CONFLICTS OF INTEREST FOR THIS LECTURE

J & J
BI
Lilly
Sanofi
Novo
AZ
Pfizer

Cardiometabolic companies
DIABETIC HEART DISEASE: A TICKING TIME BOMB

"Birth of new CV drugs for diabetes patients" ....reducing CV death and Cardiorenal events

Professor Robert Chilton
University of Texas Health Science Center
San Antonio, Texas
Director of Cath Lab
Director clinical proteomics center

Li et al. BMC Ophthalmology (2017) 17:60
OBJECTIVES

- Translational science of diabetes
- Diabetes trials
- Current treatment considerations
Rates of diabetes-related complications have declined substantially in the past two decades, but a large burden of disease persists because of the continued increase in the prevalence of diabetes.
STATINS REDUCE MAJOR CORONARY EVENTS

Event rate for major coronary events

Placebo

DM
Non DM

Statins

DM
Non DM

Secondary Prevention Trials

Primary Prevention Trials

4 to 5.1 years Cochrane Meta-analysis of randomized controlled trials

BMJ, doi:10.1136/bmj.38793.468449.AE published 3 April 2006

>2% per yr-Primary Prevention-Cochrane 2011
DIABETES IS COMPLEX

Environmental epigenetic effects

Increasing insulin resistance

Endothelial dysfunction

Cellular dysfunction

Common risk factors recognized

Treatment of numbers ≈ BP <120, LDL <50, hsCRP <0.1 etc

↑ CV risk
For > 10 yrs

Drugs primary treatment
Rarely lifestyle followed long term

Human awakening as vascular events occur
(Life span shortens 7-13 years)
YEARLY MORTALITY (DEATH) IN MEDICALLY TREATED PATIENTS BY CORONARY ANGIOGRAM

Percent DEATH per year
( not CV events)

1 vessel dx  2 vessel dx  3 vessel dx  3VDx + prox 95% LAD)
1.4  2.4  4.2  8.2

J Am Coll Cardiol. 1996;27:964–1047
WHAT PERCENTAGE ASYMPTOMATIC 30-40 YEAR OLD PEOPLE HAVE CORONARY ATHEROSCLEROSIS?

1. 10%
2. 40%
3. 50%
4. 60%
5. >70%
Atherosclerosis starts early

High Prevalence of Coronary Atherosclerosis in Asymptomatic Teenagers and Young Adults Evidence From Intravascular Ultrasound

E. Murat Tuzcu, MD; Samir R. Kapadia, MD; Eralp Tutar, MD; Khaled M. Ziada, MD; Robert E. Hobbs, MD; Patrick M. McCarthy, MD; James B. Young, MD; Steven E. Nissen, MD

Background—Most of our knowledge about atherosclerosis at young ages is derived from necropsy studies, which have inherent limitations. Detailed, in vivo data on atherosclerosis in young individuals are limited. Intravascular ultrasound provides a unique opportunity for in vivo characterization of early atherosclerosis in a clinically relevant context.

Methods and Results—Intravascular ultrasound was performed in 262 heart transplant recipients 30.9±13.2 days after transplantation to investigate coronary arteries in young asymptomatic subjects. The donor population consisted of 146 men and 116 women (mean age of 33±13.2 years). Extensive imaging of all possible (including distal) coronary segments was performed. Sites with the greatest and least intimal thickness in each CASS segment were measured in multiple coronary arteries. Sites with intimal thickness ≥0.5 mm were defined as atherosclerotic. A total of 2041 sites within 1477 segments in 574 coronary arteries (2.2 arteries per person) were analyzed. An atherosclerotic lesion was present in 136 patients, or 51.9%. The prevalence of atherosclerosis varied from 17% in individuals <20 years old to 85% in subjects ≥60 years old. In subjects with atherosclerosis, intimal thickness and area stenosis averaged 1.08±0.48 mm and 32.7±15.9%, respectively. For all age groups, the average intimal thickness was greater in men than women, although the prevalence of atherosclerosis was similar (52% in men and 51.7% in women).

Conclusions—This study demonstrates that coronary atherosclerosis begins at a young age and that lesions are present in 1 of 6 teenagers. These findings suggest the need for intensive efforts at coronary disease prevention in young adults.

(Circulation. 2001;103:2705-2710.)
What is the % CV event rate @ 10 years in type 2 diabetes patients that are overweight/obese?

1. 2%
2. 4%
3. 6%
4. 18%
5. 30%

Look AHEAD trial
What is the CV event rate per year in type 2 diabetes?

Impact of Intensive Lifestyle Intervention on Depression and Health-Related Quality of Life in Type 2 Diabetes: The Look AHEAD Trial

N=5145 overweight/obese

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Patients with Event</th>
<th>Control Group</th>
<th>Intervention Group</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead N=376</td>
<td>no.</td>
<td>no. of events (rate/100 person-yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>354</td>
<td>191 (0.84)</td>
<td>163 (0.71)</td>
<td>0.84 (0.68–1.04)</td>
<td>0.11</td>
</tr>
<tr>
<td>Fatal or nonfatal†</td>
<td>16</td>
<td>11 (0.05)</td>
<td>5 (&lt;0.02)</td>
<td>0.44 (0.15–1.26)</td>
<td>0.13</td>
</tr>
<tr>
<td>Fatal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal</td>
<td>342</td>
<td>183 (0.80)</td>
<td>159 (0.69)</td>
<td>0.86 (0.69–1.06)</td>
<td>0.16</td>
</tr>
<tr>
<td>Hospitalization for angina</td>
<td>390</td>
<td>196 (0.87)</td>
<td>194 (0.85)</td>
<td>0.97 (0.80–1.19)</td>
<td>0.79</td>
</tr>
<tr>
<td>Stroke</td>
<td>165</td>
<td>80 (0.34)</td>
<td>85 (0.36)</td>
<td>1.05 (0.77–1.42)</td>
<td>0.78</td>
</tr>
<tr>
<td>Heart failure</td>
<td>218</td>
<td>119 (0.51)</td>
<td>99 (0.42)</td>
<td>0.80 (0.61–1.04)</td>
<td>0.10</td>
</tr>
<tr>
<td>CABG</td>
<td>525</td>
<td>269 (1.21)</td>
<td>256 (1.14)</td>
<td>0.93 (0.78–1.10)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

WHICH CARDIORENAL DRUGS REDUCE CV DEATH

1. Statins
2. SGLT 2 (EMPA-REG) / GLP-1 agonist (LEADER)
3. PCSK9 inhibitor
4. DPP IV inhibitor
5. Statins + PCSK9
### MORE INTENSIVE LDL-C LOWERING & CV DEATH

No clear benefit on CV mortality

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>More Intensive Rx Arm</th>
<th>Less Intensive Rx Arm</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROVE-IT TIMI 22</td>
<td>2004</td>
<td>27</td>
<td>36</td>
<td>0.74 (0.45-1.22)</td>
</tr>
<tr>
<td>A2Z</td>
<td>2004</td>
<td>86</td>
<td>111</td>
<td>0.76 (0.57-1.01)</td>
</tr>
<tr>
<td>TNT</td>
<td>2005</td>
<td>101</td>
<td>127</td>
<td>0.80 (0.61-1.03)</td>
</tr>
<tr>
<td>IDEAL</td>
<td>2005</td>
<td>223</td>
<td>218</td>
<td>1.03 (0.85-1.24)</td>
</tr>
<tr>
<td>SEARCH</td>
<td>2010</td>
<td>565</td>
<td>572</td>
<td>0.99 (0.88-1.11)</td>
</tr>
<tr>
<td>IMPROVE-IT</td>
<td>2015</td>
<td>538</td>
<td>537</td>
<td>1.00 (0.89-1.13)</td>
</tr>
<tr>
<td><strong>Summary</strong></td>
<td></td>
<td><strong>1540</strong></td>
<td><strong>1601</strong></td>
<td><strong>0.96 (0.90-1.03)</strong></td>
</tr>
</tbody>
</table>

References:
- NEJM 2004;350:1495-504
- JAMA 2004;292:1307-16
- NEJM 2005;352:1425-35
- JAMA 2005;294:2437-45
- Lancet 2010;376:1658-69
- NEJM 2015;372:2387-97
<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial</th>
<th>Inclusion</th>
<th>N</th>
<th>Mean</th>
<th>Baseline</th>
<th>HR-MACE</th>
<th>P-superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pioglitazone</td>
<td>PROactive</td>
<td>Macrovascular disease</td>
<td>5,238</td>
<td>2.9 yrs</td>
<td>7.8%/7.9%</td>
<td>0.84 (0.72–0.98)</td>
<td>0.027</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>EMPA-REG</td>
<td>Established CV disease</td>
<td>7,028</td>
<td>2.6 yrs</td>
<td>8.07%/8.08%</td>
<td>0.86 (0.74–0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>CANVAS</td>
<td>ASCVD or &gt;2 CV risk factors</td>
<td>10,142</td>
<td>3.6 yrs</td>
<td>8.2%/8.2%</td>
<td>0.86 (0.75–0.97)</td>
<td>0.02</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>LEADER</td>
<td>High CV risk</td>
<td>9340</td>
<td>3.8 yrs</td>
<td>8.7/8.7</td>
<td>0.87 (0.78–0.97)</td>
<td>0.01</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>SUSTAIN-6</td>
<td>Established CVD, CKD or HF</td>
<td>3297</td>
<td>2 yrs</td>
<td>8.7/8.7</td>
<td>0.74 (0.58–0.95)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Chilton-2018 pending publication
Esimulin, as compared with placebo, had a lower rate of the primary composite CV outcomes

- N = 7020
- 3.1 years

Hazard ratio, 0.86 (95.02% CI, 0.74 to 0.99)
P = 0.04 for superiority

Percent of CV events

- SGLT2 Inh: 10.59%
- Placebo: 12.1%

490 of 4687 vs. 282 of 2333

Primary composite outcome was death from nonfatal myocardial infarction, or nonfatal stroke

DOI: 10.1056/NEJMoa1504720
EASD 2015
CARDIOVASCULAR DEATH: NNT 39

0.62 (0.49–0.77) <0.001

No significant effect on MI or stroke. Benefit not atherosclerotic related?

ARR=2.2%

Percentage

CV deaths
Sudden death
AMI
Stroke
Cardio Shock
Worsening HF
Other CV

Placebo
2.4

Empa
1.6

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
Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group

Abstract

Canagliflozin is a sodium-glucose cotransporter 2 inhibitor that reduces glycemia as well as blood pressure, body weight, and albuminuria in people with diabetes. We report the effects of treatment with canagliflozin on cardiovascular, renal, and safety outcomes.

Background

Methods

The CANVAS Program integrated data from two trials involving a total of 10,142 participants with type 2 diabetes and high cardiovascular risk. Participants in each trial were randomly assigned to receive canagliflozin or placebo and were followed for a mean of 188.2 weeks. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

Primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

**LEADER trial**
Heart failure and diabetes
Metabolic changes
- Abnormal ventricular relaxation
- Heart Fail. Rev. 17, 325–344
- Herz 36, 102–115

Diastolic dysfunction

Structural changes
- Abnormal ventricular arterial coupling (stiffness)

↓↓GLUT 4 uptake
- Abnormal Ca handling
- Mitochondrial dysfunction
- Endoplasmic reticulum stress
- Inflammation

Insulin resistant cardiomyocyte

↑ reactive oxygen species
↑ fibrosis / stiffness
DIASTOLIC HEART FAILURE IS COMMON IN DIABETES

- Pulmonary edema (shortness of breath)
  - Diabetes
  - Normal

End Diastolic Pressure (PCW)

LV volume (ml)

Chilton-pending publication
Risk reduction in HF hospitalization with empagliflozin vs. placebo over time

**Heart Failure Hospitalizations**

- HR 0.65 (95% CI 0.50, 0.85) p=0.0017
- HR 0.69 (95% CI 0.53, 0.91)
- HR 0.60 (95% CI 0.52, 0.92)
- HR 0.62 (95% CI 0.44, 0.83)
- HR 0.63 (95% CI 0.43, 0.93)
- HR 0.60 (95% CI 0.52, 0.92)
- HR 0.47 (95% CI 0.29, 0.76)

**Days**

- 0
- 180
- 360
- 540
- 720
- 900
- 1080
- 1260
- 1440

Young obese T2DM female with SOB

LVEDP
Left ventricular end diastolic pressure

200 ug NTG

Nitric oxide
800 cc day 1 then 150-300/day
2 cans coke in calories/day

Glycosuria
- Negative caloric balance
- HbA1C
- Urate
- Total body fat mass
- Improved metabolic inflexibility
- Inflammation
- Glucose toxicity
- Plasma uric acid
- Epicardial fat
- Inflammation

Natriuresis
- Blood pressure
- Plasma volume
- Arterial stiffness
- Myocardial stretch
- Tubulo-glomerular feedback
- Afferent arteriole constriction
- Intraglomerular hypertension
- Hyperfiltration
- Glomerular work load

MVO2-Ischemia
- Atrial/ventricular remodeling/fibrosis
- Endothelial cell activation of ACE2 - Ang1/7

SGLT2i
- Reduced CV death
- Reduced hospitalization for HF
- Reduced progression of renal dysfunction

Renal dysfunction

CV and Renal Effects of SGLT2 inhibitors: Mean BP drop 4 mmHg
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kristine Brown-Brandstätter, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulsen, F.R.C.P., Lars S. Ravn, M.D., Ph.D., William M. Sinning, M.D., Moritz Stoecker, M.D., Bernard Ziemann, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators

ABSTRACT

The cardiovascular effect of Liraglutide, a glucagon-like peptide-1 analogue, when added to standard care in patients with type 2 diabetes, remains unknown.

METHODS

In this double-blind trial, randomly assigned patients with type 2 diabetes and high cardiovascular risk to receive liraglutide or placebo. The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The primary hypothesis was that Liraglutide would be noninferior to placebo with regard to the primary outcome, with a margin of 1.30 for the upper boundary of the 95% confidence interval of the hazard ratio. No adjustments for multiplicity were performed for the prespecified exploratory outcomes.

Hazard ratio, 0.87 (95% CI, 0.73–1.05)
P = 0.14

NO benefit

LEADER trial
## CV Look @ New Cardiovascular Drugs for Type 2 Diabetes

<table>
<thead>
<tr>
<th>Trial</th>
<th>↓ CV events</th>
<th>↓ CV death</th>
<th>↓ heart failure hospitalizations</th>
<th>↓ Nephropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-SGLT2i</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CANA</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>LIRA-GLP-1</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>SEMA</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Already on standard of care

Chilton pending 2018
PRIMING VASCULAR ENDOTHELIAL CELLS FOR ENHANCED INFLAMMATORY RESPONSE

- TGRL ALONE NO INFLAMMATION IN HAEC
- TGRL ENHANCED INFLAMMATORY RESPONSE 10x TO CYTOKINE STIMULATION

HAECs were repetitively incubated with dietary levels of freshly isolated TGRL for 2 hours per day for 1 to 3 days to mimic postprandial lipidemia.

Ting et al Circ Res Feb 2007;100:000
Selective insulin resistance in liver of mice with type 2 diabetes. Insulin fails to decrease gluconeogenesis, but it continues to stimulate synthesis of fatty acids and Tg. This produces the deadly combination of hyperglycemia and hypertriglyceridemia.
Lifestyle is the best choice

Thank you

LAST slide
WHAT PERCENTAGE ASYMPTOMATIC 30-40 YEAR OLD PEOPLE HAVE CORONARY ATHEROSCLEROSIS?

1. 10%
2. 40%
3. 50%
4. 60%
5. >70%
WHAT IS THE % CV EVENT RATE @ 10 YEARS IN TYPE 2 DIABETES PATIENTS THAT ARE OVERWEIGHT/OBESE?

1. 2%
2. 4%
3. 6%
4. 18%
5. 30%

Look AHEAD trial
WHAT CELLULAR PATHWAY CONTINUES TO BE INSULIN SENSITIVE IN DIABETES

1. HMG CoA pathway
2. PPAR
3. SGLT2
4. MAP Kinase
5. PI3 kinase
WHICH CARDIORENALE DRUGS REDUCE CV DEATH

1. Statins
2. SGLT 2 (EMPA-REG) / GLP-1 Agonist (LEADER)
3. PCSK9 inhibitor
4. DPP IV inhibitor
5. Statins + PCSK9

Answer 2
....the end

Thanks