AETC AIDS Education & Training Center Program Southeast

Dyslipidemia Management in Persons Living with HIV

Andrea Levin, PharmD, BCACP

Faculty, South Florida Southeast AETC

Assistant Professor,

Nova Southeastern University College of Pharmacy

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Disclosures

- The activity planners and speakers do not have any financial relationships with commercial entities to disclose.
- The speakers will not discuss any off-label use or investigational product during the program.
- This slide set has been peer-reviewed to ensure that there are no conflicts of interest represented in the presentation

Objectives

- Identify patient specific lipoprotein goals based on current relevant guidelines
- Identify key elements to therapeutic lifestyle changes to communicate to patients
- Select an appropriate lipid lowering agent based on patient risk factors, lipoprotein levels, ASCVD risk, potential drug interactions, contraindications, and comorbidities
- Discuss patient counseling pearls including: administration, adverse effects, and monitoring parameters

Abbreviations

- Total cholesterol (TC)
- Triglycerides (TG)
- High density lipoprotein (HDL)
- Low density lipoprotein (LDL)
- Therapeutic lifestyle changes (TLC)
- Coronary heart disease (CHD)
- Creatine kinase (CK or CPK)
- Liver function tests (LFTs)
- Heterozygous familial hypercholesterolemia (HeFH)
- Homozygous familial hypercholesterolemia (HoFH)
- Atherosclerotic cardiovascular disease (ASCVD)
- Upper limit of normal (ULN)
- Within normal limits (WNL)

Dyslipidemia Definition

- Elevation in total cholesterol (TC), elevation in low density lipoprotein (LDL), elevation in triglycerides (TG), or low high density lipoprotein (HDL)
  - May be a combination of the above
- Dyslipidemia vs Hyperlipidemia?

Background

- 73.5 million (31.7%) Americans have high LDL
- Individuals with high total cholesterol are two times more likely to develop heart disease
- Only 55% of adults who need cholesterol lowering therapy have been prescribed these medications
- HIV is an independent risk factor for CVD
- ARTs can increase the risk of dyslipidemia

Should ART Be Modified?

- Lopinavir/ritonavir can cause hypertriglyceridemia.
- Consider switching a protease inhibitor to INSTI or an NNRTI
  - INSTI: dolutegravir, raltegravir, or bictegravir
  - NNRTI: rilpivirine or doravirine
- If patient is on older therapies such as stavudine or zidovudine, consider switching to tenofovir or abacavir to improve lipids.
  - Tenofovir disproxil fumarate may have lipid-lowering effects

Should ART Be Modified?

- Switching ART instead of adding lipid-lowering therapy may assist in:
  - Reducing pill burden and polypharmacy
  - Reducing cost
  - Minimizing side effects
  - Reducing the drug–drug interaction
- Could virologic suppression be impacted?
- Consideration should be given with pleiotropic effects of statins

Leading Causes of Death 2017

Condition	Number of Deaths
Heart Disease	647,457
Cancer	599,108
Accidents	169,936
Chronic lower respiratory diseases	160,201
Stroke (CVA)	146,383
Alzheimer's Disease	121,404
Diabetes	83,564
Influenza and Pneumonia	55,672
Nephritis, nephrotic syndrome	50,633
Suicide	47,173

https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm

Metabolic Syndrome

Risk Factor	Level
Abdominal obesity Men Women	Waist circumference > 102 cm (> 40 in) > 88 cm (> 35 in)
Triglycerides***	≥ 150 mg/dL
HDL cholesterol*** Men Women	 < 40 mg/dL < 50 mg/dL
Blood pressure***	Systolic ≥ 130 and/or diastolic ≥ 85 mm Hg
Fasting glucose***	≥100 mg/dl

***Drug treatment will be an alternative indicator

Detection and Evaluation

- Obtain lipoprotein levels
- Identify lipoprotein goals based on risk
- Manage through therapeutic lifestyle changes (TLC) alone (if possible) or in conjunction with pharmacologic therapy

Obtaining Lipid Levels

- Fasting lipoprotein profile should be performed when aged 20 and older
  - What about non fasting labs?
  - If TG are ≥400 mg/dl, repeat fasting labs

LDL Lab **Reference** Goals*

LDL Goal (mg/dl)	Classification
<100	Optimal
100-129	Near Optimal
130-159	Borderline High
160-189	High
≥190	Very High

***Patient Specific Goals Will Vary**

Calculated LDL

- Friedewald equation

  LDL= (TC-HDL)-(TG/5)

  - Avoid if TG >400 mg/dl or LDL is <70 mg/dl
    - Direct LDL better indicator

Other Goals

Total Cholesterol (mg/dl)	Classification
<200	Desirable
200-239	Borderline High
≥240	High

HDL (mg/dl)	Classification
Men ≥40	Optimal
Women ≥50	Optimal
Men or Women ≥60	High
Men or Women <40	Low

Triglyceride Goals

Triglyceride Goals (mg/dl)	Classification
<150	Normal
150-199	Borderline High
200-499	High
≥500	Very High

TLC Options

- Plant stanols and sterols
  - 2-3 grams may reduce LDL by 6-15%
  - Benecol ®
  - Cholestoff Supplements ®
- Psyllium
  - Reduces LDL and TC by 5-20%
- Weight controls
- Increasing physical activity and improving diet
- Increasing fatty fish consumptions
  - 20 grams will reduce CHD risk by 7%
  - Reduces TG
- Red Yeast Rice?????

Pharmacologic Options

- HMG-CoA reductase inhibitors (Statins)
- Cholesterol absorption inhibitors
- Proprotein Convertase Subtilisin Kexin Type 9 Inhibitors (PCSK9i)
- Bempedoic acid
- *Nicotinic Acid*
- *Fibric Acid derivatives (fibrates)*
- *Omega-3-fatty acids*
- *Bile Acid Sequestrants (BAS)*

Baseline Labs

- Liver Function Tests (LFTs)
  - Baseline considerations:
    - Rule out hepatic impairment if LFTs are 3 x ULN
  - LFTs should only be rechecked while on lipid lowering therapy if clinically indicated
    - Unusual fatigue or weakness, loss of appetite, upper belly pain, dark colored urine, yellowing of the skin or whites of the eyes
    - What about PLWH?
- Lipid Panel

Pharmacologic Effect on Lipid Levels

Drug Class	TC	LDL	HDL	TG
Statins	15-60% ↓	21-55% ↓	2-10% ↑	6-30% ↓
Ezetimibe --- w/statin		10-18% ↓ --- + 25% ↓		
PCSK9i	36-42% ↓	43-64% ↓		
Bempedoic Acid		15-17% ↓		
Fibrates	20-25% ↓	20-25% ↓ or ↑	6-18% ↑	20-50% ↓
BAS	20% ↓	15-25% ↓	3-5% ↑	-- or ↑
Nic. Acid	25% ↓	10-25% ↓	10-35% ↑	20-50% ↓

HMG-CoA Reductase Inhibitors

- Rosuvastatin, atorvastatin, simvastatin, pitavastatin, lovastatin, pravastatin, fluvastatin
- First line therapy to achieve LDL goals
- Reduces the risk for acute coronary syndrome for primary and secondary prevention
- Reduces the risk of stroke in secondary prevention

Statin Counseling

- Rosuvastatin, atorvastatin, pitavastatin,& fluvastatin XL can be dosed anytime
  - All other statins must be dosed at bedtime
- CYP 3A4 Considerations
  - Grapefruit juice
  - Certain ARTs
- Avoid in pregnancy
  - Discuss contraception
  - Discontinue statin therapy 1-2 months prior to pregnancy attempt
  - If pregnancy is discovered while patient is on statin, stop statin immediately
- Drug interactions/statin dosing limits/adherence
- Signs/symptoms of myopathies

Statin-Associated Muscle Symptoms (SAMS)

- Myalgia: muscle ache/weakness without CK elevation
- Myositis: muscle pain with CK elevation
- Rhabdomyolysis: muscle pain with markedly elevated CK (>10 x ULN)
  - Extensive muscle necrosis
  - Acute renal failure
  - Myoglobinuria
  - Brown urine

Drug Interactions: Statins and ART

- Contraindications with simvastatin and lovastatin:
  - Protease inhibitors
  - Potent CYP 3A4 inhibitors
  - Use of cobicistat as boosting agent with elvitegravir
- Use caution with darunavir in combination with pravastatin
- Atorvastatin and rosuvastatin may require a dose reduction with protease inhibitors, and elvitegravir/cobicistat
- Data on fluvastatin are limited, but it is not likely to interact significantly with protease inhibitors.
- Efavirenz decreases atorvastatin, pravastatin, and simvastatin levels by approximately 40 to 60%, which may require higher doses of the statin
  - Do not exceed maximum statin dose

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Nic. Acid	25% ↓	10-25% ↓	10-35% ↑	20-50% ↓

What Does the Evidence Say?

- ENHANCE was not an outcomes study
- SHARP: Ilustrated benefit of using ezetimibe plus a statin in individuals with CKD in reducing cardiovascular outcomes
- IMPROVE-IT: Illustrated some benefit in high risk cardiovascular patients with ezetimibe combined with statin therapy
- Has safety data in PLWH

Pharmacologic Effect on Lipid Levels

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Nic. Acid	25% ↓	10-25% ↓	10-35% ↑	20-50% ↓

Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) Inhibitors

- Subcutaneous injection approved with lifestyle modifications and maximally tolerated statin therapy
  - Individuals with ASCVD who require additional lowering of LDL cholesterol
- Alirocumab: Adults with heterozygous familial hypercholesterolemia (HeFH)
- Evolocumab: Adults with HeFH
  - Adults or adolescents (13-17) with homozygous familial hypercholesterolemia (HoFH)

PCSK9 Inhibitor Evidence

- Has been found to reduce LDL levels significantly when compared to combinations with ezetimibe or placebo
- Has outcomes data supporting its use in high risk CVD patients
- Has safety data in PLWH

Pharmacologic Effect on Lipid Levels

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Bempedoic Acid (Nexletol®)

- 180 mg PO once daily
- Do not exceed 20 mg of simvastatin or 40 mg of pravastatin
  - Increased risk of myopathies if above doses are exceeded
- Counseling/considerations:
  - Tendon rupture: Use with caution in adults >60 years of age, those with CKD, and/or corticosteroid use
  - Hyperuricemia: Gout
  - Avoid in pregnancy
- Monitor lipids 4-12 weeks after initiation
- Awaiting outcomes data

Pharmacologic Effect on Lipid Levels

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

Guidelines

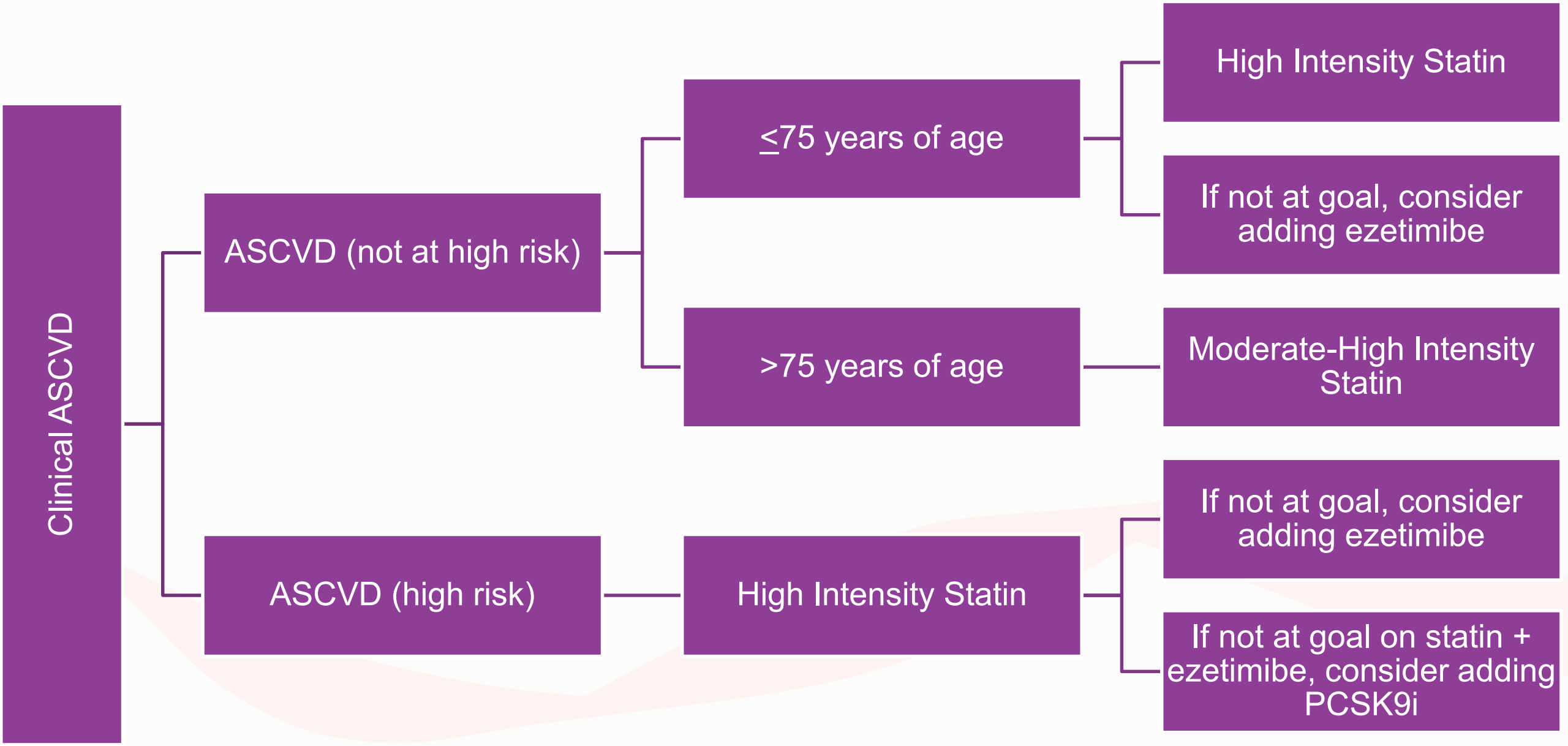
- 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk
- 2017: American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) Guidelines for the Management of Dyslipidemia and Prevention of Cardiovascular Disease
- 2013: ACC/AHA Guidelines on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults.
- 2002 with 2004 update: The National Cholesterol Education Program (NCEP) Adult Treatment Panel III

4 Major Statin Benefit Groups

- Clinical atherosclerotic cardiovascular disease (ASCVD)
- Primary elevations in LDL ≥190 mg/dl (not due to secondary causes)
- Individuals with Type I or Type II DM who are 40-75 years of age *with LDL levels of 70-189 mg/dl* without clinical ASCVD
- Individuals without clinical ASCVD or diabetes who are 40-75 years of age with LDL levels of 70-189 mg/dl and an estimated 10 year ASCVD risk ≥7.5%
  - Determined by estimated absolute 10 year risk of developing ASCVD

ASCVD

- Acute coronary syndromes
  - History of MI
  - Stable or unstable angina
  - Coronary or other arterial revascularization
- Stroke or TIA (ischemic)
- Peripheral arterial disease (atherosclerotic origin)


Clinical ASCVD
ASCVD (not at high risk)
≤75 years of age
High Intensity Statin
If not at goal, consider adding ezetimibe
>75 years of age
Moderate-High Intensity Statin
ASCVD (high risk)
High Intensity Statin
If not at goal, consider adding ezetimibe
If not at goal on statin + ezetimibe, consider adding PCSK9i

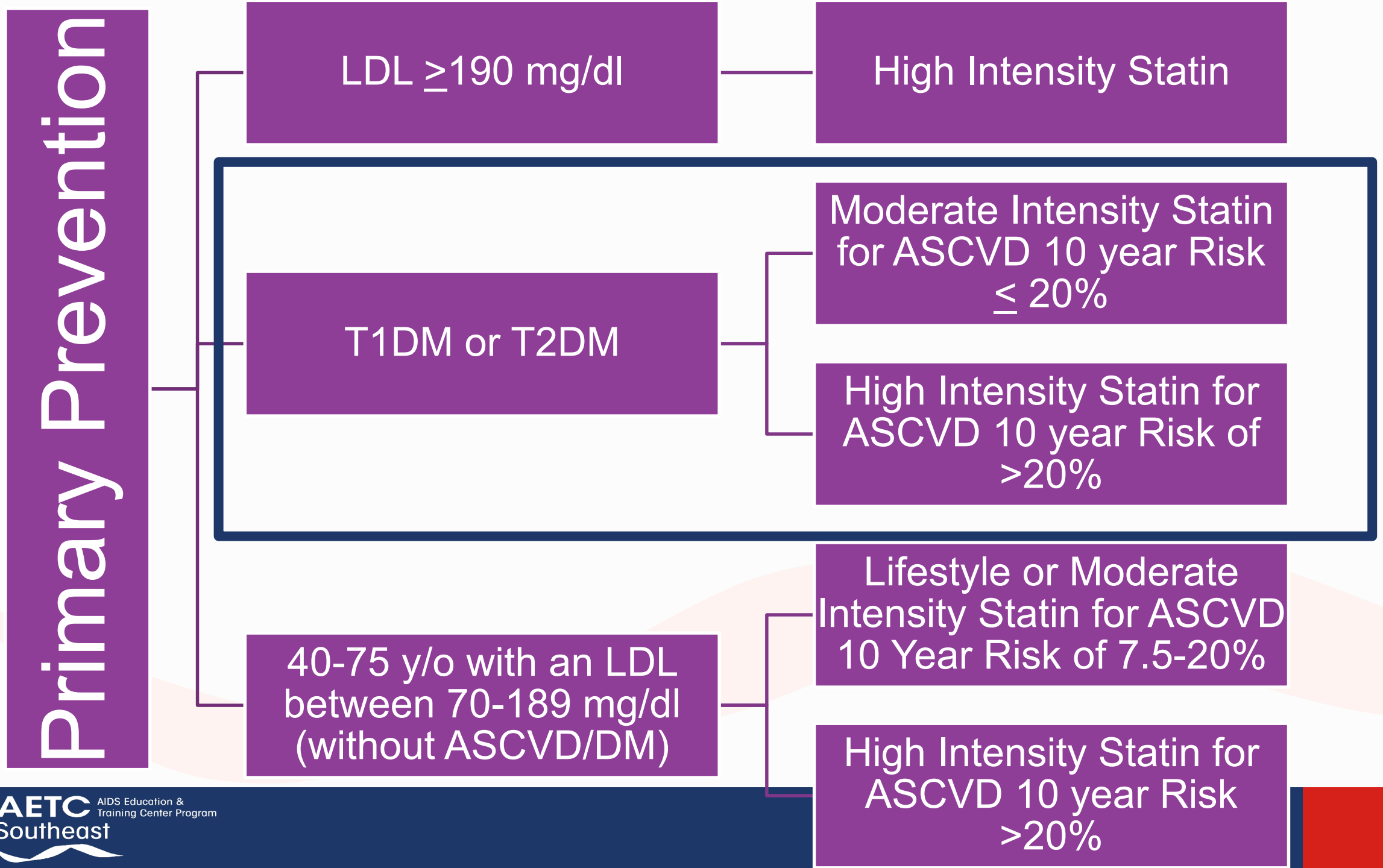
Very High Risk

Multiple ASCVD events

or

One ASCVD event + multiple high risk conditions

High Risk Conditions	
Age ≥ 65	Congestive HF
HTN	CKD ≥ Stage 3
Heterozygous FH	Smoking
Hx of PCI or CABG outside of ASCVD event	LDL >100 mg/dl despite max tolerated statin and ezetimibe
DM	


Primary Prevention
LDL ≥190 mg/dl
High Intensity Statin
T1DM or T2DM
Moderate Intensity Statin for ASCVD 10 year Risk ≤ 20%
High Intensity Statin for ASCVD 10 year Risk of >20%
40-75 y/o with an LDL between 70-189 mg/dl (without ASCVD/DM)
Lifestyle or Moderate Intensity Statin for ASCVD 10 Year Risk of 7.5-20%
High Intensity Statin for ASCVD 10 year Risk >20%

Diabetes

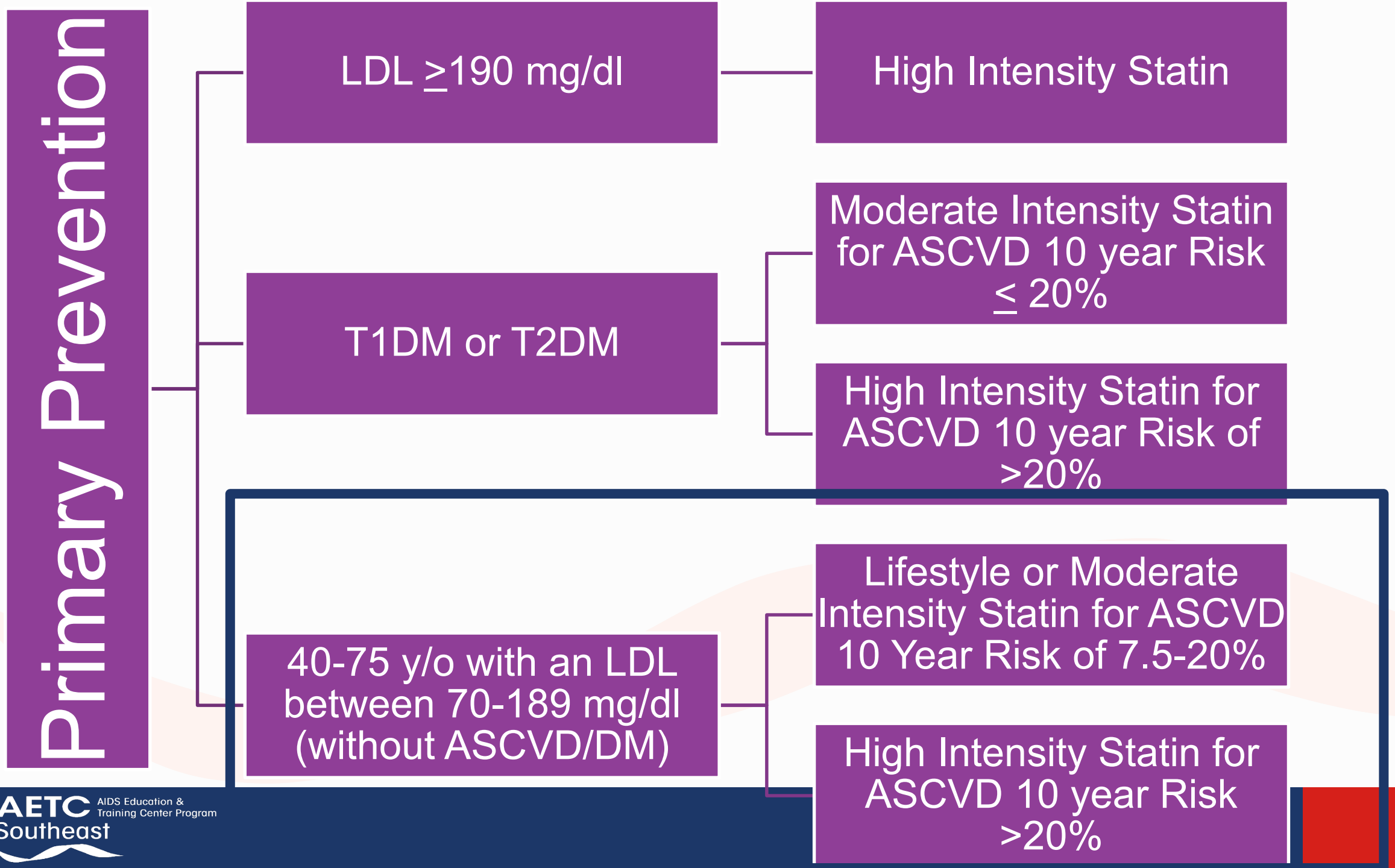
- All patients >40 y/o should be on a moderate intensity statin
- If ASCVD risk is >20% or individual is 50-75 y/o with multiple risk factors, decrease LDL by ≥50%
  - Consider adding ezetimibe to max tolerated statin dose if LDL does not decrease by ≥50%

14.4%
Baseline 10 years ASCVD Risk

vs

25.6%
Baseline 10 years ASCVD Risk

How do we approach the above 10 year ASCVD Risk Calculations?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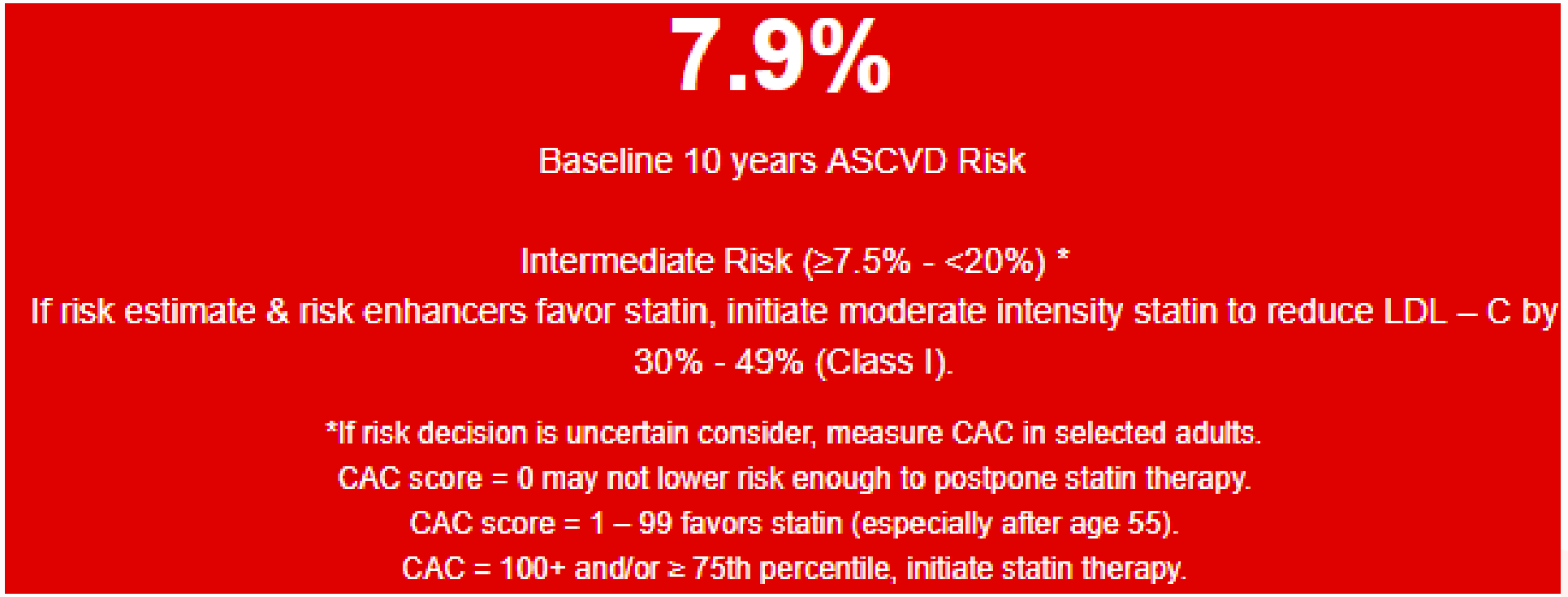


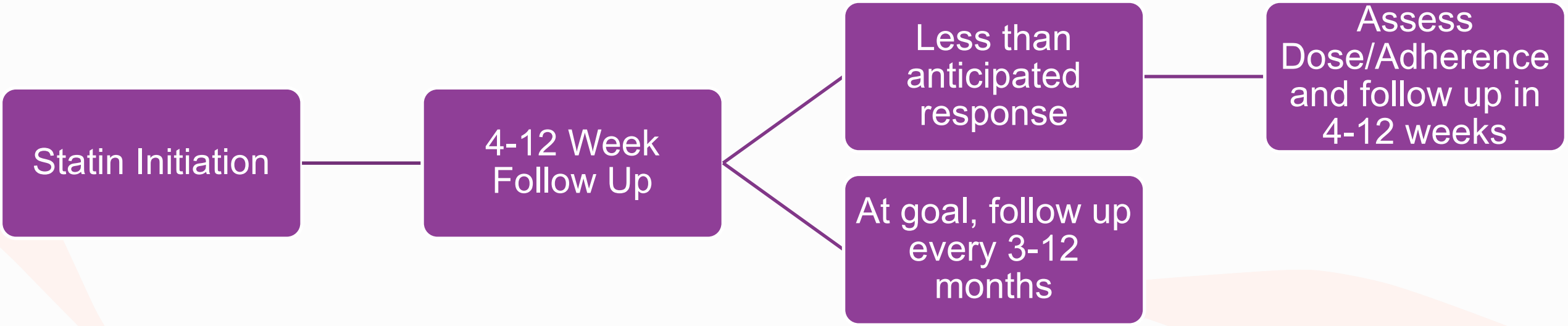
http://static.heart.org/riskcalc/app/index.html#!/baseline-risk

High, Moderate, & Low Intensity Statin Therapy

High Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily Dose LDL lowering ≥50%	Daily Dose LDL lowering 30-49%	Daily Dose LDL lowering <30%
Atorvastatin 40 and 80 mg **Rosuvastatin 20 (40) mg**	**Rosuvastatin (5) 10 mg** **Atorvastatin 10 (20) 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

****Statins in bolded red are considered primary statins**

Monitoring/Follow Up



Is the patient at goal?

- Consider the desired LDL reduction
- Consideration can me made in using an **LDL goal of <70 mg/dl** in the following statin benefit group:
  - Clinical atherosclerotic cardiovascular disease (ASCVD) with or without any of the other three statin benefit groups
    - If LDL is not <70 mg/dl on maximum tolerated statin dose, add ezetimibe

Is the patient at goal?

- Consideration can me made in using an **LDL goal of <100 mg/dl** in the following statin benefit group:
  - Primary elevations in LDL ≥190 mg/dl (not due to secondary causes)
    - If LDL is not <100 mg/dl on maximum tolerated statin dose, add ezetimibe

Ezetimibe & PCSK9 Inhibitors

- Ezetimibe can be used in any statin benefit group as an add-on agent to achieve the desired LDL goal
  - Majority of evidence supports use in high risk individuals (ie clinical ASCVD, LDL ≥190 mg/dl)
- Combination therapy with ezetimibe may be suitable for:
  - High risk patients not reaching goal on maximally tolerated statin dose
  - Individuals who cannot tolerate statins
  - Individuals with DM who do not achieve their LDL goal
- PCSK9i have evidence of benefit in individuals with clinical ASCVD, LDL ≥190 mg/dl, and/or DM as an add on to ezetimibe

HIV

- 40-75 y/o with LDL 70-189 mg/dl and ASCVD of >7.5% initiate moderate or high intensity statin
- Consider drug interactions

Other Updates: HF and CKD

- HFrEF: Consider a moderate intensity statin if life expectancy >3 years
- CKD:
  - Not on dialysis
    - 40-75 y/o with LDL 70-189 mg/dl and ASCVD of >7.5% initiate moderate intensity statin + ezetimibe
  - Dialysis:
    - Continue statin if patient already on statin but DO NOT initiate statin therapy

Patient Considerations

- Include patient in decision making
- Properly educate the patient
- Simplify regimen
- Consider cost
- Be supportive of short term goals
- Incorporate regimen into patient's daily life
- Discuss lifestyle modifications
- Adherence and self monitoring

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