Optimal Secondary Prevention following ACS in High Risk Patients

Reducing Outcomes in your Diabetic Patient

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David Fitchett MD  Disclosures

• Received CME / consultation honoraria from
  – Merck
  – Boehringer Ingelheim
  – Lilly
  – Astra Zeneca

• Steering committee member for EMPA Reg

• DMC chair for SUSTAIN 6 and PIONEER
Reducing Adverse Outcomes after ACS in Patients with Diabetes

Goals

To show:

• Diabetes increases risk of CV events
• Strategies to reduce adverse outcomes
• Changing landscape with new therapies
Why Should Cardiologists Care About Diabetes?

• DM is present in 40-50% of patients with CHD
• 70% mortality in DM due to CVD
• DM worsens impact of other CV risk factors
• DM worsens outcome of all CV syndromes
• DM impacts all aspects of CV practice
• Treatments now available with large impact on CV outcomes
Mortality following Myocardial Infarction in Patients with and without Diabetes

62,000 Patients in TIMI trials

Donohoe et al JAMA 2007;298:765
Life Expectancy Is Reduced by ~12 Years in Diabetes Patients with Previous CVD

The Emerging Risk Factors Collaboration. *JAMA* 2015;314:52
Diabetes has Major Impact on MI Recurrence

Non Diabetic Patients

- No prior MI: 3.5%
- Prior MI: 18.8%

Diabetic Patients

- No prior MI: 20.2%
- Prior MI: 45.0%

7-Year Incidence of MI

P<0.001

Impact of Diabetes on Outcomes after ACS

1 year outcomes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diabetes</th>
<th>New Diabetes</th>
<th>No Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal Reinfarction</td>
<td>10.1*</td>
<td>6.2</td>
<td>6.5</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>21.3*</td>
<td>15.7*</td>
<td>11.2</td>
</tr>
<tr>
<td>Stroke</td>
<td>3.2*</td>
<td>2.9</td>
<td>2</td>
</tr>
<tr>
<td>CV Death</td>
<td>16.2*</td>
<td>15.1*</td>
<td>10</td>
</tr>
</tbody>
</table>

VALIANT  
Aguilar et al  
_Circulation_ 2004;110;1572
In-Hospital Management of ACS in the DM Patients and Long-Term Outcomes

- Choice of revascularisation PCI vs CABG
  - Preference for CABG in multivessel CAD (FREEDOM)
- Anti-platelet agent
  - Preferential use of ticagrelor / prasugrel
  - Use of DAPT in patients managed without PCI
- Initiation / dose optimisation of
  - Statins, BP control, Use of ACEi /ARB, beta blocker
- Glycemic management
  - Glucose control
  - Need for referral?
  - Choice of drug with CV benefit / known safety

**Treatment strategies initiated during admission**

- Patient more likely to remain adherent
- Value of structured orders (admission and discharge)
Optimal Secondary Prevention on Patient with Type 2 Diabetes after ACS

• **Vascular Protection**
  Prevention of vascular events
  - Anti-platelet therapy
  - Lipid lowering
  - ACE inhibition /ARB
  - Liraglutide

• **Cardiac protection**
  Prevention of heart failure / Sudden death
  - Beta blockers
  - ACE I / ARB
  - Mineralo corticoid inhibition
  - Saccubitril / Valsartan
  - Ivabradine
  - ICD and or CRT
  - Empagliflozin

• **Risk factor management**
  Limit CAD progression
  - Smoking cessation
  - Lipid and BP control
  - Glycemia control ?
  - Rehabilitation and lifestyle
Dysfunctional Platelets in Diabetes

- Diminished platelet inhibition in patients with DM
  - ASA
  - Clopidogrel

Ferreiro J and Angiolillo D Circulation 2011;123:798
Ticagrelor and ACS Impact of Diabetes

CV Death  MI or stroke

James et al  Eur Heart J  (2010) 31, 3006
PEGASUS: Longer Term (up to 3yrs) Ticagrelor in Patients with Diabetes

Bleeding
TIMI major  HR 2.5 p<0.001
No increase in fatal bleeding, ICH or Haemorrhagic stroke

Beta-blockers and Diabetes – Implications in MI

**Concerns**

- Masking hypoglycemia
- Impaired glycogenolysis
- Worse Glucose intolerance
- Hyperosmolar hyperglycemic coma
- Susceptibility to heart failure

**Mortality reduction**

- Non DM: 33%
- DM: 48%

Enhanced Treatment Benefit in Diabetes

- BHRT = Beta-blocker Heart Attack Trial
- NMTS = Norwegian Multicentre Timolol Study
- GMT = Goteburg Metoprolol Trial

Sawicki et al J Int Med 2001;250:11
Mortality Reduced 26% by ACE Inhibtion after MI in Patients with LVEF < 40%
TRAndolapril Cardiac Evaluation Study: Increased Survival in High-Risk Patients

Association between Mean Blood Glucose and In-Hospital Mortality.

Reference Mean BG 100-<110

No diabetes

All

Diabetes

Kosiborod et al Circulation 2008;117:1018
Benefit of Tight Glycemic Control after Acute Myocardial Infarction

- STE and Non STE MI
- Blood glucose > 11 mmol/L
- N=1240
- Randomised to:
  - Intensive insulin for 24 h + multi dose insulin for 3 months
  - Early glucose target 7-10 mmol/L or
  - Usual care
- Mean FU 3.4 years

DIGAMI  Malmberg et al  JACC 1995;26:57
       Malmberg BMJ 1997;314:1512
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Patients with ACS and blood glucose > 11mmol/l may receive glycemic control to 7-10mmol/l followed by strategies to achieve long-term glucose targets. Grade C level 2

CDA Clinical Practice Guidelines 2013

DIGAMI  Malmberg et al  JACC 1995;26:57
Malmberg BMJ 1997;314:1512
Early Incretin Trials and CVD Outcomes

**EXAMINE**
- **Post MI**
- **HbA₁c Range, %**: 6.5–11.0
- **Duration of Treatment (as part of usual care)**: Alogliptin, Placebo
- **Primary End point**: Non Inferior
  - CV death, Nonfatal MI, or Nonfatal stroke

**SAVOR-TIMI²**
- **HbA₁c Range, %**: 6.5–12.0
- **Duration of Treatment (as part of usual care)**: Saxagliptin, Placebo
- **Heart failure hospitalization**: Saxagliptin 3.5%; Placebo 2.8%
- **HR 1.27 (95% CI 1.07–1.58)**
- **NNH = 142
- **Primary End point**: Non Inferior
  - CV death, Nonfatal MI, or Nonfatal stroke

**TECOS³**
- **HbA₁c Range, %**: 6.5–8.0
- **Duration of Treatment (as part of usual care)**: Sitagliptin, Placebo
- **Primary End point**: Non Inferior
  - CV death, MI, stroke, or UA

**ELIXA**
- **Post MI**
- **HbA₁c Range, %**: 7.0–11.0
- **Duration of Treatment (as part of usual care)**: Lixisenatide, Placebo
- **Primary End point**: Non Inferior
  - CV death, Nonfatal MI, or Nonfatal stroke or Hosp for Unstable Angina

**Median Duration of Follow-up**
- **SAVOR-TIMI²**
  - Year 1
  - Year 2
  - Year 3
  - Year 4
- **TECOS³**
  - Year 1
  - Year 2
  - Year 3
  - Year 4
- **ELIXA**
  - Year 1
  - Year 2
  - Year 3
  - Year 4

**EXAMINE**
- **HbA₁c Range, %**: 6.5–11.0
- **Duration of Treatment (as part of usual care)**: Alogliptin, Placebo
- **Primary End point**: Non Inferior
  - CV death, Nonfatal MI, or Nonfatal stroke
EMPA-REG OUTCOME
Trial design

- T2DM (A1C >7-10%) + high CV risk (prior MI, CAD, CVA, PVD)
- Included patients 2 months post ACS
- Prior MI in 46.5%
- Study medication given in addition to standard of care
- Primary outcome: Triple MACE: CV death, nonfatal MI, non fatal stroke
- On treatment median 2.6 years  Observation median 3.2 years

CV death

Cumulative incidence function.  
Cl, confidence interval; HR, hazard ratio.  
Hospitalisation for heart failure

HR 0.65
(95% CI 0.50, 0.85)

$p=0.0017$

Cumulative incidence function. HR, hazard ratio
Incident or worsening nephropathy and its components

<table>
<thead>
<tr>
<th>Condition</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident or worsening nephropathy</td>
<td>525/4124</td>
<td>388/2061</td>
<td>0.61 (0.53, 0.70)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>New onset macroalbuminuria</td>
<td>459/4091</td>
<td>330/2033</td>
<td>0.62 (0.54, 0.72)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Doubling of serum-creatinine*</td>
<td>70/4645</td>
<td>60/2323</td>
<td>0.56 (0.39, 0.79)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Initiation of renal replacement therapy</td>
<td>13/4687</td>
<td>14/2333</td>
<td>0.45 (0.21, 0.97)</td>
<td>0.0409</td>
</tr>
</tbody>
</table>

*Accompanied by eGFR (MDRD) ≤45 mL/min/1.73m².
Cox regression analyses.
LEADER: Liraglutide in High Risk Patients with T2 DM

- Inclusion criteria
  - Established CVD including prior MI after 14 days (31%)
    - Included 17% patients with heart failure
  - High risk for CVD

**LEADER**  Liraglutide Cardiovascular Outcome Trial

**CV death, MI, Stroke**

- Non-fatal MI  HR 0.88 (95% CI 0.75-1.03)
- Non-fatal Stroke  HR 0.89 (95% CI 0.72-1.11)
- Heart failure  HR 0.87 (95% CI 0.73-1.05)

**CV Mortality**

- Hazard ratio, 0.78 (95% CI, 0.66–0.93)
- P=0.007

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<table>
<thead>
<tr>
<th>Study</th>
<th>Patients enrolled</th>
<th>FU Yrs</th>
<th>1° Outcome ARR (p)</th>
<th>Mortality ARR (p)</th>
<th>HFH Hosp ARR (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SUSTAIN 6</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2 DM + CVD or High CV risk</td>
<td>2.1</td>
<td>2.3% (0.02)</td>
<td>26% (-0.2% ns)</td>
<td>-0.3% ns</td>
<td></td>
</tr>
<tr>
<td><strong>LEADER</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD or High CV risk</td>
<td>3.8</td>
<td>1.9% (0.01)</td>
<td>13% (1.4% 0.02)</td>
<td>0.6% ns</td>
<td></td>
</tr>
<tr>
<td><strong>EMPA REG</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2 DM + CVD</td>
<td>3</td>
<td>1.6% (0.04)</td>
<td>14% (2.6% &lt;0.001)</td>
<td>1.4% &lt;0.002</td>
<td></td>
</tr>
</tbody>
</table>

ARR Absolute risk reduction, RRR Relative risk reduction  
HFH Heart failure hospitalisation
Meta-analysis of Clinical Trials with Statin Treatment: Impact on Mortality in Diabetes

14 Trials

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Treatment</th>
<th>Control</th>
<th>RR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vascular causes:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>436 (4.6%)</td>
<td>495 (5.3%)</td>
<td>0.88 (0.75-1.03)</td>
</tr>
<tr>
<td>No diabetes</td>
<td>1112 (3.1%)</td>
<td>1465 (4.1%)</td>
<td>0.78 (0.72-0.85)</td>
</tr>
<tr>
<td><strong>Any CHD death</strong></td>
<td>1548 (3.4%)</td>
<td>1960 (4.4%)</td>
<td>0.81 (0.76-0.85)</td>
</tr>
</tbody>
</table>

Test for heterogeneity within subgroup: $x^2_1 = 2.8; p = 0.09$

<table>
<thead>
<tr>
<th>All causes:</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>1031 (11.0%)</td>
<td>1104 (11.9%)</td>
<td>0.91 (0.82-1.01)</td>
</tr>
<tr>
<td>No diabetes</td>
<td>2801 (7.9%)</td>
<td>3250 (9.1%)</td>
<td>0.87 (0.82-0.92)</td>
</tr>
<tr>
<td><strong>Any death</strong></td>
<td>3832 (8.5%)</td>
<td>4354 (9.7%)</td>
<td>0.88 (0.84-0.91)</td>
</tr>
</tbody>
</table>

Test for heterogeneity within subgroup: $x^2_1 = 0.8; p = 0.04$

Study Design

Patients stabilized post ACS ≤ 10 days:
LDL-C 1.29–3.2mM/l (or 1.29–2.6mMol/l if prior lipid-lowering Rx)

Standard Medical & Interventional Therapy

Simvastatin 40 mg

Ezetimibe / Simvastatin 10 / 40 mg

Follow-up Visit Day 30, every 4 months

Duration: Minimum 2 ½-year follow-up (at least 5250 events)

Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12
Ezetimibe in Patients with Recent ACS
CV Events

On treatment analysis
Ez/simva 29.8%  Simva 32.4%
HR 0.92  CI (0.87-0.98)
NNT 38

HR 0.93  (95% CI 0.89-0.99)
NNT 50
Major Pre-specified Subgroups

- Male
  - 34.9
  - 34.0
- Female
  - 33.3
  - 31.0
- Age < 65 years
  - 30.8
  - 29.9
- Age ≥ 65 years
  - 39.9
  - 36.4
- No diabetes
  - 30.8
  - 30.2
- Diabetes
  - 45.5
  - 40.0
- Prior LLT
  - 43.4
  - 40.7
- No prior LLT
  - 30.0
  - 28.6
- LDL-C > 2.5mmol/l
  - 31.2
  - 29.6
- LDL-C ≤ 2.5
  - 38.4
  - 36.0

*7-year event rates
*p-interaction = 0.023, otherwise > 0.05
OSLER
Impact of Evolocumab on Cumulative CV events

Hazard ratio, 0.47 (95% CI, 0.28–0.78)
P = 0.003

61% reduction of LDL
LDL on evolocumab 1.23mmol/l
FOURIER Trial Meets Primary Endpoint
AMGEN Announcement February 2 2017

FOURIER trial with evolocumab met

• Primary composite endpoint
  – cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, hospitalization for unstable angina

• Secondary composite endpoint
  – cardiovascular death, non-fatal MI or non-fatal stroke

• No new safety issues were observed.

Diabetes in 9333 of the 27,564 patients (33.9%)

Await full results and magnitude of benefit
American College of Cardiology, Washington, March 17
Secondary Prevention in Patients with Diabetes and ACS

• High risk group for CV events especially CHF and CV death

• Need to identify patients with DM

• Need to optimise all aspects of risk reduction including
  – Lifestyle management, BP, Statins, RAASi

• New opportunities with additive and potentially large benefit
  – Glucose lowering agents with CV benefit
  – Further LDL lowering with PCSK9 inhibitor