Safety of dapagliflozin in patients with type 2 diabetes mellitus and hypertension inadequately controlled by a renin-angiotensin system blocker with/without a second agent

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Background and aims: Hypertension is common in patients with type 2 diabetes mellitus (T2DM) and is often treated with an ACE inhibitor (ACEi) or an angiotensin receptor blocker (ARB) plus other antihypertensive (AHT) agents if needed. Dapagliflozin inhibits renal glucose reabsorption causing glucosuria, weight loss, diuresis and decreased BP. Dapagliflozin significantly reduced HbA1c and seated and ambulatory systolic BP versus placebo in clinical studies of patients with T2DM and hypertension. Here we describe key safety data from these studies.
Materials and methods: In two, randomized, double-blind, 12-week studies, patients with T2DM and inadequate glycaemic control (HbA1c 7.0-10.5%) and BP (seated systolic BP / diastolic BP: 140-164 / 85-104 mmHg) receiving an ACEi or an ARB (Study 1) plus a 2nd AHT drug (Study 2) were randomized to dapagliflozin 10 mg or placebo over 12 weeks. Preliminary efficacy results have been previously presented.
Results: In Study 1, 613 patients on an ACEi or ARB were randomized to treatment. In Study 2, 449 patients on an ACEi or ARB plus a 2nd AHT drug were randomized to treatment. In each study, similar proportions of dapagliflozin and placebo experienced adverse events (AEs), with few serious AEs reported. In Study 1 and 2, fewer dapagliflozin (1.0 and 0.4%, respectively) versus placebo (1.3 and 1.8%) patients withdrew due to an AE. Few hypoglycaemic events occurred (3.3 and 5.8% with dapagliflozin vs 1.3 and 2.7% with placebo), none of which led to discontinuation. No serious BP related safety issues were noted; one orthostatic hypotension AE occurred with dapagliflozin in Study 1. Serum uric acid decreased with dapagliflozin but there was no effect on serum sodium, potassium, or calcium, despite its diuretic effect (Table).
Conclusion: Dapagliflozin had a good safety profile over 12 weeks when used in combination with an ACEi or ARB ± 1AHT in patients with T2DM and inadequately controlled hypertension.

	ACEi/ARB (Study 1)	
	+ PBO (N = 311)	+ DAPA 10mg (N = 302)
At least 1 AE, N (%)	108 (35.0)	111 (36.8)
At least 1 SAE, N (%)	4 (1.3)	2 (0.7)
Calcium, mmol/L		
Baseline mean	2.37 (0.10)	2.37 (0.13)
Week 12 mean	2.37 (0.11)	2.38 (0.11)
Mean change	0.00 (−0.01, 0.01)	0.01 (−0.01, 0.03)
Potassium, mmol/L		
Baseline mean	4.48 (0.44)	4.44 (0.44)
Week 12 mean	4.52 (0.43)	4.47 (0.44)
Mean change	0.05 (0.00, 0.10)	0.03 (−0.02, 0.08)
Sodium, mmol/L		
Baseline mean	140.4 (2.94)	140.3 (2.94)
Week 12 mean	140.3 (3.02)	140.8 (3.03)
Mean change	−0.1 (−0.41, 0.21)	0.4 (0.05, 0.75)
Uric acid, µmol/L		
Baseline mean	318.24 (74.36)	321.22 (82.80)
Week 12 mean	317.06 (77.09)	299.21 (77.15)
Mean change	2.97	−16.06
	(−5.95, 11.30)	(−24.98, −7.13)
ACEi/ARB + 1 other AHT (Study 2)		
	+ PBO (N = 224)	+ DAPA 10mg (N = 225)
At least 1 AE, N (%)	93 (41.5)	98 (43.6)
At least 1 SAE, N (%)	2 (0.9)	6 (2.7)
Calcium, mmol/L		
Baseline mean	2.38 (0.10)	2.38 (0.13)
Week 12 mean	2.39 (0.11)	2.38 (0.11)
Mean change	0.01 (−0.00, 0.03)	−0.00 (−0.02, 0.02)
Potassium, mmol/L		
Baseline mean	4.39 (0.45)	4.41 (0.45)
Week 12 mean	4.44 (0.46)	4.42 (0.46)
Mean change	0.06 (0.01, 0.11)	0.00 (−0.06, 0.06)
Sodium, mmol/L		
Baseline mean	140.6 (2.96)	140.3 (2.81)
Week 12 mean	140.7 (3.11)	141.1 (2.96)
Mean change	0.0 (−0.41, 0.41)	0.8 (0.37, 1.23)
Uric acid, µmol/L		
Baseline mean	321.22 (78.22)	334.80 (94.94)
Week 12 mean	321.81 (77.39)	308.73 (90.36)
Mean change	−1.78	−25.58
	(−11.90, 8.92)	(−35.69, −14.87)

N is the number of randomized patients who took ≥1 dose of double-blind medication. Includes data after rescue. Baseline and Week 12 means are shown with standard deviations and mean changes with 95% confidence intervals. ACEi, angiotensin converting enzyme inhibitor; AE, adverse event ; AHT, antihypertensive drug; ARB, angiotensin receptor blocker; DAPA, dapagliflozin; PBO, placebo; SAE, serious adverse event
Calcium: 1 mmol/L = 4 mg/dL [Normal range:2.13–2.55 mmol/L]
Potassium: 1 mmol/L = 1 mEq/L [Normal range: 3.7–5.2 mmol/L]
Sodium: 1 mmol/L = 1 mEq/L [Normal range: 135–145 mmol/L]
Uric acid: 1 µmol/L = 0.02 mg/dL [Normal range: 208.2–428.29 µmol/L]

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