IAS Roundtable
Preventing Atherosclerotic Cardiovascular Disease in Patients with Diabetes Mellitus

Program Directors:
Jennifer G Robinson MD MPH
Raul D Santos MD MSc PhD

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

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Disclosure: Research Grants to Institution: AstraZeneca, Amgen, Sanofi-Aventis, Pfizer
The International Atherosclerosis Society would like to thank Pfizer and Upjohn for providing an unrestricted medical grant to support this educational initiative.

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: Diabetes Care in T2DM. 2019;42(Suppl. 1):S7-S12

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

Program Overview

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
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
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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.
- **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.
- **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.
- 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.


Type 2 DM is Increasing in Every Region of World

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

Diabetes: A Highly Morbid & Fatal Condition

- **Diabetes increases risk of death**
  - 1.8 fold for diabetes mortality
  - 2.3 fold for cardiovascular death

- **85% deaths in diabetic patients due to cardiovascular causes if risk factors are untreated**
  - Atherosclerotic cardiovascular disease (ASCVD) & heart failure (HF)
  - USA 1988-1994: 48% of death from cardiovascular causes
  - USA 2010-2015: 34% of deaths from cardiovascular causes due to better risk factor control

- **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

**T2DM:** Well-controlled risk factors = little or no excess risk of death, MI or stroke in next 8 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


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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

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**Diabetes >10 years ≈ CHD Risk Equivalent**

Consider a high intensity statin

Population-based prospective cohort analysis

1,860,001 adult (ages 30–90 years) of Kaiser Permanente Northern California

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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

Program Faculty
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Peter Libby MD
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Discussant
Khalid al Rasadi MD
Sultan Qaboos University, Head of Department of Biochemistry, SQU, College of Medicine and Health Sciences, Oman
Statins Reduce ASCVD & Mortality in Multiple 2° & 1° Prevention Trials

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

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

Statins with/without Diabetes

<table>
<thead>
<tr>
<th>Statin</th>
<th>Moderate Intensity</th>
<th>High-Intensity</th>
<th>LDL-C (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin 10mg</td>
<td>23%</td>
<td>34%</td>
<td>2.0</td>
</tr>
<tr>
<td>Atorvastatin 40mg</td>
<td>32%</td>
<td>42%</td>
<td>1.8</td>
</tr>
<tr>
<td>Rosuvastatin 10mg</td>
<td>25%</td>
<td>35%</td>
<td>2.5</td>
</tr>
<tr>
<td>Rosuvastatin 20mg</td>
<td>31%</td>
<td>41%</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Average ↓LDL-C for statins
- High intensity 50%
  - Atorvastatin 40-80 mg
  - Rosuvastatin 20-40 mg
- Moderate intensity 30-35%
  - Starting doses

More ↓LDL-C → More ↓ASCVD
ASCVD patients: High Intensity Statins → More ↓ASCVD & HF

Start Moderate Intensity Statin

Future patients: High Intensity Statins

Increase to High Intensity Statin

More ↓LDL-C → More ↓ASCVD & HF

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

Priority: Maximize Statin Therapy

Very high risk subgroups | Trial | Projected 10-year ASCVD risk | 5-year NNT | NNT = 11
-------------------------|------|-----------------------------|------------|-------
OHD + diabetes           | TNT  | 37%                         | 28%        | 11    |
OHD + diabetes + CKD     | TNT  | 43%                         | 28%        | 7     |

Uptitrate to high-intensity statin if possible


**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 ≥190 mg/dl on max statin
  - Consider adding ezetimibe
  - Then consider adding PCSK9 mAb


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**Diabetes Age 40-75 Years: Primary Prevention**

**2018 AHA/ACC/Multispecialty Guideline**

**Diabetes mellitus**

- **Age 40-75 years**:
  - Moderate-intensity statin
  - Regardless of 10-year ASCVD risk

**Diabetes mellitus, adult**

- **10-year ASCVD risk ≥20%**
  - If <50% LDL-C ↓ may consider adding ezetimibe to maximum statin


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**Diabetes Age <40 or >75 Years: Primary Prevention**

**2018 AHA/ACC/Multispecialty Guideline**

**Diabetes mellitus**

- **Age 20-39 years**
  - Type 1 duration ≥20 years
  - Type 2 duration ≥10 years
  - Additional risk factors


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

- **Diabetes mellitus**
  - Multiple risk factors
  - Reasonable to use High-intensity statin → LDL-C <50%

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

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

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

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

Age >75 years: More likely to have multiple comorbidities

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

13 | 14 | 15 | 16
Start Statins Earlier to Prevent More Events

Start moderate-intensity statin at 15% 10-year ASCVD risk

Start statin earlier

ASCVD progresses

MORE ASCVD EVENTS AND DEATHS PREVENTED

Advancing age

No statin

CVD events & death

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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

Faculty and Disclosures

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Department of Pediatrics, Section Molecular Genetics, University Medical Center Groningen, Netherlands
Disclosure: Unpaid Steering Committee: Kaneka; Speaker Bureau: Amgen, Sanofi, Pfizer, AstraZeneca, Merck Sharp & Dohme, Gendiag; Consultant/Advisory Board: Kaneka, Getz Pharma, Zina, Gendiag

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: Alector, Amgen, AstraZeneca, Bial, Exponent, Kowa, Merck, Novo-Nordisk, Pfizer, and Sanofi/Regeneron
Faculty and Disclosures

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

Statin Safety in Perspective

Number needed to treat for 1 year

<table>
<thead>
<tr>
<th></th>
<th>GI Bleed¹</th>
<th>Fatal GI Bleed¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>248</td>
<td>2,066</td>
</tr>
<tr>
<td>Statins</td>
<td>100,000</td>
<td>1,000,000</td>
</tr>
</tbody>
</table>

²Statins: Rhabdomyolysis
Fatal Rhabdomyolysis
Mr. L. 50 yrs.

- Fasting Glucose: 95 mg/dl
- HbA1c: 5.6%
- BMI: 26.5
- Blood pressure: 146/97 mmHg
- Estimated GFR: 58 ml/min/1.73 m²
- Micro albuminuria: Trace

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>210 mg/dl (5.4 mmol/L)</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>120 mg/dl (3.0 mmol/L)</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>32 mg/dl (0.8 mmol/L)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>285 mg/dl (3.2 mmol/L)</td>
</tr>
</tbody>
</table>

Meds: Metformin 1500 mg BID

Question: Statins Safe?

NOT SUPPORTED BY CLINICAL TRIAL EVIDENCE!
Similar rates of adverse events vs placebo
Atorvastatin Safety 80 mg vs 10 mg vs Placebo

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>10 mg</th>
<th>80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawals due to treatment-associated adverse events</td>
<td>1.24</td>
<td>4.22</td>
<td>1.24</td>
</tr>
<tr>
<td>Treatment-associated serious, non-fatal adverse events</td>
<td>0.11</td>
<td>0.06</td>
<td>0.17</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1.1</td>
<td>0.16</td>
<td>2.36</td>
</tr>
<tr>
<td>Persistent ALT or AST &gt;3x ULN†</td>
<td>0.6</td>
<td>0.04</td>
<td>0.06</td>
</tr>
<tr>
<td>Persistent CK &gt;10x ULN†</td>
<td>0.04</td>
<td>0.11</td>
<td>0.31</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>0.3</td>
<td>0.33</td>
<td>0.14</td>
</tr>
</tbody>
</table>


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


The Evidence

Low-density lipoprotein-cholesterol lowering cardiovascular disease. 5. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel

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

European Heart Journal (2017) 38, 2459–2472

>200 studies
>2 million participants
>20 million person-years f.u.
>150 000 CVD events
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
- Gallbladder
- Cataracts
- Polyneuropathy
- Sleep disturbances
- Steroid production
- Cerebral strokes

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

Statins & Stroke?

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

- Statin group - diagnosis 2 months earlier
- Cell/Animal models; not documented in humans
- Slight excess in those with DM risk factors; Statin group - diagnosis 2 months earlier
- Cell/Animal models; not documented in humans
- Modest; More likely with CYP3A inhibitors
- Greater risk reduction in some studies
- Rare
- Contraindicated during pregnancy & lactation
**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=185,732

**Meta-analysis RCTS: Hemorrhagic Stroke**

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

ICH patients (N= 3481 )

20 hospitals - 10-year FU

Statin use
30 day 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:**

Resistant 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 resistance and substantially worsened outcomes, the risk-benefit balance of discontinuing statin therapy in the post-stroke setting of ICH should be carefully considered.

**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.

**CONCLUSIONS:**

The current evidence suggests that continuing statins after ICH onset might be highly related to improvements in mortality and functional outcome. Despite this strong suggestion, randomized controlled trials should be performed to further investigate this association.
Question: Is Safer to Not Take a Statin?

Question: Is Safer to Not Take a Statin?

2 Weeks Later ER - Chest pain!

An ECG reveals new negative T waves in leads II, III, aVF, V5, and V6.

Started statin too late!!

Mr. L. 56 yrs.

ASCVD Risk Estimator Plus

Guidelines

Statin=Yes

High Intensity Statin=Yes

31% 10-y ASCVD Risk!

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Managing Symptoms During Statin Therapy

Presenter: Philip Barter MBBS PhD FRACP
Discussants: Khalid Al Rasadi MD & Jennifer Robinson MD MPH

Faculty and Disclosures

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

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Disclosure: Honoraria for Speakers Bureau: AstraZeneca, Sanofi, Pfizer; Abbott.
Advisor Board; Sanofi, Aegerion
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

Muscular Complaints in ASCOT-LLA

Atorvastatin 10 mg Daily vs. Placebo

<table>
<thead>
<tr>
<th>Period</th>
<th>Muscle related symptoms</th>
<th>HR (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLED PERIOD</td>
<td>Definite</td>
<td>1.14 (0.22)</td>
</tr>
<tr>
<td></td>
<td>Definite or probable</td>
<td>1.03 (0.72)</td>
</tr>
<tr>
<td></td>
<td>Definite, probable or possible</td>
<td>1.02 (0.69)</td>
</tr>
<tr>
<td>UNBLED PERIOD</td>
<td>The “NOCEBO” EFFECT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Definite</td>
<td>1.27 (0.13)</td>
</tr>
<tr>
<td></td>
<td>Definite or probable</td>
<td>1.41 (0.00)</td>
</tr>
<tr>
<td></td>
<td>Definite, probable or possible</td>
<td>1.17 (0.03)</td>
</tr>
</tbody>
</table>


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

![Graph showing the percentage of patients who tolerated atorvastatin 20 mg when blinded vs those who did not.](image)

Intolerant defined as "Symptoms on 2 or more statins"

### Rechallenge Successful

- **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 continued statin over the subsequent 12 months.

- 6,579 (59.1%) of the patients who had the statin discontinued were rechallenged with the same or a different statin.

- 92.2% who are rechallenged were still on a statin >12 months later.

- 43.4% were on the same statin.

- 52.4% were on a different statin.

### 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.

#### Symptom Management During Statin Therapy

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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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

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Advisory Boards: Sanofi, Aegerion

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Faculty and Disclosures

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

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

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

Formula: Non–HDL-C = Total cholesterol – HDL-C

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


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

Mean lipid levels
No statin
- LDL-C 166 mg/dL
- HDL-C 46 mg/dL
- Triglycerides 199 mg/dL

Taskinen M-S, Boren J. Atherosclerosis 2015;239:483-495

Mean lipid levels
No statin
- LDL-C 116 mg/dL
- HDL-C 46 mg/dL
- Triglycerides 199 mg/dL

Boekholdt et al JAMA. 2012;307:1302-1309
Lipid Intervention Cardiovascular Outcomes Trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td><strong>LDL-C lowering drugs</strong></td>
<td></td>
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<tr>
<td>Statins</td>
<td>ASCVD &amp; total mortality</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>ASCVD &amp; total mortality when LDL-C&gt;160 mg/dl</td>
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<tr>
<td>PCSK9 mAbs</td>
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<tr>
<td><strong>HDL-C raising drugs</strong></td>
<td></td>
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<tr>
<td>Niacin</td>
<td>Added to statin: No benefit &amp; harm in diabetic patients</td>
</tr>
<tr>
<td>CETP inhibitors</td>
<td>Added to statin: No benefit/modest benefit proportional to ↓ non-HDL-C</td>
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<tr>
<td>Inhibitors of cholesterol absorption</td>
<td></td>
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<tr>
<td>Omega-3 fatty acids</td>
<td>Added to statin: No benefit/modest benefit proportional to ↓ non-HDL-C</td>
</tr>
<tr>
<td>Triglyceride-lowering drugs</td>
<td></td>
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<tr>
<td>Icosapent ethyl 4 g/d</td>
<td>16.2% – heterogeneous evidence, modest ↓ non-fatal MI one RCT, trend toward increased bleeding</td>
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</tbody>
</table>

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


REDUCE-IT CVD Death, MI, Stroke

Icosapent ethyl 4 g/d vs mineral oil placebo × 4.9 years

Statin-treated CVD or DM+1 risk factor
Trig ≥150-<300 mg/dl
LDL-C 40-<160 mg/dl on statin
4%/year → 48%/10-y ASCVD risk
5-year NNT=28

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

IAS Roundtable
Preventing Atherosclerotic Cardiovascular Disease in Patients with Diabetes Mellitus

Program Directors:
Jennifer G Robinson MD MPH
Raul D Santos MD MSc PhD

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

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 &Philip Barter MBBS PhD FACP

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: AstraZeneca, Amgen, Boehringer Ingelheim, Pfizer

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-Aventis
ASCVD Prevention: Newer T2DM Drug Families

<table>
<thead>
<tr>
<th>GLP-1 RA</th>
<th>SGLT-2 Inhibitor</th>
<th>DPP-4 Inhibitor</th>
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<tbody>
<tr>
<td>Liraglutide (LEADER)</td>
<td>Empagliflozin (EMPA-REG)</td>
<td>Saxagliptin (SAVOR TIMI53)</td>
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<td>Semaglutide (SUSTAIN-6)</td>
<td>Canagliflozin (CANVAS)</td>
<td>Alogliptin (EXAMINE)</td>
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<td>Dapagliflozin (DECLARE)</td>
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<td>Linagliptin (CAMELINA)</td>
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<tr>
<td>Albiglutide (LIXISA)</td>
<td>Linagliptin (CAMELINA)</td>
<td></td>
</tr>
</tbody>
</table>

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

GLP-1 RA

- Liraglutide (LEADER)
- Semaglutide (SUSTAIN-6)
- Dulaglutide (HARMONY)
- Lixisenatide (EXSCEL)
- Albiglutide (LIXISA)

SGLT-2 Inhibitor

- Empagliflozin (EMPA-REG)
- Canagliflozin (CANVAS)
- Dapagliflozin (DECLARE)
- Saxagliptin (SAVOR TIMI53)
- Linagliptin (CAMELINA)

DPP-4 Inhibitor

- Alogliptin (EXAMINE)
- Sitagliptin (TECOS)
- Linagliptin (CAMELINA)

Empagliflozin and Liraglutide Reduce CVD Mortality
Liraglutide (LEADER) HR: 0.87 (95% CI: 0.73—1.05)
Semaglutide (SUSTAIN-6) HR: 1.11 (95% CI: 0.77—1.61)
Albiglutide (HARMONY) HR: 0.85 (95% CI: 0.70—1.04)
Dulaglutide (REWIND) HR: 0.93 (95% CI: 0.77—1.12)

CVD benefits of Newer T2DM drugs
Reduction in hospitalization for heart failure

Mechanisms of Action for Reducing CVD Events

**SGLT2 Inhibitor**
- 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 Receptor Agonist**
- 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

CVD Benefits of Newer T2DM Drugs

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

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

Patient has T2D* and established clinical ASCVD

Address concurrently:
- Guideline-directed medical therapy (lifestyle, antiplatelet, blood pressure, lipids) and glucose-lowering therapy (metformin).
- Consider addition of an SGLT2 inhibitor or GLP1-R agonist with demonstrated CV outcome benefit.
- Initiate clinician-patient discussion.

*Most trials of SGLT2i and GLP1-Ra 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.
Addressing Cardiovascular Risk in T2DM: A Report from ESC

Type 2 DM

YES

CV disease or risk factors

Add glucose lowering drug with evidence of CV benefit

HbA1c ≥7%

NO

Consider glucose lowering drug with evidence of CV benefit especially in patients at risk of developing CVD

Metformin

Continue guideline recommended lifestyle/diet modification and regular monitoring

YES

NO

NO

YES
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Putting It All Together

Presenter: Peter Libby MD
Discussants: Raul Santos MD MSc PhD & Jennifer Robinson MD MPH

Faculty and Disclosures

Peter Libby MD
Brigham and Women’s 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, Genentech, Kowa, Merck, Novartis, Pfizer, Sanofi-Aventis, Regeneron; Scientific Advisory Board: PMLM, Medimmune, DaVic, Angene, Merck, Gilead, Galderma, Astellas; Dr. Libby declines all personal compensation from pharma or device companies

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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

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

Additional LDL-C lowering:
- Icosapent ethyl
- Rivaroxaban if low bleeding risk
- GLP-1 agonists and SGLT-2 antagonists
- Anti-inflammatory agent??
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