SGLT2i , Diabetes and CKD care
How do we change practice

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Disclosures… Perspectives

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- Grant funding:
  - Kidney Foundation of Canada (KFOC)
  - Canadian Institute of Health Research (CIHR)
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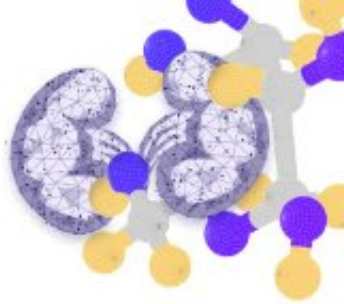
- Steering committee / DSMB
  - CREDENCE, EMPA-KIDNEY
  - NIH: Kidney Precision Medicine Project; HiLO Project
  - RESOLVE (Australian Kidney Trials Network)
  - Reata Scientific Committee
  - Gilead National Lead DKD and CKD – selonsertib)
  - Certa Therapeutics – Scientific Advisory Committee
- Participation in SGLT2 inhibitor trials
  - CREDENCE
  - DAPA-CKD
  - DIAMOND
  - EMPA-KIDNEY

Learning Objectives : Improved understanding of

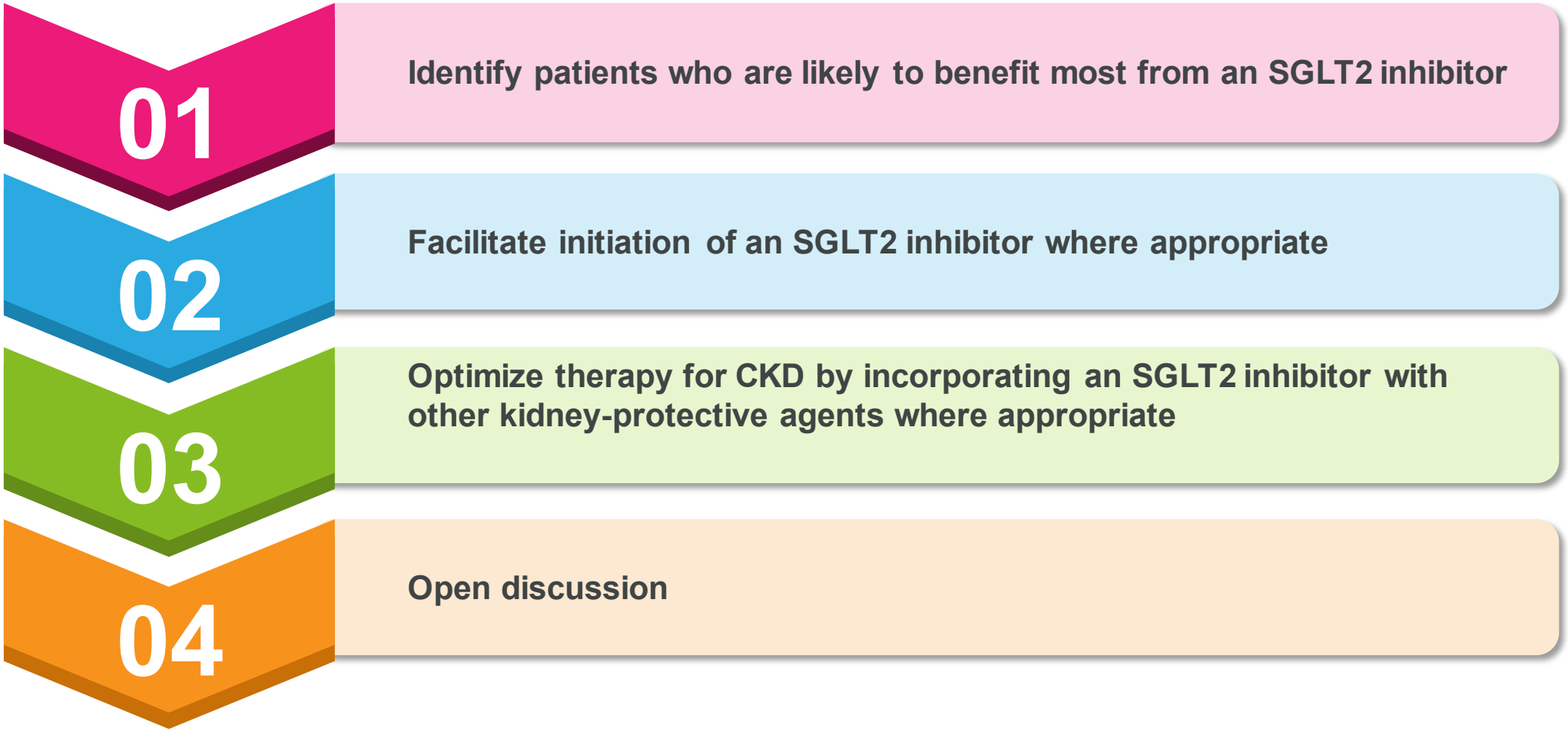


Mechanism of action of SGLT2i in protection of kidney and CV disease

Clinical trial data in different CKD populations to support use of SGLT2i

Side effects and caveats for use of SLGT2i in clinical practice.

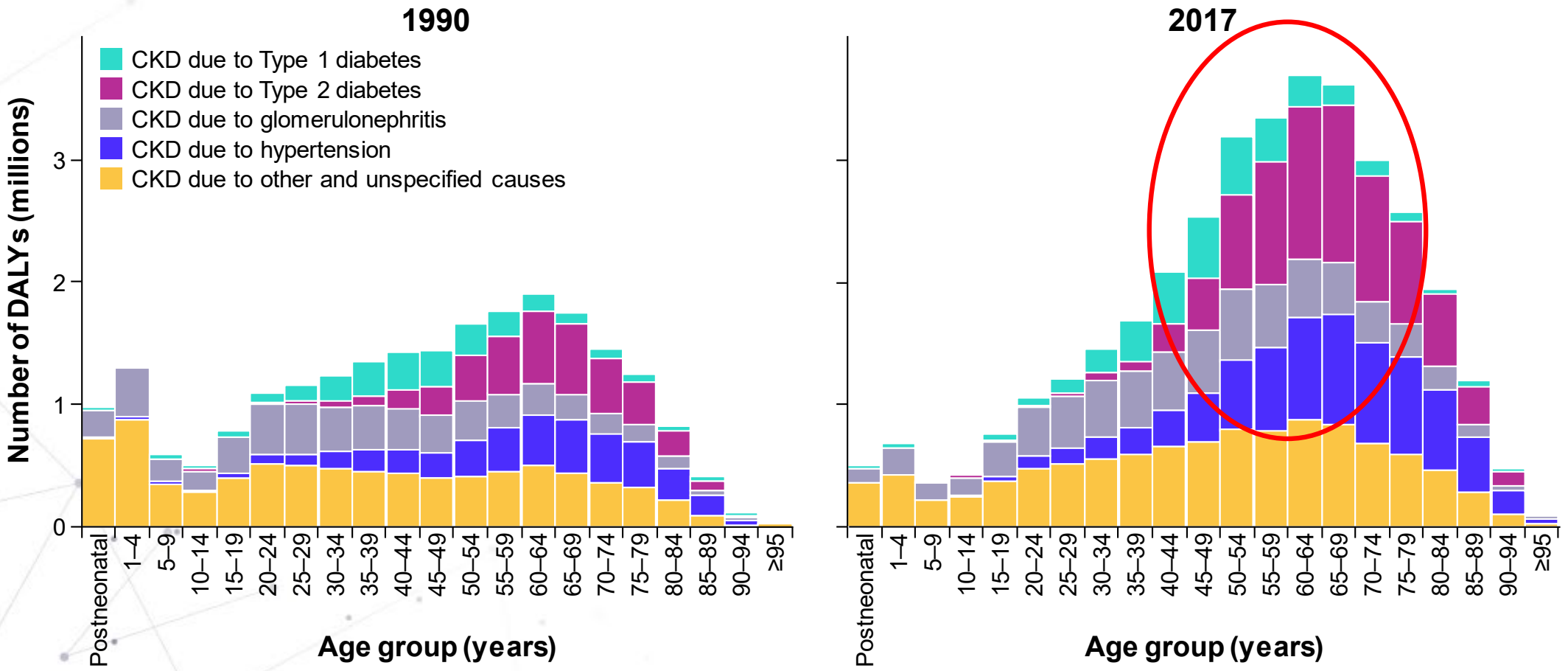
Translating improved understanding to clinical practice



CKD, chronic kidney disease; SGLT2, sodium–glucose co-transporter 2

Productive Life Years Lost Due to Premature Death or Disability in CKD

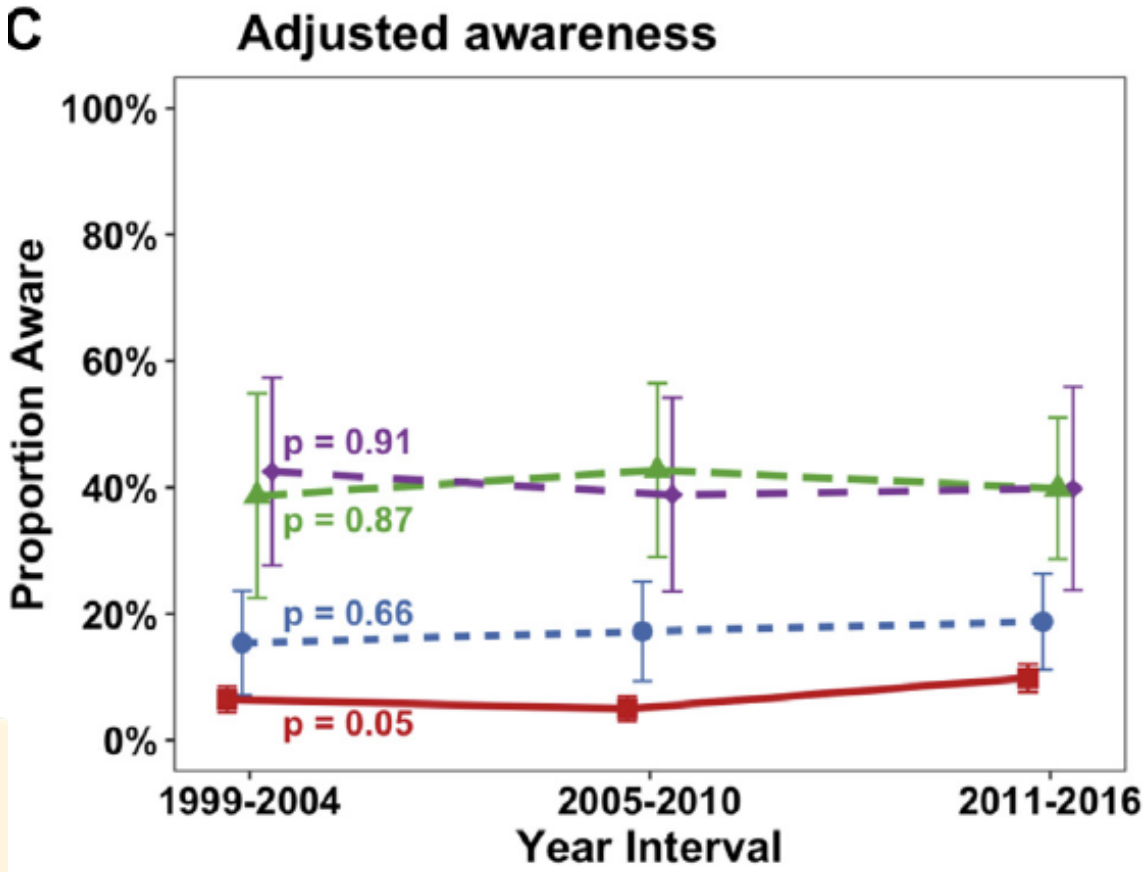
Better care for CKD is urgently needed



DALY, disability-adjusted life-year

Chronic Kidney Disease Collaborative. *Lancet* 2020;395:709–733

LOW RATES OF CKD AWARENESS AND DETECTION IN THE CURRENT ERA



Chu CD *et al. Am J Kidney Dis* 2020;76:174-183

Detection

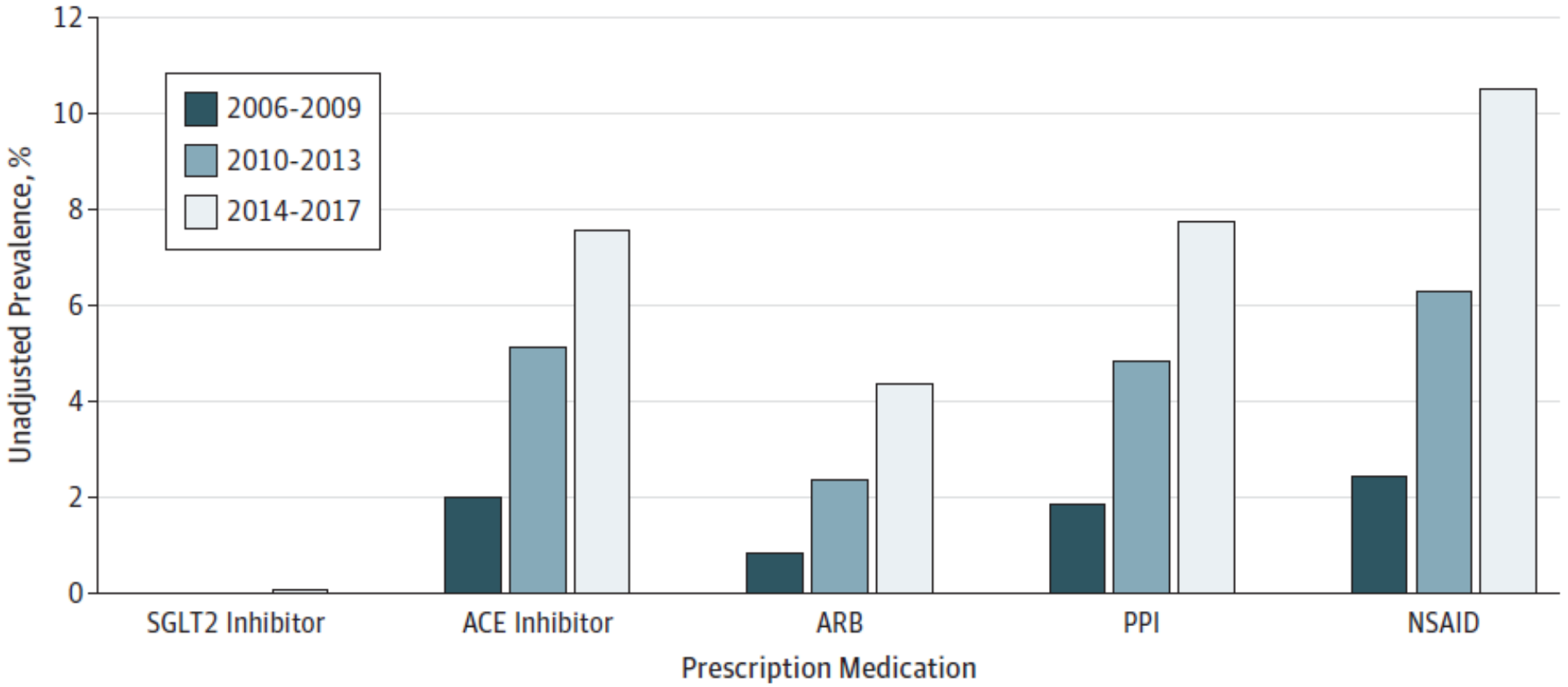
In two large US healthcare systems with a cohort of 2.6 million between 2006 and 2017, albuminuria/proteinuria was measured in 15% of patients with diabetes and CKD and in 5% of patients with diabetes and no CKD.

Risk of ESKD

- <2%
- 2% to <5%
- 5% to <15%
- ≥15%

Tuttle KR *et al. JAMA Netw Open* 2019;2:e1918169
Providence St. Joseph Health and UCLA Health

Medication Use in CKD Stages 3-5 ND Two Large US Healthcare Systems (N=660,000)



Diabetes with CKD and hypertension: ACE Inhibitor or ARB use 25%

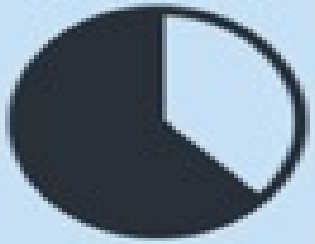
Tuttle KR *et al. JAMA Network Open* 2019;2:e1918169

Analysis of the Global Burden of Disease study highlights the global, regional, and national trends of chronic kidney disease epidemiology from 1990 to 2016

Incidence	Prevalence	Death due to CKD	Disability Adjusted Life Years (DALYs)
↑ 89% to 21 million	↑ 87% to 276 million	↑ 98% to 1.2 million	↑ 63% to 35 million

Drivers of ⊠ DALYs: Population Growth; Aging; Diabetes

Age-standardized DALYs rate



63% of burden in low and low-middle income countries

Conclusion: The global toll of CKD is significant, rising, and unevenly distributed; it is primarily driven by demographic expansion and in some regions significant tide of diabetes epidemic.

ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

Xie et al. Kidney International, 2018

Prevalence of Chronic Kidney Disease: Canada

- 1 in 10 Canadians has chronic kidney disease…4 million[1]
- The number of Canadians living with Kidney failure has grown 35% since 2008[2]
- Diabetes is the leading cause of kidney failure at 39%[2]
- 46% of new kidney failure patients are under the age of 65[2]
- Nearly 49,000 Canadians are being treated for kidney failure[2]
  - 57.5% are on dialysis
  - 42.5% have a functioning transplant
- In 2016 kidney disease was the 11th leading cause of death in Canada[3]

Adapted from The Kidney Foundation of Canada 2019 "Facing the Facts About Kidney Disease"

1. Manns B *et al,* The financial impact of advanced kidney disease on Canada Pension Plan and private disability insurance costs. *Canadian journal of kidney health and disease*. 2017 (4):1-11
2. Canadian Institute for Health Information's CORR Annual Statistics on organ replacement in Canada: dialysis, transplantation and Donation, 2008-2017 (excludes Quebec)
3. Statistics Canada. 2016

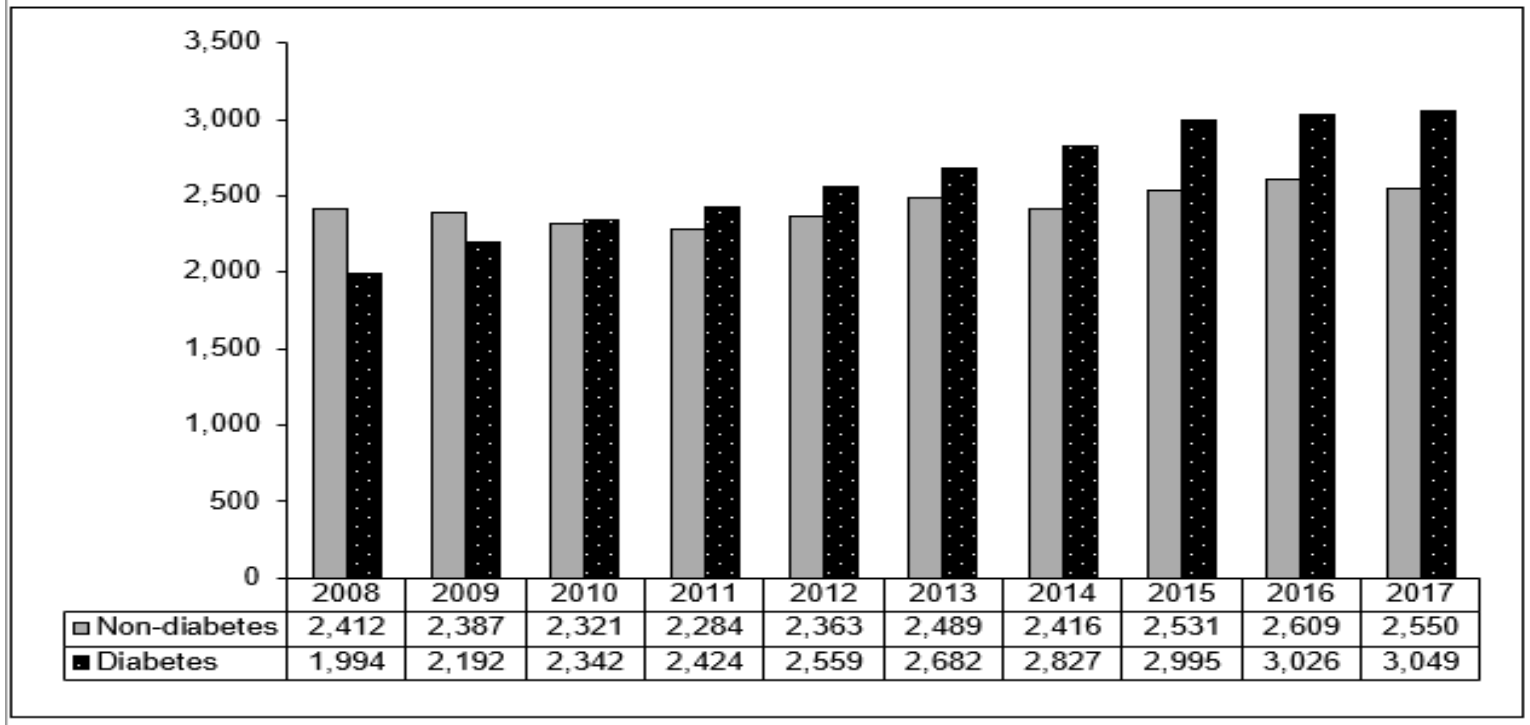
Economic impact of kidney disease

- Dialysis is the most common treatment for kidney failure and costs the health care system approximately $100,000/patient/year
- Out-of-pocket costs associated with dialysis can amount to 12.5% of a patient's income
- CKD costs the Canadian Health Care System ~ $50 billion/year
- CKD patients are less likely to be employed
  - Productivity losses
  - Additional CPP and private insurance costs of nearly **$1 billion/year**

Adapted from The Kidney Foundation of Canada 2019 "Facing the Facts About Kidney Disease"
Manns B, McKenzie S, Au F, Gignac P, Geller L. The Financial Impact of Advanced Kidney Disease on Canada Pension Plan and private disability insurance costs. CJKHD 2018

Current Canadian data describes Dialysis/ Kidney Failure due to DM growing

Figure 3 Incident end-stage kidney disease patients, with and without diabetes, Canada (excluding Quebec), 2008 to 2017 (number)

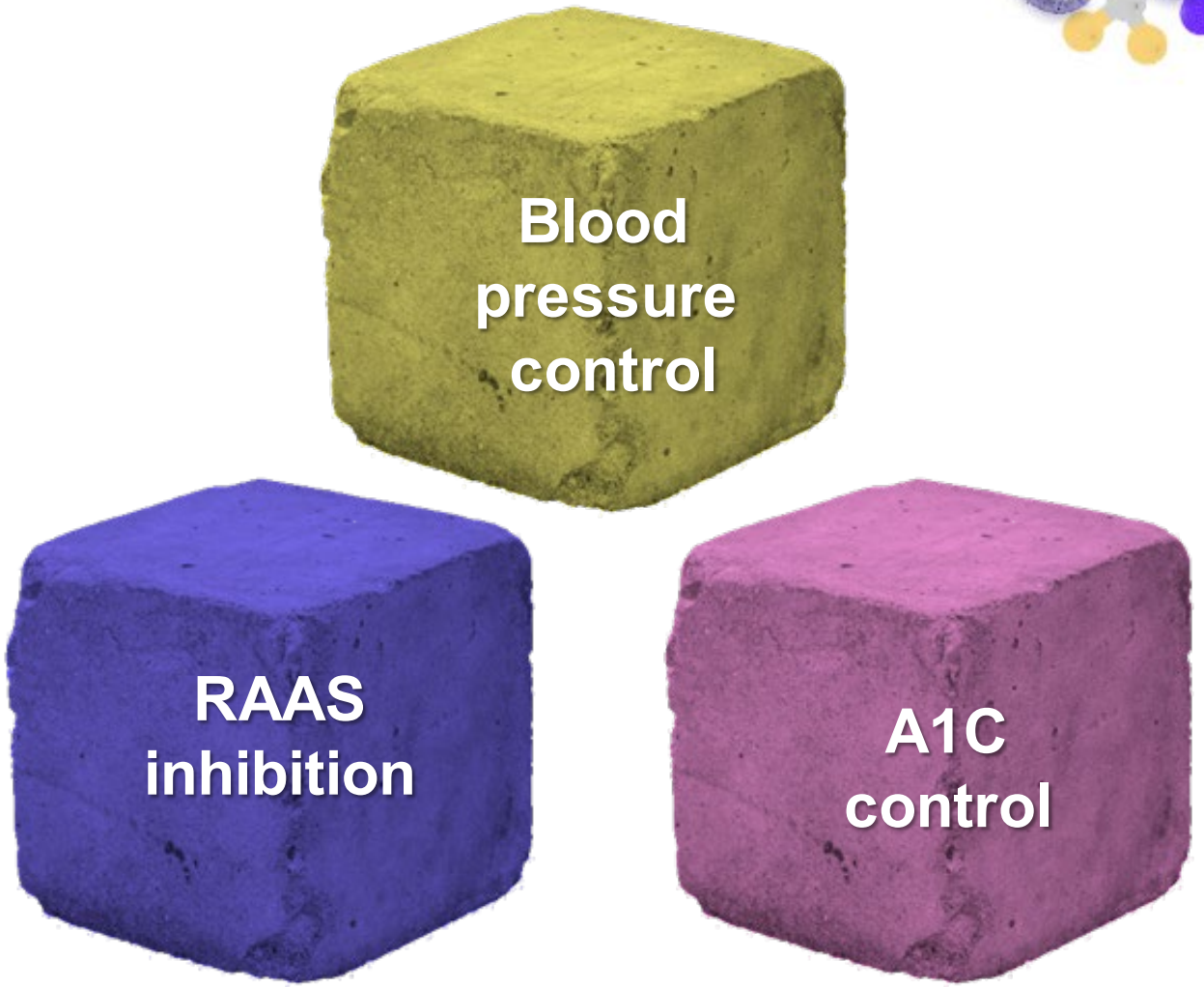


	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Non-diabetes	2,412	2,387	2,321	2,284	2,363	2,489	2,416	2,531	2,609	2,550
Diabetes	1,994	2,192	2,342	2,424	2,559	2,682	2,827	2,995	3,026	3,049

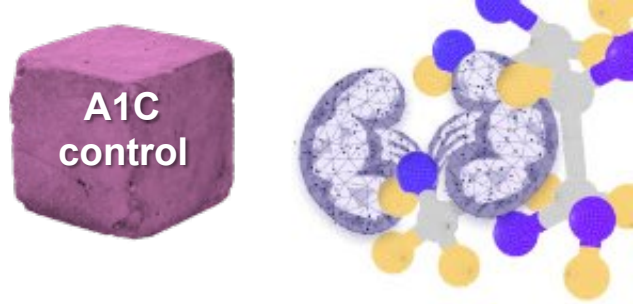
Patient diabetes status	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Non-diabetes	2,412	2,387	2,321	2,284	2,363	2,489	2,416	2,531	2,609	2,550
Diabetes	1,994	2,192	2,342	2,424	2,559	2,682	2,827	2,995	3,026	3,049

Note
Data from Quebec was not included because of significant under-reporting between 2011 and 2017.
Source
Canadian Organ Replacement Register, 2018, Canadian Institute for Health Information.

Until recently, the standard of care for CKD in patients with diabetes was based on 3 “cornerstone” treatments



But control of blood sugar has limitations with respect to some patient outcomes



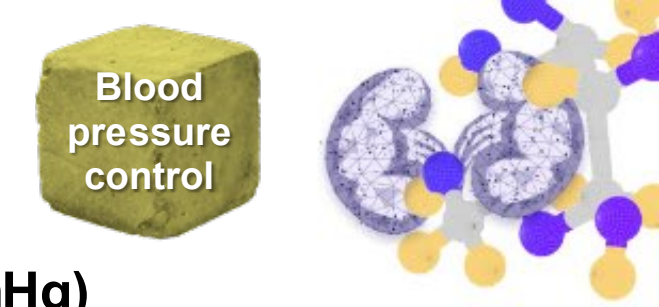
Patients who received intensive glycemic control did not seem to obtain protection against cardiovascular events[1]

Intensive treatment of A1C with targets ≤6% may increase risk of CV events and mortality for patients unable to achieve those targets[2]

While reductions in kidney events associated with A1C control are statistically and clinically significant, substantial residual risk remains

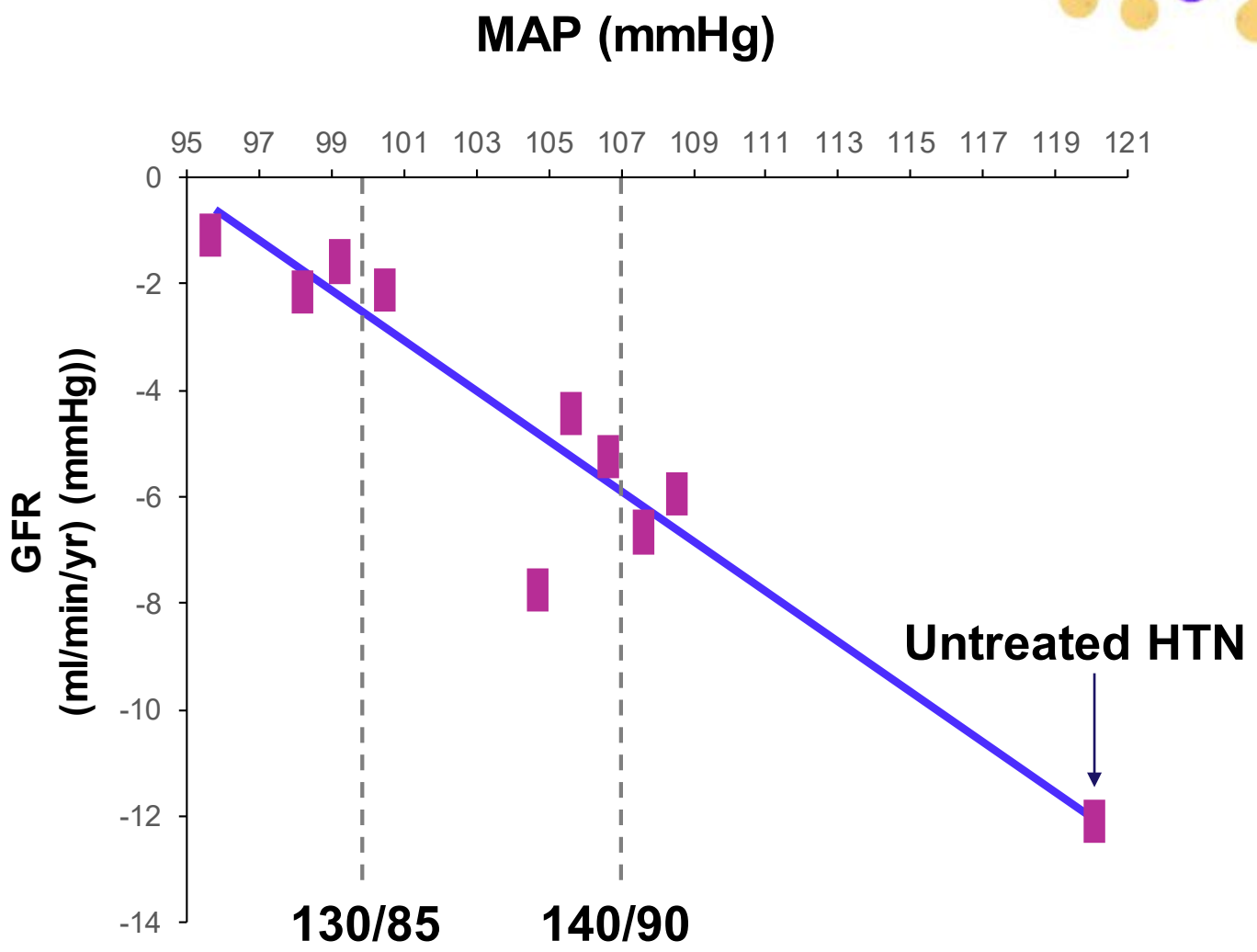
1. Diabetes Canada Clinical Practice Guidelines Expert Committee. Can J Diabetes. 2018 Apr;42 Suppl 1:S201–S209
2. Riddle et al. Diabetes Care. 2010; 33:983-990

Blood Pressure Control



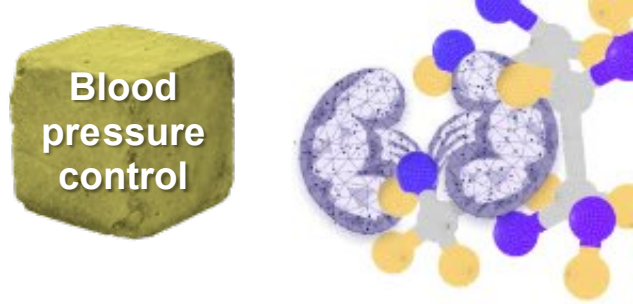
Studies in the 1990s showed that improved blood pressure control slowed eGFR decline

- Untreated hypertension:
  -10 to -12 mL/min/1.73 m^2/year
- Controlled hypertension:
  -5 to -6 mL/min/1.73 m^2/year



Bakris GL J. Clin Hypertens 1999 Oct;1(2): 141-147
Slide adapted from A. Steele

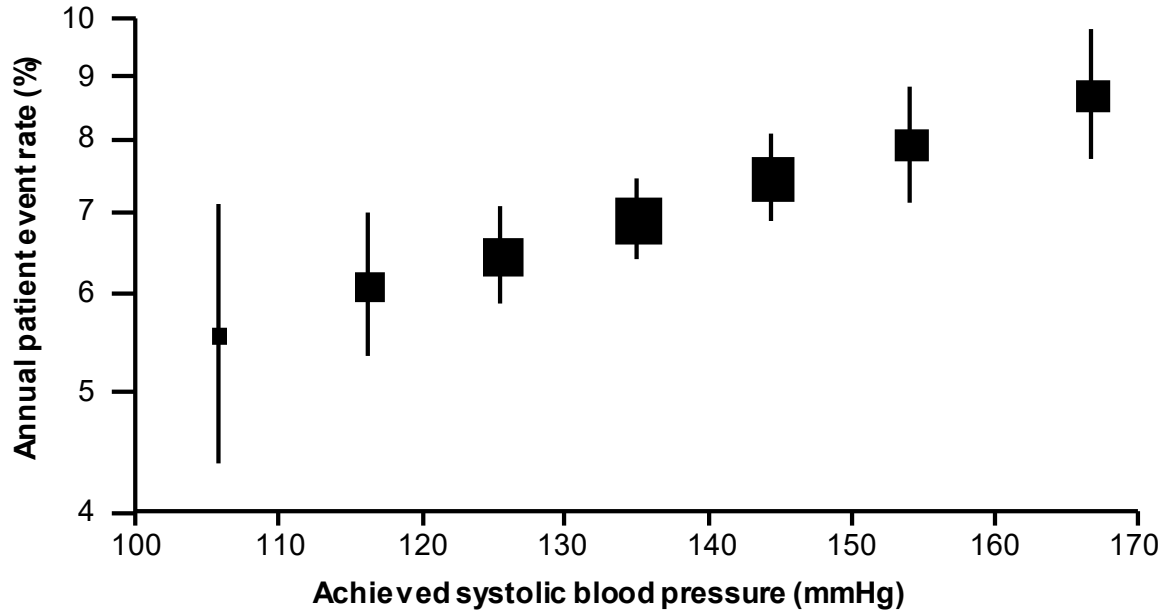
Blood Pressure Control



Analysis of achieved BP in the ADVANCE trial demonstrated a relationship between blood pressure and risk of renal events regardless of medication[1]

- Similar results were seen in an analysis from the IDNT trial[2]

Relationship between systolic blood pressure and risk of kidney events[1]

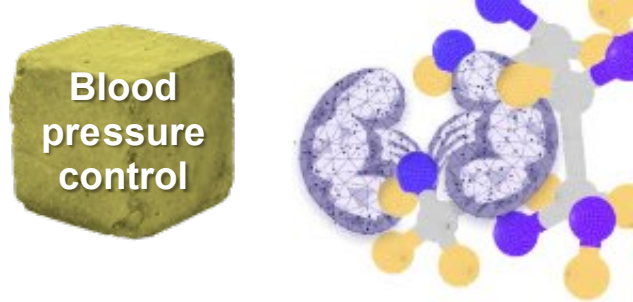


Median systolic blood pressure (mmHg)	106	116	125	135	144	154	168
No of person-years	1431	4266	9874	11983	9138	4942	3470

Composite of new-onset microalbuminuria (UACR 3.34 to 33.4 mg/mmol), new-onset macroalbuminuria (UACR >33.4 mg/mmol), doubling of serum creatinine to >200 µmol/L, or end-stage kidney disease (RRT or renal death)

1. de Galan et al. J Am Soc Nephrol. 2009; 20(4):883-892.
2. Pohl et al. J Am Soc Nephrol 16: 3027–3037, 2005.

But there are limitations to the impact of BP Control



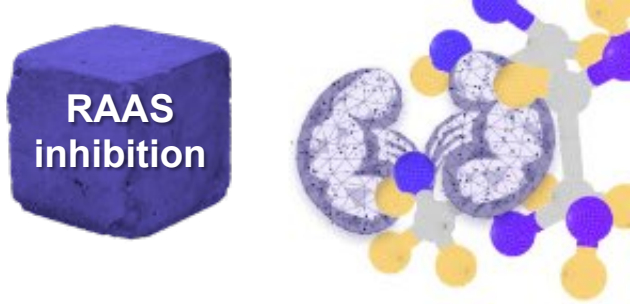
67% of Canadians with diabetes have hypertension, and 40% are not controlled[1]

Most studies have demonstrated benefits on albuminuria rather than renal function or incidence of ESRD[2]

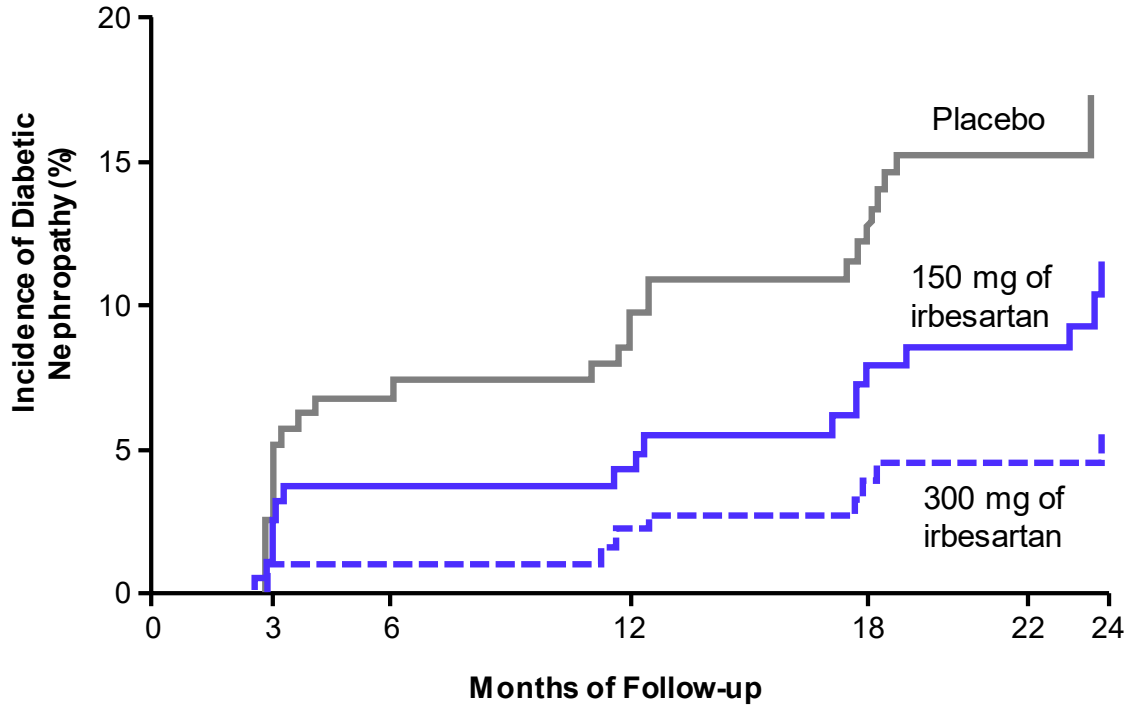
Again, substantial residual risk remains

1. Padwal et al. Can J Cardiol. 2016;32(5):687-94.
2. Diabetes Canada Clinical Practice Guidelines Expert Committee. Can J Diabetes. 2018 Apr;42 Suppl 1:S201–S209

RAAS Inhibition



- Trials of RAAS inhibitors in patients with T2D and albuminuria (3-30 mg/mmol) demonstrated a reduction in progression to overt nephropathy



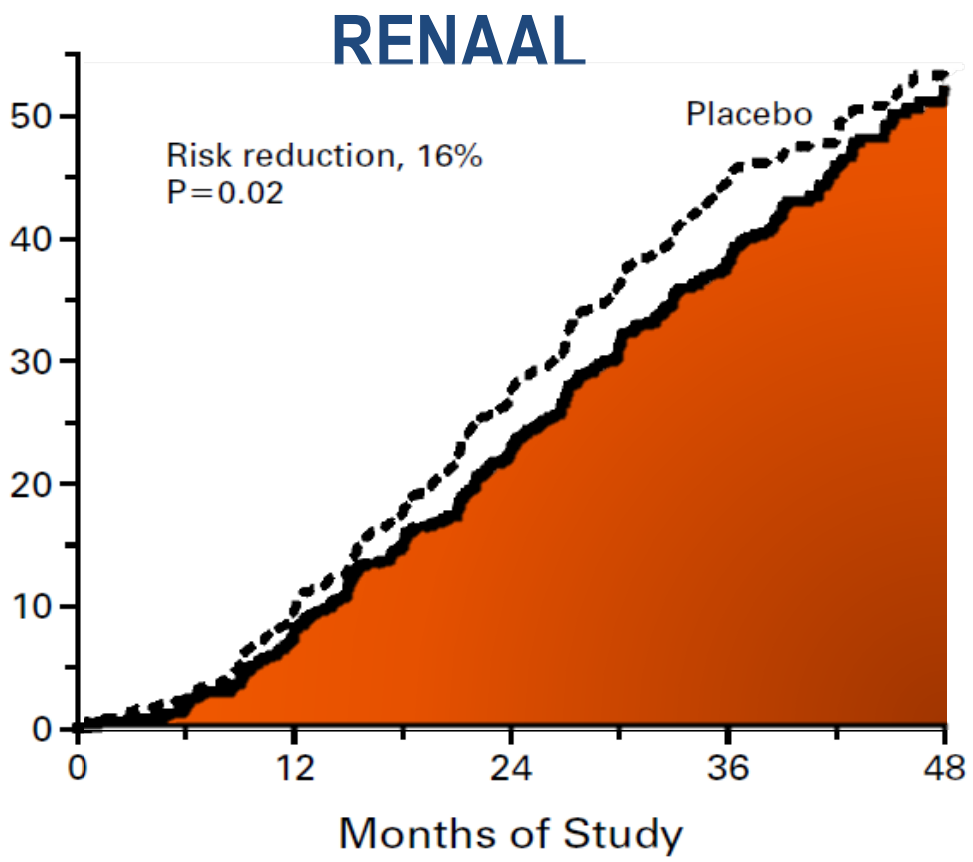
No. at Risk

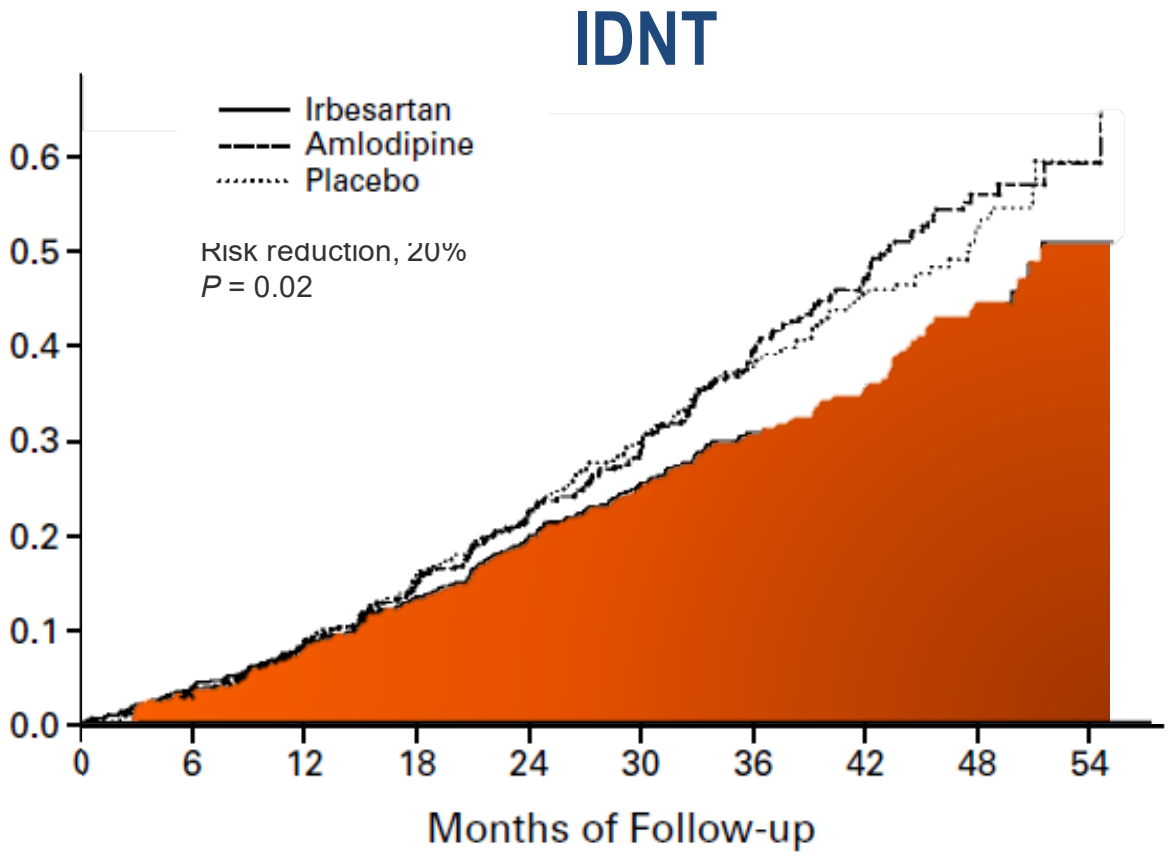
Placebo	201	201	164	154	139	129	36
150 mg of irbesartan	195	195	167	161	148	142	45
300 mg of irbesartan	194	194	180	172	159	150	49

Parving et al. N Engl J Med 2001; 345:870-878

Considerable residual renal risk still exists with current gold standards of care

Doubling of serum creatinine, ESKD, or death

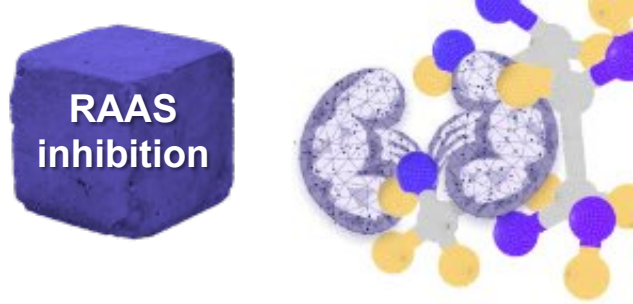




Brenner B, et al. *N Engl J Med*. 2001;345(12):861-869.

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

RAAS Inhibition has limitations (and some pts don't tolerate them)



RAAS inhibition did not seem to provide protection against cardiovascular events[1,2]

No benefits on mortality were observed[1]

While risk reductions are additive to those obtained with blood pressure control, patients with T2D and CKD remain at risk for renal and CV events

1. Brenner BM, et al New Engl J Med. 2001; 345:861-69.
2. Parving et al. N Engl J Med 2001; 345:870-878

Summary

A1C control, blood pressure control, and RAAS inhibition represent a solid foundation for treatment of patients with CKD and T2D

While these are all critical components of the standard of care, there remain important unmet needs for our patients

We can improve the lives of our patients by building further upon this foundation

Changing clinical practice : The SGLT2 inhibitor story

STUDIES IN SGLT2I

DESIGN

RESULTS CONCLUSIONS

WHY IMPACTFUL

LIMITATIONS, DOWN SIDES

SGLT2 inhibitors : new class of drugs

- CANA glaflozin
- DAPA glaflozin
- EMPA glaflozin

The first SGLT antagonist - Phlorizin

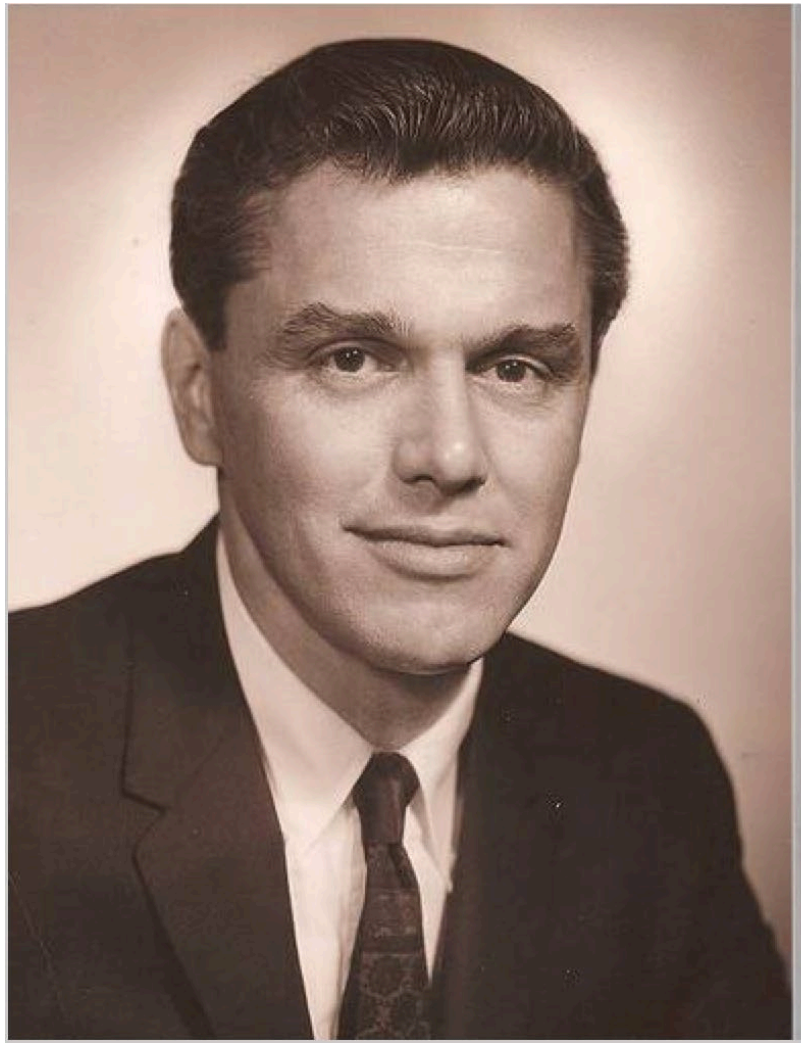
Phlorizin is a natural compound first isolated from the bark of apple trees by French chemists in 1835 and has been used to study diabetes and renal function for decades.

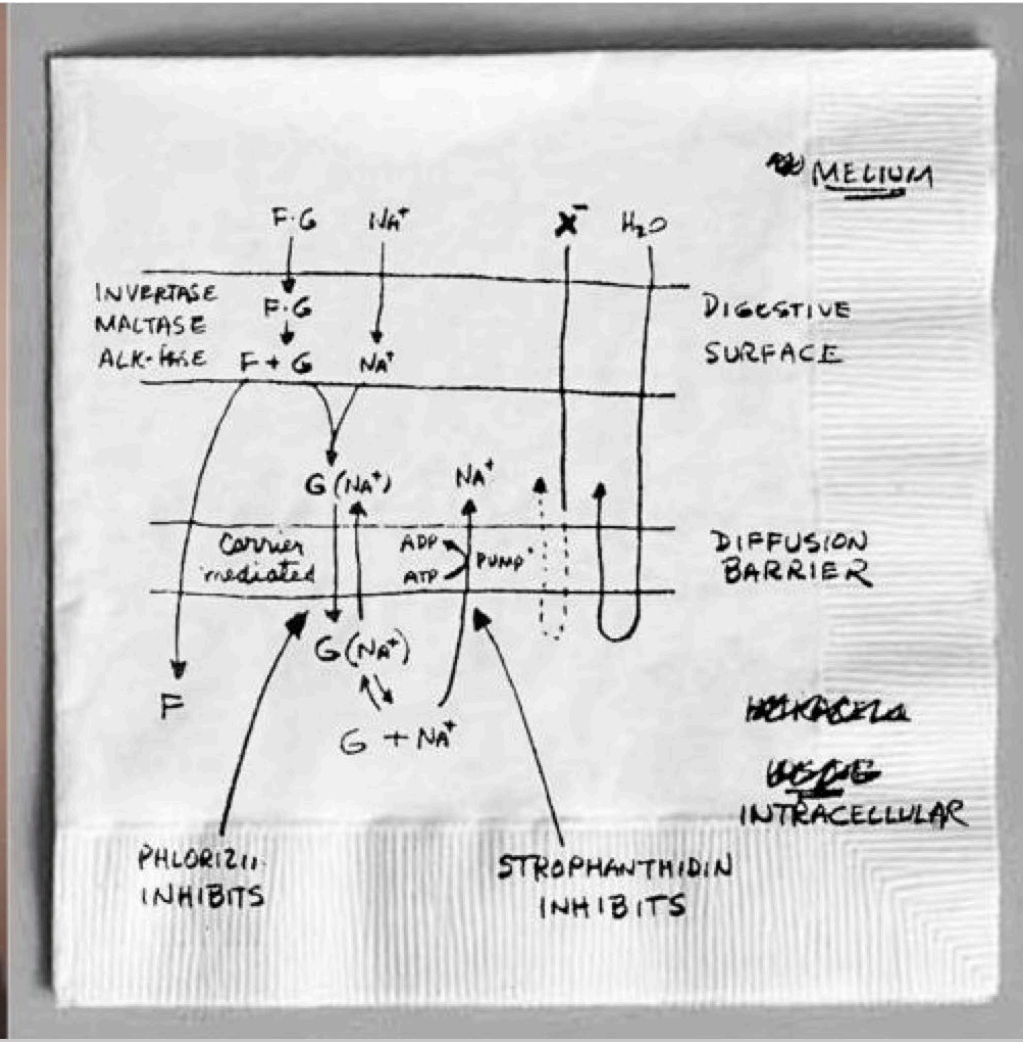
Josef von Mering

1886 – 'induced diabetes in dogs'

glycosuria, thirst, weight loss

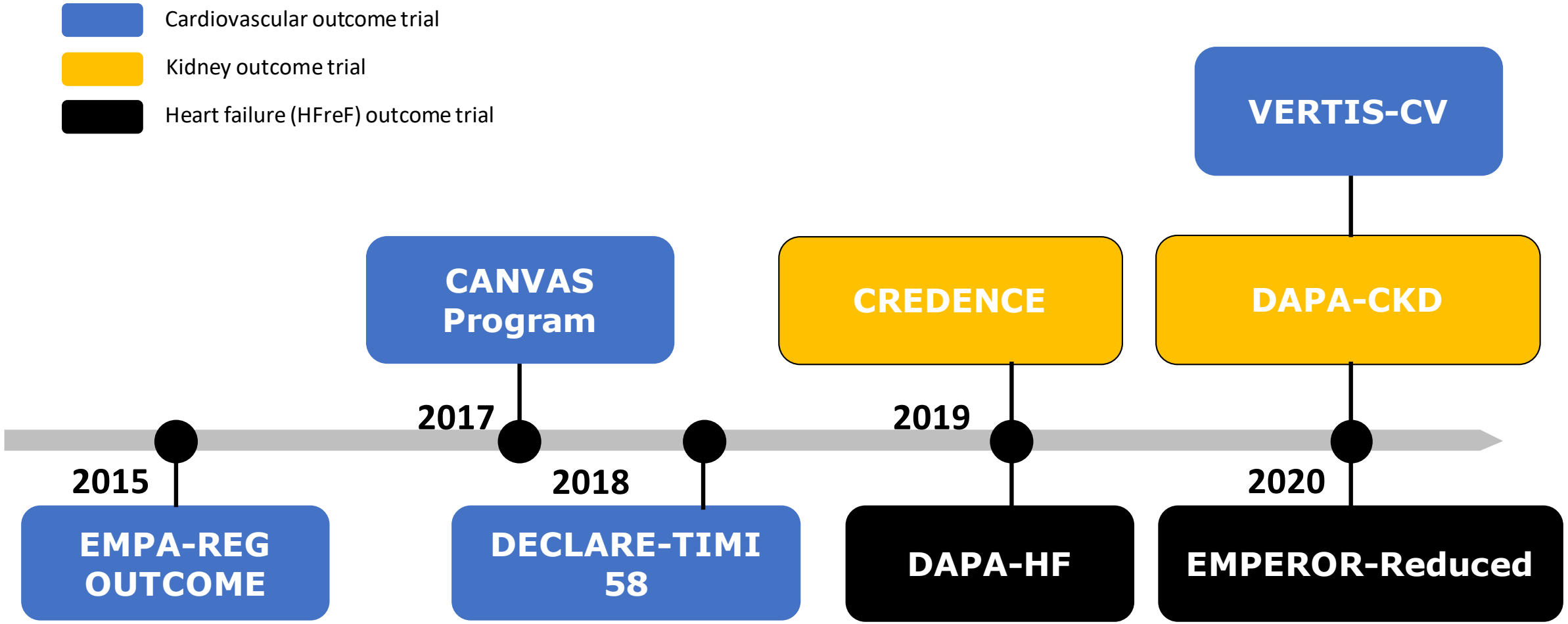
First description of co-transporter mechanism
Robert Crane 1960





Hamilton, KL. Front Physiol 2013

Key SGLT2 inhibitor trials: 2015-2020



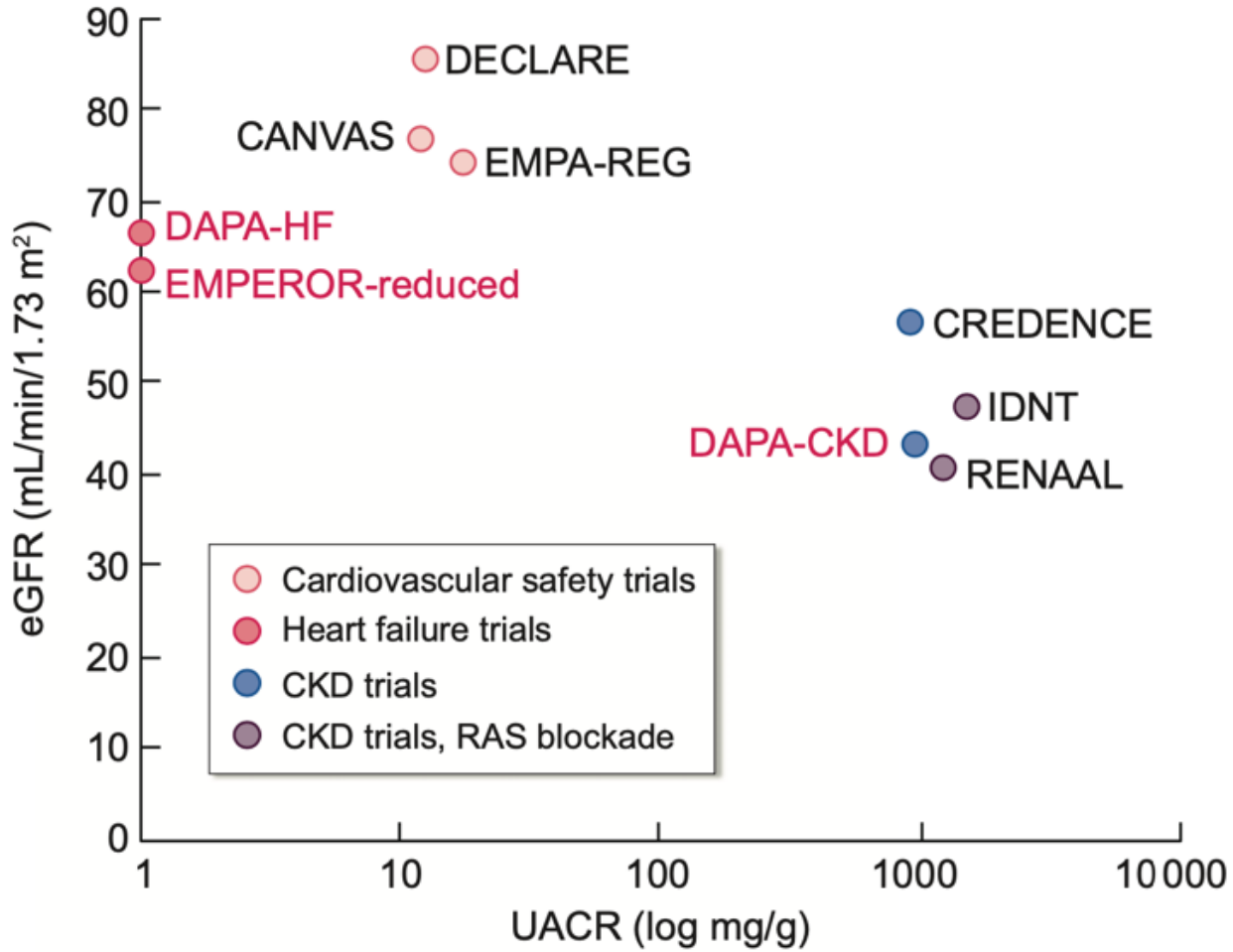
Participant characteristics in the key SGLT2 inhibitor trials

Study	EMPA-REG OUTCOME (n=7020)	CANVAS Program (n=10142)	DECLARE-TIMI 58 (n=17160)	CREDENCE (n=4401)	DAPA-CKD (n=4304)
Drug	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin	Dapagliflozin
Mean age (years)	61	63	64	63	62
Female, n (%)	2004 (29)	3633 (36)	6422 (37)	1494 (34)	1425 (33)
Median follow-up (years)	3.1	2.4	4.2	2.6	2.4
Established atherosclerotic CV disease (%)	7020 (100)	6656 (66)	(6974 (41)	2220 (50)	1610 (37)
History of heart failure, n (%)	706 (10)	1461 (14)	1724 (10)	652 (15)	468 (12)
Diabetes, n (%)	7020 (100)	10142 (100)	17160 (100)	4401 (100)	2906 (68)
eGFR, mL/min/1·73m^2, (mean)	74	76	85	56	43
eGFR <60mL/min/1·73m^2, n (%)	1819 (26)	2039 (20)	1265 (7)	2592 (59)	3850 (89)
UACR, mg/g, (median)	18	12	13	927	949
UACR >300 mg/g, n (%)	764 (11)	760 (7)	1169 (7)	4401 (100)	3859 (90)
Baseline use of RAS blockade, n (%)	5666 (81)	8116 (80)	13950 (81)	4395 (>99)	4174 (97)

Baseline kidney risk in the key SGLT2 inhibitor trials

GFR categories (mL/min/1.73 m²)	
Stage 1	≥9
Stage 2	60–
Stage 3a	45–
Stage 3b	30–
Stage 4	15–
ESKD 5	<1

E=EMPA-REG OUTCOME;



CE (DKD only)
to <90 mL/min/1.73 m²
≥300 mg/g

KD (CKD)
to <75 mL/min/1.73 m²
≥200 mg/g

DNEY (CKD)
to <75 mL/min/1.73 m²
≥200 mg/g

to <45 mL/min/1.73 m²

Heerspink et al. NDT 2020, Fernandez-Fernandez CKJ 2020

CREDENCE Trial
Canagliflozin 100 mg

Inclusion/Baseline Criteria[1]

≥30 years

Canagliflozin n=2202
Placebo n=2199

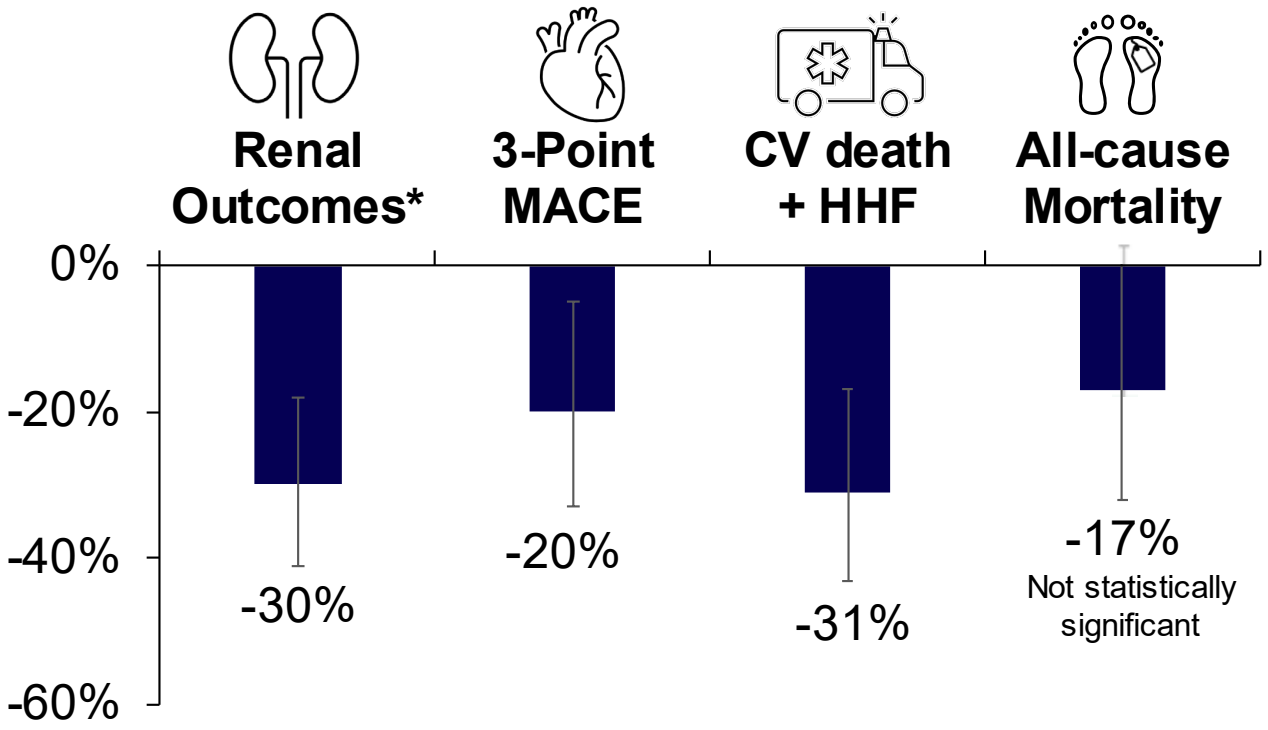
≥30 to <90 mL/min/1.73 m^2
eGFR

>33.9 to ≤565.6 mg/mmol
UACR

Confirmed T2D
A1C ≥6.5% to ≤12.0%

ACEi/ARB use **99.9%**
Mean A1C **8.3%**
Mean sBP **140.0 mmHg**

Key outcomes[2]



*Primary composite outcome: end-stage kidney disease, doubling of serum creatinine, or renal or cardiovascular death

1. Jardine MJ, et al. Am J Nephrol. 2017;46(6):462-472.
2. Perkovic et al. N Engl J Med. 2019; 380(24):2295-2306.

DAPA-CKD Trial
Dapagliflozin 10 mg

Inclusion/Baseline Criteria[1]

≥18 years
Dapagliflozin n=2152
Placebo n= 2152

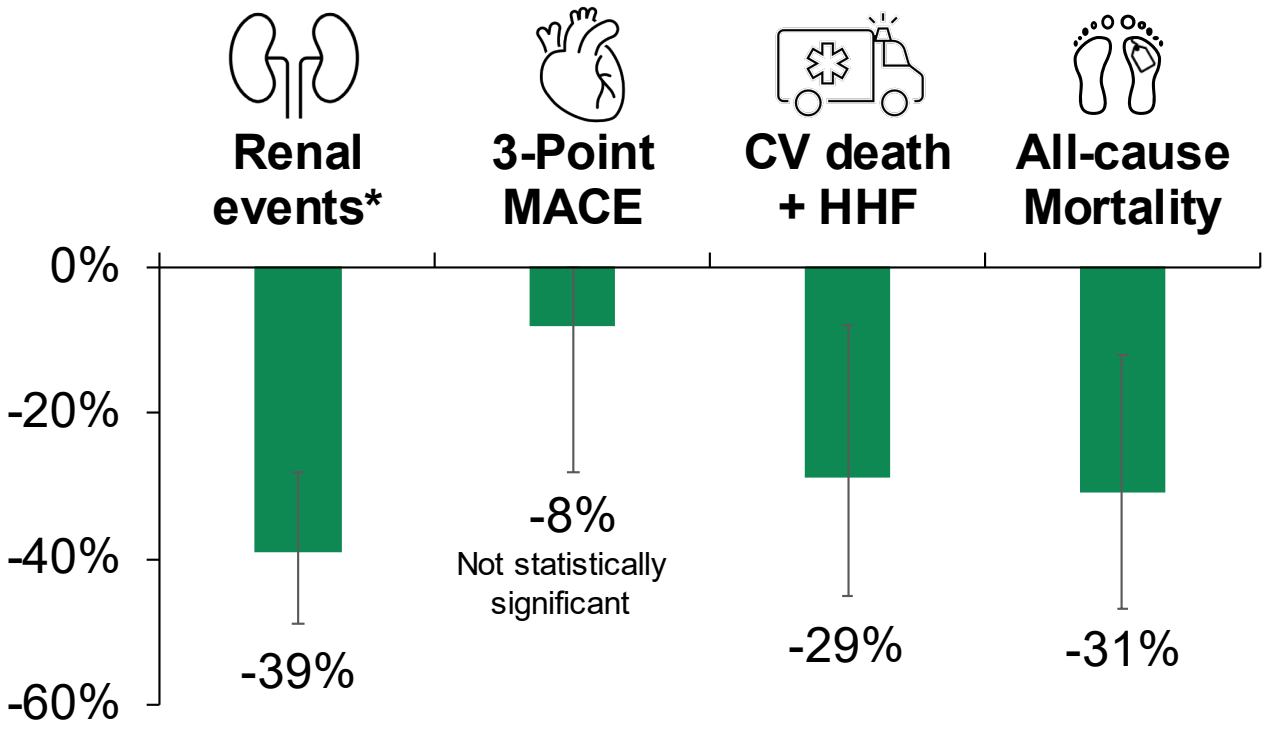
≥25 to ≤75 mL/min/1.73 m²
eGFR

>22.6 to ≤565 mg/mmol
UACR

68% with T2D

ACEi/ARB use **97%**
Mean sBP **137.4 mmHg**

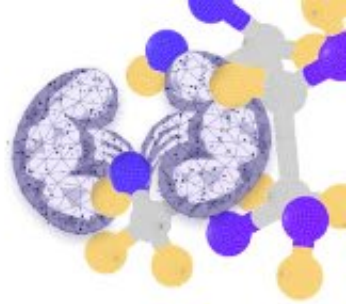
Key outcomes[2,3]



*Primary composite outcome: sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes

1. Wheeler et al. Nephrol Dial Transplant 2020;35: 1700–1711
2. Heerspink et al. N Engl J Med 2020; 383:1436-1446.
3. McMurray et al. Circulation. 2020; ePub ahead of print: 10.1161/CIRCULATIONAHA.120.051675

EMPA-KIDNEY Trial
Empagliflozin 10 mg



Inclusion Criteria[1]

≥18 years +/- T2D

Taking **ACEi/ARB**

Estimated enrollment: 6000 patients

≥20 to <45 mL/min/1.73 m²
eGFR

OR

≥45 to <90 mL/min/1.73 m²
eGFR

≥22.6 mg/mmol
UACR

Primary composite renal outcome*

Key secondary endpoints:

- Composite of CV death or HHF
- All-cause hospitalization
- All-cause mortality

*Time to first occurrence of (i) kidney disease progression (defined as ESKD, a sustained decline in eGFR to <10 mL/min/1.73 m², renal death, or a sustained decline of ≥40% in eGFR from randomization) or (ii) Cardiovascular death

US National Library of Medicine. https://www.clinicaltrials.gov/ct2/show/NCT03594110. Accessed Jan 22, 2021.

SCORED Trial
Sotagliflozin 200 or 400 mg

Inclusion/Baseline Criteria

≥18 years (≥1 major CV risk factor)
OR
≥55 years (≥2 minor CV risk factors)

Sotagliflozin n=5292 Placebo n=5292

≥25 to ≤60 mL/min/1.73 m^2
eGFR

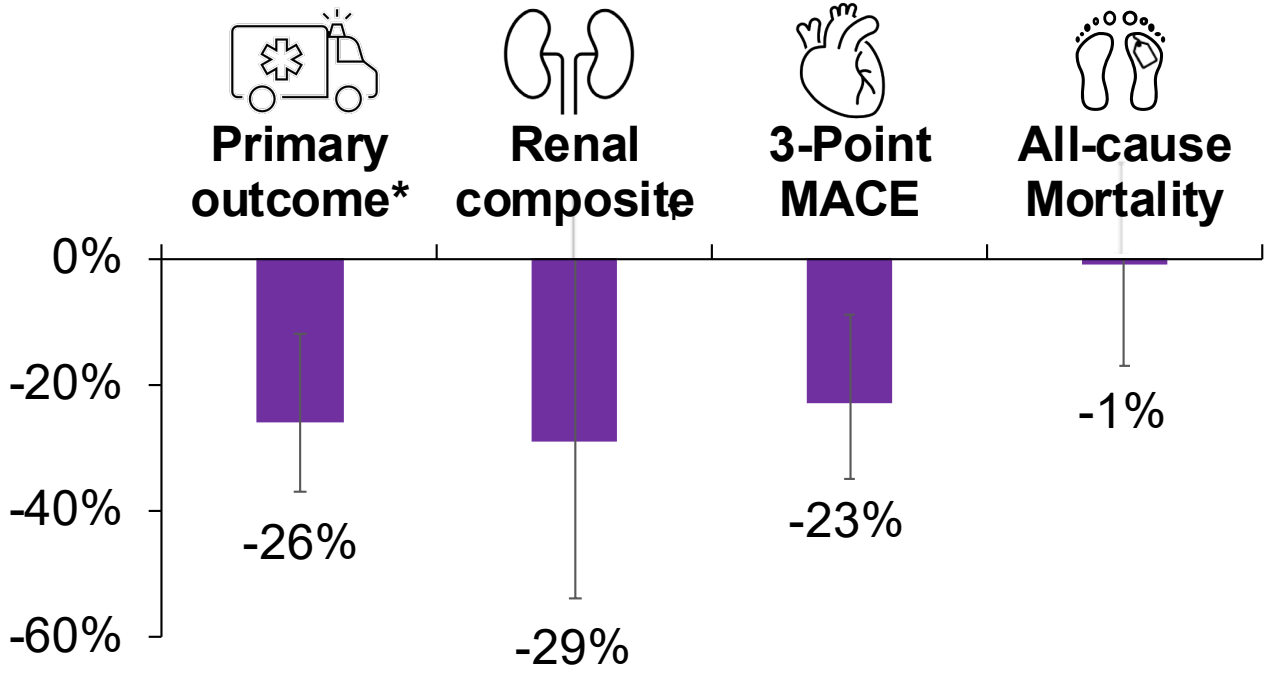
8.4 mg/mmol
Median UACR

Confirmed T2D
A1C ≥7.0%

ACEi/ARB use **88.5%**
Mean A1C **8.3%**
Median sBP **139 mmHg**

Key Outcomes

Note: Trial discontinued after 24 months of follow-up due to withdrawal of funding



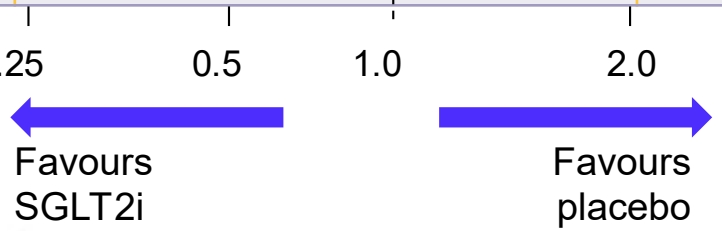
*Primary composite outcome: Total number of deaths from cardiovascular causes, hospitalizations for HF, and urgent visits for HF

†Renal composite outcome: First occurrence of a sustained decrease of ≥50% in the eGFR from baseline for ≥30 days, long-term dialysis, renal transplantation, or sustained eGFR of <15 ml/min/1.73 m^2 for ≥30 days

Bhatt et al. N Engl J Med. 2021;384(2):129-139

Renal Benefits of SGLT2 Inhibitors are Independent of A1C

	SGLT2i	Placebo	HR for primary outcome (95%CI)	P-trend
CREDENCE – Baseline A1C[1]				0.22
<8%	115/1027	144/1029	0.77 (0.61-0.99)	
≥8%	129/1174	195/1169	0.63 (0.51-0.79)	
DAPA-CKD – Presence of T2D[2]				N.R.
T2D	152/1455	229/1451	0.64 (0.52-0.79)	
No T2D	45/697	83/701	0.50 (0.35-0.72)	

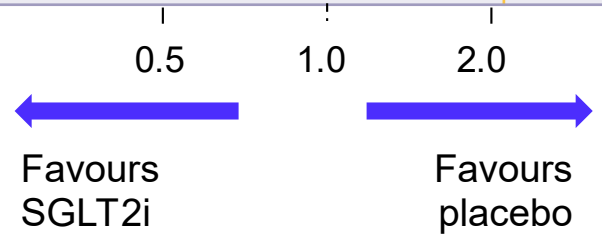


1. Perkovic et al. N Engl J Med. 2019; 380(24):2295-2306.
2. Heerspink et al. N Engl J Med 2020; 383:1436-1446.

Renal Safety of SGLT2 Inhibitors in Patients with CKD

Meta-analysis of renal AEs in patients with eGFR <60 mL/min/1.73 m^2 across 5 trials of canagliflozin, dapagliflozin, or empagliflozin

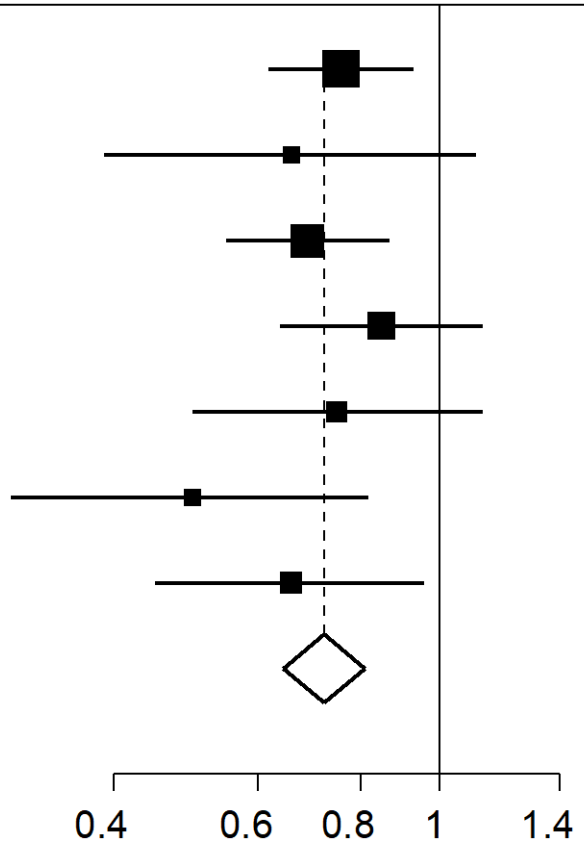
	Events (n/N)	HR/RR	$P_{heterogeneity}$
Renal-related adverse events	394/5582	1.04 (0.68-1.61)	0.11
Acute kidney injury	83/4767	0.69 (0.45-1.06)	0.63
Hyperkalemia	220/5294	0.63 (0.48-0.83)	0.90



Toyama et al. Diabetes Obes Metab. 2019;21:1237–1250.

Effect of SGLT2 inhibitors on acute kidney injury

Study	Events	Patients	RR (95% CI)	P-heterogeneity
EMPA-REG OUTCOME	401	7010	0.76 (0.62-0.93)	
CANVAS Program	58	10142	0.66 (0.39-1.11)	
DECLARE-TIMI 58	300	17160	0.69 (0.55-0.87)	
CREDENCE	184	4397	0.85 (0.64-1.13)	
DAPA-CKD	91	4298	0.75 (0.50-1.13)	
DAPA-HF	69	4736	0.50 (0.30-0.82)	
EMPEROR-Reduced	113	3730	0.66 (0.45-0.96)	
Overall (p<0.0001)			**0.72 (0.65-0.81)**	**0.67**

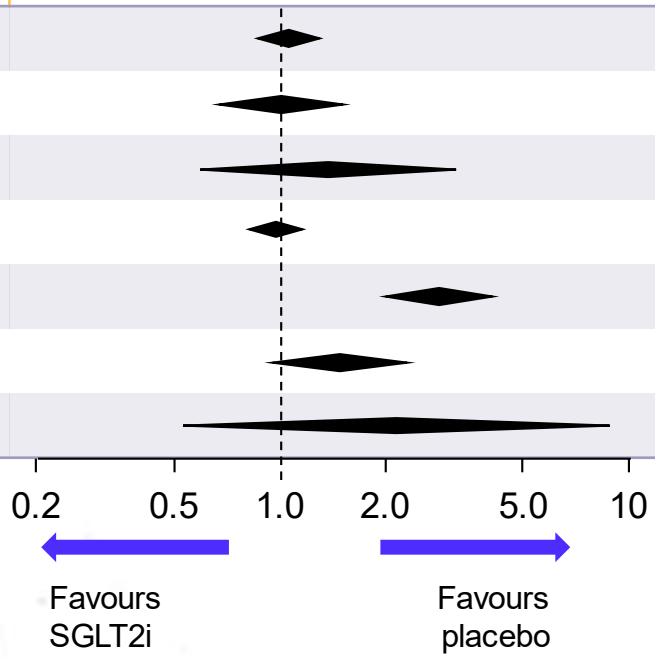


Adapted from Neuen et al. Lancet Diabetes Endocrinol 2019

Other Safety Signals

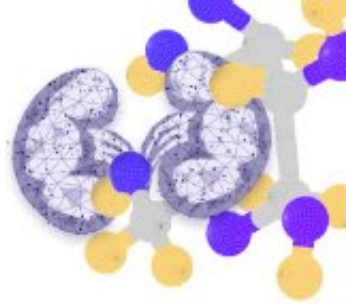
Meta-analysis of AEs in up to 10 clinical trials (including canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, and sotagliflozin)

	Events (n/N)	HR/RR	$P_{heterogeneity}$
Hypoglycemia	1292/5052	1.05 (0.85-1.32)	0.03
Fracture	238/6160	1.01 (0.67-1.52)	0.64
Amputation	106/4246	1.37 (0.58-3.25)	0.04
Urinary tract infection	703/5021	0.97 (0.81-1.16)	0.17
Genital infection	239/5776	2.86 (2.00-4.10)	0.75
Hypovolemia	297/5192	1.48 (0.94-2.32)	0.01
Diabetic ketoacidosis	10/4784	2.16 (0.51-9.09)	0.58



Toyama et al. Diabetes Obes Metab. 2019;21:1237–1250.

Summary – SGLT2i in T2D and CKD



SGLT2 inhibitors have demonstrated an ability to slow eGFR decline and reduce hard renal outcomes in clinical trials

Consistent benefits were also observed on hospitalization for heart failure, which have been shown in primary outcome trials on different patient populations

SGLT2 inhibitors may also provide benefits on 3-point MACE and overall survival in patients with T2D and CKD

Cardiorenal benefits are provided across a spectrum of kidney function

Does Dapagliflozin compared to placebo reduce the risk of kidney failure and CV events in CKD patients with and without T2DM?

DAPA-CKD

21 Countries
286 Centers

- ≥ 18 yo
- eGFR ≥ 25 to ≤ 75ml/min
- UACR ≥ 200 to ≤ 5000mg/g
- Max tolerated dose of ACEi/ARB
- With and without T2DM

Mean Age 62y, 67% ♂
eGFR 43ml/min
UACR 949mg/g
ACEi/ARB 97%
With T2DM 67.5%

MEAN FOLLOW-UP: 2.4 YEARS

N=4304

10 mg DAPAGLIFLOZIN +STANDARD CARE N=2152

PLACEBO +STANDARD CARE N=2152

Sustained ≥ 50% decline in GFR, ESKD, Renal or CV Death	Sustained ≥ 50% decline in GFR, ESKD, Renal Death	CV Death or hHF	All-cause Mortality
9.2%	6.6%	4.6%	4.7%
HR 0.61 (95% CI 0.51-0.72) p<0.001 NNT=19	HR 0.56 (0.45-0.68) p<0.001	HR 0.71 (0.55-0.92) p=0.009	HR 0.69 (0.53-0.88) p=0.004
14.5%	11.3%	6.4%	6.8%

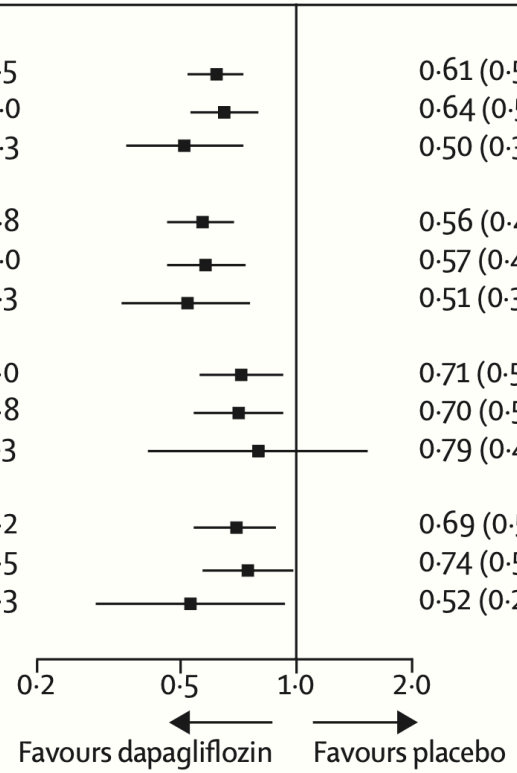
Benefit of Dapagliflozin on primary end-point was consistent in patients with and without T2DM
% of patients who discontinued the drug or who experienced SAE was similar in both groups
DKA, 2 in placebo group vs none in Dapagliflozin group
No DKA or severe hypoglycemia in patients without T2DM

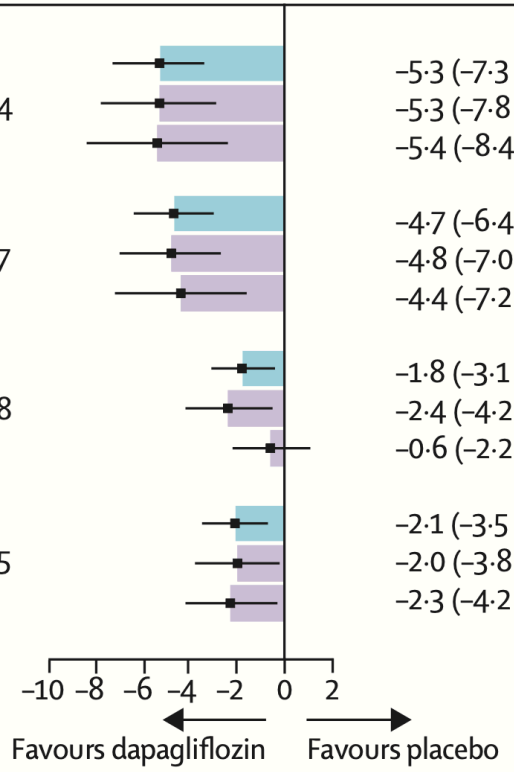
CONCLUSION: Dapagliflozin compared to placebo significantly reduced the risk of kidney failure, CV death or hospitalization for HF and all-cause mortality in patients with CKD with and without T2DM. Dapagliflozin was well-tolerated, in keeping with its established safety profile.

DAPA-CKD
Heerspink et al (2020). Dapagliflozin in Patients with Chronic Kidney Disease. *New England Journal of Medicine.* September 24,2020
DOI: 10.1056/NEJMoa2024816
Visual Abstract by: Ana Naidas, MD

Dapa: Consistent benefit irrespective of diabetes status

	Events*		Events per 100 patient-years		Hazard ratio (95% CI)	$p_{interaction}$	Absolute change in risk (95% CI)	$p_{interaction}$
	Dapagliflozin	Placebo	Dapagliflozin	Placebo				
Primary outcome								
Overall	197/2152	312/2152	4·6	7·5	0·61 (0·51–0·72)		−5·3 (−7·3 to −3·4)	
With type 2 diabetes	152/1455	229/1451	5·2	8·0	0·64 (0·52–0·79)	0·24	−5·3 (−7·8 to −2·9)	0·98
Without diabetes	45/697	83/701	3·4	6·3	0·50 (0·35–0·72)		−5·4 (−8·4 to −2·4)	
Kidney-specific composite outcome								
Overall	142/2152	243/2152	3·3	5·8	0·56 (0·45–0·68)		−4·7 (−6·4 to −3·0)	
With type 2 diabetes	103/1455	173/1451	3·5	6·0	0·57 (0·45–0·73)	0·57	−4·8 (−7·0 to −2·7)	0·80
Without diabetes	39/697	70/701	2·9	5·3	0·51 (0·34–0·75)		−4·4 (−7·2 to −1·6)	
Cardiovascular death or hospital admission for heart failure								
Overall	100/2152	138/2152	2·2	3·0	0·71 (0·55–0·92)		−1·8 (−3·1 to −0·4)	
With type 2 diabetes	85/1455	119/1451	2·7	3·8	0·70 (0·53–0·92)	0·78	−2·4 (−4·2 to −0·5)	0·11
Without diabetes	15/697	19/701	1·1	1·3	0·79 (0·40–1·55)		−0·6 (−2·2 to 1·1)	
All-cause mortality								
Overall	101/2152	146/2152	2·2	3·2	0·69 (0·53–0·88)		−2·1 (−3·5 to −0·7)	
With type 2 diabetes	84/1455	113/1451	2·6	3·5	0·74 (0·56–0·98)	0·25	−2·0 (−3·8 to −0·2)	0·85
Without diabetes	17/697	33/701	1·2	2·3	0·52 (0·29–0·93)		−2·3 (−4·2 to −0·3)	



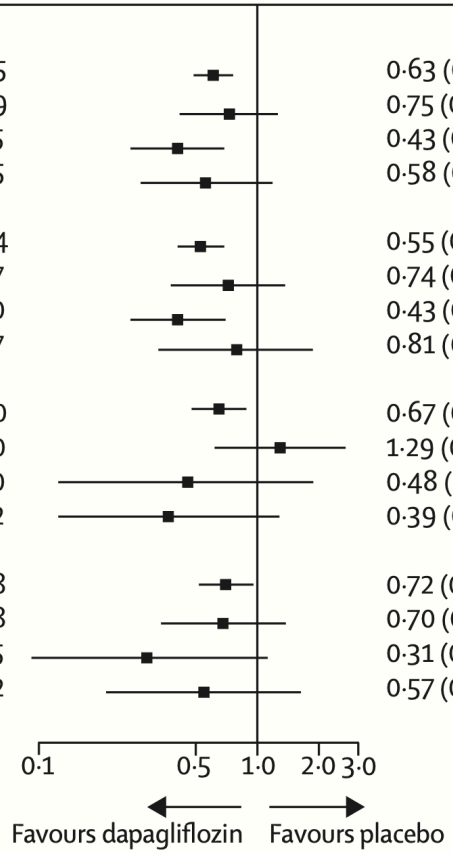


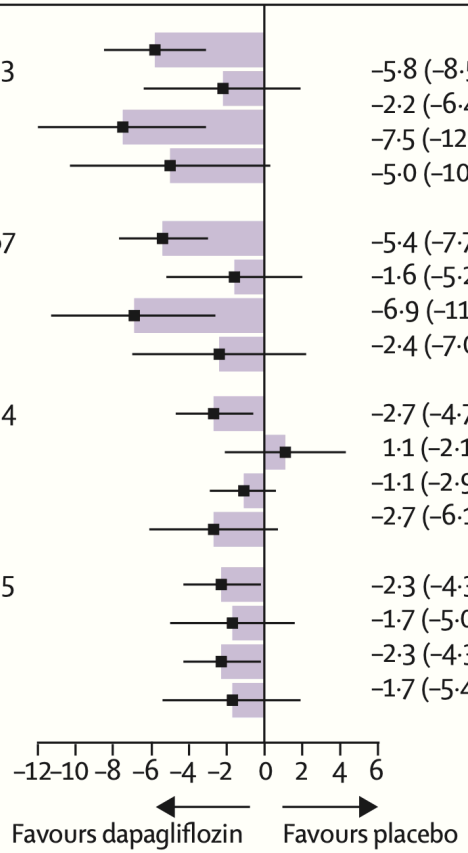
The George Institute for Global Health

Wheeler et al. Lancet D&E 2020

Consistent benefit irrespective of CKD etiology

	Events*		Events per 100 patient-years		Hazard ratio (95% CI)	$p_{interaction}$	Absolute change in risk (95% CI)	$p_{interaction}$
	Dapagliflozin	Placebo	Dapagliflozin	Placebo				
Primary outcome								
Diabetic nephropathy	139/1271	207/1239	5·4	8·5	0·63 (0·51–0·78)	0·53	–5·8 (–8·5 to –3·1)	0·37
Ischaemic or hypertensive	24/324	35/363	3·8	4·9	0·75 (0·44–1·26)		–2·2 (–6·4 to 1·9)	
Glomerulonephritis	22/343	49/352	3·4	7·5	0·43 (0·26–0·71)		–7·5 (–12·0 to –3·1)	
Other or unknown	12/214	21/198	2·9	5·5	0·58 (0·29–1·19)		–5·0 (–10·3 to 0·3)	
Kidney-specific composite outcome								
Diabetic nephropathy	93/1271	157/1239	3·6	6·4	0·55 (0·43–0·71)	0·67	–5·4 (–7·7 to –3·0)	0·16
Ischaemic or hypertensive	18/324	26/363	2·8	3·7	0·74 (0·4–1·36)		–1·6 (–5·2 to –2·0)	
Glomerulonephritis	21/343	46/352	3·3	7·0	0·43 (0·26–0·72)		–6·9 (–11·3 to –2·6)	
Other or unknown	10/214	14/198	2·5	3·7	0·81 (0·35–1·83)		–2·4 (–7·0 to –2·2)	
Cardiovascular death or hospital admission for heart failure								
Diabetic nephropathy	76/1271	107/1239	2·7	4·0	0·67 (0·50–0·90)	0·24	–2·7 (–4·7 to –0·6)	0·19
Ischaemic or hypertensive	17/324	15/363	2·5	2·0	1·29 (0·64–2·60)		1·1 (–2·1 to 4·3)	
Glomerulonephritis	3/343	7/352	0·4	1·0	0·48 (0·12–1·84)		–1·1 (–2·9 to 0·6)	
Other or unknown	4/214	9/198	0·9	2·2	0·39 (0·12–1·28)		–2·7 (–6·1 to 0·7)	
All-cause mortality								
Diabetic nephropathy	78/1271	104/1239	2·7	3·8	0·72 (0·54–0·97)	0·55	–2·3 (–4·3 to –0·2)	0·99
Ischaemic or hypertensive	14/324	22/363	2·0	2·8	0·70 (0·36–1·37)		–1·7 (–5·0 to 1·6)	
Glomerulonephritis	3/343	11/352	0·4	1·5	0·31 (0·09–1·13)		–2·3 (–4·3 to –0·2)	
Other or unknown	6/214	9/198	1·3	2·2	0·57 (0·20–1·61)		–1·7 (–5·4 to 1·9)	





Wheeler et al. Lancet D&E 2020

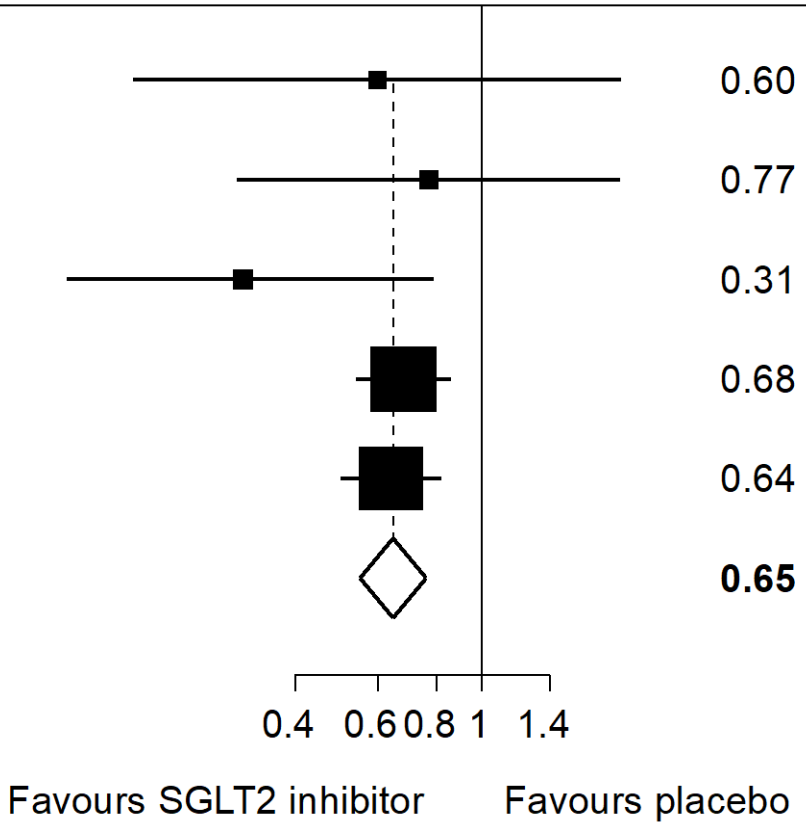
DAPA-CKD: safety results

Safety outcomes, n (%)	Dapagliflozin 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	35 (1.6)	39 (1.8)
DKA	0	2 (0.1)
Fracture	85 (4.0)	69 (3.2)
Renal-related adverse event	155 (7.2)	188 (8.7)
Major hypoglycemia	14 (0.7)	28 (1.3)
Volume depletion	127 (5.9)	90 (4.2)
Serious adverse event of volume depletion	22 (1.0)	18 (0.8)

Heerspink et al. NEJM 2020

Effect of SGLT2 inhibition on kidney failure

Study	Events	Patients	HR (95% CI)	P-heterogeneity
EMPA-REG OUTCOME	11	7020	0.60 (0.18-1.98)	
CANVAS Program	18	10142	0.77 (0.30-1.97)	
DECLARE-TIMI 58	25	17160	0.31 (0.13-0.79)	
CREDENCE	281	4401	0.68 (0.54-0.86)	
DAPA-CKD	270	4304	0.64 (0.50-0.82)	
Overall (p<0.0001)			**0.65 (0.55-0.76)**	**0.58**

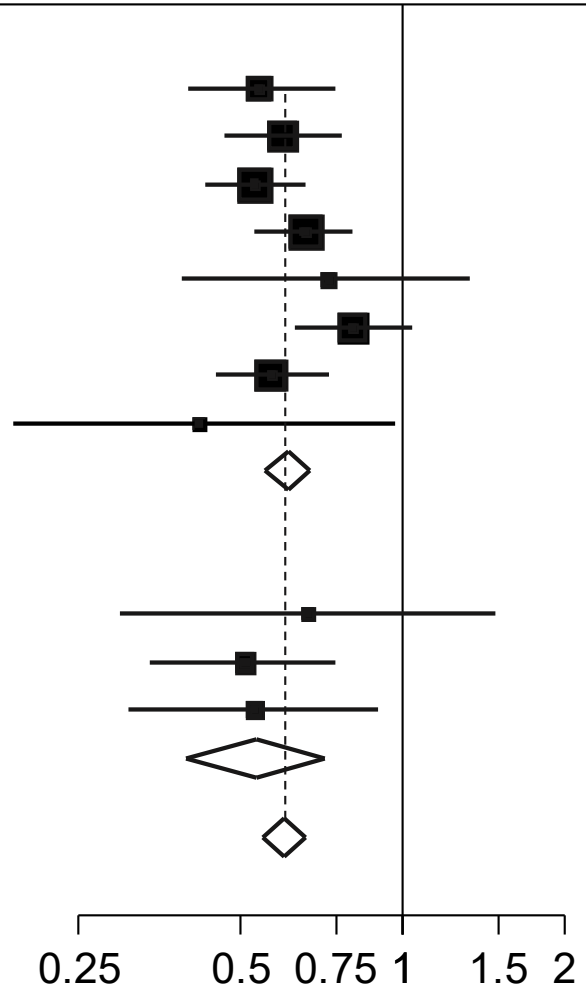


Adapted from Neuen et al. Lancet Diabetes Endocrinol 2019

SGLT2 inhibitors and kidney protection - with and without diabetes

Study	Events	Patients	HR (95% CI)
Diabetes			
EMPA-REG OUTCOME	152	6968	0.54 (0.40-0.75)
CANVAS Program	249	10142	0.60 (0.47-0.77)
DECLARE-TIMI 58	365	17160	0.53 (0.43-0.66)
CREDENCE	377	4401	0.66 (0.53-0.81)
DAPA-HF	42	2139	0.73 (0.39-1.34)
VERTIS-CV	283	8246	0.81 (0.63-1.04)
DAPA-CKD	276	2906	0.57 (0.45-0.73)
EMPEROR-Reduced	61	1856	0.42 (0.19-0.97)
Subtotal (p<0.0001)			**0.61 (0.56-0.67)**
No diabetes			
DAPA-HF	25	2605	0.67 (0.30-1.49)
DAPA-CKD	109	1398	0.51 (0.34-0.75)
EMPEROR-Reduced	27	1874	0.53 (0.31-0.90)
Subtotal (p<0.0001)			**0.54 (0.40-0.72)**
Overall (p<0.0001)			**0.60 (0.55-0.66)**

Heterogeneity between subgroups P=0.44

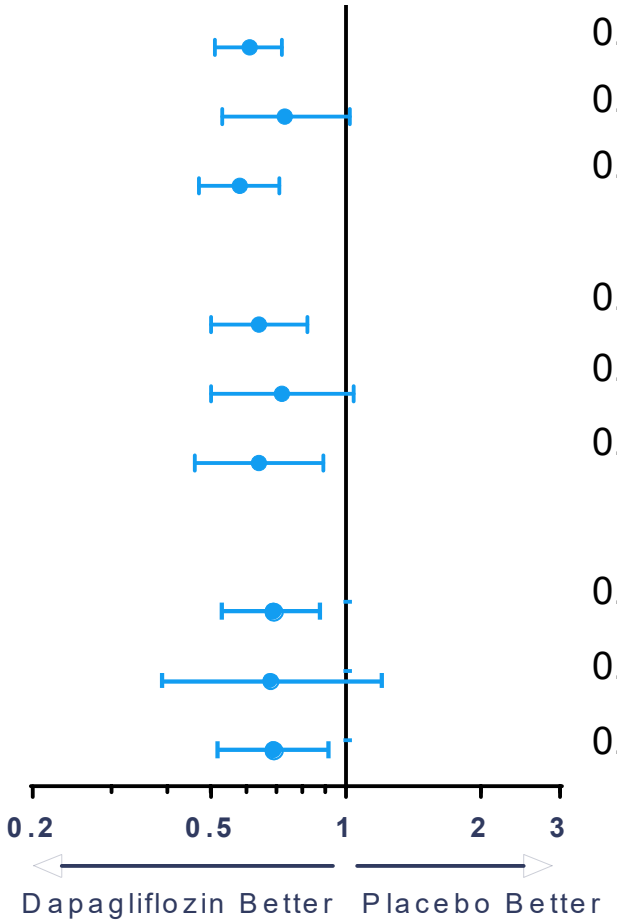


Pollock & Neuen
ACKD 2021 (accepted)

Do SGLT2i work at lower eGFR values?

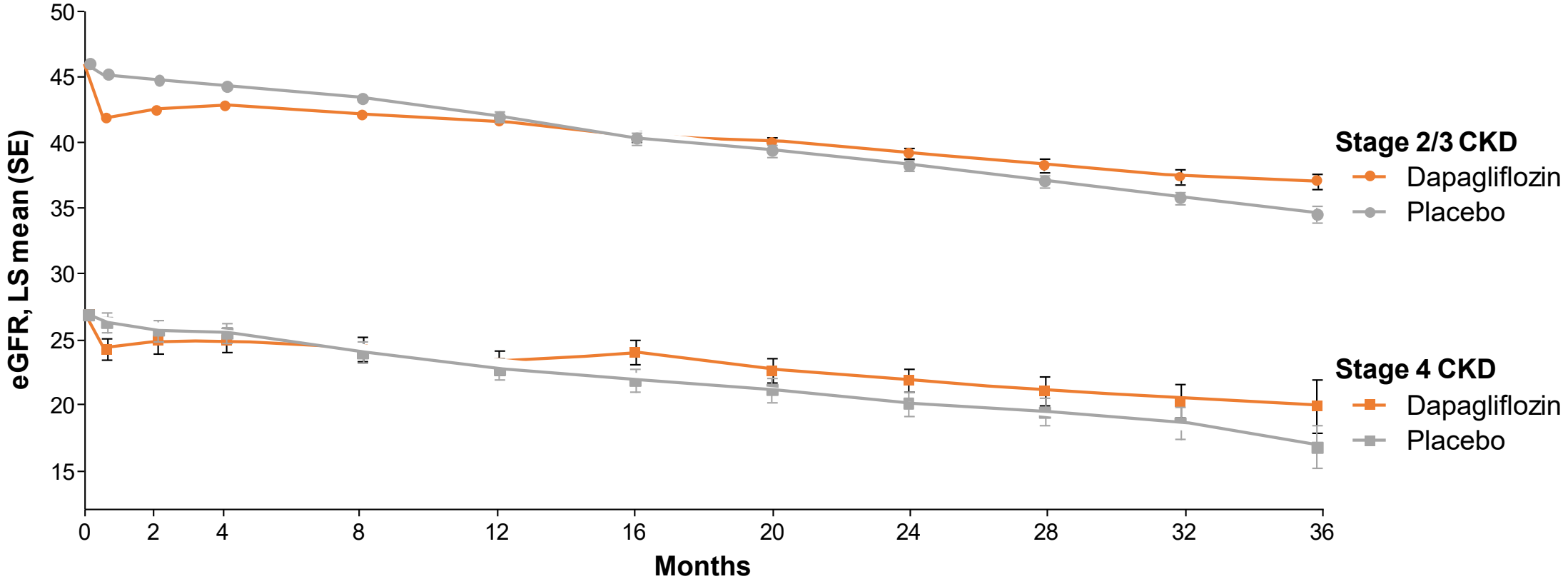
In DAPA-CKD, dapagliflozin reduced the risk of the primary outcome regardless of CKD stage

	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Hazard ratio (95% CI)	*P* value for Interaction
	No. of participants/ total no.		Events/ 100 patient-years			
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)	
Stage 4	59/293	87/331	11.1	14.9	0.73 (0.53, 1.02)	0.22
Stage 2/3	138/1859	225/1821	3.7	6.2	0.58 (0.47, 0.71)	
ESKD						
Overall	109/2152	161/2152	2.5	3.8	0.64 (0.50, 0.82)	
Stage 4	49/293	72/331	9.2	12.4	0.72 (0.50, 1.04)	0.64
Stage 2/3	60/1859	89/1821	1.6	2.4	0.64 (0.46, 0.89)	
All-cause death						
Overall	101/2152	146/2152	2.2	3.1	0.69 (0.53, 0.88)	
Stage 4	19/293	31/331	3.0	4.6	0.68 (0.39, 1.21)	0.95
Stage 2/3	82/1859	115/1821	2.0	2.9	0.69 (0.52, 0.92)	



CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease

In DAPA-CKD, dapagliflozin slowed eGFR decline in patients with Stage 4 CKD

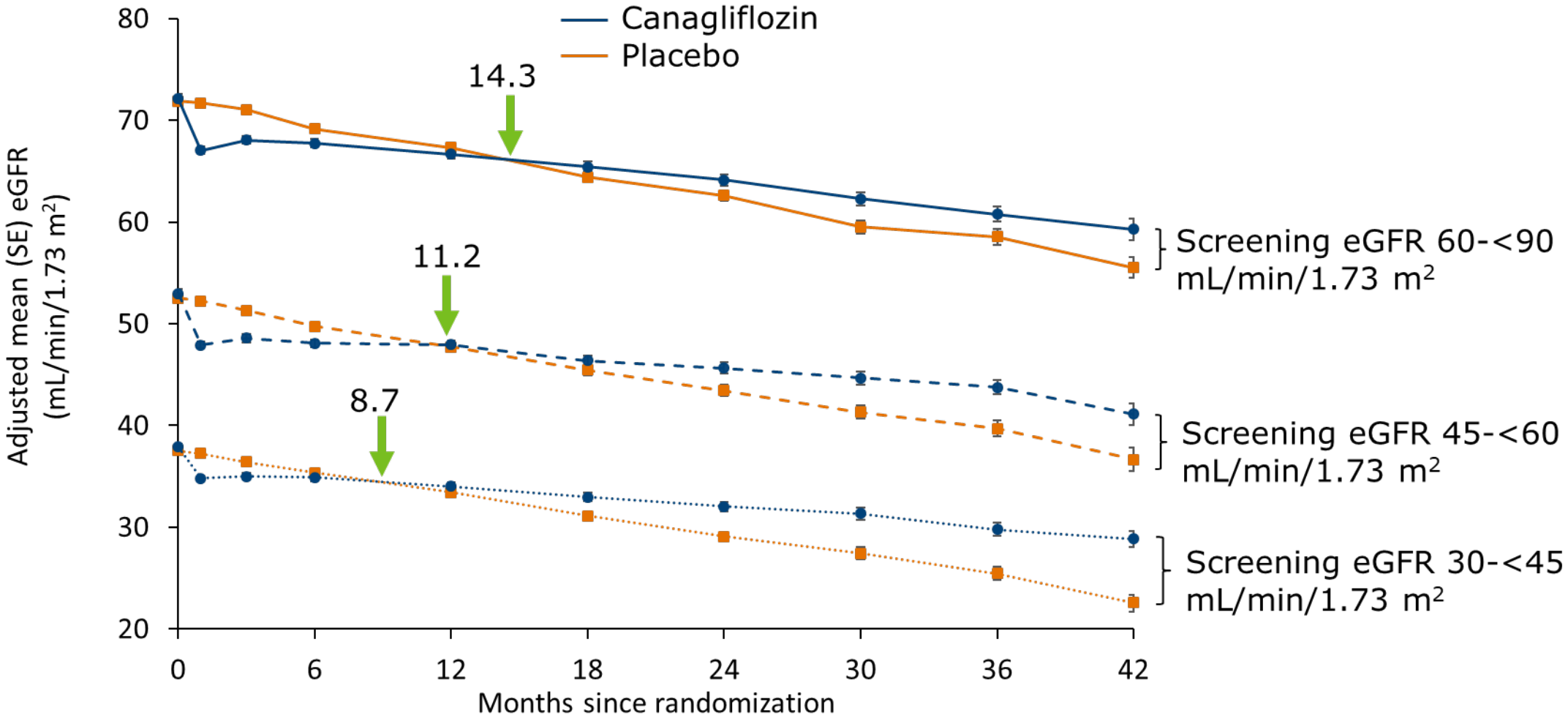


Between slope difference (SE)[a]	CKD stage 4	CKD stage 2/3
Acute, mL/min/1.73 m^2/2 weeks	–1.4 (0.5)	–2.6 (0.2)
Chronic, mL/min/1.73 m^2/year	1.8 (0.4)	1.9 (0.2)
Total, mL/min/1.73 m^2/year	1.2 (0.4)	0.9 (0.2)

Dapagliflozin vs placebo

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SE, standard error

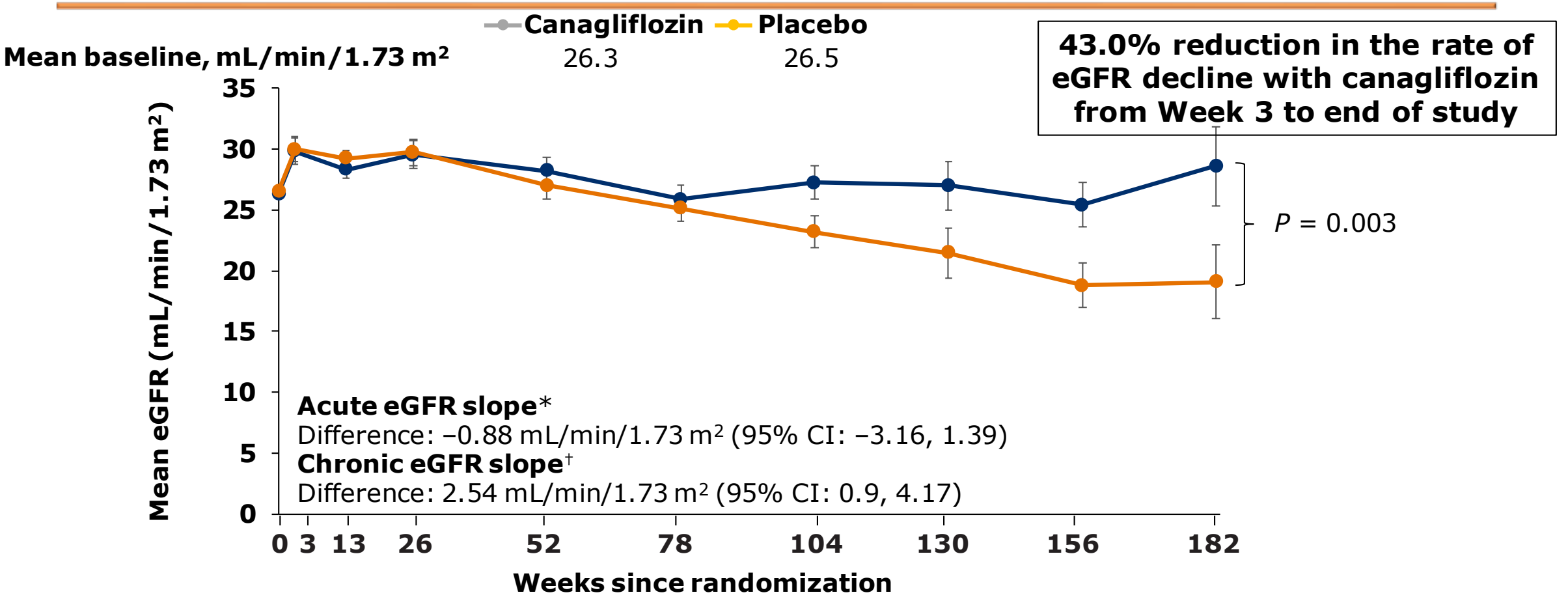
Impact of Cana on eGFR Slope by eGFR



CREDENCE

M Jardine, *JASN*, 2020. 31(5): 1128–1139

Effects of Canagliflozin on eGFR in Participants with Baseline eGFR <30 mL/min/1.73 m^2



*Measured from baseline to Week 3.
†Measured from Week 3 until the end of the study.

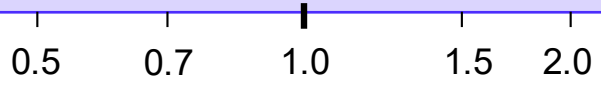
Bakris, *ASN, 2019*

Back to CV disease ……CV Limitations of RAAS Inhibition

Meta-analysis of ACEi/ARB trials showed little or no CV benefit in patients with T2D and relatively advanced CKD

- Included IDNT, RENAAL, and ADVANCE

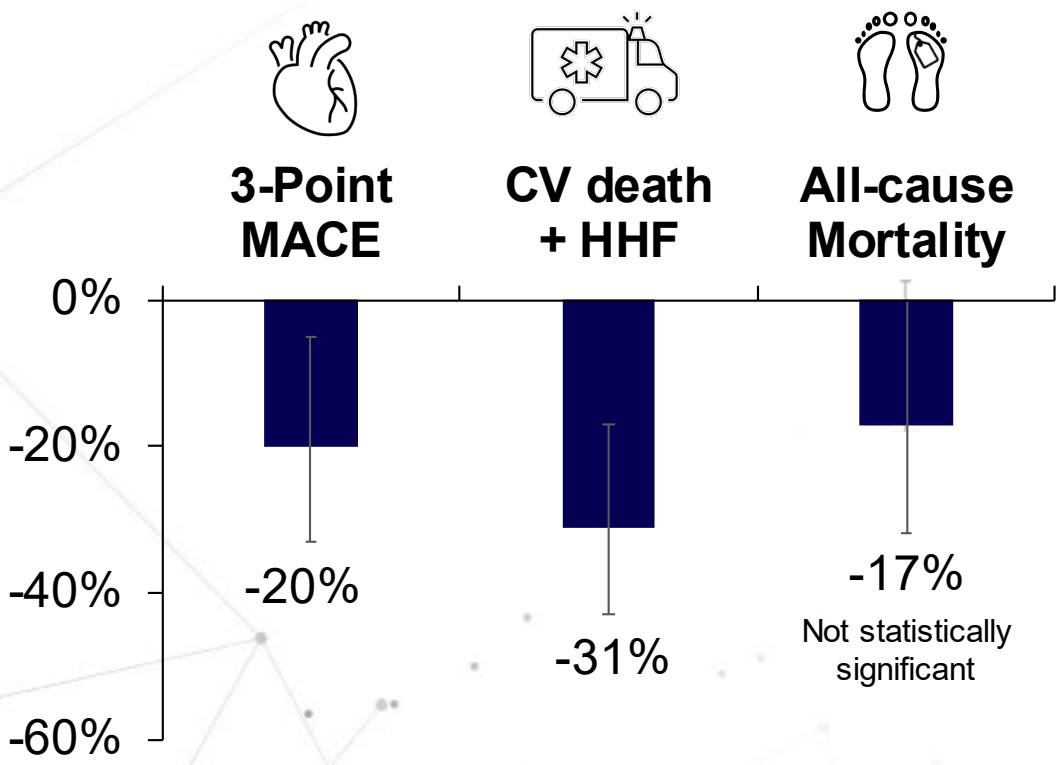
	Events			
Outcome	**ACEi/ARB**	**Control***	**Hazard Ratio (95%CI)**	**P**
All-cause mortality	362/2363	466/2946	0.97 (0.85-1.10)	0.61
CV mortality	118/1588	165/2160	1.03 (0.75-1.41)	0.85
Non-fatal CV events	284/1588	489/2160	0.90 (0.79-1.02)	0.10



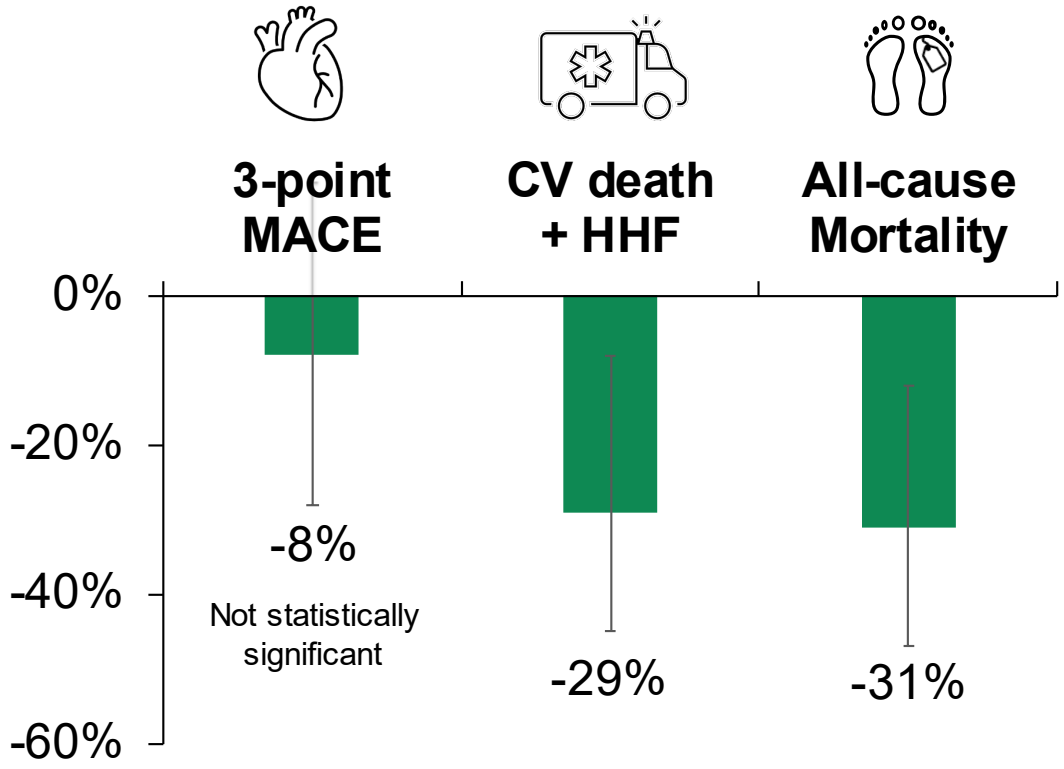
Nistor et al. Nephrol Dial Transplant. 2018;33(1):12-22.

CV Benefits of SGLT2i in CKD

CREDENCE[1]



DAPA-CKD[2,3]

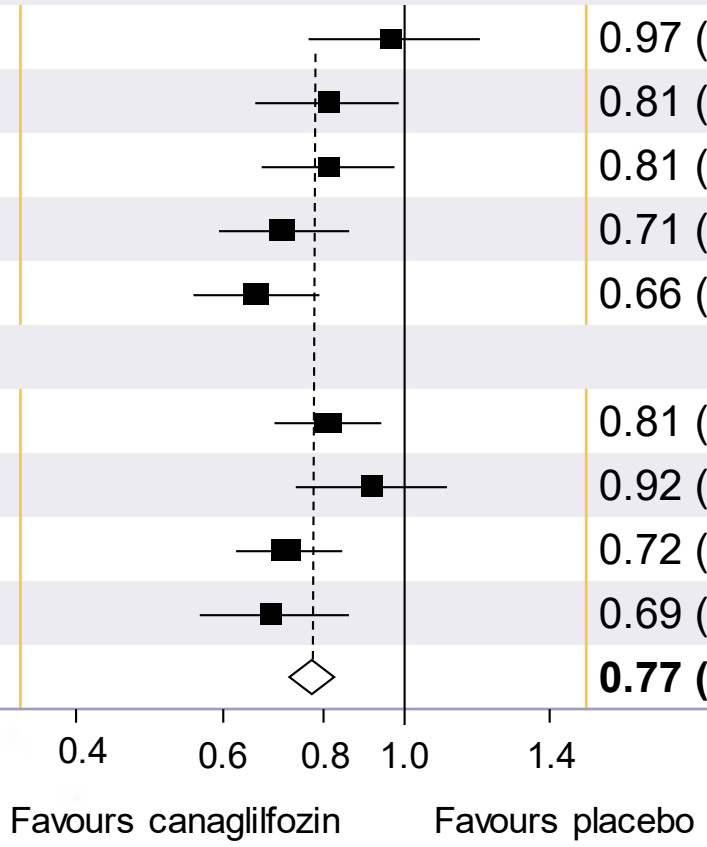


1. Perkovic et al. N Engl J Med. 2019; 380(24):2295-2306.
2. Heerspink et al. N Engl J Med 2020; 383:1436-1446.
3. McMurray et al. Circulation. 2020; ePub ahead of print: 10.1161/CIRCULATIONAHA.120.051675

Cardiorenal Benefits of SGLT2 Inhibitors Extend Across a Spectrum of Renal Function

Integrated analysis of CANVAS Program and CREDENCE data – Composite of hospitalization for heart failure, nonfatal MI, nonfatal stroke, doubling of serum creatinine, kidney failure, CV/renal death

	Events		Hazard Ratio (95%CI)	P-trend
	CANA	Placebo		
eGFR (mL/min/1.73 m²)				0.0067
≥90	172/2026	112/1545	0.97 (0.76-1.23)	
75 to <90	217/1897	177/1440	0.81 (0.66-0.99)	
60 to <75	237/1783	212/1458	0.81 (0.67-0.98)	
45 to <60	204/1310	240/1182	0.71 (0.59-0.86)	
<45	205/943	275/920	0.66 (0.55-0.79)	
UACR (mg/mmol)				0.057
<3.39	380/4028	292/3010	0.81 (0.69-0.94)	
3.4 to 34	210/1573	149/1189	0.92 (0.74-1.13)	
>34 to 249	294/1882	361/1799	0.72 (0.62-0.84)	
>249	145/459	211/494	0.69 (0.56-0.86)	
Overall	**1035/7997**	**1016/6546**	**0.77 (0.70-0.84)**	



CANA: Canagliflozin

Neuen et al. Presented at the ASN Kidney Week 2020. October 22-25, 2020.

SGLT2 Inhibition in Decompensated Heart Failure

SOLOIST Trial (Sotagliflozin 200 or 400 mg)

Inclusion/Baseline Criteria

18-85 years
Recently hospitalized for worsening heart failure
Sotagliflozin n=608 Placebo n=614

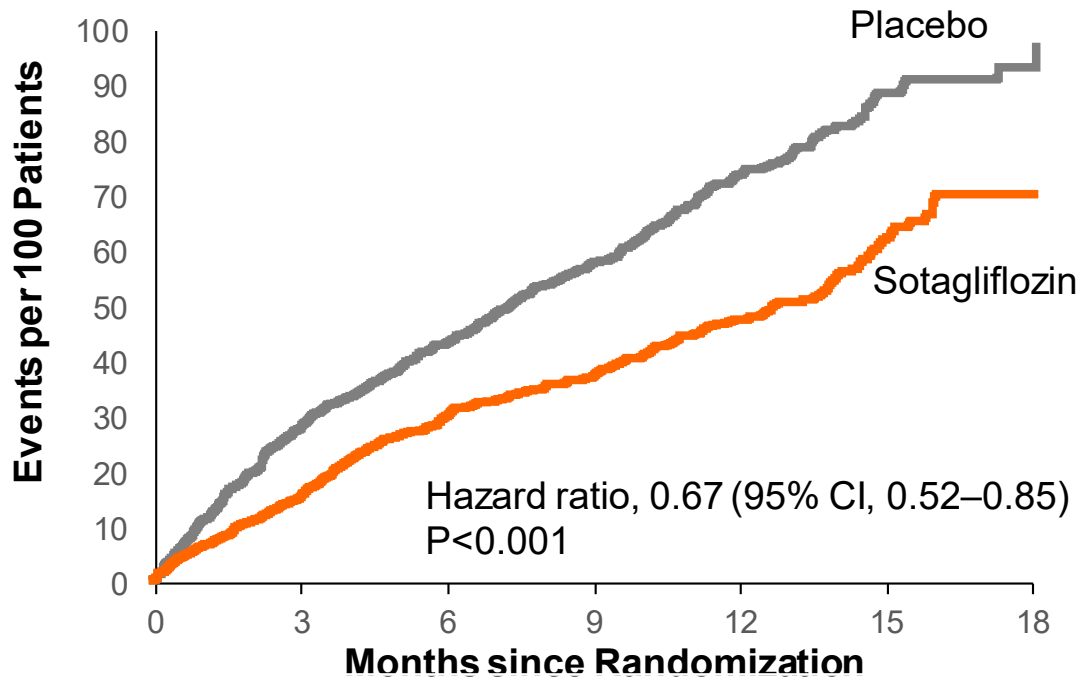
79% with LVEF <50%

Confirmed T2D
Median A1C 7.1-7.2

91.3%
Taking ACEi/ARB

Primary Outcome: Deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure

Note: Trial discontinued after 18 months of follow-up due to withdrawal of funding



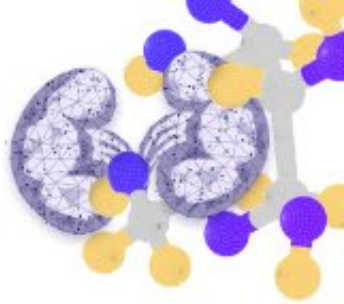
No. at Risk

Placebo	614	524	416	305	195	100	25
Sotagliflozin	608	540	430	310	209	97	29

Bhatt et al. N Engl J Med. 2021;384(2):117-128

Canadian Heart Failure Society practical guide to SGLT2 initiation

CHFS SCIC
Canadian Heart Failure Society
Société canadienne d'insuffisance cardiaque



Indications

Patients with Type 2 DM[1]
or
Patients with chronic kidney disease (eGFR 25-90, UACR>20 mg/mmol)[2]
or
Patient with chronic HFrEF[3]

Contraindications

- CLI3
- eGFR<25[4]
- Allergy or intolerance to SGLT2i[5]

Do not initiate SGLT2i

Caution

- Volume depletion[5]
- Active GMI[6]
- Hypotension (Blood pressure<95 mmHg)[*,7]
- Prior CLI
- DKA[5] [specific to DM]
- History of severe hypoglycemia[†] [specific to DM]

Delay initiation of SGLT2i until condition resolved/therapies modified to reduce risk

Outpatient Initiation

Start 10 mg od qam:
- Dapagliflozin[5]
- Empagliflozin[8]

Start 100 mg od qam:
- Canagliflozin[9]

Special Considerations

- Monitor for GMIs, counsel on proper hygiene[6]
- Concomitant dehydrating illness (SADMANS)[‡, 10]
- Borderline renal function[§, 5, 6]
- Volume depletion[‖, 5]

Potential drug-drug effects with:

Loop diuretics
- Optional dose reduction[¶] if euvolemic; 30–50% dose reduction if volume depletion occurs[3]

Follow-up

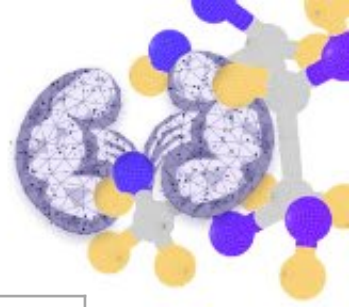
Follow up routine as per underlying condition:
- Weight[6]
- Symptoms of hypotension[6]
- Adherence[6]
- Renal function (eGFR)[**, ††, 6]
- Blood glucose[6] [specific to DM]

Insulin or SU
- If DM w/A1C<7.5, consider dose reduction (i.e., 10–20% insulin, and/or 50% SU)[11]
- If episodes of hypoglycemia[#], stop SU and dose reduce insulin[11]

Canadian Heart Failure Society. 2020. Available at: https://heartfailure.ca/sites/default/files/chfs_practical_approach_algorithm_sglt2i_0.pdf. Accessed 05/04/2021.

It can’t all be good….a deeper dive into side effects

Fracture



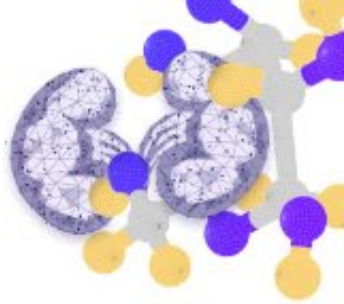
	SGLT2i (%)	*Placebo (%)*	*Hazard Ratio/Risk difference (v Pbo)*	*P value*
CREDENCE* n=4,401	1.18	1.21	0.98 (0.70, 1.37)	-
EMPA-REG* ‡ eGFR<60ml/min: n=1,819	2.0	2.3	-	-
EMPA-REG* ‡ eGFR≥60ml/min: n=5,199	1.4	1.4	-	-
CANVAS‡ n=10,142	1.54	1.19	1.26 (1.04, 1.52)	0.02
DECLARE n=17,143	5.3	5.1	1.04 (0.91, 1.18)	0.59
VERTIS CV‡ n=8,238	3.7	3.6	-	-
EMPEROR Reduced n=3,726	2.4	2.3	-	-
DAPA-HF n=4,744	2.1	2.1	-	1.00
DAPA-CKD n=4,298	3.2	4.0	-	0.22

‡ Low and high dose SGLT2 arms combined

* rates/100 pt years

Perkovic *NEJM* 2020 Neal *NEJM* 2017 Cannon NEJM 2020 Packer NEJM, 2020 Heerspink *NEJM* 2020 Wanner *NEJM* 2016
Zinman *NEJM* 2015 Wiviott *NEJM* 2019 VERTIS CV, ADA 2020 Murray *NEJM* 2019 C Arnott. *JAMA* 2020 Inzucchi, *Diabetes Care* 2018; 41(1): e4-e5

Amputation



	SGLT2i (%)	*Placebo (%)*	*Hazard Ratio/Risk difference (v Pbo)*	*P value*
CREDENCE* n=4,401	1.23	1.12	1.11 (0.79, 1.56)	-
EMPA-REG‡ N=7,020	1.9	1.8	1.01 (0.70, 1.44)	-
CANVAS‡ n=10,142	0.063	0.034	1.97 (1.41, 2.75)	<0.001
DECLARE n=17,143	1.4	1.3	1.09 (0.84, 1.40)	0.53
VERTIS CV‡§ n=8,238	2.0	1.6	-	-
EMPEROR Reduced n=3,726	0.7	0.5	-	-
DAPA-HF n=4,744	0.5	0.5		1.00
DAPA-CKD n=4,298	1.6	1.8		0.73

‡ Low and high dose SGLT2 arms combined.
§ Risk difference is for SGLT2i v pbo

Perkovic *NEJM* 2020 Neal *NEJM* 2017 Cannon NEJM 2020 Packer NEJM, 2020 Heerspink *NEJM* 2020 Inzucchi, *Diabetes Care* 2018; 41(1): e4-e5
Zinman *NEJM* 2015 Wiviott *NEJM* 2019 VERTIS CV, ADA 2020 Murray *NEJM* 2019 C Arnott. *JAMA* 2020

Volume depletion

	SGLT2i (%)	*Placebo (%)*	*Hazard Ratio*	*P value*
CREDENCE n=4,401	2.84	2.35	1.25 (0.97-1.59)	-
EMPA-REG‡ eGFR<60ml/min: n=1,819	2.8	3.6	-	
EMPA-REG*‡ eGFR≥60ml/min: n=5,199	1.8	1.6		
CANVAS* n=4,330	2.60	1.85	-	0.009
DECLARE n=17,143	2.5	2.4	1.00 (0.83, 1.21)	p=0.99
VERTIS CV‡ n=8,238	4.3	3.9	-	NS
EMPEROR Reduced n=3,726	10.6	9.9	-	-
DAPA-HF n=4,744	7.5	6.8	-	0.40
DAPA-CKD n=4,298	5.9	4.2	-	0.01

‡ Low and high dose SGLT2 arms combined.
* rates/100 pt years, collected from CANVAS alone

Perkovic *NEJM* 2020 Neal *NEJM* 2017 Cannon NEJM 2020 Packer NEJM, 2020 Heerspink *NEJM* 2020 Wanner *NEJM* 2016
Zinman *NEJM* 2015 Wiviott *NEJM* 2019 VERTIS CV, ADA 2020 Murray *NEJM* 2019 C Arnott. *JAMA* 2020 Inzucchi, *Diabetes Care* 2018; 41(1): e4-e5

Urinary Tract Infections

	SGLT2i (%)	*Placebo (%)*	*Hazard Ratio/Risk difference (v Pbo)*	*P value*
CREDENCE n=4,401	4.86	4.51	1.08 (0.90-1.29)	-
EMPA-REG* ‡ eGFR<60ml/min: n=1,819	11.0	10.4	-	-
EMPA-REG* ‡ eGFR≥60ml/min: n=5,199	6.9	7.5	-	-
CANVAS* n=4,330	4.0	3.7	-	0.38
DECLARE n=17,143	1.5	1.6	0.93 (0.73-1.18)	0.54
VERTIS CV‡§ n=8,238	12.1	10.2	-	<0.05
EMPEROR Reduced n=3,726	4.9	4.5	-	-
DAPA-HF n=4,744	0.5	0.7	-	-
DAPA-CKD n=4,298	0.9	0.7	-	-

‡ Low and high dose SGLT2 arms combined.
* rates/100 pt years, collected from CANVAS alone

Perkovic *NEJM* 2020 Neal *NEJM* 2017 Cannon NEJM 2020 Packer NEJM, 2020 Heerspink *NEJM* 2020 Wanner *NEJM* 2016
Zinman *NEJM* 2015 Wiviott *NEJM* 2019 VERTIS CV, ADA 2020 Murray *NEJM* 2019 C Arnott. *JAMA* 2020 Inzucchi, *Diabetes Care* 2018; 41(1): e4-e5

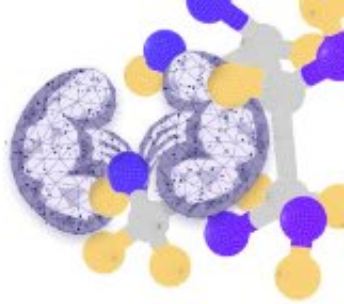
Genital Mycotic Infections

	SGLT2i (%)	*Placebo (%)*	*Hazard Ratio/Risk difference (v Pbo)*	*P value*
CREDENCE male n=2907	0.84	0.09	9.30 (2.83-30.60)	-
CREDENCE female n=1494	0.13	0.06	2.10 (1.00-4.45)	-
EMPA-REG* ‡ male n=5016	5.0	1.5		<0.001
EMPA-REG* ‡ female n=2004	10.0	2.6		<0.001
CANVAS female* n=4,330	6.88	1.75		<0.001
DECLARE n=17,143	0.9	0.1	8.36 (4.19-16.68)	<0.001
VERTIS CV‡ male n=5,769	4.4/5.1	1.2	-	<0.001
VERTIS CV‡ female n=2,477	6.0/7.8	2.4	-	<0.001
EMPEROR Reduced n=3,726	1.7	0.6	-	-
DAPA-HF n=4,744	NR	NR	-	-
DAPA-CKD n=4,298	NR	NR	-	-

* rates/100 pt years, collected from CANVAS alone

Perkovic *NEJM* 2020 Neal *NEJM* 2017 Cannon NEJM 2020 Packer NEJM, 2020 Heerspink *NEJM* 2020 Inzucchi, *Diabetes Care* 2018; 41(1): e4-e5
Zinman *NEJM* 2015 Wiviott *NEJM* 2019 VERTIS CV, ADA 2020 Murray *NEJM* 2019 C Arnott. *JAMA* 2020

Genital mycotic infections by eGFR



	Men N (%)	Women N (%)	Total	Serious % of total
Genital mycotic infections	31 (1.1%)	32 (2.1%)	91	0

	Total	CANA	Placebo	HR (95%CI)
Participants with GMIs	63	50	13	3.83 (2.08, 7.06)
Drug continued	56 (89%)	43	13	
Subsequent GMI	17	13 (30.2%)	4 (30.8%)	

CREDENCE

Amy Kang: ePoster #: PO1004
Session Title: Diabetic Kidney Disease: Clinical - 2
Session Release Date, Time: Thursday, October 22, 10:00 a.m. EDT

The Facts

SGLT2i improve outcomes in patients with DM and patients with CKD and those with established Heart disease (and all combinations)

- Kidney outcomes
- CV outcomes
- Heart Failure

Multiple RCTs concordant > 20, 000 pts!!

Biological plausibility and mechanisms

Identifiable patient profiles

This appears to be independent of hypoglycemic effects

There is no increased incidence of AKI

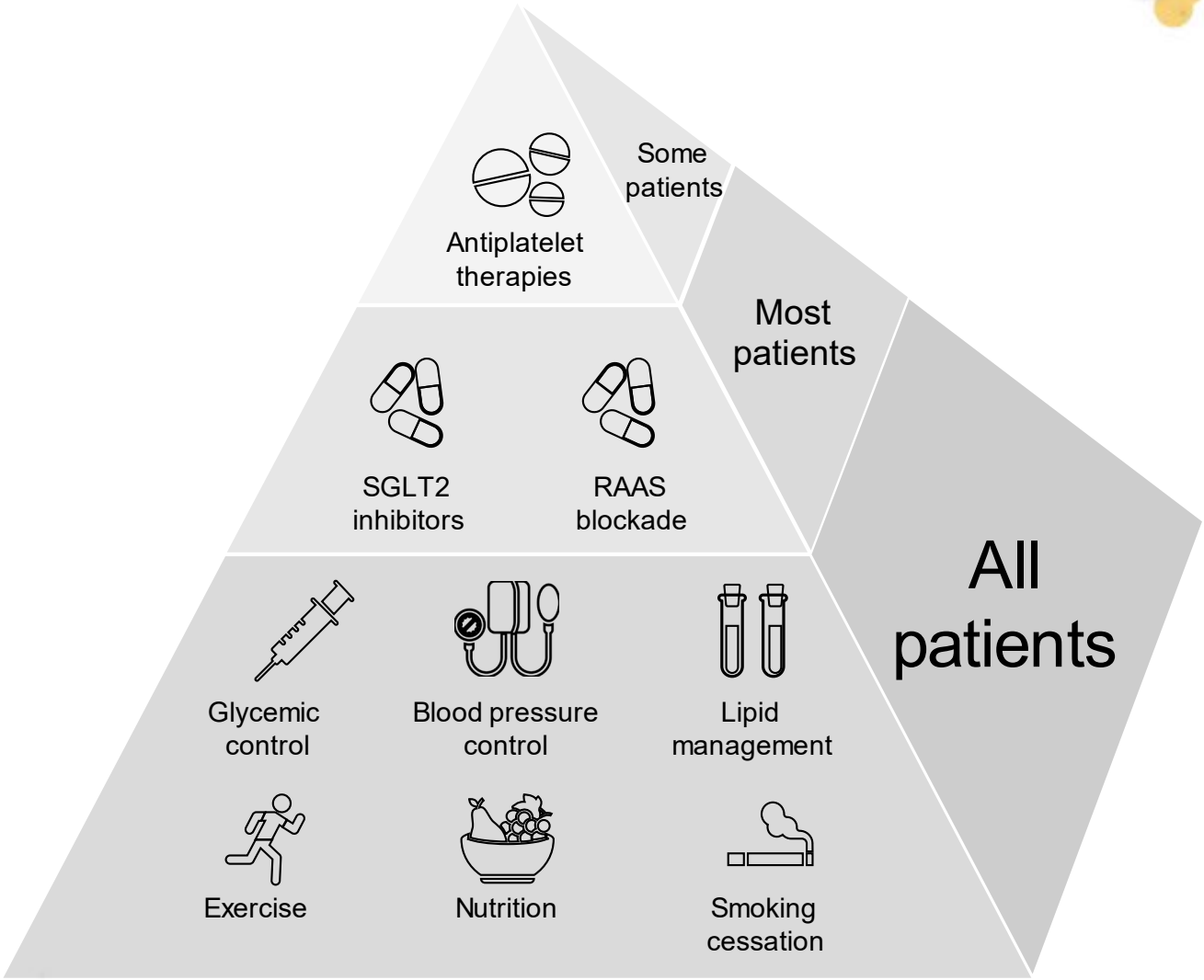
The effects appear to be across increasing categories of eGFR and uACR values in populations studied to date

The effects appear to be strong irrespective of ACEi /ARB use

Studies designed all used fixed dose of SGLT2i

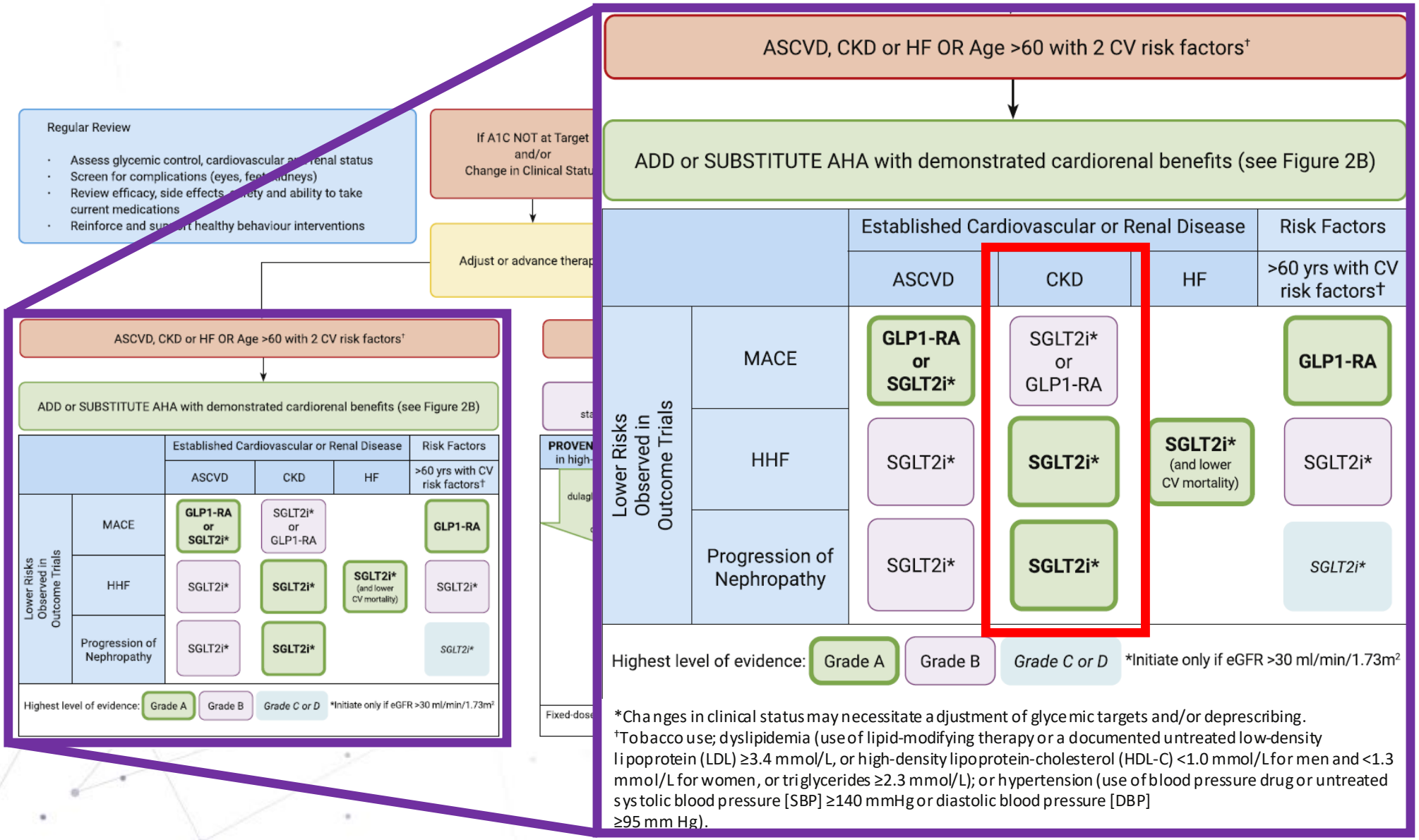
KDIGO 2020 Guidelines for Diabetes Management in CKD

- **All patients** with T2D and CKD should receive:
  - Glycemic control
  - Blood pressure control
  - Lipid management
  - Lifestyle counseling
- **Most patients** with T2D and CKD should receive:
  - ACEi or ARB
  - SGLT2 inhibitors



Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. Kidney International. 2020; 98(4S):S1-S115.

Diabetes Canada Pharmacologic Glycemic Management of Type 2 Diabetes in Adults: 2020 Update



Lipscombe et al. Can J Diabetes. 2020; 44:575-591.

SGLT2i : contextualizing the evidence into clinical practice

What I did before: Care of CKD Patients

- BP control
- Glycemic control
- Anti-proteinuric agents (RAS blockade)
- Multisciplinary care team
  - Nurse, Dietician, Social Worker
  - Pharmacist
- Regular bloodwork and urine ACR
- Regular intervals assessment
  - Education
  - Navigation
  - Surveillance

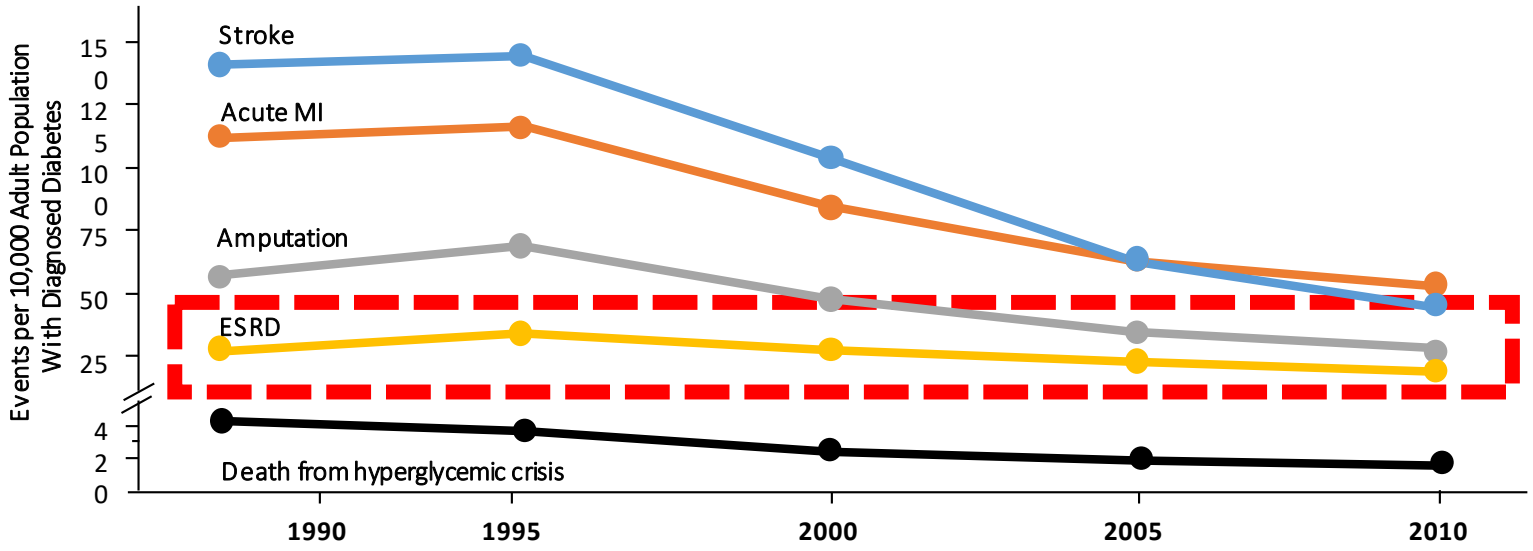
And lots of fiddling……

- Blood pressure :RAAS inhibition, B-blockers, diuretics, MRA, CCB…..
- AKI risk and management:
  - Increasing recognition of impact on trajectory and variability
  - Nephrotoxins (NSAID, AGs), ECFV contraction, procedures (dye and other)
- Protein intake
- Salt intake
- Focus on Hyperuricemia
- Calcium, Phosphate, iPTH measurement
- Life style
- CV Risk reduction: Lipid lowering

And where did this get us?

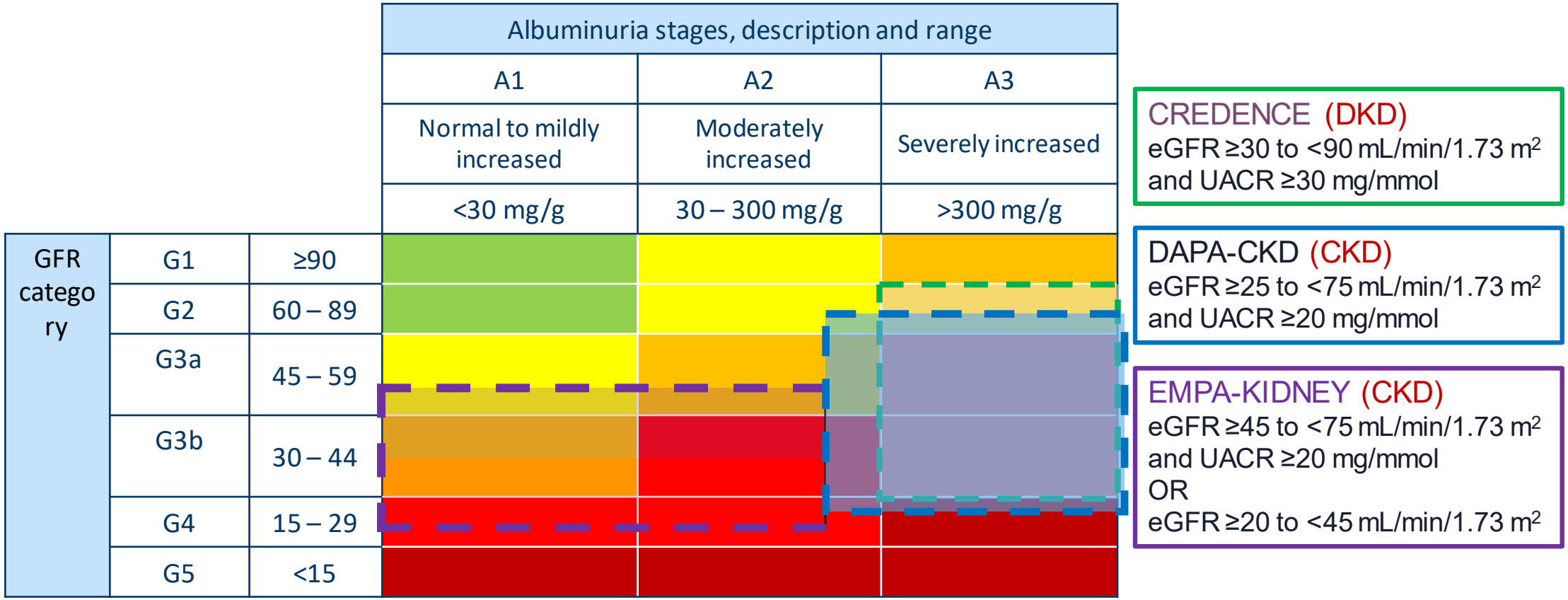
For people with diabetes… little improvement in the rate of kidney failure (ESRD)

- Rates of the other major complications in diabetes have declined
- Rates of ESRD have actually increased among older adults



ESRD, end-stage renal disease; MI: myocardial infarction.Adapted from: Gregg EW, et al. *N Engl J Med* 2014;370:1514-23.

SGLT2 Inhibitors: Primary Kidney Outcome Trials
Fixed dose, no targets, on top of best current care, international

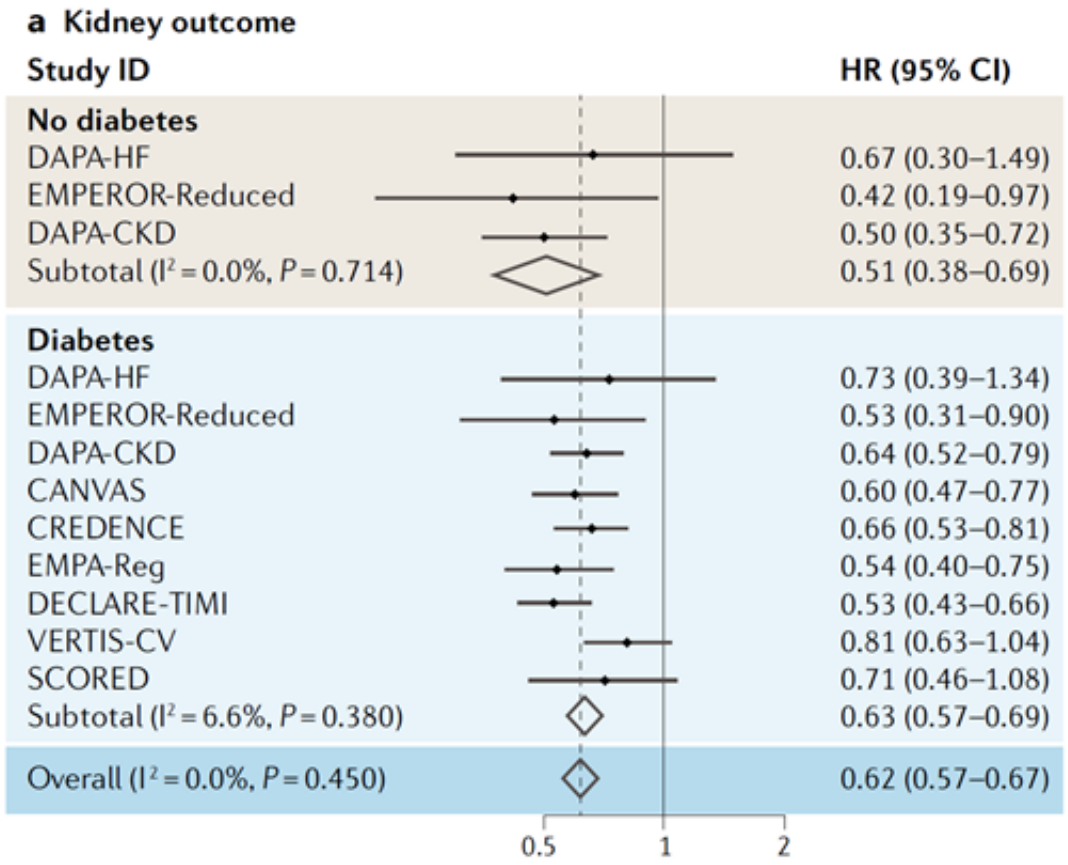


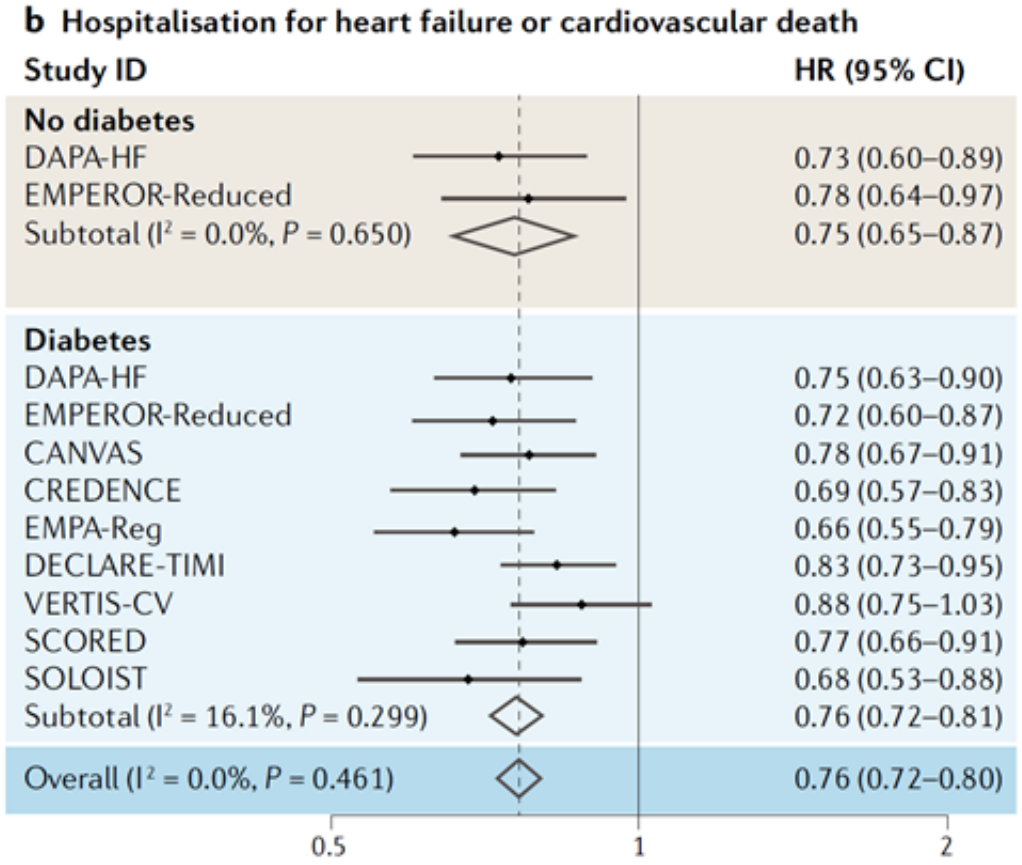
The cardiovascular outcome trials are indicated in the circles and positioned based on their mean eGFR and median UACR

CREDENCE: Perkovic et al. *N Engl J Med* 2019, 380: 2295-2306
DAPA-CKD: Heerspink et al. *N Engl J Med*. 2020; 383: 1436-1446
EMPA-KIDNEY: Ongoing; Herrington WG, et al. *Clin Kidney J*. 2018; 11:749-761.

Courtesy of Dr. Peter Rossing

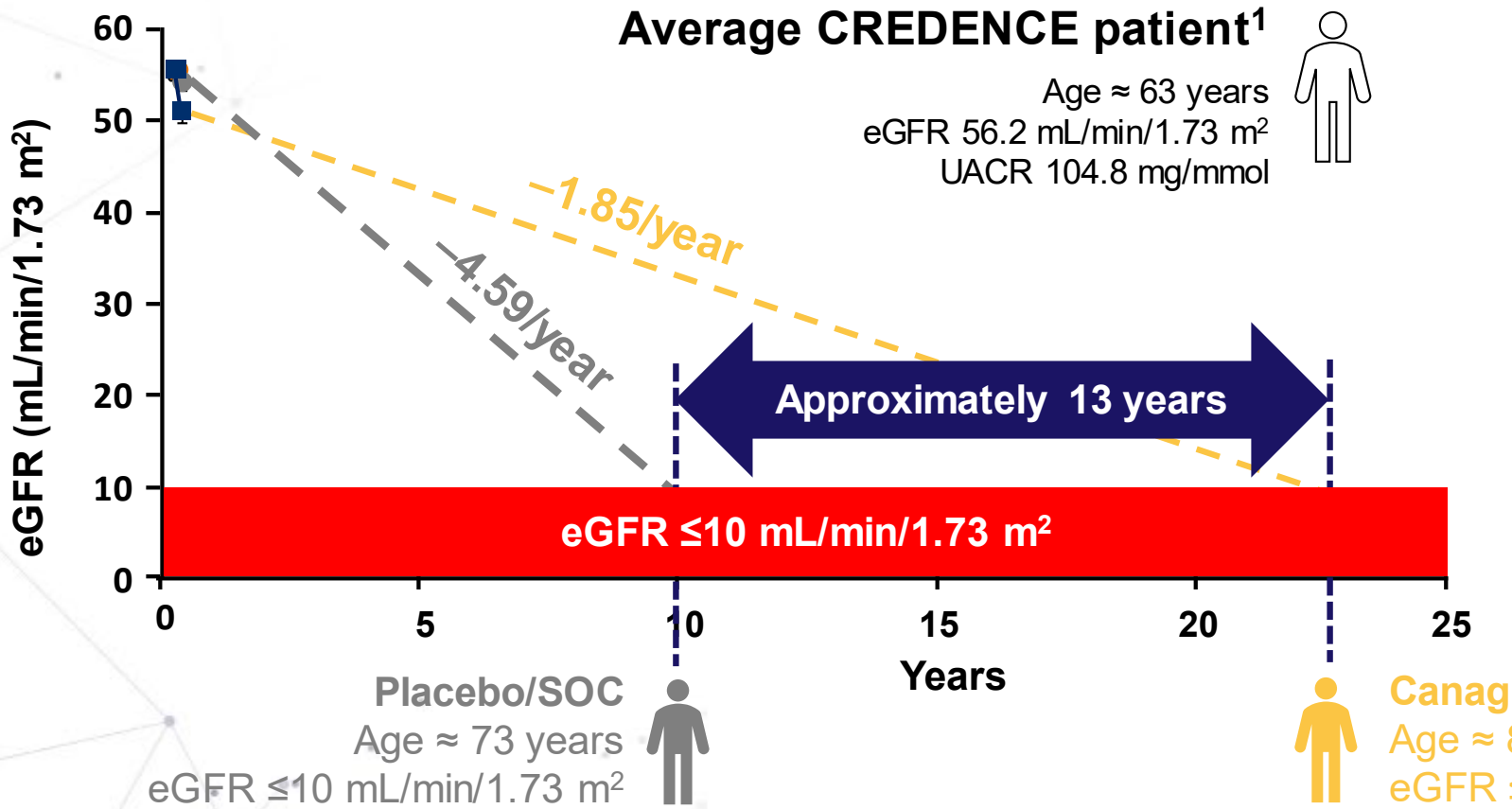
SGLT2 Inhibitors: Evidence Summary of Cardiovascular and Kidney Benefits





Kang A & Jardine M. *Nat Rev Nephrol*. 17: 83-84, 2021

SGLT2 inhibitors slow the rate of eGFR decline: Hypothetical importance of chronic eGFR slope difference



Estimated cost savings for 13-year delay of dialysis[2]

$502,554
(peritoneal)

to

$834,782
(in-center hemodialysis)

Projections are based on eGFR slopes from week 3 to end of treatment (chronic phase) and assume linear progression of eGFR decline

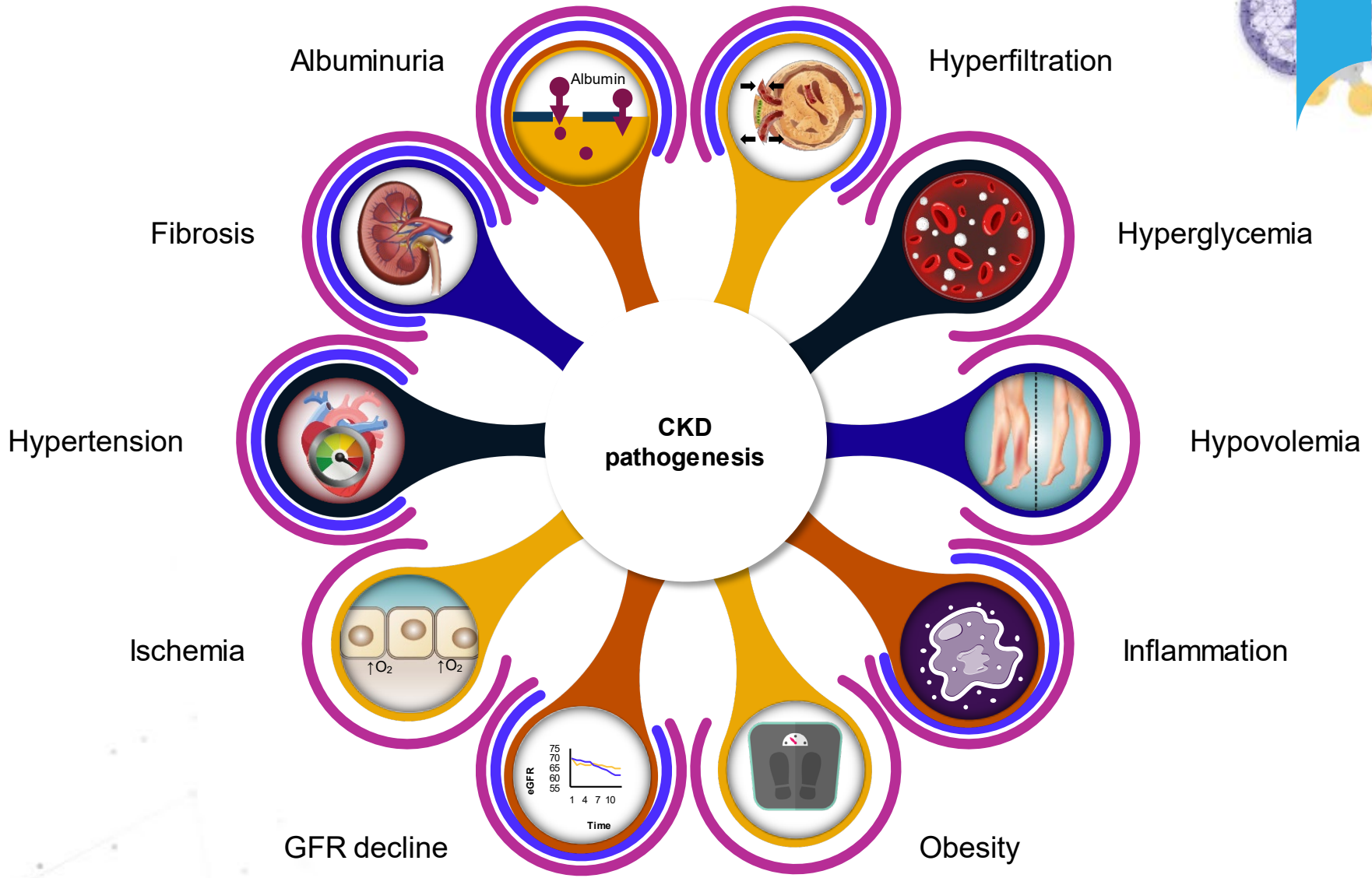
- Calculated as [(eGFR at start of chronic phase – 10 mL/min/1.73 m²) / chronic eGFR slope]

eGFR at start of chronic phase (3-week time point): Canagliflozin 100 mg/SOC 52.28 mL/min/1.73 m2, Placebo/SOC 55.45 mL/min/1.73 m2

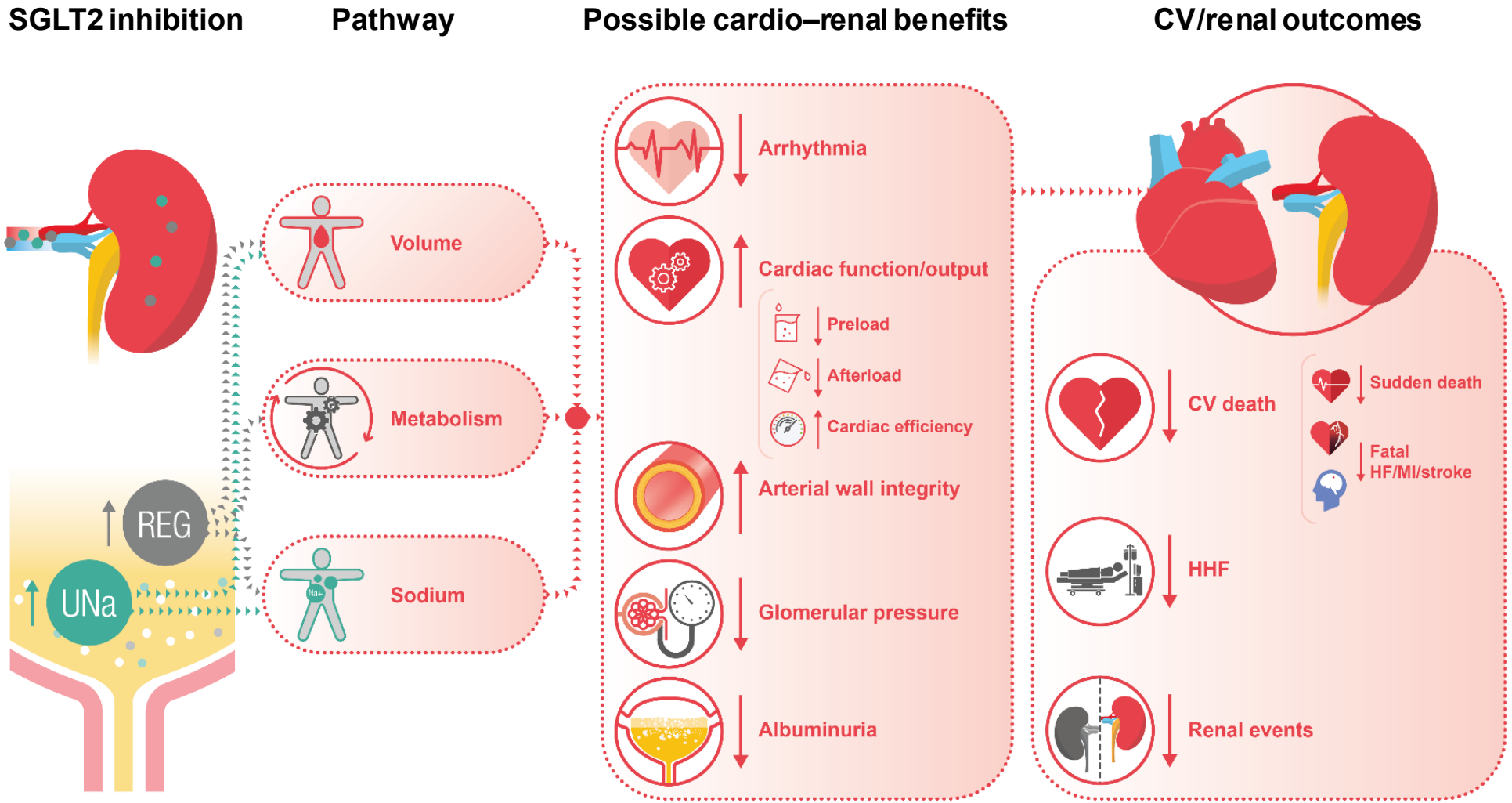
Figure adapted from: Durkin & Blais. Diabetes Ther. 2020 Dec 18. doi: 10.1007/s13300-020-00953-4.

1. Perkovic et al. N Engl J Med. 2019; 380(24):2295-2306.
2. Beaudry et al. Clin J Am Soc Nephrol. 2018;13(8):1197-1203.

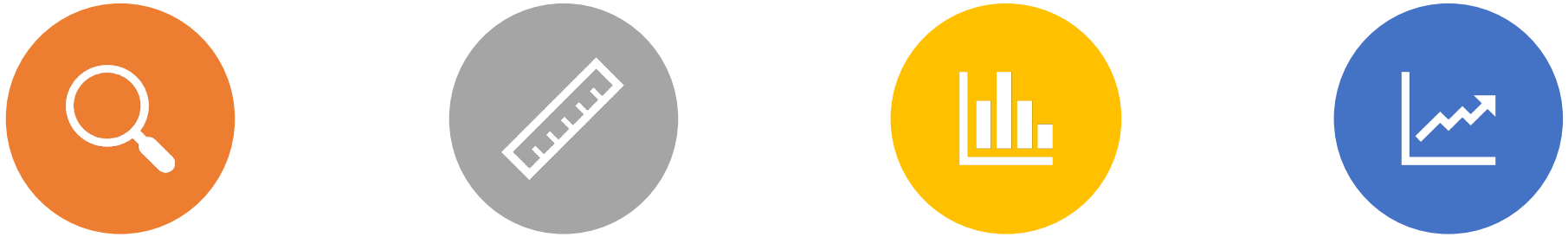
SGLT2 inhibitors
So many ways to improve outcomes



Mechanisms of Action of SGLT2 Inhibitors on hearts and kidneys



Changing clinical practice : The SGLT2 inhibitor story



STUDIES IN SGLT2I

DESIGN

RESULTS CONCLUSIONS

WHY IMPACTFUL

Translating improved understanding to clinical practice

01 Identify patients who are likely to benefit most from an SGLT2 inhibitor

02 Facilitate initiation of an SGLT2 inhibitor where appropriate

03 Optimize therapy for CKD by incorporating an SGLT2 inhibitor with other kidney-protective agents where appropriate

04 Discussion

CKD, chronic kidney disease; SGLT2, sodium–glucose co-transporter 2