CKD and SGLT2I
The sweet smell of success

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Conflict of Interest Statement

- Receipt of research grants
  Preparation of educational materials
  Attendance at drug advisory boards
  - AstraZeneca
  - Boehringer Ingelheim/Lilly Alliance
  - Merck Sharp & Dohme
  - Napp Pharmaceuticals Limited
  - Novo Nordisk
  - VPUK

The Challenge

Age of onset of Type 2 DM and Long term risk of ESRF

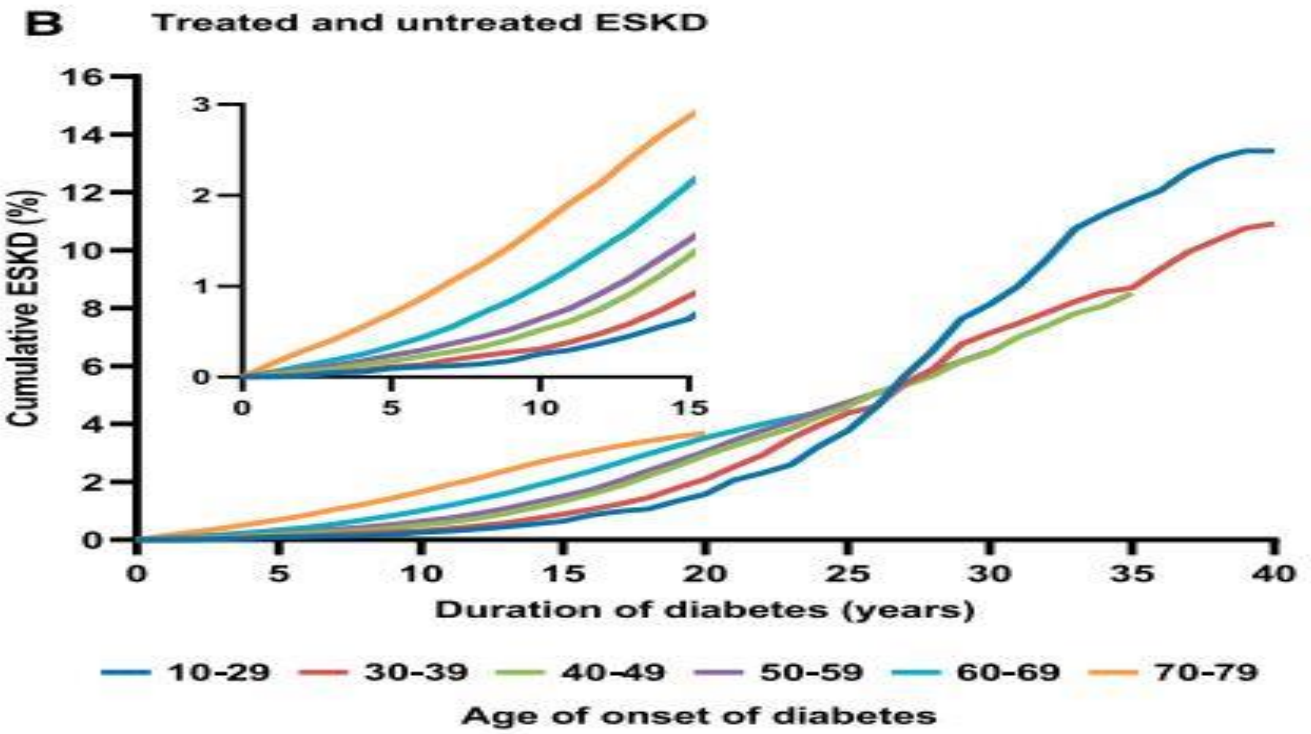
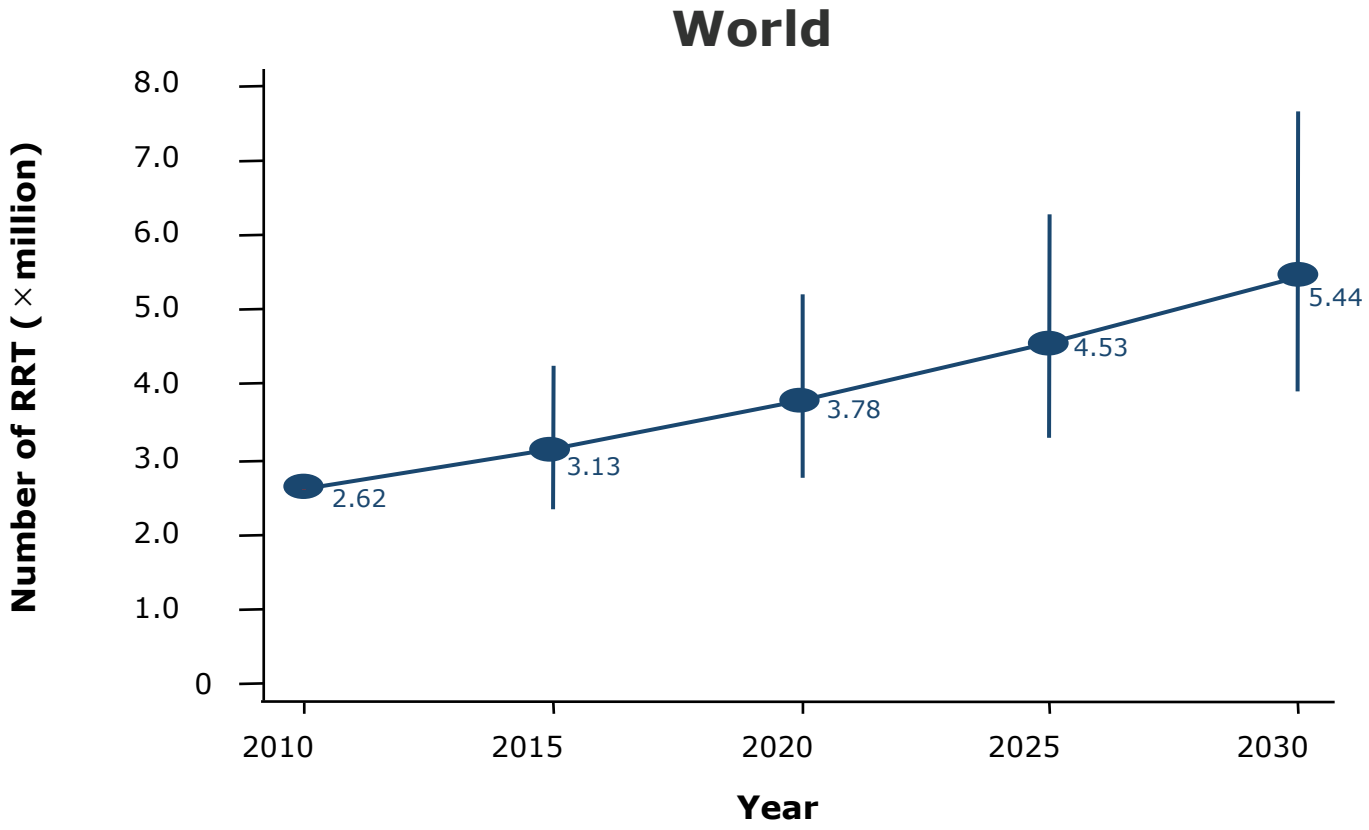


Figure 1—Cumulative incidence of ESKD by duration of type 2 diabetes stratified by age of onset of diabetes. Insets show the first 15 years of diabetes. *A*: Treated ESKD only. *B*: Treated and untreated ESKD.

- Morton et al. Diabetes Care 2020;43:1788–1795

Number of People Receiving Renal Replacement Therapy Is Projected to Double

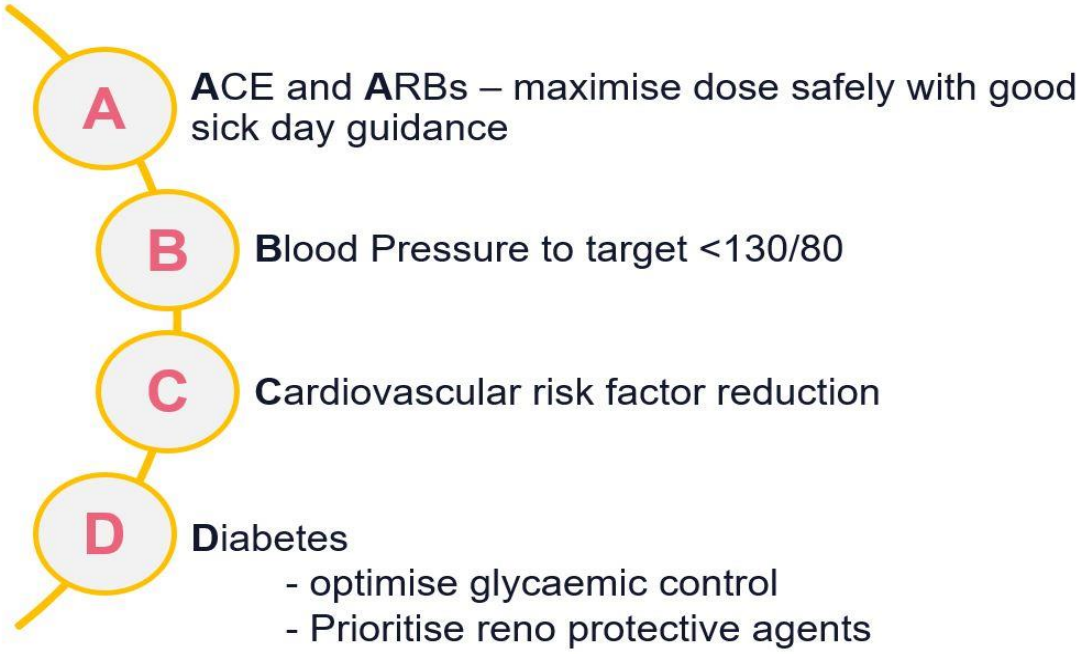


Liyanage T, et al.

The Response

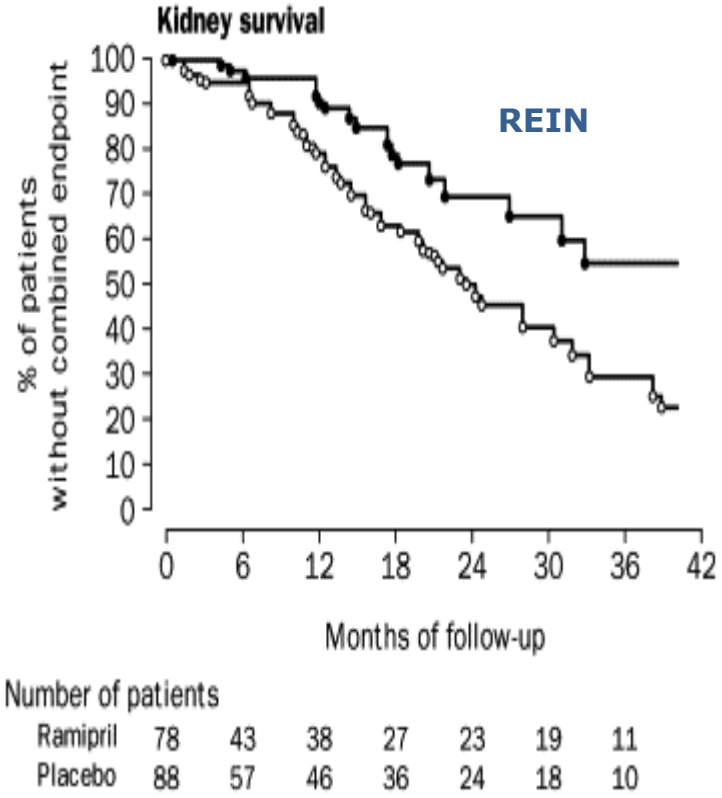
- Recognise
- Optimise
- Manage

Managing DKD up to 2019 A,B,C,D



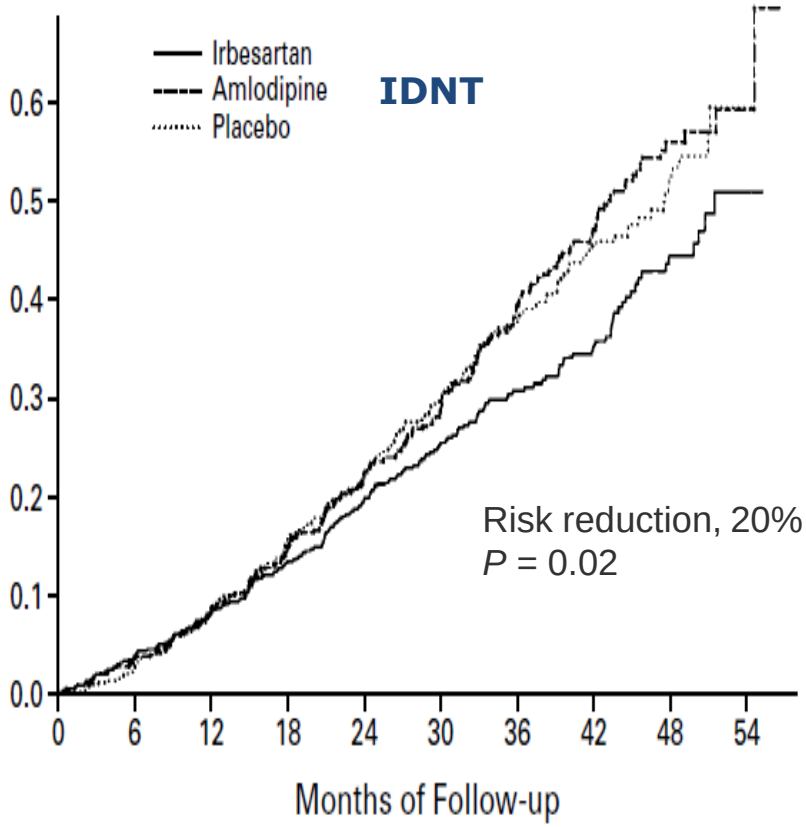
BUILT ON A FOUNDATION OF LIFESTYLE INTERVENTION AND PATIENT ENGAGEMENT

RAASi and renal protection



The GISEN Group Lancet 1997 349 1857-1863

Doubling of serum creatinine, ESKD, or death



Lewis EJ, et al. *N Eng J Med*. 2001;345(12):851-860.

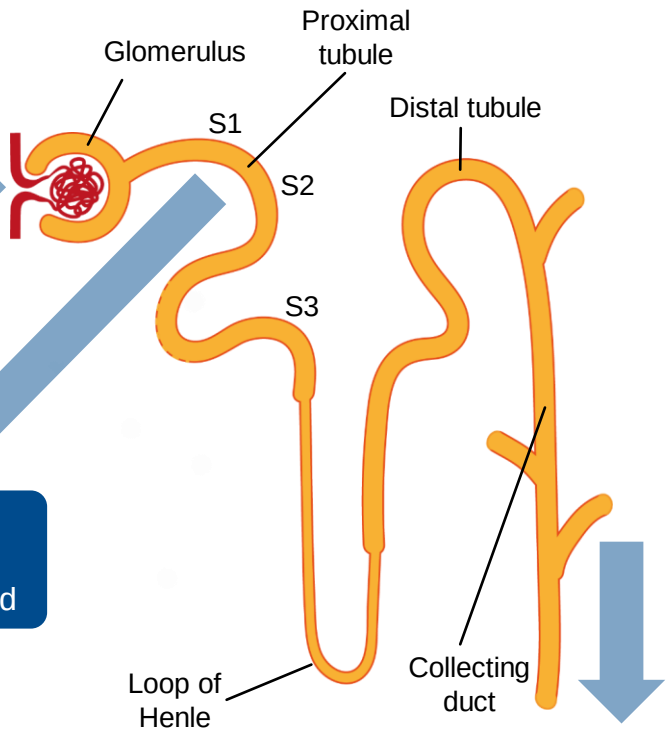
Management of DKD - 2020 onwards

a) RECOGNISE
b) ACE inhibitor/angiotensin receptor blockade
c) BP targeting
d) SGLT2I
e) CV risk reduction

Sodium and glucose filtration occurs in the glomerulus

Filtration and reabsorption of glucose takes place in the glomerulus and proximal convoluted tubule[1,2]

180 g of glucose and 25,000 mmol sodium filtered per day[2,3]



In healthy people, most of the glucose is reabsorbed from the proximal tubule back into the blood

- Urine output: 0.8 – 2 L/day[4]
- Na^+ excreted: 40 – 220 mmol/day[5]
- Very little or no glucose is excreted by healthy people[6]

1. Gerich JE. Diabet Med 2010;27:136-42.
2. Wright EM, et al. J Intern Med 2007;261:32-43.
3. Finkelstein FO, et al. Yale J Biol Med 1979;52:271-87.
4. Healthline. Urine 24-hour volume test. [Accessed October 2019]. www.healthline.com/health/urine-24-hour-volume
5. WebMD. What is a sodium urine test? February 2019. [Accessed October 2019]. www.webmd.com/a-to-z-guides/what-is-a-urine-sodium-test#2
6. Chao EC, et al. Nat Rev Drug Discov 2010;9:551-9.

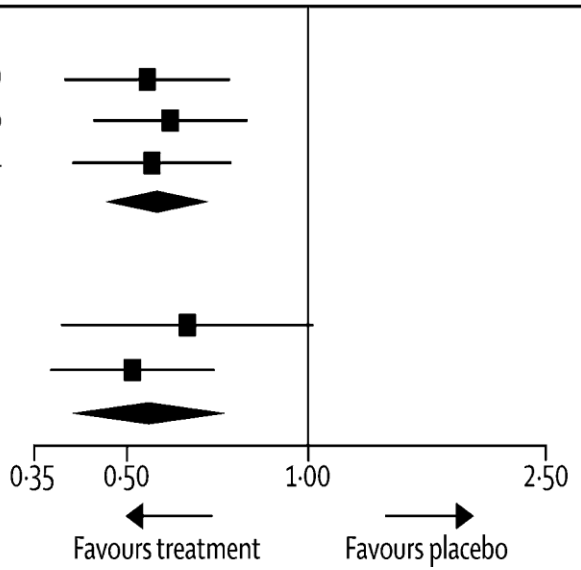
UK/INV-17012(5)a October 2019

NAPP DIABETES

SGLT2 INHIBITORS AND EFFECT ON COMPOSITE RENAL OUTCOMES - DECLINE IN GFR, ESRF OR RENAL DEATH

Imperial College Healthcare NHS Trust

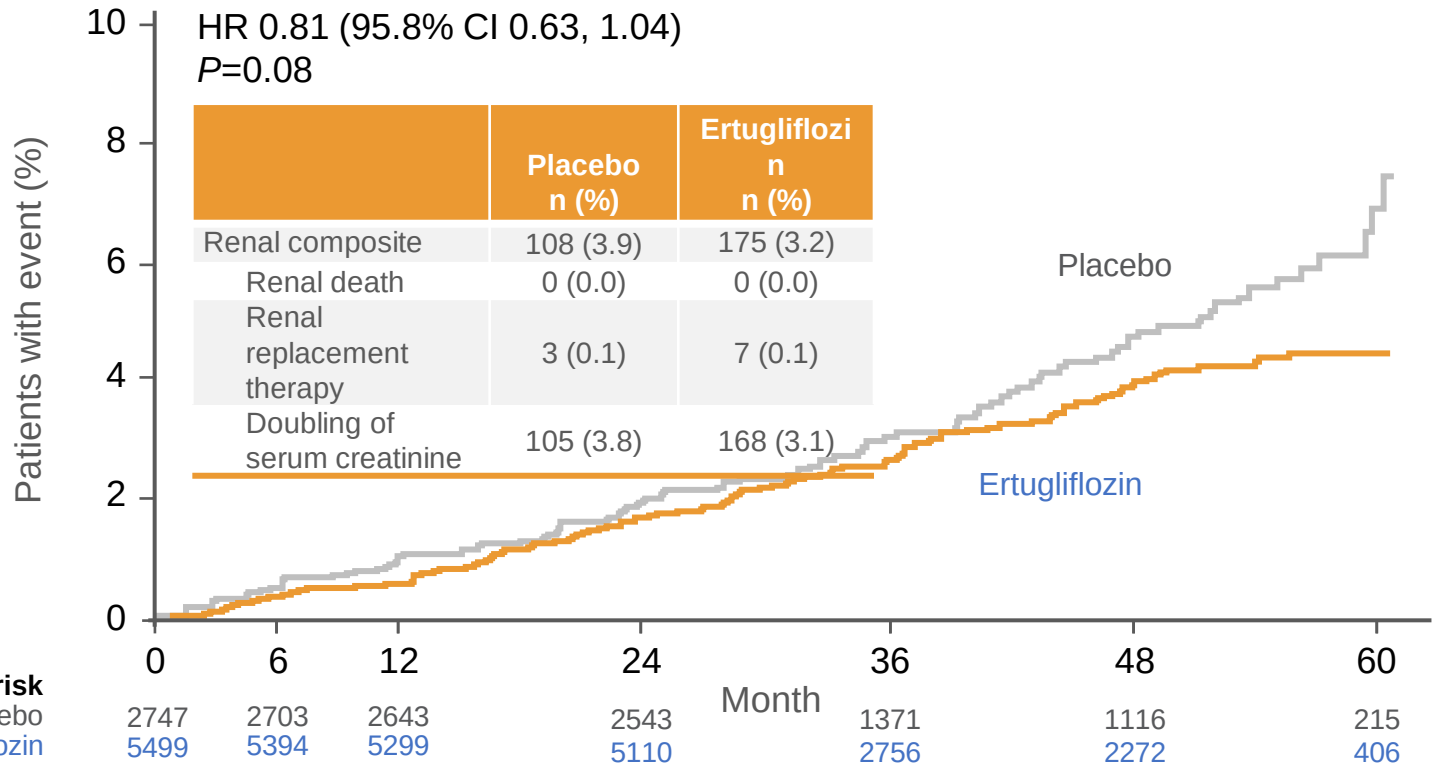
	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4645/6968	2323/6968	152	6·3	11·5	31·0		0·54 (0·40–0·75)
CANVAS Program	3756/6656	2900/6656	179	6·4	10·5	35·6		0·59 (0·44–0·79)
DECLARE-TIMI 58	3474/6974	3500/6974	183	4·7	8·6	33·4		0·55 (0·41–0·75)
Fixed effects model for atherosclerotic cardiovascular disease (p<0·0001)								**0·56 (0·47–0·67)**
Patients with multiple risk factors								
CANVAS Program	2039/3486	1447/3486	70	4·1	6·6	29·5		0·63 (0·39–1·02)
DECLARE-TIMI 58	5108/10 186	5078/10 186	182	3·0	5·9	70·5		0·51 (0·37–0·69)
Fixed effects model for multiple risk factors (p<0·0001)								**0·54 (0·42–0·71)**



Zelnicker TA et Al Lancet POL 10th November 2018

Is renal protection a class effect

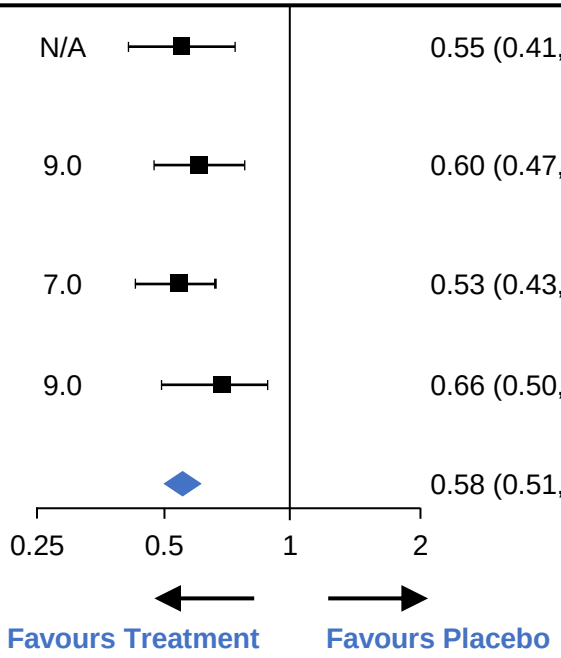
Vertis CV Renal composite[†1]
Renal death, dialysis/transplant or doubling of serum creatinine



[†]Intention-to-treat analysis set that included all randomised patients with no upper limit on the ascertainment window for the superiority outcomes (n=5499 for ertugliflozin and n=2747 for placebo). CI (95.8%) for the alpha-protected tests was adjusted at the final analysis to account for the interim analysis as per the protocol. CI, confidence interval; HR, hazard ratio. [1]Cannon CP. Evaluation of ertugliflozin efficacy and safety cardiovascular outcomes trial – VERTIS CV. American Diabetes Association Virtual Scientific Sessions. 2020.

Kidney outcomes using generally consistent definitions: Sustained ≥40% decline in eGFR, ESKD or renal death

	Treatment		Placebo		Hazard Ratio (95% CI)
	Events/N (%)	Rate per 1000 Patient-years	Events/N (%)	Rate per 1000 Patient-years	
EMPA-REG OUTCOME[1]	100/4645 (2.15)	N/A	86/2323 (3.70)	N/A	0.55 (0.41, 0.73)
CANVAS Programme[2]	124/5795 (2.14)	5.5	125/4347 (2.88)	9.0	0.60 (0.47, 0.77)
DECLARE-TIMI 58[3]	127/8582 (1.48)	3.7	238/8578 (2.77)	7.0	0.53 (0.43, 0.66)
VERTIS CV	113/5499 (2.05)	6.0	85/2747 (3.09)	9.0	0.66 (0.50, 0.88)
Pooled estimate (Q statistic *P*=0.64; I^2=0.0%)					0.58 (0.51, 0.65)



Intention-to-treat analysis set.
CI, confidence interval; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio.
[1]Perkovic V et al. *Nephrol Dial Transplant.* 2019:1–9; [2]Neal B et al. *N Engl J Med.* 2017;377:644–657; [3]Wiviott SD et al. *N Engl J Med.* 2019;380:347–357.

Primary Outcome trials

CREDENCE study design

Canagliflozin and **R**enal **E**ndpoints in **D**iabetes with **E**stablished **N**ephropathy **C**linical **E**valuation (**CREDENCE**) study

Objective: To study the effects of canagliflozin on renal endpoints in adults with type 2 diabetes and chronic kidney disease, receiving standard of care including a maximum tolerated dose of an ACEi or ARB

N = 4,401 (canagliflozin group: n = 2,202; placebo group: n = 2,199)

Two-week placebo run-in period, followed by randomisation to treatment
Follow-up at Weeks 3, 13, and 26 (face-to-face) then every 13 weeks (alternating phone/face-to-face); median follow-up: 2.62 years

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

Main 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 – ≤565.6 mg/mmol
- Stable max tolerated labelled dose of ACEi or ARB for ≥4 weeks

Exclusion criteria included: other kidney diseases, dialysis or kidney transplant; treatment with dual ACEi and ARB, direct renin inhibitor or MRA; serum K^+ >5.5 mmol/L; CV events within 12 weeks of screening; NYHA class IV heart failure; diabetic ketoacidosis or T1DM.

Standard of care (SoC) for T2DM + patients randomised 1:1 to:	Invokana (100 mg)	Placebo

Primary endpoint
ESKD, doubling of serum creatinine, or renal or CV death

Secondary endpoints (sequential testing)
1. CV death or hospitalisation for heart failure; 2. CV death, MI, or stroke; 3. Hospitalisation for heart failure; 4. ESKD, doubling of serum creatinine or renal death; 5. CV death; 6. all-cause mortality; 7. CV death, MI, stroke, hospitalisation for heart failure, or hospitalisation for unstable angina

Perkovic V, et al. N Engl J Med 2019;380:2295-306.

UK/INV-20095(1) July 2020

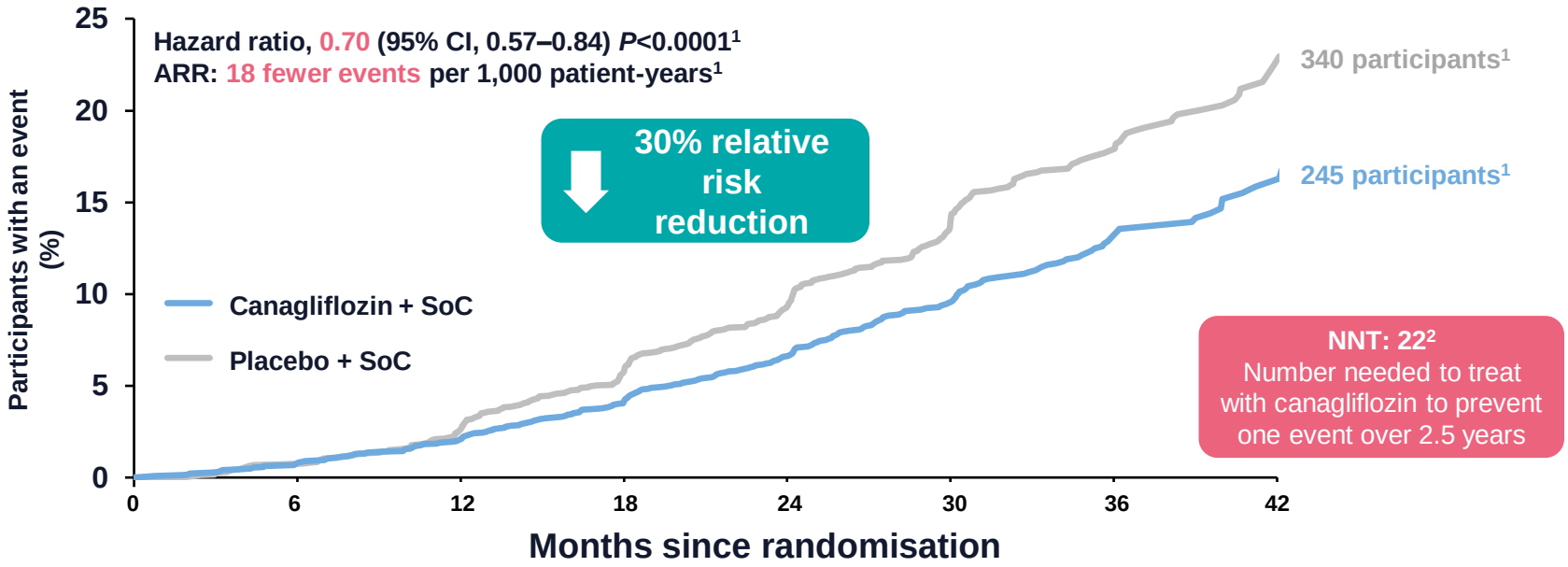
NAPP DIABETES

At baseline, patients in CREDENCE were receiving treatment to manage glycaemia and cardiovascular risk factors

- **99.9% on ACEi or ARB**
- Mean BP 140/78
- Mean HbA1C 8.3%
- 70% on statin

Perkovic V, et al. N Engl J Med 2019;380:2295-306

Invokana + SoC reduces the risk of primary renal composite (ESKD, doubling of serum creatinine, or renal or CV death) vs. placebo + SoC[1,2*]



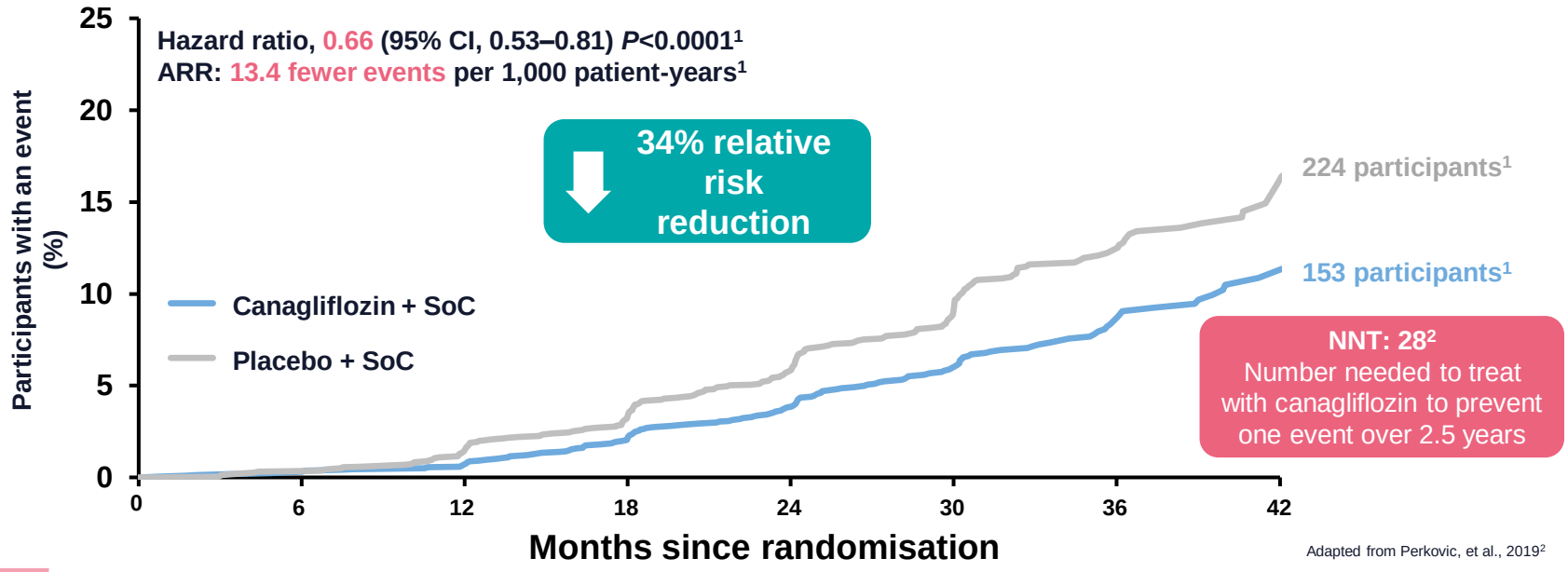
Number at risk[1]								
Placebo + SoC	2,199	2,178	2,132	2,047	1,725	1,129	621	170
Canagliflozin + SoC	2,202	2,181	2,145	2,081	1,786	1,211	646	196

*Intent-to-treat analysis set. SoC: standard of care; ESKD: end-stage kidney disease; CV: cardiovascular; ARR: absolute risk reduction.

1. Invokana 100 mg and 300 mg film-coated tablets. Summary of Product Characteristics. [Accessed July 2020]. www.medicines.org.uk/emc/product/8855
2. Perkovic V, et al. N Engl J Med 2019;380:2295-306.

NAPP DIABETES

Invokana + SoC reduces the risk of ESKD, doubling of serum creatinine, or renal death vs. placebo + SoC[1,2]



Adapted from Perkovic, et al., 2019[2]

Number at risk[2]								
Placebo + SoC	2,199	2,178	2,131	2,046	1,724	1,129	621	170
Canagliflozin + SoC	2,202	2,181	2,144	2,080	1,786	1,211	646	196

SoC: standard of care; ESKD: end-stage kidney disease; ARR: absolute risk reduction.

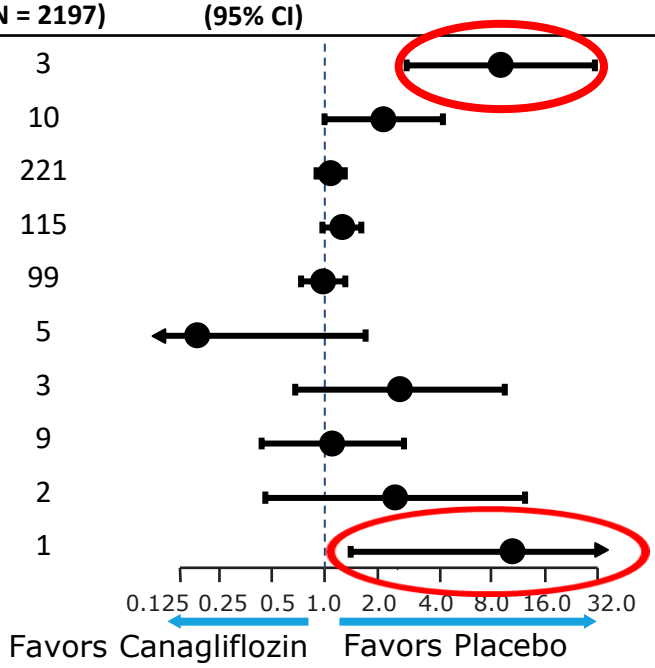
1. Invokana 100 mg and 300 mg film-coated tablets. Summary of Product Characteristics. [Accessed July 2020]. www.medicines.org.uk/emc/product/8855
2. Perkovic V, et al. N Engl J Med 2019;380:2295-306.

NAPP DIABETES

CREDENCE Other AEs of Interest

Imperial College Healthcare NHS Trust

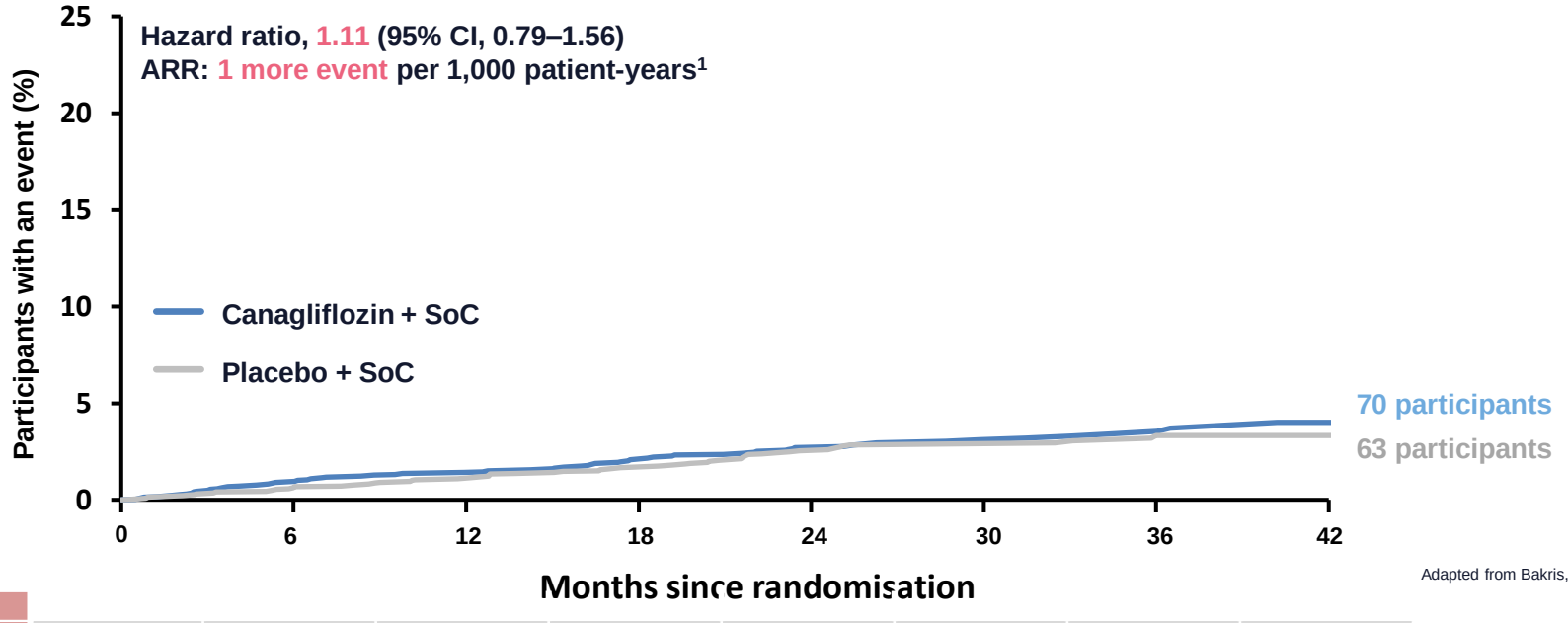
	Number of participants with an event, n		Hazard ratio (95% CI)
	Canagliflozin (N = 2200)	Placebo (N = 2197)	
Male genital mycotic infections*	28	3	9.30 (2.83–30.60)
Female genital mycotic infections†	22	10	2.10 (1.00–4.45)
Urinary tract infections	245	221	1.08 (0.90–1.29)
Volume depletion–related AEs	144	115	1.25 (0.97–1.59)
Malignancies‡	98	99	0.98 (0.74–1.30)
Renal cell carcinoma	1	5	0.20 (0.02–1.68)
Breast†	8	3	2.59 (0.69–9.76)
Bladder	10	9	1.10 (0.45–2.72)
Acute pancreatitis	5	2	2.44 (0.47–12.59)
Diabetic ketoacidosis	11	1	10.80 (1.39–83.65)



Includes all treated participants through 30 days after last dose except cancer, which includes all treated patients through the end of the trial.
*Includes male participants only (canagliflozin, n = 1439; placebo, n = 1466).
†Includes female participants only (canagliflozin, n = 761; placebo, n = 731).
‡Includes malignant tumors of unspecified type.

Perkovic V, et al. *N Engl J Med*. 2019. doi: 10.1056/NEJMoa1811744.

Safety outcomes from CREDENCE – LLA



Adapted from Bakris, et al.[2]

Number at risk								
Placebo + SoC	2,197	2,169	2,131	2,065	1,766	1,177	658	182
Canagliflozin + SoC	2,200	2,163	2,118	2,071	1,788	1,228	667	202

- Invokana 100 mg and 300 mg film-coated tablets. Summary of Product Characteristics. [Accessed July 2020]. www.medicines.org.uk/emc/product/8855
- Bakris G, et al. CREDENCE. [Accessed July 2020]. https://view.publitas.com/george-institute/credence-trial-results-and-slides/page/1

- Includes all treated patients through to the end of the trial. LLA: lower limb amputation; ARR: absolute risk reduction; SoC: standard of care.

Canagliflozin – European Commission

Change to posology (dosage) – what's new?

Invokana 100 mg	In the **absence** of severe albuminuria	Can now be **initiated down to eGFR ≥45 mL/min/1.73 m²**
	In the **presence** of severe albuminuria	Can now be **initiated down to eGFR ≥30 mL/min/1.73 m²** Continue dosing until dialysis or renal transplantation

If further glycaemic control is needed in patients with moderate or severe renal impairment, the addition of other anti-hyperglycaemic agents should be considered.

Severe albuminuria >30mg/mmol

1. Invokana 100 mg and 300 mg film-coated tablets. Summary of Product Characteristics. [Accessed July 2020]. www.medicines.org.uk/emc/product/8855

NAPP DIABETES

Is renal protection diabetes specific

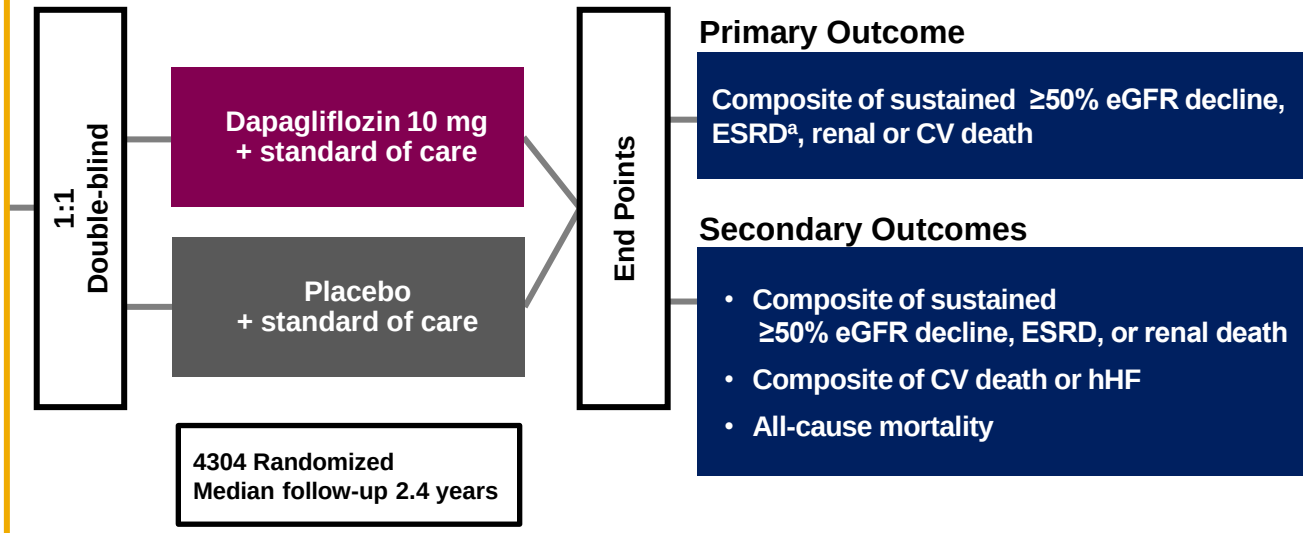
DAPA-CKD:
Dapagliflozin in Patients With Chronic Kidney Disease[1,2]

DAPACKD

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 ≥200 to ≤5000 mg/g (≥ 22.6 to ≤ 565mg/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

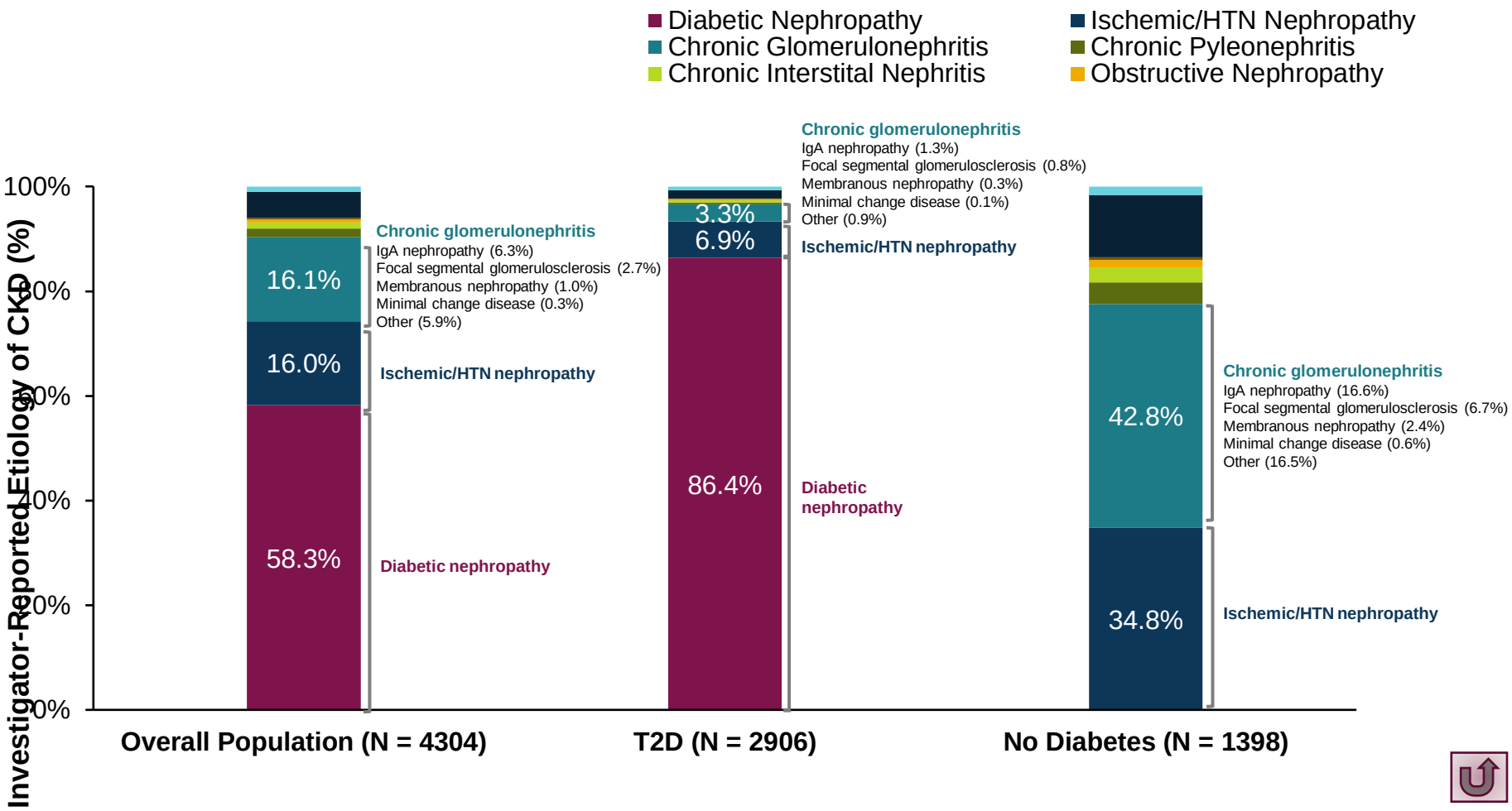


[a]ESRD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m^2 for at least 28 days.

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; ESRD = end-stage renal 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.

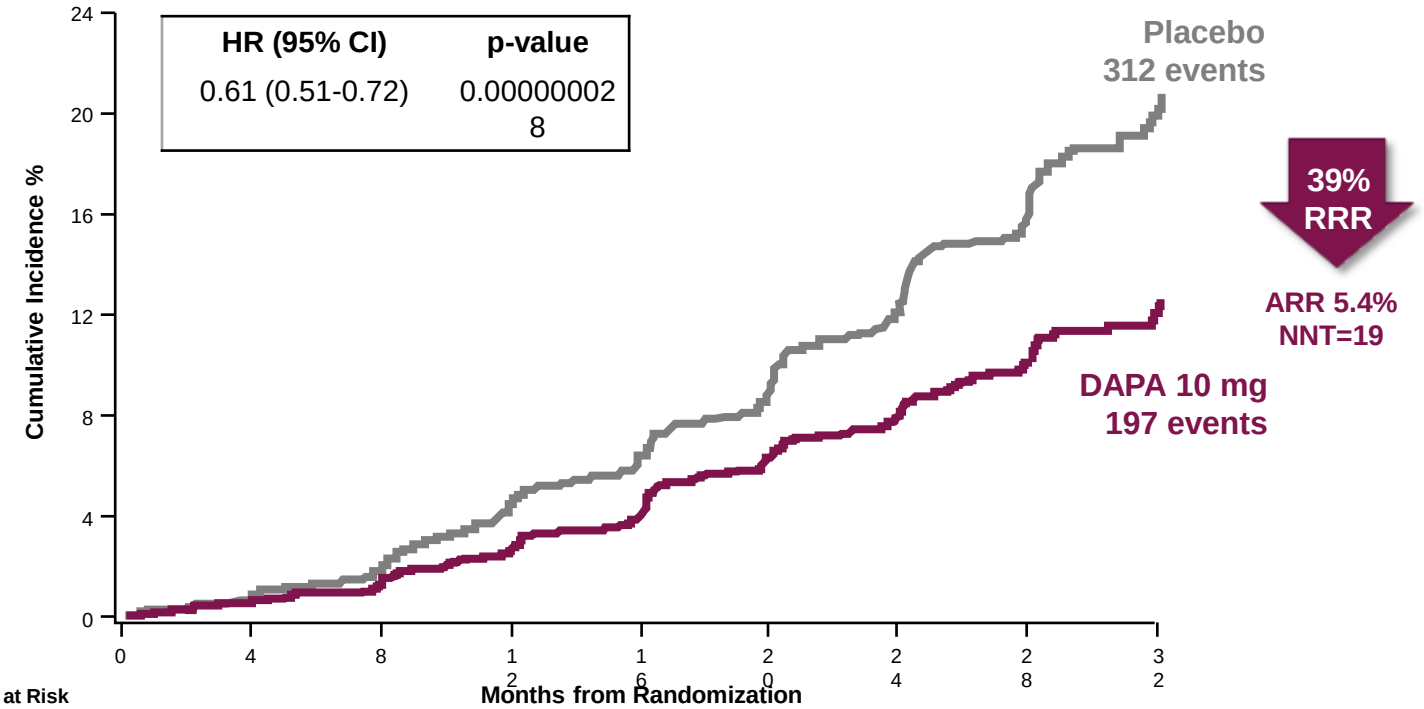
Etiology of CKD



HTN = hypertensive; IgA = immunoglobulin A; T2D = type 2 diabetes.

Wheeler DC et al. Online ahead of print. *Nephrol Dial Transplant*. 2020.

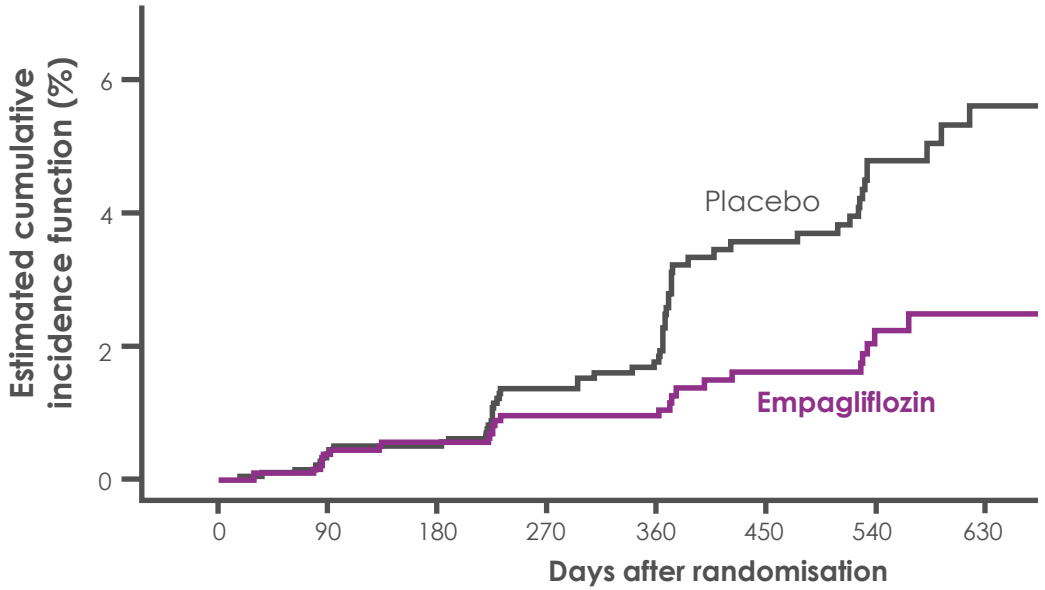
Primary Composite Outcome: Sustained ≥50% eGFR Decline, ESRD, Renal or CV Death[a]



[a]ESRD 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 ESRD when dialysis treatment was deliberately withheld for any reason.[2] CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal 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.

Composite renal endpoint (end-stage kidney disease or sustained profound decrease in eGFR)



Patients at risk

Placebo	1867	1592	1501	1136	1058	681	357	259
Empagliflozin	1863	1599	1532	1155	1062	687	391	276

RRR 50%

ARR 1.5%

HR 0.50
(95% CI 0.32, 0.77)

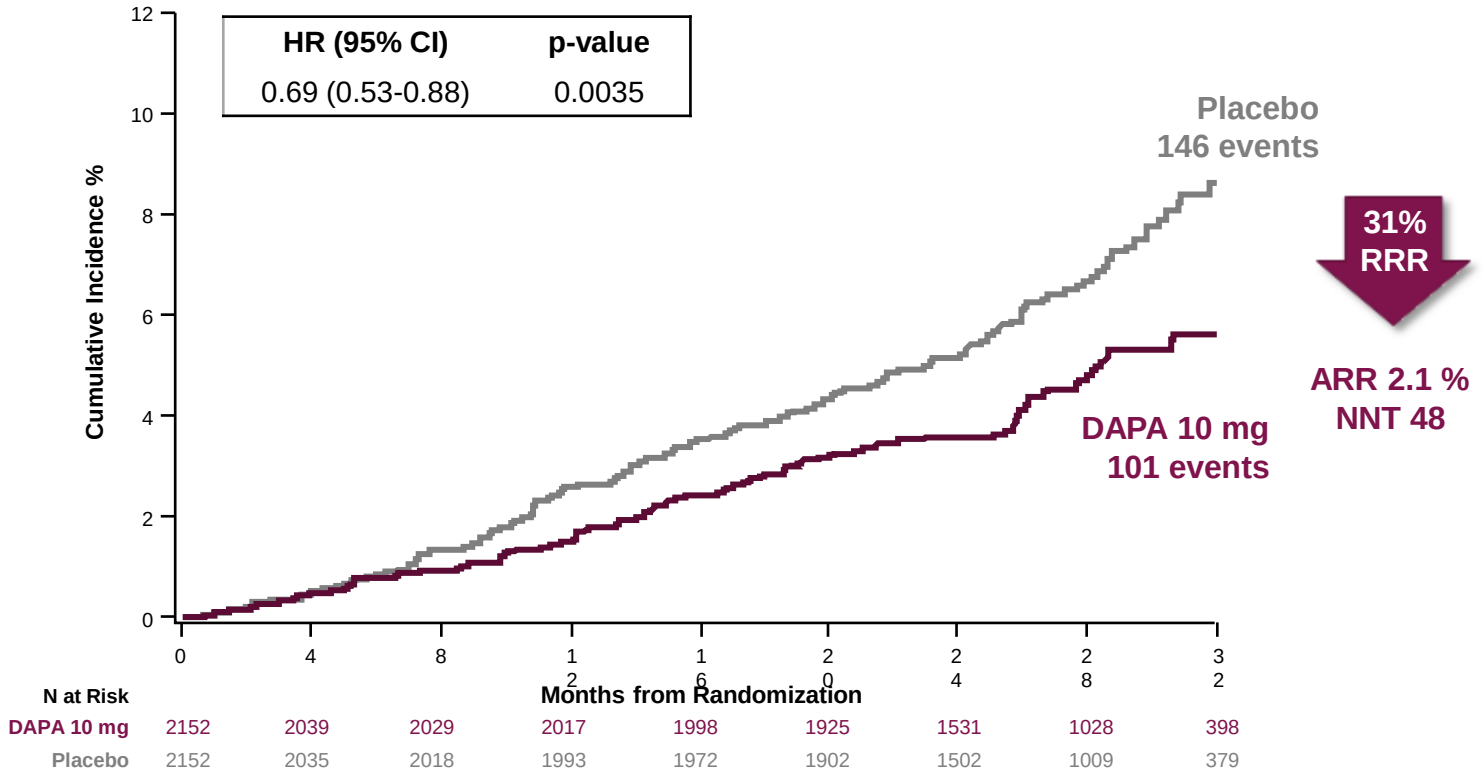
Empagliflozin:
30 patients with event
Rate: 1.6/100 patient-years
Placebo:
58 patients with event
Rate: 3.1/100 patient-years

Composite renal endpoint is defined as chronic dialysis, renal transplant, sustained reduction of ≥40% eGFR or sustained eGFR <15 ml/min/1.73 m^2 for patients with eGFR ≥30 ml/min/1.73 m^2 at baseline (<10 ml/min/1.73 m^2 for patients with eGFR <30 ml/min/1.73 m^2 at baseline). Dialysis is regarded as chronic if the frequency of dialysis is twice or more per week for at least 90 days. Cox regression model including covariates age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, and baseline LVEF. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; PY, patient years. ARR, absolute risk reduction; RRR, relative risk reduction

Packer M *et al. NEJM 2020* Aug 29. doi: 10.1056/NEJMoa2022190. Online ahead of print.

SC-GB-00245 Sept 2020

Secondary Outcome: All-cause Mortality

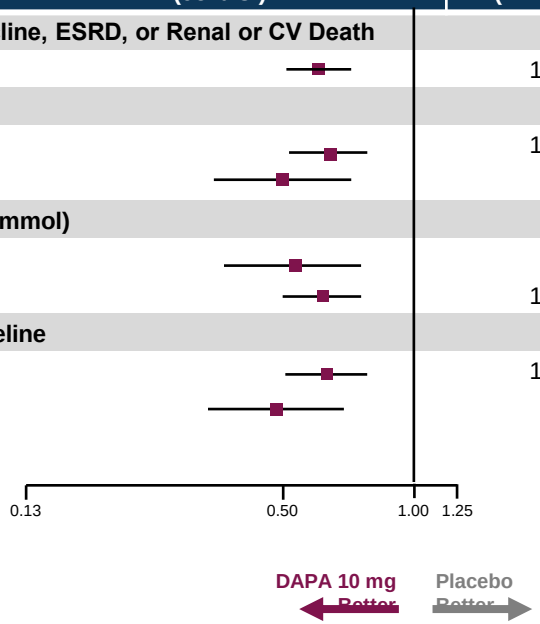


DAPA = dapagliflozin; HR = hazard ratio; RRR = relative risk reduction.

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

Primary Composite Outcome: Treatment Benefit Consistent Across Prespecified Subgroups

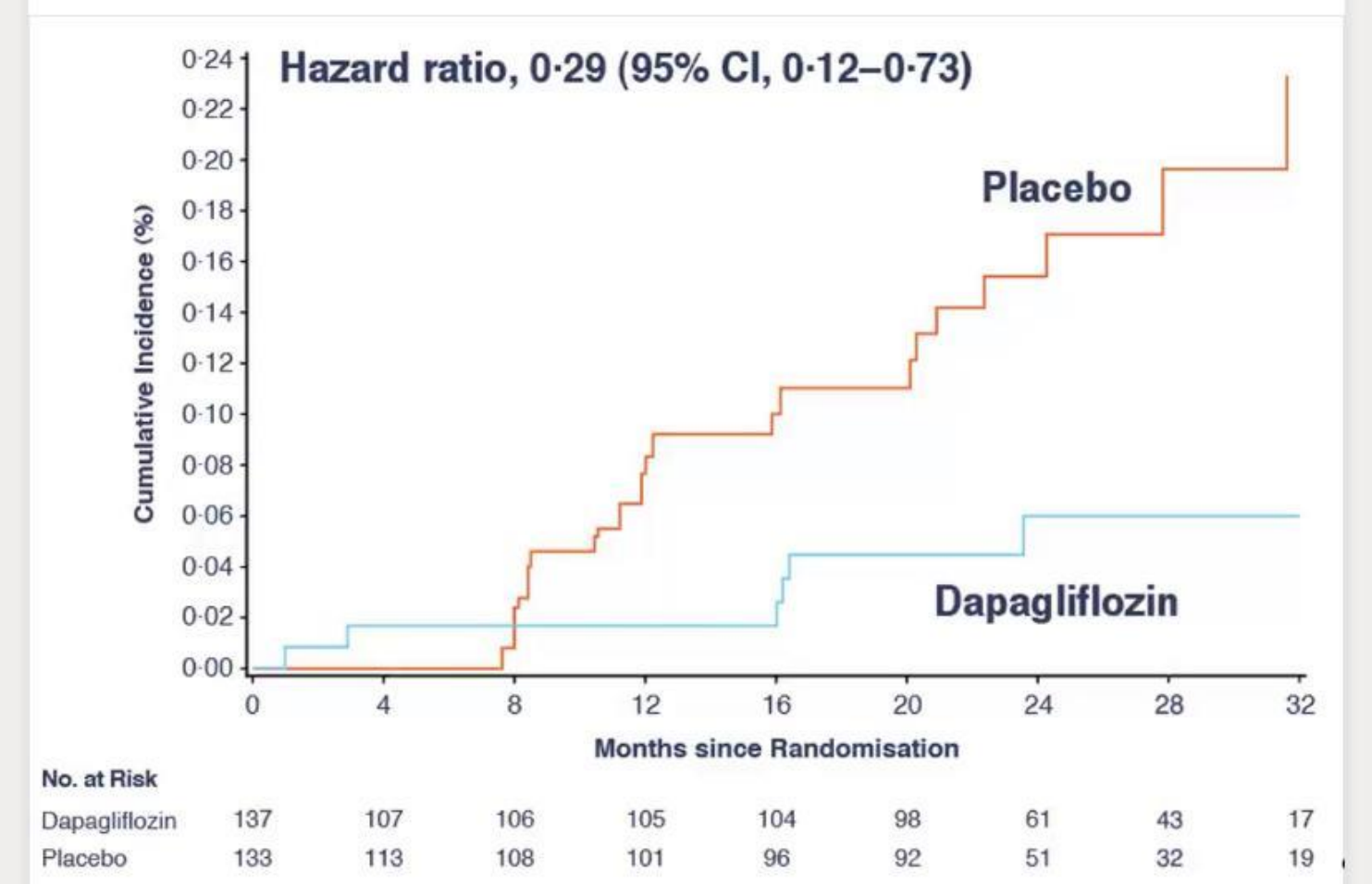
	Number of Events				
HR (95% CI)	DAPA 10 mg (N=2152)	Placebo (N=2152)	HR	95% CI	p-value Interaction
Composite of ≥50% eGFR Decline, ESRD, or Renal or CV Death					
All Patients	197	312	0.61	(0.51, 0.72)	
T2D at Baseline					0.24
Yes	152	229	0.64	(0.52, 0.79)	
No	45	83	0.50	(0.35, 0.72)	
UACR (mg/g) at Baseline (mg/mmol)					0.52
≤1000 (113)	44	84	0.54	(0.37, 0.77)	
>1000 (113)	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; ESRD = end-stage renal 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.

IgA Patients



Safety Outcomes

Safety Outcomes[a], n (%)	Dapagliflozin 10 mg (N=2149)	Placebo (N=2149)
Discontinuation of study drug	274 (12.8)	309 (14.4)
Discontinuation due to adverse event	118 (5.5)	123 (5.7)
Any serious adverse event	633 (29.5)	729 (33.9)
Adverse events of interest		
Amputation[b]	35 (1.6)	39 (1.8)
Any definite or probable diabetic ketoacidosis	0	2 (0.1)
Fracture[c]	85 (4.0)	69 (3.2)
Renal-related adverse event[c]	155 (7.2)	188 (8.7)
Major hypoglycemia[d]	14 (0.7)	28 (1.3)
Volume depletion[c]	127 (5.9)	90 (4.2)
Serious adverse events of volume depletion	22 (1.0)	18 (0.8)

[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]Adverse events with the following criteria confirmed by the investigator: i) symptoms of severe impairment in consciousness or behavior, ii) need of external assistance, iii) intervention to treat hypoglycemia, iv) prompt recovery of acute symptoms following the intervention

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

FORXIGA offers simple dosing and administration[1]

Convenient, once-daily dosing with no titration or dose adjustment required[a]

INITIATE treatment

GFR

≥15

There is limited experience with initiating treatment with dapagliflozin in patients with eGFR < 25 mL/min/1.73m2, and no experience with initiating treatment in patients with eGFR < 15 mL/min/1.73m2. Therefore, it is not recommended to initiate treatment with dapagliflozin in patients with eGFR < 15 mL/min/1.73m2 (see section 4.2).

Patients may continue on FORXIGA 10 mg once daily if eGFR falls below 15 mL/min/1.73 m^2

If GFR falls below 45 mL/min, additional glucose-lowering treatment should be considered in patients with diabetes mellitus for whom further glycaemic control is needed

DRAFT SPC information submitted for regulatory approval

[a] In patients with severe hepatic impairment, a starting dose of 5 mg is recommended. If well tolerated, the dose may be increased to 10 mg

CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; hHF, hospitalisation for heart failure; T2D, Type 2 diabetes

1. AstraZeneca AB. FORXIGA (dapagliflozin) SmPC. Available at: https://www.medicines.org.uk/emc/product/7607/smpc#gref (Accessed July 2021).

forxiga
(dapagliflozin)

SGLT2 I and clinical effectiveness

- The glycaemic efficacy of SGLT2 I **is dependent on kidney function** and efficacy is reduced in patients with eGFR <60 and unlikely to have any glycaemic lowering effect at eGFR <30

*Summary of product characteristics Canagliflozin, Empagliflozin and Dapagliflozin

SGLT2 I and clinical effectiveness

- The glycaemic efficacy of SGLT2 I **is dependent on kidney function** and efficacy is reduced in patients with eGFR <60 and unlikely to have any glycaemic lowering effect at eGFR <30
- The cardio renal beneficial efficacy of SGLT2I **is not dependent on kidney function** and continues at GFRs at which there is very little glycaemic efficacy

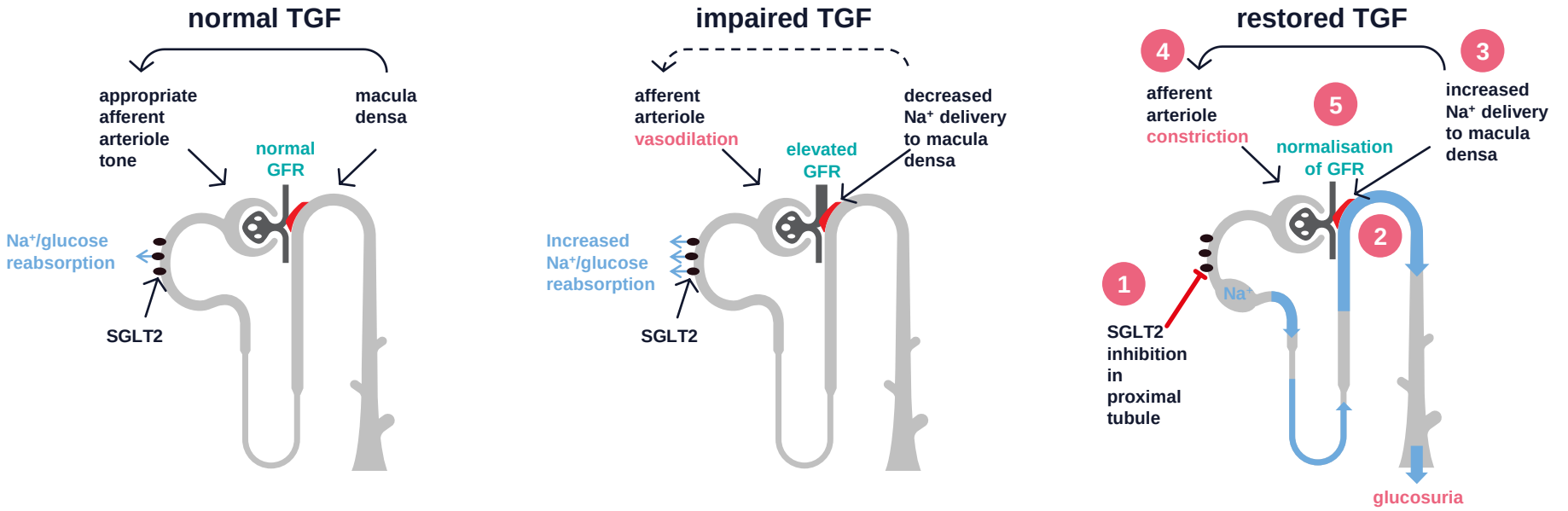
*Summary of product characteristics Canagliflozin, Empagliflozin and Dapagliflozin

Mechanisms

- Weight, BP (Not HbA1C)
- Tubuloglomerular feedback

SGLT2 inhibition – proposed mechanism for renal benefits

TGF: tubuloglomerular feedback



Normal physiology

Hyperfiltration in diabetes

SGLT2 inhibition reduces hyperfiltration via TGF

Adapted from Cherney, et al., 2014

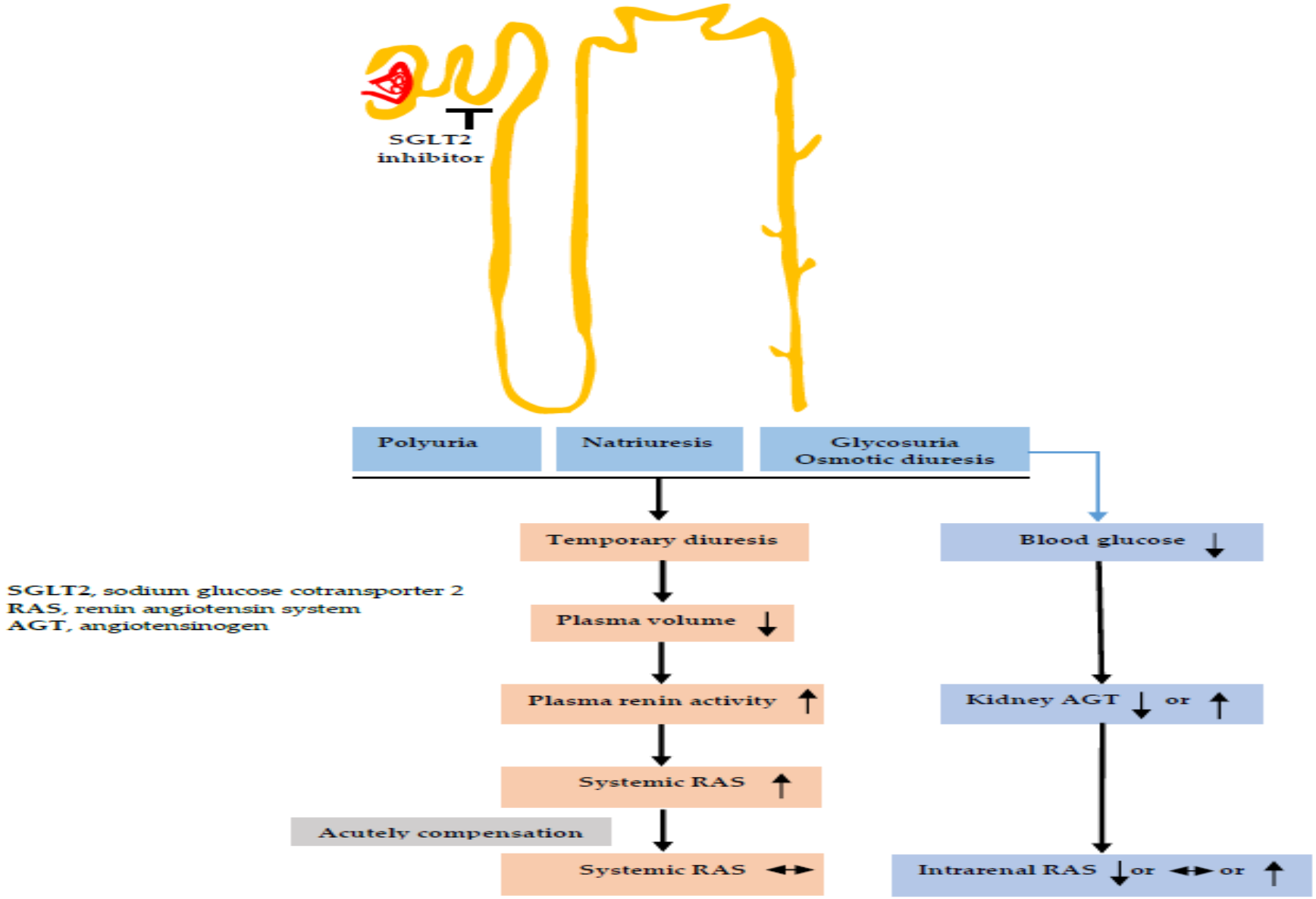
SGLT2: Sodium-glucose co-transporter 2; GFR: glomerular filtration rate.

Cherney, DZ, et al. Circulation 2014;129:587-97.

NAPP DIABETES

Mechanisms

- Weight, BP (Not HbA1C)
- Tubulo glomerular feedback
- Glorified diuretic



Ansary T *Int. J. Mol. Sci.* **2019**, *20*(3), 629;

Mechanisms

- Weight, BP (Not HbA1C)
- Tubulo glomerular feedback
- Glorified diuretic
- Distal renal tubular hypertrophy and hyperplasia
- Beta Blocker of the kidneys (Gilbert R Lancet Diab and Endo Vol 4 Issue 10 P814 2016)
- Na H exchanger inhibition (Packer Circulation 2017 137 1548)
- Podocyte stabilisation - SGLT2 on podocytes and reduction in podocyte damage in mouse proteinuric non-diabetic nephropathy (Cassis JCI insight 2018)
- Shifting fuel metabolism to ketones and lipids (Packer Diab Care 2020 43 508-511)

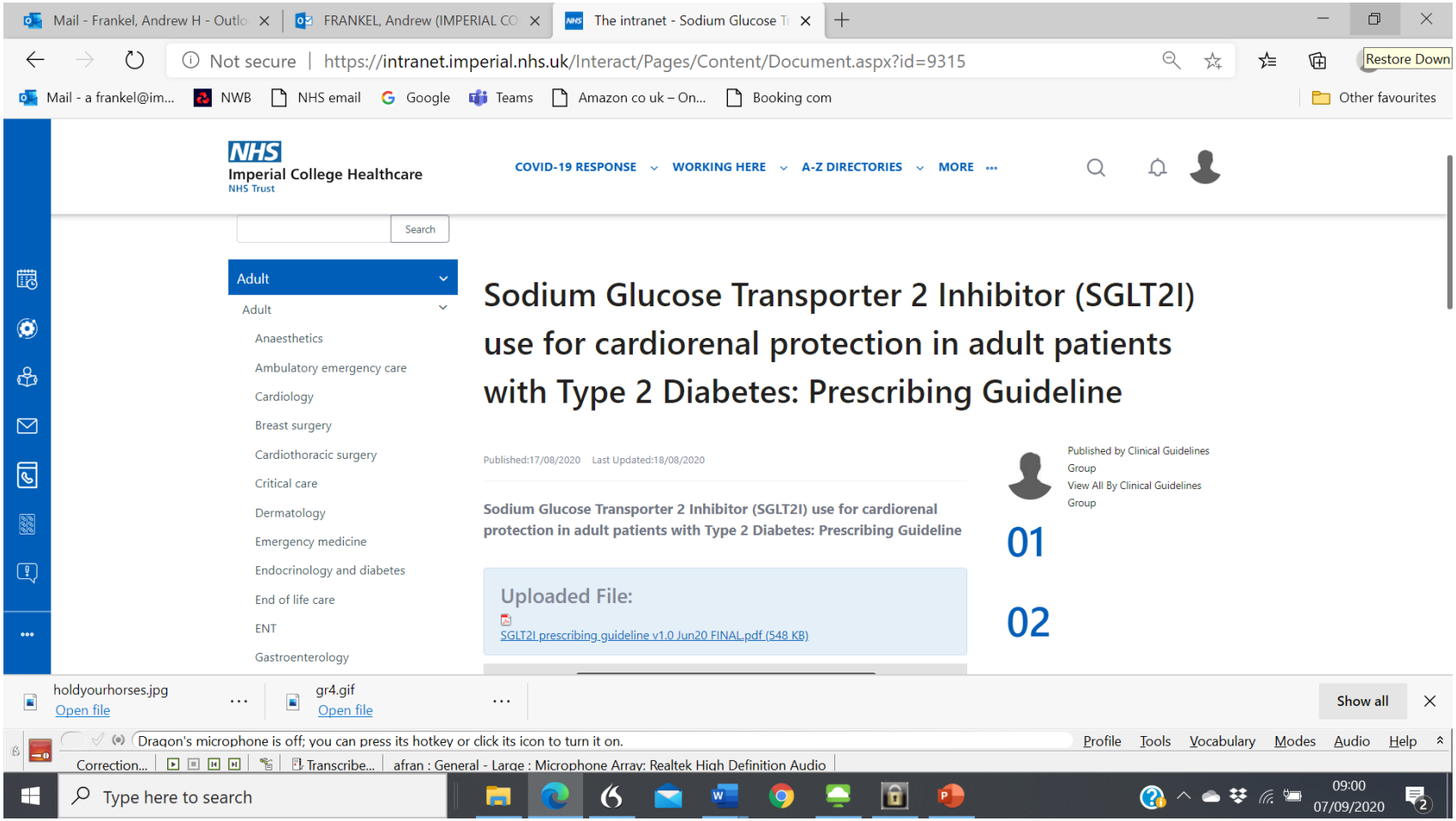
Using SGLT2I

- Licences for SGLT2I still predominantly glucocentric
- Canagliflozin can now be initiated in patients with T2DM and albuminuria down to an eGFR of 30 and continued thereafter to ESKF
- Dapagliflozin can now be used as treatment for patients with CKD irrespective of diabetes status

Hold your horses

- Licences for SGLT2I still predominantly glucocentric
- Canagliflozin can now be initiated in patients with T2DM and albuminuria down to an eGFR of 30 and continued thereafter to ESKF
- Dapagliflozin can now be used as treatment for patients with heart failure irrespective of diabetes status

SGLT2I Safe Prescribing and PIS



https://intranet.imperial.nhs.uk/Interact/Pages/Content/Document.aspx?id=9315

Cautions 1

Imperial College Healthcare NHS Trust

1. Frail elderly

2. Potential for pregnancy

3. SGLT2I should **not** be prescribed in people with type I diabetes or people with type 2 diabetes who may be at greater risk of **euglycaemic** diabetic ketosis. These individuals can still receive SGLT2Is but they should **only** be prescribed under clear direction of a diabetologist.

- Generally, most individuals will have a very low risk of this complication particularly if they are following good sick day guidance.

- Those to be aware of are those who have low beta cell functional reserve:

    a. People who have rapidly progressed to requiring insulin (within one year of diagnosis)

    b. Past history of DKA

    c. History of pancreatic disease – including alcoholic pancreatitis as a cause of their diabetes

    d. BMI <27

    e. The possibility of Latent Autoimmune Diabetes in Adults

Cautions 2

Imperial College Healthcare NHS
NHS Trust

1. Sick day guidance
2. Reiterate that if on an SGLT2I very low carbohydrate diets (or ketogenic diets) carry an increased risk of ketosis
3. In people with reasonable glycaemic control and risk of hypoglycaemia consider reducing other hypoglycaemic inducing agents when introducing SGLT2i
4. In people on diuretics consider reducing the dose
5. Give advice on the need to seek medical attention (via GP, pharmacy or urgent care centre) should they develop symptoms of a genital infection.
6. Caution is advised if the person has active peripheral vascular disease including active arterial ulceration or claudication – advice should be given on foot care
7. Even though there is no reported increased risk of UTIs with SGLT2I, care should be taken patients who may have significant lower urinary tract abnormalities or complex stones.

Imperial College Healthcare NHS
NHS Trust

Key messages

- The number of people with diabetes developing chronic kidney disease (CKD) and leading to end stage kidney failure is set to progressively increase over the next 10 years and poses challenges for the healthcare community alike
- Diabetic kidney disease carries a significant risk in relation to morbidity and mortality which is most particularly expressed in the form of cardiovascular disease
- There had been no advances made in relation to the management of patients with diabetic kidney disease since the late 1990s when inhibition of the renin angiotensin aldosterone system (RAASi) was demonstrated to provide benefit in patients with proteinuric CKD.
- There is emerging and compelling evidence now to support significant benefit for people with DKD (and indeed other forms of CKD) from sodium glucose co-transporter (2) inhibitors (SGLT2I)