SGLT2於腎臟病從預防到治療的角色

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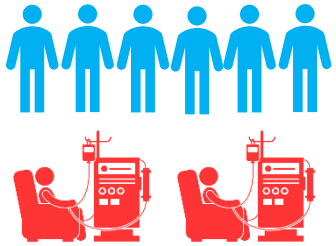
臺灣健保花費疾病前2名分別為CKD及T2D

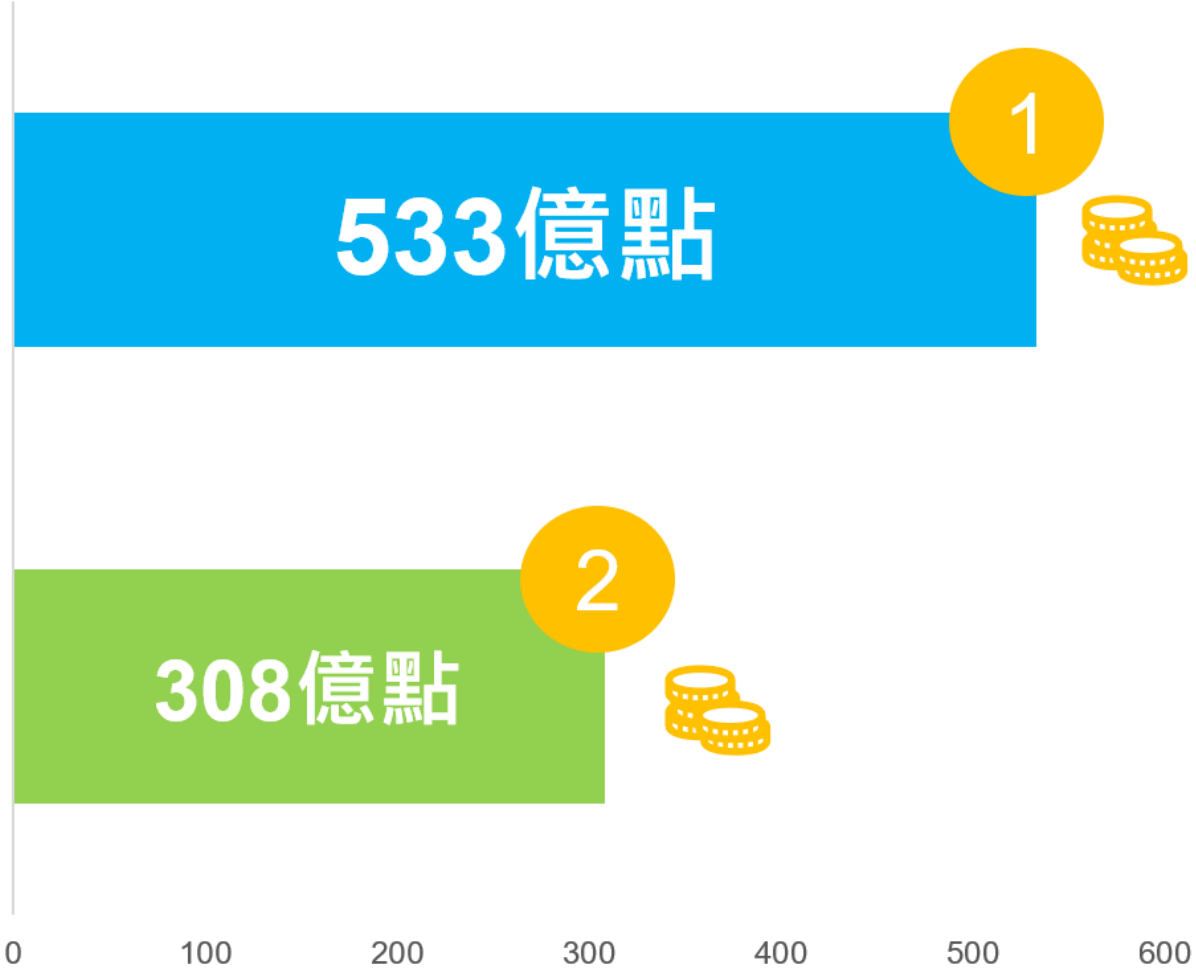
就醫人數 :5萬人

CKD: **39.7萬** (包含透析: **9.2萬**)



T2D: **153.6萬**

2019年臺灣健保花費前2名疾病及點數

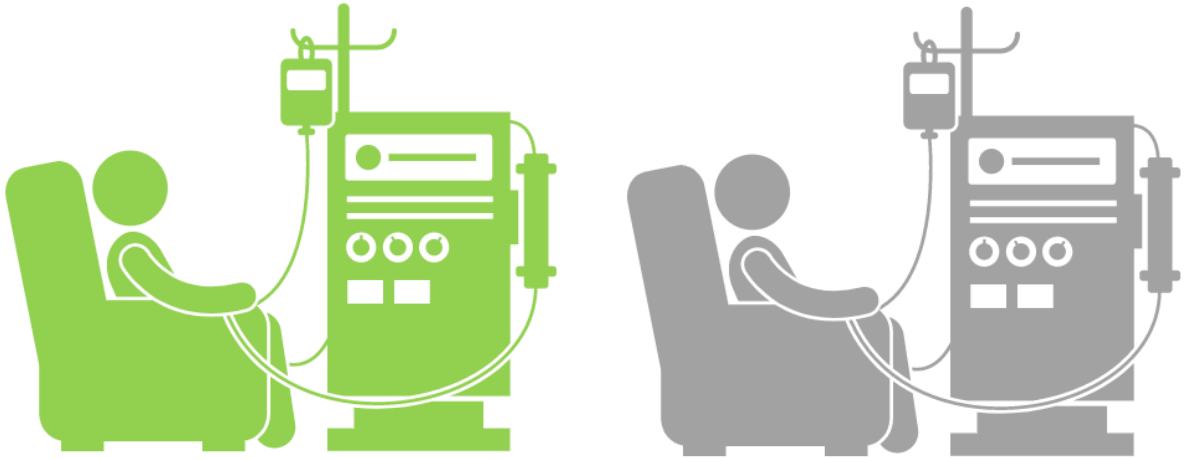


1. https://ctee.com.tw/lohas/health/299440.html 2. https://health.udn.com/health/story/5975/4717621

臺灣約每2位透析病患有1位患有糖尿病

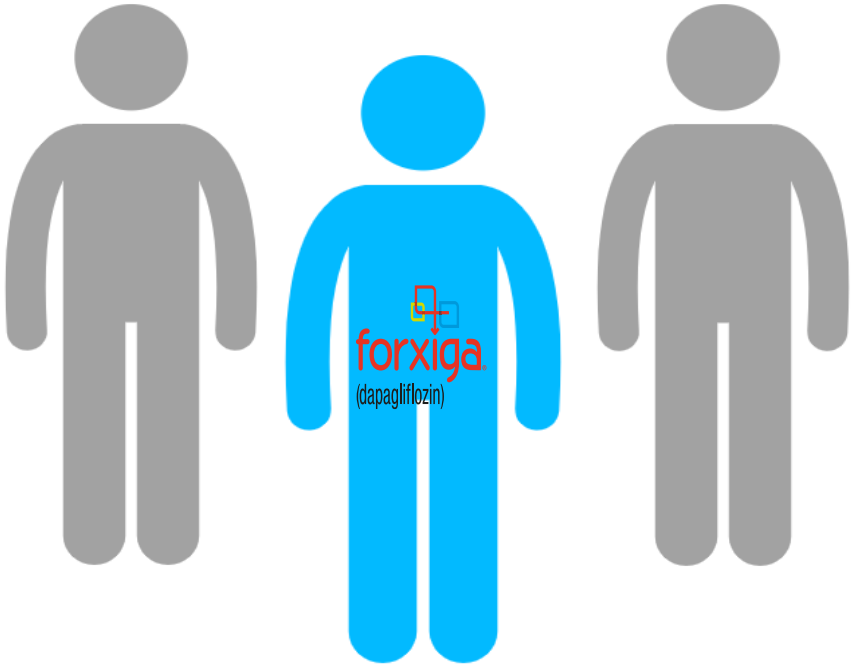
46.2% **new dialysis patients' principal diagnosis is diabetes**

In 2020 Kidney Disease in Taiwan Annual Report (data in 2018)



33.24% **patients with diabetes have nephropathy**

In Taiwan P4P program (data in 2014)



P4P: pay-for-performance

1. 2020 Kidney Disease in Taiwan Annual Report (p.56, p71) 2.. J Formos Med Assoc. 2019 Nov;118 Suppl 2:S122-S129. (Participants in P4P)

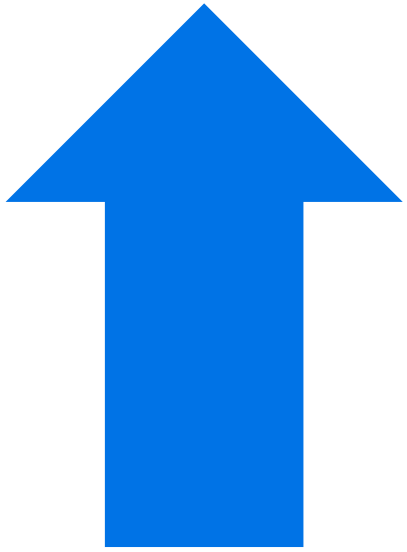
forxiga (dapagliflozin) xigduo XR Extended-Release Tablets (dapagliflozin/metformin HCl) QTERN (saxagliptin/dapagliflozin)

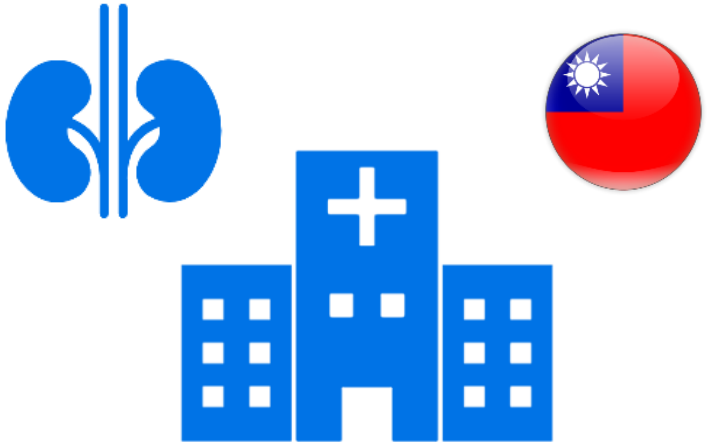
臺灣研究：罹患糖尿病增加14倍CKD或ESRD住院發生

Diabetes

vs.

non-Diabetes





Odds ratio 14.05

CKD/ESRD hospitalization

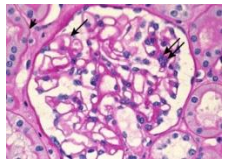
(Taiwan NHI data in 2014)

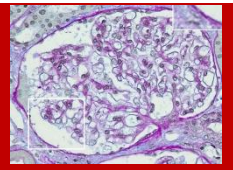
NHI: National Health Insurance

J Formos Med Assoc. 2019 Nov;118 Suppl 2:S90-S95.

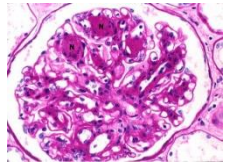
DeFronzo教授：從罹患糖尿病開始到出現白蛋白尿前的silent period是治療的關鍵期

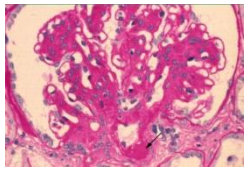
0.9	0.8	0.8	Serum Creatinine (mg/dl)	1.0	>2.0	>10
120	150	150	GFR (ml/min)	90	60	<10
0	0	10	UACR (mg/g)	>30	>100	>300


Normal glomerulus


Normoalbuminuric diabetic glomerular

“Silent Period”


Diabetic nephropathy


Advanced diabetic glomerulosclerosis

-3 0 3 TIME (years) 15 24

Onset of Diabetes

Onset of Diabetic Glomerulosclerosis

Onset of Albuminuria

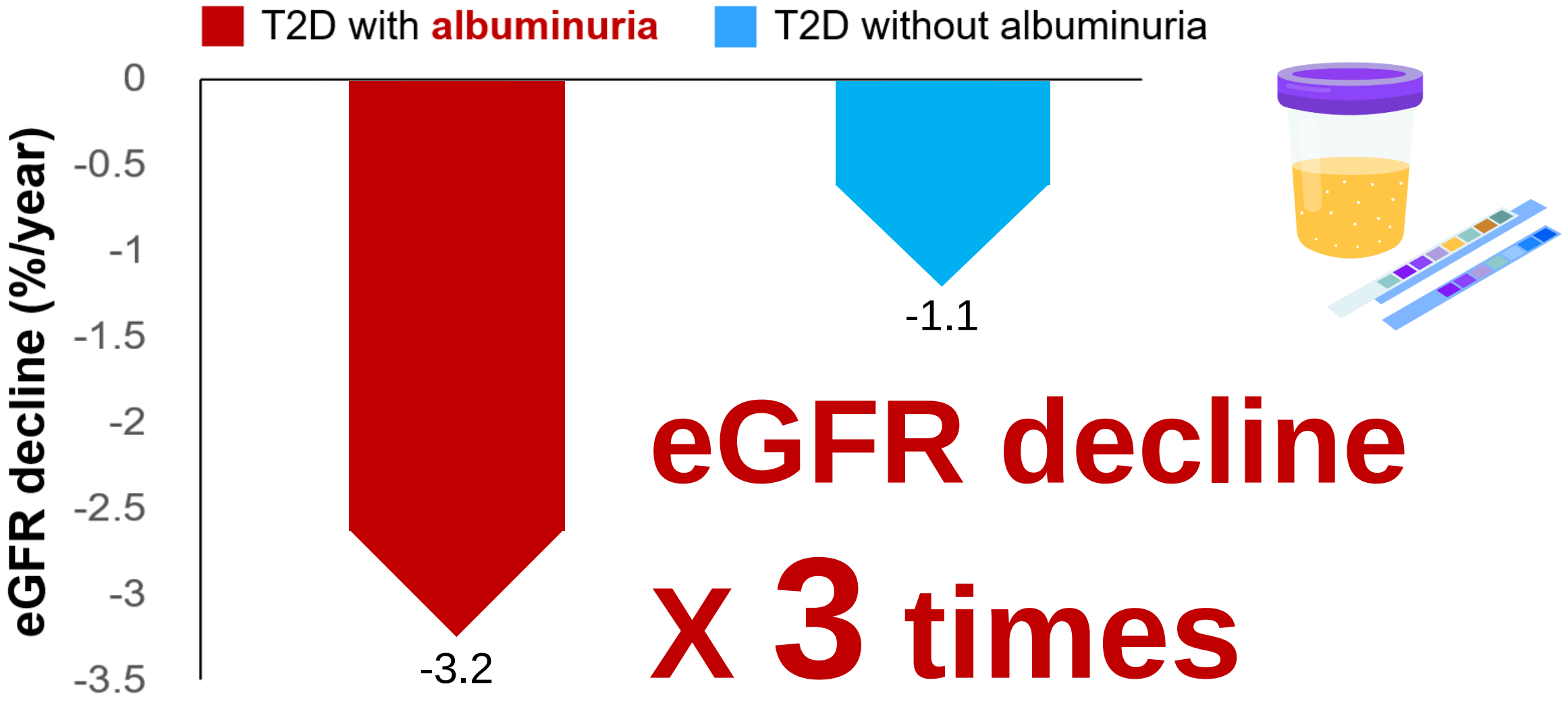
ESRD

9 years

UARC: urine albumin to creatinine ratio 1. DeFronzo, R. A. Diabetes Reviews, Vol. 3, No. 3, 01.01.1995, p. 510-564. 2. Sem Nephrol 10:184-193, 1990.

3. Sci Rep. 2018 Mar 20;8(1):4909. 4. https://somepomed.org/articulos/contents/mobipreview.htm?36/63/37883

已出現白蛋白尿的糖尿病患者，腎功能3倍速惡化



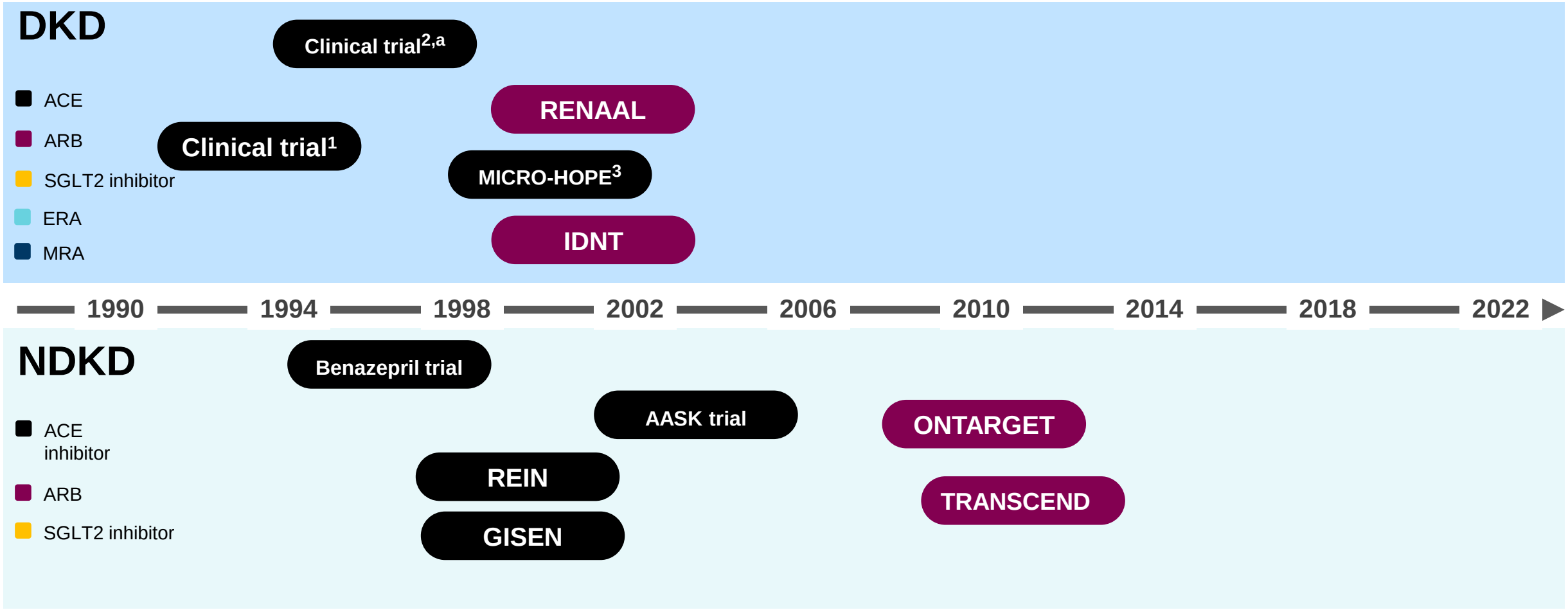
eGFR decline

x 3 times

10,185 participants with type 2 diabetes enrolled in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study

CKD was defined as eGFR<60 mL/min/1.73 m^2, albuminuria was defined as a UACR≥30 mg/g; Diabetes Care 2019 Oct; dc191438.

Clinical Trial of DKD and NDKD : Pre-SGLT2 Era

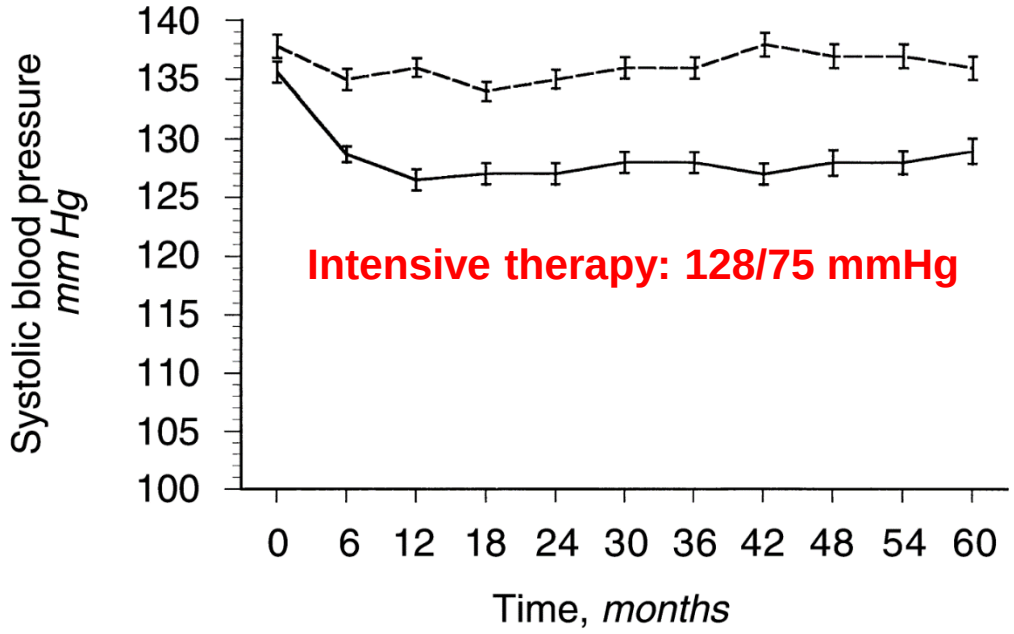


ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; NDKD, non-diabetic kidney disease; SGLT2i, sodium–glucose co-transporter 2 inhibitor

1. Lewis EJ, et al. *N Engl J Med* 1993;329:1456–1462; 2. Agardh CD, et al. *J Hum Hypertens* 1996;10:185–192; 3. HOPE Study Investigators. *Lancet* 2000;355:253–259; 4. The GISEN Group. *Lancet* 1997;349:1857–1863; 5. Chan GC, et al. *Nephrol Dial Transplant.* 2016;31:359-368; 6. Perkovic V, et al. *N Engl J Med* 2019;380:2295–2306; 7. Lancet. 2019 May 11;393(10184):1937-1947; 8. N Engl J Med 2020; 383:1436-1446; 9. ASN 2020.

積極控制血壓能減少糖尿病患的白蛋白尿惡化風險

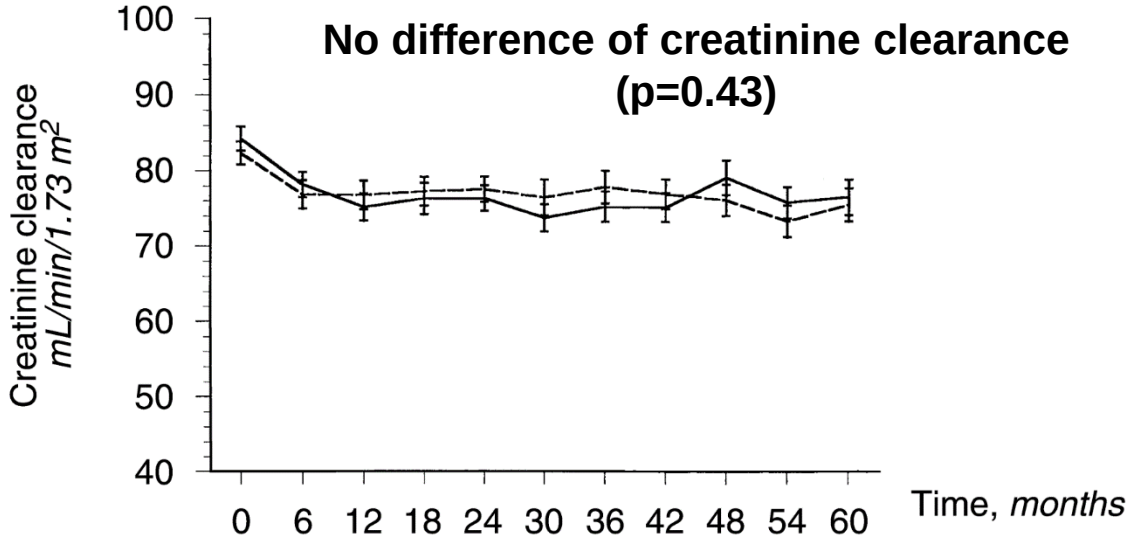
Moderate therapy : 137/81 mmHg

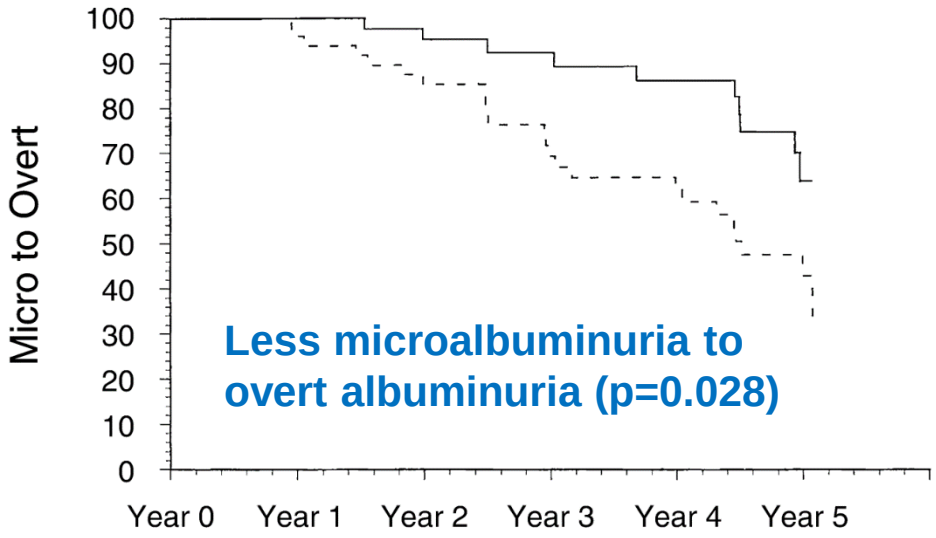


Intensive therapy: 128/75 mmHg

Intensive (*N*)	237	197	194	180	160	159
Moderate (*N*)	242	209	196	182	172	165

No difference of creatinine clearance (p=0.43)





Less microalbuminuria to overt albuminuria (p=0.028)

Intensive therapy (N=237), moderate therapy (N=243), mean follow-up was 5.3 years

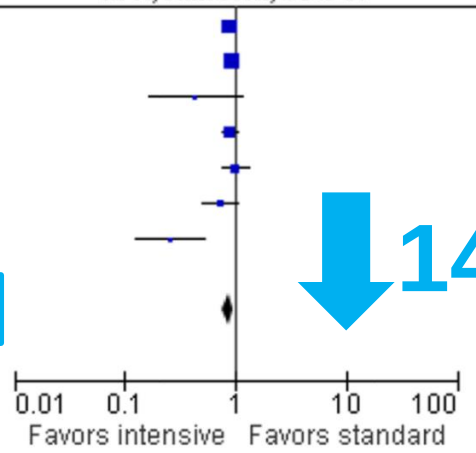
Kidney Int. 2002 Mar;61(3):1086-97.

統合分析：控制血糖能減少糖尿病患的白蛋白尿風險

Microalbuminuria

Study or Subgroup	Intensive Therapy Events	Total	Standard Therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ACCORD	720	3250	828	3273	27.3%	0.88 [0.80, 0.96]
ADVANCE	1318	5571	1434	5569	29.3%	0.92 [0.86, 0.98]
Kumamoto	5	52	11	50	1.3%	0.44 [0.16, 1.17]
UKPDS 33	368	2277	172	938	19.6%	0.88 [0.75, 1.04]
UKPDS 34	79	342	95	411	12.2%	1.00 [0.77, 1.30]
VADT	43	442	61	463	7.6%	0.74 [0.51, 1.07]
VADT Feasibility Trial	7	42	30	46	2.5%	0.26 [0.13, 0.52]
Total (95% CI)		**11976**		**10750**	**100.0%**	**0.86 [0.76, 0.96]**
Total events	2540		2631			

Heterogeneity: Tau² = 0.01; Chi² = 16.71, df = 6 (P = 0.01); I² = 64%
Test for overall effect: Z = 2.60 (P = 0.009)

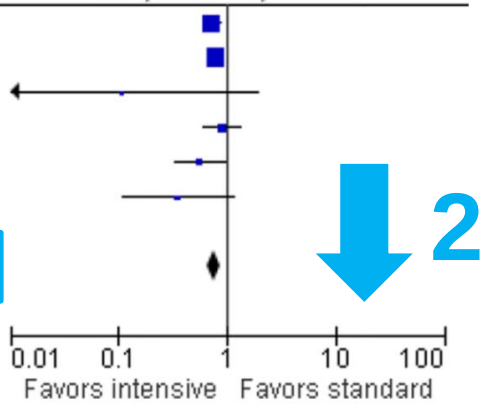


14%

Macroalbuminuria

Study or Subgroup	Intensive Therapy Events	Total	Standard Therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ACCORD	195	4397	272	4424	39.3%	0.72 [0.60, 0.86]
ADVANCE	230	5571	292	5569	42.5%	0.79 [0.67, 0.93]
Kumamoto	0	52	4	50	0.2%	0.11 [0.01, 1.94]
UKPDS 33	72	2277	33	938	10.4%	0.90 [0.60, 1.35]
VADT	20	693	36	703	6.2%	0.56 [0.33, 0.96]
VADT Feasibility Trial	3	24	10	28	1.4%	0.35 [0.11, 1.13]
Total (95% CI)		**13014**		**11712**	**100.0%**	**0.74 [0.65, 0.85]**
Total events	520		647			

Heterogeneity: Tau² = 0.00; Chi² = 5.73, df = 5 (P = 0.33); I² = 13%
Test for overall effect: Z = 4.24 (P < 0.0001)



26%

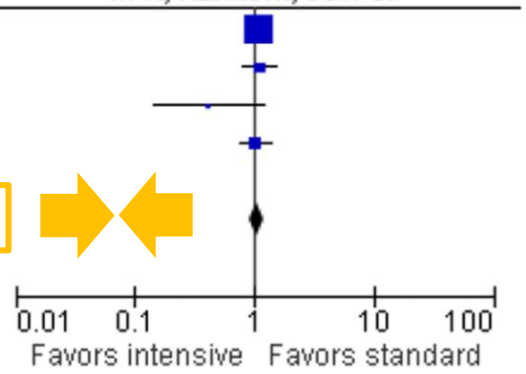
Arch Intern Med. 2012 May 28; 172(10): 761–769.

統合分析：控制血糖減少糖尿病患的腎功能惡化、ESRD風險效果有限

Doubling of Serum Creatinine

Study or Subgroup	Intensive Therapy Events	Total	Standard Therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ACCORD	392	5041	357	5035	62.5%	1.10 [0.96, 1.26]
ADVANCE	67	5571	61	5569	15.6%	1.10 [0.78, 1.55]
UKPDS 33	7	2150	7	895	1.9%	0.42 [0.15, 1.18]
VADT	78	882	78	884	20.0%	1.00 [0.74, 1.35]
Total (95% CI)		**13644**		**12383**	**100.0%**	**1.06 [0.92, 1.22]**
Total events	544		503			

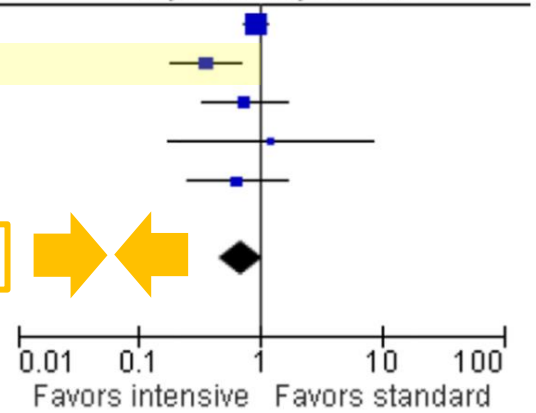
Heterogeneity: Tau² = 0.00; Chi² = 3.46, df = 3 (P = 0.33); I² = 13%
Test for overall effect: Z = 0.76 (P = 0.44)



ESRD

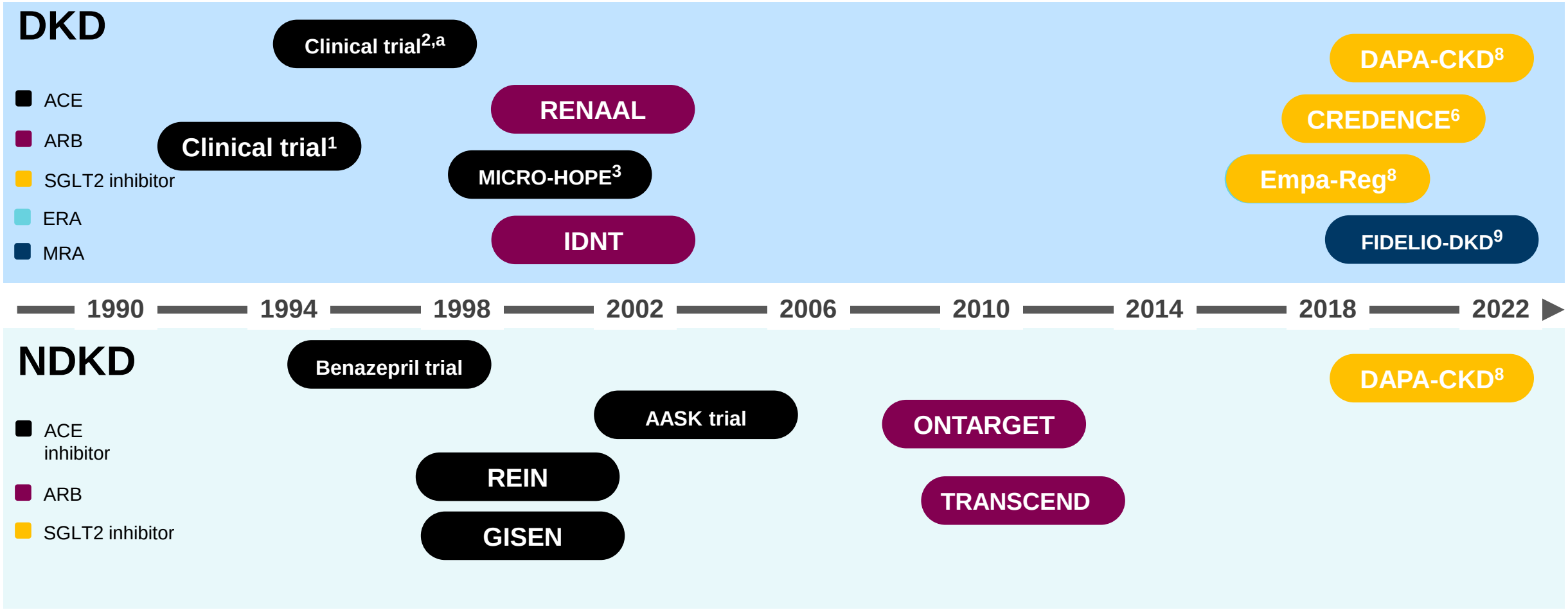
Study or Subgroup	Intensive Therapy Events	Total	Standard Therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ACCORD	138	5119	151	5115	43.2%	0.91 [0.73, 1.15]
ADVANCE	11	5571	31	5569	21.2%	0.35 [0.18, 0.70]
UKPDS 33	16	2729	9	1138	17.3%	0.74 [0.33, 1.67]
UKPDS 34	2	342	2	411	4.2%	1.20 [0.17, 8.49]
VADT	7	882	11	884	14.1%	0.64 [0.25, 1.64]
Total (95% CI)		**14643**		**13117**	**100.0%**	**0.69 [0.46, 1.05]**
Total events	174		204			

Heterogeneity: Tau² = 0.09; Chi² = 7.08, df = 4 (P = 0.13); I² = 43%
Test for overall effect: Z = 1.72 (P = 0.09)



Arch Intern Med. 2012 May 28; 172(10): 761–769.

Clinical Trial of DKD and NDKD : SGLT2 Era



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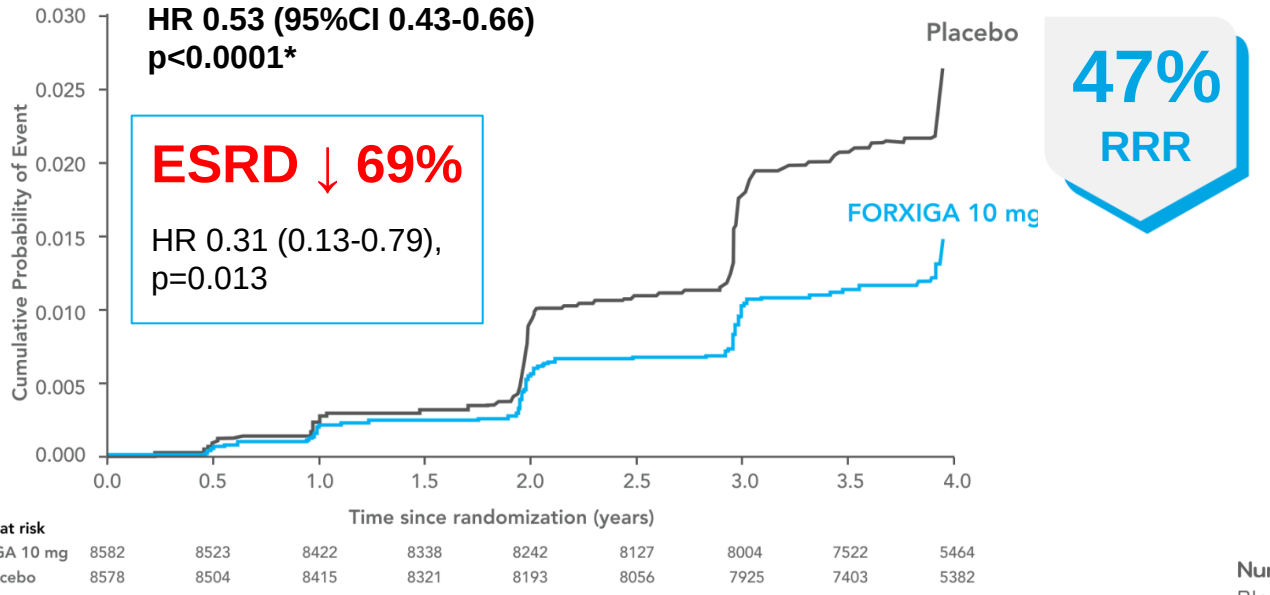
1. Lewis EJ, et al. *N Engl J Med* 1993;329:1456–1462; 2. Agardh CD, et al. *J Hum Hypertens* 1996;10:185–192; 3. HOPE Study Investigators. *Lancet* 2000;355:253–259; 4. The GISEN Group. *Lancet* 1997;349:1857–1863; 5. Chan GC, et al. *Nephrol Dial Transplant.* 2016;31:359-368; 6. Perkovic V, et al. *N Engl J Med* 2019;380:2295–2306; 7. Lancet. 2019 May 11;393(10184):1937-1947; 8. N Engl J Med 2020; 383:1436-1446; 9. ASN 2020.

FORXIGA治療T2D病患
減少腎功能惡化、ESRD或腎因性死亡

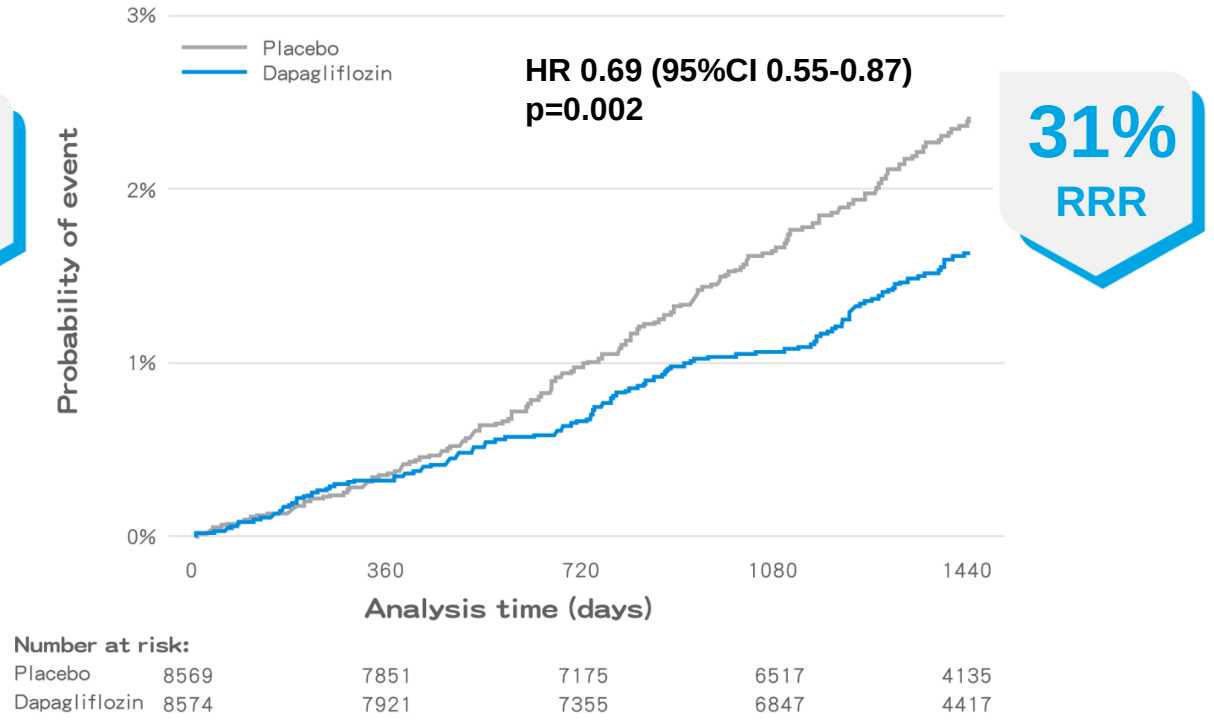
DECLARE TIMI-58

針對**9成**eGFR≥60且近**7成**UACR<30 mg/g的T2D患者使用FORXIGA 10 mg

Renal composite outcome*



Acute kidney injury



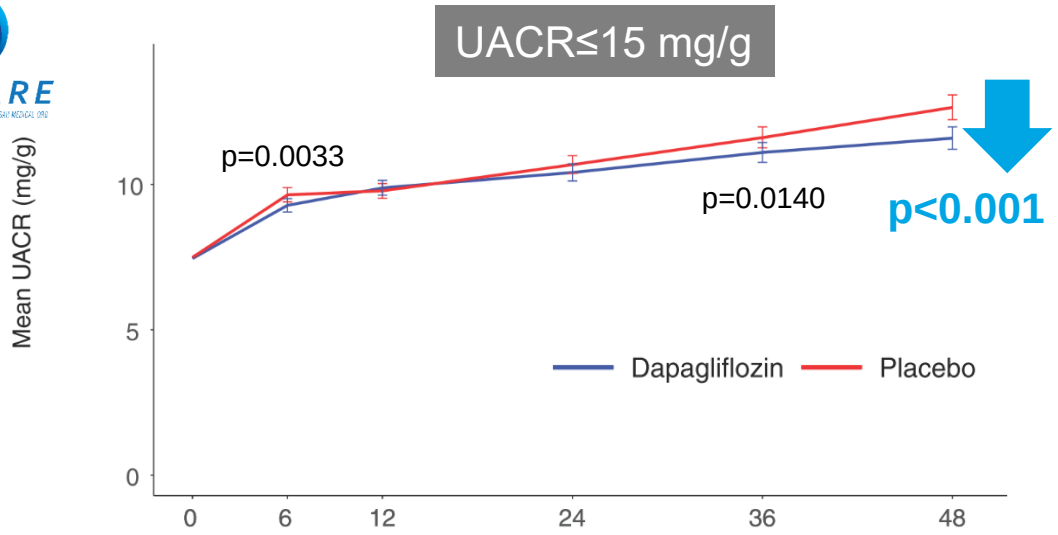
*Nominally significant, prespecified exploratory outcome; Renal composite outcome: sustained ≥40% eGFR decline to <60 mL/min/1.73 m2, ESKD, or renal death

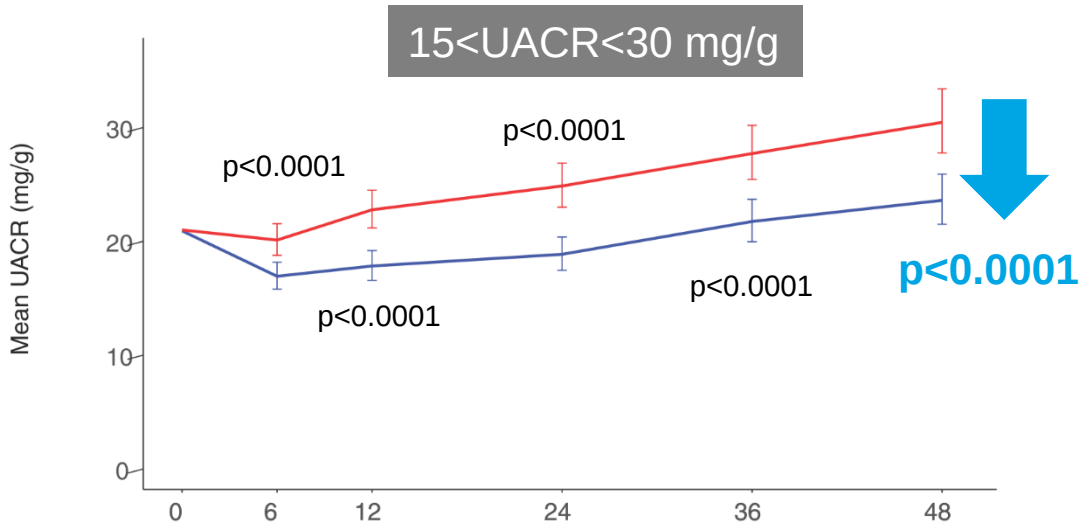
1. N Engl J Med. 2019 Jan 24;380(4):347-357. 2. Lancet Diabetes Endocrinol. 2019 Aug;7(8):606-617. 3. Diabetes Obes Metab. 2020 Aug;22(8):1357-1368.

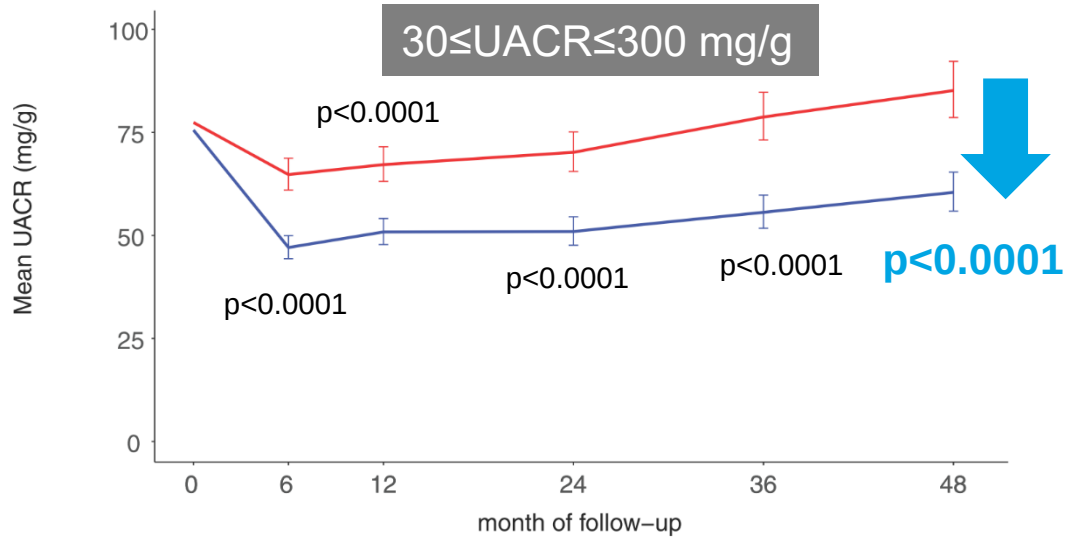
forxiga (dapagliflozin) xigduo XR Extended-Release Tablets (dapagliflozin/metformin HCl) QTERN (saxagliptin/dapagliflozin)

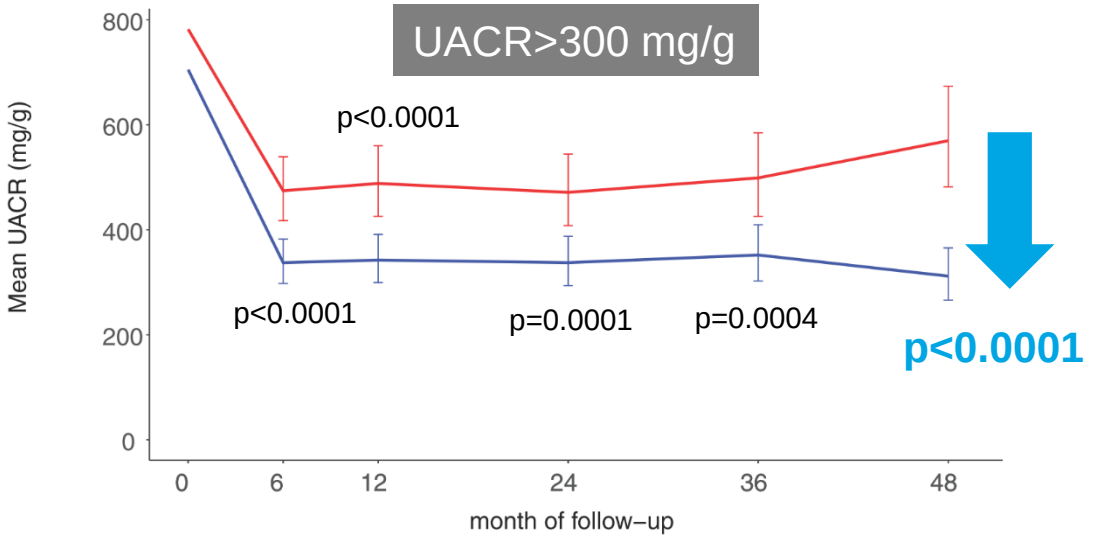
FORXIGA治療T2D減少白蛋白尿無論患者白蛋白尿分級

DECLARE TIMI-58









Diabetes Care. 2021 Aug;44(8):1805-1815.

forxiga (dapagliflozin) xigduo XR Extended-Release Tablets (dapagliflozin/metformin HCl) QTERN (saxagliptin/dapagliflozin)

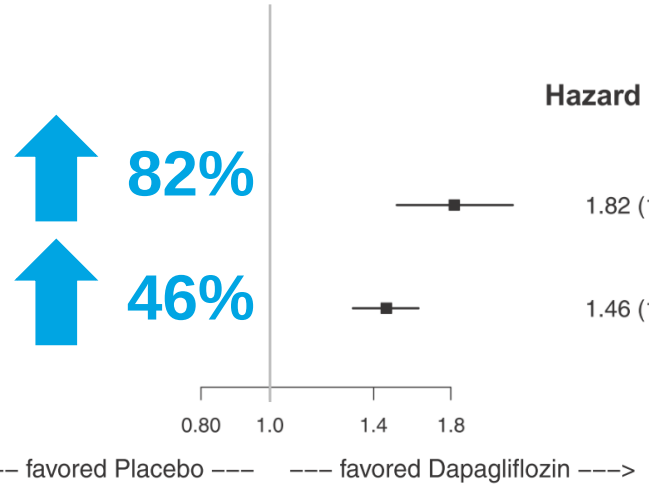
FORXIGA治療T2D有效改善白蛋白尿分期

Improvement in UACR categories

	Dapagliflozin (N=8582)			Placebo (N=8578)				
	n	N	n/N(%)	n	N	n/N(%)	Hazard ratio (95% CI)	Cox p−value
UACR to <=300 in subjects with >300 at BL	282	594	47.5%	175	575	30.4%	1.82 (1.51, 2.20)	<0.0001
UACR to <30 in subjects with 30–300 at BL	774	2017	38.4%	576	2013	28.6%	1.46 (1.31, 1.62)	<0.0001

巨量 → 微量

微量 → UACR<30

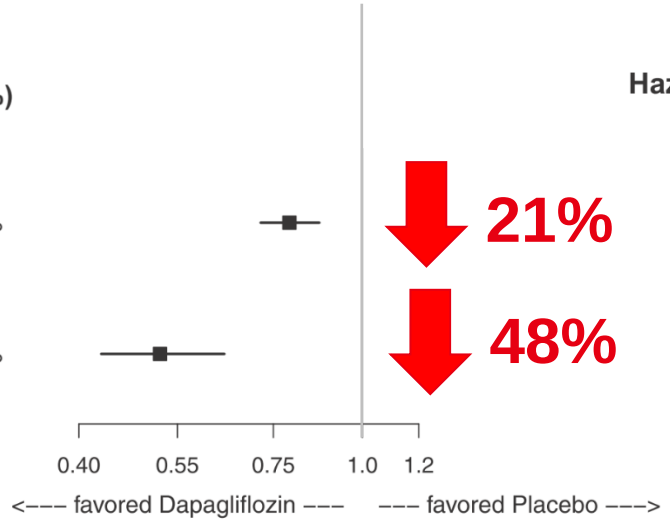


Deterioration in UACR categories

	Dapagliflozin (N=8582)			Placebo (N=8578)				
	n	N	n/N(%)	n	N	n/N(%)	Hazard ratio (95% CI)	Cox p−value
UACR to >=30 in subjects with <30 at BL	772	5819	13.3%	959	5825	16.5%	0.79 (0.72, 0.87)	<0.0001
UACR to >300 in subjects with 30–300 at BL	156	2017	7.7%	284	2013	14.1%	0.52 (0.43, 0.64)	<0.0001

<30不惡化成微量

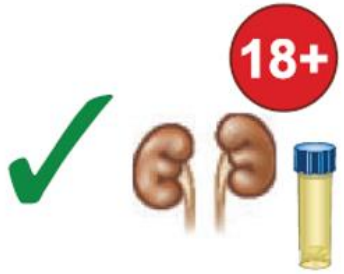
微量不惡化成巨量



Diabetes Care. 2021 Aug;44(8):1805-1815.

DAPA-CKD研究設計：收納糖尿病及非糖尿病患者

Multicentre ~ 400
Target n = 4304
Patients with and without type 2 diabetes



≥ 18 years
25–75 ml/min/1.73 m²
UACR ≥ 200 mg/g

Stable, maximum tolerated labelled daily dose, treatment with **ACE-I or ARB** for at least 4 weeks, if not contraindicated

Interventions

forxiga™ (dapagliflozin) 福適佳

1:1

Placebo

Follow-up

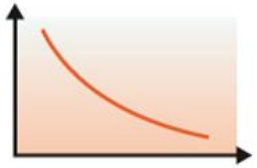
Medium

Stop Early Due to Overwhelming Efficacy

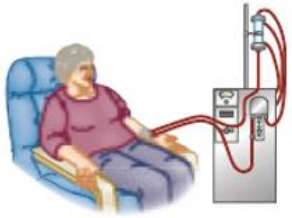
99.7% completed study

Primary outcome

Composite renal endpoint



≥ 50% decline in eGFR



End-stage kidney disease

Renal or cardiovascular death

1. Nephrol Dial Transplant. 2020 Feb 1;35(2):274-282. 2. Hiddo Lambers Heerspink present at 2020 EASD virtual meeting: Results of the DAPA-CKD trial. 24 September, 2020

DAPA-CKD baseline: 2/3糖尿病患者 1/3非糖尿病患者

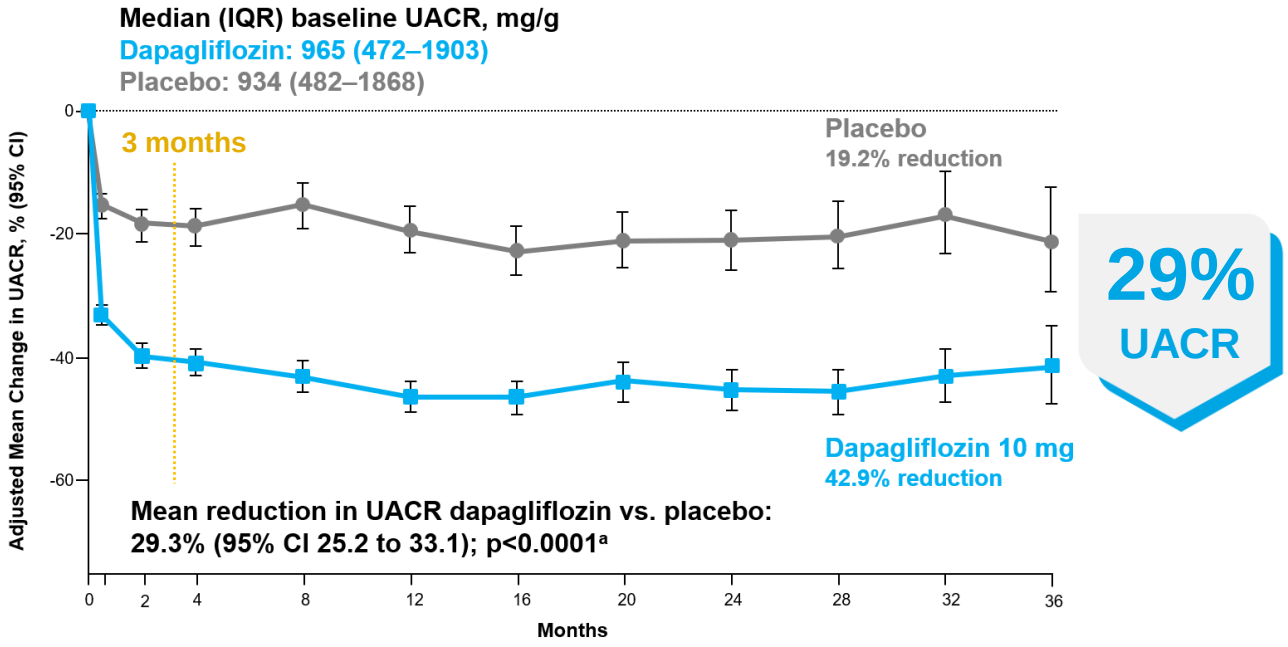
	Dapagliflozin 10 mg (N=2152)	Placebo (N=2152)
Age, years, mean	62	62
Asian, %	35	33
Type 2 diabetes, %	68	67
Without type 2 diabetes, %	32	33
Cardiovascular disease, %	38	37
Heart failure, %	11	11
Systolic blood pressure, mmHg, mean	137	137
eGFR, mL/min/1.73m^2, mean	43	43
UACR, mg/g, median	965	934
ACEi or ARB, %	97	97
Diuretic, %	43	44
Statin, %	65	65

N Engl J Med. 2020 Oct 8;383(15):1436-1446.

CKD患者使用FORXIGA能降低白蛋白尿

DAPACKD

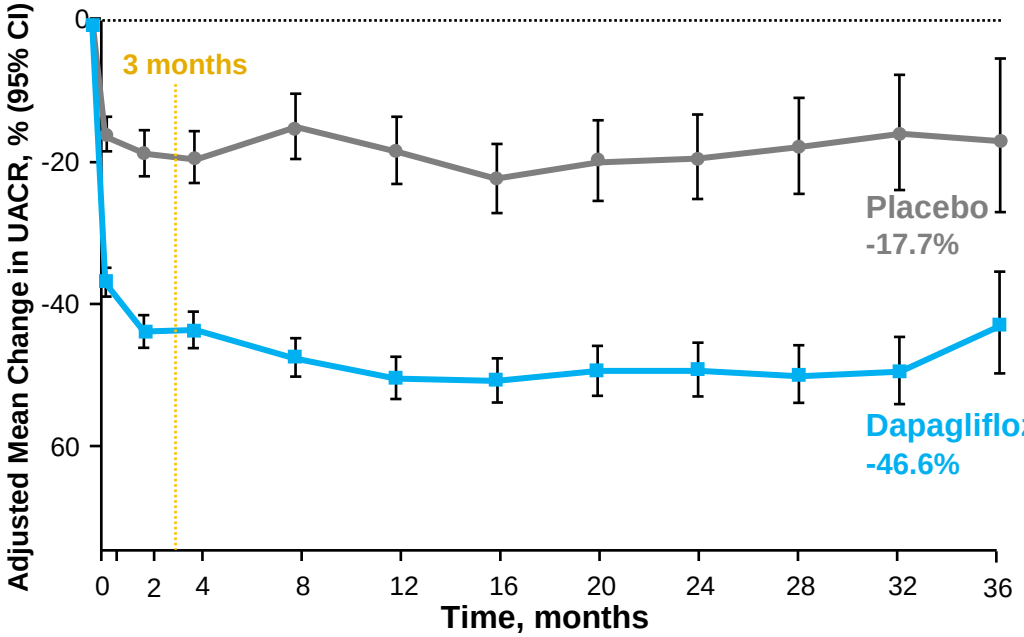
Change in albuminuria (all patients)



29% UACR

Patients with T2D

-35.1% mean reduction in UACR (dapagliflozin vs. placebo)
(95% CI -39.4, -30.6; p<0.001)



35% UACR

Median (IQR) baseline UACR, mg/g
Dapagliflozin: 1025 (473–2111) Placebo: 1005 (493–2017)

CI = confidence interval; IQR = interquartile range; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio

[a]Effect of dapagliflozin relative to placebo on UACR in the full cohort using the average coefficient of treatment to estimate the effect of dapagliflozin on the geometric mean UACR across the follow-up assessments. Jongs N et al. Presented at: ERA-EDTA Congress; June 5-8, 2021; Virtual.

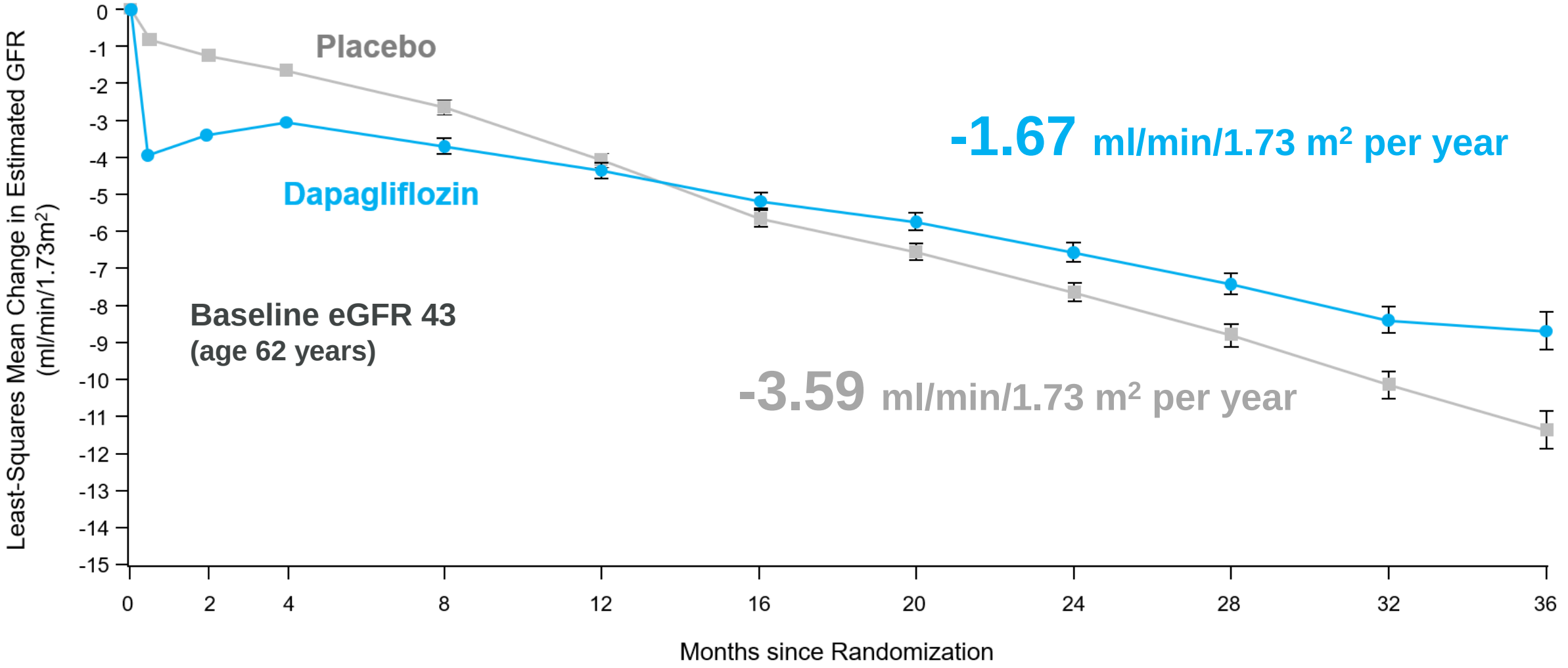
forxiga (dapagliflozin) xigduo XR Extended-Release Tablets (dapagliflozin/metformin HCl) QTERN (saxagliptin/dapagliflozin)

TW-20354 _FOR_30/6/2022

FORXIGA減緩CKD患者eGFR下降速度54%

DAPACKD

Difference of **1.92** ml/min/1.73 m^2 per year (95%CI, 1.61 to 2.24)



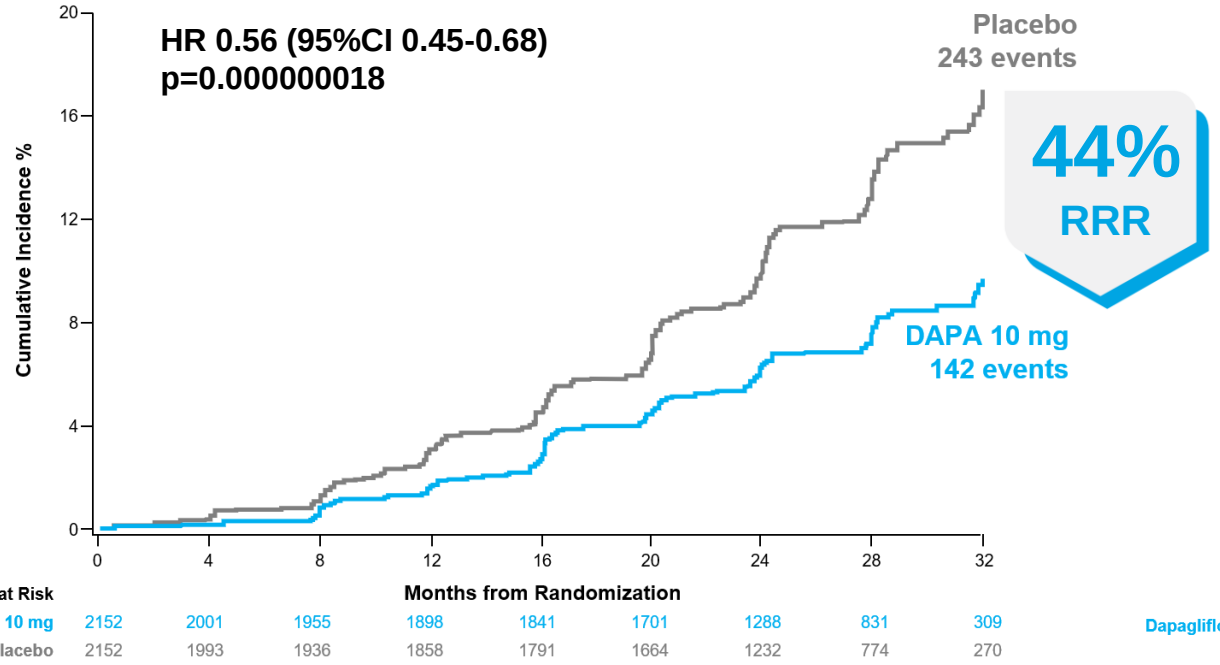
N Engl J Med. 2020 Oct 8;383(15):1436-1446.

forxiga (dapagliflozin) xigduo XR Extended-Release Tablets (dapagliflozin/metformin HCl) QTERN (saxagliptin/dapagliflozin)

FORXIGA治療CKD病患
減少腎功能惡化、ESRD或腎因性死亡

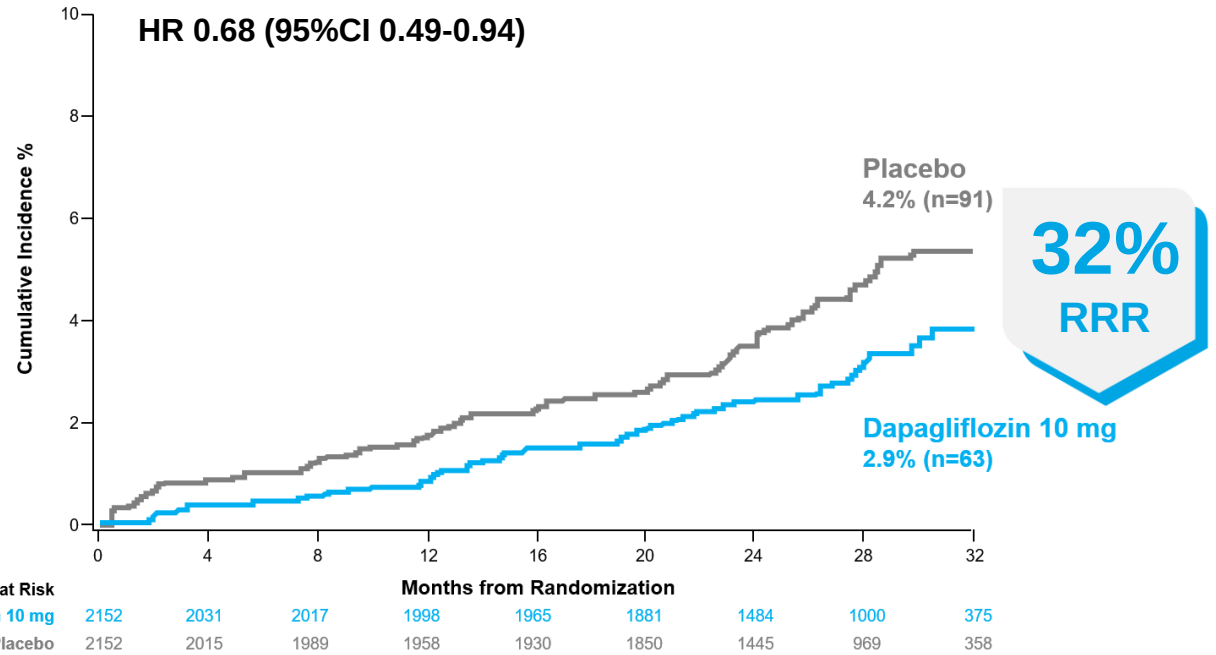
DAPACKD

Renal composite outcome



N at Risk									
DAPA 10 mg	2152	2001	1955	1898	1841	1701	1288	831	309
Placebo	2152	1993	1936	1858	1791	1664	1232	774	270

Acute kidney injury



N at Risk									
Dapagliflozin 10 mg	2152	2031	2017	1998	1965	1881	1484	1000	375
Placebo	2152	2015	1989	1958	1930	1850	1445	969	358

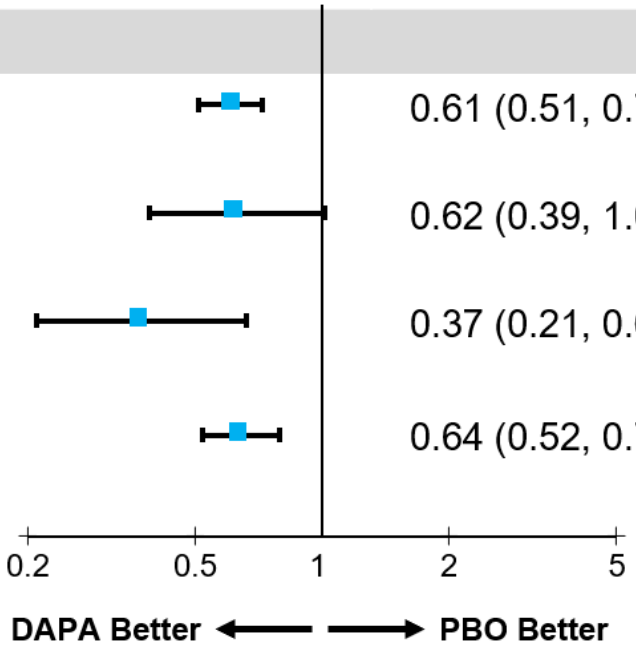
Renal composite outcome: sustained ≥50% eGFR decline, ESKD, or renal death

1. N Engl J Med. 2020 Oct 8;383(15):1436-1446. 2. Hiddo Lambers Heerspink present at 2020 EASD virtual meeting: Results of the DAPA-CKD trial. 24 September, 2020. 3. Heerspink HJL et al. Presented at: ERA-EDTA Congress; June 5-8, 2021; Virtual.

糖尿病、糖尿病前期、無糖尿病的CKD患者
使用FORXIGA一致降低腎臟惡化風險

DAPACKD

	DAPA n/N	PBO n/N	DAPA Events/100 patient-years	PBO Events/100 patient-years	Hazard Ratio (95% CI)	P-value for Interaction
Primary outcome: ≥50% eGFR decline, ESKD, kidney or CV death						
Overall	197/2152	312/2152	4.6	7.5	0.61 (0.51, 0.72)	
Normoglycemia	28/368	41/370	4.1	6.1	0.62 (0.39, 1.01)	0.19
Pre-diabetes	17/329	42/331	2.6	6.5	0.37 (0.21, 0.66)	
Type 2 diabetes	152/1455	229/1451	5.2	8.0	0.64 (0.52, 0.79)	



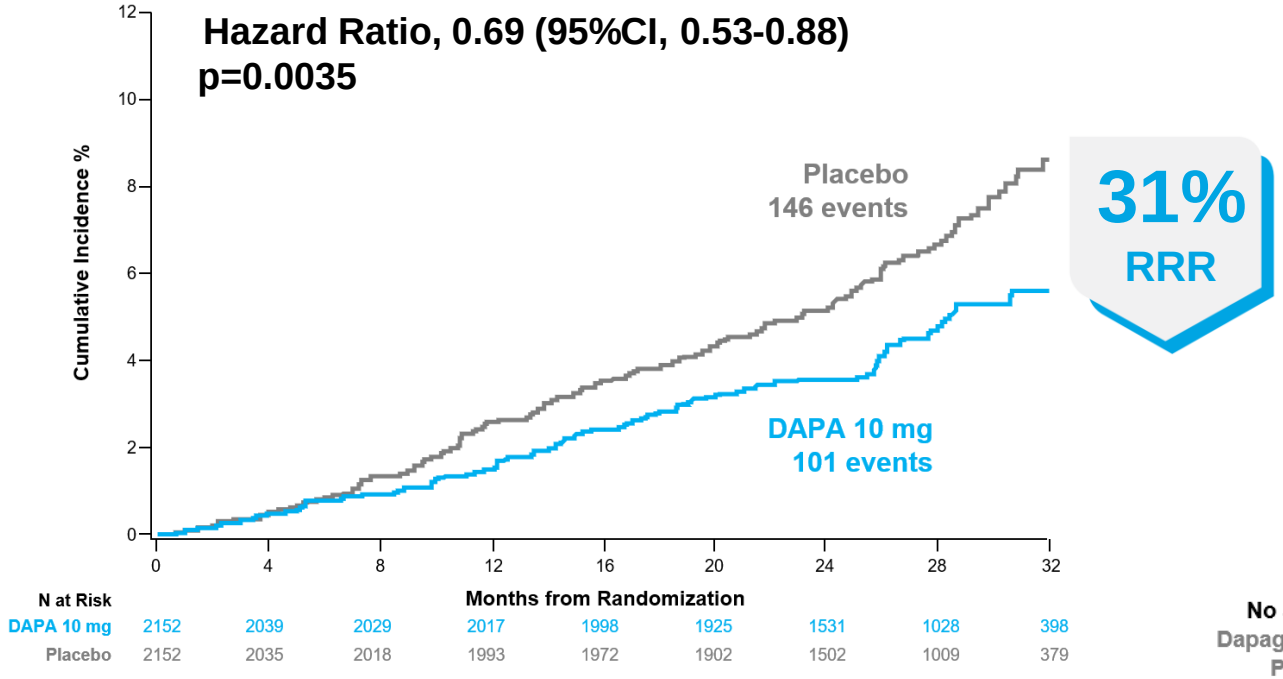
A Prespecified Analysis from DAPA-CKD

Diabetes Care. 2021 Aug;44(8):1894-1897.

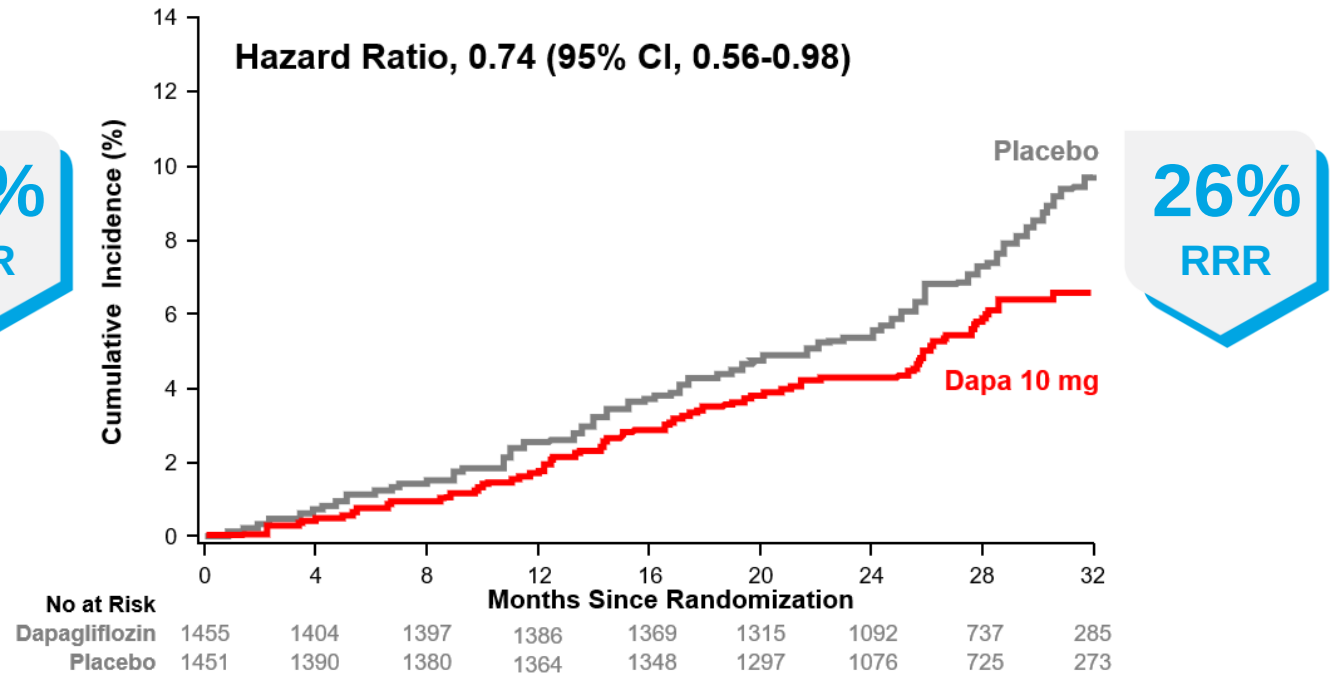
FORXIGA降低CKD患者總死亡

DAPACKD

All Patients



Patients With T2D



T2D = type 2 diabetes 1. N Engl J Med. 2020 Oct 8;383(15):1436-1446. 2. Heerspink HJL et al. Eur Heart J. 2021;42:1216-1227.

forxiga (dapagliflozin) xigduo XR Extended-Release Tablets (dapagliflozin/metformin HCl) QTERN (saxagliptin/dapagliflozin)

DAPA-CKD安全性資料

Safety outcomes[a], %	With T2D		Without T2D	
	Dapagliflozin (n=1453)	Placebo (n=1450)	Dapagliflozin (n=696)	Placebo (n=699)
Discontinuation due to AE	5.6	6.5	5.2	4.1
Any serious AE	33.2	38.8	21.6	23.9
AE of interest				
Amputation[b]	2.4	2.6	0	0.1
Any definite or probable diabetic ketoacidosis	0	0.1	0	0
Fracture[c]	4.5	3.5	2.9	2.6
Renal related adverse event[c]	8.3	10.2	4.9	5.7
Major hypoglycemia[d]	1.0	1.9	0	0
Volume depletion[c]	6.3	4.9	5.0	2.7
Discontinuation due to any AE of genital infection	0.2	0	0	0

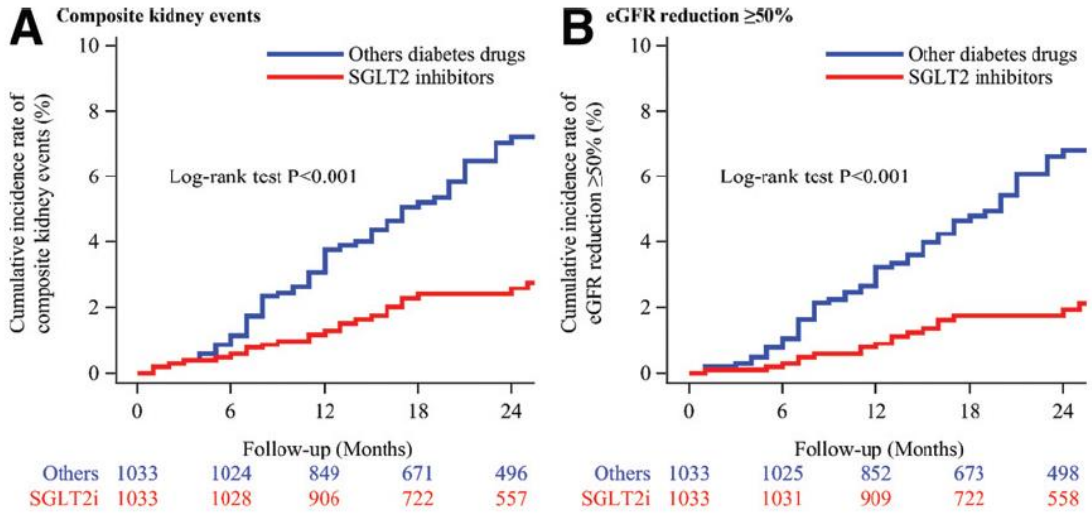
A Prespecified Analysis from DAPA-CKD

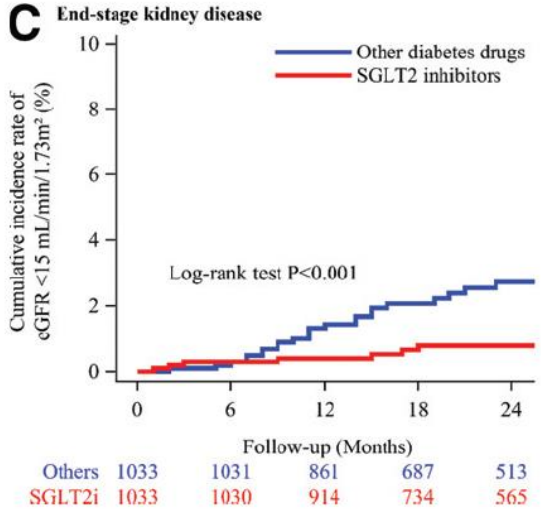
[a]Safety outcomes reported in participants on and off treatment; [b]Surgical or spontaneous/non-surgical amputation, excluding amputation due to trauma; [c]Based on pre-defined list of preferred terms; [d]AE with the following criteria confirmed by the investigator: i) symptoms of severe impairment in consciousness or behaviour, ii) need of external assistance, iii) intervention to treat hypoglycemia, iv) prompt recovery of acute symptoms following the intervention. AE = adverse event; T2D = type 2 diabetes; 1. Wheeler D. Presented at: ASN – Kidney Week 2020; October 22 – October 25, 2020. 2. Lancet Diabetes Endocrinol. 2021 Jan;9(1):22-31.

Kidney Outcomes Associated With SGLT2 Inhibitors Versus Other Glucose-Lowering Drugs in Real-world Clinical Practice: The Japan Chronic Kidney Disease Database

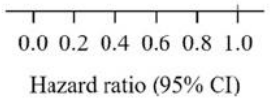
Diabetes Care 2021;44:2542–2551 | https://doi.org/10.2337/dc21-1081

Hajime Nagasu,[1] Yuichiro Yano,[2,3] Hiroshi Kanegae,[4] Hiddo J.L. Heerspink,[5] Masaomi Nangaku,[6] Yosuke Hirakawa,[6] Yuka Sugawara,[6] Naoki Nakagawa,[7] Yuji Tani,[8] Jun Wada,[9] Hitoshi Sugiyama,[10] Kazuhiko Tsuruya,[11] Toshiaki Nakano,[12] Shoichi Maruyama,[13] Takashi Wada,[14] Kunihiro Yamagata,[15] Ichiei Narita,[16] Kouichi Tamura,[17] Motoko Yanagita,[18] Yoshio Terada,[19] Takashi Shigematsu,[20] Tadashi Sofue,[21] Takafumi Ito,[22] Hirokazu Okada,[23] Naoki Nakashima,[24] Hiromi Kataoka,[25] Kazuhiko Ohe,[26] Mihoko Okada,[27] Seiji Itano,[1] Akira Nishiyama,[28] Eiichiro Kanda,[29] Kohjiro Ueki,[30] and Naoki Kashihara[1]



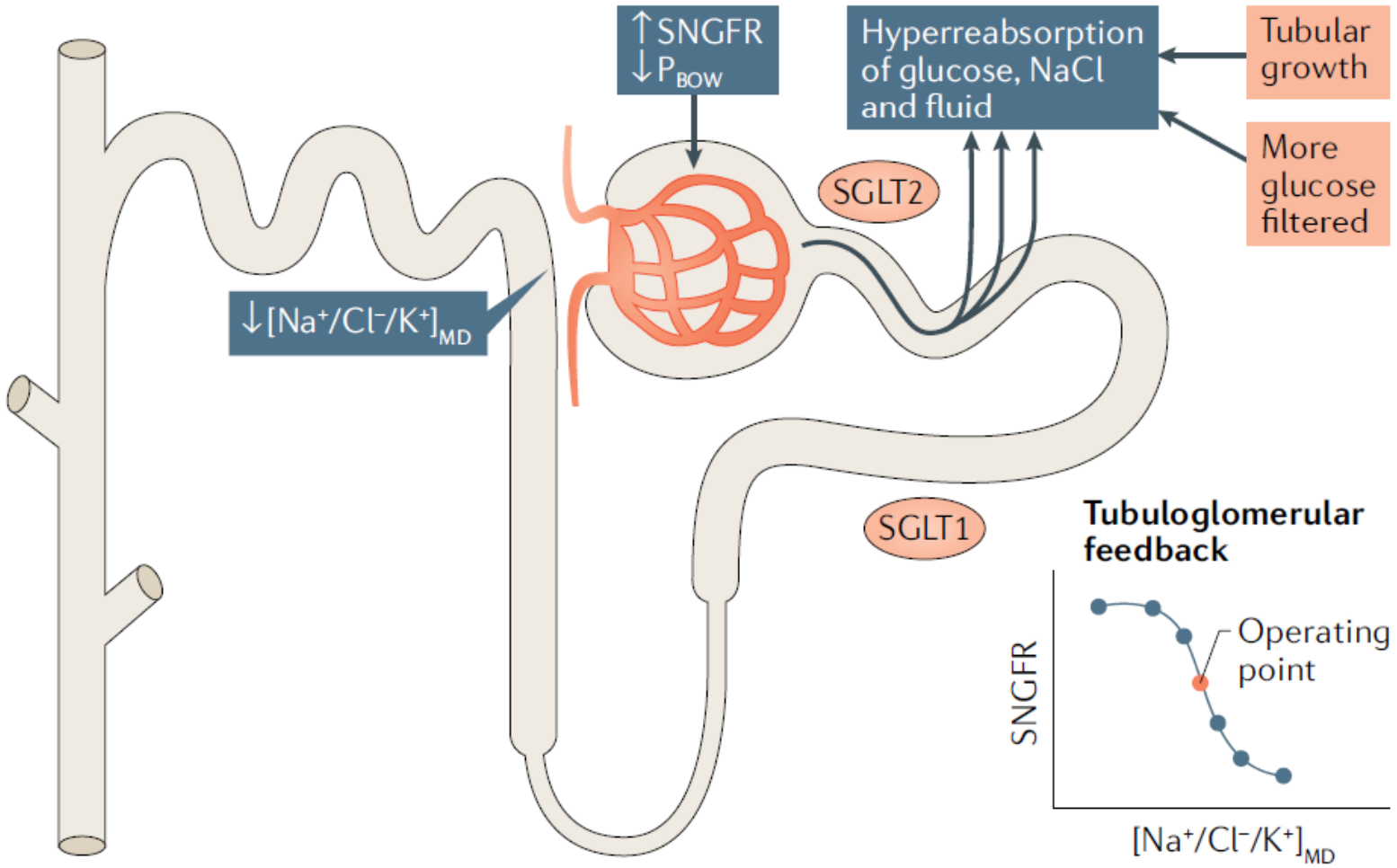


	Other diabetes drugs		SGLT2 inhibitors		Hazard ratio (95% CI)	p for interaction
	Events	Incidence rate (95% CI)	Events	Incidence rate (95% CI)		
Overall						
	73	35.7 (28.5, 44.7)	30	14.3 (10.0, 20.3)	0.40 (0.26, 0.61)	
Proteinuria at the index date						0.35
Yes	38	70.1 (51.5, 94.8)	13	22.4 (13.2, 38.0)	0.32 (0.17, 0.60)	
No	35	23.3 (16.8, 32.3)	17	11.2 (7.0, 17.8)	0.48 (0.27, 0.86)	
Rapid decline in eGFR before initiating treatments						0.81
Yes	39	64.7 (47.7, 87.2)	14	25.6 (15.3, 42.4)	0.39 (0.21, 0.72)	
No	34	23.6 (16.9, 32.8)	16	10.3 (6.4, 16.7)	0.44 (0.24, 0.79)	
eGFR <60 mL/min per 1.73m² at the index date						0.74
Yes	36	71.0 (51.7, 96.7)	16	30.1 (18.6, 48.4)	0.43 (0.24, 0.77)	
No	37	24.1 (17.5, 33.0)	14	8.9 (5.3, 14.9)	0.37 (0.20, 0.68)	
≥65 years of age at the index date						0.58
Yes	32	29.1 (20.7, 40.8)	13	13.1 (7.7, 22.3)	0.45 (0.24, 0.86)	
No	41	43.5 (32.2, 58.4)	17	15.4 (9.6, 24.5)	0.35 (0.20, 0.62)	
Use of ACE inhibitors or ARBs at the index date						0.41
Yes	39	41.8 (30.8, 56.7)	18	19.7 (12.5, 30.9)	0.47 (0.27, 0.83)	
No	34	30.6 (22.0, 42.5)	12	10.1 (5.8, 17.6)	0.33 (0.17, 0.64)	

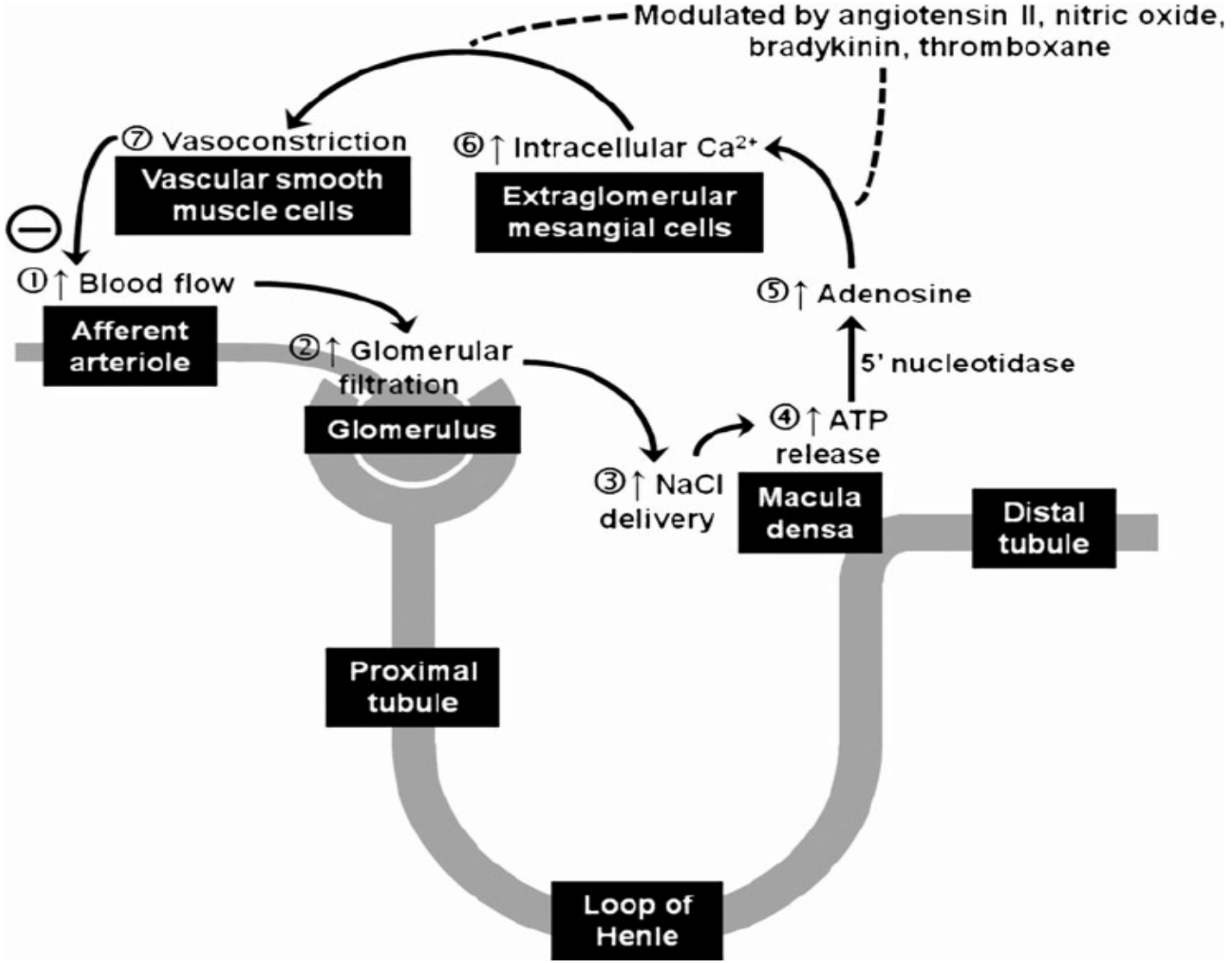


What is the Mechanism ?

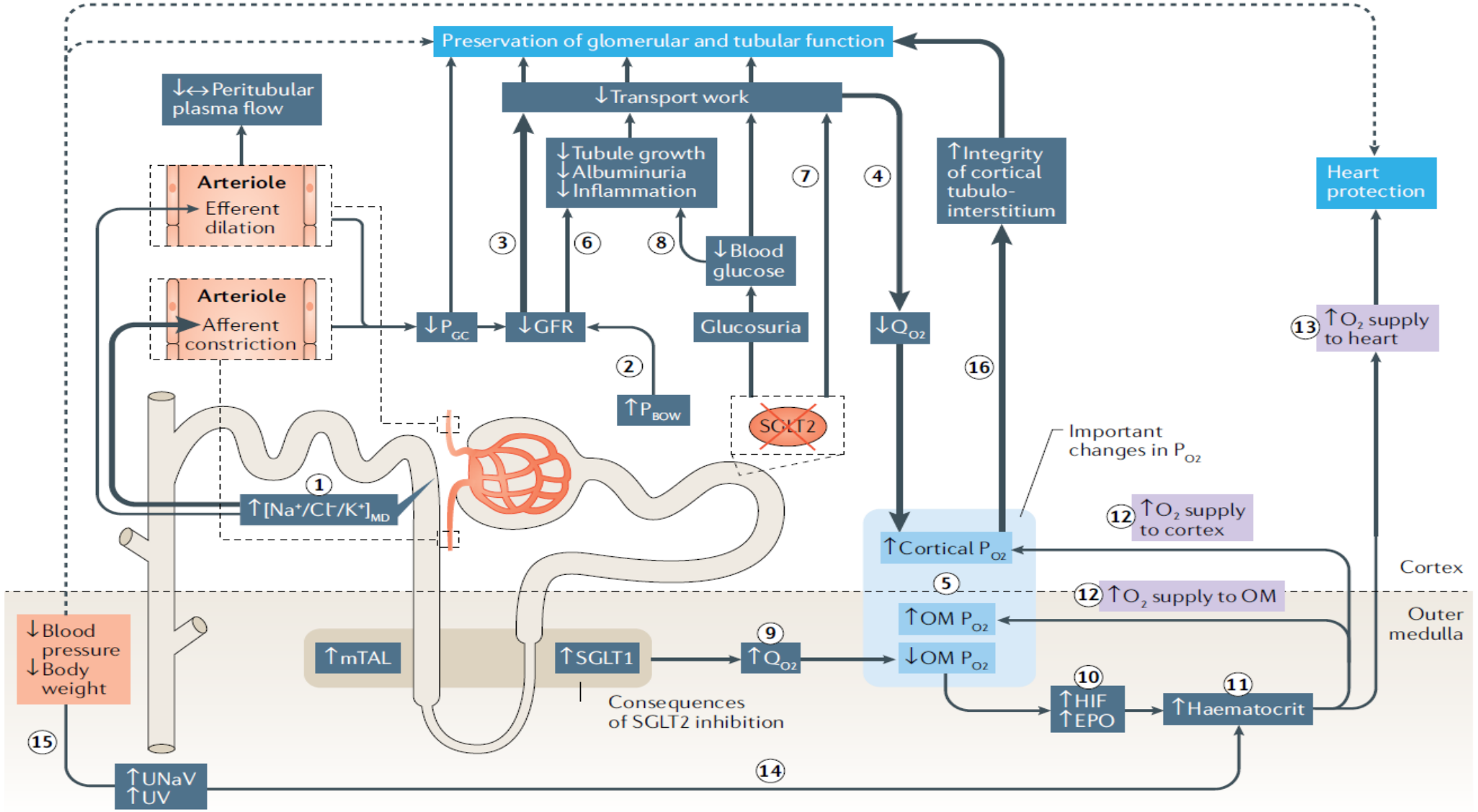
Primary Tubular Hyperreabsorption drives Hyperfiltration in Diabetes



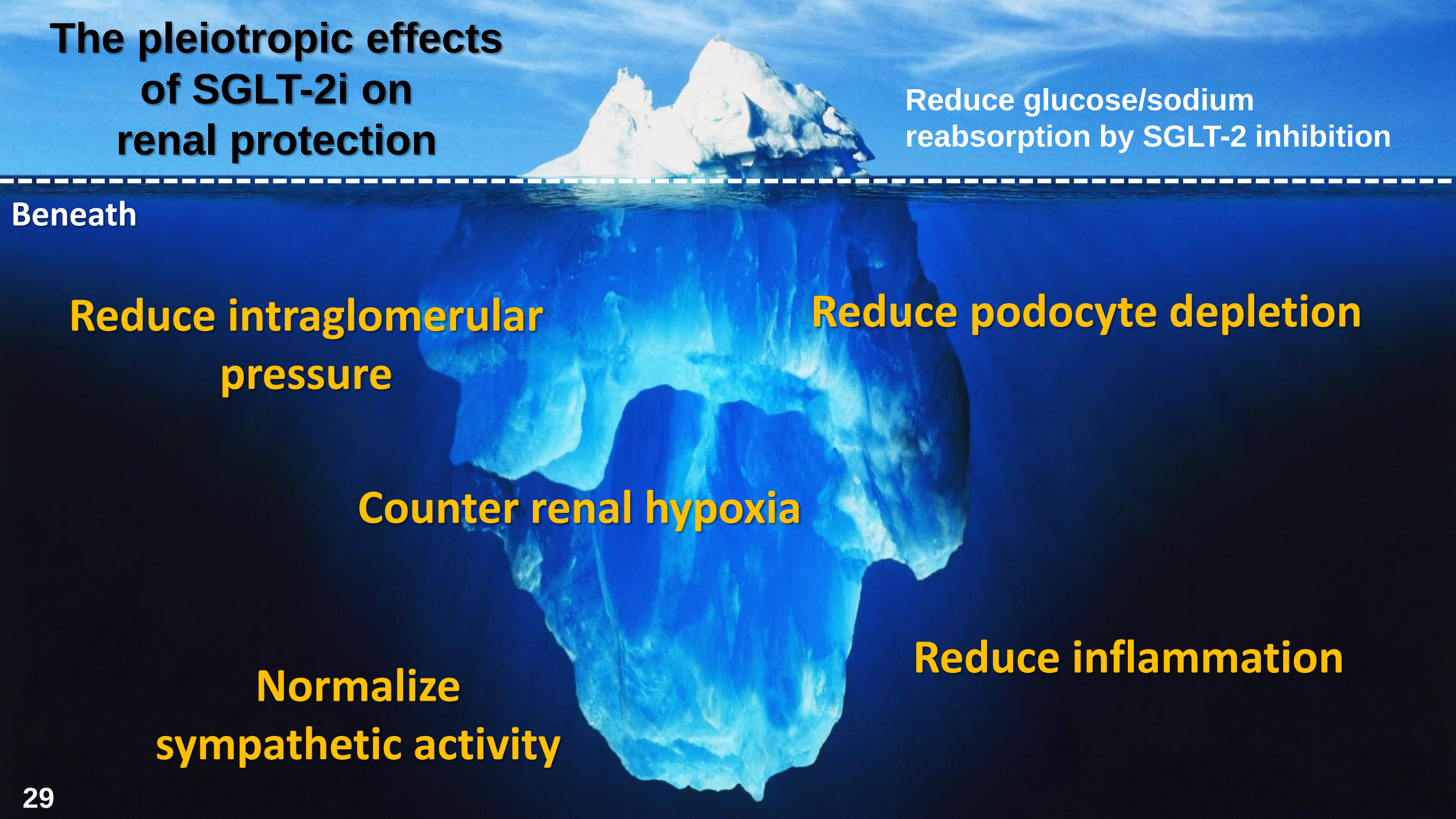
Tubuloglomerular Feedback



Mechanisms of Kidney Protection in Response to SGLT2 Inhibition



The pleiotropic effects of SGLT-2i on renal protection



Reduce glucose/sodium reabsorption by SGLT-2 inhibition

Beneath

Reduce intraglomerular pressure

Reduce podocyte depletion

Counter renal hypoxia

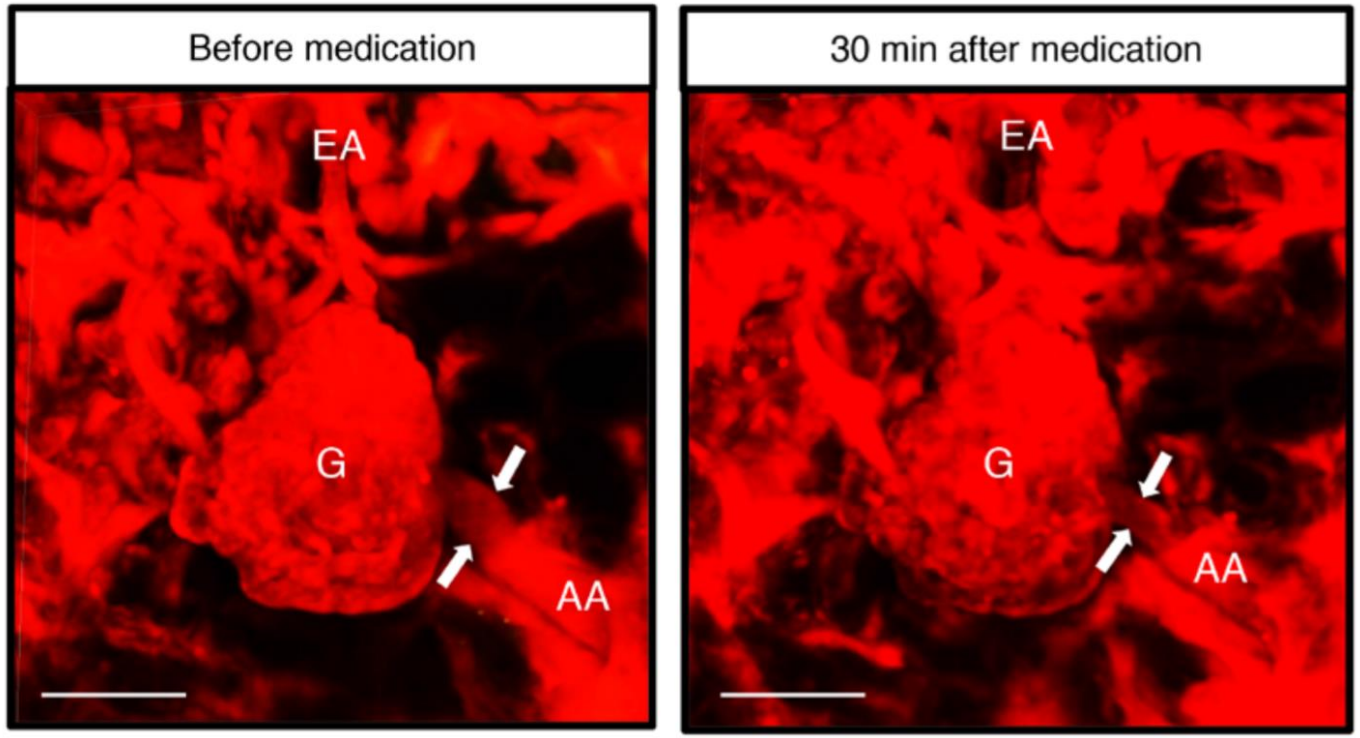
Reduce inflammation

Normalize sympathetic activity

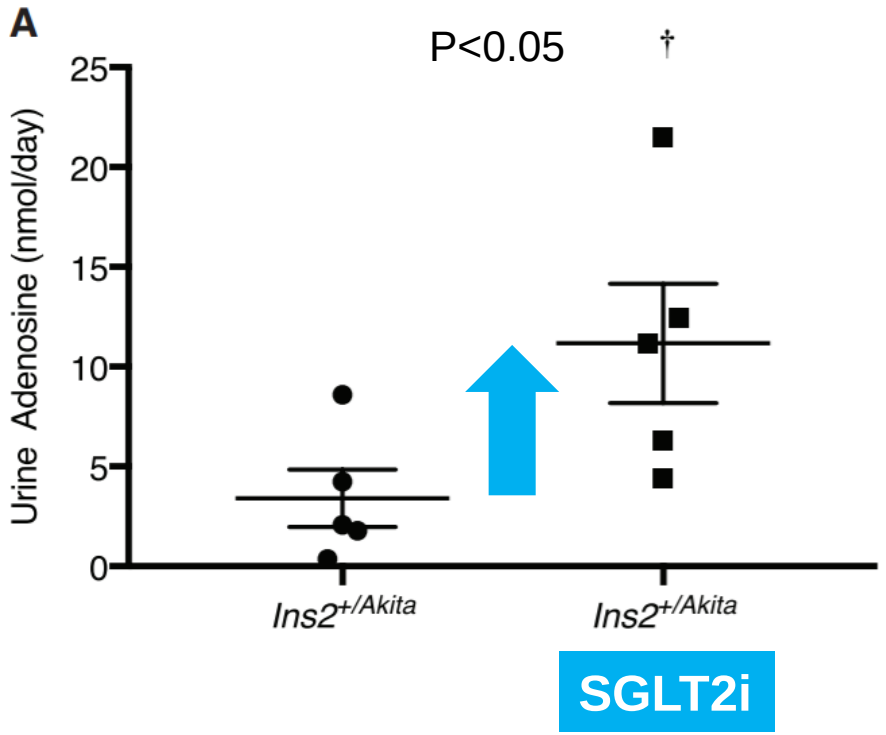
SGLT-2 inhibition constricts afferent artery mediated by adenosine

Adenosine/A1 adenosine receptor pathways play a pivotal role in the regulation of the single-nephron glomerular filtration rate via tubuloglomerular feedback mechanisms in response to SGLT-2 inhibition

In vivo imaging of afferent artery before and after SGLT-2i



Urine adenosine level increased

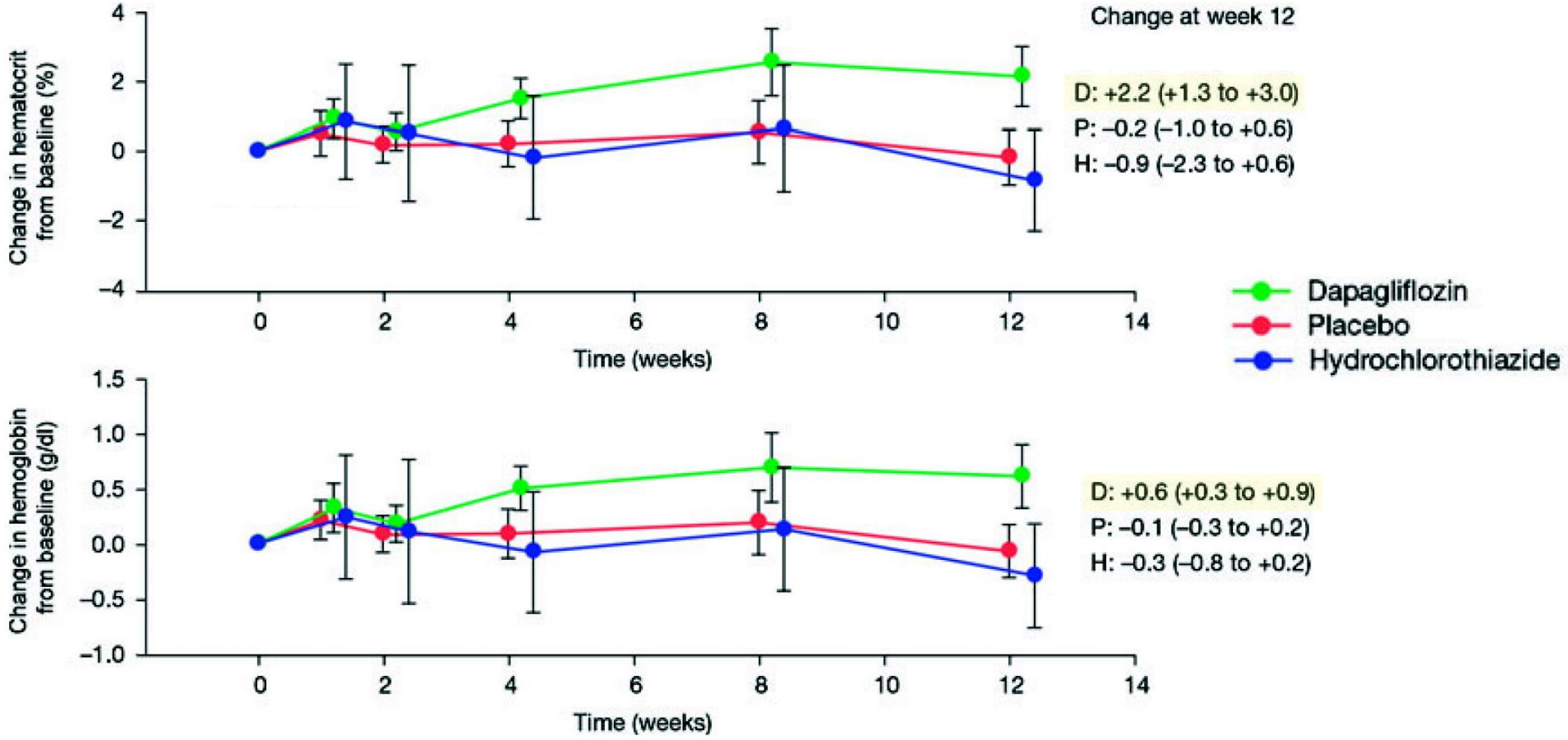


diabetic *Ins2*$_{+/Akita}$ mice

AA: afferent arteriole; G: glomerular; EA: efferent arteriole

Circulation. 2019 Jul 23;140(4):303-315.

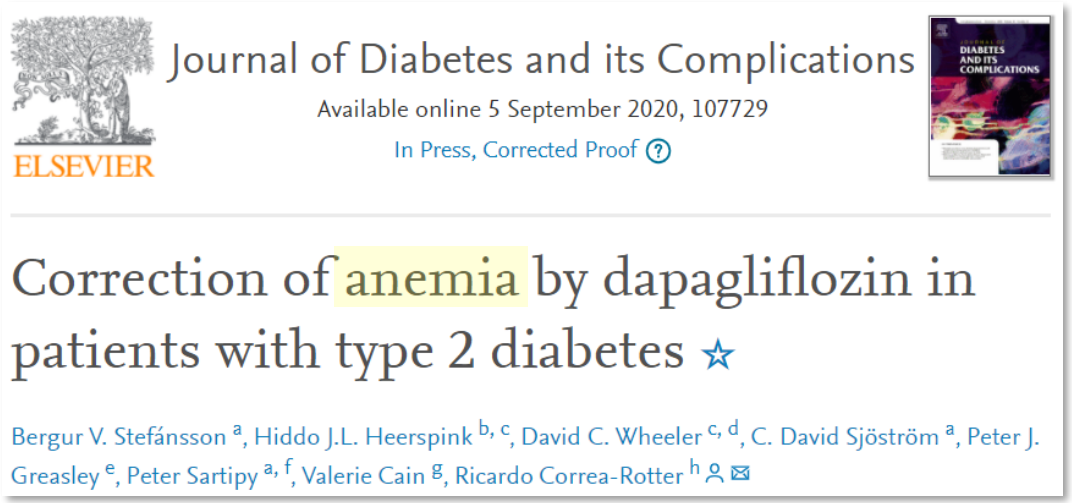
Hematocrit (+2.2%) and hemoglobin (+0.6 g/dl) appeared to increase with dapagliflozin therapy



A RCT included 75 subjects with type 2 diabetes assigned placebo, dapagliflozin 10 mg/day, or hydrochlorothiazide 25 mg/day

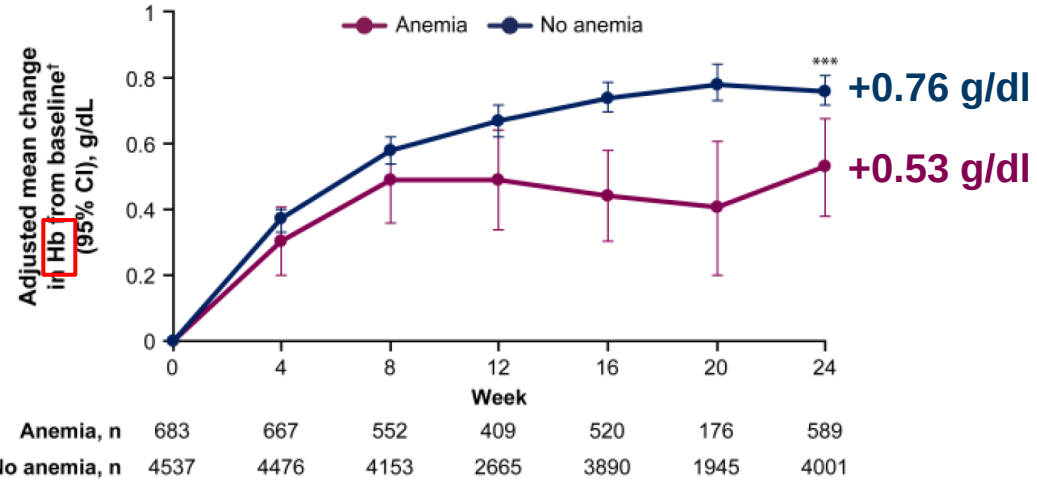
Diabetes Obes Metab. 2013 Sep;15(9):853-62.

Observed increased Hb and lower incidence of anemia in patients with Dapagliflozin therapy

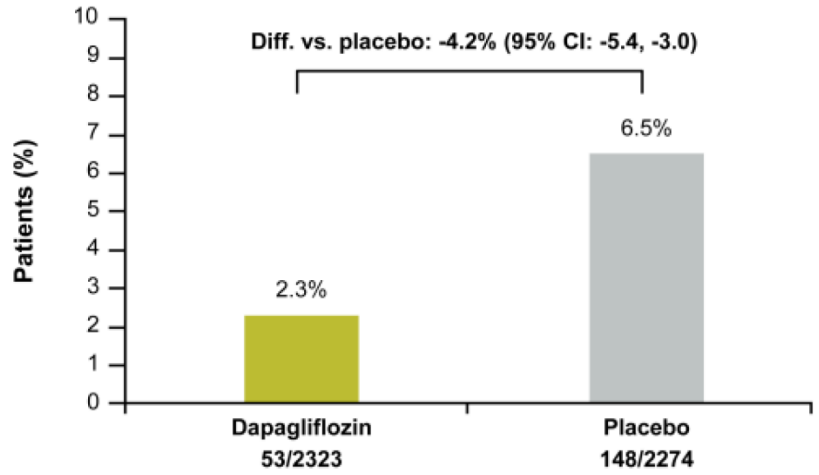


- 14 placebo-controlled, dapagliflozin (DAPA)-treatment studies (N=5325) were pooled.
- Hemoglobin increase was sustained through 24-weeks follow-up in DAPA-treated patients.
- Incidences of new-onset anemia were lower in DAPA (2.3%) vs placebo (6.5%).
- Treatment with DAPA can correct and prevent anemia in patients with type 2 diabetes.

Mean change of Hb in T2D patients treated with DAPA with and without anemia



Incidences of new-onset anemia

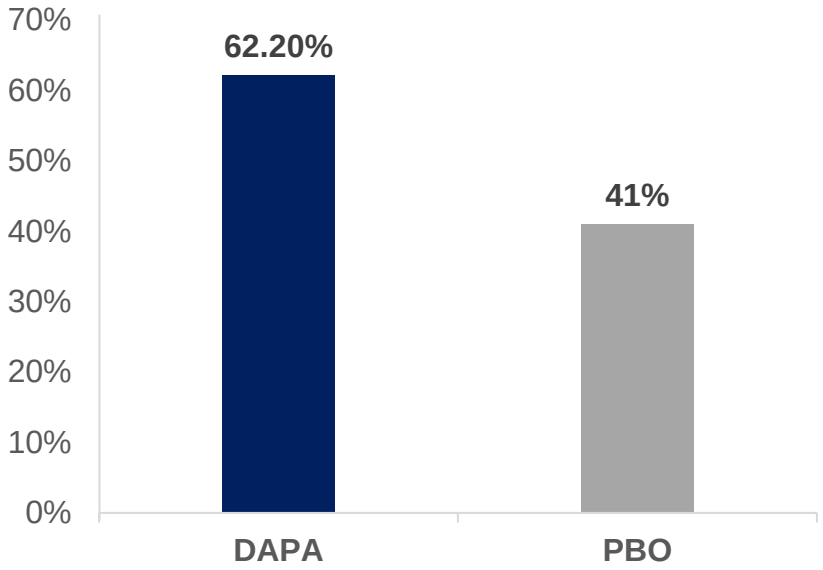


J Diabetes Complications. 2020 Dec;34(12):107729.

Dapagliflozin corrected anemia more often than placebo in DAPA-HF

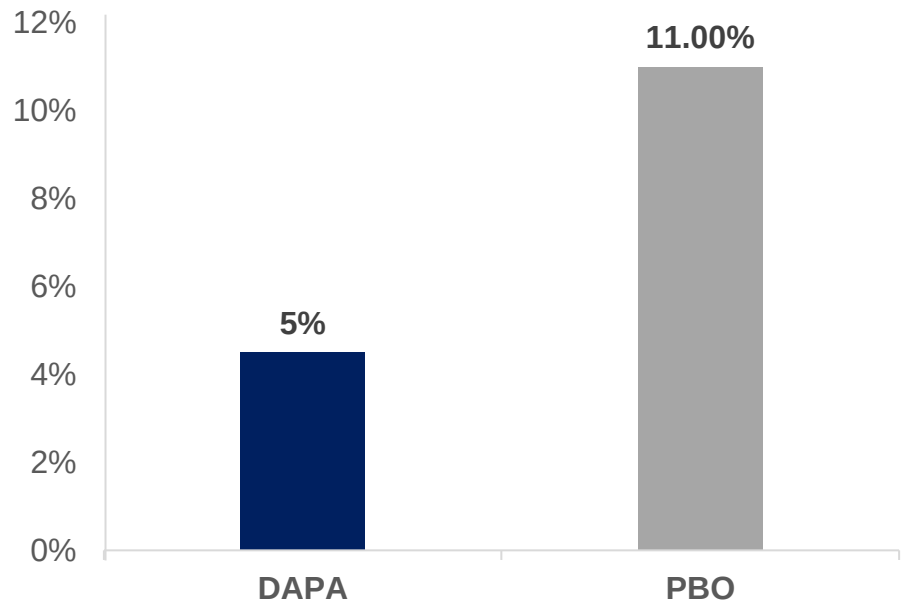
In DAPA-HF, 1032(22.0%) were anemic at baseline

Anemic → Non-anemic



Odds ratio for anemia correction of
2.37 (95% CI 1.84-3.04) p<0.001

Non-anemic → Anemic

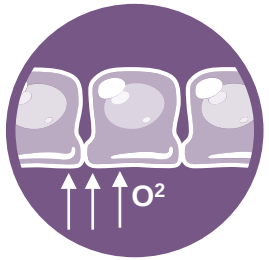


Odds ratio for development of anemia of
0.38 (95% CI 0.29-0.49); p<0.001

- Anemia was defined at baseline as a hematocrit <39% in men and <36% in women.
- Correction of anemia after randomization was defined as two consecutive hematocrit measurements above these thresholds at any time during follow up.

Eur J Heart Fail. 2021 Apr;23(4):617-628.

Dapagliflozin increases erythropoiesis and hematocrit



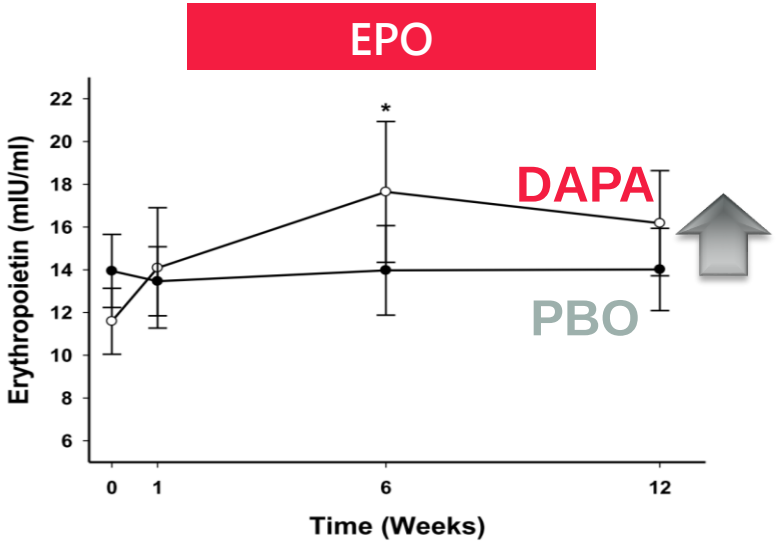
Study design：

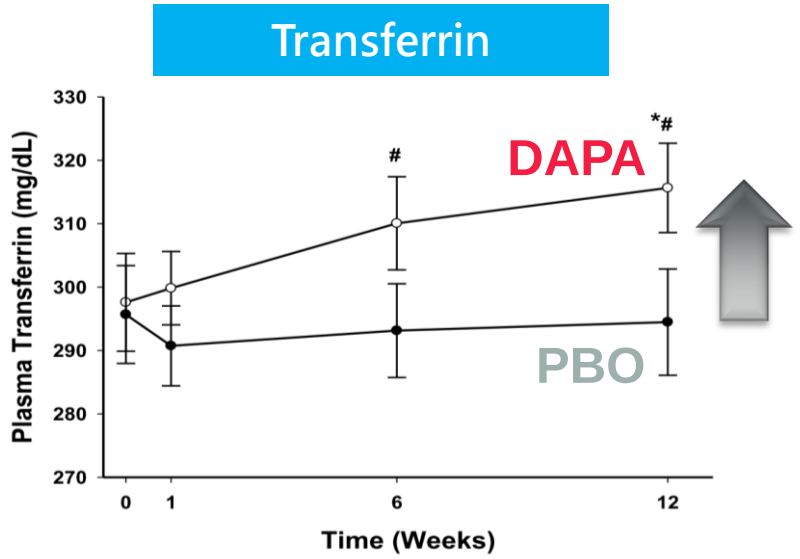
52 Patients with T2D & obesity were randomized (1:1) to either dapagliflozin (10 mg daily) or placebo for 12 weeks.

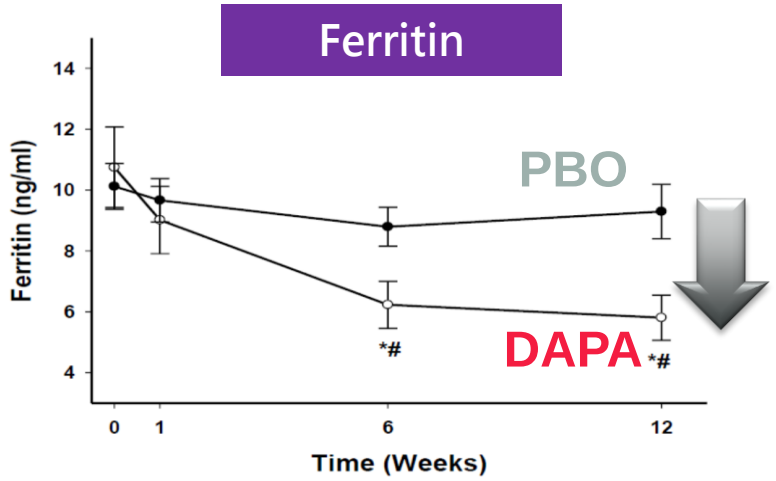
Results：

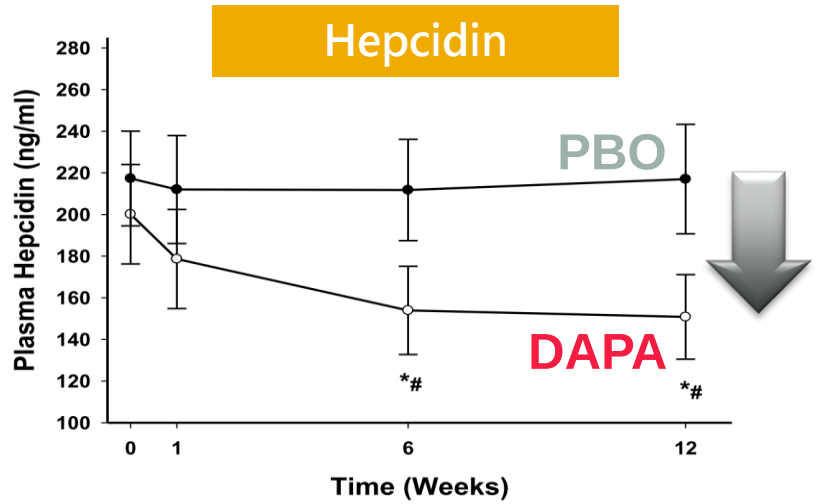
Significantly increased

Hb (+0.5 g/dl)、HCT (+2.1%)、RBC(+0.2 mil/mm^3)





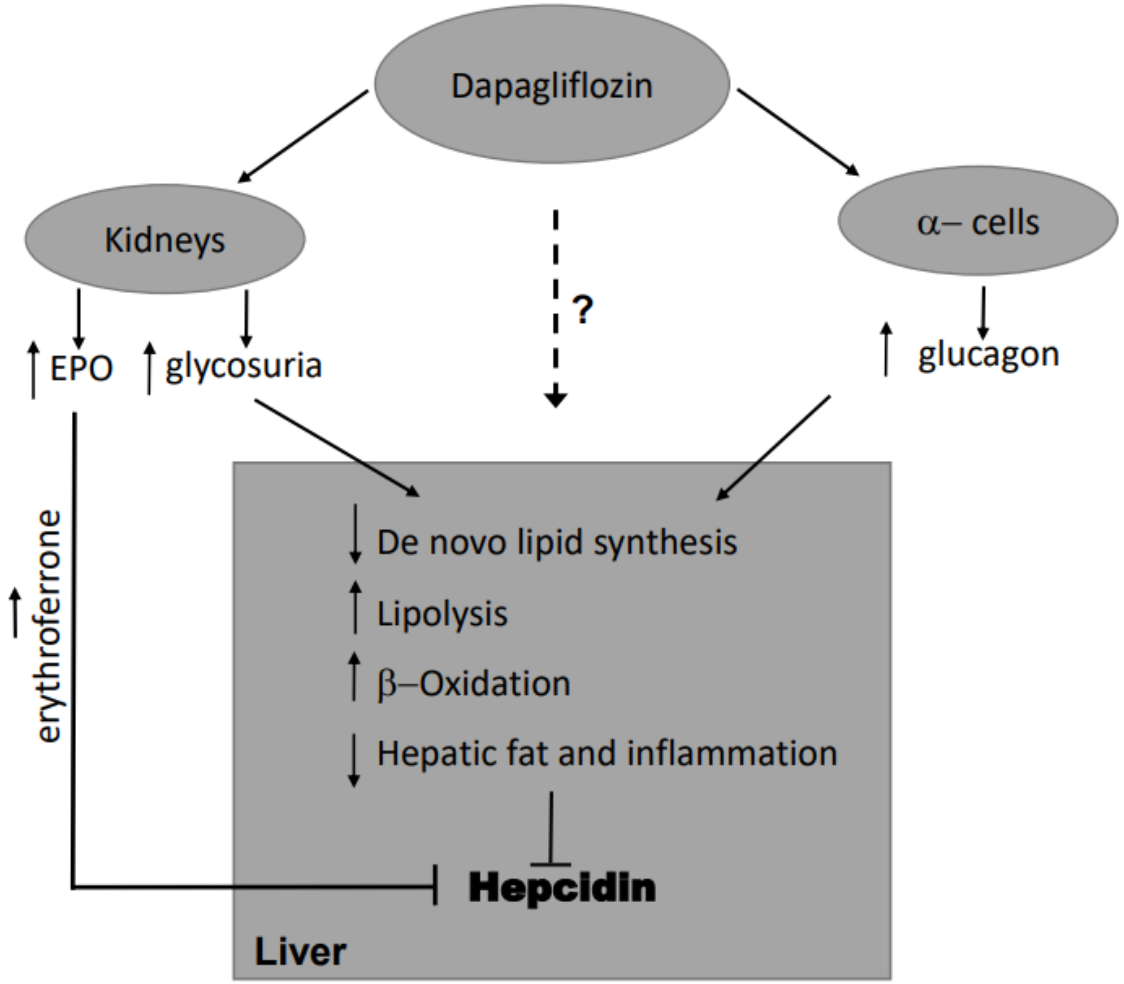




*P<0.05 compared to baseline, #P<0.05 compared to placebo

J Clin Endocrinol Metab. 2020 Apr 1;105(4):dgaa057.

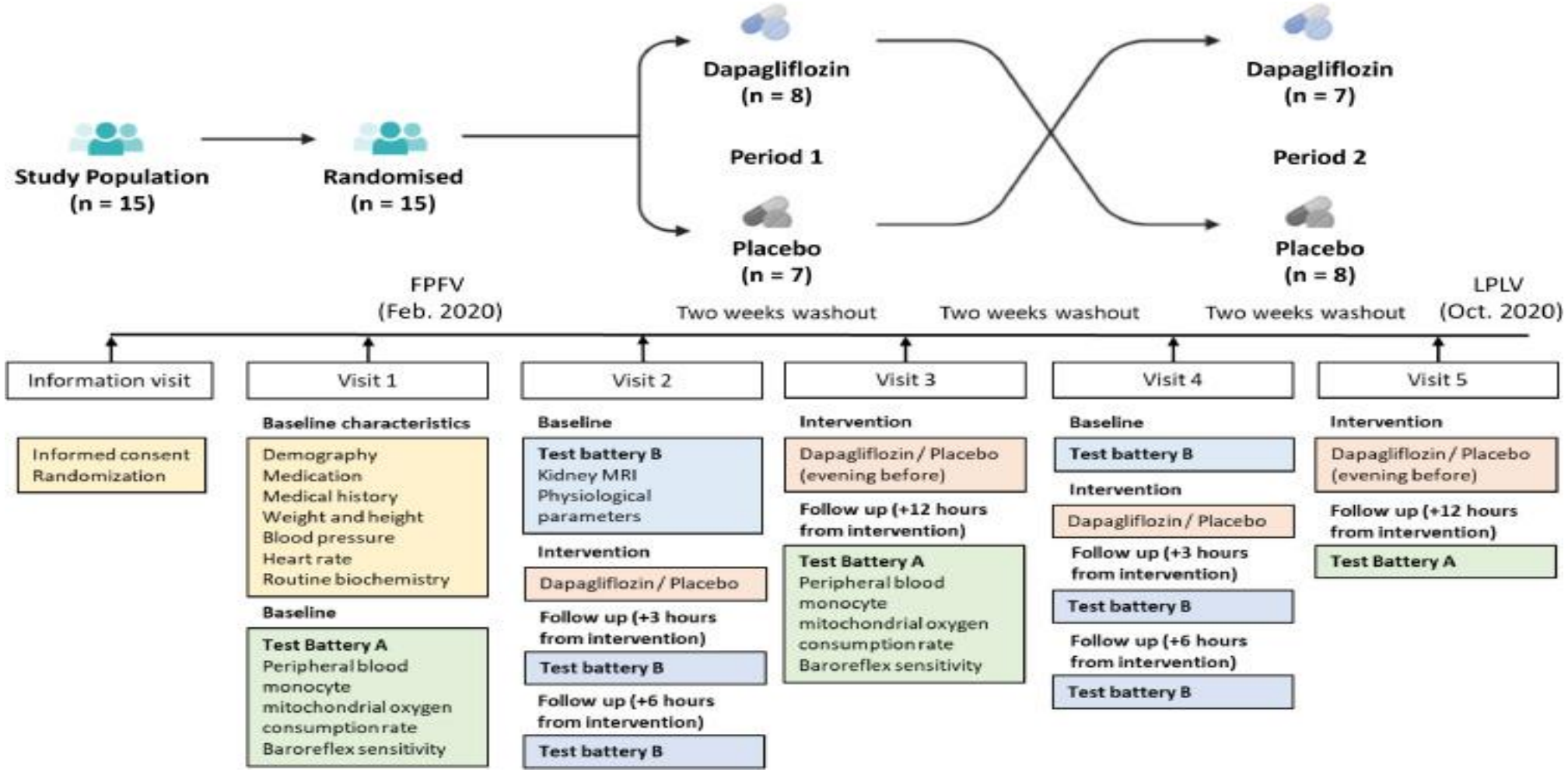
Dapagliflozin increases erythropoiesis and hematocrit



*P<0.05 compared to baseline, #P<0.05 compared to placebo

J Clin Endocrinol Metab. 2020 Apr 1;105(4):dgaa057.

Dapagliflozin improves renal cortical oxygenation via decreasing oxygen demand



A RCT enrolled 19 patients with albuminuria; MRI was used to assess renal R2* (a low value corresponds to a high tissue oxygenation), renal perfusion (arterial spin labelling) and renal artery flow (phase contrast imaging) EClinicalMedicine. 2021 Jun 28;37:100895.

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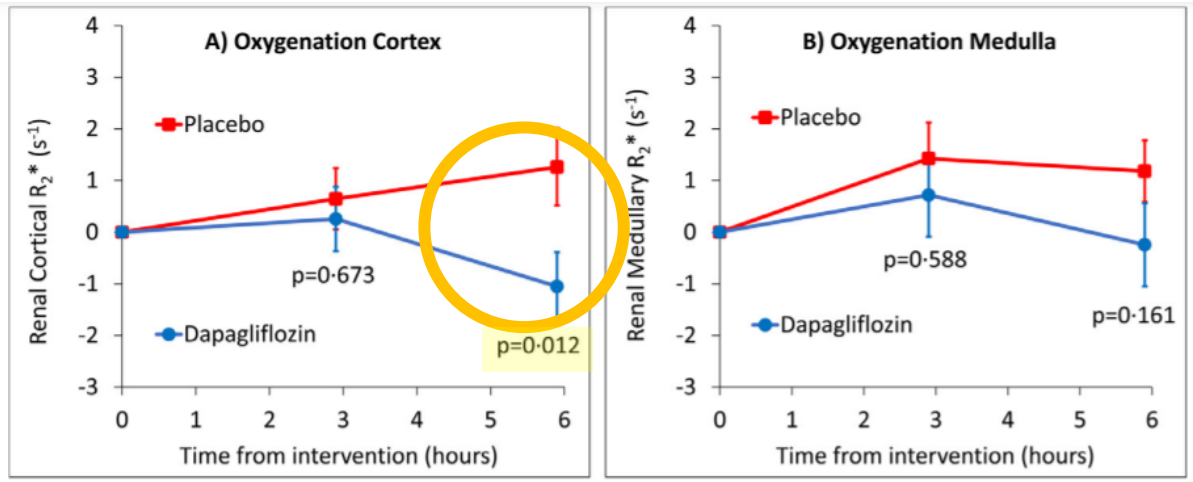
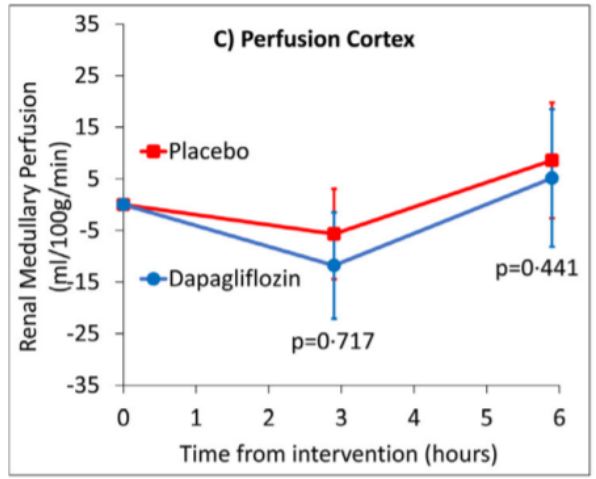
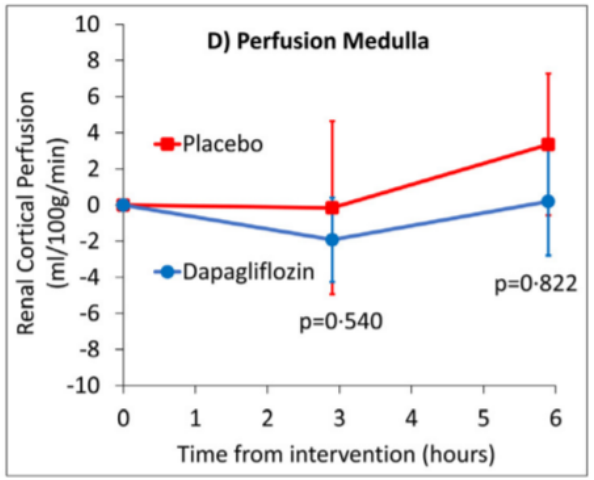
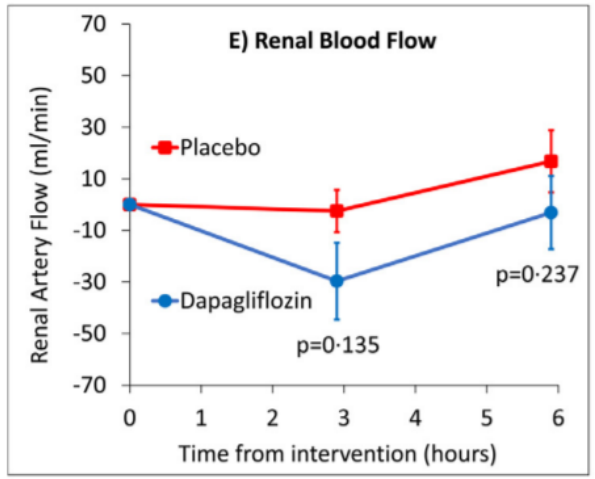


↓Oxygen demand → Improved renal cortical oxygenation



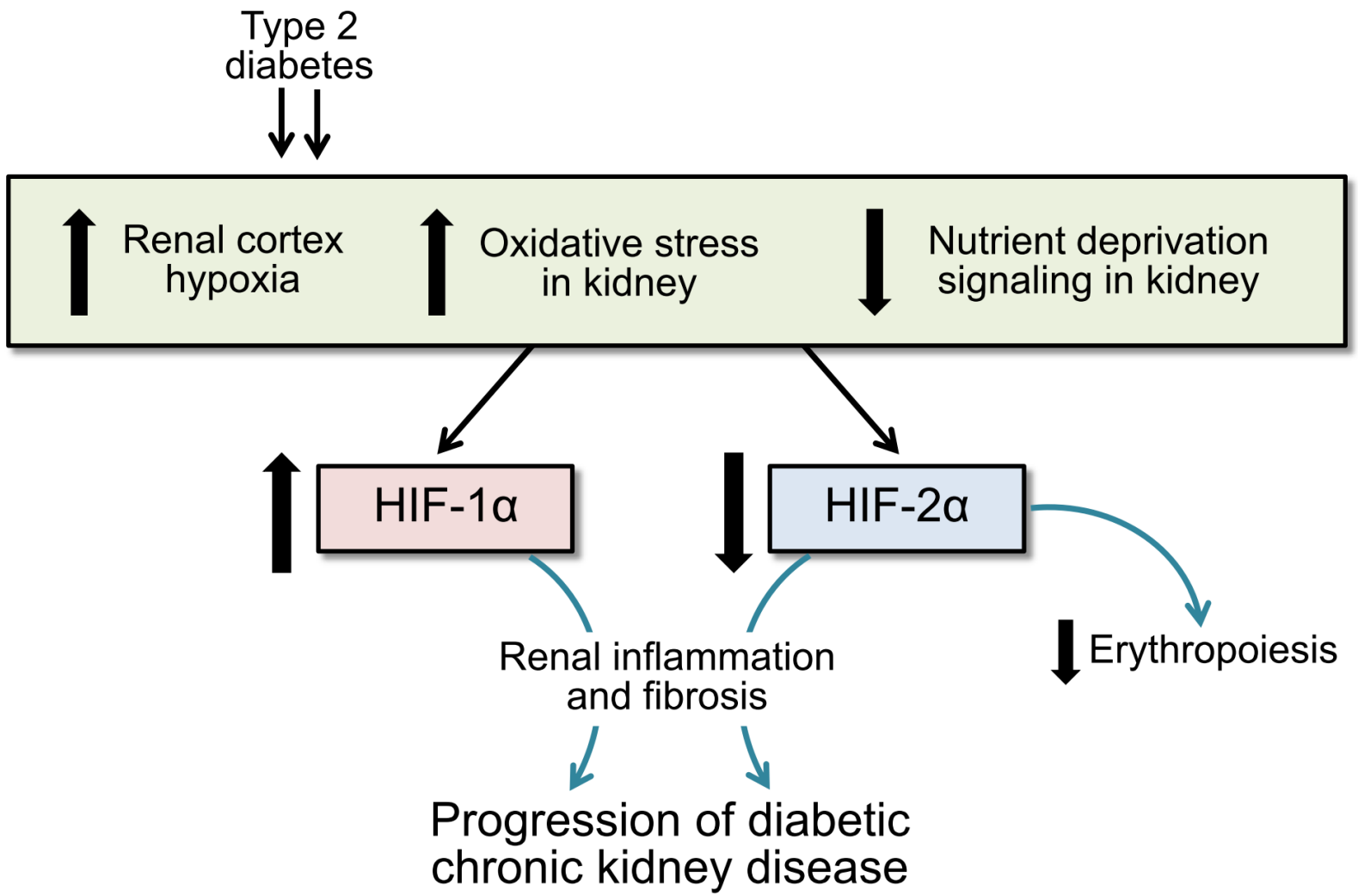




No changing renal perfusion or blood flow

A RCT enrolled 19 patients with albuminuria; MRI was used to assess renal R2* (a low value corresponds to a high tissue oxygenation), renal perfusion (arterial spin labelling) and renal artery flow (phase contrast imaging) EClinicalMedicine. 2021 Jun 28;37:100895.

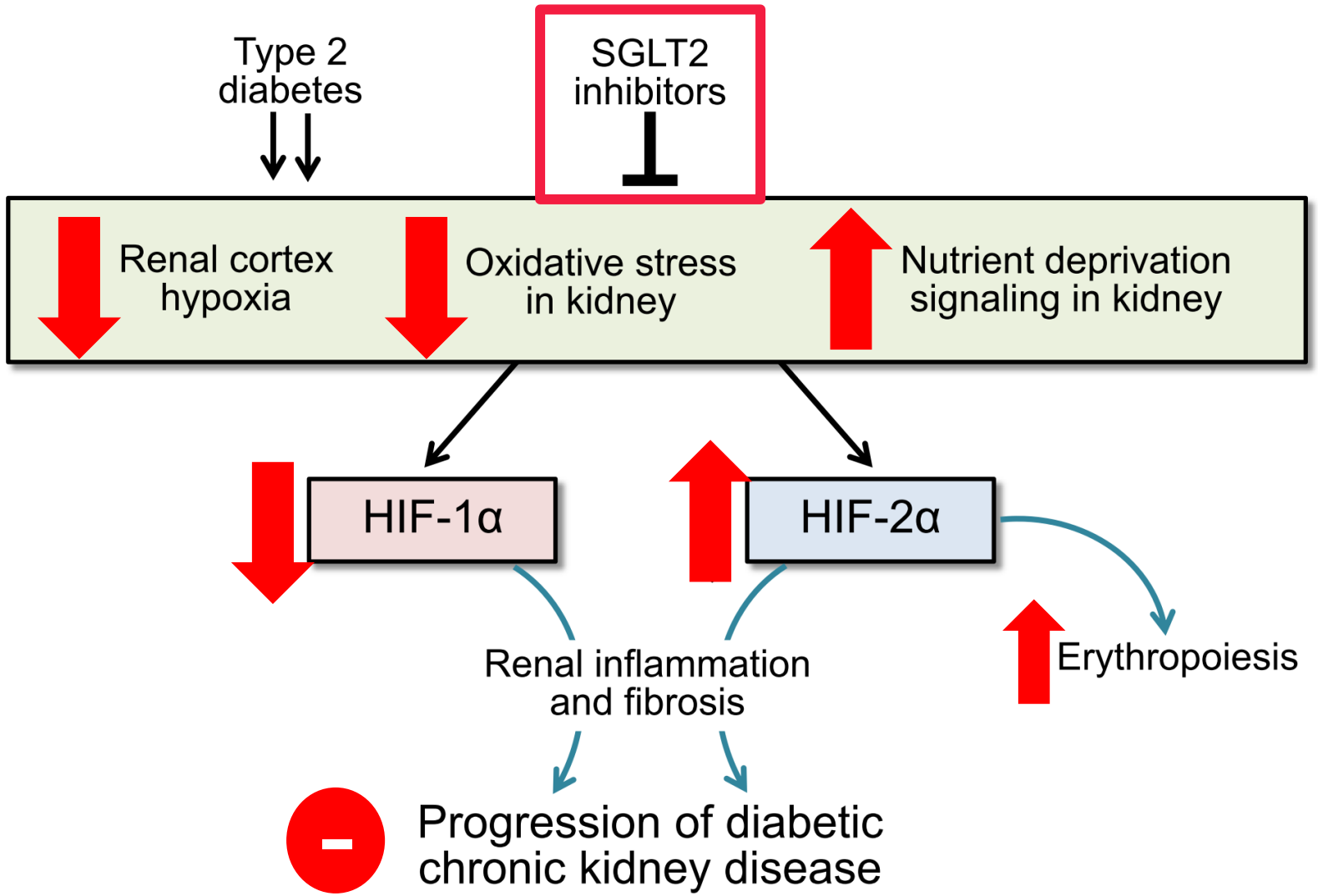
Type 2 diabetes cause both activation of HIF-1α and suppression of HIF-2α



Triggers of deranged hypoxia inducible factor (HIF) isoform signaling in type 2 diabetes and their **amelioration** with the use of SGLT-2 inhibitors and hypoxia mimetics

Am J Kidney Dis. 2021 Feb;77(2):280-286.

SGLT-2i suppress HIF-1α and activate HIF-2α and thereby augment erythropoiesis



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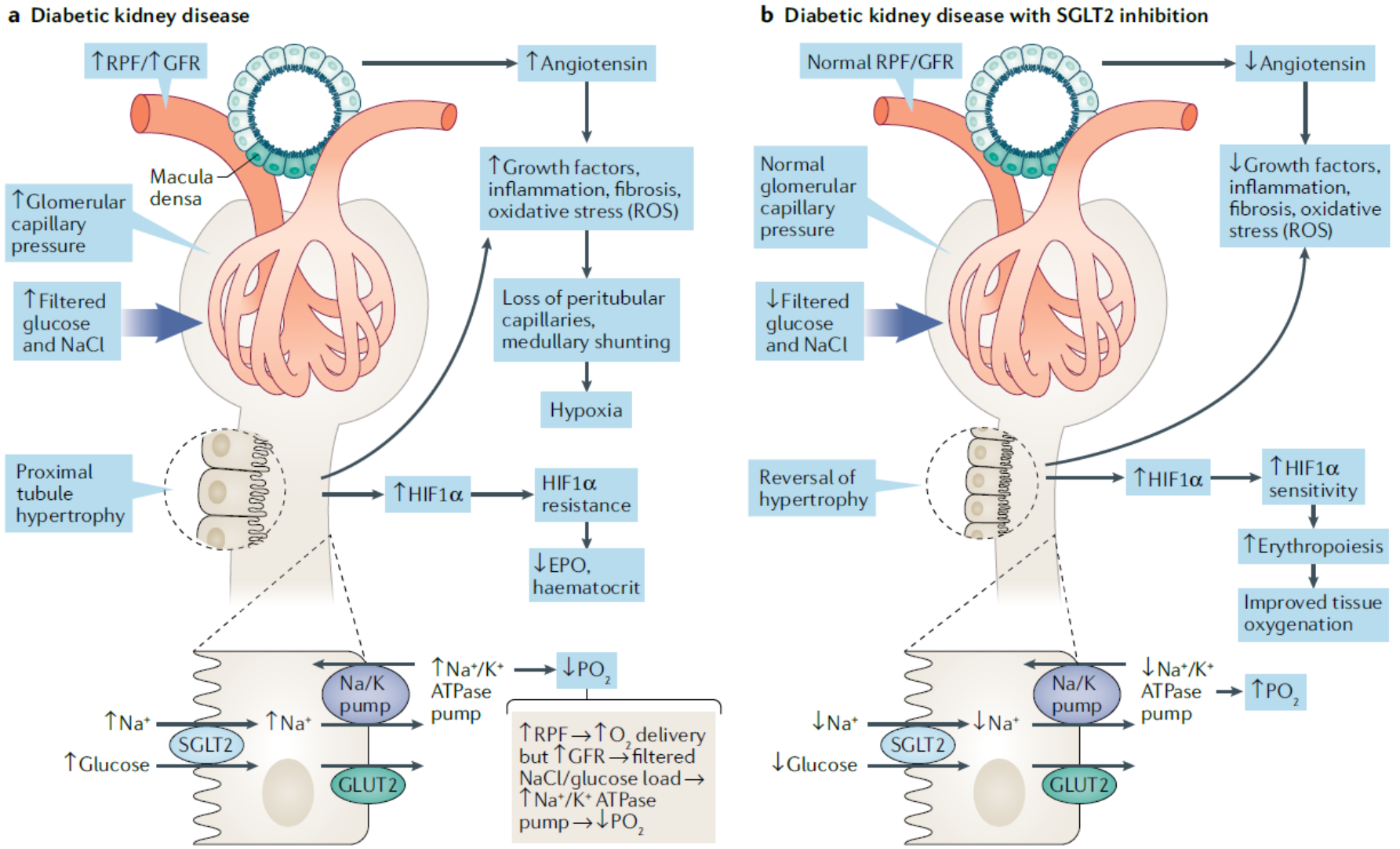
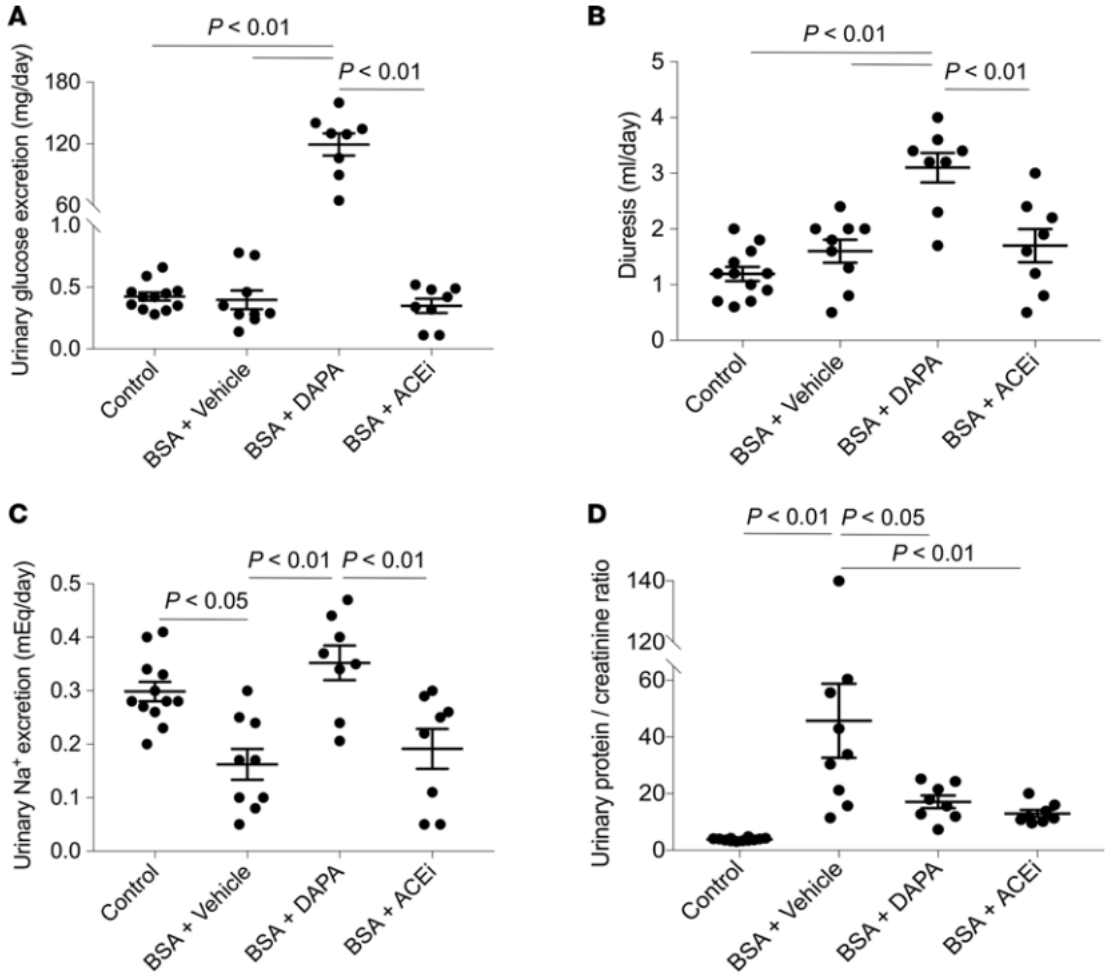
SGLT2 Improve Renal Oxygenation



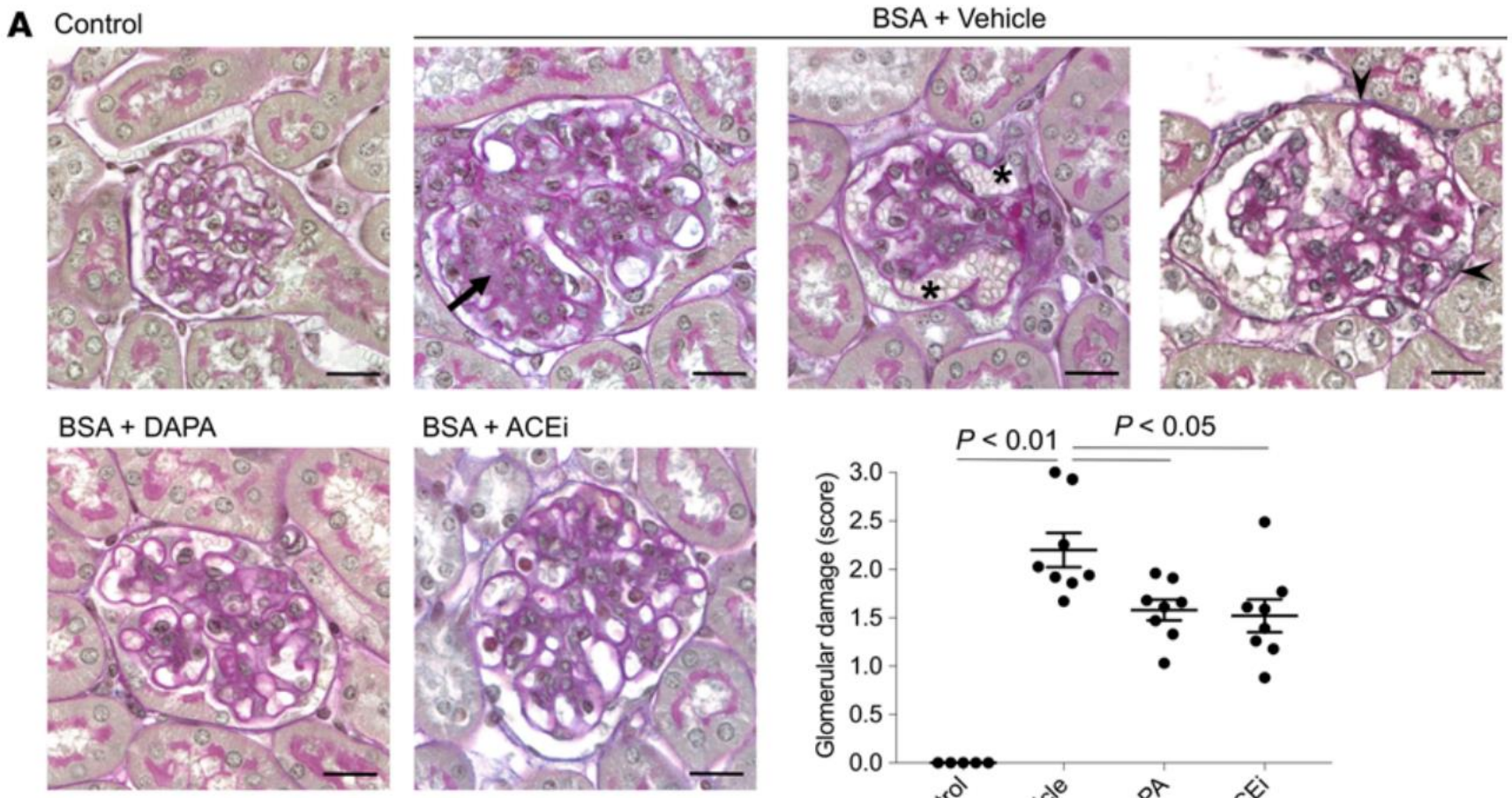
SGLT-2i limits podocyte damage in proteinuric nondiabetic nephropathy

Dapagliflozin limits podocyte depletion in mice with protein-overload proteinuria



BSA: bovine serum albumin; JCI Insight. 2018 Aug 9;3(15):e98720.

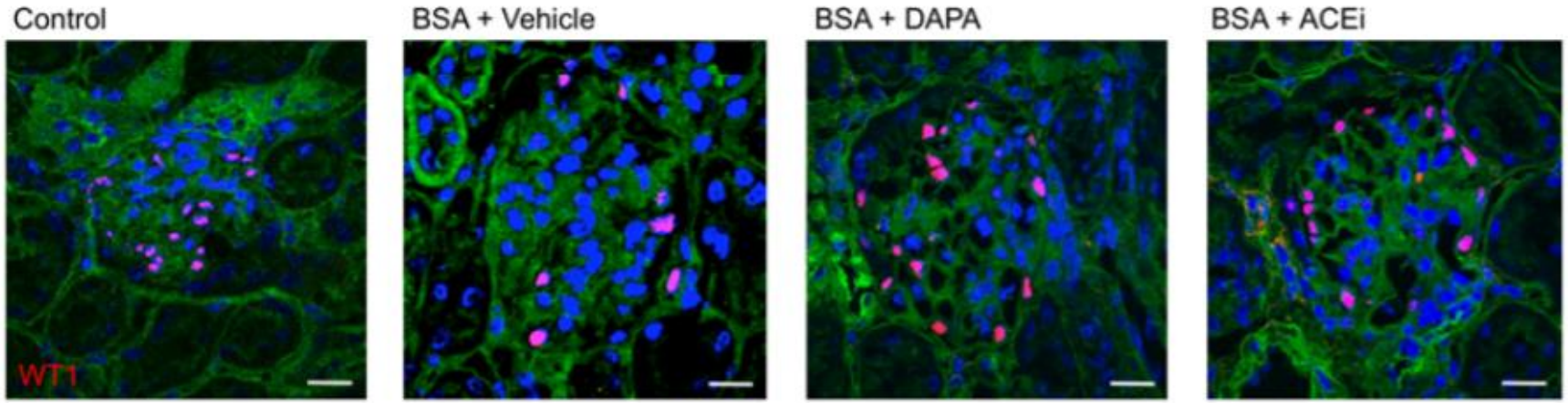
SGLT-2i limits podocyte damage in proteinuric nondiabetic nephropathy

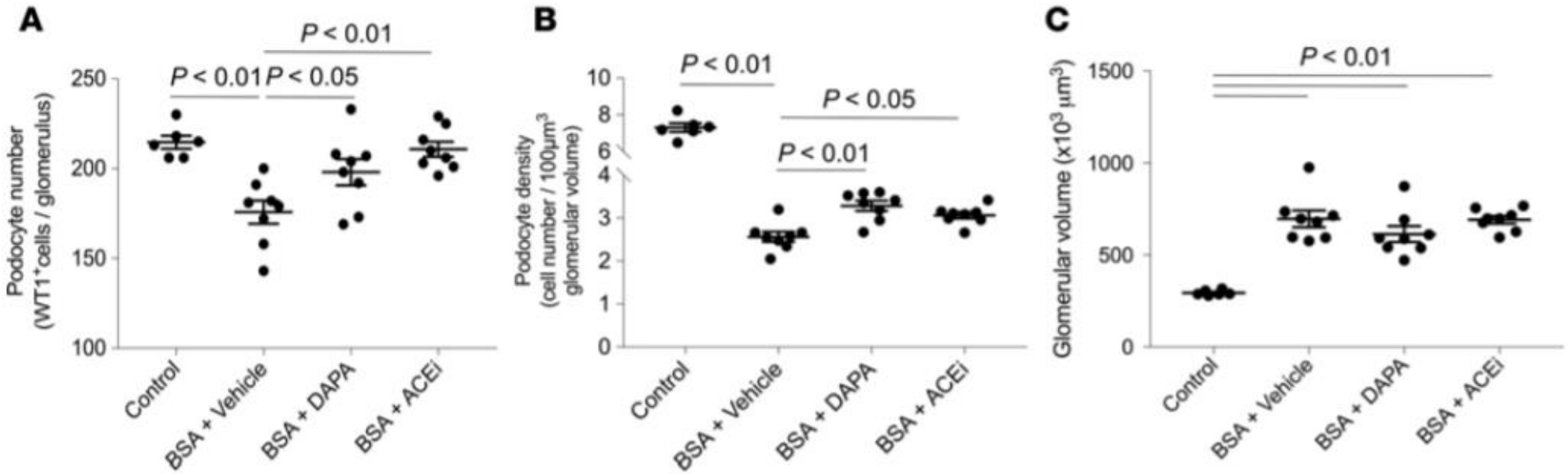


mesangial matrix expansion (arrow), glomerular capillary dilation (asterisks), and adhesions of the glomerular tuft to the Bowman's capsule (arrowheads)

BSA: bovine serum albumin; JCI Insight. 2018 Aug 9;3(15):e98720.

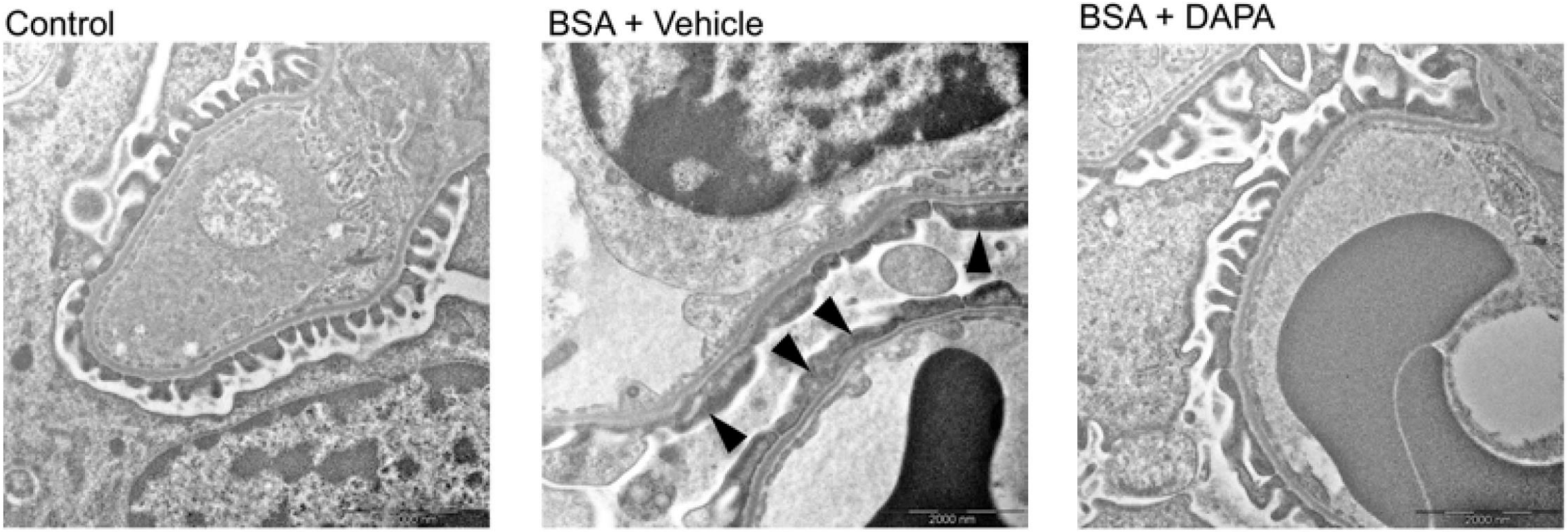
SGLT-2i limits podocyte damage in proteinuric nondiabetic nephropathy





SGLT-2i limits podocyte damage in proteinuric nondiabetic nephropathy

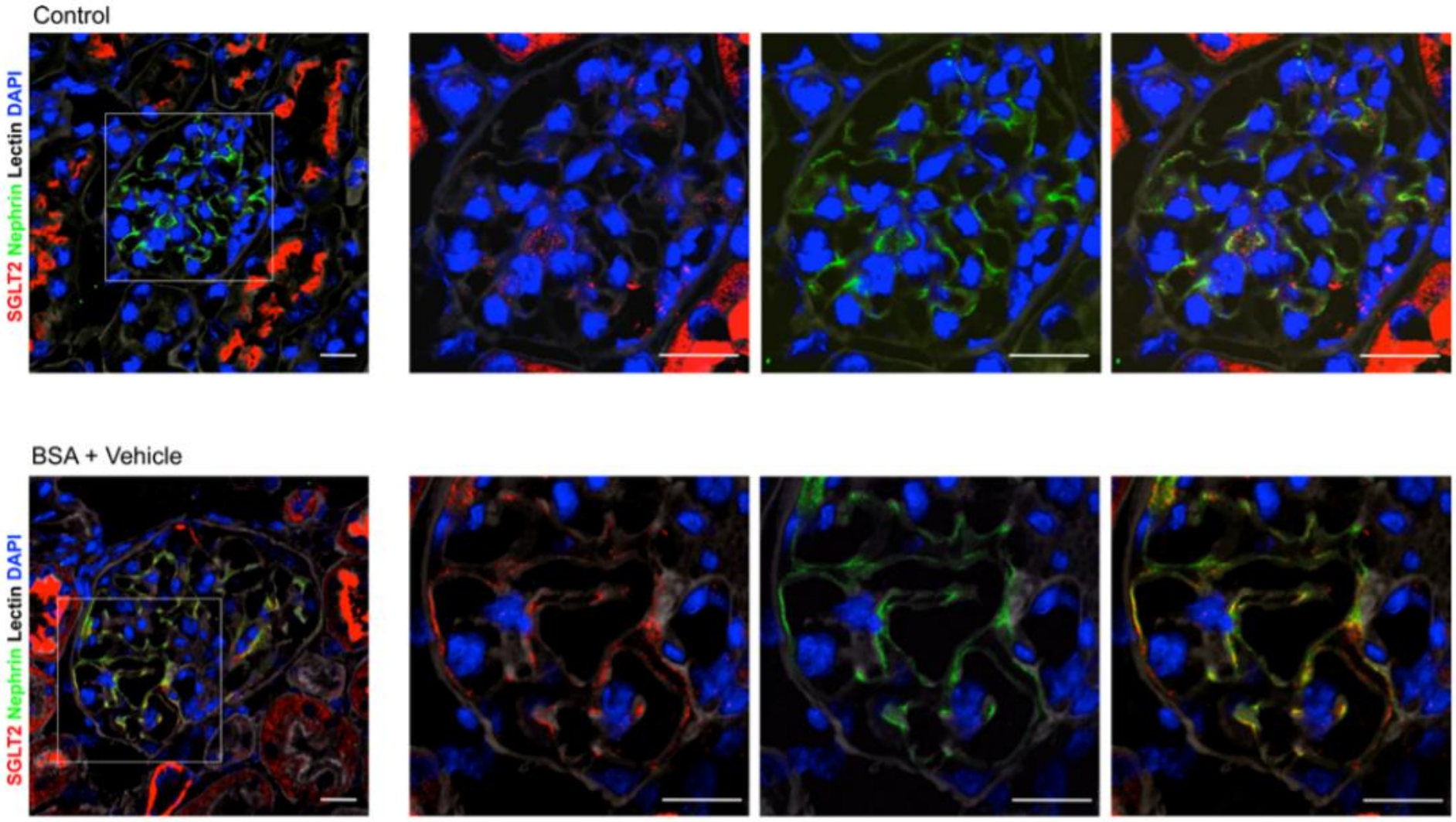
Dapagliflozin limits ultrastructural podocyte damage in mice with protein overload



Representative electron micrographs of glomeruli from control mouse and BSA-mice treated with vehicle, dapagliflozin (DAPA). Scale bars: 2,000 nm.

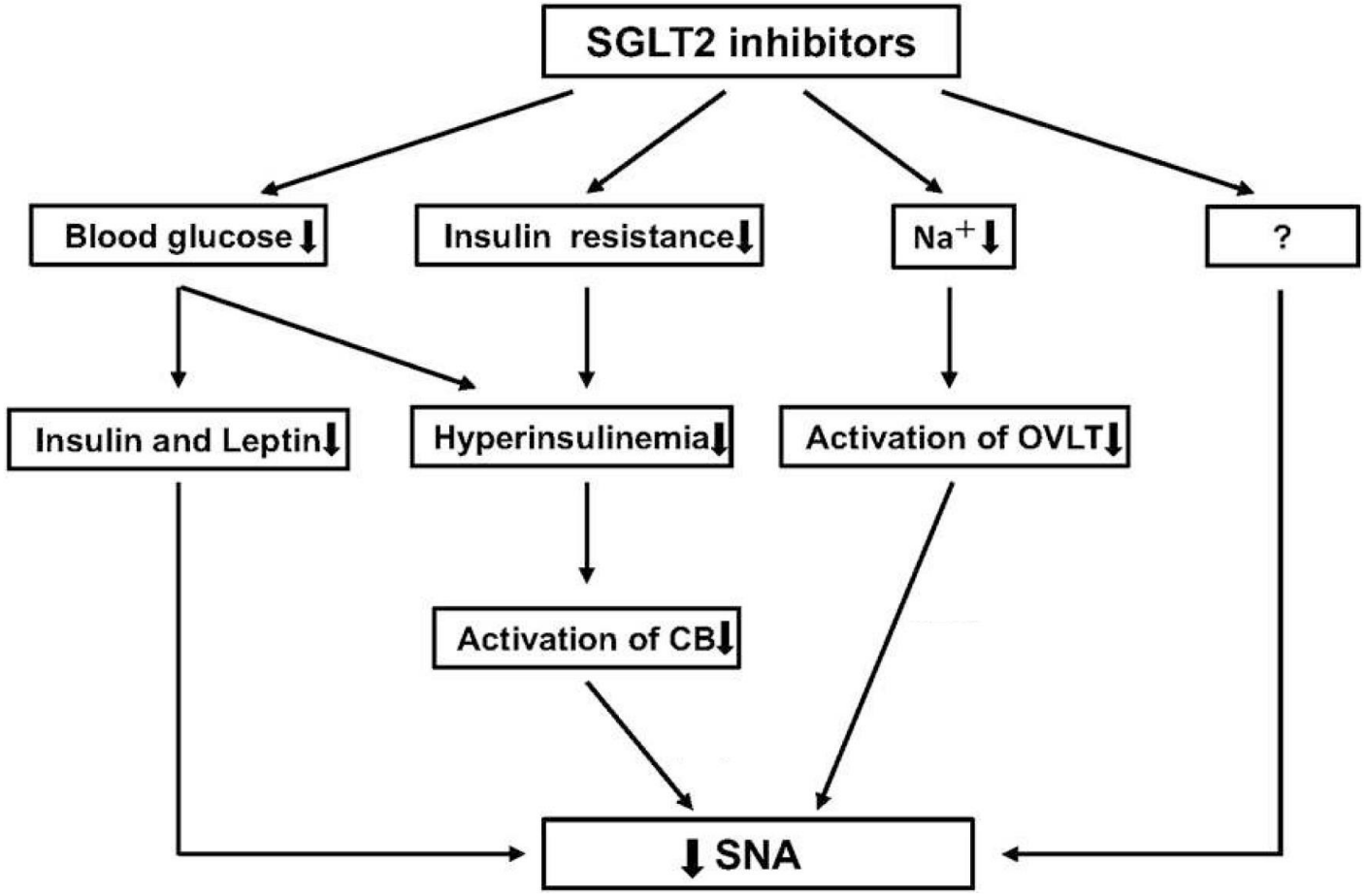
BSA: bovine serum albumin; JCI Insight. 2018 Aug 9;3(15):e98720.

SGLT-2i limits podocyte damage in proteinuric nondiabetic nephropathy

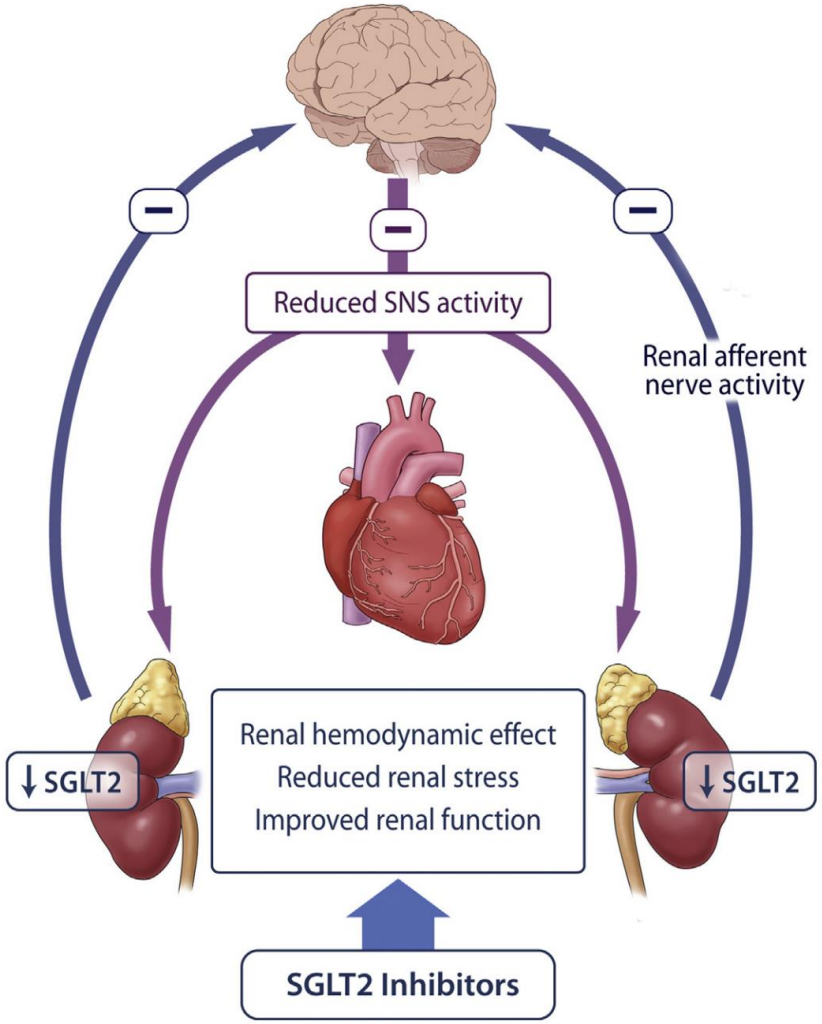


SGLT2i normalizing sympathetic nervous activity, which may be the source of its renal benefits

Possible mechanisms for reducing sympathetic nervous activity (SNA) through use SGLT-2i



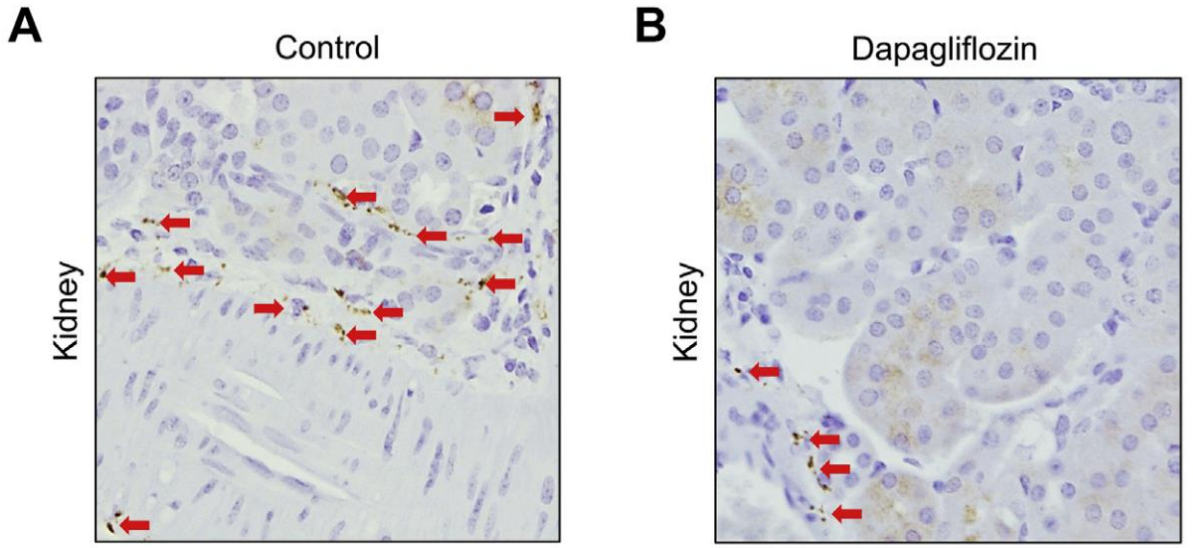
SGLT-2i secondary to reducing renal stress, may reduce afferent renal SNS activation.



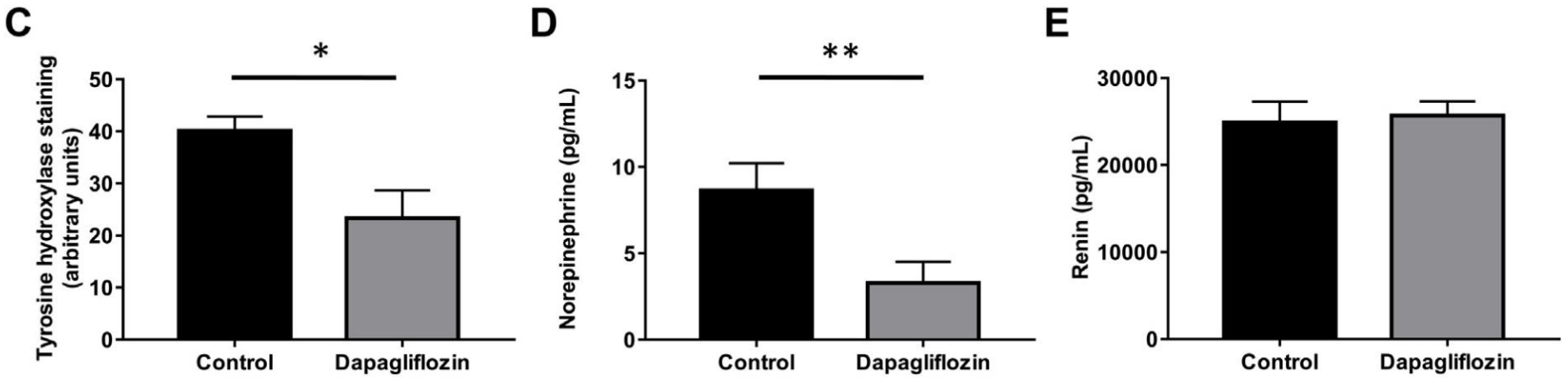
SNA: sympathetic nervous activity, OVLT: organum vasculosum laminae terminalis, CB: carotid body

1. Front Endocrinol (Lausanne). 2018 Jul 26;9:421. JACC Basic Transl Sci. 2020 Feb 24;5(2):180-182.

Inhibition of SGLT-2 Reduces Sympathetic Innervation in the Kidney of Hypertensive BPH/2J Mice



Representative immunohistochemistry images of tyrosine hydroxylase expression in kidneys from (A) untreated BPH/2J mice or (B) BPH/2J mice treated with dapagliflozin. Tyrosine hydroxylase staining is indicated with arrows. Magnification 200. (C) Quantitation of tyrosine hydroxylase expression in kidneys from BPH/2J mice, n ¼ 4 to 6 mice/group. (D) Norepinephrine content in kidneys from BPH/2J mice with or without dapagliflozin treatment, n ¼ 15 to 19 mice/group. (E) Renin concentration in serum from BPH/2J mice with or without dapagliflozin treatment, n ¼ 14 to 18 mice/group. *p ¼ 0.05; **p # 0.01



JACC Basic Transl Sci. 2020 Jan 29;5(2):169-179

SGLT-2i improves inflammation and oxidative stress

Table 2 Comparison of measurements between baseline and 12 weeks after treatment with dapagliflozin ($N = 27$)

	Baseline	12 weeks	Change	p value
HbA1c (%)	7.44 ± 0.56	6.70 ± 0.57	−0.75 ± 0.38	<0.01
Body weight (kg)	90.9 ± 16.5	87.1 ± 15.9	−3.8 ± 3.2	<0.01
eGFR (mL/min/1.73 m^2)	91.6 ± 22.3	89.5 ± 21.9	−2.1 ± 8.1	0.19
Sodium (mEq/L)	142.0 ± 2.1	141.0 ± 2.3	−1.0 ± 0.2	<0.05
Potassium (mEq/L)	4.2 ± 0.4	4.2 ± 0.4	0 ± 0	0.87
Acetoacetic acid (μmol/mL)	22.1 ± 9.6	35.5 ± 26.9	13.4 ± 29.61	<0.01
3-hydroxybutyric acid (μmol/mL)	38.2 ± 14.4	73.9 ± 69.0	35.7 ± 68.3	<0.01
Total ketone bodies (μmol/mL)	60.3 ± 20.8	109.4 ± 94.7	49.1 ± 94.1	<0.01
High-sensitivity CRP (ng/mL)	2410 ± 2814	1607 ± 1960	−803 ± 1080	<0.01
Adiponectin (μg/mL)	5.1 ± 2.3	6.7 ± 4.2	1.7 ± 2.7	<0.01
PAI-1 (mg/mL)	30.0 ± 16.8	26.8 ± 30.1	−3.2 ± 32.5	0.07

Data are expressed as mean ± standard deviation

HbA1c hemoglobin A1c, *eGFR* estimated glomerular filtration rate, *CRP* C-reactive protein, *PAI-1* plasminogen activator inhibitor-1

33%

31% Plasma 8-PGF$_{2\alpha}$

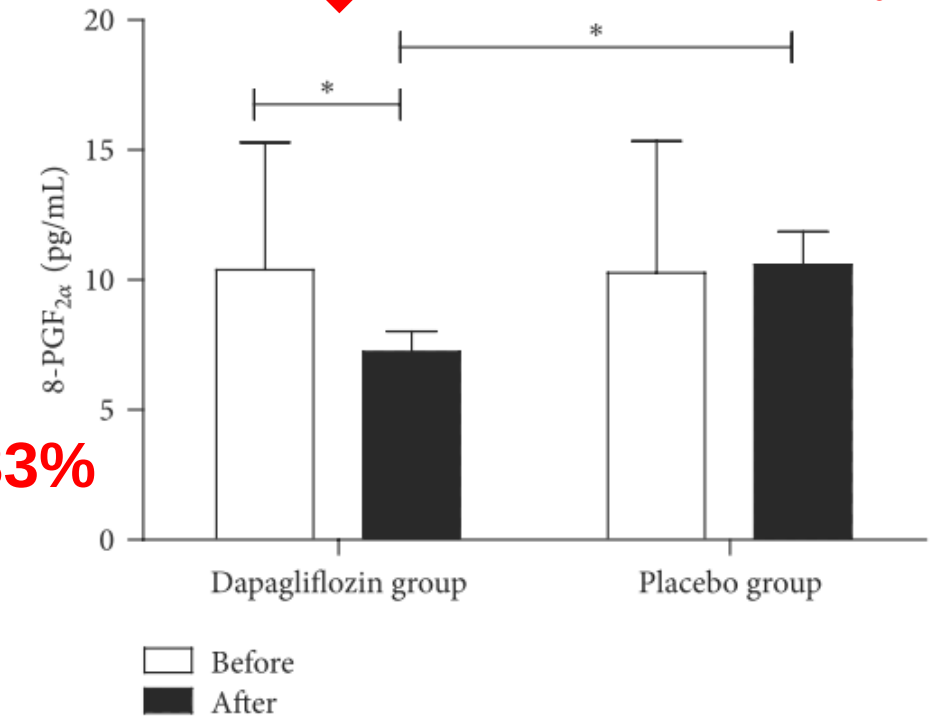


FIGURE 2: Plasma 8-PGF$_{2\alpha}$ levels in T2DM patients before (white bar) and after therapy (black bar).

A RCT enrolled 28 patients with newly diagnosed T2DM receive dapagliflozin or placebo treatment for 24 weeks[2]
8-iso PGF2α: plasma 8-iso prostaglandin F2α, biomarker of oxidative stress

1. Drugs R D. 2016 Sep;16(3):255-261. 2. J Diabetes Res. 2016;2016:5347262.

Effects of the SGLT-2i on glomerular and tubular injury markers

TABLE 1 Mean percent changes from baseline in kidney injury markers

Injury markers	Baseline[a]	Mean % change from baseline, placebo (95% CI)[b]	*P* value	Mean % change from baseline, dapagliflozin (95% CI)[b]	*P*-value
Glomerular					
IgG	2269 [875-4600]	4.3 (−12.4, 24.2)	.64	−25.3 (−38.1, −9.9)	0.01
IgG4	4 [1–8]	3.6 (−21.0, 36.0)	.80	−32.2 (−49.1, −9.7)	0.01
IgG/IgG4	920 [396-1271]	−0.9 (−24.0, 29.2)	.95	16.7(−11.9, 54.5)	0.29
IgG/Albumin	0.2 [0.2-0.3]	10.9 (1.2, 21.6)	.04	18.2 (7.0, 30.4)	<0.01
Tubular					
KIM-1	1218 [597-2705]	−0.9 (−20.4, 23.4)	.94	−23.3 (−39.8, −2.2)	0.04
NGAL	23 [13-65]	9.3 (−9.7, 32.3)	.37	−5.3 (−22.5, 15.7)	0.60
LFABP	11 [8-17]	21.2 (6.0, 38.5)	.01	22.2 (6.4, 40.4)	0.01
Inflammatory					
IL-6	3 [2-5]	−0.7 (−18.1, 20.5)	.95	−24.0 (−37.9, −7.0)	0.01
MCP-1	268 [213-413]	5.6 (−11.1, 25.5)	.54	−9.3 (−24.3, 8.7)	0.30

↓ 23%

↓ 24%

[a] Baseline data are given as median pg/24 h [25th to 75th percentile] for KIM-1, LFABP, IL-6 and MCP-1, and median ng/24 h for NGAL.

[b] All biomarkers were log transformed. Mean change in 24-hour excretion of the individual biomarker was derived by 100*(exp[least square mean change]-1). The same transformation was applied to the 95% confidence limits.

33 patients with T2D. Diabetes Obes Metab. 2018 Aug;20(8):1988-1993.

Possible mechanisms of nephroprotection of SGLT-2i in non-diabetic CKD

CLINICAL

- ↓ Proteinuria
- Improved cardiac funtion in heart failure
- ↓Blood pressure
- Osmotic diuresis
- Improved anemia
- ↓ Uric Acid

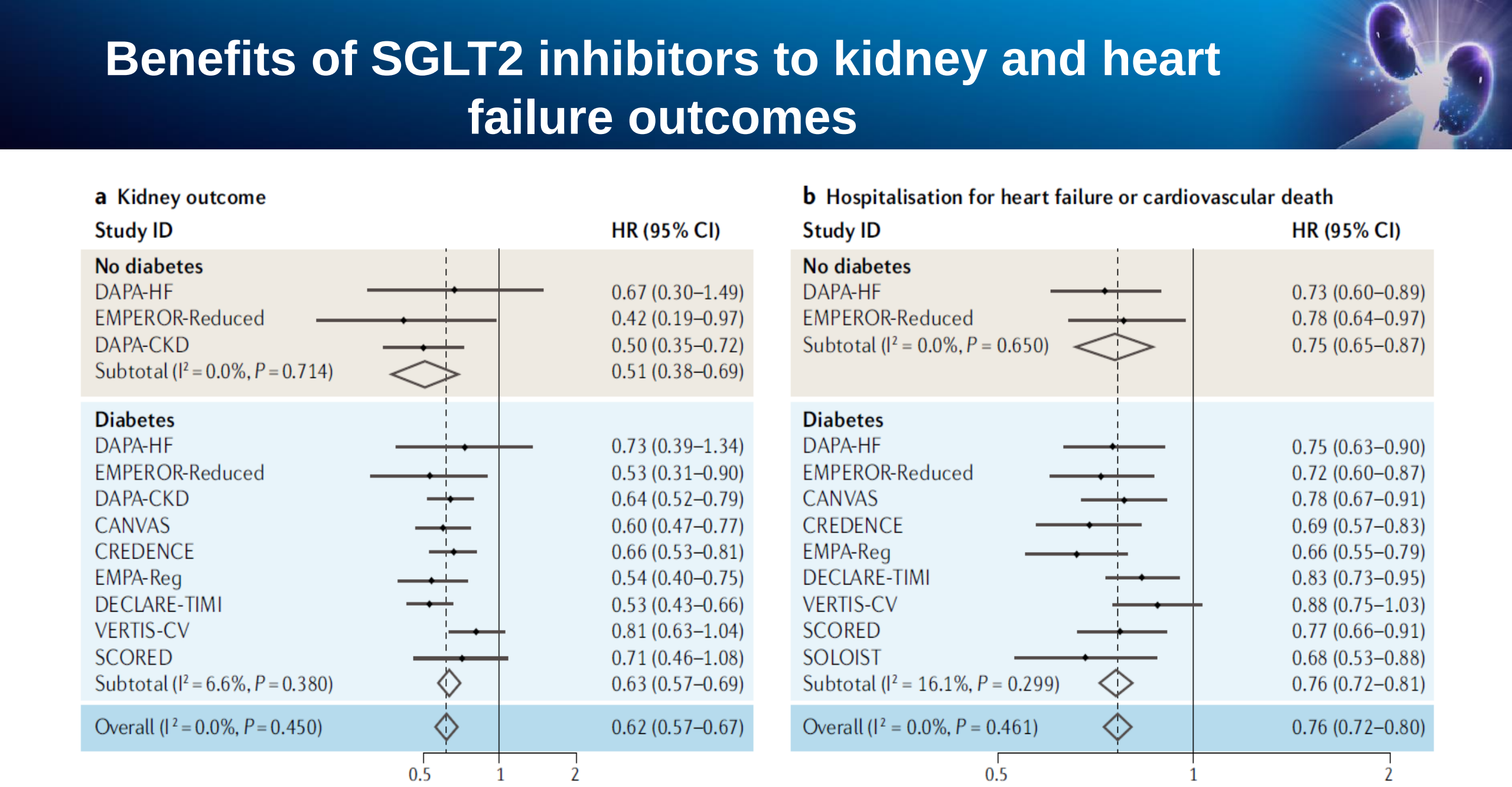
POSSIBLE NEPHROPROTECTIVE MECHANISMS IN NON-DIABETIC CHRONIC KIDNEY DISEASE

EXPERIMENTAL

- ↓ Renal fibrosis
- ↓ Apoptosis
- ↓ Oxidative stress
- ↓ Remodeling of podocyte cytoskeleton
- Improved renal hypoxia
- Preglomerular vasocontriction and postglomerular vasodilation
- ↓ Renin-Angiotensin system activity
- Modulating effects on gene expression
- ↓ Endothelin 1
- ↓Sympathetic activity
- ↑ Ketone body formation
- ↓ IL1 β and TGF-β 1 in tubular cells
- ↓ Inflammation

Drugs. 2021 Sep;81(13):1491-1511.

Benefits of SGLT2 inhibitors to kidney and heart failure outcomes



Nat Rev Nephrol. 2021 Feb;17(2):83-84

Take Home Message

1. SGLT2 plays crucial role in the progression of DKD and NDKD
2. SGLT2i improves renal outcome in both DKD and NDKD
3. SGLT2i has its role of renal protection

The End

Thanks for your listening