Redefining diabetic management based on new prospective trial (CREDENCE): time for paradigm shift

臺北市立聯合醫院 新陳代謝科
廖國盟

CAN-SLK-20180815

臨床情境

- 64 y/o male patient
- Type 2 DM since 1990
- BH: 172 cm
- BW: 77 kg
- BMI: 26
- CAD(-), CHF(-)

Brief history

- HTN(+), Hyperlipidemia (+)
- Glucophage 850 1# bid+ Januvia 100# qd
- A1c around 6.5-7.1 during 2017-2018
- Cr 1.3 , eGFR 55
- UP(+) ACR 352.7 mg/g

Question

你會把這個人的DPP-4i，

換成 SGLT-2i嗎？

爭議

- 以血糖控制的立場，換了SGLT-2i控制不一定比較好 (glucocentric)

- 以器官保護的立場，值得更換 (cardiocentric)

Glucocentric v.s Cardiocentric

降血糖帶來的
器官保護效果
并非線性

血糖 8%或9&以上，
積極控糖可以大幅降
低心腎血管疾病風險

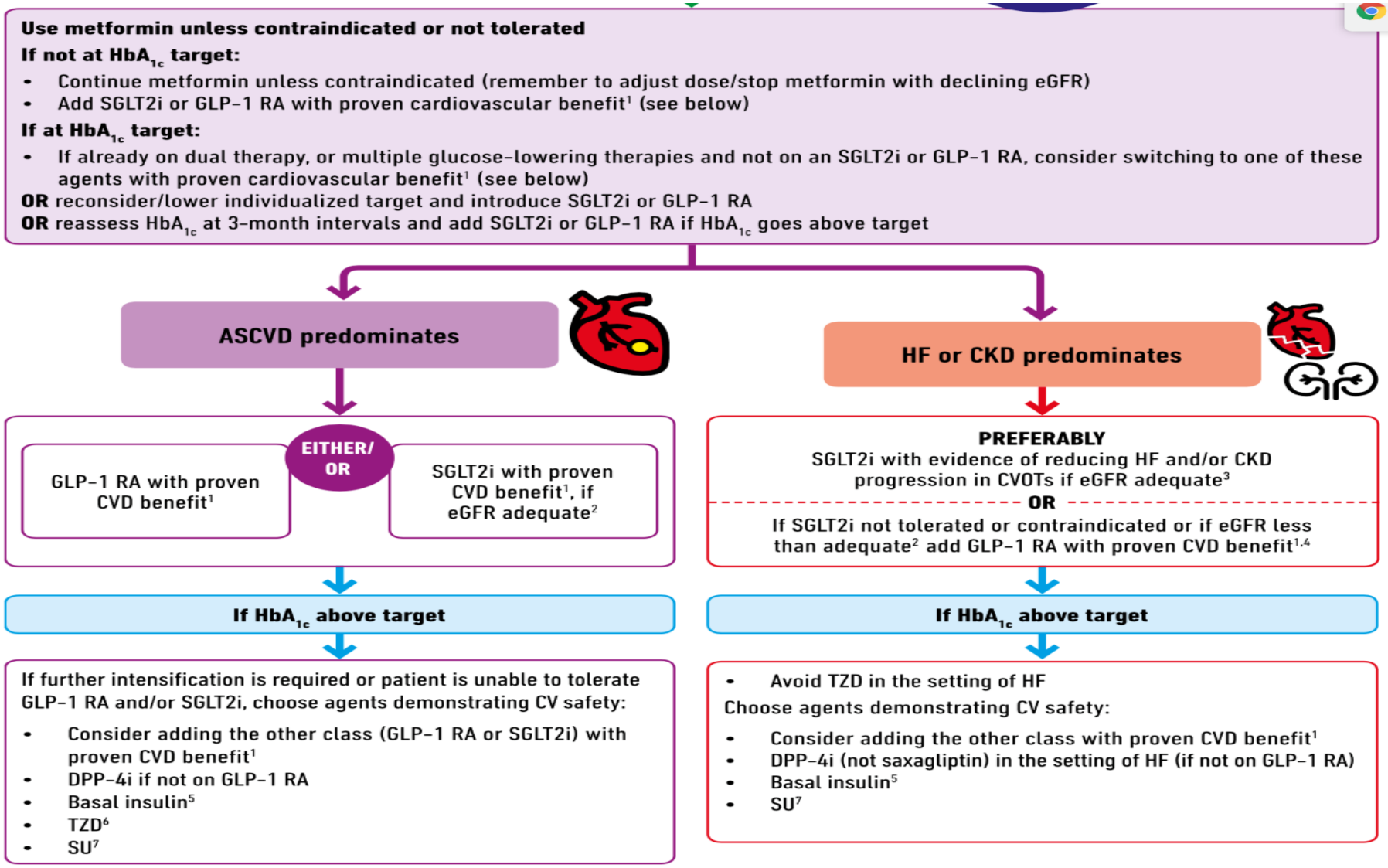
血糖控制在7%或8%以下，積極
血糖控制帶來器官保護效果有限
此時更需要使用SGLT2i這類本身
有器官保護效果的藥物

Meta科觀念
血糖最重要

CV科觀念，
血糖不重要

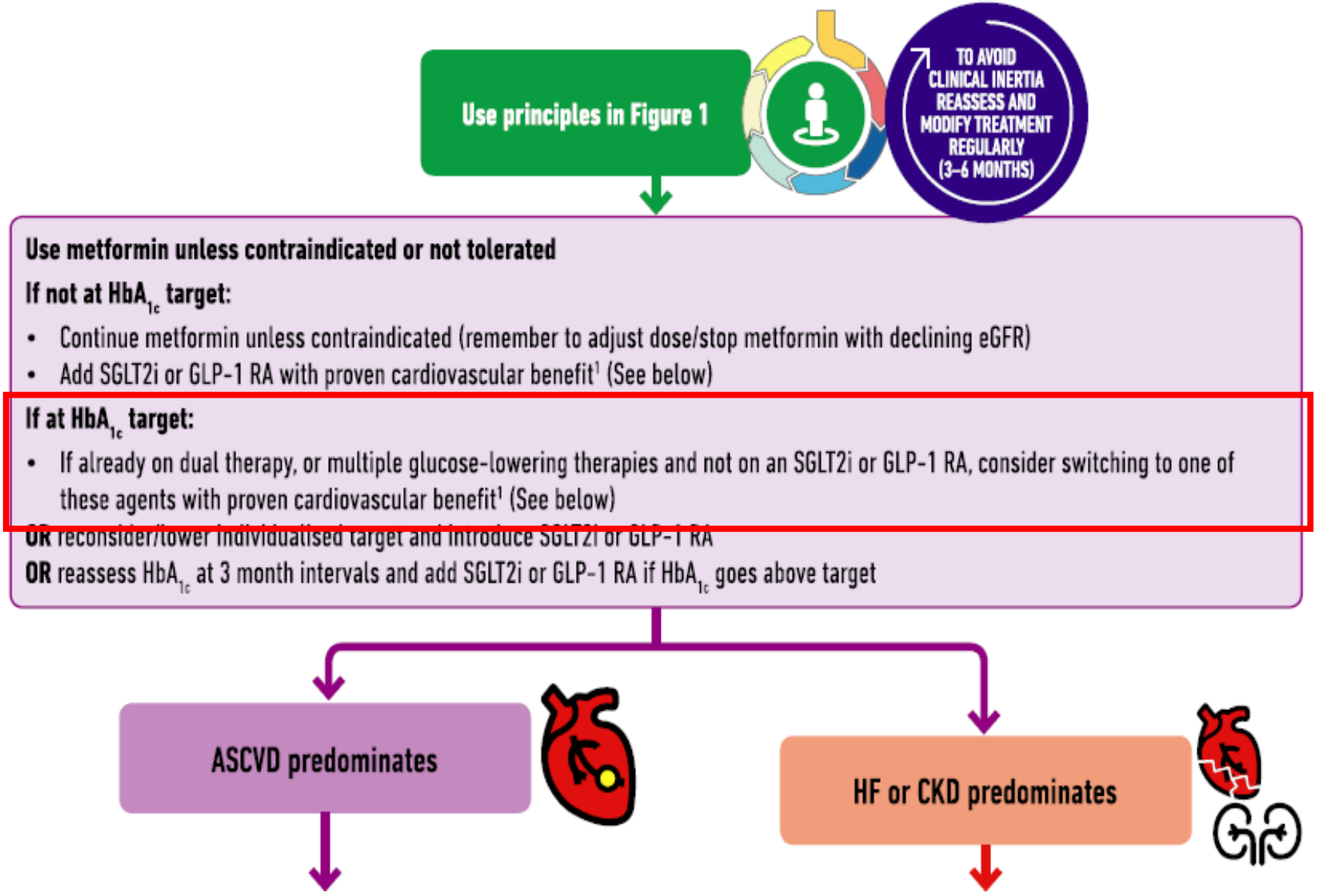
Nat Rev Dis Primers. 2015 Jul 30;1:15018. doi: 10.1038/nrdp

ADA guideline



Diabetes Care 2012; 35:1364-1379c

ADA guideline



For patients have ASCVD, HF or CKD and GFR is adequate

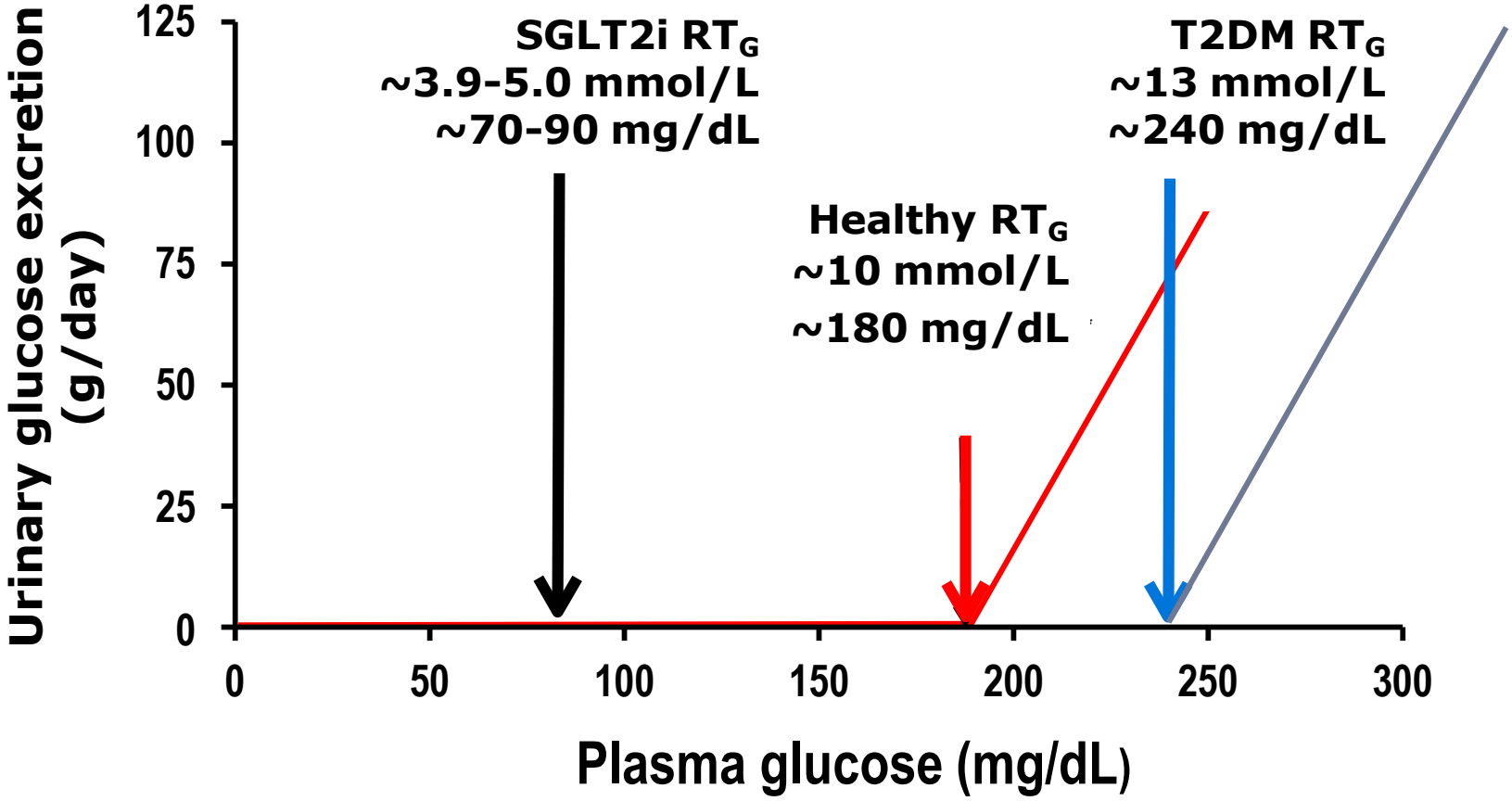
- If at A1c target: switching
- If not at A1c target: add on

SGLT2i 器官保護效果

- **Dissociation of organ protection and A1c lowering effect**

SGLT-2 i 降 A1c 最重要的 predictor 是什麼？

Renal Glucose Reabsorption



SGLT2i 血糖降低效果

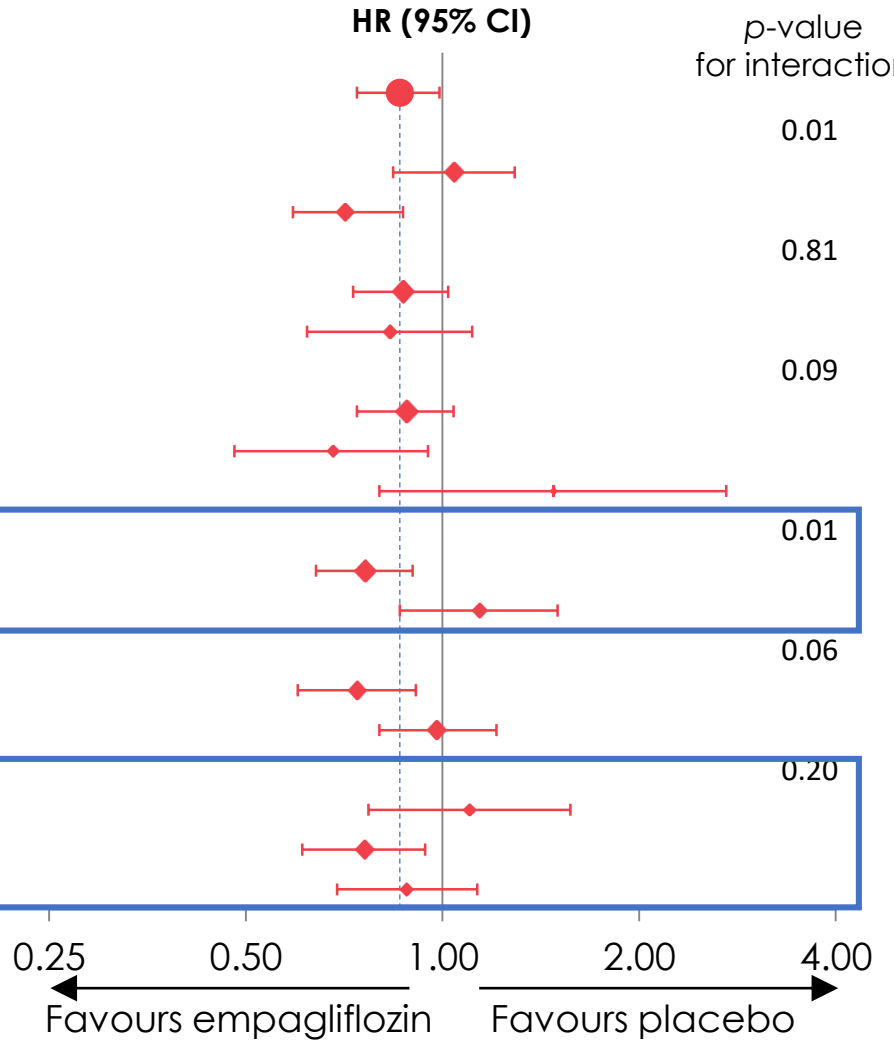
- SGLT2 排糖效果 (mg/min)=GFR (cc/min)* Blood sugar (mg/100cc)

- GFR , A1c → 決定SGLT2 效果

- GFR >90, A1c > 9→ strong responder
- GFR 60-90, A1c 7-9 → average responder
- GFR <60 A1c < 7 → poor responder

3-point MACE: subgroup analysis

	Empagliflozin	Placebo	p-value for interaction
All patients	4687	2333	
Age, years			0.01
<65	2596	1297	
≥65	2091	1036	
Sex			0.81
Male	3336	1680	
Female	1351	653	
Race			0.09
White	3403	1678	
Asian	1006	511	
Black/African-American	237	120	
HbA1c, %			0.01
<8.5	3212	1607	
≥8.5	1475	726	
Body mass index, kg/m^2			0.06
<30	2279	1120	
≥30	2408	1213	
eGFR, mL/min/1.73m^2			0.20
≥90	1050	488	
60 to <90	2425	1238	
<60	1212	607	

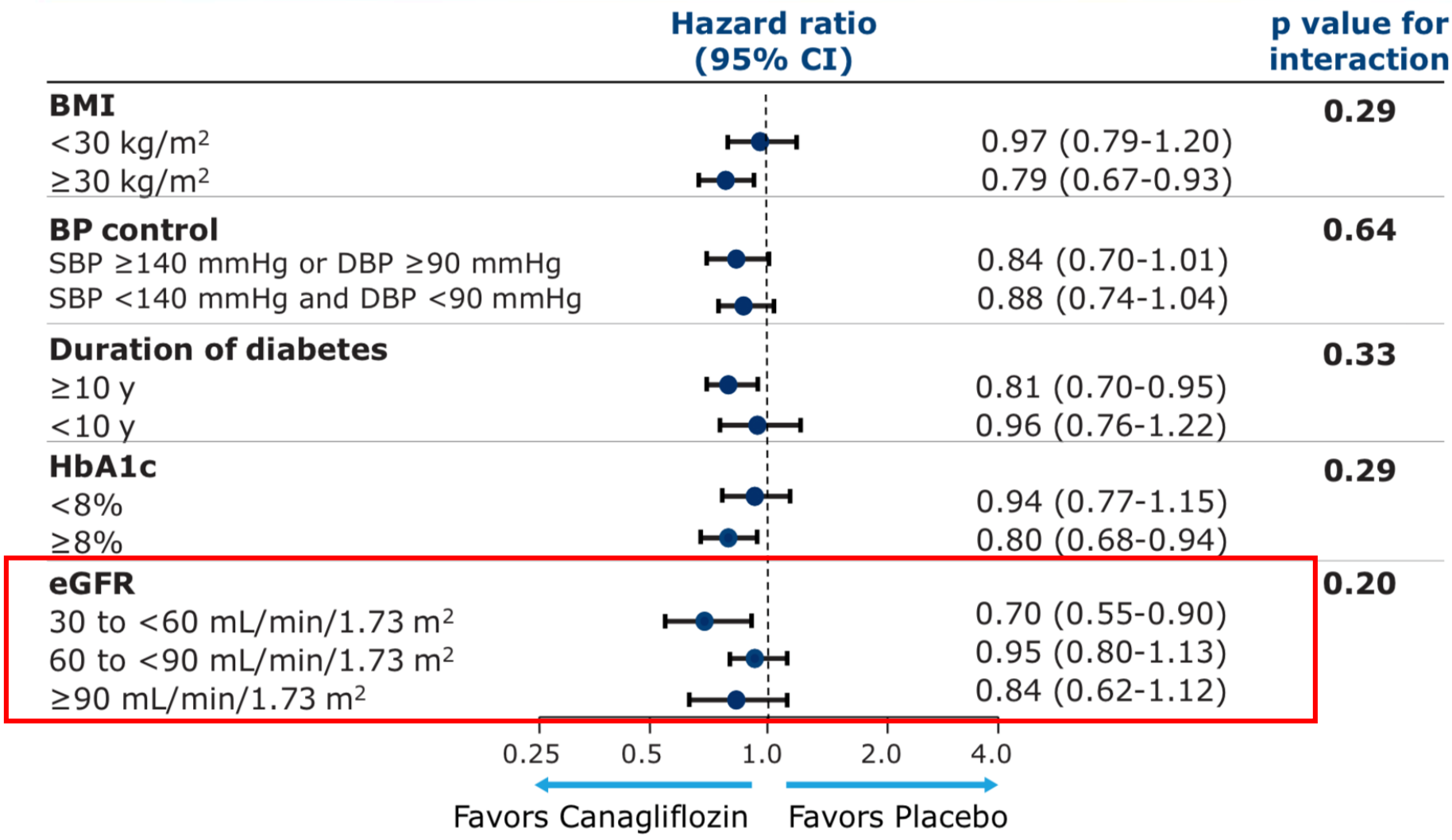


For the test of homogeneity of the treatment group difference among subgroups with no adjustment for multiple tests.
eGFR, estimated glomerular filtration rate (according to Modification of Diet in Renal Disease equation) Zinman B et al; N Engl J Med 2015; 373:2117-28.

"Safety update information. Product is not approved for CV risk reduction."

EMPA-REG OUTCOME®

Risk Factor Subgroups (Primary Outcome)



Intent-to-treat analysis

CANVAS Program

SGLT2i 器官保護效果

- SGLT-2i
- 降糖效果
- eGFR > 90 → 好
- > 60→ 可
- < 60 → 幾乎無效
- 器官保護效果→ eGFR > 30
- 器官保護機制, 一定有除了排糖之外的原因

SGLT2i 器官保護效果

	GFR30- 60	GFR>60
降糖	+	+++
心臟保護	++++	+++
腎臟保護	++++	++++
中風保護(cana)	+++	++
降體重	++	++
降血壓	++	+

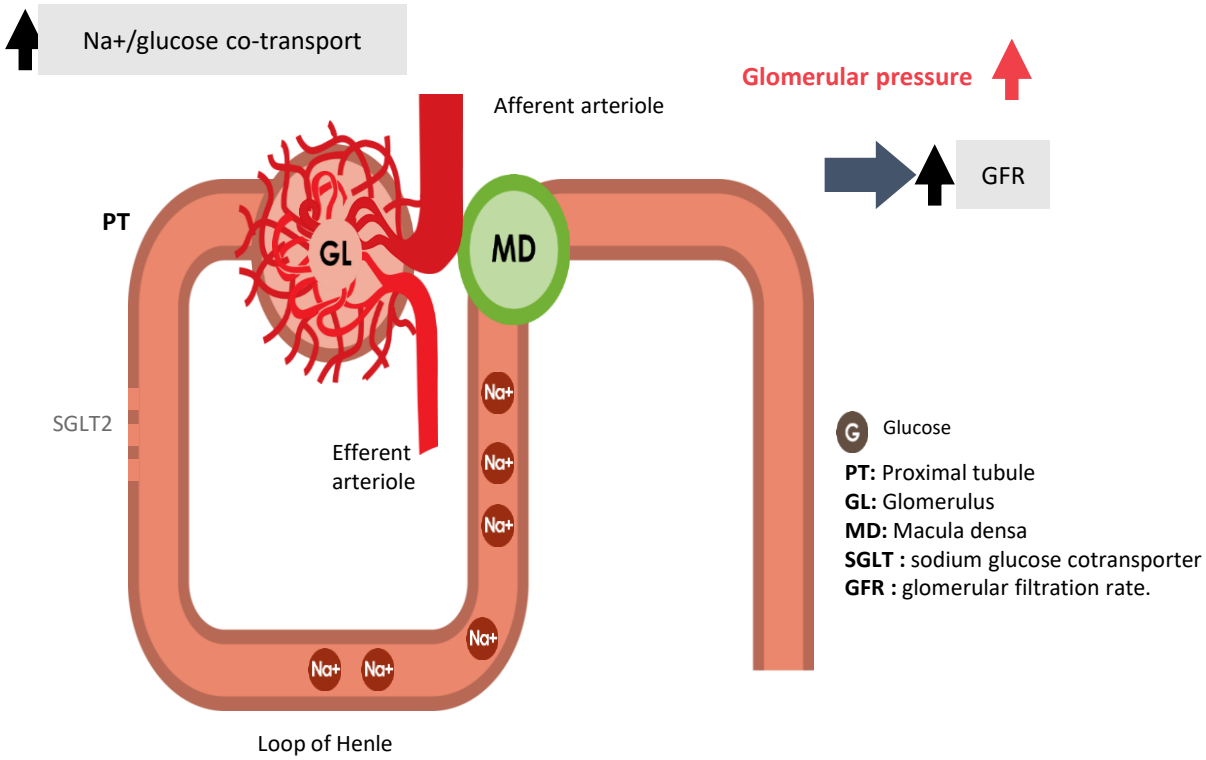
非常好的器官保護 不夠好的降糖

好的降糖藥 好的器官保護藥

Possible mechanisms for renal protective effect of SGLT-2i

- TGF
- Renal ischemia and EPO
- Oxidative stress

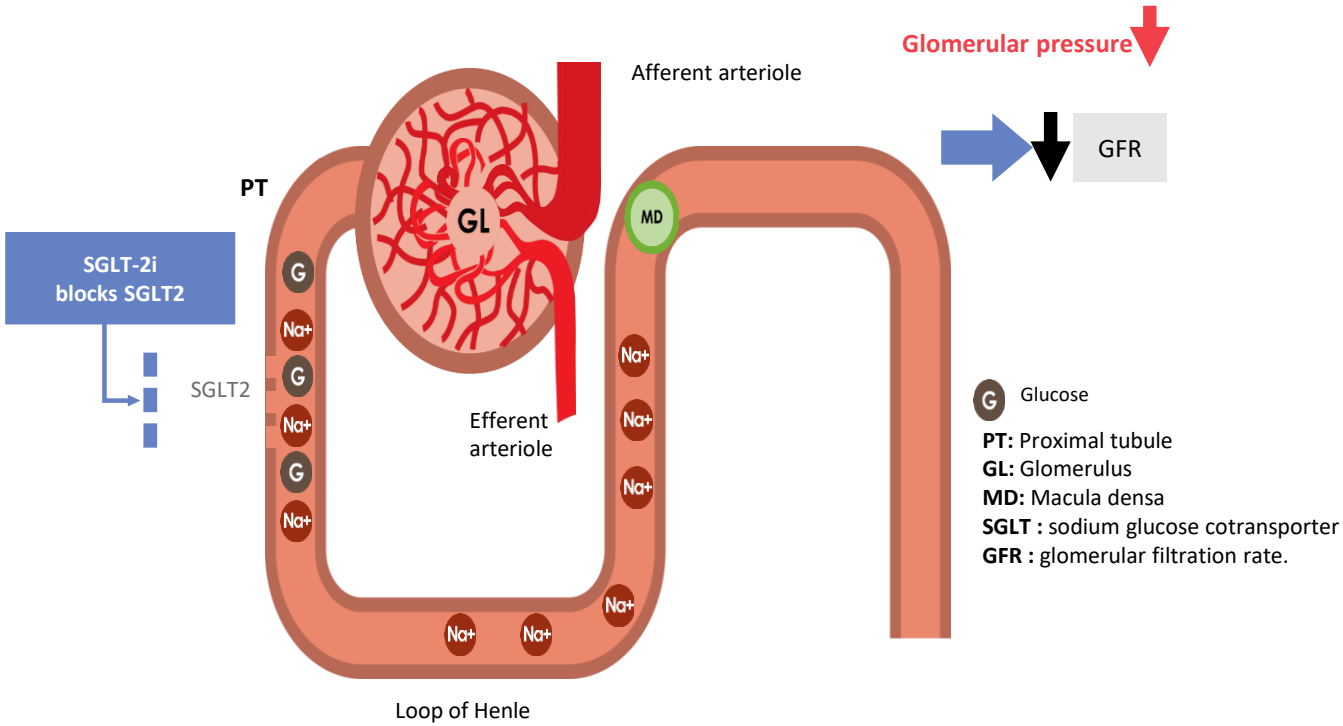
Diabetes may cause glomerular hypertension



Renal hemodynamics under hyperglycemia

Adapted from: Cherney D et al. Circulation 2014;129:587

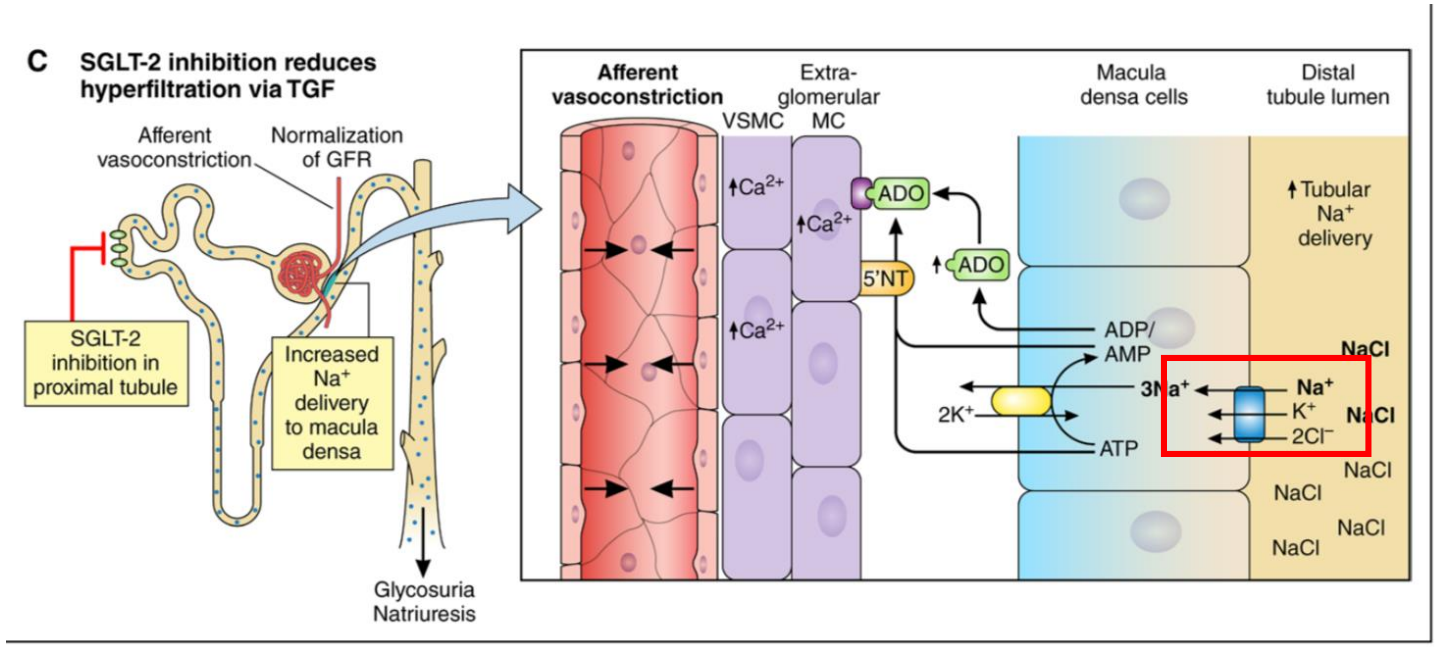
SGLT2 lowers intraglomerular pressure in T1D



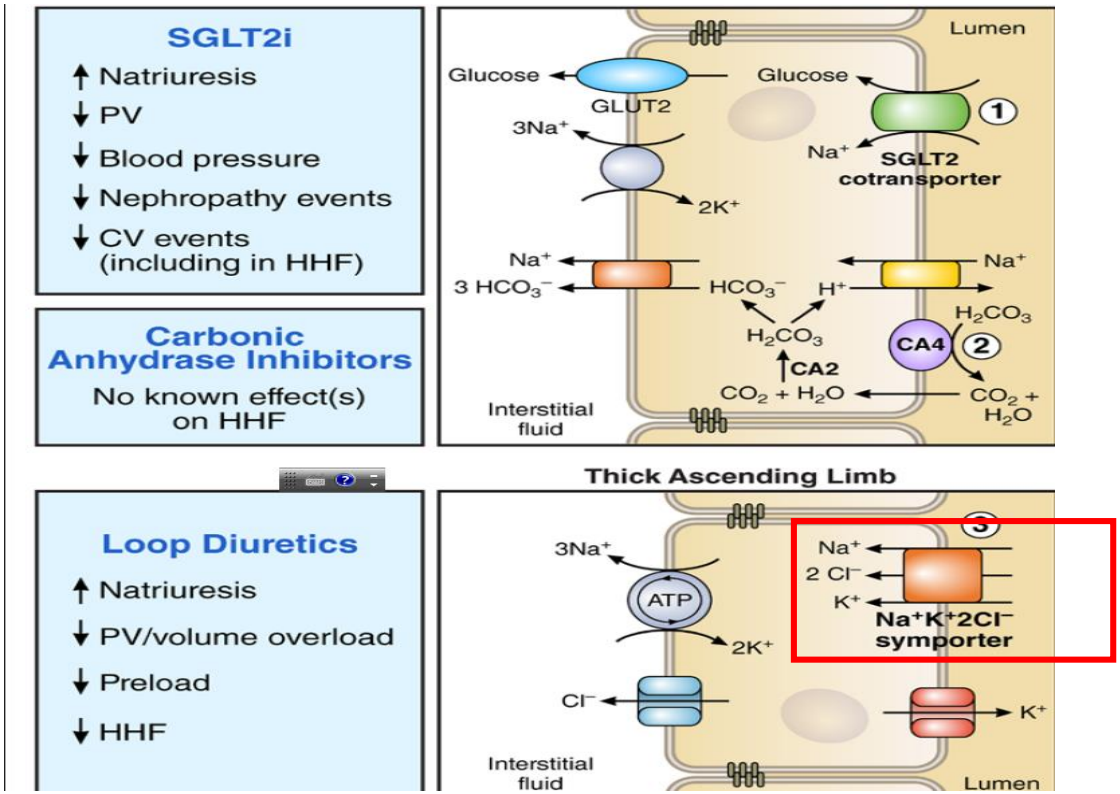
Renal hemodynamics with SGLT-2

Adapted from: Cherney D et al. Circulation 2014;129:587

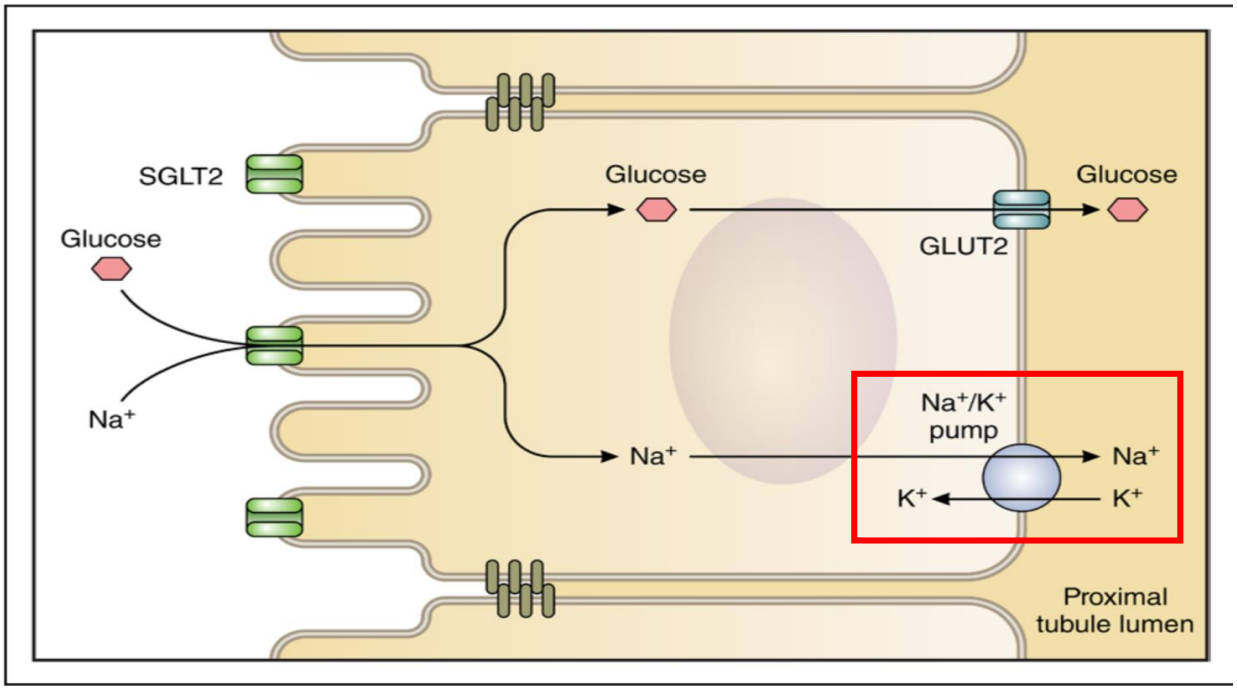
tubular glomerular feedback



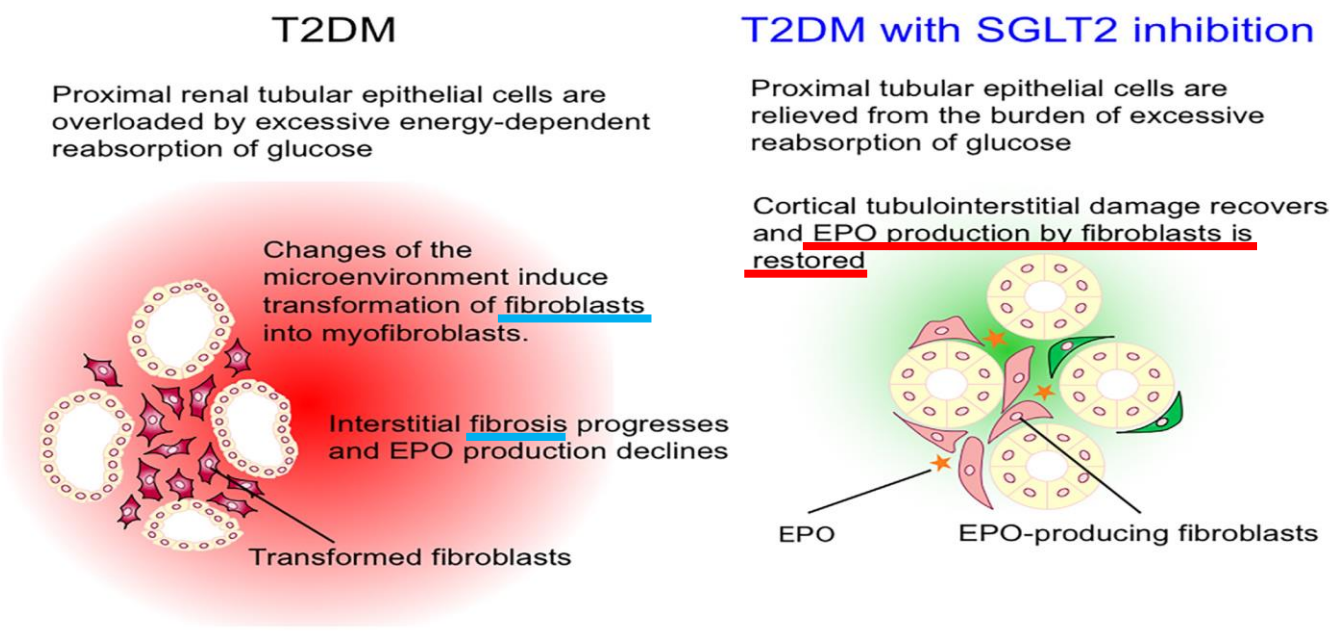
Why loop diuretic can't induce TGF



Renal ischemia and EPO



SGLT-2i therapy suppresses oxygen consumption by the proximal tubules and improves tubulointerstitial hypoxia



1. Sano M. J Cardiol. 2018 May; 71(5): 471-476.; 2. Sano M, Takei M et al. J Clin Med Res. 2016 Dec; 8(12): 844-847.

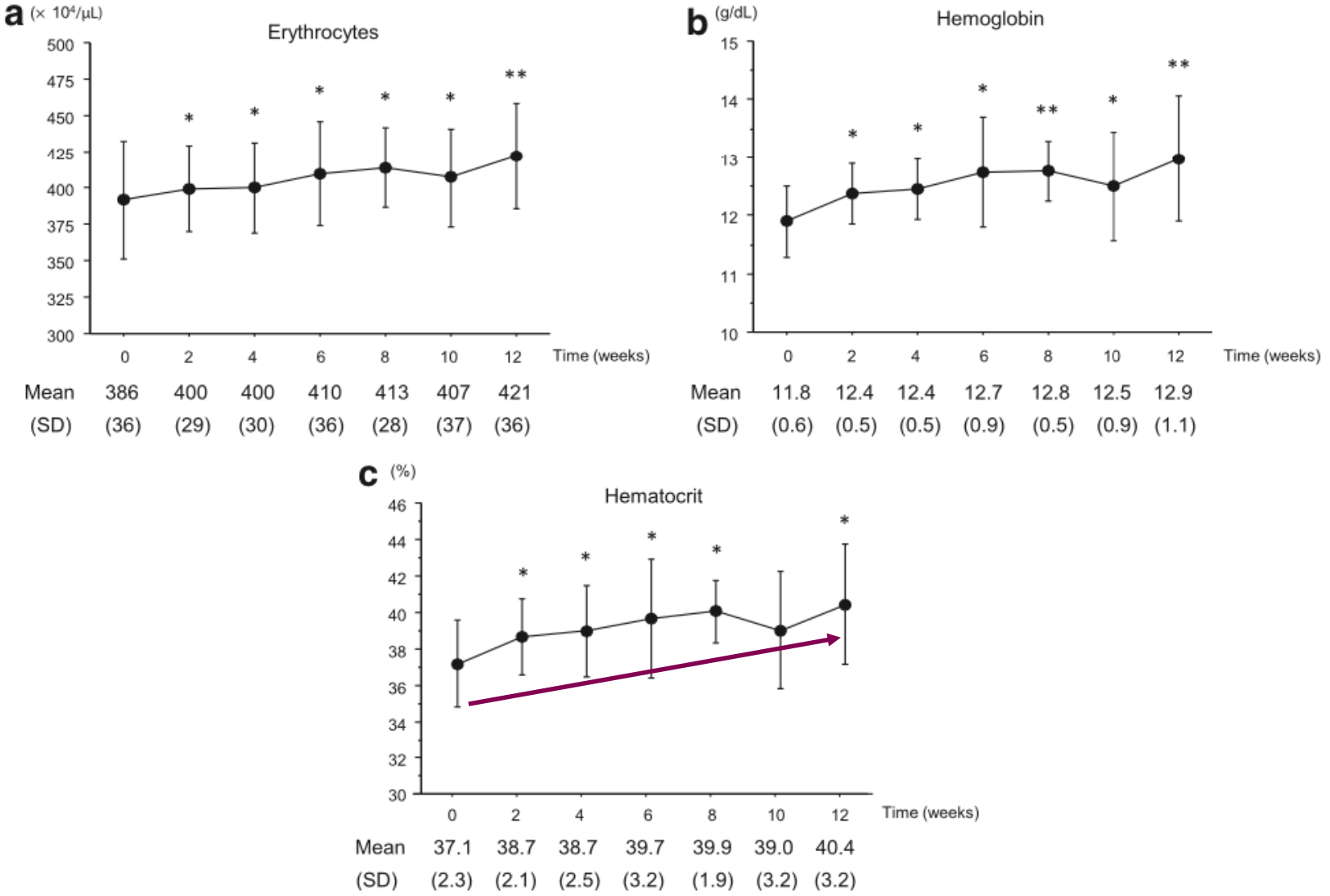
Canagliflozin Improves Erythropoiesis in Diabetes Patients with Anemia of Chronic Kidney Disease

Takashi Maruyama, MD, PhD, Hiroyuki Takashima, MD, Hidetaka Oguma, MD, Yoshihiro Nakamura, MD, Michiko Ohno, MD, Kei Utsunomiya, MD, Tetsuya Furukawa, MD, Ritsukou Tei, MD, and Masanori Abe, MD, PhD

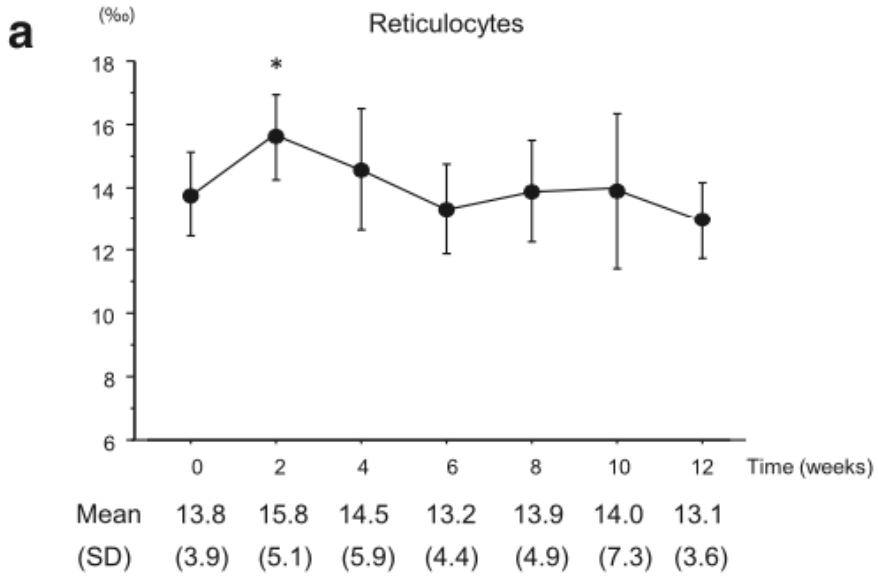
Abstract

Background: We evaluated the erythropoietic effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, in type 2 diabetes patients with anemia of chronic kidney disease.
Methods: Nine diabetes patients were enrolled and administered 100 mg canagliflozin once a day for 12 weeks. The patients received fixed doses of conventional antidiabetic drugs and renin-angiotensin system inhibitors for 8 weeks before enrollment; these drugs were continued during the study. Endpoints were changes in erythropoiesis parameters, including erythrocyte and reticulocyte count, hemoglobin, hematocrit, and serum erythropoietin (EPO) concentration from baseline to 12 weeks. All variables were measured every 2 weeks.
Results: Serum EPO concentration increased by 38 [15–62]% ($P=0.043$) between baseline and 2 and 4 weeks. Reticulocyte count transiently increased at 2 weeks. Erythropoiesis occurred after 2 weeks of canagliflozin treatment. Erythrocyte count (from $386\pm36\times10^4/\mu$L to $421\pm36\times10^4/\mu$L; $P=0.0009$), hemoglobin (from 11.8 ± 0.6 g/dL to 12.9 ± 1.1 g/dL; $P=0.0049$), and hematocrit (from $37.1\pm2.3\%$ to $40.4\pm3.2\%$; $P=0.002$) increased from baseline to study completion. Although there were no significant changes in transferrin saturation, serum ferritin levels were decreased ($P=0.003$).
Conclusions: Canagliflozin treatment led to an improvement in erythropoiesis in patients with impaired kidney function. The effect on erythropoiesis appeared to be due to an EPO production-mediated mechanism and might be independent of glycemic control; however, further studies are needed to clarify this since the present study had a small sample size and no comparator group.

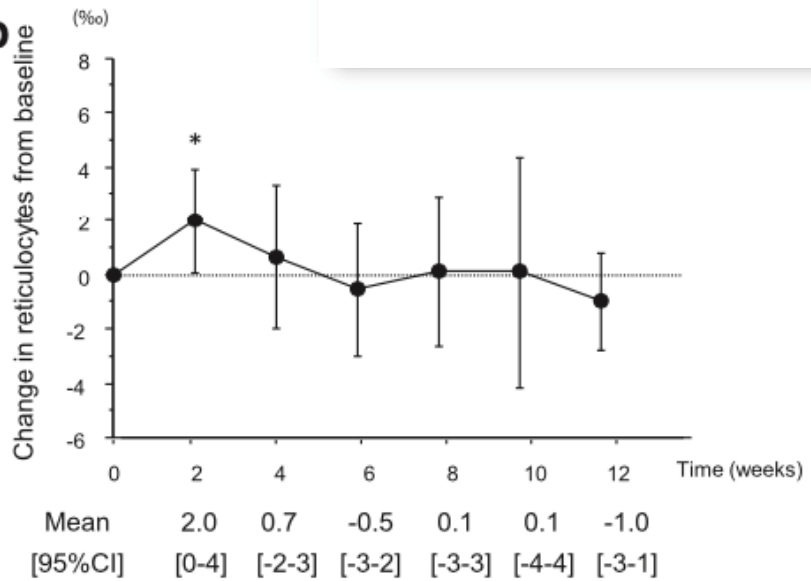
Keywords: Canagliflozin, Chronic kidney disease, Erythropoiesis, Erythropoietin, Renal anemia, Type 2 diabetes.



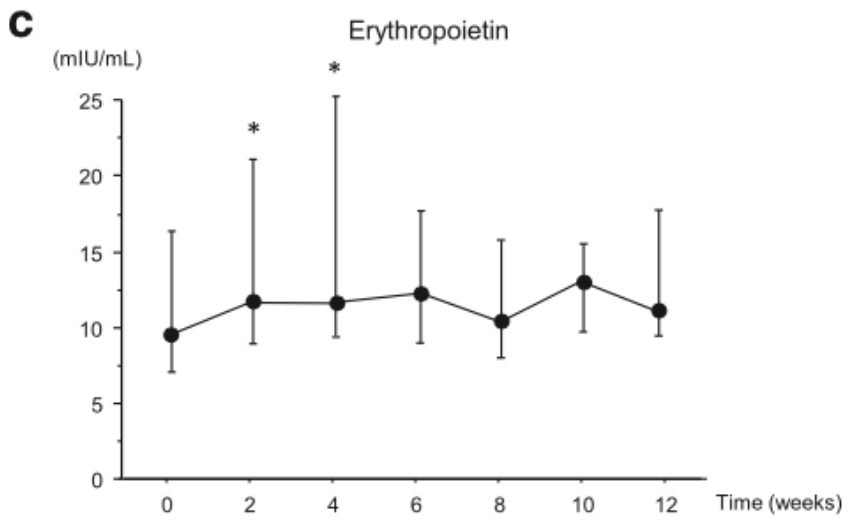
G. 1. Change in erythropoiesis profiles. **(a)** Changes in erythrocyte count at each time point. Data are expressed as an ± SD. **(b)** Changes in hemoglobin level at each time point. Data are expressed as mean ± SD. **(c)** Changes in matocrit level at each time point. Data are expressed as mean ± SD. $*P < 0.05$; $**P < 0.01$ versus baseline. SD, standard viation.



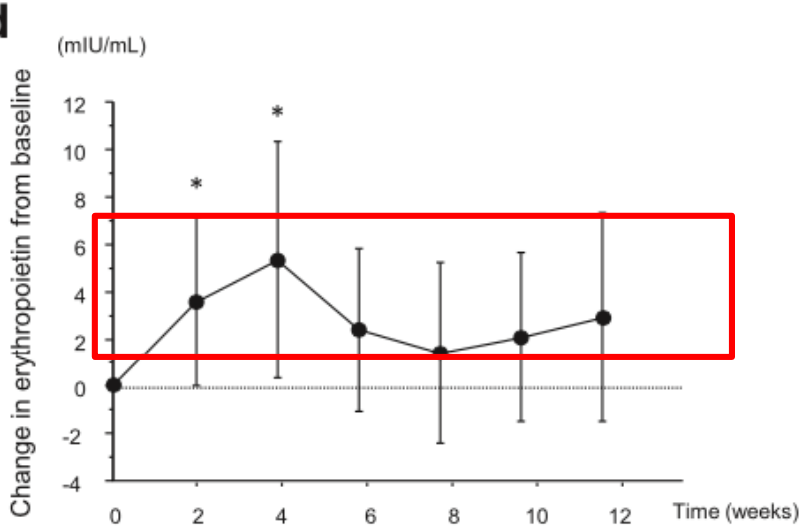
	0	2	4	6	8	10	12
Mean	13.8	15.8	14.5	13.2	13.9	14.0	13.1
(SD)	(3.9)	(5.1)	(5.9)	(4.4)	(4.9)	(7.3)	(3.6)



	0	2	4	6	8	10	12
Mean	2.0	0.7	-0.5	0.1	0.1	-1.0	
[95%CI]	[0-4]	[-2-3]	[-3-2]	[-3-3]	[-4-4]	[-3-1]	



	0	2	4	6	8	10	12
Median	9.6	12.2	11.4	11.7	9.9	13.0	11.4
[IQR]	[7-18]	[9-22]	[9-25]	[9-17]	[8-16]	[10-15]	[9-18]



	0	2	4	6	8	10	12
Mean	3.6	5.3	2.4	1.4	2.1	2.9	
[95%CI]	[0-7]	[0-10]	[-1-6]	[-2-5]	[-1-6]	[-1-7]	

Univariable analysis show changes from baseline in hematocrit and hemoglobin mediated the most on the HR for CV Death in EMPA REG

	HR for CV death with empagliflozin vs. placebo (95% CI)	Percentage mediation
Unadjusted	0.615 (0.491, 0.770)	
Adjusted for		
HbA_{1c}	0.624 (0.496, 0.785)	3.0
FPG	0.665 (0.529, 0.837)	16.1
SBP	0.593 (0.473, 0.743)	−7.5
DBP	0.614 (0.490, 0.769)	−0.3
Heart rate	0.621 (0.495, 0.780)	2.0
LDL-C	0.596 (0.475, 0.748)	−6.5
HDL-C	0.636 (0.506, 0.799)	6.9
logTG	0.604 (0.482, 0.758)	−3.7
FFAs	0.586 (0.463, 0.741)	−9.9
logUACR	0.649 (0.518, 0.815)	11.1
eGFR (MDRD)	0.631 (0.504, 0.790)	5.3
eGFR (CKD-EPI)	0.632 (0.505, 0.791)	5.6
Weight	0.579 (0.461, 0.727)	−12.4
BMI	0.578 (0.460, 0.726)	−12.8
WC	0.598 (0.477, 0.750)	−5.8
Hematocrit	0.791 (0.626, 1.000)	51.8
Hemoglobin	0.780 (0.619, 0.983)	48.9
Albumin	0.696 (0.555, 0.873)	25.5
Uric acid	0.693 (0.553, 0.869)	24.6

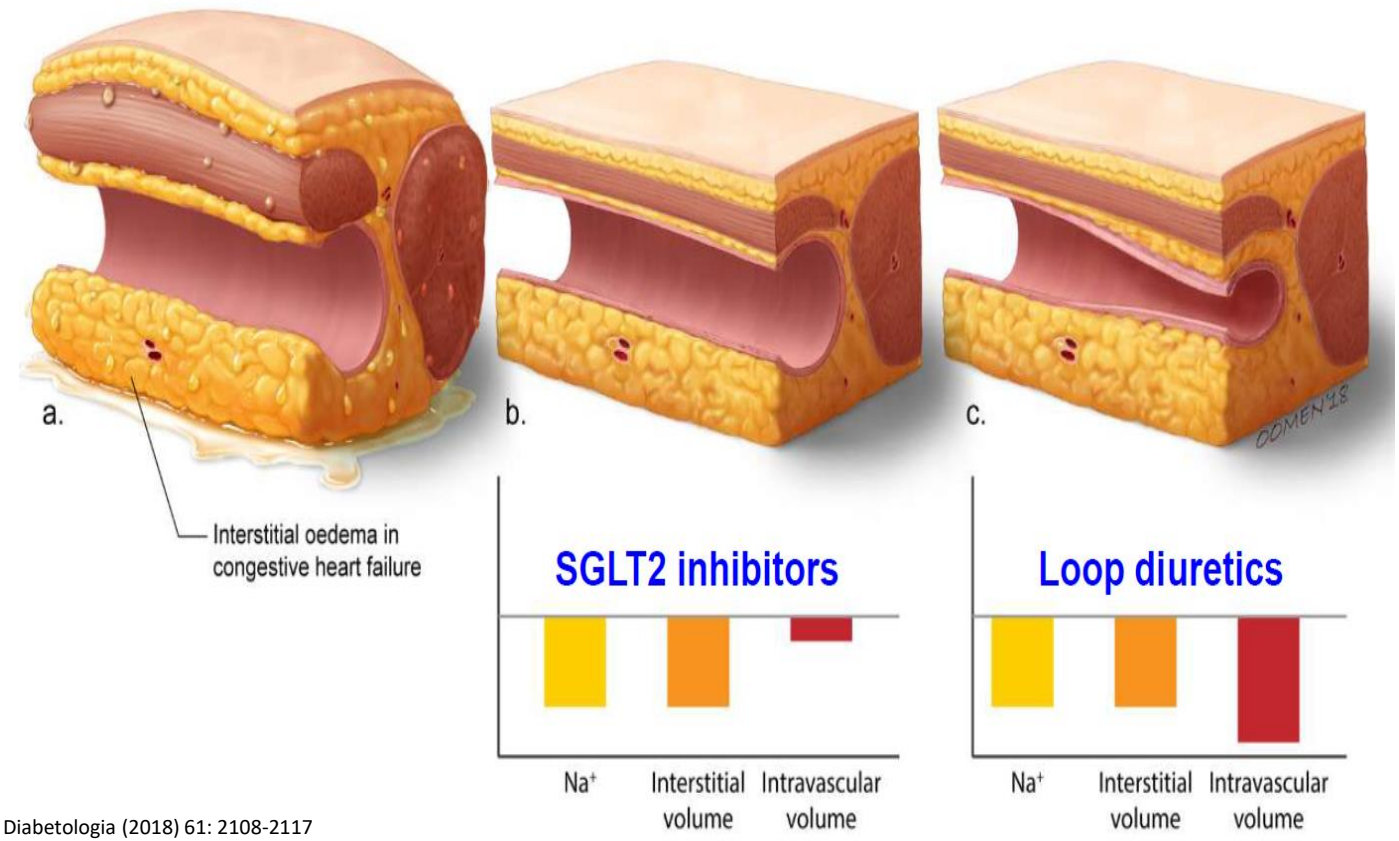
American Diabetes Association. Diabetes Care

Univariable mediation analysis of risk of CV death with Empa versus placebo: time-dependent covariate analysis adjusting for the change from baseline in each variable

FFA, free fatty acid; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; TG, triglyceride; WC,
waist circumference.

Diabetes Care 2018 Feb; 41(2): 356-363.

SGLT2i may differentially regulate the interstitial vs intravascular compartment when compared with loop diuretics

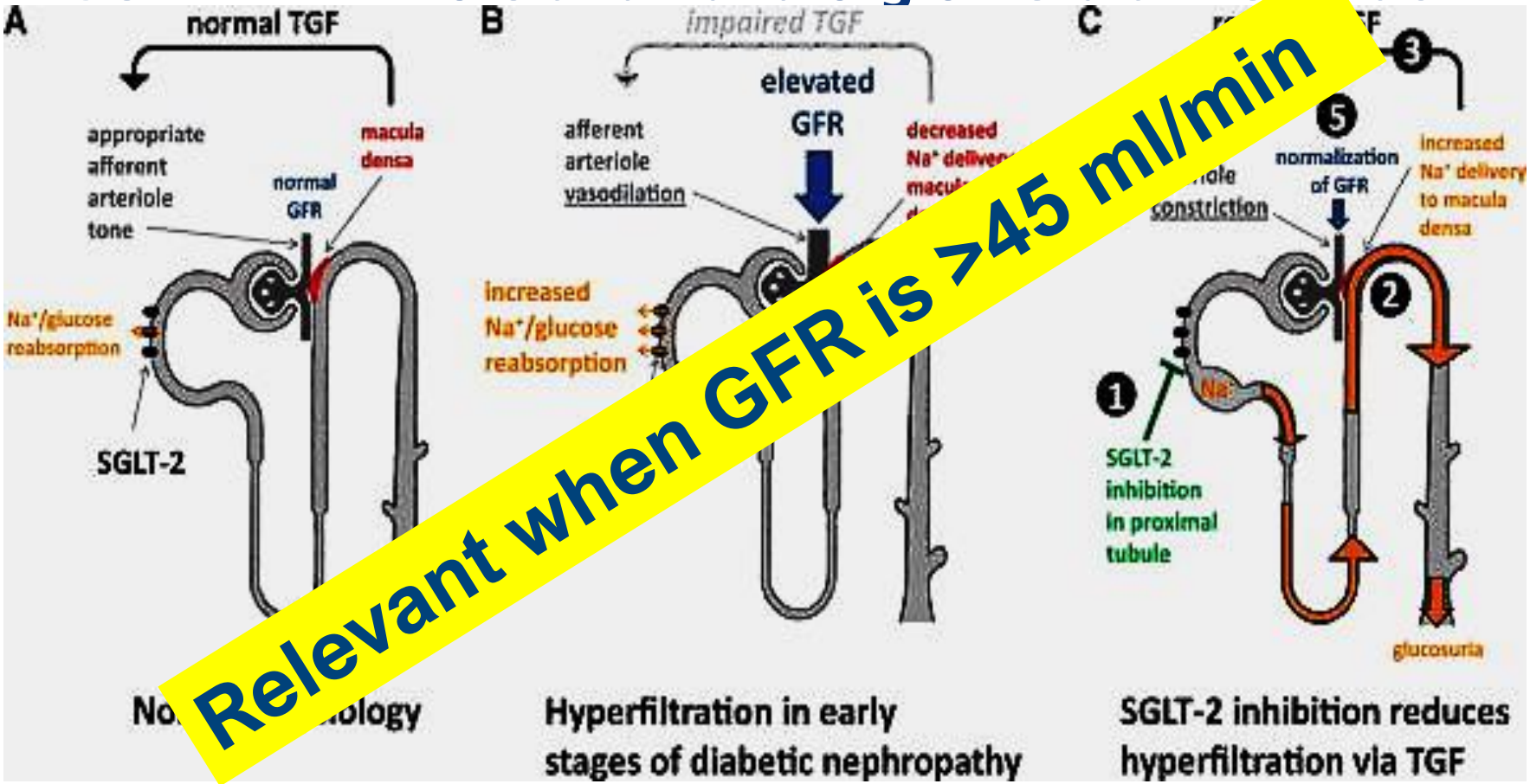


Diabetologia (2018) 61: 2108-2117

Osmotic diuresis different from loop diuresis

- **Reduce interstitial edema**
- **Loop diuretics sparing**
- **Prevent prerenal azotemia**
- **Reduce reflex tachycardia**
- **Reduce RAS activation**

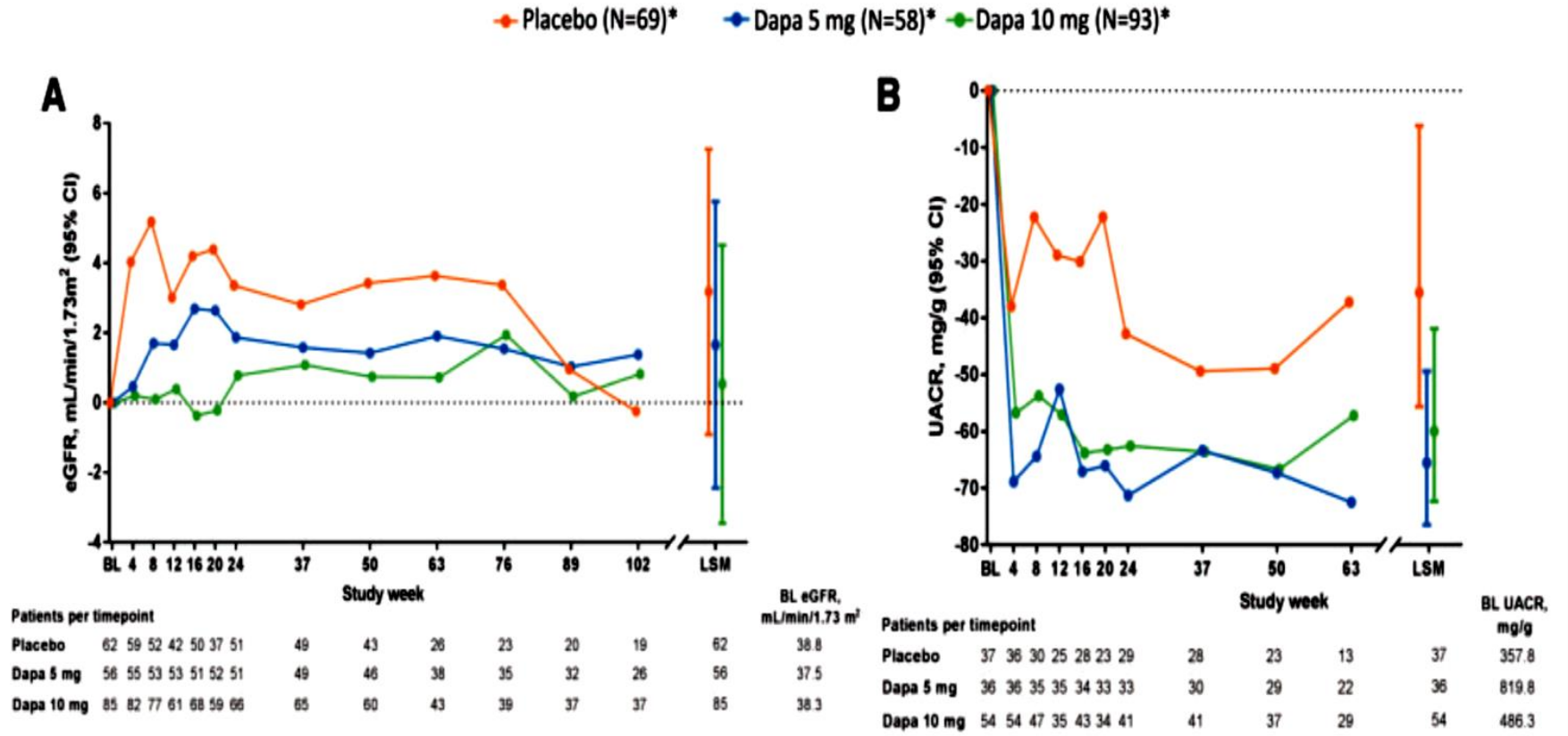
SGLT2 inhibitors and Tubulo-glomerular Feedback



Relevant when GFR is >45 ml/min

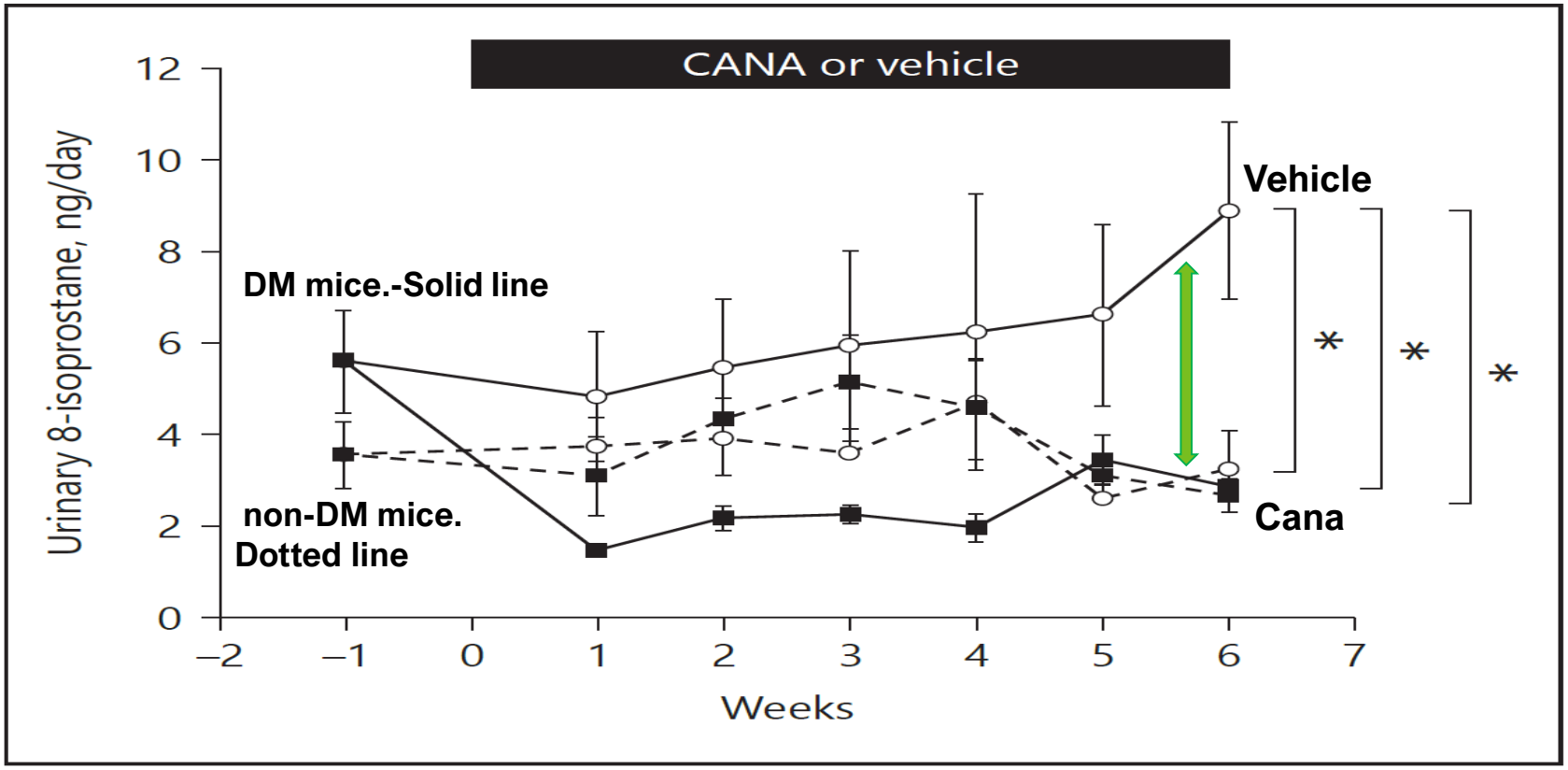
Cherney DZ Circulation 129(5):587-97, 2014

Changes in parameters of kidney function (Stages 3b & 4 CKD) over time during treatment with placebo or dapagliflozin: (A) eGFR, (B) UACR



Dekkers Cj et.al. Nephrol Dial Transplant (2018) 33: 2005–2011

Effects of CANA on renal oxidative stress in T2DM mice.



Woods TC et.al. Am J Nephrol 2019;49:331–341

Case 1

- 55 y/o female patient
- Type 2 DM since 2016
- BH: 157 cm
- BW: 88 kg
- BMI: 35.7

Brief history

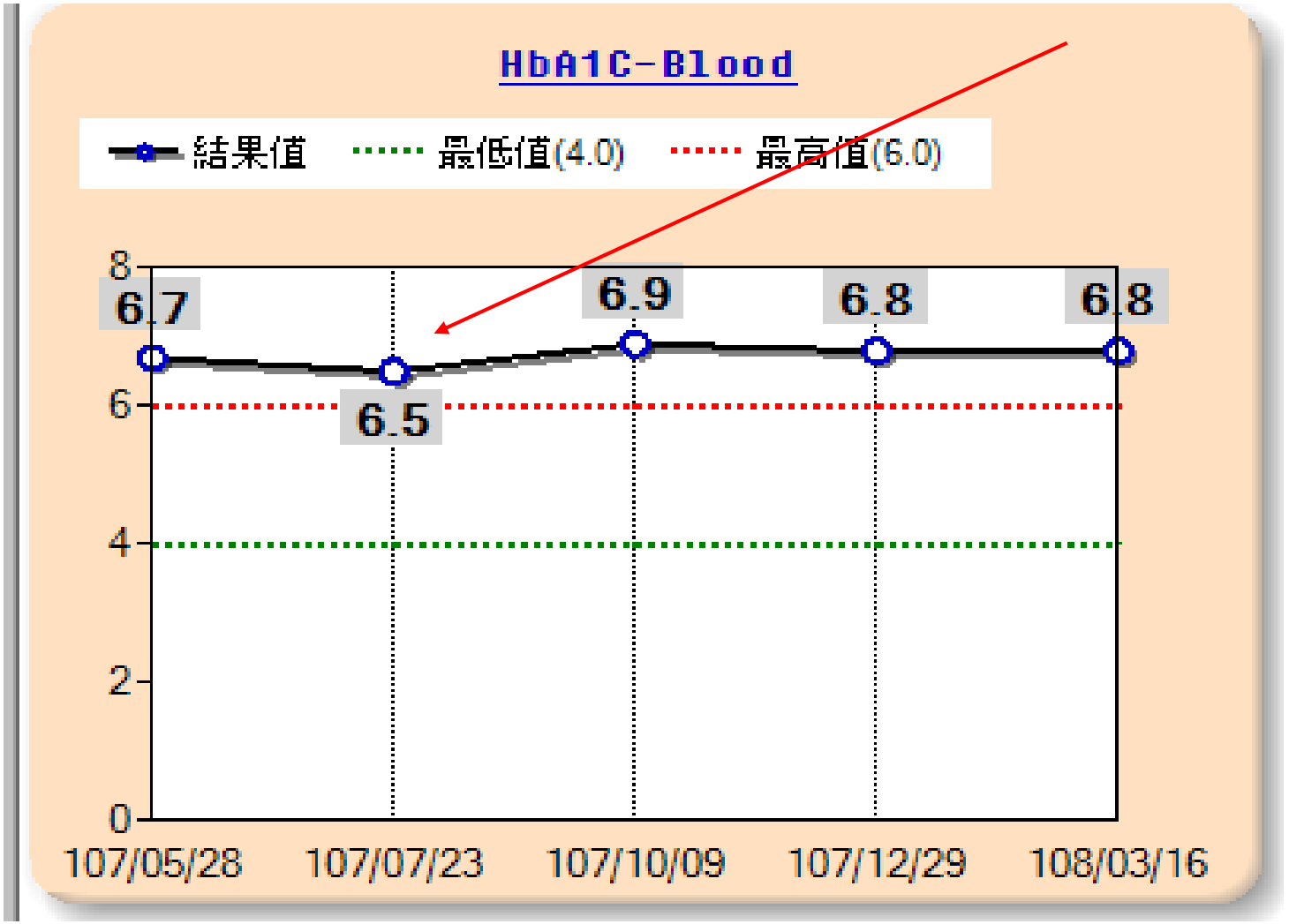
- type 2 DM diagnosed since 2016
- Under Glucophage 500 mg 1# bid + Januvia 1# qd
- A1c 6.5- 7
- GFR 87
- Urine protein 3+
- ACR 792 mg/g (2018/7/23)

Brief history

- Cr 0.7 GFR 87
- BP Under Micardis for blood pressure control
- → change regimen to Glucophage 500 mg 1# bid+ canaglu 100 mg qd

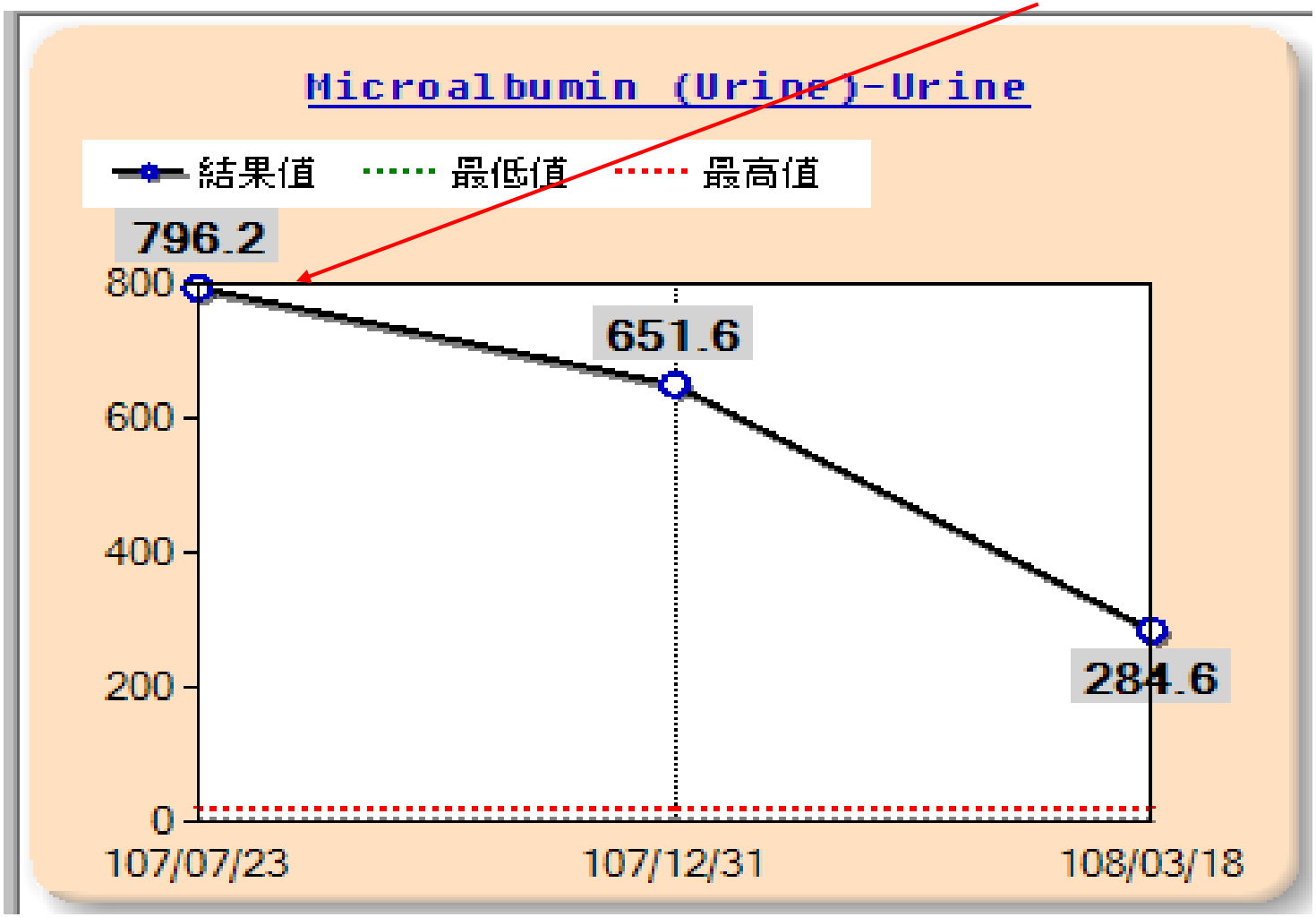
Case 1

Start Canaglu

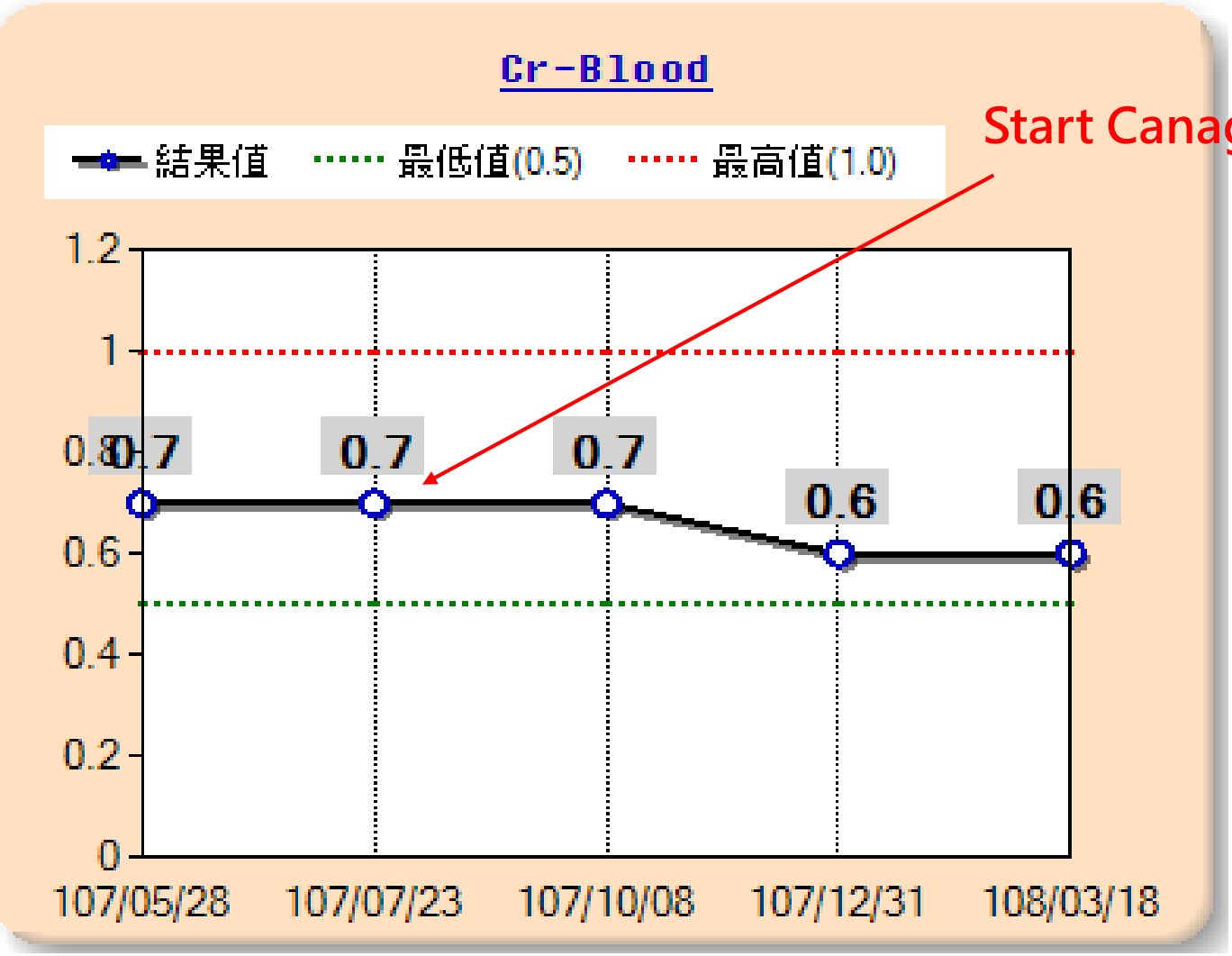


Case 1

Start canaglu



Case 1


Cr-Blood
結果值
最低值(0.5)
最高值(1.0)
Start Canaglu
1.2
1
0.8
0.6
0.4
0.2
0
0.7
0.7
0.7
0.6
0.6
107/05/28
107/07/23
107/10/08
107/12/31
108/03/18

Case 1

- Current medication

  Glucophage 500 mg 1# bid+ Canaglu 100 mg qd

- ACR:796 mg/g→ 284 mg/g
- BW : 88->85 Kg
- Cr 0.7-> 0.6

Case 2

- 71 y/o female patient
- Type 2 DM since 2006
- BH: 148 cm
- BW: 58 kg
- BMI: 26.4

Brief history

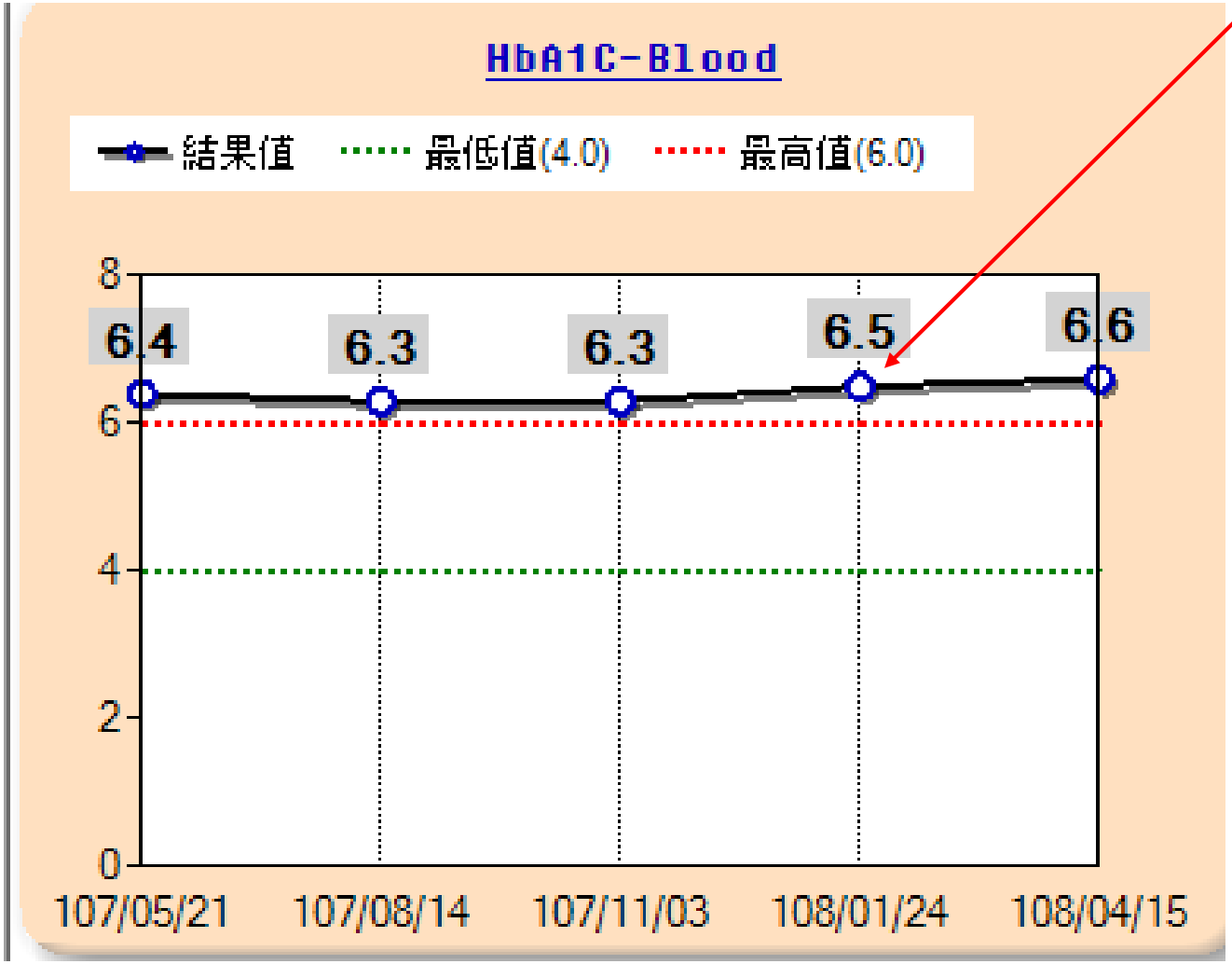
- type 2 DM diagnosed since 2006
- Under actosmet 850 mg 1# bid
- A1c 6.3->6.8
- MA(+)
- ACR 58.9 mg/g (2018/5/21)

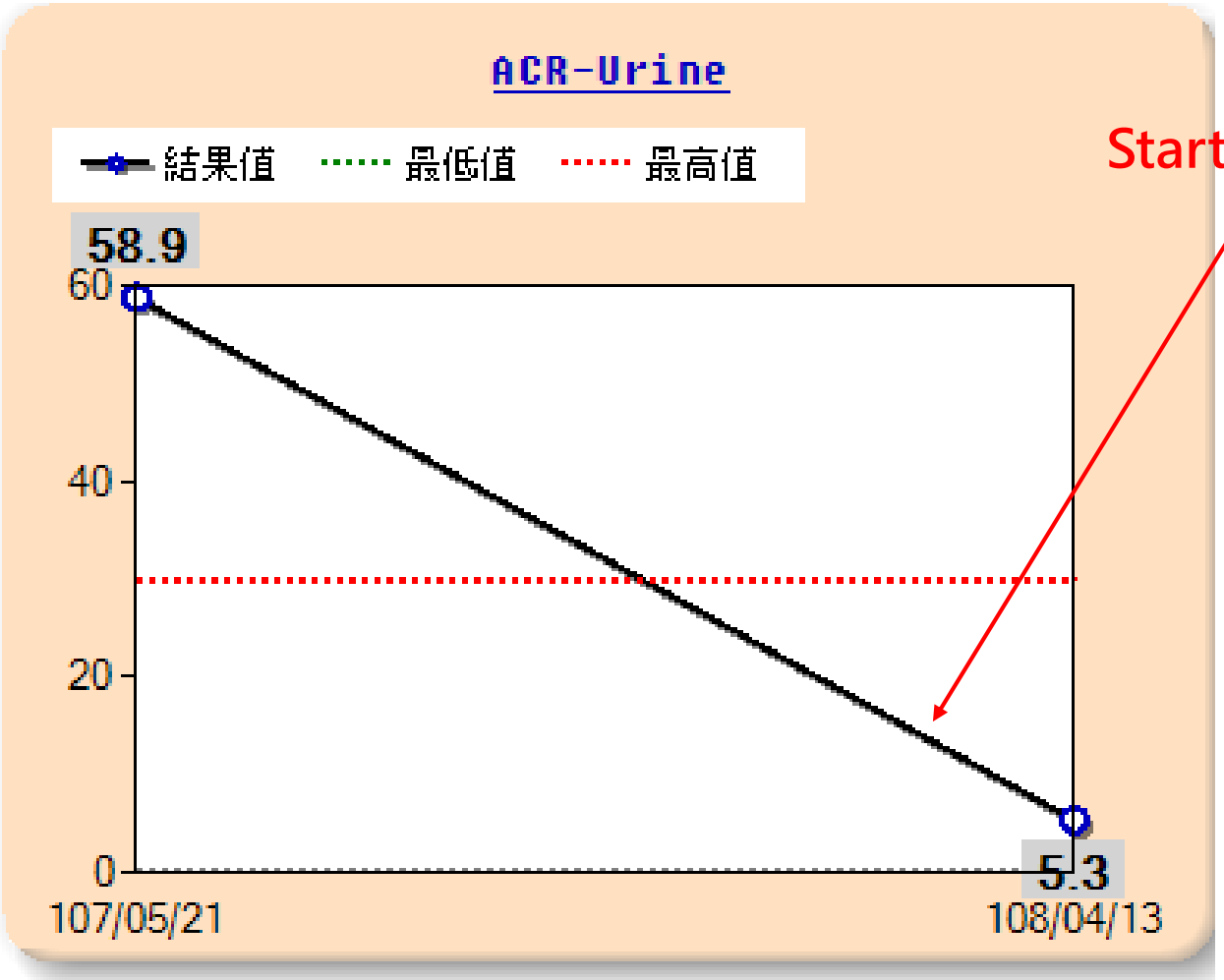
Case 2

- Cr 0.8 GFR 71
- BP Under Olmetec 40 mg for blood pressure control
- → change regimen to Glucophage 850 mg 1# bid+ canaglu 100 mg qd

Case 2

Start Canaglu




ACR-Urine
結果值
最低值
最高值
58.9
60
40
20
0
5.3
107/05/21
108/04/13
Start canaglu

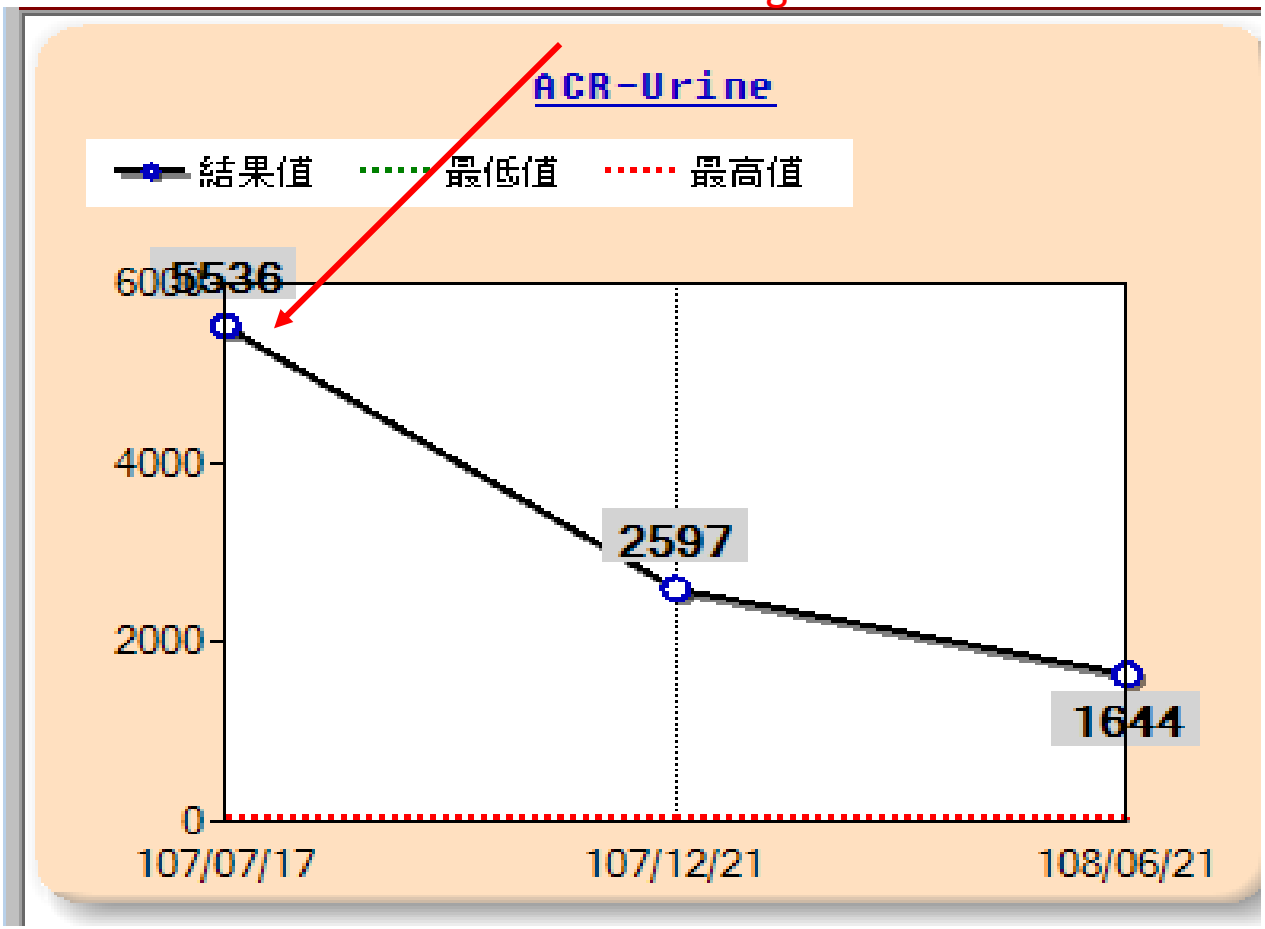
Summary

- Current medication

  Glucophage 850 mg 1# bid+ Canaglu 100 mg qd

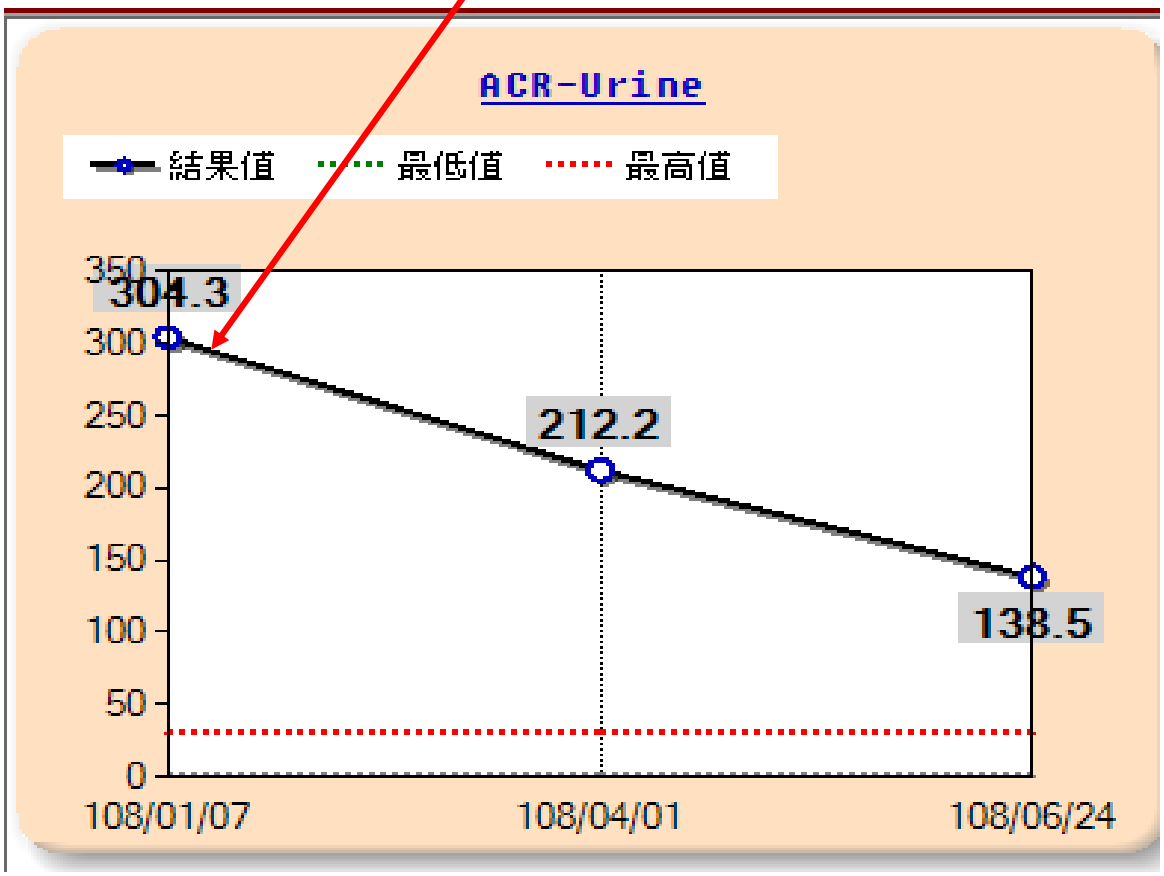
- ACR:58 mg/g→ 5.3 mg/g
- BW : 58->54 Kg
- Cr 0.8-> 0.9

Start canaglu



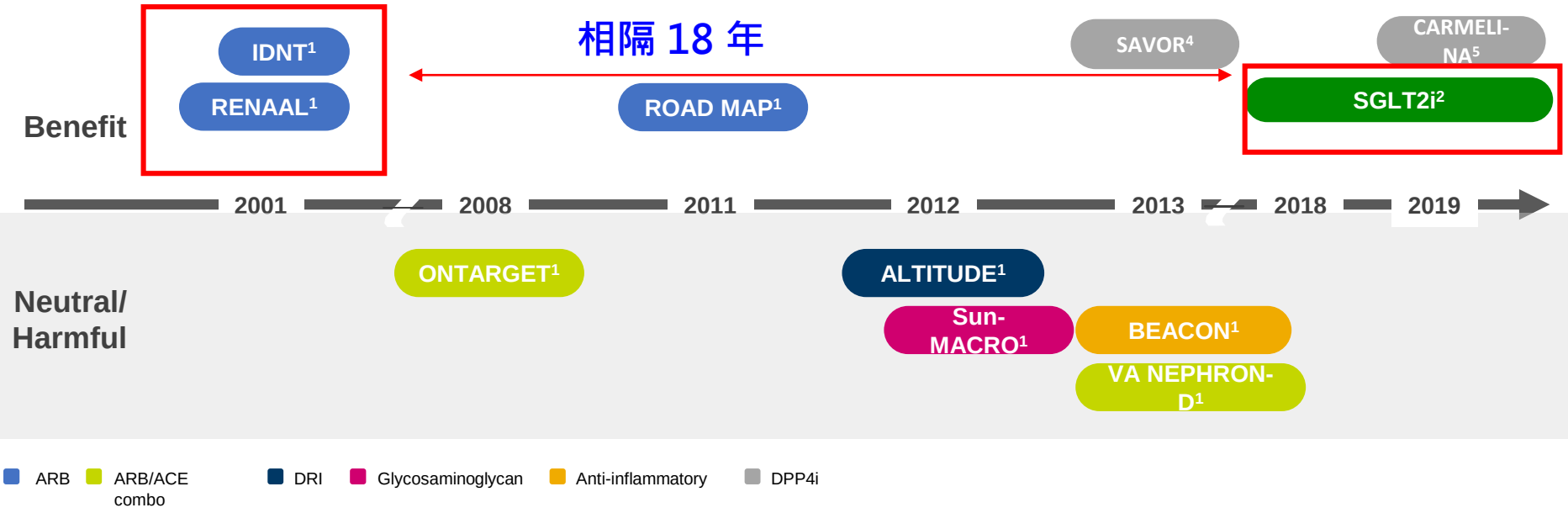
62 y/o male , GFR 47

Start canaglu



49 y/o male GFR 75

Before SGLT2i, the options to prevent new onset or worsening renal function are limited



ONTARGET, BEACON demonstrated increased risk of events.

ALTITUDE, Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints; ARB, angiotensin receptor blocker; ACE, angiotensin-converting enzyme; BEACON, Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes Mellitus; DRI, dopamine reuptake inhibitor; IDNT, Irbesartan Diabetic Nephropathy Trial; ONTARGET, Ongoing Telmisartan Along and in Combination with Ramipril Global Endpoint Trial; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; SGLT2i, sodium-glucose cotransporter 2 inhibitor; Sun-MACRO, Sulodexide macro-albuminuria; VA NEPHRON-D, Veterans Affairs Nephropathy in Diabetes.

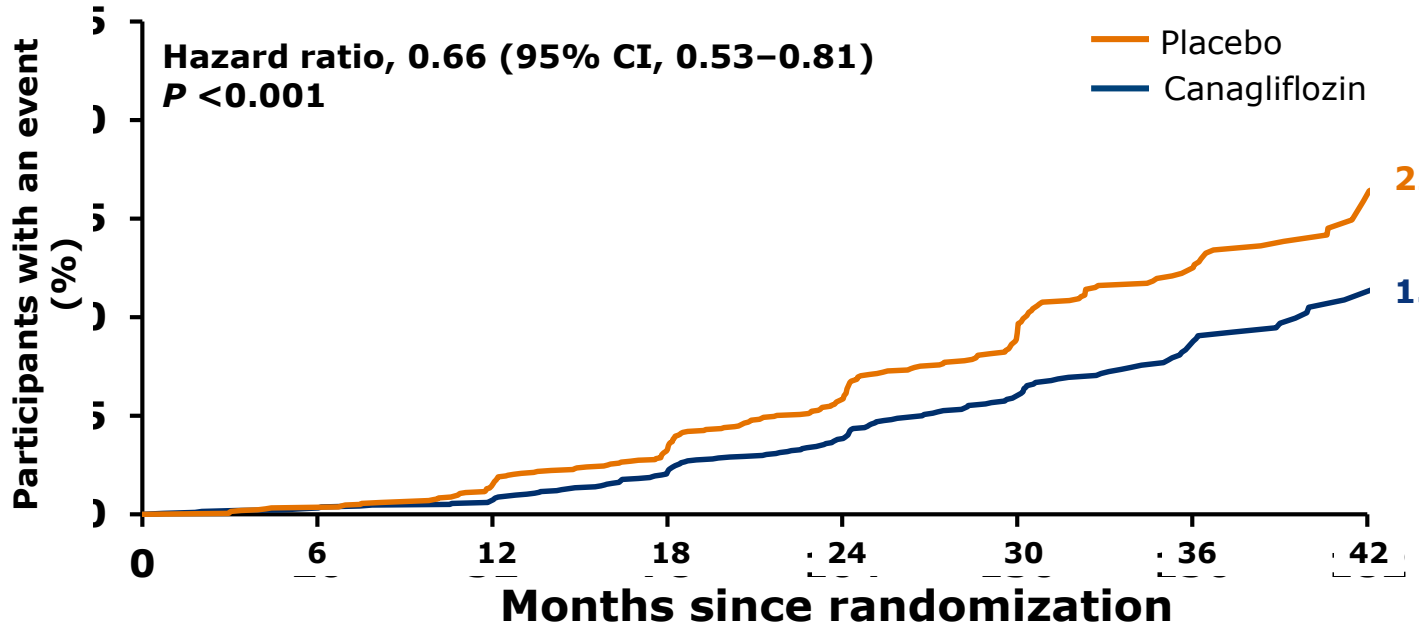
1. Chan GC, et al. *Nephrol Dial Transplant.* 2016;31:359-368. **2.** Janssen press release downloaded 25 September 2018 https://www.janssen.com/phase-3-credence-renal-outcomes-trial-invokanar-canagliflozin-being-stopped-early-positive-efficacy. ; 3.Diabetes Care 2017;40:69 – 76; 4. .JAMA. 2019;321(1):69-79;

Canagliflozin and Renal E
with Established N

N

Stopped Early for Overwhelming Efficacy-
No Safety Issues

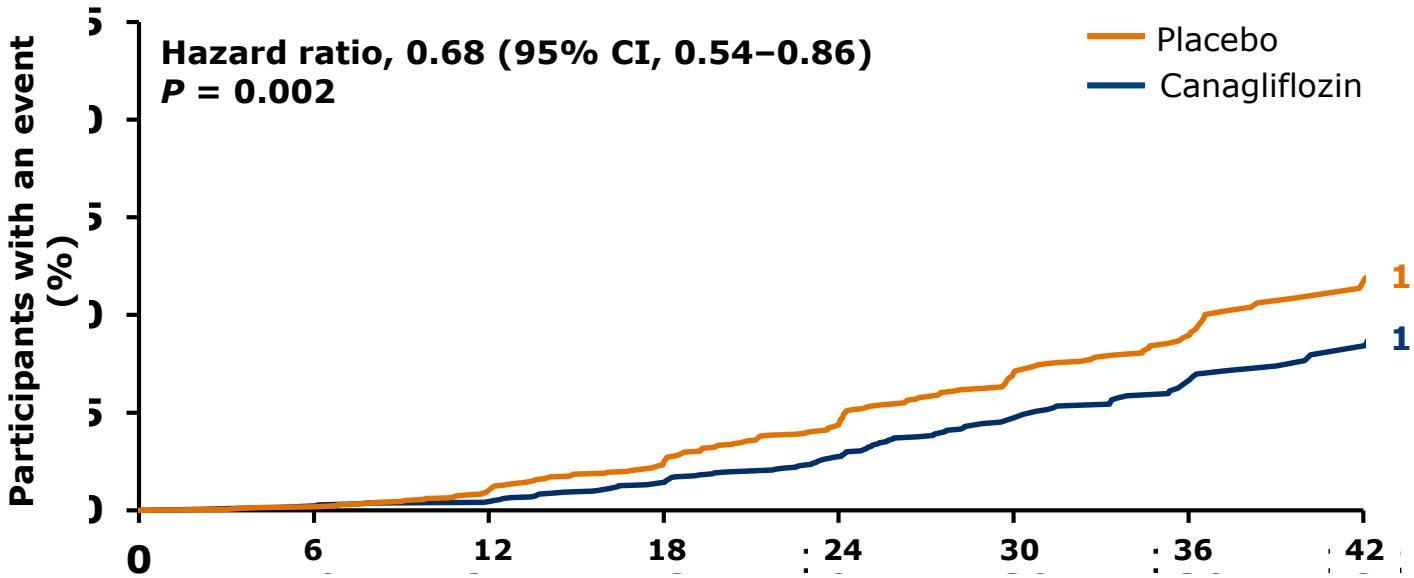
ESKD, Doubling of Serum Creatinine, or Renal Death



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

CREDENCE

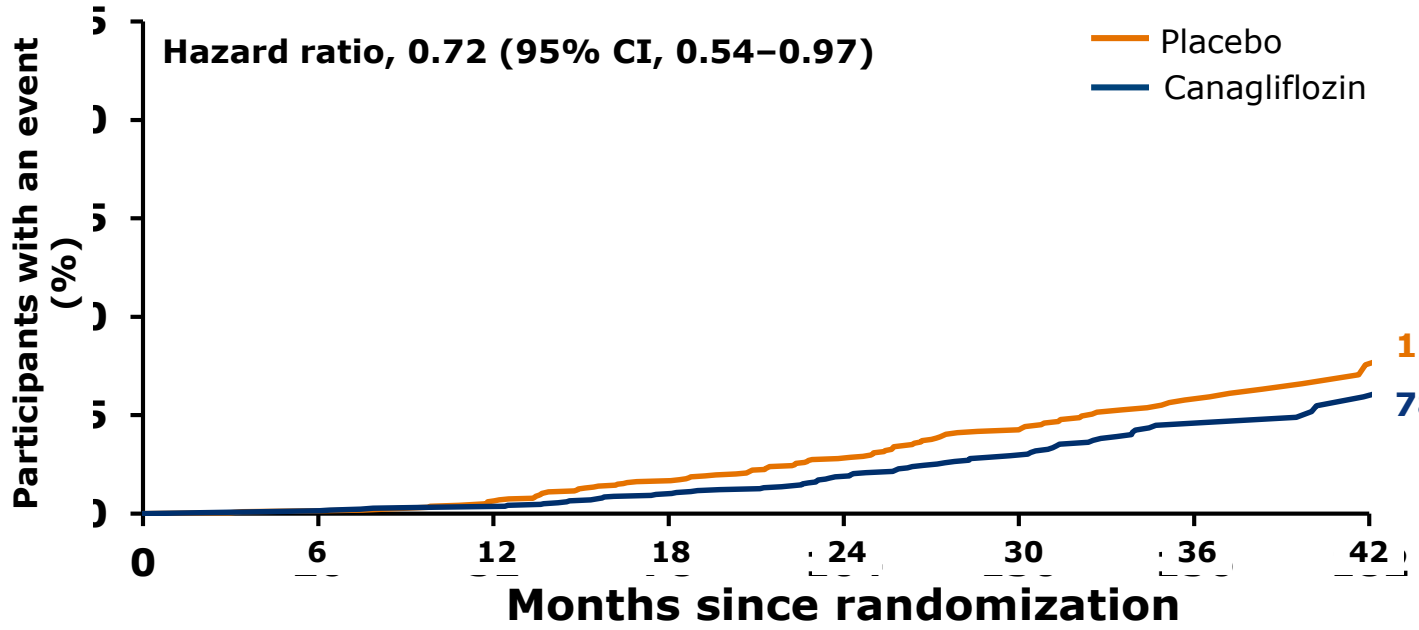
End-stage Kidney Disease



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

CREDENCE

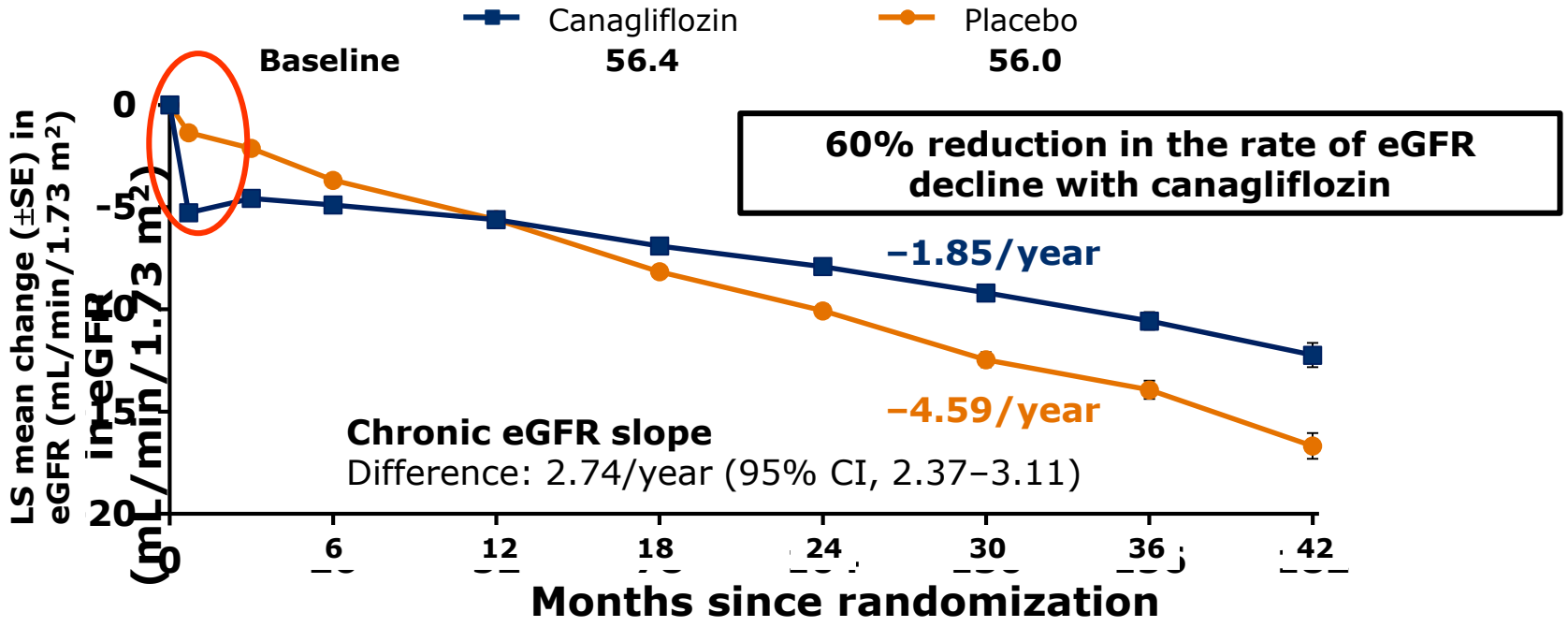
Dialysis, Kidney Transplantation, or Renal Death*



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

CREDENCE

Acute and Long-term Effects on eGFR



No. of Participants

Placebo	2178	2084	1985	1882	1720	1536	1006	583	210
Canagliflozin	2179	2074	2005	1919	1782	1648	1116	652	241

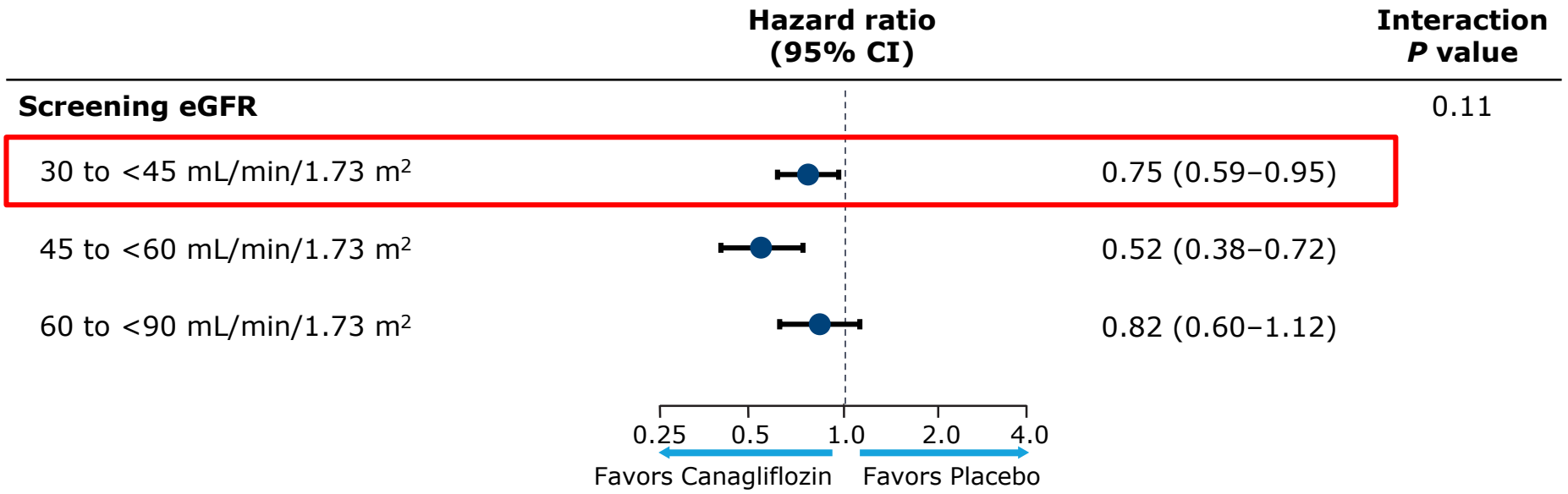
Perkovic V, et al. *N Engl J Med*. 2019. doi: 10.1056/NEJMoa1811744.

On treatment

Canagliflozin slows progression to ESRD for more than 20 years

- **GFR 60, UP(+)**
- **No intervention→ -10 / year → 5 years progressed to ESRD**
- **Add RAS blockade→ -5 /year→ 10 years progressed to ESRD**
- **Add Canagliflozin→ -1.85/year→ 27 years progressed to ESRD**

Primary Outcome: Benefits in eGFR 30 to <45 Subgroup



NNT in patients with eGFR 30 to <45 mL/min/1.73 m²

目前 G F R **30-45** 仍未取得 **indication**

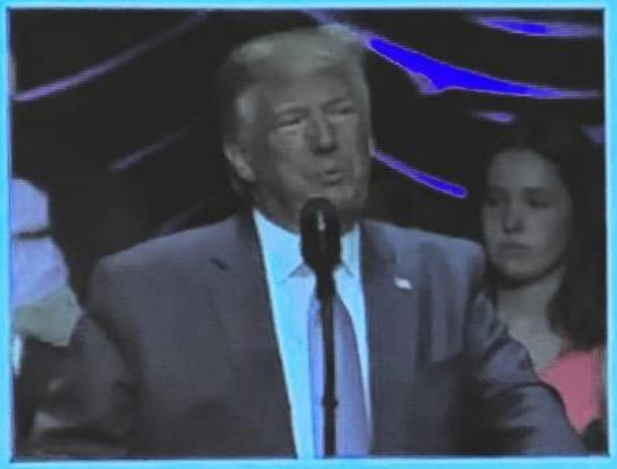
CREDENCE

HEALTH • MEDICINE

How Trump's Executive Order Could Save Lives by Transforming How the U.S. Treats Kidney Disease

TIME

JULY 11, 2019



The policy is intended to improve kidney care in three major ways:

1. Emphasizing more effective and convenient treatments
2. Making more kidneys available for transplant
3. Improving preventive care and education with the goal of reducing the number of people who develop end-stage renal disease by 25% by 2030

去年健保支出最高10大疾病排行

排行	治病項目	醫療費用	就醫人數
1	慢性腎臟疾病	約513.78億元	36.4萬人
2	糖尿病	約291.68億元	145.9萬人
3	齒齦炎及牙周疾病	約171.02億元	877.8萬人
4	齲齒	約167.09億元	578.5萬人
5	高血壓	約139.20億元	177萬人
6	到院抗腫瘤治療	約125.42億元	7.5萬人
7	呼吸衰竭	約124.24億元	4.1萬人
8	慢性缺血性心臟病	約118.41億元	37.7萬人
9	思覺失調症	約113.58億元	10.6萬人
10	急性上呼吸道感染	約103.76億元	852萬人

資料來源：衛福部健保署

Four conditions to add Canagliflozin as second line therapy

- CKD
- CHF
- ASCVD
- Diabesity

Other conditions suitable for Canagliflozin use

- Add on insulin therapy
- High glucose variability
- Shifting from other OADs (esp: SUs, TZDs, DPP-4i)
- NASH

In relation to other OADs

- SUs: reduce dose
- TZD: add on , may reduce to half dose
- Insulin: reduce basal insulin dose 10-20%
- DPP-4i: switching
- GLP-1 analog : add on
- 請確保 血糖控制不受影響

ADA Standards of Care Updated With Renal Guidance Based on CREDENCE

- "The CREDENCE trial was the first sodium-glucose cotransporter 2 (SGLT2) inhibitor trial to assess renal-specific primary outcomes and ended early due to efficacy. Incorporating these findings into the Standards of Care now gives providers the latest evidence-based recommendations to treat people with type 2 diabetes and diabetes-related chronic kidney disease…"
  - William T. Cefalu, MD, Chief Scientific, Medical and Mission Officer of the ADA[1]
- **Based on the Grade A evidence from the CREDENCE trial, the ADA *living guidelines* (updated on June 3, 2019)[2] propose the following:**
  - "For patients with type 2 diabetes and diabetic kidney disease, consider use of an SGLT2 inhibitor in patients with **an eGFR ≥30 mL/min/1.73 m²** and particularly in those with >300 mg/g albuminuria to reduce risk of CKD progression, cardiovascular events, or both."

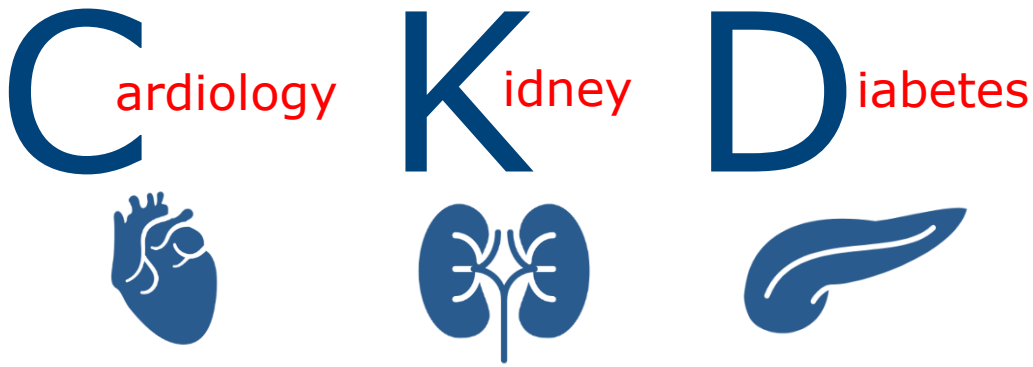
1. American Diabetes Association. http://www.diabetes.org/newsroom/press-releases/2019/updates-standards-medical-care-diabetes.html. Accessed June 5, 2019.
2. American Diabetes Association. *Standards of Medical Care in Diabetes–2019*. http://care.diabetesjournals.org/content/42/Supplement_1. Last updated June 3, 2019. Accessed June 5, 2019.

Use of Canagliflozin in Clinical Practice for Patients With T2DM

Canagliflozin as Treatment for Cardiovascular Disease

Canagliflozin as Treatment for Chronic Kidney Disease

Canagliflozin as Treatment for Diabetes



Presented at the 79th Scientific Sessions of the American Diabetes Association;
June 11, 2019; San Francisco, CA.

CREDENCE