Case 1

Mark

Diabetes & Cardiovascular Disease

Learning Objectives

Upon completion of this case based session, participants will be able to:

01 Assess your patients with diabetes for risk of macro and microvascular disease

02 Use the ABCDES of vascular protection for your patients with diabetes

03 Use appropriate additional therapies to help reach the LDL-C target

Case 1
Follow Up Diabetes Visit

Mark
63 years old

Mark's History

- T2DM for 8 years
- Myocardial Infarction 3 years ago (DES stent)
- Hypertension x 10 years
- Past smoker

Physical Exam

- BMI 32.6 kg/m^2
- BP 128/78 mmHg
- HR 78 regular
- No Retinopathy
- No Neuropathy
- Rest of exam normal

DES: drug eluting stent

Case 1
Follow Up Diabetes Visit

Mark
63 years old

Medications

- Metformin/Sitagliptin 50/1000 mg BID
- Empagliflozin 10 mg OD
- ASA 81 mg
- Rosuvastatin 20 mg OD *(unable to tolerate 40 mg due to myalgias)*
- Ezetimibe 10 mg OD
- Ramipril 10 mg OD
- Amlodipine 10mg OD

Labs

- A1C 6.9%
- eGFR 64 ml/min
- ACR 5 mg/mmol
- TC 4.3 mmol/L
- LDL-C 2.4 mmol/L
- HDL-C 1.1 mmol/L
- TG 1.5 mmolL

Vascular Protection Checklist

- ✓ **A** • A1C – optimal glycemic control (usually ≤7%)
- ✓ **B** • BP – optimal blood pressure control (< 130/80 mmHg)
- ✓ **C** • Cholesterol – LDL-C <2.0 mmol/L or >50% reduction if treatment is indicated
- ✓ **D** • Drugs to protect the heart
  A – ACEi or ARB | S – Statin | A – ASA if indicated | SGLT2i / GLP-1RA → with demonstrated CV benefit if type 2 DM with CVD and A1C not at target
- ✓ **E** • Exercise / Healthy Eating
- ✓ **S** • Smoking cessation

ACEi, angiotensin converting enzyme inhibitor; *ARB*, angiotension receptor blocker; *CV*, cardiovascular; *CVD*, cardiovascular disease; *DM*, diabetes mellitus

Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes. 2018;42(Suppl 1):S1-S325

Case 1

Vascular Protection Checklist

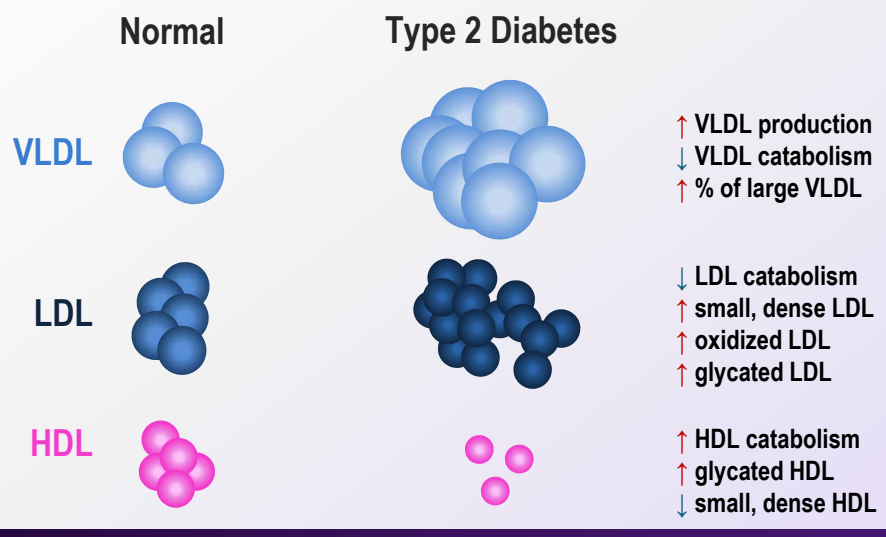
- **A** • A1C **≤7%**
- **B** • BP **<130/80 mmHg**
- **C** • LDL-C **≤2.0 mmol/L**
- **D** • Drugs to protect the heart
  - **A – ACEI or ARB**
  - **S – Statin**
  - **A – ASA if indicated**
  - **SGLT2i / GLP-1RA**
- **E** • Exercise/Eating
- **S** • Smoking cessation

Mark

- ✓ **A** • A1C **6.9%**
- ✓ **B** • BP **128/78 mmHG**
- ✗ **C** • LDL-C **2.4 mmol/L**
- ✓ **D** • Drugs to protect the heart
  - ✓ **Ramipril 10 mg**
  - ✓ **Rosuvastatin 20 mg (ezetimibe 10 mg)**
  - ✓ **ASA 81 mg**
  - ✓ **Empagliflozin 10 mg**
- ⚠ **E** • Exercise/Eating – **Trying**
- ✓ **S** • Smoking cessation – **Doesn't Smoke**

Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes. 2018;42(Suppl 1):S1-S325

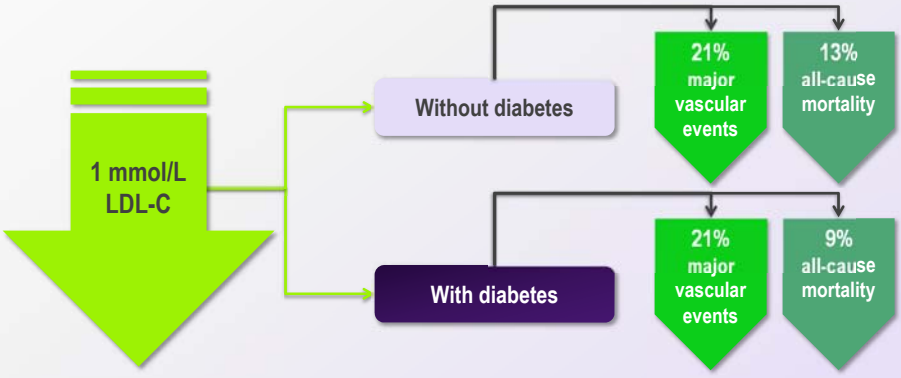
Lipid Abnormalities in Type 2 Diabetes



Apo, apolipoprotein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.
Adapted from Vergès B. Diabetologia. 2015;58:886-99

Cholesterol Treatment Trialists' Collaboration Lipid Lowering Benefits of Statins in Diabetes

14 randomized trials of statin therapy
Treatment duration ≥2 years | Mean follow-up of 4.3 years
N=71,370 without diabetes | N=18,686 with diabetes



Adapted from Cholesterol Treatment Trialists' (CTT) Collaborators. Lancet. 2008;371:117-25.

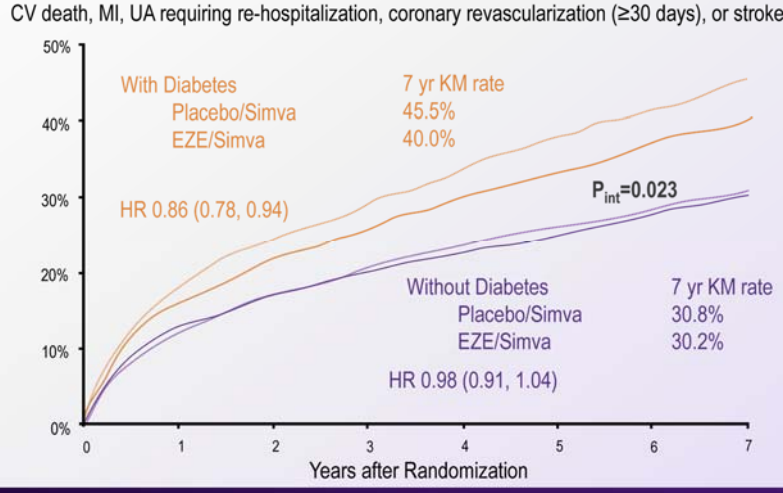
Second-Line Lipid-Modifying Medications

Drug class* Generic name* (tradename)	Principal effects	Other considerations
Bile acid sequestrants (BAS) ▪ Cholestyramine resin ▪ Colesevelam ▪ Colestipol HCl	▪ Lowers LDL-C	▪ GI intolerability, which worsens with increasing doses ▪ May elevate TG ▪ Colesevelam has A1C lowering effect
Cholesterol absorption inhibitor ▪ Ezetimibe	▪ Lowers LDL-C	▪ Less effective than statins as monotherapy ▪ Effective when used in combination with a statin to further lower LDL-C
Fibrates ▪ Bezafibrate ▪ Fenofibrate ▪ Gemfibrozil	▪ Lowers TG ▪ Variable effect on LDL-C ▪ Highly variable effect on HDL-C (more effective at raising HDL-C when baseline TG is high)	▪ May increase creatinine and homocysteine levels; however, favorable effects on renal function have been noted with long-term fenofibrate treatment; possible benefit of fenofibrate on retinopathy ▪ Do not use gemfibrozil in combination with a statin due to increased risk of myopathy and rhabdomyolysis
Nicotinic acid ▪ Extended-release niacin ▪ Immediate-release niacin) ▪ Long-acting (e.g. "no-flush") **not recommended**	▪ Raises HDL-C ▪ Lowers TG ▪ Lowers LDL-C ▪ Lowers Lp(a)	▪ To be used selectively and cautiously but not to be used prior to trials of ezetimibe or BAS ▪ Can cause dose-related deterioration of glycemic control ▪ Long-acting niacin should **not** be used due to increased hepatotoxicity and decreased efficacy
PCSK9 Inhibitor ▪ Alirocumab ▪ Evolocumab	▪ Lowers LDL-C ▪ Lowers Lp(a)	▪ Injection site reactions ▪ CV risk reduction shown in one randomized clinical trial of secondary prevention, including in a subset with type 2 diabetes

Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes. 2018;42(Suppl 1):S1-S325

IMPROVE-IT

Ezetimibe Add-on to Simvastatin was Beneficial in Persons with ACS and Diabetes



CV, cardiovascular; MI, myocardial infarction; UA, unstable angina.
Giguliano RP et al. Benefit of adding ezetimibe to statin therapy on cardiovascular outcomes and safety in patients with vs without diabetes: the IMPROVE-IT trial.. Presented at the European Society of Cardiology Congress; August 30, 2015; London, England.

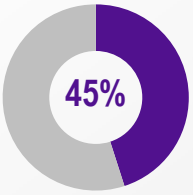
Recommendations for Lipid Management in Diabetes

- For people with diabetes with indications for lipid-lowering therapy, treatment should be initiated with a **statin**[1] to achieve LDL-C consistently **<2.0 mmol/L**[2] **or >50% reduction** of LDL-C from baseline[3].
  - Alternative targets and respective goals are **apo B <0.8 g/L and non-HDL-C <2.6 mmol/L**[4].

1 [Grade A, Level 1]
2 [Grade C, Level 3]
3 [Grade D, Consensus]
4 [Grade C, Level 3]

Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes. 2018;42(Suppl 1):S1-S325

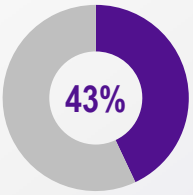
Many High-Risk Canadian Patients Treated with Statins Are Not at LDL-C Goal



DYSIS[1]

Canadian high-risk patients are NOT at LDL-C target[1*] (< 2.0 mmo/L)

- 88% of patients received a 'potent' statin with suboptimal dose
- 14% of patients received additional lipid-lowering agent



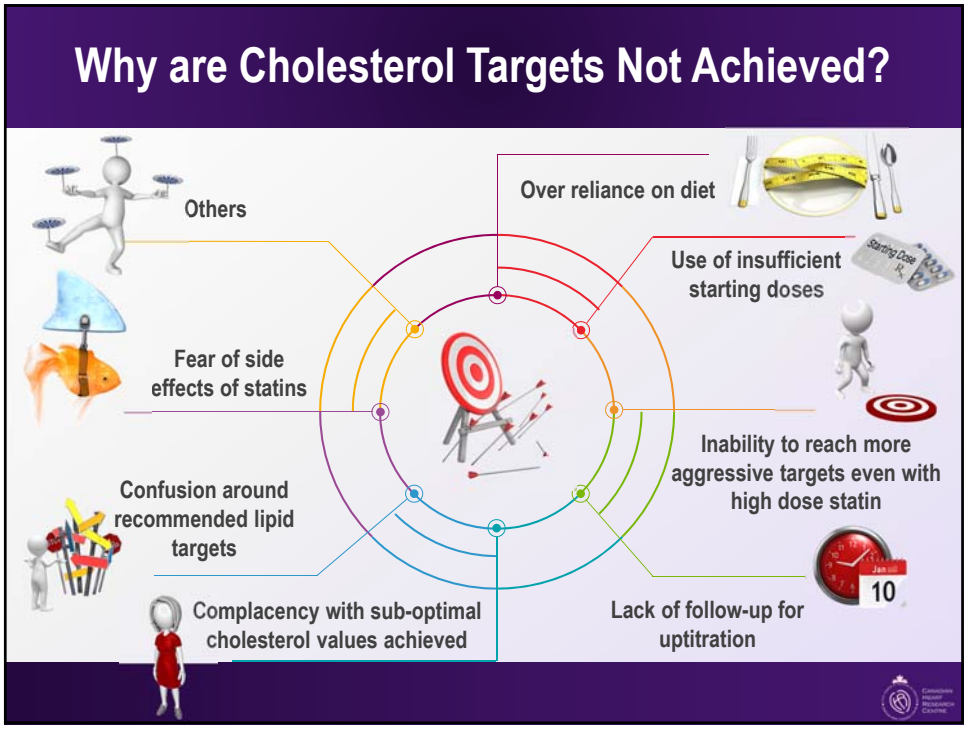
DM-SCAN[2]

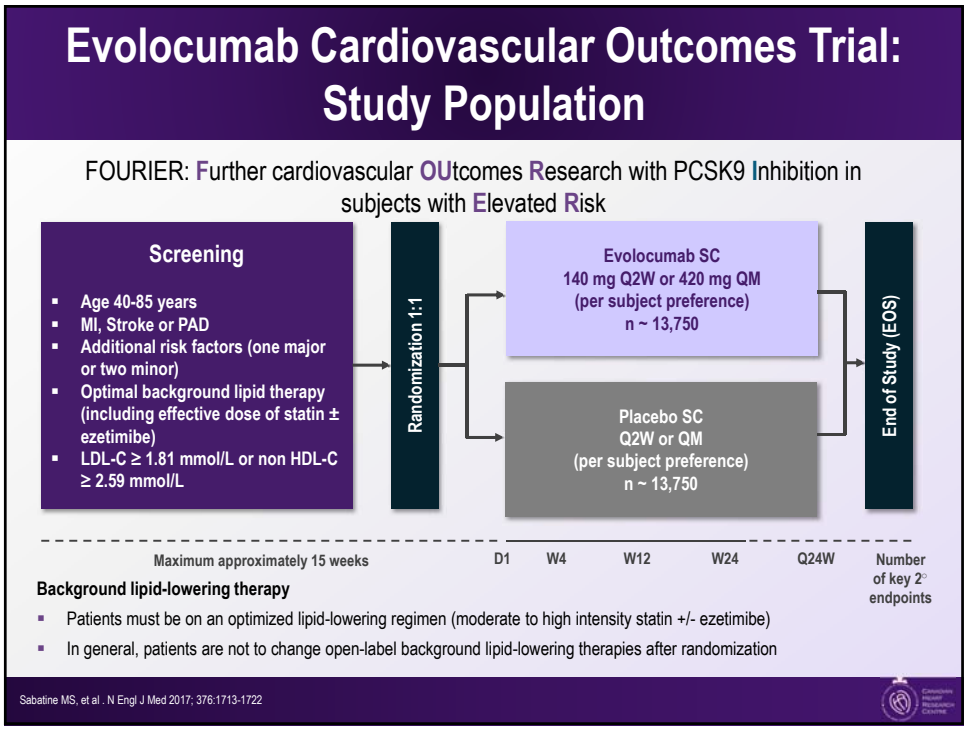
Canadian patients with diabetes are NOT at LDL-C target[†] (≤ 2.0 mmo/L)

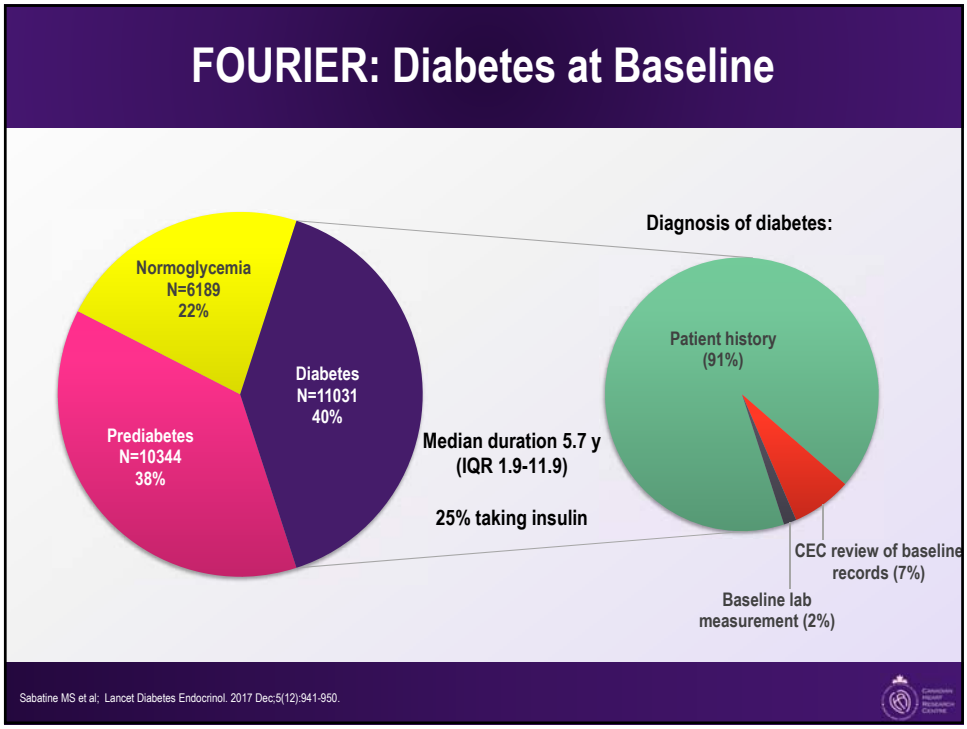
- 82% of patients were on a lipid-lowering agent

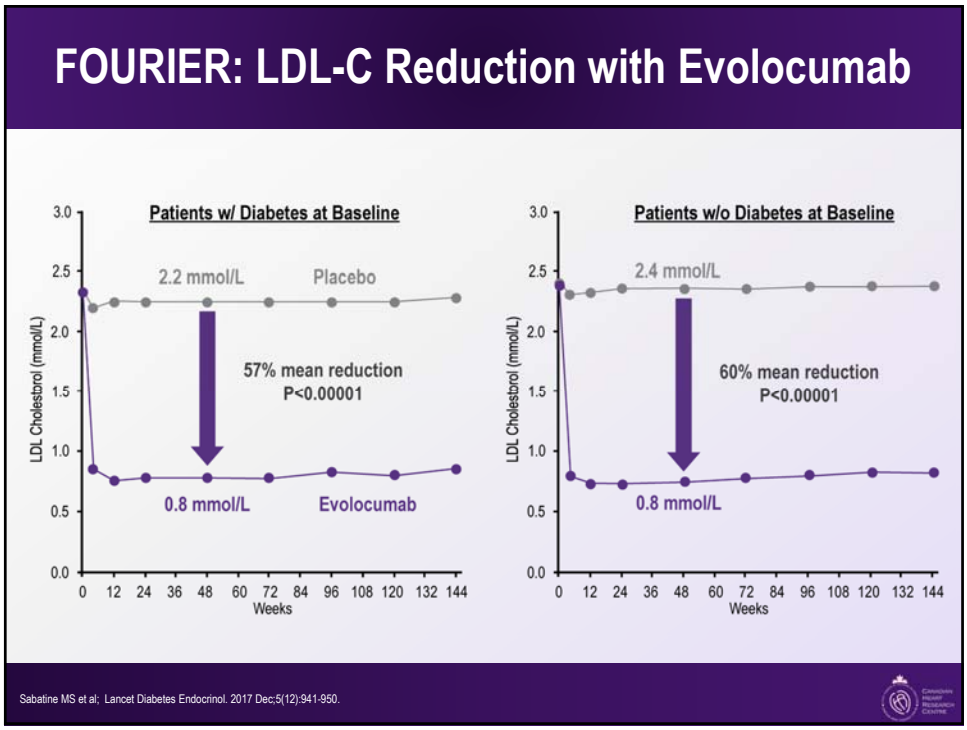
*High risk = *coronary artery disease, peripheral arterial disease, cerebrovascular disease, diabetes mellitus or Framingham 10-year risk score ≥20%. DYSIS Study – 2,436 patients, 1913 high risk patients.*
†N = 5,069

1. Goodman SG et al. on behalf of the DYSIS Canadian Investigators. Can J Cardiol. 2010;26:e330-e335.
2. Leiter LA et al. on behalf of the DM-SCAN investigators. Can J Diabetes. 2013;37:82-89.

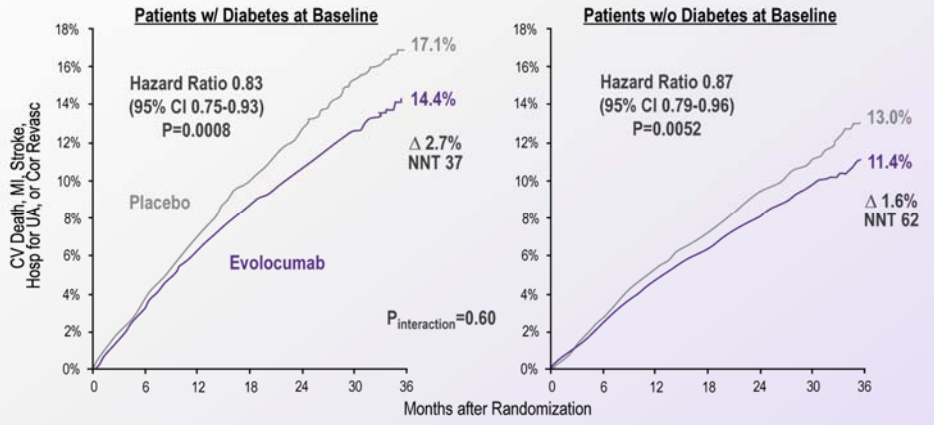

Why are Cholesterol Targets Not Achieved?
Others
Over reliance on diet
Use of insufficient starting doses
Fear of side effects of statins
Inability to reach more aggressive targets even with high dose statin
Confusion around recommended lipid targets
Complacency with sub-optimal cholesterol values achieved
Lack of follow-up for uptitration


Evolocumab Cardiovascular Outcomes Trial: Study Population
FOURIER: Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk
Screening
Age 40-85 years
MI, Stroke or PAD
Additional risk factors (one major or two minor)
Optimal background lipid therapy (including effective dose of statin ± ezetimibe)
LDL-C ≥ 1.81 mmol/L or non HDL-C ≥ 2.59 mmol/L
Randomization 1:1
Evolocumab SC
140 mg Q2W or 420 mg QM
(per subject preference)
n ~ 13,750
Placebo SC
Q2W or QM
(per subject preference)
n ~ 13,750
End of Study (EOS)
Maximum approximately 15 weeks
D1
W4
W12
W24
Q24W
Number of key 2° endpoints
Background lipid-lowering therapy
Patients must be on an optimized lipid-lowering regimen (moderate to high intensity statin +/- ezetimibe)
In general, patients are not to change open-label background lipid-lowering therapies after randomization
Sabatine MS, et al . N Engl J Med 2017; 376:1713-1722


FOURIER: Diabetes at Baseline
Normoglycemia
N=6189
22%
Diabetes
N=11031
40%
Prediabetes
N=10344
38%
Median duration 5.7 y
(IQR 1.9-11.9)
25% taking insulin
Diagnosis of diabetes:
Patient history
(91%)
CEC review of baseline
records (7%)
Baseline lab
measurement (2%)
Sabatine MS et al; Lancet Diabetes Endocrinol. 2017 Dec;5(12):941-950.

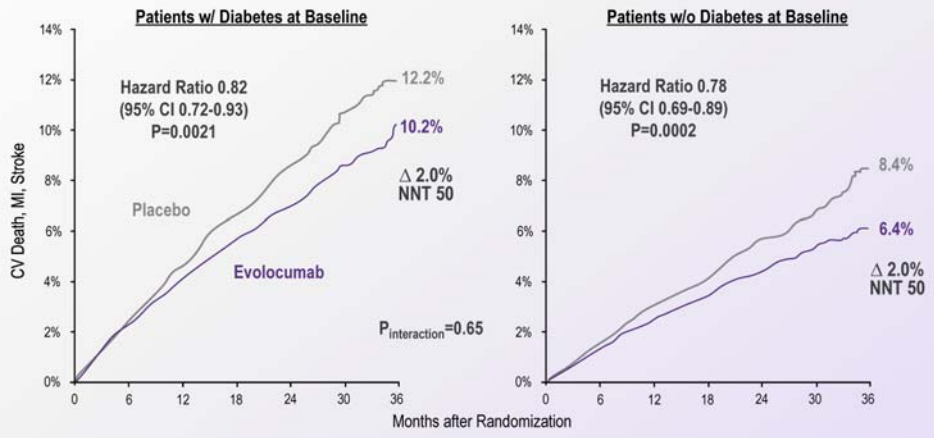

FOURIER: LDL-C Reduction with Evolocumab
Patients w/ Diabetes at Baseline
2.2 mmol/L
Placebo
57% mean reduction
P<0.00001
0.8 mmol/L
Evolocumab
LDL Cholesterol (mmol/L)
Weeks
Patients w/o Diabetes at Baseline
2.4 mmol/L
60% mean reduction
P<0.00001
0.8 mmol/L
Sabatine MS et al; Lancet Diabetes Endocrinol. 2017 Dec;5(12):941-950.

FOURIER: Effect of Evolocumab on Primary Endpoint



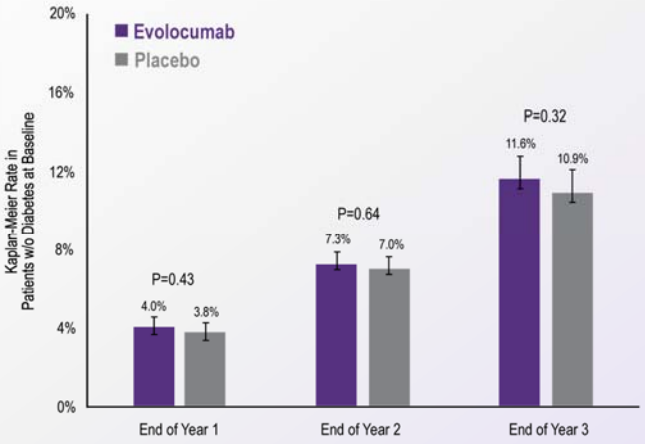
Sabatine MS et al; Lancet Diabetes Endocrinol. 2017 Dec;5(12):941-950.

FOURIER: Effect of Evolocumab on Key Secondary Endpoint



Sabatine MS et al; Lancet Diabetes Endocrinol. 2017 Dec;5(12):941-950.

FOURIER: New-Onset Diabetes



In all patients w/o diabetes at baseline (1294 incident cases in 16,510 patients):

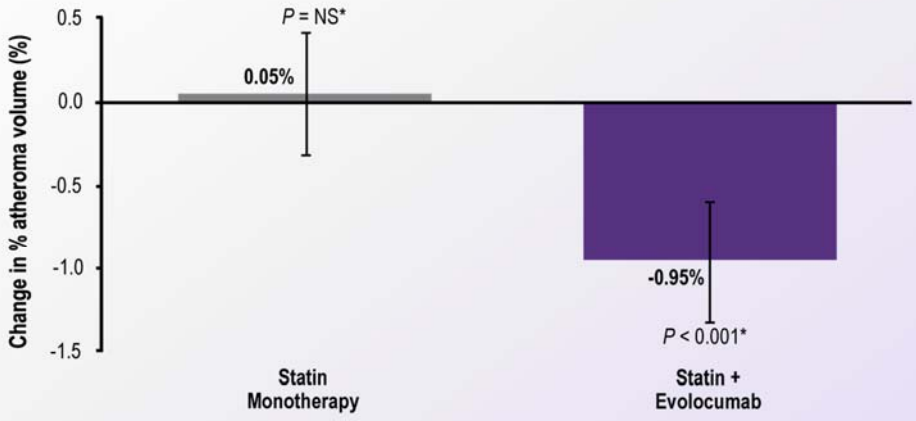
HR 1.05 (95% CI 0.94-1.17)

In patients w/ prediabetes at baseline (1163 incident cases in 10,338 patients):

HR 1.00 (95% CI 0.89-1.13)

Sabatine MS et al; Lancet Diabetes Endocrinol. 2017 Dec;5(12):941-950.

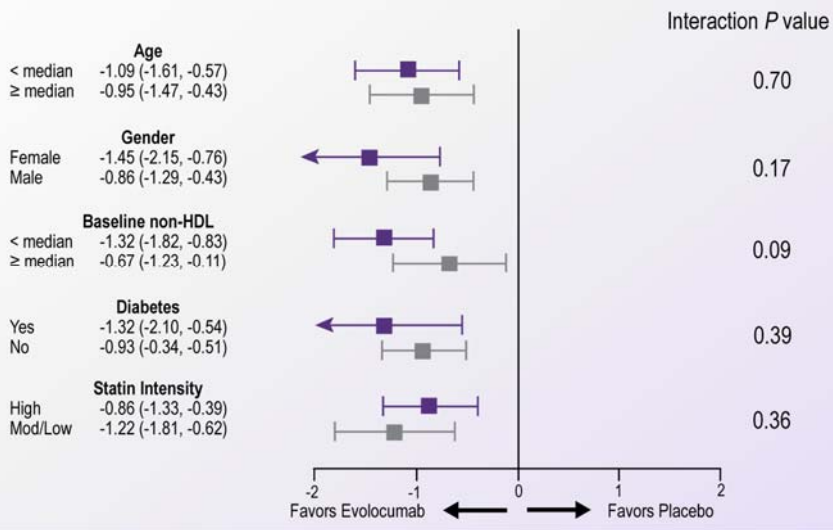
GLAGOV: Primary Endpoint
Nominal Change in PAV from Baseline to Week 78



Difference between groups: -1.0% (-1.8 to -0.64); *P* < 0.001

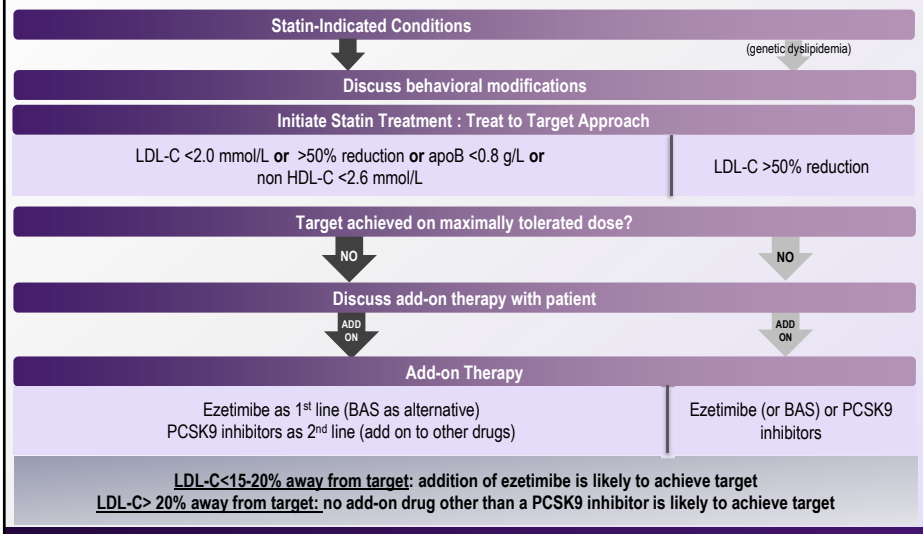
Nicholls SJ, et al. JAMA. 2016;316(22):2373-2384. doi:10.1001/jama.2016.16951

GLAGOV:
Interaction: Selected Prespecified Subgroups (PAV)



Nicholls SJ, et al. JAMA. 2016;316(22):2373-2384. doi:10.1001/jama.2016.16951

2016 Canadian Guidelines for Management of Dyslipidemia



Anderson and al., Can Journal of Cardiol, 32 (11); 1263-82. Apo, apolipoprotein; BAS, bile acid sequestrant; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol.

Summary

- Statin monotherapy may not achieve targets in all patients
- Previous add-ons to statin are suboptimal
- PCSK9 inhibitors appear to have similar efficacy and safety in individuals with and without diabetes (with greater absolute risk reduction) and with no apparent adverse effects on glycemia