# 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

American Diabetes Association. Diabetes Care 2022;45 (suppl 1):S144

# ASCVD (Atherosclerotic cardiovascular disease)

- Acute coronary syndromes
- History of 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

- For all patients regardless of risk factors
- Mediterranean or DASH diet:
  - Rich in fruits, vegetables, low fat diary products
  - Reduce saturated and total fat
  - ↑ Intake of omega-3 fatty acid, fibers, plant sterols in **diet**
- Physical activity
- Weight control
- Smoking cessation

American Diabetes Association. Diabetes Care 2022;45 (suppl 1):S144
ACC/AHA guidelines. J Am Coll Cardiol 2018 10.1016/j.jacc.2018.11.003

# Statins in DM

**ASCVD**
All ages

High intensity statin

# Statins in diabetes

## Age ≥40 years

High intensity statin if:

- 10-year ASCVD risk ≥20%
- Or Age 50-75
- Or ≥2 CV risk factors (HTN, smoking, CKD, albuminuria, family history of premature CVD)

Generally moderate intensity statin

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

# Statins in diabetes age 20-39 years

## ADA guidelines

***Consider*** moderate intensity statin

If multiple CV risk factors

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# Statins in diabetes 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

# Which Statin to use?

# Statins in diabetes: primary CVD prevention

1) CARDS trial:
   - High CV risk patients (at least 1 CV risk factor)
   - **Atorvastatin 10 mg**
   - ↓ CV events (MI, stroke)
2) HPS trial: (subgroup with DM)
   - High CV risk patients
   - **Simvastatin 40 mg**
   - ↓ CV events (MI, stroke)

CARDS trial. Lancet 2004;364:685
HPS trial. Lancet 2003;361:2005

# CASE 1: approach

- Patient with DM & ≥40 years
  - So needs statin
  - Generally moderate intensity
- If ASCVD risk ≥20% or age 50-75 or ≥2 CV risk factors = use high intensity
- So, for this patient: 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 4.2 mmol (160 mg)
- Advised for statin
- ALT 72 (normal <40), AST 45 (normal <40)
- **How to approach?**
- **Start statin?**

# CASE 2: approach

- The patient needs evaluation for liver disease before staring statin:
  - **History: medications, alcohol, travel,…**
  - **Hepatitis B virus (HBsAg)**
  - **Hepatitis C virus (HCV Ab)**
  - **Liver ultrasound**
- Many patients have fatty liver

# 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 4.2 mmol (160 mg)
- Atorvastatin 40 mg started
- On follow up after 2 months, he reports muscle pain
- **How to manage?**

# Statin-related myopathy

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

# Statin-related adverse muscle events

- Starts weeks to months after starting statin
- **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.

# Risk factors for statin-related myopathy

- High-intensity statin
- Advanced age (>65 years)
- Female gender
- Vitamin D deficiency
- Untreated hypothyroidism
- Alcohol
- Kidney or liver disease
- Recent major surgery
- Medications:
  - Fibrates, Diltiazem, Verapamil, Macrolides, Amiodarone, Antifungals, Cyclosporine, protease inhibitors

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

# Management of Statin-related adverse muscle events

- If patient cannot tolerate: stop statin
- Wait for symptoms to resolve. Check CK
- Manage accordingly:

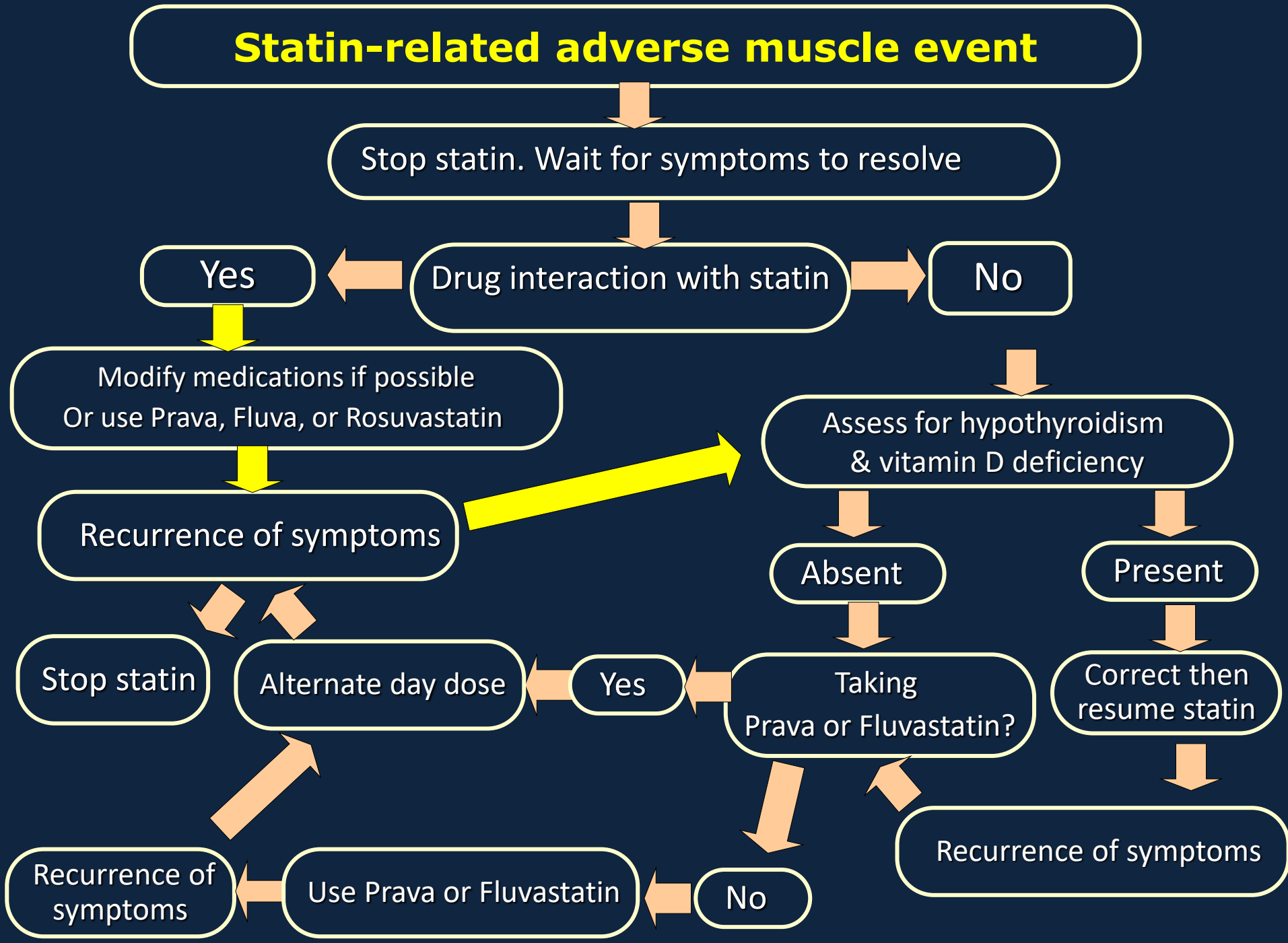
1) Drug interaction:
    - Change interacting medication if possible
    - If not possible, change statin to Fluva, Prava, or Rosuvastatin

2) If symptoms recur, assess for vit. D def. & hypothyroidism
    - Treat then resume same statin
    - If symptoms recur, change to Fluva, Prava, or Rosuvastatin

# Recurrence of Statin-related adverse muscle events

- Switch to another statin
  - Lowest risk : Fluvastatin
  - Also Pravastatin has low risk
  - Can use low dose rosuvastatin (5 or 10 mg qd)
- If symptoms recur:
  - May try low intensity statin
  - Use every other day dosing (of above)
- If still symptoms, stop statin
  - Use non-statin agents

American Diabetes Association. Diabetes Care 2022;45 (suppl 1):S144
Joy T, Hegele R. Ann Intern Med 2009;150:858


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 80 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**: <2.6 mmol (100 mg)
  - **ASCVD**: <1.8 mmol (70 mg)
- Assess adherence
- How was response to statin?
  - Look at LDL before starting statin
  - Some patients have less than expected response
  - Some patients have different responses to statins
    - **Consider switching statins**

# Non-statin therapy in DM

**1) Patients with ASCVD:**

- On maximally tolerated statin & **LDL ≥1.8 mmol** (70 mg)
- Add Ezetimibe or PCSK-9 inhibitor (based on desired LDL reduction, cost, patient preferences, route of administration)

**2) Patients without ASCVD, 10-y risk ≥20%:**

- On maximally tolerated statin with LDL reduction of <50% or **LDL ≥2.6 mmol** (100 mg)
- Optional: *consider* Ezetimibe

American Diabetes Association. Diabetes Care 2022;45 (suppl 1):S144
ACC/AHA guidelines. J Am Coll Cardiol 2017;70:1785

# 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

# Non-statin therapy: Bile acid sequestrants

- ↓ Bile acid absorption
- Cholestyramine, Colestipol, Colesevelam
- Reduces LDL by 15-30%
- GI side effects (diarrhea, constipation, gases)
- Can ↑ TG levels
- Consider if ezetimine is not tolerated

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
- On metformin, gliclazide, oral estrogen contraceptive
- BMI  34, Normal B.P.
- HbA1c  12
- LDL 2.8  mmol (110 mg), TG 9 mmol (820 mg), HDL 0.6 mmol (25 mg)

# 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.

# Triglycerides in DM: ADA recommendations

- Triglycerides target: <1.7 mmol (150 mg)
- Combination of Statin + Fibrate:
  - Has not been shown to ↓ CV events
  - Is generally not recommended
- If TG ≥5.7 mmol (500 mg):
  - Evaluate for secondary causes and consider treatment to reduce the risk of acute pancreatitis

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# 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
  - 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 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

# 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 2022;45 (suppl 1):S144
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 high risk for CVD
- Non-statin therapy if LDL above target on maximally tolerated statin in ASCVD or high-risk patients
- Assess cause of severe hyperTG; treat if persistent