UPDATES IN CARDIOLOGY:
LIPID AND DIABETIC MANAGEMENT

Clint Allred, MD, FACC
DISCLOSURES

• None
Retraction and Repudication of "Mediterranean Diet vs. Western Diet for Cardiovascular Disease with a Lower Risk of Ischemic Stroke" (NEJM 2018;378:1279-90).

Summary
Background
Syphilis is commonly observed in returned travelers. The purpose of this study was to determine the effectiveness of the Malarone (a combination of an antimalarial drug and an antiplasmodial agent) in the prevention of malaria and to determine the incidence of adverse events. The results of this study indicate that Malarone is effective in the prevention of malaria and has a low incidence of adverse events.

Figure 2. An atrial view of the MitraClip device (Abbott Vascular) grasping both leaflets of the mitral valve.
Reprint of: Positive Psychological Well-Being and Cardiovascular Disease

Peter
Colin
Mary
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Eric S. Kim, PhD, a Hayami K. Koga, MD, MPH, c Emily H. Feig, PhD, b,c  Donald M. Lloyd-Jones, MD, MSc, f
Martin E.P. Seligman, PhD, e  Darwin R. Labarte, MD, MPH, PhD f
LEARNING OBJECTIVES

1. Review updated Lipid Guideline including the role of non-statin means to treat hyperlipidemia

1. Review diabetic management strategies for the cardiac patient
Primary Prevention: Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle

Age 0-19 y
Lifestyle to prevent or reduce ASCVD risk
Diagnosis of Familial Hypercholesterolemia → statin

Age 20-39 y
Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk
Consider statin if family history premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)

Age 40-75 y and LDL-C ≥70-<190 mg/dL (≥1.8-<4.9 mmol/L) without diabetes mellitus
10-year ASCVD risk percent begins risk discussion

ASCVD Risk Enhancers:
- Family history of premature ASCVD
- Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g., preeclampsia, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (e.g., South Asian ancestry)

Lipid/Biomarkers:
- Persistently elevated triglycerides (≥275 mg/dL, ≥2.6 mmol/L)

In selected individuals if measured:
- hs-CRP ≥2.0 mg/L
- Lp(a) levels >50 mg/dL or >125 nmol/L
- apoB ≥1.30 mg/dL
- Ankle-brachial index (ABI) <0.9

Risk discussion: Emphasize lifestyle to reduce risk factors (Class I)

Risk discussion: If risk enhancers present then risk discussion regarding moderate-intensity statin therapy (Class IIB)

Risk discussion: If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49% (Class I)

Risk discussion: Initiate statin to reduce LDL-C ≥50% (Class I)

If risk decision is uncertain:
Consider measuring CAC in selected adults:
- CAC = zero (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
- CAC = 1-99 favors statin (especially after age 55)
- CAC = 100+ and/or ≥75th percentile, initiate statin therapy

LDL-C ≥190 mg/dL (≥4.9 mmol/L)
No risk assessment; High-intensity statin (Class I)

Diabetes mellitus and age 40-75 y
Moderate-intensity statin (Class I)

Diabetes mellitus and age 40-75 y
Risk assessment to consider high-intensity statin (Class IIa)

Age >75 y
Clinical assessment, Risk discussion

Grundy et al 2018 JACC
Figure 1. Secondary Prevention in Patients With Clinical ASCVD

Clinical ASCVD

Healthy Lifestyle

ASCVD not at very high-risk*  

Age ≤75 y

High-intensity statin (Goal: ↓ LDL-C ≥50%) (Class I)

If high-intensity statin not tolerated, use moderate-intensity statin (Class I)

If on maximal statin therapy and LDL-C ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe may be reasonable (Class IIb)

Age >75 y

Initiation of moderate- or high-intensity statin is reasonable (Class IIa)

Continuation of high-intensity statin is reasonable (Class IIa)

If on maximal statin and LDL-C ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe is reasonable (Class IIa)

If PCSK9-I is considered, add ezetimibe to maximal statin before adding PCSK9-I (Class I)

High-intensity or maximal statin (Class I)

If on clinically judged maximal LDL-C lowering therapy and LDL-C ≥70 mg/dL (≥1.8 mmol/L), or non-HDL-C ≥100 mg/dL (≥2.6 mmol/L), adding PCSK9-I is reasonable (Class IIa)

Dashed arrow indicates RCT-supported efficacy, but is less cost effective

Very high-risk* ASCVD
Very high risk of future ASCVD events

- Major ASCVD Events
  - Recent ACS (within the past 12 mo)
  - History of MI (other than recent ACS event listed above)
  - History of ischemic stroke
  - Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation)

- High-Risk Conditions
  - Age >65 y
  - Heterozygous familial hypercholesterolemia
  - History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
  - Diabetes mellitus
  - Hypertension
  - CKD (eGFR 15-59mL/min/1.73m²)
  - Current smoking
  - Persistently elevated LDL-C (LDL-C >100mg/dL) despite maximally tolerated statin therapy and ezetimibe
  - History of congestive HF

Grundy et al 2018
IMPROVE-IT

<table>
<thead>
<tr>
<th>Years since Randomization</th>
<th>Simvastatin–ezetimibe</th>
<th>Simvastatin</th>
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<tr>
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<td>9077</td>
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Hazard ratio, 0.936 (95% CI, 0.89–0.99)  
P=0.016

Simvastatin monotherapy
Simvastatin–ezetimibe

ARR: 2%
RRR: 5.7%
NNT 50

Cannon et al. NEJM 2015
Figure 1. Secondary Prevention in Patients With Clinical ASCVD

Clinical ASCVD

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Continuation of high-intensity statin is reasonable (Class IIa)

Very high-risk* ASCVD

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If on maximal statin and LDL-C ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe is reasonable (Class IIa)

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Grundy et al 2018
EVOLOCUMAB – (REPATHA)

Schwartz et al. NEJM 2018

Alirocumab (Praluent)

Sabatine et al. NEJM 2017

Schwartz et al NEJM 2018
FIGURE. Mechanism of LDL-C Reduction via PCSK9 Inhibition

Without a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, PCSK9 binds to the low-density lipoprotein (LDL) receptor (LDLR) leading to lysosomal degradation of LDLRs. With PCSK9 inhibition (eg, via monoclonal antibodies [mAb] binding), the binding of PCSK9 to LDLRs is blocked, which stimulates recycling of the LDLR and leads to increased LDLR expression at the cell membrane. The increase in LDL receptor expression then leads to an increase in low-density lipoprotein cholesterol (LDL-C) binding and catabolism.

ABSTRACT

Sabatine et al. NEJM 2017

ARR: 1.5%
NNT: 67

Schwartz et al. NEJM 2018

ARR: 1.6%
NNT: 62
PCSK9I COST EFFECTIVENESS (MID 2018 $)

- "Low Value"
- "Good Value"

Hlatky et al. JACC. 2017;70:2677-87

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Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*

ARR: 4.8%
NNT: 21
CARDIOVASCULAR RISK REDUCTION AND TYPE 2 DIABETES MELLITUS
UKPDS 33: Intensive Glycemic Control Significantly Reduces Microvascular Complications

Figure 9.1—Glucose-lowering medication in type 2 diabetes: overall approach. For appropriate context, see Fig. 4.1. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOTs, cardiovascular outcomes trials; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione. Adapted from Davies et al. (39).
Timeline of Major Diabetes Outcomes Trials

**Blue** = Intensive vs standard control using same set of glucose-lowering agent(s)
**Purple** = Intensive control with a specific agent vs standard care
**Red** = Placebo- or active-controlled study
* = FDA-mandated cardiovascular safety trial

ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; CANVAS, Canagliflozin Cardiovascular Assessment Study; DCCT, Diabetes Control and Complications Trial; DEVOTE, Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events; EXAMINE, Examination of Cardiovascular Outcomes with Allogliflozin versus Standard of Care; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; EMPA-REG, EMPA-REG OUTCOME trial; Exenatide Study of Cardiovascular Event Lowering; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; ORIGIN, Outcome Reduction with an Initial Glagagine Intervention; PROActive, Prospective Pioglitazone Clinical Trial in Macrovascular Events; RECORD, Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes; SAVOR-TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction; STOP-NIDDM, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus; SUSTAIN, Trial to Evaluate Cardiovascular and Other Long-Term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.
Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34)

Metformin v Diet

1° outcomes:
- Composite of “any DM endpoint”
  - 32% RRR (p=0.002)
- DM related death
  - 42% risk reduction (p=0.002)
- All cause mortality
  - 36% risk reduction (p=0.01)

2° Analysis Metformin v SU/Insulin
- Composite of “any DM endpoint”
  - 26% RRR (p=0.003)
- DM related death
  - NS (p=0.11)
- All-Cause Mortality
  - 29% RRR (p=0.02)
Primary Outcome:
Annual rate of nonfatal MI, nonfatal stroke or CV death
Effects of Intensive Glucose Lowering in Type 2 Diabetes

The Action to Control Cardiovascular Risk in Diabetes Study Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intensive Therapy (N=5128)</th>
<th>Standard Therapy (N=5123)</th>
<th>P Value</th>
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<tr>
<td><strong>Hypoglycemia — no. (%)</strong></td>
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<td>Requiring medical assistance</td>
<td>338 (10.9)</td>
<td>179 (3.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Requiring any assistance</td>
<td>338 (10.9)</td>
<td>261 (5.1)</td>
<td>&lt;0.001</td>
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<td><strong>Fatal or nonfatal heart failure — no. (%)</strong></td>
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<td>132 (4.0)</td>
<td>124 (2.4)</td>
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<td>Motor vehicle accident in which patient was driver — no./total no. (%)</td>
<td>9/5033 (0.2)</td>
<td>14/5036 (0.3)</td>
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<tr>
<td>Any nonhypoglycemic serious adverse event — no. (%)</td>
<td>131 (2.1)</td>
<td>82 (1.6)</td>
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<td>Fluid retention — no./total no. (%)</td>
<td>3541/5053 (70.1)</td>
<td>1378/5054 (66.8)</td>
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<td><strong>Clinical measures</strong></td>
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<td><strong>Weight gain &gt;10 kg since baseline — no./total no. (%)</strong></td>
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<td>1399/5053 (27.8)</td>
<td>713/5042 (14.3)</td>
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<td>Alanine aminotransferase &gt;4 times ULN — no./total no. (%)</td>
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<td>77/5061 (1.5)</td>
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<td>Low-density lipoprotein cholesterol — mg/dl</td>
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<td>90.6±34.0</td>
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<td>Blood pressure — mm Hg</td>
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<td>Systolic</td>
<td>126.4±16.7</td>
<td>127.6±17.2</td>
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<td>Diastolic</td>
<td>66.9±10.5</td>
<td>67.7±10.6</td>
<td>&lt;0.001</td>
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<td><strong>Cigarette-smoking status — no. (%)</strong></td>
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<td>Current (previous 30 days)</td>
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<td>528 (9.9)</td>
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<td><strong>Use of nonglycemic medication — no./total no. (%)</strong></td>
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<td>Antihypertensive</td>
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<td>4714/5123 (92.0)</td>
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<td>1753/4970 (75.5)</td>
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<td>Beta-blocker</td>
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<td>2450/5037 (48.6)</td>
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<td>Statin</td>
<td>4412/5039 (88.0)</td>
<td>4425/5054 (87.6)</td>
<td>0.54</td>
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</table>
Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes

The ADVANCE Collaborative Group*
**Timeline of Major Diabetes Outcomes Trials**

- **DCCT** (1995)
- **UKPDS/UKPDS Metformin** (1995)
- **STOP-NIDDM** (2000)
- **PROActive** (2005)
- **ACCORD** (2010)
- **VADT** (2010)
- **ORIGIN** (2010)
- **SAVOR-TIMI** (2011)
- **TECOS** (2014)
- **LEADER** (2014)
- **DEVOTE** (2015)
- **EXCLSA** (2015)
- **ADVANCE** (2008)
- **RECORD** (2008)
- **EXAMINE** (2015)
- **ELIXA** (2015)
- **EMPA-REG** (2015)
- **SUSTAIN 6** (2015)
- **CANVAS** (2015)
- **EXCEL** (2015)

**Blue** = Intensive vs standard control using same set of glucose-lowering agent(s)
**Purple** = Intensive control with a specific agent vs standard care
**Red** = Placebo- or active-controlled study

* = FDA-mandated cardiovascular safety trial

**ACCORD**, Action to Control Cardiovascular Risk in Diabetes; **ADVANCE**, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; **CANVAS**, Canagliflozin Cardiovascular Assessment Study; **DCCT**, Diabetes Control and Complications Trial; **DEVOTE**, Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events; **EXAMINE**, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; **ELIXA**, Evaluation of Lixisenatide in Acute Coronary Syndrome; **EMPA-REG**, EMPA-REG OUTCOME trial; **EXENATE** Study of Cardiovascular Event Lowering; **LEADER**, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; **ORIGIN**, Outcome Reduction with an Initial Glargine Intervention; **PROActive**, Prospective Pioglitazone Clinical Trial in Macrovascular Events; **RECORD**, Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes; **SAVOR-TIMI**, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction; **STOP-NIDDM**, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus; **SUSTAIN**, Trial to Evaluate Cardiovascular and Other Long-Term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; **TECOS**, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; **UKPDS**, United Kingdom Prospective Diabetes Study; **VADT**, Veterans Affairs Diabetes Trial.
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators
Figure 1. Cardiovascular Outcomes and Death from Any Cause.

Shown are the cumulative incidence of the primary outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) (Panel A), cumulative incidence of death from cardiovascular causes (Panel B), the Kaplan–Meier estimate for death from any cause (Panel C), and the cumulative incidence of hospitalization for heart failure (Panel D) in the pooled empagliflozin group and the placebo group among patients who received at least one dose of a study drug. Hazard ratios are based on Cox regression analyses.
Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes


A. Cardiovascular Death or Hospitalization for Heart Failure

B. MACE

C. Renal Composite

D. Death from Any Cause

No. at Risk
Placebo: 8578 8485 8387 8259 8127 8003 7880 7767 5362
Dapagliflozin: 8582 8517 8413 8222 8110 7970 7497 5445

No. at Risk
Placebo: 8578 8433 8281 8129 7969 7805 7649 7137 5158
Dapagliflozin: 8582 8466 8303 8166 8017 7873 7708 7237 5225

No. at Risk
Placebo: 8578 8508 8422 8326 8200 8056 7932 7409 5380
Dapagliflozin: 8582 8533 8436 8347 8248 8136 8009 7534 5472

No. at Risk
Placebo: 8578 8542 8484 8414 8337 8258 8184 7741 5715
Dapagliflozin: 8582 8554 8495 8437 8369 8305 8207 7763 5715
Semaglutide Cardiovascular Outcomes
SUSTAIN-6 (2016)

A Primary Outcome

Hazard ratio, 0.74 (95% CI, 0.58–0.95)
P<0.001 for noninferiority
P=0.02 for superiority

B Nonfatal Myocardial Infarction

Hazard ratio, 0.74 (95% CI, 0.51–1.08)
P=0.12

C Nonfatal Stroke

Hazard ratio, 0.61 (95% CI, 0.38–0.99)
P=0.04

D Death from Cardiovascular Causes

Hazard ratio, 0.98 (95% CI, 0.65–1.48)
P=0.92

No. at Risk

Placebo 1649 1616 1586 1567 1534 1508 1479
Semaglutide 1648 1619 1601 1584 1568 1543 1524

No. at Risk

Placebo 1649 1624 1598 1587 1562 1542 1516
Semaglutide 1648 1623 1609 1595 1582 1560 1543

No. at Risk

Placebo 1649 1629 1611 1597 1571 1548 1528
Semaglutide 1648 1630 1619 1606 1593 1572 1558

No. at Risk

Placebo 1649 1637 1623 1617 1600 1584 1566
Semaglutide 1648 1634 1627 1617 1607 1589 1579
Completed and ongoing CVOTs (6–14,39,44–58). 3-P, 3-point; 4-P, 4-point; 5-P, 5-point.

William T. Cefalu et al. Dia Care 2018;41:14-31
A CARDIOLOGIST’S PRACTICAL GUIDE TO USING SGLT2i

Candidates for Initiation

Selection of Drug and Dose

Pre-Initiation Safety Screen

Prescription of SGLT2i

Long-Term Continuation

Patients with T2DM with or at High Risk for CV Disease, Already on Metformin

Below Individualized HbA1c Target:
Switch non-metformin oral therapies (e.g., sulfonylureas) to a SGLT2i

Above Individualized HbA1c Target:
Consider SGLT2i initiation

Drug Type
Canagliflozin, dapagliflozin, & empagliflozin with similar efficacy profile in reducing HF events

Starting Dose (once daily in AM)
- Canagliflozin (100mg)
- Dapagliflozin (5mg)
- Empagliflozin (10mg)
- Ertugliflozin (5mg)

Metformin+SGLT2i Combination Therapies
Consider to limit non-adherence and pill burden

Stable Hemodynamic and Clinical Status
Pre-Initiation eGFR must be above:
- 60 mL/min/1.73 m² (dapagliflozin, ertugliflozin)
- 45 mL/min/1.73 m² (canagliflozin, empagliflozin)

Anticipatory Guidance
Consider diuretic dose reduction

Patient Counseling
- Genital/perineal hygiene
- Orthostatic hypotension
- Regular foot exams
- Symptoms of DKA
- Avoid excessive alcohol

Multidisciplinary Care
Close communication with other providers, including PCPs and endocrinologists

Follow-up and Monitoring
- Serial assessment of renal function, body weights, blood pressure, and symptoms
- Dose upitation guided by need for glycemic control
- Ensure adherence to SGLT2i, other therapies, and therapeutic lifestyle
- Multidisciplinary care team follow-up

Vardeny et al JACC HF 2019:169-172
• Estimated that ~5% of eligible DM-CV patients are prescribed SGLT2-I

• <5% of current prescriptions generated by cardiologists
BOTTOM LINE

• Statins first line for lipid lowering therapy
  – Ezetimibe is second line agent.
  – PCSK9 inhibitors should be reserved for very high risk patients with careful consideration to cost

• Significant CV event reduction has been established with SGLT2-I and GLP1-RA
QUESTION

• 65 yo F history of coronary artery disease (10 mo ago w NSTEMI presentation – mid LAD 90%), HLD, obesity HTN,
• At time of NSTEMI placed on atorvastatin 40
• 3 weeks after statin initiation she develops petechial rash.
• PCP transitions to simvastatin with recurrence of rash, no further statin challenge given
• Diet – bad (McD weekly, Pepsi, Coke, chips, candy, lots of red meat)
• Physical activity – sedentary (BMI 41)
<table>
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<th>Component</th>
<th>NSTEMI</th>
<th>RASH</th>
<th>Off Statin</th>
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<td>10/2017</td>
<td>3/2018</td>
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<tr>
<td>Total Cholesterol</td>
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<td>109</td>
<td>183</td>
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<tr>
<td>LDL Calculated</td>
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<td>HDL</td>
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<tr>
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<td>169</td>
<td>381</td>
</tr>
<tr>
<td>Non-HDL</td>
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<td>87</td>
<td>153</td>
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Agrees to try rosuvastatin 10mg
**QUESTION**

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<th>Atorva 40 Rash</th>
<th>Off Statin</th>
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<td>Non-HDL</td>
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<td>87</td>
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</tbody>
</table>

What do you recommend in light of the patient’s “on-therapy” lipid profile?

a) No change to therapy  
b) Addition of PCSK9 inhibitor Evolocumab  
c) Addition of ezetimibe 10mg daily  
d) Increase dose of Rosuvastatin to 20mg daily
REFERENCES

- Cannon et al. Simulation of lipid-lowering therapy intensification in a population with atherosclerotic cardiovascular disease. JAMA Cardiol. 2017 Sep 1;2(9):959-966
- Hlatky et al. PCSK9 inhibitors; economics and policy. J Am Col Card. 2017;70:2677-87