Dapagliflozin in renal impairment: Association of British Clinical Diabetologists (ABCD) Nationwide Dapagliflozin Audit

M Yadagiri, S Bain, T Robinson, JP Wilding, T Pang, B Mcgowan, P Winocour, V Oguntolu, J Clarke, H Partridge, IW Gallen, K Adamson, REJ Ryder

On behalf of the ABCD nationwide dapagliflozin audit contributors

ADA, San Diego
11, June, 2017
Disclosures

- Dr Bob Ryder has received speaker fees, consultancy fees and/or educational sponsorships from AstraZeneca, GI Dynamics, Janssen, Novo Nordisk, Sanofi-Aventis and Takeda
PHOTOGRAPHY PROHIBITED

Please do not take photos during this presentation
ABCD nationwide audits

• Assess safety and efficacy of new diabetes therapies as they come into real clinical use from phase 3 clinical trials
• Secure on-line
• Anonymised
ABCD nationwide exenatide and liraglutide audits

- Real-life data
  - >13000 patients from
  - >150 centres
  - >500 contributors

- There have been (by 2015)
  - 12 published papers
  - 23 abstracts
  - 13 oral presentations

http://www.diabetologists-abcd.org.uk/GLP1_Audits/PresentationsPostersAbstractsExenatide.htm
http://www.diabetologists-abcd.org.uk/GLP1_Audits/PresentationsPostersAbstractsLiraglutide.htm
SGLT2 inhibitors – a chance to learn in the same way about a new class

- Canagliflozin
- Dapagliflozin
- Empagliflozin

ABCD nationwide dapagliflozin audit

• Launched October 2014
• Findings so far .....
## Year 1 Audit Overview – October 2015

<table>
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<tbody>
<tr>
<td>Centres</td>
<td>44</td>
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<tr>
<td>Contributors</td>
<td>129</td>
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<tr>
<td>Number of Patients</td>
<td>943</td>
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<tr>
<td>Age (years)</td>
<td>56.7±10.4</td>
</tr>
<tr>
<td>Sex [Males(%)]</td>
<td>55.9%</td>
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<tr>
<td>Duration of diabetes (years)*</td>
<td>11.4 (6–16)</td>
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<tr>
<td>Baseline HbA₁₅ (mmol/mol)</td>
<td>80.2±16.1</td>
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<tr>
<td>Baseline HbA₁₅(%)</td>
<td>9.5±1.5</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>37.0±13.3</td>
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<tr>
<td>Baseline weight (kg)</td>
<td>103.3±22.7</td>
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<tr>
<td>Duration of follow up (months)*</td>
<td>6.4 (0–12.3)</td>
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vs Combined Clinical Trials – Dapagliflozin

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<tr>
<td></td>
<td>8.0</td>
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<td>32.2</td>
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</table>

* Reported as mean±SD or median (IQR)*

Data presented at ABCD autumn meeting, November 2015
Reductions in HbA\textsubscript{1c}: RCT data vs. ABCD audit

Adjusted mean change from baseline HbA\textsubscript{1c} (%) at 24 weeks

- Monotherapy\textsuperscript{1} -0.89\textsuperscript{*}
- Add-on to metformin\textsuperscript{2} -0.84\textsuperscript{*}
- Add-on to an SU\textsuperscript{3} -0.82\textsuperscript{*}
- Add-on to metformin + an SU\textsuperscript{4} -0.86\textsuperscript{*}
- Add-on to a DPP-4 inhibitor ± metformin\textsuperscript{5} -0.5\textsuperscript{*}
- Add-on to insulin ± OADs\textsuperscript{6} -0.96\textsuperscript{*}

AbCD Audit -0.89\textsuperscript{*}

Baseline HbA\textsubscript{1c} 8.01\% 7.92\% 8.07\% 8.08\% 7.9\% 8.57\% 9.5\%


Data presented at AbCD autumn meeting, November 2015
**Weight loss: RCT data vs. ABCD audit**

<table>
<thead>
<tr>
<th>Monotherapy(^1)</th>
<th>Add-on to metformin(^2)</th>
<th>Add-on to an SU(^3)</th>
<th>Add-on to metformin + an SU(^4)</th>
<th>Add-on to a DPP-4 inhibitor ± metformin(^5)</th>
<th>Add-on to insulin ± OADs(^6)</th>
<th>ABCD Audit</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>(-2.7^*)</td>
</tr>
<tr>
<td>Baseline weight (kg)</td>
<td>94.2</td>
<td>86.3</td>
<td>80.6</td>
<td>88.6</td>
<td>91.0</td>
<td>94.5</td>
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Data presented at ABCD autumn meeting, November 2015
ALT response to dapagliflozin

Data presented at DUK annual professional conference, Glasgow, March 2016
Dapagliflozin – improvements sustained

Data presented at ADA meeting, New Orleans, June 2016
Figure 1: Change in HbA1c stratified by background diabetes therapy

Data are adjusted mean and estimated difference (ED) were analysed by ANCOVA with baseline HbA1c and eGFR as covariates. DD; diabetes drugs

Data presented at ADA meeting, New Orleans, June 2016
ABCD dapagliflozin audit

Data presented at ADA meeting, New Orleans, June 2016

ABCD liraglutide audit

Effect of dapagliflozin on HbA1c and weight after its addition to various combinations of other diabetes medications: ABCD nationwide dapagliflozin audit*

EASD 2016 Poster Presentation: M. Yadagiri, P. Sen Gupta, R.E.J. Ryder et al on behalf of all ABCD nationwide dapagliflozin audit contributors
Dapagliflozin in Renal Impairment – FDA

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FARXIGA safely and effectively. See full prescribing information for FARXIGA.

FARXIGA (dapagliflozin) tablets, for oral use
Initial U.S. Approval: 2014

----------INDICATIONS AND USAGE------------------
FARXIGA is a sodium-glucose cotransporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)

Limitation of use:
• Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis. (1.1)

----------DOSAGE AND ADMINISTRATION-----------------
• The recommended starting dose is 5 mg once daily, taken in the morning, with or without food. (2.1)
• Dose can be increased to 10 mg once daily in patients tolerating FARXIGA who require additional glycemic control. (2.1)
• Assess renal function before initiating FARXIGA. Do not initiate FARXIGA if eGFR is below 60 mL/min/1.73 m². (2.2)
• Discontinue FARXIGA if eGFR falls persistently below 60 mL/min/1.73 m². (2.2)

• Hypoglycemia: In patients taking insulin or an insulin secretagogue with FARXIGA, consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia. (5.3)
• Genital mycotic infections: Monitor and treat if indicated. (5.4)
• Increased LDL-C: Monitor and treat per standard of care. (5.5)
• Bladder Cancer: An imbalance in bladder cancers was observed in clinical trials. FARXIGA should not be used in patients with active bladder cancer and should be used with caution in patients with a prior history of bladder cancer. (5.6)
• Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with FARXIGA or any other antidiabetic drug. (5.7)

----------ADVERSE REACTIONS-----------------
• The most common adverse reactions associated with FARXIGA (5% or greater incidence) were female genital mycotic infections, nasopharyngitis, and urinary tract infections. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS-----------------
• Pregnancy: There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)

https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202293s003lbl.pdf
2.2 Patients with Renal Impairment

Assessment of renal function is recommended prior to initiation of FARXIGA therapy and periodically thereafter.

FARXIGA should not be initiated in patients with an eGFR less than 60 mL/min/1.73 m².

No dose adjustment is needed in patients with mild renal impairment (eGFR of 60 mL/min/1.73 m² or greater).

FARXIGA should be discontinued when eGFR is persistently less than 60 mL/min/1.73 m² [see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)].

https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202293s003lbl.pdf
Aims

- To evaluate the efficacy of dapagliflozin real clinical use in
  - mild renal impairment (eGFR 60-90 ml/min)
  - moderate renal impairment (eGFR 30-59 ml/min)
In view of FDA guidance, how is it possible to get data on dapagliflozin in patients with eGRF 30-59?

- Because clinician’s, at least in the UK, do not necessarily prescribe according to medication license .....
The ABCD audit

• Collected anonymised data of real patients treated with dapagliflozin in the UK
  – patient age, gender, diabetes duration, ethnicity
  – diabetes medications;
  – HbA1c, weight, eGFR
  – lipids;
  – blood pressure;
  – adverse events and dapagliflozin discontinuation
ABCD nationwide dapagliflozin audit

<table>
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<th>Data Input</th>
<th>Oct 2014 – Jan 2017</th>
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<td>Centres</td>
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<td>Contributors</td>
<td>156</td>
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<td>Number of patients</td>
<td>2027</td>
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Methods

• Data from ABCD Dapagliflozin Audit (2014-2017)
• Selection criteria:

Baseline HbA1c and eGFR + Follow up HbA1c

4.3 (3.0-7.0) months

• Patients categorised into 3 groups depending on baseline eGFR:
  • Group 1: eGFR > 90 ml/min
  • Group 2: eGFR 60-90 ml/min
  • Group 3: eGFR 30-59 ml/min
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>57.2±10.0</td>
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<tr>
<td>Duration of Diabetes (years)*</td>
<td>7.0 (1.9-13.0)</td>
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<tr>
<td>Sex [Males (%)]</td>
<td>58.4</td>
</tr>
<tr>
<td>Baseline ALT (U/l)</td>
<td>40.1±21.5</td>
</tr>
<tr>
<td>Baseline HbA1c (mmol)</td>
<td>80.4±15.3</td>
</tr>
<tr>
<td>Baseline HbA1c (%)</td>
<td>9.5±1.5</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>35.8±7.4</td>
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<tr>
<td>Weight (Kg)</td>
<td>102.6±22.3</td>
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Reported as (Mean±SD) or Median(IQR)*

Vs Combined Clinical Trials - Dapagliflozin

8.0

32.2
### Audit Characteristics (n=880)

<table>
<thead>
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<tr>
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Vs Combined Clinical Trials - Dapagliflozin

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</table>
## Baseline Characteristics

<table>
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<tr>
<th>N (%)</th>
<th>Gr 1 (&gt;90ml/min) n= 185 (21%)</th>
<th>Gr 2 (60-90ml/min) n= 651 (74%)</th>
<th>Gr 3 (30-59ml/min) n=43 (5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males(%)</td>
<td>58.7</td>
<td>59.0</td>
<td>65.1</td>
</tr>
<tr>
<td>Age(yrs)♦</td>
<td>52.4±10.2</td>
<td>58.3±9.4</td>
<td>64.4±9.6</td>
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<tr>
<td>T2DM duration(years)*</td>
<td>11.0(7.0-15.0)</td>
<td>8.2(3.9-12.3)</td>
<td>15.0(11.0-20.0)</td>
</tr>
<tr>
<td>HbA1c(mmol)♦</td>
<td>82.6±16.2</td>
<td>80.3±17.5</td>
<td>78.1±16.0</td>
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<tr>
<td>HbA1c(%)♦</td>
<td>9.7±1.4</td>
<td>9.5±1.5</td>
<td>9.3±1.4</td>
</tr>
<tr>
<td>Weight(Kg)♦</td>
<td>106.8±22.1</td>
<td>101.2±22.4</td>
<td>105.9±18.3</td>
</tr>
<tr>
<td>BMI(Kg/m²)♦</td>
<td>37.2±7.8</td>
<td>35.3±7.3</td>
<td>37.1±6.1</td>
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<tr>
<td>ALT(U/l)♦</td>
<td>33.7±18.1</td>
<td>42.9±22.4</td>
<td>30.3±13.6</td>
</tr>
<tr>
<td>SBP(mm Hg)♦</td>
<td>136.4±16.9</td>
<td>135.0±15.6</td>
<td>137.6±17.6</td>
</tr>
</tbody>
</table>

Reported as (Mean±SD)♦ or Median(IQR)*
Results – HbA1c (%)

-1.1±1.1, p<0.001

-0.9±1.4, p<0.001

-0.2±1.8, p=0.510

Grp1 (eGFR >90) n=185
Grp2 (eGFR 60-90) n=651
Grp3 (eGFR 30-59) n=43
Results - Weight

- **Grp1 (eGFR > 90)**
  - Weight: -3.2 ± 5.2, p < 0.001
  - n = 183

- **Grp2 (eGFR 60-90)**
  - Weight: -2.1 ± 4.8, p < 0.001
  - n = 653

- **Grp3 (eGFR 30-59)**
  - Weight: -3.5 ± 7.7, p = 0.003
  - n = 47
Results - BMI

BMI (Kg/m²)

-1.1±1.7, p<0.001

-1.2±2.7, p=0.004

-0.8±1.8, p<0.001

Grp1 (eGFR>90) n=181
Grp2 (eGFR 60-90) n=529
Grp3 (eGFR 30-59) n=44
Results – Systolic BP

- Grp1 (eGFR > 90)
  - n=169
  - Systolic Blood Pressure: 130±3.8 mmHg, p=0.003

- Grp2 (eGFR 60-90)
  - n=629
  - Systolic Blood Pressure: 130±2.8 mmHg, p<0.001

- Grp3 (eGFR 30-59)
  - n=45
  - Systolic Blood Pressure: 130±3.3 mmHg, p=0.231
Results - Alanine Aminotransferase

ALT (U/l) - Alanine Aminotransferase

- Grp1 (eGFR > 90) n=87: -4.7 ± 13.8, p=0.002
- Grp2 (eGFR 60-90) n=259: -6.6 ± 15.6, p<0.001
- Grp3 (eGFR 30-59) n=26: -4.0 ± 8.0, p=0.018
Conclusion

• Dapagliflozin reduces HbA1c, weight, BMI, systolic BP and ALT by statistically and clinically significant amounts in normal and mild renal impairment

• In moderate renal impairment, there is a reduction in weight and ALT but has no significant impact on HbA1c or systolic BP
ABCD nationwide dapagliflozin audit contributors
The following are those whom we know about.


England

Scotland

Wales

Northern Ireland
Belfast (Belfast): Johnston PC, Nugent A. Northern Trust (Antrim Area Hospital): Kennedy A, Strzelecka A.

Acknowledgment
The ABCD nationwide dapagliflozin audit is an independent audit supported by an unrestricted grant from Astra Zeneca
Somewhat similar results from a clinical trial

Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control

Donald E. Kohan, Paola Fioretto, Weihua Tang and James F. List

In patients with diabetes, glycemic improvement by sodium-glucose cotransporter-2 inhibition depends on the kidney's ability to filter glucose. Dapagliflozin, a sodium-glucose cotransporter-2 inhibitor, reduces hyperglycemia in patients with diabetes and normal or mildly impaired renal function. In this randomized, double-blind, placebo-controlled study we assessed daily treatment with dapagliflozin in 252 patients with inadequately controlled type 2 diabetes and moderate renal impairment. The primary endpoint, the mean change in HbA1c, was not statistically different from placebo after 24 weeks (−0.41% and −0.44% for 5- and 10-mg doses, respectively, and −0.32% for placebo). The mean change from baseline was −1.54 and −1.80% for

Current medications for treating type 2 diabetes mellitus (T2DM) target the pancreas, liver, intestines, muscle, or adipose tissue and act by increasing insulin secretion or action, or by improving insulin sensitivity. The sodium-glucose cotransporter-2 (SGLT2), located in the renal proximal tubule, reabsorbs the majority of filtered glucose. Inhibition of renal glucose reabsorption via inhibition of SGLT2, an insulin-independent process, represents a novel approach to treating T2DM.

Several clinical trials with dapagliflozin, a potent and selective SGLT2 inhibitor, showed that it reduces hyperglycemia and improves glycemic control in patients with T2DM. These trials examined dapagliflozin as monotherapy or in combination therapy.