Supplementary Material

Article title: Dapagliflozin and Empagliflozin in Paediatric Indications: a Systematic Review and Meta-Analysis

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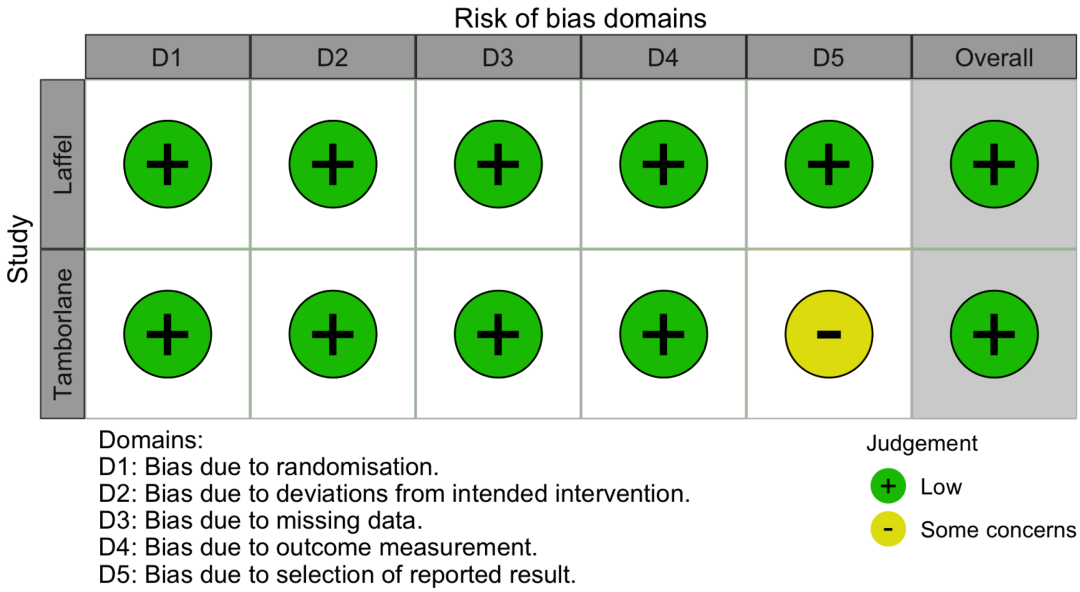
1. Supplementary Figure



Supplementary Figure 1. Risk of bias of papers included in the meta-analysis of empagliflozin / dapagliflozin use in adolescents with T2DM. Risk of bias was assessed according to five categories as recommended by the Cochrane collaboration: selection bias (D1), performance bias (D2), detection bias (D3), attrition bias (D4) and reporting bias (D5).

2. Suplementary Tables

Supplementary Table 1: Data from n=2 clinical studies on dapagliflozin in chronic heart failure (n=38 patients) and proteinuric chronic kidney disease (n=9 patients). Continuous data are provided as median and interquartile range or mean and standard deviation (SD).

Combined outcomes in heart failure and chronic kidney disease			
eGFR			ns
Before	115	[78-136]	
End of follow-up	101	[77-125]	
Blood glucose			ns
Before	5.3	±0.74	
End of follow-up	5.2	±0.65	
Haemoglobin			ns
Before	123	±29	
End of follow-up	133	±25	
Sodium			ns
Before	136	±3.3	
End of follow-up	138	±3.5	

Supplementary Table 2: Data from n=3 paediatric studies on dapagliflozin (n=57 patients), n=1 paediatric study on empagliflozin (n=27 patients). Continuous data are provided as median and interquartile range, proportions are provided as absolute numbers and percentages.

	N (studies)	
Diagnosis		
Type 1 Diabetes mellitus	2	
Type 2 Diabetes mellitus	2	
Type of study		
PK	1	
PD	1*	
PK-PD	2*	
Single-dose	4	
Multiple dose	0	
Length of study [days]	12	[7-21]

Pharmacokinetics dapagliflozin (n=3 studies, n=2 cohorts)

	2.5mg dose group n=14	5mg dose group n=16	10mg dose group n=49
T_{max} [h] (1 study)	1.50 (0.8-2.0)#	0.96 (0.6-1.5) #	0.88 (0.8-4.0) #
C_{max} [ng/mL (CV%)] (2 studies, 1 cohort, 3 doses)	24.8 (CV 34%)	48.4 (CV 41%)	118.0 (CV 35%)
V_d [L (CV%)] (1 study with 3 dose group, synthesis of 2 studies for 10mg dose group)	468 (CV 34%)	343 (CV 45%)	130 (CV n.a.) ◊
$t_{1/2}$ [h, SD] (1 study)	14.1 +/- 5.59	10.3 +/- 3.72	10.7 +/- 2.16
CL [L/h] (CV%)	24.5 (CV 26%)	25.1 (CV 27%)	20.3 (CV n.a.) ♣
AUC_{0-24} [ng * h / mL (CV%)] ✚	101 (CV 23%)	199 (CV 29%)	517 (combined, weighted mean)
Covariates			Body weight Δ

Pharmacokinetics empagliflozin (n=1 study, n=1 cohort)

	5mg dose group n=9	10mg dose group n=8	25mg dose group n=10
t_{max} [h]	1.5 (absolute range 0.95-7.92)	1.3 (absolute range 0.97-4.17)	1.8(absolute range 0.50-4.0)
C_{max} [nmol/L (CV%)]	175 (54.2%)	211 (59.1%)	692 (57.3%)
V_d (L) *(calculated)*	101.3	185.9	137.1
$t_{1/2}$ [h (CV%)]	7.03 (18.9%)	7.61 (27.0%)	8.09 (26.8%)
CL (L/h) *(calculated)*	10.0	16.9	11.7
AUC_{0-24h} [nmol * h/L (CV%)]	1110 (42.7%)	1310 (18.9%)	4720 (27.4%)

Covariates	not investigated (rich PK study)

* Parkinson et al [37] (PD study) and Tirucherai et al [38] (PKPD study) were both based on the same cohort of n=24 adolescents with type 2 diabetes mellitus

\# these values represent the absolute range

◊ we report here the weighted mean. More specificically: in Tirucherai et al [Tirucherai et al., 2016] (n=8 participants in the 10mg dose group) 355 L (CV 34%), in Busse [36] (n=33 participants) et al 75.5 L (CV not reported, RSE 5.6%).

♣ We provide here the weighted mean (between Tirucherai [38], 23.5L/h, n=8 participants, and Busse [36], 19.5L/h, 33 participants). CV was 25% for 8 patients, not available for the remaining 33 patients (who, however, showed a RSE of the estimated clearance of 3.4%

✚ Tirucherai [38] (n=23 patients) and Parkinson [37] (n=20 patients) report on the same cohort, but provide slightly different results. Given the major number of participants presented, we report here the results from Tirucherai (n=23) [38]. The results for 10mg is the weighted mean between the cohort from Tirucherai [38] (n=23 patients) and Busse [36] (n=33 patients).

∆ Only in the model by Busse et al. [36]