Vascular harmony

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University of Texas Health Science Center
Director of Cardiac Catheterization labs
Director of clinical proteomics
INTERHEART trial: 9 modifiable risk factors account for 90% of myocardial infarctions

Lancet 2004; 364: 937–52
Overview of the largest world Pandemic……Obesity / diabetes

- Heart
- Peripheral vascular disease
- Diabetes is complex
- Smoking Diabetes
- Blood vessel lining
- Eyes
- Kidney
- Diabetes Blood pressure
- Diabetes Blood pressure
Healthy lifestyle: healthy endothelial cells

(1.6 trillion cells) lining 60,000 miles of blood vessels

Inside look at your blood vessel

Oscillatory blood pressure (hypertension)

Biological biomarkers
- Genetics
- Age

Metabolic biomarkers
- Inflammation
- Lipids
- BNP
- Troponin
- Glucose
- Insulin resistance

Mechanical biomarkers
- Blood pressure
- Pulse wave velocity
- Central aortic pressure
Healthy endothelial cells
“endothelial cells dysfunction years ahead of risk factors”

Antioxidants
Nitric oxide
tPA
Others

Human glycocalyx

Vascular wall cell signaling

Aging
Genetics

Metabolics

Inflammation
LIPIDS
Insulin resistance
Epigenetics
Others

Introduction

Oscillatory blood pressure (hypertension)
Diabetes and heart disease
Significantly related to BMI

Damaged by free radicals (ROS)

1-3 horsepower on average

Sustain about 0.25 hp
World class 0.54 hp
Never rests….at least not for long

Fuel plant

Most common fuel
Sugar
Free fatty acids
Ketones

38 lbs/ATP per day
nothing beats healthy weight loss and lifestyle

Absolute risk reduction

Drugs

Normal weight/exercise

Rough estimates

Percentage

0
10
20
30
40

95% failure rate
Diabetes (≈80% HT / bad lipids)

Longer you have disease more free radial damage
CV EVENT REDUCED BY CONTROLLING MULTIPLE RISK FACTORS

- **STENO-2 TRIAL**
- **13.3 YEARS OF FOLLOW-UP**
- **PATIENTS ACTIVELY INVOLVED**

Intensively target Healthy lifestyle
Control BP, Lipids, Glucose vs Control

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**Effect of a Multifactorial Intervention on Mortality in Type 2 Diabetes**


**ABSTRACT**

Intensified multifactorial intervention — with tight glucose regulation and the use of renin-angiotensin system blockers, aspirin, and lipid-lowering agents — has been shown to reduce the risk of nonfatal cardiovascular disease among patients with type 2 diabetes mellitus and microalbuminuria. We evaluated whether this approach would have an effect on the rates of death from any cause and from cardiovascular disease.

STENT-2 RESULTS - 13 YEARS LATER

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intensive Therapy</th>
<th></th>
<th>Conventional Therapy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>No. of Events</td>
<td>No. of First Events</td>
<td>No. of Patients</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>24</td>
<td>24</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>9</td>
<td>9</td>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>8</td>
<td>9</td>
<td>7</td>
<td>21</td>
</tr>
<tr>
<td>Stroke</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td>Coronary-artery bypass grafting</td>
<td>8</td>
<td>8</td>
<td>5</td>
<td>13</td>
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<tr>
<td>Percutaneous coronary intervention</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Revascularization</td>
<td>6</td>
<td>8</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Amputation</td>
<td>6</td>
<td>10</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>All cardiovascular events</td>
<td>25</td>
<td>51</td>
<td>48</td>
<td>158</td>
</tr>
</tbody>
</table>
A Nephropathy

B Retinopathy

Picture review of diabetes and vascular disease

.......adjusted for current proven outcome results

There is no primary and secondary prevention......its all atherosclerosis

Lifestyle still wins
The eye of diabetes

Normal Retina  Diabetic Retina
Protecting your kidney with diabetes

SGLT 2 inhibitors

Diabetes
- Weight loss
- Sodium loss
- Water loss
- Reduce kidney damage

Natriuresis effect on tubuloglomerular feedback
- Afferent arteriole
- Macula densa

↑ Tubuloglomerular feedback leads to afferent constriction
↓ Intraglomerular hypertension
↓ Proteinuria

Na⁺/glucose cotransport inhibition with SGLT2 inhibitors

↓ Blood pressure
↓ Arterial stiffness
↓ Na⁺ Glucose
↓ Weight HbA1c
# Risk Categories and LDL-C Treatment Goals

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Risk factors/10-year risk</th>
<th>Treatment goals</th>
</tr>
</thead>
</table>
| **Extreme risk**    | - Progressive ASCVD including unstable angina in individuals after achieving an LDL-C <70 mg/dL  
- Established clinical cardiovascular disease in individuals with DM, stage 3 or 4 CKD, or HeFH  
- History of premature ASCVD (<55 male, <65 female)                                                                                                           | <55  | <80  | <70 |
| **Very high risk**  | - Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20%  
- DM or stage 3 or 4 CKD with 1 or more risk factor(s)  
- HeFH                                                                                                           | <70  | <100 | <80 |
| **High risk**       | - ≥2 risk factors and 10-year risk 10%-20%  
- DM or stage 3 or 4 CKD with no other risk factors                                                                                                              | <100 | <130 | <90 |
| **Moderate risk**   | ≤2 risk factors and 10-year risk <10%                                                                                                                                                                                | <100 | <130 | <90 |
| **Low risk**        | 0 risk factors                                                                                                                                                                                                            | <130 | <160 | NR  |
30 y/o/ Hispanic
Type 2 DM male
A1c 8.5
Obese
HDL low
High triglycerides
Biopsy proven
NASH

8 months before

NIRS-IVUS
Glucosecentric approach: failed to reduce CV events

Target glucose number

Glucose-centered approach

EVENT drive endpoint after EMPA-REG / LEADER

Treatment for diabetes patients 7.5% risk in 10 years

Decreased CV death
Decreased CV events
Reduced progression of kidney disease
Reduced hospital readmission for HF

2015
Strategies for Multivessel Revascularization in Patients with Diabetes

Michael E. Farkouh, M.D., Michael Domanski, M.D., Lynn A. Sleeper, Sc.D., Flora S. Siami, M.P.H.,
George Dangas, M.D., Ph.D., Michael Mack, M.D., May Yang, M.P.H., David J. Cohen, M.D.,
Yves Rosenberg, M.D., M.P.H., Scott D. Solomon, M.D., Akshay S. Desai, M.D., M.P.H.,
Bernard J. Gersh, M.B., Ch.B., D.Phil., Elizabeth A. Magnuson, Sc.D., Alexandra Lansky, M.D.,
Robin Boineau, M.D., Jesse Weinberger, M.D., Krishnan Ramanathan, M.B., Ch.B., J. Eduardo Sousa, M.D., Ph.D.,
Jamie Rankin, M.D., Balram Bhargava, M.D., John Buse, M.D., Whady Hueb, M.D., Ph.D., Craig R. Smith, M.D.,
Victoria Muratov, M.D., M.P.H., Sameer Bansilal, M.D., Spencer King III, M.D., Michel Bertrand, M.D.,
and Valentin Fuster, M.D., Ph.D., for the FREEDOM Trial Investigators*
5-year % rate of Death/MI/Stroke:

5-Year Event Rates (overall): 26.6% PCI vs. 18.7% CABG

J Am Coll Cardiol 2014;64:1189–97
New cardiovascular agents for diabetes patients

CV death
Renal vascular protection
Heart failure
Peripheral artery disease

Reduced weight
Reduced BP
**Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes**

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Pichette, M.D., Eric B. Million, Ph.D., Stefan Hartel, Ph.D., Michaela Matthes, Dipl., and Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woehrle, M.D., Uli C. Broedel, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

**Abstract**

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.

**B Death from Cardiovascular Causes**

Hazard ratio: 0.62 (95% CI, 0.49–0.77)  
P<0.001

![Graph showing death from cardiovascular causes over time with placebo and empagliflozin](chart.png)
Hazard ratio, 0.85 (95% CI, 0.74–0.99) 
P=0.04 for superiority

Hazard ratio, 0.62 (95% CI, 0.49–0.77) 
P<0.001

Hazard ratio, 0.68 (95% CI, 0.57–0.82) 
P<0.001

Hazard ratio, 0.65 (95% CI, 0.50–0.85) 
P=0.002
### Table 2: Adjudicated CV Death by Subcategory

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=2333</th>
<th>Empa 10 N=2345</th>
<th>Empa 25 N=2342</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with CV death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Acute MI</td>
<td>137 (5.9)</td>
<td>90 (3.8)</td>
<td>82 (3.5)</td>
</tr>
<tr>
<td>- Sudden death</td>
<td>38 (1.6)</td>
<td>30 (1.3)</td>
<td>23 (1.0)</td>
</tr>
<tr>
<td>- Worsening of heart failure</td>
<td>19 (0.8)</td>
<td>7 (0.3)</td>
<td>4 (0.2)</td>
</tr>
<tr>
<td>- Cardiogenic shock</td>
<td>3 (0.1)</td>
<td>1 (&lt;0.1)</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>- Stroke</td>
<td>11 (0.5)</td>
<td>9 (0.4)</td>
<td>7 (0.3)</td>
</tr>
<tr>
<td>- Other cardiovascular death</td>
<td>55 (2.4)</td>
<td>37 (1.6)</td>
<td>37 (1.6)</td>
</tr>
<tr>
<td>- Fatal event not assessable</td>
<td>53 (2.3)</td>
<td>34 (1.4)</td>
<td>37 (1.6)</td>
</tr>
</tbody>
</table>
In people with clinical cardiovascular disease in whom glycemic targets are not met, an SGLT2 inhibitor with demonstrated cardiovascular outcome benefit should be added to antihyperglycemic therapy to reduce the risk for cardiovascular and all-cause mortality (Grade A, Level 1A for empagliflozin)
**CLOSING COMMENTS**

2 treatments known to extend life expectancy/CV death in diabetes

Metabolic treatment

<table>
<thead>
<tr>
<th>Trial</th>
<th>↓ CV events</th>
<th>↓ CV death</th>
<th>Kidney protection</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-SGLT2I</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CANA</td>
<td>Yes</td>
<td>No</td>
<td>YES</td>
</tr>
<tr>
<td>LIRA-GLP-1</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>SEMA</td>
<td>Yes</td>
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</tr>
<tr>
<td>Statins</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>PCSK9</td>
<td>Yes</td>
<td>No</td>
<td>NO</td>
</tr>
</tbody>
</table>

New era- cardiorenal agents for T2DM