IAS Roundtable

Preventing Atherosclerotic Cardiovascular Disease in Patients with Diabetes Mellitus

Program Directors:

Jennifer G Robinson MD MPH

Raul D Santos MD MSc PhD

1

IAS Expert Panel/Disclosures

Khalid al Rasadi MD

Sultan Qaboos University, Head of Department of Biochemistry, SQU, College of Medicine and Health Sciences, Oman

Disclosure: *Honoraria for Speakers Bureau: AstraZeneca, Sanofi, Pfizer, Abbott. Advisory Boards: Sanofi, Aegerion*

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Disclosure: *Consultant/Advisory Board/Speaker Honorarium for Amgen, Pfizer and Sanofi-Regeneron*

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Disclosure: *Unpaid Steering Committee: Kaneka; Speaker Bureau: Amgen, Sanofi, Pfizer, Astra-Zeneca, Merck Sharp & Dohme, Getz Pharma, Gendiag; Consultant/Advisory Board: Kaneka, Getz Pharma, Zora, Gendiag*

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IAS Expert Panel/Disclosures

Peter Libby MD

Brigham and Womens Hospital and Mallinckrodt Professor of Medicine, Harvard Medical School, United States of America

Disclosure: *Grant/Research support: Novartis; Unpaid Consultant and/or Unpaid Steering or Executive Committee of Clinical Trials: Amgen, AstraZeneca, Esperion, GlaxoSmithKline, Kowa, Merck, Novartis, Pfizer, Sanofi-Aventis-Regeneron; Scientific Advisory Board: IFM, Medimmune, DalCor, Amgen, Novartis, Corvidia, Olatec, Xbiotech; Dr. Libby declines all personal compensation from pharma or device companies*

Jennifer G Robinson MD MPH

Professor, Departments of Epidemiology & Medicine, Director, Prevention Intervention Center Department of Epidemiology, University of Iowa, United States of America

Disclosure: *Research grants to Institution: Acasti, Amarin, Amgen, Astra-Zeneca, Esai, Esperion, Merck, Novartis, Novo-Nordisk, Regeneron, Sanofi, Takeda; Consultant: Amgen, Medicines Company, Merck, Novartis, Novo-Nordisk, Pfizer, Regeneron, Sanofi*

3

IAS Expert Panel/Disclosures

Raul D Santos MD MSc PhD,

Associate Professor and Director Lipid Clinic Heart Institute (InCor) University of Sao Paulo Medical School Hospital, Researcher Hospital Israelita Albert Einstein, Sao Paulo-Brazil

Disclosure: *Consulting/Speaking/Research activities from: Akcea, Amgen, AstraZeneca, Biolab, Esperion, Kowa, Merck, Novo-Nordisk, Pfizer, and Sanofi/Regeneron.*

Dong Zhao MD. PhD,

Professor, Department of Epidemiology, Beijing Institute of Heart, Lung & Blood Vessel Diseases, Capital Medical University Beijing Anzhen Hospital, Beijing, China

Disclosure: *Research Grants to Institutions: Astra-Zeneca, Amgen, Boehringer-Ingelheim, Pfizer*

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The International Atherosclerosis Society would like to thank Pfizer and Upjohn for providing an unrestricted medical grant to support this educational initiative.

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Statement of Need - Diabetic Patients

- 33-49% of patients still do not meet targets for A1C, blood pressure, or lipids in US – *Even more do not in many low-and middle income countries*
- Only 14% of patients meet targets for all A1C, BP, lipids, and nonsmoking status - *Even fewer do in many low-and middle income countries*
- Progress in CVD risk factor control is slowing
- System-level improvements are needed

Improving Care and Promoting Health in Populations:
Standards of Medical Care in Diabetes - 2019. Diabetes Care 2019;42(Suppl. 1):S7-S12

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Program Objective

- Provide a better understanding of the evidence-based management of the diabetic patient to reduce ASCVD risk
- Focus on statins and newer diabetes drugs

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Program Overview
Integrated Learning Modules

1. Natural history and ASCVD risk stratification in T2DM
2. Statins, LDL-C lowering and prevention of ASCVD in T2DM
3. Safety of statin therapy and low LDL-C in T2DM
4. Managing symptoms during statin therapy
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Natural History and Atherosclerotic Cardiovascular Disease (ASCVD) Risk Stratification in Diabetes Mellitus

Presenter: Raul Santos MD MSc PhD

Discussants: Jennifer Robinson MD MPH & Dong Zhao MD PhD

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Faculty and Disclosures

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Diabetes Mellitus (DM) Diagnosis (Type 1 & 2)

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*

OR

2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.*

OR

A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*

OR

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

*"In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

FPG= Fasting plasma glucose; PG= postprandial glucose; OGTT= oral glucose tolerance test; DCCT= Diabetes Treatment and Control Trial
American Diabetes Association. **2. Classification and Diagnosis of Diabetes:** ***Standards of Medical Care in Diabetes—2019.***
Diabetes Care 2019 Jan; 42(Supplement 1): S13-S28

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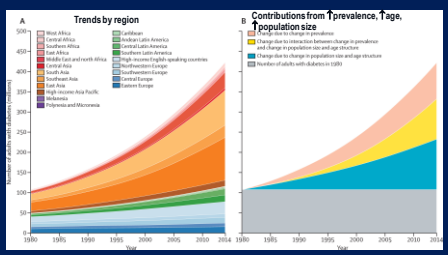
Type 2 DM is Increasing in Every Region of World

Due to poor diets, less physical activity, increasing obesity & aging populations



NCD RisC. Lancet 2016; 10027: 1513-30

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Diabetes: A Highly Morbid & Fatal Condition

- **Diabetes increases risk of death**
  - 1.8-fold for **all-cause mortality**
  - 2.3-fold for **cardiovascular death**
  - Women ≈ Men
- **85% deaths in diabetic patients due to cardiovascular causes** if risk factors are untreated
  - Atherosclerotic cardiovascular disease (ASCVD) & heart failure (HF)
  - US 1988-1994: 48% of death from cardiovascular causes
  - US 2010-2015: 34% of deaths from cardiovascular causes due to better risk factor control
    - Statins
    - Blood pressure
    - ACEI/ARB
- **Diabetes increases risk of heart failure**
  - 11% increase in HF risk per 1 mmol/L (18 mg/dL) higher glucose level
- Along with increased risk of renal failure, neuropathy/amputation, and blindness

Seshashi SRK et al. N Engl J Med 2011; 364: 829-841; Liu L, et al. World J Diab 2016; 7: 449-461;
NCD RisC. Lancet 2016; 10027: 1513-30; Rawshani A, et al NEJM 2018; 379-633-644; Khan H, et al J Card Fail 2014; 20: 584-592

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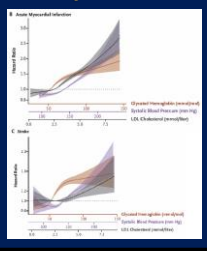
T2DM: *Well-controlled risk factors = little or no excess risk* of death, MI or stroke in next 6 years

- HbA1c <7% (<53 mmol/mole)
- LDL-C <100 mg/dl (<2.5 mmol/L)
- Blood pressure <140/<80 mm Hg
- Nonsmokers
- No micro or macroalbuminuria



Rawshani A, et al NEJM 2018; 379-633-644

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Diabetes – Risk Stratification for Statin Therapy
2018 AHA/ACC/Multispecialty Guideline

Diabetes Primary Prevention

Age 40-75 years

- At least moderate intensity statin for everyone (I A)
- High intensity statin if risk factors (IIa B-NR)

- **Age 20-39 years** (IIb C-LD)
  - Moderate intensity statin if multiple ASCVD & Diabetes risk factors

Estimate 10-year ASCVD risk*
- Age
- Sex
- Race
- Blood pressure & antihypertensive medication
- Total cholesterol
- HDL-cholesterol,
- Smoking

Diabetes risk-enhancing factors
- Long duration
  - ≥10 years T2DM
  - ≥20 years T1DM
- Albuminuria ≥30 mcg
- eGFR <60 mL/min/1.73 m²
- Retinopathy
- Neuropathy
- ABI <0.9

NR nonrandomized data; **LD** limited data
***ASCVD risk estimator**. *http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate*
Grundy SM, et al. J Am Coll Cardiol 2019; 73: 3168-3209

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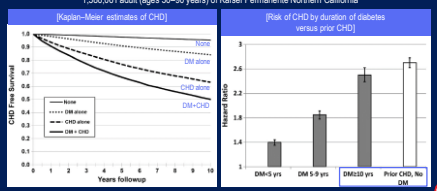
Diabetes ≥10 years ≈ CHD Risk Equivalent
Consider a high intensity statin

Population-based prospective cohort analysis
1,586,061 adult (ages 30–90 years) of Kaiser Permanente Northern California



Rana JS, et al. J Gen Intern Med. 2016; 1(4):387–93

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Statins, LDL-C Lowering, and Prevention of Atherosclerotic Cardiovascular Disease (ASCVD) in Diabetes Mellitus (DM)

Presenter: Jennifer G Robinson MD MPH

Discussants: Peter Libby MD & Khalid al Rasadi MD

3

Program Faculty

Presenter

Jennifer G Robinson MD MPH

Professor, Departments of Epidemiology & Medicine, Director, Prevention Intervention Center Department of Epidemiology, University of Iowa, United States of America

Discussant

Peter Libby MD

Brigham and Womens Hospital and Mallinckrodt Professor of Medicine, Harvard Medical School, United States of America

Discussant

Khalid al Rasadi MD

Sultan Qaboos University, Head of Department of Biochemistry, SQU, College of Medicine and Health Sciences Oman

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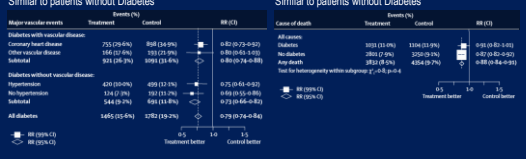
Statins Reduce ASCVD & Mortality in Multiple 2° & 1° Prevention Trials

21% ↓ASCVD per ↓LDL-C 1 mmol/L
Similar to patients without Diabetes

12% ↓ Mortality per ↓LDL-C 1 mmol/L
Similar to patients without Diabetes



ASCVD = Atherosderotic Cardiovascular Disease
1 mmol/L = 39 mg/dL
CTT. Lancet 2008; 371: 117-175

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More ↓LDL-C→ More ↓ASCVD

ASCVD patients: High Intensity Statins → More ↓ASCVD & HF

Start Moderate Intensity Statin

- 22% RRR ASCVD
- 10% RRR HF

Increase to High Intensity Statin

- Additional 15 - 20% RRR ASCVD
- Additional 21 - 25% RRR HF

Average ↓ LDL-C for statins

- High intensity 50%
  - Atorvastatin 40-80 mg
  - Rosuvastatin 20-40 mg
- Moderate intensity 30-35%
  - Starting doses

RRR= Relative risk reduction
CTT. Lancet 2010; 376: 1670-81; Preiss D, et al Eur Heart J 2015; 36: 1536-46

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Priority: Maximize Statin Therapy

Very high risk subgroups	Trial	Projected 10-year ASCVD risk	
		Moderate-intensity statin	High-intensity statin
CHD + diabetes	TNT	37%	28%
CHD + diabetes + CKD	TNT	43%	28%

5-year NNT = 11

NNT = 7

Uptitrate to high-intensity statin if possible!

Robinson JG, et al. J Am Coll Cardiol 2016;68:2412–2421

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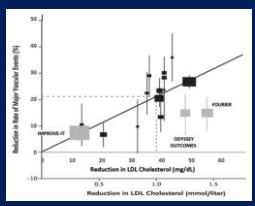
Statins Are First Line ASCVD Risk Reduction Therapy



- Statins: ↓ LDL-C 1 mmol/l (39 mg/dl) → ↓ ASCVD events ≈22%
- Ezetimibe modestly lowers LDL-C → Modestly ↓ ASCVD events
- PCSK9 mAbs ↓ LDL-C 50-65% → Less benefit when LDL-C <100 mg/dl on high/moderate intensity statins

CTT. Lancet 2005; 366: 1267-78; Cannon C, et al. NEJM 2015; 372: 2387097; Sabatine M, et al. NEJM 2017; 376: 1713-22; Schwartz G, et al. NEJM 2018; 379: 2097-2107.

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Diabetes – Secondary Prevention

2018 AHA/ACC/ADA/Multispecialty cholesterol guideline

DM & ASCVD = Very high ASCVD risk

- **Age ≤75 years**
  - **High intensity statin → ↓LDL-C 50%**
- **Age >75 years or safety concerns**
  - **Moderate intensity statin**
- **If LDL-C ≥70 mg/dl on max statin**
  - Consider adding ezetimibe
  - Then consider adding PCSK9 mAb

Grundy SM, et al. J Am Coll Cardiol 2019; 73: 3168-3209

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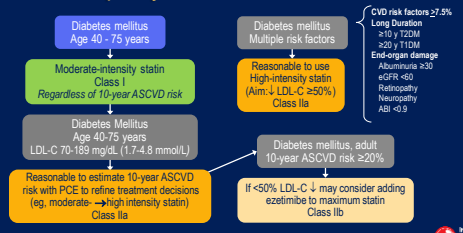
Diabetes Age 40-75 Years: Primary Prevention

2018 AHA/ACC/Multispecialty Guideline



Grundy SM, et al. J Am Coll Cardiol 2019; 73: 3168-3209

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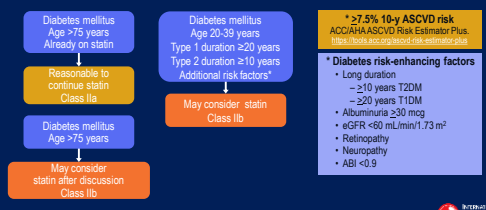
Diabetes Age <40 or >75 Years: Primary Prevention *2018 AHA/ACC/Multispecialty Guideline*



Grundy SM, et al. J Am Coll Cardiol 2019; 73: 3168-3209

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After Maximizing Statin Therapy, What is the ASCVD benefit of Further Lowering LDL-C?

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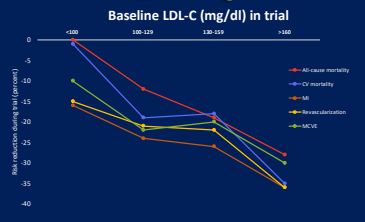
Greater Mortality & ASCVD Risk Reduction When LDL ≥100 mg/dl



Total mortality
Additional **10%** RR per 40 mg/dl higher baseline LDL-C

CV mortality
Additional **14%** RR per 40 mg/dl higher baseline LDL-C

From Navarese EP, Robinson JG (co-primary authors). JAMA 2018; 319: 1566-1579

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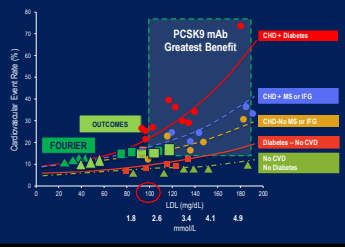
Log Linear Association LDL-C & CV Event Reduction Statin & PCSK9 mAb Trials



Diminishing returns from lowering LDL-C <100 mg/dl

CVD, cardiovascular disease; IFG, impaired fasting glucose; LDL-C, low-density lipoprotein cholesterol; mAb, monoclonal antibody; MS, metabolic syndrome; PCSK9, proprotein convertase subtilisin/kinexin type 9. Risk curve concept: Robinson JG, Stone NJ. *Am J Cardiol.* 2006;98:1405-1408.; FOURIER median of baseline LDL-C quartiles from Sabatine M, *et al.* Presented ACC Scientific Sessions; March 2017; Washington DC; Schwartz G, *et al. N Engl J Med 2019;* 379: 2097-2017

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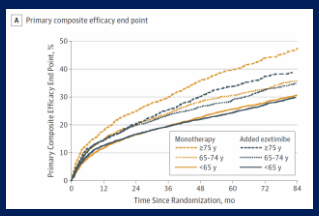
IMPROVE-IT: Ezetimibe Added to Statin Only Beneficial in ACS When Age ≥75 Years



Age ≥75 years: More likely to have multiple comorbidities

Bach RG, et al JAMA Cardiol 2019; doi: 10.1001/jamacardio.209.2306. Online July 17, 2019.

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Once Statin Therapy Maximized,

- Most benefit to adding nonstatin when LDL-C ≥100 mg/dl
- LDL-C <100 mg/dl
  - Ezetimibe - ACS age≥75 years with comorbidities only group to benefit
  - PCSK9 inhibiting monoclonal antibodies - Reasonable cost-effectiveness only in extremely high risk patients

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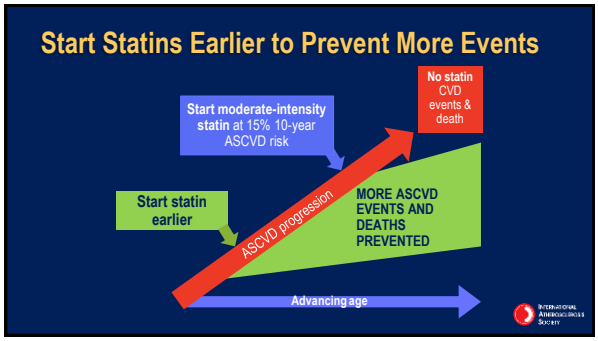
Start Statins Earlier to Prevent More Events
No statin
CVD events & death
Start moderate-intensity statin at 15% 10-year ASCVD risk
Start statin earlier
ASCVD progression
MORE ASCVD EVENTS AND DEATHS PREVENTED
Advancing age

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Safety of Statin Therapy in T2DM

Presenter: Peter Lansberg MD PhD

Discussants: Raul Santos MD MSc PhD & Dong Zhao MD PhD

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Faculty and Disclosures

Peter Lansberg MD PhD
Department of Pediatrics, Section Molecular Genetics, University Medical Center Groningen, Netherlands

Disclosure: *Unpaid Steering Committee: Kaneka; Speaker Bureau: Amgen, Sanofi, Pfizer, Astra-Zeneca, Merck Sharp & Dohme, Getz Pharma, Gendiag; Consultant/Advisory Board: Kaneka, Getz Pharma, Zora, Gendiag*

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Mr. L. 50 yrs.

Fasting Glucose :	95 mg/dl
HbA_{1C}:	5.6 %
BMI:	26.5
Blood pressure:	146/97 mmHg
Estimated GFR:	58 ml/min/1.73 m^2
Micro albuminuria:	Trace
Total cholesterol:	210 mg/dl (5.4 mmol/l)
LDL-cholesterol:	120 mg/dl (3.0 mmol/L)
HDL-cholesterol:	32 mg/dl (0.8 mmol/L)
Triglycerides:	285 mg/dl (3.2 mmol/L)

Meds: Metformin 1500 mg BID

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Question:

Statins Safe?

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Similar rates of adverse events vs placebo
Atorvastatin Safety 80 mg vs 10 mg vs Placebo

49 clinical trials - 14 236 patients

Adverse event (% of patients)	10 mg (n=7258)	80 mg (n=4798)	Placebo (n=2180)
Withdrawals due to treatment-associated adverse events	2.36	1.75	1.24
Treatment-associated serious, non-fatal adverse events	0.16	0.52	4.22
Myalgia	2.85	2.67	1.24
Treatment-related myalgia	1.36	1.5	0.69
Persistent ALT or AST >3x ULN†	0.11	0.6	0.17
Persistent CK >10x ULN†	0	0.06	0
Rhabdomyolysis	0	0	0
Albuminuria	0.11	0.04	0
Hematuria	0.33	0.31	0.14

Newman C, et al. Am J Cardiol 2006;97:61–67

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Claimed by Some:

"Statin treatment in the run-in period leads to exclusion of statin intolerant patients and therefore overestimates adherence"

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Identical Rates of Muscle Symptoms in 42 Placebo- RCT's

Only 3 of 42 studies → Drug run-in phase

11.7% vs 11.4% (SE 0.25) NS

Ganga HV, Slim HB, Thompson PD.A systematic review of statin-induced muscle problems in clinical trials. Am Heart J. 2014;168:6-15

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The Evidence

Review

Interpretation of the evidence for the efficacy and safety of statin therapy

CURRENT OPINION

Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel

>200 studies
>2 million participants
>20 million person/years f.u.
>150 000 CVD events

Lancet. 2017 Feb 11;389(10066):602

European Heart Journal (2017) 38, 2459–2472

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Statin Side Effects

- ✓ Muscle complaints
- ✓ Rhabdomyolysis
- ✓ Auto Immune Myositis
- ✓ New onset diabetes
- ✓ Teratogenicity
- ✓ Drug interactions
- ✓ Pharmacogenetic effects

- ? *Hemorrhagic stroke*
- ? *Reproduction*

- ~~Cancer~~
- ~~Liver damage~~
- ~~Cognitive function/memory loss~~
- ~~Acute pancreatitis~~
- ~~Erectile dysfunction~~
- ~~Cataract~~
- ~~Tendonitis~~
- ~~Polyneuropathy~~
- ~~Sleep disturbances~~
- ~~Steroid production~~
- ~~Infections~~

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40 mg Atorvastatin → ↓2 mmol/l LDL-C
Treat 10,000 patients for 5 years:

Myopathy	→ 5 cases
Rhabdomyolysis	→ 1 case
Diabetes	→ 50 – 100 cases
Hemorrhagic stroke	→ 5 – 10 cases

Symptomatic adverse complaints:

Muscle pain - weakness	→ 50 - 100 cases (0.5% -1.0%)
	Same rate as placebo/control group

Lancet. 2017 Feb 11;389(10069):602

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Statin Side Effects

Side effect	RCT evidence
Autoimmune myositis	Extremely rare
New onset diabetes	Slight excess in those with DM risk factors; Statin group- diagnosis 2 months earlier
Teratogenicity	Cell/Animal models; not documents in humans
Drug interactions	Modest; More likely with CYP3A inhibitors
Pharmacogenetic effects	Greater risk reduction in some studies
Hemorrhagic stroke	Rare
Reproduction	Contraindicated during pregnancy & lactation

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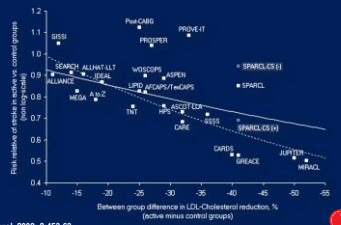
Stroke Risk and LDL Lowering

1 mmol (39 mg) ↓LDL-C stroke → Stroke ↓21% (95% CI 6.3 to 33.5%, p<0.001)

Total n=165,732



Amarenco P, Labreuche J. Lancet Neurol. 2009; 8:453-63

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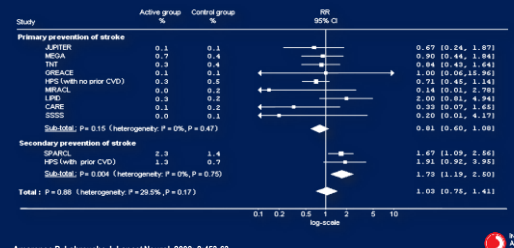
Meta-analysis RCTS: Hemorrhagic Stroke



Amarenco P, Labreuche J. Lancet Neurol. 2009; 8:453-63

22

Effect of Statin Use During Hospitalization for Intracerebral Hemorrhage on Mortality and Discharge Disposition

JAMA Neurol. 2014 Nov;71(11):1364-71

ICH patients (N= 3481)
20 hospitals - 10-year FU

Statin use
30 days post ICH **survival**
OR:4.25 (3.46-5.23; P<.001)

Statin discontinuation
30 days post ICH **survival**
OR:0.16 (0.12-0.21; P<.001)

CONCLUSIONS AND RELEVANCE:
Inpatient statin use is associated with improved outcomes after ICH, and the cessation of statin use is associated with worsened outcomes after ICH. Given the association between statin cessation and substantially worsened outcomes, the risk-benefit balance of discontinuing statin therapy in the acute setting of ICH should be carefully considered.

23

Statins and the risk of intracerebral haemorrhage in patients with stroke: systematic review and meta-analysis

CONCLUSIONS:
Irrespective of stroke subtype, there were non-significant trends towards future ICH with statins. However, this risk was **overshadowed by substantial and significant improvements in mortality and functional outcome among statin users.**

J Neurol Neurosurg Psychiatry. 2019 Jan;90(1):75-83.

Meta-analysis of Statin Use for the Acute Therapy of Spontaneous Intracerebral Hemorrhage

J. Humberto Tapia Pérez, MD,* O. Can Yildiz, MD,† Thomas Schneider, PhD, MD,† and Christopher Nimsky, PhD, MD*

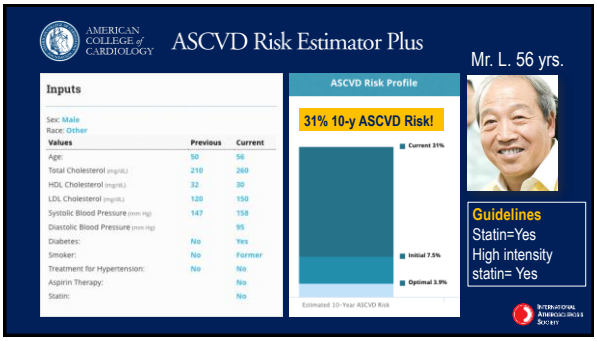
CONCLUSIONS:
The current evidence suggests that **continuing statin after ICH onset might be highly related to improvement of the outcome of patients with ICH.** Despite this strong suggestion, randomized controlled trials should be performed to further investigate this association.

Journal of Stroke and Cerebrovascular Diseases 2019 Jun;28(6):1703-1709

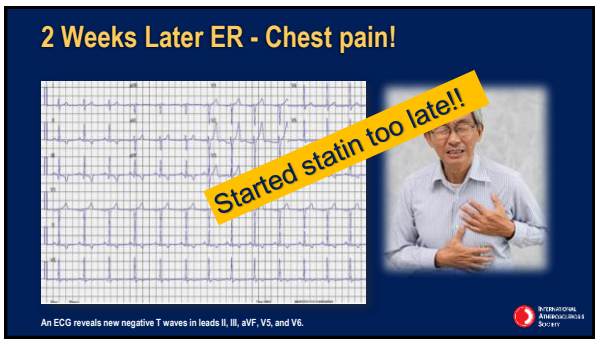
24


Question:
Is Safer to Not Take a Statin?

25


AMERICAN COLLEGE of CARDIOLOGY
ASCVD Risk Estimator Plus
Mr. L. 56 yrs.
Inputs
Sex: Male
Race: Other
Values
Previous
Current
Age:
50
56
Total Cholesterol (mg/dL)
210
260
HDL Cholesterol (mg/dL)
32
30
LDL Cholesterol (mg/dL)
120
150
Systolic Blood Pressure (mm Hg)
147
158
Diastolic Blood Pressure (mm Hg)
95
Diabetes:
No
Yes
Smoker:
No
Former
Treatment for Hypertension:
No
No
Aspirin Therapy:
No
Statin:
No
ASCVD Risk Profile
31% 10-y ASCVD Risk!
Current 31%
Initial 7.5%
Optimal 3.9%
Estimated 10-Year ASCVD Risk
Guidelines
Statin=Yes
High intensity statin= Yes

26


2 Weeks Later ER - Chest pain!
Started statin too late!!
An ECG reveals new negative T waves in leads II, III, aVF, V5, and V6.

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IAS Roundtable

Preventing Atherosclerotic Cardiovascular Disease in Patients with Diabetes Mellitus

Program Directors:

Jennifer G Robinson MD MPH

Raul D Santos MD MSc PhD

1

Program Overview
Integrated Learning Modules

1. **Natural history and ASCVD risk stratification in T2DM**
2. Statins, LDL-C lowering and prevention of ASCVD in T2DM
3. Safety of statin therapy in T2DM
4. **Managing symptoms during statin therapy**
5. Residual dyslipidemia in T2DM and implications for ASCVD prevention
6. Role of Newer T2DM drugs (SGLPT2, GLP-1) for ASCVD prevention
7. Putting It All Together

2

Managing Symptoms During Statin Therapy

Presenter: Philip Barter MBBS PhD FRACP

Discussants: Khalid al Rasadi MD & Jennifer Robinson MD MPH

3

Faculty and Disclosures

Philip Barter, MBBS, PhD, FRACP
School of Medical Sciences, University of New South Wales, Sydney, Australia
Disclosure: *Consultant/Advisory Board/Speaker Honorarium for Amgen, Pfizer and Sanofi-Regeneron*

Khalid al Rasadi MD
Sultan Qaboos University, Head of Department of Biochemistry, SQU, College of Medicine and Health Sciences, Oman
Disclosure: *Honoraria for Speakers Bureau: AstraZeneca, Sanofi, Pfizer, Abbott. Advisory Boards: Sanofi, Aegerion*

4

Faculty and Disclosures

Dong Zhao MD. PhD,
Professor, Department of Epidemiology, Beijing Institute of Heart, Lung & Blood Vessel Diseases, Capital Medical University Beijing Anzhen Hospital, Beijing, China
Disclosure: *Research Grants to Institutions: Astra-Zeneca, Amgen, Boehringer-Ingelheim, Pfizer*

5

Many Patients Have Symptoms During Statin Therapy…

But few symptoms are due to statin

- STATINS ARE SAFE: Same rate Adverse Events (AEs) in statin & control groups (moderate vs high intensity /open label groups) in randomized controlled trials
  - Muscle
  - Liver
  - Cognition
  - Etc,
- New diabetes: Onset 2 months earlier in statin vs control group
- CTT meta-analysis: rare cases of serious myopathy/rhabdomyolysis and hemorrhagic stroke

ASCVD risk-reduction benefit far exceeds any potential harm from statin therapy

Grundy SM, et al. J Am Coll Cardiol 2019; 73: 3168-3209; Newman CB, et al. *Arterioscler Thromb Vasc Biol.* 2018;38:e08-e09. doi: 10.1161/ATV.0000000000000073.; Robinson JG. *Curr Opin Lipidol.* 2015;25:225–235; CTT Collaborators. *Lancet.* 2012; 380: 581-590; Armitage J. Lancet 2007;370:1781–90; Stone NJ, Robinson JG, et al. *J Am Coll Cardiol.*2014;63:2889–2934.

6

Muscular Complaints in ASCOT-LLA Atorvastatin 10 mg Daily vs. Placebo

BLINDED PERIOD – Muscle related symptoms — No effect

Definite	HR 1.14 p = 0.27
Definite or probable	HR 1.03 p = 0.72
Definite, probable, or possible	HR 1.02 p = 0.69

UNBLINDED PERIOD — The "NOCEBO" EFFECT

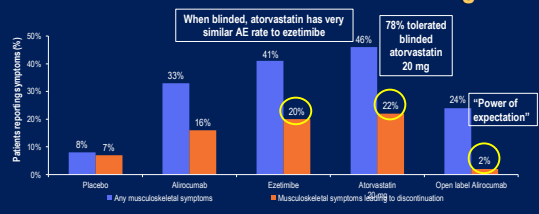
Definite	HR 1.27 p = 0.13
Definite or probable	HR 1.41 p = 0.006
Definite, probable, or possible	HR 1.17 p = 0.03

Up to 40% increase

Gupta A et. al. Lancet. 2017; 389: 2473–2481.

7

~75–80% of Statin of "Intolerant" Patients Can Tolerate Blinded atorvastatin 20 mg



Intolerant defined as "Symptoms on 2 or more statins"

Moriarty PM, et al. J Clin Lipidol 2015;9:758–769; Nissen SE et al. *JAMA.* 2016;315:1580-1590

8

Rechallenge Successful

A retrospective cohort study
107,835 adults who received a statin prescription

18,778 patients had statin-related events.

11,124(59.2%) of the patients who had the statin discontinued at least temporarily discontinued statin

6,579 (59.1%) of the patients who had the statin discontinued were rechallenged statin over the subsequent 12 months

92.2% who are rechallenged were still on a statin >12 months later
- ✓ **47.6% were on the same statin**
- ✓ 52.4% were on the different statin

Zhang H et al. Ann Intern Med 2013;159:75-6

9

Symptom Management During Statin Therapy
Combating the Nocebo Effect

1. **Discontinue** statin until the symptoms are resolved
2. **Build trust - Talk *with* patients** (not at them)
3. **Reassurance:** Statins are among the safest drugs yet developed; serious safety issues are rare and are greatly outweighed by the cardiovascular benefits of the agents

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Symptom Management During Statin Therapy
Combating the Nocebo Effect

3. **Manage expectations**
   - ASCVD & mortality benefits from statins
   - Avoid pain catastrophizing – Can you still do what you need/want to do?
4. **Rechallenge** - with the same or lower dose of statin
5. **Repeat** - If muscle symptoms recur, discontinue statin and rechallenge with progressively lower doses of the same or a different statin
   - Large majority of patients tolerate less-frequent or lower doses of statin

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2

Residual Dyslipidemia in Type 2 Diabetes Mellitus (DM) and Implications for Atherosclerotic Cardiovascular Disease (ASCVD) Prevention

Presenter: Khalid al Rasadi MD

Discussants: Raul Santos MD MSc PhD & Phillip Barter MBBS PhD FRACP

3

Faculty and Disclosures

Khalid al Rasadi MD
Sultan Qaboos University, Head of Department of Biochemistry, SQU, College of Medicine and Health Sciences, Oman
Disclosure: *Honoraria for Speakers Bureau: AstraZeneca, Sanofi, Pfizer, Abbott. Advisory Boards: Sanofi, Aegerion*

Raul D Santos MD MSc PhD,
Associate Professor and Director Lipid Clinic Heart Institute (InCor) University of Sao Paulo Medical School Hospital, Researcher Hospital Israelita Albert Einstein, Sao Paulo-Brazil
Disclosure: *Consulting/Speaking/Research activities from: Akcea, Amgen, AstraZeneca, Biolab, Esperion, Kowa, Merck, Novo-Nordisk, Pfizer, and Sanofi/Regeneron.*

4

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Philip Barter, MBBS, PhD, FRACP
School of Medical Sciences, University of New South Wales, Sydney, Australia
Disclosure: *Consultant/Advisory Board/Speaker Honorarium for Amgen, Pfizer and Sanofi-Regeneron*

5

Lipids in Diabetes

- Diabetes → Hepatic overproduction & delayed clearance of fasting and post-prandial atherogenic triglyceride-rich lipoproteins
- Atherogenic dyslipidemia common – 35-50% of diabetes patients
  - ↑ Triglyceride-rich lipoproteins → ↑Triglyceride levels
    - Chylomicron remnants, VLDL, LDL, IDL
  - ↑ small, dense LDL
  - ↓ HDL-C

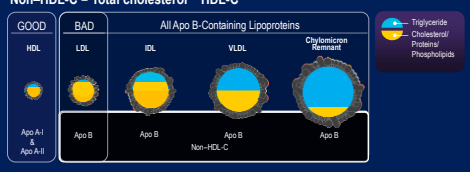
Mean lipid levels
No statin
- LDL-C 116 mg/dL
- HDL-C 46 mg/dL
- Triglyceride 189 mg/dL

Taskinen M-J, Boren J. Atherosclerosis 2015; 239: 483-495;
Cheung BM, et al. Am J Med 2009; 122: 443-453: US 1999-2002 3% on statins

6

Non–HDL-C is a Measure of All Atherogenic Particles

Non–HDL-C = Total cholesterol − HDL-C



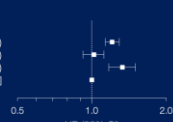
Executive Summary of the Third Report of NCEP ATP III. *JAMA*. 2001;285:2486–2497.
Blaha MJ, et al. *J Clin Lipidol*. 2008;2:267–273.
Ballantyne CM, *Clinical Lipidology: A companion of Braunwald's Heart Disease*. Philadelphia, PA: Saunder Elsevier; 2009

7

Association of LDL Cholesterol, Non–HDL Cholesterol, and Apolipoprotein B Levels with Risk of Cardiovascular Events Among Patients Treated with Statins *A Meta-analysis*

Figure 3. Risk of Major Cardiovascular Events by LDL and non-HDL Cholesterol Categories

Target Level				
LDL-C	Non–HDL-C	No. of Major Cardiovascular Events	Total No. of Participants	HR (95% CI)
≥100 mg/dL	≥130 mg/dL	1877	10419	1.21 (1.13-1.29)
≥100 mg/dL	<130 mg/dL	467	2873	1.02 (0.92-1.12)
<100 mg/dL	≥130 mg/dL	283	1435	1.32 (1.17-1.50)
<100 mg/dL	<130 mg/dL	2760	23426	1.00 [Reference]



Boekholdt et al JAMA. 2012;307:1302-1309

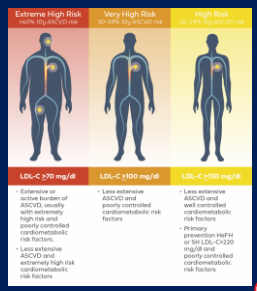
8

Lipid Intervention Cardiovascular Outcomes Trials

Drug	Outcome
LDL-C lowering drugs	
Statins	↓ASCVD & total mortality
Ezetimibe	↓ASCVD
PCSK9 mAbs	↓ASCVD (& total mortality when LDL-C ≥100 mg/dl)
HDL-C raising drugs	
Niacin	Added to statin: No benefit & harm in diabetic patients
CETP inhibitors	Added to statin: No benefit/modest benefit proportional to ↓non-HDL-C
Triglyceride-lowering drugs	
Fibrates	Modest ↓ASCVD proportional to ↓non-HDL-C
Omega-3 fatty acids	1 gm – heterogeneous evidence; modest ↓nonfatal MI one RCT
	Icosapent ethyl 4 gm – 25% ↓ASCVD; ↑edema, atrial fibrillation, bleeding trend

9

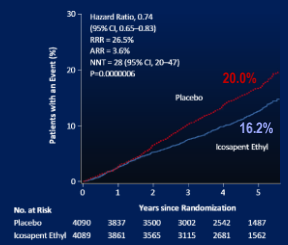
Statement on Enhancing the value of PCSK9 inhibiting monoclonal antibodies in statin-treated patients



Robinson JG, et al. J Clin Lipidol 2019; online ahead of print

10

REDUCE-IT CVD Death, MI, Stroke



Icosapent ethyl 4 g/d vs mineraol oil placebo X 4.9 years

Statin-treated
CVD or DM+≥1 risk factor
Trig ≥150-<500 mg/dl
LDL-C 40-≤100 mg/dl on statin

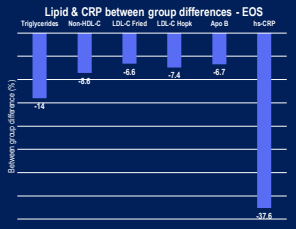
4%/year → **≈40% 10-y ASCVD risk**
5-year NNT=28

Bhatt D, et al. N Engl J Med 2019; 380: 11-22

11

REDUCE-IT Mechanism of Action?

- Lipid changes do not explain ASCVD risk reduction
- Baseline median levels
  - Triglyceride 217 mg/dl
  - LDL-C median 74 mg/dl
  - hs-CRP 2.2 mg/L
- Trend toward increased bleeding



Bhatt D, et al. N Engl J Med 2019; 380: 11-22

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IAS Roundtable

Preventing Atherosclerotic Cardiovascular Disease in Patients with Diabetes Mellitus

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Raul D Santos MD MSc PhD

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Role of Newer Type 2 Diabetes Mellitus (DM) Drugs (SGLT2 Inhibitor, GLP-1 RA) for Atherosclerotic Cardiovascular Disease (ASCVD) Prevention

Presenter: Dong Zhao MD PhD

Discussants: Peter Libby MD & Phillip Barter MBBS PhD FACP

3

Faculty and Disclosures

Dong Zhao MD. PhD,
Professor, Department of Epidemiology, Beijing Institute of Heart, Lung & Blood Vessel Diseases, Capital Medical University Beijing Anzhen Hospital, Beijing, China
Disclosure: *Research Grants to Institutions: Astra-Zeneca, Amgen, Boehringer-Ingelheim, Pfizer*

Philip Barter, MBBS, PhD, FRACP
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4

Faculty and Disclosures

Peter Libby MD
Brigham and Womens Hospital and Mallinckrodt Professor of Medicine, Harvard Medical School, United States of America

Disclosure: *Grant/Research support: Novartis; Unpaid Consultant and/or Unpaid Steering or Executive Committee of Clinical Trials: Amgen, AstraZeneca, Esperion, GlaxoSmithKline, Kowa, Merck, Novartis, Pfizer, Sanofi-Aventis-Regeneron; Scientific Advisory Board: IFM, Medimmune, DalCor, Amgen, Novartis, Corvidia, Olatec, Xbiotech; Dr. Libby declines all personal compensation from pharma or device companies*

5

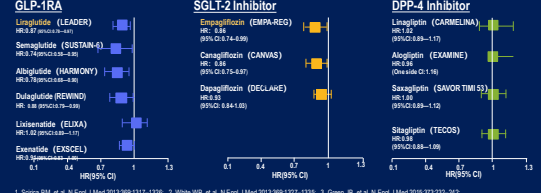
ASCVD Prevention: Newer T2DM Drug Families

GLP-1RA	SGLT-2 Inhibitor	DPP-4 Inhibitor
Liraglutide (LEADER)	Empagliflozin (EMPA-REG)	Saxagliptin (SAVOR TIMI53)
Semaglutide (SUSTAIN-6)		
Albiglutide (HARMONY)	Canagliflozin (CANVAS)	Alogliptin (EXAMINE)
Dulaglutide (REWIND)		
	Dapagliflozin (DECLARE)	Sitagliptin (TECOS)
Exenatide (EXSCEL)		
Lixisenatide (ELIXA)		Linagliptin (CARMELINA)

1. Scirica BM, et al. N Engl J Med 2013;369:1317–1326; 2. White WB, et al. N Engl J Med 2013;369:1327–1335; 3. Green JB, et al. N Engl J Med 2015;373:232–242; 4. 2018 EASD presentation; 5. Pfeffer MA, et al. N Engl J Med. 2015;373(23):2247–57; 6. Marso SP, et al. N Engl J Med. 2016;375:311–22; 7.Marso SP, et al. N Engl J Med. 2016;375:1834–44; 8. Holman RR, et al. N Engl J Med. 2017;377(13):1228–39; 9. Hernandez AF, et al. Lancet. 2018 Oct 1; 10. Neal B, et al. N Engl J Med. 2017 Aug 17;377(7)644-657; 11.Zinman, B. et al. N Engl J Med. 2017; 373 (22)2117-2128; 12. DOI: 10.1056/NEJMoa1812389

6

CVD Benefits of Newer T2DM Drugs Reduction in the Risk of MACE



1. Scirica BM, et al. N Engl J Med 2013;369:1317–1326; 2. White WB, et al. N Engl J Med 2013;369:1327–1335; 3. Green JB, et al. N Engl J Med 2015;373:232–242; 4. 2018 EASD presentation; 5. Pfeffer MA, et al. N Engl J Med. 2015;373(23):2247–57; 6. Marso SP, et al. N Engl J Med. 2016;375:311–22; 7.Marso SP, et al. N Engl J Med. 2016;375:1834–44; 8. Holman RR, et al. N Engl J Med. 2017;377(13):1228–39; 9. Hernandez AF, et al. Lancet. 2018 Oct 1; 10. Neal B, et al. N Engl J Med. 2017 Aug 17;377(7)644-657; 11.Zinman, B. et al. N Engl J Med. 2017; 373 (22)2117-2128; 12. DOI: 10.1056/NEJMoa1812389

7

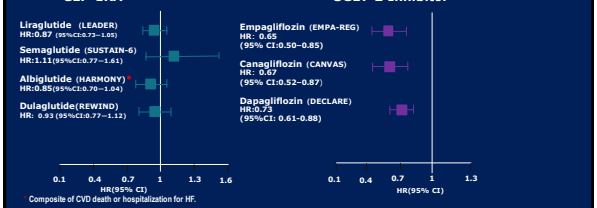
Empagilflozin and Liraglutide Reduce CVD Mortality

1. Yusuf S, et al. N Engl J Med. 2000;342:145–153;2.Scandinavian Simvastatin Survival Study Group Lancet 1994; 344: 1383–89. 3.Cannon CP et al NEJM 2004;350:1495-504;4.Sabatine MS et al. NEJM 2017 376:1713-1722;5.Schwartz GG et al. NEJM 2018;379:2097-2107;6.Marso SP, et al. N Engl J Med. 2016;375:311–22;7.Zinman, B. et al. N Engl J Med. 2015; 373 (22)2117-2128;

8

CVD benefits of Newer T2DM drugs

Reduction in hospitalization for heart failure



* Composite of CVD death or hospitalization for HF.

1. Marso SP, et al. N Engl J Med. 2016;375:311–22; 2.Marso SP, et al. N Engl J Med. 2016;375:1834–44; 3. Hernandez AF, et.al, Lancet. 2018 392:1519; 4.Gerstein HC. et al. Lancet 2019 394:121-130 5.Zinman, B. et al. N Engl J Med. 2015; 373 (22)2117-2128; 6. Neal B, et al. N Engl J Med. 2017 Aug 17;377(7)644-657; 7.Wiviott S.D. et al. N Engl J Med 2019;380:347-57

9

Mechanisms of Action for Reducing CVD Events

SGLT2 Inhibitor	GLP1 Receptor Agonist
• SGLT2 • sodium-glucose cotransporter 2 in proximal tubule of nephron responsible for 90% of urinary glucose reabsorption • SGLT2 inhibition: • Increases glucosuria in proportion to hyperglycemia • Diuretic & natriuretic effects → ↓ Blood pressure & weight loss	• GLP1 • glucagon-like peptide 1 is released from distal ileum & colon after eating • GLP1 receptor agonist: • ↑ glucose-dependent insulin secretion • ↓ glucagon secretion • Delays gastric emptying → Satiety → Weight loss

10

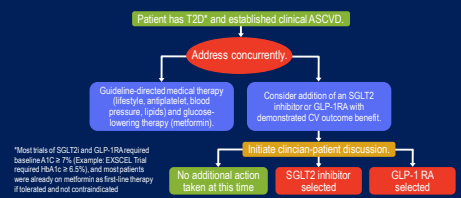
CVD Benefits of Newer T2DM Drugs

- Important to note that CV benefits occurred in statin-treated patients with LDL-C <100 mg/dl

Das SR, et al. J Am Coll Cardiol 2018; 72: 3200-3223

11

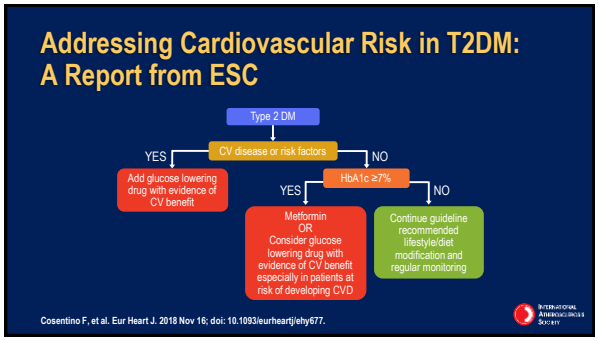
2018 ACC Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients with T2 DM and ASCVD



*Most trials of SGLT2i and GLP-1RA required baseline A1C ≥ 7% (Example: EXSCEL Trial required HbA1c ≥ 6.5%), and most patients were already on metformin as first-line therapy if tolerated and not contraindicated

Das SR, et al. J Am Coll Cardiol 2018; 72: 3200-3223

12


Addressing Cardiovascular Risk in T2DM: A Report from ESC
Type 2 DM
CV disease or risk factors
YES
NO
Add glucose lowering drug with evidence of CV benefit
HbA1c ≥7%
YES
NO
Metformin
OR
Consider glucose lowering drug with evidence of CV benefit especially in patients at risk of developing CVD
Continue guideline recommended lifestyle/diet modification and regular monitoring
Cosentino F, et al. Eur Heart J. 2018 Nov 16; doi: 10.1093/eurheartj/ehy677.

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Putting It All Together

Presenter: Peter Libby MD

Discussants: Raul Santos MD MSc PhD & Jennifer Robinson MD MPH

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Faculty and Disclosures

Peter Libby MD

Brigham and Womens Hospital and Mallinckrodt Professor of Medicine, Harvard Medical School, United States of America

Disclosure: *Grant/Research support: Novartis; Unpaid Consultant and/or Unpaid Steering or Executive Committee of Clinical Trials: Amgen, AstraZeneca, Esperion, GlaxoSmithKline, Kowa, Merck, Novartis, Pfizer, Sanofi-Aventis-Regeneron; Scientific Advisory Board: IFM, Medimmune, DalCor, Amgen, Novartis, Corvidia, Olatec, Xbiotech; Dr. Libby declines all personal compensation from pharma or device companies*

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Disclosure: *Consulting/Speaking/Research activities from: Akcea, Amgen, AstraZeneca, Biolab, Esperion, Kowa, Merck, Novo-Nordisk, Pfizer, and Sanofi/Regeneron.*

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Disclosure: *Research grants to Institution: Acasti, Amarin, Amgen, Astra-Zeneca, Esai, Esperion, Merck, Novartis, Novo-Nordisk, Regeneron, Sanofi, Takeda; Consultant: Amgen, Medicines Company, Merck, Novartis, Novo-Nordisk, Pfizer, Regeneron, Sanofi*

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Cardiovascular Risk Reduction in Patients with Diabetes Mellitus (DM)

- The approach should be holistic – not siloed
- T2DM patient management mandates a global approach
- We need to adopt a concerted strategy that transcends the usual disciplinary boundaries to serve our patients best
- We should not be constrained by our specialty training but work with our patients to address multiple facets of risk and apply the exciting new advances to optimize outcomes

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Cardiovascular Risk Reduction in Patients with Diabetes Mellitus

- The holistic approach should include
  - Lifestyle intervention (weight control and physical activity: LOOKAHEAD, Pascal's Wager)
  - Smoking cessation
  - Control of blood pressure

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Cardiovascular Risk Reduction in Patients with Diabetes Mellitus

- The holistic approach should include
  - Maximal statin therapy – High intensity statin if higher risk
  - Adding nonstatin therapy in highest risk patients if LDL-C ≥100 mg/dl
  - Once LDL-C <100 mg/dl – Several options for further ASCVD risk reduction
    - Additional LDL-C lowering
    - Icosapent ethyl
    - Rivaroxaban if low bleeding risk
    - GLP-1 agonists and SGLT-2 antagonists
    - Anti-inflammatory agent??

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Cardiovascular Risk Reduction in Patients with Diabetes Mellitus

- The holistic approach should include
  - Glucose management to improved microvascular outcomes
  - Use of GLP-1 agonists and SGLT-2 antagonists as *cardiovascular drugs*

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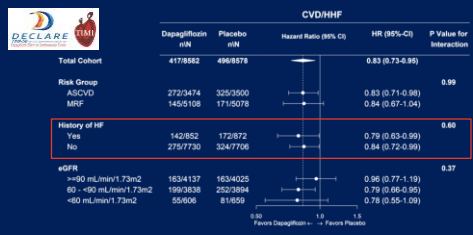
Effect on CVD/HF in Key Subgroups



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