# 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

THOMAS SJ CRABTREE,[1,2,3] ALEX BICKERTON,[4] KETAN DHATARIYA,[5,6] ALISON GALLAGHER,[7] JACKIE ELLIOTT,[8] KAREN ADAMSON,[9] IAN GALLEN,[10] DENNIS BARNES,[11] SIVA SIVAPPRIYAN,[11] ISKANDER IDRIS,[1,2] ROBERT EJ RYDER[3] ON BEHALF OF ALL SGLT2i AUDIT CONTRIBUTORS*

**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 ($HbA_{1c}$), 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 $HbA_{1c}$, 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±10.4years, $HbA_{1c}$ 75.3±17.2 mmol/mol, BMI 33.9±7.1kg/m$^2$ and 61.2% female were included. Over median follow-up of 1.7 years, $HbA_{1c}$ 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/m$^2$ (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 $HbA_{1c}$ 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 $HbA_{1c}$ 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 $HbA_{1c}$ 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.

[1] Faculty of Medicine and Health Sciences, University of Nottingham, Nottingham, UK
[2] Department of Diabetes & Endocrinology, University Hospitals of Derby and Burton NHS Trust, Derby, UK
[3] Department of Diabetes & Endocrinology, Sandwell & West Birmingham Hospitals NHS Trust, Birmingham, UK
[4] Department of Diabetes & Endocrinology, Yeovil General Hospital NHS Trust, Yeovil, UK
[5] Department of Diabetes & Endocrinology, The Norfolk and Norwich University Hospitals NHS Trust, Norwich, UK
[6] Norwich Medical School, University of East Anglia, Norwich, UK
[7] Department of Diabetes, University Hospitals of Leicester NHS Trust, Leicester, UK
[8] Department of Diabetes & Endocrinology, Sheffield Teaching Hospitals NHS Trust, Sheffield, UK
[9] Department of Diabetes & Endocrinology, St John's Hospital, Livingston, UK
[10] Department of Diabetes and Endocrinology, Royal Berkshire Hospital NHS Trust, Reading, UK
[11] Department of Diabetes and Endocrinology, Maidstone and Tunbridge Wells NHS Trust, Maidstone, UK

* See acknowledgement

**Address for correspondence:** Dr Tom Crabtree
Royal Derby Hospital, Uttoxeter Road, Derby, DE22 3NE, UK
E-mail: T.Crabtree@nhs.net

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**Key words:** SGLT2, real-world, $HbA_{1c}$, weight, blood pressure

## Introduction

Sodium-glucose co-transporter-2 inhibitors (SGLT2i) have been in use in UK practice for close to 10 years,[1] 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 ($HbA_{1c}$) and weight reductions across the class, as well as reductions in systolic blood pressure (SBP),[2] differences in efficacy between agents have also been reported: canagliflozin, for example, has been associated with larger $HbA_{1c}$ reductions.[3] 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 SGLT2i 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.[4,5] 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.[6]

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.[7]

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,[8-10] and examined cross-class effects on renal function and albuminuria.[11] The aim of this analysis is to report $HbA_{1c}$, weight and SBP outcomes across the SGLTi 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.[12] Outcomes of interest included change in glycated $HbA_{1c}$, weight, body mass index (BMI) and SBP. For each outcome, change from baseline was assessed using multivariate linear regression adjusting for key confounders: $HbA_{1c}$, 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 $HbA_{1c}$ was 9.7 mmol/mol (95% CI 9.5-10.0; $p<0.001$). When adjusting for confounders, $HbA_{1c}$ reduced by 10 mmol/mol (95% CI 9.8-10.2; $p<0.001$). By agent, $HbA_{1c}$ reductions were observed in association with all three agents as follows: empagliflozin, $HbA_{1c}$ -10.6 mmol/mol (95% CI 10.4-10.9; $p<0.001$); canagliflozin, $HbA_{1c}$ -9.8 mmol/mol (95% CI 9.1-10.4; $p<0.001$) and dapagliflozin, $HbA_{1c}$ -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 $HbA_{1c}$ 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/m$^2$ (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

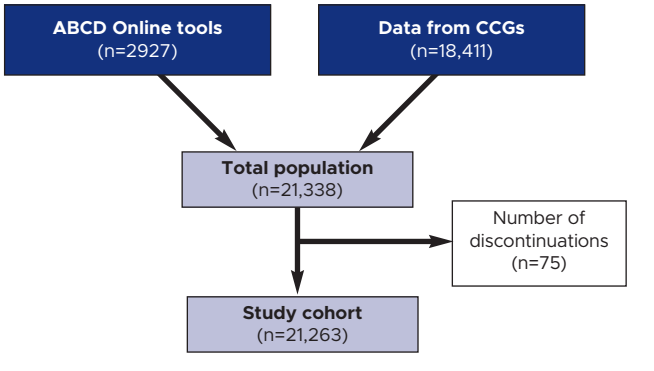


**Table 1.** Baseline characteristics of the cohort

| | Empagliflozin | Canagliflozin | Dapagliflozin | Total |
|---|---|---|---|---|
| n= | 11,231 | 2,257 | 7,775 | 21,263 |
| Age, mean±SD | 60.0±10.4 | 60.1±10.6 | 60.0±10.3 | 60.0±10.4 |
| Gender, % male | 61.5% | 62.0% | 60.6% | 61.2% |
| Weight (kg), mean±SD | 96.6±22.0 | 97.8±21.9 | 98.7±22.2 | 97.5±22.1 |
| Weight (kg), range | 56.0-254.0 | 56.0-208.4 | 57.2-239.0 | 56.0-254.0 |
| BMI (kg/m$^2$), mean±SD | 33.7±7.0 | 34.0±7.6 | 34.2±7.0 | 33.9±7.1 |
| BMI (kg/m$^2$), range | 21.9-140.9 | 21.5-138.4 | 22.3-129 | 21.5-140.9 |
| Diabetes duration (years), median (IQR) | 8.2 (4.3-12.5) | 8.2 (4.0-12.5) | 7.9 (4.2-12.0) | 8.1 (4.2-12.3) |
| $HbA_{1c}$ (%), mean±SD | 9.1±2.1 | 9.1±1.6 | 9.0±2.7 | 9.1±2.3 |
| $HbA_{1c}$ (%), range | 6.3-18.5 | 6.2-16.5 | 6.2-18.1 | 6.2-18.5 |
| $HbA_{1c}$ (mmol/mol), mean±SD | 75.8±17.2 | 76.0±17.6 | 74.6±17.1 | 75.3±17.2 |
| $HbA_{1c}$ (mmol/mol), range | 45.4-178.7 | 44.3-156.8 | 44.3-174.3 | 44.3-178.7 |
| eGFR (mL/min/1.73m$^2$), mean±SD | 82.0±13.5 | 79.3±13.5 | 81.6±12.7 | 81.6±13.2 |
| Systolic blood pressure (mmHg), Mean±SD | 129±19 | 132±15 | 132±15 | 130±17 |
| Systolic blood pressure (mmHg), range | 70-248 | 80-194 | 96-226 | 70-248 |
| 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) |
| Thiazolinedione, 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) |

**Figure 2.** Bar chart showing adjusted change in $HbA_{1c}$ from baseline with empagliflozin, canagliflozin and dapagliflozin. Error bars represent 95% confidence intervals

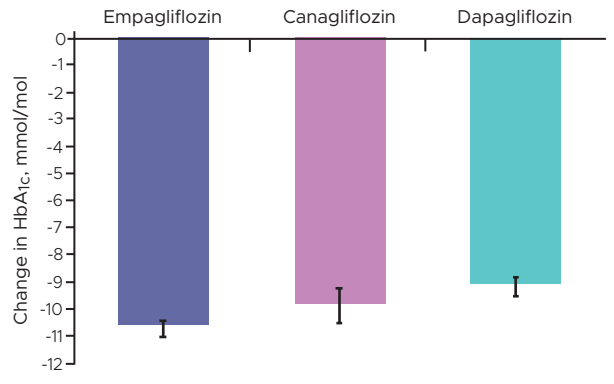
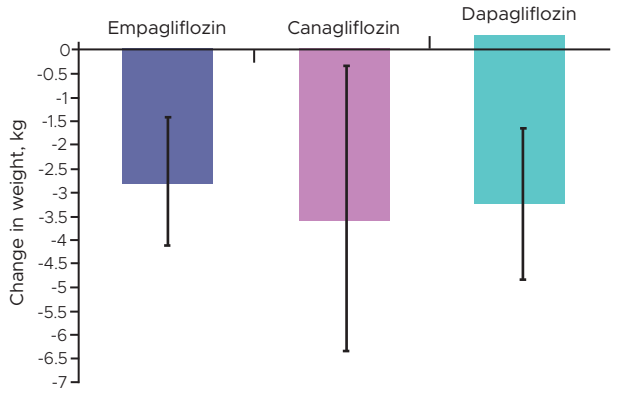



**Figure 3.** Bar chart showing adjusted change in weight from baseline with empagliflozin, canagliflozin and dapagliflozin. Error bars represent 95% confidence intervals




was 1.1 kg/m$^2$ (95% CI 0.8-1.5; p<0.001) across the class and by agent: empagliflozin, BMI -1.0 kg/m$^2$ (95% CI 0.5-1.5; p<0.001); canagliflozin, BMI -1.3 kg/m$^2$ (95% CI 0.2-2.3; p=0.02) and for dapagliflozin 1.2 kg/m$^2$ (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

**Figure 4.** Bar chart showing adjusted change in body mass index from baseline with empagliflozin, canagliflozin and dapagliflozin. Error bars represent 95% confidence intervals

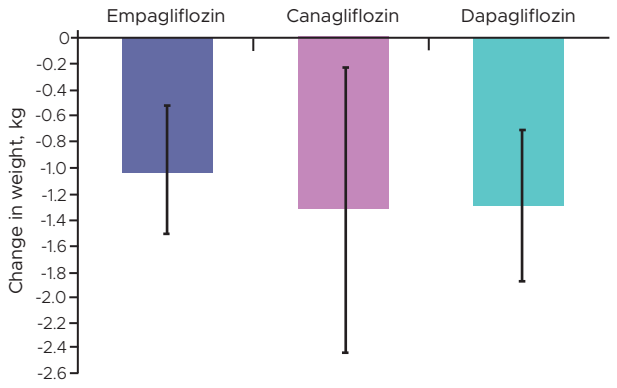
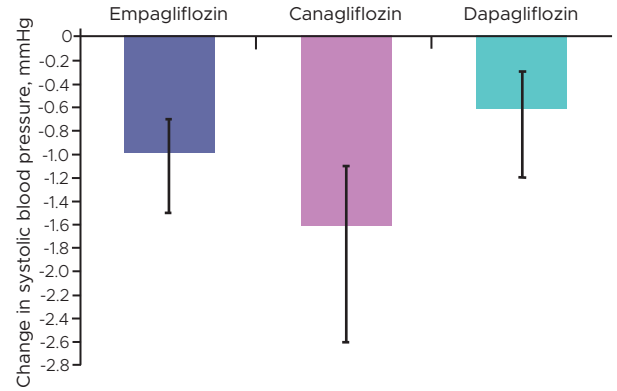



**Figure 5.** Bar chart showing adjusted change in systolic blood pressure from baseline with empagliflozin, canagliflozin and dapagliflozin. Error bars represent 95% confidence intervals




analysing complete data only for weight, BMI and $HbA_{1c}$. Those with complete data for SBP had larger reductions and this may make the results reported less reliable. The amount of missing data for each variable and sensitivity analysis are reported in Appendix 2 online at www.bjd-abcd.com.

## Discussion

Our study demonstrates $HbA_{1c}$, 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,[13] our cohort was heavier (97.5 kg vs 86.4 kg in EMPA-REG) and had higher baseline $HbA_{1c}$ (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, $HbA_{1c}$ reductions exceeded those observed in randomised controlled trials, even when correcting for baseline $HbA_{1c}$, with reductions of 10 mmol/mol observed compared to 6-7 mmol/mol in a published meta-analysis.[14] However, the baseline $HbA_{1c}$ 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 $HbA_{1c}$ 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 $HbA_{1c}$ reductions, perhaps due to the additional moderate effect of canagliflozin on inhibiting sodium-glucose co-transport 1 in the gut.[2,15] 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.[14,16] 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 SLGT2i 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.[2,14]

## 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

**Key messages**

- In the real-world reductions in $HbA_{1c}$ and weight are observed across all SGLT2 inhibitors
- $HbA_{1c}$ reductions observed with empagliflozin were significantly greater than with dapagliflozin
- Otherwise, no differences between drugs was noted and they are broadly comparable across other key outcomes

patients (i.e. greater $HbA_{1c}$, weight and SBP at baseline). Data examining the link between these medications and hard cardiorenal endpoints in the ABCD audits are needed to establish that these improvements translate into improved outcomes for users.


**Conflict of interest** TSJC has received personal fees from Sanofi, NovoNordisk, 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.
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**Acknowledgement** SGLT2i audit contributors - see Appendix 3 online at www.bjd-abcd.com.

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## Appendix 1 - Missing data – n (%)

| | Empagliflozin | Canagliflozin | Dapagliflozin | Total |
|---|---|---|---|---|
| n= | 11,231 | 2,257 | 7,775 | 21,263 |
| Weight | 301 (2.6) | 73 (3.2) | 179 (2.3) | 553 (2.6) |
| BMI | 423 (3.8) | 171 (7.6) | 662 (2.3) | 1,256 (5.9) |
| Diabetes duration | 522 (4.6) | 197 (8.7) | 771 (9.9) | 1,490 (7.0) |
| $HbA_{1c}$ | 25 (0.2) | 8 (0.4) | 43 (0.5) | 76 (0.4) |
| eGFR | 135 (1.2) | 43 (1.9) | 247 (3.1) | 425 (2.0) |
| Systolic blood pressure | 101 (0.9) | 32 (1.4) | 98 (1.2) | 231 (1.0) |

## Appendix 2 - Missing data and sensitivity analysis

| | Number missing | Sensitivity analysis (95% CI) |
|---|---|---|
| $HbA_{1c}$, mmol/mol | 375 | -9.7 (-9.4, -9.9) |
| Weight, kg | 2,721 | -3.1 (-2.1, -4.1) |
| BMI, $kg/m^2$ | 3,381 | -1.4 (-1.4, -1.4) |
| Systolic blood pressure, mmHg | 2,288 | -2.2 (-2.0, -2.5) |

## Appendix 3 - The SGLT2i audit contributors

Details to follow