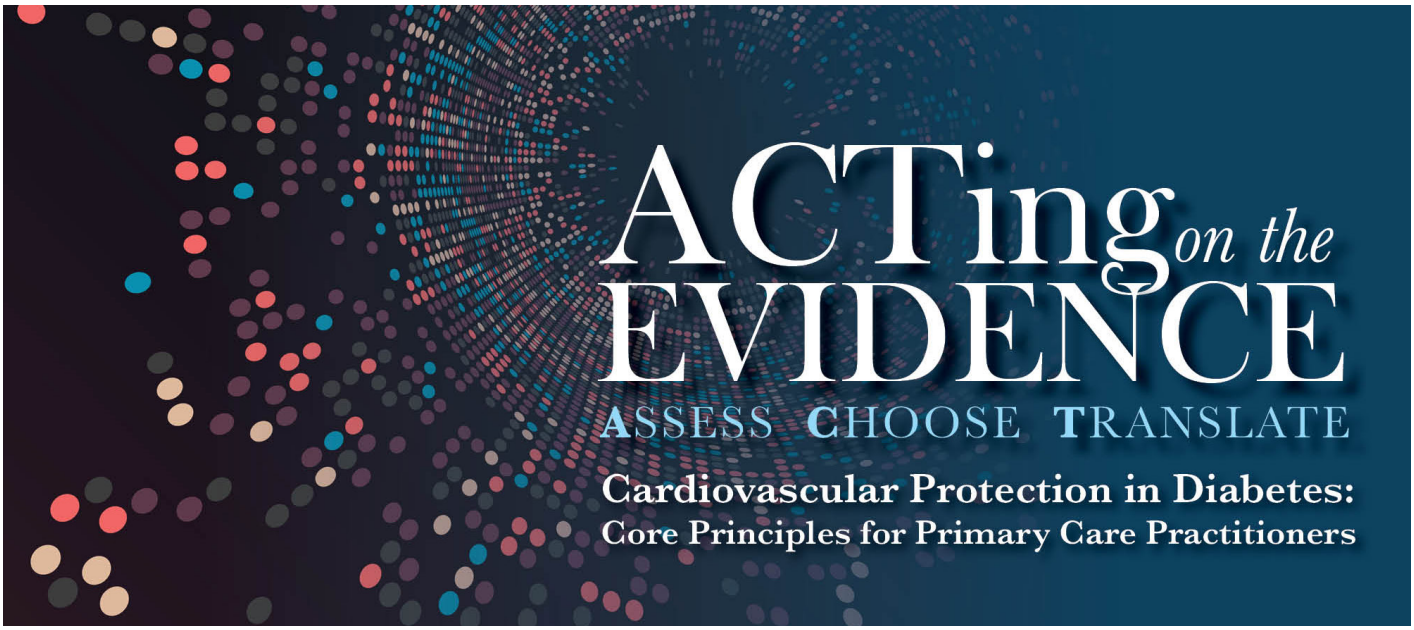

Evidence for the renal benefits of SGLT-2 inhibitors in diabetes

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Module 5: Renal benefits of SGLT-2 inhibitors in diabetes

Introduction

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Chronic kidney disease remains an important complication of type 2 diabetes mellitus (T2DM); control of risk factors and the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are foundational therapy, paramount to reducing diabetic kidney disease. Three large cardiovascular outcomes trials (CVOTs) with sodium-glucose co-transporter-2 (SGLT-2) inhibitors have now provided data that these agents similarly reduce renal events, quite profoundly, across a broad spectrum of patients with or without established cardiovascular disease. Many other ongoing trials will evaluate the efficacy of SGLT-2 inhibitors as a renal protective strategy in people with or without diabetes, with established renal disease, and renal disease in heart failure.

Mechanism of action of SGLT-2 inhibitors – proposed renal protective pathways

SGLT-2 inhibitors limit the reabsorption of both glucose and sodium in the proximal tubule of the kidney, resulting in glycosuria and natriuresis.[1] There is overlap between the SGLT-2 mechanisms suggested to be involved in renal protection with those mechanisms that have been proposed to explain their cardiovascular benefit (Figure 1);[2] both direct and indirect mechanisms may mediate the renal protection of these agents.

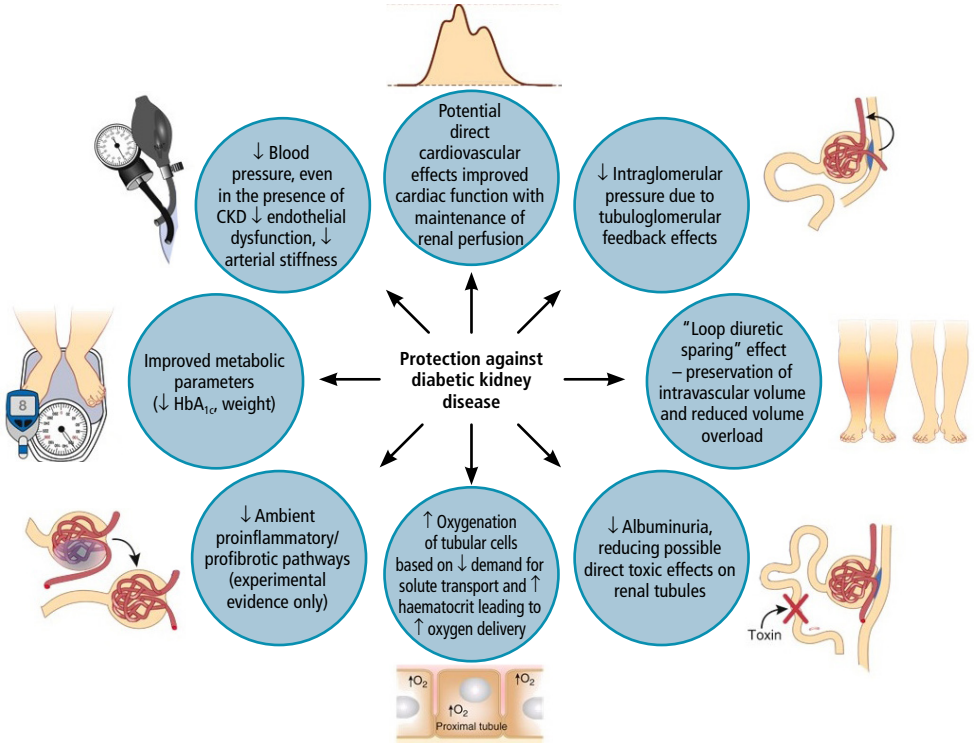


Figure 1. Proposed renal protective pathways of SGLT-2 inhibitors

Other modules

Module 1
Cardiovascular prevention and heart failure in diabetes

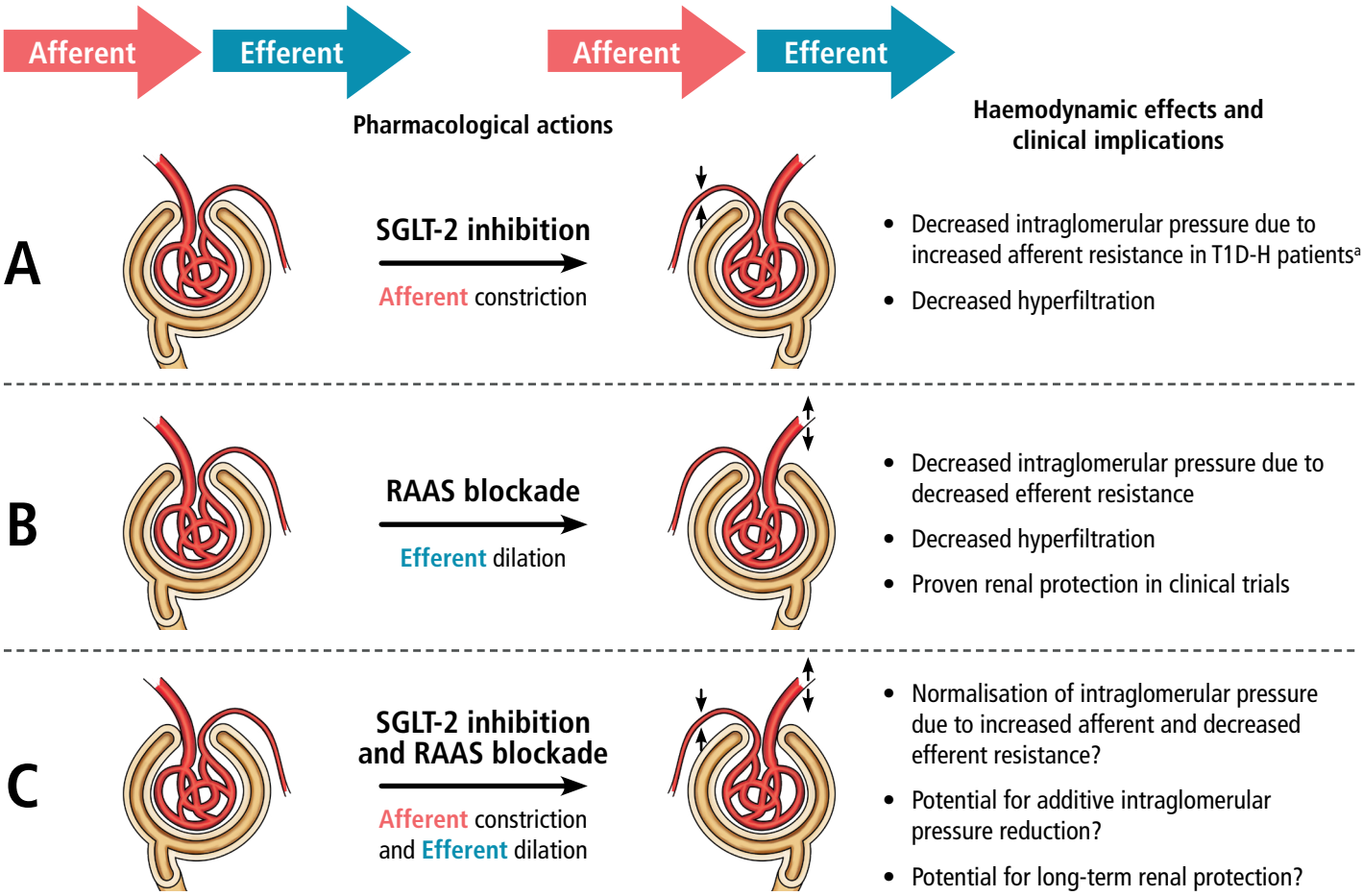
Module 2
Cardiovascular outcome trials in diabetes

Module 3
Renal protection in type 2 diabetes

Module 4
Review of renal therapies prior to SGLT-2 inhibitors

Module 6
Safety of SGLT-2 inhibitors and side-effects

SGLT-2 inhibitors promote relative afferent arteriole vasoconstriction, thereby reducing intraglomerular hypertension;[3] renin-angiotensin-aldosterone system (RAAS) blockers act on efferent arteriole vasodilatation to reduce intraglomerular hypertension. The combination of SGLT-2 inhibitors and RAAS blockers is complementary, with the potential for additive reductions in intraglomerular pressure that benefit the kidney (Figure 2).



RAAS: renin–angiotensin–aldosterone system; T1D-H: type 1 diabetes hyperfiltration
[a] SGLT-2 inhibitors are not indicated for use in type 1 diabetes in South Africa

Figure 2. Clinical implications of the pharmacological actions and haemodynamic effects of SGLT-2 inhibition and RAAS blockade

What is the evidence of SGLT-2 inhibitor benefit for renal function preservation?

A starting point from which to understand the significance of the SGLT-2 inhibitors, canagliflozin, dapagliflozin and empagliflozin, arises from evidence-based data.

A comparative study of canagliflozin versus glimepiride has shown that canagliflozin preserved renal function in relatively low-risk individuals with normal renal function, compared to the ongoing decline seen in patients on sulphonylurea treatment (Figure 3).[4] The estimated glomerular filtration rate (eGFR) slope reductions are greater with the sulphonylurea compared to the SGLT-2 inhibitor and that relationship remains consistent even in people with urine albumin-to-creatinine ratios (UACRs) >3.4mg/mmol. In fact, eGFR slopes are steeper with sulphonylurea therapy than those seen in the overall population (Figure 4).[5] The DERIVE study of dapagliflozin demonstrated an initial dip in eGFR, explained as a recalibration secondary to afferent arteriole vasoconstriction and due to changing intraglomerular haemodynamics and intraglomerular pressures.

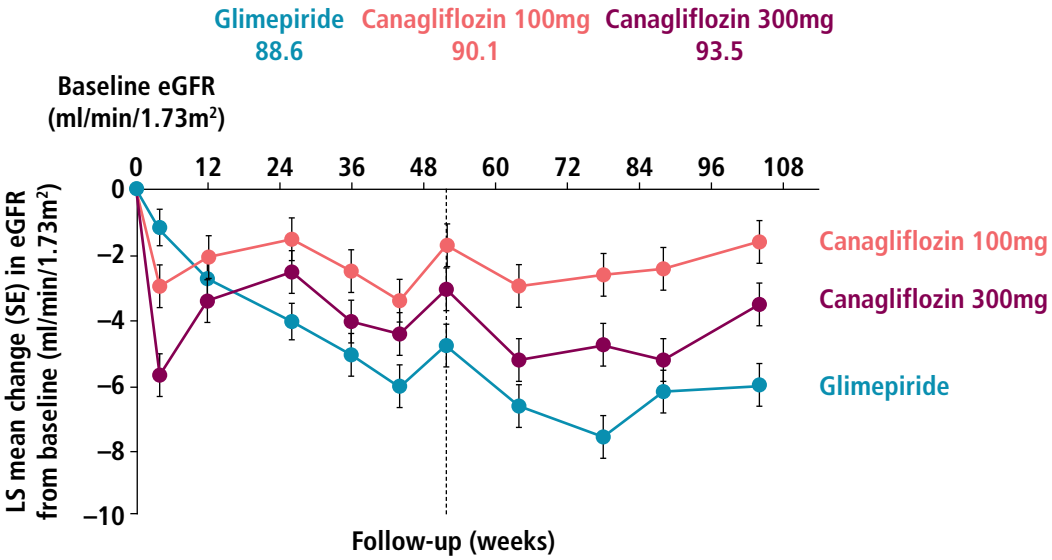
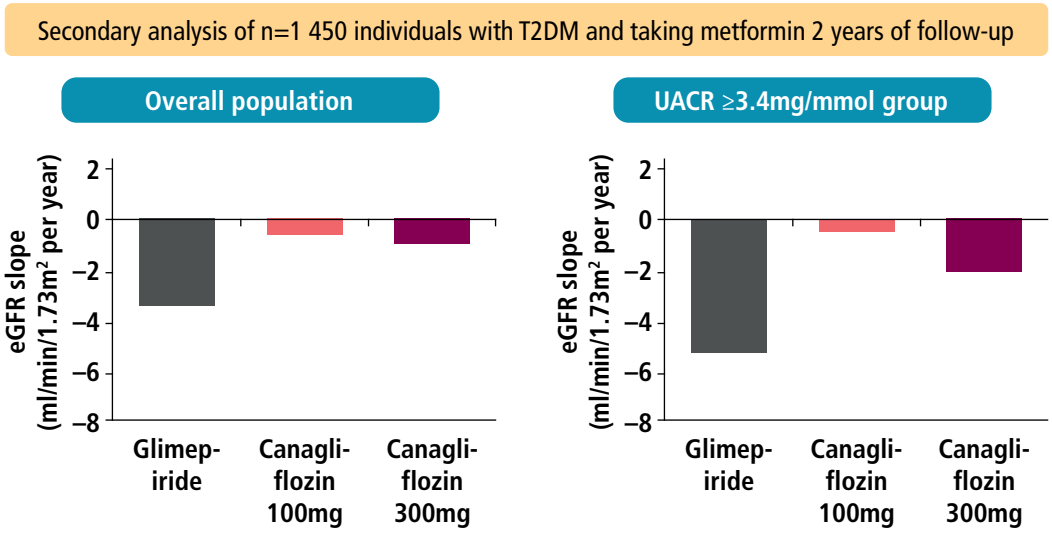


Figure 3. Canagliflozin preserves renal function in low-risk individuals with normal renal function



eGFR: estimated glomerular filtration rate; UACR: urinary albumin-to-creatinine ratio

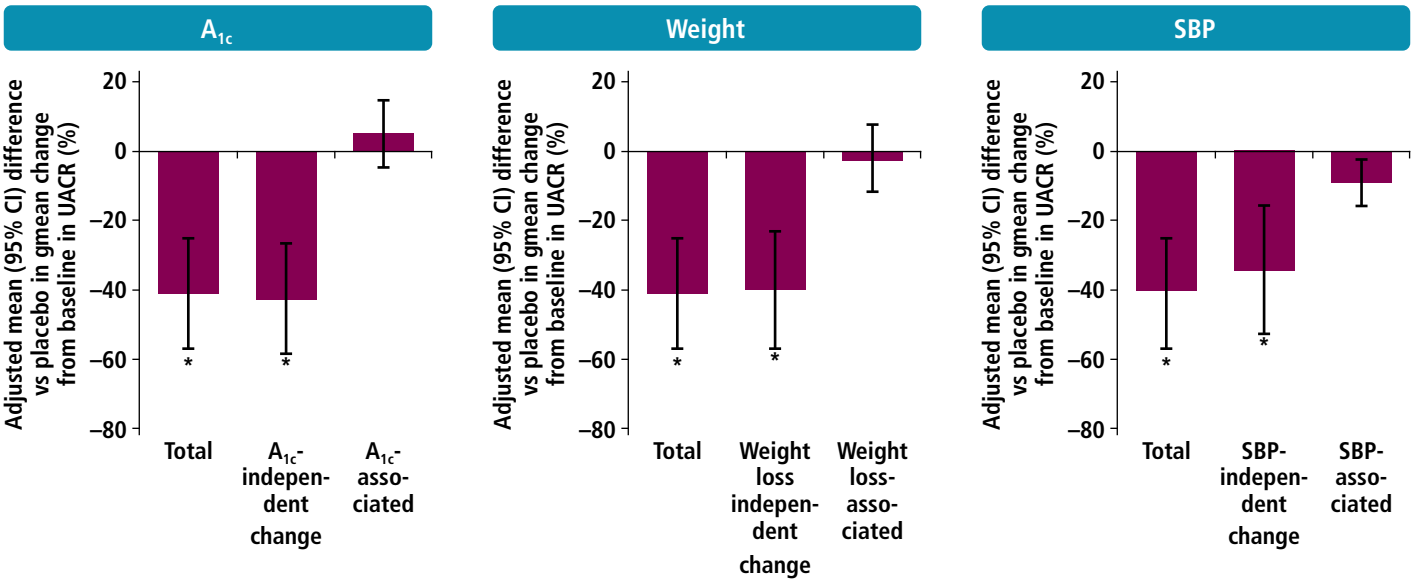
Figure 4. Canagliflozin slows eGFR decline

The haemodynamic benefits persist despite a lack of HbA_{1c} reduction, particularly at the lower GFRs

It is important to understand that the renal protective benefits of an SGLT-2 inhibitor are distinct and independent of changes in HbA_{1c}, weight and blood pressure. Pooled analyses with empagliflozin from five phase III randomised controlled trials of patients with either microalbuminuria or macroalbuminuria assessed the proportion of the benefit dependent on or independent of HbA_{1c}, weight or blood pressure. The percentage change in geometric mean UACR from baseline to week 24 was independent of HbA_{1c}, weight and blood pressure changes (Figure 5).[6]

The impact of empagliflozin on HbA_{1c} and systolic blood pressure as stratified by GFR is important. With declining GFR, the HbA_{1c} lowering efficacy is reduced substantially. In addition, with declining GFR there is no reduction in the blood pressure lowering efficacy of empagliflozin (Figure 6); if anything, the effect on blood pressure tends to be greater when the GFR is lower. The haemodynamic benefits persist despite a lack of HbA_{1c} reduction, particularly at the lower GFRs.

Pooled analysis of 5 Phase III RCTs with T2DM cohorts
n=636 with microalbuminuria (UACR 3.4–34mg/mol) | n=215 with macroalbuminuria (UACR >34mg/mol)



Primary assessment was the % change in gmean UACR from baseline to week 24

CKD: chronic kidney disease; gmean: geometric mean; RCT: randomised trail; SBP: systolic blood pressure; T2DM: type 2 diabetes; UACR: urinary albumin-to-creatinine ratio.
*P<0.05 (treated set; last observation carried forward).

Figure 5. Empagliflozin-mediated UACR changes are largely independent of HbA_{1c}, systolic blood pressure and weight

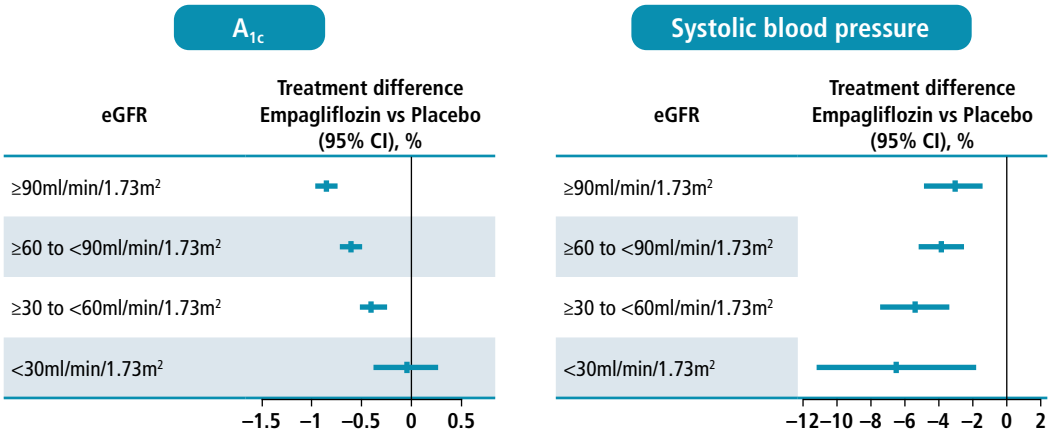


Figure 6. Impact of empagliflozin on HbA_{1c} and systolic blood pressure as stratified by eGFR

EMPA-REG OUTCOME: What have we learned about renal outcomes with empagliflozin treatment?

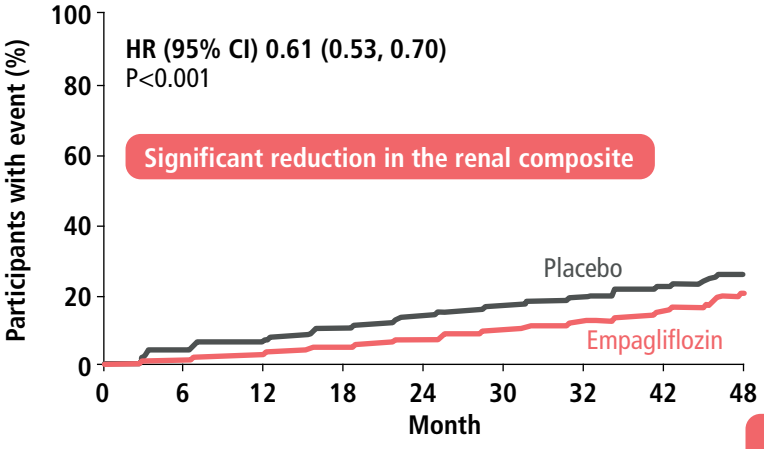
EMPA-REG OUTCOME evaluated 7 000 patients randomised to one of three arms: placebo, empagliflozin 10mg and empagliflozin 25mg. These T2DM patients all had established cardiovascular disease or atherosclerotic cardiovascular disease (ASCVD). For the outcome of major adverse cardiovascular events (MACE), empagliflozin treatment achieved superiority. There was a 35% reduction of the heart failure outcome in actively treated patients.

Renal composite in EMPA-REG OUTCOME

The point estimates of the renal outcomes all favour empagliflozin and the hazard ratios are profound, indicative of an approximate 50% RRR

The renal outcome was a composite of progression to macroalbuminuria, a doubling of serum creatinine with an eGFR <45ml/min/1.73m^2, initiation of renal replacement therapy (RRT) or death from renal disease. A profound 39% relative risk reduction (RRR) for the renal endpoint was demonstrated with empagliflozin versus placebo (Figure 7).[7]

There are various markers by which the renal outcomes can be measured: incident or worsening nephropathy by itself; progression to macroalbuminuria; reduction of serum creatinine levels that were accompanied by an eGFR <45ml/min/1.73m^2; initiation of RRT; or the composite of doubling of serum creatinine accompanied by an eGFR <45ml/min/1.73m^2, initiation of RRT or death from renal disease. The individual outcomes from EMPA-REG are shown in Figure 8. The point estimates of the renal outcomes all favour empagliflozin and the hazard ratios are profound, indicative of an approximate 50% RRR.



- Progression to macroalbuminuria
- Doubling of serum creatinine with an eGFR of ≤45ml/minute/1.73m^2
- Initiation of renal-replacement therapy
- Death from renal disease

No signal of increased acute kidney injury risk

Figure 7. EMPA-REG OUTCOME: renal composite

Outcome	Placebo		Empagliflozin		HR (95% CI)	P-value
	No. with event/ No. analysed (%)	Rate/1 000 patient years	No. with event/ No. analysed (%)	Rate/1 000 patient years		
Incident or worsening nephropathy or CV death	497/2102 (23.6)	95.9	675/4170 (16.2)	60.7	0.61 (0.55–0.69)	<0.001
Incident or worsening nephropathy	388/2061 (18.8)	76.0	525/4124 (12.7)	47.8	0.61 (0.53–0.70)	<0.001
Progression to macroalbuminuria	330/2033 (16.2)	64.9	459/4091 (11.2)	41.8	0.62 (0.54–0.72)	<0.001
Doubling of serum creatinine level accompanied by an eGFR ≤45ml/min/1.73m^2	60/2323 (2.6)	9.7	70/4645 (1.5)	5.5	0.56 (0.39–0.79)	<0.001
Initiation of renal replacement therapy	14/2333 (0.6)	2.1	13/4687 (0.3)	1.0	0.45 (0.21–0.97)	0.04
Doubling or serum creatinine level accompanied by an eGFR ≤45ml/min/1.73m^2, initiation of renal replacement therapy or death from renal disease	71/2323 (3.1)	11.5	81/4646 (1.7)	6.3	0.54 (0.40–0.75)	<0.001
Incident albuminuria in patients with a normal albumin level at baseline	703/1374 (51.2)	266.0	1430/2779 (51.5)	252.5	0.95 (0.87–1.04)	0.25

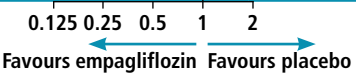
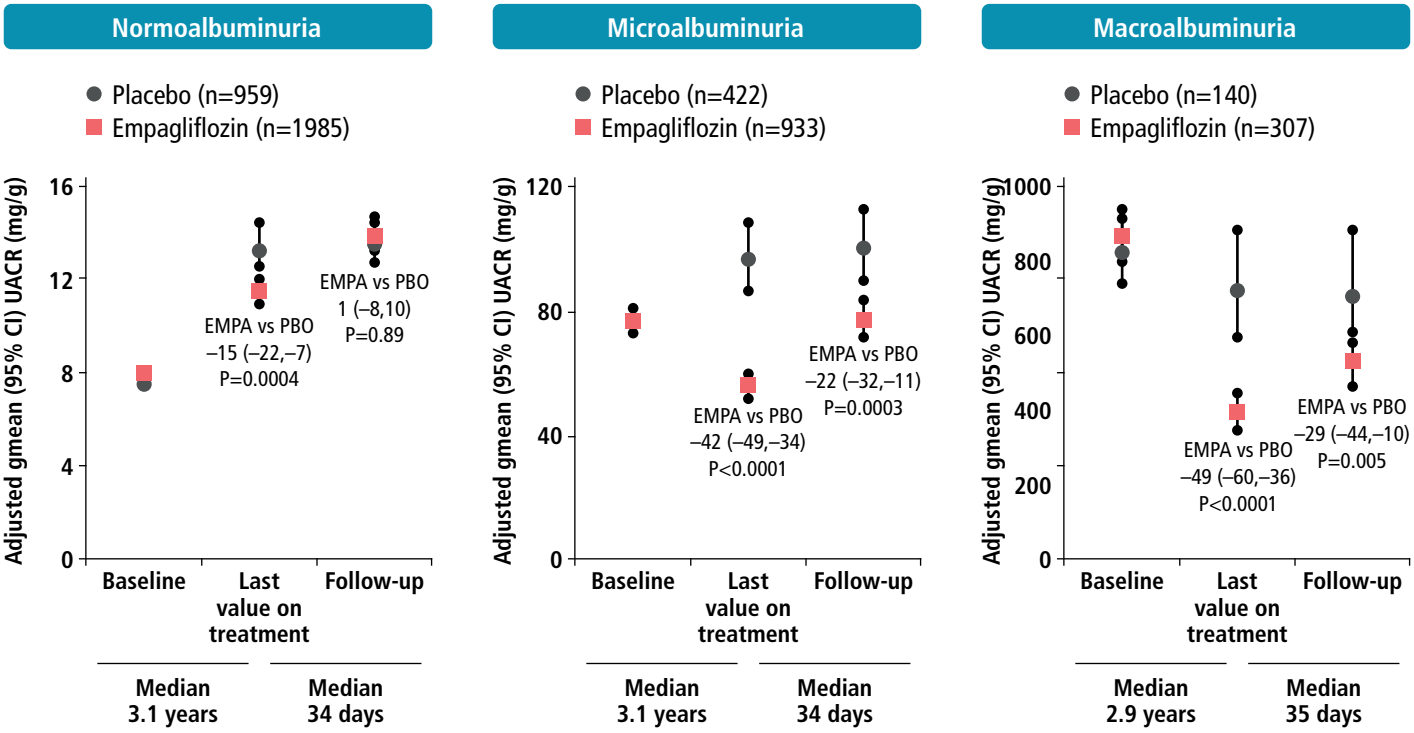


Figure 8. EMPA-REG OUTCOME: individual renal outcome measures

What are the effects of empagliflozin on eGFR by albuminuria status?

In examining the impact of empagliflozin on GFR in people with normoalbuminuria, microalbuminuria and macroalbuminuria, a noticeable stabilisation of the GFR is observed with empagliflozin compared to a decline in GFR observed in the placebo group across patients with normo-, micro- or macroalbuminuria. Empagliflozin demonstrated a profound reduction in UACR in patients with micro- and macroalbuminuria (Figure 9).[6]



gmean: geometric mean; UACR: urinary albumin-to-creatinine ratio.

Figure 9. EMPA-REG OUTCOME: effects of empagliflozin on UACR by albuminuria status

What is the relationship between glycaemia and renal protection?

In respect of the interaction between glycaemia and renal protection after week 12, the evidence of reduced incident or worsening nephropathy clearly favours empagliflozin treatment. Clearly, the benefit of an SGLT-2 inhibitor on incident or worsening nephropathy is totally independent of changes in HbA_{1c} and also independent of baseline HbA_{1c} level.[8]

Outcome	No. with event/No. analysed (%) Placebo	Empagliflozin	HR (95% CI)	P-interaction value
Incident or worsening nephropathy				
All patients	388/2061 (18.8)	524/4124 (12.7)	0.61 (0.53–0.70)	
All patients, adjusted for baseline and time-dependent control of A_{1c} (<7.5%)	388/2061 (18.8)	525/4123 (12.7)	0.65 (0.57–0.74)	
Baseline A_{1c}				
<7.0%	27/111 (24.3)	37/264 (14.0)	0.55 (0.34–0.91)	
7.0 to <8.0%	170/933 (18.2)	214/1814 (11.8)	0.60 (0.49–0.73)	0.6907
8.0 to <9.0%	126/704 (17.9)	161/1348 (11.9)	0.58 (0.46–073)	
≥9.0%	65/313 (20.8)	113/697 (16.2)	0.72 (0.53–0.98)	
Incident or worsening nephropathy after week 12				
All patients	368/2027 (18.2)	513/4089 (12.5)	0.63 (0.55–0.72)	
Change in A_{1c} from baseline to week 12				
Reduction ≥median	104/611 (17.0)	301/2595 (11.6)	0.63 (0.50–0.78)	
Reduction <median	264/1416 (18.6)	212/1493 (14.2)	0.70 (0.58–0.84)	0.4628
Reduction ≥0.5%	89/504 (17.7)	268/2376 (11.3)	0.58 (0.46–0.74)	
Reduction <0.5% or increase	279/1532 (18.3)	245/1712 (14.3)	0.72 (0.61–0.86)	0.1593
Reduction ≥0.3%	127/731 (17.4)	343/2860 (12.0)	0.64 (0.52–0.78)	
Reduction <0.3% or increase	241/1296 (18.6)	170/1228 (13.8)	0.68 (0.56–0.83)	0.6575

Figure 10. EMPA-REG OUTCOME: the effects of empagliflozin on incident or worsening nephropathy stratified by HbA_{1c}

What have we learned about renal protection from the CANVAS Program?

CANVAS studied a mixed population of 10 000 T2DM patients with and without established ASCVD, randomised to placebo, canagliflozin 100mg and canagliflozin 300mg. Recruited patients had an eGFR >30ml/min/1.73m^2, as was also the case in the EMPA-REG OUTCOME trial. With regard to the primary cardiovascular outcomes from the CANVAS Program, MACE was reduced by 14% and hospitalisation for heart failure by 33%. These differences appeared quite early in the trial.

Renal composite of the CANVAS Program

The renal outcome was a composite of a 40% reduction in eGFR, requirement for RRT or death from renal causes. There was a 40% RRR, highly statistically significant, in favour of canagliflozin versus placebo (Figure 11).[9] The composite renal outcome and all of the individual renal outcome components were reduced, including the cardiorenal outcome with canagliflozin. There was no increased signal of acute kidney injury (AKI) and there were indications that the use of an SGLT-2 inhibitor is beneficial with regard to AKI. Progression of albuminuria was also reduced, with a 27% RRR. The effects of canagliflozin to prevent GFR decline occurred across the various strata of eGFR, relative to placebo.

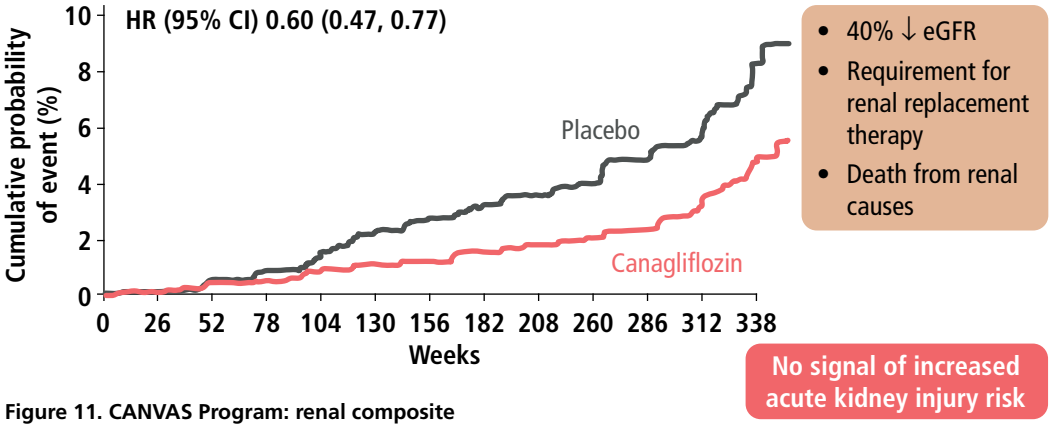


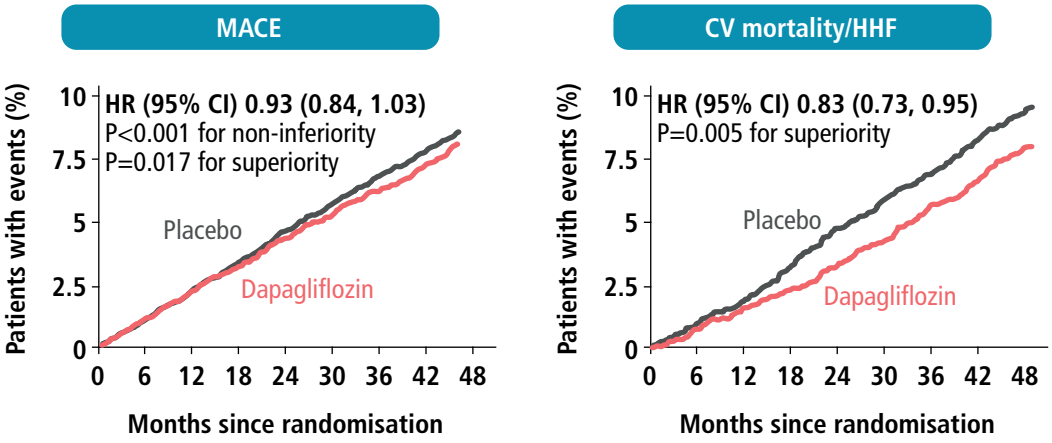
Figure 11. CANVAS Program: renal composite

DECLARE-TIMI 58: dapagliflozin and renal function

The DECLARE-TIMI 58 study included about 60% of patients in primary prevention, 40% in secondary prevention; it is the largest and the longest of all of the three SGLT-2 inhibitor studies and also the broadest in terms of the populations that it enrolled

Of the 17 000 T2DM patients enrolled in DECLARE-TIMI 58, dapagliflozin use in primary prevention was evaluated in 60% of patients, with the remaining 40% being assessed in respect of dapagliflozin used as secondary prevention. This is the largest and the longest of all of the three SGLT-2 inhibitor studies, and also the broadest in terms of the populations that it enrolled.

Patients were randomised to placebo or dapagliflozin and the trial was event-driven, with a median follow-up of 4.2 years. Dual primary outcomes were MACE, with a 7% RRR that is not statistically superior but clearly non-inferior, and the outcome of cardiovascular mortality and heart failure, reduced by 17% with a p-value of 0.0054 for superiority (Figure 12).[9]



CV: cardiovascular; HHF: hospitalisation for heart failure; MACE: major adverse cardiovascular events

Figure 12. DECLARE-TIMI 58: MACE and cardiovascular mortality/hospitalisation for heart failure

Renal composite of DECLARE-TIMI 58

The composite renal outcome included a 40% reduction in eGFR, end-stage renal disease (ESRD), and renal or cardiovascular death. This outcome was substantially reduced in the dapagliflozin treatment arm, with a 24% RRR, in a very broad population of patients primarily at much lower risk than the EMPA-REG and CANVAS cohorts and, most importantly, excluding people with eGFR <60ml/min/1.73m^2. The DECLARE-TIMI 58 results relate to quite healthy patients from a renal standpoint and despite this, dapagliflozin treatment demonstrated a significant renal benefit. There was no significant increase in AKI and numerically fewer cases of AKI were seen in people treated with dapagliflozin (Figure 13).

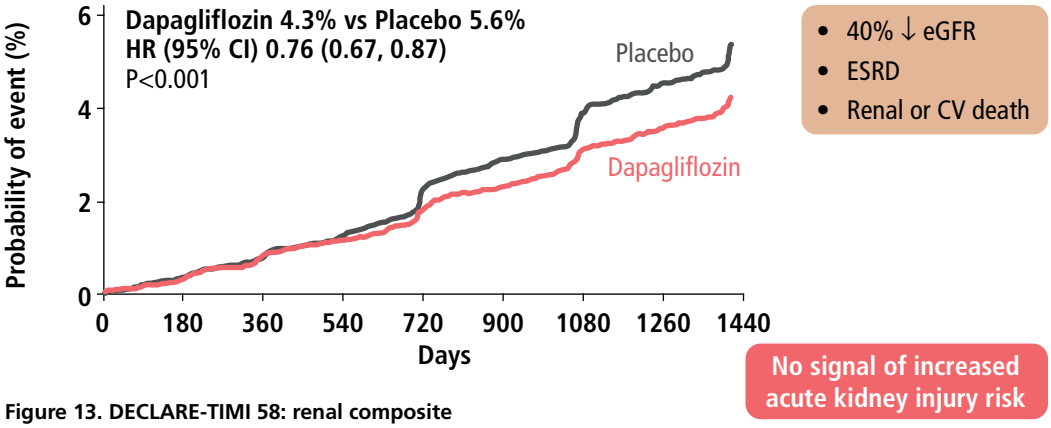


Figure 13. DECLARE-TIMI 58: renal composite

Key outcomes by baseline renal function

Key trial outcomes by baseline renal function include a 40% reduction in eGFR, and a very significant 24% RRR for ESRD, or renal or cardiovascular death, with no statistical heterogeneity in patients across the three categories of eGFR (Figure 14).

I think this is a profound moment to recognise the unbelievable and unprecedented renal protective benefits that are being observed with these agents in both primary and secondary prevention populations and in many cases on top of ACE inhibitors and adequate blood pressure control

eGFR stratum	n/N		HR (95% CI)	P-interaction value
	Placebo	Canagliflozin		
CV death/Hospitalisation for heart failure	**496/8578**	**417/8582**	**0.83 (0.75–0.95)**	**0.37**
<60	86/659	55/606	0.78 (0.55–1.09)	
60 to <90	252/3894	199/3838	0.79 (0.66–0.95)	
>90	163/4025	163/4137	0.96 (0.77–1.19)	
MACE	**803/8759**	**756/8582**	**0.93 (0.84–1.03)**	**0.99**
<60	104/659	85/606	0.92 (0.69–1.23)	
60 to <90	390/3894	367/3838	0.95 (0.82–1.09)	
>90	309/4025	304/4137	0.94 (0.80–1.10)	
40% ↓ eGFR, ESRD, or renal or CV death	**480/8578**	**370/8582**	**0.76 (0.67–0.87)**	**0.97**
<60	76/659	53/606	0.77 (0.64–1.09)	
60 to <90	240/3894	182/3838	0.76 (0.63–0.93)	
>90	164/4025	135/4137	0.79 (0.63–0.99)	

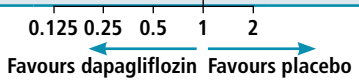


Figure 14. DECLARE-TIMI 58: key outcomes by baseline renal function

Secondary prevention of renal events in established cardiovascular disease

Meta-analyses of data from those with established cardiovascular disease in the EMPA-REG, CANVAS and DECLARE cohorts indicate almost identical individual benefits of each of the SGLT-2 inhibitors, as well as the class benefit, in secondary prevention. Hazard ratios of 0.54 in EMPA-REG, 0.59 in CANVAS and 0.55 in DECLARE were observed, with a cumulative overall RRR of 44% for renal events (Figure 15). In patients with T2DM and multiple risk factors, DECLARE demonstrated a significant reduction in renal events, even in people without established cardiovascular disease, of the order of 50%.[10] "I think this is a profound moment to recognise the unbelievable and unprecedented renal protective benefits that are being observed with these agents in both primary and secondary prevention populations and in many cases on top of ACE inhibitor treatment and adequate blood pressure control," Dr Verma stated.

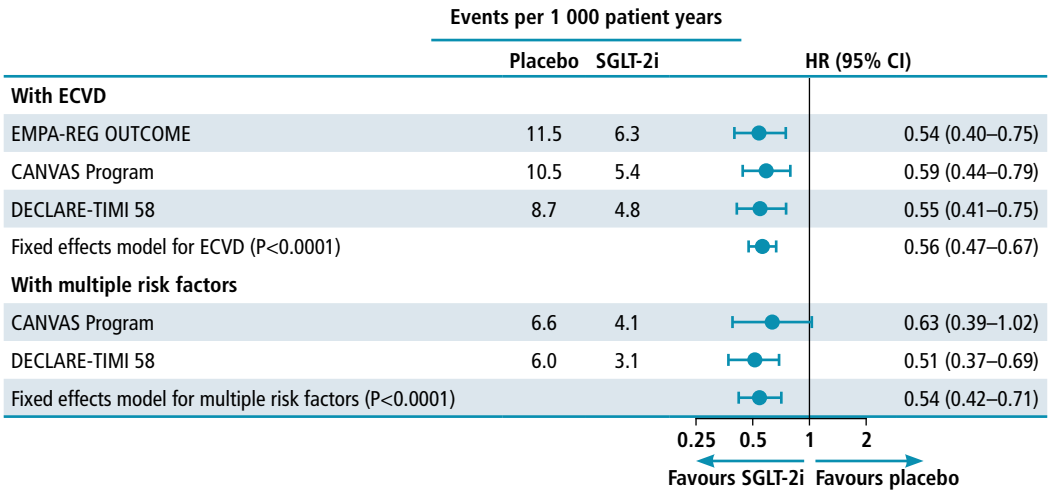


Figure 15. Secondary prevention: progression of renal disease with SGLT-2 inhibitors in the presence of established cardiovascular disease

Meta-analyses of data from those with established cardiovascular disease in the EMPA-REG, CANVAS and DECLARE cohorts indicate almost identical individual benefits of each of the SGLT-2 inhibitors, as well as the class benefit, in secondary prevention

The cardiorenal hypothesis for heart failure protection

A nephrocentric perspective of the cardiorenal hypothesis for heart failure protection with SGLT-2 inhibitors suggests that these agents facilitate proximal tubular natriuresis that triggers tubuloglomerular feedback; a reduction in intraglomerular hypertension is then responsible for reductions in albuminuria and preservation of renal function. The reduced blood pressure and arterial stiffness, along with the reduced cardiac afterload, improve 'spilling' conditions and facilitate left ventricular remodelling. Preservation of systemic sodium and water homeostasis facilitates maintenance of euvolaemia, reducing cardiac preload, myocardial wall stress and further optimising filling conditions (Figure 16).[1] Overall reductions in renal systemic inflammation also have an effect on left ventricular remodelling.

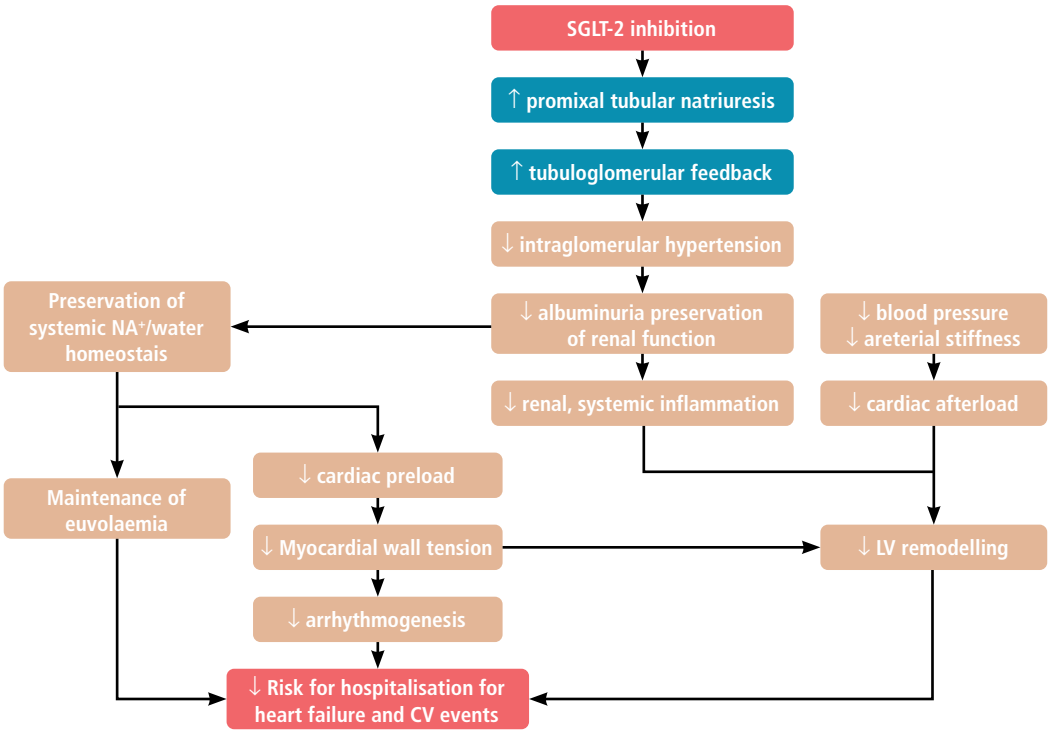


Figure 16. A nephrocentric perspective of the cardiorenal hypothesis for heart failure protection with SLGT-2 inhibitors[1]

SGLT-2 inhibitor CVOTs and renal outcome trials – currently announcing results

DAPA-CKD and DELIGHT have announced their results recently while EMPA-KIDNEY's results are expected mid-2022. CREDENCE is a dedicated diabetic kidney disease trial of diabetes patients with HbA_{1c} 6.5-10.5, GFRs between 30 and 90ml/min/1.73m^2 with UACRs >34 and <565 on maximally tolerated ACE inhibitors or ARBs and randomised to canagliflozin 100mg versus placebo. This trial was stopped early on the achievement of prespecified efficacy criteria that included the primary composite of ESRD, doubling of serum creatinine, renal or cardiovascular death on top of standard of care (results announced, available online).[11] Other upcoming trials with renal data using dapagliflozin have recently been stopped early because of the overwhelming efficacy of the drug, according to the independent data monitoring committees.

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