Real-world cross-comparison of metabolic outcomes with different sodium-glucose co-transporter 2 inhibitors agents in adults with type 2 diabetes: results from the Association of British Clinical Diabetologists audit programme

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Abstract
Sodium-glucose co-transporter-2 inhibitors (SGLT2i) have demonstrated significant efficacy in improving cardiorenal and metabolic outcomes. However, whether there are differences between agents remain unclear. We therefore assessed changes in haemoglobin A1c (HbA1c), weight, body mass index (BMI) and systolic blood pressure (SBP) across the class; and between agents.

Methods: Individuals using empagliflozin (E), canagliflozin (C) or dapagliflozin (D) in the ABCD audits were included provided that data were available for the outcomes of interest. Multivariate linear regression analysis was used to assess adjusted change in HbA1c, weight, BMI and SBP and to compare outcomes between drugs. Analyses were performed in Stata 17.

Results: 21,263 individuals (E=11,231; C=2,257; D=7,775) with mean ±SD age 60.0±10.4 years, HbA1c 75.3±17.2 mmol/mol, BMI 33.9±7.1kg/m² and 61.2% female were included. Over median follow-up of 1.7 years, HbA1c reduced by 10.0 mmol/mol (95% CI 9.8-10.2; p<0.001); weight reduced by 3.2 kg (95% CI 2.2-4.1; p<0.001); BMI reduced by 1.1 kg/m² (95% CI 0.8-1.5; p<0.001) and SBP reduced by 0.9 mmHg (95% CI 0.7-1.1; p<0.001). Empagliflozin was associated with larger HbA1c reduction than dapagliflozin and canagliflozin (-10.6 mmol/mol [E] vs -9.8 mmol/mol [C] vs -9.1 mmol/mol [D]; p<0.001 for both). Canagliflozin was associated with statistically larger SBP reductions compared to dapagliflozin (-1.6 mmHg [C] vs 0.6 mmHg [D]). No differences were noted in weight and BMI change between drugs. Discontinuation of SGLT2i therapy was rare, only occurring in 0.35% (75/21,338).

Our cohort has individuals with higher baseline weight and HbA1c compared to published trial data and may be more generalisable to a UK population.

Conclusion: SGLT2i are very well tolerated and are associated with improvements in multiple metabolic and clinical parameters in UK real-world practice. Relatively small differences were observed between agents for HbA1c and SBP reduction, but not for weight reduction. Further work should focus on establishing the association between individual SGLT2i agents and hard cardiorenal end points in the real world.

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Key words: SGLT2, real-world, HbA1c, weight, blood pressure

Introduction
Sodium-glucose co-transporter-2 inhibitors (SGLT2i) have been in use in UK practice for close to 10 years, with different SGLT2i agents being utilised in clinical practice according to local formulary and clinical guidelines. While meta-analysis of randomised controlled trials highlights significant
haemoglobin A1c (HbA1c) and weight reductions across the class, as well as reductions in systolic blood pressure (SBP),
differences in efficacy between agents have also been reported: canagliflozin, for example, has been associated with
larger HbA1c reductions. The relative efficacy of individual SGLT2i agents therefore remains unclear. Nonetheless, notable
improvements in multiple metabolic outcomes, as well as other mechanisms of action, mean that the SGLT2 class has
proven efficacy in placebo-controlled trials in reducing the risk of long-term cardiovascular (CV) and renal morbidity and
reducing all-cause mortality. Further research has promoted the use of these drugs in people without diabetes for
management of proteinuric and non-proteinuric chronic kidney disease as well as in heart failure with preserved or reduced
ejection fraction.

The National Institute for Health and Care Excellence (NICE) recognises the strong evidence to support the use of SGLT2i
and recommends their use earlier in pathways, especially for individuals with established CV disease, with high 10-year risk
of CV events or with multiple risk factors.

Although randomised controlled trials provide the gold standard for clinical evidence, evidence from the real world is vital
to understand how these findings translate into clinical practice, where individuals may have more broad baseline
characteristics and be less closely monitored. The Association of British Clinical Diabetologists (ABCD) audit programmes of
SGLT2i started in 2014 and have been providing real-world insights into their use ever since. We have previously reported
outcomes across individual SGLT2i drugs and examined cross-class effects on renal function and albuminuria. The aim
of this analysis is to report HbA1c, weight and SBP outcomes across the SGLT2i class, and to look for any observed differences
in efficacy between individual SGLT2i agents in the real world.

Methods
Data for this observational cohort study were received via two routes. First, from secondary care services via the ABCD
canagliflozin, empagliflozin and dapagliflozin audits, using routinely collected data entered into the secure online tools.
This was integrated with data received from primary care clinical commissioning groups in regions participating in the audit
programme via Eclipse. Individuals with available baseline and follow-up data for the outcomes of interest were included. The
most recent follow-up period was used for this analysis.

Baseline characteristics were reported using simple descriptive statistics. Missing data were managed by generating
ten sets of imputations using multiple chained equations and Rubin’s rules were applied for all analyses. Outcomes of
interest included change in glycated HbA1c, weight, body mass index (BMI) and SBP. For each outcome, change from baseline
was assessed using multivariate linear regression adjusting for key confounders: HbA1c, weight, blood pressure, diabetes
duration, SGLT2i drug, estimated glomerular filtration rate, gender and age. Statistical significance was defined as p<0.05.
Comparisons between each drug were adjusted for multiple comparisons using Bonferroni corrections. Sensitivity analysis
using non-imputed data only was performed. All analyses were performed in Stata 17.

Ethics and funding
The audit programme is independent and funded by the ABCD. Since it was an audit, no ethical approval was required. The
ABCD audits are approved by the ABCD Caldicott Guardian and the Confidentiality Advisory Group.

Results
In total, 21,263 individuals using SGLT2i were included in this analysis: 11,231 using empagliflozin, 2,257 using canagliflozin and
7,775 using dapagliflozin. The flow chart for inclusion of individuals in the analysis is displayed in Figure 1. Median follow-up
time was 1.7 years (IQR 0.9-2.8 years). Discontinuation rates were low, only 75/21,338. The baseline characteristics of the
cohort, and for each group, are shown in Table 1. The degree of missing data across all drugs was small and consistent
between drugs (Appendix 1 online at www.bjd-abcd.com).

Across the SGLT2i class, unadjusted change in HbA1c was 9.7 mmol/mol (95% CI 9.5-10.0; p<0.001). When adjusting for
confounders, HbA1c reduced by 10 mmol/mol (95% CI 9.8-10.2; p<0.001). By agent, HbA1c reductions were observed in
association with all three agents as follows: empagliflozin, HbA1c -10.6 mmol/mol (95% CI 10.4-10.9; p<0.001); canagliflozin, HbA1c
-9.8 mmol/mol (95% CI 9.1-10.4; p<0.001) and dapagliflozin, HbA1c -9.1 mmol/mol (95% CI 8.7-9.4; p<0.001). These results are
illustrated in Figure 2. Empagliflozin was associated with statistically larger HbA1c reductions than canagliflozin (p=0.03)
and dapagliflozin (p<0.001).

Unadjusted change in mean weight was -3.1 kg (95% CI 2.2-4.0; p<0.001). An adjusted change in weight of -3.2 kg (95% CI
2.2-4.1; p<0.001) was observed with no significant differences between all three drugs (p=1.00 for all comparisons). Adjusted
for confounders, weight changed by -2.8 kg (95% CI 1.5-4.2; p<0.001) with empagliflozin; by -3.6 kg (95% CI 0.6-6.6; p=0.02)
with canagliflozin and by 3.5 kg (95% CI 1.9-5.1; p<0.001) with dapagliflozin. Before adjusting for confounders, BMI reduced by
1.1 kg/m² (95% CI 0.8-1.4; p<0.001). Adjusted reduction in BMI

![Figure 1. Flow chart for number of individuals included in the study](https://www.bjd-abcd.com)
was 1.1 kg/m² (95% CI 0.8-1.5; p<0.001) across the class and by agent: empagliflozin, BMI -1.0 kg/m² (95% CI 0.5-1.5; p<0.001); canagliflozin, BMI -1.3 kg/m² (95% CI 0.2-2.3; p=0.02) and for dapagliflozin 1.2 kg/m² (95% CI 0.7-1.8; p<0.001). There was no significant difference between agents in their association with BMI change. These results are illustrated in Figure 3 (weight) and Figure 4 (BMI).

The results for SBP change are shown in Figure 5. Unadjusted change in SBP was -0.8 mmHg (95% CI 0.5-1.0; p<0.001). Adjusting for confounders, SBP decreased by 0.9 mmHg (95% CI 0.7-1.1; p<0.001). Reductions in SBP were significant for all three drugs: empagliflozin, SBP -1.0 mmHg (95% CI 0.7-1.2; p<0.001); canagliflozin, SBP -1.6 mmHg (95% CI 1.1-2.2; p<0.001) and for dapagliflozin, SBP -0.6 mmHg (95% CI 0.3-0.9; p<0.001). Reductions with canagliflozin were larger than those seen with dapagliflozin (p=0.005), but otherwise no significant differences were noted between drugs.

Sensitivity analyses revealed no significant differences when

Table 1. Baseline characteristics of the cohort

<table>
<thead>
<tr>
<th></th>
<th>Empagliflozin</th>
<th>Canagliflozin</th>
<th>Dapagliflozin</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>11,231</td>
<td>2,257</td>
<td>7,775</td>
<td>21,263</td>
</tr>
<tr>
<td>Age, mean±SD</td>
<td>60.0±10.4</td>
<td>60±10.6</td>
<td>60.0±10.3</td>
<td>60.0±10.4</td>
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<tr>
<td>Gender, % male</td>
<td>61.5%</td>
<td>62.0%</td>
<td>60.6%</td>
<td>61.2%</td>
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<td>Weight (kg), mean±SD</td>
<td>96.6±22.0</td>
<td>97.8±21.9</td>
<td>98.7±22.2</td>
<td>97.5±22.1</td>
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<td>Weight (kg), range</td>
<td>56.0-254.0</td>
<td>57.2-239.0</td>
<td>56.0-254.0</td>
<td>56.0-254.0</td>
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<tr>
<td>BMI (kg/m²), mean±SD</td>
<td>33.7±7.0</td>
<td>34.0±7.6</td>
<td>34.2±7.0</td>
<td>33.9±7.1</td>
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<tr>
<td>BMI (kg/m²), range</td>
<td>21.9-140.9</td>
<td>21.5-138.4</td>
<td>22.3-129</td>
<td>21.5-140.9</td>
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<td>Diabetes duration (years), median (IQR)</td>
<td>8.2 (4.3-12.5)</td>
<td>8.2 (4.0-12.5)</td>
<td>7.9 (4.2-12.0)</td>
<td>8.1 (4.2-12.3)</td>
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<td>HbA₁c, %, mean±SD</td>
<td>9.1±2.1</td>
<td>9.1±1.6</td>
<td>9.0±2.7</td>
<td>9.1±2.3</td>
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<td>HbA₁c, %, range</td>
<td>6.3-18.5</td>
<td>6.2-16.5</td>
<td>6.2-18.1</td>
<td>6.2-18.5</td>
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<td>HbA₁c (mmol/mol), mean±SD</td>
<td>75.8±17.2</td>
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<td>74.6±17.1</td>
<td>75.3±17.2</td>
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<td>HbA₁c (mmol/mol), range</td>
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<td>44.3-174.3</td>
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<td>eGFR (mL/min/1.73m²), mean±SD</td>
<td>82.0±13.5</td>
<td>79.3±13.5</td>
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<td>Systolic blood pressure (mmHg), Mean±SD</td>
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<td>132±15</td>
<td>132±15</td>
<td>130±17</td>
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<tr>
<td>Systolic blood pressure (mmHg), range</td>
<td>70-248</td>
<td>80-194</td>
<td>96-226</td>
<td>70-248</td>
</tr>
</tbody>
</table>

Concomitant diabetes drugs

| Metformin, n (%) | 9,164 (81.6) | 1,704 (75.5) | 6,046 (77.8) | 16,914 (79.6) |
| Sulphonylurea, n (%) | 3,252 (29.0) | 686 (38.4)   | 2,237 (28.8) | 6,175 (29.0)  |
| Dipeptidyl peptidase-4 inhibitor, n (%) | 2,154 (19.2) | 525 (23.3)   | 1,668 (21.5) | 4,347 (20.4)  |
| Thiazolidinedione, n (%) | 344 (3.1)    | 60 (2.7)     | 111 (1.4)    | 515 (2.4)     |
| Glucagon-like peptide-1 agonists, n (%) | 459 (4.1)    | 57 (2.5)     | 331 (4.3)    | 847 (4.0)     |
| Insulin, n (%) | 1,432 (12.8) | 172 (7.6)    | 788 (10.1)   | 2,392 (11.3)  |
Discussion

Our study demonstrates HbA1c, weight, BMI and SBP reductions associated with all three SGLT2i drugs commonly used in UK clinical practice. As is often the case with real-world data, our cohort consists of individuals with more broad baseline characteristics. As an example, in comparison to EMPA-REG, our cohort was heavier (97.5 kg vs 86.4 kg in EMPA-REG) and had higher baseline HbA1c (9.1% vs 8.1% in EMPA-REG) but were generally younger (60.0 years vs 63.1 years in EMPA-REG).

In our study, HbA1c reductions exceeded those observed in randomised controlled trials, even when correcting for baseline HbA1c, with reductions of 10 mmol/mol observed compared to 6-7 mmol/mol in a published meta-analysis. However, the baseline HbA1c in our study was higher, which may account for the larger reductions. Weight reductions were also larger (3.2 kg vs 1.8 kg).

Comparing the agents, empagliflozin was statistically associated with larger HbA1c reductions than both dapagliflozin and canagliflozin but differences between the drugs were clinically relatively small. This is in contrast to a published network meta-analysis which suggests canagliflozin was associated with the largest HbA1c reductions, perhaps due to the additional moderate effect of canagliflozin on inhibiting sodium-glucose co-transport 1 in the gut. Additionally, there were some differences in the number of individuals using various concomitant medications, and these may account for some of these differences (see Table 1). As an example, a larger number of canagliflozin users were taking sulphonylureas and fewer were taking insulin – it is possible that insulin may have been titrated alongside the other medications, causing this discrepancy.

SBP reductions were smaller than in randomised controlled trials (−0.9 mmHg vs −4.45 mmHg) and in published meta-analyses. The reasons for this are unclear and may be related to compliance or concomitant adjustment in other medications which we were unable to account for. Dapagliflozin was associated with larger SBP reductions than canagliflozin, although again the clinical significance of such a small difference is likely to be negligible. All drugs had similar impacts on weight and BMI, with no differences noted across the class.

Strengths and limitations

This study utilises data from a large number of real-world SGLT2i users, is likely to be generalisable to a UK clinic population and uses recognised statistical methods to account for missing data (often a problem with observational datasets). As they are observational data, however, they may be limited by unmeasured confounding factors – notably ethnicity is absent from our data set and would be important to explore further in future work. Data on concomitant antihypertensive use were limited and therefore not accounted for within the analysis – the blood pressure result should therefore be interpreted with caution. Nevertheless, the findings of this study mirror those seen by meta-analyses of randomised controlled trials, supporting the validity of the findings.

Conclusions

SGLT2i are very well tolerated and are associated with real-world improvements in multiple metabolic and clinical parameters; whilst differences between drugs were observed, the clinical relevance of these differences is unclear given that the magnitudes of the variances were quite small. Our findings on the relative effectiveness of individual SGLT2i agents were slightly discordant to the relative efficacy of individual SGLT2i reported in randomised clinical trials. These differences may reflect differences in baseline characteristic of real-world
patients (i.e. greater HbA₁c, weight and SBP at baseline). Data examining the link between these medications and hard cardio-renal endpoints in the ABCD audits are needed to establish that these improvements translate into improved outcomes for users.

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*Conflict of interest* TSJC has received personal fees from Sanofi, Novo Nordisk, Lilly, Abbott Diabetes Care, Dexcom and Insulet. REJR has received speaker fees and/or consultancy fees and/or educational sponsorships from Abbott, Besins, BioQuest, Morphic Medical and Novo Nordisk. AB, KD, AG, JE, KA, IQ, DB, SS, IL: None.

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*Acknowledgement* SGLT2i audit contributors - see Appendix 3 online at www.bjd-abcd.com.

References
Appendix 1 - Missing data – n (%)

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<th>Empagliflozin</th>
<th>Canagliflozin</th>
<th>Dapagliflozin</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>11,231</td>
<td>2,257</td>
<td>7,775</td>
<td>21,263</td>
</tr>
<tr>
<td>Weight</td>
<td>301 (2.6)</td>
<td>73 (3.2)</td>
<td>179 (2.3)</td>
<td>553 (2.6)</td>
</tr>
<tr>
<td>BMI</td>
<td>423 (3.8)</td>
<td>171 (7.6)</td>
<td>662 (2.3)</td>
<td>1,256 (5.9)</td>
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<tr>
<td>Diabetes duration</td>
<td>522 (4.6)</td>
<td>197 (8.7)</td>
<td>771 (9.9)</td>
<td>1,490 (7.0)</td>
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<td>HbA1c</td>
<td>25 (0.2)</td>
<td>8 (0.4)</td>
<td>43 (0.5)</td>
<td>76 (0.4)</td>
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<tr>
<td>eGFR</td>
<td>135 (1.2)</td>
<td>43 (1.9)</td>
<td>247 (3.1)</td>
<td>425 (2.0)</td>
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<td>101 (0.9)</td>
<td>32 (1.4)</td>
<td>98 (1.2)</td>
<td>231 (1.0)</td>
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Appendix 2 - Missing data and sensitivity analysis

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<tr>
<td>Weight, kg</td>
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<td>BMI, kg/m²</td>
<td>3,381</td>
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<td>Systolic blood pressure, mmHg</td>
<td>2,288</td>
<td>-2.2 (-2.0, -2.5)</td>
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</table>

Appendix 3 - The SGLT2i audit contributors

Details to follow