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SGLT2 Inhibitors

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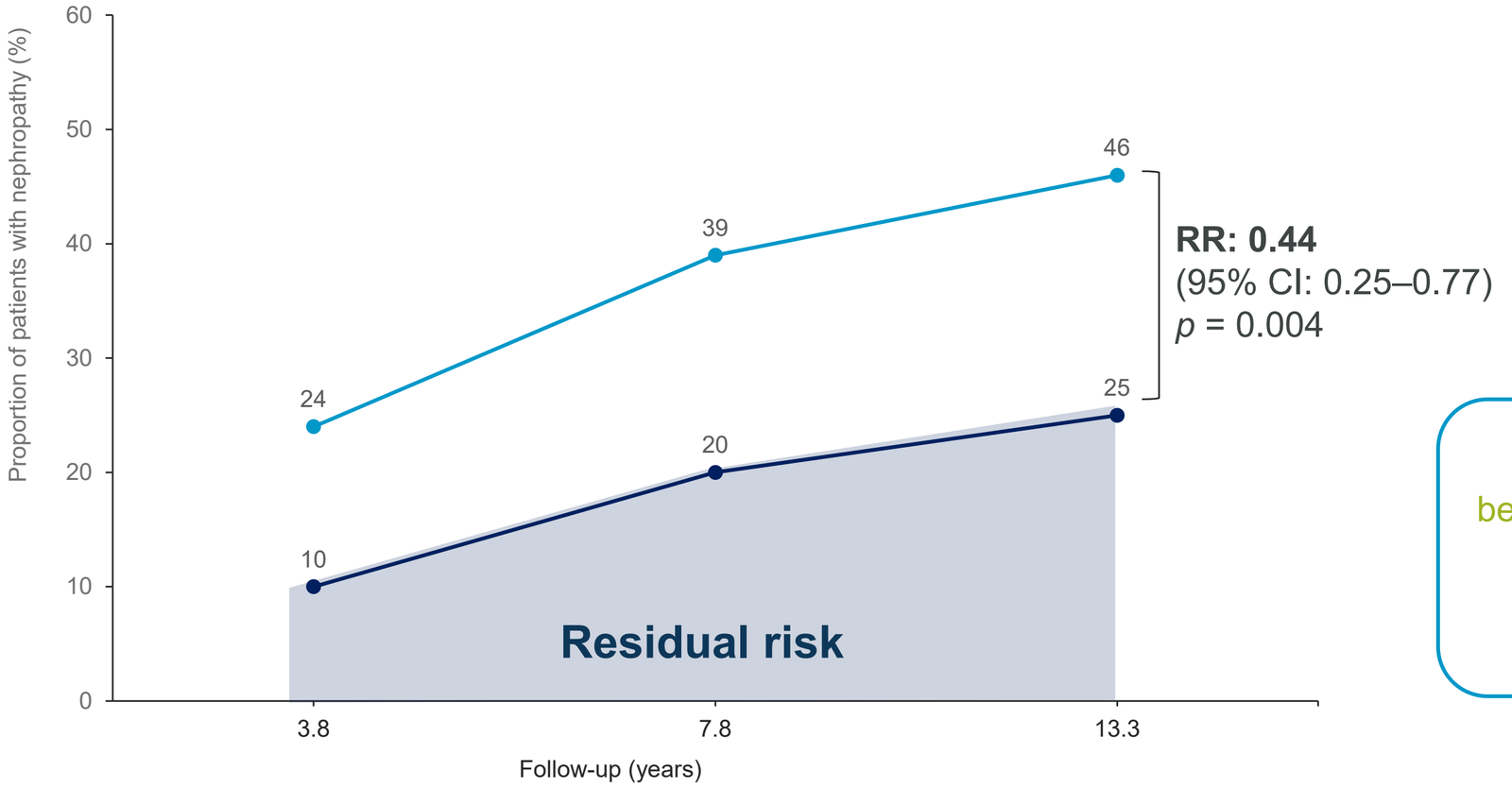
STENO-2 Study: Optimal Risk Factor Management Does Not Eliminate Risk of Diabetic Nephropathy[a]

Residual nephropathy risk in patients randomized to multifactorial intensive medical therapy[b,1]



Intensive treatment:
behaviour modification and therapies targeting hyperglycaemia, hypertension, dyslipidaemia and microalbuminuria[2]

aDiabetic nephropathy was defined as a urinary albumin excretion of more than 300 mg/24 hours in two of three consecutive sterile urine specimens; bAntidiabetic therapy, antihypertensive agents, statins, aspirin, vitamins C and E2
CI, confidence interval; RR, relative risk
Fioretto P et al. Nat Rev Endocrinol. 2010;6:19–25
Gaede P *et al. Lancet*. 1999;353:617–622

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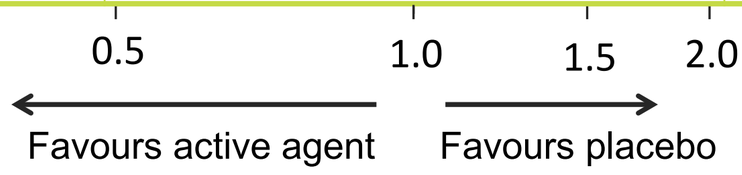
Exploratory Data from Cardiovascular Outcome Trials (CVOTs) – GLP-1 Receptor Agonists

- GLP-1RA medications did not protect against substantial loss of kidney function*, ESKD, or death due to kidney disease in CVOTs
  - Patients in GLP-1RA CVOTs had renal function similar to patients in SGLT2i CVOTs
- However, they do provide a significant reduction in progression to macroalbuminuria

	Patients	Events	HR (95%CI)
ELIXA	6063	76	1.16 (0.74–1.83)
LEADER	9340	184	0.89 (0.67–1.19)
SUSTAIN-6	3297	32	1.28 (0.64–2.58)
EXSCEL	12914	519	0.88 (0.74–1.05)
Fixed effects (p = 0.24)			0.92 (0.80–1.06)



*Defined as sustained doubling of serum creatinine or a 40% decline in estimated glomerular filtration rate

CVOT, cardiovascular outcome trial; ESKD, end-stage kidney disease; GLP-1RA, glucagon-like peptide-1 receptor agonists; SGLT2i, sodium-glucose cotransporter-2 inhibitor

Zelnicker et al. *Circulation*. 2019;139:2022–2031.

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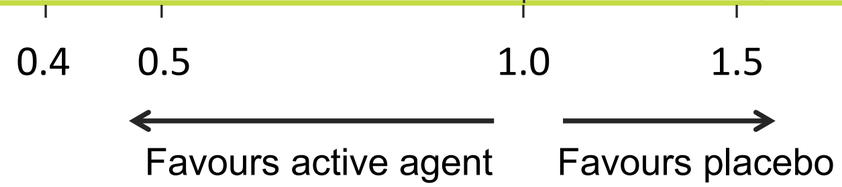
Exploratory Data from Cardiovascular Outcome Trials (CVOTs) – SGLT2 Inhibitors

In exploratory analyses of CVOT data, SGLT2i medications protected against substantial loss of kidney function*, ESKD, or death due to kidney disease in CVOTs

- In contrast, GLP-1RA medications were not effective on this endpoint and only provided a significant reduction in progression to macroalbuminuria

	Patients	Events	HR (95%CI)
EMPA-REG OUTCOME	6968	152	0.54 (0.40–0.66)
CANVAS Program	10142	249	0.60 (0.47–0.77)
DECLARE-TIMI 58	17160	365	0.53 (0.43–0.75)
Overall p <0.001			0.55 (0.48–0.64)



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Zelnicker et al. *Circulation*. 2019;139:2022–2031.

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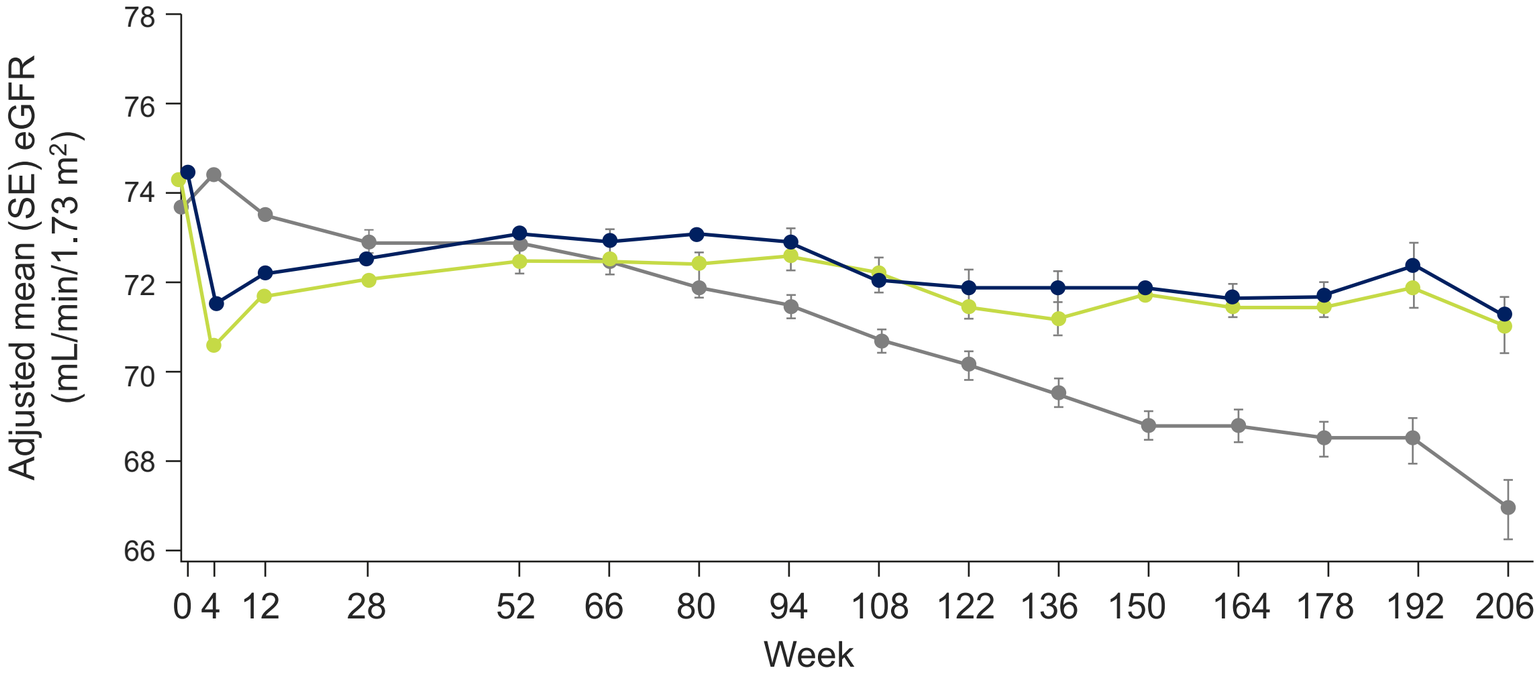
EMPA-REG Kidney Function

eGFR over time



Placebo	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448	171
Empagliflozin 10 mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513	193
Empagliflozin 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524	216

Mixed model repeated measures analysis in the treated set (OC-AD)

eGFR, estimated glomerular filtration rate

Wanner C, et al. J Am Soc Nephrol. 2018 Nov;29(11):2755-2769.

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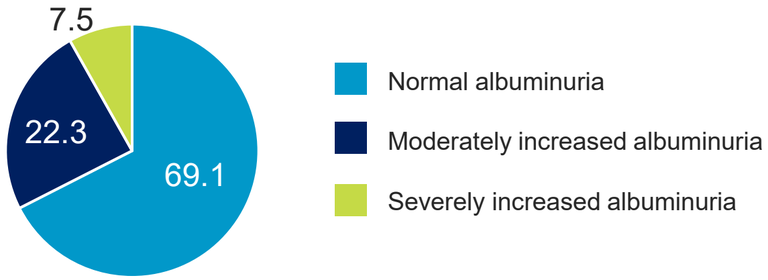
Renal Data From the CANVAS Trial

Effect of Canagliflozin on Renal and Cardiovascular Outcomes Across Different Levels of Albuminuria: Data From the CANVAS Program

METHODS

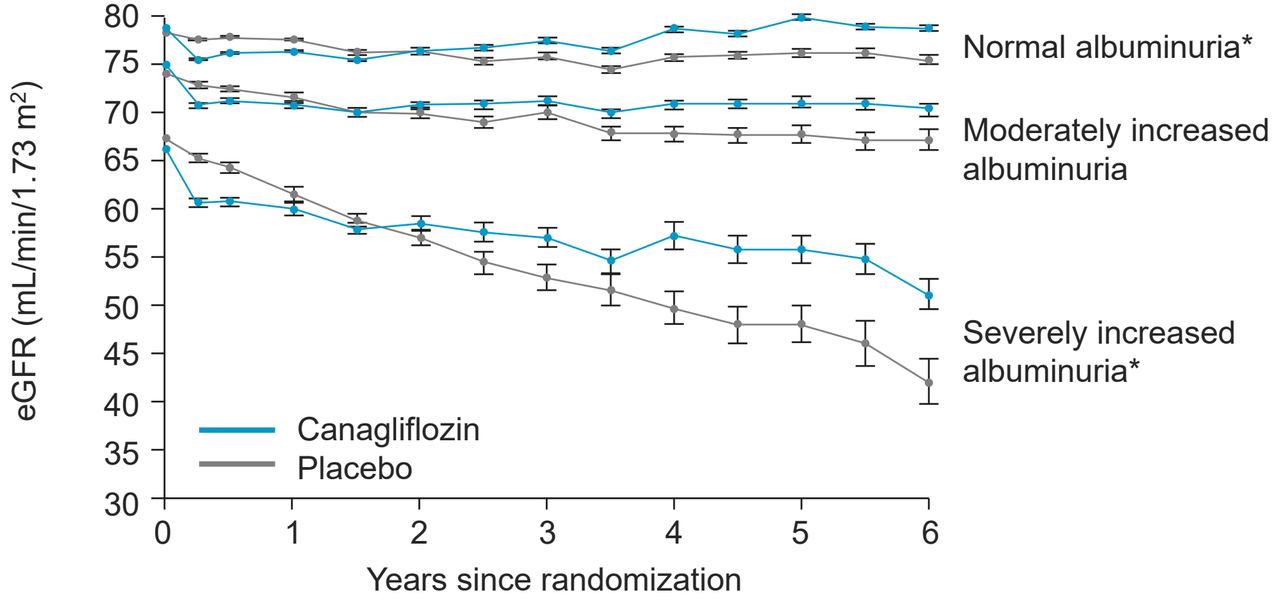
10,142 patients with T2DM

Canagliflozin Placebo



Note: 1.1% of patients did not have a UACR measurement at baseline.

RESULTS



Conclusion The proportional effects of canagliflozin on renal and cardiovascular outcomes are mostly consistent across different levels of albuminuria, but benefits are greatest in people with severely increased albuminuria

*Clinically significant difference
T2DM, type 2 diabetes mellitus; UACR, urine albumin-creatinine ratio
Neuen BL, et al. *J Am Soc Nephrol*. 2019 Nov;30(11):2229-2242.

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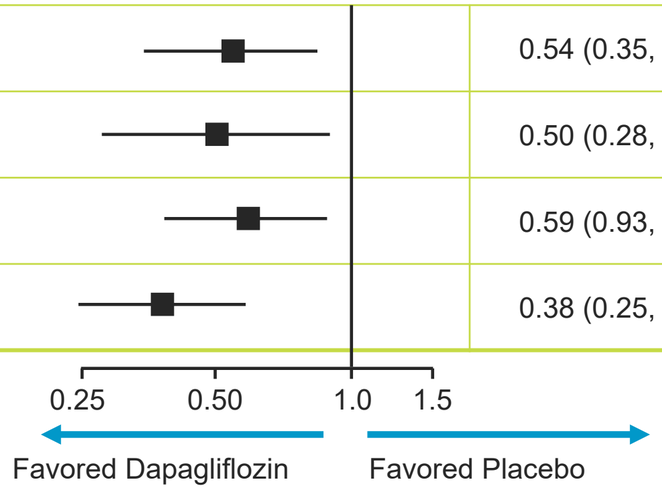
The Effect of Dapagliflozin on Albuminuria in DECLARE-TIMI 58

DECLARE-TIMI 58 Trial/Sub-group analysis: Treatment effect of dapagliflozin vs. placebo on composite renal-specific outcomes according to baseline UACR categories

	Dapagliflozin		Placebo				
	n/N (%)	KM event rate	n/N (%)	KM event rate	HR (95% CI)	P value	P value for interaction
Renal-Specific composite endpoint							
UACE <-15 mg/g	33/4538 (0.7%)	0.7%	60/4528 (1.3%)	1.3%	0.54 (0.35, 0.83)	0.0048	0.4801
15 < UACR < 30 mg/g	17/1281 (1.3%)	1.3%	35/1296 (2.7%)	2.4%	0.50 (0.28, 0.89)	0.0190	
30 <= UACR <=300 mg/g	39/2017 (1.9%)	2.0%	66/2013 (3.2%)	3.3%	0.59 (0.93, 0.87)	0.0082	
300 < UACE mg/g	31/594 (5.2%)	4.8%	75/575 (13%)	12.8%	0.38 (0.25, 0.58)	<0.0001	



*Clinically significant difference
T2DM, type 2 diabetes mellitus; UACR, urine albumin-creatinine ratio
Mosenzon O, et al. Diabetes Care. 2021 Aug;44(8):1805-1815.

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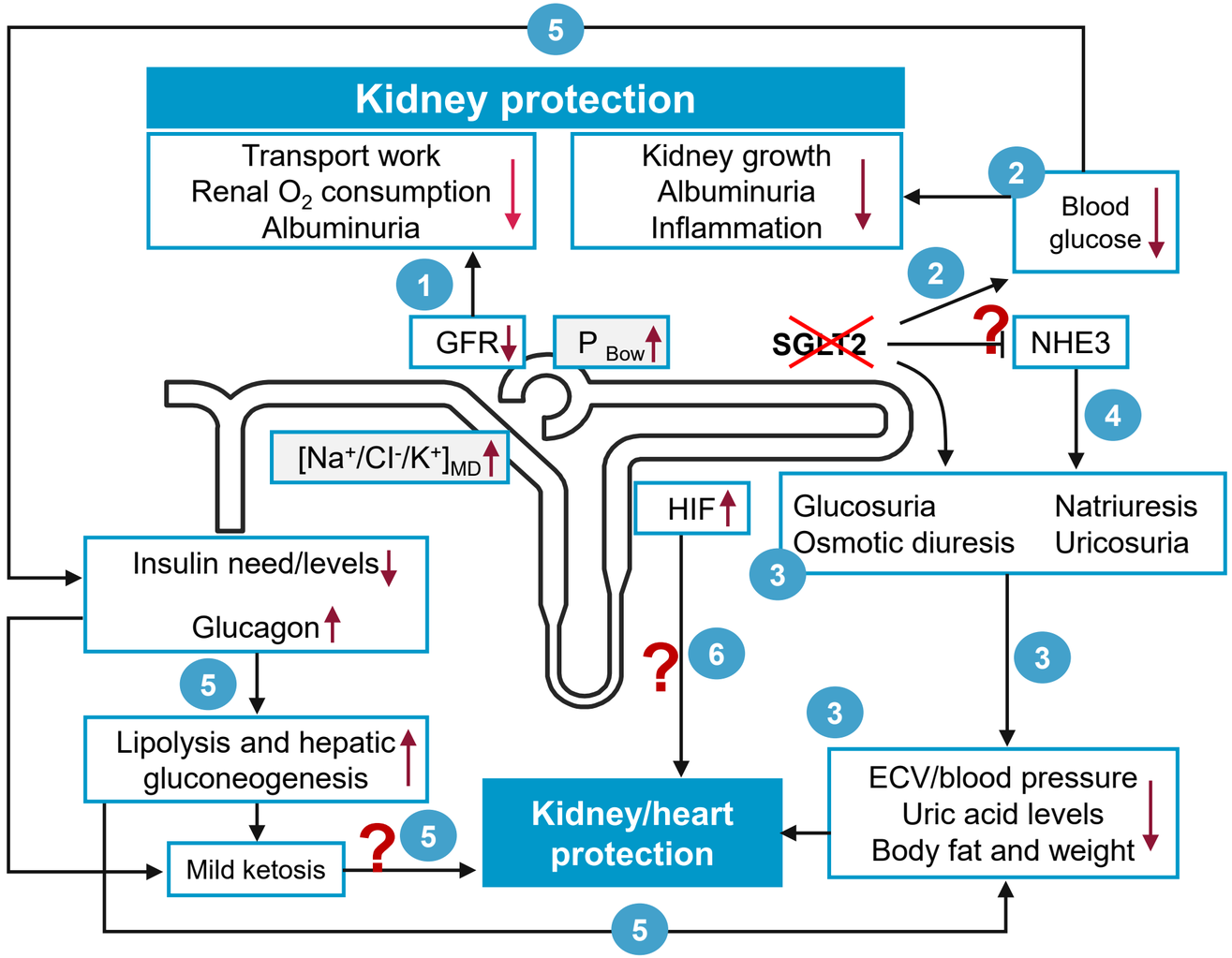
SGLT2i and the Kidney: Many Potential Mechanisms



Proposed Renal Protective Mechanisms:

- TGF restoration, reduced GH and reduced O_2 consumption/ beta-blocker effect
- Lowered BG, inflammation
- Osmotic diuresis, uricosuric, low BP and ECFV
- NHE3 inhibition, natriuresis
- Reduced insulin levels, increased glucagon, lipolysis, mild ketosis
- Enhanced renal HIF

TGF, tubuloglomerular feedback; NHE3, Na+/H+-exchanger 3; HIF, hypoxia-inducible factor; BG, blood glucose; BP, blood pressure; ECFV, extracellular fluid volume; SGLT2, sodium glucose cotransporter 2; GFR, glomerular filtration rate; GH, glomerular hyperfiltration

Adapted from: Vallon V, Thomson SC. Diabetologia 2017;60:215-25.

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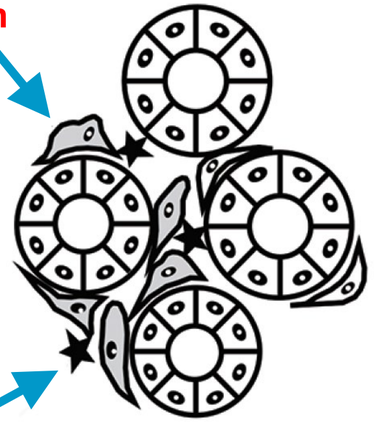
Hypoxia Hypothesis

SGLT2 inhibition also exhibits a "β-blocker effect":
↓ proximal tubular O_2 consumption, ↓ hypoxia

Normal State

Neural crest-derived fibroblasts produce erythropoietin



Healthy renal tubules

Erythropoietin

SGLT2 inhibitor

With Diabetes

High oxygen requirement of the proximal tubules due to excessive glucose reabsorption

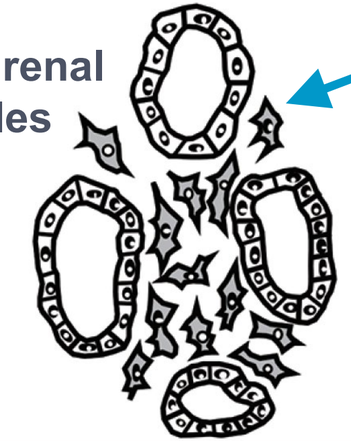
↓

Tubulointerstitial hypoxia

↓

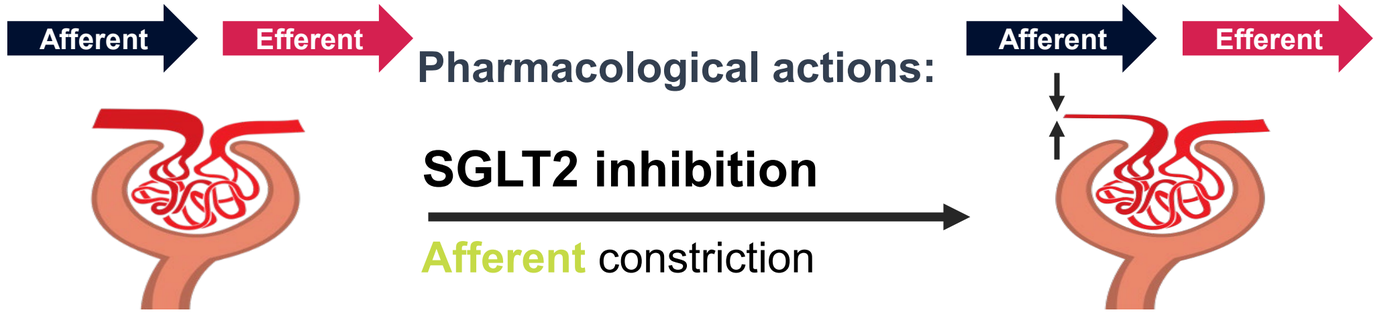
Transformation into dysfunctional fibroblasts producing less erythropoietin

Injured renal tubules



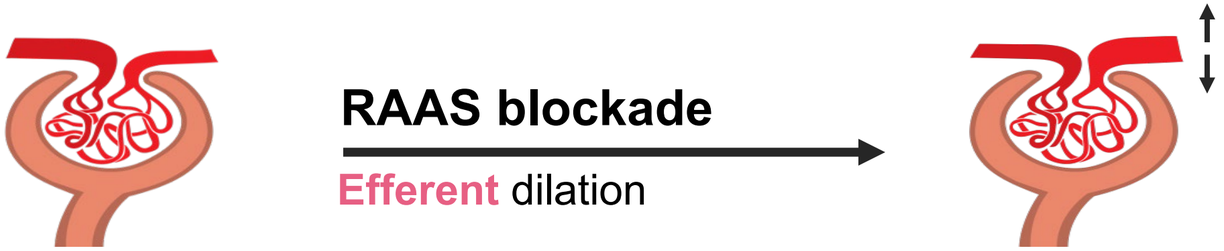
SGLT2i, sodium-glucose cotransporter-2 inhibitor
Adapted from: Sano M, et al. i2016;8:844-47.

Comparative effect of SGLT2 vs. RAAS Inhibition or Combined Therapy on Renal Segmental Resistances

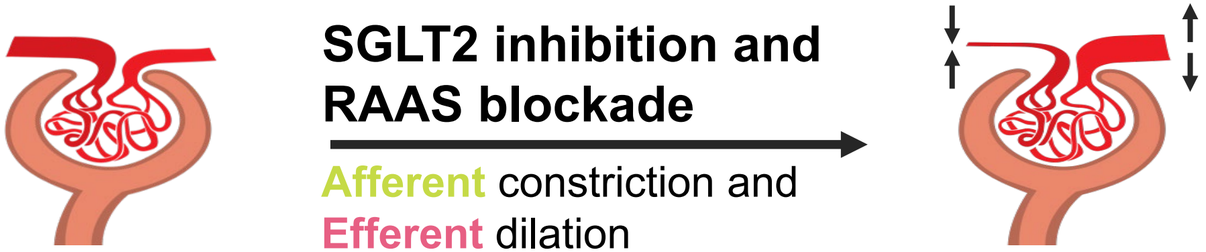


Hemodynamic effects and clinical implications:

- Decreased intraglomerular pressure due to increased afferent resistance in T1D-H patients
- Decreased hyperfiltration



- Decreased intraglomerular pressure due to decreased efferent resistance
- Decreased hyperfiltration
- Proven renal protection in clinical trials



- Normalisation of intraglomerular pressure due to increased afferent and decreased efferent resistance?
- Potential for additive intraglomerular pressure reduction?
- Potential for long-term renal protection?

RAAS, renin–angiotensin–aldosterone system; SGLT2, sodium–glucose co-transporter 2; T1D-H, type 1 diabetes with hyperfiltration
Adapted from: Skrtić M, et al. *Diabetologia* 2014;57:2599–602.

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Results from One Trial of SGLT2i Agents with Primary Renal Outcomes Have been Reported

	CREDENCE[1,2]	DAPA-CKD[3,4]	EMPA-KIDNEY[5]
No. of patients	4401	4000	5000
Treatment arms	CANA 100 mg vs. PBO	DAPA (5, 10 mg) vs. PBO	EMPA vs. PBO
Patient population	CKD + T2D Must be taking max. labelled or tolerated ACEi/ARB	CKD ± T2D Must be taking max. labelled ACEi/ARB if not medically contraindicated	CKD ± T2D Must be taking clinically appropriate doses of ACEi/ARB unless not tolerated or not indicated
Kidney function inclusion criteria (eGFR units: mL/min/1.73 m²)	eGFR ≥30 to <90 AND UACR >33.9 mg/mmol 60% to have eGFR ≥30 to <60	eGFR ≥25 to <75 AND UACR ≥22.6 mg/mmol	eGFR ≥20 to <45 OR eGFR ≥45 to <90 with UACR ≥22.6 mg/mmol
Primary endpoint	Composite of ESKD, doubling of sCr, renal or CV death	Composite of ≥50% sustained decline in eGFR, ESKD, CV or renal death	Composite of CV death, kidney disease progression (ESKD, renal death or a sustained decline of ≥40% in eGFR)
Start	2014	2017	2018
Completion	Complete: Stopped early due to achievement of efficacy endpoint	Complete: Stopped early due to achievement of efficacy endpoint (data not yet reported)[5]	2022

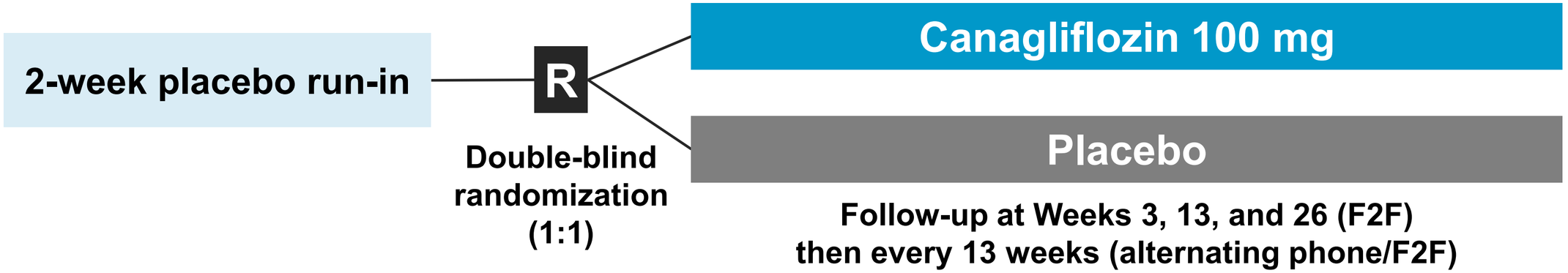
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; PBO, placebo; SCr, serum creatinine; T2D, type 2 diabetes; UACR, urine albumin-creatinine ratio

1. Perkovic et al., *N Engl J Med* 2019, DOI: 10.1056/NEJMoa1811744
2. Jardine MJ et al., *Am J Nephrol* 2017;46:462–472;
3. ClinicalTrials.gov Identifier: NCT03036150;
4. AstraZeneca Inc. Press release. March 30, 2020. Available at: https://www.astrazeneca.com/media-centre/press-releases/2020/farxiga-phase-iii-dapa-ckd-trial-will-be-stopped-early-after-overwhelming-efficacy-in-patients-with-chronic-kidney-disease.html. Accessed April 7, 2020.
5. ClinicalTrials.gov Identifier: NCT03594110.

CREDENCE: Study Design

Key inclusion criteria
- ≥30 years of age
- T2DM and HbA1c 6.5–12.0%
- eGFR 30–90 mL/min/1.73 m^2
- UACR 33.9–565 mg/mmol (300–5000 mg/g)
- Stable maximum tolerated or labelled dose of ACEi or ARB for ≥4 weeks

Key exclusion criteria
- Other kidney diseases, dialysis, or kidney transplant
- Dual ACEi and ARB; direct renin inhibitor; MRA
- Serum K+ >5.5 mmol/L
- CV events within 12 weeks of screening
- NYHA class IV heart failure
- Diabetic ketoacidosis or T1DM



Participants continued treatment if eGFR was <30 mL/min/1.73 m^2 until chronic dialysis was initiated, or kidney transplant occurred.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; UACR, urinary albumin-to-creatinine ratio

Adapted from: Jardine MJ, et al. *Am J Nephrol* 2017;46:462–72.

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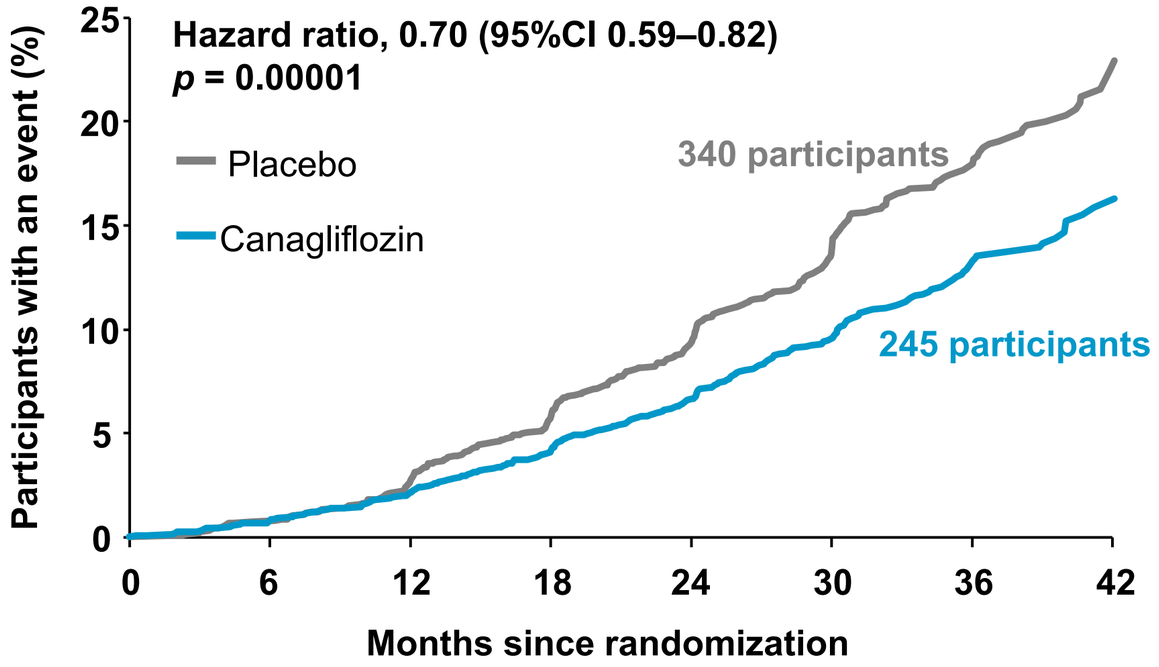
CREDENCE Primary Endpoint

- Patients in CREDENCE received fixed-dose canagliflozin 100 mg in addition to the standard of care
- Primary composite endpoint of **ESKD, doubling of serum creatinine, and renal/CV death** was reduced by 30%

CREDENCE primary endpoint: Composite of ESKD, doubling of serum creatinine, and renal or CV death



No. at risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

ESKD, end-stage kidney disease

Perkovic et al. *N Engl J Med*. 2019; 380(24):2295-2306.

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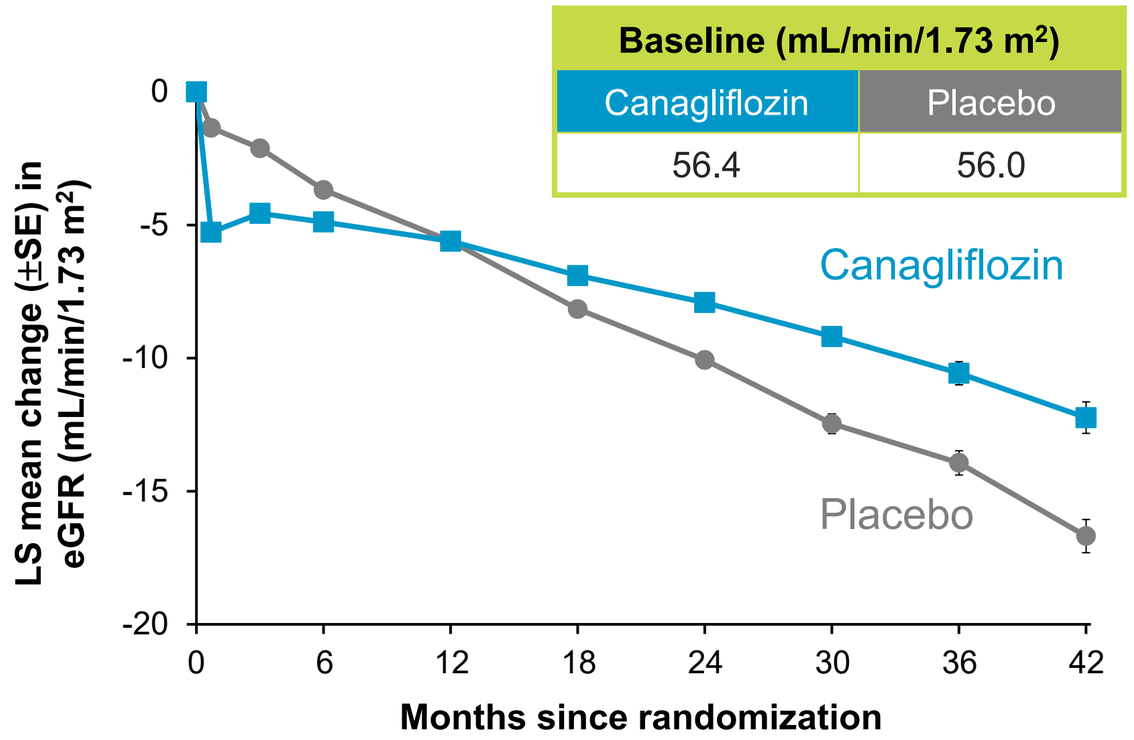
CREDENCE: Effect on eGFR Decline

- In CREDENCE, canagliflozin was associated with a slower **long-term** decline in eGFR despite initial reversible hemodynamic drop[1]
- Placebo represents eGFR decline in modern standard of care (99.9% of patients taking ACEi/ARB)[1]
  - In IDNT, irbesartan slowed eGFR decline by roughly 1.2 mL/min/1.73 m^2 per year[2]

eGFR Changes in CREDENCE[1]

	First 3 weeks (mL/min/1.73 m^2)	Thereafter (mL/min/1.73 m^2 per year)
Placebo (±SD)	–0.55 ± 0.25	–4.59 ± 0.14
Canagliflozin (±SD)	–3.72 ± 0.25	–1.85 ± 0.13
Difference (95%CI)	–3.17 (–3.87 to –2.47)	2.74 (2.37 to 3.11)

eGFR changes in CREDENCE[1]



No. at risk								
Placebo	2178	1985	1882	1720	1536	1006	583	210
Canagliflozin	2179	2005	1919	1782	1648	1116	652	241

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate

1. Perkovic et al. *N Engl J Med*. 2019 Jun 13;380(24):2295-230.
2. Evans et al. *Nephrol Dial Transplant*. 2012 Jun;27(6):2255-63.

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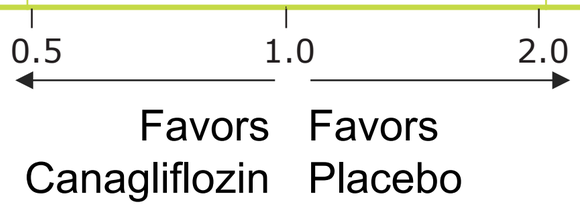
CREDENCE – Renal Safety

	Number of participants with an event, n		Hazard ratio (95%CI)
	Canagliflozin (N = 2200)	Placebo (N = 2197)	
All AEs	1784	1860	0.87 (0.82–0.93)
All serious AEs	737	806	0.87 (0.79–0.97)
All renal-related AEs*	290	388	0.71 (0.61–0.82)
Hyperkalemia	151	181	0.80 (0.65–1.00)
Acute kidney injury	86	98	0.85 (0.64–1.13)



Includes all treated participants through 30 days after last dose.
*Defined as AEs coded by MedDRA as “Renal And Urinary Disorders”

AE, adverse event
Perkovic V, et al. *N Engl J Med*. 2019;380(24):2295-2306.

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DAPA-CKD:
Dapagliflozin in Patients With Chronic Kidney Disease[1,2]

Objective

To assess whether treatment with dapagliflozin, compared with placebo, reduced the risk of renal and CV events in patients with CKD with or without T2D, and who were receiving standard of care including a maximum tolerated dose of an ACEi or ARB

Key Inclusion Criteria

- ≥18 years of age
- eGFR ≥25 to ≤75 mL/min/1.73m^2
- UACR ≥22.6 to ≤565 umol/mmol
- Stable max tolerated dose of ACEi/ARB for ≥4 weeks
- With and without T2D

Key Exclusion Criteria

- T1D
- Polycystic kidney disease, lupus nephritis, ANCA-associated vasculitis
- Immunosuppressive therapy ≤6 months prior to enrollment

1:1 Double-blind

- Dapagliflozin 10 mg + standard of care
- Placebo + standard of care

4304 Randomized
Median follow-up 2.4 years

End Points

Primary Outcome

Composite of sustained ≥50% eGFR decline, ESKD[a], renal or CV death

Secondary Outcomes

- Composite of sustained ≥50% eGFR decline, ESKD, or renal death
- Composite of CV death or hHF
- All-cause mortality

[a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m^2 for at least 28 days.
ACEi, angiotensin-converting enzyme inhibitor; ANCA, anti-neutrophil cytoplasmic antibody; ARB, angiotensin-receptor blocker; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; hHF, hospitalization for heart failure; T1D, type 1 diabetes; T2D, type 2 diabetes; UACR, urinary albumin-to-creatinine ratio.

1. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282;
2. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.

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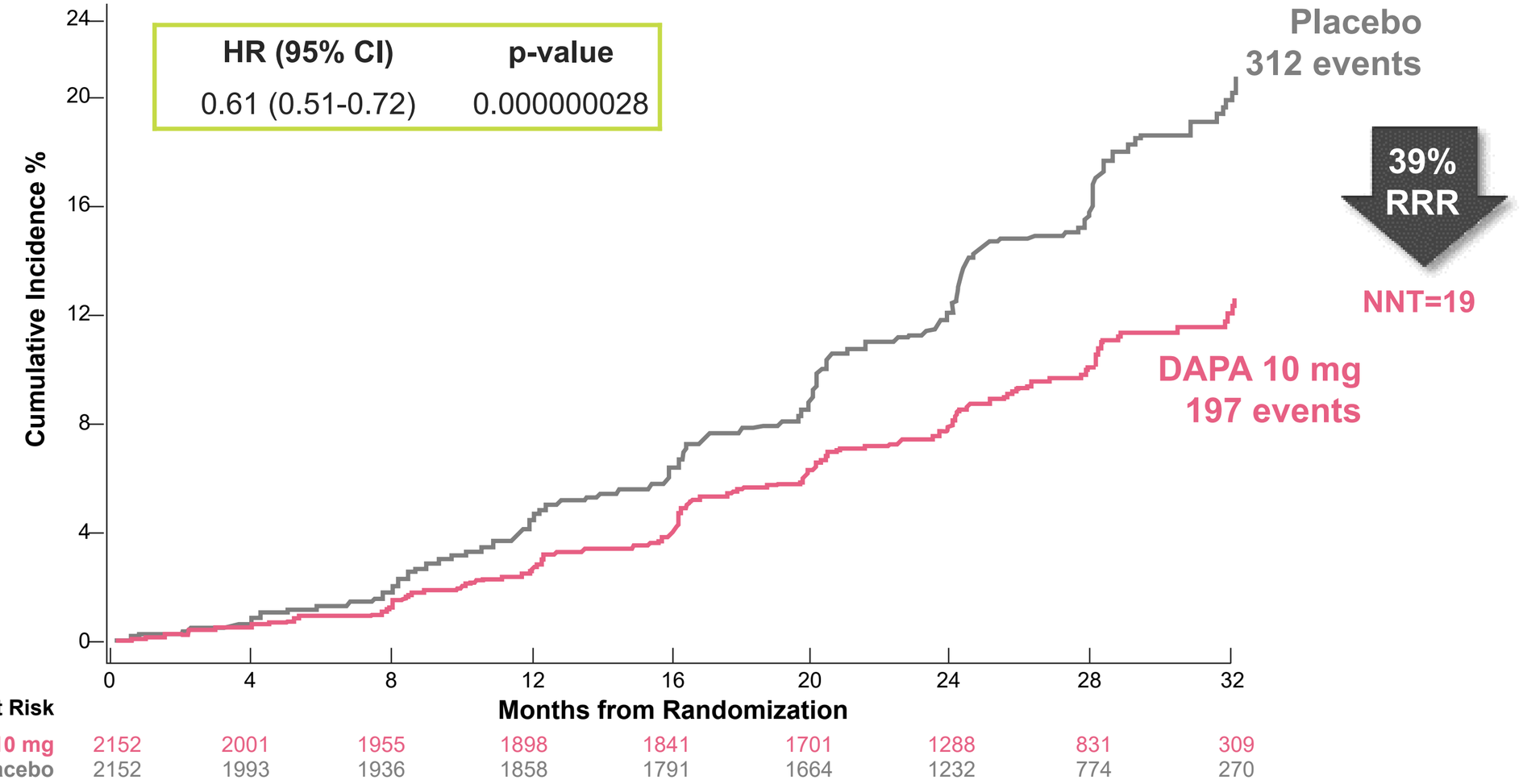
Primary Composite Outcome:
Sustained ≥50% eGFR Decline, ESKD, Renal or CV Death[a]



[a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m^2 for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason.[2] CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR, hazard ratio; NNT, number needed to treat; RRR, relative risk reduction.

1. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.
2. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282.

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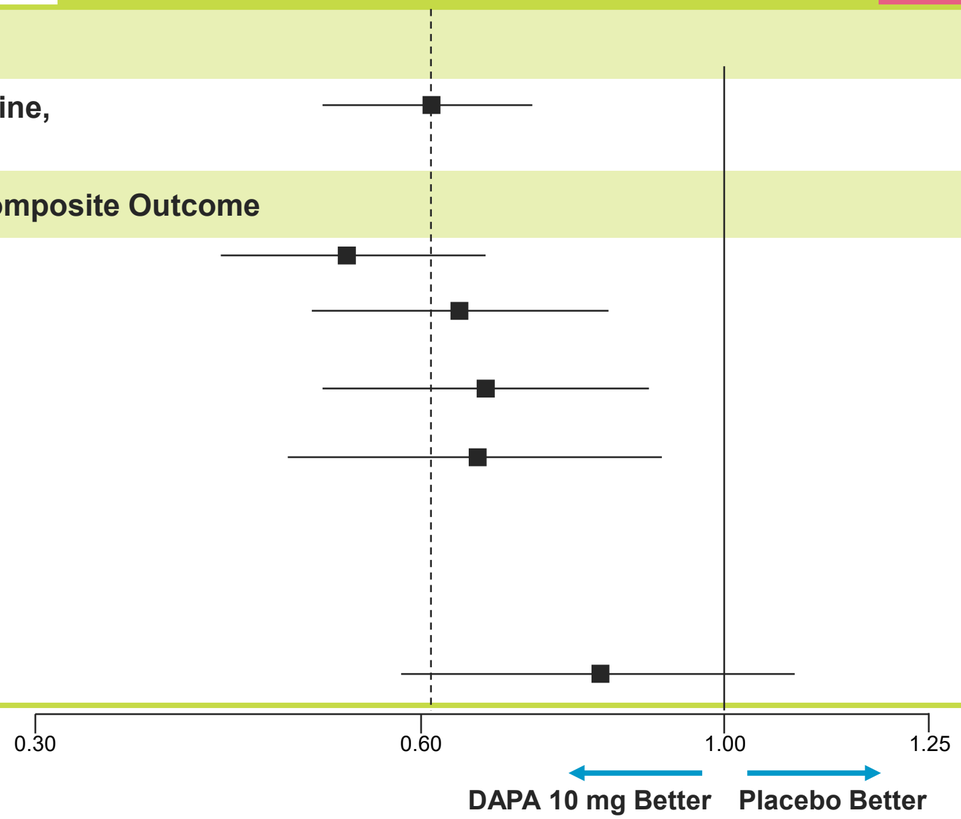
Individual Components of the Primary Composite Outcome

	HR (95% CI)	Number of Events: DAPA 10 mg (N=2152)	Number of Events: Placebo (N=2152)	HR	95% CI	p-value
Primary Composite Outcome						
Composite of ≥50% eGFR Decline, ESKD, or Renal or CV Death		197	312	0.61	(0.51, 0.72)	0.000000028
Components of the Primary Composite Outcome						
≥50% eGFR Decline		112	201	0.53	(0.42, 0.67)	<0.0001
ESKD		109	161	0.64	(0.50, 0.82)	0.0004
eGFR <15mL/min/1.73m^2		84	120	0.67	(0.51, 0.88)	0.0045
Chronic Dialysis		68	99	0.66	(0.48, 0.90)	0.0080
Transplantation		3	8	NC		
Renal Death		2	6	NC		
CV Death		65	80	0.81	(0.58, 1.12)	0.2029



CV, cardiovascular; DAPA, dapagliflozin; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio; NC, not calculable

Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.

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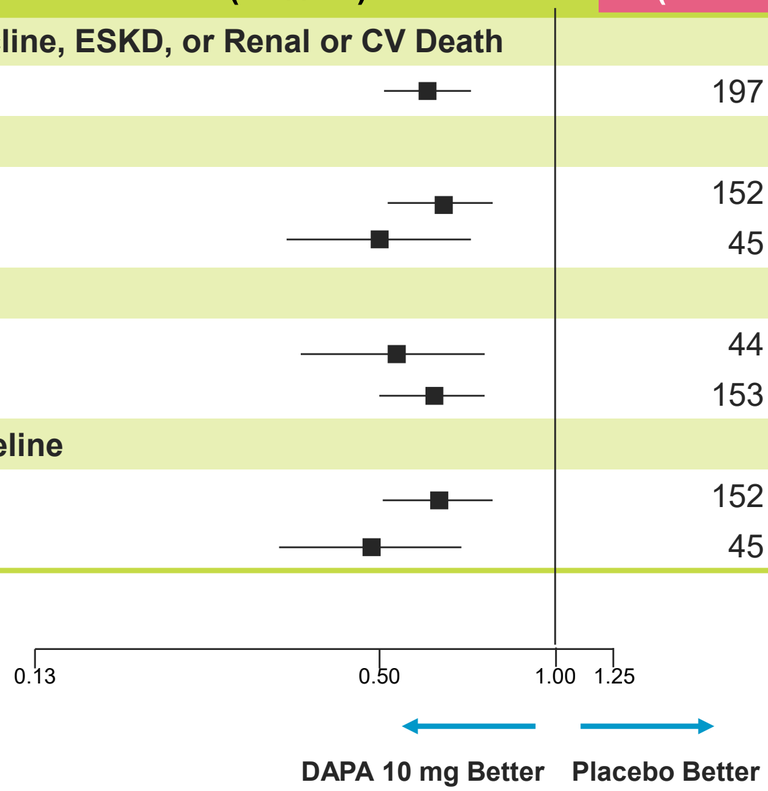
Primary Composite Outcome: Prespecified Subgroup Analyses

	Number of Events				
	DAPA 10 mg (N=2152)	Placebo (N=2152)	HR	95% CI	p-value Interaction
Composite of ≥50% eGFR Decline, ESKD, or Renal or CV Death					
All Patients	197	312	0.61	(0.51, 0.72)	
T2D at Baseline					0.24
Yes	152	229	0.64	(0.52, 0.79)	
No	45	83	0.50	(0.35, 0.72)	
UACR (mg/g) at Baseline					0.52
≤1000	44	84	0.54	(0.37, 0.77)	
>1000	153	228	0.62	(0.50, 0.76)	
eGFR (mL/min/1.73m^2) at Baseline					0.22
<45	152	217	0.63	(0.51, 0.78)	
≥45	45	95	0.49	(0.34, 0.69)	



CV, cardiovascular; DAPA, dapagliflozin; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio; T2D, type 2 diabetes; UACR, urinary albumin-to-creatinine ratio.

Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.

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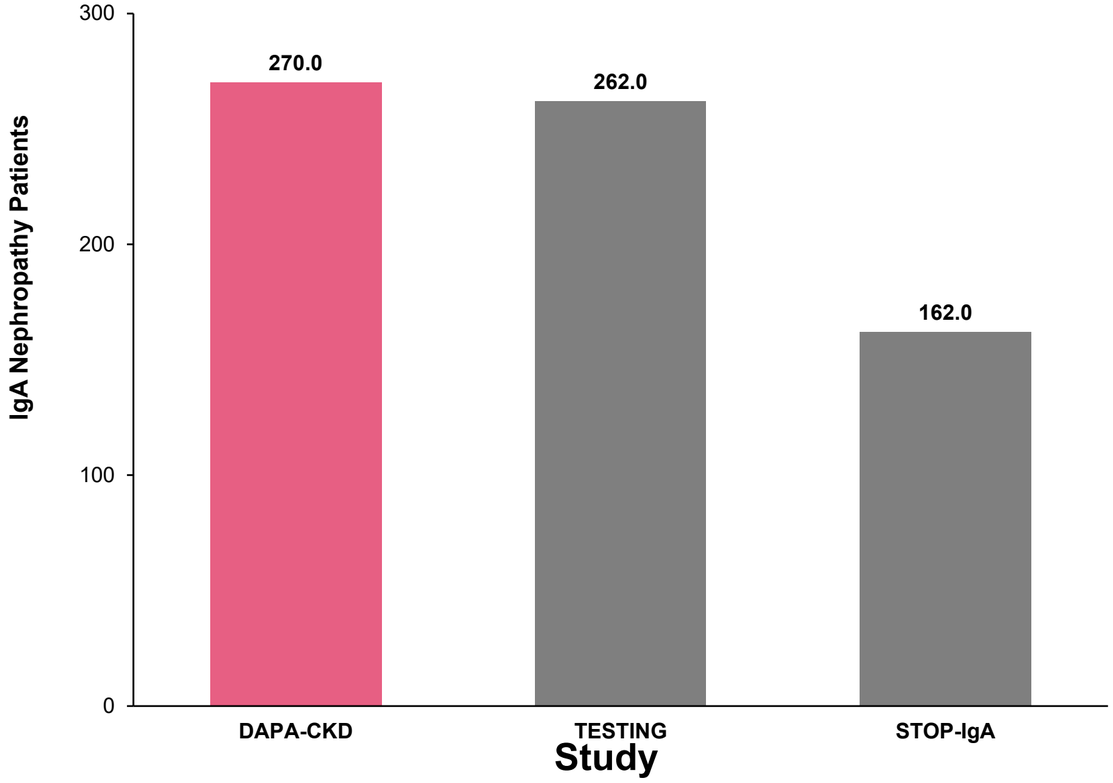
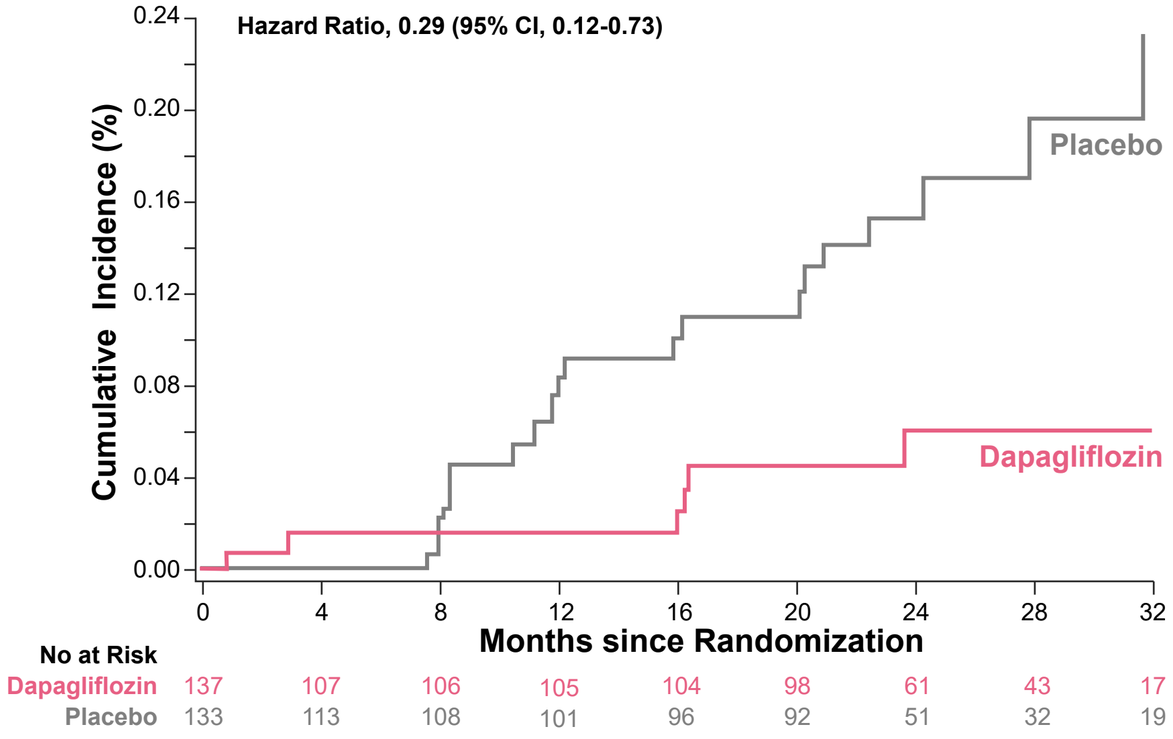
Further Exploring the Effect of Dapagliflozin by Causes Of Kidney Disease in DAPA-CKD – IgA Nephropathy

Number of participants with IgA nephropathy in clinical trials[1]



Primary outcome in participants with IgA nephropathy[2]



1. Wheeler DC et al. *Nephrol Dial Transplant*. 2020;35:1700–1711;
2. Wheeler DC. Presented at: ASN – Kidney Week 2020; October 22 – October 25, 2020.

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Doubling of Serum Creatinine, ESKD, or Death

	N	Albuminuria	Baseline renal function	Median Follow-up	2xCr, ESKD, renal death # of events	Relative risk reduction
IDNT[1]	1715	Median ACR: 210 mg/mmol	Mean Cr: 148 µmol/L	2.6 years	644	20%
RENAAL[2]	1513	Median ACR: 140 mg/mmol	Mean Cr: 168 µmol/L	3.4 years	686	16%
CREDENCE[3,4] **(99.9% on RAASi)**	4401	Median ACR: 105 mg/mmol	Median eGFR 56.2	2.6 years	377	30%
DAPA-CKD (97% on RAASi)	4304 2906 DM 1398 No DM	Median ACR: 107 mg/mmol 115 mg/mmol 97 mg/mmol	Median eGFR 43.1 43.8 41.7	2.4 years	509	39% 36% 50%

ACR, albumin-creatinine ratio; DM, diabetes mellitus eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; RAASi, renin-angiotensin aldosterone system

1. Lewis EJ, et al. N Eng J Med. 2001;345(12):851-860.
2. Brenner B, et al. N Engl J Med. 2001;345(12):861-869.
3. Perkovic et al. N Engl J Med. 2019; 380(24):2295-2306
4. Jardine MJ, et al. *Am J Nephrol* 2017;46:462–72

SGLT2i Product Monographs: Cardiovascular & Renal Indications in Canada

FORXIGA® Add-On Combination in Patients with CV Risk Factors or Established CV Disease: FORXIGA is indicated as an adjunct to diet, exercise, and standard of care therapy to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and CV risk factors or established CV disease

FORXIGA is indicated in adults, as an adjunct to standard of care therapy, for the treatment of **HFrEF** to reduce the risk of CV death, hospitalization for heart failure and urgent heart failure visit

FORXIGA is indicated to reduce the risk of sustained eGFR decline, ESRF, and CV and renal death in adults with CKD.

JARDIANCE® Add-on Combination in Patients with Established CV Disease: JARDIANCE is indicated as an adjunct to diet, exercise and standard care therapy to reduce the incidence of CV death in patients with type 2 diabetes mellitus and established cardiovascular disease who have inadequate glycemic control

INVOKANA® Add-On Combination in Patients with Established CV Disease: INVOKANA is indicated as an adjunct to diet, exercise, and standard of care therapy to reduce the risk of major adverse CV events (CV death, nonfatal myocardial infarction and nonfatal stroke) in adults with type 2 diabetes mellitus and established CVD.

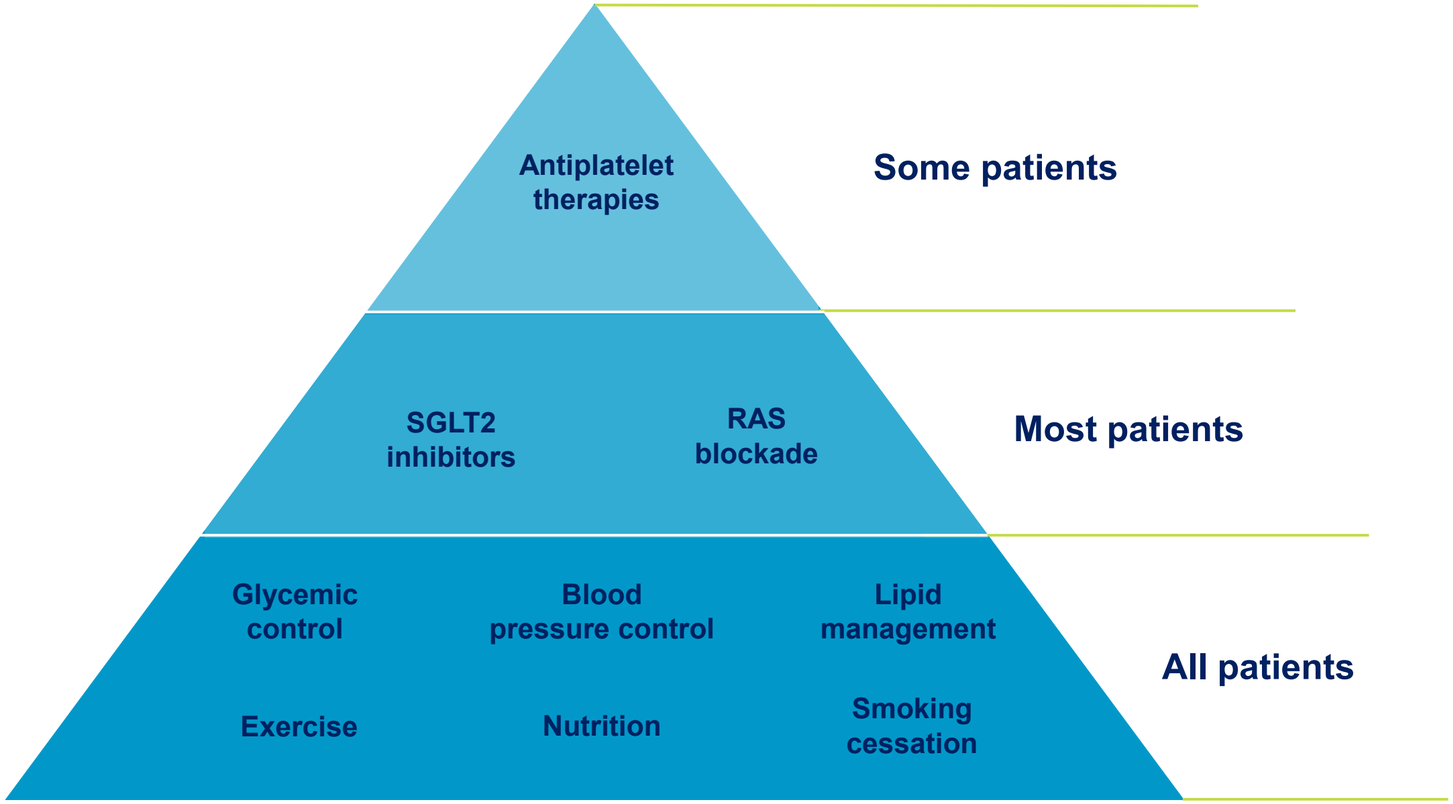
Patients with Diabetic Nephropathy: INVOKANA® is indicated as an adjunct to diet, exercise, and standard of care therapy to reduce the risk of ESKD, doubling of serum creatinine, and CV death in adult patients with type 2 diabetes mellitus and diabetic nephropathy with albuminuria (>33.9 mg/mmol).

CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular death; eGFR, estimated glomerular filtration rate; ESRF, end-stage renal failure; HFrEF, heart failure with reduced ejection fraction; SGLT2i, Sodium-glucose linked transporter inhibitor;

Forxiga product monograph, AstraZeneca (Canada) August 2020. Invokana product monograph, Janssen Inc. (Canada) January 2020,. Jardiance product monograph, Boehringer Ingelheim (Canada) Ltd, April 2020

2020 KDIGO: Comprehensive Care in Patients with Diabetes and CKD

Patients with diabetes and CKD should be treated with a comprehensive strategy to reduce risks of kidney disease progression and cardiovascular disease.



CKD, chronic kidney disease
de Boer IH et al. *Kidney Int*. 2020;98:839-848

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