



Flozyny w praktyce klinicznej - pacjent CRM

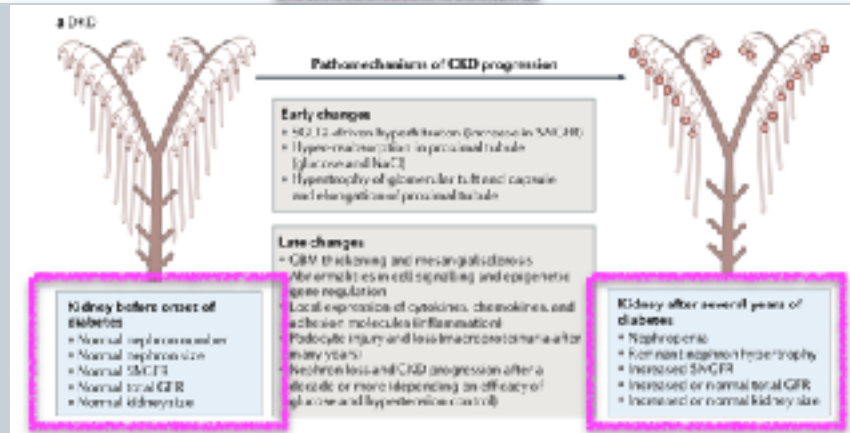
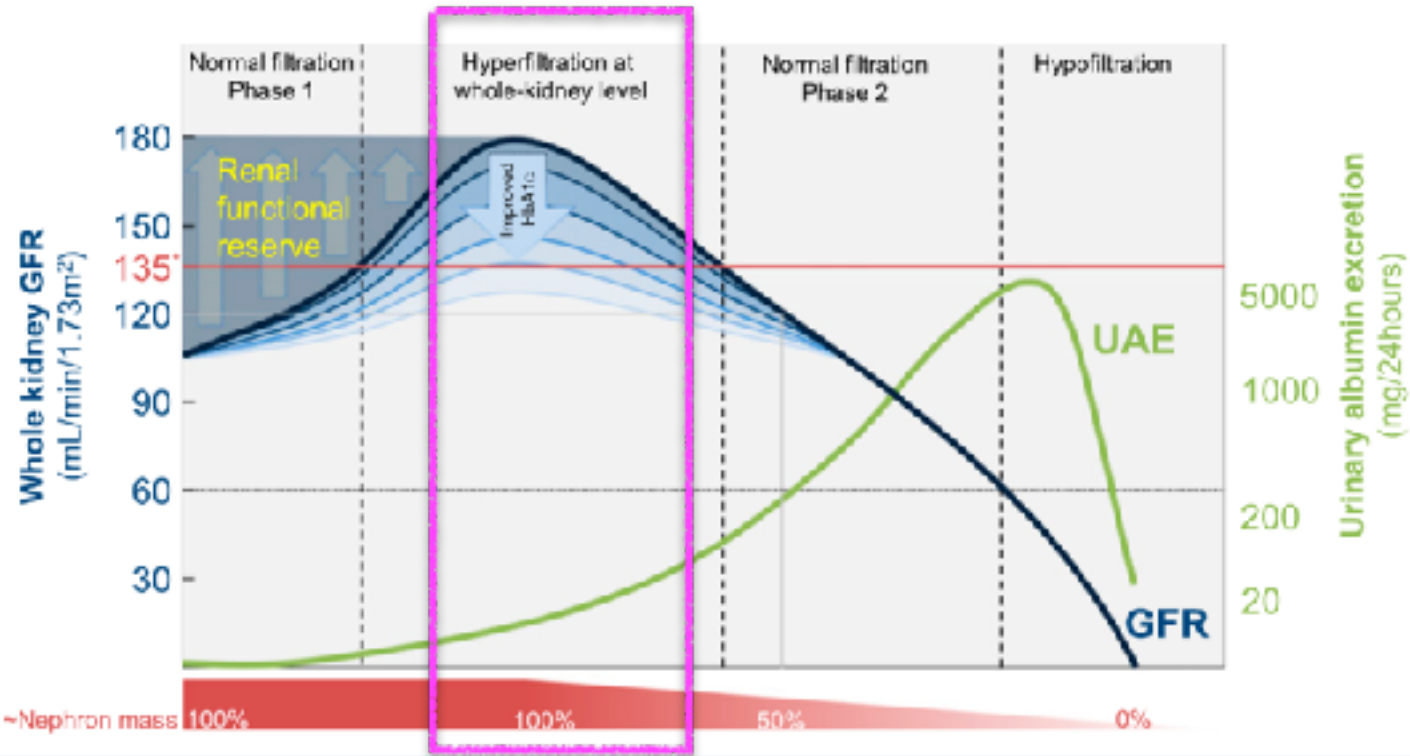
Krzysztof Wróblewski

Klinika Chorób Wewnętrznych i Nefrodiabetologii, UM w Łodzi

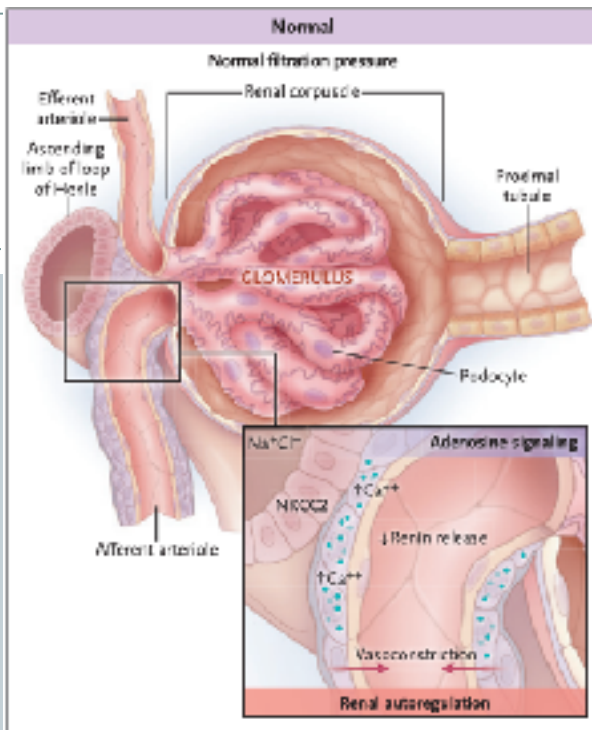


11/05/2023

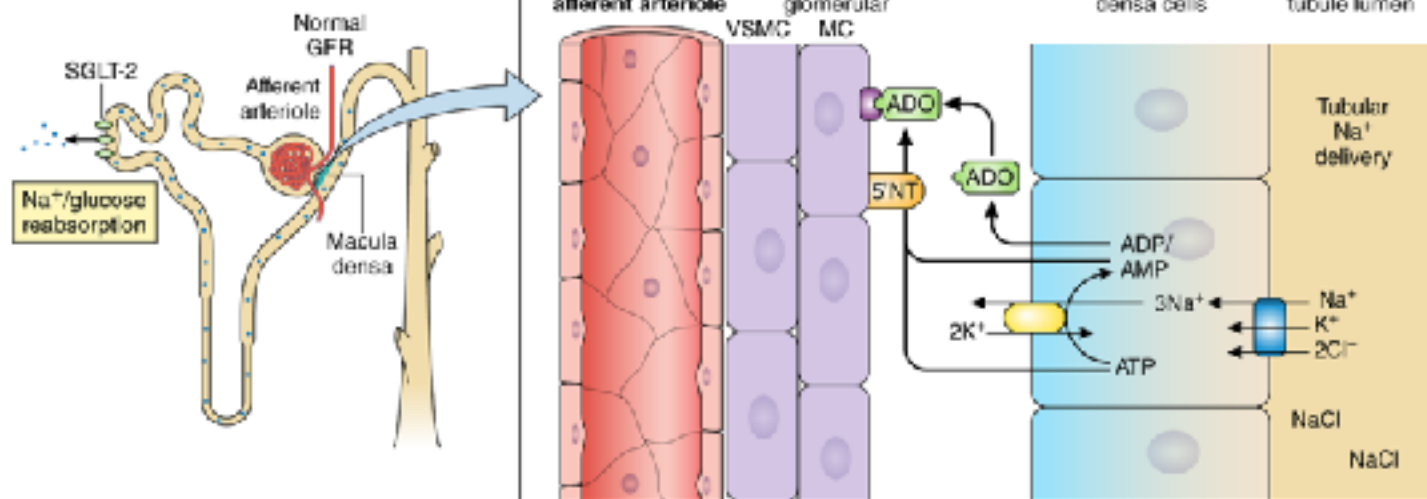
DM a nerki



kluczem jest plamka

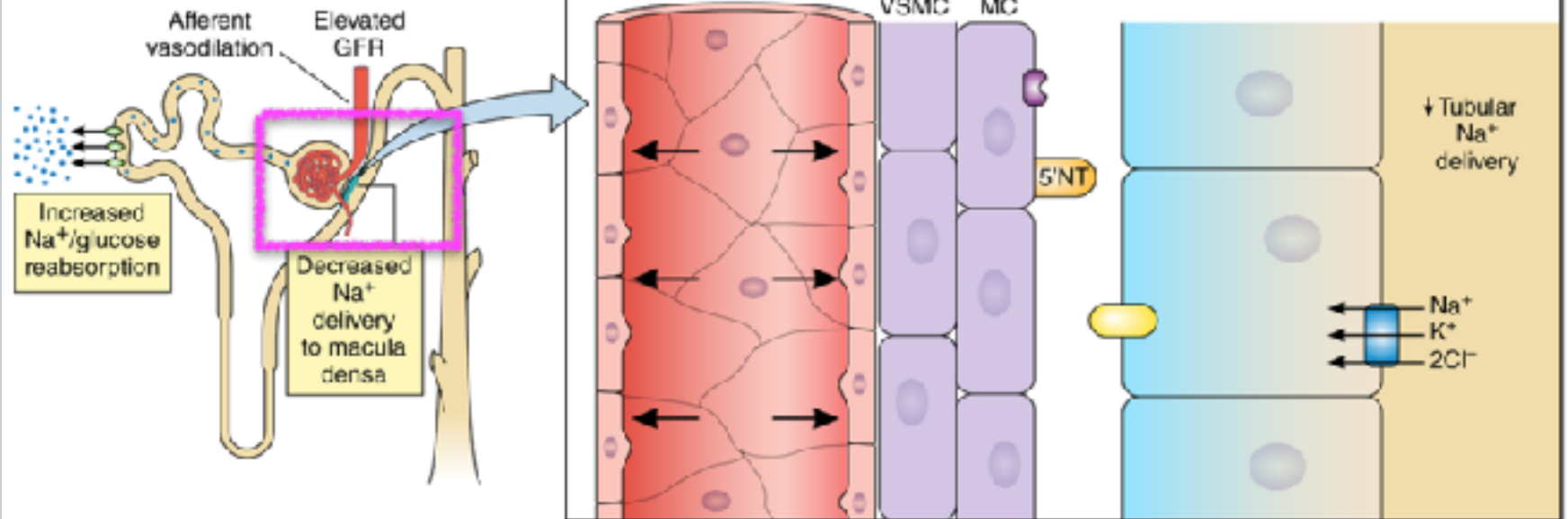


A Normal physiology



DM

B Hyperfiltration in early stages of diabetic nephropathy



CLINICAL IMPLICATIONS OF BASIC RESEARCH

The clinical implications of basic research studies are based on findings that demonstrate a causal relationship between a disease and a specific intervention. However, the path between the laboratory and the bedside is not always straightforward. The path from basic research to clinical practice is often a long and winding one, and it is important to understand the limitations of basic research in predicting clinical outcomes. The following are some of the limitations of basic research in predicting clinical outcomes:

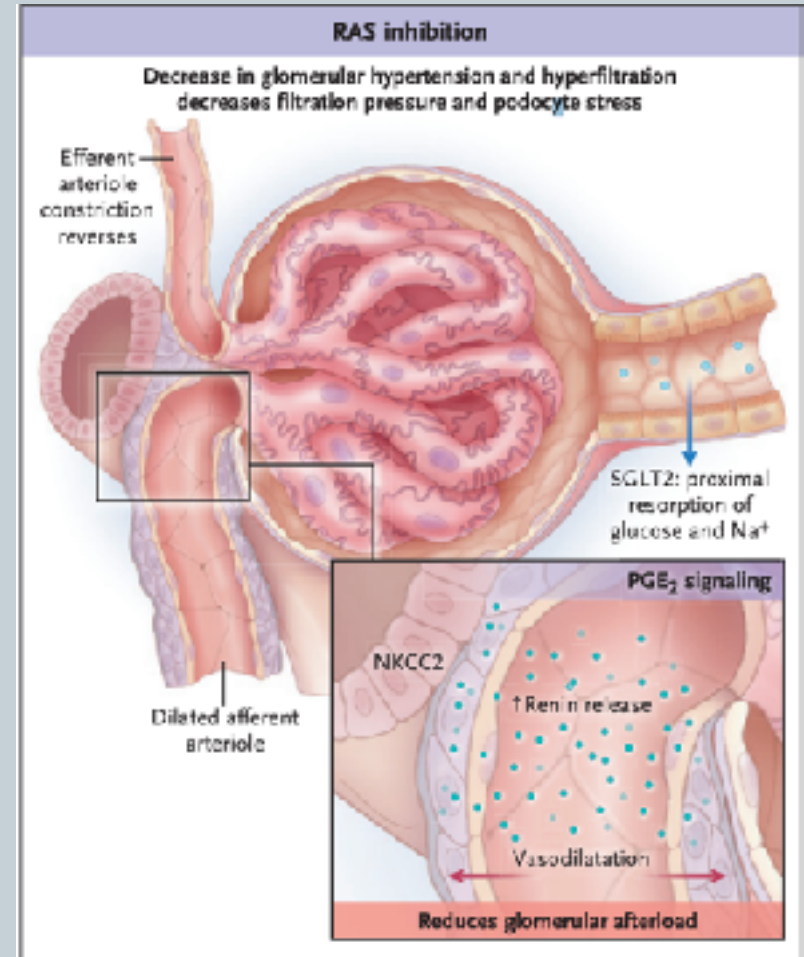
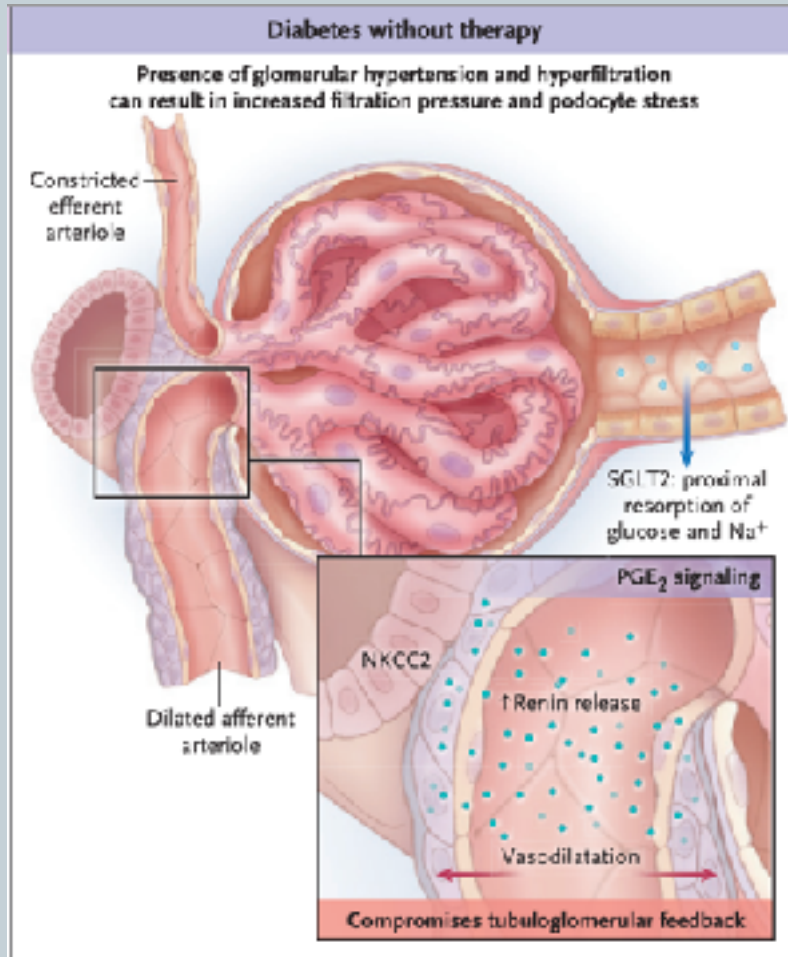
BASED ON FINDINGS OF CLINICAL OBSERVATION

John A. Jorgensen, M.D., Editor

Nephron Protection in Diabetic Kidney Disease

—Harapachon Anders, M.D., John H. Davis, Ph.D., and Ravi Thirumangalakudi, M.D.

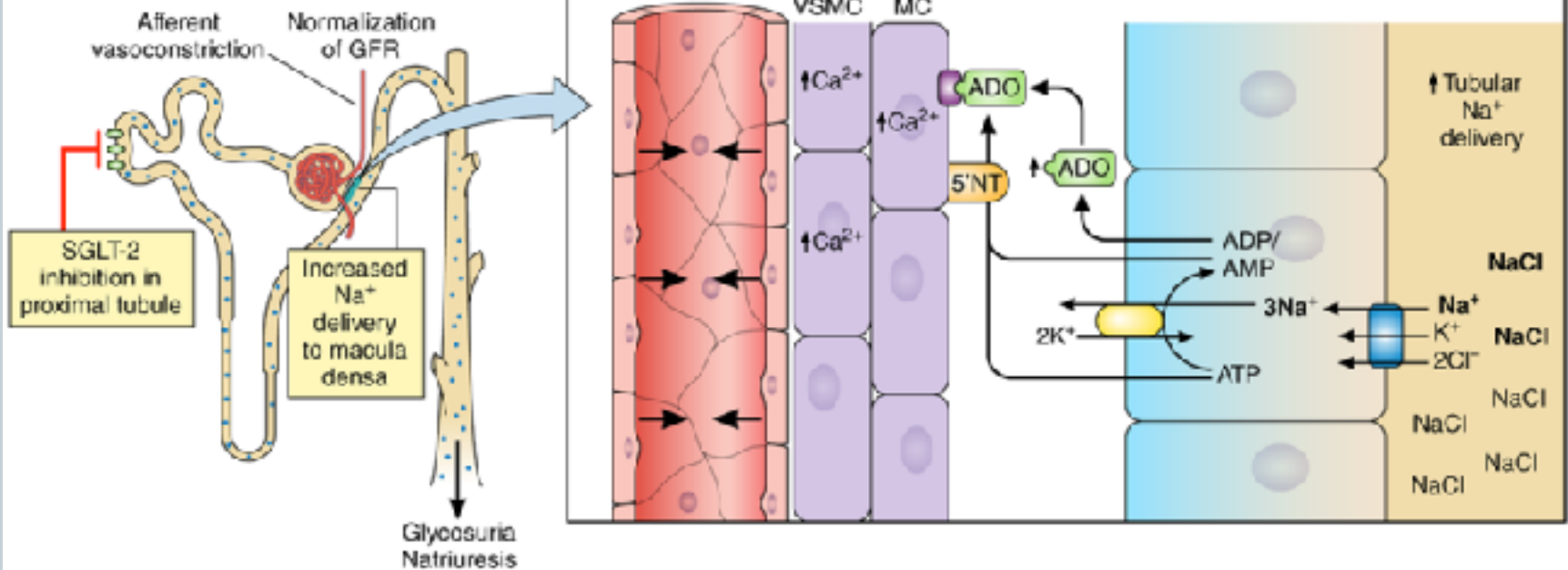
ACEI/ARB w DM



iSGLT2



C SGLT-2 inhibition reduces hyperfiltration via TGF



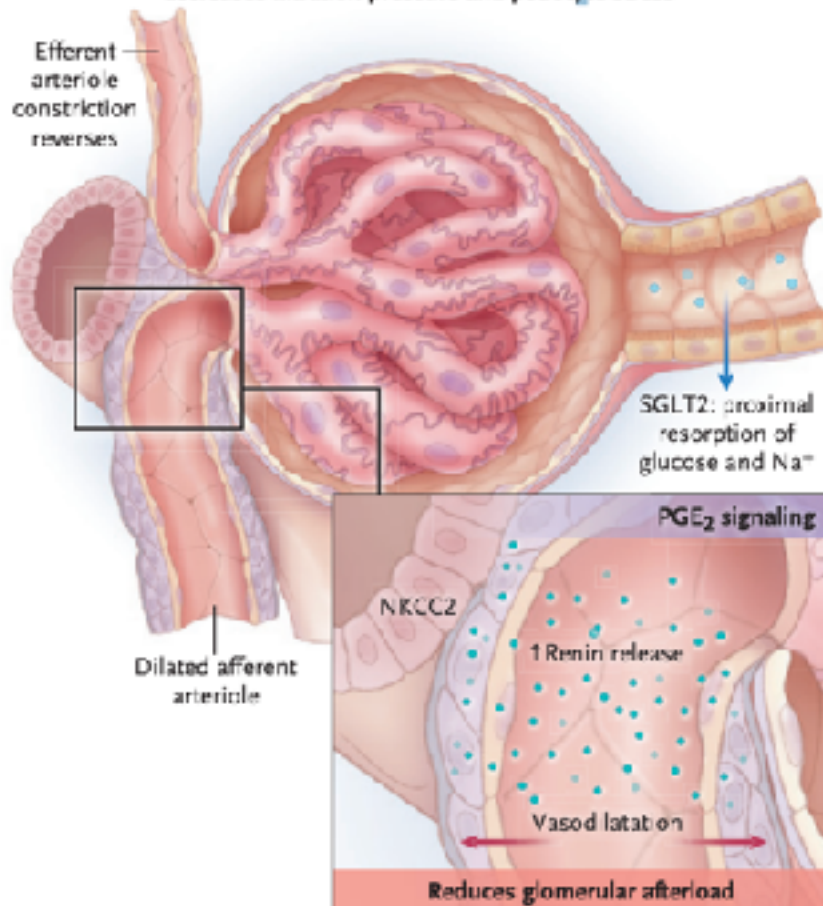
⇓ hiperfiltracji, ⇓ reabsorpcji glukozy

ACEI vs iSGLT2



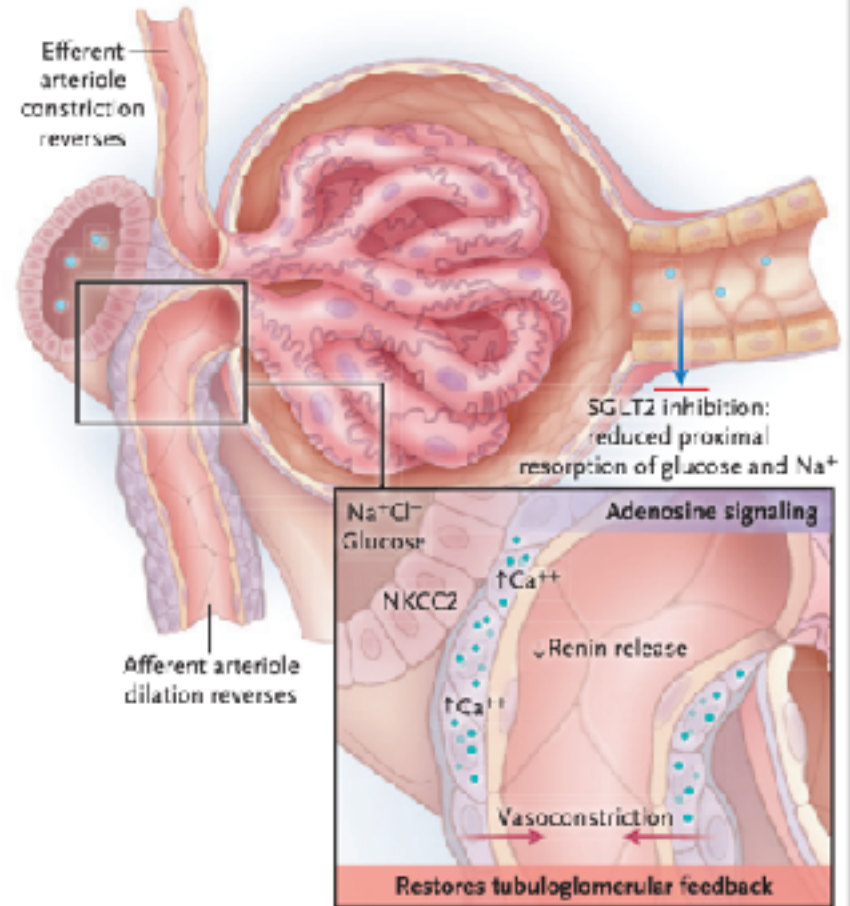
RAS inhibition

Decrease in glomerular hypertension and hyperfiltration decreases filtration pressure and podocyte stress



SGLT2 inhibition

Normalization of filtration pressure and podocyte stress



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*

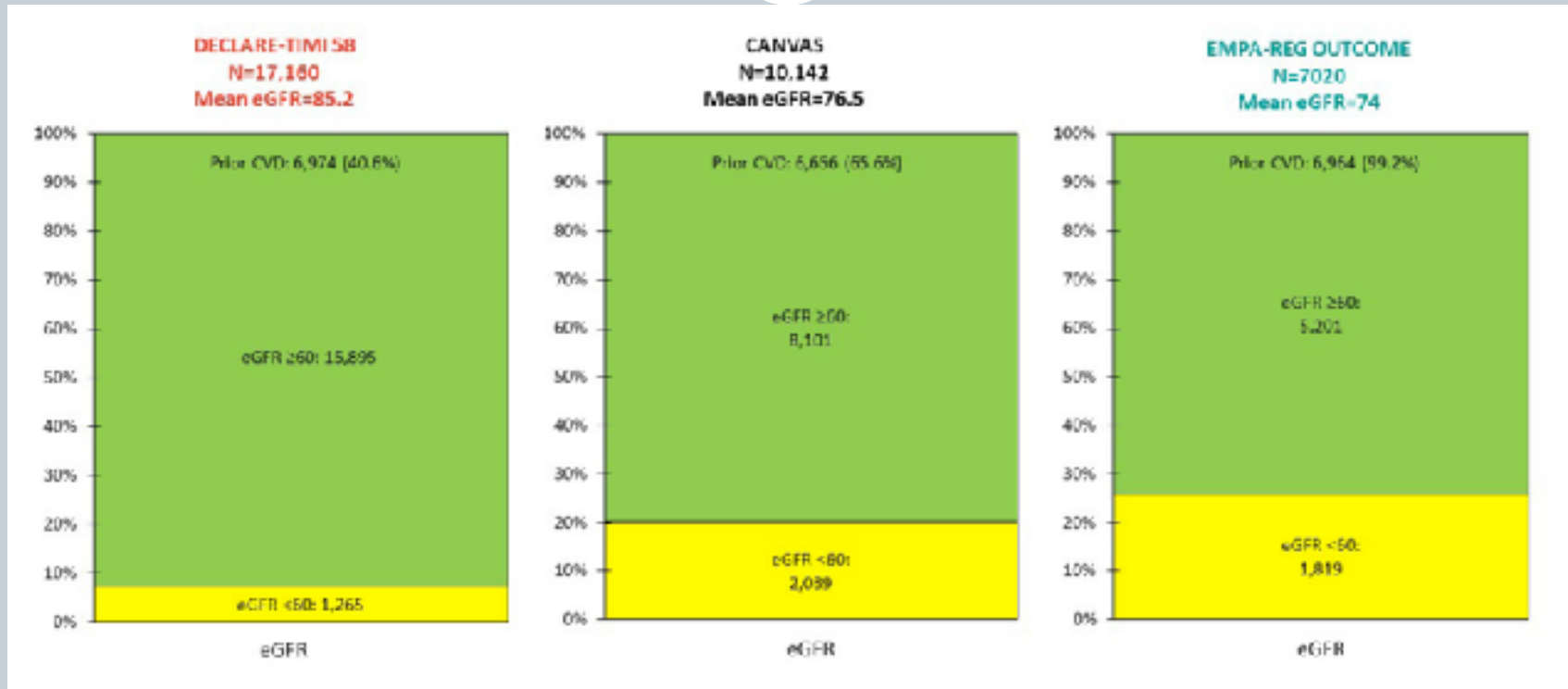
2017

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*

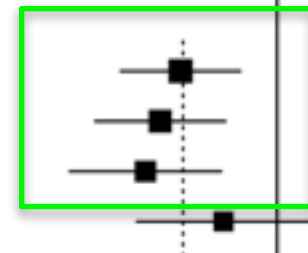
2019





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	



0.25 0.5 0.75 1 1.5
SGLT2i better Placebo better

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

OR

Trials Department of Population Health and Genomics and the SGLT2 Inhibitor Meta-Analysis Early 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 cardiovascular complications. Some other trials recruiting patients with and without diabetes were designed to assess outcomes separately in patients without diabetes.

iSGLT2 a serce w populacji bez DM2

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

OCTOBER 9, 2020

VOL. 382 NO. 16

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

N. Wicker, S.D. Anker, J. Butler, G. Filippatos, E.J. Ferrero, P. Carson, J. Januzzi, S. Verma, H. Tsutsui, M. Bruckmann, W. Jamal, K. Kimura, J. Schnee, C. Keller, D. Coccaro, E. Sacchi, M. Böhm, D.-J. Cho, V. Chopra, E. Chuquillure, N. Giannetti, S. Janssens, J. Zhang, J.R. González Juanatey, S. Kaul, H.-P. Brunner-La Rocca, E. Merkely, E.J. Nicholls, S. Perrone, L. Riffa, P. Ponikvarski, M. Sirtori, M.-F. Serrano, J. Spinar, I. Squire, S. Taddei, C. Wanner, and F. Zamora, for the EMPEROR-Reduced Trial Investigators*

2020

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

OCTOBER 14, 2021

VOL. 385 NO. 16

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

S.D. Anker, J. Butler, G. Filippatos, J.-P. Ferreira, E. Sacchi, M. Böhm, H.-P. Brunner-La Rocca, D.-J. Cho, V. Chopra, E. Chuquillure Valenzuela, N. Giannetti, J.E. Gomez Mesa, E. Janssens, J.L. Januzzi, Szlachetka-Juanatey, B. Merx, S.J. Nicholls, S.V. Perrone, L.L. Riffa, P. Ponikvarski, M. Sirtori, D. Sim, I. Squire, S. Taddei, H. Tsutsui, S. Verma, D. Vineranu, J. Zhang, F. Carson, C.S.P. Lam, N. Marx, L. Satta, W. Jamal, S. Schmidt, J.M. Schnee, M. Bruckmann, S.J. Pocock, F. Zamora, and M. Packer, for the EMPEROR Preserved Trial Investigators*

2021

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikvarski, M.S. Sabatine, I.S. Anand, J. Böhlövák, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozd, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Ljungman, B. Merkely, J.C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. Schou, S. Tereshchenko, S. Verma, C. Held, D.L. DeMets, K.F. Docherty, P.S. Jhund, O. Bengtsson, M. Sjöstrand, and A.-M. Langkilde, for the DAPA-HF Trial Committees and Investigators*

2019



KIDNEY DISEASE PROGRESSION

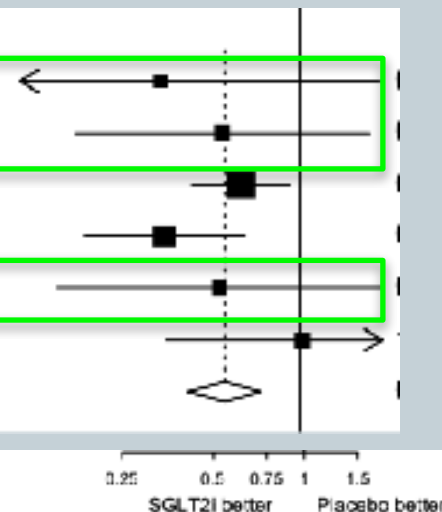
Median
baseline uACR
(mg/g) participants

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		



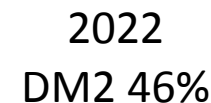
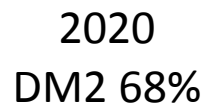
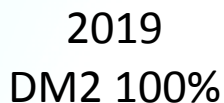
Impact of diabetes on the effects of sodium glucose
co-transporter-2 inhibitors on kidney outcomes:
a collaborative [meta-analysis](#) of large placebo-controlled trials



For the Department of Medicine, Harvard Medical School, and the SGLT2i Alliance, Boston, MA, USA

Summary

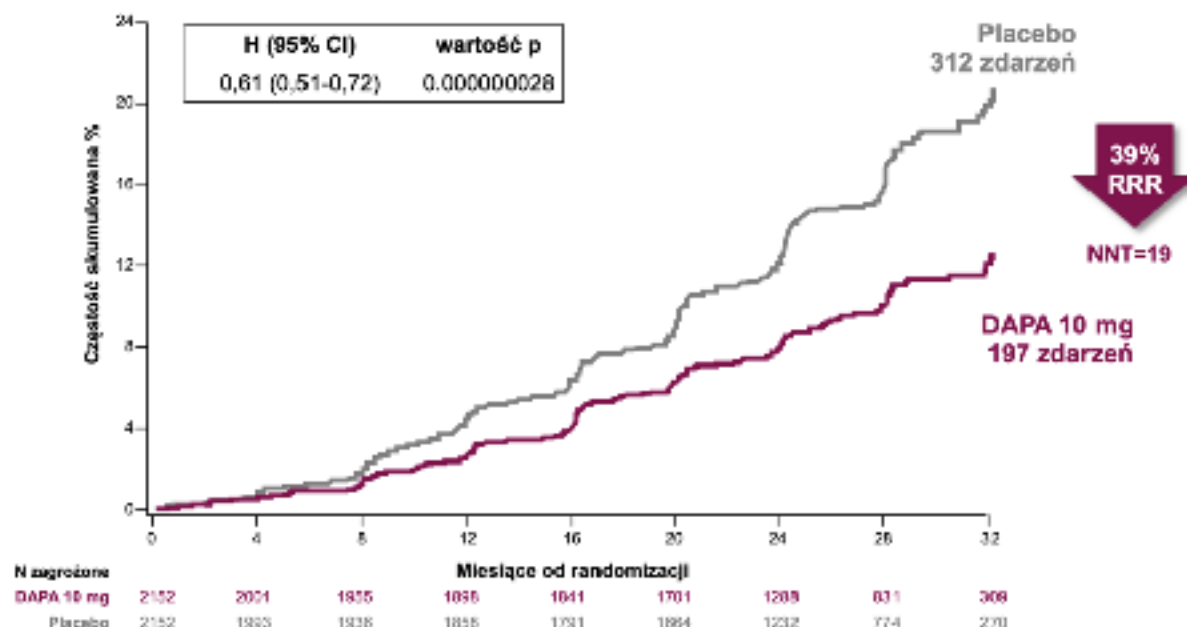
Background Large trials have shown that sodium glucose co-transporter 2 (SGLT2) inhibitors reduce the risk of adverse kidney and cardiovascular outcomes in patients with heart failure or chronic kidney disease, or with type 2 diabetes and high risk of cardiovascular disease. Some other trials involving patients with and without diabetes were designed to assess outcomes separately in patients without diabetes.



DAPA-CKD



**Pierwszorzędowy punkt końcowy:
trwała redukcja eGFR $\geq 50\%$, ESKD, zgon nerkowy lub s-n ^a**



Highland Trial Protocol (2019) 1: 13
doi: 10.1016/j.ijid.2019.02.023



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

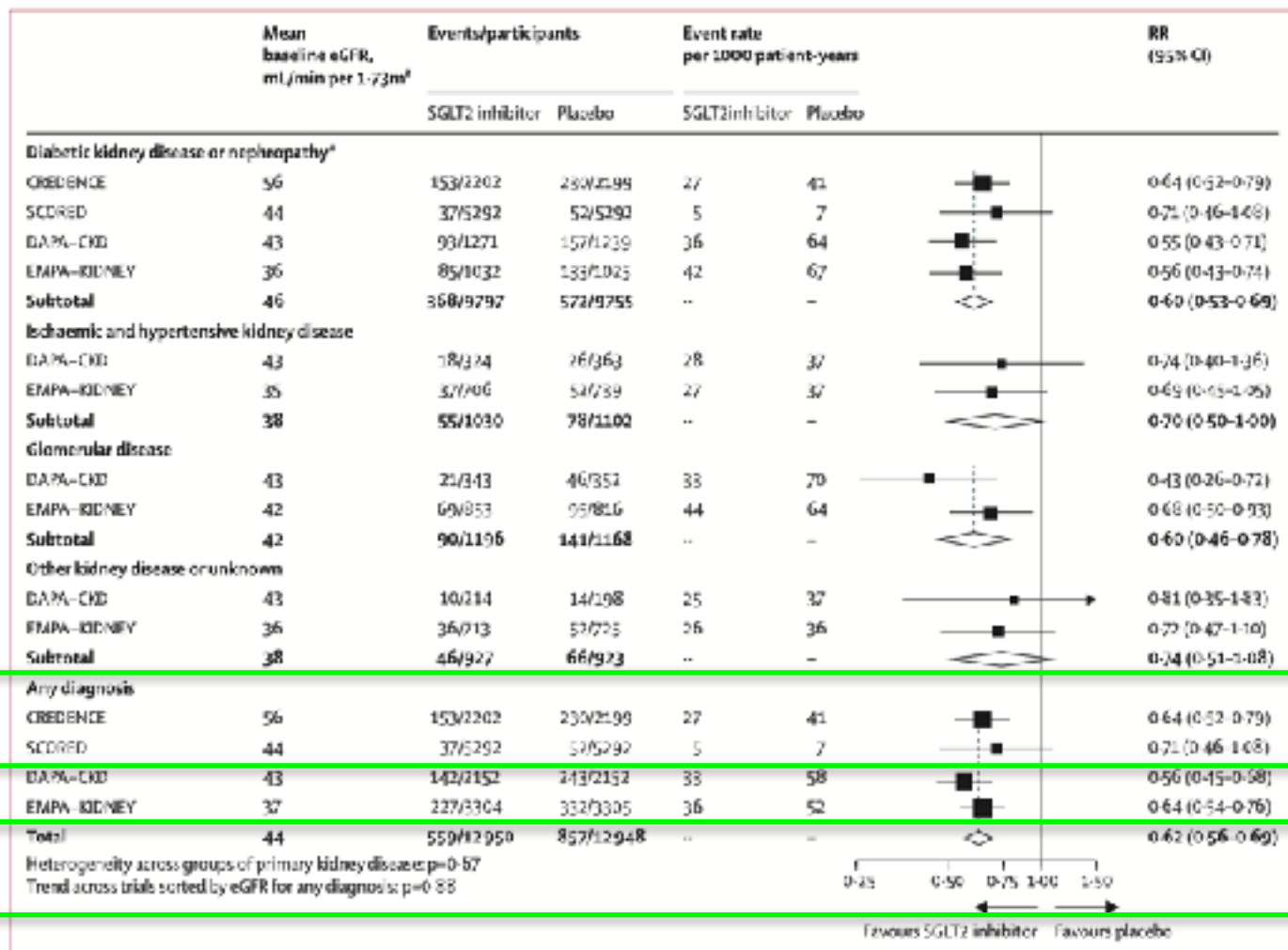
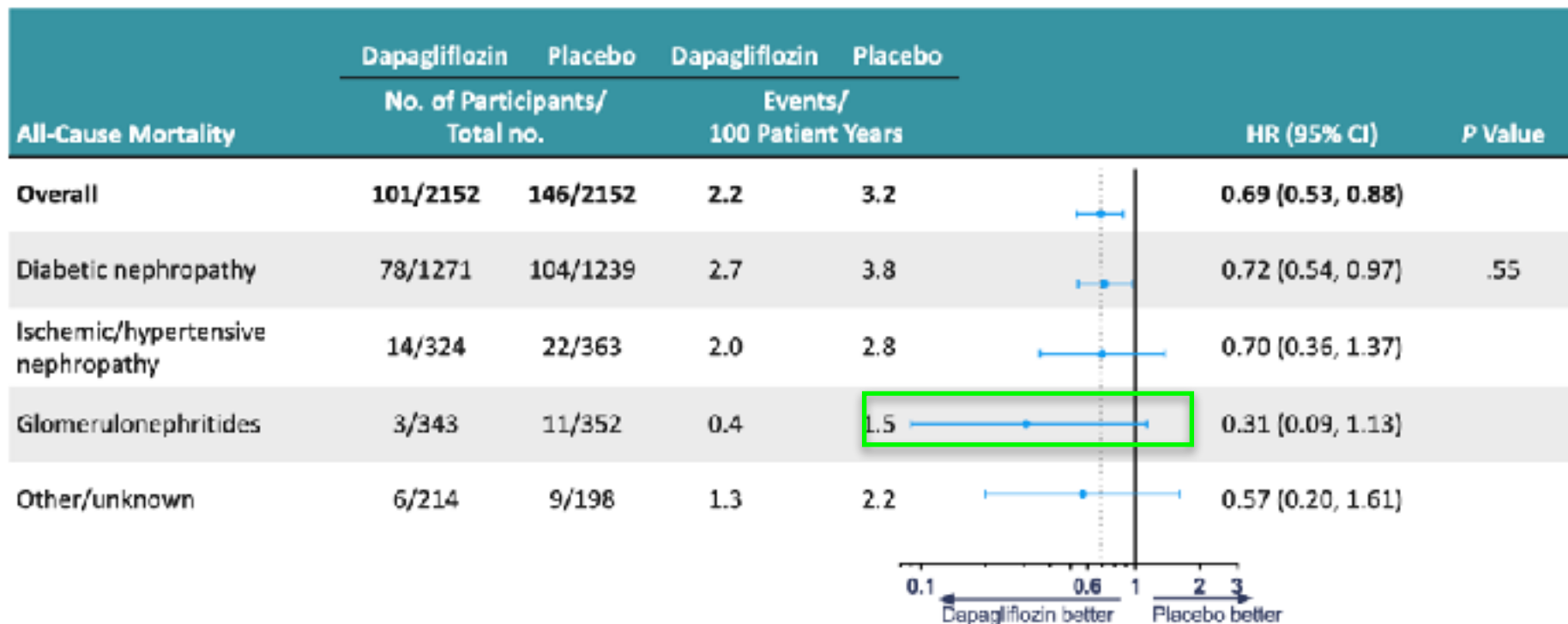


Figure 2: Effect of sodium glucose co-transporter-2 inhibition on kidney disease progression by presumed primary kidney disease (chronic kidney disease trials only)

PChN bez DM



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

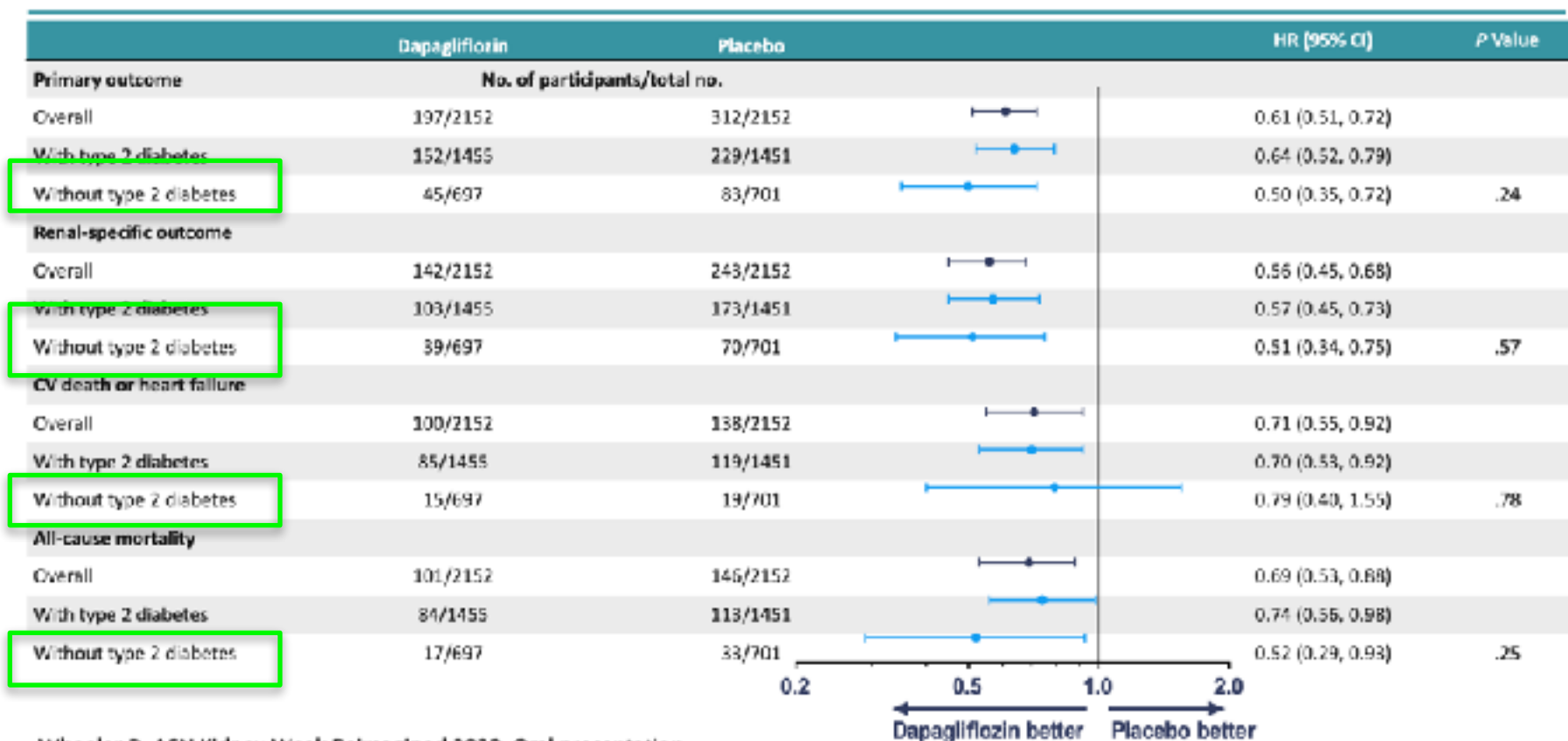


DAPA-CKD



DAPA-CKD

Primary and Secondary Outcomes by Diabetes Status

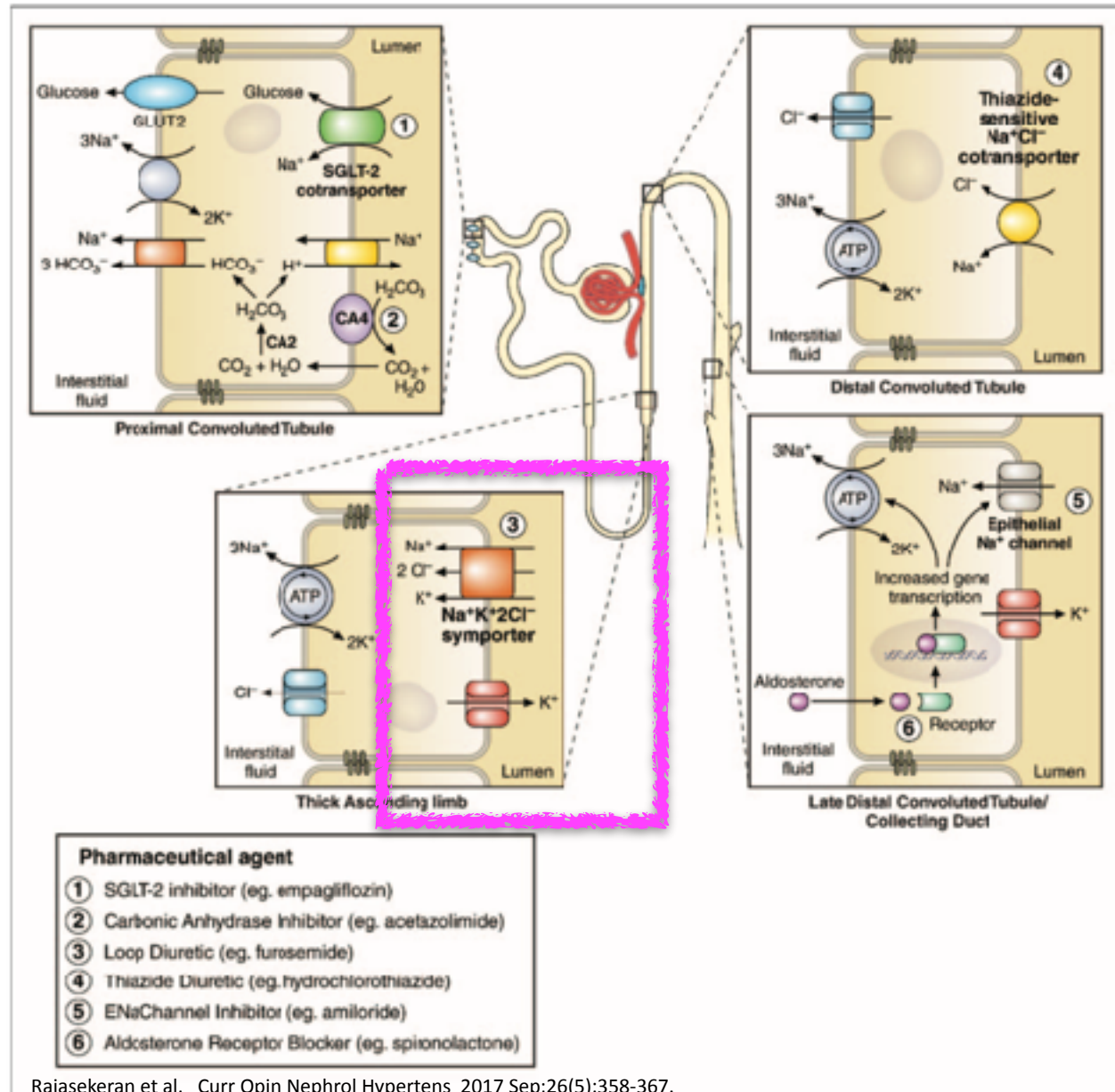


Wheeler D. ASN Kidney Week Reimagined 2020. Oral presentation.

iSGLT2 - czy tylko efekt hemodynamiczny?



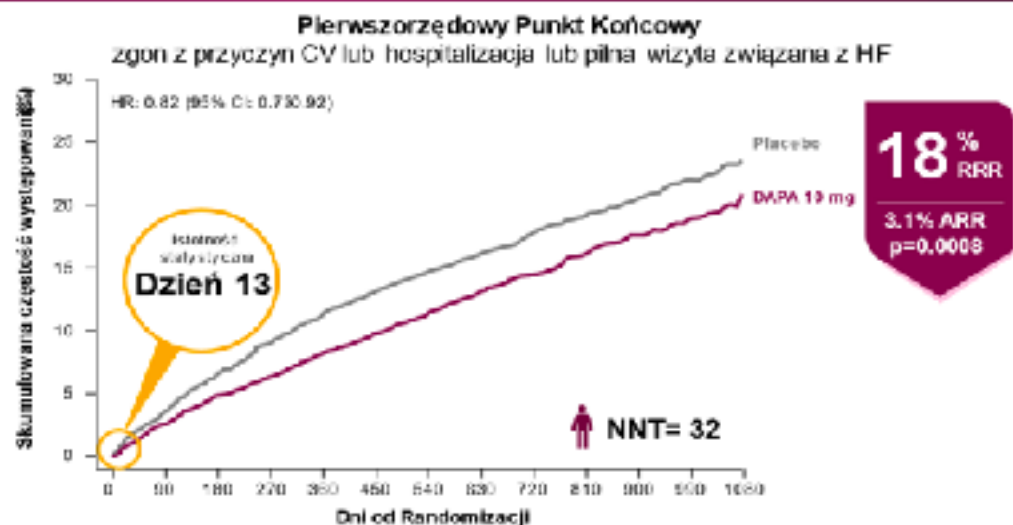
- iSGLT2 i diuretyki - czy to ten sam efekt działania?
- skąd się bierze efekt kardioprotekcyjny, skoro iSGLT2 nie są zlokalizowane w sercu?
- co to jest kompleksowa nefroptotekcja?



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

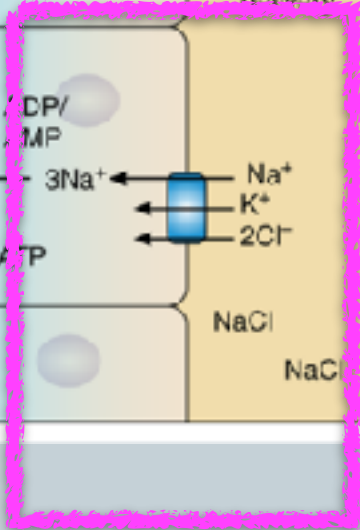


DELIVER



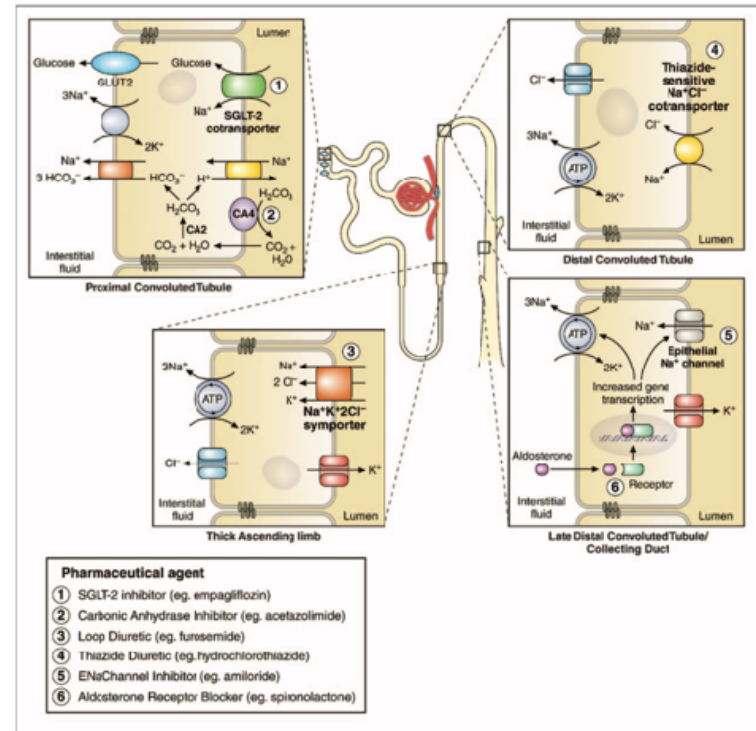
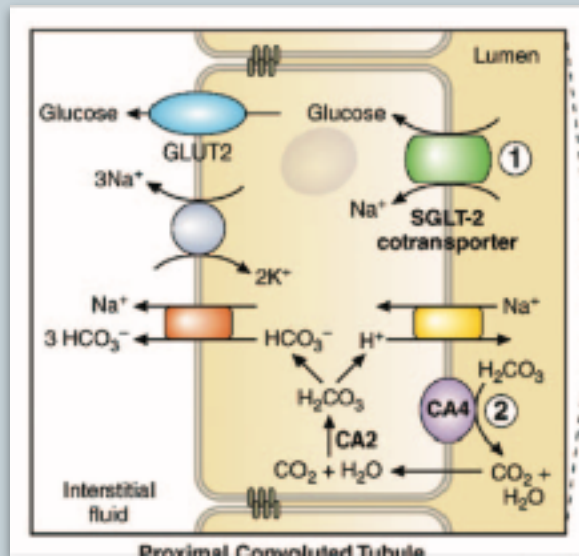
ARR - bezwzględne zmniejszenie ryzyka; CV - sercowo-naczyniowe; DAPA - dapagliflozyna; HF - niewydolność serca; HR - współczynnik ryzyka; LVEF - frakcja wyrzutowa lewej komory serca; RRR - względne zmniejszenie ryzyka.

Rysunek 1. Wyniki pierwszorzędnego 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)



cewka bliższa - hot topic !

Sodium-glucose cotransporter-2 inhibitors Rajasekaran *et al.*



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

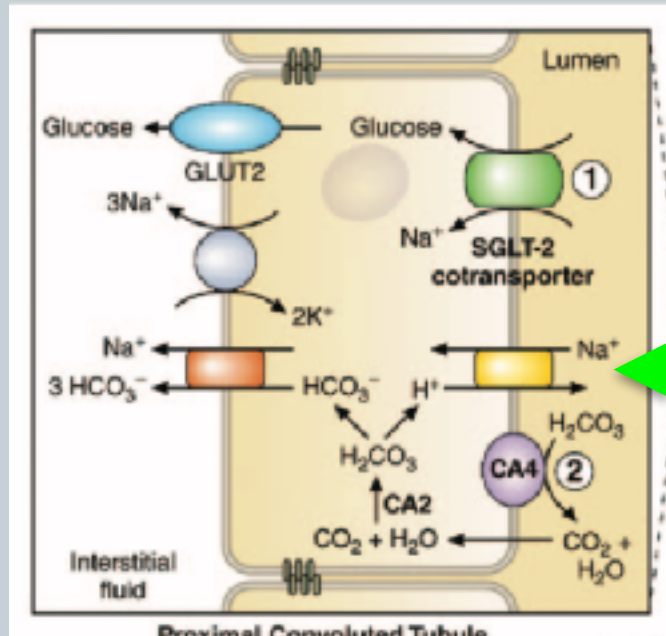
Wilfried Mullens^{1,2*}, Jeroen Dauw^{1,3}, Pieter Martens¹, Evelyne Meekers^{1,2},

iSGLT2 - czy tylko efekt hemodynamiczny?

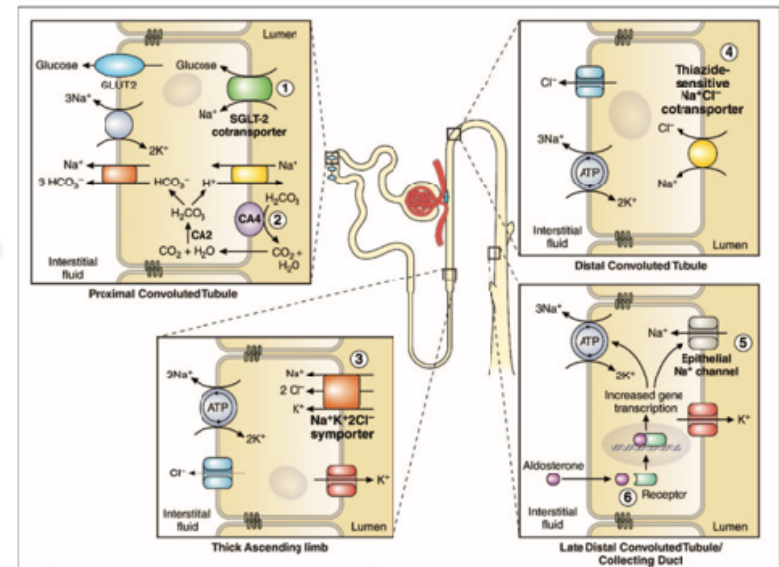


- iSGLT2 i diuretyki - czy to ten sam efekt działania?
- skąd się bierze efekt kardioprotekcyjny, skoro iSGLT2 nie są zlokalizowane w sercu?
- co to jest kompleksowa nefroptotekcja?

iSGLT2 i NHE



Sodium-glucose cotransporter-2 inhibitors Rajasekaran *et al.*



Pharmaceutical agent

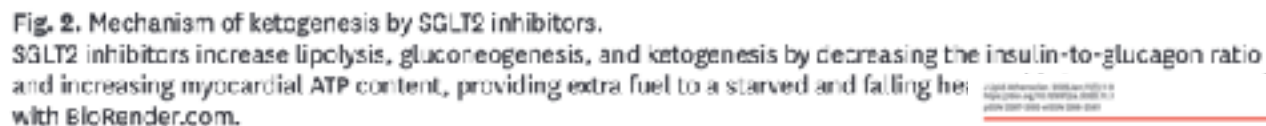
- ① SGLT-2 inhibitor (eg. empagliflozin)
- ② Carbonic Anhydrase Inhibitor (eg. acetazolamide)
- ③ Loop Diuretic (eg. furosemide)
- ④ Thiazide Diuretic (eg. hydrochlorothiazide)
- ⑤ ENaC Inhibitor (eg. amiloride)
- ⑥ Aldosterone Receptor Blocker (eg. spironolactone)

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 Ca^{2+} wewnątrz komórki -> uszkodzenie komórki (włóknienie, stan zapalny, apoptoza) -> uszkodzenie całego narządu
- aktywacja NHE3 wzmacnia aktywność nerkowego układu współczulnego





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SGLT2 Inhibitors and Ketone Metabolism in Heart Failure

Muhammad Saadullah Ghossein , Suzanne M. Voorhes , Salva E. Faridat ,
Muhammad A. Al-Sayid , S. Saad-Whitcomb 

metabolizm w sercu

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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VOL. 77, NO. 12, 2021

THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Therapeutic Potential of Ketone Bodies for Patients With Cardiovascular Disease



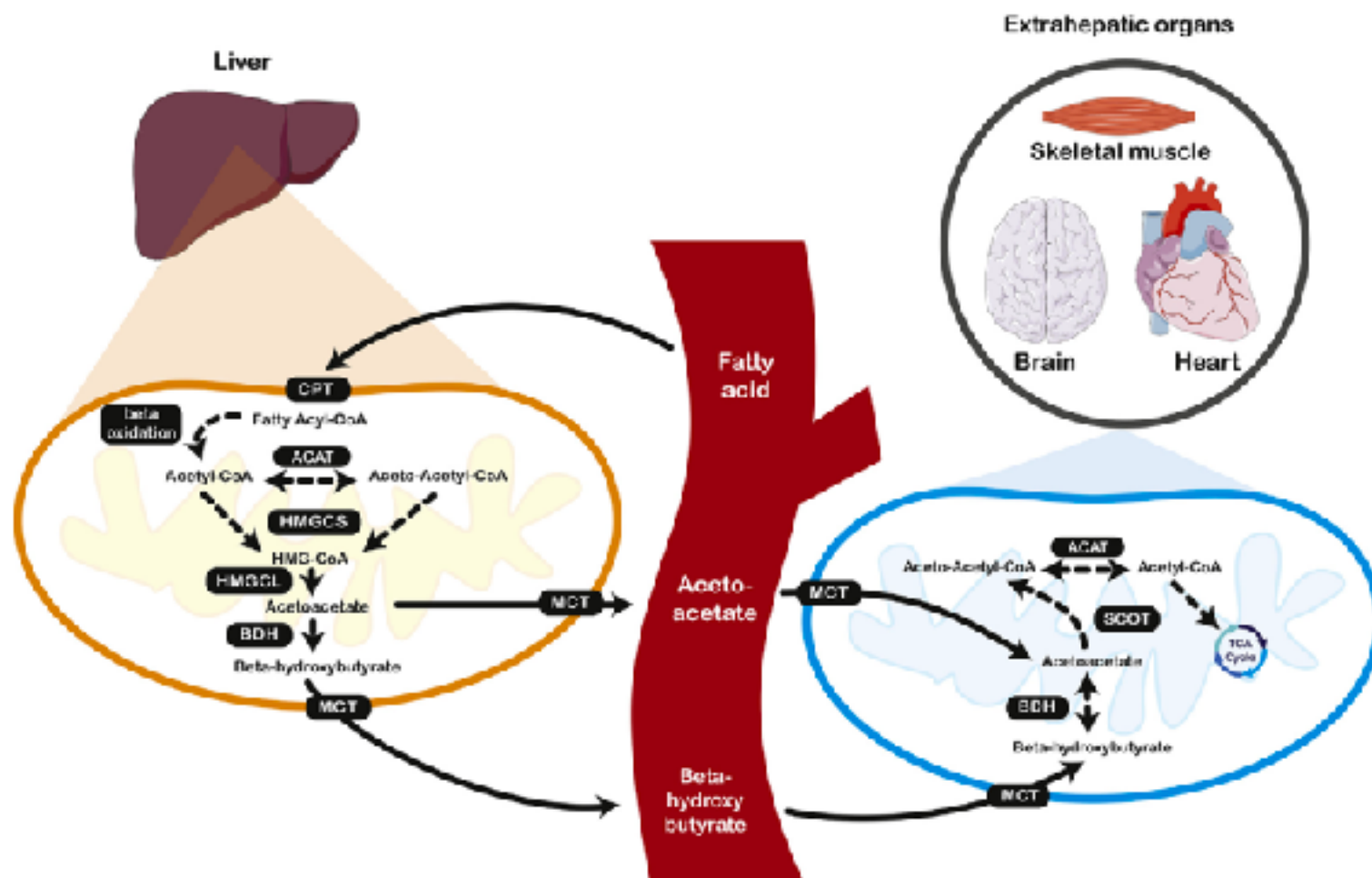
JACC State-of-the-Art Review

Salva R. Varista, MD, PhD,¹ Cher Sin Chong, PhD,^{1,2} Juan J. Badimon, PhD,³ Daniel P. Kelly, MD,⁴
Rudolf A. de Boer, MD, PhD,⁵ B. Daan Westenbrink, MD, PhD⁶

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 metabolized to 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 dehydrogenases; HMG-CoA = hydroxymethylglutaryl-CoA; HMGCS = HMG-CoA lyase; HMGCL = HMG-CoA synthase; SCOT = succinyl-CoA:3-oxoacid CoA transferase; TCA = tricarboxylic acid.

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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

Edwin S. Yeh, MD, PhD¹, Qing Xia, PhD², Anne J. Badier, PhD³, David P. Kelly, MD⁴,
Rodrigo de Bona, MD, PhD⁵, Dan Wassenaar, MD, PhD⁶

REVIEW

Open Access

Ketone bodies: from enemy to friend and guardian angel



Hubert Rahn^{1,2}, Kristin Gempel², Nereu Fölsing², Martina Leumann-Schaller³, Henner C. Schöberl⁴ and
Seyhan Merin^{1,2} *

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



SGLT2 Inhibitors

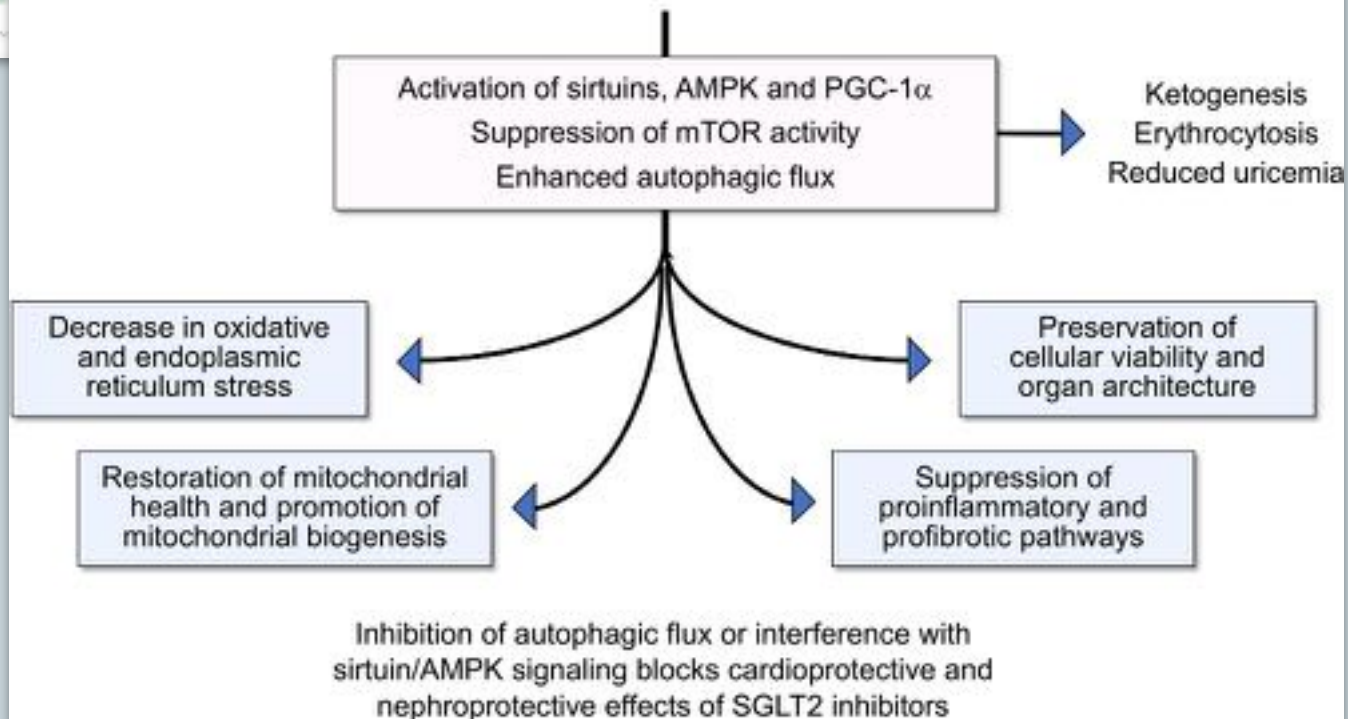
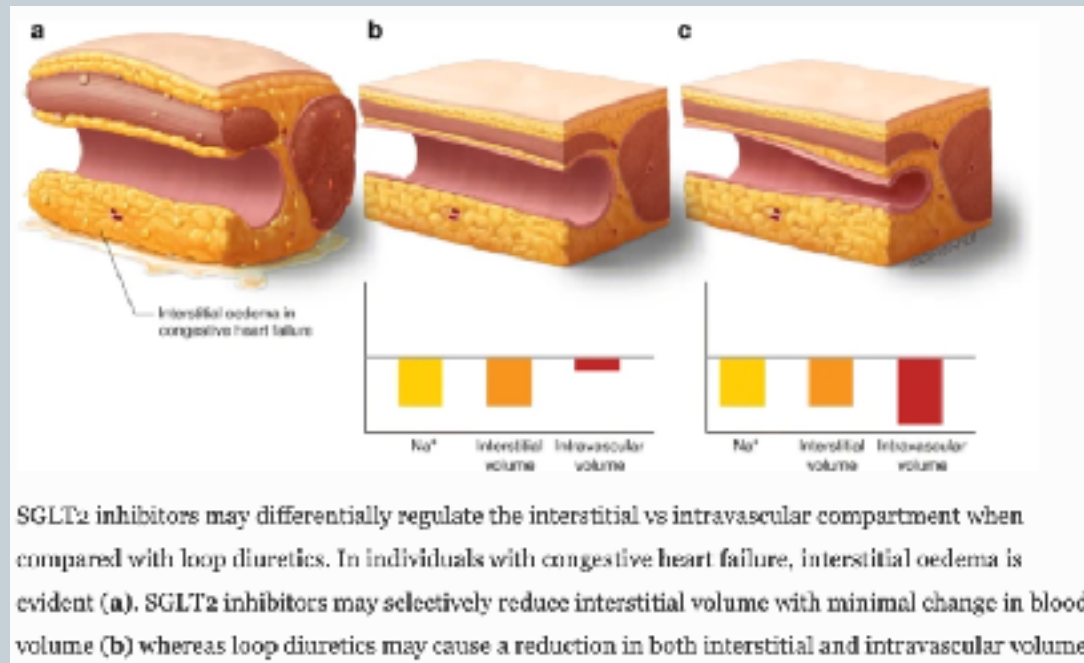


Diagram illustrating the proposed mechanism of action of the smart diuretic:

- INHIBITION OF SODIUM-HYDROGEN EXCHANGER
- ↑ MITOCHONDRIAL ENERGY EFFICIENCY
- “SMART DIURETIC”



iSGLT2 i układ współczulny



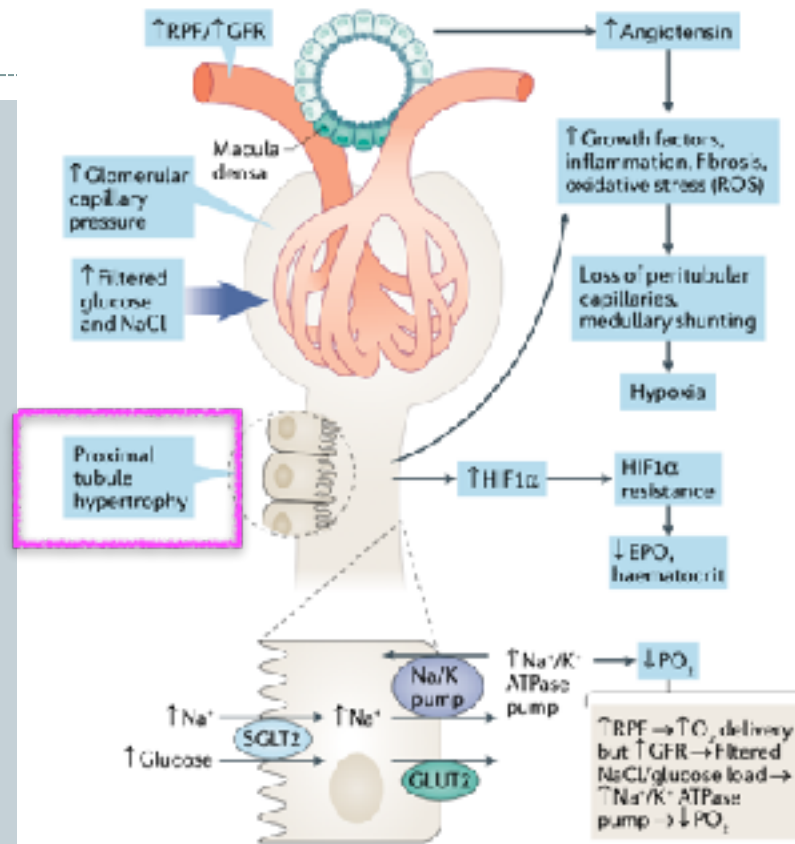
- iSGLT2 zmniejszają odruch neurohumoralny, który wywołują diuretyki pętlowe na skutek spadku objętości wewnątrznaczyniowej
- iSGLT2 nie zwiększają aktywności reninowej osocza

dlaczego?

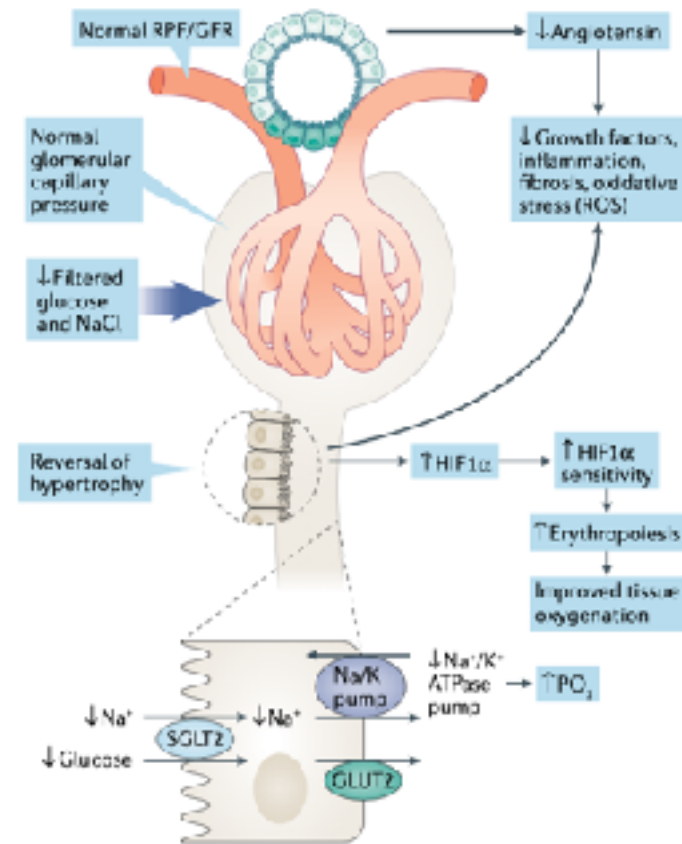


- występuje efekt kardioprotekcyjny, skoro iSGLT2 nie są zlokalizowane w sercu?
- należy stosować iSGLT2, skoro efekt diuretyczny wywołują.... diuretyki?
- w nefroprotekcji nie tylko wyhamowanie filtracji ma znaczenie?

a Diabetic kidney disease



b Diabetic kidney disease with SGLT2 inhibition



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. David Mazer, Gregory M.E. Hare, Philip W. Connolly, Richard E. Gilbert, Nadine Shehata, Adrian Quan, Hwee Teoh, Lawrence A. Leiter, Bernard Zelman, Peter Jini, Fei Zuo, Nikhil Misra, Krivka E. Thope, Ronald M. Goldenberg, Andrew T. Yan, Kim A. Connolly, and Suboch Yerna

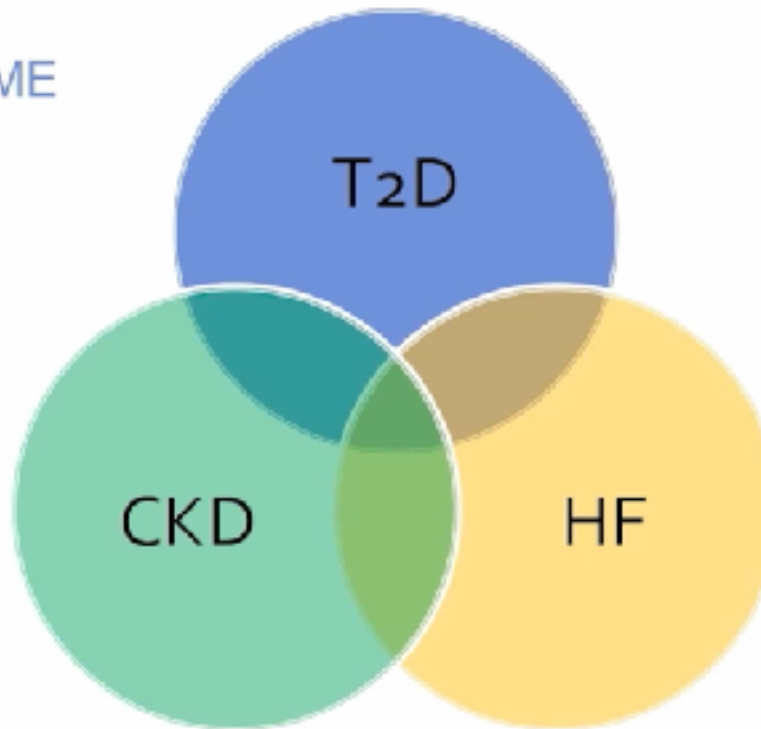
Originally published 11 Nov 2019 | <https://doi.org/10.1181/CIRCULATIONAHA.119.014036> | Circulation, JDrull

pacjent CRM
pełne spektrum działania iSGLT2



EMPA-REG OUTCOME
CANVAS
DECLARE-TIMI 58
VERTIS-CV

CREDENCE
DAPA-CKD
SCORED
EMPA-Kidney



DAPA-HF
EMPEROR-Reduced
SOLOIST
EMPEROR-Preserved
DELIVER

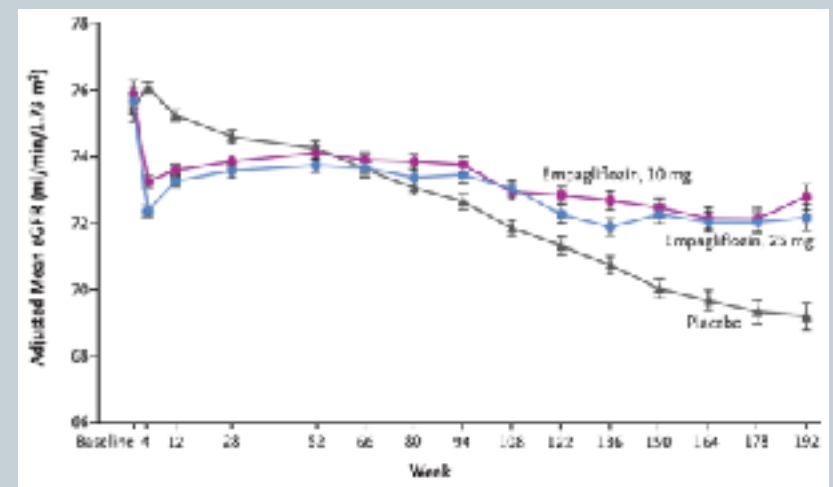
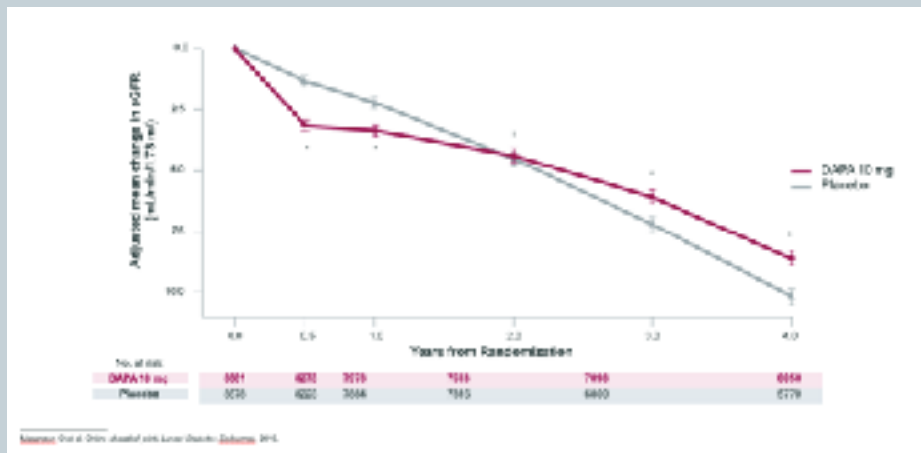
pacjent CRM (cardio-renal-metabolic)



iSGLT2

aspekty praktyczne

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



**Dapagliflozin and Cardiovascular Outcomes
in Type 2 Diabetes**

EMPHATICALLY, WE CAN SAY THAT THE
 DRUGS ARE THE KEY

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetics

Christopher Packer, M.D., Silvio L. Inzucchi, M.D., John M. Jakulin, M.D.,
 David Fickman, M.D., Michaela M. Gassmann, M.D.,
 Michaela Malinova, PhD, Renshaw, Carl P. Jorgensen, B.S., Ph.D.
 Hans-J. Vanders, M.C., Ulf C. Bevilacqua, B.S., Edward Zander, M.D.,
 for the EMPA-REG, EMPA-REG, EMPA-REG

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=32290)	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=30932)	275 (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)	■	

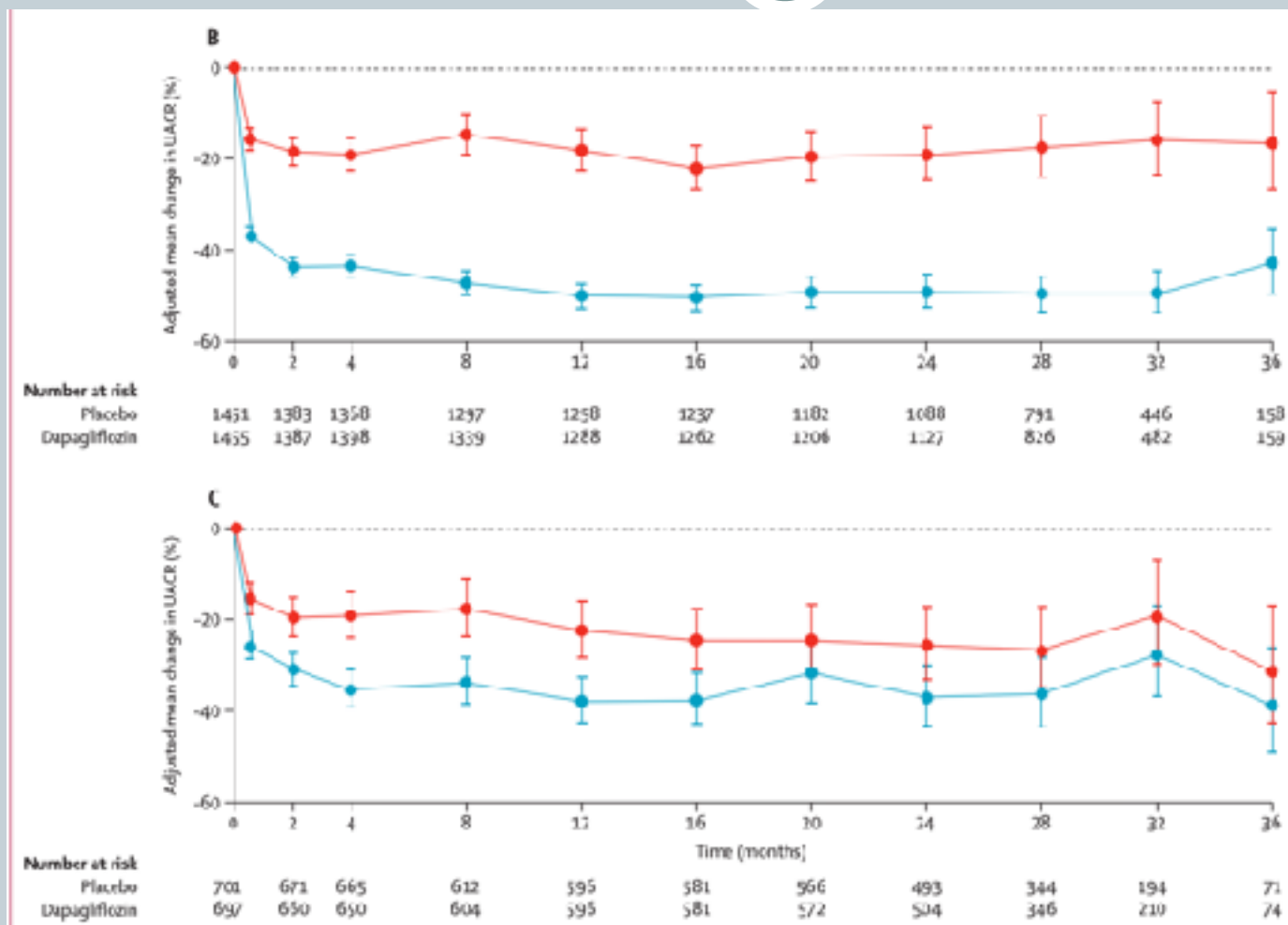
JAMA Internal Medicine | Original Investigation

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 N. Paik, MD, ScD, MPH; Ethan A. Hirsch, PhD; Elisabetta Di Lorenzo, MD, ScD

aspekty praktyczne zmiana w UACR

Lancet Diabetes Endocrinol
2020;9:755-66
Published Online
October 4, 2021
[https://doi.org/10.1016/S2213-8587\(21\)00343-6](https://doi.org/10.1016/S2213-8587(21)00343-6)



● 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 ^d	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)

Medical Risk Translation (2020) 1: 12
doi: 10.1038/s41530-020-0021-1



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



SGLT2 inhibitors and the risk of infections: a systematic review and meta-analysis of randomised controlled trials

Robert Packer¹, Massimo Giuseppe Sirtori^{2,3}, Gianni Gennari⁴, Laurent Nazarey^{5,6}, Diana R. L. Ho⁷, Erik Andersson^{8,9}

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Abstract

Aims There is concern about the infection-related safety profile of sodium-glucose co-transporter 2 (SGLT-2) inhibitors. We aimed to determine the effect of SGLT-2 inhibitors on urinary and other infections via systematic review and meta-analysis of randomised controlled trials (RCTs).

Methods We conducted a systematic search of Medline, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov to identify double-blind RCTs enrolling ≥ 40 patients with type 2 diabetes which compared SGLT-2 inhibitor to placebo or active comparator. Two independent reviewers extracted data and appraised study quality. Data were pooled using random-effects models.

Results Eighty-six RCTs involving 50,880 patients were included. SGLT-2 inhibitors increased the risk of genital infection compared to placebo (relative risk (RR) 3.17 95% CI 2.59–3.93, P 0.001) and active comparator (RR 3.05, 95% CI 2.14–4.42, P 0.001). The risk of urinary tract infection (UTI) was not increased with SGLT-2 inhibitors compared to placebo (RR 1.08, 95% CI 0.95–1.23, P 0.25) or active comparator (RR 1.08, 95% CI 0.95–1.23, P 0.25). In drug-specific analyses, only dapagliflozin 40 mg daily was associated with a significantly increased risk of UTI compared to placebo (RR 1.33, 95% CI 1.10–1.61, P 0.002). SGLT-2 inhibitors were associated with a reduced risk of gastroenteritis (RR 0.53, 95% CI 0.30–0.92, P 0.02) but not with the risk of respiratory tract infections.

Conclusions Compared to placebo, SGLT-2 inhibitors are associated with an increased risk of genital tract infections. Although there is no association with urinary tract infections and UTI, higher doses of dapagliflozin are associated with an increased risk.

Keywords Sodium-glucose co-transporter 2 (SGLT-2) inhibitor; Type 2 diabetes mellitus; Infections; Adverse events; Systematic review; Meta-analysis

Introduction

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors are a novel class of anti-hyperglycaemic agents used in the treatment of type 2 diabetes mellitus. The majority of

Managed by Academic Press.

Supplementary material for this article is available at <https://doi.org/10.1136/bmjopen-2018-025496>. It contains supplementary material, which is available to authorised users.

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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 Nuffield 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.

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

Josip A. Borucki^{1,2}, Tina Todorovic^{3,4}, Karim^{5,6}, Ivana Mustajica⁷, Marko Karamic⁸, Josko Badić⁹, Duska Glasnović⁹, Domenico D'Amico¹⁰

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³Department of Nephrology and Endocrinology, University Hospital of Split, Split, Croatia

⁴Department of Cardiology and Thoracic Sciences, IBCS Pericardium Policlínica & Gemelli, Università Cattolica SacroCuore, Rome, Italy

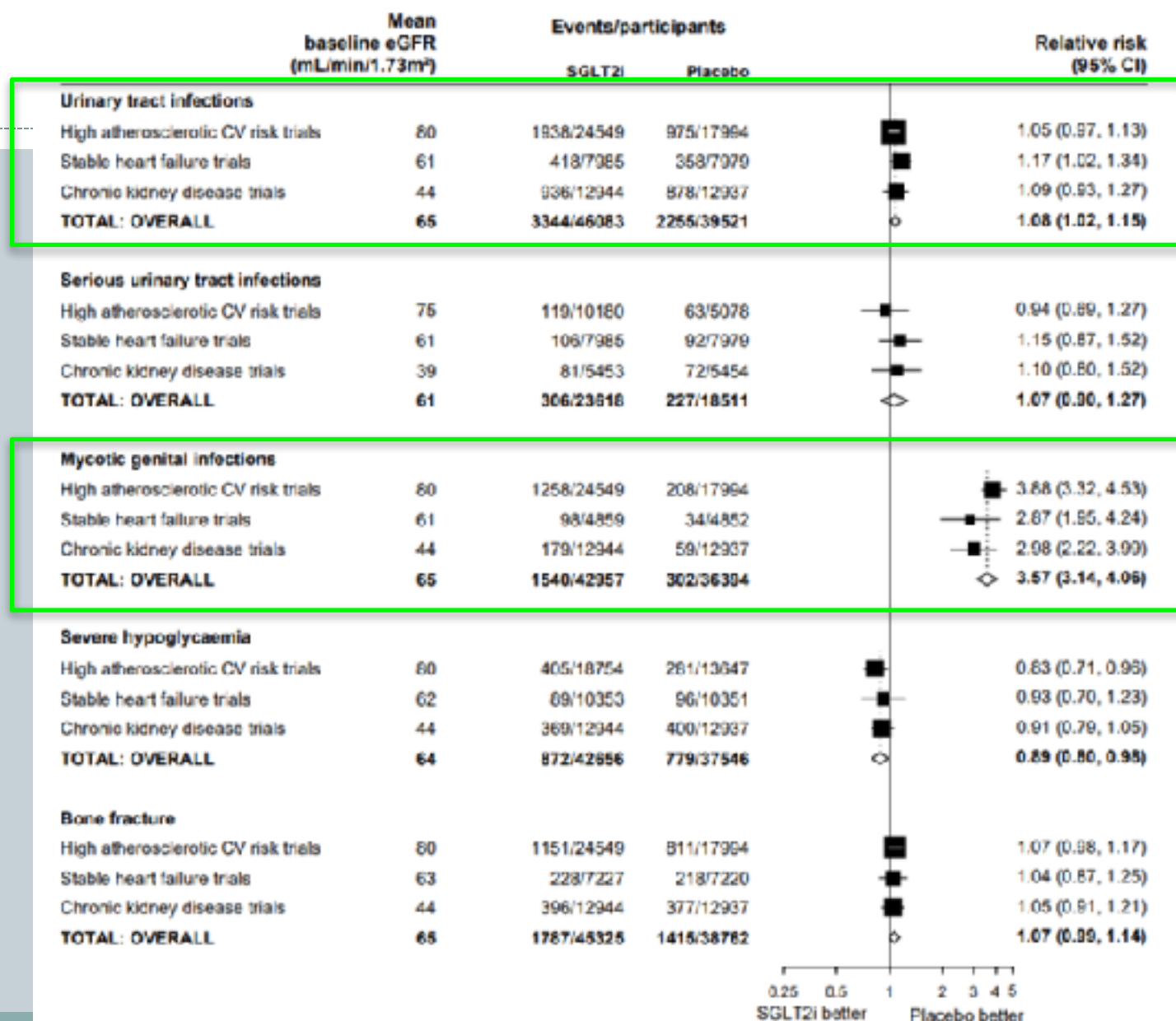
Open access

Research

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

Jennifer R Derrnan,¹ Catherine A Grandy,¹ Eugene Chibrikov,¹ Carlo A Mena,^{1,2} Kris Auvey-Basdar,³ Karissa Johnston,³ Michelle Swab,³ Jenna Hachey,¹ Denise C. Janssen,¹ Hui Huiyan,¹ John-Michael Gammon^{1,2}

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



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 Boer¹, Kamlesh Khunti², Tami Sadusky³, Katherine R. Tuttle⁴, Joshua J. Neumiller⁵,
Connie M. Rhee⁶, Sylvia E. Rosas⁷, Peter Rossing^{8,9} and George Bakris¹⁰

nowe rekomendacje ADA/KDIGO

04/10/2022

Lifestyle



Healthy diet



Physical activity



Smoking cessation



Weight management



First-line drug therapy

SGLT2i
(initiate if eGFR ≥ 20 ;
continue until dialysis
or transplant)

Metformin
(if eGFR ≥ 30)

**RAS inhibitor at maximum
tolerated dose (if HTN*)**

**Moderate- or
high-intensity statin**

Regular reassessment
of glycemia, albuminuria,
BF, CVD risk, and lipids

Additional risk-based therapy

GLP-1 RA if needed to
achieve individualized
glycemia target

**Other glucose-lowering
drugs** if needed to
achieve individualized
glycemia target

Nonsteroidal MRA[†] if
ACR ≥ 30 mg/g and
normal potassium

**Dihydropyridine CCB
and/or diuretic*†** if
needed to achieve
individualized BP target

Steroidal MRA if
needed for resistant
hypertension
if eGFR ≥ 15

**Antiplatelet
agent for
clinical ASCVD**

**Ezetimibe, PCSK9i,
or icosapent ethyl** if
indicated based on
ASCVD risk and lipids

■ T2D only
■ All patients
(T1D and T2D)

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 ^a	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 ^a (saxagliptin)	Intermediate	Low	Neutral	High
Insulin	Neutral	Neutral	Neutral	Highest	High	Gain	High (analog) 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

(dapagliflozyna)

NOWOŚĆ!

Cukrzyca typu 2

(Aktualizacja warunków refundacyjnych¹⁻⁴)

Cukrzyca typu 2, u pacjentów leczonych co najmniej dwoma lekami hipoglikemizującymi, z $HbA_{1c} \geq 7,5\%$ oraz bardzo wysokim ryzykiem sercowo-naczyniowym rozumianym jako:



potwierdzona choroba sercowo-naczyniowa

lub

uszkodzenie innych narządów objawiające się poprzez:



białkomoczą lub przerost lewej komory lub retinopatię

lub

obecność ≥ 3 głównych czynników ryzyka spośród:

- wiek ≥ 55 lat dla mężczyzn, wiek ≥ 60 lat dla kobiet
- dyslipidemia
- nadciśnienie tętnicze
- palenie tytoniu
- otyłość

Niewydolność serca

(wskazanie refundowane)¹⁻⁴



Przewlekła niewydolność serca u dorosłych pacjentów z obniżoną frakcją wyrzutową lewej komory serca (LVEF $\leq 40\%$)

oraz

utrzymującymi się objawami choroby w klasie II-IV NYHA pomimo zastosowania terapii opartej na ACEi (lub ARB/ARNi)

i

lekach z grupy beta-adrenolityków oraz jeśli wskazane u antagonistach receptora mineralokortykoidów

Przewlekła choroba nerek

(wskazanie refundowane)¹⁻⁴



Przewlekła choroba nerek u dorosłych pacjentów z:

- $eGFR < 60 \text{ mL/min/1,73 m}^2$
- albuminuria (UACR) $\geq 200 \text{ mg/g}$
- oraz leczonych terapią opartą na ACEi/ARB nie krócej niż 4 tygodnie lub z przeciwwskazaniami do tych terapii

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

kryteria refundacyjne DM2



- **Rozszerzenie aktualnego wskazania refundacyjnego, tj.:**
- zmniejszenie wymogu z $\text{HbA1c} \geq 8,0\%$ na $\text{HbA1c} \geq 7,5\%$
- 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 Boer¹, Kamlesh Khunti², Tami Sadosky³, Katherine R. Tuttle⁴, Joshua J. Neumiller⁵,
Connie M. Rhee⁶, Sylvia E. Rosas⁷, Peter Rossing^{8,9} and George Bakris¹⁰

Who and when to screen?

T1D Yearly starting 5 years after diagnosis

T2D Yearly starting at diagnosis

How to screen?



Spot urine ACR



and

eGFR

What to do with a positive result?



Repeat and confirm:

- Evaluate possible temporary or spurious causes
- Consider using cystatin C and creatinine to more precisely estimate GFR
- Only persistent abnormalities define CKD



Initiate evidence-based treatments

What defines CKD diagnosis?



Persistent urine ACR ≥ 30 mg/g
and/or



Persistent eGFR < 60 mL/min/1.73 m²
and/or



Other evidence of kidney damage

iSGLT2 w praktyce



Journal of the American Heart Association

Volume 11, Issue 5, 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



Tamara T. Milder^{1,2,3,4,5}, Sophie L. Stocker^{6,7}, Melissa Royce⁸, Richard O. Day^{9,10}, Jerry R. Greenfield^{11,12}

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

News | Medicine | Medical News

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

Patricia M. Zetter, PhD
February 27, 2023

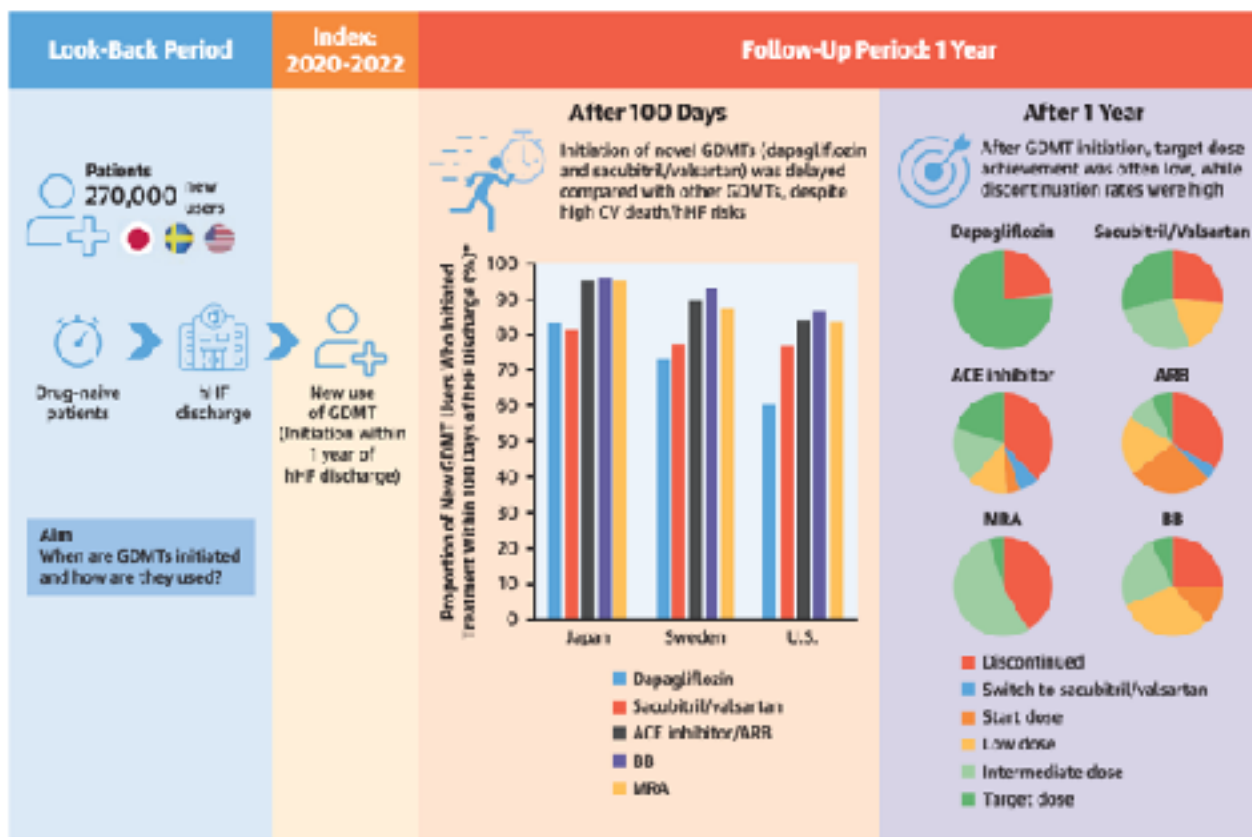
[Access to Small, NJ](#)

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



CENTRAL ILLUSTRATION Initiation, Titration to Target Dose, and Discontinuation of GDMTs Among New Users of GDMTs After hHF, in Japan, Sweden, and the United States



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

stosowanie iSGLT2 - wskazówki praktyczne



KI REPORTS
ki-reports.org

Prescribing SGLT2 Inhibitors in Patients With CKD: Expanding Indications and Practical Considerations

Edvin Yau^{1,2,3}, Ali Uthman^{1,2,3}, Ibrahim Altawy^{1,2} and David Z.L. Cheng^{1,2}

¹Division of Nephrology, Department of Medicine, University Health Sciences, Toronto, Ontario, Canada and ²Department of Medicine, University of Toronto, Toronto, Ontario, Canada

- iSGLT2 to leki bezpieczne
- iSGLT2 to leki o działaniu plejotropowym
- iSGLT2 to leki **3 w 1** (kardio-nefroprotekcja 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 **ACR** wyjaśnić pacjentowi skutki stosowania leku - nasilona diureza (nagła), **parcie na pęcherz (pacjent kojarzy z infekcją)**
- czasowe wstrzymanie leku przed dużym zabiegiem operacyjnym

Neuen B et al. CMAJ 2019 October 15;191:E1128-3

<https://kdigo.org/guidelines/diabetes-ckd/>

Puckrin R et al. Acta Diabetol, 2018 May;55(5):503-514