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## Original research

# Clinical risk factors predicting genital fungal infections with sodium–glucose cotransporter 2 inhibitor treatment: The ABCD nationwide dapagliflozin audit

Ken Yan Thong<sup>a,\*</sup>, Mahender Yadagiri<sup>b</sup>, Dennis Joseph Barnes<sup>c</sup>,  
David Stuart Morris<sup>d</sup>, Tahseen Ahmad Chowdhury<sup>e</sup>, Ling Ling Chuah<sup>f</sup>,  
Anthony Michael Robinson<sup>g</sup>, Stephen Charles Bain<sup>h</sup>,  
Karen Ann Adamson<sup>i</sup>, Robert Elford John Ryder<sup>b</sup>, ABCD Nationwide  
Dapagliflozin Audit contributors<sup>1</sup>

<sup>a</sup> School of Medicine and Pharmacology, University of Western Australia, Perth, Australia

<sup>b</sup> Department of Diabetes, Endocrinology and Lipid Metabolism, City Hospital, Birmingham, UK

<sup>c</sup> Diabetes/Endocrinology Services, The Tunbridge Wells Hospital, Pembury, UK

<sup>d</sup> Bridgnorth Medical Practice, Northgate Health Centre, Shropshire, UK

<sup>e</sup> Department of Diabetes, The Royal London Hospital, London, UK

<sup>f</sup> Croydon Health Services NHS Trust, Croydon, UK

<sup>g</sup> Department of Endocrinology, Royal United Hospitals, Bath, UK

<sup>h</sup> Abertawe Bro Morgannwg University Board, Swansea, UK

<sup>i</sup> Diabetes Department, St John's Hospital, Livingston, UK

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## ABSTRACT

**Introduction:** Treatment of type 2 diabetes with sodium–glucose cotransporter 2 (SGLT2) inhibitors may result in genital fungal infections. We investigated possible risk factors for developing such infections among patients treated with the SGLT2 inhibitor dapagliflozin.

**Methods:** The Association of British Clinical Diabetologists (ABCD) collected data on patients treated with dapagliflozin in routine clinical practice from 59 diabetes centres. We assessed possible associations of patient's age, diabetes duration, body mass index, glycated haemoglobin, renal function, patient sex, ethnicity and prior genital fungal infection, urinary tract infection, urinary incontinence or nocturia, with the occurrence of  $\geq 1$  genital fungal infection within 26 weeks of treatment.

**Results:** 1049 out of 1116 patients (476 women, 573 men) were analysed. Baseline characteristics were, mean  $\pm$  SD, age  $56.7 \pm 10.2$  years, BMI  $35.5 \pm 6.9$  kg/m<sup>2</sup> and HbA<sub>1c</sub>  $9.4 \pm 1.5\%$ . Only patient sex (13.2% women vs 3.3% men) and prior history of genital fungal infection (21.6% vs 7.3%) were found to be associated with occurrence of genital fungal infections

\* Corresponding author at: Department of Diabetes and Endocrinology, Rockingham General Hospital, Elanora Drive, Rockingham, WA 16168, Australia. Fax: +61 8 95994737.

E-mail address: [kythong@gmail.com](mailto:kythong@gmail.com) (K.Y. Thong).

<sup>1</sup> See Appendix A.

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after dapagliflozin treatment, adjusted OR 4.22 [95%CI 2.48,7.19],  $P < 0.001$  and adjusted OR 2.41 [95% CI 1.04,5.57],  $P = 0.039$ , respectively.

**Conclusion:** Women and patients with previous genital fungal infections had higher risks of developing genital fungal infections with dapagliflozin treatment.

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## 1. Introduction

Type 2 diabetes is characterised by several pathophysiological disruptions including defects in insulin secretion by the pancreas, increased hepatic glucose output and increased insulin resistance in the muscle. It is also now recognised that an adaptive increase in glucose reabsorption in the kidney tubules, mediated by sodium–glucose cotransporters 1 and 2 (SGLT1 and SGLT2), limits glucosuria and contributes to glucose dysregulation in type 2 diabetes. SGLT2, being higher in capacity and lower in affinity than SGLT1, has become a viable target for pharmacotherapy [1].

Initially available SGLT2 inhibitors include dapagliflozin, canagliflozin and empagliflozin. Among other effects, treatment with SGLT2 inhibitors results in increased glucosuria and natriuresis, and leads to improvements in glycaemia, body weight and blood pressure among patients with type 2 diabetes [1,2]. A recent trial utilising empagliflozin has also demonstrated treatment-led reduction in hospitalisation for heart failure and cardiovascular deaths among patients with type 2 diabetes with high cardiovascular risk [3]. SGLT2 inhibitors are recommended as an option for second or third line therapy in addition to metformin by a joint position statement by the American Diabetes Association and European Association for the Study of Diabetes [4].

Adverse events associated with SGLT2 inhibitor treatment include genital fungal infections, urinary tract infection, volume-related events (hypotension, syncope or dehydration), hypoglycaemia and rarely, ketoacidosis [5–7]. Of these, genital fungal infections appear to be the most prevalent and consistent finding among various trials involving SGLT2 inhibitors. Diabetes patients are at an increased risk of genital fungal infections compared with non-diabetes patients [8]. By inducing glucosuria, treatment with SGLT2 inhibitors likely increases this risk further [9]. Manifestations include vulvo-vaginal infections in female patients and balanitis or balanoposthitis in male patients. Typically, trials of SGLT2 inhibitors have shown genital fungal infections to be more common among women, occur early after treatment initiation (within 24 weeks), and are usually not severe enough to warrant treatment discontinuation [9,10].

The Association of British Clinical Diabetologists (ABCD) is the diabetes specialist society in the UK. ABCD has been conducting nationwide audits of new diabetes therapies once they become available for use in routine clinical practice, including thus far audits on the glucagon-like peptide-1 receptor agonists exenatide twice daily, liraglutide and exenatide once weekly, as well as on dapagliflozin, canagliflozin and insulin degludec. These audits hoped to accelerate learning of the new therapies and extend surveillance of adverse events

in a real-world setting. All the audits bear similar designs including nationwide solicitation but voluntary participation of diabetes centres, collection of data of patients on certain diabetes treatments based on routine treatment decisions and clinical justification of their use, and utilisation of purpose-built audit software to collect pre-specified audit queries. We utilised data from the current ABCD dapagliflozin audit in an attempt to identify clinical predictors for developing genital fungal infections among patients treated with dapagliflozin.

## 2. Methods

### 2.1. Subjects

ABCD invited diabetes centres in hospitals and primary care across UK to submit de-identified data of patients routinely treated with dapagliflozin 10 mg daily. A few diabetes centres from Hong Kong, Brazil and Australia were also invited to participate as “proof of concept” that a larger scale international audit database can be achieved. Between October 2014 and September 2016, 59 diabetes centres enrolled and submitted varying degrees of data depending on date of participation, the frequency of patients’ health visits and duration of dapagliflozin treatment that had taken place.

Data requested included patients’ age, sex, ethnicity as well as pre- and post-dapagliflozin treatment information including diabetes treatments, glycated haemoglobin ( $HbA_{1c}$ ), body weight, body mass index (BMI), systolic and diastolic blood pressure, lipid parameters, alanine transaminotransferase and creatinine, whenever these data were available. We accepted laboratory results from individual participating centres. Contributors were asked to identify prior history of genital fungal infections and urinary tract infections within the previous one year, urinary incontinence, nocturia, as well as to report these events or any-other adverse events after treatment.

The audit received data on 1116 patients with at least one follow-up visit after dapagliflozin was initiated. Sixty-four patients with less than 12 weeks data contribution or follow-up, this not being due to discontinuation of dapagliflozin within 12 weeks of initiation, were excluded. Three patients were excluded due to previous SGLT2 inhibitor use. Data on the remaining 1049 patients were analysed.

### 2.2. Outcome and risk variables

Patients were divided into those who developed  $\geq 1$  genital fungal infection within 26 weeks of treatment and those who did not. We included genital fungal infection proven by microbiology or clinical examination or when there were suggestive

**Table 1 – Baseline characteristics (continuous variables) and their association with genital fungal infections among patients treated with dapagliflozin.**

	n	≥1 Genital fungal infection		P value
		Yes	No	
Age (years)	1049	56 ± 11	57 ± 10	0.47
Duration of diabetes (years)	1048	11 ± 6	12 ± 7	0.27
HbA <sub>1c</sub> (%; mmol/mol)	1045	9.2 ± 1.5; 77 ± 16	9.4 ± 1.5; 79 ± 16	0.18
Body mass index (kg/m <sup>2</sup> )	1023	34.0 ± 7.4	35.4 ± 6.9	0.53
eGFR* (ml/min/1.73 m <sup>2</sup> )	932	92 ± 18	90 ± 18	0.32

Variables are shown as mean ± SD.

eGFR; estimated glomerular filtration rate, calculated by the CKD-EPI equation.

symptoms such as pruritus or redness in the genital area. We then assessed possible associations of patient's age, duration of diabetes, BMI, HbA<sub>1c</sub>, estimated glomerular filtration rate (eGFR), sex, ethnicity, previous genital fungal infection, previous urinary tract infection, previous urinary incontinence and previous nocturia with the development of genital fungal infections. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

### 2.3. Statistical analyses

Univariate associations were tested using Student's t-test and Chi-Square analysis for continuous and categorical variables, respectively. Fisher's exact test was used for categorical variables when the number of events was less than five. Variables with statistically significant association in univariate analyses ( $P < 0.05$ ) were entered into a binary logistic regression analysis. Analyses were performed combining female and male patients together and then separately to exclude sex-specific interactions. Statistical analyses were performed using Minitab<sup>®</sup> Release 14 (Minitab Ltd., Coventry, UK).

## 3. Results

The overall proportion of patients reporting ≥1 treatment emergent genital fungal infections was 82/1049 (7.8%). The majority (95.1%) of the reports of genital fungal infection occurred in the first follow-up visit, which occurred at a median of 18 [interquartile range 13–26] weeks after starting dapagliflozin. 109 (10.4%) patients discontinued dapagliflozin permanently within 26 weeks, 25 (2.4%) due to issues with genital fungal infections.

Baseline characteristics of patients (476 women and 573 men) and possible association with subsequent genital fungal infections are shown in **Tables 1 and 2**. Genital fungal infections were more common among women (13.2%) compared with men (3.3%) (difference  $P < 0.001$ ). Patients reporting a history of genital fungal infections were also more likely to have infection after dapagliflozin treatment compared with patients who did not report such a history (21.6% vs 7.3%,  $P = 0.007$ ). Women with prior history of genital fungal infection were at the greatest risk with 27.6% of these patients developing treatment-emergent genital fungal infections. No other variables were found to be associated with the occurrence of genital fungal infections, either analysed among the entire cohort or by the sexes separately. In a simple two-variable

logistic regression, the likelihood for developing genital fungal infections for female sex and previous genital fungal infections were, adjusted odds ratio and 95% confidence interval, OR 4.22 [95%CI 2.48,7.19],  $P < 0.001$  and OR 2.41 [95%CI 1.04,5.57],  $P = 0.039$ , respectively.

## 4. Discussion

Our study, utilising “real-life” clinical data, identified patient sex and prior history of genital fungal infection to be the only risk factors for developing genital fungal infections with dapagliflozin treatment. Only a small proportion of patients discontinued dapagliflozin due to such infections.

Results from our study are similar to clinical trial data of SGLT2 inhibitors. In a pooled analysis of clinical trials utilising dapagliflozin 10 mg, the incidence of genital fungal infection was 9.7% among women and 4.2% in men. The incidence of genital fungal infection among patients with a history of genital infections was 25.0% [9]. In a pooled analysis of trials utilising canagliflozin 100 mg and 300 mg, the incidence of genital fungal infections were 10.4% and 11.4% in women and 4.2% and 3.7% in men, respectively. Women with a previous history of vulvovaginitis had a higher incidence of treatment emergent genital fungal infection (29.0%) in the same analysis. Treatment discontinuation due to genital fungal infection occurred in 0.9% and 0.5% of the canagliflozin 100 mg and 300 mg groups, respectively [10]. In a large cardiovascular outcome study of empagliflozin, pooled events for the 10 mg and 25 mg dose showed the incidence of genital fungal infection to be 10.0% in women and 5.0% in men [3].

We did not identify other risk factors for developing genital fungal infection with dapagliflozin treatment to help with treatment decisions in the clinical setting. Baseline HbA<sub>1c</sub> was not a risk factor, a similar finding noted by Johnsson et al. [9] and Nyirjesy et al. [10]. In contrast, Nyirjesy et al. has reported more frequent genital fungal infection among women with younger age or higher BMI (but not among men) [10]. A low incidence of vulvovaginal infections (<5%) was observed in a study of canagliflozin treatment among Japanese patients with type 2 diabetes [11] but we did not find a lower incidence of infections in our Asian cohort. A low incidence of genital fungal infections was also observed in type 2 diabetes patients with moderate renal impairment treated with canagliflozin [12], possibly due to attenuated effects of urinary glucose excretion in patients with reduced renal function. We did not find an effect of renal function on developing genital fungal

**Table 2 – Baseline characteristics (categorical variables) and their association with genital fungal infections among 1049 patients treated with dapagliflozin.**

	≥1 Genital fungal infection		P value
	Yes	No	
Sex			
Female	63 (13.2)	413 (86.8)	<0.001
Male	19 (3.3)	554 (96.7)	
Ethnicity (n = 947)			
Caucasian	51 (7.1)	671 (92.9)	–
Asian	20 (10.8)	166 (89.2)	0.11 (vs Caucasian)
Afro-Caribbean	3 (10.7)	25 (89.3)	0.49 (vs Caucasian)
Mixed	1 (9.1)	10 (90.9)	–
Previous genital fungal infection <1 year			
Yes	8 (21.6)	29 (78.4)	0.007
No	74 (7.3)	938 (92.7)	
Previous urinary tract infection <1 year			
Yes	2 (9.5)	19 (90.5)	0.68
No	80 (7.8)	948 (92.2)	
History of urinary incontinence			
Yes	2 (15.4)	11 (84.6)	0.27
No	80 (7.7)	956 (92.3)	
History of nocturia			
Yes	11 (13.6)	70 (86.4)	0.06
No	71 (7.3)	897 (92.7)	

Variables are shown as n (%).

infection in our study. However, only 5.3% of patients with calculated eGFR in our study had eGFR below 60 ml/min/1.73 m<sup>2</sup>. Dapagliflozin is not licensed for patients with eGFR below 60 ml/min/1.73 m<sup>2</sup> [13].

Our study suggests that women with a history of genital fungal infections should be counselled closely with regards to the risks of genital infection with dapagliflozin treatment. Nonetheless, the risks of treatment should be weighed against the beneficial metabolic profile associated with treatment. When starting SGLT2 inhibitor treatment, patients may need to be told to look out for the specific symptoms of genital fungal infections. A management plan if genital infections occur should also be considered, be it to self-treat with topical or oral antifungal therapy, or to seek medical review. Recurrent genital infections should prompt consideration of an alternative diabetes treatment.

The strength of our study includes having a large number of participating centres with different ethnic groups studied and having pre-specified queries on genital fungal infection and urinary symptoms before and after treatment. The limitations include the possibility of under-reporting of events due to patient drop-outs or poor recall of events. The number of patients with previous urinary tract infections or urinary incontinence was also very small so we may not have detected a significant interaction with the occurrence of genital fungal infection.

## 5. Conclusion

Women and patients with previous genital fungal infections are at higher risk of developing genital fungal infections with dapagliflozin treatment. A history of genital fungal infection should be routinely obtained when considering SGLT2 inhibitor treatment, and women should be given closer con-

sideration both in terms of the decision to start treatment and for monitoring of adverse events.

## Conflict of interest

DSM and KAA have worked as consultants on the 'Expert on Demand Programme' for Astra Zeneca, providing education and advice on the use of dapagliflozin. SCB has received honoraria, research funding and attended advisory boards funded by Astra Zeneca. KYT, MY, DJB, TAC, LLC, AMR, KAA, REJR have no conflicts of interest to declare.

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## Appendix A.

*ABCD nationwide dapagliflozin audit – initial setup, maintenance and nationwide analysis:* Ryder REJ, Adamson K, Bailey CJ, Walton C, Thong KY, Sen Gupta P, Cull ML, Yadagiri M. Statistician: Blann A.



## England

Aintree University Hospital NHS Foundation Trust (University Hospital Aintree): Wilding J, Yunus A. Barts Health NHS Trust (St Bartholomew's Hospital): Glynn N, Leslie RDG. Barts Health NHS Trust (The Royal London Hospital): Chowdhury T, Coppack SW. Bridgnorth Medical Practice (Bridgnorth Medical Practice): Morris D. Bromley CCG (Selsdon Park Medical Practice): Cheah Y, Lovie K. County Durham And Darlington NHS Foundation Trust (Darlington Memorial Hospital): Kamaruddin S, Khan U, Partha P, Peter P, Tarigopula G, Tee SA. Doncaster And Bassetlaw Hospitals NHS Foundation Trust (Bassetlaw Hospital): Chaturvedi P, Payne G. Dorset County Hospital NHS Foundation Trust (Dorset County Hospital): Graja A, Macklin A, Wotherspoon F. Dudley Group Hospitals NHS Foundation Trust (Russells Hall Hospital): Pang T. East and North Hertfordshire NHS Trust (Queen Elizabeth II Hospital): Phylactou M, Darzy K, Winocour P. East Kent Hospitals University NHS Foundation Trust (Ashford Hospital): Chuah L, Richards J. East Sussex Healthcare NHS Trust (Conquest Hospital): Ahmad S, Batson D, Castro E, Combes A, Dashora U, Govindan R, Kumar S, Moor C, Ravelo M. Frimley Park Hospital NHS Foundation Trust (Frimley Park Hospital): Bingham E, Kurera I, Zaman M. Great Western Hospitals NHS Foundation Trust (The Great Western Hospital): Bhattacharya B, Broughton C, Ghaffar I. Guy's And St Thomas' NHS Foundation Trust (Guy's And St Thomas' NHS Foundation Trust): Joshi M, McGowan B. Hampshire Hospitals NHS Foundation Trust (Royal Hampshire County Hospital): Chong JLV. Hull and East Yorkshire Hospitals NHS Trust (Hull Royal Infirmary): Sathyapalan T, Varghese J, Walton C. King's College Hospital NHS Foundation Trust (Orpington Hospital): Allinson R, Allitt C, Amo-Konado S, Barratt M, Cheah YS, Cunningham S, Fisher N, Hopkins D, Hussey S, Lewis D, Lovegrove-Saville L, Mukuva P, Mustafa O. King's College Hospital NHS Foundation Trust (PRINCESS ROYAL UNIVERSITY HOSPITAL): Burwell S, Cheah Y, Mensah N, Mukuv P, O'Donnell H, Whight E. Lancashire Teaching Hospitals NHS Foundation Trust (Chorley And South Ribble Hospital): Balmuri LMR, Imtiaz K. Leicester General Hospital (Leicester General Hospital): Gallagher A, Gohil S. London Medical, London (Private): Abraham R, Palik E, Willis C. London North West Healthcare NHS Trust (Brent Community Services): Anthony J, Carroll M, Godambe S, McCabe-Hughes F, Murali KS, Ogida L, Patel N, St-John J. Maidstone And Tunbridge Wells NHS Trust (The Tunbridge Wells Hospital): Agarwal G, Barnes D, Billings D, Butler C, Cairns S, Crosby Z, Danby T, Haq M, Ryan A. Pennine Acute Hospitals NHS Trust (North Manchester General Hospital): Tarpey S. Pennine Acute Hospitals NHS Trust (Royal Oldham Hospital): Tarpey S. Royal United Hospital Bath NHS Trust: Robinson T. Sandwell And West Birmingham Hospitals NHS Trust (Cape Hill Medical Centre, GP): Gardner G. Sandwell And West Birmingham Hospitals NHS Trust (City Hospital Birmingham): Bajwa R, Basu A, Cull M L, De P, Lee B, Kaur A, Pickles O, Ryder R E J, Sen Gupta P, Taylor N, Wyres, M, Yadagiri M. Sandwell And West Birmingham Hospitals NHS Trust (Tower Hill Medical Centre, Dr DK Nandis Practice, GP): Bath S, Chiam W. Sandwell And West Birmingham Hospitals NHS Trust (Norvic Family Practice, GP): Charm E, Littlewood Z, Pathan A, Wyres M. Sandwell

And West Birmingham Hospitals NHS Trust (Sherwood House Medical Practice, GP): Hoffman H. Sandwell And West Birmingham Hospitals NHS Trust (Sundial Lane Surgery, Dr K Akhtar, GP): Akhtar R, Baker O, Durk D, Woakes E, Wyres M. Sandwell And West Birmingham Hospitals NHS Trust (Park House Surgery, GP): Baker O, Hallan P. Sheffield Teaching Hospitals NHS Foundation Trust (Northern General Hospital): Hunt L Scott A. Southern Health NHS Foundation Trust (Fenwick Hospital): Ayling C, Fayers K, Price H, McDonald M, Thorne K, Woodman S. Stockport NHS Foundation Trust (Buxton Cottage Hospital): Bell R. Stockport NHS Foundation Trust (Kingsgate House): Bell R. Stockport NHS Foundation Trust (Stockport NHS Foundation Trust): Bell R. Surrey and Sussex Healthcare NHS Trust (East Surrey Hospital): Brockett K, Clark J. The Royal Bournemouth And Christchurch Hospitals NHS Foundation Trust (Royal Bournemouth General Hospital): Hampton K, Partridge H, Walker J, Williams E. The Royal Wolverhampton NHS Trust (New Cross Hospital): Aziz U, Lekakou L, Oguntolu V. Whitstable Medical Practice (Dr Jm Ribchester & Partners, GP): Brice R, Rollings R, Sansom H.

## Scotland

Forth Valley Acute Hospitals NHS Trust: Barwell N, Buchanan L. Greater Glasgow & Clyde: Huang F, Jones G. NHS Fife (Victoria Hospital, Kirkcaldy): Baird J, Burns D, Chalmers J, Creagh M. Royal Infirmary of Edinburgh NHS Trust: Reid H. West Lothian NHS Trust: Adamson K, Reid H, Vanlook L. Western General Hospitals NHS Trust: Reid H.

## Wales

Abertawe Bro Morgannwg University NHS Trust (Morrison Hospital): Bain S C, Eyles J, Kumar P, Min T, Price D, Stephens JW. Abertawe Bro Morgannwg University NHS Trust (Neath Port Talbot Hospital): Chokor M, Peter R. Abertawe Bro Morgannwg University NHS Trust (Singleton Hospital): Bain S C, Eyles J. Abertawe Bro Morgannwg University NHS Trust (Swansea University): Bain S C, Eyles J. Betsi Cadwalader University Healthboard (Wrexham Maelor Hospital): Ahmad S, Khalily N, Stanaway S. Cardiff And Vale NHS Trust: Roberts A.

## Northern Ireland

Altnagelvin hospital, Londonderry Black N. Belfast Trust (Belfast City): Johnston PC, Nugent A. Northern Trust (Antrim Area Hospital): Kennedy A, Strzelecka A. Northern Trust (Causeway Hospital): Abouzaid M, Rooney D. Tyrone County Hospital: Black N, Hameed A.

## Hong Kong

Hong Kong UMP: Tsang Man Wo.

## Brazil

Hospital Universitario Evangelico de Curitiba: Biagini GLK.

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