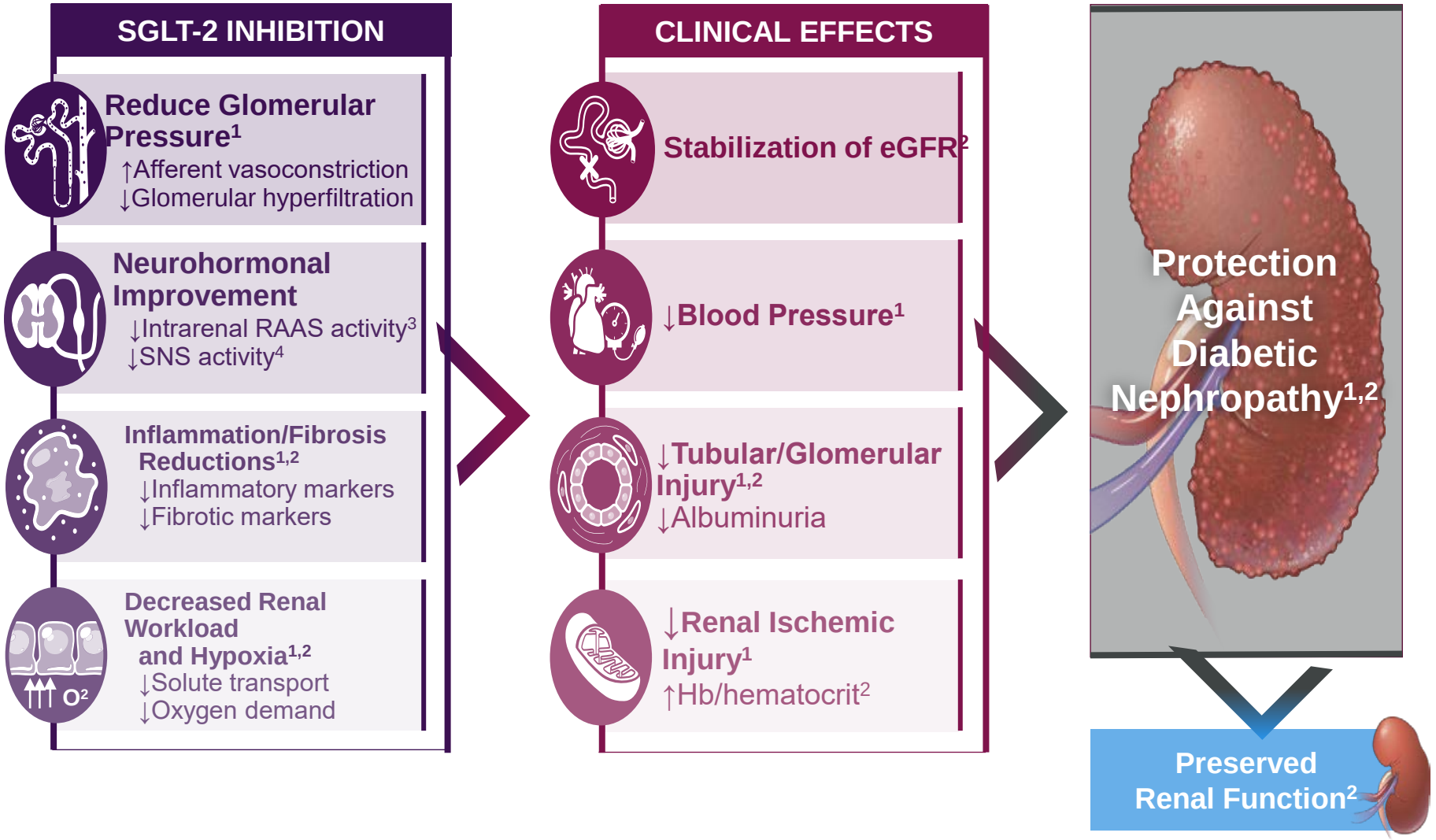
SID
Società Italiana
di Diabetologia
fondata nel 1964

SGLT2: effetti sulle complicanze renali

Stefania Ghilotti
IRCCS Maugeri Pavia

Potential Effects By Which SGLT-2 Inhibition Improves Renal Outcomes

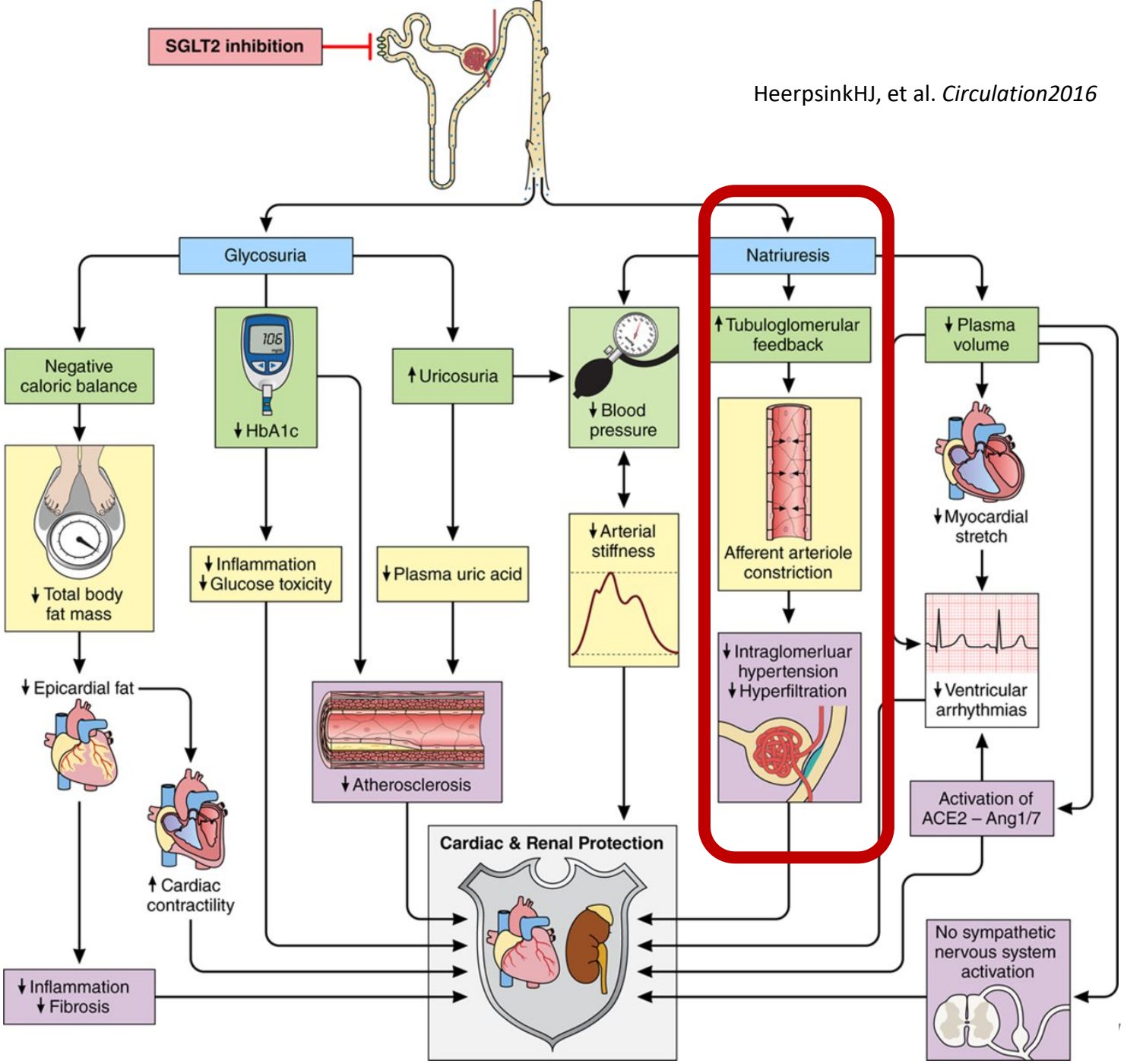


eGFR=estimated glomerular filtration rate; Hb=hemoglobin; RAAS=renin angiotensin aldosterone system; SNS=sympathetic nervous system.

1. Heerspink HJL, et al. *Kidney Int*. 2018; 2. Tamargo J. *Eur Cardiol*. 2019; 3. Shin SJ, et al. *PLoS One*. 2016;. 4. Sano M. *J Cardiol*. 2018.

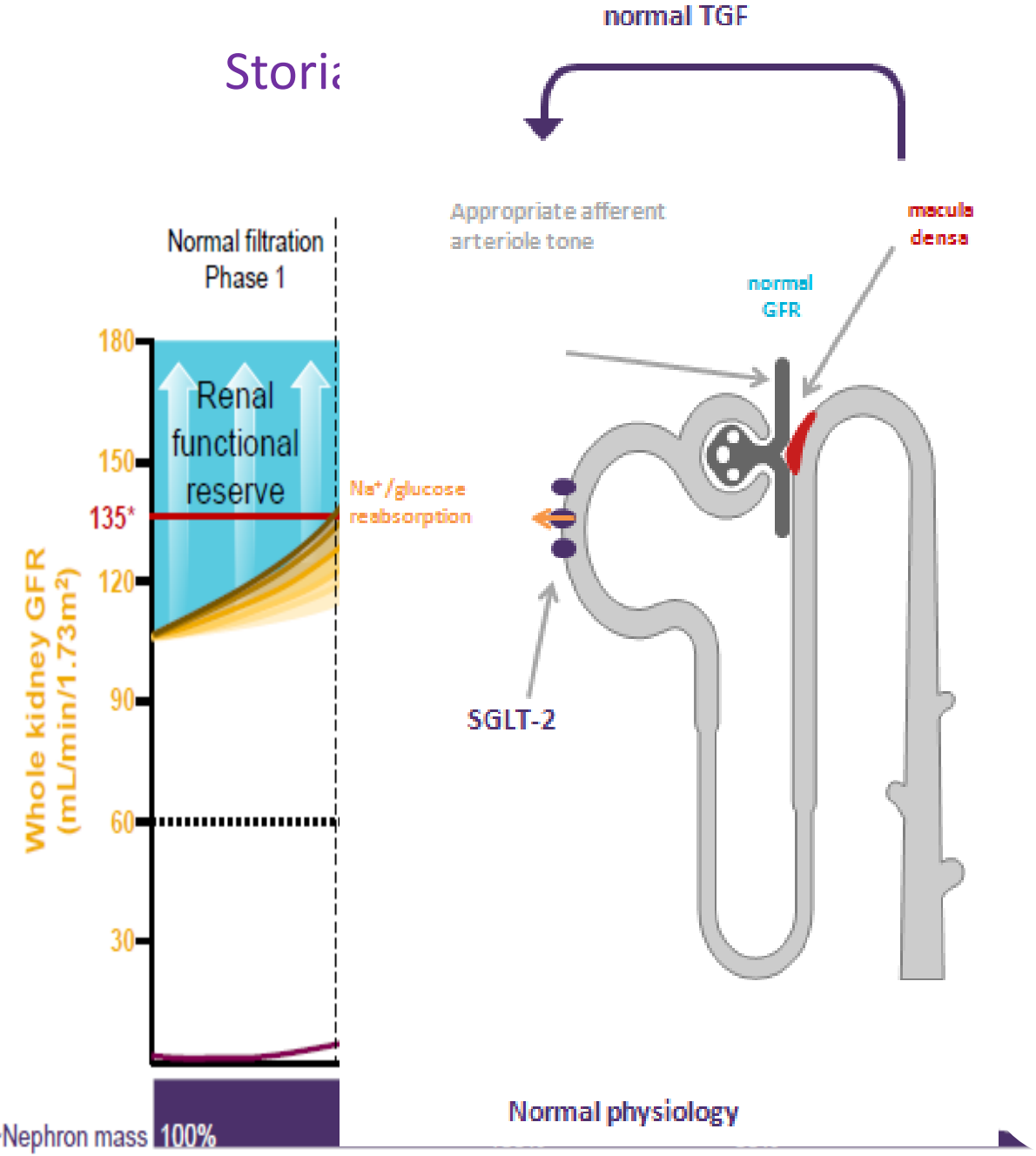
Potenziali effetti di protezione renale degli SGLT2-i

- Emodinamici
- Risparmio energetico e miglioramento ipossia
- Metabolici
- Anti-infiammatori e riprogrammazione cellulare
- Simpatici



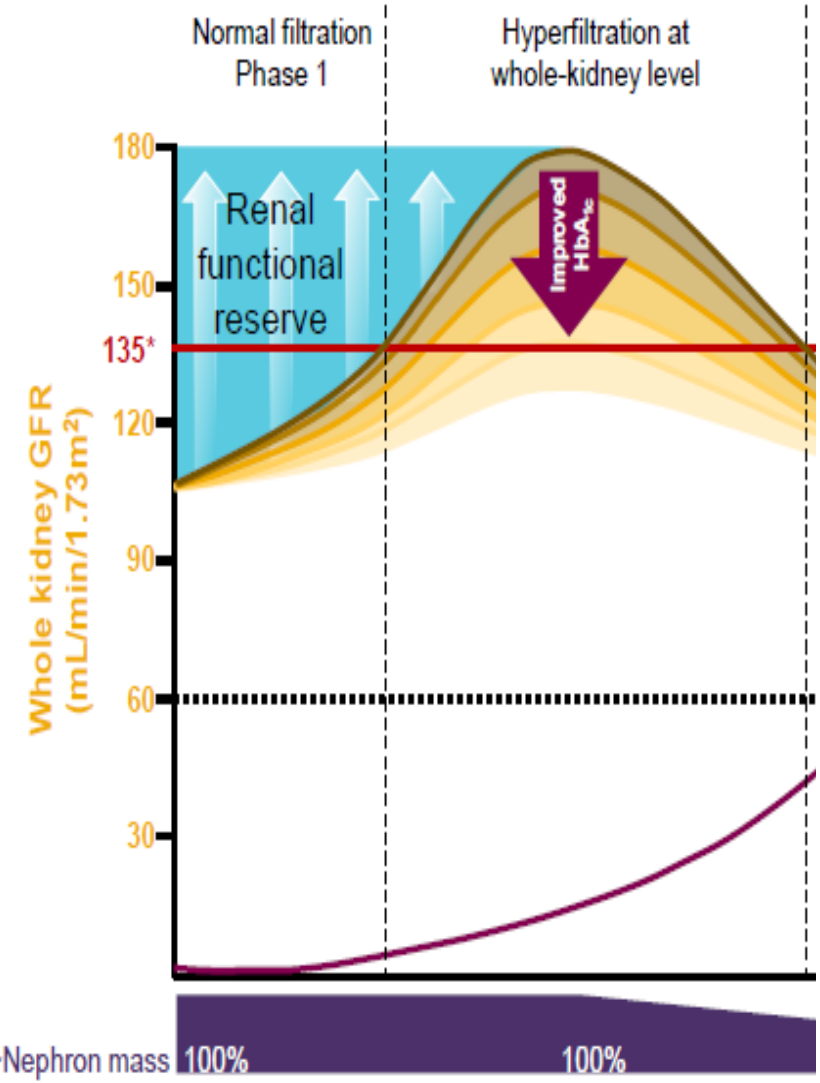
HeerpsinkHJ, et al. *Circulation2016*

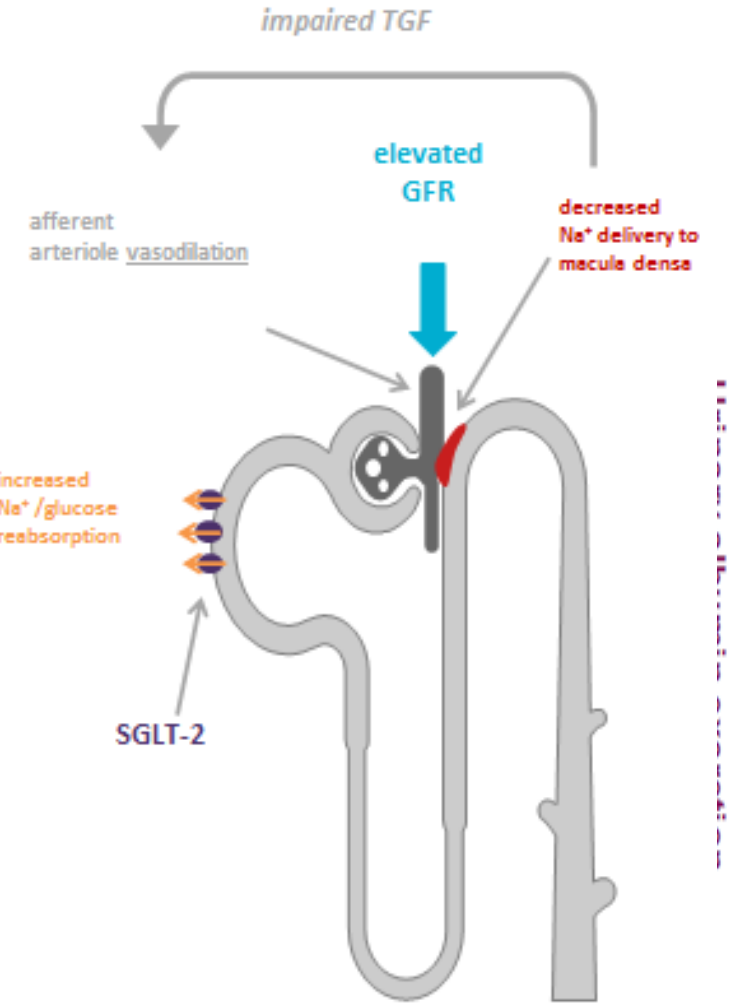
Stori



Tonneijck, J Am Soc Nephrol 2017

Storia naturale della nefropatia diabetica

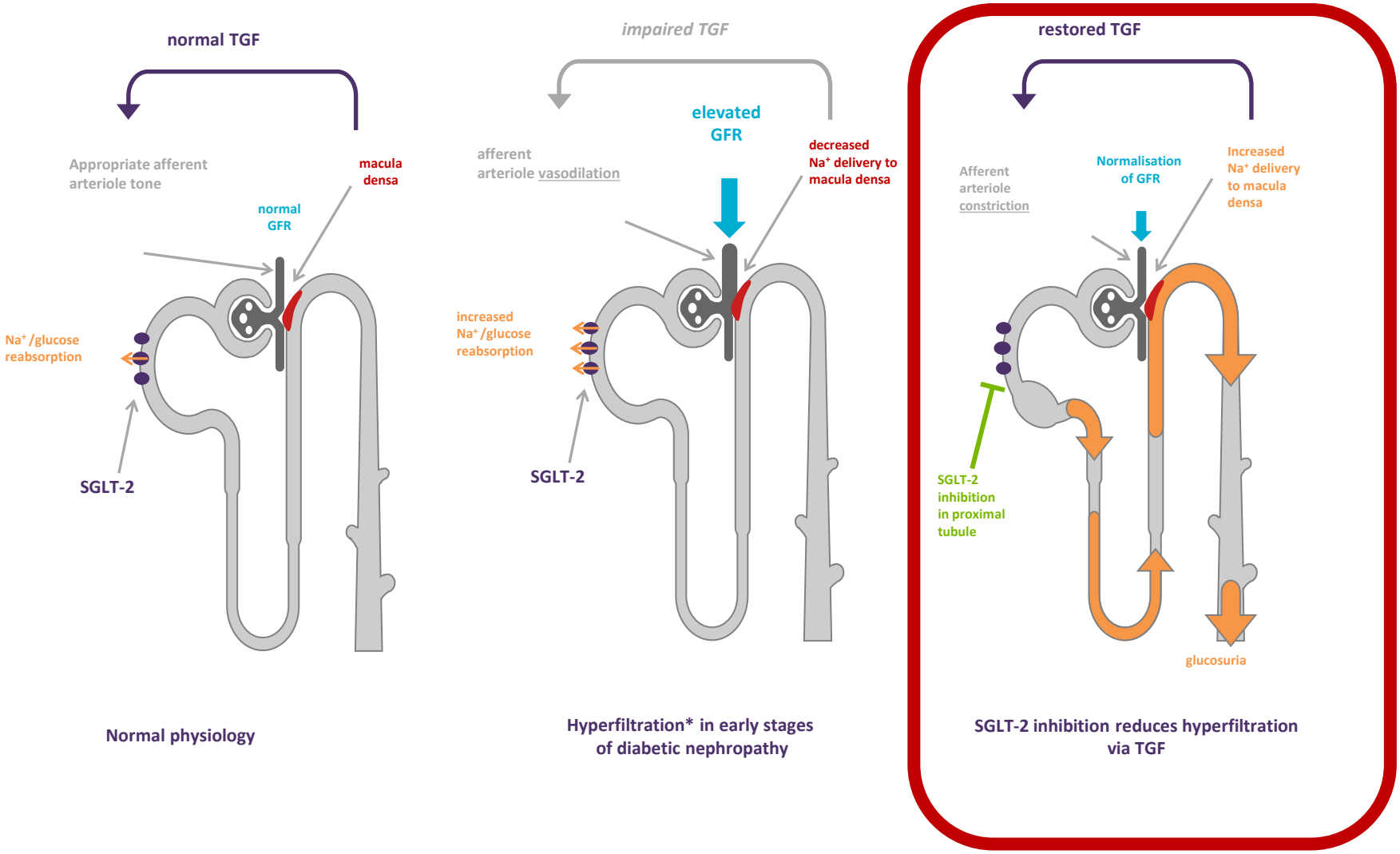




Hyperfiltration* in early stages
of diabetic nephropathy

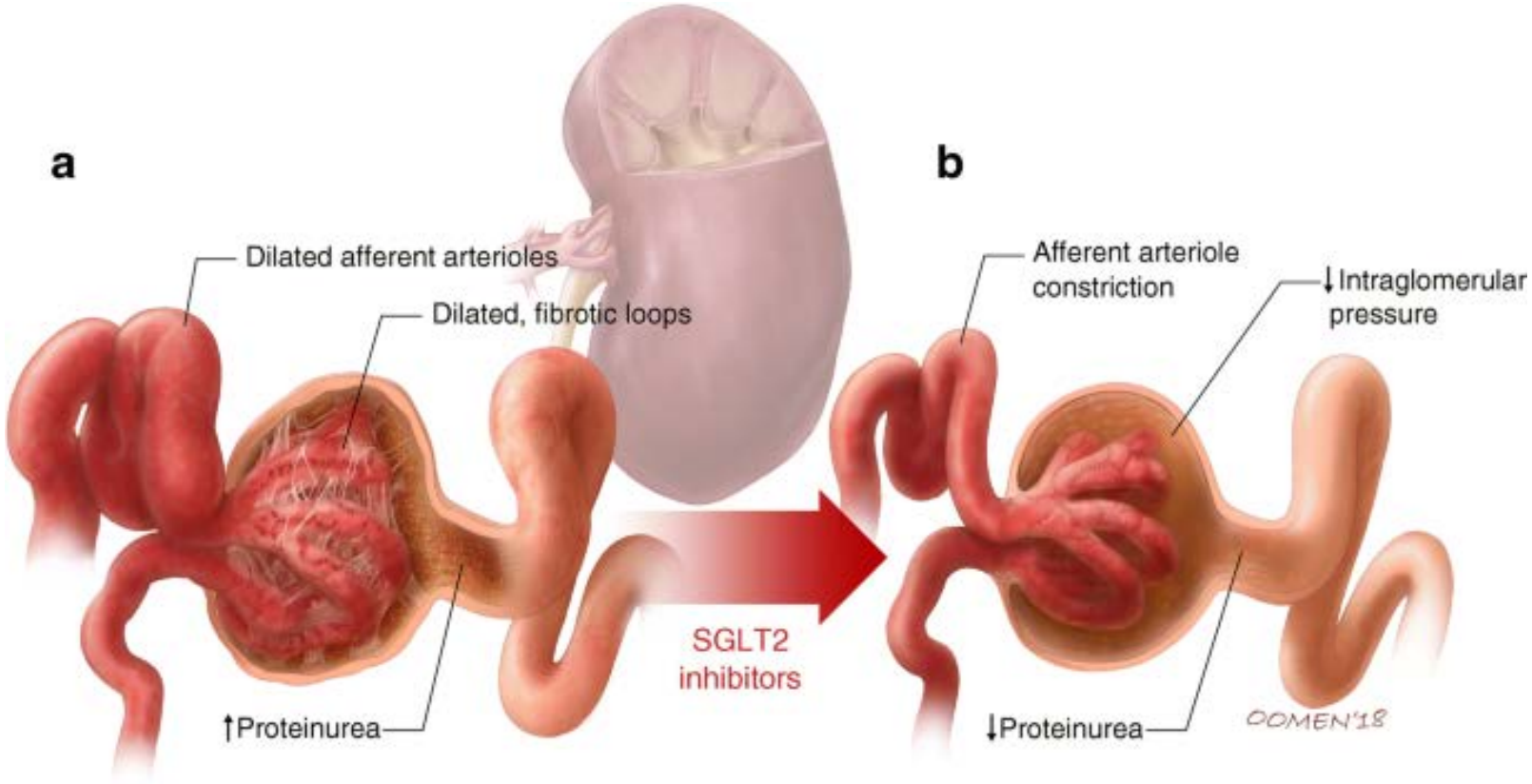
Tonneijck, J Am Soc Nephrol 2017

Regolazione del feed-back tubulo-glomerulare e riduzione dell'iperfiltrazione con SGLT2 i



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

Verma, Diabetologia (2018)

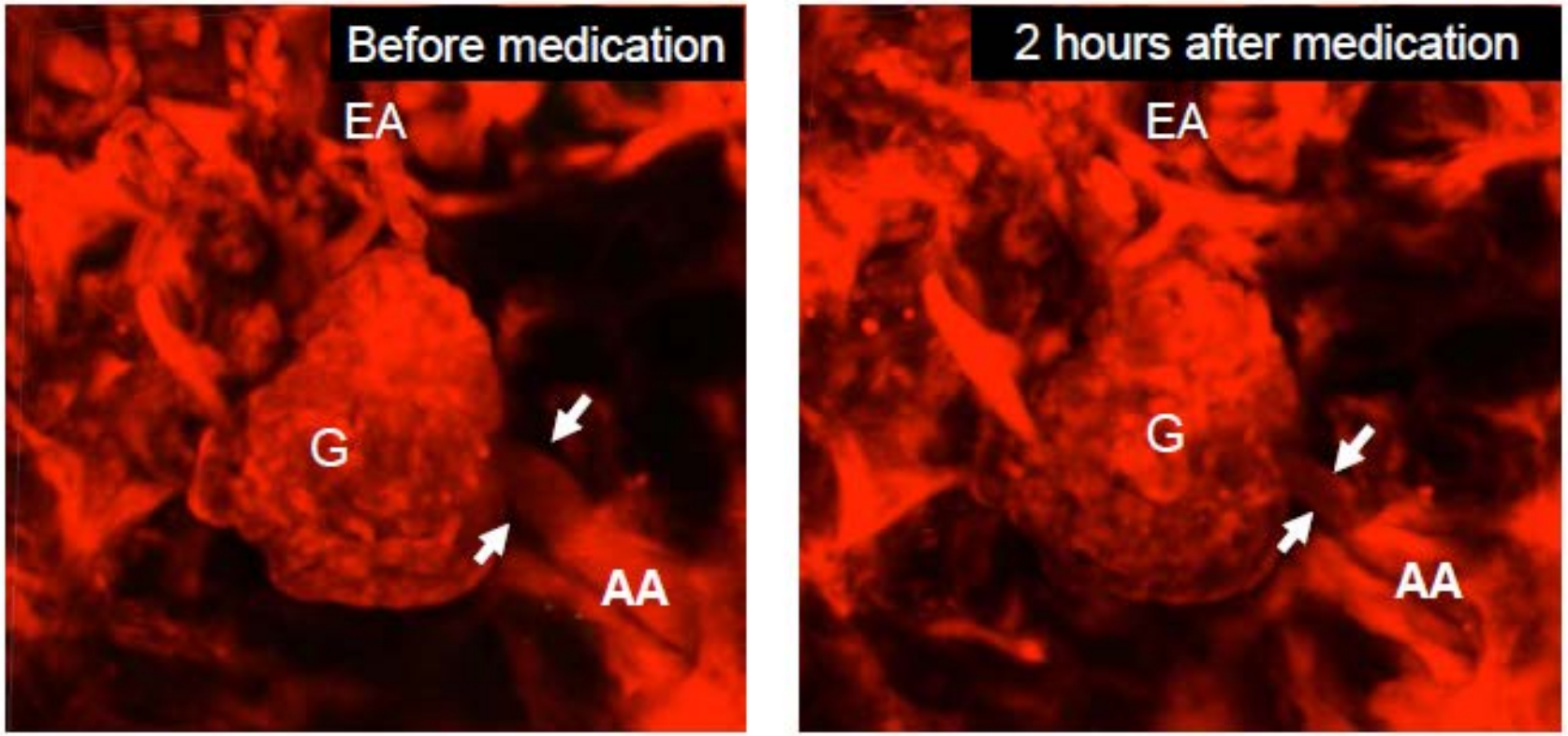


Diabetes is associated with afferent arteriolar dilatation, which leads to high intraglomerular pressure and hyperfiltration. Ongoing barotrauma to the glomerulus may lead to proteinuria

(**a**). SGLT2 inhibitors, through tubuloglomerular feedback, promote afferent arteriolar vasoconstriction. This in turn serves as a mechanism to reduce intraglomerular hypertension and provide nephroprotection (**b**).

G. Oomen 2018.

Immagini in vivo di vasocostrizione dell'arteriola afferente dopo SGLT2 inibitore



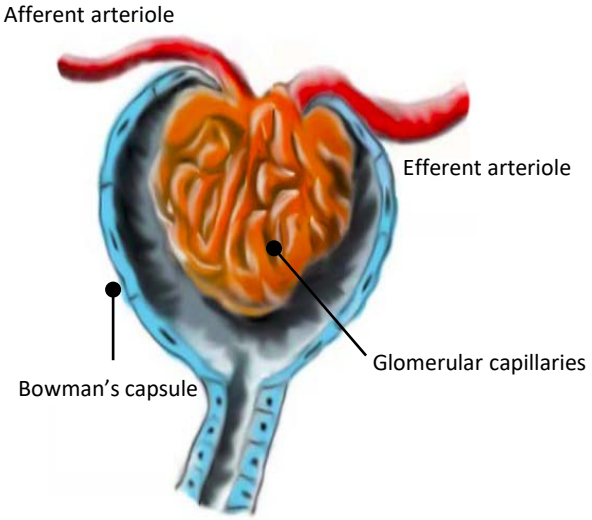
Kidokoro ed at Circulation 2019

Riduzione dell'iperfiltrazione renale mediata dall'effetto complementare di SGLT2 inibitori e blocco del RAAS

SGLT2 inhibitors

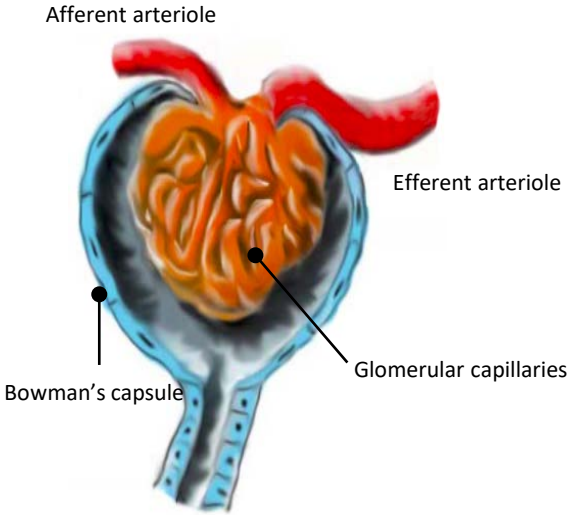
Afferent constriction[1-3]

Due to increased Na+ delivery to the macula densa[1-3]



RAAS blockade

Efferent vasodilation[1]



CLINICAL IMPLICATIONS

- **Decreased glomerular pressure[1,3]**
- **Reduction in albuminuria[1,2]**

- **Decreased glomerular pressure[1,3]**
- **Reduction in albuminuria[4]**

1. Van Bommel EJ, et al. *Clin J Am Soc Nephrol*. 2017;12(4):700-710. 2. Seidu S, et al. *Prim Care Diabetes*. 2018;12(3):265-283. 3. Cherney DZ, et. al. *Circula*
Feb 4;129(5):587-97. 4. Heerspink HJ, et al. *Diabetes Care*. 2011;34 Suppl 2:S325-9. 5. Adapted from: Shiraishi M, et al. *FASEB J*. 2003;17(15):2284-6.

Potenziali effetti di protezione renale degli SGLT2-i

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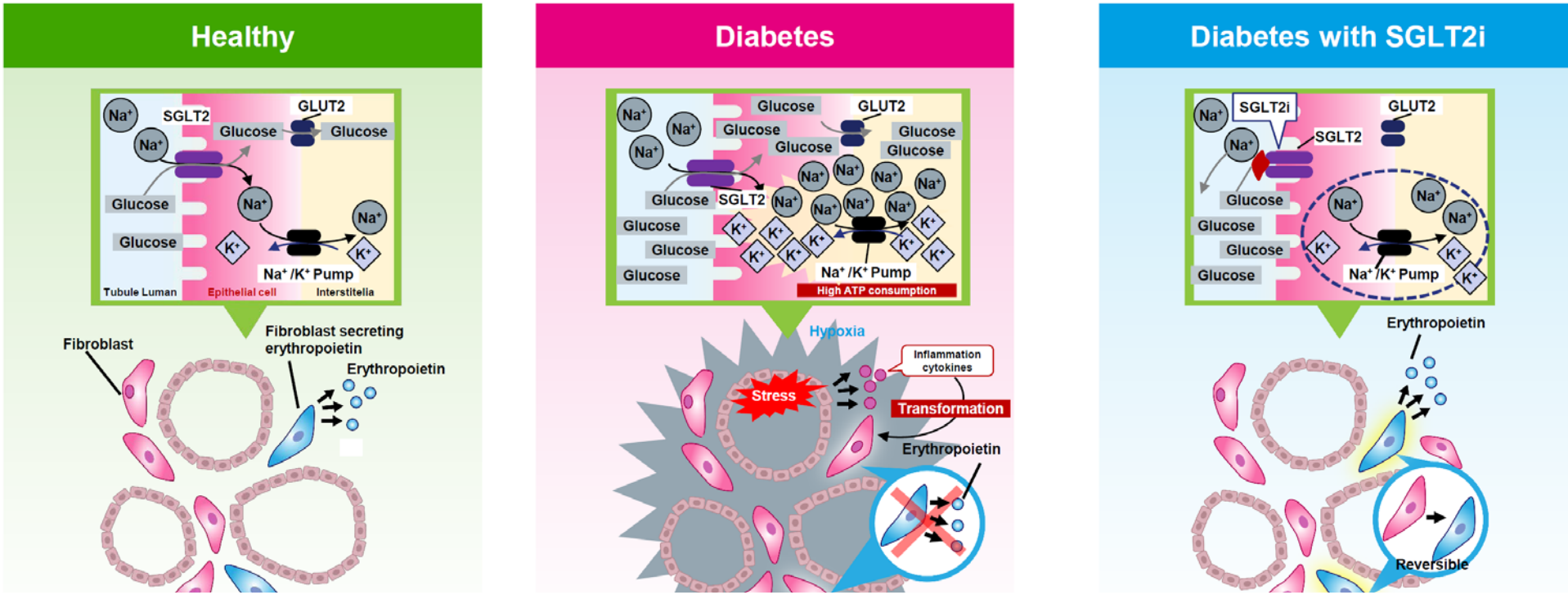
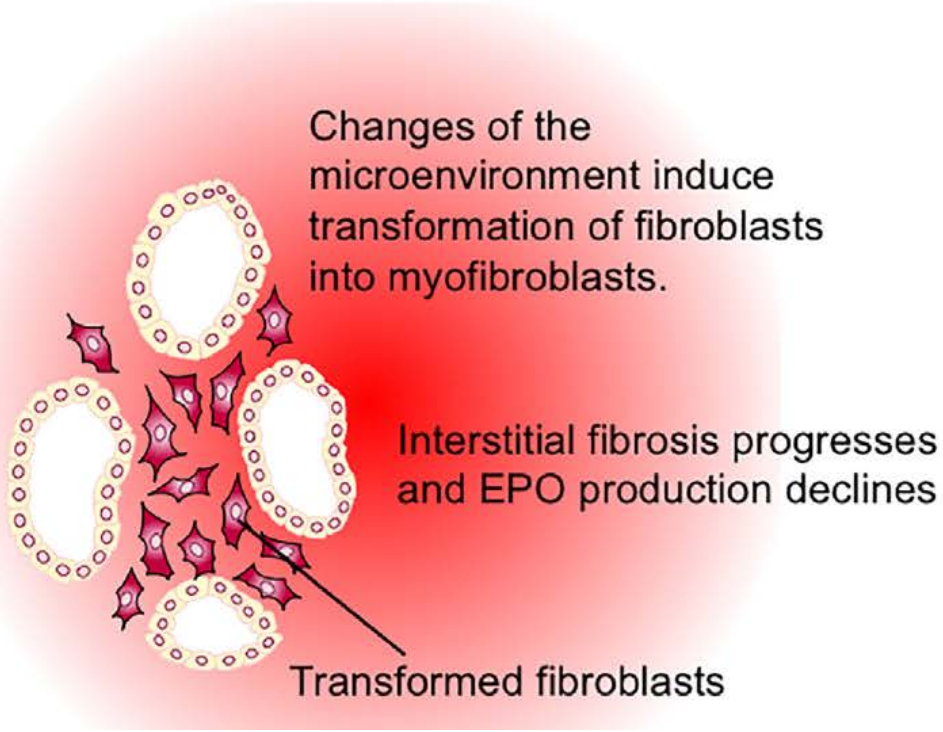
Gli SGLT2-i riducono il lavoro renale, contrastano **l'ipossia renale** (riduzione spesa energetica e aumento EPO)



Sano and Goto Circulation 2019

T2DM

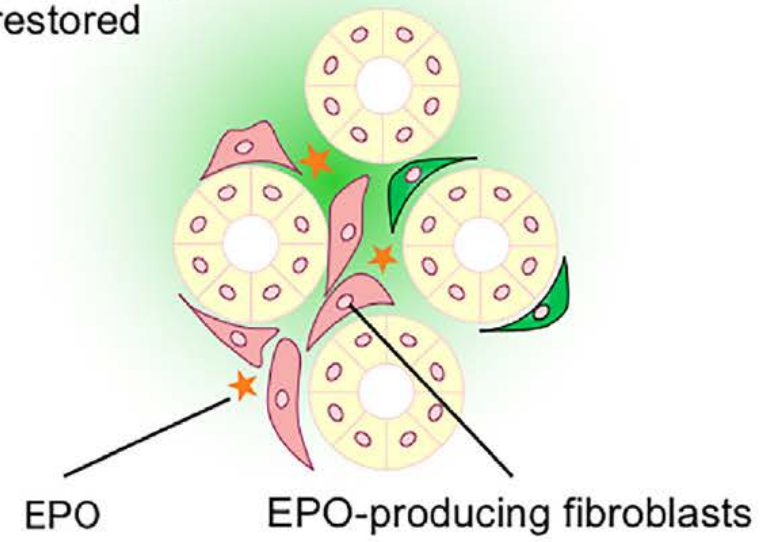
Proximal renal tubular epithelial cells are overloaded by excessive energy-dependent reabsorption of glucose



T2DM with SGLT2 inhibition

Proximal tubular epithelial cells are relieved from the burden of excessive reabsorption of glucose

Cortical tubulointerstitial damage recovers and EPO production by fibroblasts is restored



Sano, Journal of Cardiology 71 (2018)

Potenziali effetti di protezione renale degli SGLT2-i

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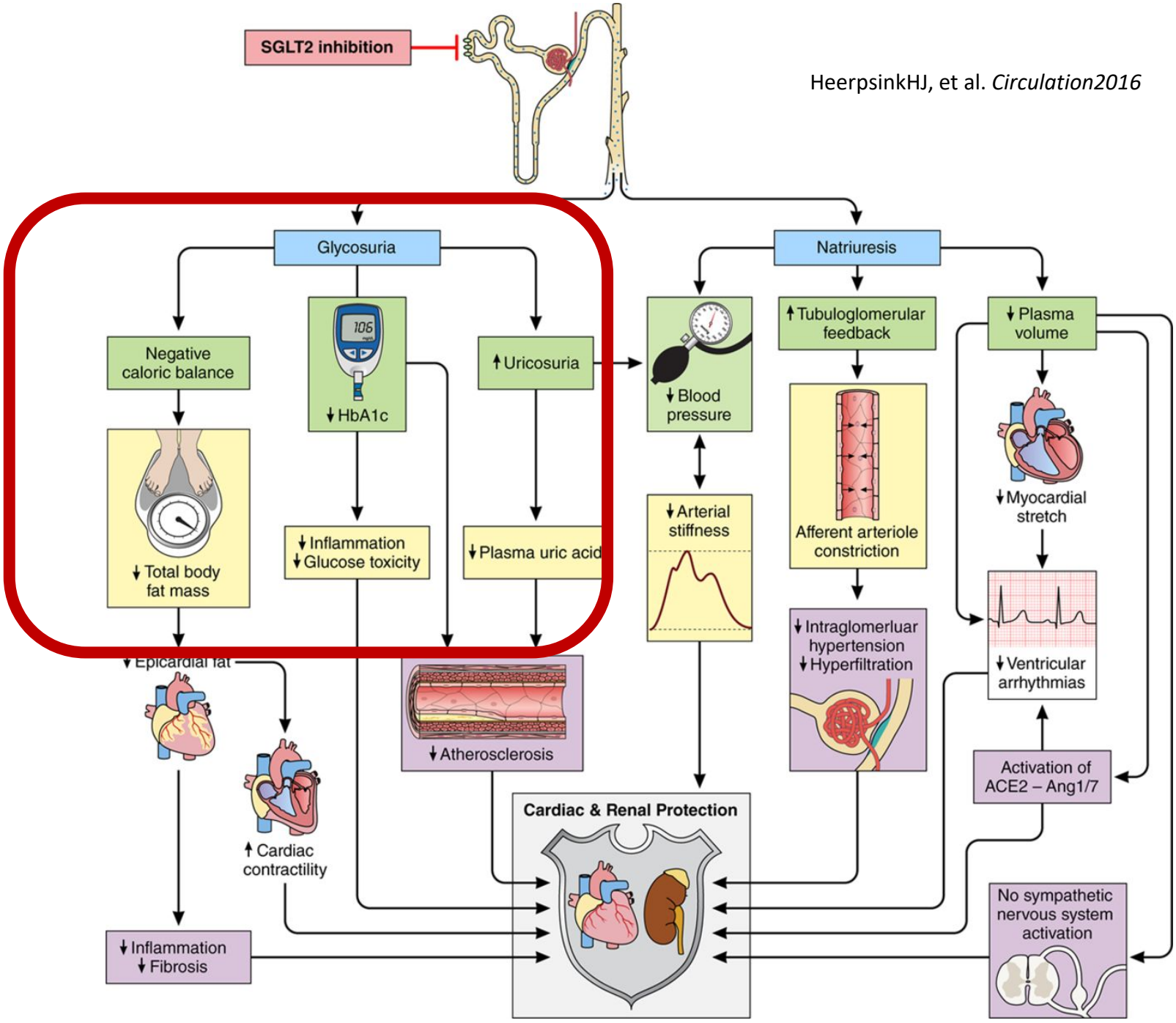
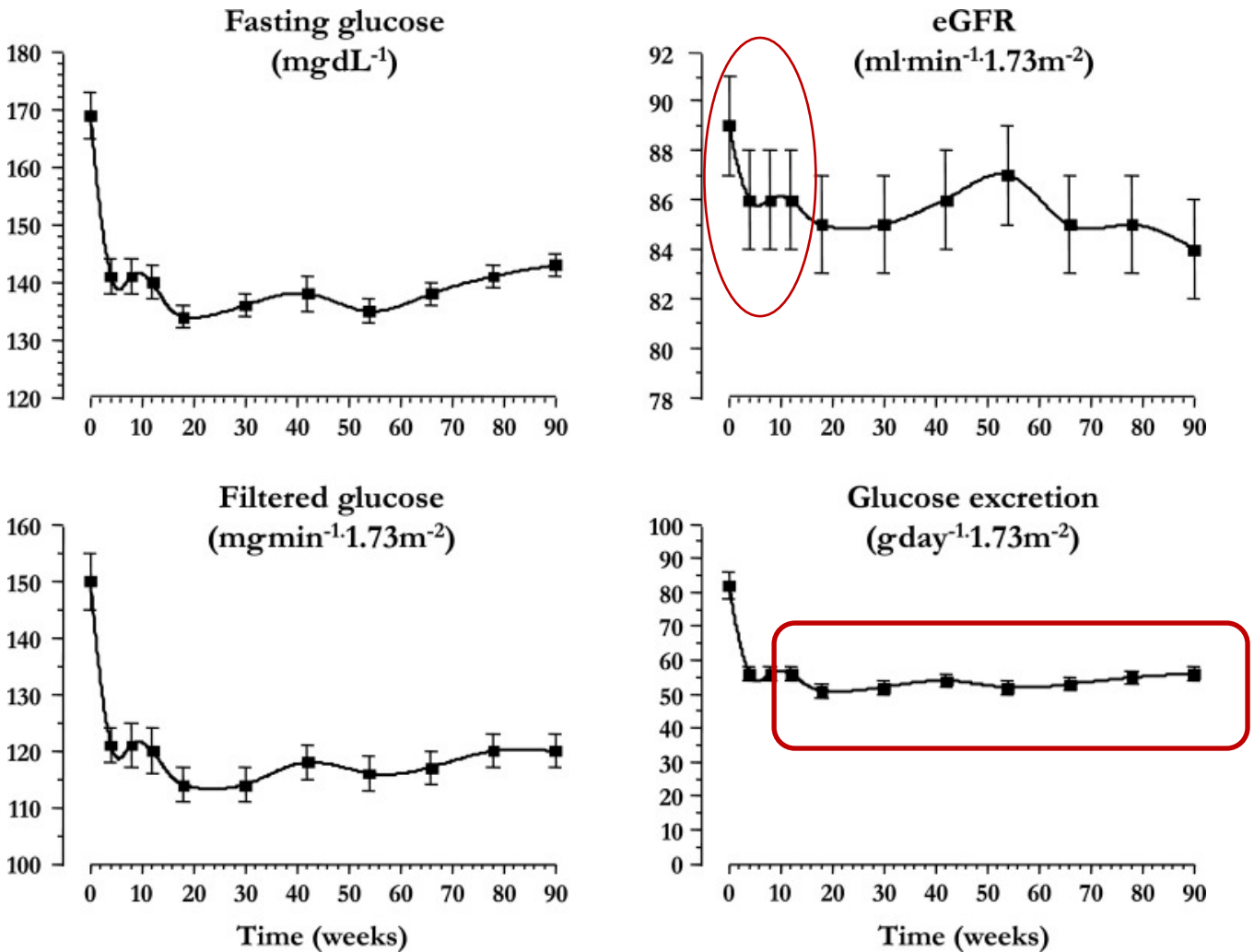


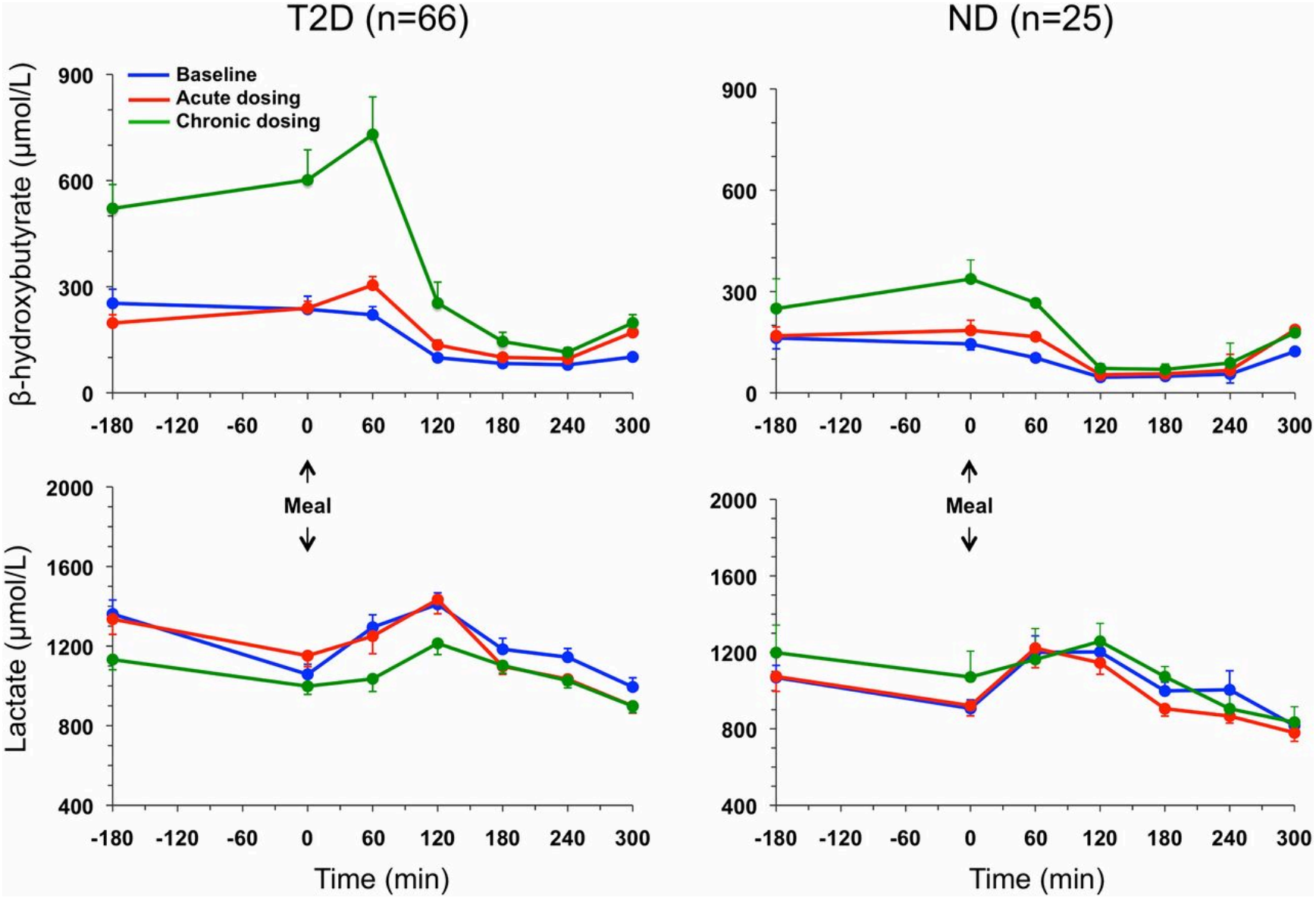
HeerpsinkHJ, et al. *Circulation2016*

Energy Balance After Sodium–Glucose Cotransporter 2 Inhibition

Giulia Ferrannini,[1] Thomas Hach,[2] Susanne Crowe,[2] Arjun Sanghvi,[3] Kevin D. Hall,[3] and Ele Ferrannini[4]

Diabetes Care 2015;38:1730–1735 | DOI: 10.2337/dc15-0355

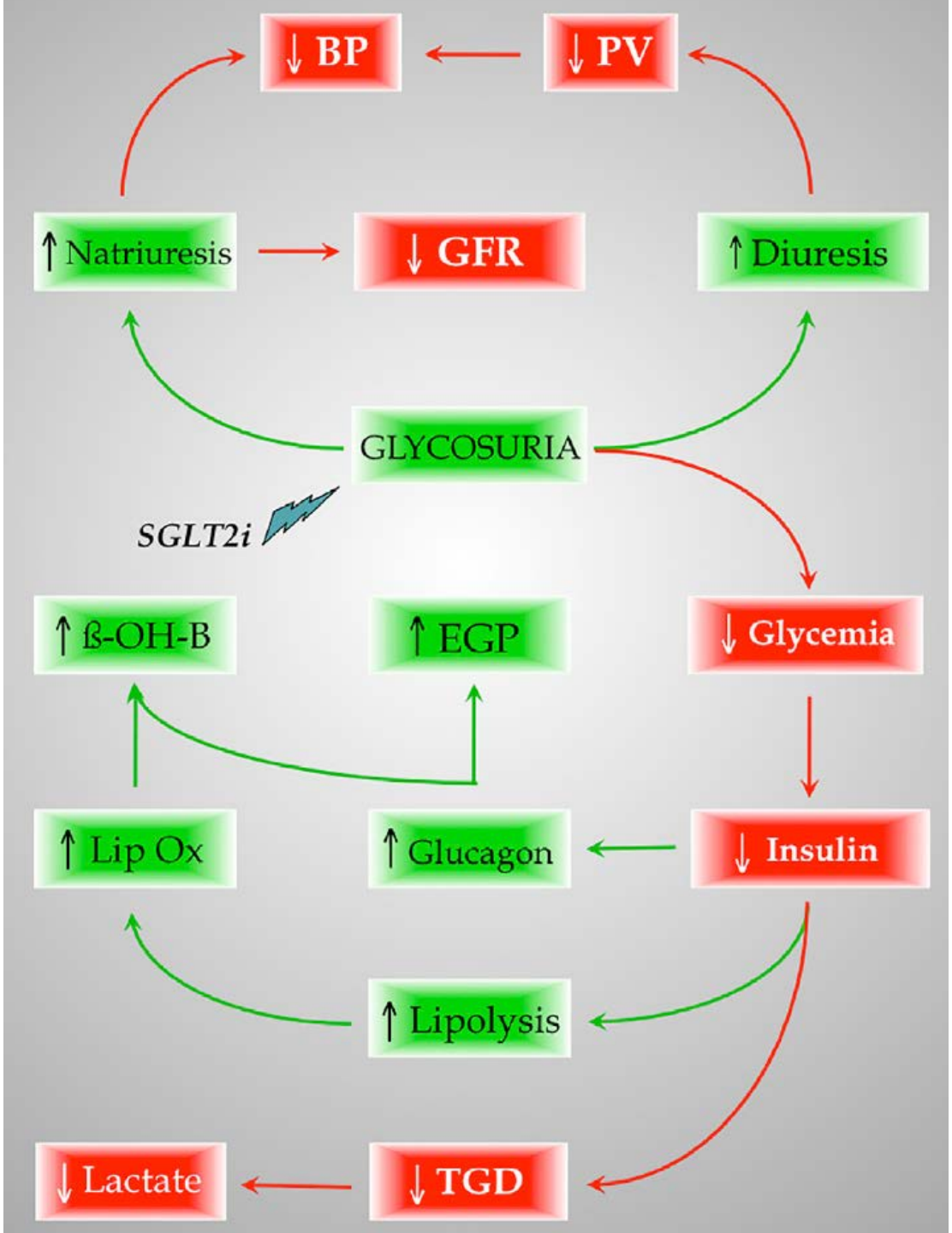




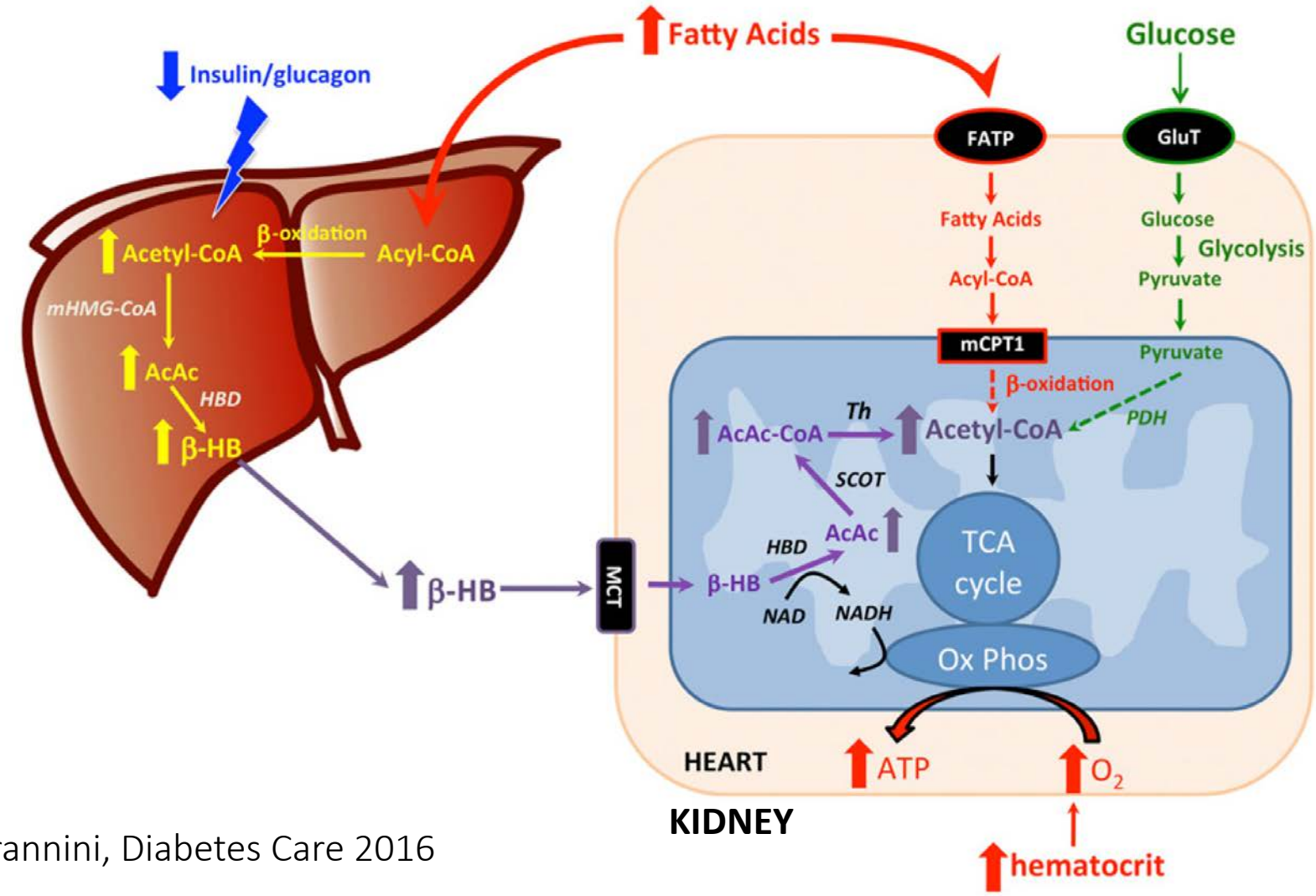
Ferranini Diabetes 2016;65:1190–1195

Schematic representation of the main metabolic and hemodynamic effects of SGLT2-induced inhibition of renal glucose reabsorption in humans. GFR, glomerular filtration rate; BP, blood pressure; PV, plasma volume; EGP endogenous glucose production; Lip Ox, lipid oxidation; TGD, tissue glucose disposal; b-OH-B, b-hydroxybutyrate. Red boxes stand for decrease andgreen boxes for increase; red lines imply a negative effect, green lines a positive one.

Ferranini Cell Metabolism 2017

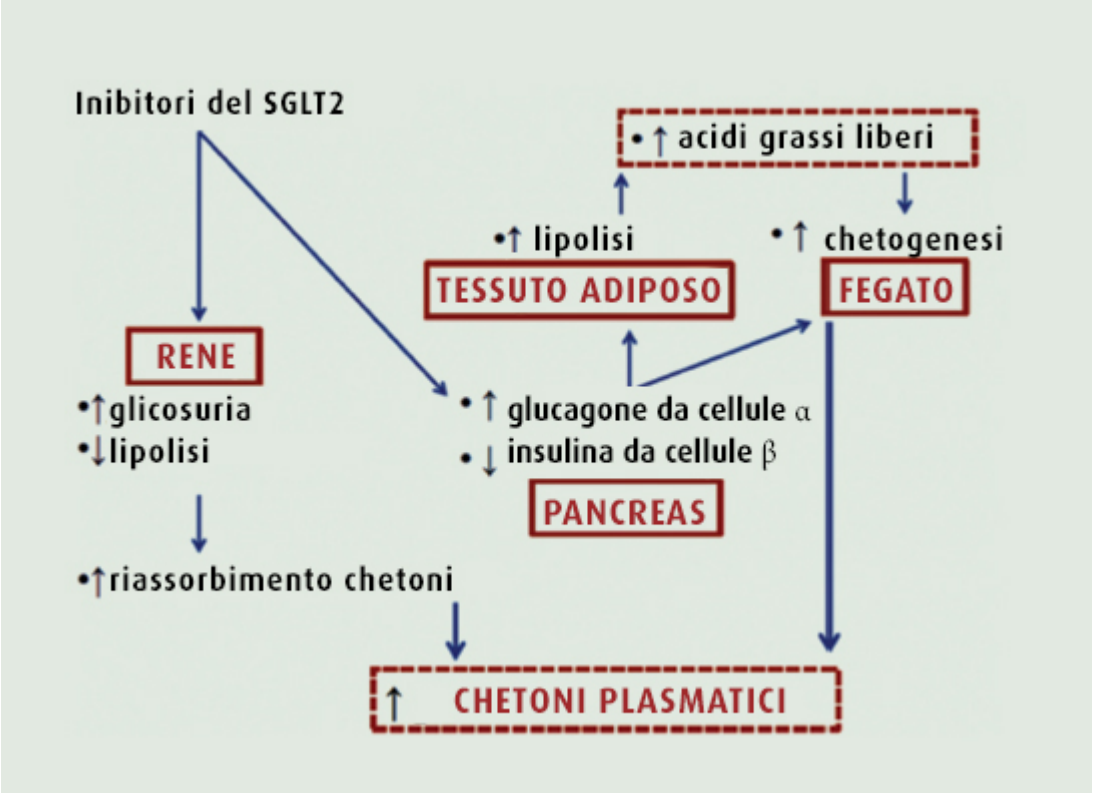


A“Thrifty Substrate” Hypothesis



Ferrannini, Diabetes Care 2016

Chetoacidosi euglicemica



- Bassa riserva di cellule beta pancreatiche funzionanti;
-condizioni che portano ad una limitata assunzione di cibo o grave disidratazione;
- riduzione di insulina;
- incremento del fabbisogno insulinico a causa di malattia acuta;
- intervento chirurgico;
- abuso di alcol

Potenziali effetti di protezione renale degli SGLT2-i

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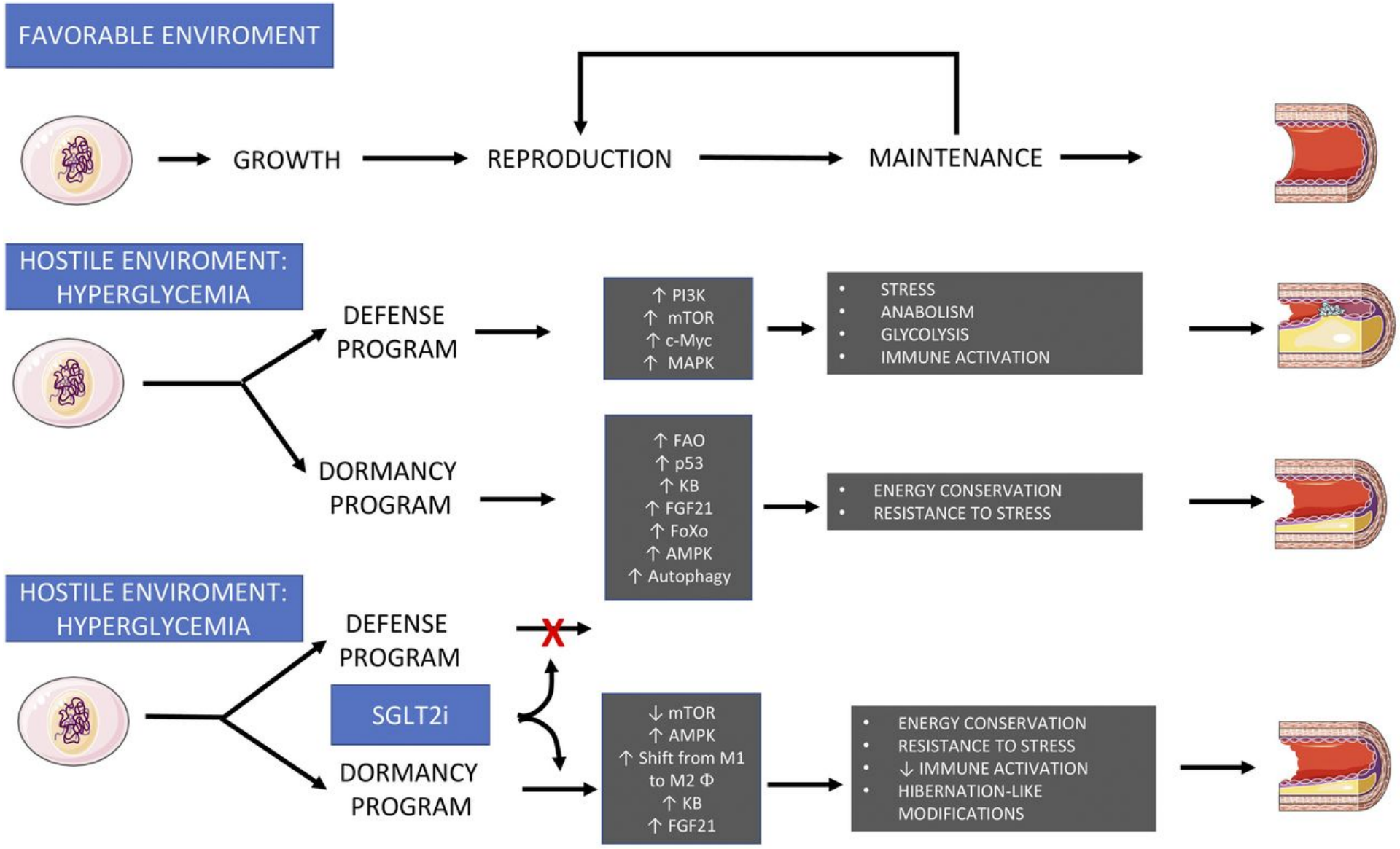
- **Anti-infiammatori e riprogrammazione cellulare**
- Simpatici



Avogaro Diabetes Care 2020

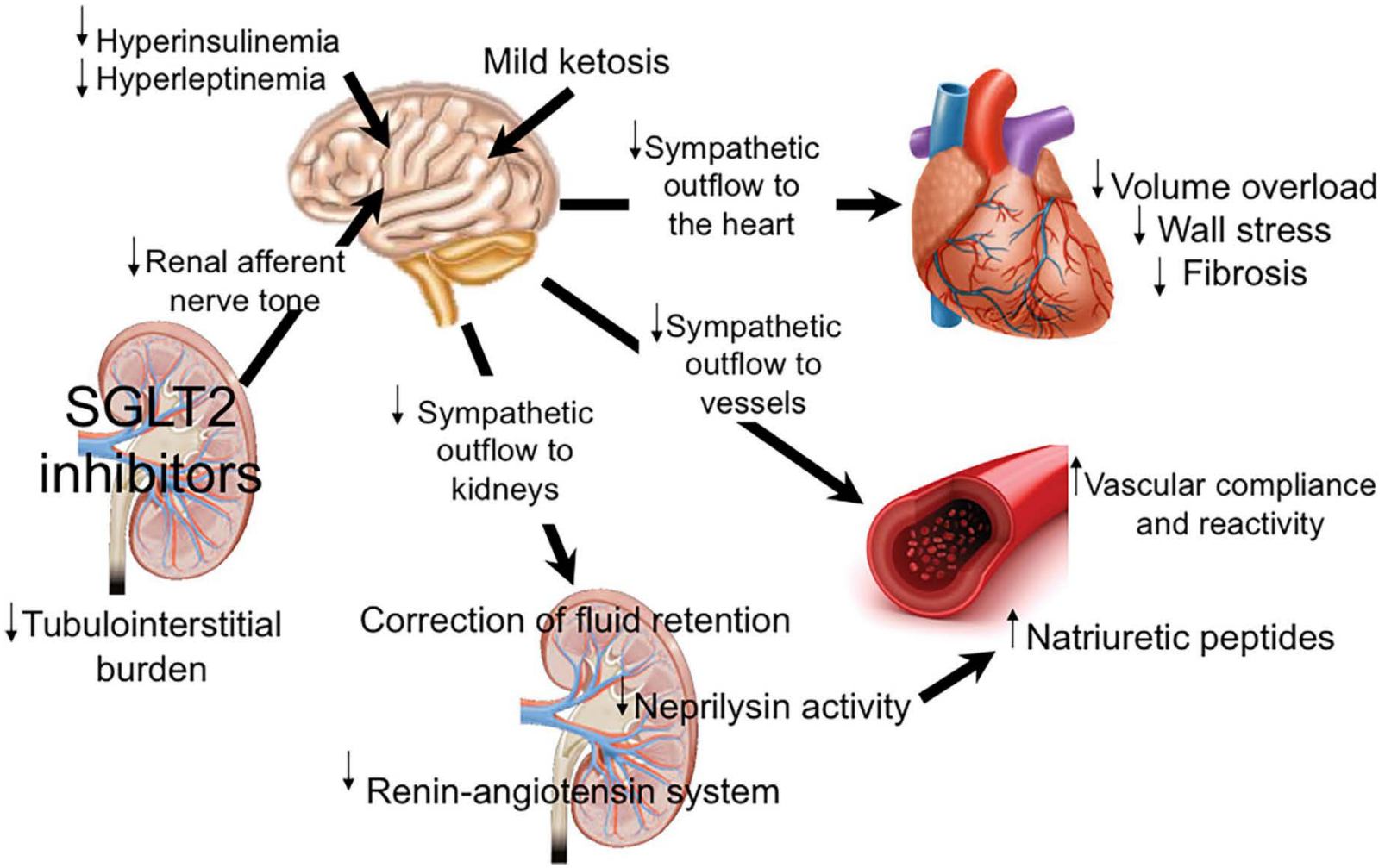
Potenziali effetti di protezione renale degli SGLT2-i

- Emodinamici
- Ipossia e risparmio energetico
- Metabolici
- Anti-infiammatori e riprogrammazione cellulare
- **Simpatici**

A new class of drugs for heart failure: SGLT2 inhibitors reduce sympathetic overactivity

Motoaki Sano (MD, PhD, FJCC)*

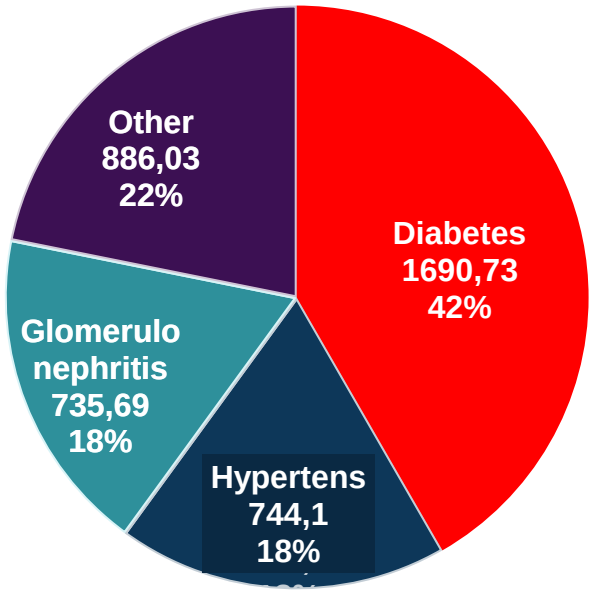
Sano, Journal of Cardiology (2018)



SGLT-2i potrebbe ridurre l' attività simpatica renale e centrale

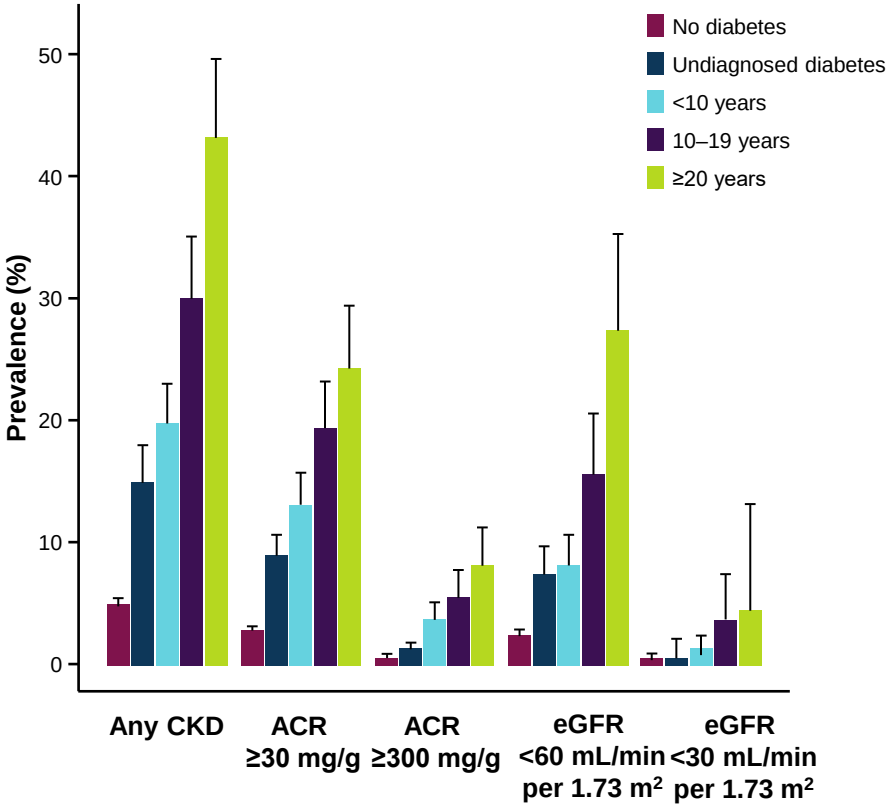
Diabetes is the single greatest risk factor for CKD, with the prevalence of CKD increasing with the duration of diabetes

Age-standardized global prevalence rate of CKD by cause per 100,000 persons in 2016[1]



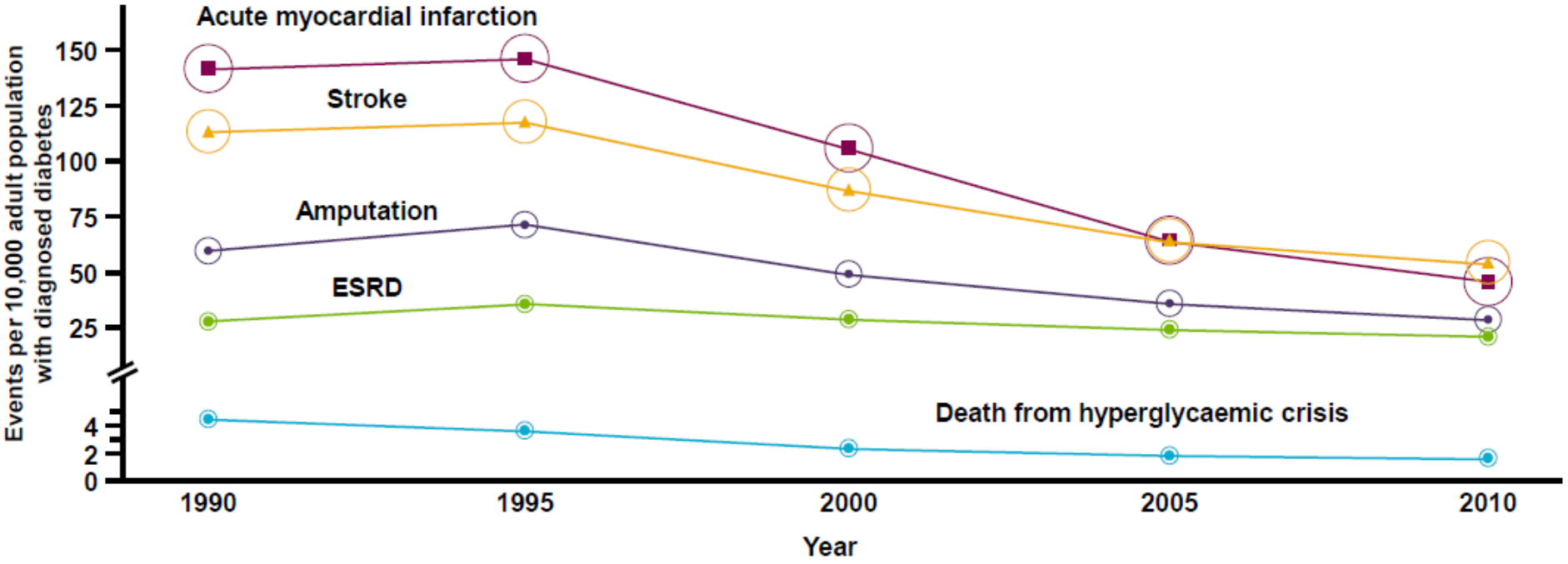
Diabetes caused the greatest rate of age-standardized DALYs in patients with CKD, in comparison with other causes[2]

Presence of CKD among adults in the USA, depending on duration of diabetes[3]



ACR, albumin:creatinine ratio; CKD, chronic kidney disease; DALY, disability-adjusted life year; eGFR, estimated glomerular filtration rate

1. Xie Y, et al. *Kidney Int* 2018
2. ;Global Burden of Disease Collaborators 2017. *Lancet* 2018;
3. 3. Zelnick LR, et al. *Clin J Am Soc Nephrol* 2017;12:1984–1990



ESRD, end-stage renal disease

Gregg EW, et al. *New Engl J Med2014;*

CVOT OUTCOMES RENALI: OUTCOMES SECONDARI

EMPA-REG OUTCOME®

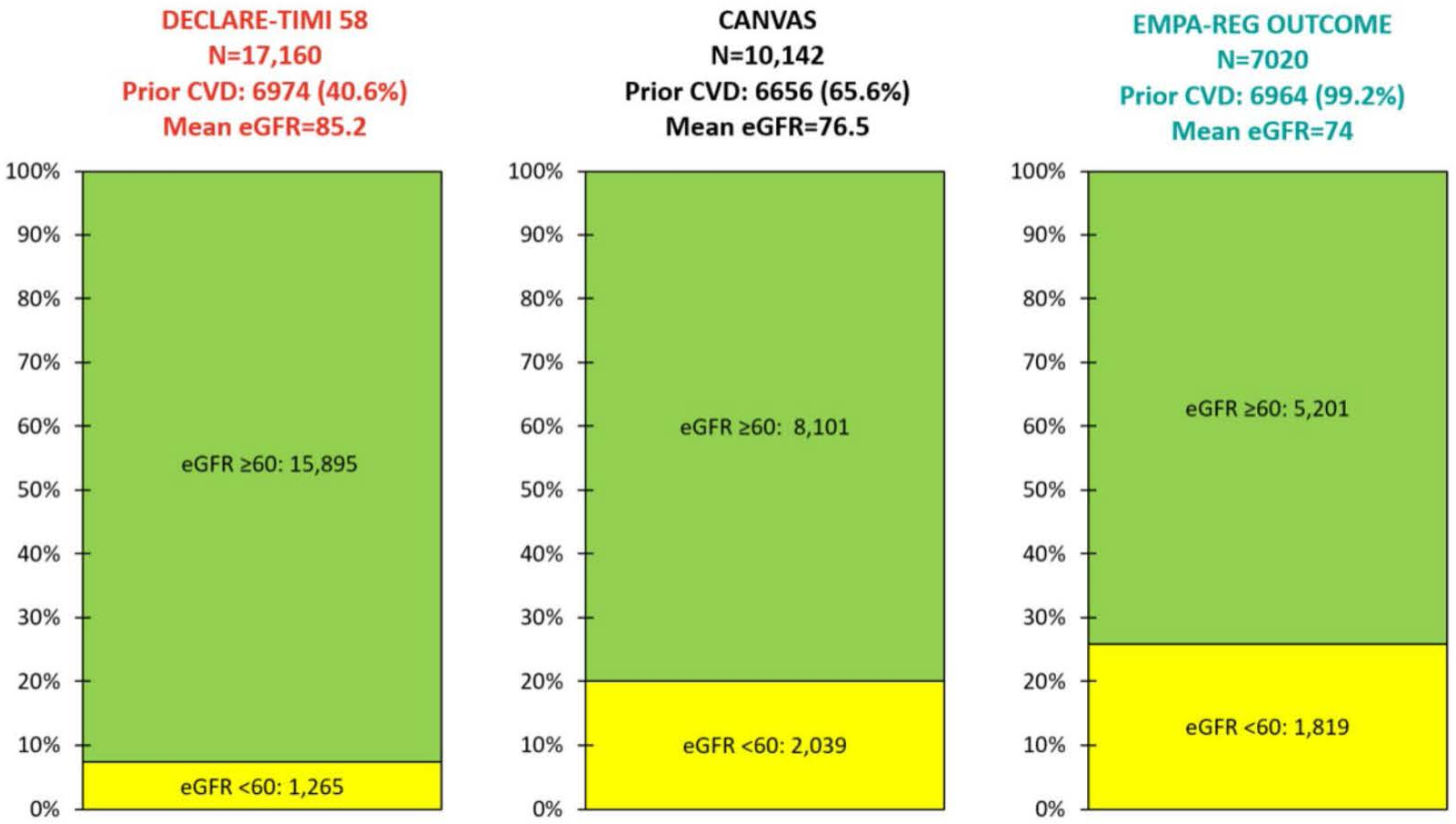
2015	2016	2017	2018	2019	2020
Secondary renal endpoints as progression to macroalbuminuria (urinary albuminto-creatinine ratio, >300 mg of albumin per gramof creatinine); a doubling of the serum creatininelevel, accompanied by an eGFR of ≤45; the initiation of renal-replacement therapy; or death from renal disease.		**Secondary renal endpoints[3,4]:** • Progression of albuminuria • ≥40% decrease in eGFR to <60 mL/min/1.73 m^2, ESRD, or death from renal causes CANVAS Program	**Secondary renal composite endpoint[5,6]** • Decrease of ≥40% eGFR to <60 mL/min/1.73 m^2, ESRD, or death from renal causes DECLARE TIMI-58		**Secondary renal endopoint** Sustained ≥40% reduction in eGFR, renal-replacement therapy (dialysis or transplantation) or death from renal causes **VERTIS**

CKD, chronic kidney disease; CV, cardiovascular; CVOT, cardiovascular outcomes trial; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; ESRD, end-stage renal disease; SGLT2, sodium–glucose co-transporter 2; T2D, Type 2 diabetes; UACR, urine albumin:creatinine ratio

Wanner C, et al. *N Engl J Med* 2016;.; Perkovic V, et al. *Lancet Diabetes Endocrinol* 2018. Clin4; Mosenzon O, et al. *Lancet Diabetes Endocrinol* 2019;. Perkovic V, et al. *N Engl J Med* 2019; 8. McMurray JJV, et al. *N Engl J Med* 2019

Class effects of SGLT2 inhibitors on cardiorenal outcomes

Aaron Y. Kluger[1,2*], Kristen M. Tecson[1,2,3], Andy Y. Lee[4,5], Edgar V. Lerma[6], Janani Rangaswami[7,8], Norman E. Lepor[9,10], Michael E. Cobble[11] and Peter A. McCullough[1,3,4,5]



Kluger *et al. Cardiovasc Diabetol (2019)*

The NEW ENGLAND JOURNAL of MEDICINE

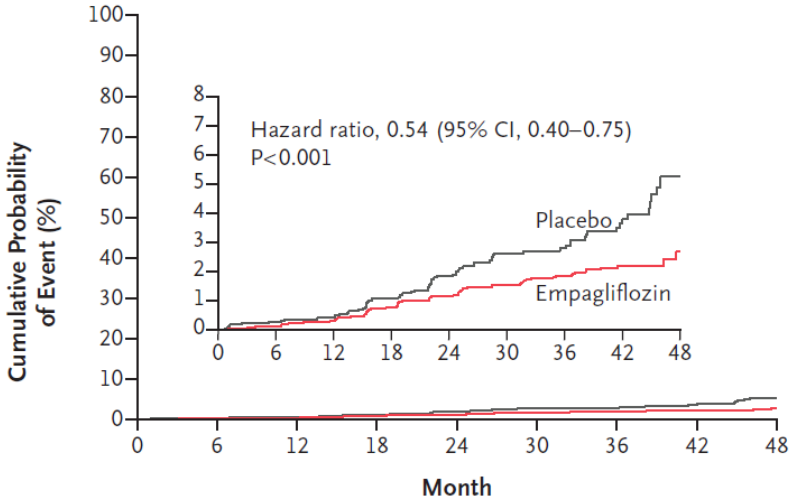
ORIGINAL ARTICLE

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Maximilian von Eynatten, M.D., Michaela Mattheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D., for the EMPA-REG OUTCOME Investigators*

4124 patients

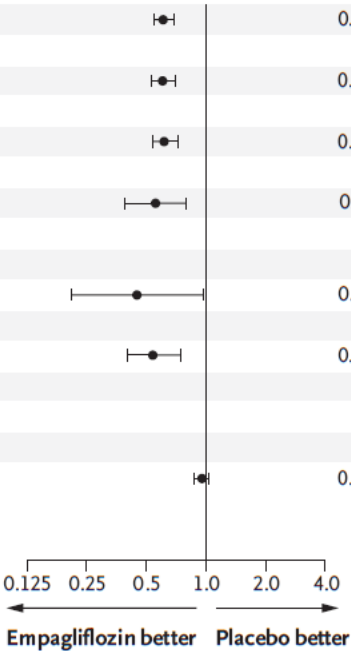
Post Hoc Renal Composite Outcome



No. at Risk

Empagliflozin	4645	4500	4377	4241	3729	2715	2280	1496	360
Placebo	2323	2229	2146	2047	1771	1289	1079	680	144

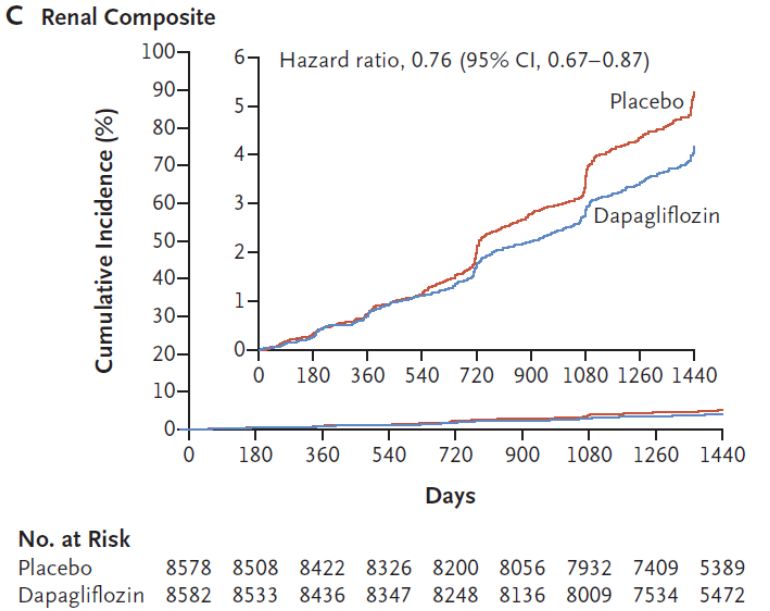
Renal Outcome Measure	Empagliflozin: *no. with event/ no. analyzed (%)*	Empagliflozin: *rate/1000 patient-yr*	Placebo: *no. with event/ no. analyzed (%)*	Placebo: *rate/1000 patient-yr*	Hazard Ratio (95% CI)	P Value
Incident or worsening nephropathy or cardiovascular death	675/4170 (16.2)	60.7	497/2102 (23.6)	95.9	0.61 (0.55–0.69)	<0.001
Incident or worsening nephropathy	525/4124 (12.7)	47.8	388/2061 (18.8)	76.0	0.61 (0.53–0.70)	<0.001
Progression to macroalbuminuria	459/4091 (11.2)	41.8	330/2033 (16.2)	64.9	0.62 (0.54–0.72)	<0.001
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2	70/4645 (1.5)	5.5	60/2323 (2.6)	9.7	0.56 (0.39–0.79)	<0.001
Initiation of renal-replacement therapy	13/4687 (0.3)	1.0	14/2333 (0.6)	2.1	0.45 (0.21–0.97)	0.04
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2, initiation of renal-replacement therapy, or death from renal disease	81/4645 (1.7)	6.3	71/2323 (3.1)	11.5	0.54 (0.40–0.75)	<0.001
Incident albuminuria in patients with a normal albumin level at baseline	1430/2779 (51.5)	252.5	703/1374 (51.2)	266.0	0.95 (0.87–1.04)	0.25



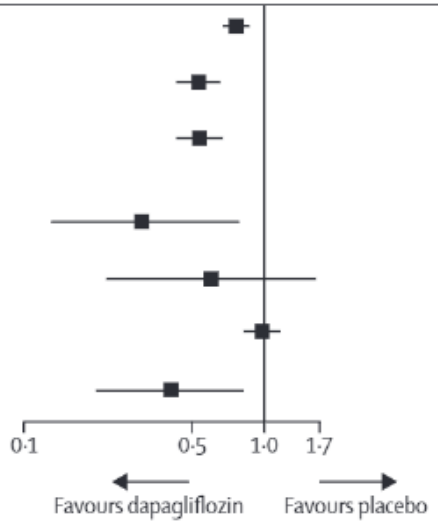
Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE–TIMI 58 randomised trial

Ofri Mosenzon, Stephen D Wiviott, Avivit Cahn, Aliza Rozenberg, Ilan Yanuv, Erica L Goodrich, Sabina A Murphy, Hiddo J L Heerspink, Thomas A Zelniker, Jamie P Dwyer, Deepak L Bhatt, Lawrence A Leiter, Darren K McGuire, John P H Wilding, Eri T Kato, Ingrid A M Gause-Nilsson Martin Fredriksson, Peter A Johansson, Anna Maria Langkilde, Marc S Sabatine, Itamar Raz

17160 patients, 10.186 without CVD



	Dapagliflozin group		Placebo group		Hazard ratio (95% CI)	p value
	n/N (%)	Kaplan-Meier event rate (4 years)	n/N (%)	Kaplan-Meier event rate (4 years)		
Composite cardiorenal outcome	370/8582 (4·3%)	4·2%	480/8578 (5·6%)	5·3%	0·76 (0·67–0·87)	<0·0001
Composite renal-specific outcome	127/8582 (1·5%)	1·5%	238/8578 (2·8%)	2·6%	0·53 (0·43–0·66)	<0·0001
Sustained eGFR decrease ≥40% to eGFR <60mL/ min per 1·73m²	120/8582 (1·4%)	1·4%	221/8578 (2·6%)	2·5%	0·54 (0·43–0·67)	<0·0001
End-stage renal disease	6/8582 (0·1%)	0·1%	19/8578 (0·2%)	0·2%	0·31 (0·13–0·79)	0·013
Renal death	6/8582 (0·1%)	0·1%	10/8578 (0·1%)	0·1%	0·60 (0·22–1·65)	0·32
Cardiovascular death	245/8582 (2·9%)	2·7%	249/8578 (2·9%)	2·7%	0·98 (0·82–1·17)	0·83
End-stage renal disease or renal death	11/8582 (0·1%)	0·1%	27/8578 (0·3%)	0·3%	0·41 (0·20–0·82)	0·012



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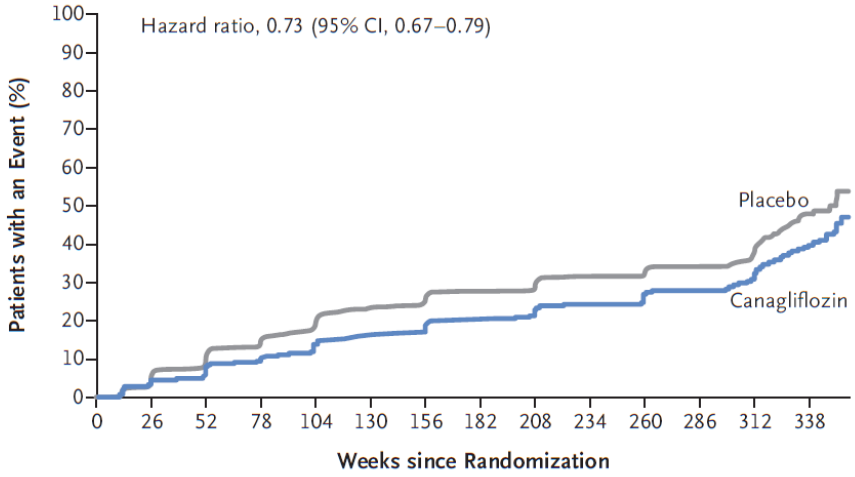
ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

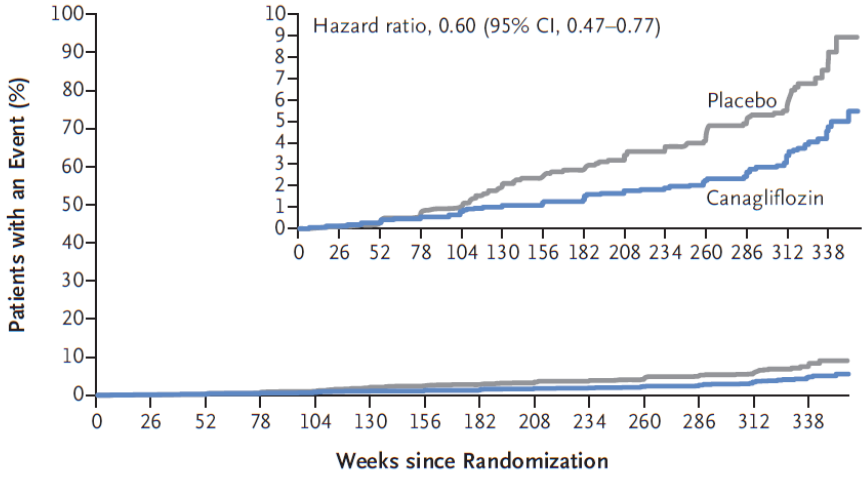
Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group*

C Progression of Albuminuria



No. at Risk														
Placebo	3819	3473	3096	2700	1690	877	724	652	626	565	548	485	303	67
Canagliflozin	5196	4791	4475	4027	2968	1951	1730	1593	1528	1408	1354	1213	775	185

D Composite of 40% Reduction in eGFR, Requirement for Renal-Replacement Therapy, or Death from Renal Causes



No. at Risk														
Placebo	4347	4287	4227	4151	3029	1674	1274	1253	1229	1202	1173	1148	819	229
Canagliflozin	5795	5737	5664	5578	4454	3071	2654	2623	2576	2542	2495	2450	1781	493

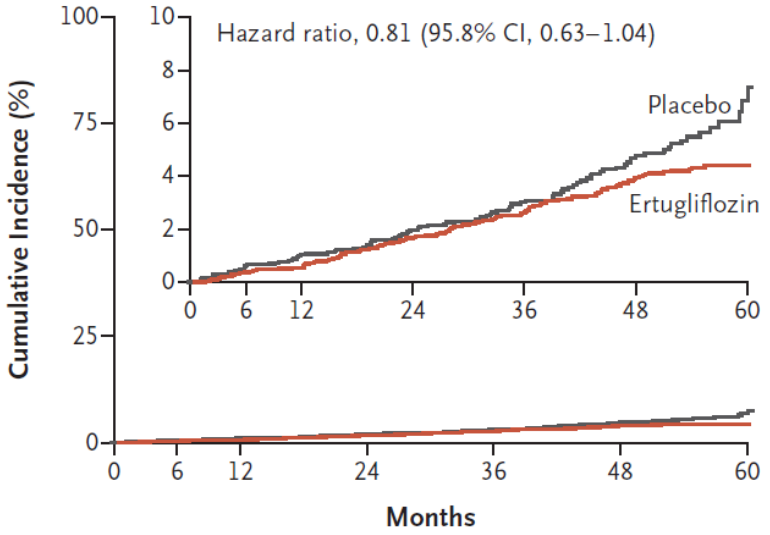
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes

C.P. Cannon, R. Pratley, S. Dagogo-Jack, J. Mancuso, S. Huyck, U. Masiukiewicz, B. Charbonnel, R. Frederich, S. Gallo, F. Cosentino, W.J. Shih, I. Gantz, S.G. Terra, D.Z.I. Cherney, and D.K. McGuire, for the VERTIS CV Investigators*

D Composite Renal Outcome Event

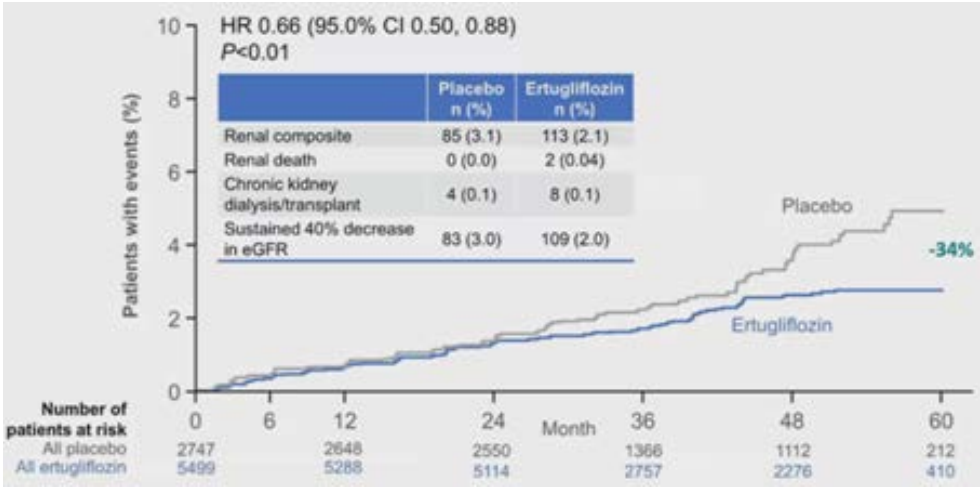


No. at Risk

Placebo	2747	2703	2643	2543	1371	1116	215
Ertugliflozin	5499	5394	5299	5110	2756	2271	406

Death from renal causes,
Renal replacement therapy,
Doubling of the serum creatinine level

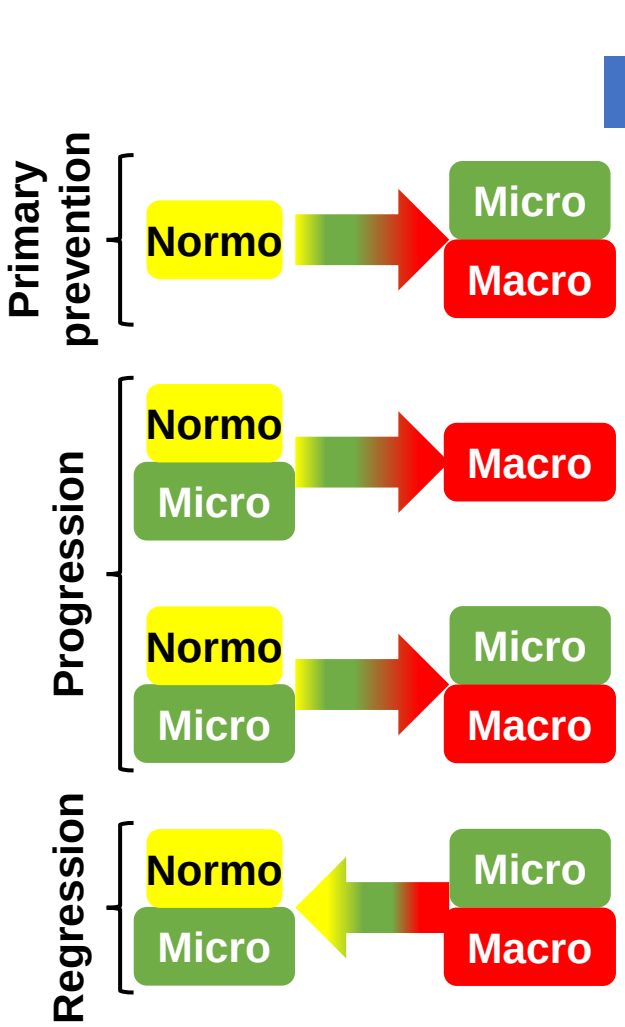
Cherney DZ annual meating EAS 2020



Death from renal causes,
Renal replacement therapy,
Susteined 40% reduction in eGFR: HR 0.65

Progressione albuminuria: HR 0.79, p<0.01
Regresssione albuminuria:HR 1.23, p<0.01

The beneficial effect of SGLT2i on ALBUMINURIA is consistent across trials



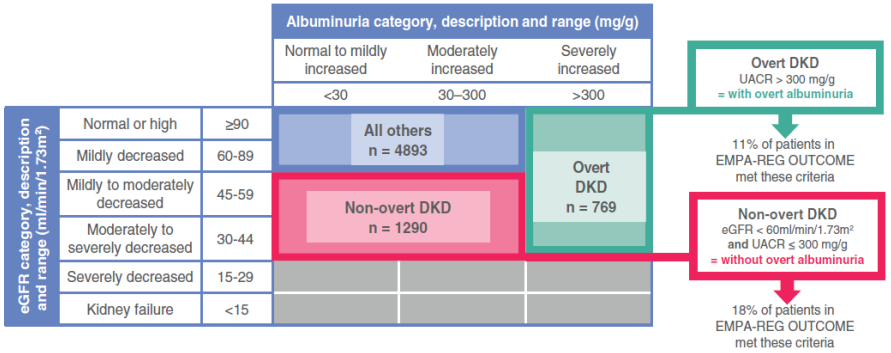
	DECLARE-TIMI 58[1]	CANVAS program[2]	EMPA-REG OUTCOME[2]
Primary prevention: Normo → Micro/Macro	↓ 21% 0.79 (0.72, 0.87)[a]	↓ 20% 0.80 (0.73, 0.88)[b]	↓ 16% 0.84 (0.74, 0.95)[b]
Progression: Normo/Micro → Macro	↓ 46% 0.54 (0.45, 0.65)[a]	↓ 42% 0.58 (0.50, 0.68)[b]	↓ 38% 0.62 (0.54, 0.72)[c]
Progression: Normo/Micro → Micro/Macro	↓ 27% 0.73 (0.67, 0.79)[a]	↓ 27% 0.73 (0.67, 0.79)[b]	↓ 33% 0.67 (0.59, 0.77)[d]
Regression: Micro/Macro → Normo/Micro	↑ 54% 1.54 (1.40, 1.69)[a]	↑ 70% 1.70 (1.51, 1.91)[b]	↑ 61% 1.61 (1.34, 1.94)[d]

[a]Exploratory outcome; [b]Sustained exploratory outcome; [c]Secondary outcome; [d]Sustained post-hoc outcome
macro, macroalbuminuria; micro, microalbuminuria; normo, normoalbuminuria

1. Raz I, et al. Presented at 79th Scientific Sessions of the American Diabetes Association; June 7th–11th, 2019; San Francisco, CA, USA; 244-OR; 2. Barutta F, et al. *Diabetes Metab Res Rev* 2019;35:e3171

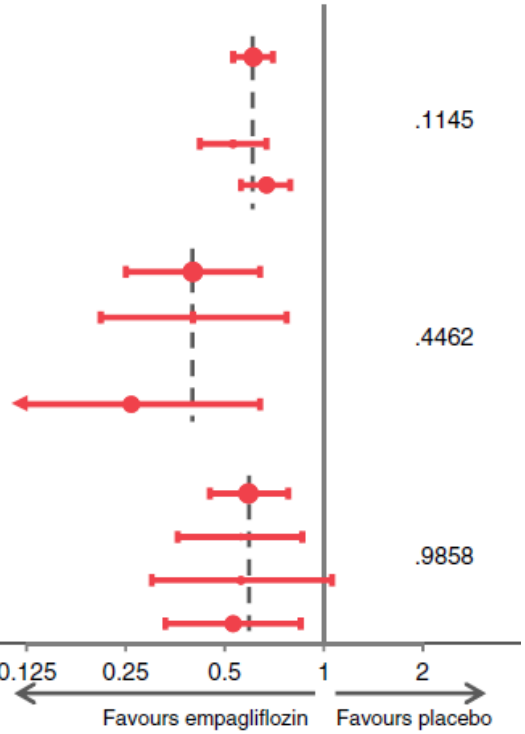
Consistent effects of empagliflozin on cardiovascular and kidney outcomes irrespective of diabetic kidney disease categories: Insights from the EMPA-REG OUTCOME trial

Christoph Wanner MD[1] | Silvio E. Inzucchi MD[2] | Bernard Zinman MD[3] | Audrey Koitka-Weber PhD[1,4,5] | Michaela Mattheus Dipl Biomath[6] | Jyothis T. George MD[4] | Maximilian von Eynatten MD[4] | Sibylle J. Hauske MD[4,7] | EMPA-REG OUTCOME Investigators



(B)

	Empagliflozin n event/N	Empagliflozin %	Placebo n event/N	Placebo %	Hazard ratio (95% CI)	Interaction *P*-value
Incident or worsening nephropathy**						
All patients	525/4124	12.7	388/2061	18.8	0.61 (0.53, 0.70)	
Overt DKD	NA	NA	NA	NA	NC	.1145
Non-overt DKD	150/829	18.1	128/431	29.7	0.53 (0.42, 0.67)	
All others	332/3219	10.3	228/1589	14.3	0.67 (0.56, 0.79)	
Hard kidney endpoint†						
All patients	31/4645	0.7	37/2323	1.6	0.40 (0.25, 0.65)	
Overt DKD	17/504	3.4	19/260	7.3	0.40 (0.21, 0.77)	.4462
Non-overt DKD	6/838	0.7	5/438	1.1	NC	
All others	7/3253	0.2	13/1609	0.8	0.26 (0.10, 0.64)	
Alternative kidney endpoint‡						
All patients	108/4645	2.3	87/2323	3.7	0.59 (0.45, 0.78)	
Overt DKD	49/504	9.7	36/260	13.8	0.56 (0.36, 0.86)	.9858
Non-overt DKD	21/838	2.5	18/438	4.1	0.56 (0.30, 1.06)	
All others	36/3253	1.1	33/1609	2.1	0.53 (0.33, 0.85)	

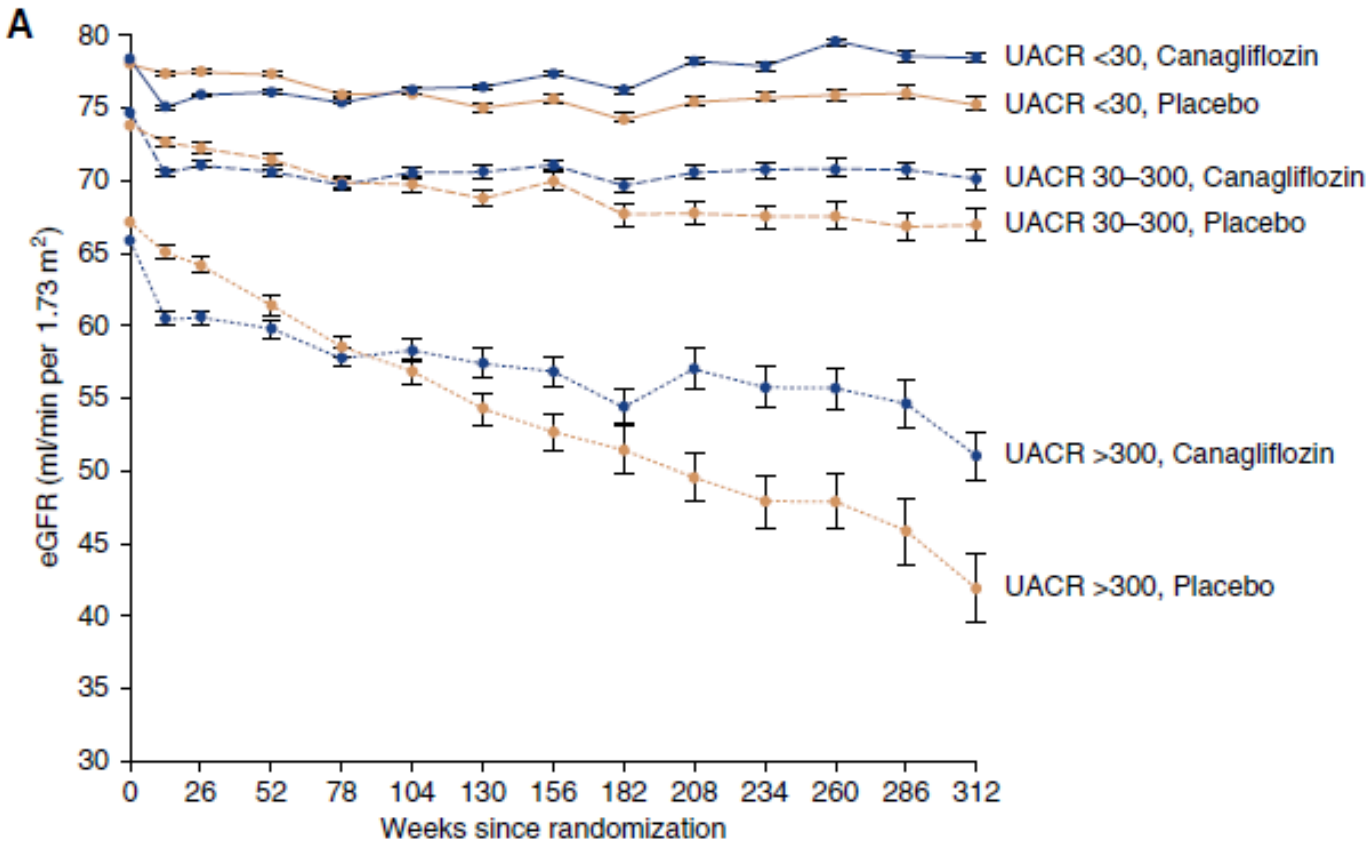


Empagliflozin may improve kidney outcomes and slow the progression of kidney disease in type 2 diabetes patients with DKD, irrespective of its clinical form, both with or without the presence of overt albuminuria.

Diab Obes Met 2020

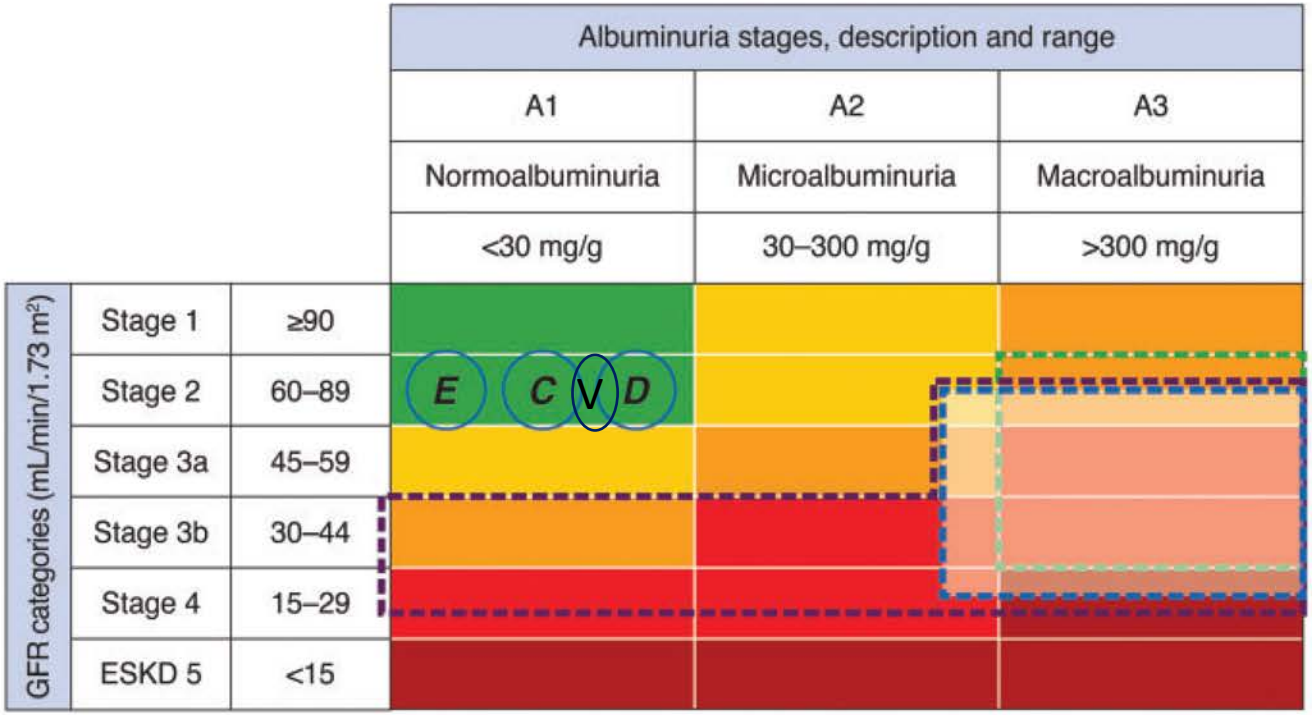
Effect of Canagliflozin on Renal and Cardiovascular Outcomes across Different Levels of Albuminuria: Data from the CANVAS Program

Brendon L. Neuen,[1] Toshiaki Ohkuma,[1] Bruce Neal,[1] David R. Matthews,[2] Dick de Zeeuw,[3] Kenneth W. Mahaffey,[4] Greg Fulcher,[5] Qiang Li,[1] Meg Jardine,[1] Richard Oh,[6] Hiddo L. Heerspink,[1,3] and Vlado Perkovic[1]



Canagliflozin slowed the loss of kidney function across all UACR subgroups. Effect of canagliflozin as indicated by (A) adjusted mean eGFR over time

CVOT e SGLT2-i : FOCUS SU CKD



CREDENCE (DKD only)
eGFR ≥30 to <90 mL/min/1.73 m²
and UACR ≥300 mg/g

DAPA-CKD (CKD)
eGFR ≥25 to <75 mL/min/1.73 m²
and UACR ≥200 mg/g

EMPA-KIDNEY (CKD)
eGFR ≥45 to <75 mL/min/1.73 m²
and UACR ≥200 mg/g
OR
eGFR ≥20 to <45 mL/min/1.73 m²

H.J.L. Heerspink, Nephrol Dial Transplant (2020)

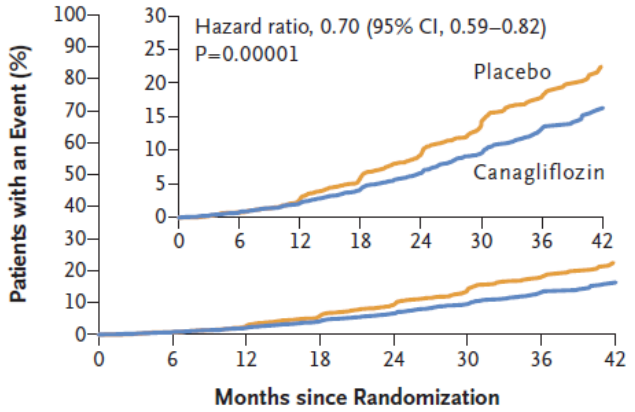
Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

The NEW ENGLAND JOURNAL of MEDICINE

V. Perkovic, M.J. Jardine, B. Neal, S. Bompoint, H.J.L. Heerspink, D.M. Charytan, R. Edwards, R. Agarwal, G. Bakris, S. Bull, C.P. Cannon, G. Capuano, P.-L. Chu, D. de Zeeuw, T. Greene, A. Levin, C. Pollock, D.C. Wheeler, Y. Yavin, H. Zhang, B. Zinman, G. Meininger, B.M. Brenner, and K.W. Mahaffey, for the CREDENCE Trial Investigators*

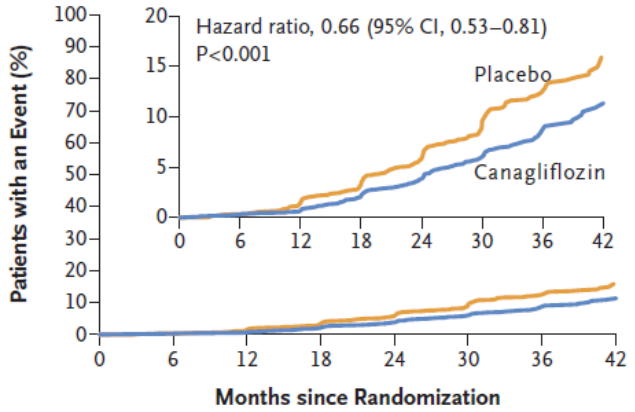
June 13, 2019

A Primary Composite Outcome



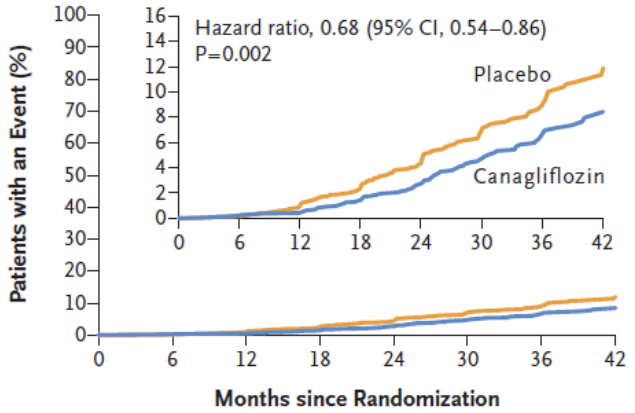
No. at Risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

B Renal-Specific Composite Outcome



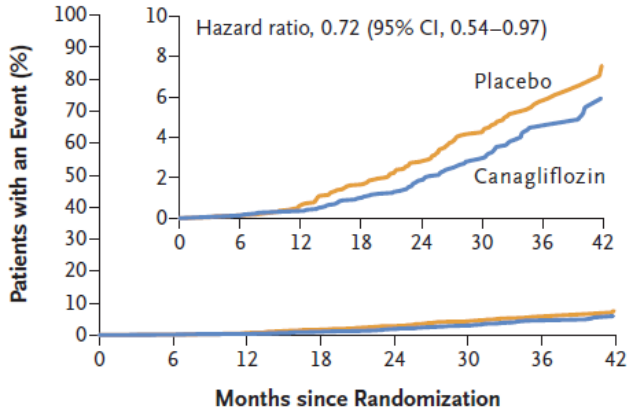
No. at Risk								
Placebo	2199	2178	2131	2046	1724	1129	621	170
Canagliflozin	2202	2181	2144	2080	1786	1211	646	196

C End-Stage Kidney Disease



No. at Risk								
Placebo	2199	2182	2141	2063	1752	1152	641	178
Canagliflozin	2202	2182	2146	2091	1798	1217	654	199

D Dialysis, Kidney Transplantation, or Renal Death



No. at Risk								
Placebo	2199	2183	2147	2077	1776	1178	653	180
Canagliflozin	2202	2184	2148	2100	1811	1236	661	199

Type 2 diabetes and albuminuric chronic kidney disease 12900 pz

IC: eGFR of 30 to <90 albuminuria >300 to 5000) and were treated with renin–angiotensin system blockade.

Primary composite Outcome:
-**end-stage kidney disease** (dialysis, transplantation, or a sustained egfr<15)
- **doubling of creatinine,**
- **death from renal or cardiovascular causes**

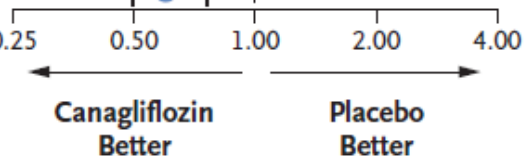
Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

The NEW ENGLAND JOURNAL of MEDICINE

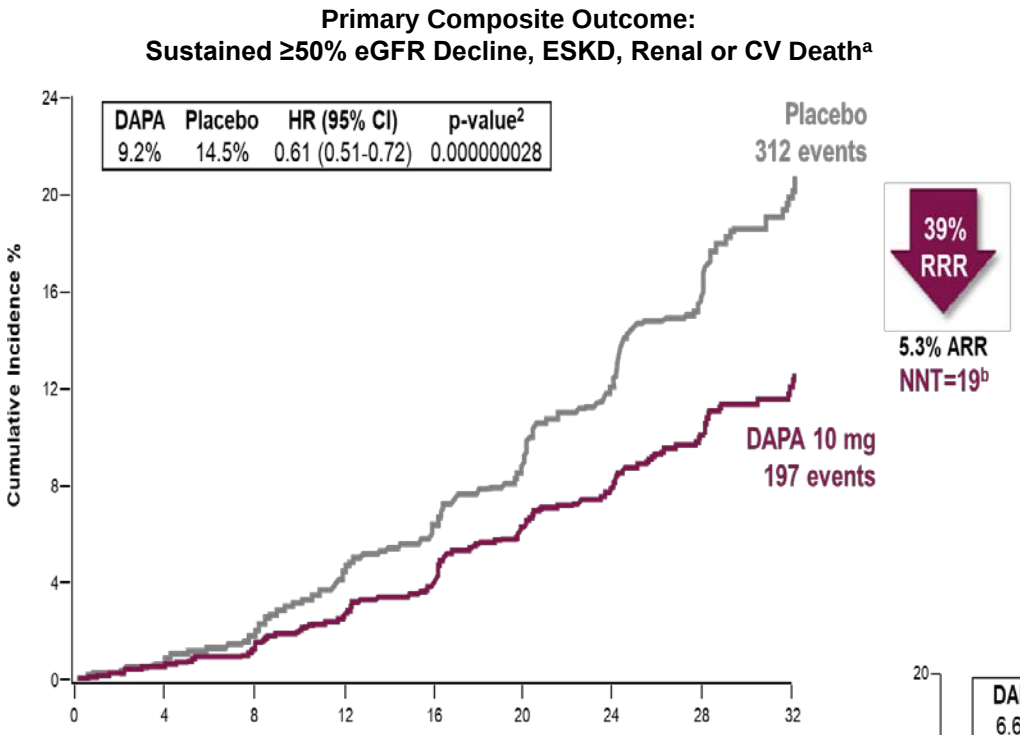
V. Perkovic, M.J. Jardine, B. Neal, S. Bompoint, H.J.L. Heerspink, D.M. Charytan, R. Edwards, R. Agarwal, G. Bakris, S. Bull, C.P. Cannon, G. Capuano, P.-L. Chu, D. de Zeeuw, T. Greene, A. Levin, C. Pollock, D.C. Wheeler, Y. Yavin, H. Zhang, B. Zinman, G. Meininger, B.M. Brenner, and K.W. Mahaffey, for the CREDENCE Trial Investigators*

June 13, 2019

Subgroup	Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients/total no.		*events/1000 patient-yr*			
Primary composite outcome of ESKD, doubling of serum creatinine, or renal or CV death						
Screening estimated GFR						0.11
30 to <45 ml/min/1.73 m^2	119/657	153/656	72.2	95.4	0.75 (0.59–0.95)	
45 to <60 ml/min/1.73 m^2	56/640	102/639	33.4	63.1	0.52 (0.38–0.72)	
60 to <90 ml/min/1.73 m^2	70/905	85/904	29.9	36.5	0.82 (0.60–1.12)	
Baseline UACR						0.49
≤1000	69/1185	88/1163	22.0	28.8	0.76 (0.55–1.04)	
>1000	176/1017	252/1036	69.6	100.8	0.67 (0.55–0.81)	
Renal-specific composite outcome of ESKD, doubling of serum creatinine, or renal death						
Screening estimated GFR						0.18
30 to <45 ml/min/1.73 m^2	85/657	115/656	51.6	71.7	0.71 (0.53–0.94)	
45 to <60 ml/min/1.73 m^2	33/640	66/639	19.7	40.8	0.47 (0.31–0.72)	
60 to <90 ml/min/1.73 m^2	35/905	43/904	14.9	18.5	0.81 (0.52–1.26)	
Baseline UACR						0.16
≤1000	29/1185	31/1163	9.2	10.2	0.90 (0.54–1.50)	
>1000	124/1017	193/1036	49.1	77.2	0.61 (0.49–0.76)	

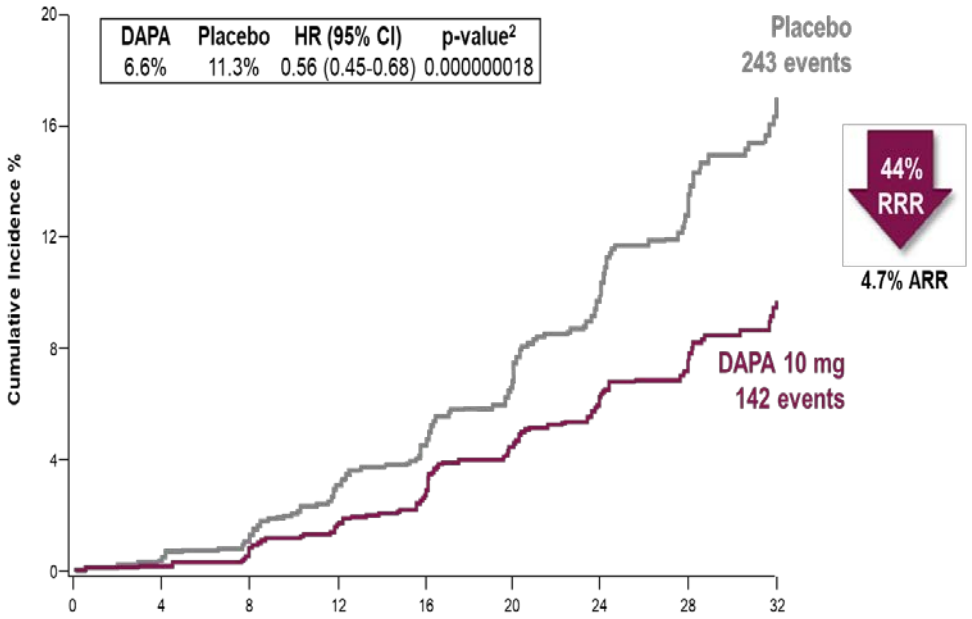


DAPA CKD



Demonstrated a significant and clinically relevant reduction in:

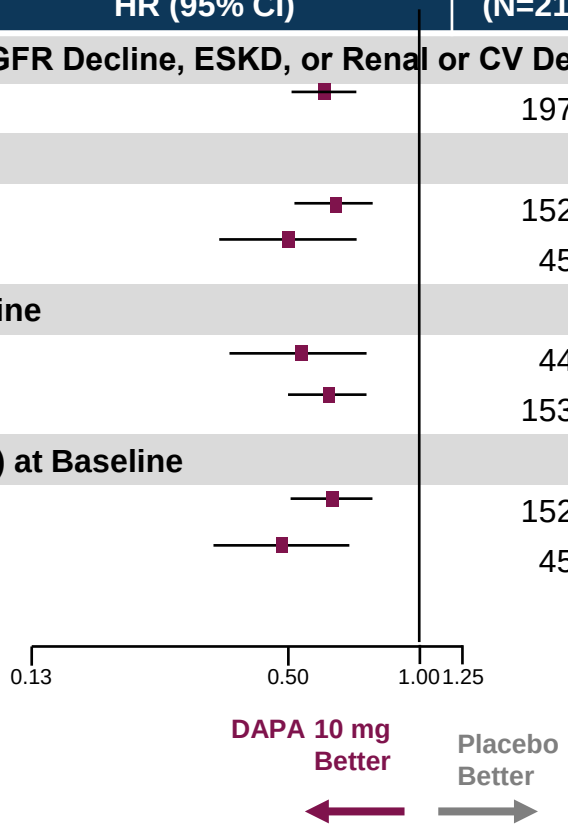
- Primary Renal Outcome
- Renal Specific Outcome



Heerspink HJL et al. *N Engl J Med*. 2020

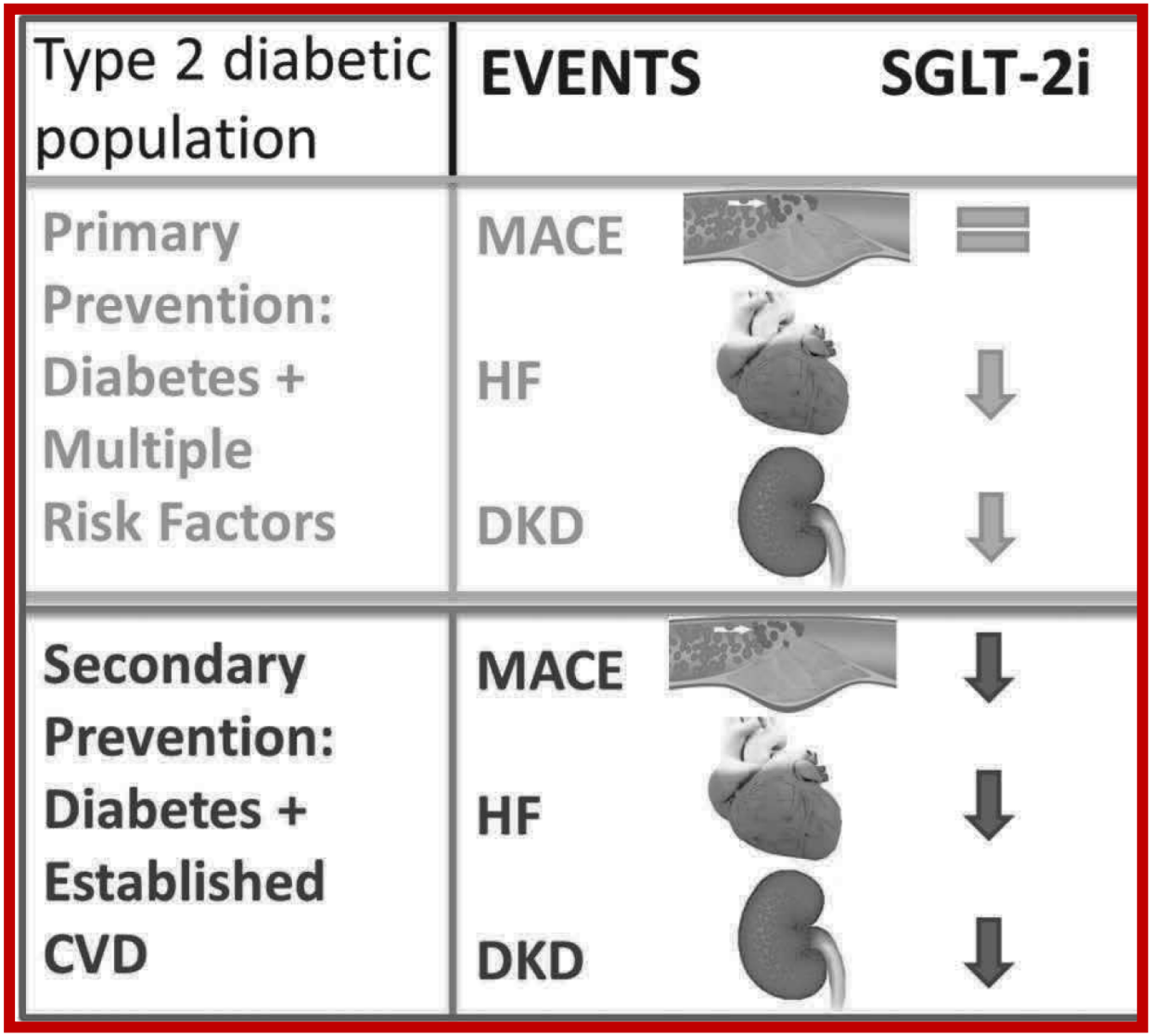
DAPA DKC Primary Composite Outcome: Treatment Benefit Consistent Across Subgroups

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



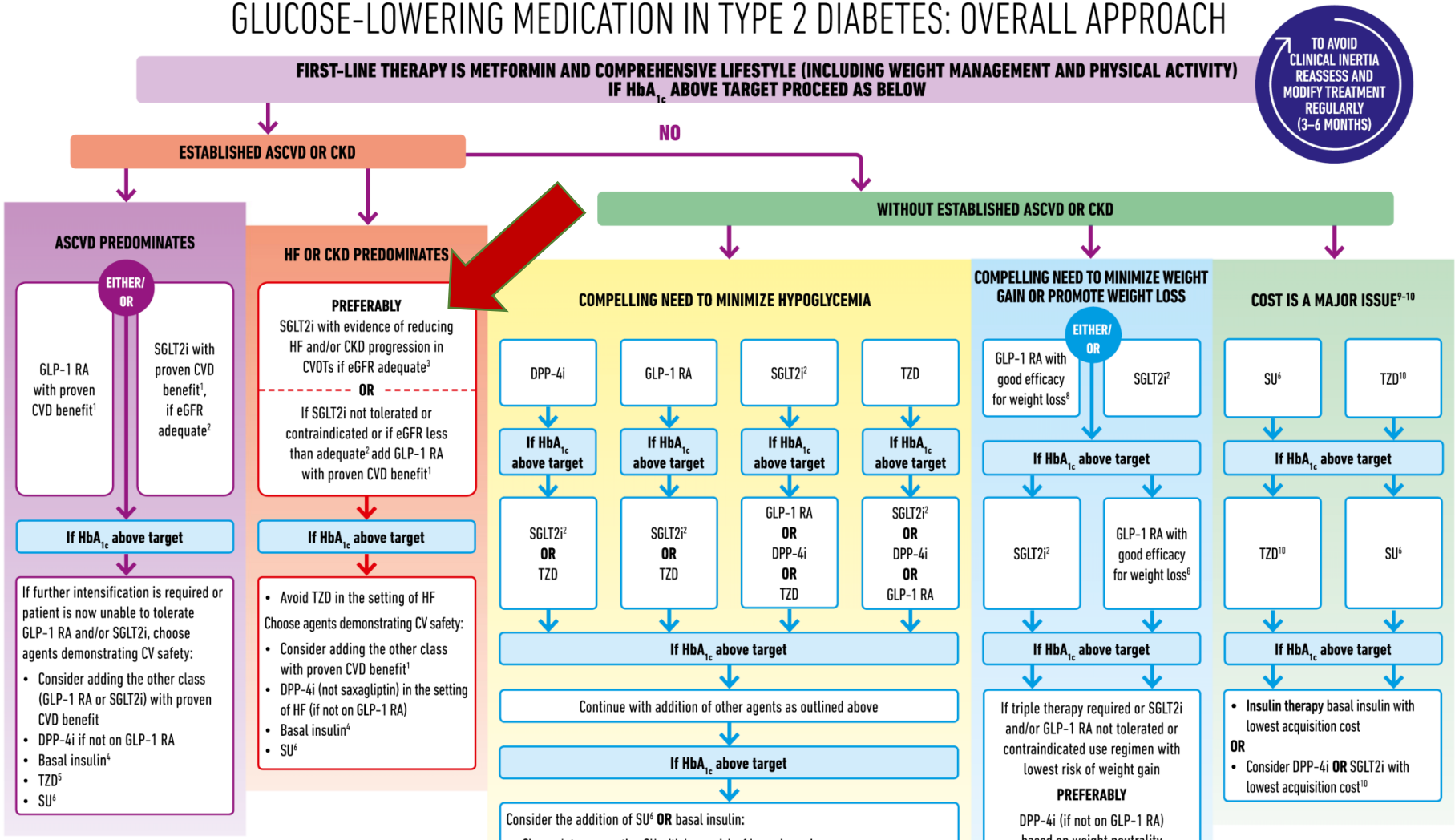
CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio. 1. Heerspink HJL et al. Online ahead of print. *N Engl J Med*. 2020; 2. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 – September 1, 2020.

	CREDENCE[1-3]	Dapa-CKD[4-5]	EMPA-KIDNEY[5-6]
SGLT2 inhibitor	Canagliflozin vs placebo	Dapagliflozin vs placebo	Empagliflozin vs placebo
Population	**DKD incl.** ✓ T2D x Non-DM x T1D	**CKD incl.** ✓ T2D ✓ Non-DM x T1D	**CKD incl.** ✓ T2D ✓ Non-DM ✓ T1D
No. of patients	4401	4000	~5000
Key inclusion criteria	eGFR ≥30 to <90 ml/min/1.73 m^2 **and** UACR >300 mg/g	eGFR ≥25 to ≤75 ml/min/1.73 m^2 **and** UACR ≥200 mg/g	eGFR ≥20 to <45 ml/min/1.73 m^2 **or** eGFR ≥45 to <90 ml/min/1.73 m^2 and UACR ≥200 mg/g
Primary outcome	Composite of ESKD, doubling of serum creatinine, or renal or CV death	Composite of ≥50% sustained decline in eGFR or reaching ESKD, or renal or CV death	Composite of ≥40% sustained decline in eGFR or reaching ESKD, or renal or CV death
Key secondary outcomes	Composite of CV death or HHF All-cause mortality	Composite of CV death or HHF All-cause mortality	Composite of CV death or HHF All-cause hospitalisation All-cause mortality
Start date **Estimated completion date**	February 2014 Completed*	February 2017 Completed	~November 2018 ~June 2022
No. of countries	34	21	7



Giugliano el at, Diabetes Obes Metab. 2020

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries, TZDs relatively more expensive and DPP-4i relatively cheaper

Linee guida ADA-EASD 2018

FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)

INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF†

NO

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

CONSIDER INDEPENDENTLY OF BASELINE A1C OR INDIVIDUALIZED A1C TARGET

IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW

ASCVD PREDOMINATES

- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 years with coronary, carotid or lower extremity artery stenosis >50%, or LVH)

PREFERABLY

GLP-1 RA with proven CVD benefit[1]

OR

SGLT2i with proven CVD benefit[1] if eGFR adequate[2]

If A1C above target

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit[1]
- DPP-4i if not on GLP-1 RA
- Basal insulin[4]
- TZD[5]
- SU[6]

HF OR CKD PREDOMINATES

- Particularly HFrEF (LVEF <45%)
- CKD: Specifically eGFR 30-60 mL/min/1.73 m² or UACR >3 mg/g, particularly UACR >30 mg/g

PREFERABLY

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[2]

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1]

If A1C above target

- Avoid TZD in the setting of HF

Choose agents demonstrating CV safety:

- For patients on a SGLT2i, consider adding GLP-1 RA with proven CVD benefit[1]
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin[4]
- SU[6]

COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA

DPP-4i	GLP-1 RA	SGLT2i[2]	TZD
If A1C above target			
SGLT2i[2] **OR** TZD	SGLT2i[2] **OR** TZD	GLP-1 RA **OR** DPP-4i **OR** TZD	SGLT2i[2] **OR** DPP-4i **OR** GLP-1 RA

If A1C above target

Continue with addition of other agents as outlined above

If A1C above target

Consider the addition of SU[6] **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycemia
- Consider basal insulin with lower risk of hypoglycemia[7]

COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

GLP-1 RA with good efficacy for weight loss[8] — EITHER/OR — SGLT2i[2]

If A1C above target

SGLT2i[2] | GLP-1 RA with good efficacy for weight loss[8]

If A1C above target

If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain

PREFERABLY

DPP-4i (if not on GLP-1 RA) based on weight neutrality

If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:

• SU[6] • TZD[5] • Basal insulin

COST IS A MAJOR ISSUE[9-10]

SU[6]	TZD[10]
If A1C above target	
TZD[10]	SU[6]

If A1C above target

- **Insulin therapy** basal insulin with lowest acquisition cost

OR

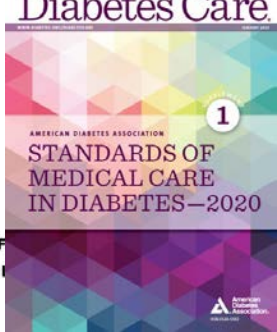
- Consider DPP-4i **OR** SGLT2i with lowest acquisition cost[10]

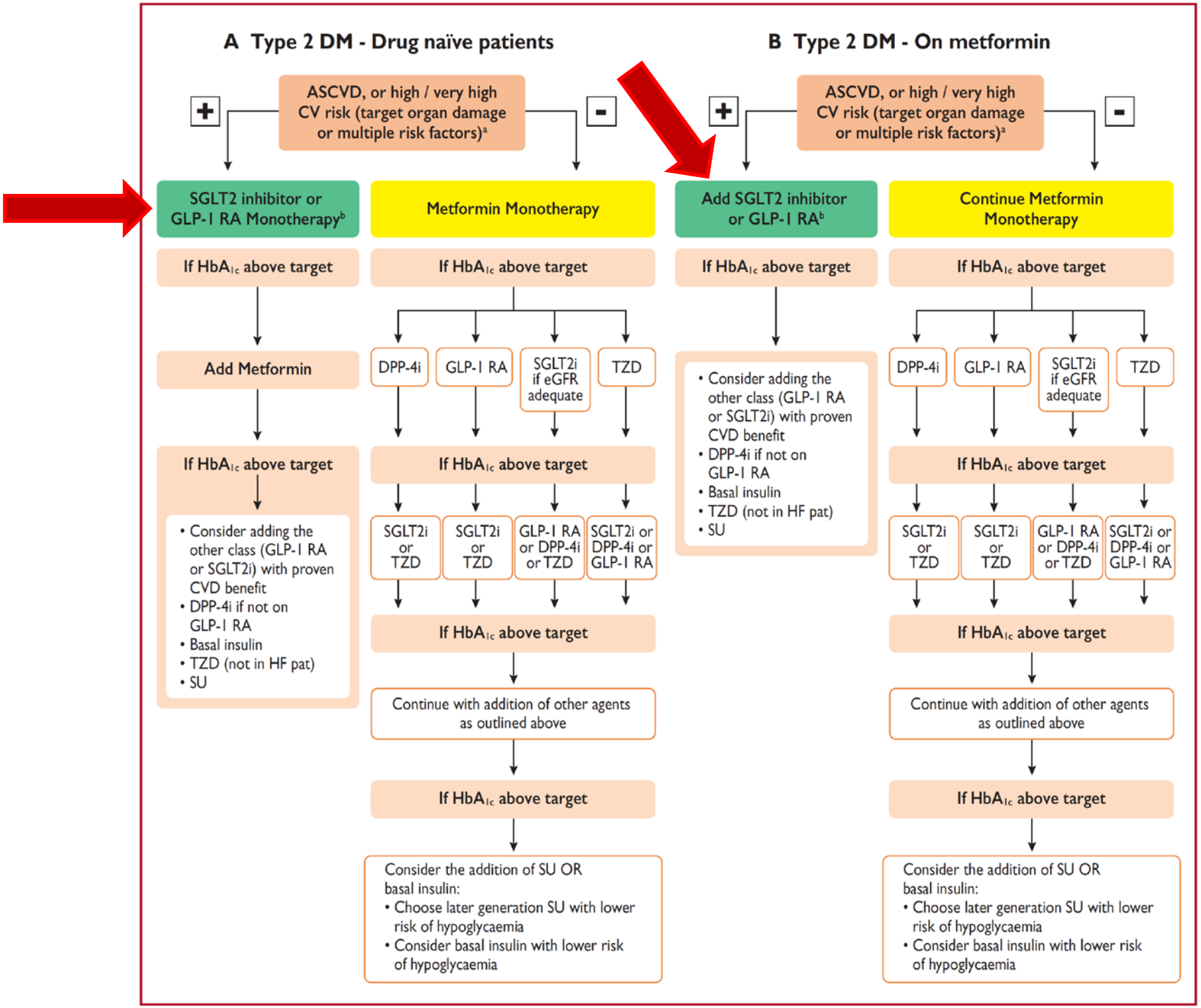
1. Proven CVD benefit means it has label indication of reducing CVD events
2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozen has primary heart failure outcome data from DAPA-HF
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU to lower risk of hypoglycemia, Glimepiride has shown similar CV safety to DPP-4i
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

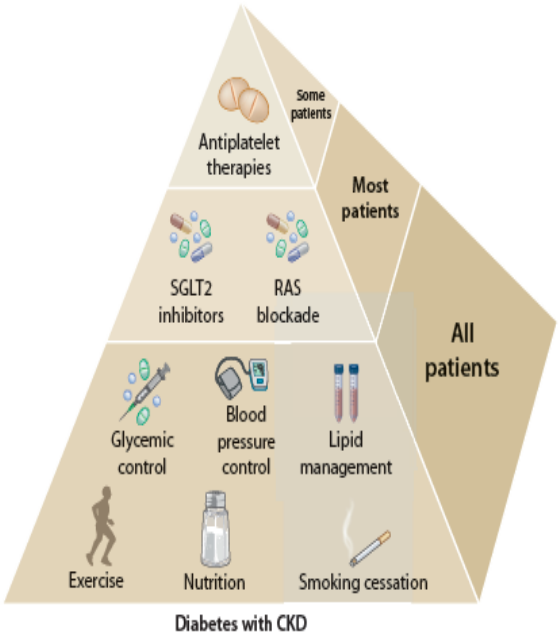
LVH = Left Ventricular Hypertrophy; HFrEF = Heart F

UACR = Urine Albumin-to-Creatinine Ratio; LVEF = L




A Type 2 DM - Drug naïve patients
B Type 2 DM - On metformin
ASCVD, or high / very high CV risk (target organ damage or multiple risk factors)[a]
+
-
SGLT2 inhibitor or GLP-1 RA Monotherapy[b]
Metformin Monotherapy
Add SGLT2 inhibitor or GLP-1 RA[b]
Continue Metformin Monotherapy
If HbA1c above target
Add Metformin
DPP-4i
GLP-1 RA
SGLT2i if eGFR adequate
TZD
SGLT2i or TZD
GLP-1 RA or DPP-4i or TZD
SGLT2i or DPP-4i or GLP-1 RA
• Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
• DPP-4i if not on GLP-1 RA
• Basal insulin
• TZD (not in HF pat)
• SU
Continue with addition of other agents as outlined above
Consider the addition of SU OR basal insulin:
• Choose later generation SU with lower risk of hypoglycaemia
• Consider basal insulin with lower risk of hypoglycaemia

Comprehensive management of diabetes and CKD



Lifestyle therapy

Physical activity
Nutrition
Weight loss

First-line therapy

Metformin

eGFR < 45	eGFR < 30	Dialysis
Reduce dose	Discontinue	Discontinue

+

SGLT2 inhibitor

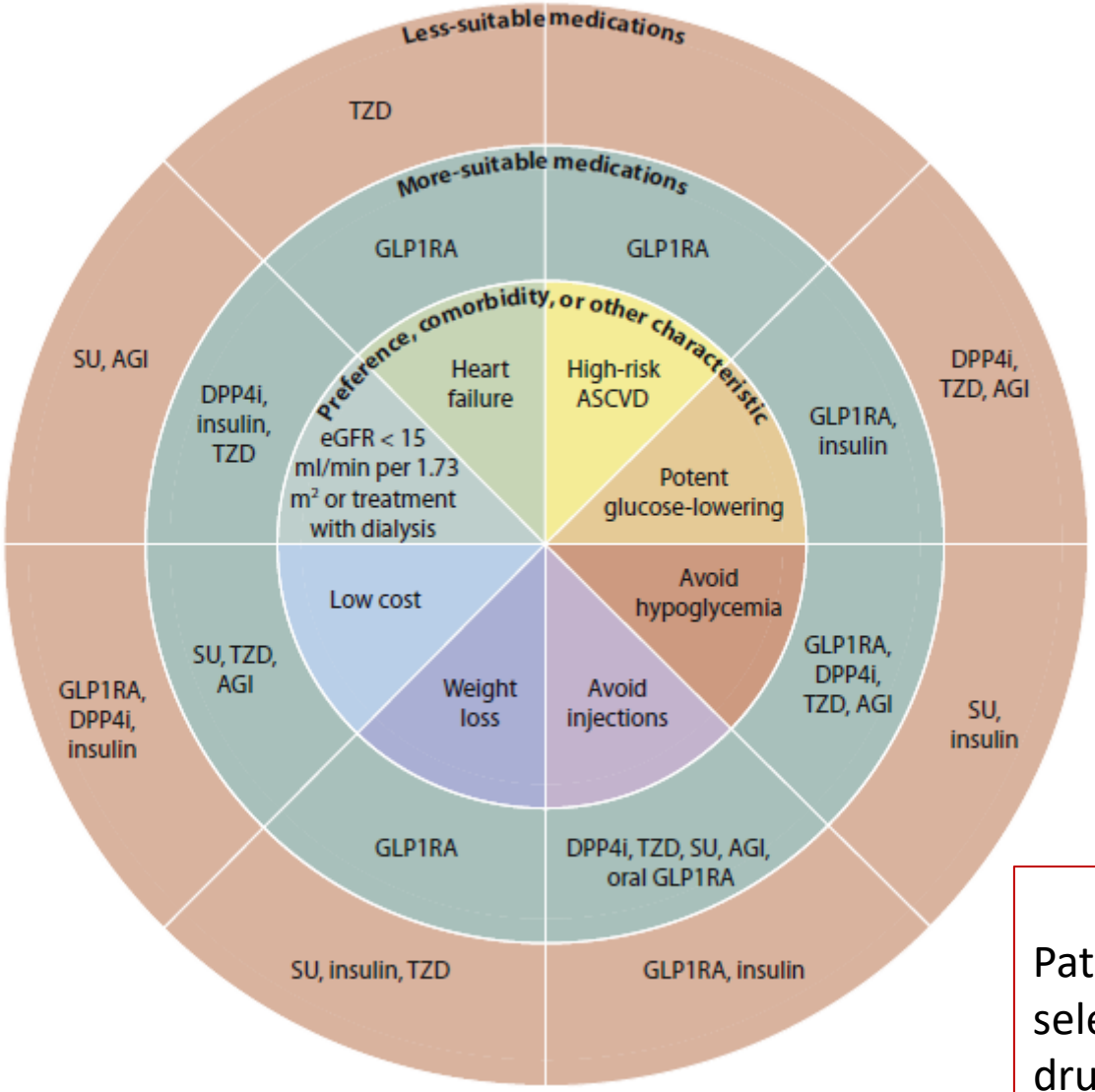
eGFR < 30	Dialysis
Do not initiate	Discontinue

Additional drug therapy as needed for glycemic control

- GLP-1 receptor agonist (preferred)
- DPP-4 inhibitor
- Insulin
- Sulfonylurea
- TZD
- Alpha-glucosidase inhibitor

- Guided by patient preferences, comorbidities, eGFR, and cost
- Includes patients with eGFR < 30 ml/min per 1.73 m^2 or treated with dialysis
- See Figure 20

KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease, 2020 Oct, Kidney International

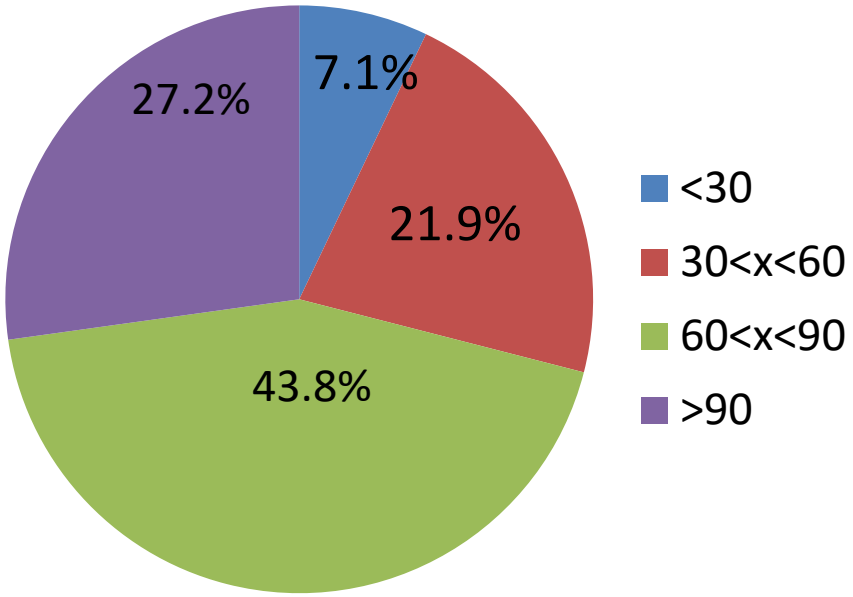


Patient factors influencing the selection of glucose-lowering drugs other than SGLT2i and metformin in T2D and CKD.

Grazie per l’attenzione

Annali AMD 2020

Andamento per 4 classi di filtrato



Soggetti con micro/macroalb %