Heart failure and diabetes: SGLT-2 inhibition, a paradigm shift?

John McMurray
BHF Cardiovascular Research Centre,
University of Glasgow & Queen Elizabeth
University Hospital, Glasgow.
Heart failure in diabetes

Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored

John J V McMurray, Hertzel C Gerstein, Rury R Holman, Marc A Pfeffer

*Lancet Diabetes Endocrinol* 2014; 2: 843–51

- Trying to put heart failure on the diabetes map
- Omission of heart failure from “MACE” endpoint recommended by FDA in clinical trials
- Emphasising frequency and prognostic importance of heart failure relative to other cardiovascular events
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 Mattheus, 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

The key findings in EMPA-REG

Heart failure Hospitalization

Cardiovascular mortality

Hazard ratio, 0.65 (95% CI, 0.50–0.85)  
P=0.002

Hazard ratio, 0.62 (95% CI, 0.49–0.77)  
P<0.001
Key Questions about SGLT-2 inhibitors and heart failure (HF)

- How is HF prevented by SGLT-2 inhibitors?
- Why is mortality reduced by SGLT-2 inhibitors?
- Can we use SGLT-2 inhibitors to treat established HF?
Prevention of heart failure

- Direct myocardial action – Improved cardiac (systolic/diastolic function)? Inotropic, lusitropic or metabolic effect?
- Indirect myocardial action – Anti-ischaemic effect? Reduced myocyte necrosis?
- Other myocardial effects – Extra-cellular matrix effect?
- Antiarrhythmic effect – Atrial arrhythmias?
- Blood pressure lowering – Vasodilator action? Sodium/volume reduction?
- Renal effect(s) – Diuresis/natriuresis? preservation/improvement in eGFR?
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Ketone ("super-fuel") hypothesis

Can a Shift in Fuel Energetics Explain the Beneficial Cardiorenal Outcomes in the EMPA-REG OUTCOME Study? A Unifying Hypothesis
Sunder Mudaliar, Sindura Alloju, and Robert R. Henry

CV Protection in the EMPA-REG OUTCOME Trial: A "Thrifty Substrate" Hypothesis
Ele Ferrannini,1 Michael Mark,2 and Eric Mayoux2

Empagliflozin’s Fuel Hypothesis: Not so Soon
Gary D. Lopaschuk1,∗ and Subodh Verma2,∗
1Cardiovascular Translational Science Institute, University of Alberta, Edmonton, AB T6G 2S2, Canada
2Division of Cardiac Surgery, Keenan Research Centre, Li Ka Shing Knowledge Institute, St. Michael’s Hospital, University of Toronto, ON M5S, Canada

Cell Metabolism 24, August 9, 2016
Which fuel is most efficient?
Prevention of heart failure

- Direct myocardial action – Improved cardiac (systolic/diastolic function)? Inotropic, lusitropic or metabolic effect?

- Indirect myocardial action – Anti-ischaemic effect? Reduced myocyte necrosis?

- Other myocardial effects – Extra-cellular matrix effect?

- Antiarrhythmic effect – Atrial arrhythmias?

- Blood pressure lowering – Vasodilator action? Sodium/volume reduction?

- Renal effect(s) – Diuresis/natriuresis? preservation/improvement in eGFR?
**EMPA-REG: Primary composite endpoint**

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

Cox regression analysis. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio; CV, cardiovascular; MI, myocardial infarction.

*95.02% CI
Prevention of heart failure

- Direct myocardial action – Improved cardiac (systolic/diastolic function)? Inotropic, lusitropic or metabolic effect?
- Indirect myocardial action – Anti-ischaemic effect? Reduced myocyte necrosis?
- Other myocardial effects – Extra-cellular matrix effect?
- **Antiarrhythmic effect – Atrial arrhythmias?**
- Blood pressure lowering – Vasodilator action? Sodium/volume reduction?
- Renal effect(s) – Diuresis/natriuresis? preservation/improvement in eGFR?
Prevention of heart failure

- Direct myocardial action – Improved cardiac (systolic/diastolic function)? Inotropic, lusitropic or metabolic effect?
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- Renal effect(s) – Diuresis/natriuresis? preservation/improvement in eGFR?
Cardiac (patho-)physiology – after-load, pre-load, arterial stiffness

- Diuresis/natriuresis – reduced intravascular volume, pre-load
- Arterial stiffness – intra-vascular sodium
Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis


www.thelancet.com  Published online December 23, 2015
BP reduction is extremely effective in reducing the risk of developing HF.

<table>
<thead>
<tr>
<th></th>
<th>Studies</th>
<th>Intervention</th>
<th>Control</th>
<th>RR (95% CI) per 10 mm Hg reduction in systolic blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major cardiovascular events</td>
<td>55</td>
<td>13209</td>
<td>14068</td>
<td>0.80 (0.77–0.83)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>56</td>
<td>4862</td>
<td>5301</td>
<td>0.83 (0.78–0.88)</td>
</tr>
<tr>
<td>Stroke</td>
<td>54</td>
<td>4635</td>
<td>5378</td>
<td>0.73 (0.68–0.77)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>43</td>
<td>3284</td>
<td>3760</td>
<td>0.72 (0.67–0.78)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>16</td>
<td>890</td>
<td>834</td>
<td>0.95 (0.84–1.07)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>57</td>
<td>9775</td>
<td>9998</td>
<td>0.87 (0.84–0.91)</td>
</tr>
</tbody>
</table>
Do only patients with a very high BP benefit?

**SPRINT**
- BP 139.7/78.1 mmHg
- Heart failure – HR 0.62 (0.45, 0.84); P=0.002

**EMPA-REG**
- BP 135.5/76.7 mmHg
- Heart failure – HR 0.65 (0.50, 0.85); P=0.002
EMPA-REG Outcome: Change in SBP

All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat).

X-axis: timepoints with reasonable amount of data available for pre-scheduled measurements.
### How much BP reduction?

#### Mean BP difference

<table>
<thead>
<tr>
<th>5-year risk of stroke</th>
<th>Active (n/N)</th>
<th>Control (n/N)</th>
<th>Mean BP difference, mm Hg</th>
<th>Risk difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4.0%</td>
<td>175/10493</td>
<td>286/14743</td>
<td>4.4/3.0</td>
<td>-1.06 (-1.53 to 0.60)</td>
</tr>
<tr>
<td>4.0–5.4%</td>
<td>196/5608</td>
<td>266/6648</td>
<td>6.1/3.1</td>
<td>-1.05 (-1.87 to 0.23)</td>
</tr>
<tr>
<td>5.4–7.2%</td>
<td>205/4145</td>
<td>257/4529</td>
<td>7.5/3.5</td>
<td>-1.49 (-2.67 to 0.32)</td>
</tr>
<tr>
<td>&gt;7.2%</td>
<td>206/2781</td>
<td>255/2870</td>
<td>6.1/2.6</td>
<td>-1.78 (-3.35 to 0.22)</td>
</tr>
</tbody>
</table>

#### 5-year risk of CHD

<table>
<thead>
<tr>
<th>5-year risk of CHD</th>
<th>Active (n/N)</th>
<th>Control (n/N)</th>
<th>Mean BP difference, mm Hg</th>
<th>Risk difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5%</td>
<td>164/10373</td>
<td>251/14382</td>
<td>5.0/3.1</td>
<td>-0.47 (-0.90 to 0.05)</td>
</tr>
<tr>
<td>5–7%</td>
<td>183/5646</td>
<td>232/6950</td>
<td>5.5/3.2</td>
<td>-0.28 (-1.03 to 0.47)</td>
</tr>
<tr>
<td>7–11%</td>
<td>182/4187</td>
<td>233/4630</td>
<td>6.3/2.8</td>
<td>-1.14 (-2.20 to 0.07)</td>
</tr>
<tr>
<td>&gt;11%</td>
<td>189/2870</td>
<td>225/2997</td>
<td>6.2/2.9</td>
<td>-1.57 (-3.19 to 0.04)</td>
</tr>
</tbody>
</table>

#### 5-year risk of heart failure

<table>
<thead>
<tr>
<th>5-year risk of heart failure</th>
<th>Active (n/N)</th>
<th>Control (n/N)</th>
<th>Mean BP difference, mm Hg</th>
<th>Risk difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.6%</td>
<td>102/14560</td>
<td>119/20070</td>
<td>4.8/3.1</td>
<td>-0.12 (-0.36 to 0.11)</td>
</tr>
<tr>
<td>2.6–4.5%</td>
<td>104/4503</td>
<td>118/4839</td>
<td>6.7/3.0</td>
<td>-0.26 (-0.99 to 0.47)</td>
</tr>
<tr>
<td>4.5–7.0%</td>
<td>101/2362</td>
<td>120/2376</td>
<td>7.2/2.9</td>
<td>-1.04 (-2.52 to 0.44)</td>
</tr>
<tr>
<td>&gt;7.0%</td>
<td>90/1651</td>
<td>131/1674</td>
<td>6.3/2.8</td>
<td>-3.28 (-5.30 to 1.25)</td>
</tr>
</tbody>
</table>

#### 5-year risk of cardiovascular death

<table>
<thead>
<tr>
<th>5-year risk of cardiovascular death</th>
<th>Active (n/N)</th>
<th>Control (n/N)</th>
<th>Mean BP difference, mm Hg</th>
<th>Risk difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5%</td>
<td>190/12870</td>
<td>274/17732</td>
<td>4.6/3.0</td>
<td>-0.30 (-0.64 to 0.05)</td>
</tr>
<tr>
<td>5–8%</td>
<td>203/4967</td>
<td>261/5788</td>
<td>5.9/3.0</td>
<td>-0.78 (-1.67 to 0.11)</td>
</tr>
<tr>
<td>8–13%</td>
<td>212/2985</td>
<td>252/3138</td>
<td>7.4/3.3</td>
<td>-1.68 (-3.32 to 0.05)</td>
</tr>
<tr>
<td>&gt;13%</td>
<td>220/2254</td>
<td>243/2301</td>
<td>8.4/3.4</td>
<td>-1.20 (-3.36 to 0.96)</td>
</tr>
</tbody>
</table>

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Mean BP difference

6.3/2.8mmHg
Antihypertensive Treatment and Development of Heart Failure in Hypertension

A Bayesian Network Meta-analysis of Studies in Patients With Hypertension and High Cardiovascular Risk

Sebastiano Sciarretta, MD; Francesca Palano, MD; Giuliano Tocci, MD; Rossella Baldini, PhD; Massimo Volpe, MD

Prevention of HF: Diuretics are the most effective anti-hypertensives
Critical components of the action of diuretics (and SGLT2 inhibitors?) in preventing HF
Are patients with T2DM particularly sensitive to even small sodium/volume changes?

**RECORD: Development of heart failure**

Cumulative incidence (%)

![Graph showing cumulative incidence over months for Rosiglitazone and Control groups.](image-url)
Could lowering BP with a diuretic have the rapid benefit seen in EMPA-REG?

Heart failure Hospitalization

Cardiovascular mortality

Hazard ratio, 0.65 (95% CI, 0.50–0.85)
P=0.002

Hazard ratio, 0.62 (95% CI, 0.49–0.77)
P<0.001
HYVET: How quickly does reducing BP work?

The New England Journal of Medicine

Treatment of Hypertension in Patients 80 Years of Age or Older

Nigel S. Beckett, M.B., Ch.B., Ruth Peters, Ph.D., Astrid E. Fletcher, Ph.D., Jan A. Staessen, M.D., Ph.D., Lisheng Liu, M.D., Dan Dumitrascu, M.D., Vassil Stoyanovsky, M.D., Riitta L. Antikainen, M.D., Ph.D., Yuri Nikitin, M.D., Craig Anderson, M.D., Ph.D., Alli Belhani, M.D., Françoise Forette, M.D., Chakravarthi Rajkumar, M.D., Ph.D., Lutgarde Thijs, M.Sc., Winston Banya, M.Sc., and Christopher J. Bulpitt, M.D., for the HYVET Study Group*

HYVET: How quickly does reducing BP work?

![Graph showing the effect of reducing blood pressure over time.](image-url)
Prevention of heart failure

- Direct myocardial action – Improved cardiac (systolic/diastolic function)? Inotropic, lusitropic or metabolic effect?

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- Blood pressure lowering – Vasodilator action? Sodium/volume reduction?

- Renal effect(s) – Diuresis/natriuresis? preservation/improvement in eGFR?
The cardio-renal axis is critical in heart failure
Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Maximilian von Eynatten, M.D., Michaela Mattheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D., for the EMPA-REG OUTCOME Investigators

EMPA-REG Outcome: Change in eGFR

Adjusted Mean eGFR (ml/min/1.73 m^2)

Week

Baseline 4 12 28 52 66 80 94 108 122 136 150 164 178 192

Empagliflozin, 10 mg
Empagliflozin, 25 mg
Placebo
Key Questions about SGLT-2 inhibitors and heart failure (HF)

• How is HF prevented by SGLT-2 inhibitors?
• Why is mortality reduced by SGLT-2 inhibitors?
• Can we use SGLT-2 inhibitors to treat established HF?
The key findings in EMPA-REG

Heart failure Hospitalization

- Hazard ratio, 0.65 (95% CI, 0.50–0.85)
- P=0.002

Cardiovascular mortality

- Hazard ratio, 0.62 (95% CI, 0.49–0.77)
- P<0.001
Heart failure events with rosiglitazone in type 2 diabetes: data from the RECORD clinical trial

Michel Komajda¹,², John J.V. McMurray³, Henning Beck-Nielsen⁴, Ramon Gomis⁵, Markolf Hanefeld⁶, Stuart J. Pocock⁷, Paula S. Curtis⁸, Nigel P. Jones⁹, and Philip D. Home¹⁰
RECORD: Design

People on monotherapy

Metformin

Randomly allocated to dual

Add rosiglitazone (continue metformin)

Add sulfonylurea (continue metformin)

Sulfonylurea

Add rosiglitazone (continue sulfonylurea)

Add metformin (continue sulfonylurea)

Mean follow-up: 5.5 years
Rescue therapy:
Rosiglitazone groups: (i) intensify to triple oral therapy; (ii) stop rosiglitazone and start insulin.
Metformin + SU groups: start insulin
**Prognosis following hospitalisation for HF in RECORD**

<table>
<thead>
<tr>
<th>Event</th>
<th>Rosiglitazone (n = 2220)</th>
<th>Control (n = 2227)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with HF events (fatal and non-fatal)</td>
<td>61</td>
<td>29</td>
</tr>
<tr>
<td>First HF event fatal</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Survived first HF event</td>
<td>57</td>
<td>29</td>
</tr>
<tr>
<td><strong>All-cause death (%)</strong></td>
<td>17 (30)</td>
<td>8 (28)</td>
</tr>
<tr>
<td>HF death</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Other CV death^a</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Other death</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Further non-fatal HF event (%)</td>
<td>7 (12)</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Other non-fatal CV event (%)</td>
<td>13 (23)</td>
<td>10 (34)</td>
</tr>
<tr>
<td>No other CV event (%)</td>
<td>26 (46)</td>
<td>15 (52)</td>
</tr>
</tbody>
</table>

**Overall mortality 6.6%**
HF in diabetes is really deadly

- Overall mortality: 4.8%
- Mortality in patients hospitalized with HF 26.1%
Two main modes of death in heart failure

- Sudden death
- Heart failure
What type of heart failure?

HFREF or HFPEF?

Normal  HFREF  HFPEF
What do we know about undiagnosed HF/ left ventricular dysfunction in diabetes?

High prevalence of previously unknown heart failure and left ventricular dysfunction in patients with type 2 diabetes

L. J. M. Boonman-de Winter • F. H. Rutten • M. J. M. Cramer • M. J. Landman • A. H. Liem • G. E. H. M. Rutten • A. W. Hoes

- 581 patients ≥60 years with T2DM and without a diagnosis of HF
- 27.7% undiagnosed HF (4.8% HFREF; 22.9% HFPEF)
- LVEF <45% 0.7%; LVEF 45-55% 11.2%
- LV diastolic dysfunction 25.1%
Key Questions about SGLT-2 inhibitors and heart failure (HF)

- How is HF prevented by SGLT-2 inhibitors?
- Why is mortality reduced by SGLT-2 inhibitors?
- Can we use SGLT-2 inhibitors to treat established HF?
HF: Patho-physiological basis of treatment

Myocardial injury

Left ventricular systolic dysfunction

Perceived reduction in circulating volume and pressure

Systemic vasoconstriction
Renal sodium and water retention

Neurohumoral activation
- SNS
- RAAS
- ET, AVP etc
Myocardial injury

Left ventricular systolic dysfunction

Perceived reduction in circulating volume and pressure

Neurohumoral activation
- SNS
- RAAS
- ET, AVP etc

ACE inhibitors
Beta-blockers
MRAs

Systemic vasoconstriction
Renal sodium and water retention

Diuretics
Diuretics

Peripheral oedema

Pulmonary oedema

Accumulation of fluid in the air sacs (alveoli) in the lungs
Treatment of heart failure – similar patho-physiological considerations

- Direct myocardial action – Improved cardiac (systolic/diastolic function)? Inotropic, lusitropic or metabolic effect?
- Indirect myocardial action – Anti-ischaemic effect? Reduced myocyte necrosis?
- Other myocardial effects – Extra-cellular matrix effect?
- Antiarrhythmic effect – Atrial arrhythmias? Ventricular arrhythmias?
- Blood pressure lowering – Vasodilator action? Sodium/volume reduction?
- Renal effect(s) – Diuresis/natriuresis? preservation/improvement in eGFR?
- Systemic effects – Neurohumoral, anti-inflammatory etc.
### EMPA-REG Outcome

**Outcomes according to heart failure status at baseline**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No HF at baseline (n=7020)</th>
<th>HF at baseline (n=706)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death or HF hospitalization</td>
<td>0.66 (0.55, 0.79)</td>
<td>0.72 (0.50, 1.04)</td>
</tr>
<tr>
<td>HF death or HF hospitalization</td>
<td>0.61 (0.47, 0.79)</td>
<td>NR</td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>0.65 (0.50, 0.85)</td>
<td>0.75 (0.48, 1.19)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.89 (0.82, 0.96)</td>
<td>0.79 (0.52, 1.20)</td>
</tr>
</tbody>
</table>

*Placebo/empagliflozin hazard ratio*

*Pham et al Trends in Cardiovascular Medicine 2016 in press*
Mechanistic studies in heart failure

Rationale and design of a randomized trial to test the safety and non-inferiority of canagliflozin in patients with diabetes with chronic heart failure: the CANDLE trial

Canagliflozin

Research into the effect of SGLT2 inhibition on left ventricular remodelling in patients with heart failure and diabetes mellitus (REFORM) trial rationale and design

Dapagliflozin
Jardiance® (empagliflozin) to be studied for the treatment of people with chronic heart failure

- New studies will evaluate the effect of Jardiance® for the treatment of chronic heart failure
- There are approximately 26 million people worldwide, and 5.7 million people in the U.S., suffering from chronic heart failure
- The studies build on results from the landmark EMPA-REG OUTCOME® trial

Ingelheim, Germany and Indianapolis, US, 19 April, 2016 – Boehringer Ingelheim and Eli Lilly and Company
Summary and conclusions

- The effect of empagliflozin in preventing HF can probably partly (but probably not wholly) explained by a diuretic/antihypertensive and renal actions
- A beneficial myocardial metabolic effect has also been postulated
- The HF phenotype in EMPA-REG is unknown
- Whether SGLT2 inhibitors might be effective in treating HF is a key and unanswered question
- The diuretic/natriuretic actions and preservation of GFR are appealing attributes from a HF therapy perspective
- Other potential beneficial mechanisms possible and worthy of further exploration