CVOT IN DIABETES: IMPLICATIONS FOR SGLT2 INHIBITORS?
Causes of death in Diabetes

- CV disease: 17.3%
- Diabetes: 1.3%
- Cancer: 7.6%
- Respiratory: 4.2%

Rates of CV events in Diabetes patients per 10,000 person-years:

- MI: 97
- Stroke: 151
- Heart failure: 243

Framingham 5 X increase in diabetes
Onset of CV event can be sudden
Management of type 2DM: 2016 state of the art

CV endpoints / death
- Atrial fibrillation
- Diastolic dysfunction
- Hypoglycemia/syncope
- Microvascular endpoints

Remaining clinical challenges

Prevention
- Eye disease prevention
- Diabetes vasculopathy / PVDx
HYPERTENSION

MACROVASCULAR EVENTS

ACS
Heart failure
Stroke
PVDx

MICROVASCULAR EVENTS

#1 Blindness
Kidney
Neuropathy

All important

HIGH RISK CV PATIENTS
60 YEAR OLD MALE

Years of life remaining

Healthy: 20
CAD: 12.6
MI: 10.8
CHF: 4
Stroke: 7.8

Framingham 40 year follow up
N=5070

Eur Heart J 2002; 23: 458–466
CASE 1
43 Y/O HISPANIC MALE HAD FFR OF LAD 0.85...HAS CHEST PAIN

1. **Medical treatment with global risk reduction**
2. **ASA and treat risk factors**
3. **ASA and antiplatelet and treat risk factors**
4. **Stent vessel due to hazy nature of LAD and then treat with ASA and antiplatelet for 2 years?**

Metformin for diabetes HbA1c 8.9 in lab
DEFER study: background

- **Fractional Flow Reserve**, calculated from coronary pressure measurement, is an accurate, invasive, and lesion-specific index to demonstrate or exclude whether a particular coronary stenosis can cause reversible ischemia.

- **FFR** can be determined easily, in the cath-lab, immediately prior to a planned intervention.

**FFR based strategy for PCI in equivocal stenosis** (DEFER – Study)

Patients scheduled for PCI without Proof of Ischemia (n=325)
Patients scheduled for PCI without Proof of Ischemia (n=325)

Randomization

- deferral of PTCA (167)
  - FFR $\geq 0.75$ (91)
    - No PTCA
    - DEFER Group
  - FFR < 0.75 (76)
    - PTCA
- performance of PTCA (158)
  - FFR < 0.75 (68)
    - PTCA
  - FFR $\geq 0.75$ (90)
    - PTCA
    - PERFORM Group
Less CV events in patients deferred with FFR > 0.75 (.80)

J Am Coll Cardiol. 2007;49(21):2105-2111
Just returned to ER with chest pain...cath 6 months ago
PATIENT HAD DRUG ELUTING STENT PLACED POST ANTERIOR MI...YOUR RECOMMENDATION FOR DUAL ANTIPLATELET TREATMENT IN THIS DIABETES PATIENT

1. **ASA AND ANTIPLATELET FOR 1 YEAR**
2. **ASA ONLY**
3. **ASA AND ANTIPLATELET FOR 2 YEARS**
4. **JUST GIVE STATINS WITH ASA POST DES**

DOI: 10.1161/CIRCULATIONAHA.115.016783
DUAL ANTIPLATELETS POST MI IN DIABETES PATIENT UP TO 30 MONTHS IS **MAYBE** BENEFICIAL

**Diabetes**

8257/11648

**ASA AntiP**

**DOi: 10.1161/CIRCULATIONAHA.115.016783**
Conclusions—In patients with DM, continued thienopyridine beyond 1-year after coronary stenting is associated with reduced risk of MI, although this benefit is attenuated when compared with patients without DM.

DOI: 10.1161/CIRCULATIONAHA.115.016783
Short look at incretins
**Introduction**

- **SAVOR**
  - Reduction in CV death: 2-5% per yr
  - Reduction in heart failure: 7-8% per yr
  - Reduction in all cause mortality: 4.5% per yr

- **EXAMINE**
  - CV event rate per year

- **TECOS**
  - CV event rate per year

- **EMPA-REG**
  - SGLT2 inhibitors
  - Reduction in CV death
  - Reduction in heart failure
  - Reduction in all cause mortality

- **DPP 4 inhibitors**
  - HbA1c
  - Safe & well tolerated

- **SDF1**
  - Diastolic stiffness Platelets

**Aspirin Statins SGLT2 Lifestyle**
Cardiovascular endpoint trials in diabetes
What is the estimated **CV event rate in 1 year** for type 2 diabetes patients with ACS

Acute coronary syndrome within 15-90 days, age ≥ 18 post treatment...EXAMINE

1. <1%
2. 2-3%
3. 7-8%
4. 20%

Hazard ratio, 0.96 (upper boundary of the one-sided repeated CI, 1.16)
Type 2 diabetes (A1c ≥6.5% and ≤8.0%)
≥50 years old
Preexisting vascular disease

Primary Composite Cardiovascular Outcome

Time to first occurrence of:
Cardiovascular-related death
Nonfatal myocardial infarction
Nonfatal stroke
Hospitalization for unstable angina

TECOS

Green JB et al. NEJM 2015; DOI: 10.1056/NEJMoa1501352
A Primary Cardiovascular Outcome

- Hazard ratio, 0.98 (95% CI, 0.89–1.08)
- P=0.65

C Hospitalization for Heart Failure

- Hazard ratio, 1.00 (95% CI, 0.83–1.20)
- P=0.98

TECOS
Overview - DPPIV inhibitor trials
<table>
<thead>
<tr>
<th></th>
<th>SAVOR-16492</th>
<th>EXAMINE-5380</th>
<th>TECOS-14671</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient type</td>
<td>CAD-stable</td>
<td>ACS</td>
<td>CAD stable</td>
</tr>
<tr>
<td>Yearly CV events</td>
<td>2-3%</td>
<td>7-8%</td>
<td>4-5%</td>
</tr>
<tr>
<td>Age</td>
<td>65</td>
<td>61</td>
<td>61</td>
</tr>
<tr>
<td>HT</td>
<td>81%</td>
<td>83%</td>
<td>75-80%</td>
</tr>
<tr>
<td>Statins</td>
<td>Large %</td>
<td>90%</td>
<td>80%</td>
</tr>
<tr>
<td>ACE blockers</td>
<td>82%</td>
<td>79%</td>
<td></td>
</tr>
<tr>
<td>HbA1c</td>
<td>8.0</td>
<td>8.0</td>
<td>7.2</td>
</tr>
<tr>
<td>Hx of HF</td>
<td>12.7%</td>
<td>27.8%</td>
<td>18%</td>
</tr>
<tr>
<td>Hx of CAD</td>
<td>78%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>GFR 30-50cc</td>
<td>13.6</td>
<td>30-60</td>
<td>9.3%</td>
</tr>
<tr>
<td>Insulin</td>
<td>40%</td>
<td>30%</td>
<td>23%</td>
</tr>
</tbody>
</table>
HEART FAILURE HOSPITALIZATION WITH DDP-4 INHIBITOR RECENT CVOTs

% Hospitalization for Heart Failure

<table>
<thead>
<tr>
<th>Drug</th>
<th>SAVOR</th>
<th>EXAMINE</th>
<th>TECOS</th>
<th>ALL 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.5%</td>
<td>3.9%</td>
<td>3.1%</td>
<td>3.4%</td>
</tr>
<tr>
<td></td>
<td>2.8%</td>
<td>3.3%</td>
<td>3.1%</td>
<td>3.0%</td>
</tr>
</tbody>
</table>

1.14 (0.97-1.34)  
P = NS  
All 3

Significant++

Not significant

+++ (3.5% vs. 2.8%; hazard ratio, 1.27; 95% CI, 1.07 to 1.51; P = 0.007)

3-4 years

Chilton 2015
Drugs reducing CV events in diabetes

- Aspirin
- Statins
- Beta blockers & CCB
- RAAS blockers
- Thiazide “like” diuretics
- ? Metformin
- ? PPAR
- Hypoglycemic drugs
- EMPA-REG

All have off target side effects

Others drugs in small studies
Cardiovascular endpoint trials in diabetes

CV death

Heart failure

All cause mortality

Cardiovascular endpoint trials in diabetes
CV Benefits of BP Reduction in Type 2 Diabetes

- UKPDS 38: 32% reduction in diabetes related death
- ADVANCE: 18% reduction in risk of CV death
- EMPA-REG: 38% reduction in risk of CV death

<table>
<thead>
<tr>
<th>SBP reduction</th>
<th>UKPDS 38</th>
<th>ADVANCE</th>
<th>EMPA-REG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
<td>5.6</td>
<td>4</td>
</tr>
</tbody>
</table>
Biomechanics of vulnerable vascular wall

- Necrotic core
- Thin fibrous cap
- Wall stress (BP)
  - Stress concentrations form within the fibrotic cap due to stiffness of the cap with respect to the normal vessel wall
- Endothelial cells (dysfunctional)
  - ↑ ROS
  - ↑ MCP
- Vascular wall
  - ↑ Macrophages
  - ↑ MMPs
- Blood vessel wall
- Intravascular Ultrasound
- NIRS - lipids
- Thin cap
- Atherosclerosis
- Lipid/necrotic core Yellow
CV IMPLICATIONS OF SGLT2 INHIBITION

• **Glucose excreted in the urine as a consequence of SGLT2 inhibition equates to about 200–300 calories each day. (Weight loss of 2–3 kg) (4–6 pounds)**

• **Chronic osmotic diuresis caused by glycosuria**
  - Dose-related increases in 24 hour urinary volumes of between 107 - 470 mL
  - **Sodium loss**

• **5 mm Hg blood pressure reduction**

• **Mild increase in LDL, HDL and decrease in triglycerides**

• **Lipids by NMR**
  - Dose related increase in LDL (NMR), Apo B, LDL particle number
  - Dose related increase in HDL
  - More impressive drop in triglycerides that is dose related

Kidney Int Suppl 2011: S20–S27
Diabetes Care 2009; 32: 650–657
Diabetes 2011; 60 (Suppl 1): A582–A643
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 Matheus, 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

ABSTRACT

BACKGROUND
The effects of empagliflozin, an inhibitor of sodium–glucose cotransporter 2, in addition to standard care, on cardiovascular morbidity and mortality in patients with type 2 diabetes at high cardiovascular risk are not known.

METHODS
We randomly assigned patients to receive 10 mg or 25 mg of empagliflozin or placebo once daily. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, as analyzed in the pooled empagliflozin group versus the placebo group. The key secondary composite outcome was the primary outcome plus hospitalization for unstable angina.

RESULTS
A total of 7020 patients were treated (median observation time, 3.1 years). The primary outcome occurred in 490 of 4687 patients (10.5%) in the pooled empagliflozin group and in 282 of 2333 patients (12.1%) in the placebo group (hazard ratio in the empagliflozin group, 0.86; 95.02% confidence interval, 0.74 to 0.99; P=0.04 for superiority). There were no significant between-group differences in the rates of myocardial infarction or stroke, but in the empagliflozin group there were significantly lower rates of death from cardiovascular causes (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction), hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction), and death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction). There was no significant between-group difference in the key secondary outcome (P=0.08 for superiority). Among patients receiving empagliflozin, there was an increased rate of genital infection but no increase in other adverse events.
CV DEATH, MI AND STROKE: PRIMARY ENDPOINT

<table>
<thead>
<tr>
<th>Event</th>
<th>Patients with event/analysed</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-point MACE</td>
<td>490/4687 282/2333</td>
<td>0.86</td>
<td>(0.74, 0.99)*</td>
<td>0.0382</td>
<td></td>
</tr>
<tr>
<td>CV death</td>
<td>172/4687 137/2333</td>
<td>0.62</td>
<td>(0.49, 0.77)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>213/4687 121/2333</td>
<td>0.87</td>
<td>(0.70, 1.09)</td>
<td>0.2189</td>
<td></td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>150/4687 60/2333</td>
<td>1.24</td>
<td>(0.92, 1.67)</td>
<td>0.1638</td>
<td></td>
</tr>
</tbody>
</table>

*favours empagliflozin
<table>
<thead>
<tr>
<th>Favours empagliflozin</th>
<th>Favours placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>2.00</td>
</tr>
<tr>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

4-point MACE 490/4687 282/2333 0.86 (0.74, 0.99)* 0.0382
**WAIST CIRCUMFERENCE-CARDIOLOGY RISK FACTOR**

**Week**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Empagliflozin 10 mg</th>
<th>Empagliflozin 25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2259</td>
<td>2272</td>
<td>2273</td>
</tr>
<tr>
<td>12</td>
<td>1869</td>
<td>2183</td>
<td>2209</td>
</tr>
<tr>
<td>28</td>
<td>2110</td>
<td>2155</td>
<td>2157</td>
</tr>
<tr>
<td>52</td>
<td>1562</td>
<td>1644</td>
<td>1648</td>
</tr>
<tr>
<td>108</td>
<td>1220</td>
<td>1285</td>
<td>1329</td>
</tr>
<tr>
<td>164</td>
<td>418</td>
<td>475</td>
<td>486</td>
</tr>
<tr>
<td>220</td>
<td>34</td>
<td></td>
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</tr>
</tbody>
</table>
CV mortality (MI, CVA) drives the primary endpoint

DOI: 10.1056/NEJMoa1504720
EASD 2015
No significant effect on MI or stroke.

Benefit not atherosclerotic related?

All deaths not attributed to the categories of CV death and not attributed to a non-CV cause were presumed CV deaths.

DOI: 10.1056/NEJMoa1504720
EASD 2015
Immediate benefit

Cumulative Incidence of

Hazard ratio, 0.65 (95% CI, 0.50–0.85)
P=0.002
OSMOTIC DIURESIS / BP / DIASTOLIC DYSFUNCTION IMPROVEMENT?

Heart failure hospitalization

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Control</th>
<th>Empa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hosp for HF</td>
<td>4.1</td>
<td>2.7</td>
</tr>
<tr>
<td>Hosp for HF/death</td>
<td>8.5</td>
<td>5.7</td>
</tr>
</tbody>
</table>

BP difference 4/2 mm Hg

- Hosp for HF: 0.65 (0.50–0.85), P<0.002
- Hosp for HF/death: 0.66 (0.55–0.79), P<0.001

Excluded stroke
BP difference 4/2 mm Hg
SGLT2 inhibitor significantly improves arterial stiffness in diabetes

<table>
<thead>
<tr>
<th>Sex</th>
<th>Placebo</th>
<th>Empa</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
<th>PP (mmHg)</th>
<th>MAP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>424</td>
<td>927</td>
<td>-3.8 (-5.1, -2.6)***</td>
<td>-1.5 (-2.3, -0.7)***</td>
<td>-2.3 (-3.3, -1.3)***</td>
<td>-2.3 (-3.2, -1.5)***</td>
</tr>
<tr>
<td>Female</td>
<td>401</td>
<td>725</td>
<td>-3.4 (-4.7, -2.0)***</td>
<td>-1.2 (-2.0, -0.3)**</td>
<td>-2.2 (-3.2, -1.1)***</td>
<td>-1.9 (-2.8, -1.0)***</td>
</tr>
<tr>
<td>Interaction p-value</td>
<td>p=0.598</td>
<td>p=0.546</td>
<td>p=0.851</td>
<td>p=0.526</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Measure of arterial stiffness

ADA 2015 Chilton et al
Possible hemodynamic mechanisms
Increased stiffness: increased atherosclerosis the reflected wave arrives at the heart closer to systole, placing a greater load on the heart-increased work.
ASCOT: Differing effect of statin added to β-blocker-based or CCB-based therapy


*Atenolol (50–100 mg) ± bendroflumethiazide (1.25–2.5 mg)
†Amlodipine (5–10 mg) ± perindopril (4–8 mg)
CAFÉ in ASCOT
Affects of Reduced Central Aortic Pressure

Examples of peripheral (A) and corresponding derived central aortic (B) waveforms from patients of equal age treated with atenolol (solid line) or amlodipine (broken line) as monotherapy, achieving equivalent brachial blood pressures.

Primary objective: a comparison of the effects of the 2 treatment regimens on central aortic pressures derived from applanation tonometry.

- Conduit Artery Function Evaluation (CAFÉ) trial
- Sphygmocor
- Substudy of ASCOT BPLA (n=2199)
- Compared central aortic pressure
  - Amlodipine group
  - Atenolol group

Circ March 7, 2006; 113:000
Abdominal aorta

“This is about as normal as an adult aorta in America get”

↑ CV risk factors + diabetes
Precath patient with diabetes

40% of individuals with PAD have no leg pain

Heart Disease and Stroke Statistics 2015 Update AHA
<table>
<thead>
<tr>
<th></th>
<th>Euglycemia</th>
<th>Hyperglycemia</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Empagliflozin</td>
<td>p-value</td>
<td>Baseline</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>111.2 ± 8.9</td>
<td>108.5 ± 8.7</td>
<td>0.02</td>
<td>112.1 ± 9.8</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>63.6 ± 8.5</td>
<td>63.1 ± 8.1</td>
<td>0.6191</td>
<td>65.2 ± 8.3</td>
</tr>
<tr>
<td>Pulse (beats per minute)</td>
<td>74.2 ± 13.1</td>
<td>71.8 ± 13.8</td>
<td>0.1885</td>
<td>72.0 ± 11.0</td>
</tr>
<tr>
<td>Vascular parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radial augmentation index (%)</td>
<td>−52.0 ± 16.1</td>
<td>−57.0 ± 16.7</td>
<td>0.0001</td>
<td>−47.9 ± 17.3</td>
</tr>
<tr>
<td>Carotid radial pulse wave velocity (m/s)</td>
<td>7.3 ± 1.1</td>
<td>6.7 ± 0.9</td>
<td>0.0001</td>
<td>7.9 ± 1.1</td>
</tr>
</tbody>
</table>

↑↑ 1 m/s PWV -- risk increase of 15% for cardiovascular events and all-cause mortality
A  Normal

- Endothelium
- Collagen
- Elastic Fibers
- Pericytes/mesenchymal stem cells

B  Arterial remodeling

- Mechanical stretch
- Shear stress
- Collagen deposition
- Elastic Fiber Degradation
- TGF-β
- IL-1
- Synthetic VSMC
- VSMC hyperplasia
- Migration
- Calcification
- Osteogenic VSMC
- Phenotype switching
- Matrix vesicle release

Increased Wall Thickness

A  Normal

- Systolic BP
- Pulse Pressure
- Reflected Wave
- Forward Traveling Wave

B  Arterial Stiffness

- Augmentation

↑↑↑ pulse wave velocity
Possible mechanisms involved in CV benefits of SGLT2

- Wall stress
- Waist circumference / adipocytes
- Arterial wall stiffness
- Metabolic changes
- Sympathetic nervous system
- Glucose
- Lipids
- Insulin
- Leptin
- Circadian rhythm
- Reactive oxygen species / inflammation
- Endothelium
- Other
- Microvascular

Chilton 2015 pending publication
Heart needs a diet

Global risk reduction best choice
Cardiovascular treatment of diabetes: **REDUCE CV deaths!!**

- **SAVOR EXAMINE TECOS**
  - Safe, no hypoglycemia or HF
  - No CV benefit

- **EMP Agliflozin**
  - Safe and no significant hypoglycemia
  - Reduces significantly CV death

- **Metformin**
  - CV reduction?
PREVENT ONE DEATH (NNT)

Simvastatin\(^1\) for 5.4 years

30

High CV risk
5% diabetes, 26% hypertension

Ramipril\(^2\) for 5 years

56

High CV risk
38% diabetes, 46% hypertension

Empagliflozin for 3 years

39

T2DM with high CV risk
92% hypertension

Pre-ACEi/ARB era

Pre-statin era

1994

2000

2015

Pre-ACEi/ARB era

<29% statin

>75% statin

>80% ACEi/ARB

1. 4S investigator. Lancet 1994; 344: 1383-89;