Dyslipidemia in diabetes

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Session objectives

- Recognize the indications for statins in diabetes
- Discuss the management of specific side effects of statins
- Explain the indications for non-statin therapies
- Describe the approach and management of hypertriglyceridemia

CASE 1

- A 52-year-old man with DM 2 & hypertension
- No smoking
- B.P. 125/70
- Total cholesterol 4.4 mmol (170 mg), LDL 2.4 mmol (95 mg), HDL 1.0 mmol (40 mg), TG 1.9 mmol (170 mg)
- **How to approach lipids?**

Statin therapy in DM

- Categorize the patient:
  - With ASCVD (secondary prevention)
  - Without ASCVD (primary prevention)
- Assess 10-year ASCVD risk using ACC/AHA calculator for patients without ASCVD
- Statins for:
  - ASCVD
  - Age ≥40 years

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ASCVD (Atherosclerotic cardiovascular disease)

- Acute coronary syndromes
- Myocardial infarction
- Stable or unstable angina
- Coronary or other arterial revascularization
- Stroke or TIA
- Peripheral arterial disease

ACC/AHA guidelines. J Am Coll Cardiol 2018 10.1016/j.jacc.2018.11.003

Lifestyle changes

- Mediterranean or DASH diet
- Reduction of saturated and trans fat
- ↑ Intake of n-3 fatty acid, fibers, plant stanols/sterols in **diet**
- Physical activity
- Weight control
- Smoking cessation

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Statins in DM

ASCVD
All ages

High intensity statin

Statins in diabetes:
primary prevention

Age ≥40 years

Moderate intensity statin

- Age 40-75 with no CV risk
- Age ≥75 years

High intensity statin if:

- Age 40-75 & ≥1 CV risk factor(s): (HTN, smoking, CKD, albuminuria, family history of premature CVD)

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Statins in diabetes:
primary prevention
(age 20-39 years)

ADA guidelines

- ***Consider*** moderate intensity statin if **multiple** CV risk factors

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Statins in diabetes primary prevention (age 20-39 years)

ACC/AHA guidelines

- **Consider** statin if any of the following:
  - DM 2 for ≥10 years or DM 1 for ≥20 years
  - Albuminuria
  - eGFR <60
  - Retinopathy
  - Neuropathy
  - Ankle brachial index <0.9

ACC/AHA Guidelines. J Am Coll Cardiol 2018 10.1016/j.jacc.2018.11.003

Moderate-intensity statins

- **Lower LDL by 30 to 49%:**
  - Atorvastatin 10 or 20 mg qd
  - Fluvastatin XL 80 mg qd
  - Lovastatin 40 or 80 mg qd
  - Pitavastatin 1, 2, or 4 mg qd
  - Pravastatin 40 or 80 mg qd
  - Rosuvastatin 5 or 10 mg qd
  - Simvastatin 20 or 40 mg qd

High-intensity statins

- **Lower LDL by ≥50%**
  - Atorvastatin 40 or 80 mg qd
  - Rosuvastatin 20 or 40 mg qd

LDL targets: ADA guidelines

No ASCVD → LDL <1.8 mmol (70 mg)

ASCVD → LDL <1.3 mmol (55 mg)

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CASE 1: approach

- Patient with DM & ≥40 years
  - So needs statin
- As patient's age is 40-75 y with CVD risk factor (hypertension):
  - Use high intensity statin

Labs before starting statins?

- **ALT:**
- Baseline
- Should they be monitored?
- No need to monitor unless symptoms of hepatic dysfunction develop or patient is on other medications that may affect liver function

ACC/AHA Guidelines. J Am Coll Cardiol 2018 10.1016/j.jacc.2018.11.003
www.fda.org

F/U after starting statin

- Measure lipids after 1-3 months from starting
- Then every year
- Measure lipids if changing dose or treatment
- To assess response & adherence
- Moderate-intensity statins: ↓ LDL 30-49%
- High-intensity statins: ↓ LDL ≥50%

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CASE 2

- A 55-year-old man with DM 2
- LDL 3.2 mmol (123 mg)
- Advised for statin
- ALT 72 (normal <40), AST 45 (normal <40)
- **How to approach?**
- **Start statin?**

CASE 2: approach

- Evaluation for liver disease before staring statin:

1) History:

- Medications/supplements, alcohol, prior hepatitis, IV illicit drug use, travel

2) Examination:

- **Signs of chronic liver disease**

3) Labs:

- Hepatitis B virus (surface Ag)
- Hepatitis C virus (Antibodies)

4) Liver ultrasound

Starting statin with baseline high ALT

- Education:
  - Importance of follow up
  - Symptoms (abdominal pain, vomiting, jaundice)
    - **If so, stop statin and early follow up**
- Monitor ALT

CASE 2: follow up

- Hepatitis B and Hepatitis C virus serology: negative
- Liver ultrasound: fatty liver
- Rosuvastatin 20 mg qd started
- **After 3 months**
  - ALT 100 (was 72)
  - AST 70 (was 45)
- **PLAN?**

Statin-induced liver injury

- Increased ALT after staring statin
- Rate: 0.5-3%
- **If ALT <3 times upper limit of normal:**
  - Continue statin
  - Monitor ALT every 2-3 months or earlier if symptoms (abdominal pain, vomiting, jaundice)

Statin-induced liver injury

- **If ALT >3 times upper limit of normal or symptoms:**
  - Stop statin. Monitor ALT/AST
  - When ALT returns to baseline:
    - Can challenge with another statin (Pravastatin appears to be the safest)
    - Avoid the same statin

Can Statins be used in chronic liver disease?

- Yes, if liver disease is stable
- Can be used in compensated cirrhosis
- Avoid in decompensated cirrhosis & acute liver failure
- Monitor ALT:
  - Before starting statin
  - When increasing dose
  - And periodically

Moctezuma-Velázquez C, et al. Curr Treat Options Gastroenterol 2018;16:226

CASE 3

- A 62-year-old man with type 2 DM and hypertension
- LDL 3.2 mmol (123 mg)
- Atorvastatin 40 mg started
- On follow up after 2 months, he reports muscle pain
- **How to manage?**

Statin-associated muscle symptoms

- **History**:
  - Onset of muscle symptoms
  - Nature of symptoms
  - Severity of symptoms (mild, tolerable, frequency..)
  - Symptoms interfere with daily activities?
  - On other medications?
- **Physical exam**

Statin-associated muscle symptoms

- **Symptoms:**
  - Muscle pain or tenderness
  - Muscle cramping or stiffness
  - Muscle weakness (difficult to get out of chair or climb stairs)
  - Fatigue

- Usually bilateral, proximally (arms, shoulder, hips, legs)
- Some have back pain

- **Onset:**
  - Weeks to months (within 6 months of starting statin)

Risk factors for statin-associated muscle symptoms

- High-intensity statin
- Advanced age (>65 years)
- Female gender
- Vitamin D deficiency
- Untreated hypothyroidism
- Alcohol
- Kidney or liver disease
- Recent major surgery
- Low BMI
- Medications:

Fibrates, Glucocorticoids, Diltiazem, Verapamil, Clarithromycin, Amiodarone, Antifungals, Cyclosporine, Protease inhibitors

Joy T, Hegele R. Ann Intern Med 2009;150:858

Statin-associated muscle symptoms

- **Degrees:**

1) Myalgia (muscle aches, soreness, stiffness, tenderness, cramps)

2) Myopathy (muscle weakness, with or without ↑ in serum CK)

3) Myositis (muscle inflammation)

4) Myonecrosis (↑ in serum CK)

5) Rhabdomyolysis (myonecrosis with myoglobinuria or acute kidney injury)

National Lipid Association. J Clin Lipidol 2014;8(3 Suppl):S58.

Management of statin associated muscle symptoms

- If symptoms are mild, continue statin and observe
- If patient cannot tolerate: stop statin
- Wait for the symptoms to resolve (usually 4-6 weeks)
- If there are other conditions:

1) Drug interaction:
   - Change interacting medication if possible

2) If clinically indicated, assess for vitamin D deficiency & hypothyroidism
   - Treat and challenge with the same statin

Management of statin-associated muscle symptoms

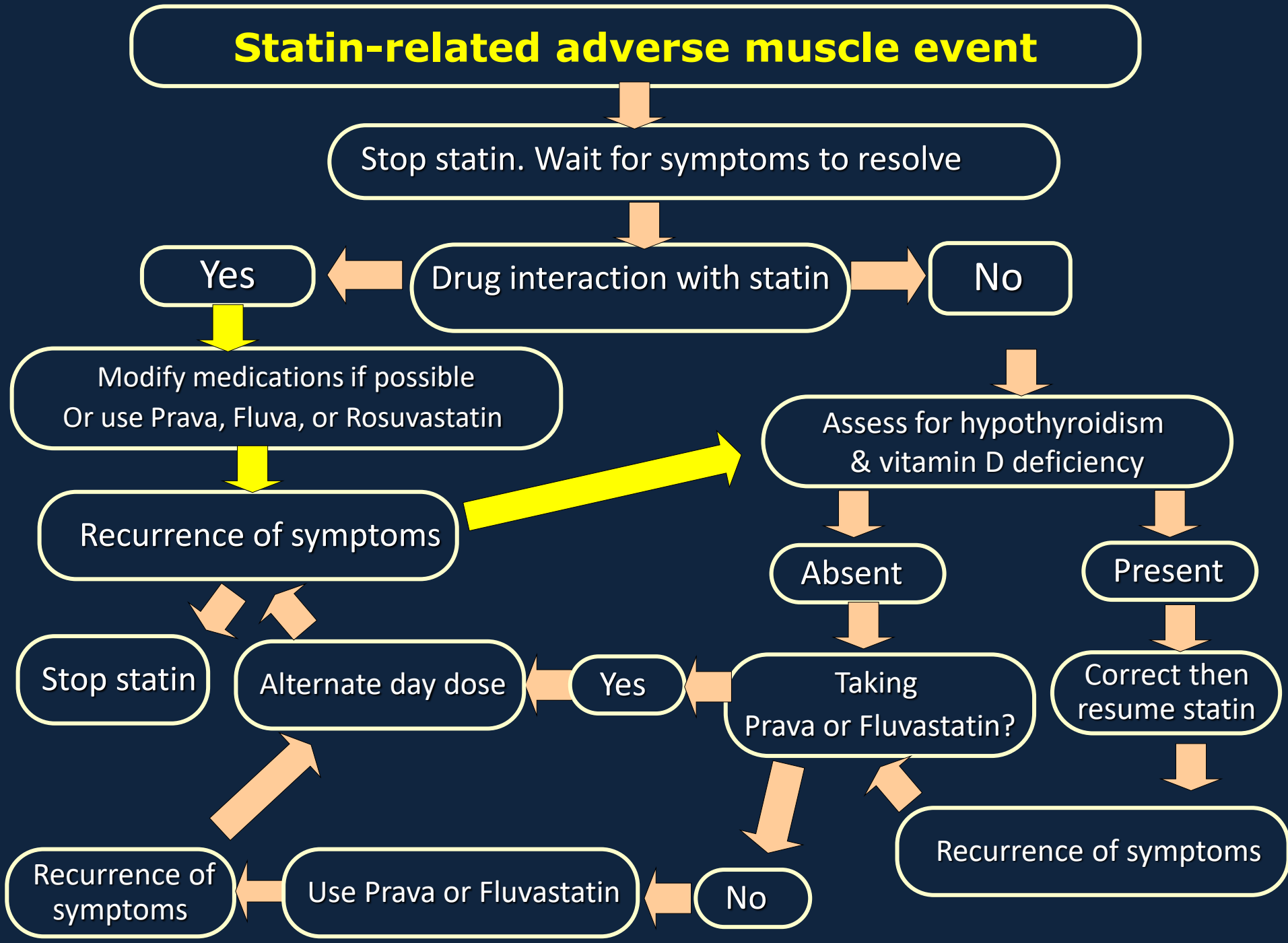
- If severe symptoms:
  - Check creatinine kinase (CK)
  - If CK >5 times upper limit of normal:
    - Stop statin
    - Follow CK
    - Monitor CK and symptoms
  - If CK >10 times:
    - Assess for rhabdomyolysis (very rare)
    - Check kidney function
    - May need hospitalization

Berberich AJ, Hegele RA. Endocr Rev 2022;43:611

Management of statin-associated muscle symptoms

- When symptoms resolve:
  1) Change to a different statin
  2) If symptoms recur:
     - Switch to Fluvastatin or Pravastatin
  3) If symptoms recur:
     - Use alternate day atorvastatin or rosuvastatin
  4) If symptoms recur:
     - Stop statin
     - Use non-statin agents

Berberich AJ, Hegele RA. Endocr Rev 2022;43:611


Statin-related adverse muscle event
Stop statin. Wait for symptoms to resolve
Drug interaction with statin
Yes
No
Modify medications if possible
Or use Prava, Fluva, or Rosuvastatin
Recurrence of symptoms
Stop statin
Alternate day dose
Yes
Assess for hypothyroidism
& vitamin D deficiency
Absent
Present
Taking
Prava or Fluvastatin?
Correct then
resume statin
Recurrence of symptoms
No
Use Prava or Fluvastatin
Recurrence of
symptoms

CASE 4

- A 62-year-old woman with DM 2, hypertension & coronary artery disease (prior acute MI)
- Following lifestyle changes
- BMI 29, blood pressure controlled
- Atorvastatin 40 mg, insulin, Metformin, Empagliflozin, ACEI, beta blocker, aspirin
- LDL 2.8 mmol (110 mg) , HDL 1.3 mmol (40 mg) TG 1.4 mmol (130 mg)
- **How would you approach lipids?**

Case approach

- LDL targets in DM:
  - **General with no ASCVD**: <1.8 mmol (70 mg)
  - **With ASCVD**: <1.3 mmol (55 mg)
- Patient did not achieve target LDL despite being on high intensity statin
- Assess adherence
- Doubling dose (atorvastatin to 80 mg) will ↓ LDL by <10%

Indications for non-statin therapy in DM

1) ASCVD with LDL ≥1.3 mmol (55 mg)

2) Age 40-75 y and multiple CV risk factors

with LDL ≥1.8 mmol (70 mg)

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Non-statin therapy: Ezetimibe

- Inhibits absorption of cholesterol
- Can be used alone or with statin
- Reduces LDL by 15-20%
- Well-tolerated
- Generic is available

ACC/AHA guidelines. J Am Coll Cardiol 2018 10.1016/j.jacc.2018.11.003
ACC guidelines. J Am Coll Cardiol 2017;70(14):1785

Non-statin therapy: PCSK-9 inhibitors

- Monoclonal antibodies
- Inhibit the enzyme “Proprotein convertase subtilisin/kexin type 9” which binds to LDL receptor
- Alirocumab, Evolocumab
- Lower LDL by 35-65%
- Use alone or with statin
- Subcutaneous injection, every 2 or 4 weeks
- Very high cost

ACC/AHA guidelines. J Am Coll Cardiol 2018 10.1016/j.jacc.2018.11.003
ACC guidelines. J Am Coll Cardiol 2017;70(14):1785

CASE 5

- A 38-year-old woman with DM 2 for 4 years
- On metformin, gliclazide, sitagliptin, oral estrogen contraceptive
- BMI 34.2, Normal B.P.
- HbA1c 12.2, LDL 2.8 mmol (110 mg), TG 9 mmol (820 mg), HDL 0.6 mmol (25 mg)
- **How would you approach?**

Serum triglycerides

- <1.7 mmol (150 mg): **Normal**
- 1.7-2.2 mmol (150-199 mg): **borderline high**
- 2.23-5.6 mmol (200-499 mg): **high**
- ≥5.7 mmol (≥500 mg): **Very high**

NCEP/ATP III Guidelines.

Secondary causes of very high TG

- Uncontrolled DM
- Alcohol
- Nephrotic syndrome
- CKD
- Liver disease
- Hypothyroidism
- Drugs (estrogens, steroids, β-Blockers, tamoxifen, immunosuppressive, antiretroviral)

Endocrine Society guidelines. J Clin Endocrinol Metab 2012;97:2969

Back to our case

- TG 9 mmol (820 mg)
- The patient has very high TG [≥5.7 mmol (500 mg)]
- Need to look for secondary causes:
  - A1c 12.2
  - She is on estrogen contraceptive
  - Normal kidney function, no proteinuria
  - No alcohol use
  - TSH is normal
- **Uncontrolled glucose & estrogen can ↑ TG**

Case 5: PLAN

- Control glucose:
  - Insulin is indicated (which will help ↓ TG)
- Stop OCP:
  - Change to another contraceptive method
- Advise diet and weight loss
- F/U lipids in 2-3 months
- May consider treatment from the start especially if TG >11 mmol (>1000 mg) or can wait till secondary causes are treated
  - Then if TG is still very high [≥5.7 mmol (500 mg)] to start treatment

Treatment of very high TG

- **Fibrates**:
  - Most effective; reduce TG by ≥50%

  1) Fenofibrate: comes in several forms:
     - Nanocrystal formulation 145 mg daily taken without regard to meals
     - Micronized capsules 200 mg daily taken with dinner
     - As fenofibric acid (also called choline fenofibrate);

       145 mg daily without regard to meals

  2) Gemfibrozil 600 mg bid (can ↑ risk of myopathy when used with statins)

Treatment of very high TG

- **Omega-3 fatty acids**:
  - Lower TG by up to 45%
  - Can be used alone or combined with fibrates
  - Can increase LDL cholesterol
  - Dose: 1-2 grams bid
- **Statins:**
  - Can lower TG by 20-40%
  - High intensity statins are more effective

Triglycerides in DM: ADA recommendations

- Triglycerides target: <1.7 mmol (150 mg)
- For very high TG ([≥5.7 mmol (500 mg)]:
  - Evaluate for secondary causes
  - Can start with statin (if patient is a candidate)
  - If TG is still very high, can add fibrate or omega-3
- For high TG [1.7-5.6 mmol (150-499 mg)]:
  - Combination of Statin + Fibrate has not been shown to ↓ CV events
  - Treatment is generally not recommended

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Icosapent ethyl for 1ry & 2ry prevention of ASCVD in DM

- Icosapent ethyl (EPA)
- Note: usual omega-3 has EPA & DHA (no benefit)
- Patients with ASCVD or DM with CV risk on statin with controlled LDL levels
- Elevated triglycerides [1.5-5.6 mmol (135-499 mg)]
- Reduction of cardiac events, stroke and CV mortality
- ADA: consider to reduce CV risk (level A)

American Diabetes Association. Diabetes Care 2023;46 (suppl 1):S158
REDUCE-IT trial. New Eng J Med 2019;380:11;www.fda.gov

Low HDL-cholesterol

- <1 mmol (40 mg) in men; <1.3 mmol (50 mg) in women
- Low HDL is a risk factor for CAD
- Raising HDL levels did not lower the risk of CVD
- Physical activity, smoking cessation, weight loss
- Statin + Niacin is not recommended. May ↑ stroke

American Diabetes Association. Diabetes Care 2023;46 (suppl 1):S158
HPS-2 THRIVE study. N Engl J Med 2014;371:203; AIM-HIGH study. N Eng J Med 2011;365:2255
ACC/AHA Guideline. Circulation 2014;129 (Suppl 2)

Summary: key points

- Statins for patients with DM age ≥40
- Moderate intensity statin in general
- High intensity statin if any CV risk factor
- Non-statin therapy if LDL above target on maximally tolerated statin in ASCVD or high-risk patients
- Assess causes of severe hyperTG (≥500 mg); treat if persistent