevated LDL-C≥100 mg/dL.

‡ Risk Enhancers: Family history of premature ASCVD, persistently elevated LDL-C ≥160 mg/dl, chronic kidney disease, metabolic syndrome, conditions specific to women (e.g. pre-eclampsia, premature menopause), inflammatory disease (especially psoriasis, RA, or HIV), ethnicity (e.g. South Asian ancestry), Lipid/biomarkers; persistently elevated triglycerides (≥175 mg/dL), If measured: hs-CRP ≥2.0 mg/L, Lp(a) levels ≥50 mg/dL or ≥125 nmol/l, apoB ≥130 mg/dL especially at higher levels of Lp(a), ABI <0.9.

Lecture Quiz

Q1: A 35-year-old man with no history of cardiac or other vascular disease asks how often he should have routine cholesterol screening. Which of the following is the best answer?

A. Every 3 months
B. Annually
C. Every 5 years
D. Every 7-10 years

Q2: A 38-year-old man presents to your clinic following a health fair screening of his cholesterol level because he was told that it is high. He watches his diet, plays tennis, exercises 3 to 5 times per week, and appears to be in good physical condition. He is a nonsmoker and has no family history of cardiovascular disease. His profile is total cholesterol 202 mg/dL, HDL 45 mg/dL, LDL 128 mg/dL, and triglycerides 145 mg/dL. Following a review of this patient's profile, which of the following would you recommend?

A. Administer gemfibrozil.
B. Administer HMG-CoA reductase inhibitor.
C. Administer low-dose niacin and slowly increase to achieve 3 g daily.
D. Suggest he continue his current diet and exercise program.

Q3: Which of the following patients is the best candidate for lifestyle modification alone rather than lipid-lowering medications?

A. A 60-year-old diabetic male smoker with a recent myocardial infarction: cholesterol 201 mg/dL, HDL 47 mg/dL, and LDL 138 mg/dL
B. A 62-year-old diabetic man: cholesterol 210 mg/dL, HDL 27 mg/dL, and LDL 146 mg/dL
C. A57-year-old asymptomatic woman: cholesterol 235mg/dL,HDL92mg/dL, and LDL 103 mg/dL
D. A 39-year-old man with nephrotic syndrome: cholesterol 285 mg/dL, HDL 48 mg/dL, LDL 195 mg/dL

Q4: Which of the following patients meets criteria for the diagnosis of the metabolic syndrome?

A. A man with waist circumference of 110 cm, well- controlled diabetes mellitus with fasting plasma glucose of 98 mg/dL, and blood pressure of 140/75 mmHg
B. A woman with triglycerides of 180 mg/dL, waist cir- cumference of 75 cm, and polycystic ovary syndrome
C. A man with nonalcoholic liver disease, obstructive sleep apnea, and blood pressure of 135/90 mmHg
D. A woman with high-density lipoprotein (HDL) of 54 mg/dL, blood pressure of 125/80 mmHg, and fasting plasma glucose of 85 mg/dL

Q5: You are managing a patient with the metabolic syn- drome. She is an obese woman with poorly controlled dia- betes and dyslipidemia. Her HbA1C is 8.8% and fasting plasma glucose is 195 mg/dL. Low-density lipoprotein (LDL) cholesterol is 98 mg/dL and triglycerides are 276 mg/dL. Her medications include insulin, atorvastatin, hy- drochlorothiazide, and aspirin. What is the best option for a medication to treat this patient's hypertriglyceridemia?

A. Cholestyramine
B. Colestipol
C. Ezetimibe
D. Fenofibrate
E. Nicotinic acid

Answers: Q1:C | Q2:D | Q3:C | Q4:A | Q5:D

THANKS!!

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Send us your feedback:
We are all ears!