Treatment of diabetic kidney disease: landmark studies and tribulations

Sydney C.W. TANG
Chronic kidney disease is a global public health problem

Estimated CKD Burden: 8 – 16% worldwide (Jha V, et al. Lancet 2013)
Chronic kidney disease (CKD): an increasingly common cause of death: 1990 to 2013

Top 50 Causes of death: a systematic analysis for the Global Burden of Disease Study

1990 mean rank (95% UI)

1. Lower respiratory infections
2. Diarrhoeal diseases
3. Premature birth
4. Ischaemic heart disease
5. Cerebrovascular disease
6. Neonatal encephalopathy
7. Tuberculosis
8. Malnutrition
9. Congenital anomalies
10. Road injuries
11. COPD
12. Measles
13. Drowning
14. Protein-energy malnutrition
15. Meningitis
16. Self-harm
17. Neonatal sepsis
18. Cirrhosis
19. Tetanus
20. Lung cancer
21. Maternal disorders
22. Syphilis
23. Intentional violence
24. Stomach cancer
25. Fire and heat
26. Diabetes
27. HIV/AIDS
28. Asthma
29. Liver cancer
30. Other cardiovascular
31. Falls
32. Rheumatic heart disease
33. Typhoid fever
34. Hypertensive heart disease
35. Iron-deficiency anaemia
36. Chronic kidney disease
37. Whooping cough
38. Colorectal cancer
39. Leukaemia
40. Pneumonia disease
41. Breast cancer
42. Cardiomyopathy
43. Pulmonary aspiration
44. Alzheimer’s disease
45. Oesophageal cancer

36 Chronic kidney disease

2013 mean rank (95% UI)

1. Ischaemic heart disease
2. Lower respiratory infections
3. Cerebrovascular disease
4. Diarrhoeal diseases
5. Road injuries
6. HIV/AIDS
7. Premature birth
8. Malaria
9. Neonatal encephalopathy
10. Congenital anomalies
11. Tuberculosis
12. COPD
13. Cirrhosis
14. Self-harm
15. Lung cancer
16. Neoplasms
17. Chronic kidney disease
18. Protein-energy malnutrition
19. Drowning
20. Liver cancer
21. Intentional violence
22. Malaria
23. Hypertensive heart disease
24. Stomach cancer
25. Maternal disorders
26. Colorectal cancer
27. Asthma
28. Falls
29. Alzheimer’s disease
30. Breast cancer
31. Cardiomyopathy
32. Anaemia
33. Other cardiovascular
34. Fire and heat
35. Syphilis
36. Sickle cell
37. Typhoid fever
38. Oesophageal cancer
39. Leukaemia
40. Intestinal larval disease
41. Rheumatic heart disease
42. Pneumonia disease
43. Measles
44. Pancreatic cancer
45. Iron-deficiency anaemia

19 Chronic kidney disease

2013 mean rank (95% UI)
The number of people with type 2 diabetes is increasing in every country.
The Diabetes Epidemic

387 million people have diabetes; by 2035, this will rise to 592 million.

179 million people with diabetes are undiagnosed.

The greatest number of people with diabetes are between 40 and 59 years of age.

IDF Diabetes Atlas 2014
Outline

• The burden of diabetic kidney disease in Asia
• Landmark clinical trials on treatment and tribulations
• Recent clinical trials
  – Investigational
  – Novel
• Future perspectives
Japan

- Population: 127 million
### Chronic Kidney Disease Japan Cohort Study (CKD-JAC)

<table>
<thead>
<tr>
<th></th>
<th>No diabetes</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No CGN</td>
<td>CGN</td>
</tr>
<tr>
<td>No diabetes</td>
<td>909</td>
<td>948</td>
</tr>
<tr>
<td></td>
<td>30.5%</td>
<td>31.8%</td>
</tr>
</tbody>
</table>

N = 2977

Imai et al. Clin Exp Nephrol 2010
Causes of incipient dialysis

JSDT

Diabetic nephropathy 43.8%
Chronic glomerulonephritis 18.8%
Hypertensive nephrosclerosis
Trends in % Incident Counts - by Diagnosis, 1996 - 2013

49.6% incident patients were diabetic
Nephrology in China

Zhi-Hong Liu

- China has a high prevalence of chronic kidney disease (CKD); an increasing prevalence of hypertension, obesity and type 2 diabetes mellitus, and an ageing population will exacerbate the burden of CKD.
- The current leading cause of CKD in China is glomerular disease, followed by diabetic nephropathy; IgA nephropathy is the most common glomerular disease.

Taiwan
Diabetes became the top leading cause of ESRD
Increase of incidence of aged group after launching of NHI

Diabetes, aged, and health insurance are majors for increase of ESRD.

Yang & Hwang, NDT, 2008
Treated ESRD mortality

Taiwan Society of Nephrology data
Other developed Asian Countries

ESRD Registry Committee,
Korean Society of Nephrology
Figure 3.1.2.4: Incidence of Patients on Dialysis by Mode of Dialysis and Etiology, 1999 – 2013
### What about in developing Asian Countries?

#### Table 15: Distribution of New Dialysis Patients according to Primary Renal Disease and Mode of Dialysis, 2013

<table>
<thead>
<tr>
<th>PRIMARY RENAL DISEASE</th>
<th>HD</th>
<th>PD</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGN, Biopsy Proven</td>
<td>98 (0.72)</td>
<td>5 (0.66)</td>
<td>103 (0.72)</td>
</tr>
<tr>
<td>Crescentic glomerulonephrits</td>
<td>2</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Crescentic Pauci immune</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Diffuse glomerulosclerosis</td>
<td>3</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Diffuse proliferative glomerulonephrits</td>
<td>4</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>17</td>
<td>1</td>
<td>18</td>
</tr>
</tbody>
</table>

#### Table 2.1.8: Primary Renal Diseases 2004-2013

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>New Dialysis patients</td>
<td>2901</td>
<td>3155</td>
<td>3681</td>
<td>4070</td>
<td>4604</td>
<td>4920</td>
<td>5252</td>
<td>6009</td>
<td>6541</td>
<td>6222</td>
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<tr>
<td>% Unknown cause</td>
<td>25</td>
<td>23</td>
<td>23</td>
<td>25</td>
<td>26</td>
<td>26</td>
<td>27</td>
<td>28</td>
<td>22</td>
<td>17</td>
</tr>
<tr>
<td>% Diabetes Mellitus</td>
<td>53</td>
<td>55</td>
<td>57</td>
<td>57</td>
<td>57</td>
<td>58</td>
<td>58</td>
<td>57</td>
<td>59</td>
<td>61</td>
</tr>
<tr>
<td>% GN/SLE</td>
<td>6</td>
<td>7</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>% Polycystic kidney</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>% Obstructive Nephropathy</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>% Toxic Nephropathy</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>% Hypertension</td>
<td>10</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>8</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>% Others</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

21ST REPORT OF THE MALAYSIAN DIALYSIS AND TRANSPLANT REGISTRY 2013
Cambodia

- So far, no reliable data on the incidence and prevalence of ESRD & CKD in Cambodia.

- In a recent study carried out in MoPoTsyo (an NGO Health Center in the Takeo province of Cambodia):
  - Over one-half of Cambodians with DM had a reduced eGFR (60 ml/min/1.73 m²).

An Estimation of the Prevalence and Progression of Chronic Kidney Disease in a Rural Diabetic Cambodian Population

Bernadette Thomas¹*, Maurits van Pelt², Rajnish Mehrotra¹, Cassianne Robinson-Cohen³, James LoGerfo⁴
CKD population in Sri Lanka

- Estimates only
- >75% due to DM, HT and CGN
- DM alone 36%
- Diabetic population in SL 12% = 2.5 million
- by 2030-? 5 million
- DBN – 30% to 50% will develop CKD (all stages) = 0.81 million
- Estimated prevalence of HT in SL = 2 million
The Indian CKD registry confirms the emergence of DN as the pre-eminent cause of CKD in the country as a whole.
Nepal

- No formal registry in Nepal in relation to CKD and ESRD. So, very little is known about the pattern of the ESRD.

- **It is presumed that diabetes mellitus is the commonest cause of ESRD**, followed by CGN and hypertension. (Sharma et al. Journal of Nepal Medical Association 2001; Adhikary Land Simkhada R. Kathmandu Medical college Journal 2005)

- A single hospital based retrospective study from the capital city (Kathmandu) from 1990 to 1999 found that three most common causes of ESRD were Glomerulonephritis (36%), Diabetes mellitus (16.8%), and hypertension (13.7%). (Khakhurel S et al. Journal of Nepal Medical Association 2009).

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Personal communication with Sharma S, Nepal Society of Nephrology
Incidence of end stage renal disease on renal replacement therapy in Nepal (1990-1999)

Hada R¹, Khakurel S¹, Agrawal RK¹, Kafle RK², Bajracharya SB³ and Raut KB⁴
¹National Academy of Medical Sciences, Bir Hospital, ²National Kidney center, ³Shree Birendra Hospital, Chhauni, ⁴Tribhuban University Teaching Hospital

Table 1: Annual incidence of ESRD with renal replacement therapy in Nepal

<table>
<thead>
<tr>
<th>Years</th>
<th>Total number of ESRD on RRT</th>
<th>Total population of Nepal b (in million)</th>
<th>Total number of ESRD on RRT per million population (pmp)</th>
<th>Estimated incidence of ESRD with 100 pmp per year as par with South Asian countries⁵⁶⁷</th>
<th>Proportion of patient receiving RRT in % c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>61</td>
<td>17.9²</td>
<td>3.4</td>
<td>1790</td>
<td>0.18</td>
</tr>
<tr>
<td>1991</td>
<td>68</td>
<td>18.4</td>
<td>3.6</td>
<td>1840</td>
<td>0.19</td>
</tr>
<tr>
<td>1992</td>
<td>97</td>
<td>19.0</td>
<td>5.1</td>
<td>1900</td>
<td>0.26</td>
</tr>
<tr>
<td>1993</td>
<td>78</td>
<td>19.5</td>
<td>4.0</td>
<td>1950</td>
<td>0.20</td>
</tr>
<tr>
<td>1994</td>
<td>125</td>
<td>20.0</td>
<td>6.25</td>
<td>2000</td>
<td>0.31</td>
</tr>
<tr>
<td>1995</td>
<td>134</td>
<td>20.5</td>
<td>6.53</td>
<td>2050</td>
<td>0.31</td>
</tr>
<tr>
<td>1996</td>
<td>159</td>
<td>21.2</td>
<td>7.5</td>
<td>2120</td>
<td>0.35</td>
</tr>
<tr>
<td>1997</td>
<td>189</td>
<td>21.6</td>
<td>8.75</td>
<td>2160</td>
<td>0.40</td>
</tr>
<tr>
<td>1998</td>
<td>212</td>
<td>22.1</td>
<td>9.59</td>
<td>2210</td>
<td>0.43</td>
</tr>
<tr>
<td>1999</td>
<td>270</td>
<td>22.7</td>
<td>11.89</td>
<td>2270</td>
<td>0.52</td>
</tr>
<tr>
<td>1393 (100%)</td>
<td></td>
<td>Average – 6.0</td>
<td></td>
<td>Average – 0.31%</td>
<td></td>
</tr>
</tbody>
</table>
Burden of CKD, Proteinuria, and Cardiovascular Risk Among Chinese, Mongolian, and Nepalese Participants in the International Society of Nephrology Screening Programs

Sanjib Kumar Sharma, MD,1 Hequn Zou, MD,2 Ariunaa Togtokh, MD,3 Bogdan Ene-Iordache, EngD,4 Sergio Carminati, IT,4 Andrea Remuzzi, EngD,4,5 Natasha Wiebe, MMath, PStat,6 Bharati Ayyalasomayajula, PhD,6 Norberto Perico, MD,4 Giuseppe Remuzzi, MD, FRCP,4,7 and Marcello Tonelli, MD, SM7,8,9

Figure 1. Location of screening centers.
Key messages:
Total screened: 11,394 participants
Decreased eGFR (60 mL/min/1.73 m²): 7.3%-14%
Proteinuria on dipstick: 2.4%-10%
Hypertension: 26%-36%
**Diabetes:** 3%-8%
Obesity (body mass index > 30 kg/m²): 2%-20%

Sharma SK, et al. AJKD 2010
CLINICAL STUDY

End stage renal disease in Brunei Darussalam – report from the first Brunei Dialysis Transplant Registry (BDTR)

Jackson Tan

Table 3. Incidence of presumptive etiological diseases (2011).

<table>
<thead>
<tr>
<th>Disease</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>57.1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21.4</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>9.8</td>
</tr>
<tr>
<td>Obstruction</td>
<td>2.7</td>
</tr>
<tr>
<td>Polycystic kidneys</td>
<td>0.9</td>
</tr>
<tr>
<td>Others</td>
<td>8.1</td>
</tr>
</tbody>
</table>
USRDS 2014 Report

DM: 43.5%

40-50%

~60%
DN as the etiology of dialysis therapy

![Bar chart showing prevalence and incidence of DN from 2007 to 2012. Prevalence in blue, incidence in red.](Thailand Renal Replacement Report 2011, Nephrology Society of Thailand)
Outline

• The burden of diabetic kidney disease in Asia
• **Landmark clinical trials on treatment and tribulations**
• Recent clinical trials
  – Investigational
  – Novel
• Future perspectives
Full Review

Diabetic nephropathy: landmark clinical trials and tribulations

Gary C.W. Chan and Sydney C.W. Tang

Division of Nephrology, Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong
ARB: RENAAL & IDNT

Risk reduction, 28%
P=0.002


Lewis EJ, N Eng J Med 2001
ACE inhibitors in diabetic nephropathy

Strippoli GF, BMJ 2004
ONTARGET – Renal composite

Mann JF, J Hypertens 2013
DEPARTMENT OF VETERANS AFFAIRS VETERANS HEALTH ADMINISTRATION (VHA) PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP), AND CENTER FOR MEDICATION SAFETY (VA MEDSAFE)

DUAL RENIN-ANGIOTENSIN ALDOSTERONE SYSTEM BLOCKADE IN DIABETIC NEPHROPATHY AND INCREASED ADVERSE EVENTS

I. ISSUE
Recently, the VA Cooperative Study, “Combination Angiotensin Receptor Blocker and Angiotensin-Converting Enzyme Inhibitor for Treatment of Diabetic Nephropathy (VA NEPHRON-D)” had medications terminated early per recommendations of the Data Monitoring Committee. The decision was based on a greater number of observed acute kidney injury events and hyperkalemia in the combination angiotensin receptor blocker (ARB), losartan, and angiotensin-converting enzyme inhibitor (ACEI), lisinopril, therapy group compared to patients receiving an ARB plus placebo. These outcomes, combined with additional evidence on the use of combination therapy with an ACEI and ARB in general, suggest VA consider implications in practice, especially for patients who are being prescribed combination therapy for a potential benefit on kidney outcomes.
VA-NEPHRON-D: Significantly increased SAE

**Acute Kidney Injury**

Hazard Ratio (HR) 1.7 (95% CI 1.3-2.2)

**Hyperkalemia**

Hazard Ratio (HR) 2.8 (95% CI 1.8-4.3)

Dual blockade in patients with DN

Catala-Lopez F, Rev Esp Cardiol 2013
ALTITUDE: Outcomes

Parving, N Eng J Med 2012 (ALTITUDE study)
Aldosterone antagonists

Aldo antagonist +ACEi/ARB
Vs ACEi /ARB alone

Proteinuria
Change in GFR
Incidence of hyperkalaemia

Spironolactone
Eplerenone
Total

Navaneethan et al, Clinical JASN 2009
4.1: We recommend that adults with diabetes and CKD ND with urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office BP is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. (1B)

4.2: We suggest that adults with diabetes and CKD ND with urine albumin excretion >30 mg per 24 hours (or equivalent*) whose office BP is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. (2D)

4.3: We suggest that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*). (2D)

4.4: We recommend that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion >300 mg per 24 hours (or equivalent*). (1B)
Finerenone

- Finerenone (BAY94-8862) is a novel nonsteroidal MRA that has greater receptor selectivity than spironolactone and better receptor affinity than eplerenone in vitro.
- May be able to address the unmet medical need of safely managing albuminuria without adversely affecting serum K in patients with type 2 DN.
Effect of Finerenone on Albuminuria in Patients With Diabetic Nephropathy
A Randomized Clinical Trial

George L. Bakris, MD; Rajiv Agarwal, MD; Juliana C. Chan, MD; Mark E. Cooper, MD, PhD; Ron T. Gansevoort, MD, PhD; Hermann Haller, MD, PhD; Giuseppe Remuzzi, MD; Peter Rosing, MD; Roland E. Schmieder, MD; Christina Nowack, MD; Peter Kolkhof, PhD; Amer Joseph, MBBS; Alexander Pieper, DipStat; Nina Kimmeskamp-Kirschbaum, PhD; Luis M. Ruilope, MD, PhD; for the Mineralocorticoid Receptor Antagonist Tolerability Study—Diabetic Nephropathy (ARTS-DN) Study Group

OBJECTIVE To evaluate the safety and efficacy of different oral doses of the nonsteroidal mineralocorticoid receptor antagonist finerenone, given for 90 days to patients with diabetes and high or very high albuminuria who are receiving an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker.

Inclusion: T2DM, UACR ≥ 30 mg/g, eGFR > 30 (30-45: on a non-K sparing diuretic); on an RAS blocker, serum potassium ≤ 4.8 mmol/L.

Primary outcome variable: UACR at day 90 vs at baseline

N = ~ 90+ / Rx group (1.25, 2.5, 7.5, 10, 15, 20 mg daily)
N = 94 in matching control group
Change in Least Squares Mean UACR

Weir MR. Nat Rev Nephrol Oct 13, 2015

"...finerenone might amplify the antiproteinuric effects of RAS inhibitors"

Demographic Characteristics of Patients Treated With Placebo or Finerenone, 1.25-20mg/d

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo (n = 94)</th>
<th>Finerenone, mg/d</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>1.25 (n = 96)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.5 (n = 92)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 (n = 100)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.5 (n = 97)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 (n = 98)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15 (n = 125)</td>
<td></td>
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<tr>
<td></td>
<td>20 (n = 119)</td>
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<table>
<thead>
<tr>
<th>UACR</th>
<th></th>
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<tbody>
<tr>
<td>Median (range), mg/g</td>
<td></td>
<td></td>
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<tr>
<td>182.9 (15.0-3056)</td>
<td>216.8 (14.1-2707)</td>
<td></td>
</tr>
<tr>
<td>158.9 (21.2-4020)</td>
<td>174.8 (27.9-2649)</td>
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<tr>
<td>166.4 (10.7-4948)</td>
<td>249.5 (30.4-3917)</td>
<td></td>
</tr>
<tr>
<td>210.1 (21.2-4144)</td>
<td>202.7 (4.4-2298)</td>
<td></td>
</tr>
<tr>
<td>Geometric mean (CV %), mg/g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>188.4 (169.8)</td>
<td>227.1 (162.6)</td>
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</tr>
<tr>
<td>196.1 (192.0)</td>
<td>191.2 (189.0)</td>
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</tr>
<tr>
<td>180.3 (190.1)</td>
<td>230.7 (171.0)</td>
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</tr>
<tr>
<td>204.7 (193.1)</td>
<td>204.1 (171.9)</td>
<td></td>
</tr>
<tr>
<td>Albuminuria, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (≥30–&lt;300 mg/d)</td>
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<td></td>
</tr>
<tr>
<td>58 (61.7)</td>
<td>54 (56.3)</td>
<td></td>
</tr>
<tr>
<td>62 (67.4)</td>
<td>64 (64.0)</td>
<td></td>
</tr>
<tr>
<td>63 (64.9)</td>
<td>56 (57.1)</td>
<td></td>
</tr>
<tr>
<td>74 (59.2)</td>
<td>66 (55.5)</td>
<td></td>
</tr>
<tr>
<td>Very high (≥300 mg/d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>34 (36.2)</td>
<td>38 (39.6)</td>
<td></td>
</tr>
<tr>
<td>28 (30.4)</td>
<td>34 (34.0)</td>
<td></td>
</tr>
<tr>
<td>31 (32.0)</td>
<td>42 (42.9)</td>
<td></td>
</tr>
<tr>
<td>46 (36.8)</td>
<td>48 (40.3)</td>
<td></td>
</tr>
<tr>
<td>Serum potassium, mean (SD), mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.3 (0.48)</td>
<td>4.32 (0.43)</td>
<td>4.30 (0.43)</td>
</tr>
<tr>
<td>4.31 (0.33)</td>
<td>4.3 (0.42)</td>
<td>4.3 (0.42)</td>
</tr>
<tr>
<td>4.3 (0.46)</td>
<td>4.3 (0.44)</td>
<td>4.3 (0.44)</td>
</tr>
<tr>
<td>eGFR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD), mL/min/1.73 m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>72.2 (20.4)</td>
<td>66.1 (21.9)</td>
<td>67.4 (20.2)</td>
</tr>
<tr>
<td>67.1 (22.2)</td>
<td>67.5 (21.9)</td>
<td>67.0 (20.9)</td>
</tr>
<tr>
<td>67.5 (23.6)</td>
<td>66.0 (22.2)</td>
<td></td>
</tr>
<tr>
<td>≤60 mL/min/1.73 m², No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26 (27.7)</td>
<td>41 (42.7)</td>
<td>35 (38.0)</td>
</tr>
<tr>
<td>41 (41.0)</td>
<td>39 (40.2)</td>
<td>44 (44.9)</td>
</tr>
<tr>
<td>50 (40.0)</td>
<td>52 (43.7)</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine, mean (SD), mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1 (0.3)</td>
<td>1.2 (0.4)</td>
<td>1.2 (0.4)</td>
</tr>
<tr>
<td>1.2 (0.4)</td>
<td>1.2 (0.4)</td>
<td>1.2 (0.4)</td>
</tr>
<tr>
<td>1.2 (0.3)</td>
<td>1.2 (0.4)</td>
<td>1.2 (0.4)</td>
</tr>
</tbody>
</table>

Serial eGFR and serum K levels

60% had eGFR >60 ml/min
2/3 on loop/thiazide
Modest BP reduction

The role of glycemic control
Glomerulocentric view:
Cellular mechanisms of diabetic glomerulosclerosis

Adapted from Masaon RM. J Am Soc Nephrol 2003
Diabetic substrates

Pathways / molecules
- NK-κB (↑)
- PKC (↑)
- ERK1/2 (↑)
- p38 (↑)
- CDK (↓)
- STAT-1 (↑)
- TLRs (↑)
- ROS (↑)
- Smad (↑)
- KKS (↑)

Downstream events promulgated
- Cell cycle arrest, cell hypertrophy and senescence
- Upregulated inflammatory chemokines/ cytokines
- Secretion of profibrotic cytokines and ECM proteins
- EMT (debatable)

Intensive glucose control improves kidney outcomes in patients with type 2 diabetes

Vlado Perkovic, Hiddo Lambers Heerspink, John Chalmers, Mark Woodward, Min Jun, Qiang Li, Stephen MacMahon, Mark E. Cooper, Pavel Hamet, Michel Marre, Carl Erik Mogensen, Neil Poulter, Giuseppe Mancia, Alan Cass, Anushka Patel, and Sophia Zoungas, for the ADVANCE Collaborative Group
Intensive glucose control improves kidney outcomes in patients with type 2 diabetes

Vlado Perkovic\textsuperscript{1}, Hiddo Lambers Heerspink\textsuperscript{2}, John Chalmers\textsuperscript{1}, Mark Woodward\textsuperscript{1,3}, Min Jun\textsuperscript{1}, Qiang Li\textsuperscript{1}, Stephen MacMahon\textsuperscript{1,4}, Mark E. Cooper\textsuperscript{5}, Pavel Hamet\textsuperscript{6}, Michel Marre\textsuperscript{7}, Carl Erik Mogensen\textsuperscript{8}, Neil Poulter\textsuperscript{9}, Giuseppe Mancia\textsuperscript{10}, Alan Cass\textsuperscript{1}, Anushka Patel\textsuperscript{1} and Sophia Zoungas\textsuperscript{1,11}, for the ADVANCE Collaborative Group

<table>
<thead>
<tr>
<th>Event</th>
<th>Number of events</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESRD</td>
<td>27</td>
<td>0.35</td>
<td>(0.15–0.83)</td>
<td>0.01</td>
</tr>
<tr>
<td>Renal death</td>
<td>37</td>
<td>0.85</td>
<td>(0.45–1.63)</td>
<td>0.63</td>
</tr>
<tr>
<td>ESRD or renal death</td>
<td>59</td>
<td>0.64</td>
<td>(0.38–1.08)</td>
<td>0.09</td>
</tr>
<tr>
<td>Sustained doubling &gt;200</td>
<td>84</td>
<td>0.83</td>
<td>(0.54–1.27)</td>
<td>0.38</td>
</tr>
<tr>
<td>Doubling to &gt;200</td>
<td>129</td>
<td>1.15</td>
<td>(0.82–1.63)</td>
<td>0.42</td>
</tr>
<tr>
<td>New macroalbuminuria</td>
<td>393</td>
<td>0.70</td>
<td>(0.57–0.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>New microalbuminuria</td>
<td>2752</td>
<td>0.91</td>
<td>(0.85–0.98)</td>
<td>0.01</td>
</tr>
</tbody>
</table>
ADVANCE: New or worsening nephropathy

**Hazard ratios**

<table>
<thead>
<tr>
<th>BP arm</th>
<th>Favours Per-Ind</th>
<th>Favours Placebo</th>
<th>Relative risk reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td></td>
<td></td>
<td>18% (-1 to 32)</td>
</tr>
<tr>
<td>Standard</td>
<td></td>
<td></td>
<td>18% (-7 to 37)</td>
</tr>
<tr>
<td>Intensive</td>
<td></td>
<td></td>
<td>17% (-12 to 38)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Glucose arm</th>
<th>Favours Intensive</th>
<th>Favours Standard</th>
<th>Relative risk reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td></td>
<td></td>
<td>19% (2 to 34)</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td>20% (-4 to 39)</td>
</tr>
<tr>
<td>Per-Ind</td>
<td></td>
<td></td>
<td>18% (-9 to 39)</td>
</tr>
</tbody>
</table>

**Annual event rate %**

- **Hazard ratio**: 0.5 1.0 2.0
- **Relative risk reduction (95% CI)**
  - Favouring Intensive
  - Favouring Placebo

*RRR 33%, P=0.005

*Perkovic, J Am Soc Nephrol. 2009*
Role of statin in diabetic patients with nephropathy
SHARP : CV events

Risk ratio 0.83 (0.74–0.94)
Logrank 2P=0.0022

Placebo
Eze/simv

SHARP- subgroup analyses

Statins in CKD - meta analysis
Risk of CV events by kidney function

Renal effects of atorvastatin and rosuvastatin in patients with diabetes who have progressive renal disease (PLANET I): a randomised clinical trial

Dick de Zeeuw, Deborah A Anzalone, Valerie A Cain, Michael D Cressman, Hiddo J Lambers Heerspink, Bruce A Molitoris, John T Monyak, Hans-Henrik Parving, Giuseppe Remuzzi, James R Sowers, Donald GVildt*
Albuminuria reduction in patients with diabetic kidney disease
Stages of nephropathy in diabetes

<table>
<thead>
<tr>
<th>Stage</th>
<th>Annual transition rate in T2DM</th>
<th>Annual risk of all-cause death in T2DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normoalbuminuria</td>
<td>2.0%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>2.8%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>2.3%</td>
<td>4.6%</td>
</tr>
<tr>
<td>S-creat. &gt;175 μmol/l or ESKD</td>
<td></td>
<td>19.2%</td>
</tr>
</tbody>
</table>

Adapted from: UKPDS 64. *Kidney Int* 2003; 63: 225-32
Activation of inflammatory and fibrogenic pathways in proximal tubular epithelial cells by ultrafiltered proteins
Activation of inflammatory and fibrogenic pathways in proximal tubular epithelial cells by ultrafiltered proteins

Inflammation and T cell recruitment
Accumulation of fibroblasts
Fibrosis

Reduction in albuminuric and protection from renal endpoint - RENAAL

De Zeeuw, Kidney Int, 2004
Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis

Meta-analysis of 1.2 M subjects from 21 studies

Lancet 2010; 375: 2073–81
Drug-Induced Reduction in Albuminuria Is Associated with Subsequent Renoprotection: A Meta-Analysis

Hiddo J. Lambers Heerspink, Tobias F. Kröpelin, Jarno Hoekman, and Dick de Zeeuw, on behalf of the Reducing Albuminuria as Surrogate Endpoint (REASSURE) Consortium

Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Medline and EMBASE 1950 – 2014
Mean FU > 1,000 patient-yrs
Reported ESRD outcomes with longitud UACR measured
21 trials with 78,342 pts and 4,183 ESRD events

for each 30% reduction in albuminuria, the risk of ESRD decreased by 23.7%
(95% confidence interval, 11.4% to 34.2%; P=0.001)
Outline

• The burden of diabetic kidney disease in Asia
• Landmark clinical trials on treatment and tribulations
• Recent clinical trials
  – Investigational
  – Novel
• Future perspectives
Full Review
Diabetic nephropathy: landmark clinical trials and tribulations
Gary C.W. Chan and Sydney C.W. Tang
Division of Nephrology, Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong

- Investigational
  - Antioxidants: NAC, Nex inhibitors etc
  - PKC inhibition: Ruboxistaurin
  - Antifibrotic therapies: Anti-TGF-β Ab
  - XO inhibitors: Allopurinol, febuxostat
  - Chemokine modulation: Anti-CCR2/5
  - Matrix metalloproteinase inhibition

- Novel
  - DPP-4 inhibitors
  - SGLT-2 inhibitors
  - Selective ET receptor antagonism
  - VDR activators
  - MRA

- Established
  - RAS blockade: ACEI, ARB
  - Blood pressure control
  - Glycemic regulation
The Chemokine and Cytokine storm in the diabetic kidney

1. Diabetic milieu
   hyperglycemia, AGE, hyperinsulinemia, hemodynamic alterations, ROS, Angiotensin II
2. Protein Overload
3. Glomerular ultra-filtrated growth factors

Tang SC, et al. NDT 2013
The effect of CCR2 inhibitor CCX140-B on residual albuminuria in patients with type 2 diabetes and nephropathy: a randomised trial

Dick deZeeuw, Pirow Bekker, Elena Henkel, Christopher Hasslacher, Joanna Gouni-Berthold, Heidrun Mehling, Antonia Potarca, Vladimir Tesar, Hiddo J Lamers Heerspink, Thomas J Schall, for the CCX140-B Diabetic Nephropathy Study Group*

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>Placebo (n=64)</th>
<th>5 mg CCX140-B (n=63)</th>
<th>10 mg CCX140-B (n=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine (μmol/L)*</td>
<td>111.4 (42.5)</td>
<td>112.3 (42.0)</td>
<td>117.6 (47.3)</td>
</tr>
<tr>
<td>eGFR (mL/min per 1.73 m²)</td>
<td>64.2 (26.1)</td>
<td>62.4 (24.2)</td>
<td>61.1 (25.1)</td>
</tr>
<tr>
<td>Uₘₐ₁ (mg/g)†</td>
<td>440 (351–550)</td>
<td>363 (287–460)</td>
<td>438 (345–557)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>41 (64%)</td>
<td>45 (71%)</td>
<td>36 (55%)</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>23 (36%)</td>
<td>18 (29%)</td>
<td>25 (39%)</td>
</tr>
<tr>
<td>ACE inhibitors plus angiotensin receptor blockers</td>
<td>0</td>
<td>0</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Insulin and insulin analogues</td>
<td>33 (52%)</td>
<td>23 (37%)</td>
<td>29 (45%)</td>
</tr>
<tr>
<td>Biguanides (metformin)</td>
<td>36 (56%)</td>
<td>40 (64%)</td>
<td>33 (51%)</td>
</tr>
<tr>
<td>Sulphonamides, urea derivatives</td>
<td>18 (28%)</td>
<td>21 (33%)</td>
<td>15 (23%)</td>
</tr>
</tbody>
</table>
Primary Endpoint

UACR changes from baseline during 52 weeks were
-2% for placebo (95% CI –11% to 9%),
-18% for 5 mg CCX140-B (–26% to –8%), and
-11% for 10 mg CCX140-B (–20% to –1%).
<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Least-squares mean (95% CI)</th>
<th>n</th>
<th>Least-squares mean (95% CI)</th>
<th>p value vs placebo</th>
<th>5 mg CCX140-B</th>
<th>n</th>
<th>Least-squares mean (95% CI)</th>
<th>p value vs placebo</th>
<th>10 mg CCX140-B</th>
<th>n</th>
<th>Least-squares mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td></td>
<td>-2.6 (-4.6 to -0.6)</td>
<td>57</td>
<td>-2.4 (-4.4 to -0.4)</td>
<td>0.88</td>
<td>58</td>
<td>-3.8 (-5.9 to -1.8)</td>
<td>0.39</td>
<td>52</td>
<td>-0.8 (-0.29 to 0.13)</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td></td>
<td>0.12 (-0.08 to 0.33)</td>
<td>58</td>
<td>0.16 (-0.05 to 0.36)</td>
<td>0.58</td>
<td>57</td>
<td>0.08 (-0.13 to 0.39)</td>
<td>0.08</td>
<td>52</td>
<td>-0.8 (-0.29 to 0.13)</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)</td>
<td></td>
<td>-0.38 (-0.36 to 1.11)</td>
<td>58</td>
<td>-0.74 (-1.49 to 0.01)</td>
<td>0.01</td>
<td>56</td>
<td>-0.37 (-1.13 to 0.39)</td>
<td>0.08</td>
<td>52</td>
<td>-0.37 (-1.13 to 0.39)</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Fasting plasma insulin (pmol/L)</td>
<td></td>
<td>-48.9 (-106.6 to 8.8)</td>
<td>58</td>
<td>-14.5 (-73.0 to 44.1)</td>
<td>0.40</td>
<td>56</td>
<td>-1.20 (-5.77 to 3.38)</td>
<td>0.61</td>
<td>52</td>
<td>-1.20 (-5.77 to 3.38)</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>HOMA-IR</td>
<td></td>
<td>-2.24 (-6.59 to 2.31)</td>
<td>58</td>
<td>-1.37 (-5.88 to 3.14)</td>
<td>0.59</td>
<td>56</td>
<td>-1.37 (-5.88 to 3.14)</td>
<td>0.59</td>
<td>52</td>
<td>-1.37 (-5.88 to 3.14)</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td>Phosphorus (mmol/L)</td>
<td></td>
<td>0.06 (0.03 to 0.10)</td>
<td>57</td>
<td>0.03 (-0.01 to 0.07)</td>
<td>0.20</td>
<td>58</td>
<td>0.03 (-0.01 to 0.07)</td>
<td>0.20</td>
<td>52</td>
<td>0.03 (-0.01 to 0.07)</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Blood urea nitrogen (mmol/L)</td>
<td></td>
<td>0.34 (-0.27 to 0.96)</td>
<td>57</td>
<td>0.49 (-0.13 to 1.11)</td>
<td>0.74</td>
<td>58</td>
<td>0.49 (-0.13 to 1.11)</td>
<td>0.74</td>
<td>52</td>
<td>0.49 (-0.13 to 1.11)</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>Plasma MCP-1 (pg/mL)</td>
<td></td>
<td>423 (4.4 to 80.3)</td>
<td>58</td>
<td>697 (32.1 to 107.3)</td>
<td>0.31</td>
<td>58</td>
<td>697 (32.1 to 107.3)</td>
<td>0.31</td>
<td>52</td>
<td>697 (32.1 to 107.3)</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>Urine MCP-1 to creatinine ratio (%)</td>
<td></td>
<td>26 (3 to 55)</td>
<td>57</td>
<td>46 (19 to 79)</td>
<td>0.84</td>
<td>57</td>
<td>46 (19 to 79)</td>
<td>0.84</td>
<td>47</td>
<td>29 (3 to 61)</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>Plasma CCX140 at week 52 (ng/mL), mean (SD)</td>
<td>57</td>
<td>1265 (379)</td>
<td>NA</td>
<td>57</td>
<td>1265 (379)</td>
<td>NA</td>
<td>55</td>
<td>2299 (1057)</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
UACR is reduced by 36% and 44% in the 0.75 mg and 1.25 mg groups compared to a 2% increase in the placebo group.
Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): a randomised controlled trial

Dick de Zeeuw, Rajiv Agarwal, Michael Amdahl, Paul Audhya, Daniel Coyne, Tushar Garimella, Hans-Henrik Parving, Yili Pritchett, Giuseppe Remuzzi, Eberhard Ritz, Dennis Andress

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=93)</th>
<th>1 µg paricalcitol (n=93)</th>
<th>2 µg paricalcitol (n=95)</th>
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</thead>
<tbody>
<tr>
<td><strong>Urinary albumin-to-creatinine ratio (mg/mmol)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>94 (81)</td>
<td>101 (94)</td>
<td>92 (86)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>73 (30-128)</td>
<td>71 (33-139)</td>
<td>68 (28-133)</td>
</tr>
<tr>
<td><strong>Serum creatinine (µmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>180 (79)</td>
<td>172 (56)</td>
<td>170 (63)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>39 (17)</td>
<td>40 (15)</td>
<td>42 (18)</td>
</tr>
<tr>
<td><strong>eGFR (mL/min per 1.73 m²)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>39 (17)</td>
<td>40 (15)</td>
<td>42 (18)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>38 (25-50)</td>
<td>37 (27-52)</td>
<td>37 (28-55)</td>
</tr>
</tbody>
</table>
Change in UACR and eGFR

Change in UACR from baseline to the last measurement during treatment
Renal glucose handling in humans

In “normal” individuals:
- Approximately **900mmol (180g)** of glucose is filtered by the kidneys daily.¹
- In animal models,
  - ~90% reabsorbed in the S1 and S2 segments of the proximal tubule via SGLT2.²
  - Remainder reclaimed in the S3 segment¹,³
- Minimal glucose is excreted by the kidney
- **In hyperglycaemic individuals:** glucose reabsorption by the kidney effectively doubles

---

Renal glucose handling in humans

Investigational
- Antioxidants (NAC, lipoenolamine, etc)
- T2D inhibitors (Rouvièrein)
- Anti-insulin therapies (Anti-DOR-A Abs)
- K+ inhibitors (Alogliptin, Trazacostin)
- Oxidative stress (Anti-COR2/5)
- Metalloproteinase inhibition

Novel
- SGLT-2 inhibitors
- Anti-premature aging
- Selective ET receptor antagonists
- MRA antagonists
- NHE

Established
- DPP-4 inhibitors
- ACE inhibitors
- Blood pressure control
- Glycemic regulation

Graph:
- Rate of glucose filtration / reabsorption / excretion (mg/min)
- Plasma glucose (mg/dL)
- Tm
- Filtered
- Excreted
- Reabsorbed
- Threshold

Renal glucose handling in humans
Enhanced renal tubular glucose reabsorption contributes to hyperglycaemia in T2DM

- Hyperglycaemia results in increased glucose filtered at the glomerulus and glucose reabsorption operates at the transport maximum (i.e. if normal glucose is 5 mM/L glucose and Tm is 10 mM/L glucose then twice the amount of glucose is reabsorbed if BSL is 10 mM/L or above)

- SGLT2 and GLUT transporter numbers are increased, thus Tm is increased
Enhanced renal tubular glucose reabsorption contributes to hyperfiltration in diabetes

- Reduced Na+ delivery to the distal nephron
- Leading to activation of the macula densa within the JG apparatus to adjust the tone of the afferent glomerular arterioles to increase glomerular filtration (tubuloglomerular feedback mechanism)
- Hyperfiltration in the early stages of diabetic nephropathy delivers more glucose to the tubule and hence more ‘available’ to be reabsorbed

Renal corpuscle: The structure on the left in blue and pink is the renal corpuscle. The structure on the right is the renal tubule. The blue structure (A) is the Bowman's capsule (2 and 3). The pink structure is the glomerulus with its capillaries. At the left, blood flows from the afferent arteriole (9), through the capillaries (10), and out the efferent arteriole (11). The mesangium is the pink structure inside the glomerulus between the capillaries (5a) and extending outside the glomerulus (5b). Macula densa is #7.

Pathophysiology of type 2 diabetes: deterioration over 20 years

Onset of diabetes

Primary prevention
Secondary prevention
Tertiary prevention

GFR

Hyperfiltration
Onset nephropathy

Glomerulomegaly
Renal hypertrophy

ESRD

Urine protein excretion (g/24 h)

Years after diabetes onset

0 5 10 15 20 25 30

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

This article was published on September 17, 2015, at NEJM.org.
Key inclusion and exclusion criteria

• Key inclusion criteria
  – Adults with type 2 diabetes
  – BMI ≤45 kg/m²
  – HbA1c 7–10%*
  – Established cardiovascular disease
    • Prior myocardial infarction, coronary artery disease, stroke, unstable angina or occlusive peripheral arterial disease

• Key exclusion criteria
  – eGFR <30 mL/min/1.73m² (MDRD)
### Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=2333)</th>
<th>Empagliflozin 10 mg (n=2345)</th>
<th>Empagliflozin 25 mg (n=2342)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1c, %</strong></td>
<td>8.08 (0.84)</td>
<td>8.07 (0.86)</td>
<td>8.06 (0.84)</td>
</tr>
<tr>
<td><strong>Time since diagnosis of type 2 diabetes, years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>423 (18.1)</td>
<td>406 (17.3)</td>
<td>434 (18.6)</td>
</tr>
<tr>
<td>&gt;5 to 10</td>
<td>571 (24.5)</td>
<td>585 (24.9)</td>
<td>590 (25.2)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>1339 (57.4)</td>
<td>1354 (57.7)</td>
<td>1318 (56.3)</td>
</tr>
<tr>
<td><strong>LDL cholesterol, mg/dL</strong></td>
<td>84.9 (35.3)</td>
<td>86.3 (36.7)</td>
<td>85.5 (35.2)</td>
</tr>
<tr>
<td><strong>eGFR, mL/min/1.73m² (MDRD)</strong></td>
<td>73.8 (21.1)</td>
<td>74.3 (21.8)</td>
<td>74.0 (21.4)</td>
</tr>
<tr>
<td>≥90 mL/min/1.73m²</td>
<td>488 (20.9%)</td>
<td>519 (22.1%)</td>
<td>531 (22.7%)</td>
</tr>
<tr>
<td>60 to &lt;90 mL/min/1.73m²</td>
<td>1238 (53.1%)</td>
<td>1221 (52.1%)</td>
<td>1204 (51.4%)</td>
</tr>
<tr>
<td>&lt;60 mL/min/1.73m²</td>
<td>607 (26.0%)</td>
<td>605 (25.8%)</td>
<td>607 (25.9%)</td>
</tr>
</tbody>
</table>

Data are n (%) or mean (SD) in patients treated with ≥1 dose of study drug.
HbA1c

Placebo
Empagliflozin 10 mg
Empagliflozin 25 mg

Adjusted mean (SE) HbA1c (%)

Week

Placebo: 2294 2272 2188 2133 2113 2063 2008 1967 1741 1456 1241 1109 962 705 420 151
Empagliflozin 10 mg: 2296 2272 2218 2150 2155 2108 2072 2058 1805 1520 1297 1164 1006 749 488 170
Empagliflozin 25 mg: 2296 2280 2212 2152 2150 2115 2080 2044 1842 1540 1327 1190 1043 795 498 195
Weight

Adjusted mean (SE) weight (kg)

<table>
<thead>
<tr>
<th>Week</th>
<th>Placebo</th>
<th>Empagliflozin 10 mg</th>
<th>Empagliflozin 25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2285</td>
<td>2290</td>
<td>2283</td>
</tr>
<tr>
<td>12</td>
<td>1915</td>
<td>1913</td>
<td>1891</td>
</tr>
<tr>
<td>28</td>
<td>1893</td>
<td>1894</td>
<td>1891</td>
</tr>
<tr>
<td>52</td>
<td>1891</td>
<td>1894</td>
<td>1891</td>
</tr>
<tr>
<td>108</td>
<td>1891</td>
<td>1894</td>
<td>1891</td>
</tr>
<tr>
<td>164</td>
<td>1891</td>
<td>1894</td>
<td>1891</td>
</tr>
<tr>
<td>220</td>
<td>1891</td>
<td>1894</td>
<td>1891</td>
</tr>
</tbody>
</table>
3-point MACE

Empagliflozin 10 mg
HR 0.85
(95% CI 0.72, 1.01)
p=0.0668

Empagliflozin 25 mg
HR 0.86
(95% CI 0.73, 1.02)
p=0.0865

Cumulative incidence function. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio
CV death

Cumulative incidence function. HR, hazard ratio
Hospitalisation for heart failure

HR 0.65
(95% CI 0.50, 0.85)
p = 0.0017

Cumulative incidence function. HR, hazard ratio.
All-cause mortality

HR 0.68  
(95% CI 0.57, 0.82)  
p<0.0001  

Kaplan-Meier estimate. HR, hazard ratio
## Adverse events consistent with genital infection

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=2333)</th>
<th>Empagliflozin 10 mg (n=2345)</th>
<th>Empagliflozin 25 mg (n=2342)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Rate</td>
<td>n (%)</td>
</tr>
<tr>
<td>Events consistent with genital infection</td>
<td>42 (1.8%)</td>
<td>0.73</td>
<td>153 (6.5%)</td>
</tr>
<tr>
<td>Serious events</td>
<td>3 (0.1%)</td>
<td>0.05</td>
<td>5 (0.2%)</td>
</tr>
<tr>
<td>Events leading to discontinuation</td>
<td>2 (0.1%)</td>
<td>0.03</td>
<td>19 (0.8%)</td>
</tr>
<tr>
<td>By sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>25 (1.5%)</td>
<td>0.60</td>
<td>89 (5.4%)</td>
</tr>
<tr>
<td>Female</td>
<td>17 (2.6%)</td>
<td>1.09</td>
<td>64 (9.2%)</td>
</tr>
</tbody>
</table>

Rate = per100 patient-years
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*

This article was published on June 14, 2016, at NEJM.org.
eGFR over time

• Empa (10 or 25 mg daily) dropped eGFR by around 4 ml/min (from 74 to 70 – 71) over the initial 4 weeks, which became stable over the 4-year treatment period.

• The placebo group pursued a steady decline in eGFR from 74 to 67 ml/min at the end of the trial.
A Incident or Worsening Nephropathy

Hazard ratio, 0.61 (95% CI, 0.53–0.70)
P<0.001

No. at Risk
Empagliflozin: 4124, 3994, 3848, 3669, 3171, 2279, 1887, 1219, 290
Placebo: 2061, 1946, 1836, 1703, 1433, 1016, 833, 521, 106
Doubling of sCr, initiation of RRT or death from renal disease

**B Post Hoc Renal Composite Outcome**

- Cumulative Probability of Event (%)

  - Hazard ratio, 0.54 (95% CI, 0.40–0.75)
  - P < 0.001

- No. at Risk
  - Empagliflozin: 4645, 4500, 4377, 4241, 3729, 2715, 2280, 1496, 360
  - Placebo: 2323, 2229, 2146, 2047, 1771, 1289, 1079, 680, 144

- Month

- Graph showing cumulative probability over time with Kaplan-Meier curves for Empagliflozin and Placebo groups.
<table>
<thead>
<tr>
<th>Event</th>
<th>N with event Empa</th>
<th>N with event Placebo</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>New onset or worsening of nephropathy</td>
<td>525/4124</td>
<td>388/2061</td>
<td>0.61</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>New onset albuminuria</td>
<td>459/4091</td>
<td>330/2033</td>
<td>0.62</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2x sCr</td>
<td>70/4645</td>
<td>60/2323</td>
<td>0.56</td>
<td>0.0009</td>
</tr>
<tr>
<td>RRT</td>
<td>13/4687</td>
<td>14/2333</td>
<td>0.45</td>
<td>0.0409</td>
</tr>
</tbody>
</table>

• From March 2013, when canagliflozin was approved, to October 2015, FDA received reports of 101 confirmable cases of AKI, some requiring hospitalization/dialysis, with canagliflozin or dapagliflozin use.

• In half of the cases, AKI occurred within 1 month of starting the drug, and most patients improved after stopping it.

• Some cases occurred in patients who were younger than 65 years. Some patients were dehydrated, had low BP, or were taking other medicines that can affect the kidneys.

http://www.fda.gov/Drugs/DrugSafety/ucm505860.htm
Recommendations from FDA

- Consider factors that may predispose patients to AKI prior to starting SGLT2i, e.g. decreased blood volume; CKD; CHF; and taking other medications such as diuretics, ACE, ARBs, and NSAIDs.
- Assess kidney function prior to starting SGLT2i and monitor periodically thereafter.
- If AKI occurs, promptly discontinue the drug and treat the kidney impairment.
Evidence based treatments in people with diabetic nephropathy

1. Risk factor modification / Patient education
2. RAS blockade
   - ARB or ACEI
   - DRI: no evidence
   - MRA: possibly the newer compounds
3. BP lowering
4. Glycaemic control
5. Lipid lowering
6. Novel approaches for albuminuria reduction
   - ET antagonist: short term: ↓ albuminuria; 4-year trial ongoing
   - CCR2 inhibition: initial data encouraging
   - VDR activator: cost
7. SGLT2 inhibition: ↓ CV events; ? renoprotective