INFLUENCING CV RISK WITH ANTIHYPERGLYCEMIC AGENTS: SGLT2 INHIBITORS AND INCRETIN BASED THERAPIES

“Novel new cardiorenal agents for diabetes”

Nephro-protective

Heart-protective

Vascular protective
Type 2 diabetes patients
CONFLICTS OF INTEREST

Medical research with multiple companies, governmental and private industry

Lecture today involves more than companies with FDA approval of these compounds
Clinical translational pathobiology
HT diabetes patient and the interventional cardiology patient

Hispanic T2DM with BP 142/87
Normal Texas Weight (BMI 33)
Welder with 5 children 3x wives

Cath due to atypical chest pain
HbA1c 8.2 metformin
HT - HCTZ

1 year later
Routine day
Acute MI: 3 am

- High incidence of undiagnosed diabetes in acute myocardial infarction patients

Percentage of patients seen by cardiologist without known diabetes

Young Hispanic male
BP 145/70
CC 45 cc/min
Low HDL
High triglycerides
Blood sugar at MI 304
HbA1c 8.8

Eur Heart J. 2004;25:1880

BENEFICIAL DIABETES KIDNEY PROTECTION WITH SGLT2 INHIBITORS

...you or your family have diabetes...LOOK...on top of ACEI/ARB
No Rx drug is free of side effects

BEST: Great lifestyle with hand picked parents

Incretins: GLP 1 agonist
- LEADER
- SUSTAIN-6

SGLT2 inhibitors
- EMPA REG
- CANVAS

....High quality clinical trials with cost of > 3 billion dollars
Major factor effecting oxygen consumption

Heart rate
Blood pressure
Heart size
Afterload

↓ MVO2-reduces ischemia

Wall thickness

Laplace's law

BP
ARTERIAL COMPLIANCE REDUCES AFTERLOAD ON HEART

60% of microcirculation is fed during diastole
What's new
SGLT2 inhibitor pathophysiology
CV AND RENAL EFFECTS OF SGLT2 INHIBITORS

SGLT2i
800 cc fluid 24-48 hours
300 cc / day
2 cans coke
TRANSLATIONAL BIOLOGY OF NEW CV AGENT SGLT2 INHIBITORS

Patient perspective
- Weight loss
- Lower BP
- Less shortness of breath

Osmotic diuresis / natriuresis (plasma volume contraction)

- eGFR ↓↓ 5 cc/min/1.73m²
- ↓ 30-40% albuminuria

↓↓ SBP 4-6 mm

(Activation of renal tubuloglomerular feedback)

↑↑ macula densa sodium / chloride delivery

Afferent vasoconstriction

800 cc fluid acutely
150-300 cc daily
2 cans of coke in calories per day

Adapted from Heerspink
48 y/o Hispanic women
Type 2 diabetes

300 cc of NS
Very SOB

Patient very short of breath

Diuretic IV

LVEDP
Left ventricular end diastolic pressure

Chilton
**Significant Reduction in Pulse Wave Velocity with SGLT2 Inhibitor**

- **N=40**
- **Hyperglycemic clamp**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>8 wks EMP25</th>
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</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>8</td>
<td>7.5</td>
</tr>
<tr>
<td><strong>SBP 112</strong></td>
<td>7</td>
<td>6.5</td>
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<tr>
<td><strong>HR 72</strong></td>
<td></td>
<td>6</td>
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<tr>
<td><strong>Noradr level .77</strong></td>
<td></td>
<td>6</td>
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<tr>
<td><strong>8 weeks EMP25</strong></td>
<td>5.5</td>
<td>5</td>
</tr>
<tr>
<td><strong>SBP 110</strong></td>
<td>5</td>
<td></td>
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<tr>
<td><strong>HR 70</strong></td>
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<tr>
<td><strong>Noradr level .70</strong></td>
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**Carotid PW Velocity m/s**

- **Baseline**: 7.9, P<0.0001
- **8 wk EMP25**: 6.9, P<0.0017

*Cardiovascular Diabetology 2014, 13:28*
### High Quality Prospective Randomized CV Endpoint Trials

<table>
<thead>
<tr>
<th>CV Benefits</th>
<th>↓ CV events</th>
<th>↓ CV death</th>
<th>↓ Hospitalization for HF</th>
<th>% events/yr</th>
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</thead>
<tbody>
<tr>
<td><strong>SGLT2 inhibitors</strong></td>
<td>EMPA</td>
<td></td>
<td>+</td>
<td>4.5%</td>
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<tr>
<td></td>
<td>CANVAS</td>
<td>-</td>
<td>+</td>
<td>4.95%</td>
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<tr>
<td><strong>GLP1 agonist</strong></td>
<td>LEADER</td>
<td>-/+</td>
<td>-</td>
<td>3.7%</td>
</tr>
<tr>
<td></td>
<td>SUSTAIN-6</td>
<td></td>
<td>-</td>
<td>4.5%</td>
</tr>
<tr>
<td><strong>DPPIV inhibitors</strong></td>
<td>SAVOR</td>
<td>-</td>
<td>-</td>
<td>2.5%</td>
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<tr>
<td></td>
<td>EXAMINE</td>
<td>-</td>
<td>-</td>
<td>7-8%</td>
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<tr>
<td></td>
<td>TECOS</td>
<td>-</td>
<td>-</td>
<td>3.25%</td>
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<tr>
<td><strong>NEPI/AT1</strong></td>
<td>PARADIGM</td>
<td>+</td>
<td>+</td>
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<tr>
<td></td>
<td>HF</td>
<td></td>
<td></td>
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<tr>
<td><strong>Lipid lowering</strong></td>
<td>STATINS-4S</td>
<td>+</td>
<td>-</td>
<td>1.7%</td>
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<tr>
<td></td>
<td>PCSK9 I</td>
<td>+</td>
<td>-</td>
<td>4.86%</td>
</tr>
<tr>
<td></td>
<td>FOURIER</td>
<td>+</td>
<td>-</td>
<td>3.8%</td>
</tr>
</tbody>
</table>

*ONLY if significant*

Chilton pending publication
New CV drugs for diabetes that reduce CV death
>80% have hypertension

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

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BACKGROUND
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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.
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NEJM 2015;373:2117
## SGLT 2 INHIBITORS AND CV EVENTS

### EMPA-REG
- **CV death**: ↓↓↓ 38%
- **Stroke-NS MI-NS**: Primary MACE: -14%, Heart failure hosp: -35%

### CANVAS
- **CV death (NS)**: ↓13%
- **Stroke-NS MI-NS**: Primary MACE: -14%, Heart failure hosp: -33%

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Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke
GLP 1 AGONIST AND CV EVENTS

- **LEADER**:
  - CV death: ↓22%
  - Stroke: NS
  - MI: NS
  - Percentage: -13

- **SUSTAIN-6**:
  - CV death (NS): ↓2%
  - Stroke: ↓39%
  - MI: NS
  - Percentage: -26

- **EXSCEL**:
  - CV death (NS): ↓12%
  - Stroke: NS
  - MI: NS
  - Percentage: -9

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Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke
HIGH RISK CV OUTCOME TRIALS

- **4S trial**
  - NNT: 30
  - Event rate per year: 1.7%

- **HOPE**
  - NNT: 56
  - Event rate per year: 3.5

- **EMPA-REG**
  - NNT: 38
  - Event rate per year: 4.5

- **LEADER**
  - NNT: 53
  - Event rate per year: 4

**Summary**: Liraglutide for 3.5 years, Ramipril for 3 years, Empagliflozin for 3 years, Simvastatin for 5.4 years.

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