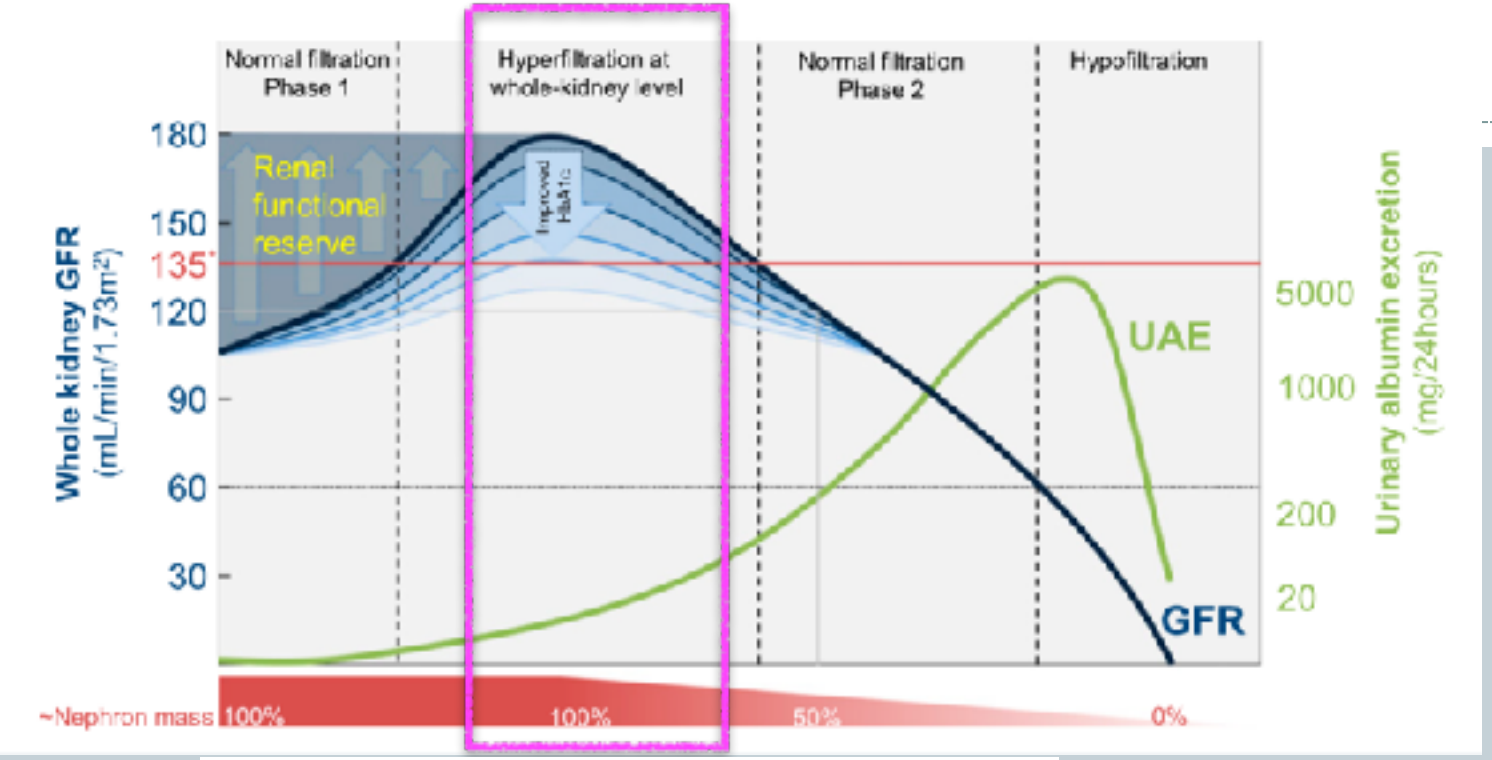
Flozyny w praktyce klinicznej - pacjent CRM

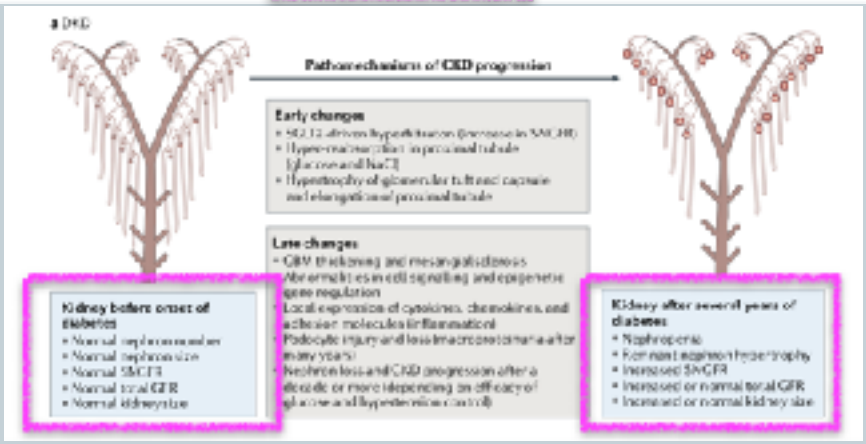
Krzysztof Wróblewski

Klinika Chorób Wewnętrznych i Nefrodiabetologii, UM w Łodzi

11/05/2023

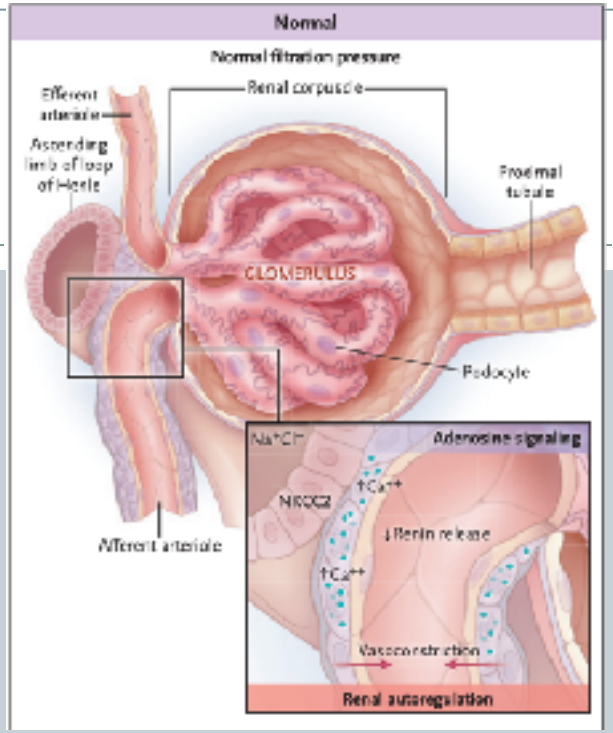
DM a nerki

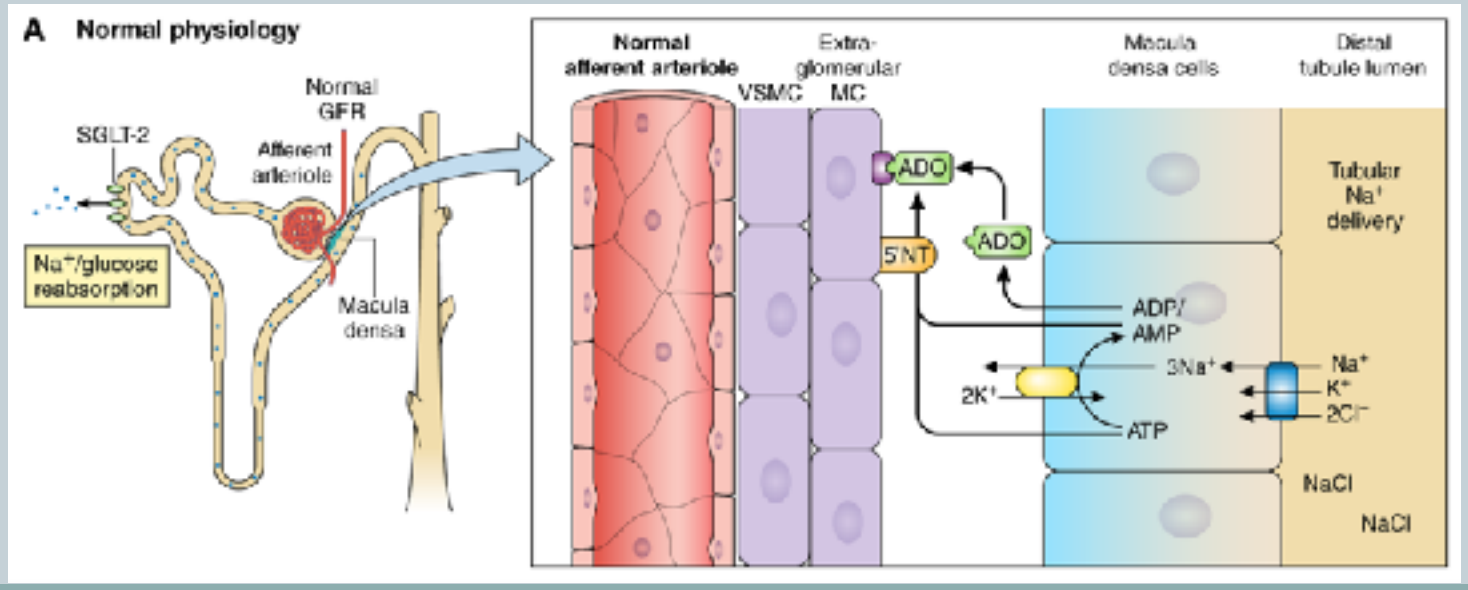




Tonneijck J et al. J Am Soc Nephrol 28, 2017: 1023-1039
HJ Anders, Nat Rev Nephrol. 2018 Jun;14(6):361-377

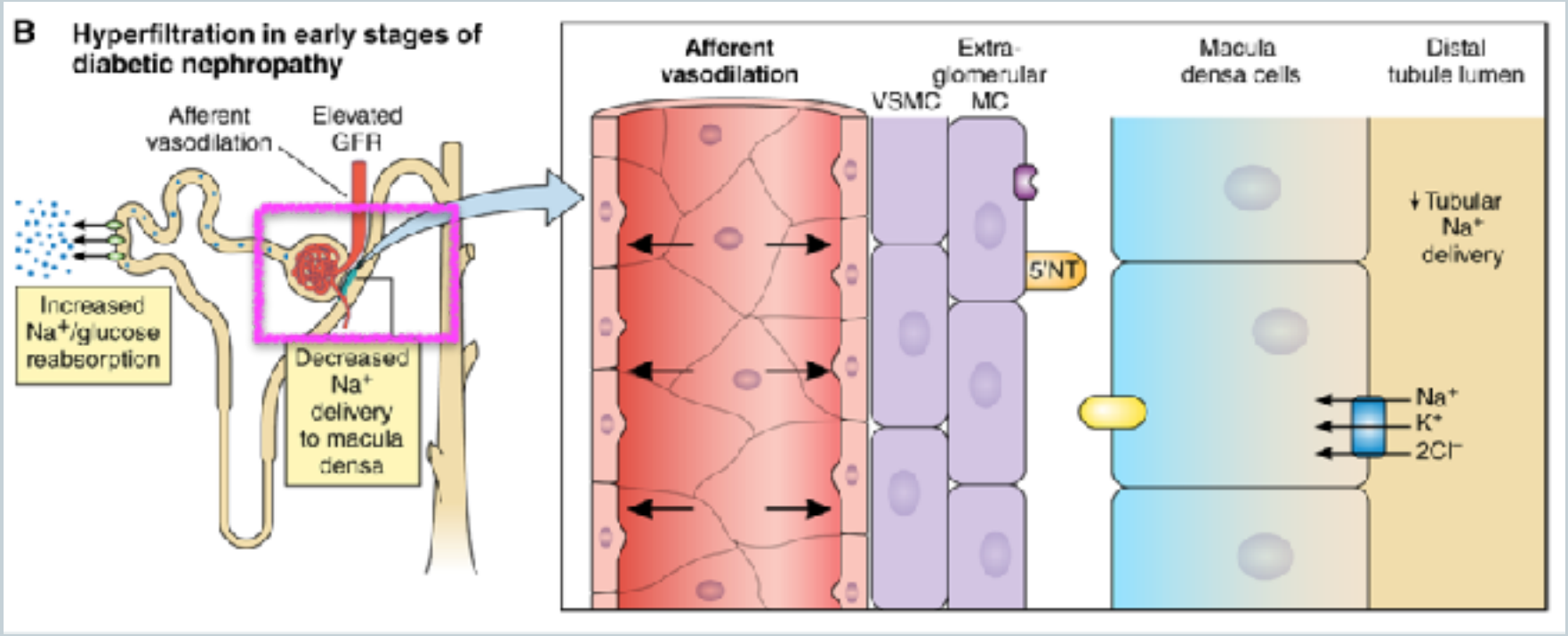
kluczem jest plamka





Heerspink H et al. Circulation. 2016;134:752–772

DM

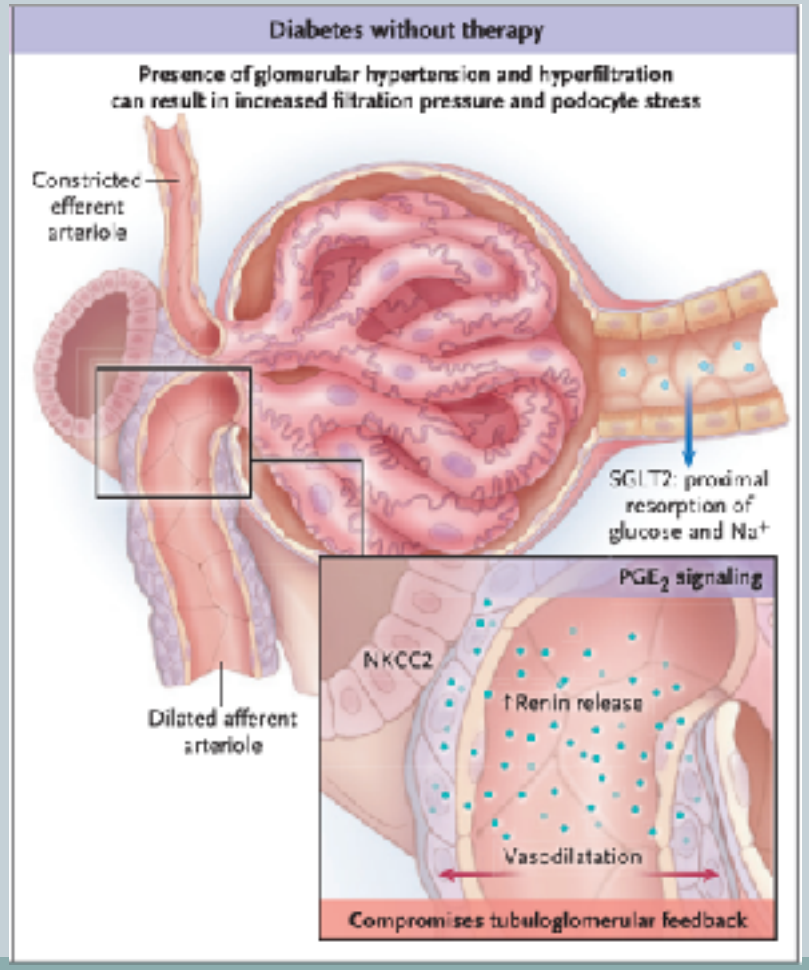


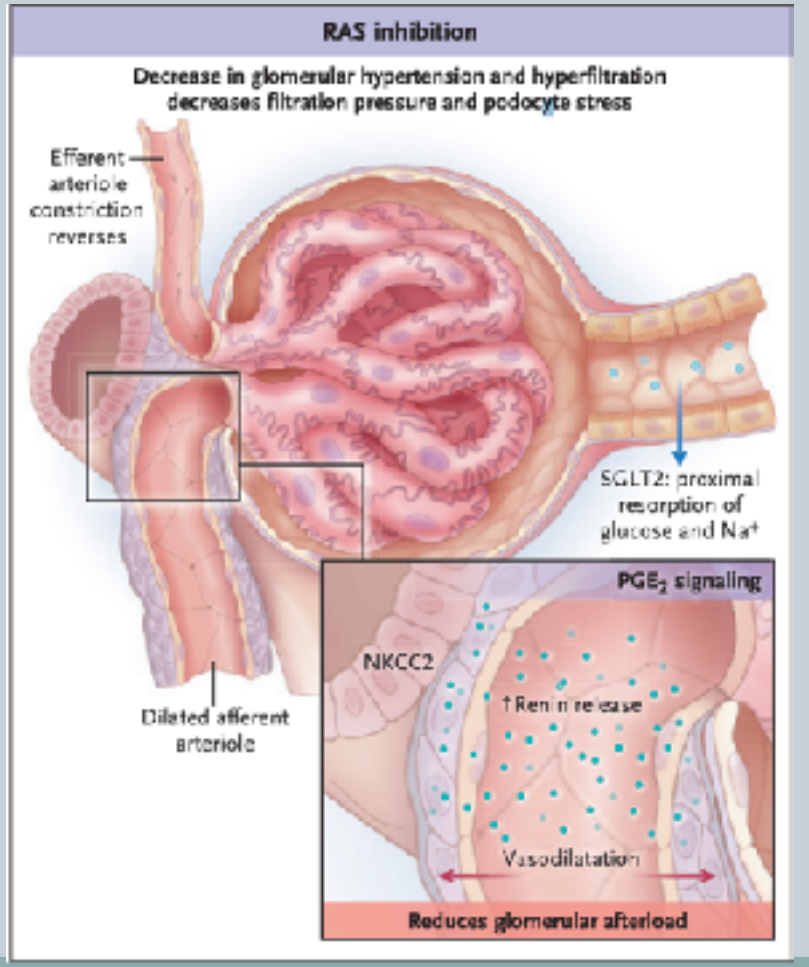
Heerspink H et al. Circulation. 2016;134:752–772


CLINICAL IMPLICATIONS OF BASIC RESEARCH

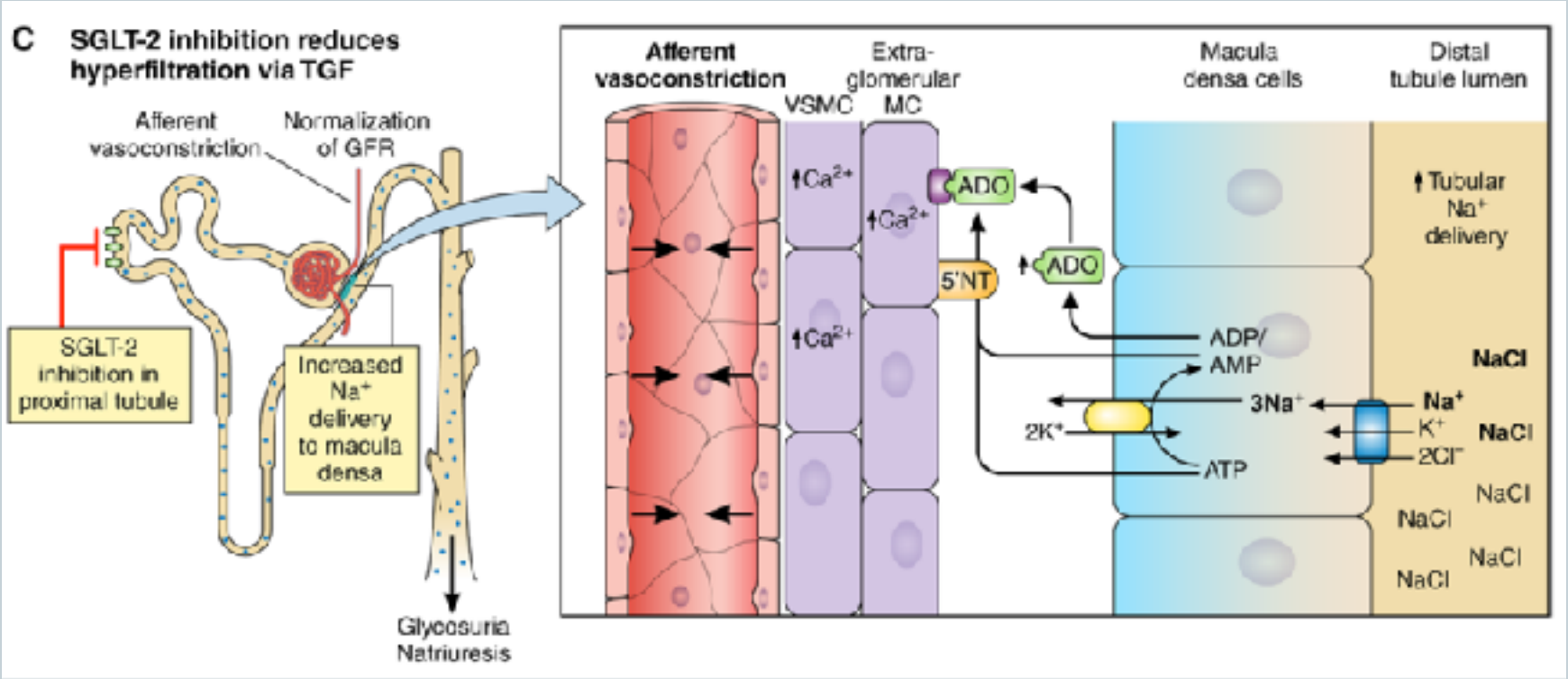
Nephron Protection in Diabetic Kidney Disease

ACEI/ARB w DM





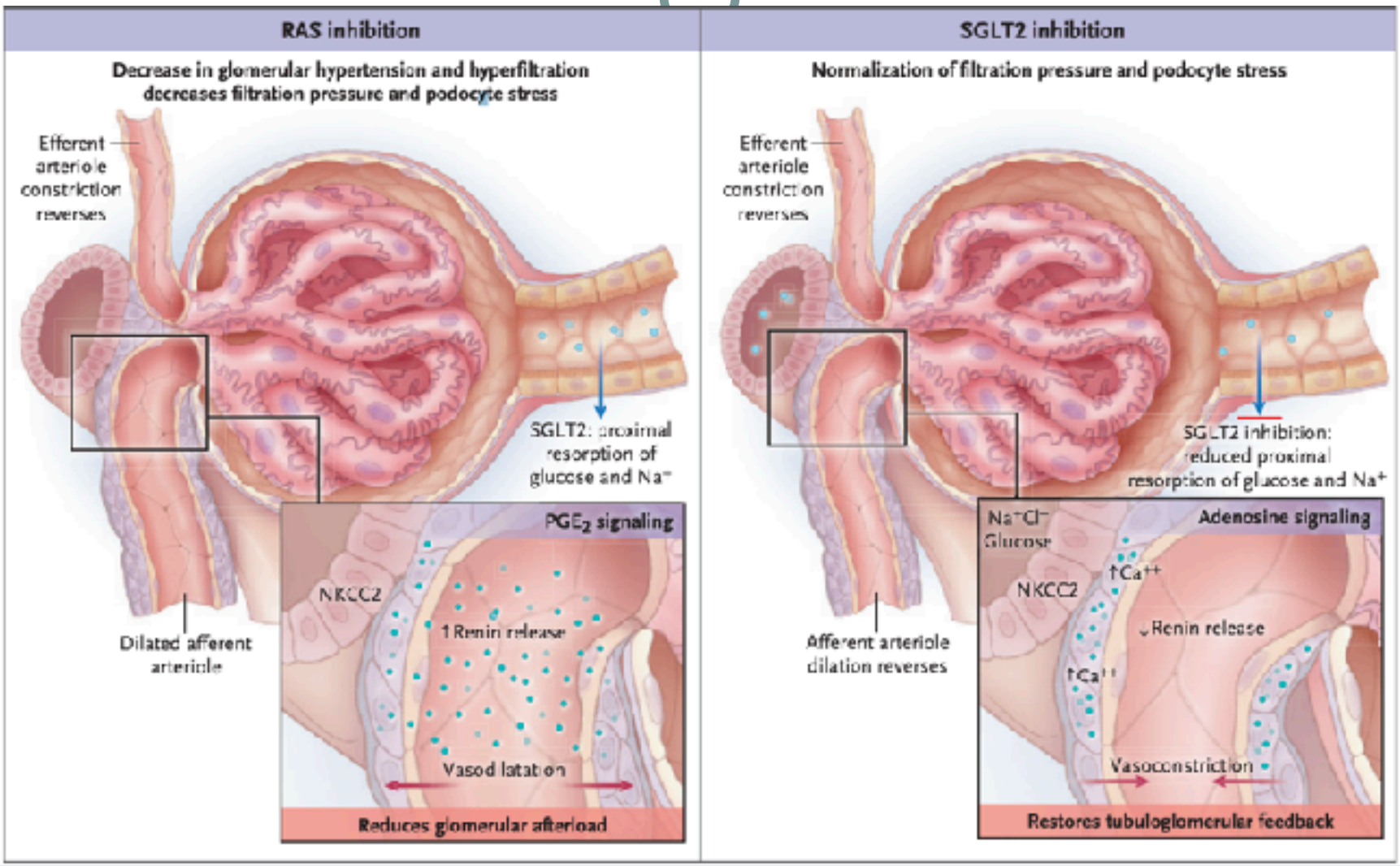
iSGLT2



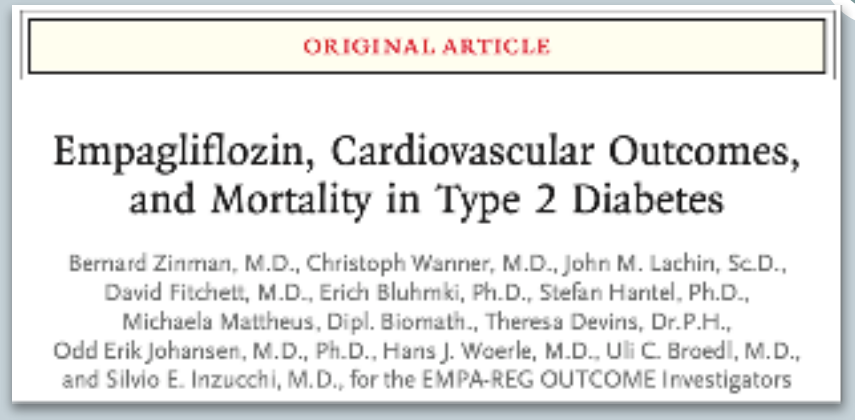
⇓ hiperfiltracji, ⇓ reabsorpcji glukozy

Heerspink H et al. Circulation. 2016;134:752–772

ACEI vs iSGLT2



iSGLT2 a serce w populacji DM2

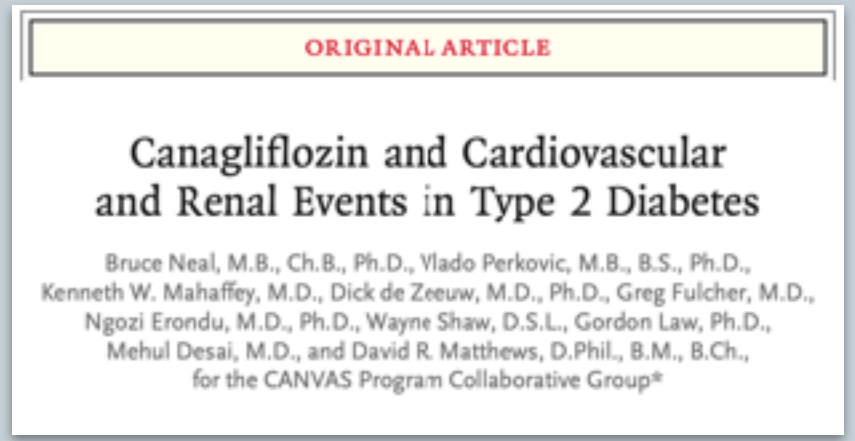


ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

2015

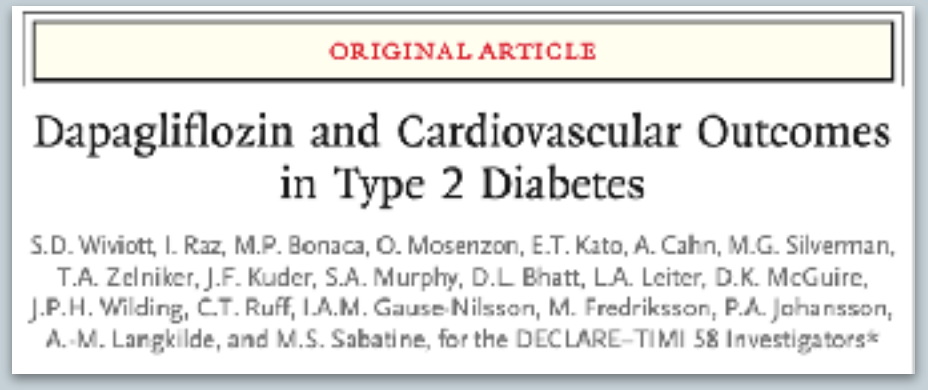


ORIGINAL ARTICLE

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*

2017

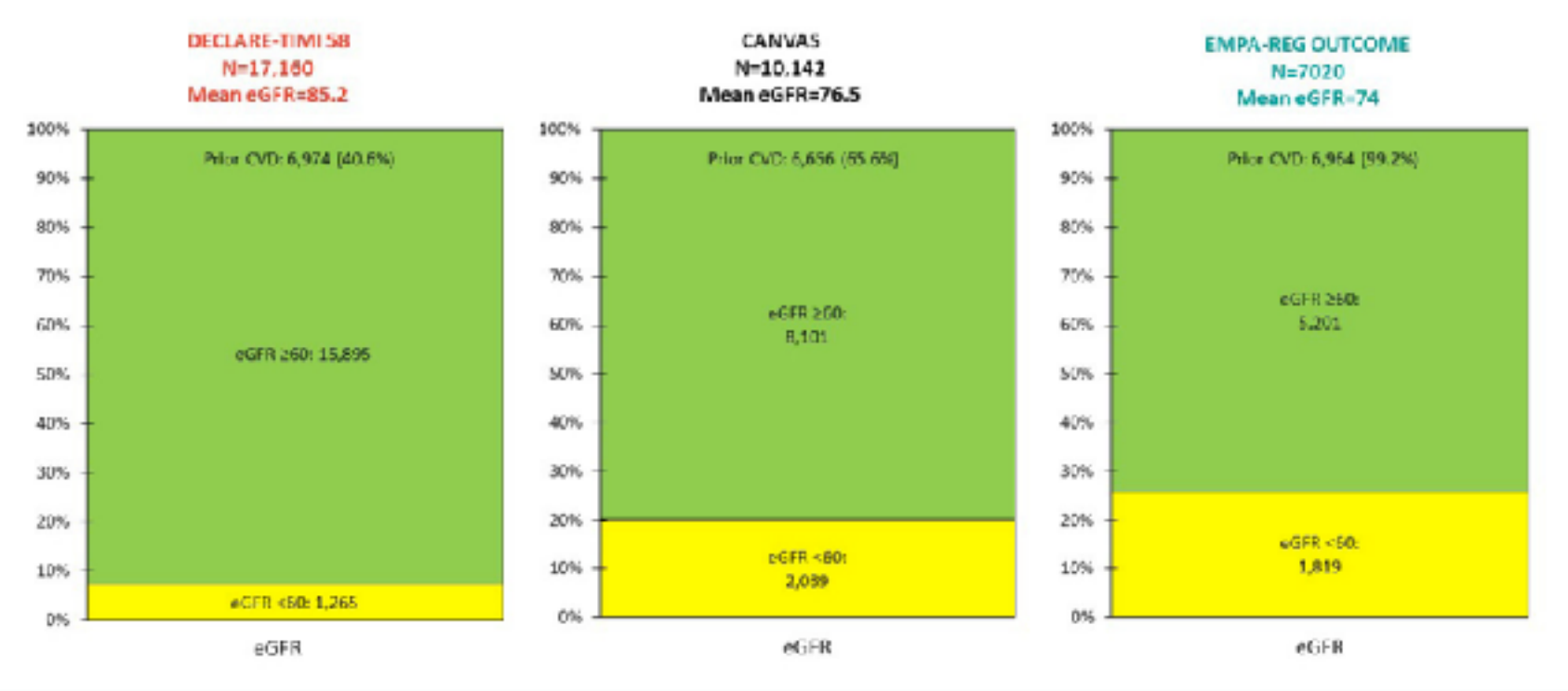


ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, A.-M. Langkilde, and M.S. Sabatine, for the DECLARE–TIMI 58 Investigators*

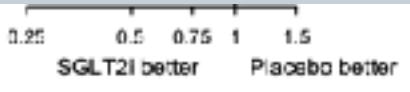
2019

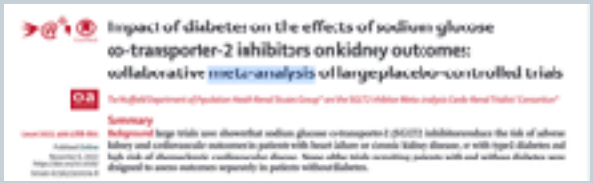


Kluger AJ et al. Rev Cardiovasc Med. 2018 Jun 30;19(2):41-49

KIDNEY DISEASE PROGRESSION

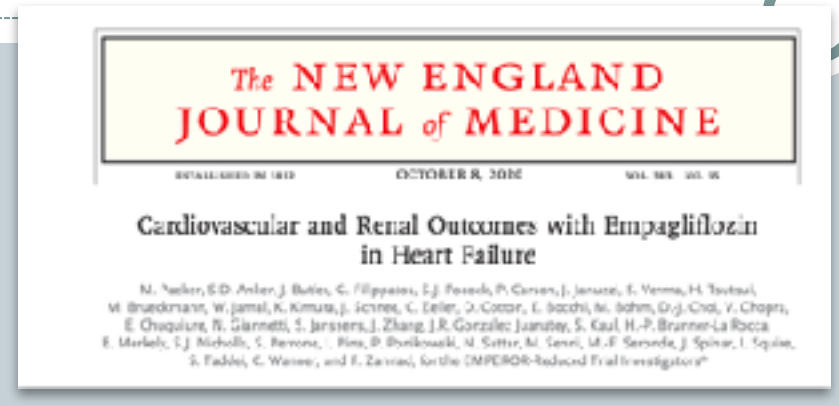
	Median baseline uACR (mg/g)	Number of events/ participants		Rate per 1000 patient years	
				SGLT2i	Placebo
Diabetes					
CANVAS Program	12	80/5795	81/4347	3.6	5.8
DECLARE-TIMI 58	13	56/8582	102/8578	1.6	3.0
EMPA-REG OUTCOME	18	51/4645	47/2323	4.0	7.6
VERTIS CV	19	49/5499	32/2747	2.6	3.4



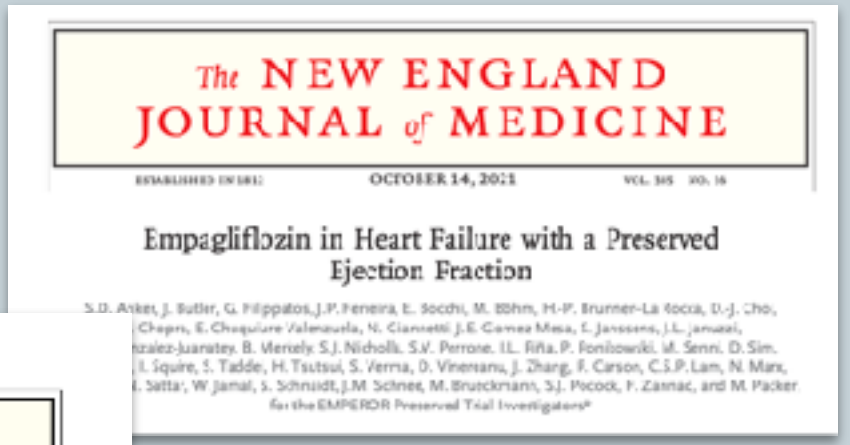

Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials

Summary

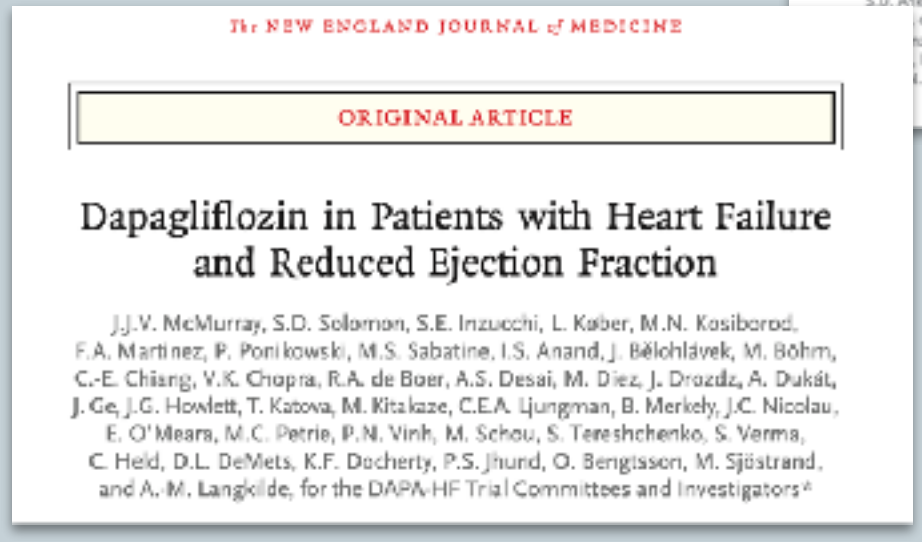
iSGLT2 a serce w populacji bez DM2



2020



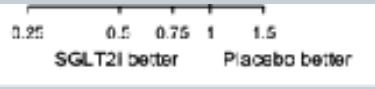
2021

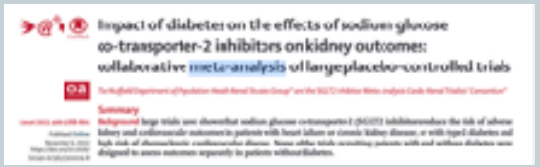


2019

KIDNEY DISEASE PROGRESSION

	Median baseline uACR (mg/g)	Number of events/ participants		Rate per 1000 patient years	
				SGLT2i	Placebo
No diabetes					
EMPEROR-REDUCED	15	5/936	10/938	5.2	10
EMPEROR-PRESERVED	16	12/1531	18/1519	4.5	6.9
EMPA-KIDNEY	380	119/1779	157/1790	35	47
DAPA-CKD	861	39/697	70/701	29	53
DAPA-HF		10/1298	15/1307	5.0	8.0
DELIVER		17/1551	17/1557	5.0	4.9
Subtotal: NO DIABETES		**202/7792**	**287/7812**		




Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials

iSGLT2 w populacji z i bez DM2
badania nefrologiczne

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

2019
DM2 100%

Dapagliflozin in Patients with Chronic Kidney Disease

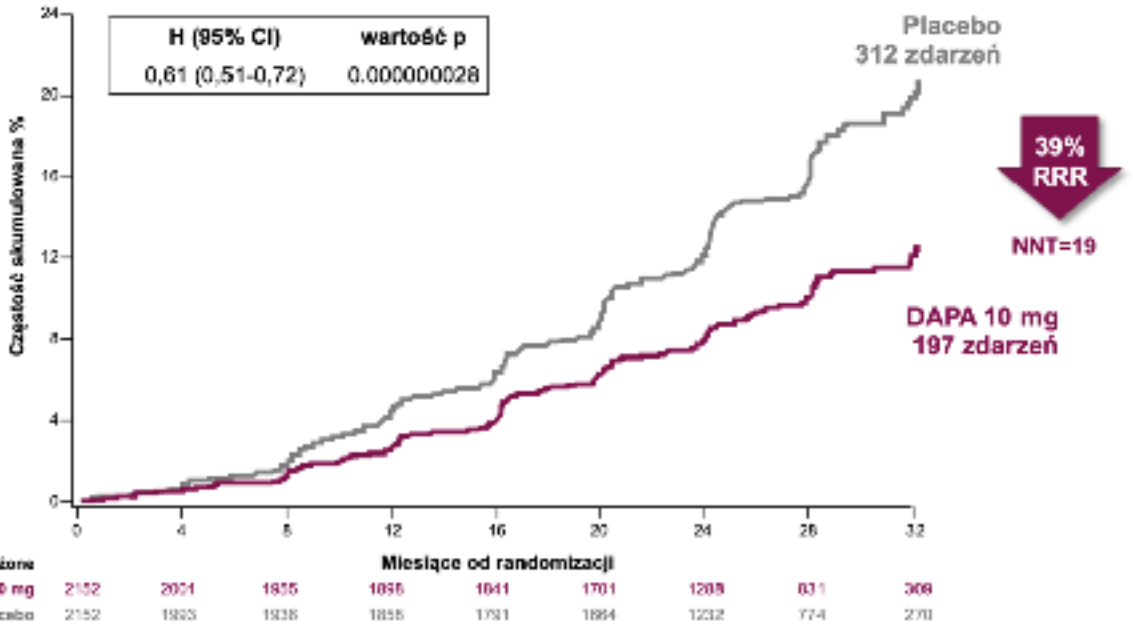
2020
DM2 68%

Empagliflozin in Patients with Chronic Kidney Disease

2022
DM2 46%

DAPA-CKD

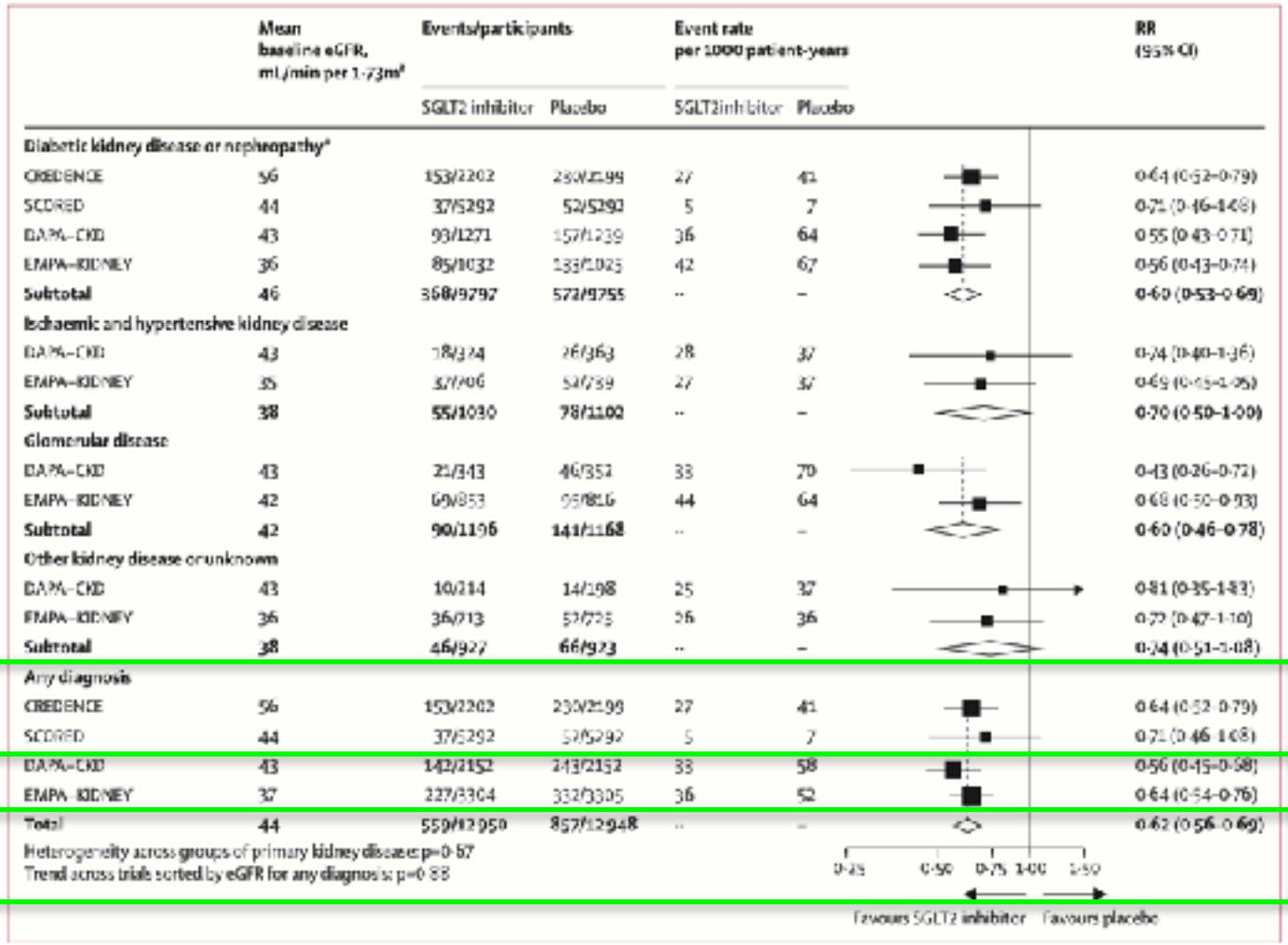
Pierwszorzędowy punkt końcowy: trwała redukcja eGFR ≥ 50%, ESKD, zgon nerkowy lub s-n [a]



ndt

The dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD) trial: baseline characteristics

iSGLT2 w populacji z i bez DM2 badania nefrologiczne



	Mean baseline eGFR, ml/min per 1·73m²	Events/participants		Event rate per 1000 patient-years		RR (95% CI)
		SGLT2 inhibitor	Placebo	SGLT2 inhibitor	Placebo	
Diabetic kidney disease or nephropathy*						
CREDENCE	56	153/2202	269/2599	27	41	0·64 (0·52–0·79)
SCORED	44	37/5292	52/5292	5	7	0·71 (0·46–1·08)
DAPA-CKD	43	93/1271	157/1239	36	64	0·55 (0·43–0·71)
EMPA-KIDNEY	36	85/1032	133/1025	42	67	0·56 (0·43–0·74)
Subtotal	46	368/9797	572/9755	..	–	**0·60 (0·53–0·69)**
Ischaemic and hypertensive kidney disease						
DAPA-CKD	43	78/374	26/363	28	37	0·74 (0·40–1·36)
EMPA-KIDNEY	35	57/706	52/739	27	37	0·69 (0·45–1·05)
Subtotal	38	135/1080	78/1102	..	–	**0·70 (0·50–1·00)**
Glomerular disease						
DAPA-CKD	43	21/343	46/351	33	70	0·43 (0·26–0·72)
EMPA-KIDNEY	42	69/853	95/816	44	64	0·68 (0·50–0·93)
Subtotal	42	90/1196	141/1168	..	–	**0·60 (0·46–0·78)**
Other kidney disease or unknown						
DAPA-CKD	43	10/214	14/198	25	37	0·81 (0·35–1·83)
EMPA-KIDNEY	36	36/713	53/725	26	36	0·72 (0·47–1·10)
Subtotal	38	46/927	66/923	..	–	**0·74 (0·51–1·08)**
Any diagnosis						
CREDENCE	56	153/2202	269/2599	27	41	0·64 (0·52–0·79)
SCORED	44	37/5292	52/5292	5	7	0·71 (0·46–1·08)
DAPA-CKD	43	142/2152	243/2152	33	58	0·56 (0·45–0·68)
EMPA-KIDNEY	37	227/3304	332/3305	36	52	0·64 (0·54–0·76)
Total	44	559/12950	857/12948	..	–	**0·62 (0·56–0·69)**

Heterogeneity across groups of primary kidney diseases p=0·57
Trend across trials sorted by eGFR for any diagnosis p=0·88

0·25 0·50 0·75 1·00 1·50

Favours SGLT2 inhibitor Favours placebo

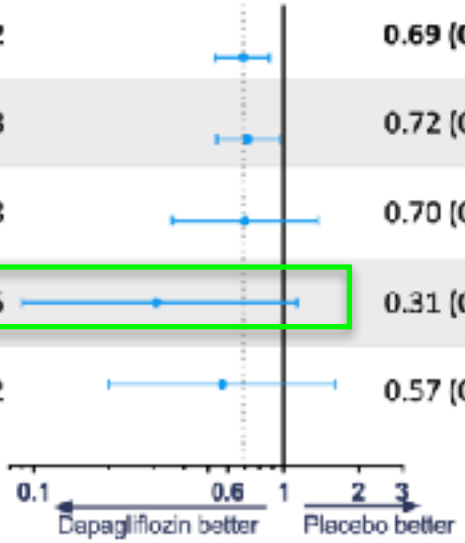
Figure 2: **Effect of sodium glucose co-transporter-2 inhibition on kidney disease progression by presumed primary kidney disease (chronic kidney disease trials only)**

Lancet 2022; 400: 1788–801

PChN bez DM

Secondary Outcome: All-Cause Mortality According to Underlying Cause of Kidney Disease

All-Cause Mortality	Dapagliflozin No. of Participants/ Total no.	Placebo No. of Participants/ Total no.	Dapagliflozin Events/ 100 Patient Years	Placebo Events/ 100 Patient Years	HR (95% CI)	*P* Value
Overall	**101/2152**	**146/2152**	**2.2**	**3.2**	**0.69 (0.53, 0.88)**	
Diabetic nephropathy	78/1271	104/1239	2.7	3.8	0.72 (0.54, 0.97)	.55
Ischemic/hypertensive nephropathy	14/324	22/363	2.0	2.8	0.70 (0.36, 1.37)	
Glomerulonephritides	3/343	11/352	0.4	1.5	0.31 (0.09, 1.13)	
Other/unknown	6/214	9/198	1.3	2.2	0.57 (0.20, 1.61)	



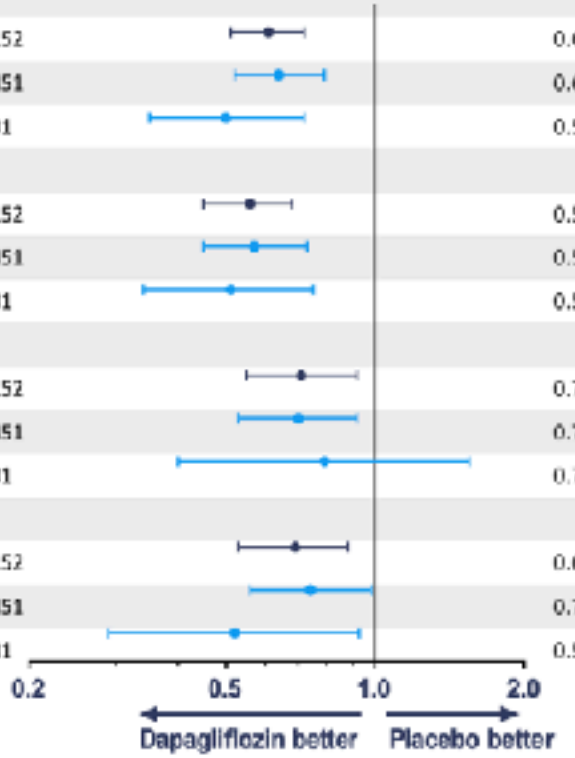
Wheeler D. ASN Kidney Week Reimagined 2020. Oral presentation.

DAPA-CKD

DAPA-CKD

Primary and Secondary Outcomes by Diabetes Status

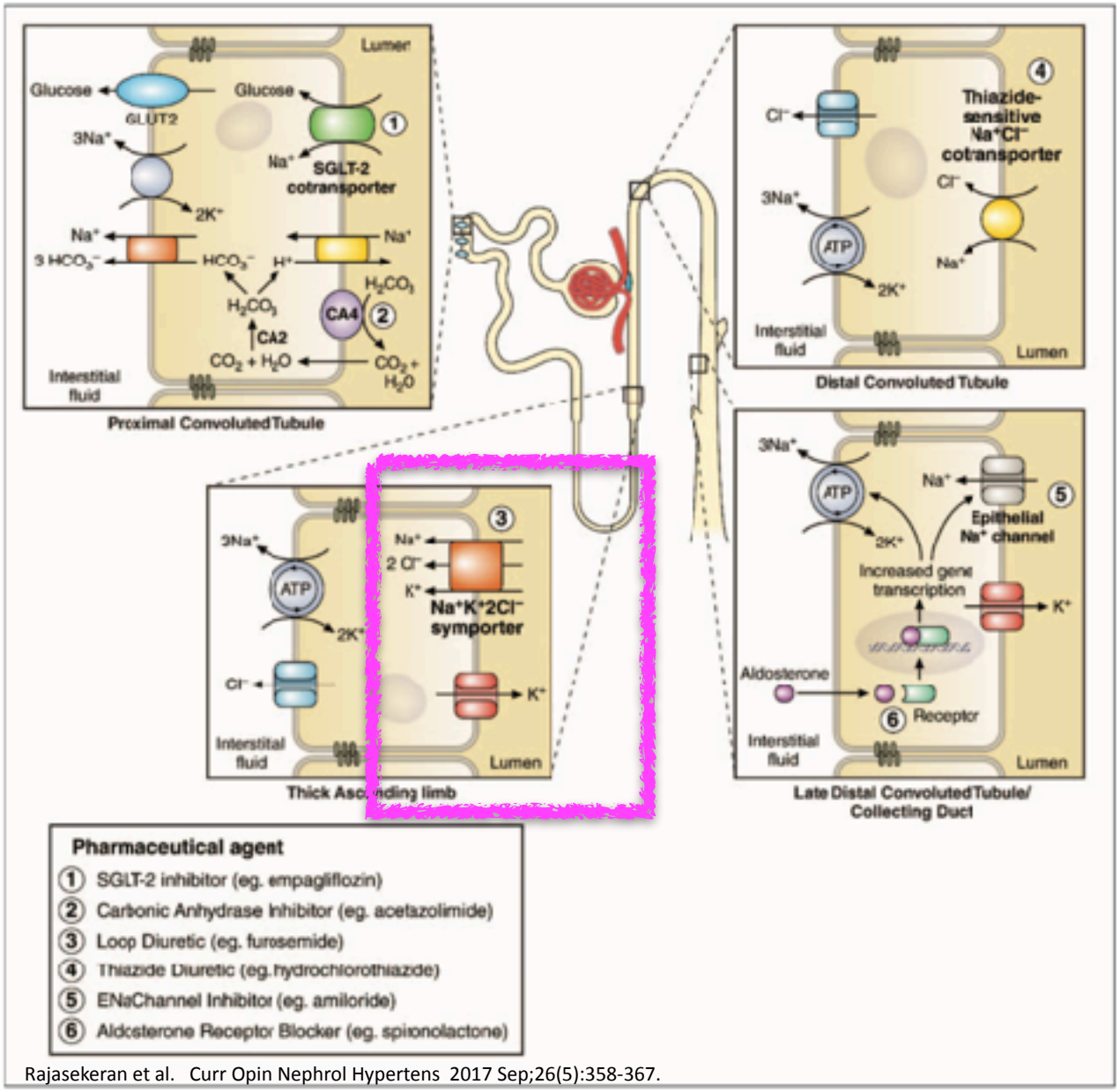
	Dapagliflozin	Placebo	HR (95% CI)	*P* Value
Primary outcome	**No. of participants/total no.**			
Overall	197/2152	312/2152	0.61 (0.51, 0.72)	
With type 2 diabetes	152/1455	229/1451	0.64 (0.52, 0.79)	
Without type 2 diabetes	45/697	83/701	0.50 (0.35, 0.72)	.24
Renal-specific outcome				
Overall	142/2152	243/2152	0.56 (0.45, 0.68)	
With type 2 diabetes	103/1455	173/1451	0.57 (0.45, 0.73)	
Without type 2 diabetes	39/697	70/701	0.51 (0.34, 0.75)	.57
CV death or heart failure				
Overall	100/2152	138/2152	0.71 (0.55, 0.92)	
With type 2 diabetes	85/1455	119/1451	0.70 (0.53, 0.92)	
Without type 2 diabetes	15/697	19/701	0.79 (0.40, 1.55)	.78
All-cause mortality				
Overall	101/2152	146/2152	0.69 (0.53, 0.88)	
With type 2 diabetes	84/1455	113/1451	0.74 (0.56, 0.98)	
Without type 2 diabetes	17/697	33/701	0.52 (0.29, 0.93)	.25



Wheeler D. ASN Kidney Week Reimagined 2020. Oral presentation.

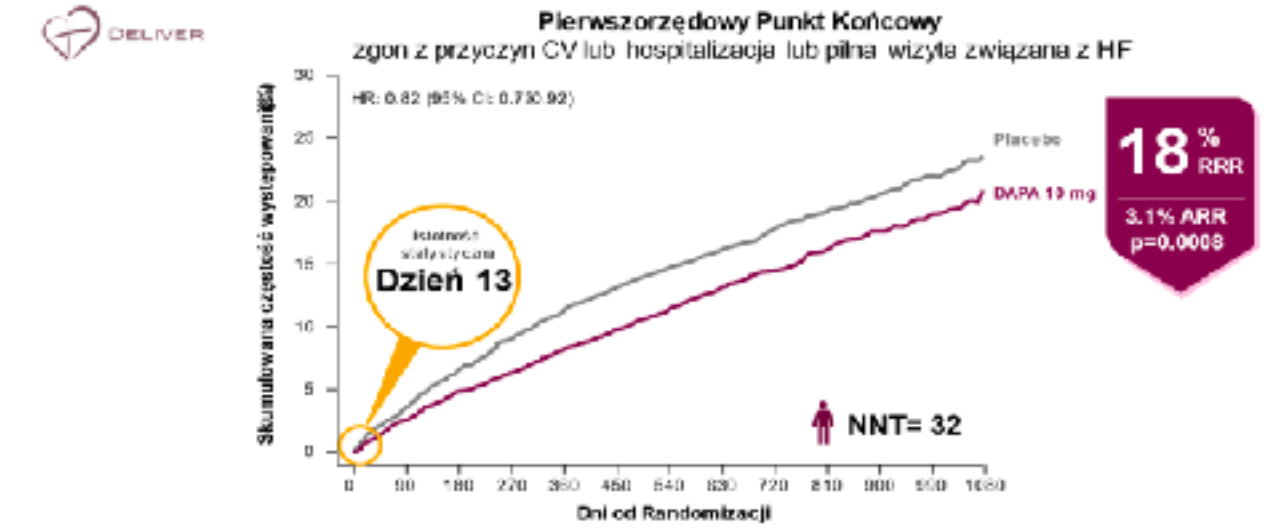
iSGLT2 - czy tylko efekt hemodynamiczny?

- iSGLT2 i diuretyki - czy to ten sam efekt działania?
- skąd się bierze efekt kardioprotekcyjny, skoro iSGLT2 nie są zlokalizowane w sercu?
- co to jest kompleksowa nefroptotekcja?

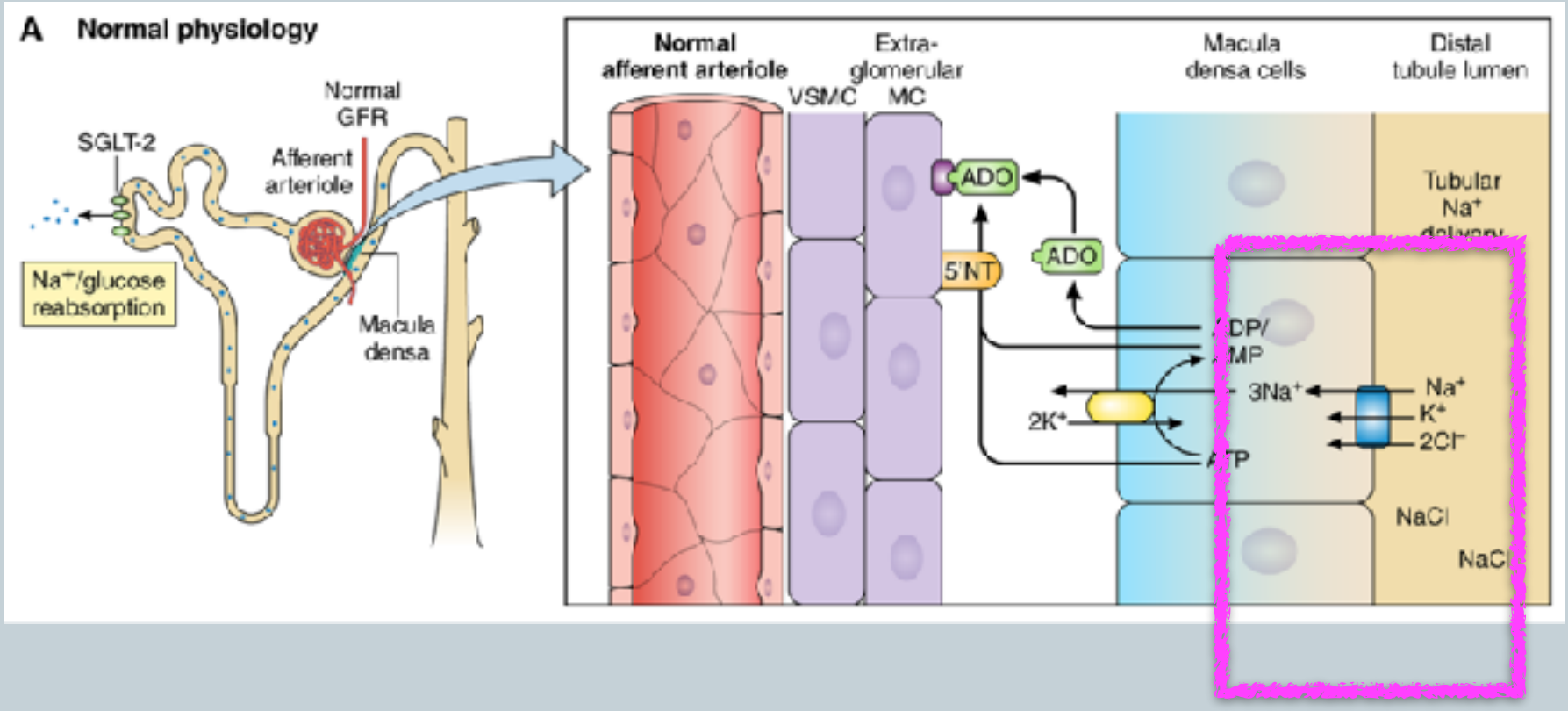


Rajasekeran et al. Curr Opin Nephrol Hypertens 2017 Sep;26(5):358-367.

Dapagliflozyna istotnie redukowała ryzyko zgonu z przyczyn sercowo-naczyniowych lub pogorszenia HF u pacjentów z LVEF >40%

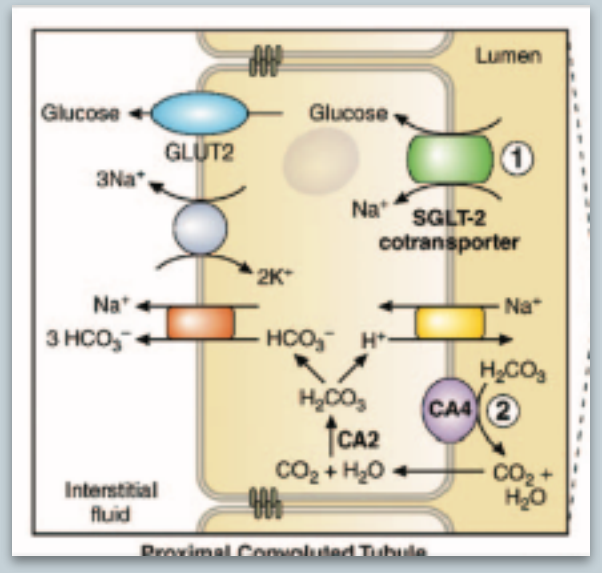


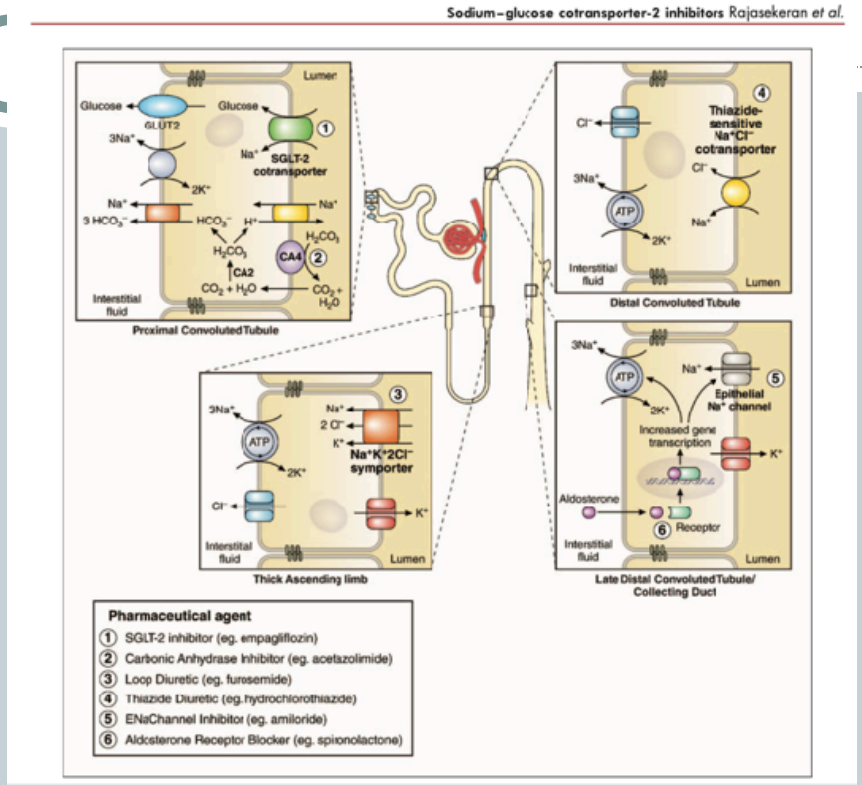
Rysunek 1. Wyniki pierwszorzędowego punktu końcowego badania DELIVER (Salomon SD. Et al.; N Engl J Med. 2022;387(12):1089-1098. doi:10.1056/NEJMoa2206286; Vaduganathan M. et.al.; JAMA Cardiol. 2022;doi:10.1001/jamacardio.2022.3750)



Heerspink H et al. Circulation. 2016;134:752–772

cewka bliższa - hot topic !





ESC
European Journal of Heart Failure (2012)
RESEARCH ARTICLE

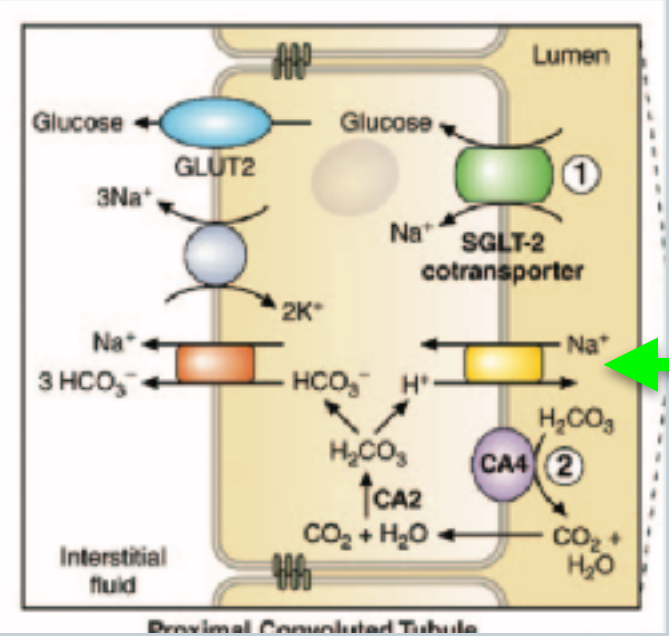
Acetazolamide in Decompensated Heart Failure with Volume Overload trial (ADVOR): baseline characteristics

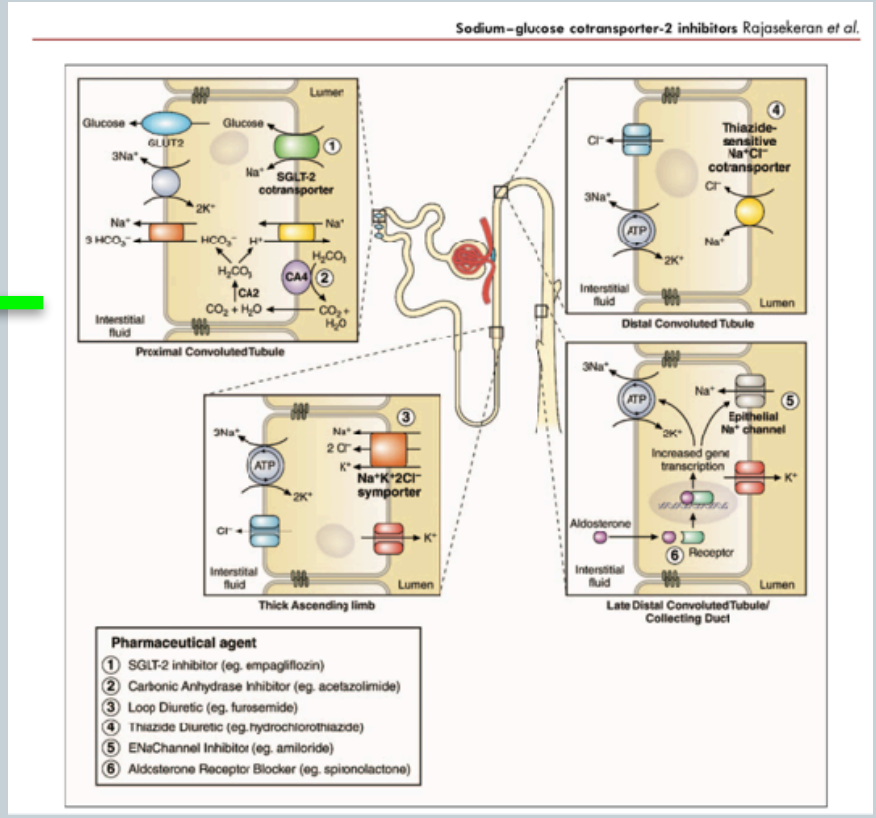
Wilfried Mullens[1,2*], Jeroen Dauw[1,2], Pieter Martens[1], Evelyne Meekers[1,2],

iSGLT2 - czy tylko efekt hemodynamiczny?

- iSGLT2 i diuretyki - czy to ten sam efekt działania?
- skąd się bierze efekt kardioprotekcyjny, skoro iSGLT2 nie są zlokalizowane w sercu?
- co to jest kompleksowa nefroptotekcja?

iSGLT2 i NHE


Lumen
Glucose
GLUT2
Glucose
1
3Na+
Na+
SGLT-2
cotransporter
2K+
Na+
3 HCO3−
HCO3−
H+
Na+
H2CO3
CA4
2
H2CO3
CA2
CO2 + H2O
CO2 + H2O
Interstitial fluid
Proximal Convoluted Tubule


Sodium–glucose cotransporter-2 inhibitors Rajasekeran et al.
Proximal Convoluted Tubule
Thick Ascending limb
Distal Convoluted Tubule
Late Distal Convoluted Tubule/ Collecting Duct
Thiazide-sensitive Na+Cl− cotransporter
Epithelial Na+ channel
Increased gene transcription
Aldosterone
Receptor
Na+K+2Cl− symporter
Pharmaceutical agent
1 SGLT-2 inhibitor (eg. empagliflozin)
2 Carbonic Anhydrase Inhibitor (eg. acetazolamide)
3 Loop Diuretic (eg. furosemide)
4 Thiazide Diuretic (eg. hydrochlorothiazide)
5 ENaChannel Inhibitor (eg. amiloride)
6 Aldosterone Receptor Blocker (eg. spironolactone)

NHE

- aktywacja **NHE** (sodium–hydrogen exchangers (NHEs) odpowiada za CHF (**NHE1**) i DKD (**NHE3** w cewkach bliższych, **NHE1** w komórkach mezangialnych)
- aktywacja NHE -> wzrost Na+ i Ca2+ wewnątrz komórki -> uszkodzenie komórki (włóknienie, stan zapalny, apoptoza) -> uszkodzenie całego narządu
- aktywacja NHE3 wzmaga aktywność nerkowego układu współczulnego

Ni et al. Cardiovasc Diabetol (2020) 19:98

DeFronzo et al. Nat Rev Nephrol2021 May;17(5):319-334.

iSGLT2 i ketogeneza
wróg stał się przyjacielem

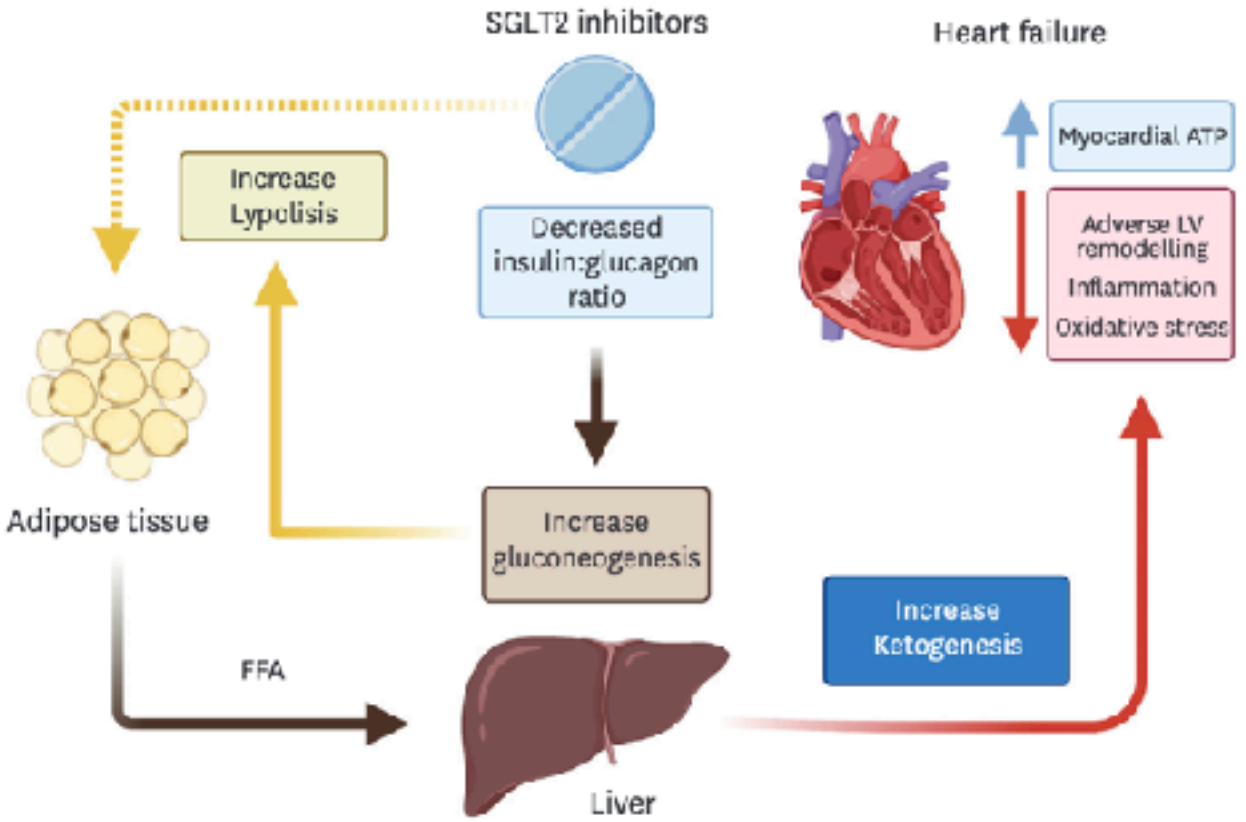
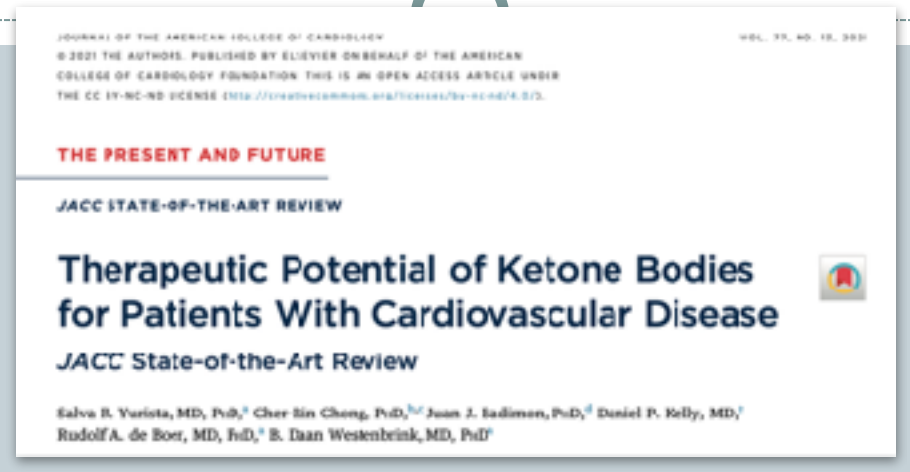


Fig. 2. Mechanism of ketogenesis by SGLT2 inhibitors.
SGLT2 inhibitors increase lipolysis, gluconeogenesis, and ketogenesis by decreasing the insulin-to-glucagon ratio and increasing myocardial ATP content, providing extra fuel to a starved and failing he
with BioRender.com.
ATP, adenosine triphosphate; FFA, free fatty acids; LV, left ventricular; SGLT2, sodium-

metabolizm w sercu



JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 77, NO. 22, 2021

THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Therapeutic Potential of Ketone Bodies for Patients With Cardiovascular Disease

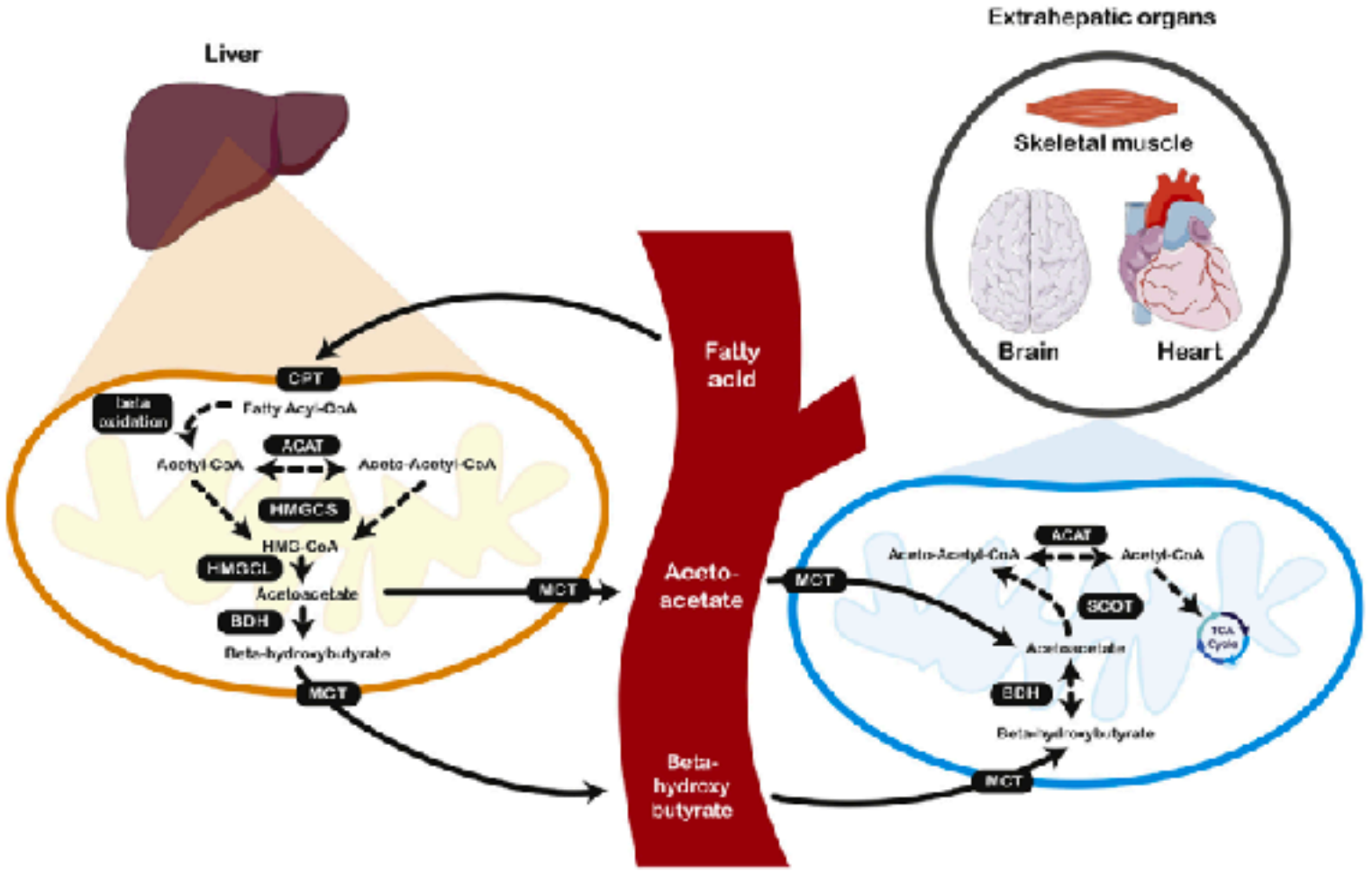
JACC State-of-the-Art Review

Eelva B. Yurista, MD, PhD,[a] Cher-Yin Cheng, PhD,[b,c] Juan J. Badimon, PhD,[d] Daniel P. Kelly, MD,[e] Rudolf A. de Boer, MD, PhD,[a] B. Daan Westenbrink, MD, PhD[a]

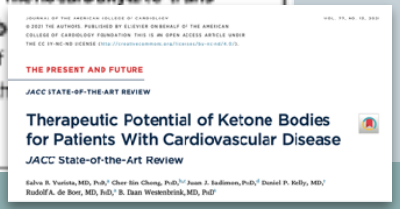
CARDIAC METABOLISM IN NORMAL HEART AND HEART DISEASE

KETONE BODIES: PLEIOTROPIC EFFECTS BEYOND CARDIAC ENERGETICS

FIGURE 1 Metabolic Pathways of Ketone Bodies in Liver and Extrahepatic Organs



Fatty acids are transported to mitochondria by carnitine palmitoyltransferase 1 (CPT1) and subsequently, ketone bodies acetoacetate (AcAc), beta-hydroxybutyrate (βOHB) and acetone are synthesized from acetyl-CoA that is derived from β-oxidation. AcAc and βOHB are released into the circulation by monocarboxylate transporters (MCTs). After internalization in extra-hepatic tissues, AcAc and βOHB are converted back to acetyl-CoA, which is subsequently metab
generate ATP. Acetone is not metabolically active and is either excreted through urine or exhaled. Part of illustration elements courtesy of
ACAT = acetoacetyl-CoA thiolase; ATP = adenosine triphosphate; BDH = beta-hydroxybutyrate dehydrogenase; HMG-CoA = hydroxymeth
HMGCS = HMG-CoA lyase HMGCL = HMG-CoA synthase; SCOT = succinyl-CoA:3-ketoacid CoA transferase; TCA = tricarboxylic acid.


THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Therapeutic Potential of Ketone Bodies for Patients With Cardiovascular Disease

JACC State-of-the-Art Review

BMC Medicine

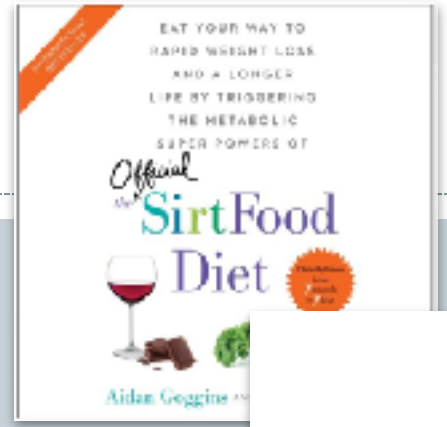
REVIEW Open Access

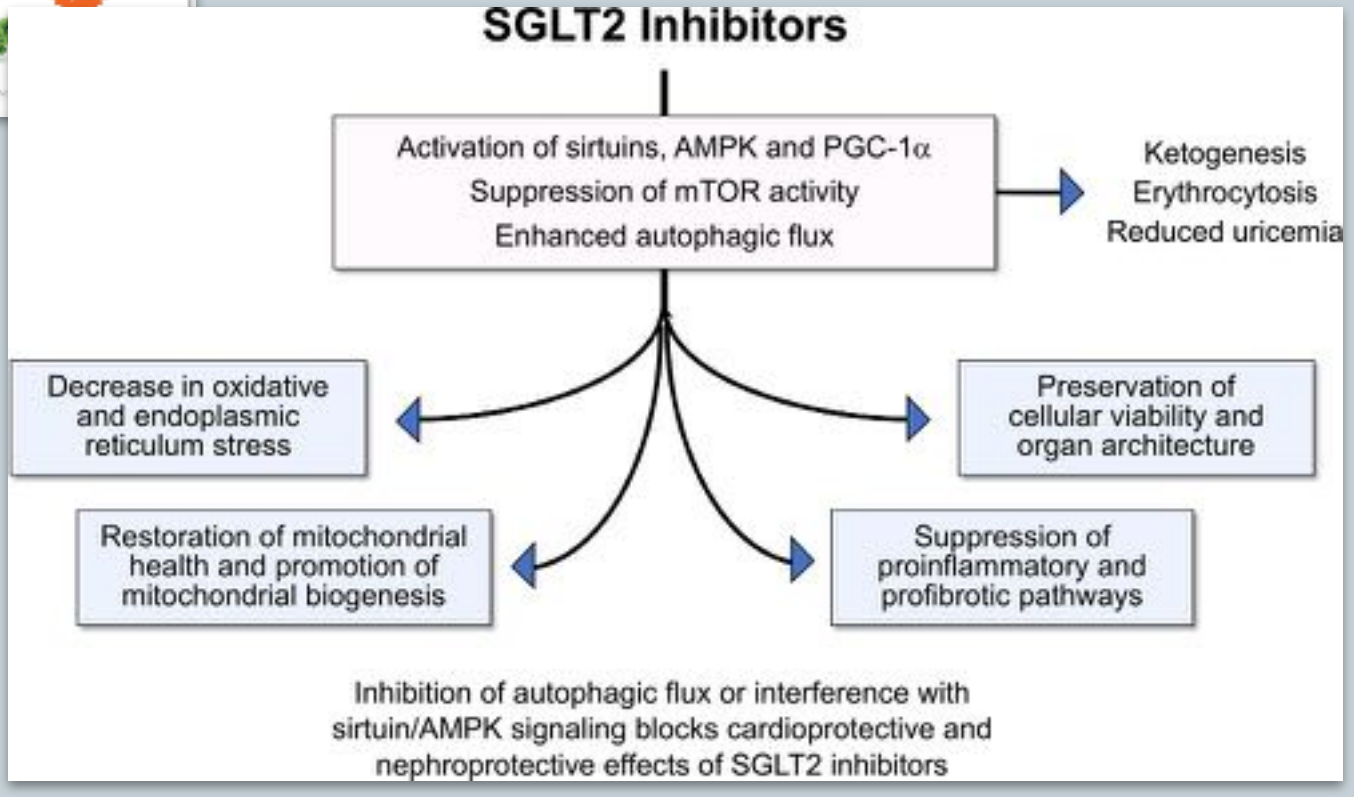
Ketone bodies: from enemy to friend and guardian angel

Table 1 Ranges of ketone body levels in human plasma in different physiological conditions

Physiological condition	β-Hydroxybutyrate concentration in plasma (range in mmol/l)
Normal circadian variation	0.1–0.4
After prolonged exercise	0.3–2
After 1–2 days of fasting	1–2
After 2–3 weeks of fasting	5–7
After 1–3 weeks of ketogenic diet	0.5–5
During diabetic ketoacidosis	3–25

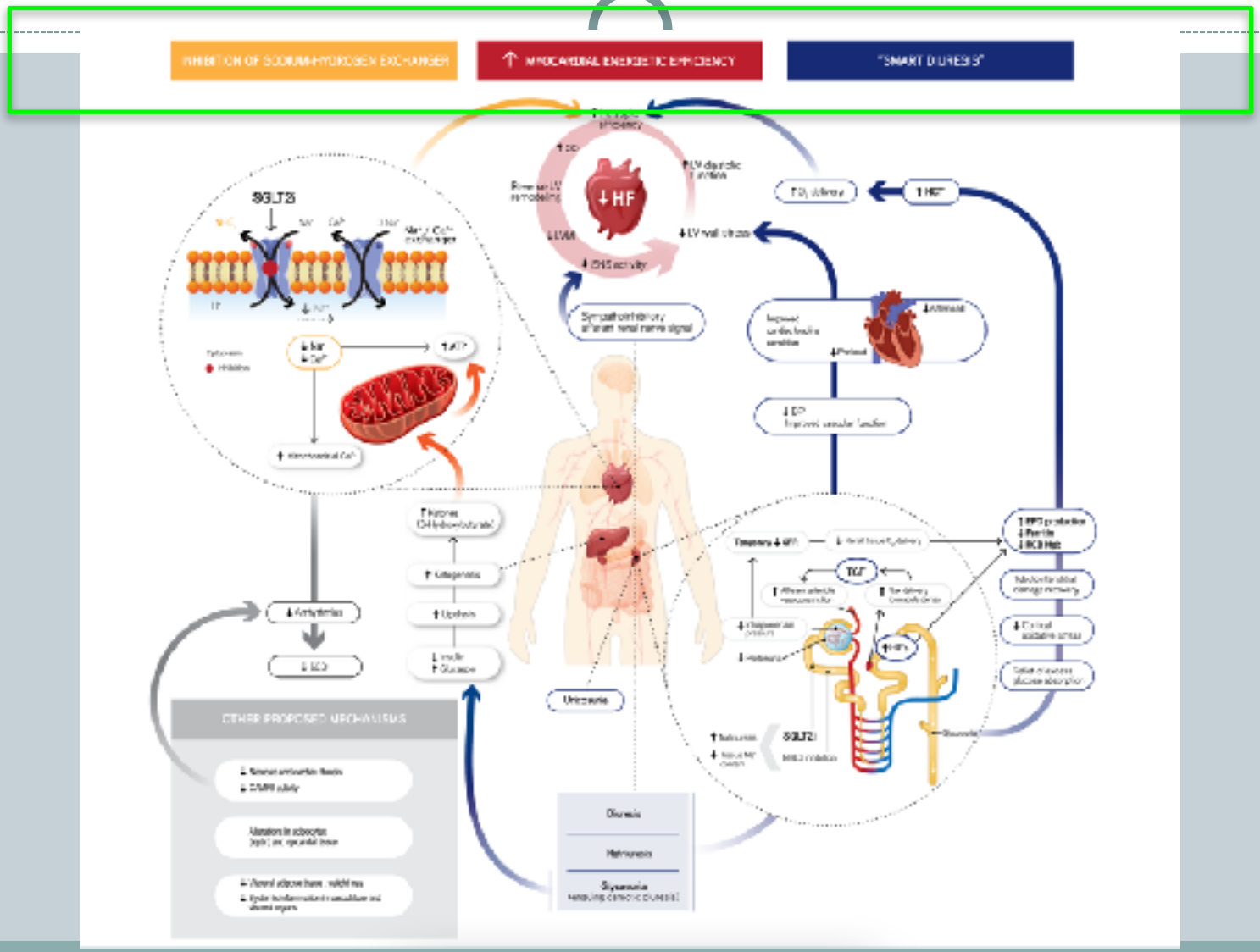
iSGLT2 and more



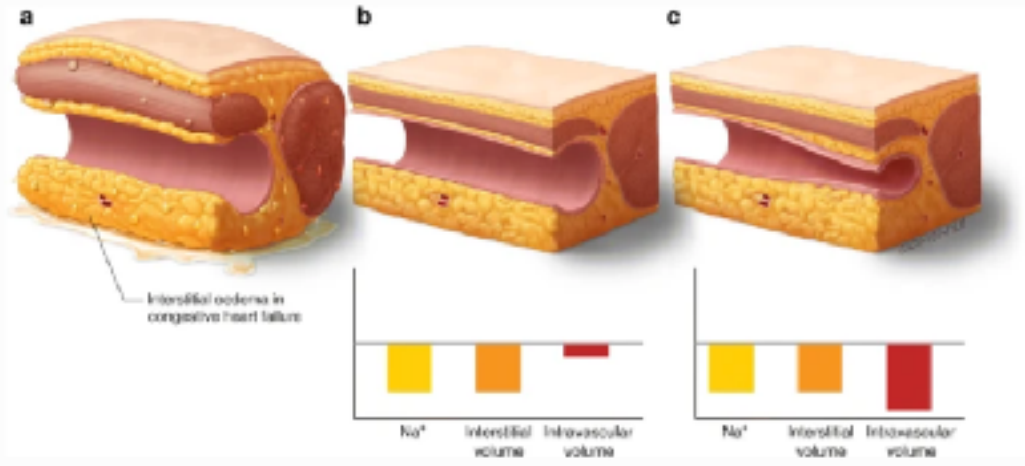


Milton Packer. Circulation. Critical Reanalysis of the Mechanisms Underlying the Cardiorenal Benefits of SGLT2 Inhibitors and Reaffirmation of the Nutrient Deprivation Signaling/Autophagy Hypothesis, Volume: 146, Issue: 18, Pages: 1383-1405, DOI: (10.1161/CIRCULATIONAHA.122.061732)

działanie bezpośrednie oraz działanie pośrednie - NHE + poprawa wydolności energetycznej kardiomiocytów



iSGLT2 i układ współczulny



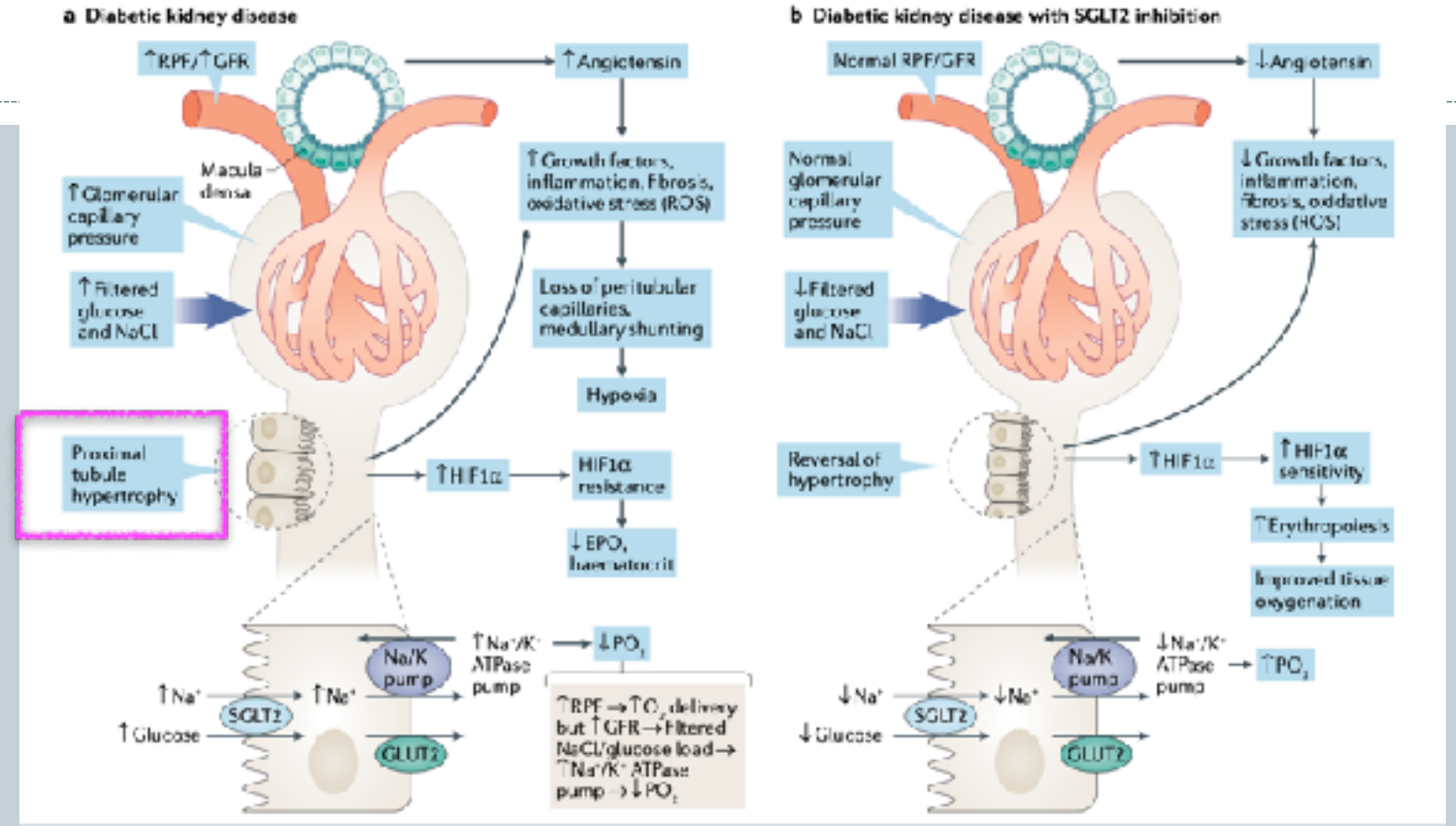
SGLT2 inhibitors may differentially regulate the interstitial vs intravascular compartment when compared with loop diuretics. In individuals with congestive heart failure, interstitial oedema is evident (**a**). SGLT2 inhibitors may selectively reduce interstitial volume with minimal change in blood volume (**b**) whereas loop diuretics may cause a reduction in both interstitial and intravascular volume

- iSGLT2 zmniejszają odruch neurohumoralny, który wywołują diuretyki pętlowe na skutek spadku objętości wewnątrznaczyniowej
- iSGLT2 nie zwiększają aktywności reninowej osocza

Verma S, & McMurray J. Diabetologia 2018, 61, 2108–2117.

dlaczego?

- występuje efekt kardioprotekcyjny, skoro iSGLT2 nie są zlokalizowane w sercu?
- należy stosować iSGLT2, skoro efekt diuretyczny wywołują…. diuretyki?
- w nefroprotekcji nie tylko wyhamowanie filtracji ma znaczenie?



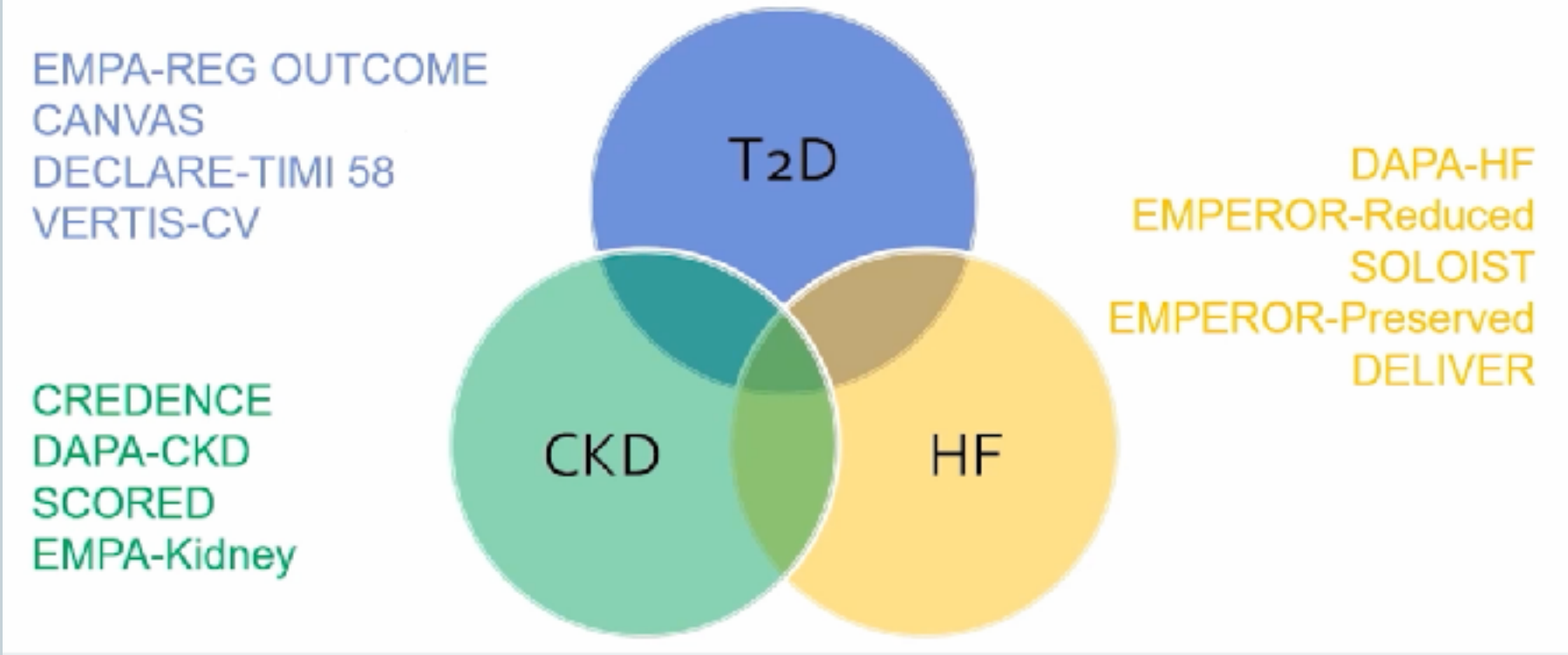
DeFronzo, R. A., Reeves, W. B., & Awad, A. S. (2021, 17(5), 319–334.

Effect of Empagliflozin on Erythropoietin Levels, Iron Stores and Red Blood Cell Morphology in Patients with Type 2 Diabetes and Coronary Artery Disease

C. Davic Mazer, Gregory M.T. Hare, Philip W. Connelly, Richard E. Gilbert, Nadine Shehata, Adrian Quan, Hwee Teoh, Lawrence A. Leiter, Bernard Zinman, Peter Jüni, Fei Zuo, Nikhil Mistry, Kevin E. Thorpe, Ronald M. Goldenberg, Andrew T. Yan, Kim A. Connelly, and Subodh Verma

Originally published 1 Nov 2019 | https://doi.org/10.1161/CIRCULATIONAHA.119.041035 | Circulation. ;0:null

pacjent CRM
pełne spektrum działania iSGLT2

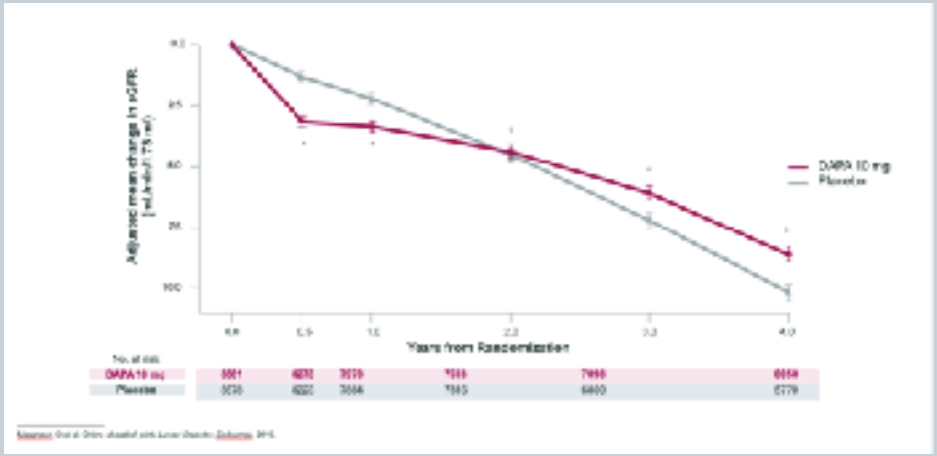


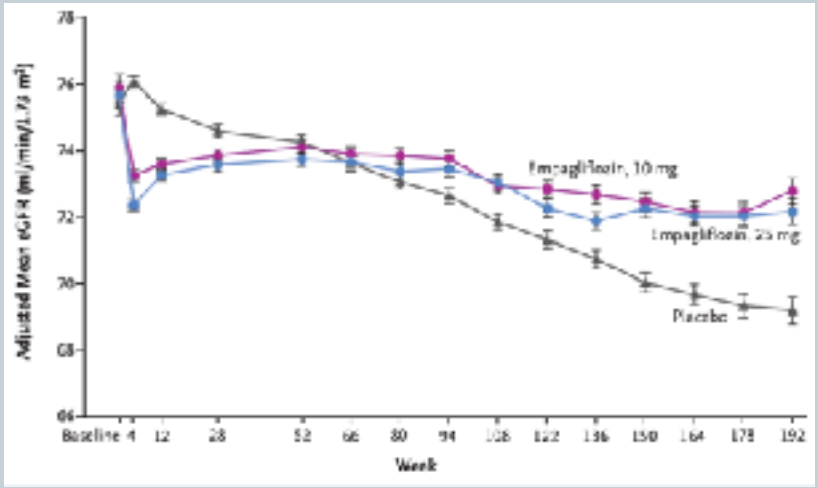
pacjent CRM (cardio-renal-metabolic)

iSGLT2
aspekty praktyczne

- wpływ na eGFR i stęż. kreatyniny
- AKI
- wpływ na UACR
- bezpieczeństwo

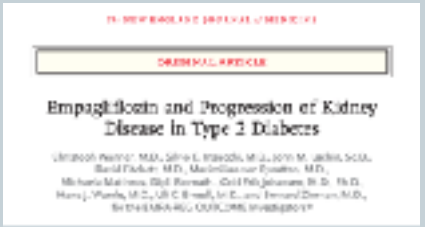
aspekty praktyczne
wpływ na eGFR






ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes


ORIGINAL ARTICLE

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

aspekty praktyczne
AKI

	SGLT2 inhibitor events, No. (IR/1000 PY)	DPP-4 inhibitor events, No. (IR/1000 PY)	RD/1000 PY (95% CI)	HR (95% CI)	SGLT2 inhibitor vs DPP-4 inhibitor, relative scale: Favors SGLT2 / Favors DPP-4
Acute kidney injury					
Subgroup HbA_{1c} <7.5% (n=24052)	162 (19.55)	220 (27.22)	-7.68 (-12.37 to -2.99)	0.72 (0.59 to 0.89)	
Subgroup HbA_{1c} 7.5%-9% (n=32 290)	211 (18.92)	295 (27.03)	-8.11 (-12.12 to -4.11)	0.70 (0.59 to 0.84)	
Subgroup HbA_{1c} >9% (n=30 932)	225 (23.25)	268 (30.05)	-6.80 (-11.51 to -2.09)	0.79 (0.66 to 0.94)	
Overall population (n=87274)	598 (20.54)	783 (28.05)	-7.60 (-10.15 to -5.04)	0.73 (0.66 to 0.81)	

JAMA InternalMedicine | Original Investigation

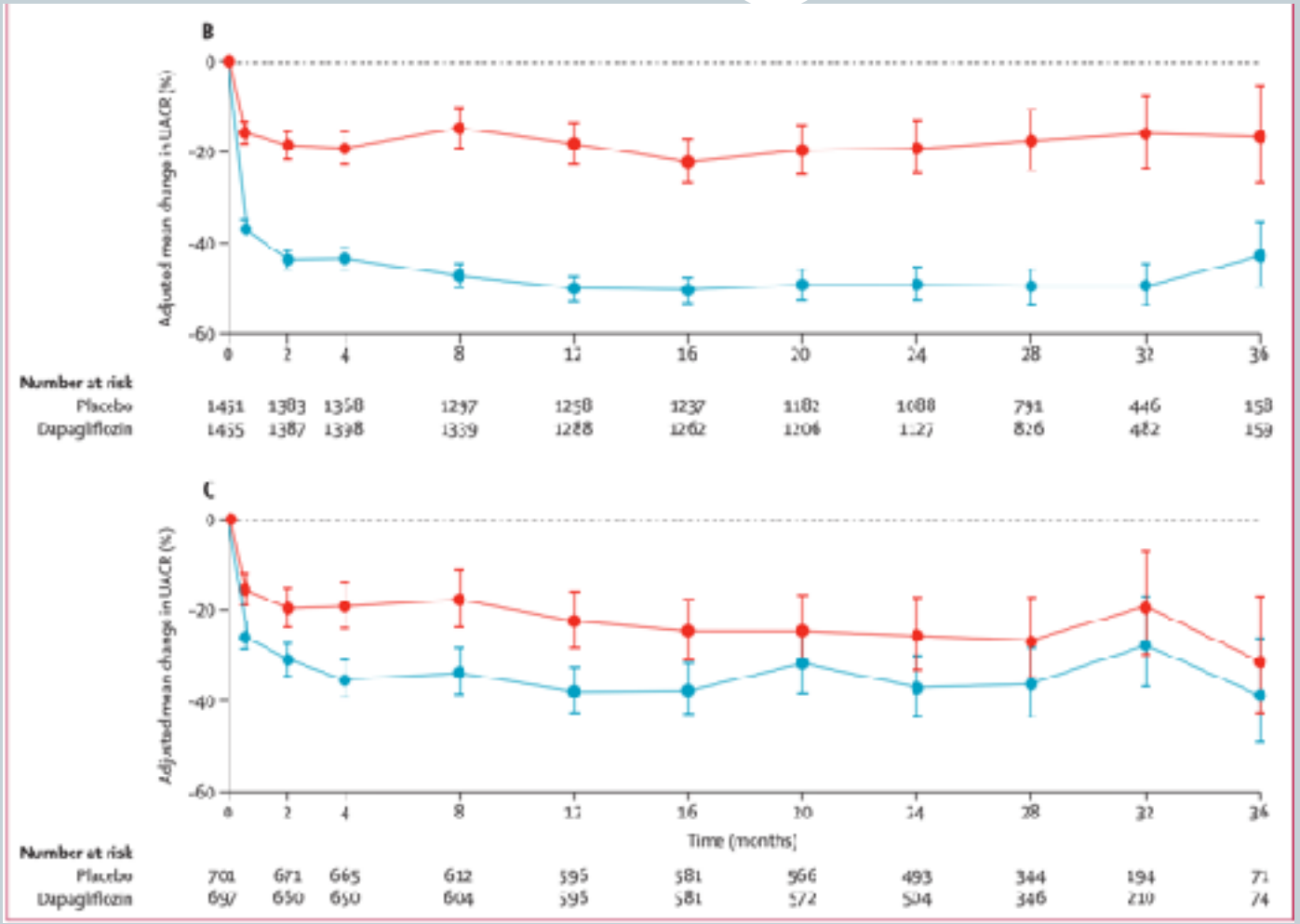
Comparing Effectiveness and Safety of SGLT2 Inhibitors vs DPP-4 Inhibitors in Patients With Type 2 Diabetes and Varying Baseline HbA_{1c} Levels

Elvira D'Andrea, MD, PhD; Deborah J Wexler, MD MSc; Seoyoung C. Kim, MD ScD; Julie M. Paik, MD, ScD, MPH; Ethan Ali, PhD; Elisabetta Patorno, MD, DrPH

JAMA Internal Medicine March 2023 Volume 183, Number 3

aspekty praktyczne
zmiana w UACR

Lancet Diabetes Endocrinol
2021; 9: 755-66
Published Online
October 4, 2021
https://doi.org/10.1016/
S2213-8587(21)00244-4



- DM
- bez DM

spadek UACR do nawet 30% już po 2 tyg. leczenia

aspekty praktyczne
bezpieczeństwo

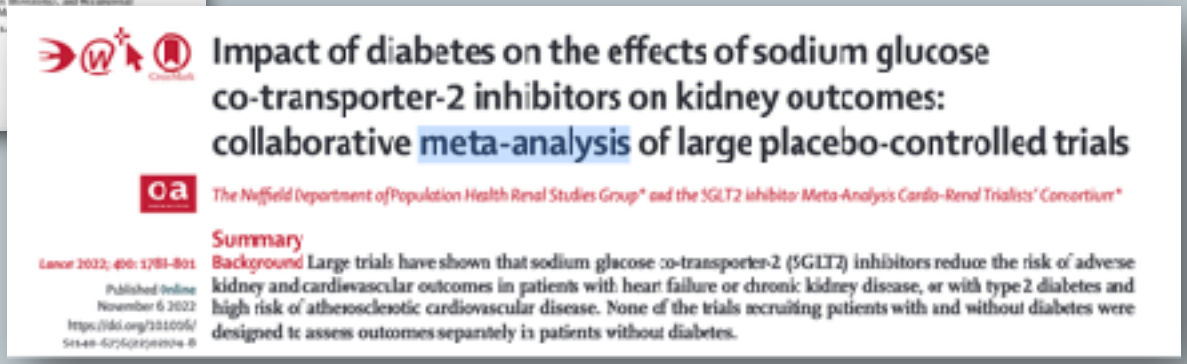
Zdarzenia[a], n (%)	Dapagliflozyna 10 mg (N=2149)	Placebo (N=2149)
Przerwanie udziału w badaniu	274 (12.8)	309 (14.4)
Przerwanie udziału w badaniu z powodu zdarzenia niepożądanego	118 (5.5)	123 (5.7)
Każde poważne zdarzenie niepożądane	633 (29.5)	729 (33.9)
Zdarzenia niepożądane będące przedmiotem zainteresowania:		
Amputacja[b]	35 (1.6)	39 (1.8)
Stwierdzona lub prawdopodobna cukrzycowa kwasica ketonowa	0	2 (0.1)
Złamania[c]	85 (4.0)	69 (3.2)
Zdarzenie niepożądane związane z nerkami[a]	155 (7.2)	188 (8.7)
Ciężka hipoglikemia[d]	14 (0.7)	28 (1.3)
Niedobór płynów[e]	127 (5.9)	90 (4.2)
Poważne działania niepożądane związane z niedoborem płynów	22 (1.0)	18 (0.8)

SGLT-2 inhibitors and the risk of infections: a systematic review and meta-analysis of randomized controlled trials

SGLT2 inhibitors and the risk of urinary tract infections in patients with heart failure: A pooled analysis examining safety endpoints

Open access Research

BMJ Open Comparative safety of the sodium glucose co-transporter 2 (SGLT2) inhibitors: a systematic review and meta-analysis



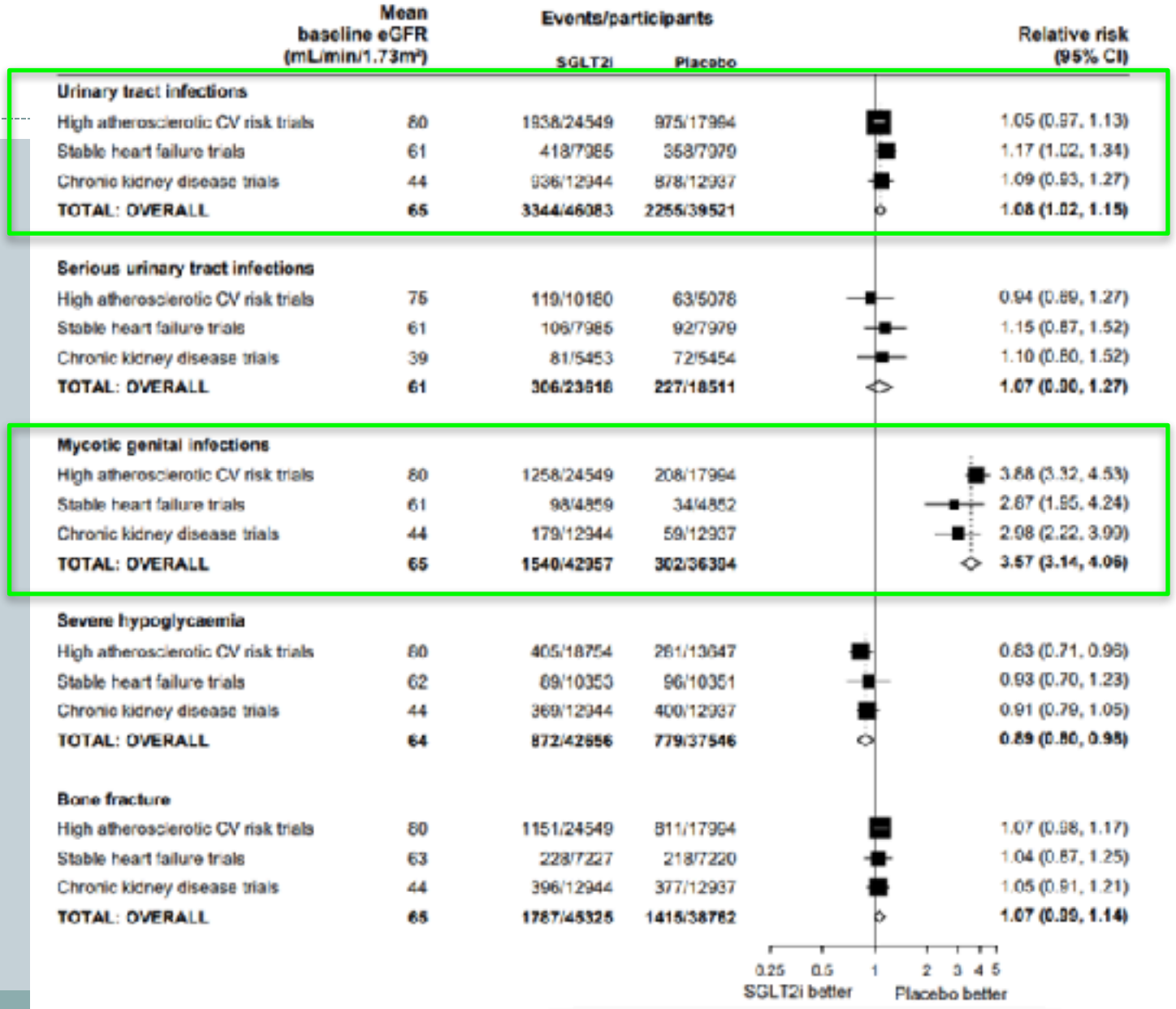
Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials

The Neffield Department of Population Health Renal Studies Group* and the SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium*

Summary

Background Large trials have shown that sodium glucose co-transporter-2 (SGLT2) inhibitors reduce the risk of adverse kidney and cardiovascular outcomes in patients with heart failure or chronic kidney disease, or with type 2 diabetes and high risk of atherosclerotic cardiovascular disease. None of the trials recruiting patients with and without diabetes were designed to assess outcomes separately in patients without diabetes.

iSGLT-2 zwiększają ryzyko infekcji genitalnych, **nie zwiększają** ryzyka ZUM

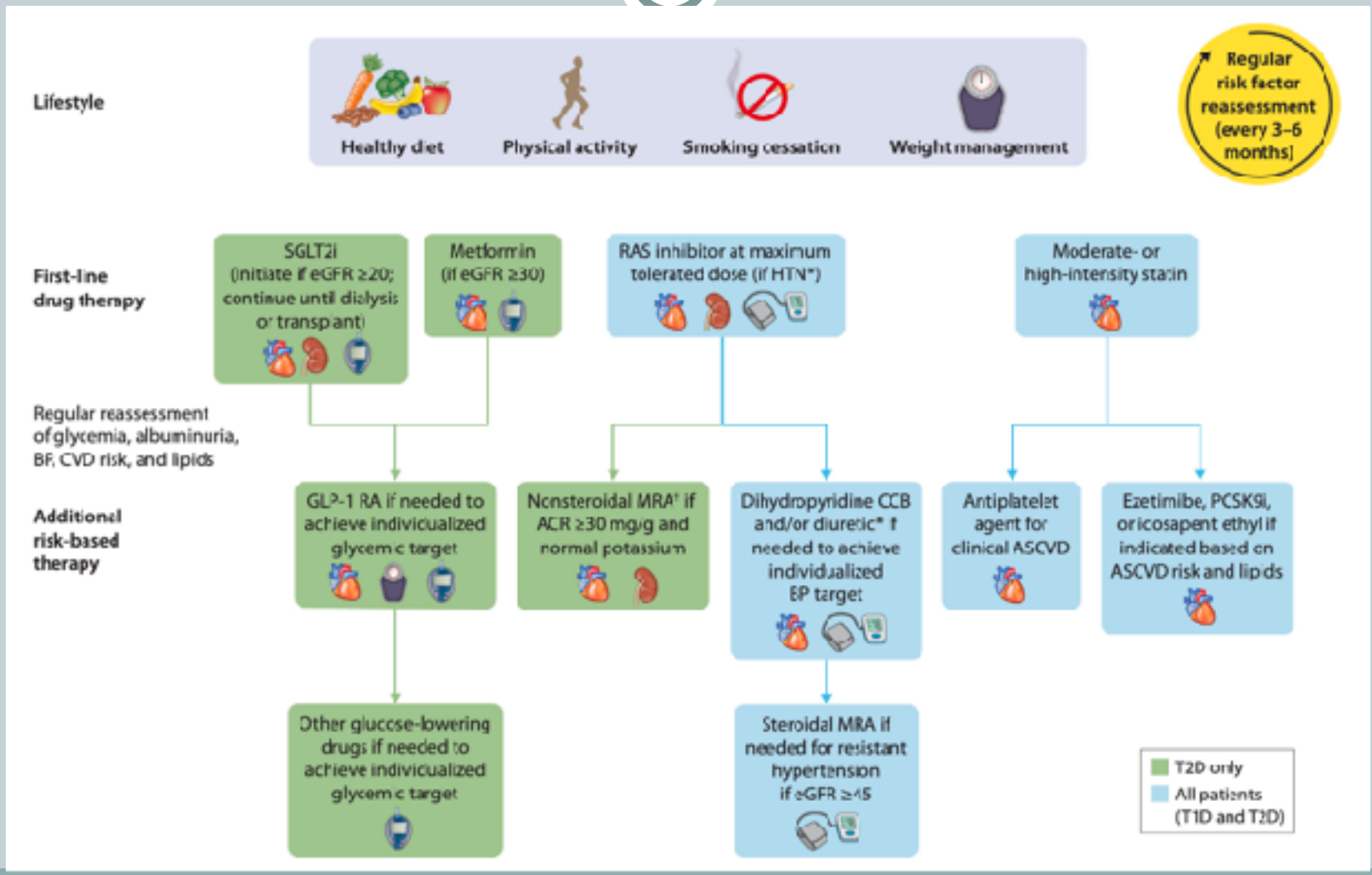

Mean baseline eGFR (mL/min/1.73m²)
Events/participants
SGLT2i
Placebo
Relative risk (95% CI)
Urinary tract infections
High atherosclerotic CV risk trials 60 1838/24549 975/17994 1.05 (0.97, 1.13)
Stable heart failure trials 61 418/7085 358/7079 1.17 (1.02, 1.34)
Chronic kidney disease trials 44 936/12944 878/12937 1.09 (0.93, 1.27)
TOTAL: OVERALL 65 3344/46083 2255/39521 1.08 (1.02, 1.15)
Serious urinary tract infections
High atherosclerotic CV risk trials 75 119/10160 63/5078 0.94 (0.69, 1.27)
Stable heart failure trials 61 106/7985 92/7979 1.15 (0.87, 1.52)
Chronic kidney disease trials 39 81/5453 72/5454 1.10 (0.80, 1.52)
TOTAL: OVERALL 61 306/23618 227/18511 1.07 (0.90, 1.27)
Mycotic genital infections
High atherosclerotic CV risk trials 60 1258/24549 208/17994 3.88 (3.32, 4.53)
Stable heart failure trials 61 98/4859 34/4852 2.87 (1.95, 4.24)
Chronic kidney disease trials 44 179/12944 59/12937 2.98 (2.22, 3.99)
TOTAL: OVERALL 65 1540/42357 302/36304 3.57 (3.14, 4.06)
Severe hypoglycaemia
High atherosclerotic CV risk trials 60 405/18754 261/13947 0.83 (0.71, 0.96)
Stable heart failure trials 62 69/10353 96/10351 0.93 (0.70, 1.23)
Chronic kidney disease trials 44 369/12944 400/12937 0.91 (0.79, 1.05)
TOTAL: OVERALL 64 872/42556 779/37546 0.89 (0.80, 0.98)
Bone fracture
High atherosclerotic CV risk trials 60 1151/24549 811/17994 1.07 (0.98, 1.17)
Stable heart failure trials 63 228/7227 218/7220 1.04 (0.87, 1.25)
Chronic kidney disease trials 44 396/12944 377/12937 1.05 (0.91, 1.21)
TOTAL: OVERALL 65 1787/45325 1415/38782 1.07 (0.99, 1.14)
0.25 0.5 1 2 3 4 5
SGLT2i better
Placebo better

nowe rekomendacje ADA/KDIGO 04/10/2022

www.kidney-international.org consensus report

Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO)

Ian H. de Boer[1], Kamlesh Khunti[2], Tami Sadusky[3], Katherine R. Tuttle[4], Joshua J. Neumiller[5], Connie M. Rhee[6], Sylvia E. Rosas[7], Peter Rossing[8,9] and George Bakris[10]



ChPL

	dapagliflozyna [1]	empagliflozyna [2]	canagliflozyna [3]
DM2	√ ⩾25	√ ⩾60 (10mg->25 mg) ⩾30 -60 (10 mg)	√ >60 (100 mg -> 300 mg) ⩾30 -60 (100mg)
CHF	√ ⩾25	√ ⩾20 (10 mg)	x
PChN	√ ⩾25	x	x

https://www.astrazeneca.pl/content/dam/az-pl/SPC/SPC_Forxiga_10mg.pdf **Charakterystyka Produktu Leczniczego, 03.02.2023r.**

https://www.boehringer-ingelheim.pl/sites/pl/files/documents/poland_pdf/jardiance/jardiance_chpl_21.07.2022.pdf

https://www.ema.europa.eu/en/documents/product-information/invokana-epar-product-information_pl.pdf

Table 2 | Considerations for selecting glucose-lowering agents in patients with T2D and CKD[2,17]

	Progression of CKD	ASCVD	Heart failure	Glucose-lowering efficacy	Hypoglycemia risk	Weight effects	Cost
Metformin	Neutral	Potential benefit	Potential benefit	High	Low	Neutral	Low
SGLT2 inhibitors	Benefit[a]	Benefit[c]	Benefit	Intermediate	Low	Loss	High
GLP-1 receptor agonists	Benefit[b]	Benefit[c]	Potential benefit	High	Low	Loss	High
DPP-4 inhibitors	Neutral	Neutral	Potential risk[c] (saxagliptin)	Intermediate	Low	Neutral	High
Insulin	Neutral	Neutral	Neutral	Highest	High	Gain	High (analogs) Low (human)
Sulfonylureas	Neutral	Neutral	Neutral	High	High	Gain	Low
Thiazolidinediones	Neutral	Potential benefit (pioglitazone)	Increased risk	High	Low	Gain	Low
α-Glucosidase inhibitors	Neutral	Neutral	Neutral	Intermediate	Low	Neutral	Low

Neutral

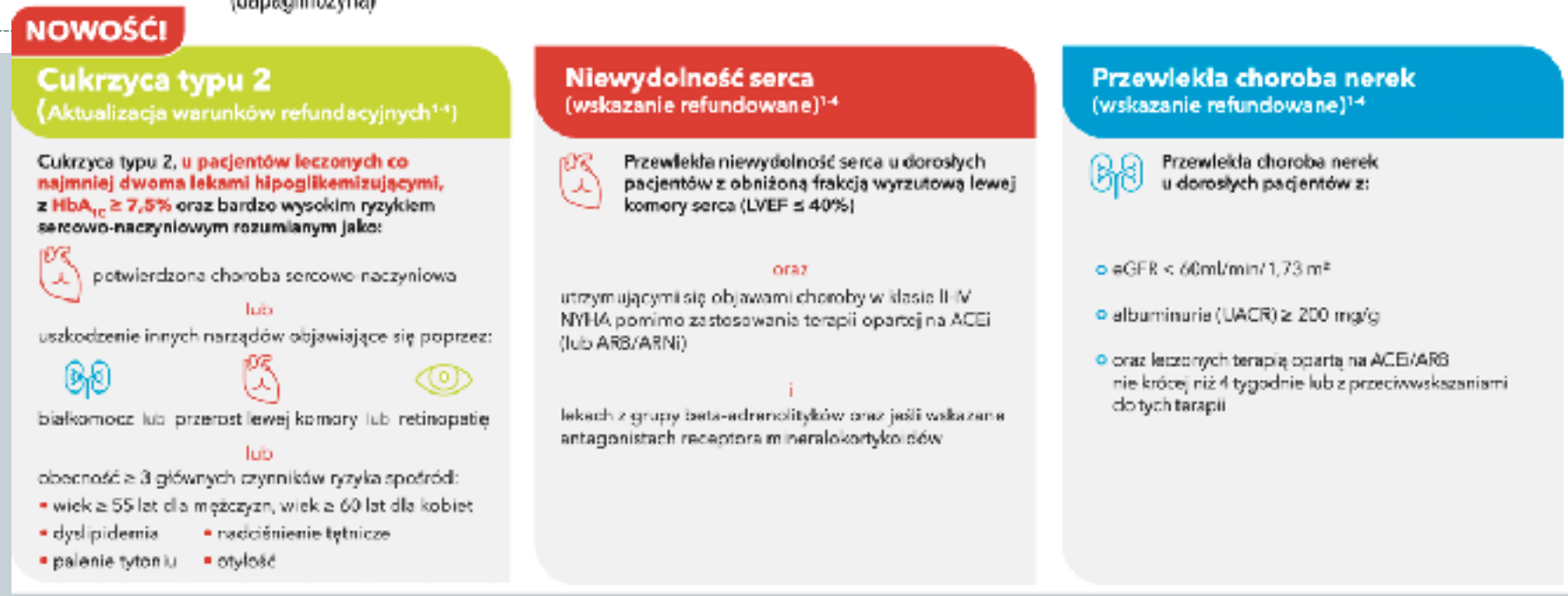
Potential benefit or intermediate glucose-lowering efficacy

Benefit (organ protection, high efficacy, low hypoglycemia risk, weight loss, or low cost)

Potential risk or high cost to patient

Increased risk for adverse effects

Kidney International (2022) 102, 974–989



Dnia 3 lutego 2023 r. dapagliflozyna uzyskała rozszerzone wskazanie w leczeniu przewlekłej objawowej niewydolności serca w całym spektrum frakcji wyrzutowej lewej komory (HFrEF, HFmrEF, HFpEF)1

Charakterystyka produktu leczniczego Forxiga® 10mg z dnia 03.02.2023r dostępna na stronie: https://www.astrazeneca.pl/content/dam/az-pl/SPC/SPC_Forxiga_10mg.pd

kryteria refundacyjne DM2

- **Rozszerzenie aktualnego wskazania refundacyjnego, tj.:**

- zmniejszenie wymogu z HbA1c ≥ 8,0% na HbA1c ≥ 7,5%
- usunięcie ograniczenia w zakresie braku stosowania insuliny przez pacjenta przed zastosowaniem leków flozynowych
- usunięcie konieczności 6 miesięcznego okresu stosowania dwóch leków przed włączeniem do leczenia lekami flozynowymi

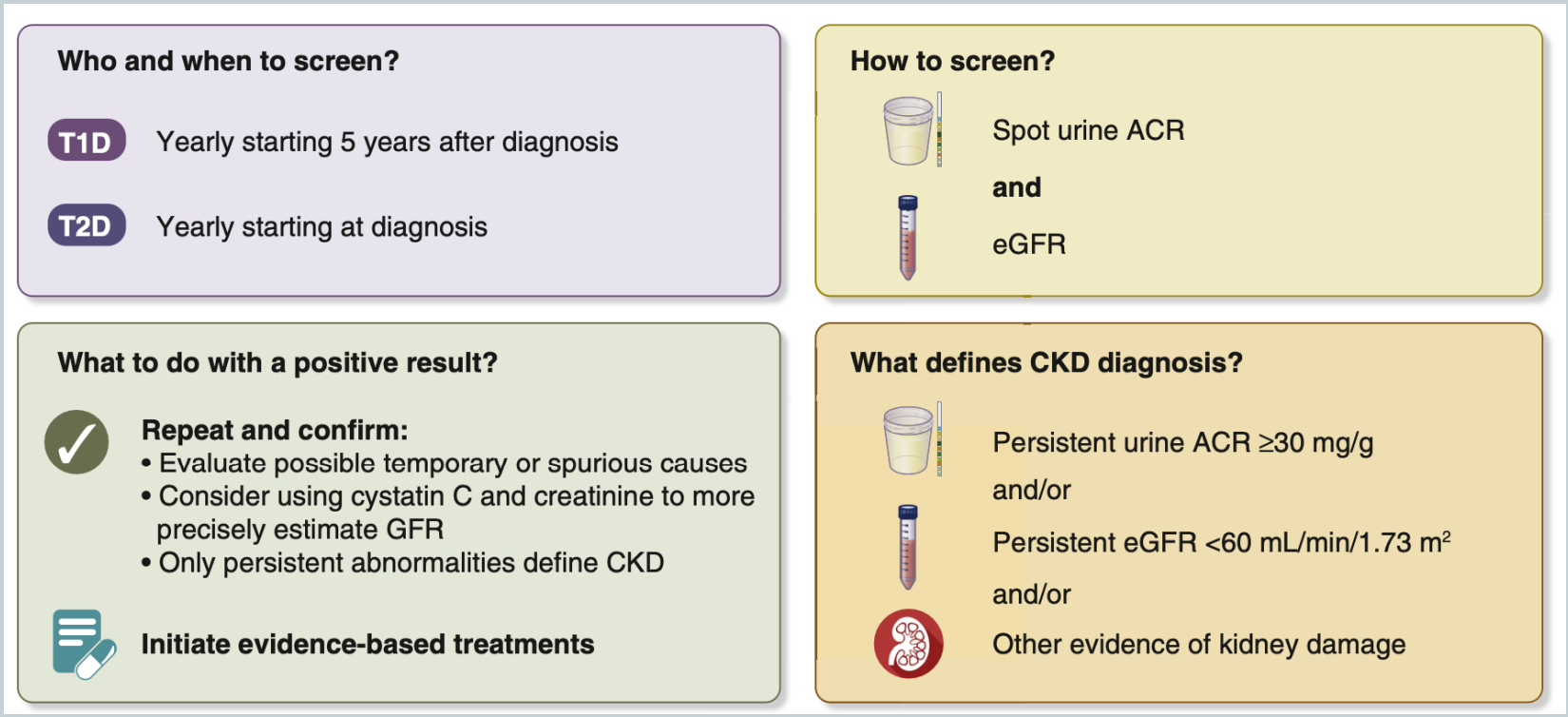
https://www.nowosciwdiabetologii.com/

https://www.nowosciwdiabetologii.com/

https://pulsmedycyny.pl/nowe-obwieszczenie-refundacyjne-od-1-wrzesnia-2022-mz-wylicza-zmiany-1159148

Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO)

Ian H. de Boer[1], Kamlesh Khunti[2], Tami Sadusky[3], Katherine R. Tuttle[4], Joshua J. Neumiller[5], Connie M. Rhee[6], Sylvia E. Rosas[7], Peter Rossing[8,9] and George Bakris[10]



iSGLT2 w praktyce

Journal of the American Heart Association
Volume 11, Issue 9, 3 May 2022
https://doi.org/10.1161/JAHA.121.023811

- This analysis of a near–census-level audit of the US retail prescriptions shows that since 2015, cardiologists have increased use of SGLT2is and GLP-1RAs 12-fold and 4-fold, respectively.
- Nonetheless, cardiologists accounted for <2% of all SGLT2i and GLP-1RA use in 2020.

Prescribing of SGLT2 inhibitors in primary care: A qualitative study of General Practitioners and Endocrinologists

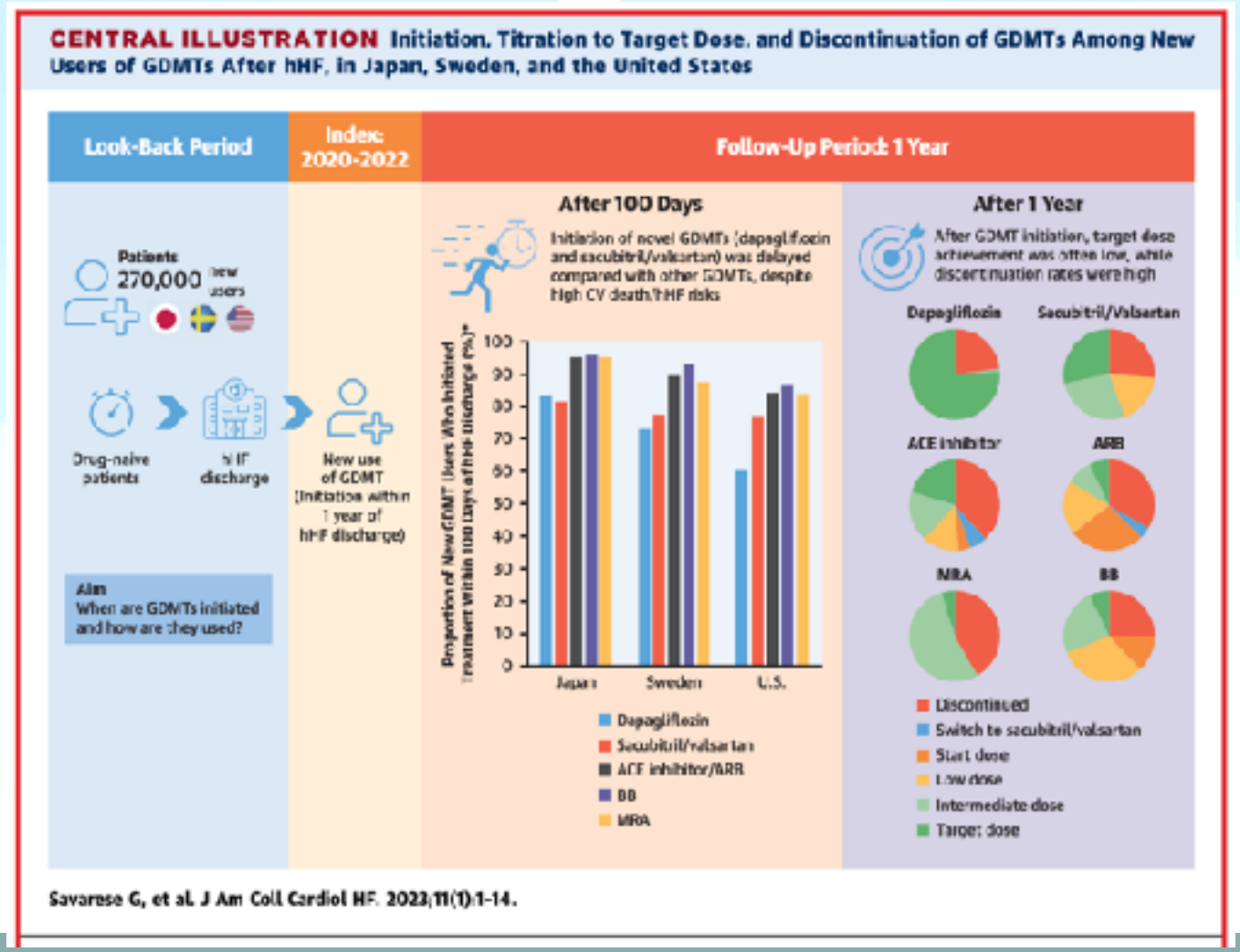
Tamsen T. Milder, Sophie L. Stocker, Melissa Heyworth, Richard O. Day, Jerry R. Greenfield

Reluctance
Reduced appreciation of cardiovascular benefits
Ease of access to Endocrinologist
Less frequently managing type 2 diabetes
Complexity of therapeutic options
Experience of patients with adverse effects

< 10% of Eligible Type 2 Diabetes Patients Get New but Pricey Drugs

Among these 1133 people — who represent more than 22 million American adults with type 2 diabetes who fit the 2022 criteria — a scant 3.7% were actually taking a GLP-1 agonist and 5.3% were taking an SGLT2 inhibitor.

iSGLT2 w praktyce



Savarese G, et al. J Am Coll Cardiol HF. 2023;11(1):1-14.

stosowanie iSGLT2 - wskazówki praktyczne

- iSGLT2 to leki bezpieczne
- iSGLT2 to leki o działaniu plejotropowym
- iSGLT2 to leki **3 w 1** (kardio-nefroprotrekcja i efekt metaboliczny)
- przy iSGLT2 właściwa edukacja pacjenta: nasilona diureza (nagła), parcie na pęcherz (pacjent kojarzy z infekcją)
- przy iSGLT2 zmniejszenie dawek innych leków (diuretyków)
- nacisk na higienę osobistą
- kontrola SCr zwykle po 4- 6 tyg, akceptowalny wzrost SCr do 30%
- wzrost SCr nie zawsze wynika ze stosowania iSGLT2 - wyklucz inne przyczyny
- IPOM (Indywidualny Plan Opieki Medycznej) - opieka koordynowana w POZ - > oznaczenie ACRwyjaśnić pacjentowi skutki stosowania leku - nasilona diureza (nagła), parcie na pęcherz (pacjent kojarzy z infekcją)
- czasowe wstrzymanie leku przed dużym zabiegiem operacyjnym

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