When Statins Aren’t Enough: Appropriate Therapies for High-Risk Patients with Diabetes

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Clinical ASCVD

LDL-C ≥ 190 mg/dL

Diabetes
Type 1 or 2
Age 40-75 yr

≥7.5% estimated
10-yr ASCVD risk +
age 40-75 yr

• High-intensity statin if age ≤ 75 yr
• Moderate-intensity statin if age > 75 yr or not candidate for high-intensity

High-intensity statin

Moderate-intensity statin

High-intensity statin if 10-yr ASCVD risk ≥ 7.5%

Moderate-to-high intensity statin

ASCVD = atherosclerotic cardiovascular disease

ACC/AHA 2013 Blood Cholesterol Guideline: Statin Benefit Groups

J Am Coll Cardiol 2013;2889-934
2013 ACC/AHA Cholesterol Guidelines
Recommendations on Use of Non-Statins

• Clinicians treating high risk patients who have a
  – Less than anticipated response to statins
  – Unable to tolerate recommended intensity of a statin
  – Completely statin intolerant

• High risk patients
  • ASCVD + age < 75 years
  • Baseline LDL-C $\geq$ 190 mg/dL
  • Age 40-75 years + diabetes mellitus
2013 ACC/AHA Cholesterol Guidelines

Recommendations on Use of Non-Statins

• Before starting non-statin
  – Emphasize adherence to lifestyle modifications & statin
  – Exclude secondary causes of dyslipidemia
• Preferentially prescribe drugs that provide ASCVD risk-reduction benefits that outweigh the potential for side effects and interactions, and patient preferences
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

A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways

Endorsed by the National Lipid Association

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2017 Focused Update: 40-75 yr (no ASCVD) + Diabetes + Baseline LDL-C 70-189 mg/dL

- Algorithm did not change regarding the use of ezetimibe and not using PCSK9 inhibitors
- Clarified statements within the text of manuscript to distinguish patients with or without high risk features
  - retinopathy
  - CKD [eGFR <60 mL/min/1.73 m²]
  - albuminuria [urinary albumin/creatinine ratio >30 mg/g]
  - elevated Lp(a) [>30 mg/dL]
  - hs-CRP [>2 mg/dL], or
  - presence of subclinical atherosclerosis

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2017 Focused Update: 40-75 yr (no ASCVD) + Diabetes + Baseline LDL-C 70-189 mg/dL

**FIGURE 4 | Patients Aged 40-75 years without Clinical ASCVD and with Diabetes and Baseline LDL-C 70-189 mg/dL, on Statin for Primary Prevention**

- Patients aged 40-75 years without clinical ASCVD and with diabetes and baseline LDL-C 70-189 mg/dL, on statin for primary prevention

  - Patient has ≥50% LDL-C reduction (may consider LDL-C <100 mg/dL or may consider non-HDL-C <130 mg/dL in patients with diabetes) on maximally tolerated statin*

    - **NO**
      1. Address statin adherence.
      2. Intensify lifestyle (may consider phytosteryl).
      3. Evaluate for statin intolerance if unable to tolerate moderate-intensity statin.†
      4. Consider referral to lipid specialist if statin intolerant.

    - **YES**
      Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.

  - Patient has ≥50% LDL-C reduction (may consider LDL-C <100 mg/dL or may consider non-HDL-C <130 mg/dL in patients with diabetes) on maximally tolerated statin*

    - **NO**
      Optimal non-statin medications to consider

    - **YES**
      Decision for no additional medication

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*Based on the American College of Cardiology (ACC) and the American Heart Association (AHA) 2017 Focused Update for the ACC/AHA 2013 Guideline on the Prevention, Detection, Evaluation, and Management of High Blood Cholesterol in Adults.

†For the small proportion of patients in this group with 10-year ASCVD risk <7.5% and no other high-risk features, starting with moderate-intensity statin to achieve 30-40% LDL-C reduction (may consider LDL-C <100 mg/dL or non-HDL-C <130 mg/dL) is acceptable. If this level of LDL-C reduction is not achieved, consider increasing to high-intensity statin.

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2017 Focused Update: 40-75 yr (no ASCVD) + Diabetes + Baseline LDL-C 70-189 mg/dL + 10-yr ASCVD <7.5% without high risk features

- Acceptable to start with moderate-intensity statin to achieve 30-49% LDL-C reduction (may consider LDL-C <100 mg/dL or non-HDL-C <130 mg/dL)
- May increase to high-intensity statin, if LDL-C reduction is not achieved

For the small proportion of patients in this group with 10-year ASCVD risk <7.5% and no other high-risk features, starting with moderate-intensity statin to achieve 30-49% LDL-C reduction (may consider LDL-C <100 mg/dL or non-HDL-C <130 mg/dL) is acceptable. If this level of LDL-C reduction is not achieved, consider increasing to high-intensity statin.

Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.

high risk features = retinopathy; CKD [eGFR <60 mL/min/1.73 m²]; albuminuria [urinary albumin/creatinine ratio >30 mg/g]; elevated Lp(a) [>30 mg/dL]; hs-CRP [>2 mg/dL], or presence of subclinical atherosclerosis
2017 Focused Update: 40-75 yr (no ASCVD) + Diabetes + Baseline LDL-C 70-189 mg/dL + 10-yr ASCVD ≥7.5% or high risk features

- May add non-statin medication (ezetimibe)

high risk features = retinopathy; CKD [eGFR <60 mL/min/1.73 m²]; albuminuria [urinary albumin/creatinine ratio >30 mg/g]; elevated Lp(a) [>30 mg/dL]; hs-CRP [>2 mg/dL], or presence of subclinical atherosclerosis

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Case 1

10-yr ASCVD risk ≥7.5% or high risk features

- 55 YO Caucasian male
- PMH: type 2 diabetes, HTN
- Social: Nonsmoker
- Meds: metoprolol, ramipril, metformin, atorvastatin 40 mg
- Vitals WNL
- Metabolic panel – WNL
- eGFR > 60 mL/min/1.73m²
- HgbA1c 9.1%
- Lipids (mg/dL): TC 189, TG 171, HDL-C 45, LDL-C 110
  - Non-HDL-C 144
- 10-year ASCVD Risk 11.4%

http://dx.doi.org/10.1016/j.jacc.2017.07.745
Case 2
10-yr ASCVD risk <7.5% or high risk features

- 55 YO African American female
- PMH: type 2 diabetes, CKD
- Social: Nonsmoker
- Meds: ramipril, metformin, atorvastatin 40 mg
- Vitals WNL
- Metabolic panel – WNL
- eGFR 30 mL/min/1.73m²
- HgbA1c 7.3 %
- Lipids (mg/dL): TC 148, TG 165, HDL-C 45, LDL-C 70
  - Non-HDL-C 103
- 10-year ASCVD Risk 5.4%
Summary: 2017 Focused Update: 40-75 yr (no ASCVD) + Diabetes + Baseline LDL-C 70-189 mg/dL

• Algorithm did not change regarding the use of ezetimibe and not using PCSK9 inhibitors
• Text continues to emphasize need to identify patients with 10-yr ASCVD risk \( \geq 7.5\% \) or with high risk features
  • May consider addition of ezetimibe for some patients
• Encourage
  • Estimation of 10-yr ASCVD risk
  • Screening for high risk features

high risk features = retinopathy; CKD [eGFR <60 mL/min/1.73 m²]; albuminuria [urinary albumin/creatinine ratio >30 mg/g]; elevated Lp(a) [>30 mg/dL]; hs-CRP [>2 mg/dL], or presence of subclinical atherosclerosis

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EMPARY-REG

• Population: type 2 diabetes + established CVD
  • n = 7020; mean age 63 years, mean A1c 8.1%
  • eGFR > 30 mL/min/1.73 m²
• Study arms: empagliflozin 10 mg, 25 mg, or placebo
• Median follow-up 3.1 years
• Primary composite outcome: death from CV causes, nonfatal MI, or nonfatal stroke
  • Empagliflozin (aggregate data) 10.5% versus placebo 12.1% (HR 0.86, 95% CI 0.74-0.99, p<0.001 for non-inferiority; p=0.04 for superiority)
  • Primarily driven by ↓ CV death (3.7% versus 5.9%; HR 0.62, 95% CI 0.49-0.77, p<0.001)
• Subgroup analysis may provide additional information to identify patient groups with net clinical benefit or harm
CANVAS Program

- Population: type 2 diabetes + high CVD risk
  - n = 10,142; mean age 63.3 years, mean A1c 8.2%
  - eGFR > 30 mL/min/1.73 m²
- Study arms: canagliflozin 300 mg, 150 mg, or placebo
- Mean follow-up 188.2 weeks
- Primary composite outcome: death from CV causes, nonfatal MI, or nonfatal stroke
  - Canagliflozin (aggregate data) 26.9 participants versus placebo 31.5 participants (HR 0.86, 95% CI 0.75-0.97, p<0.001 for non-inferiority; p=0.02 for superiority)
  - None of components showed a difference
- Subgroup analysis may provide additional information to identify patient groups with net clinical benefit or harm
LEADER

• Population: type 2 diabetes + high CVD risk
  • n = 9340; mean age 64 years, mean A1c 8.7%
• Study arms: liraglutide or placebo
• Median follow-up 3.8 years
• Primary composite outcome: death from CV causes, nonfatal MI, or nonfatal stroke
  • Liraglutide 13.0% versus placebo 14.9% (HR 0.87, 95% CI 0.78-0.97, p<0.001 for non-inferiority; p=0.01 for superiority)
  • Primarily driven by ↓ CV death (4.7% versus 6.0%; HR 0.78, 95% CI 0.66-0.93, p=0.007)
• Subgroup analysis may provide additional information to identify patient groups with net clinical benefit or harm