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Hey #NephSky!
Welcome to a new #Medsky #Skytorial brought to you by @kireports.bsky.social
Our author is @brianrifkin.bsky.social nephrologist in Hattiesburg, MS
Please check out #KIReportsCommunity educational #blogposts too!

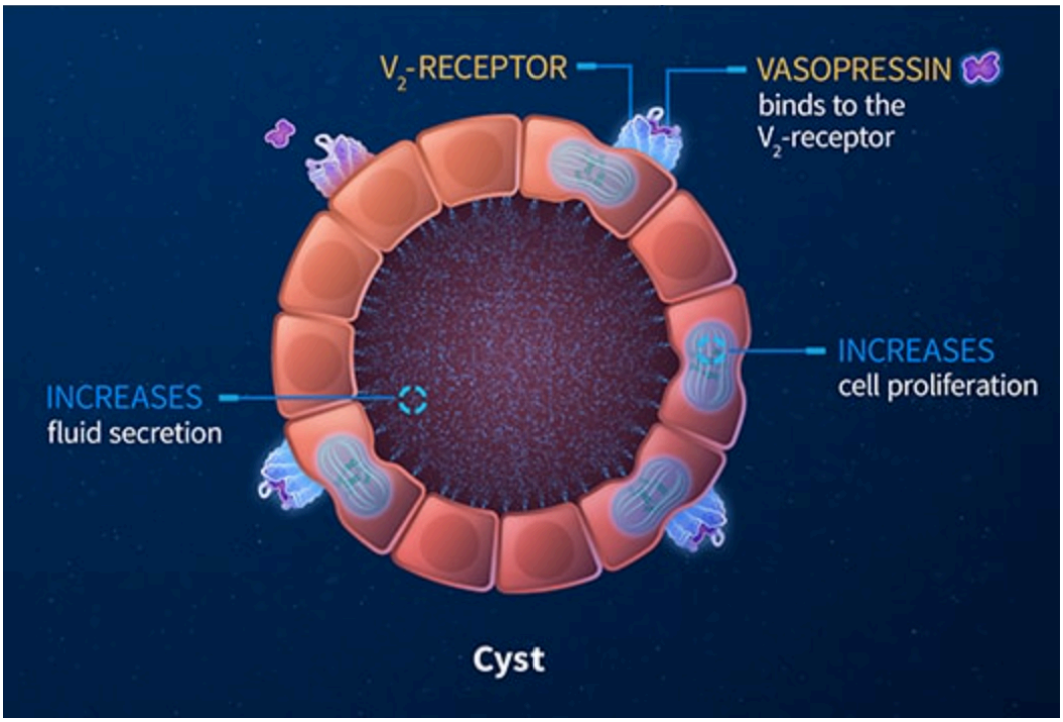
2/
Our topic:
Use of dapagliflozin (SGLT2 inhibitor) in patients with autosomal dominant polycystic kidney disease (ADPKD) concurrently on tolvaptan therapy. There are no conflicts of interest.
#MedSky #NephSky
Article: Open-Label, Randomized, Controlled, Crossover Trial on the Effect of Dapagliflozin in Patients With ADPKD Receiving Tolvaptan

3/
Autosomal dominant polycystic kidney disease (ADPKD) is estimated to affect up to 12 million individuals and is the 4th most common cause of renal replacement therapy worldwide. In fact, @KDIGO.org has just released its first comprehensive ADPKD guidelines in 2025.

4/
How about a quick quiz- which medication has been approved for slowing the progression of eGFR decline in patients with ADPKD?

-SGLT2i
-GLP-1 RA
-tolvaptan
-nsMRA

5/
The answer is tolvaptan, a vasopressin V2 antagonist & “aquaretic”.
Vasopressin ⬆️cell proliferation & fluid secretion in renal cysts. This may ⬆️ the number & size of cysts in addition to total kidney volume (TKV) in ADPKD.
Let’s 👀 at studies of tolvaptan in ADPKD.



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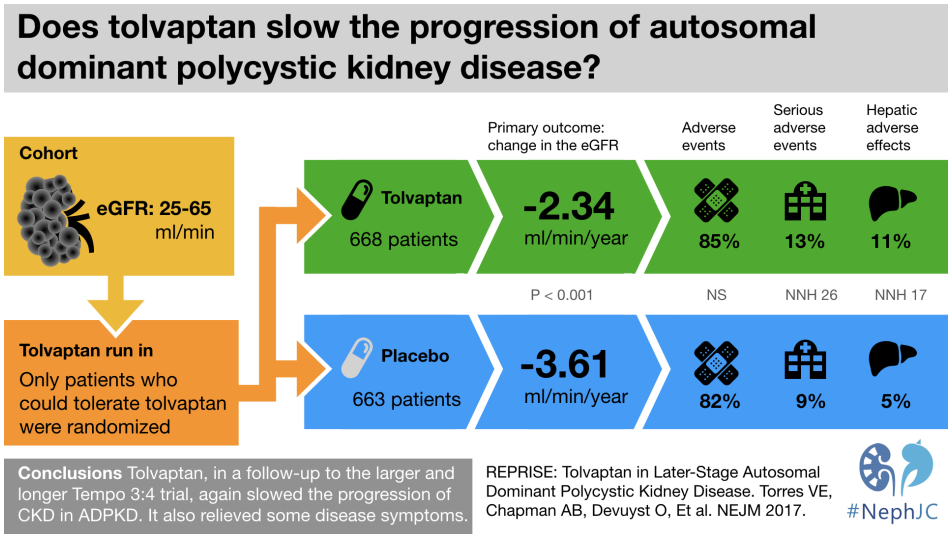
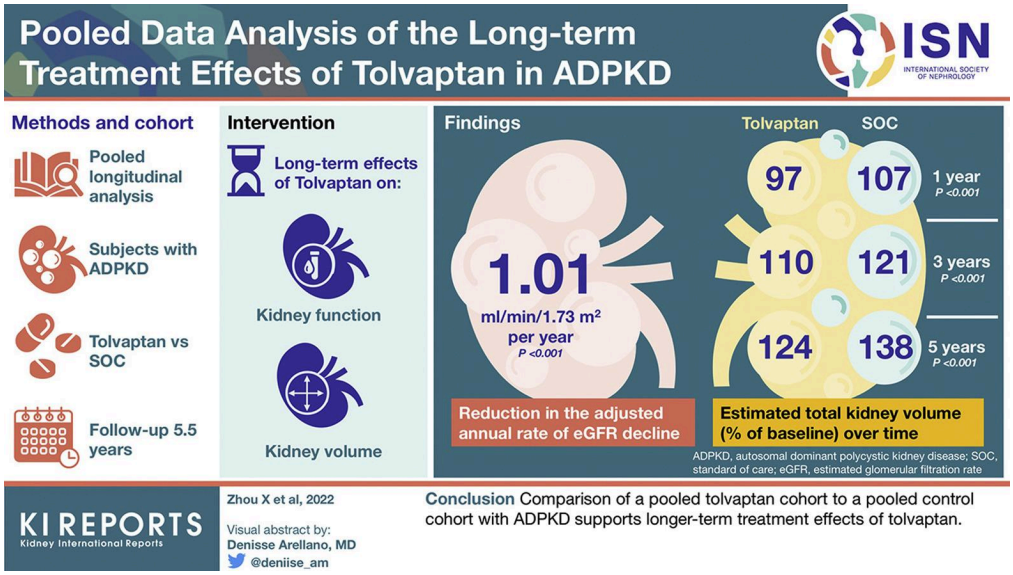
TEMPO 3:4
Tolvaptan slowed the rate of height adjusted total kidney volume (htTKV) & decline in eGFR vs placebo over a 3-yrs. Pts who received tolvaptan had a ⬆️frequency of discontinuation related to ⬆️aquaresis (thirst, polyuria, nocturia) & liver toxicity- 15.4% vs 5%.

6/
REPRISE
Included patients with ADPKD & eGFR of 25-65 ml/min. Tolvaptan resulted in a slower eGFR decline vs placebo at 1-year.
The decline of eGFR was: −2.34 ml/min/yr with tolvaptan versus −3.61 ml/min/yr with placebo. ($p< 0.001$)



7/
OVERTURE
Observational, longitudinal study ➡️ 3409 ADPKD pts, followed for 1-3 years. Higher baseline measured height adjusted total kidney volume (htTKV) was once again associated with worse ADPKD-related clinical outcomes- abdomen girth, UACR & eGFR decline rate.

8/
OVERTURE
⬆️ htKTV was also associated with worse scores on multiple measures of patient-reported QoL, productivity, physical function & healthcare utilization. In pts at ⬇️risk of ESKD, the risks of tolvaptan may outweigh the benefits.
But what about SGLT2 inhibitors in CKD?



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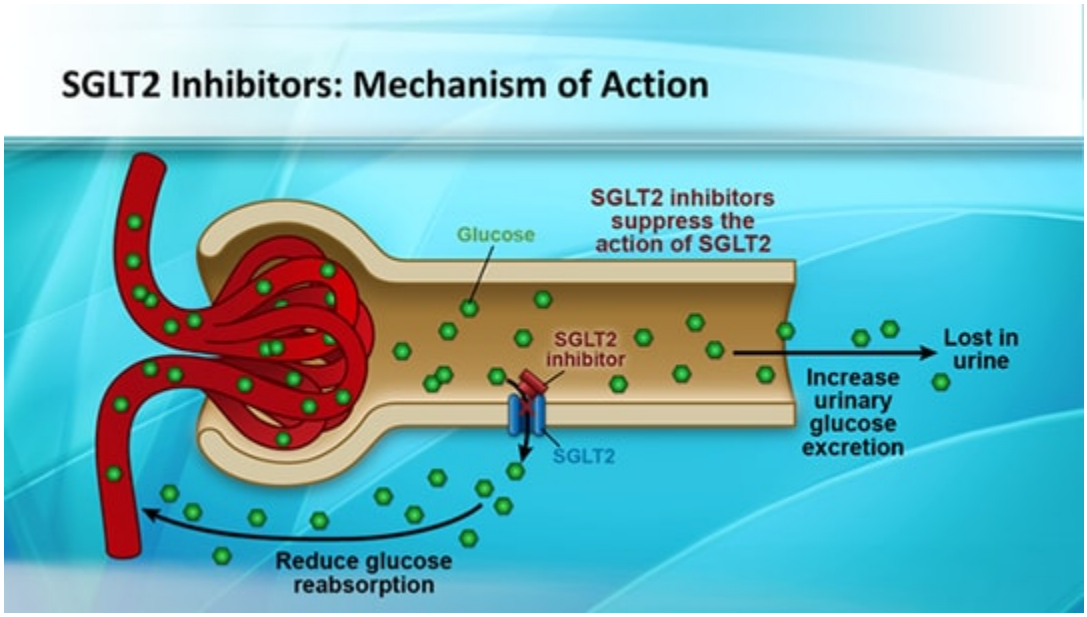
SGLT2 inhibitors
Block glucose reabsorption in the proximal tubule of the kidney, ⬆️glucosuria & ⬇️hyperglycemia. They also ⬇️intraglomerular pressure, inflammation & oxidative stress. Benefits are seen in pts with proteinuria (with/without DM), CKD & CHF.



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SGLT2 inhibitors have shown benefits in a wide variety of patients with kidney & cardiovascular diseases, with impressive improvements in outcomes. Prior studies of SGLT2i in ADPKD animal models had yielded conflicting results concerning cyst growth & eGFR decline.

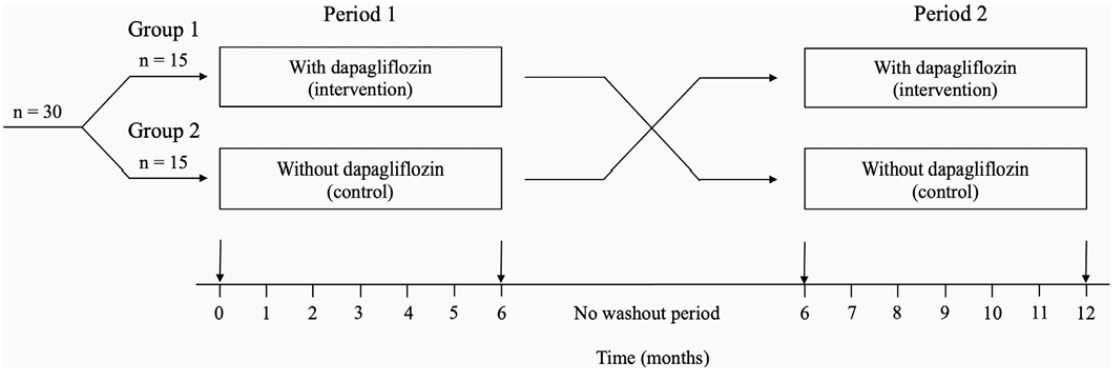
Selected Clinical Trials of SGLT2 inhibitors in CVD and CKD

	N	T2DM	CKD (eGFR)	1° Composite Outcome	HR (95 CI)	Takeaway
EMPA-REG OUTCOME	7,020	100%	25.9% (74)	CV death, nonfatal MI, or nonfatal stroke	0.86 (0.74-0.99)	Empagliflozin lowered CV events in T2DM + ASCVD; signal for SGLT2i in HF and CKD.
CANVAS	10,142	100%	21.9% (76)	CV death, nonfatal MI, or nonfatal stroke	0.86 (0.75-0.97)	Canagliflozin lowered CV events in T2DM + ASCVD or ASCVD risk; signal for SGLT2i in HF and CKD.
DECLARE-TIMI 58	17,160	100%	9.2% (85)	1. CV death or HHF* 2. MACE	*0.83 (0.73-0.95)	Dapagliflozin lowered CV death or HHF, but had no effect on MACE, in T2DM + ASCVD or ASCVD risk.
CREDENCE	4,401	100%	100% (56)	ESKD, 2x SCr, renal or CV death	0.70 (0.59-0.82)	Canagliflozin lowered adverse kidney events in CKD + T2DM; first renal outcomes trial in SGLT2i.
DAPA-CKD	4,304	67%	100% (43)	≥50% decline eGFR, ESKD, renal or CV death	0.61 (0.51-0.72)	Dapagliflozin lowered adverse kidney events for patients with CKD, with or without T2DM.
DAPA-HF	4,744	42%	41% (66)	CV death or worsening HF	0.74 (0.65-0.85)	Dapagliflozin improved HF outcomes in HFrEF on GDMT, with or without T2DM.
EMPEROR-REDUCED	3,730	50%	48% (62)	CV death or HHF	0.75 (0.65-0.86)	Empagliflozin improved HF outcomes in HFrEF on GDMT, with or without T2DM.

T2DM – type 2 diabetes mellitus; CKD – chronic kidney disease; eGFR – estimated glomerular filtration rate; CV – cardiovascular; MI – myocardial infarction, ASCVD – atherosclerotic cardiovascular disease; SCr – serum creatinine; ESKD – end-stage kidney disease; HF – heart failure; GDMT – guideline-directed medical therapy; MACE – major adverse cardiac events; HHF – hospitalization for heart failure

11/
Outpatients from centers in Japan were recruited from December 2021 - March 2024. Adults with ADPKD & receiving ⬆️ dose tolvaptan (> 60 mg daily for 3 months) with an eGFR >25 ml/min, TKV > 750 & annual growth rate >5% were eligible. Patients with DM were excluded.

12/
Due to concerns about the safety of dapagliflozin in patients with ADPKD the study was open-label. To ⬇️ the number of recruits, a cross-over design was adopted. Pts received dapagliflozin 10 mg with tolvaptan or just tolvaptan for 6 month intervals.



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Patients had bloodwork done every 1-2 months. Patients also underwent CT or MRI at six month intervals to assess TKV. Adherence to dapagliflozin, but not tolvaptan, was monitored by the treating nephrologist.

14/
The 1° outcome was the rate of eGFR decline. Given the known decline in eGFR when initiating SGLT2 inhibitors, chronic slope (1-6 months) was used rather than total slope (from baseline). eGFR equations, including both creatinine and cystatin C, were used.

15/
2° outcomes included changes in TKV and body weight, plasma vasopressin levels, and 24-hour urine volume, osmolarity, and albuminuria.

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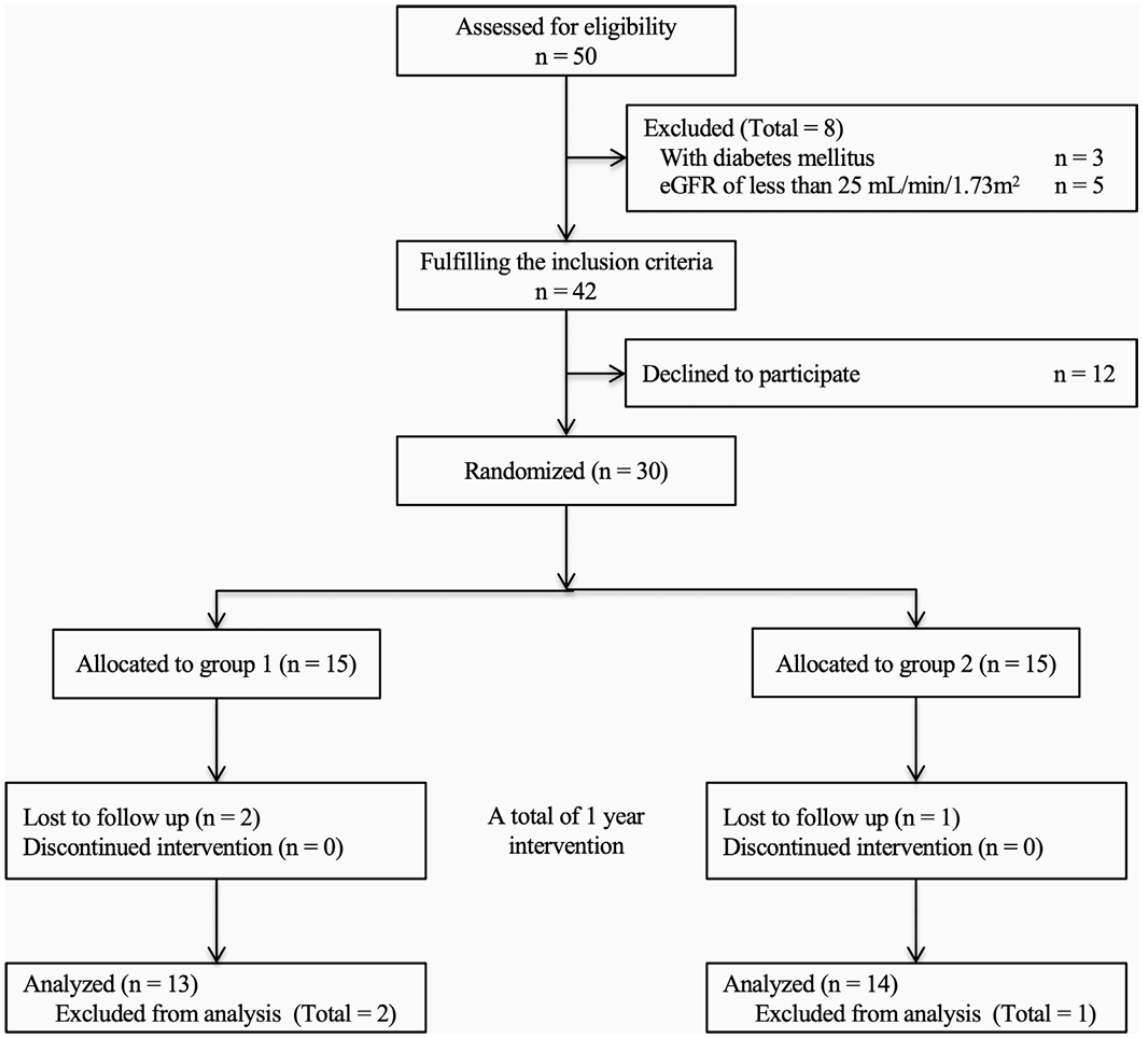
30 patients were randomized into 2 groups of 15 to receive dapagliflozin for the first six months or second six month interval. Three patients were lost to follow-up leaving 13 patients in group one and 14 patients in group 2.



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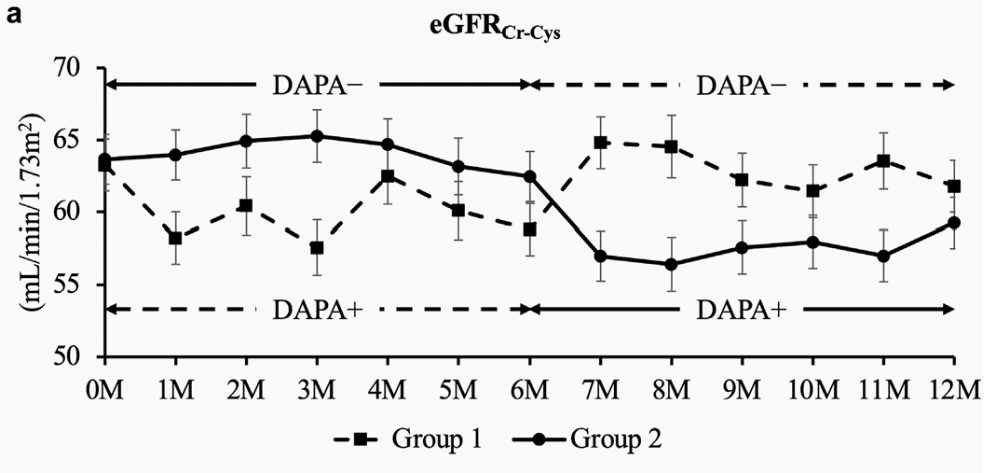
Baseline characteristics did not differ significantly between groups, except for TKV and htTKV which were higher in group 1 (1414 vs 1012, p =0.08 and 822 vs 624, p =0.07 respectively). Because of the crossover design, differences between groups had minimal effect on outcomes.

Variables	All (n = 27)	Group 1 (n = 13)[a]	Group 2 (n = 14)[b]	P-value
Age (yr)	49.7 ± 12.1	49.2 ± 13.3	50.2 ± 11.4	0.84
Male/female (% male)	14/13 (52%)	5/8 (38%)	9/5 (64%)	0.26
Family history of ADPKD	4 (15%)	2 (15%)	2 (14%)	0.79
Hypertension (%)	22 (81%)	11 (85%)	11 (79%)	1
Use of RAS inhibitors (%)	18 (67%)	10 (77%)	8 (57%)	0.42
Tolvaptan (mg)	102.8 ± 24.2	95.2 ± 25.9	109.8 ± 21.1	0.12
Duration of tolvaptan treatment (years)	2.3 (0.5–6.2)	3.0 (0.3–6.1)	2.1 (1.2–5.8)	0.66
BMI (kg/m^2)	23.3 ± 2.9	24.0 ± 3.2	22.7 ± 2.5	0.25
Systolic BP (mmHg)	132.7 ± 12.5	131.8 ± 9.8	133.4 ± 14.7	0.77
Diastolic BP (mmHg)	84.2 ± 7.9	84.7 ± 6.3	83.8 ± 9.2	0.77
Mean BP (mmHg)	100.4 ± 8.5	100.4 ± 6.3	100.3 ± 10.3	0.97
Complications of ADPKD				
Liver cyst	23 (85%)	10 (77%)	13 (93%)	0.33
Brain aneurysm	2 (7%)	1 (8%)	1 (7%)	1
Valvular disease	7 (26%)	5 (38%)	2 (14%)	0.18
Mayo imaging classification, n (%)				0.36
1B	7 (26%)	2 (15%)	5 (36%)	
1C	15 (56%)	7 (54%)	8 (57%)	
1D	4 (15%)	3 (23%)	1 (7%)	
1E	1 (4%)	1 (8%)	0 (0%)	

ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; BP, blood pressure; CCVD, cerebrovascular/cardiovascular disease; RAS, renin–angiotensin aldosterone system.
[a]Dapagliflozin treatment was initiated in group 1.
[b]Group 2 was initiated on treatment without dapagliflozin.

18/
The slopes of eGFR decline were flattened during the periods in which pts received SGLT2i. The carryover effect of discontinuing SGLT2i was negligible. Models confirmed that eGFR (cr-cys) est mean was greater during the periods when pts received dapagliflozin.



19/
2° outcomes
The 6 month change in TKV was ⬇️ by SGLT2i use. Urine osms, but not volume, was ⬆️ in pts receiving SGLT2i. There was no effect on albuminuria, however, all patients had under 150 mg/d at baseline. Finally, SBP (but not DBP) were ⬇️ in the dapagliflozin group.

Variables	Dapagliflozin +	Dapagliflozin −	*P*-value
TKV change (%/6 mo)	−0.44 ± 4.91	5.04 ± 8.09	0.01
BW change (kg/6 mo)	−0.69 ± 1.42	0.56 ± 1.49	0.01
Urine volume (ml)	4,472 ± 1,389	4,328 ± 1,299	0.51
Urinary osmolarity (mOsm)	184.4 ± 51.1	165.3 ± 47.9	0.05
Urine albumin (mg/d)	36.4 ± 90.1	44.5 ± 86.0	0.62
L-FABP (μg/gCr)	5.25 ± 6.09	4.96 ± 5.92	0.39
Plasma vasopressin (pg/ml)	4.52 ± 2.02	3.58 ± 1.72	0.002
Systolic BP (mmHg)	123.0 ± 13.1	128.4 ± 10.1	0.04
Diastolic BP (mmHg)	81.9 ± 7.7	84.1 ± 7.7	0.31
Mean BP (mmHg)	95.6 ± 8.8	98.9 ± 7.6	0.13
Pulse pressure (mmHg)	51.9 ± 9.9	57.3 ± 5.8	0.08

BP, blood pressure; BW, body weight; L-FABP, liver-type fatty acid-binding protein; TKV, total kidney volume.
For variables, the values at 6 months of each trial were obtained.

20/
Safety
There were 2 COVID infections (3 total) and 1 kidney cyst infection in patients on dapagliflozin. There were no recorded episodes of hypoglycemia. Cyst hemorrhage, subarachnoid hemorrhage and hospitalizations were not recorded during the study period.

21/
Special precautions were used to select ADPKD pts with severe disease who had already qualified, & were actively using tolvaptan. The authors did observe a rise in serum vasopressin levels in patients on dapagliflozin, but also an improvement in eGFR slope over the short term.

22/
This trial did not look at dapagliflozin as a monotherapy or in patients with less severe ADPKD who did not qualify for tolvaptan. Longer randomized trials with more heterogeneous groups of ADPKD pts will have to be done before SGLT2i can be recommended for pts with ADPKD.

23/
This has been @brianrifkin.bsky.social with another @KIReports.bsky.social learning opportunity. Hope to see you back to learn more at this handle soon.