Title: SGLT2 inhibitor canagliflozin does not increase risk of non-genital skin and soft tissue infections in people with type 2 diabetes mellitus.

Subtitle: A pooled post-hoc analysis from the CANVAS and CREDENCE randomized double-blind trials.

Short running title: Non-genital SSTI in Canagliflozin trials

Authors

Amy Kang MBBS (Hons)[1,2,3], Brendan Smyth PhD[1,4,5], Brendon L Neuen MBBS (Hons)[1], Hiddo JL Heerspink PhD[1,6], Gian Luca Di Tanna PhD[1], Hong Zhang MD[8], Clare Arnott PhD[1,9], Carinna Hockham PhD[1], Rajiv Agarwal MD[10], George Bakris MD[11], David M Charytan MD[12], Dick de Zeeuw PhD[6], Tom Greene PhD[13], Adeera Levin MD[14], Carol Pollock PhD[15,16], David C Wheeler MD[17], Kenneth W Mahaffey MD[18], Vlado Perkovic PhD[1,2], Meg J Jardine PhD[1,4,19]

Affiliations

1. The George Institute for Global Health, University of New South Wales, Sydney, New South Wales, Australia
2. University of New South Wales, Sydney, New South Wales, Australia
3. Department of Nephrology, Prince of Wales Hospital, Sydney, New South Wales, Australia
4. NHMRC Clinical Trials Centre, University of Sydney, Sydney, New South Wales, Australia
5. Department of Renal Medicine, St George Hospital, Sydney, New South Wales, Australia
6. Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
7. The Charles Perkins Centre, University of Sydney, Sydney, New South Wales, Australia
8. Renal Division of Peking University First Hospital, Beijing, China
9. Department of Cardiology, Royal Prince Alfred Hospital, Sydney Medical School, Sydney,

New South Wales, Australia

10. Indiana University School of Medicine and VA Medical Center, Indianapolis, IN, USA
11. Department of Medicine, University of Chicago Medicine, Chicago, IL, USA
12. Nephrology Division, New York University Langone Medical Center, New York University School of Medicine, New York, NY, USA
13. University of Utah, Salt Lake City, UT, USA
14. Division of Nephrology, University of British Columbia, Vancouver, British Columbia, Canada
15. Kolling Institute of Medical Research, Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia
16. Royal North Shore Hospital, Sydney, New South Wales, Australia
17. Department of Renal Medicine, University College London Medical School, London, United Kingdom
18. Stanford Center for Clinical Research, Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA
19. Concord Repatriation General Hospital, Sydney, New South Wales, Australia

Corresponding author: Dr Amy Kang The George Institute for Global Health, akang@georgeinstitute.org.au

Word count: 3029

Tables: 1

Figures: 4

Twitter summary: #Canagliflozin did not increase risk of non-genital #skin or soft tissue infections in #CANVAS or #CREDENCE, reassuring for use of #SGLT2 inhibitors

Structured Abstract

Aims: Sodium glucose cotransporter 2 inhibitors (SGLT2i) may disrupt the skin's protective hypertonic microenvironment. We assessed whether canagliflozin affects risk of non-genital SSTIs (skin and soft tissue infections).

Materials and Methods: We performed a post-hoc pooled individual participant analysis of the CANVAS and CREDENCE trials that randomized people with type 2 diabetes at high cardiovascular risk and/or with chronic kidney disease to either canagliflozin or placebo. Investigator-reported adverse events were assessed by two blinded authors following pre-determined criteria for non-genital SSTI. Risk of non-genital SSTI, overall and within pre-specified subgroups, and risk of non-genital fungal SSTI, were analyzed using Cox regression models. Factors associated with non-genital SSTI were assessed using multivariable Cox regression models.

Results: Overall 903 (6%) of 14,531 participants experienced non-genital SSTIs over 26 months median follow-up. No difference was observed in non-genital SSTI rates between canagliflozin and placebo (24.0 events/1000 person-years versus 23.9 events/1000 person-years, respectively; HR 0.97 [95% CI 0.85-1.11], p=0.70), with consistent results across subgroups (all p interaction>0.05). The risk of recurrent events and non-genital fungal infection also did not differ significantly between canagliflozin and placebo (HR 1.06 [0.94-1.19], p=0.32 and HR 1.18 [0.88-1.60], p=0.27, respectively). Baseline factors independently associated with non-genital SSTI were younger age, male sex, higher body mass index, higher glycated haemoglobin, lower eGFR, established peripheral vascular disease and history of neuropathy.

Conclusions: Canagliflozin did not affect risk of non-genital SSTI or non-genital fungal SSTI compared to placebo. These findings suggest that any SGLT2i-mediated change in skin microenvironment is unlikely to have meaningful clinical consequences.

Introduction

Sodium glucose cotransporter 2 inhibitors (SGLT2i) offer cardiovascular, kidney and mortality benefits,[1, 2] to individuals with type 2 diabetes, heart failure and chronic kidney disease.[3-5] As indications for and uptake of this drug class continues to rise,[6, 7] understanding potential adverse effects is increasingly important.

The skin is the body's first defence against external micro-organisms and a storage site for excess sodium.[8-10] The high sodium content of the skin may be protective against micro-organisms and activate white cells.[11] The kidney regulates an average of 90g of total body sodium.[12] Approximately 25g of sodium is reabsorbed by sodium glucose cotransporter 2 receptor dependent pathways each day. By blocking this, SGLT2i promote sodium excretion, reduce total body sodium and water, and contribute to beneficial blood pressure and cardiovascular effects,[13, 14] but could also reduce skin hypertonicity[15, 16] and impair the skin's antimicrobial barrier, leading to skin and soft tissue infections.

There is clinical concern for a broader risk of skin and soft tissue infection (SSTI) apart from the recognised risk of genital mycotic infections with SGLT2i. This concern was fed by 1) case reports of necrotising fasciitis in post-marketing surveillance; 2) an association between canagliflozin and osteomyelitis in post-marketing data-mining of the FDA;[17] 3) an over-representation of infectious events and necrotising fasciitis in people taking SGLT2i in a worldwide post-marketing surveillance database;[18] and 4) an increased risk of amputation in participants randomized to canagliflozin in the CANVAS[19] trial, primarily driven by infection.[20] The higher incidence of amputation in participants on canagliflozin appears to be an anomaly and potentially chance finding of CANVAS, as no other adequately powered studies replicated this finding.[21-23]. However, as SSTI, osteomyelitis and amputation could be part of the same pathological pathway, whether SSTI is associated with SGLT2i requires exploration.

Few studies have explored if SGLT2i carry a broader risk of non-genital SSTI, remote from the local effects of glycosuria. To date, large-scale SGLT2i clinical outcome trials have only reported limited non-genital SSTIs of interest. A meta-analysis of the published randomized evidence did not find an increased risk of bacterial skin infections (necrotising fasciitis, abscess, cellulitis or erysipelas) with SGLT2i use but had only 394 events in 69,573 people.[24] Another study described skin complications of SGLT2i in post-marketing surveillance, but focused on hypersensitivity and allergic reactions to the drug class without a clear comparator group.[25]

We aimed to describe non-genital SSTIs in the CANVAS and CREDENCE trials, and to determine if the rate of non-genital SSTI differed between participants allocated to canagliflozin versus placebo, overall or in any subgroup. We also aimed to assess patient factors associated with non-genital SSTIs in people with diabetes mellitus at high cardiovascular and/or renal risk.

Materials and Methods

Study design and participants

The CANVAS Program [19, 26] and CREDENCE trial [27, 28] are both large parallel, double-blind randomized, placebo-controlled multi-centre trials comparing outcomes for participants randomised to canagliflozin to participants randomised to placebo. Study designs and conduct have been previously described.[26, 27] Briefly, the CANVAS Program (comprised of the CANVAS and the CANVAS-R trials) assigned 10,142 people with type 2 diabetes and high cardiovascular risk to either oral canagliflozin or placebo and the CREDENCE trial assigned 4,401 people with type 2 diabetes and albuminuric kidney disease to either oral canagliflozin or placebo. In the CANVAS trial, participants were randomized 1:1:1 to canagliflozin 100mg daily, canagliflozin 300mg daily or placebo. In the CANVAS-R trial participants were randomized 1:1 to canagliflozin initially dosed at 100mg daily with the option of up-titration to 300mg daily after week 13, or placebo. In the CREDENCE trial, participants were randomized 1:1 to 100mg of canagliflozin daily or placebo.

Adverse events were collected as part of safety monitoring and assessed at every study visit in all trials. However, in the CANVAS-R trial, only serious adverse events or events leading to drug discontinuation were reported to the central safety committee and were available for analysis in the current study. This analysis was post-hoc and adverse events were categorized after data-lock.

Outcomes

The primary outcome of this *post-hoc* analysis was non-genital SSTI adverse events. As non-genital SSTI were not an adverse event of interest in any of the trials, non-genital SSTI was pre-defined by two blinded authors (AK and BS). All Medical Dictionary for Regulatory Activities (MedDRA) terms with a body system or organ class of "Infections and Infestations", "Skin and subcutaneous tissue disorders" or "Musculoskeletal and connective tissue disorders" were reviewed and classified as SSTI or not-SSTI with discrepancies resolved by consensus. Assessors were aware of the primary trial results but were blinded to treatment allocation relating to adverse events. The MeDRA terms used to define non-genital SSTI and fungal non-genital SSTI are listed in the Supplementary Appendix. Our definition of SSTI did not include genital mycotic infections as this group of infections are a recognised, specific and previously reported complication of SGLT2i,[19, 28] likely driven by a different pathophysiological pathway related to the local effects of glucosuria. Infections were categorized as bacterial, fungal or other skin infections, or soft tissue infections. Pre-specified secondary outcomes for this analysis were fungal non-genital SSTI, non-fungal non-genital SSTI and non-genital SSTI requiring hospitalisation.

Statistical analysis

We performed pooled analyses of the CANVAS and CREDENCE trials to assess the risk of non-genital SSTIs. The primary analysis was conducted in all treated participants through to 30 days after the last drug dose (on-treatment analysis), which is more conservative for adverse effect analyses. A pre-specified sensitivity analysis was performed in all randomized participants. Baseline characteristics were summarized as means with standard deviations, medians with inter-quartile ranges, or frequencies and percentages. For the primary outcome and secondary outcomes hazard ratios (HRs)

and 95% confidence intervals (CIs) were estimated with Cox regression models with a frailty component to account for the inclusion of distinct studies. The proportional hazards assumption was checked visually on the first imputed dataset using cumulative sums of residuals and by Kolmogorov-type Supremum test. Recurrent event analyses were conducted using the Anderson Gill method.[29] No correction for multiple comparisons were made. Annualised incidence rates were calculated per 1000 person-years of follow-up.

Exploratory analyses assessed whether risk of non-genital SSTIs differed in pre-specified subgroups based on participant characteristics (age, sex, race, region, body mass index, glycated haemoglobin, diabetes duration, eGFR, peripheral vascular disease, smoking, neuropathy and heart failure). Dose effect was assessed in the CANVAS trial, which randomly assigned participants to different doses of canagliflozin. The placebo group was randomly split into 2, to allow comparison between the 100mg and 300mg canagliflozin arms. In the CREDENCE trial only one dose of canagliflozin was tested.

Factors associated with non-genital SSTIs were determined by Cox regression in multivariable models using pre-selected baseline variables selected from known risk factors and biological plausibility. Collinearity for continuous variables (age, eGFR, body mass index and glycated haemoglobin) was assessed visually and when detected the variable considered to be more clinically relevant was entered into the model. Age and duration of diabetes mellitus were collinear, preventing duration of diabetes being entered as a variable in the multivariable analysis. Age, eGFR, body mass index and glycated haemoglobin were analysed as linear variables. The unadjusted risk of non-genital SSTI was graphed as a restricted cubic spline with knots at the 10^{th}, 50^{th} and 90^{th} centiles for pre-selected variables of interest: eGFR, glycated haemoglobin, body mass index and age. All analyses were conducted in SAS Enterprise Guide 7.1 with SAS/STAT 14.1 (SAS Institute, Cary NC, USA). In all analyses, two-sided $p<0.05$ were considered to be statistically significant.

Role of the funding source

Although the trials were funded by Janssen Research and Development, this analysis was independently designed and conducted by the authors and did not receive support from Janssen or any other external source.

Results

A total of 14,531 participants were included in the current analysis. The mean age was 63 years, and 10,866 (75%) were White. At baseline, 3,155 (22%) had a history of peripheral vascular disease and 5,252 (36%) had a diagnosis of neuropathy (Supplementary table 1).

There were 498 MeDRA terms within “Infections and Infestations”, “Skin and subcutaneous tissue disorders” and “Musculoskeletal and connective tissue disorders”, of which 57 were agreed to represent SSTI (Supplementary table 2 and 3).

During the trial, 903 (6%) participants experienced non-genital SSTIs over a median of 26 months follow-up at a rate of 23.9 events per 1000 person-years (Supplementary table 2). There were 861 skin and 42 soft tissue infections (Supplementary table 4). The most frequent MeDRA terms were “cellulitis” (n=237, 26.2%), “fungal skin infection” (n=237, 8%) and “gangrene” (n=51, 5.6%), respectively (Supplementary table 2). Four cases of necrotising fasciitis/ Fournier’s gangrene were reported, of which 3/7,990 were in the canagliflozin arms and 1/6,541 were in the placebo arms and all participants recovered (Table 1).

No difference was observed in the rate of non-genital SSTIs between canagliflozin and placebo arms (24.0 events/1000 person-years versus 23.9 events/1000 person-years, respectively; HR 0.97 [95% CI 0.85-1.11], p=0.70), with consistent results across participant subgroups (all p interaction>0.05). The results were consistent across participant subgroups and between trials (Figure 1 and 2) (all p interaction>0.05).

Similarly, no difference was detected in the secondary analyses, including rates of non-genital fungal SSTI or non-fungal SSTI with canagliflozin compared to placebo (Table 2). There was also no difference detected in the rate of hospitalised SSTI (HR 0.92 [95% CI 0.72-1.17], p=0.49) with canagliflozin compared to placebo. There were 1,258 recurrent (first and subsequent) non-genital SSTI over the assessed period and no difference in the recurrent event analysis with canaglifozin compared to placebo (HR 1.06 [0.94-1.19], p=0.32).

There was no suggestion of a dose-dependent effect, with similar risk between doses of canagliflozin (HR 1.17 [95% CI 0.88-1.55] versus HR 1.06 [95% CI 0.80-1.40] for the 100mg and 300mg canagliflozin arms in the CANVAS trial respectively, p interaction=0.64). Results were similar in the pre-specified sensitivity analyses (Supplementary table 5).

The study drug was continued after most first events. The drug dose was not changed in 755 (84%) cases. Of those, 132/449 (29%) in the canagliflozin group and 61/306 (20%) in the placebo group had a subsequent event whilst on treatment. Drug was interrupted in 81 (9%) cases and in the remaining 67 (7%) of first events, drug was withdrawn or already withdrawn at the time of the event.

Non-genital SSTI was associated with lower eGFR. Risk was non-linear for glycated haemoglobin and body mass index and rose after an HbA1c of 8% and body mass index of 30 kg/m^2. In contrast, risk of SSTI declined after 60 years of age. Independent associations with SSTI included male sex, higher body mass index, higher glycated haemoglobin, insulin requirement, established peripheral vascular disease and neuropathy (Figure 3). Older age was independently associated with a reduced risk of SSTI.

Discussion

In the largest randomized analysis by event rate assessing the risk of non-genital SSTIs with SGLT2i, we found that participants with type 2 diabetes mellitus at high cardiovascular and/or renal risk who received canagliflozin were not at increased risk of non-genital SSTI compared to those who received

placebo. This finding was consistent across participant subgroups and between trials. There was also no difference in the risk of recurrent events or non-genital fungal infections between those who received canagliflozin or placebo. Factors associated with non-genital SSTIs in this cohort of people with type 2 diabetes mellitus were younger age, male sex, and markers of diabetes severity (higher body mass index, higher glycated haemoglobin, insulin requirement, peripheral vascular disease and neuropathy) at baseline.

SGLT2i induce naturesis[30] producing sustained sodium shift out of the skin. A randomised trial of 59 people with type 2 diabetes mellitus found dapagliflozin reduced skin sodium content by 6% at 6 weeks compared to baseline[15] and a randomised trial of 79 participants with heart failure found empagliflozin reduced skin sodium content by 6% at 3 months compared to baseline.[16] Longer term studies are yet to be conducted. 24-hour urine samples were not collected in CANVAS or CREDENCE, preventing an assessment of naturesis in either study or correlation between naturesis and risk of non-genital SSTI in this analysis. Although SGLT2i reduce skin sodium content, our clearly neutral findings suggest that either the effect on the sodium content in the skin is of negligible antimicrobial consequence or that other benefits of SGLT2i, such as improvement in glycaemic control, kidney function, oedema or weight, which are also important determinants of risk of infections,[31] mitigate this risk.

Mycotic genital infections are a recognised complication of SGLT2i, assumed to be caused by the delivery of glucose to the genital area by glucosuria. In both CANVAS and CREDENCE, canagliflozin was associated with a higher risk of genital mycotic infections in both men and women.[19, 28] As these results were previously published and the mechanism of the adverse event is believed to be distinct, mycotic genital infections were not included in this analysis.

Our results, together with limited data from other randomized trials,[24] provides reassurance that SGLT2i do not increase the risk of non-genital SSTI in people with type 2 diabetes mellitus and atherosclerotic cardiovascular disease and/or diabetic kidney disease and suggests that associations

between non-genital SSTI and SGLT2i may be due to the higher prevalence of risk factors for non-genital SSTI among people in whom SGLT2i were initially indicated. This is particularly relevant as the indications for SGLT2i broaden to other diseases including chronic kidney disease and heart failure, irrespective of the presence or absence of diabetes mellitus.[32-36]

Our results help us to understand risk factors for skin and soft tissue infections in people with type 2 diabetes mellitus. People with diabetes mellitus are particularly susceptible to skin infections and are three times more likely to suffer skin infections than the general population,[37] with higher risk of both typical and atypical skin infections.[38] However, the relative contribution of diabetes mellitus itself,[39] complications of diabetes (kidney disease, peripheral vascular disease, neuropathy) or common comorbidities (such as obesity and smoking) and medications used to treat diabetes mellitus to the risk of infection is difficult to ascertain. This analysis found markers of diabetes severity (higher body mass index, higher glycated haemoglobin, insulin requirement, peripheral vascular disease and neuropathy) were independently associated with risk of non-genital SSTI. Hyperglycaemia creates a chronic inflammatory state that impairs leucocyte function[40] and increases susceptibility to infection. Independently, obesity is believed to impair the immune system and also specifically increases the risk of skin infections by increasing the risk of pressure areas and skin breakdown, lymphoedema and impairing circulation and wound healing.[41] The Fremantle Diabetes Study, an observational study of 1,294 participants, found prior recent infection-related hospitalization, along with disease complications (obesity, albuminuria, and retinopathy) at baseline were independently associated with risk of hospitalisation for infection.[31] Similarly, an English primary care cohort of 85,312 participants with type 1 or type 2 diabetes mellitus found glycaemic control was independently associated with risk of hospitalisation for infection.[42] Another study used two-sample Mendelian randomization in the genome-wide association study of 171,322 participants and found a causal relationship between obesity and SSTI.[43] Previous studies have also found associations between insulin requirement and risk of infection.[44] Insulin is not a first-line therapy for type 2 diabetes mellitus and is generally initiated after failure of first line therapies or if first line therapies are

contraindicated (such as in advanced chronic kidney disease).[45] The independent association with risk of non-genital SSTI is likely the result of residual confounding where insulin requirement is a marker of disease severity. Although, it is possible that the medication itself increases risk of SSTI, or that our findings are the result of detection bias where people requiring insulin therapy are more likely to be diagnosed with infection. Conversely, although we found no association between metformin use and SSTI, previous studies found metformin use is associated with reduced risk of bacterial pneumonia[46, 47] and better outcomes after sepsis,[48] potentially due to the anti-inflammatory effects of metformin,[49] or metformin may act as a surrogate marker for healthcare access or kidney function.

Although older age is commonly believed to be a risk factor for all types of infection, we found that younger, rather than older, age was associated with risk of non-genital SSTI. This finding is supported by previous studies of people with diabetes mellitus that found younger people were more likely to suffer skin infections.[50] However different relationships have been described for other types of infections. One study found older age predicted generalised bacterial infections,[31] while another study described varying relationships between age and infection, depending on the type of infection.[51] Possible explanations for a different relationship between age and SSTI compared to other types of infection, include the protective skin sodium barrier, which becomes more hypertonic with increasing age.[10] Alternative explanations include more aggressive disease in younger onset diabetes mellitus[52, 53] with greater risk of complications including SSTI. In addition, selection bias may disproportionately affect older people such that only older people with fewer comorbidities are part of clinical research.[54]

In our analysis, male gender was associated with risk of non-genital SSTI. This is supported by the findings of previous studies in people with diabetes mellitus[31] linking male sex to risk of generalised bacterial infections. Women appear to be at greater risk of hypersensitivity and allergic reactions from SGLT2i.[55] Reasons for greater vulnerability to skin and soft tissue infections in men are not clear but

may be related to hormonal differences or differences in received health care[56] and subsequent complications of diabetes mellitus.

In our analysis, race was not associated with risk of SSTI. However, the vast majority (75%) of participants were of White ethnicity, limiting the generalizability of the findings to other ethnicities. The possibility that the risk of skin and soft tissue infections varies between ethnicities and/or geographies remains. Multiple previous studies have described healthcare inequities in the risk of infection in minority racial groups in both the general population[31, 57] and in people with diabetes mellitus.[58]

Strengths and Limitations

This large individual participant level data analysis of randomized trials provides three times as many events as the preceding studies and thus greater power to detect a difference in SSTI. The trials successfully recruited people at-risk who were older and had worse markers of diabetes severity than registries of people with diabetes mellitus.[59] However, this analysis also has several limitations. This was a *post-hoc* analysis using investigator-reported adverse events where investigators may have different reporting thresholds and different methods for categorising adverse events. However, these factors should not systematically favour either arm of the trials. In addition, this analysis was not powered to look specifically at the rare complication of necrotising fasciitis. Furthermore, like many other trials in diabetes mellitus, women were under-represented. Caution should be exercised in generalising our results to other SGLT2i as some meta-analyses have found differences in risk of other infections between agents,[60] and in extending our findings to populations without type 2 diabetes.

Conclusion

Canagliflozin did not increase the risk of skin and soft tissue infections overall or in any subgroup, in participants with type 2 diabetes mellitus at high cardiovascular or renal risk. Our results provide reassurance for the use of SGLT2i and suggest that high rates of skin and soft tissue infections may be due to underlying risk from diabetes mellitus itself and its complications. Factors associated with skin and soft tissue infections in this cohort of people with type 2 diabetes mellitus included some traditional markers of worse diabetic control at baseline, younger age and male gender.

Acknowledgements

Author contributions

Design and oversight of the CANVAS and CREDENCE studies were provided by VP, MJ, CP, RA, GB, DMC, DdZ, HJLH, TG, AL, BN, DCW, HZ, BZ, KWM. MJ and AK conceptualized the present study. Adverse events were categorized by AK and BS. The analysis was designed and performed by AK, with expert review and revision provided by GLDT. Figures were produced by AK. The manuscript was drafted by AK and interpretation of the analysis provided by CA, BS, BLN, HJLH, BN, HZ, CH, RA, GB, DMC, DdZ, TG, AL, CP, DCW, BZ, KWM, VP and MJ. All authors had full access to the data on request and AK and BN verified all the data in the study. All authors reviewed the manuscript and have agreed to publication of the final version.

The CANVAS and CREDENCE studies were sponsored by Janssen Research and Development, and was conducted collaboratively by the sponsor, an academic-led steering committee, and an academic research organization, George Clinical. This *post-hoc* analysis of the CANVAS and CREDENCE trials was not specifically funded. The funders were not involved in the design, analysis, reporting, or decision to submit this manuscript for publication. AK is supported by an NHMRC Postgraduate Scholarship (1150349) via the University of New South Wales, an Australian Government Research Training Program Fee Offset and has received a George Institute Scholarship. BS is supported by the Jacquot Research Establishment Award from the Royal Australasian College of Physicians. We thank the participants in the trials and thank the study investigators, who are listed in the Supplementary Appendix to the primary CANVAS and CREDENCE study publications.

Disclosures

AL is on the steering committee for the CREDENCE trial and has received travel support from Janssen. BLN has received fees for advisory boards, scientific presentations, speaker fees, steering committee

roles and travel support from American Diabetes Association, AstraZeneca, Bayer, Boehringer and Ingelheim, Cambridge Healthcare Research, Janssen, and Medscape with all honoraria paid to his institution. CA is supported by an NHMRC/MRFF Priority Investigator Grant and a NSW Health EMCR Grant and is an employee of the George Institute for Global Health. She is responsible for the secondary analysis program for the CANVAS Program and CREDENCE trial. She has received honoraria from Astra Zeneca and Amgen. CP has served on the steering committee for CREDENCE, has been a speaker for Janssen Cilag, advisory board member and speaker for Astra Zeneca, speaker for Eli Lilly and Boehringer Ingelheim. DdZ has served on advisory boards and/or been a speaker for Bayer, Boehringer Ingelheim, Fresenius, Mitsubishi-Tanabe, Travere Pharmaceuticals; Steering Committees and/or speaker for AbbVie and Janssen; Data Safety and Monitoring Committees for Bayer. Honoraria paid to Institution and consultant/speaker. DCW has an ongoing consultancy contract with AstraZeneca and has received payments from Amgen, Astellas, Boehringer Ingelheim, Bayer, GlaxoSmithKline, Gilead, Janssen, Mundipharma, Merck Sharpe and Dohme, Tricida, Vifor and Zydus. DMC has personal fees or fees paid by Janssen Pharmaceuticals to the Baim Institute for work on the CREDENCE trial steering committee. He has received consulting fees from Amgen, CSL Behring, Eli Lilly, Fresenius, Gilead, Medtronic/Covidien, Merck, Novo Nordisk, Zoll, AstraZeneca, Glaxo Smith Kline, PLC Medical and Allena Pharmaceuticals, and has received research support from Medtronic and Amgen. GB has received support from T32 NIH grant DK07011 and is a consultant to Bayer, KBP Biosciences, Ionis, Alynylam, AstraZeneca, Quantum Genomics, Novo Nordisk, Dia Medica Therapeutics and inREGEN. HJLH has served as a consultant for AbbVie, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Chinook, CSL Pharma, Fresenius, Gilead, Janssen, Merck, Mundipharma, Mitsubishi Tanabe and Retrophin and has received grant support from AbbVie, AstraZeneca, Boehringer Ingelheim and Janssen. HZ has received fees for steering committee roles and travel support from Janssen. KM has received research support from Afferent, Amgen, Apple, Inc, AstraZeneca, Cardiva Medical, Inc, Daiichi, Ferring, Google (Verily), Johnson & Johnson, Luitpold, Medtronic, Merck, National Institutes of Health, Novartis, Sanofi, St. Jude, and Tenax. KM also has

served as a consultant (speaker fees for continuing medical education events only) for Abbott, Ablynx, AstraZeneca, Baim Institute, Boehringer Ingelheim, Bristol-Myers Squibb, Elsevier, GlaxoSmithKline, Johnson & Johnson, MedErgy, Medscape, Mitsubishi, Myokardia, National Institutes of Health, Novartis, Novo Nordisk, Portola, Radiometer, Regeneron, Springer Publishing, and University of California, San Francisco. RA reports receiving personal fees and nonfinancial support from Bayer Healthcare Pharmaceuticals Inc.; receiving personal fees and nonfinancial support from Akebia Therapeutics, Boehringer Ingelheim, Eli Lilly and Vifor Pharma; serving as a member of data safety monitoring committees for Chinook and Vertex Pharmaceuticals; serving as a member of steering committees of randomized trials for Akebia Therapeutics and Bayer, serving as associate editor for the American Journal of Nephrology and Nephrology Dialysis and Transplantation and as an author for UpToDate; and receiving research grants from the US Veterans Administration and the National Institutes of Health Technology Services. TG has received grant or consulting support for statistical consultations from Janssen, DURECT, Pfizer, Astrazeneca, CSL, and Boehringer-Ingleheim. VP serves as a Board Director for St. Vincents Health Australia, George Clinical and several Medical Research Institutes. He has led or served on the Steering Committees of trials funded by Abbvie, Bayer, GSK, Boehringer Ingelheim, Eli Lilly, Gilead, Janssen Novartis, Novo Nordisk, Otsuka, Pfizer, Retrophin/Travere, and Tricida. VP also reports having receiving honoraria for scientific presentations and/or advisory board attendance from Abbvie, Amgen, Astra Zeneca, Bayer, Baxter, Boehringer Ingelheim, Chinook, Durect, Eli Lilly, Gilead, GSK, Janssen, Merck, Mitsubishi Tanabe, Mundipharma, Novartis, Novo Nordisk, Pharmalink, Pfizer, Reata, Relypsa, Roche, Sanofi, and Servier. MJ J is responsible for research projects that have received funding from Amgen, Baxter, CSL, Dimerix, Eli Lilly, Gambro, and MSD; has received Advisory, Steering Committee and/or speaker fees from Akebia, Amgen, Astra Zeneca, Baxter, Bayer, Boehringer Ingelheim, Chinook, CSL, Janssen, MSD, Roche and Vifor; with any consultancy, honoraria or travel support paid to her institution.

AK, BS, CH and GLDT have no conflicts of interest to declare.

Data sharing

Data from this study are available in the public domain via the Yale University Open Data Access Project (http://yoda.yale.edu/). This includes deidentified individual participant data, data definition specification, annotated case report form, protocol with amendments and primary statistical analysis plan.

Figure Legends

Figure 1 a and b

Risk of non-genital skin and soft tissue infection from canagliflozin versus placebo Hazard Ratio (95% CI) overall and by trial.

Figure 2

Risk of non-genital skin and soft tissue infection from canagliflozin versus placebo Hazard Ratio (95% CI) by pre-specified subgroups.

Figure 3

Factors associated with non-genital skin and soft tissue infections.

Figure 4a, b, c and d

Unadjusted risk of non-genital skin and soft tissue infections by eGFR, glycated haemoglobin, body mass index and age.

Tables

Table 1. Non-genital skin and soft tissue infection event numbers and outcomes

Outcome	Canagliflozin 7,990	Placebo 6,541	All 14,531
All events	533	370	903
Serious adverse events	131	98	229
Hospitalised	128	98	226
Fatal events	1	3	4
Necrotising fasciitis/ Fournier's gangrene	3	1	4

Table 2. Secondary analyses

	Canagliflozin		**Placebo**		**Hazard ratio [95% CI], p value**
	n/N	**Rate**	**n/N**	**Rate**	
Non-genital Fungal infection	118/7,990	5.1	68/6,541	4.2	HR 1.18 [0.88-1.60], p=0.27
Non-fungal infection	450/7,990	20.0	314/6,541	20.1	HR 0.96 [95% CI 0.83-1.11], p=0.61
SSTI requiring hospitalization	153/7,990	6.6	121/6,541	7.5	HR 0.92 [95% CI 0.72-1.17], p=0.49

References

1. Neuen, B.L., et al., *SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis.* The Lancet Diabetes & Endocrinology, 2019. **7**(11): p. 845-854.
2. Arnott, C., et al., *Sodium-Glucose Cotransporter 2 Inhibition for the Prevention of Cardiovascular Events in Patients With Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis.* J Am Heart Assoc, 2020. **9**(3): p. e014908.
3. Das Sandeep, R., et al., *2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes.* Journal of the American College of Cardiology, 2020. **76**(9): p. 1117-1145.
4. de Boer, I.H., et al., *Executive summary of the 2020 KDIGO Diabetes Management in CKD Guideline: evidence-based advances in monitoring and treatment.* Kidney International, 2020. **98**(4): p. 839-848.
5. Herrington, W.G., et al., *Empagliflozin in Patients with Chronic Kidney Disease.* N Engl J Med, 2023. **388**(2): p. 117-127.
6. Dennis, J.M., et al., *Time trends in prescribing of type 2 diabetes drugs, glycaemic response and risk factors: A retrospective analysis of primary care data, 2010–2017.* 2019. **21**(7): p. 1576-1584.
7. Adhikari, R., et al., *National Trends in Use of Sodium-Glucose Cotransporter-2 Inhibitors and Glucagon-like Peptide-1 Receptor Agonists by Cardiologists and Other Specialties, 2015 to 2020.* 2022. **11**(9): p. e023811.
8. Lemoine, S., et al., *Tissue Sodium Storage in Patients With Heart Failure: A New Therapeutic Target?* 2021. **14**(11): p. e012910.
9. Kopp, C., et al., *²³Na Magnetic Resonance Imaging of Tissue Sodium.* 2012. **59**(1): p. 167-172.
10. Kopp, C., et al., *23Na magnetic resonance imaging-determined tissue sodium in healthy subjects and hypertensive patients.* Hypertension, 2013. **61**(3): p. 635-40.
11. Jantsch, J., et al., *Cutaneous Na+ storage strengthens the antimicrobial barrier function of the skin and boosts macrophage-driven host defense.* Cell metabolism, 2015. **21**(3): p. 493-501.
12. Strazzullo, P. and C. Leclercq, *Sodium.* Advances in nutrition (Bethesda, Md.), 2014. **5**(2): p. 188-190.
13. Thomas, M.C. and D.Z.I. Cherney, *The actions of SGLT2 inhibitors on metabolism, renal function and blood pressure.* Diabetologia, 2018. **61**(10): p. 2098-2107.
14. Ye, N., et al., *Blood Pressure Effects of Canagliflozin and Clinical Outcomes in Type 2 Diabetes and Chronic Kidney Disease: Insights From the CREDENCE Trial.* Circulation, 2021. **143**(18): p. 1735-1749.
15. Karg, M.V., et al., *SGLT-2-inhibition with dapagliflozin reduces tissue sodium content: a randomised controlled trial.* Cardiovascular diabetology, 2018. **17**(1): p. 5-5.
16. Kolwelter, J., et al., *The SGLT2 inhibitor empagliflozin reduces tissue sodium content in patients with chronic heart failure: results from a placebo-controlled randomised trial.* Clin Res Cardiol, 2023. **112**(1): p. 134-144.
17. Hui Zhao, M.Y., Ziran Li, et al. , *Sodium-glucose co-transporter-2 inhibitors (SGLT2i) treatment and risk of osteomyelitis: a pharmacovigilance study of the FAERS database.*, in *Authorea.* .
18. Zhou, X., et al., *Safety of SGLT2 Inhibitors: A Pharmacovigilance Study from 2013 to 2021 Based on FAERS.* 2021. **12**.
19. Neal, B., et al., *Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes.* N Engl J Med, 2017. **377**(7): p. 644-657.
20. Matthews, D.R., et al., *Effects of canagliflozin on amputation risk in type 2 diabetes: the CANVAS Program.* Diabetologia, 2019. **62**(6): p. 926-938.

21. Arnott, C., et al., *The effect of canagliflozin on amputation risk in the CANVAS program and the CREDENCE trial.* Diabetes Obes Metab, 2020. **22**(10): p. 1753-1766.
22. Heyward, J., et al., *Association between sodium-glucose cotransporter 2 (SGLT2) inhibitors and lower extremity amputation: A systematic review and meta-analysis.* PLOS ONE, 2020. **15**(6): p. e0234065.
23. Baigent, C., et al., *Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials.* The Lancet, 2022. **400**(10365): p. 1788-1801.
24. Silverii, G.A., et al., *Fournier's gangrene and sodium-glucose co-transporter-2 inhibitors: A meta-analysis of randomized controlled trials.* Diabetes Obes Metab, 2020. **22**(2): p. 272-275.
25. Sakaeda, T., et al., *Susceptibility to serious skin and subcutaneous tissue disorders and skin tissue distribution of sodium-dependent glucose co-transporter type 2 (SGLT2) inhibitors.* Int J Med Sci, 2018. **15**(9): p. 937-943.
26. Neal, B., et al., *Rationale, design and baseline characteristics of the CANagliflozin cardioVascular Assessment Study-Renal (CANVAS-R): A randomized, placebo-controlled trial.* Diabetes Obes Metab, 2017. **19**(3): p. 387-393.
27. Jardine, M.J., et al., *The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) Study Rationale, Design, and Baseline Characteristics.* Am J Nephrol, 2017. **46**(6): p. 462-472.
28. Perkovic, V., et al., *Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy.* N Engl J Med, 2019. **380**(24): p. 2295-2306.
29. Andersen, P.K., and Gill, R. D. , *Cox's Regression Model Counting Process: A Large Sample Study.* Annals of Statistics 1982. **10**: p. 1100–1120.
30. Kawasoe, S., et al., *Mechanism of the blood pressure-lowering effect of sodium-glucose cotransporter 2 inhibitors in obese patients with type 2 diabetes.* BMC Pharmacology and Toxicology, 2017. **18**(1): p. 23.
31. Hamilton, E.J., et al., *Incidence and Predictors of Hospitalization for Bacterial Infection in Community-Based Patients with Type 2 Diabetes: The Fremantle Diabetes Study.* PLOS ONE, 2013. **8**(3): p. e60502.
32. Kang, A. and M.J. Jardine, *SGLT2 inhibitors may offer benefit beyond diabetes.* Nature Reviews Nephrology, 2021. **17**(2): p. 83-84.
33. Heerspink, H.J.L., et al., *Dapagliflozin in Patients with Chronic Kidney Disease.* N Engl J Med, 2020. **383**(15): p. 1436-1446.
34. McMurray, J.J.V., et al., *Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction.* N Engl J Med, 2019. **381**(21): p. 1995-2008.
35. Packer, M., et al., *Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure.* N Engl J Med, 2020. **383**(15): p. 1413-1424.
36. Anker, S.D., et al., *Effect of Empagliflozin on Cardiovascular and Renal Outcomes in Patients With Heart Failure by Baseline Diabetes Status - Results from the EMPEROR-Reduced Trial.* Circulation, 2020.
37. Benfield, T., J.S. Jensen, and B.G. Nordestgaard, *Influence of diabetes and hyperglycaemia on infectious disease hospitalisation and outcome.* Diabetologia, 2007. **50**(3): p. 549-54.
38. Shah, B.R. and J.E. Hux, *Quantifying the Risk of Infectious Diseases for People With Diabetes.* 2003. **26**(2): p. 510-513.
39. Grossmann, V., et al., *Profile of the Immune and Inflammatory Response in Individuals With Prediabetes and Type 2 Diabetes.* 2015. **38**(7): p. 1356-1364.
40. Pettersson, U.S., et al., *Increased recruitment but impaired function of leukocytes during inflammation in mouse models of type 1 and type 2 diabetes.* PloS one, 2011. **6**(7): p. e22480-e22480.

41. Pugliese, G., et al., *Obesity and infectious diseases: pathophysiology and epidemiology of a double pandemic condition.* International Journal of Obesity, 2022. **46**(3): p. 449-465.
42. Critchley, J.A., et al., *Glycemic Control and Risk of Infections Among People With Type 1 or Type 2 Diabetes in a Large Primary Care Cohort Study.* Diabetes Care, 2018. **41**(10): p. 2127-2135.
43. Hu, H., et al., *The causal relationship between obesity and skin and soft tissue infections: A two-sample Mendelian randomization study.* Frontiers in Endocrinology, 2022. **13**.
44. Donnelly, J.P., et al., *Association of Diabetes and Insulin Therapy With Risk of Hospitalization for Infection and 28-Day Mortality Risk.* Clin Infect Dis, 2017. **64**(4): p. 435-442.
45. *Standards of Medical Care in Diabetes—2019 Abridged for Primary Care Providers.* 2019. **37**(1): p. 11-34.
46. Yen, F.S., et al., *Metformin use and the risk of bacterial pneumonia in patients with type 2 diabetes.* Sci Rep, 2022. **12**(1): p. 3270.
47. Mor, A., et al., *Rates of Community-based Antibiotic Prescriptions and Hospital-treated Infections in Individuals With and Without Type 2 Diabetes: A Danish Nationwide Cohort Study, 2004–2012.* Clinical Infectious Diseases, 2016. **63**(4): p. 501-511.
48. Gómez, H., et al., *Association of Metformin Use During Hospitalization and Mortality in Critically Ill Adults With Type 2 Diabetes Mellitus and Sepsis*.* Critical Care Medicine, 2022. **50**(6).
49. Cameron, A.R., et al., *Anti-Inflammatory Effects of Metformin Irrespective of Diabetes Status.* Circ Res, 2016. **119**(5): p. 652-65.
50. Jia, L., et al., *Incidence and risk factors for developing infection in patients presenting with uninfected diabetic foot ulcers.* PloS one, 2017. **12**(5): p. e0177916-e0177916.
51. Kim, E.J., et al., *Diabetes and the Risk of Infection: A National Cohort Study.* Diabetes Metab J, 2019. **43**(6): p. 804-814.
52. Hubert, K., et al., *Type 2 diabetes phenotype and progression is significantly different if diagnosed before versus after 65 years of age.* J Diabetes Sci Technol, 2008. **2**(1): p. 82-90.
53. Bjornstad, P., et al., *Long-Term Complications in Youth-Onset Type 2 Diabetes.* N Engl J Med, 2021. **385**(5): p. 416-426.
54. Smyth, B., et al., *Representativeness of Randomized Clinical Trial Cohorts in End-stage Kidney Disease: A Meta-analysis.* JAMA Intern Med, 2019. **179**(10): p. 1316-24.
55. Yokote, K., et al., *Real-world evidence for the safety of ipragliflozin in elderly Japanese patients with type 2 diabetes mellitus (STELLA-ELDER): final results of a post-marketing surveillance study.* Expert Opinion on Pharmacotherapy, 2016. **17**(15): p. 1995-2003.
56. Tseng, C.-L., et al., *Are there gender differences in diabetes care among elderly medicare enrolled veterans?* Journal of General Internal Medicine, 2006. **21**(3): p. S47-S53.
57. Mayr, F.B., et al., *Infection rate and acute organ dysfunction risk as explanations for racial differences in severe sepsis.* Jama, 2010. **303**(24): p. 2495-503.
58. Meng, Y.-Y., et al., *Racial and Ethnic Disparities in Diabetes Care and Impact of Vendor-Based Disease Management Programs.* Diabetes Care, 2016. **39**(5): p. 743-749.
59. Rawshani, A., et al., *Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes.* 2018. **379**(7): p. 633-644.
60. Li, D., et al., *Urinary tract and genital infections in patients with type 2 diabetes treated with sodium-glucose co-transporter 2 inhibitors: A meta-analysis of randomized controlled trials.* Diabetes Obes Metab, 2017. **19**(3): p. 348-355.