Risk of urogenital infections in non-diabetic patients treated with sodium glucose transporter 2 (SGLT2) inhibitors. Systematic review and meta-analysis

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Supplementary Table 1.
Data extracted from the included studies (PICO Tables).

Authors, year	Population	Intervention	Outcomes
Anker 2021 EMPEROR-Preserved	5988 patients with class II–IV heart failure and an ejection fraction of more than 40% with or without diabetes	Empagliflozin (10 mg once daily) or placebo in addition to usual therapy empagliflozin (n = 2996) placebo (n = 2989) median of 26.2 months	Empagliflozion versus placebo Patients with any adverse event 2574 (85.9) *vs* 2585 (86.5) Patients with any serious adverse event 1436 (47.9) *vs* 1543 (51.6) Urinary tract infections 297 (9.9) vs 243 (8.1) Complicated urinary tract infections 57 (1.9) *vs* 45 (1.5) Genital infections 67 (2.2) *vs* 22 (0.7) Complicated genital infections 8 (0.3) *vs* 8 (0.3)

Supplementary information from https//www.g-ba.de /bewertungsverfahren /nutzenbewertung/810/			Empagliflozion versus placebo Diabetic UTI 148/1465 *vs* 131/1471 Complicated UTI 29/1465 *vs* 25/1471 Genital infections 37/1465 *vs* 14/1471 Complicated genital infections Non-diabetic UTI 149/1531 *vs* 112/1518 Complicated UTI 28/1531 *vs* 20/1518 Genital infections 30/1531 *vs* 8/1518 Complicated genital infections
Abraham 2021 EMPERIAL-Reduced EMPERIAL-Preserved	HF patients with reduced EF (HFrEF) (< 40%, n = 312) EMPERIAL-Reduced or preserved EF (> 40%, n = 315) EMPERIAL-Preserved evaluating the effect on exercise ability and patient reported outcomes in patients with and without T2D	Empagliflozin 10 mg placebo for 12 weeks	Empagliflozin 10 mg versus placebo Diabetics Complicated urinary tract infections 2/173 *vs* 1/175 Genital infections 2/173 *vs* 1/175 Non diabetics Complicated urinary tract infections 0/136 *vs* 1/136 Genital infections 1/136 *vs* 0/136
Bays 2014	Overweight and obese subjects (body mass index [BMI] > 27 and > 50 kg/m^2 376 subjects without diabetes mellitus	Canagliflozin 50, 100, or 300 mg or placebo once day 12 weeks	Canagliflozin 50+100+300 versus placebo Urinary tract infections 10/98+7/93+8/96 *vs* 6/89 Vulvovaginal mycotic infections 8/98+5/93+14/96 *vs* 1/89 Genital mycotic infection – men 0/12+ 0/17+1/10 *vs* 0/14 Genital mycotic infection – women 12/86+ 10/76+19/86 *vs* 3/75
Cherney 2020 DIAMOND	53 adult patients (aged 18-75 years, mean 51+/-13) 32% women chronic kidney disease, without a diagnosis of diabetes 24-h urinary protein > 500 mg and <= 3500 mg eGFR) at least 25 mL/min	Dapagliflozin then placebo (n = 27) placebo then dapagliflozin (n = 26) 6 wks Cross-over	Dapagliflozin *vs* placebo Urinary tract infection 1/53 *vs* 0/52 Genital infection 1/53 *vs* 0/52

Herrington 2023 EMPA-KIDNEY	DM2 6609 (46%)		Empagliflozin (N=3304) Placebo (N=3305) Serious urinary tract infection 52/3304 (1.6%) 54/3305 (1.6%) Serious genital infection 1/3304 (< 0.1%) 1/3305 (< 0.1%)
Hollander 2017	obese or overweight without type 2 diabetes patients (n = 335, aged 18–65 years, BMI 30 to to < 50 kg/m^2 or BMI > 27 to < 50 with hypertension and/or dyslipidemia	Placebo (n = 82) canagliflozin 300 mg (n = 84) phentermin 15 mg (n = 85) canagliflozin+phenermin (n = 83) orally once daily	Canagliflozin *vs* phentermine *vs* canagliflozion+phentermin Genital mycotic infections - Women 7/84 *vs* 0/85 *vs* 5/83 *vs* 0/82 Genital mycotic infections - Men 0/84 *vs* 0/85 *vs* 0/83 *vs* 0/82 Urinary tract infections 4/84 *vs* 1/85 *vs* 2/83 *vs* 0/82
Lundkvist 2016 (Diabetes Ob Metab)	50 obese adults without diabetes (aged 18-70 years; body mass index 30-45 kg/m^2)	Dapagliflozin 10 mg once daily plus subcutaneous long-acting exenatide 2 mg once weekly (n = 25) placebo (n = 24)	Urinary tract infections 2/25 *vs* 1/24 Acute pyelonephritis 1/25 *vs* 0/24 Urinary tract infection 0/25 *vs* 1/24 Fungal urinary tract infection 1/25 *vs* 0/24 Genital infections 1/25 *vs* 0/24 Vaginal infection 1/25 *vs* 0/24
McMurray 2019 DAPA-HF	Patients with New York Heart Association class II, III, or IV heart failure and an ejection fraction of 40% or less N = 4744	Dapagliflozin N = 2373 Placebo N = 2371 Diabetes 993 (41.8) 990 (41.8)	Dapagliflozin (n = 2368) *vs* placebo (n = 2368) Urinary tract infection 11/2368 *vs* 17/2368 Urosepsis 4/2368 *vs* 7/2368 Pyelonephritis acute 2 *vs* 0 Pyelocystitis 1 *vs* 0 Pyelonephritis 1 *vs* 1 Cystitis 0 *vs* 1 Renal abscess 0 *vs* 1 Urinary tract infection Staphylococcal 0 *vs* 1 Balanoposthitis 0 *vs* 1 Fournier 0 *vs* 1

Packer 2020 EMPEROR reduced	3730 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less EMPEROR reduced with and without DM2	Empagliflozin (10 mg once daily) placebo in addition to recommended therapy Diabetes mellitus 927 (49.8) *vs* 929 (49.8)	Empagliflozin (n=1863) *vs* Placebo (n=1863) Urinary tract infections 91/186383/1863 Complicated urinary tract infections 1971863 15/1863 Genital infections 31/186312/1863 Complicated genital infections 6/1863 5/1863 (0.3)
Supplementary information from *Anker SD et al* Circulation 2021; 143:337-349			Empagliflozin *vs* placebo Diabetics Urinary tract infections 52/927 *vs* 49/926 Genital infections 18/927 *vs* 4/926 Non diabetics Urinary tract infection 39/936 *vs* 34/937 Genital infections 13/936 *vs* 8/937
Reis 2022	40 adult non-diabetic HF patients with a left ventricular ejection fraction (LVEF) < 50%	Dapagliflozin 10 mg *vs* HF medication 20+20 6 months	Dapagliflozin 10 mg *vs* controls Urinary tract infection 1/20 *vs* 0/20
Solomon 2022 DELIVER	N = 6236 N = 3150 (50%) Preserved Ejection Fraction Heart Failure	Dapagliflozin 10 mg (n = 3126) Placebo (n = 3127)	Dapagliflozin *vs* Placebo Urinary tract infection 30/3126 *vs* 32/3127 Discontinuation due to urinary tract infection 11/3126 *vs* 6/3127

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Wheeler 2021 DAPA-CKD	4304 participants urinary albumin-to-creatinine ratio of 200–5000 mg/g eGFR) 25–75 mL/min per 1·73m²	Dapagliflozin 10 mg once daily N = 2152 placebo N = 2152 Patients with DM dapagliflozin n = 1453 placebo n = 1450 Patients without DM dapagliflozin n = 696 placebo n = 699 Median follow up 2·4 years (IQR 2·0–2·7)	Any SAE of urinary tract infection DM 23/1453 *vs* 14/1450 no DM 26/696 *vs* 4/699 Urinary tract infection DM 17/1453 *vs* 10/1450 No DM 3/696 *vs* 3/690 Pyelonephritis acute DM 2/1453 *vs* 1/1450 no DM 3/696 *vs* 0/699 Cystitis DM 1/1453 *vs* 2/1450 No DM 0/696 *vs* 0/699 Escherichia urinary tract infection DM 1/1453 *vs* 0/1450 No DM 0/696 *vs* 0/699 Pyonephrosis DM 1/1453 *vs* 0/1450 No DM 0/696 *vs* 0/699 Urinary tract infection bacterial DM 1/1453 *vs* 0/1450 No DM 0/696 *vs* 0/699 Urogenital infection bacterial DM 1/1453 *vs* 0/1450 No DM 0/696 *vs* 0/699 Pyelonephritis DM 0/1453 *vs* 1/1450 No DM 1/696 *vs* 1/699 Any SAE of genital infection DM 3/1453 *vs* 0/1450 No DM 0/696 *vs* 07699 Balanoposthitis DM 1/1453 *vs* 0/1450 No DM 0/696 *vs* 0/699 Urogenital infection bacterial DM 1/1453 *vs* 0/1450 No DM 0/696 *vs* 0/699 Vulval cellulitis DM 1/1453 *vs* 0/1450 No DM 0/696 *vs* 0/699

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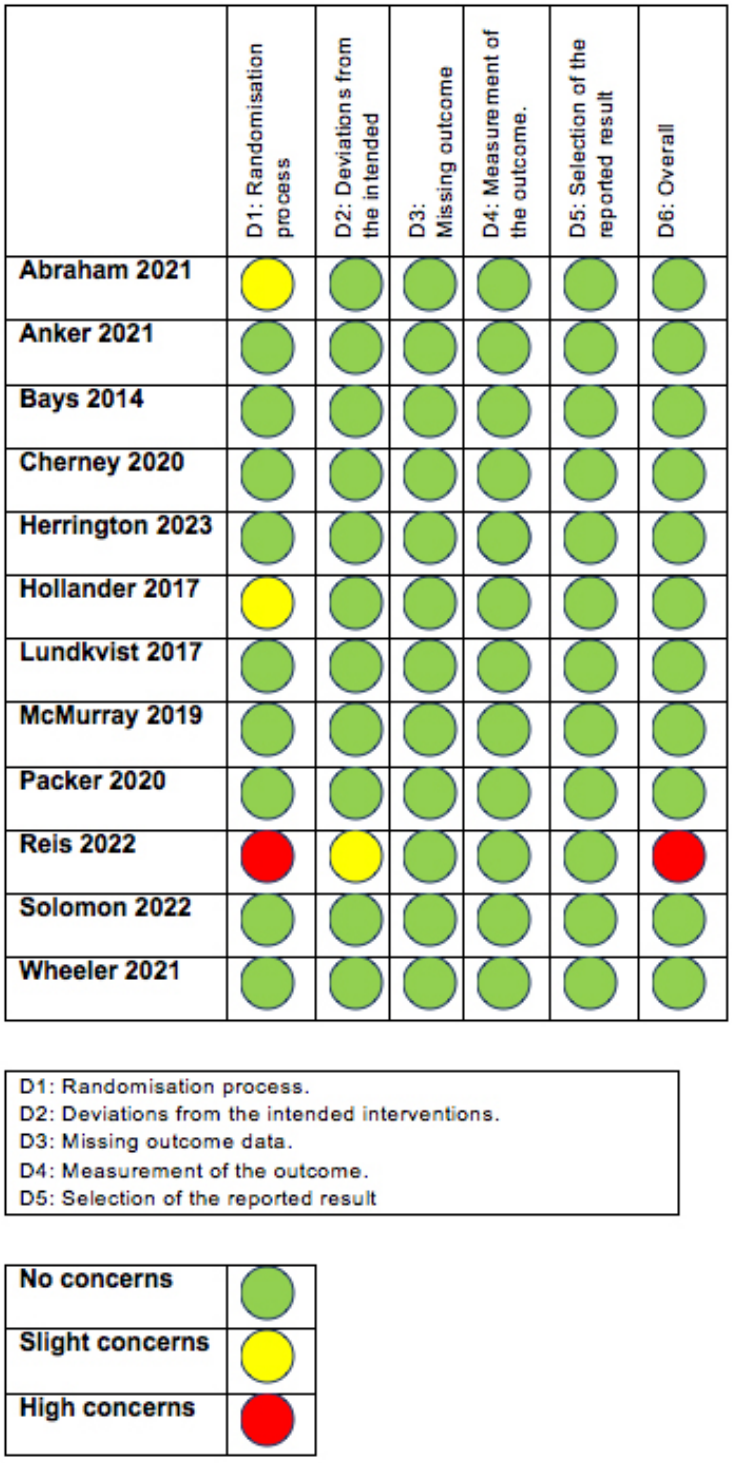
Risk of Bias

Supplementary Figure 1.
Risk of Bias (RoB) 2 assessment of risk of bias in randomised control trialspresented.
The values at the right of the no-effect bar show higher odds of infection in diabetic patients.



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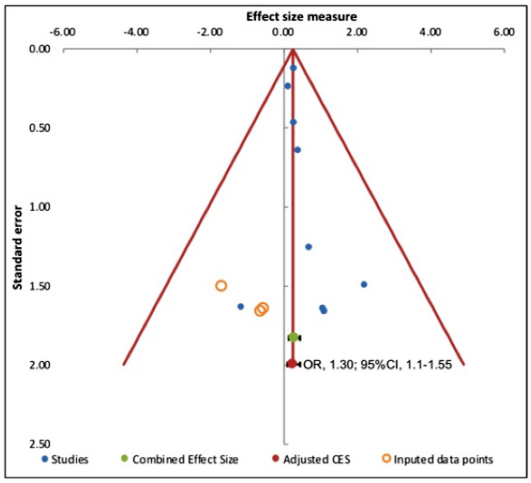
Tools to assess study quality were tailored to study design. The risk of bias in randomised control trials was assessed using the Risk of Bias (RoB) 2 assessment tool as prescribed by the Cochrane Methods 1,2. Data is shown in table S2 (Supplementary Table 2). Study quality was independently assessed by two reviewers (DH and HP) against pre-defined criteria. Disagreements were resolved by discussion. Risk of bias was not used to exclude studies. We anticipated identifying too few studies to assess publication bias.

Comments

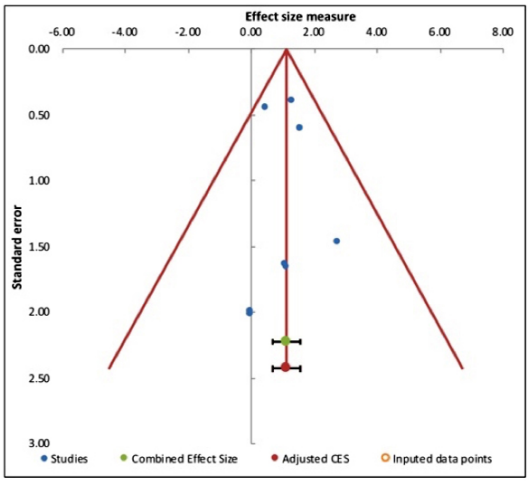
Abraham - Slight differences between the two groups. Domain 1 slight concerns.
Anker - No concerns
Bays - No concerns
Cherney - No concerns
Herrington - No concerns
Hollander - Single blinded study. Domain 1 slight concerns. Small sample sizes.
Lundquist - No concerns
McMurray - No concerns
Packer - No concerns
Reis - Not blinded. I am not sure the allocation sequence concealed until participants were enrolled and assigned to interventions also carers and people delivering the interventions were aware of participants' assigned intervention during the trial.
Salomon - No concerns
Wheeler - No concerns

Funnel plots

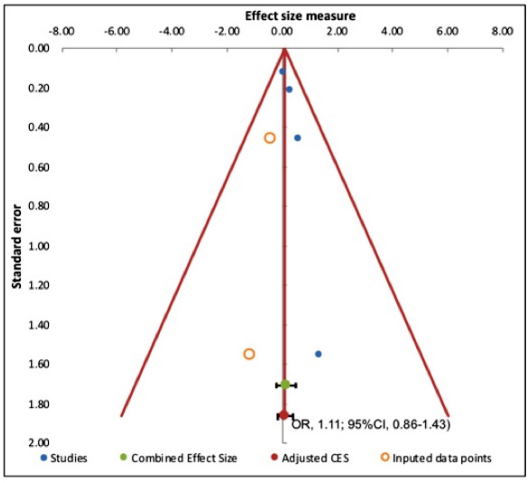
Supplementary Figure 2.
Publication bias assessment in pooled analyses including at least 4 trials. The effect size is presented as the logarithm of the odds ratios. If missing studies (open orange circles) are imputed by the "trim-and-fill" analysis, adjusted odds ratios (red dots) and 95% confidence intervals are presented in the plots.



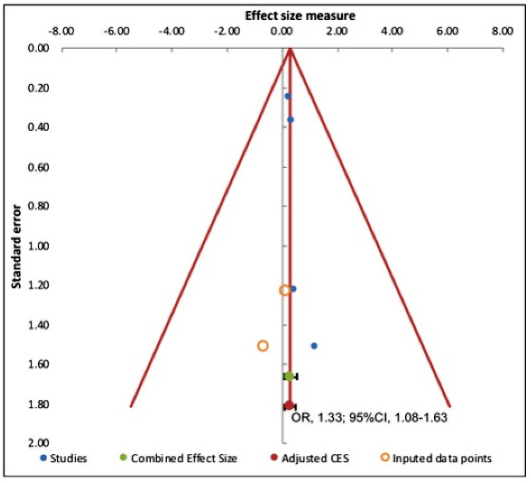
UTI in non-diabetics; SGLTi vs Placebo



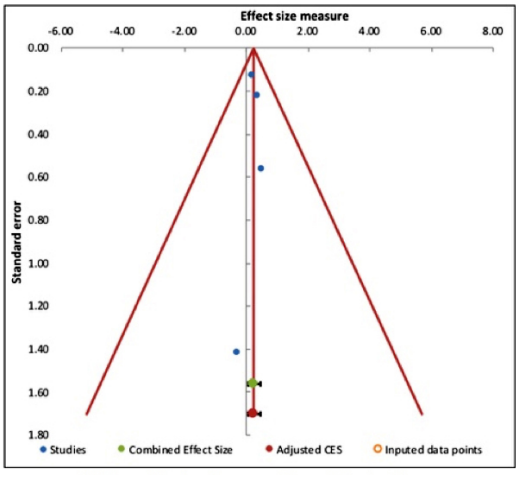
Genital infections in non-diabetics; SGLTi vs Placebo



UTI – Diabetics vs Non Diabetics; patients on SGLTi



Genital infections – Diabetics vs Non Diabetics; patients on SGLTi



UTI – Diabetics vs Non Diabetics; patients on Placebo

Summary of findings

Supplementary Table 2.

Effect of SGLT2 inhibitors or placebo on urogenital infections

Patient or population: male or female patients with or without diabetes
Settings: outpatient
Intervention: SGLT2 inhibitors (SGLT2i)
Comparison: placebo
Outcome: onset of urinary tract infections (UTI) or genital infections (GI)

Endpoint, Comparison, Condition	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies or comparisons)	Quality of the evidence (GRADE)	Comments
	Assumed control risk	Corresponding intervention risk				
	Comparison	Intervention				
Urinary tract infections, SGLT2i vs. placebo, non-diabetic subjects	44.41 per 1000	58.21 per 1000 (47.78 to71.21)	OR 1.33 (1.08 to 1.65)	7326 (9)	⊕⊝⊝⊝ Very low	*Reasons for downgrading:* - risk of bias - probable publication bias - Indirectness of evidence (Surrogate endpoint)
Genital infections, SGLT2i *vs.* placebo, non-diabetic subjects	5.34 per 1000	16.42 per 1000 (10.04 to 26.80)	OR 3.11 (1.89 to 5.13)	7326 (9)	⊕⊕⊕⊝ Moderate	*Reasons for upgrading:* - large magnitude of effect *Reasons for downgrading:* - risk of bias - Indirectness of evidence (Surrogate endpoint)
Urinary tract infections, diabetic *vs.* non-diabetic subjects treated with SGLT2i	58.81 per 1000	67.03 per 1000 (55.47 to 80.96)	OR 1.15 (0.94 to 1.41)	7317 (4)	⊕⊕⊝⊝ Low	*Reasons for downgrading:* - probable publication bias - Indirectness of evidence (Surrogate endpoint)
Genital infections, diabetic *vs.* non-diabetic subjects treated with SGLT2i	13.33 per 1000	18.05 per 1000 (14.26 to 22.72)	OR 1.36 (1.07 to 1.72)	7317 (4)	⊕⊕⊝⊝ Low	*Reasons for downgrading:* - probable publication bias - Indirectness of evidence (Surrogate endpoint)
Urinary tract infections, diabetic *vs.* non-diabetic subjects taking placebo	45.89 per 1000	58.85 per 1000 (477.64 to 72.29)	OR 1.30 (1.04 to 1.62)	7312 (4)	⊕⊕⊕⊝ Moderate	*Reasons for downgrading:* - Indirectness of evidence (Surrogate endpoint)
Genital infections, diabetic *vs.* non-diabetic subjects taking placebo	4.86 per 1000	5.49 per 1000 (2.09 to 14.35)	OR 1.13 (0.43 to 2.98)	7312 (4)	⊕⊕⊕⊝ Moderate	*Reasons for downgrading:* - Indirectness of evidence (Surrogate endpoint)

The corresponding intervention risk (and its 95% confidence interval) is based on the assumed control risk in the comparison group and the relative effect of the intervention (and its 95% CI).
It is calculated from the odds ratio using the formula:
OR x ACR/[1-ACR + (OR x ACR)]
CI: Confidence Interval; OR: Odds Ratio; ACR: Assumed Control Risk

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.