# Redefining Diabetic Management: Time for a Paradigm Change

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廖國盟

CAN-SLK-20180815

# Case

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 1# qd

A1c around 6.9->7.5 during 2017-2018

Cr 1.3 , eGFR 55

MA(+) ACR 352.7 mg/g

# Question

你會把這個病人的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
- 以器官保護的立場，值得更換

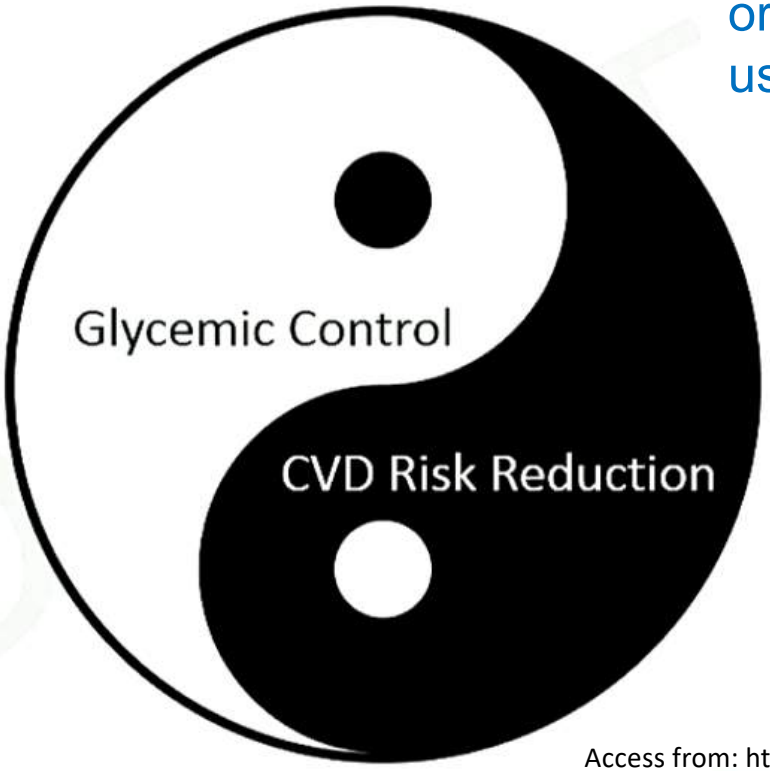
# Outline

- Update of Guideline for T2DM Management
- Mechanism of of Cardiorenal  effect of SGLT-2i
- Organ Protection Effect of Canagliflozin for DM Patient
- SGLT-1/SGLT-2 inhibition

# Preventing Complications

Every 1% A1c reduction is not equal with regard to organ protection while using different OADs

According to UKPDS results, every 1% A1c reduction automatically translate to 14% reduction of macrovascular complications, and over 30% reduction microvascular complications




Access from: https://professional.diabetes.org/2018EASDconsen

**Use metformin unless contraindicated or not tolerated**

**If not at $HbA_{1c}$ target:**

- Continue metformin unless contraindicated (remember to adjust dose/stop metformin with declining eGFR)
- Add SGLT2i or GLP-1 RA with proven cardiovascular benefit[1] (see below)

**If at $HbA_{1c}$ target:**

- If already on dual therapy, or multiple glucose-lowering therapies and not on an SGLT2i or GLP-1 RA, consider switching to one of these agents with proven cardiovascular benefit[1] (see below)

**OR** reconsider/lower individualized target and introduce SGLT2i or GLP-1 RA

**OR** reassess $HbA_{1c}$ at 3-month intervals and add SGLT2i or GLP-1 RA if $HbA_{1c}$ goes above target

## ASCVD predominates

GLP-1 RA with proven CVD benefit[1]

**EITHER/ OR**

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

**If $HbA_{1c}$ above target**

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

- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit[1]
- DPP-4i if not on GLP-1 RA
- Basal insulin[5]
- TZD[6]
- SU[7]

## HF or CKD predominates

**PREFERABLY**

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]

**OR**

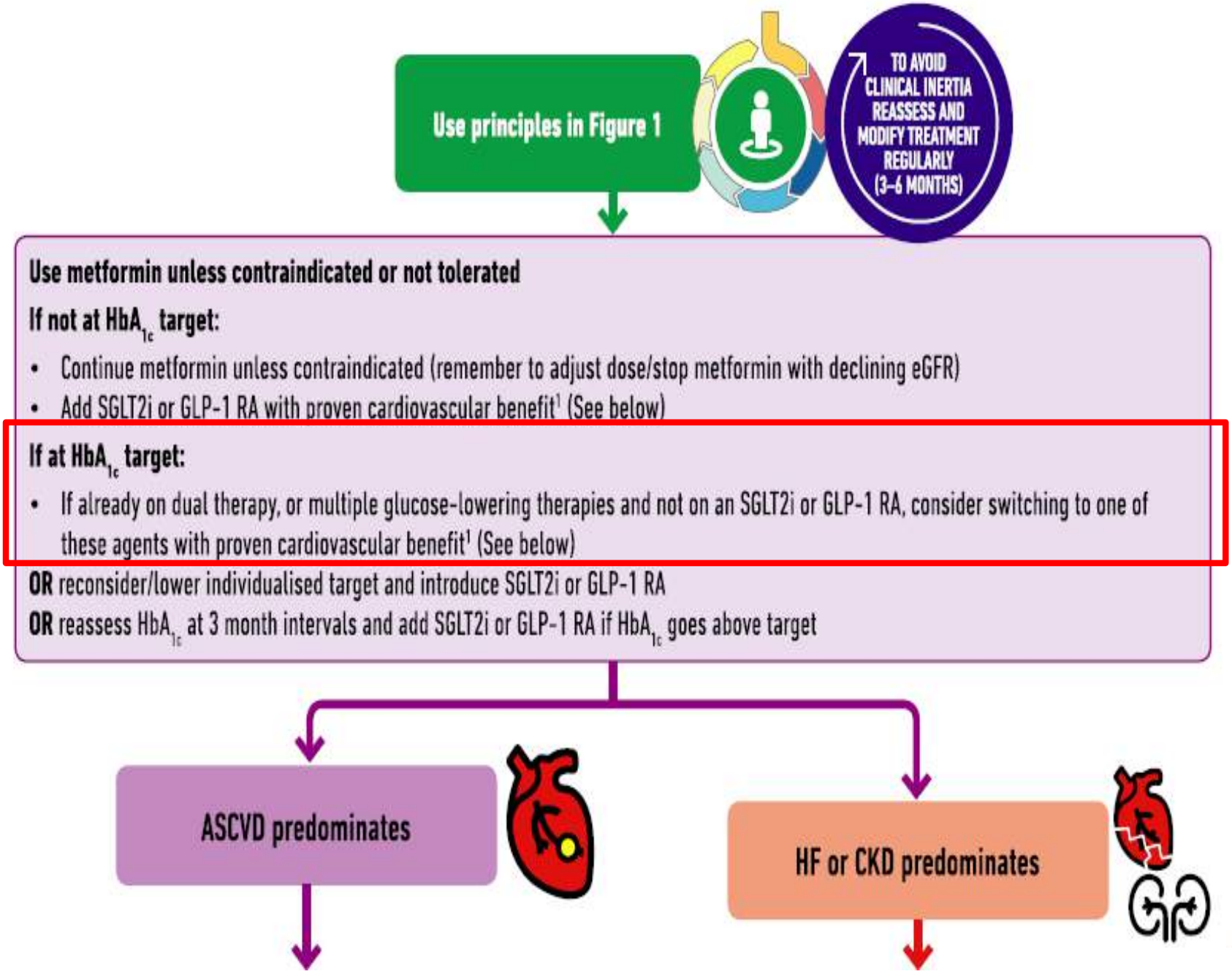
If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1,4]

**If $HbA_{1c}$ above target**

- Avoid TZD in the setting of HF

Choose agents demonstrating CV safety:

- Consider adding the other class with proven CVD benefit[1]
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin[5]
- SU[7]

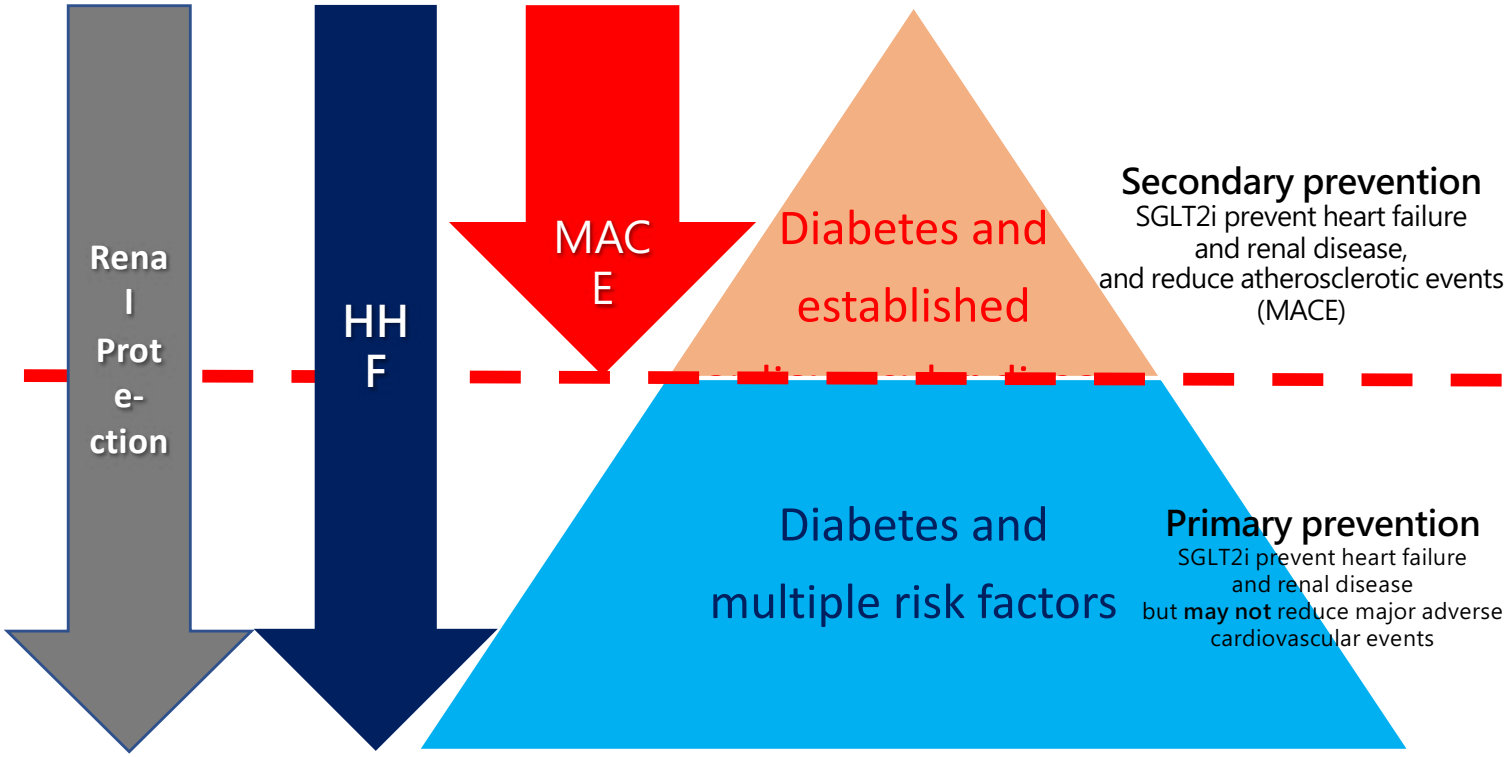

Use principles in Figure 1
TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
Use metformin unless contraindicated or not tolerated
If not at HbA1c target:
• Continue metformin unless contraindicated (remember to adjust dose/stop metformin with declining eGFR)
• Add SGLT2i or GLP-1 RA with proven cardiovascular benefit[1] (See below)
If at HbA1c target:
• If already on dual therapy, or multiple glucose-lowering therapies and not on an SGLT2i or GLP-1 RA, consider switching to one of these agents with proven cardiovascular benefit[1] (See below)
OR reconsider/lower individualised target and introduce SGLT2i or GLP-1 RA
OR reassess HbA1c at 3 month intervals and add SGLT2i or GLP-1 RA if HbA1c goes above target
ASCVD predominates
HF or CKD predominates

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

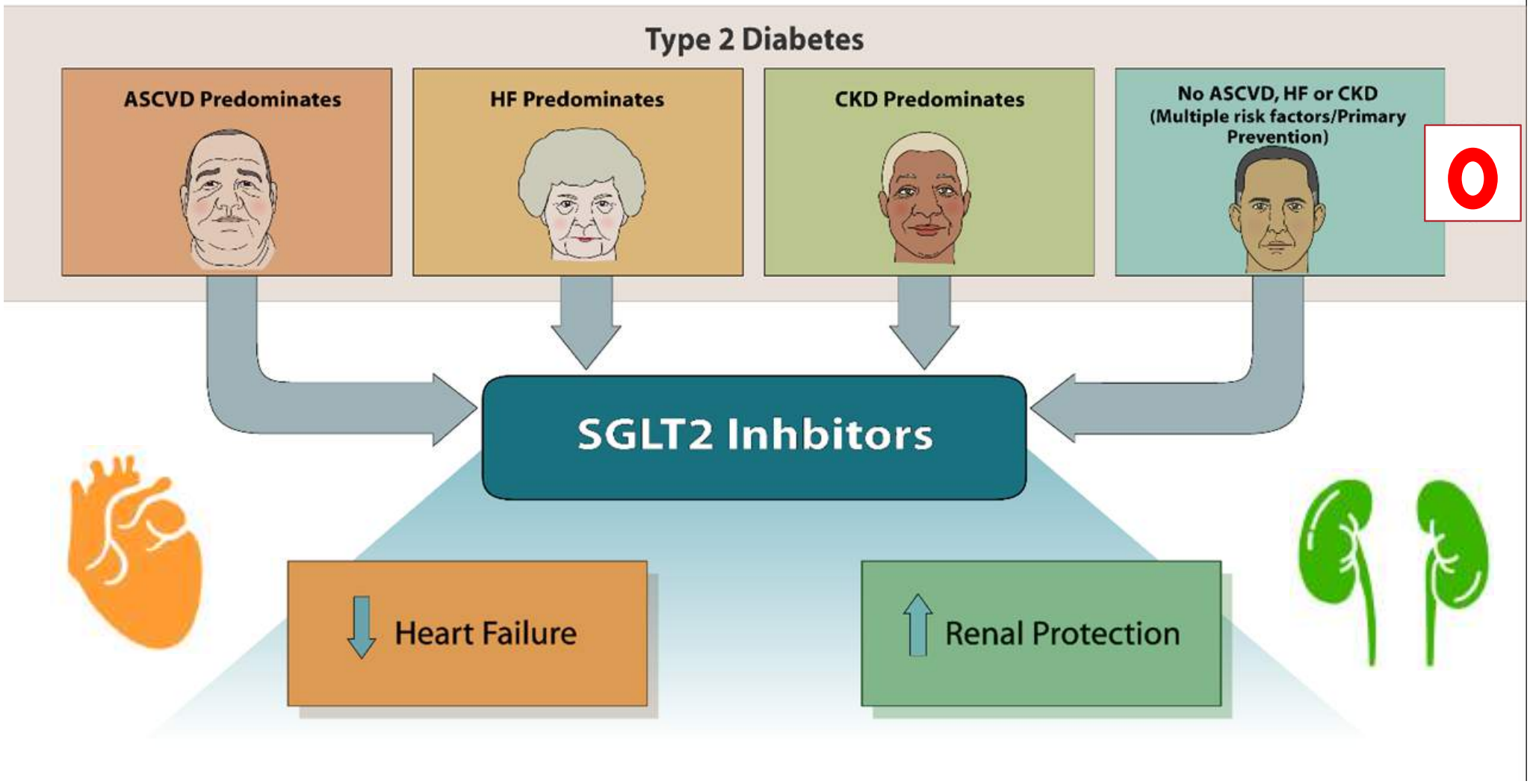
**If at A1c target: switching**

**If not at A1c target: add on**

# Pump, pipes, and filter : do SGLT2 inhibitors cover it all?




www.thelancet.com Published online November 10, 2018
http://dx.doi.org/10.1016/S0140-6736(18)32824-1


Type 2 Diabetes
ASCVD Predominates
HF Predominates
CKD Predominates
No ASCVD, HF or CKD
(Multiple risk factors/Primary
Prevention)
SGLT2 Inhbitors
Heart Failure
Renal Protection


THE LANCET
"Sabatine and colleagues' meta-analysis...provides compelling evidence that SGLT2i should now be considered as first-line therapy after metformin in most people with type 2 diabetes..."
Editorial
World Report
Articles
Articles
Review

# Outline

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# SGLT2i 器官保護效果

- Dissociation of organ protection and A1c lowering effect

- Dissociation of natriuresis effect and glcosuric effect

TYPE 2 DIABETES-THE WAY FORWARD

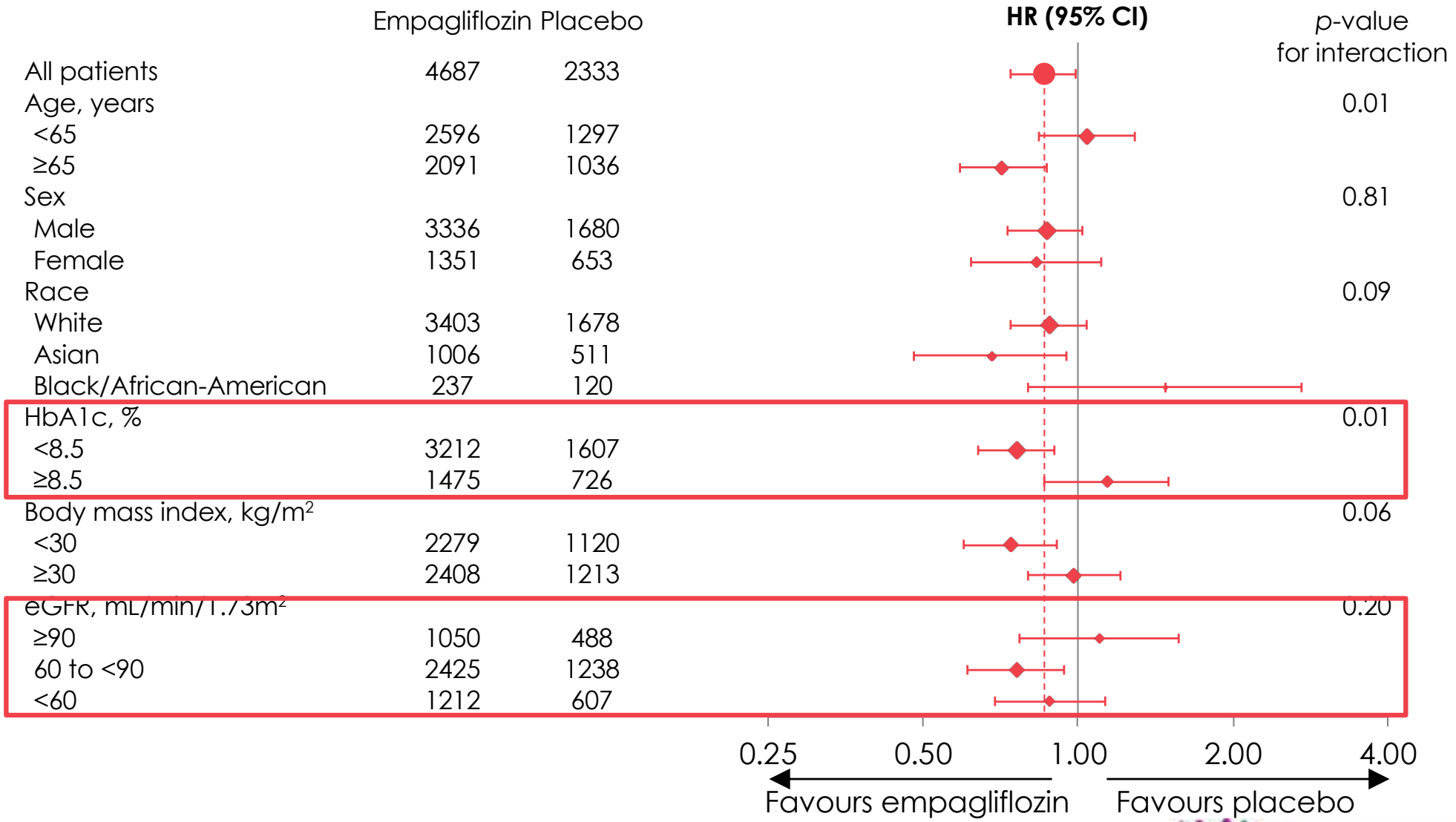
- SGLT2 排糖效果 (mg/min)

- =GFR (cc/min)* Blood sugar (mg/100cc)

- GFR , A1c → 決定SGLT2 效果

TYPE 2 DIABETES-THE WAY FORWARD

# 3-point MACE: subgroup analysis

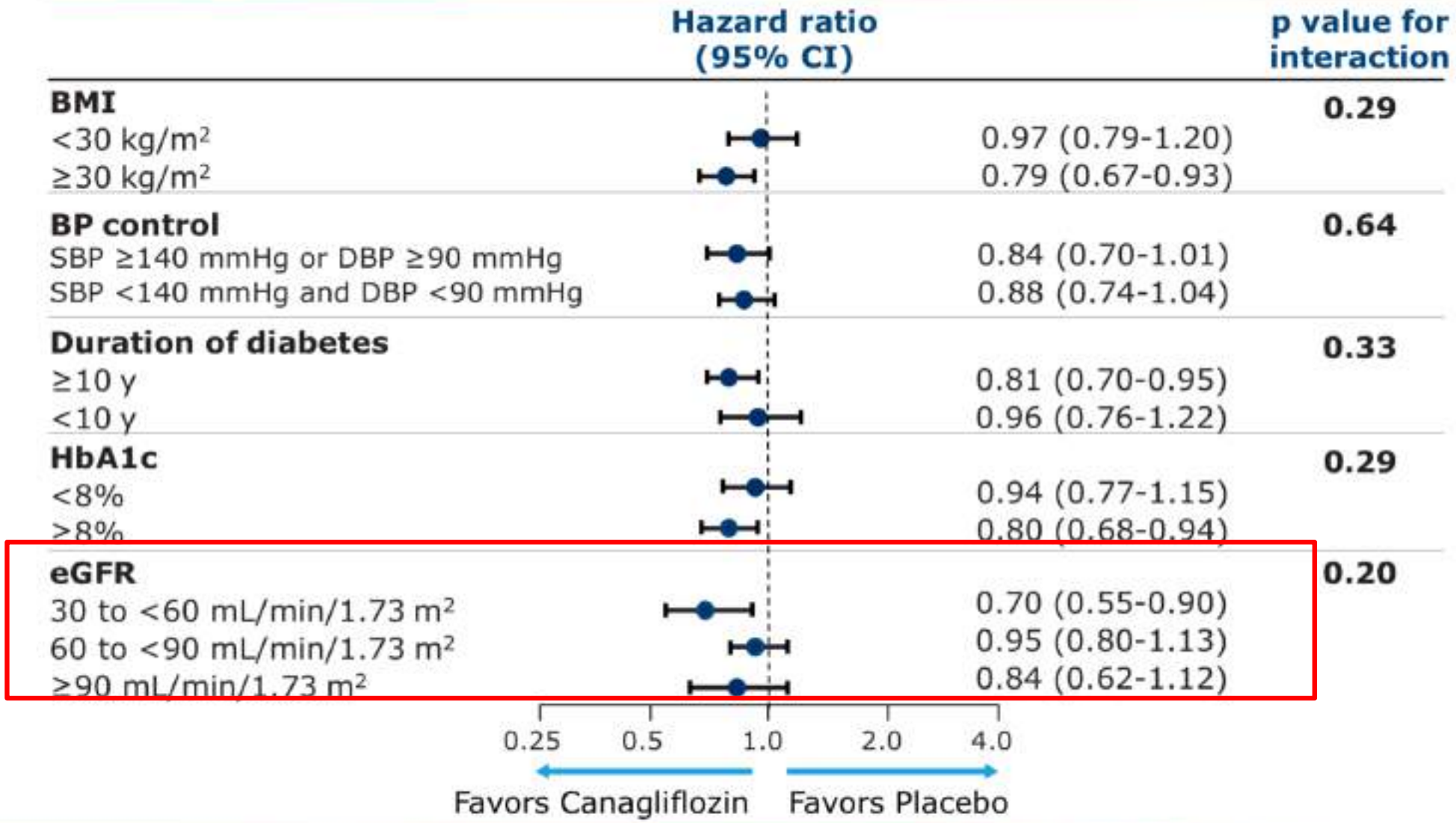



For the test of homogeneity of the treatment group difference among subgroups with no adjustment for multiple tests. eGFR, estimated glomerular filtration rate (according to Modification of Diet in Renal Disease equation) Zinman B et al; N Engl J Med 2015; 373:2117-28.

"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

# UNCOUPLING OF NATRIURESIS AND GLYCOSURIC EFFECT WHEN GFR < 60

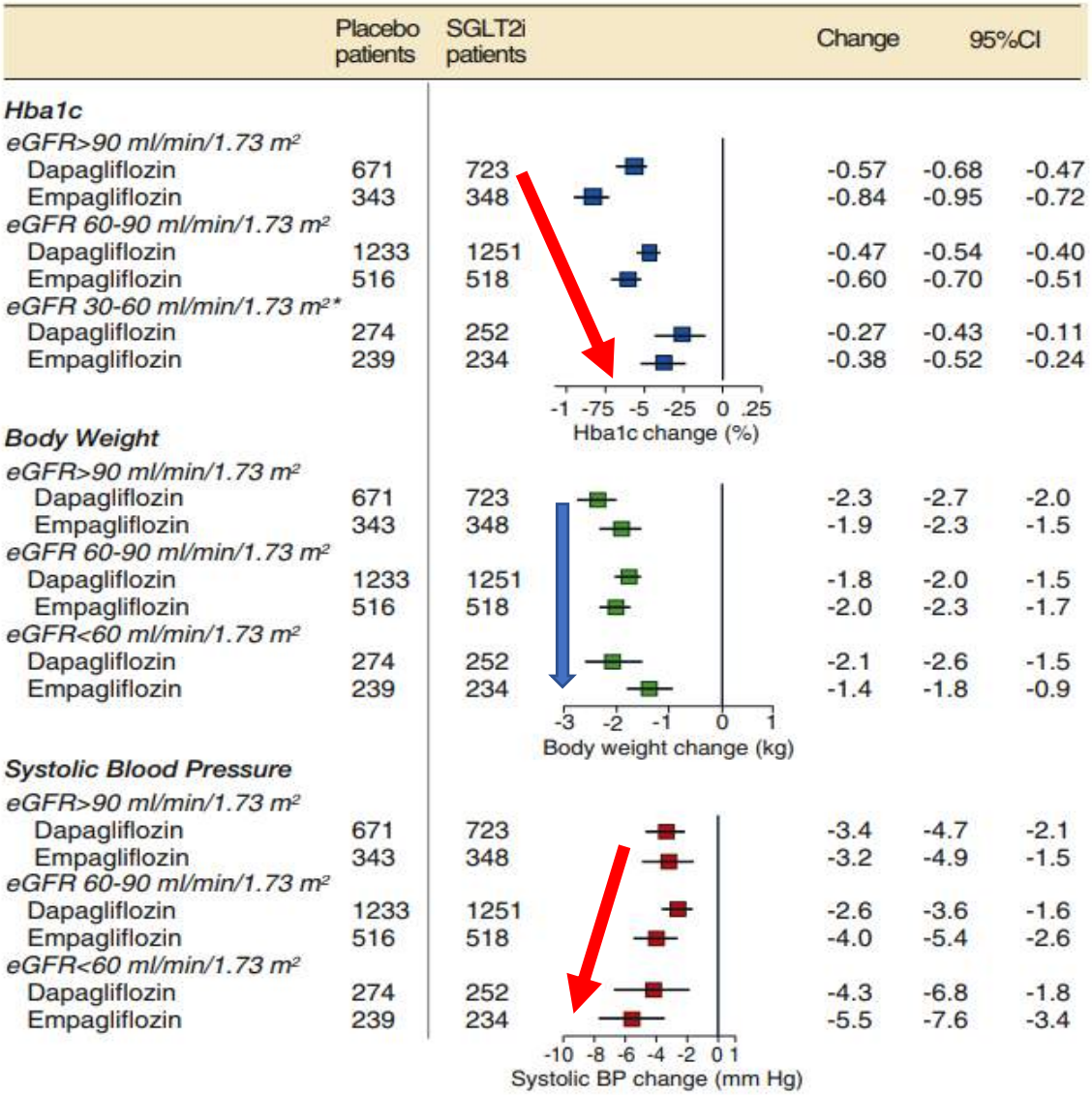



**Figure 2 | Glycemic, weight, and systolic blood pressure lowering effects of empagliflozin[38] and dapagliflozin[57] at chronic kidney disease stages 1, 2, and 3.** eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; SGLT2, sodium-glucose cotransport-2.

- 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

TYPE 2 DIABETES-THE WAY FORWARD

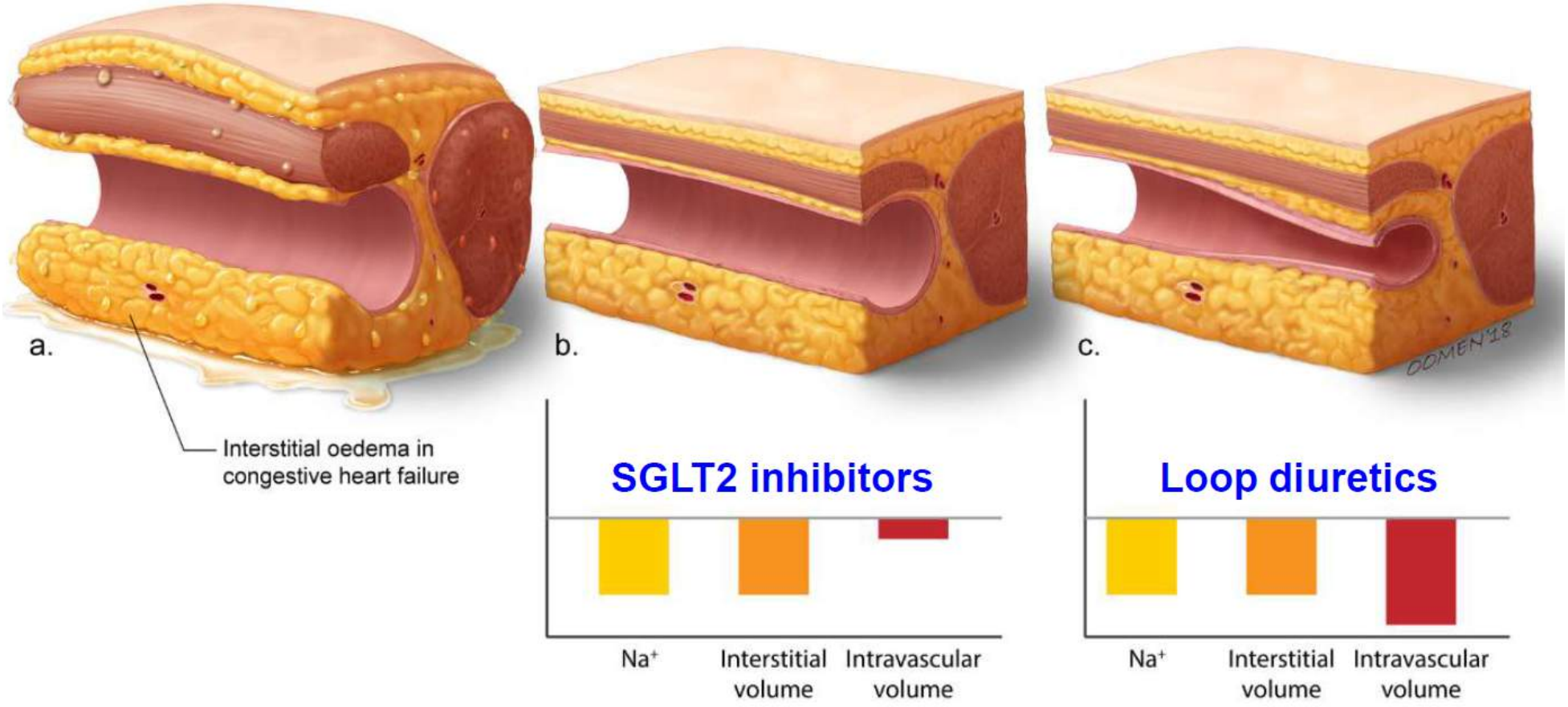
| | GFR30- 60 | GFR>60 |
|---|---|---|
| 降糖 | + | +++ |
| 心臟保護 | ++++ | +++ |
| 腎臟保護 | +++ | ++++ |
| 中風保護(cana) | +++ | ++ |
| 降體重 | ++ | ++ |
| 降血壓 | ++ | + |

# Possible mechanisms for cardiac protective effect of SGLT-2i

- Osmotic diuresis
- NHE 1
- Ketone body

TYPE 2 DIABETES-THE WAY FORWARD

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

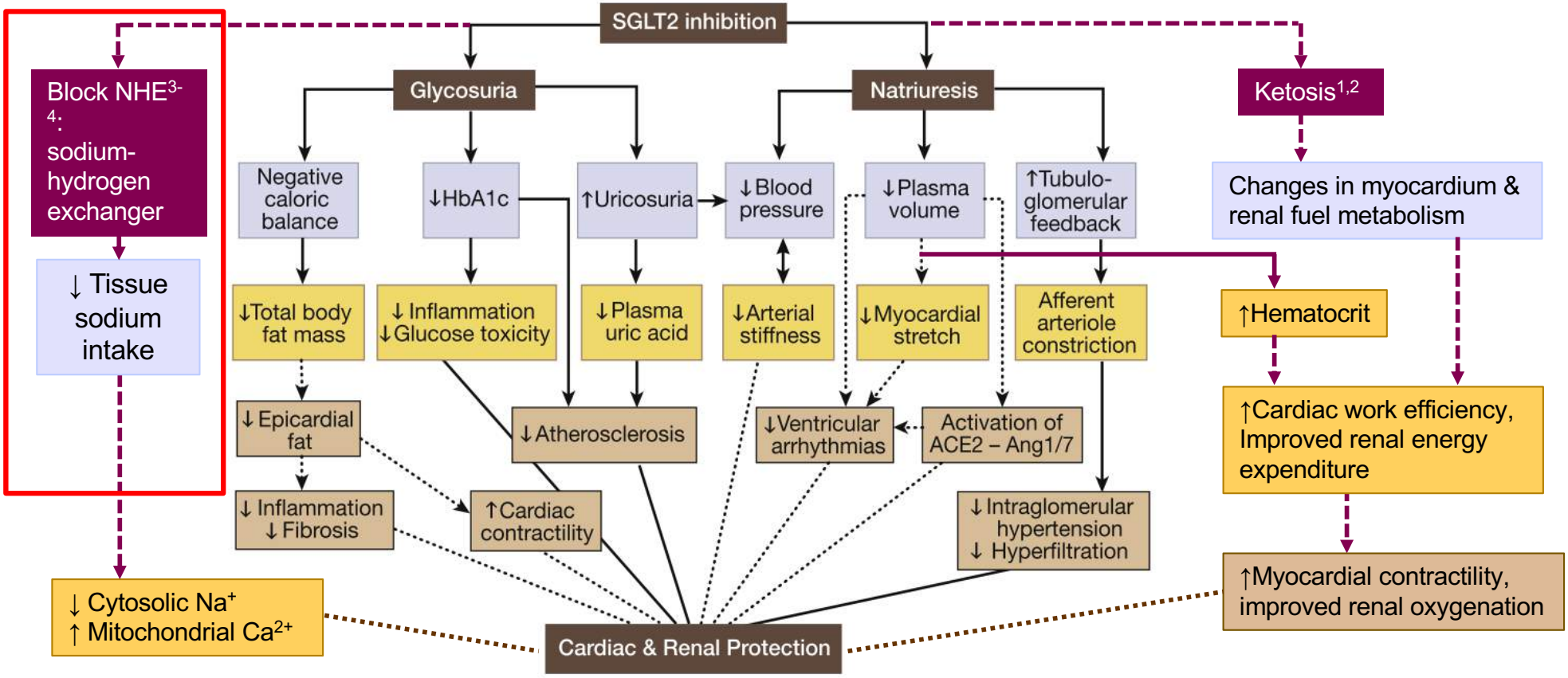



Diabetologia (2018) 61:2108 – 2117

# Osmotic diuresis different from loop diuresis

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

# Proposed Mechanisms of CV & Renal Benefits of SGLT-2 inhibitors

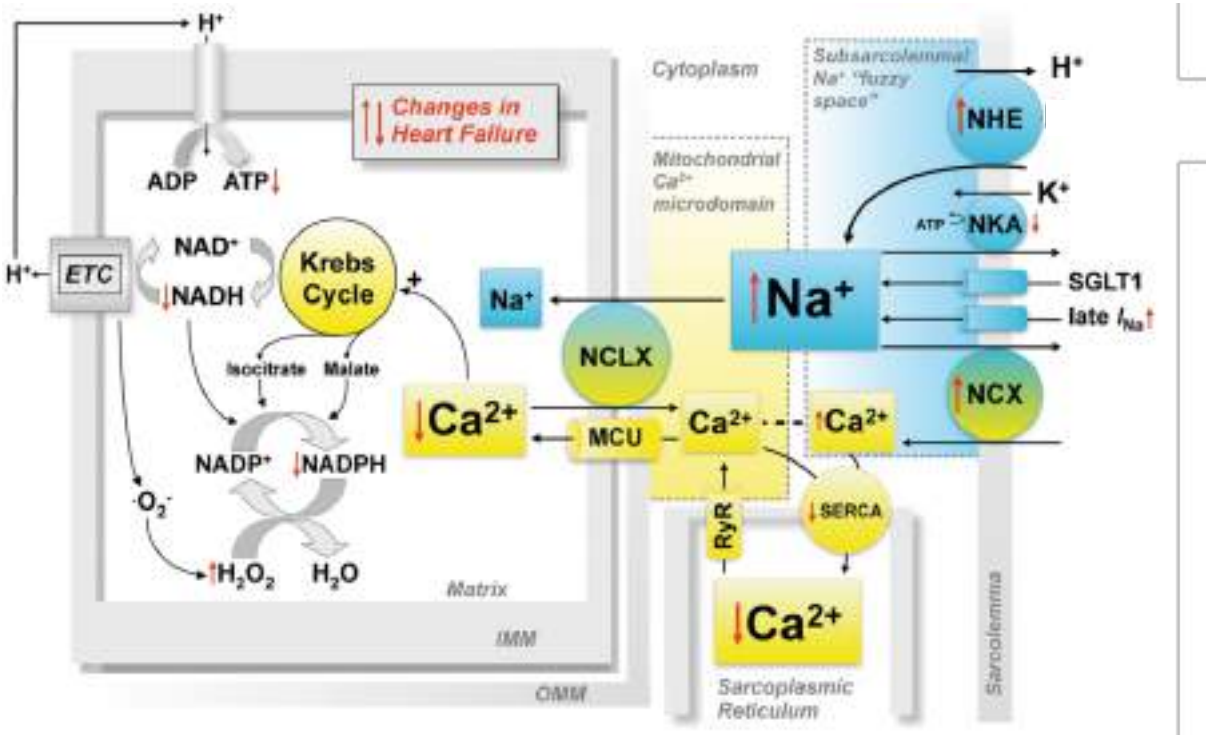



The figure adapted from Kidney Int. 2016 Mar;89(3):524-6., with additional ketosis and NHE hypothesis depicted based on data from

1. Diabetes Care 2016;39:1115-1122., 2. Diabetes Care 2016;39:1108-1114., 3. JAMA Cardiol. 2017 Sep 1;2(9):1025-1029. 4. Cardiovasc Res. 2018 Jan 1;114(1):12-18.

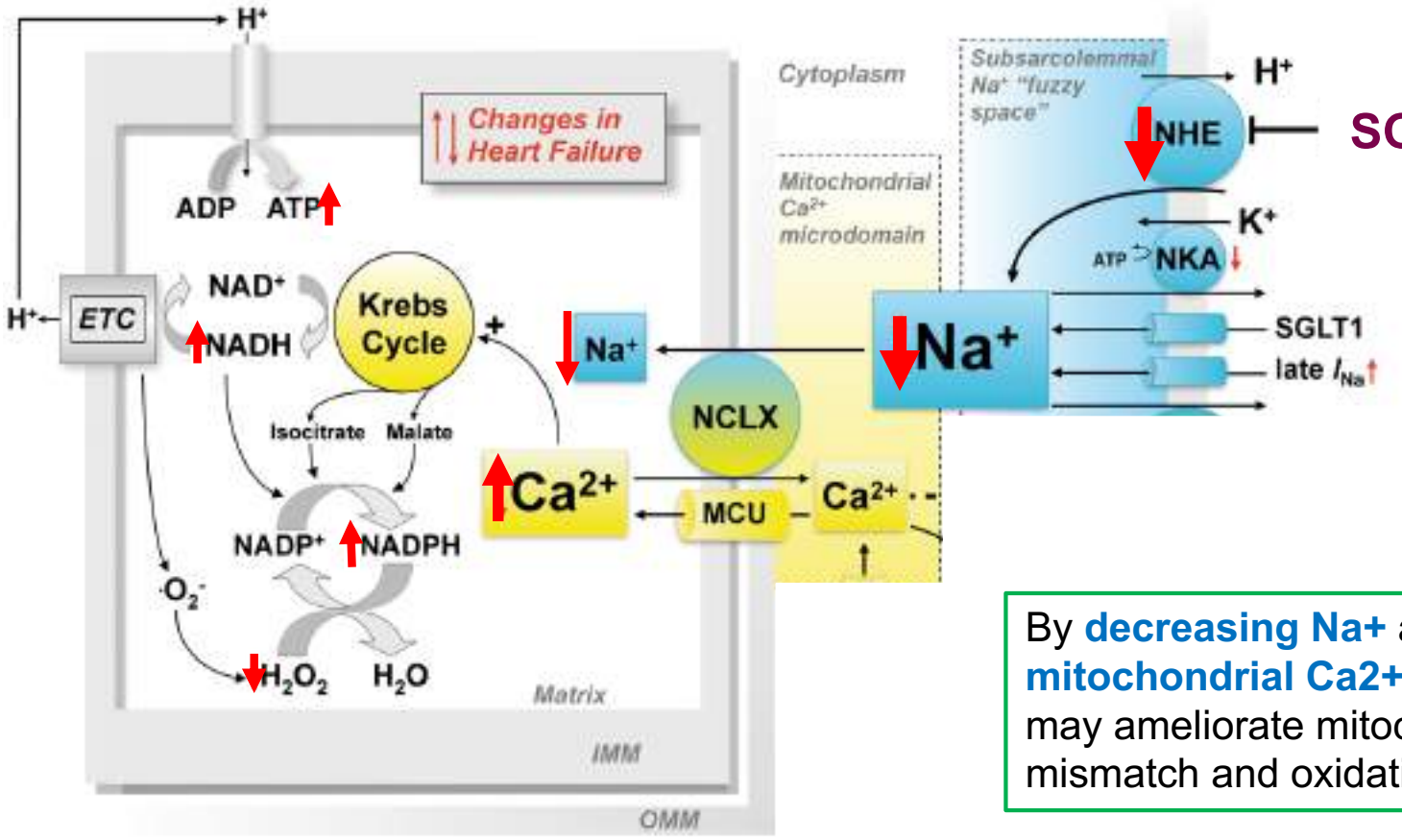
# The sodium hypothesis[1] : Sodium and calcium balance in heart failure patients

- Up-regulation and increased activity of NHE ($Na^+/H^+$ Exchanger) were found in patients with heart failure[2]




1. Bertero E. et al. 2017 Cardiovascular Research. https://doi.org/10.1093/cvr/cvx149 ; 2. International Journal of Cardiology 128 (2008) 147–149 ; 3.Diabetologia. 2017 Dec 2. doi: 10.1007/s00125-017-4509-7

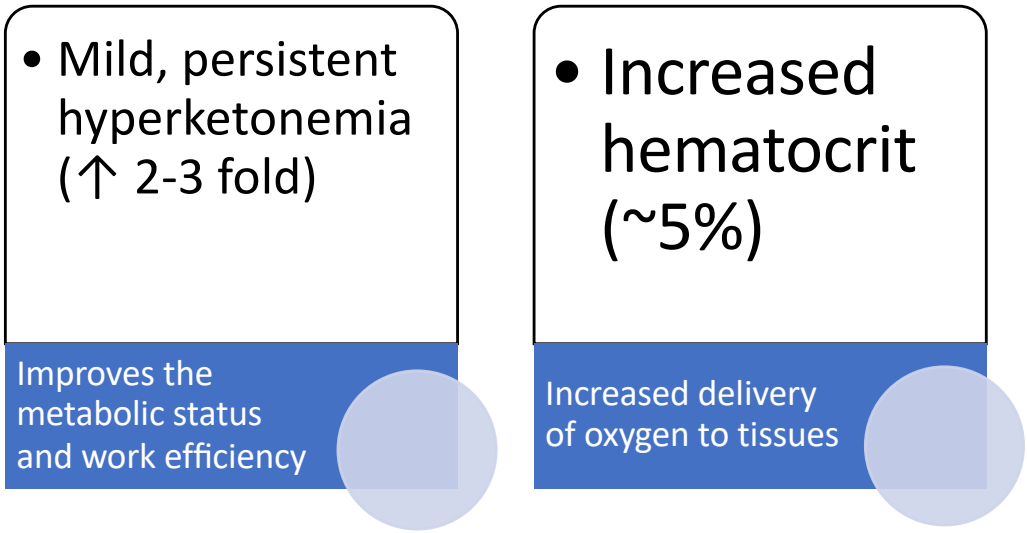
# SGLT2 reduced sodium intake and maintained calcium level




By **decreasing Na+** and restoring **mitochondrial Ca2+** handling, SGLT2i may ameliorate mitochondrial energetic mismatch and oxidative stress.

Bertero E. et al. 2017 Cardiovascular Research. https://doi.org/10.1093/cvr/cvx149

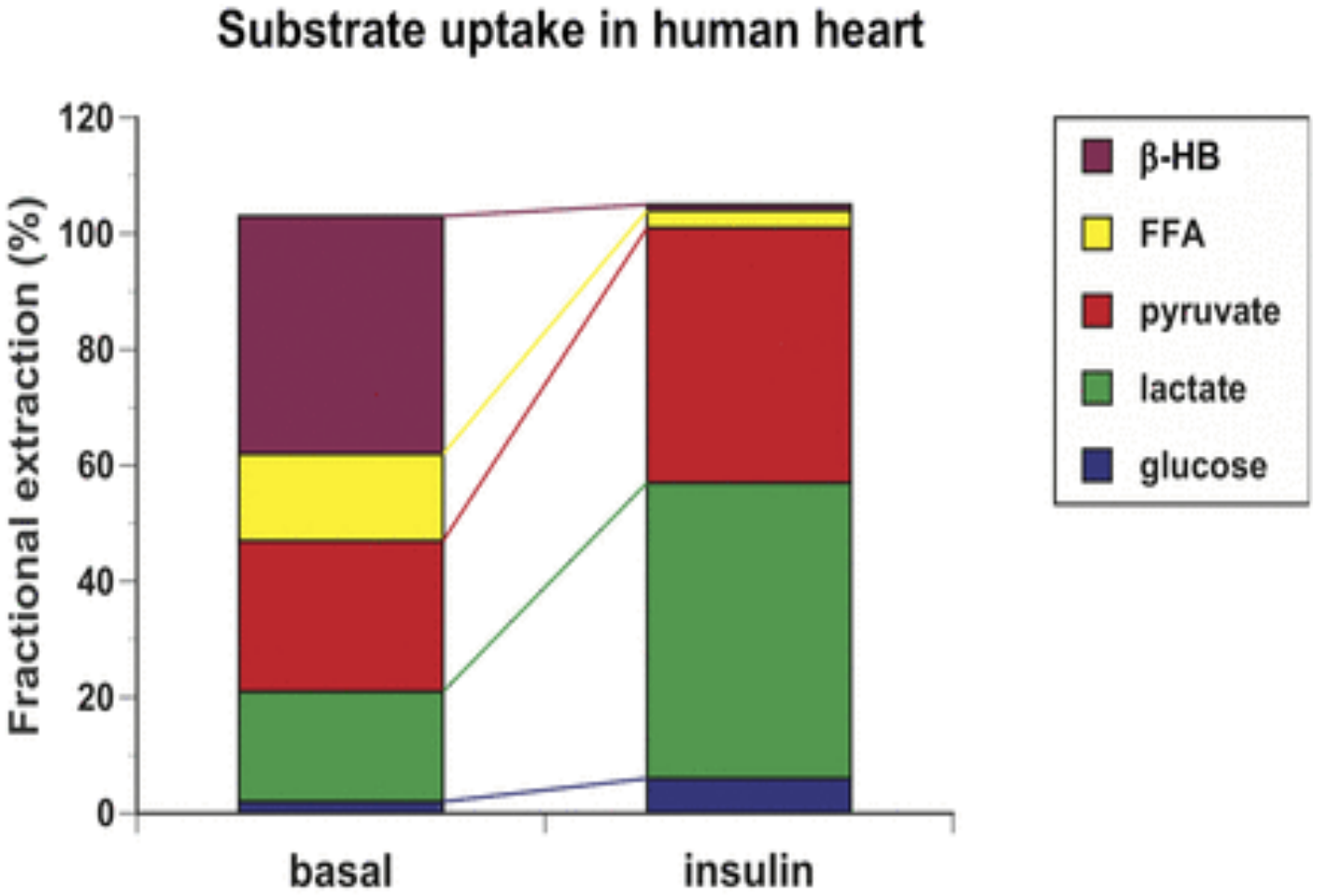
# How SGLT2i help change in organ fuel energetics ?



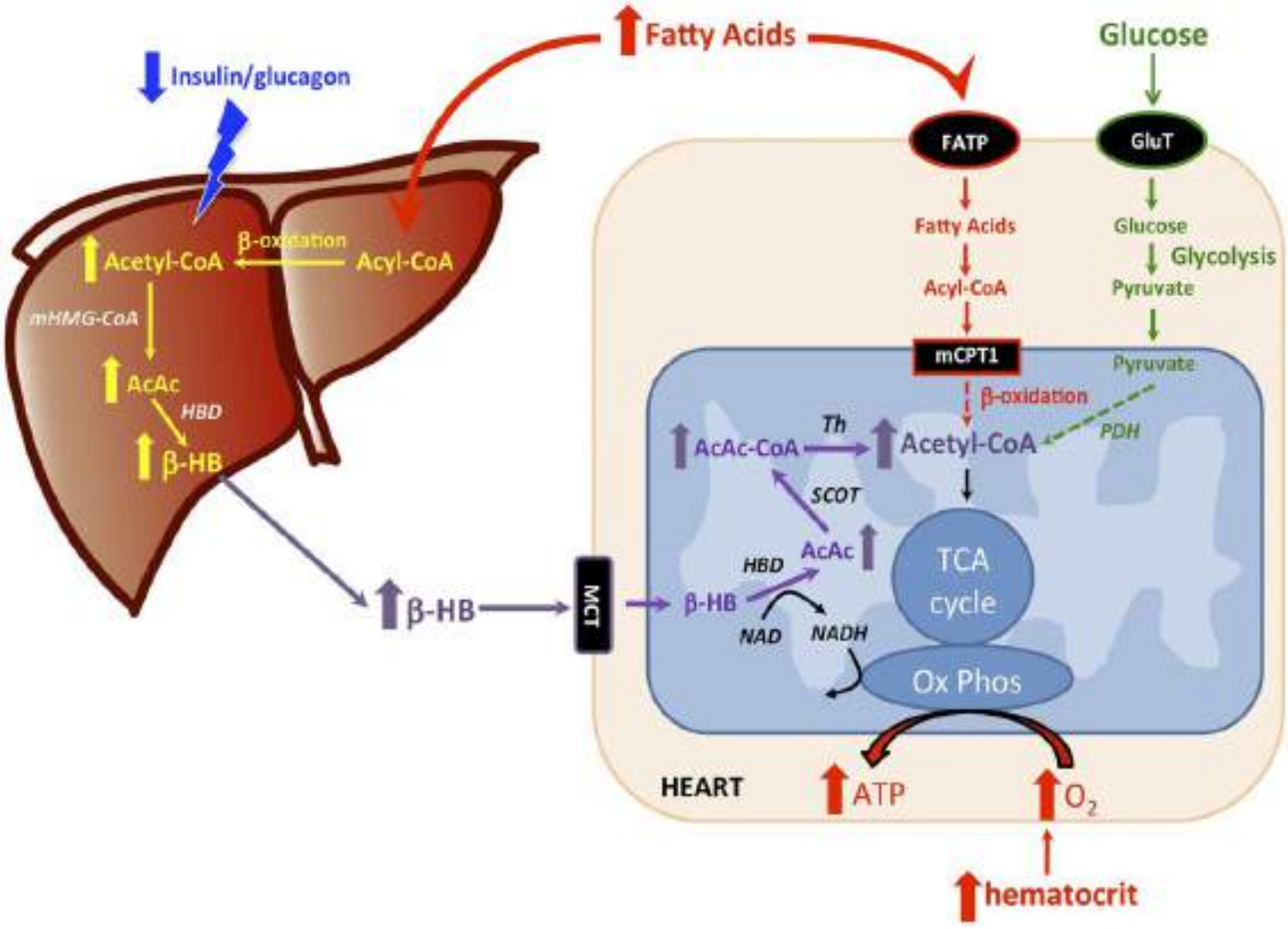

- **Ele Ferrannini et al. Diabetes Care 2016;39:1108-1114**


28

# Thrifty substrate theory



# Thrifty substrate theory

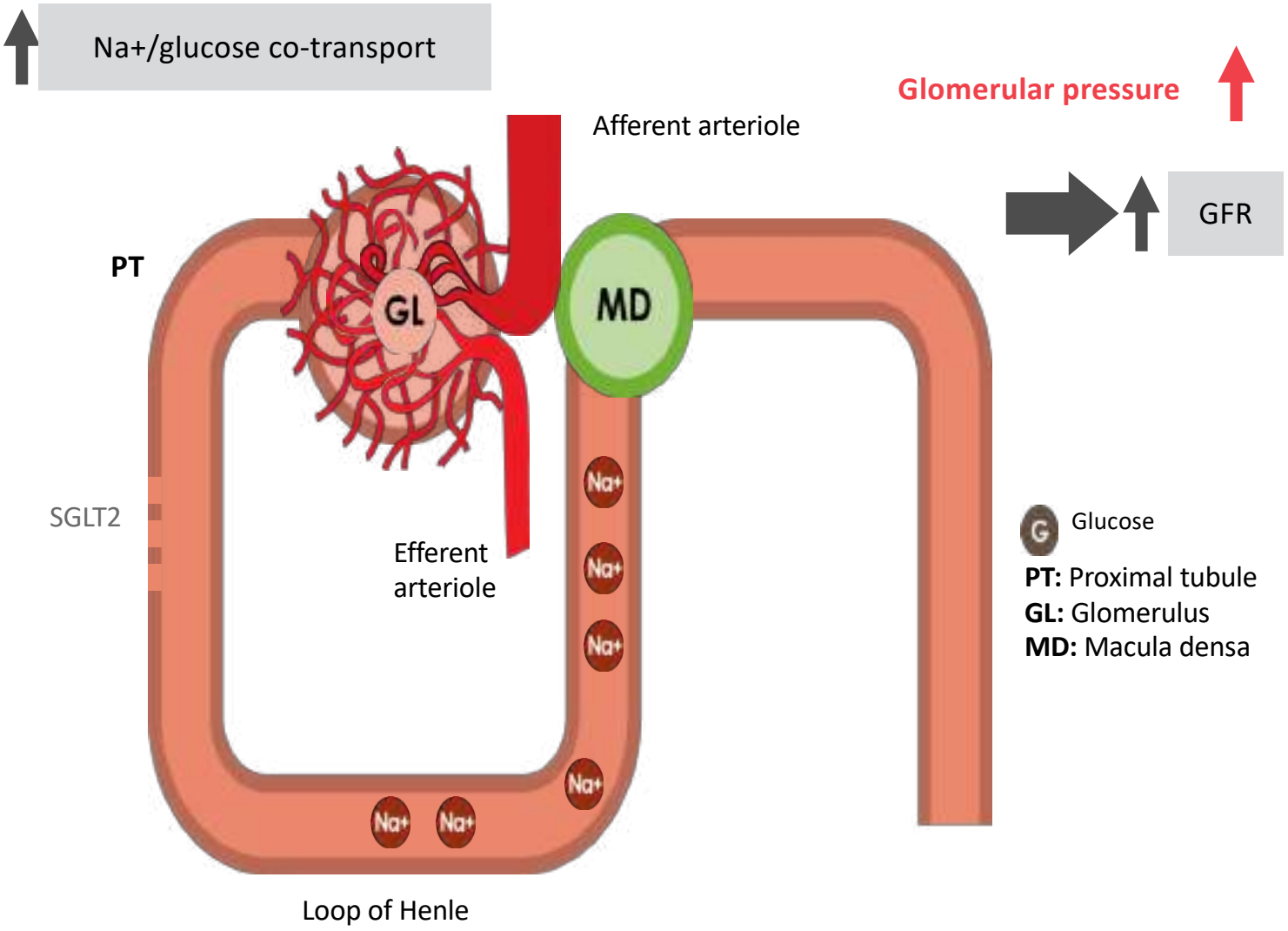


# Possible mechanisms for renal protective effect of SGLT-2i

- TGF
- NHE 3
- Ketone body
- Renal ischemia and EPO

TYPE 2 DIABETES-THE WAY FORWARD

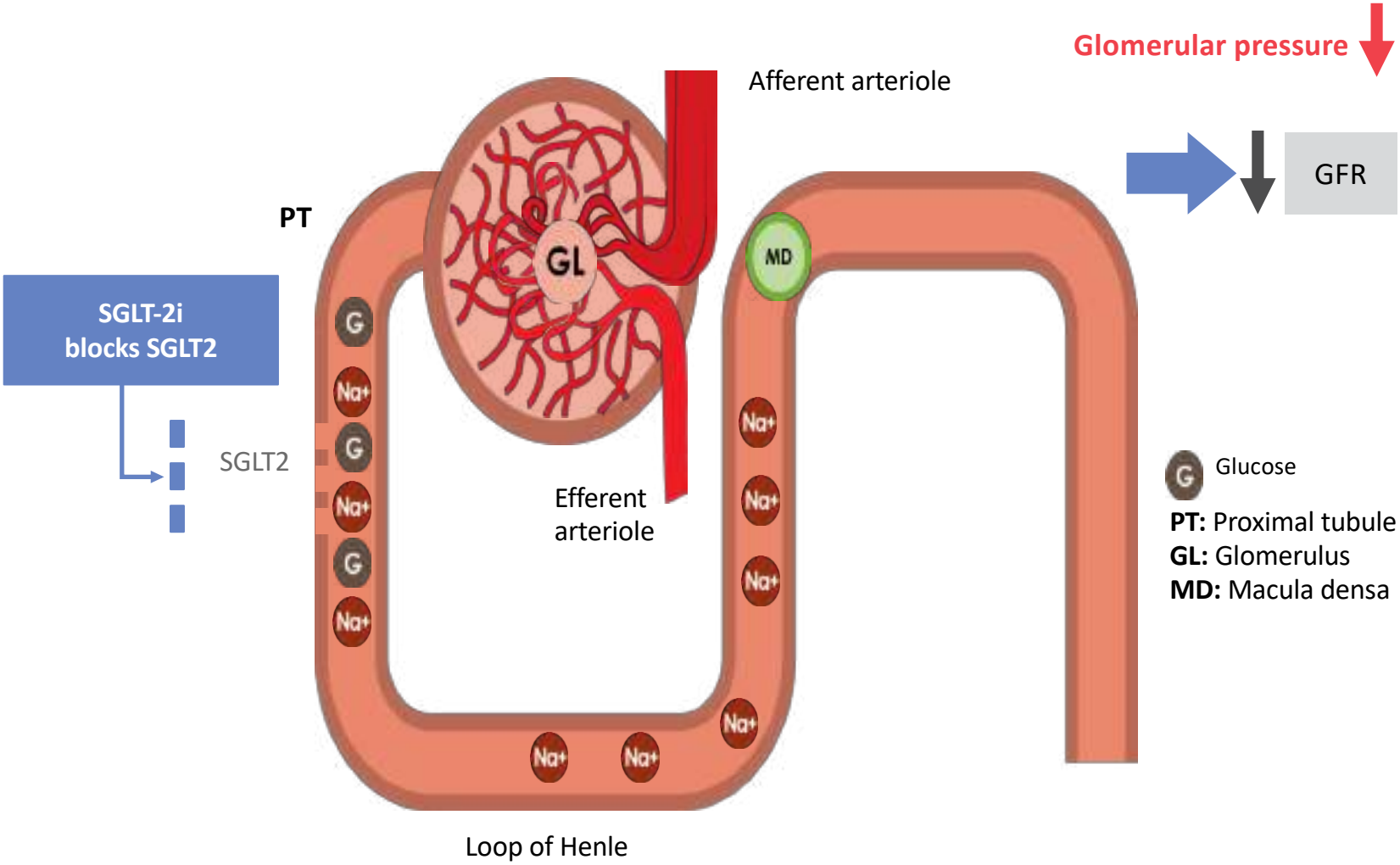
## Diabetes may cause glomerular hypertension




**Renal hemodynamics under hyperglycemia**

SGLT, sodium glucose cotransporter; GFR, glomerular filtration rate.
Adapted from: Cherney D *et al. Circulation* 2014;129:587

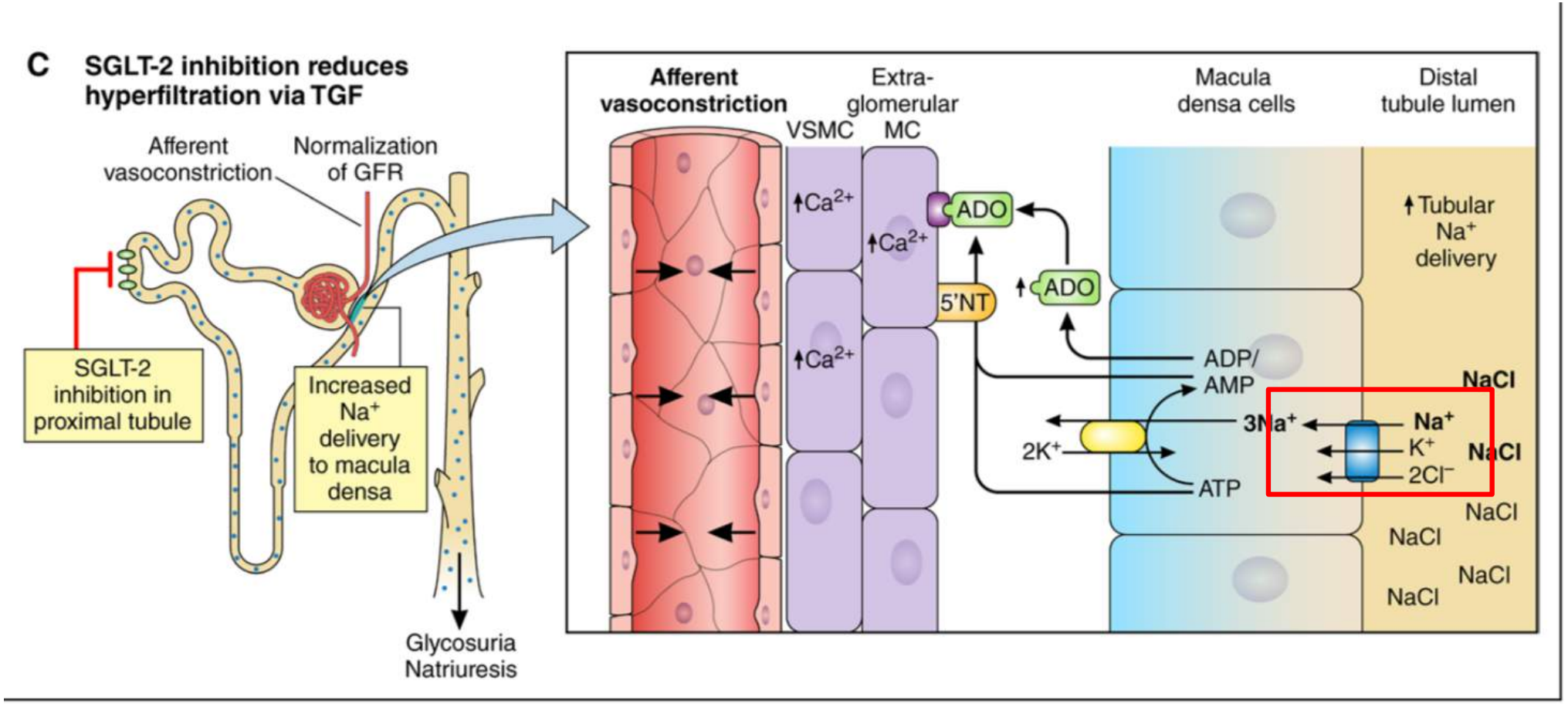
## SGLT2 lowers intraglomerular pressure in T1D




## Renal hemodynamics with SGLT-2

SGLT, sodium glucose cotransporter; GFR, glomerular filtration rate.
Adapted from: Cherney D *et al. Circulation* 2014;129:587

# tubular glomerular feedback



# Why loop diuretic can’t induce TGF

**SGLT2i**

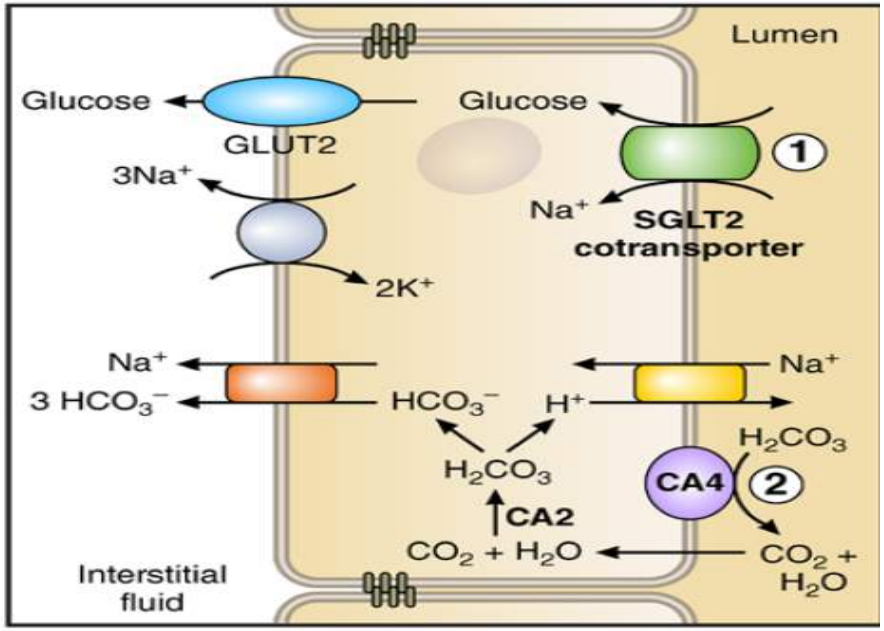
- ↑ Natriuresis
- ↓ PV
- ↓ Blood pressure
- ↓ Nephropathy events
- ↓ CV events (including in HHF)

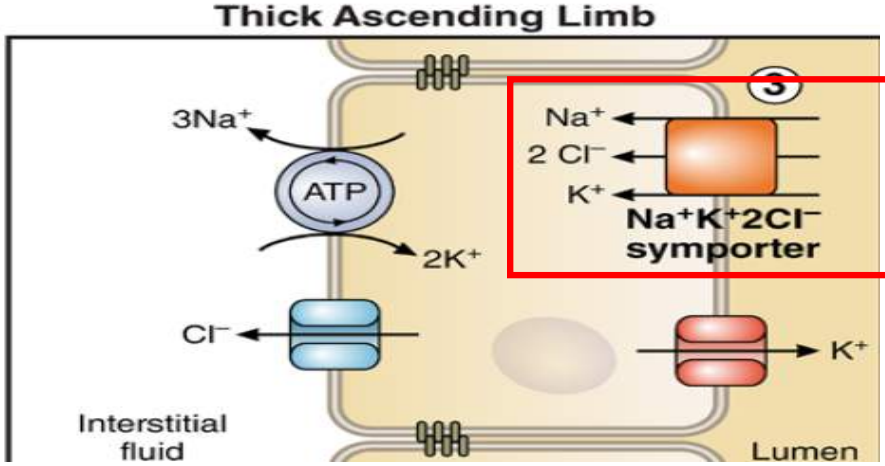
**Carbonic Anhydrase Inhibitors**

No known effect(s) on HHF

**Loop Diuretics**

- ↑ Natriuresis
- ↓ PV/volume overload
- ↓ Preload
- ↓ HHF



# SGLT-2i and NHE3

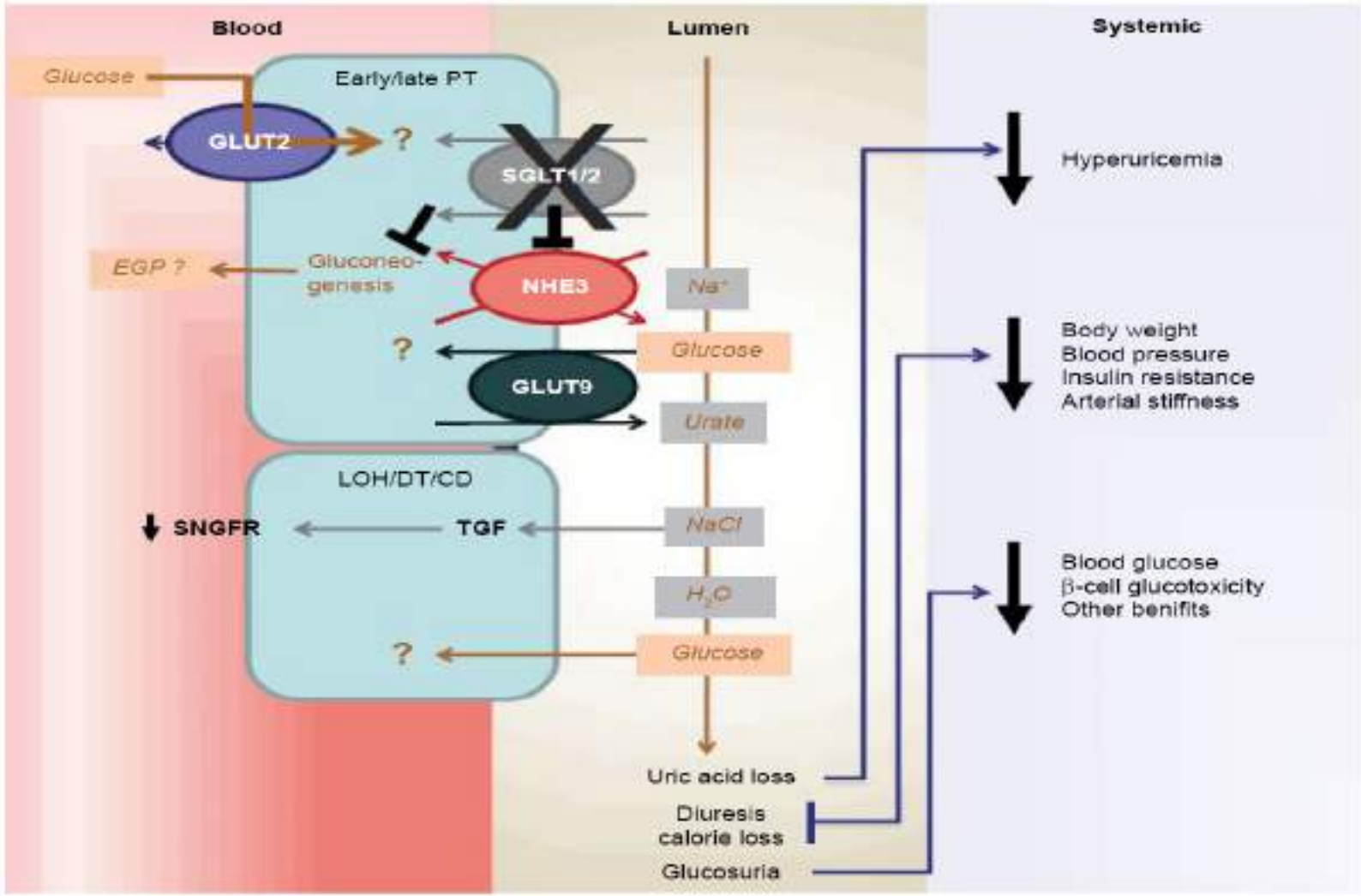
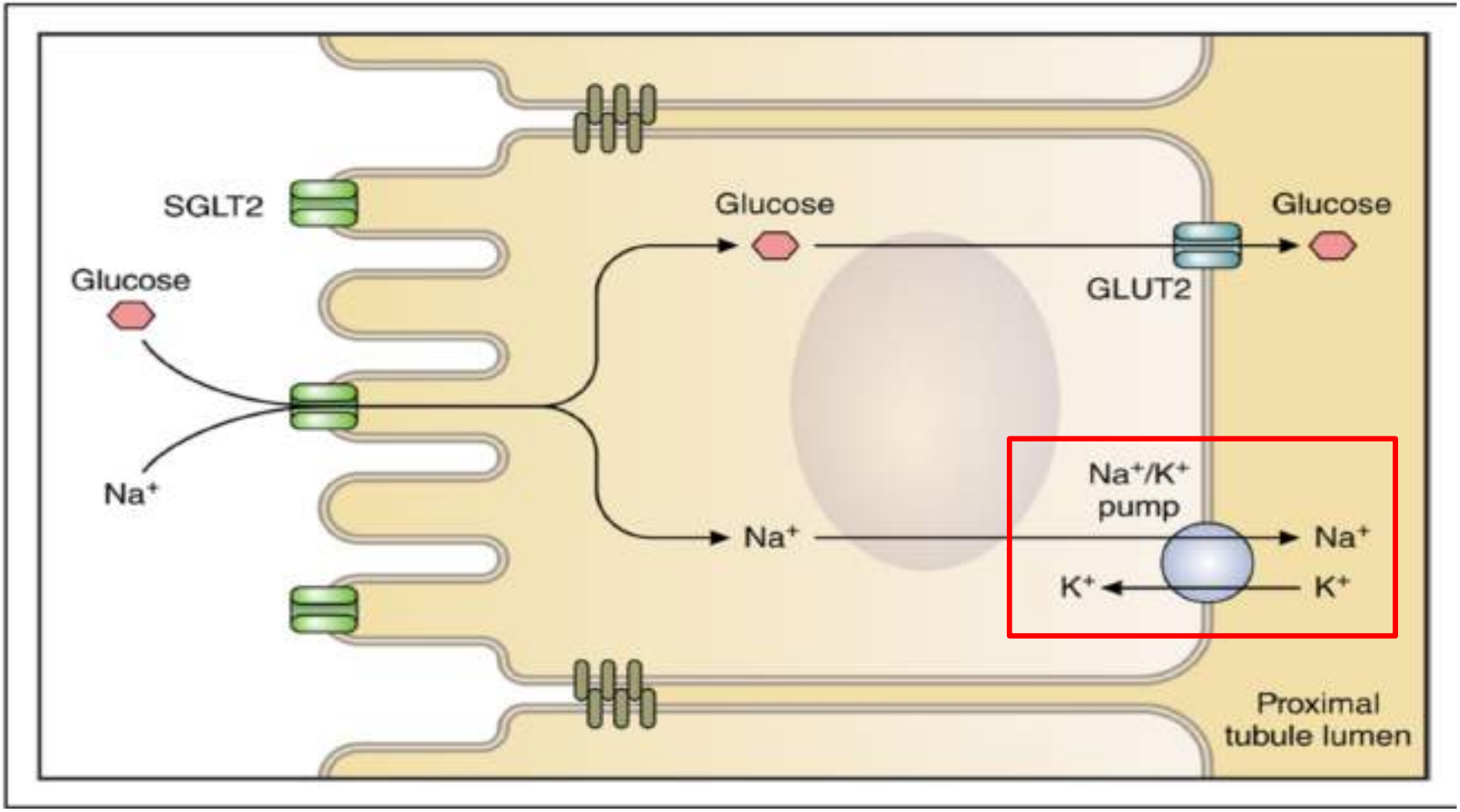



**Figure 2** Downstream renal effects of SGLT1 and SGLT2 inhibition.
**Note:** Reproduced from Gallo LA, Wright EM, Vallon V. Probing SGLT2 as a therapeutic target for diabetes: basic physiology and consequences. *Diab Vasc Dis Res.* 2015;12(2):78–89,[4] copyright ©2015 by (SAGE Publications). Reprinted by Permission of SAGE Publications, Ltd.
**Abbreviations:** GLUT, glucose transporter; SGLT, sodium glucose transporter; PT, proximal tubule; LOH, loop of Henle; DT, distal tubule; CD, collecting duct; NHE3, sodium hydrogen exchanger-3; EGP, endogenous glucose production; SNGFR, single nephron glomerular filtration rate; TGF, tubuloglomerular feedback.

# Renal ischemia and EPO



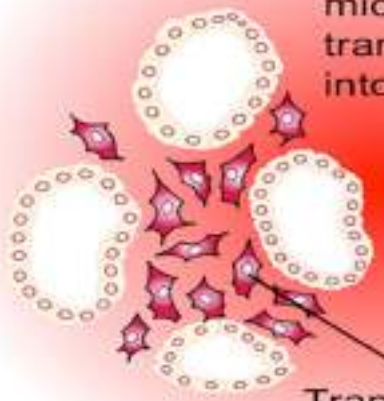
# SGLT-2i therapy suppresses oxygen consumption by the proximal tubules and improves tubulointerstitial hypoxia

## T2DM

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

Changes of the microenvironment induce transformation of fibroblasts into myofibroblasts.

Interstitial fibrosis progresses and EPO production declines

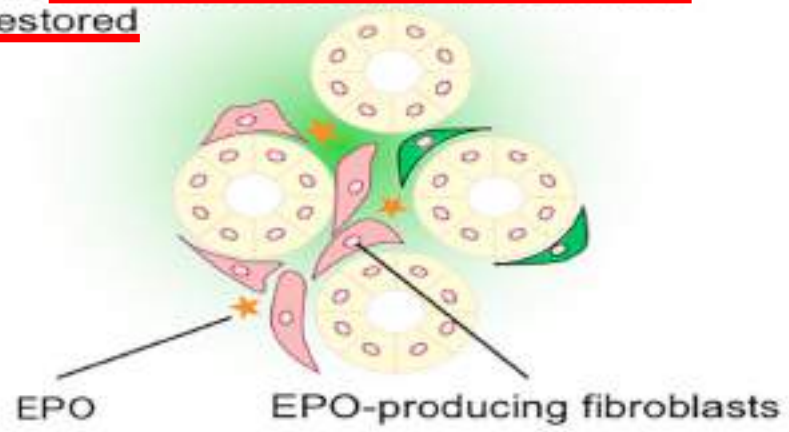


Transformed fibroblasts

## T2DM with SGLT2 inhibition

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

Cortical tubulointerstitial damage recovers and EPO production by fibroblasts is restored



EPO

EPO-producing fibroblasts

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.

# 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.

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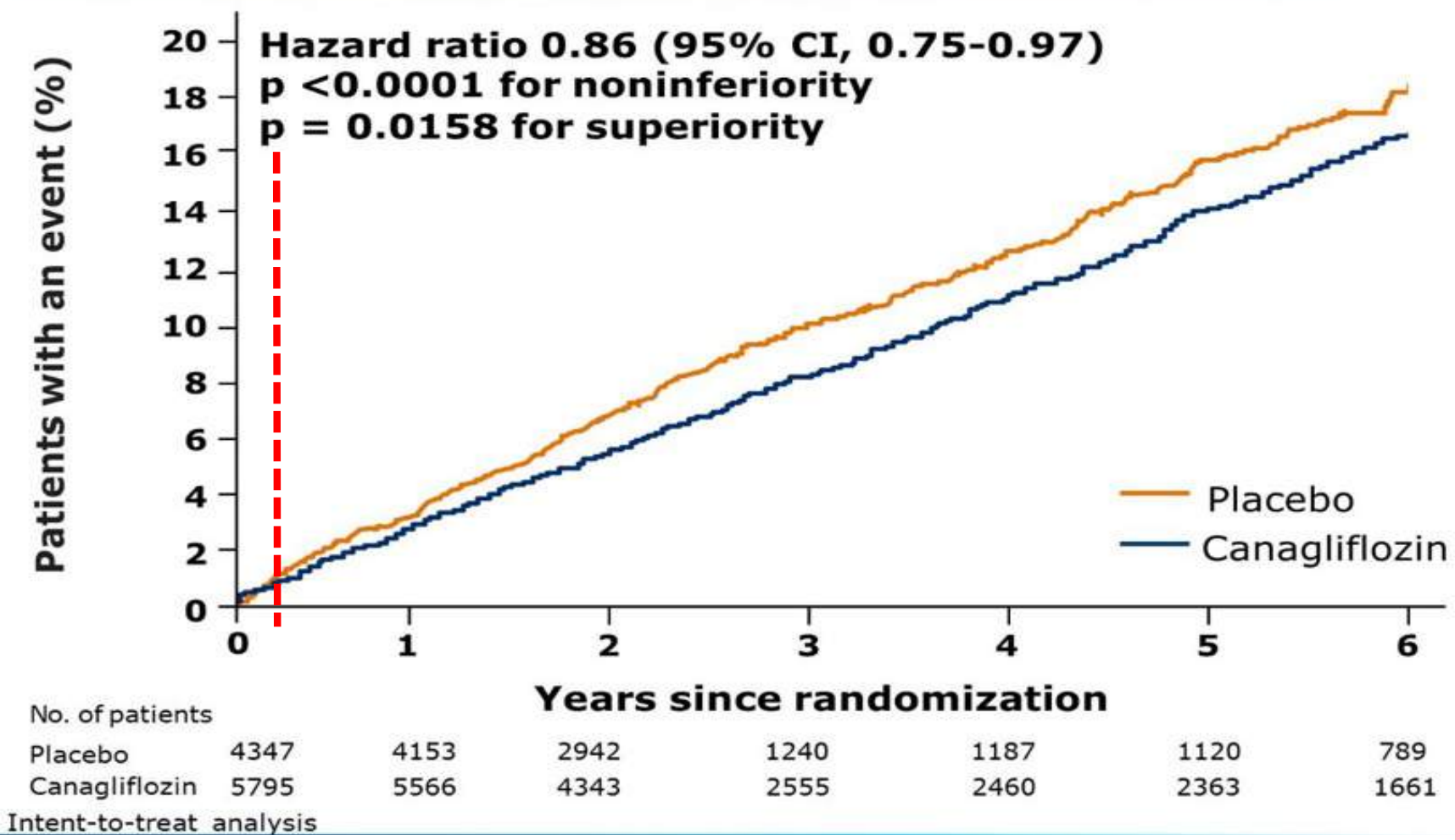
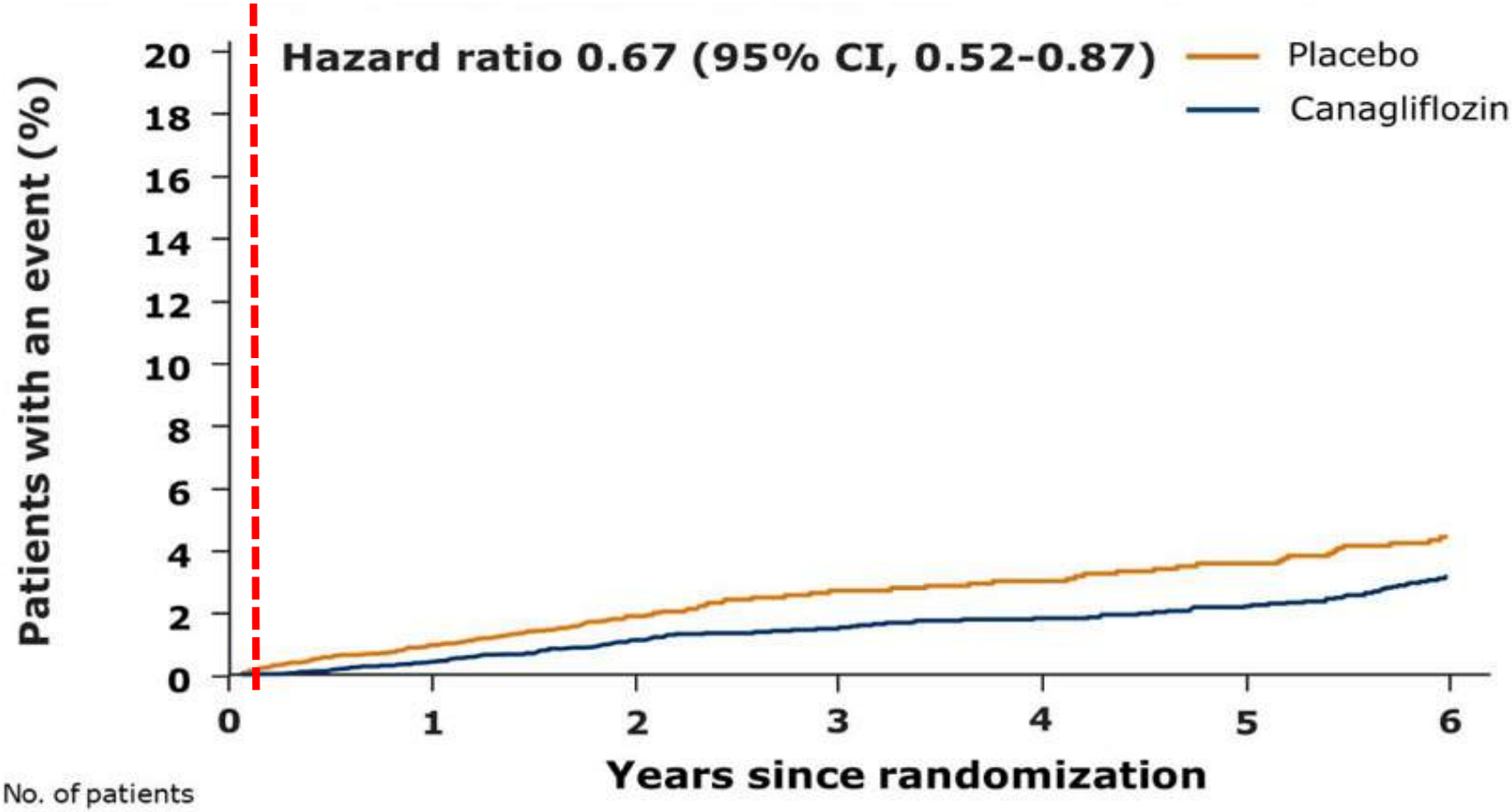
# Primary Mace Outcome

## CV Death, Non-fatal Myocardial Infarction or Non-fatal Stroke



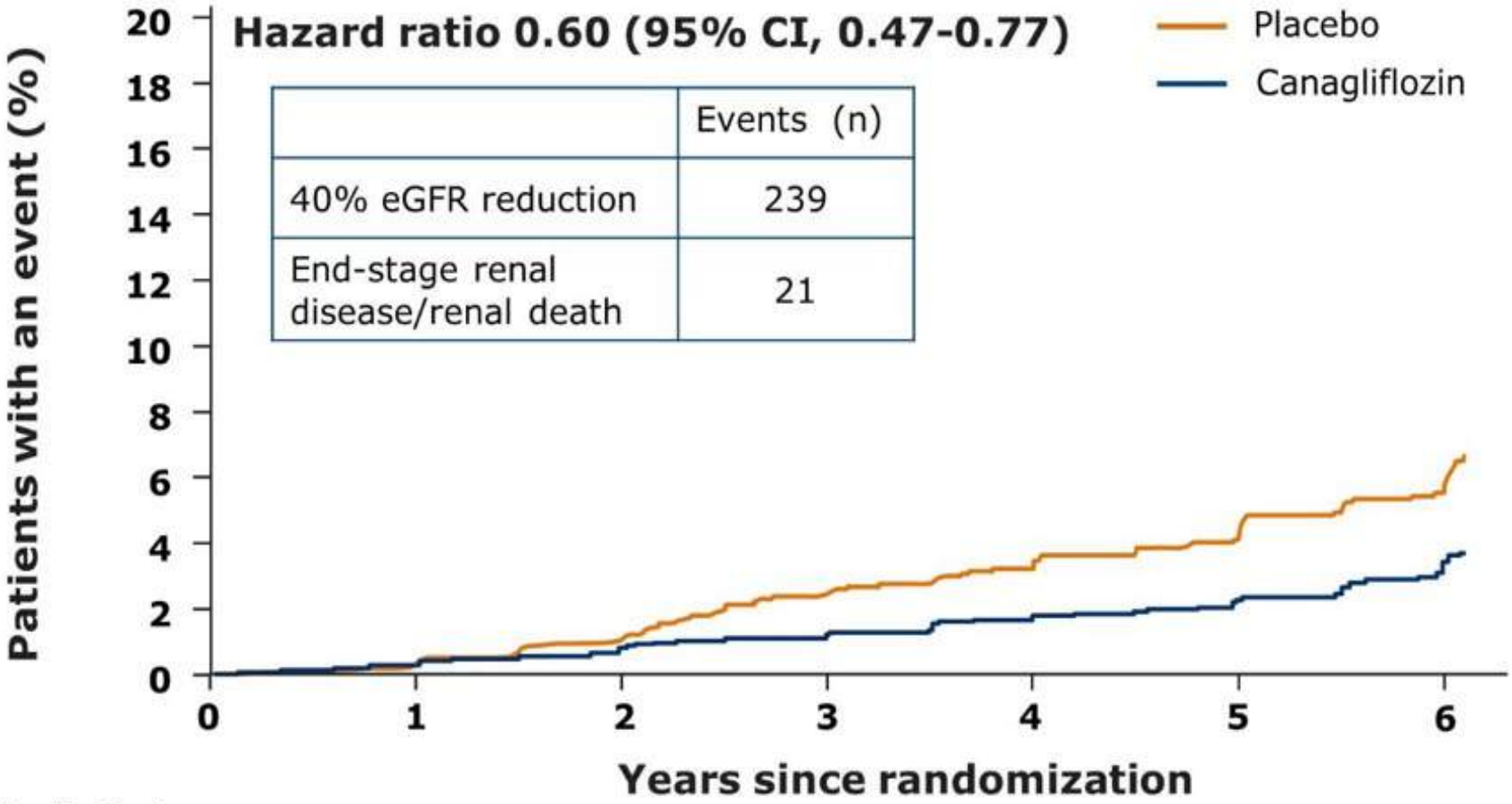

N Engl J Med 2017; 377:644-657 (Ref. 9)

# Hospitalization for Heart Failure




N Engl J Med 2017; 377:644-657 (Ref. 9)

# Composite of 40% Reduction in eGFR, End-stage Renal Disease, or Renal Death




N Engl J Med 2017; 377:644-657 (Ref. 9)

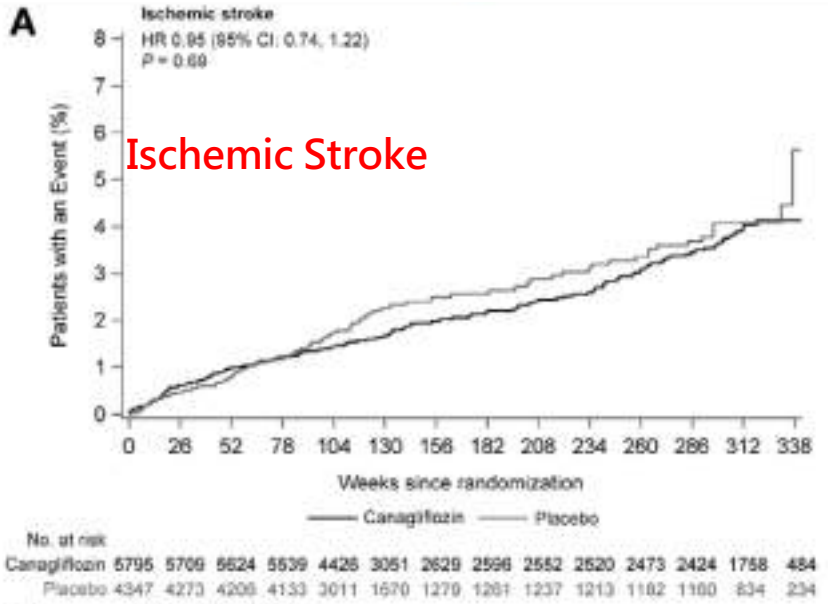
# Canagliflozin and Stroke in Type 2 Diabetes Mellitus Results From the Randomized CANVAS Program Trials

| | Number of participants with an event | Participants with an event per 1000 patient-years | | HR (95% CI) |
|---|---|---|---|---|
| | | Canagliflozin | Placebo | |
| **All stroke** | 309 | 7.93 | 9.62 | 0.87 (0.69, 1.09) |
| Ischemic | 253 | 6.70 | 7.51 | 0.95 (0.74, 1.22) |
| Hemorrhagic | 30 | 0.53 | 1.29 | 0.43 (0.20, 0.89) |
| Undetermined | 29 | 0.80 | 0.79 | 1.04 (0.48, 2.22) |
| Fatal | 39 | 0.95 | 1.18 | 0.84 (0.44, 1.59) |
| Nonfatal | 274 | 7.12 | 8.39 | 0.90 (0.71, 1.15) |
| **TIA*** | 88 | 2.32 | 2.59 | 0.86 (0.56, 1.32) |
| **All stroke or TIA*** | 377 | 9.93 | 11.49 | 0.89 (0.73, 1.10) |

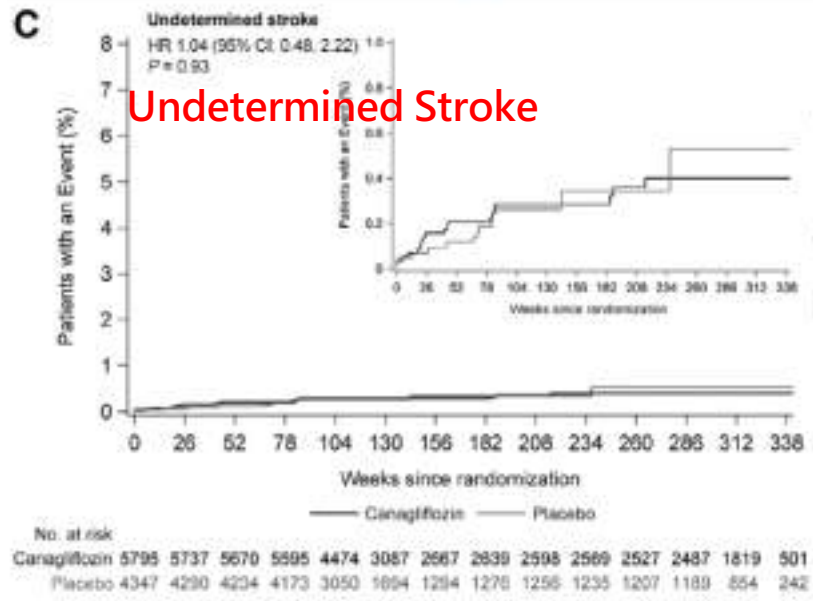

*TIAs were not adjudicated but based upon adverse event reports made by site investigators.

*Stroke*. 2019;50:00-00. DOI: 10.1161/STROKEAHA.118.023009

# Canagliflozin and Stroke in Type 2 Diabetes Mellitus Results From the Randomized CANVAS Program Trials

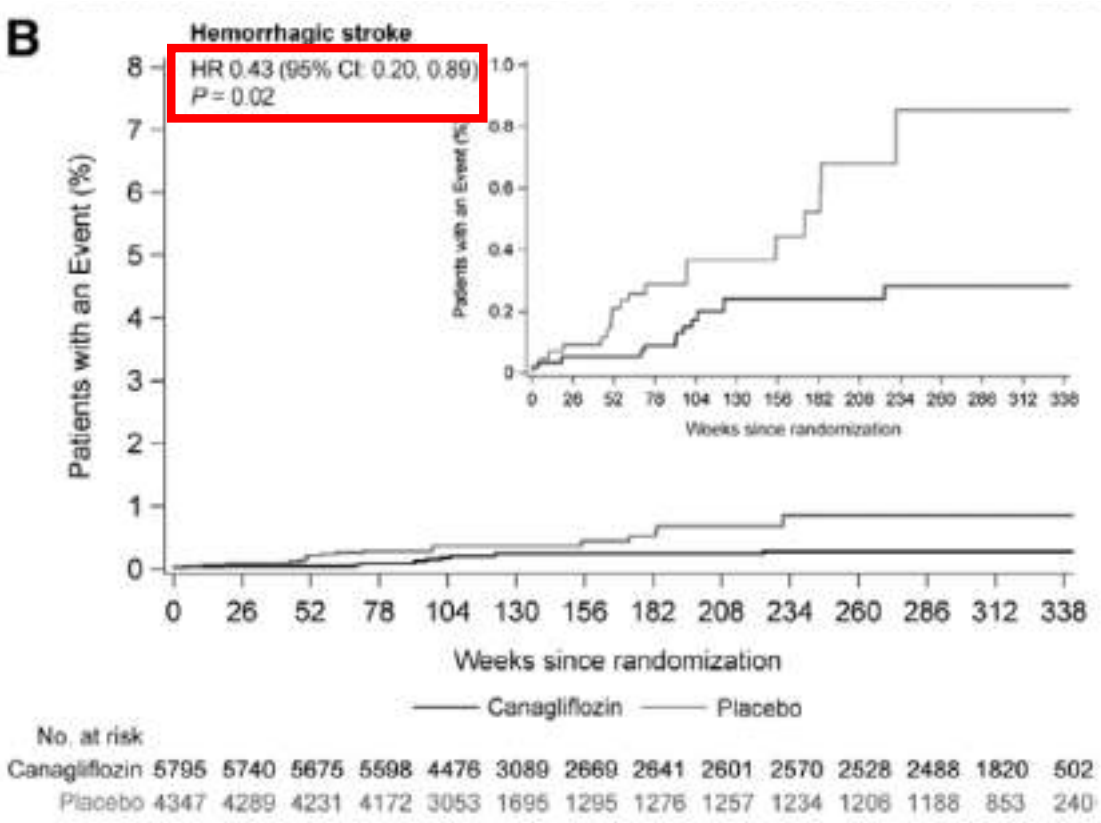



Ischemic Stroke




Undetermined Stroke

Hemorrhagic Stroke




***Stroke*. 2019;50:00-00. DOI: 10.1161/STROKEAHA.118.023009**

# Canagliflozin and Stroke in Type 2 Diabetes Mellitus Results From the Randomized CANVAS Program Trials

**Table 1. Effects of Canagliflozin on Possible Intermediate Markers of Stroke Risk**

| | Change From Baseline to the Last Measurement* | | Mean Treatment Difference (95% CI)† | *P* Value |
|---|---|---|---|---|
| | Canagliflozin | Placebo | | |
| Systolic BP, mmHg | −4.86 (0.19) | −1.73 (0.22) | −3.14 (−3.71, −2.57) | <0.001 |
| Diastolic BP, mmHg | −3.21 (0.11) | −2.39 (0.13) | −0.82 (−1.15, −0.48) | <0.001 |
| Body weight, kg | −3.21 (0.08) | −0.81 (0.09) | −2.40 (−2.64, −2.17) | <0.001 |
| HbA1c, % | −0.42 (0.02) | −0.03 (0.02) | −0.39 (−0.44, −0.34) | <0.001 |
| HDL-C, mmol/L | 0.04 (0.00) | −0.01 (0.00) | 0.05 (0.04, 0.06) | <0.001 |
| LDL-C, mmol/L | 0.08 (0.01) | −0.03 (0.01) | 0.12 (0.08, 0.15) | <0.001 |
| Ratio of LDL-C to HDL-C, % | 0.32 (1.09) | −0.70 (1.31) | 1.02 (−2.33, 4.36) | 0.55 |
| Triglycerides, mmol/L | 0.08 (0.02) | 0.02 (0.02) | 0.06 (0.00, 0.11) | 0.04 |
| Total cholesterol, mmol/L | 0.14 (0.01) | −0.04 (0.02) | 0.18 (0.14, 0.22) | <0.001 |
| Hematocrit, % | 1.63 (0.05) | −0.90 (0.06) | 2.53 (2.38, 2.68) | <0.001 |
| Albumin:creatinine ratio, mg/g | 21.01 (6.30) | 84.55 (7.49) | −63.55 (−82.73, −44.36) | <0.001 |
| eGFR, mL/min per 1.73 $m^2$ | −1.82 (0.19) | −3.87 (0.23) | 2.05 (1.47, 2.62) | <0.001 |

***Stroke*. 2019;50:00-00. DOI: 10.1161/STROKEAHA.118.023009**

# Canagliflozin and Cardiovascular Outcomes in Patients with Chronic Kidney Disease

Circulation

ORIGINAL RESEARCH ARTICLE

## Cardiovascular and Renal Outcomes With Canagliflozin According to Baseline Kidney Function

### Data From the CANVAS Program

*Circulation.* 2018;138:1537–1550

# Canagliflozin and Cardiovascular Outcomes in Patients with Chronic Kidney Disease(eGFR<60)

A. MACE HR: 0.70

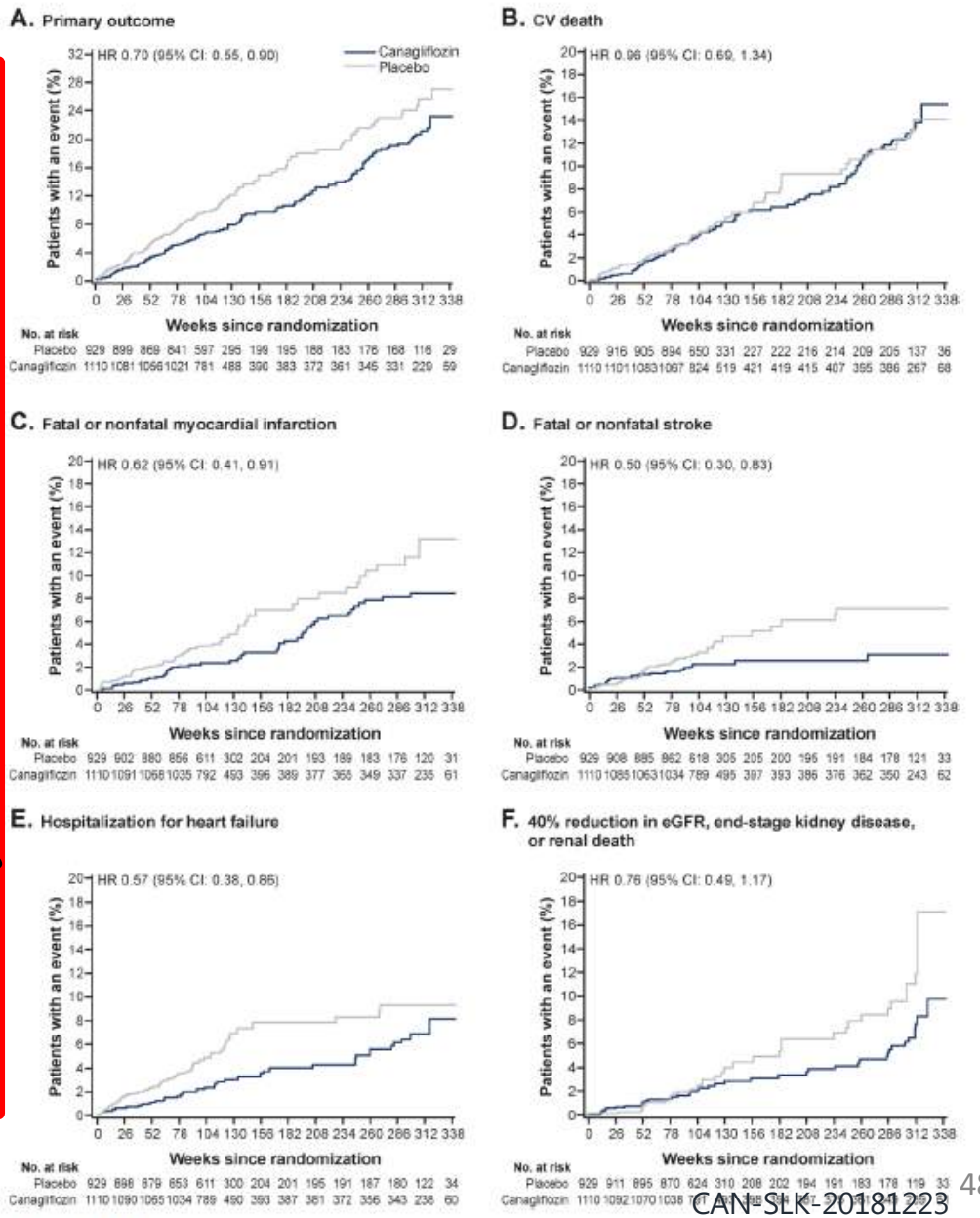
B. CV Death HR: 0.93

C. Fatal & non-Fatal MI
HR: 0.62

D. Fatal & non-Fatal Stroke
HR: 0.50

E. Hospitalization of HF
HR: 0.57

F. 40% Reduction of eGFR、ESRD & Renal Death
HR: 0.76

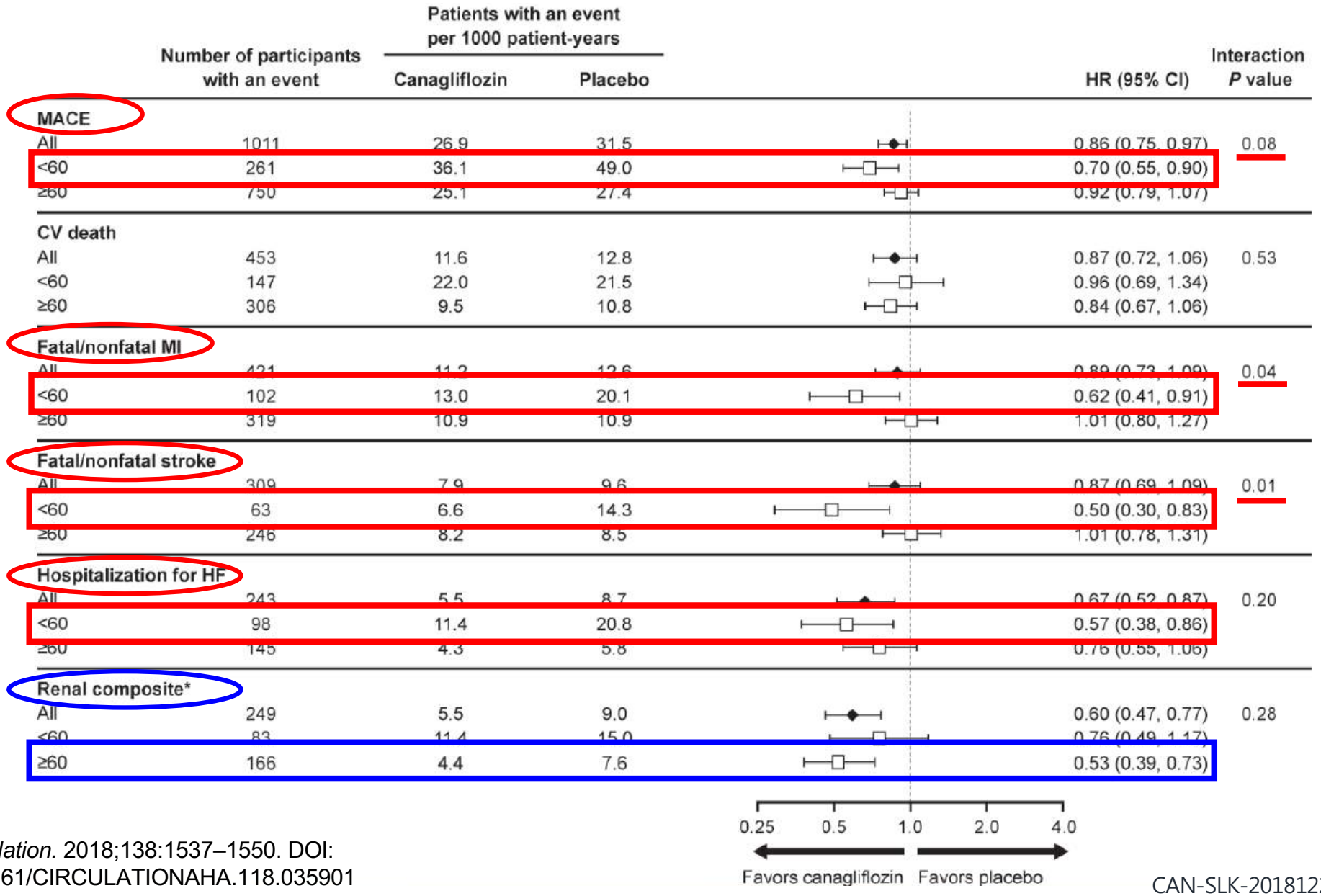



*Circulation.* 2018;138:1537–1550. DOI: 10.1161/CIRCULATIONAHA.118.035901



CAN-SLK-20181223

# Canagliflozin and Cardiovascular Outcomes in Patients with Chronic Kidney Disease

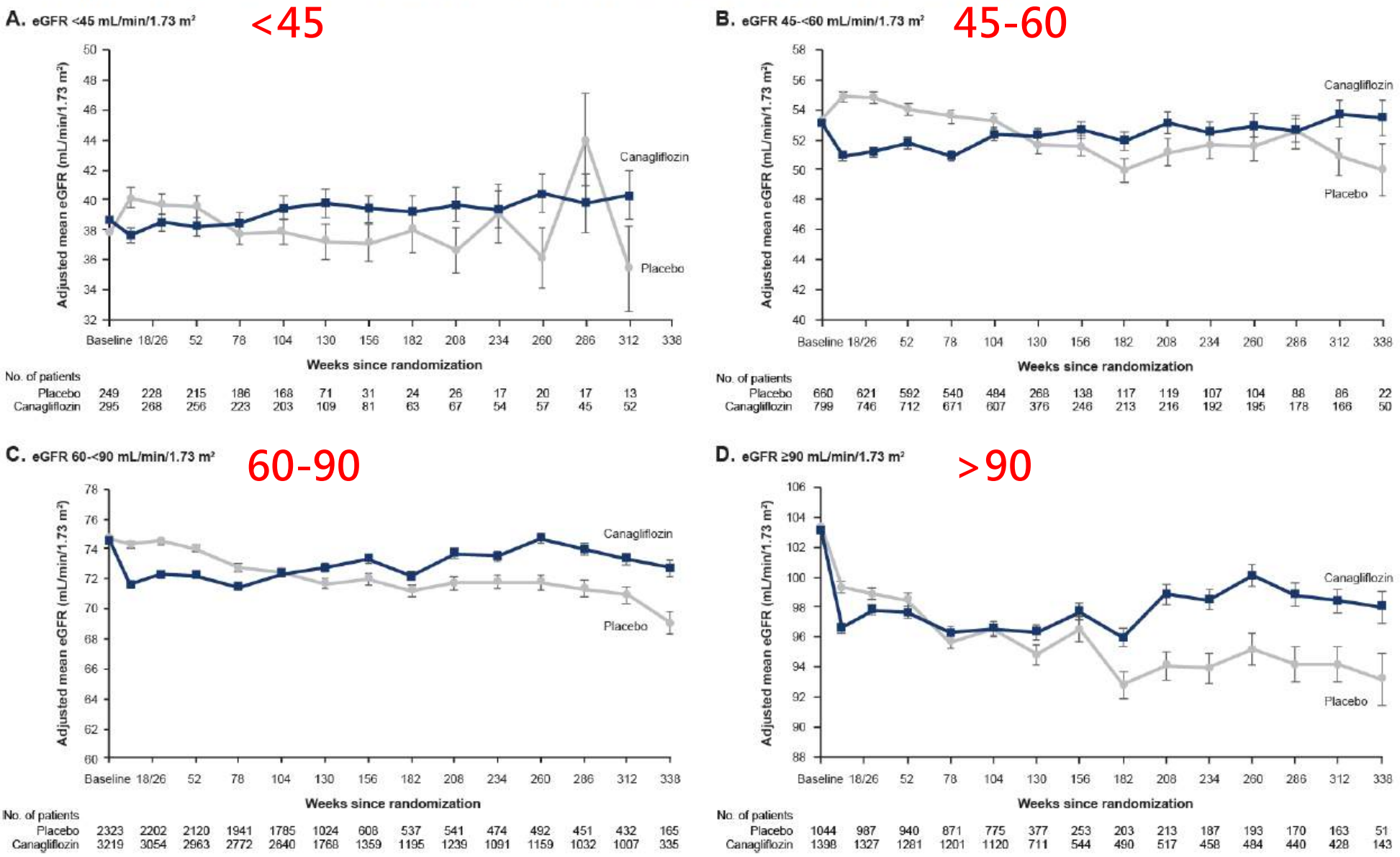


| | Number of participants with an event | Patients with an event per 1000 patient-years | | HR (95% CI) | Interaction *P* value |
|---|---|---|---|---|---|
| | | Canagliflozin | Placebo | | |
| **MACE** | | | | | |
| All | 1011 | 26.9 | 31.5 | 0.86 (0.75, 0.97) | 0.08 |
| <60 | 261 | 36.1 | 49.0 | 0.70 (0.55, 0.90) | |
| ≥60 | 750 | 25.1 | 27.4 | 0.92 (0.79, 1.07) | |
| **CV death** | | | | | |
| All | 453 | 11.6 | 12.8 | 0.87 (0.72, 1.06) | 0.53 |
| <60 | 147 | 22.0 | 21.5 | 0.96 (0.69, 1.34) | |
| ≥60 | 306 | 9.5 | 10.8 | 0.84 (0.67, 1.06) | |
| **Fatal/nonfatal MI** | | | | | |
| All | 421 | 11.2 | 12.6 | 0.89 (0.73, 1.09) | 0.04 |
| <60 | 102 | 13.0 | 20.1 | 0.62 (0.41, 0.91) | |
| ≥60 | 319 | 10.9 | 10.9 | 1.01 (0.80, 1.27) | |
| **Fatal/nonfatal stroke** | | | | | |
| All | 309 | 7.9 | 9.6 | 0.87 (0.69, 1.09) | 0.01 |
| <60 | 63 | 6.6 | 14.3 | 0.50 (0.30, 0.83) | |
| ≥60 | 246 | 8.2 | 8.5 | 1.01 (0.78, 1.31) | |
| **Hospitalization for HF** | | | | | |
| All | 243 | 5.5 | 8.7 | 0.67 (0.52, 0.87) | 0.20 |
| <60 | 98 | 11.4 | 20.8 | 0.57 (0.38, 0.86) | |
| ≥60 | 145 | 4.3 | 5.8 | 0.76 (0.55, 1.06) | |
| **Renal composite*** | | | | | |
| All | 249 | 5.5 | 9.0 | 0.60 (0.47, 0.77) | 0.28 |
| <60 | 83 | 11.4 | 15.0 | 0.76 (0.49, 1.17) | |
| ≥60 | 166 | 4.4 | 7.6 | 0.53 (0.39, 0.73) | |



*Circulation.* 2018;138:1537–1550. DOI: 10.1161/CIRCULATIONAHA.118.035901

# Change in eGFR over time with canagliflozin and placebo with eGFR



# New Indication for INVOKANA® (canagliflozin) to Reduce the Risk of Major Adverse Cardiovascular Events (MACE)

October 30, 2018

## Invokana Approved to Reduce Risk of Major Adverse Cardiovascular Events

Janssen announced that the Food and Drug Administration (FDA) has approved Invokana (canagliflozin) to reduce the risk of major cardiovascular (CV) events, including myocardial infarction (MI), stroke or death due to a CV cause in adults with type 2 diabetes (T2D) who have established CV disease. The new indication also applies to Invokamet (canagliflozin, metformin HCl) and Invokamet XR (canagliflozin, metformin HCl ext-rel) tablets.


*Invokana is a sodium-glucose co-transporter 2 (SGLT2) inhibitor*

"This FDA approval makes Invokana the only oral type 2 diabetes treatment indicated to reduce the risk of heart attack, stroke or CV death," said James List, MD, PhD, Global Therapeutic Area Head, Cardiovascular & Metabolism, Janssen Research & Development, LLC. "It is an important step forward for patients and the physicians who treat them."

# PI of Invokana vs. Jardiance

**1 INDICATIONS AND USAGE**

INVOKANA® (canagliflozin) is indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD).

**1 INDICATIONS AND USAGE**

JARDIANCE is indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus,
- to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease.

Ref . PI of Invokana (2018/10)
PI of Jardiance (2018/10)

# CREDENCE Study Early Termination for Positive Findings

janssen | Johnson & Johnson

JANSSEN GLOBAL change location › SEARCH

## Phase 3 CREDENCE Renal Outcomes Trial of INVOKANA® (canagliflozin) is Being Stopped Early for Positive Efficacy Findings

Jul 16, 2018
United States

- INVOKANA® has the potential to be the first new therapy in more than 15 years for slowing the progression of chronic kidney disease in patients with type 2 diabetes

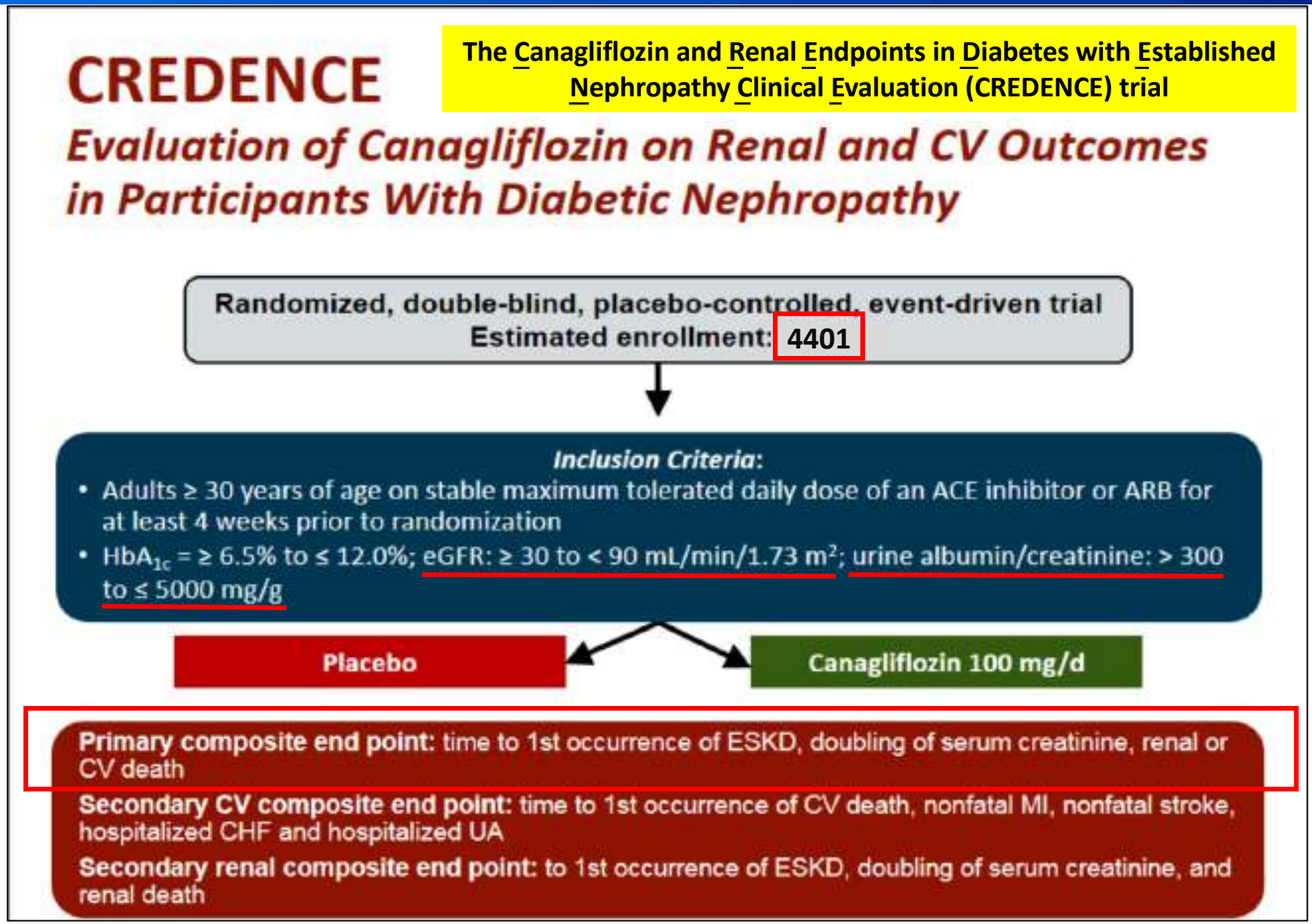
- Worldwide, 160 million patients with type 2 diabetes are at risk for developing chronic kidney disease[i]

- CREDENCE assessed INVOKANA® for renal protection by evaluating the risk reduction of the composite endpoint of time to dialysis or kidney transplantation, doubling of serum creatinine, and renal or cardiovascular death, when used in addition to standard of care

RARITAN, N.J., July 16, 2018 -- The Janssen Pharmaceutical Companies of Johnson & Johnson today announced that the Phase 3 CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) clinical trial, evaluating the efficacy and safety of INVOKANA® (canagliflozin) versus placebo when used in addition to standard of care for patients with chronic kidney disease (CKD) and type 2 diabetes (T2D), is being stopped early based on the achievement of pre-specified efficacy criteria.

https://www.janssen.com/phase-3-credence-renal-outcomes-trial-invokanar-canagliflozin-being-stopped-early-positive-efficacy

# Patient Enrollment and End Points



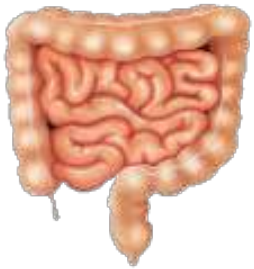

https://www.medscape.org

# Outline

- Update of Guideline for T2DM Management
- Mechanism of of Cardiorenal  effect of SGLT-2i
- Organ Protection Effect of Canagliflozin for DM Patient
- SGLT-1/SGLT-2 inhibition

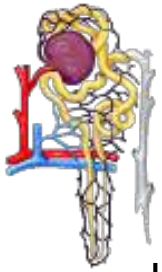
# Effect of SGLT1 / SGLT2

## Intestine SGLT1



- Main uptake mechanism for glucose and galactose in the intestine
- S2 and S3 segments of the proximal renal tubule are responsible for ~10% of the renal glucose re-absorption
- High-affinity ($K_m$ = ~0.5 mM), low-capacity transporter which transfers glucose and sodium with a $Na^+$:glucose coupling ratio of 2

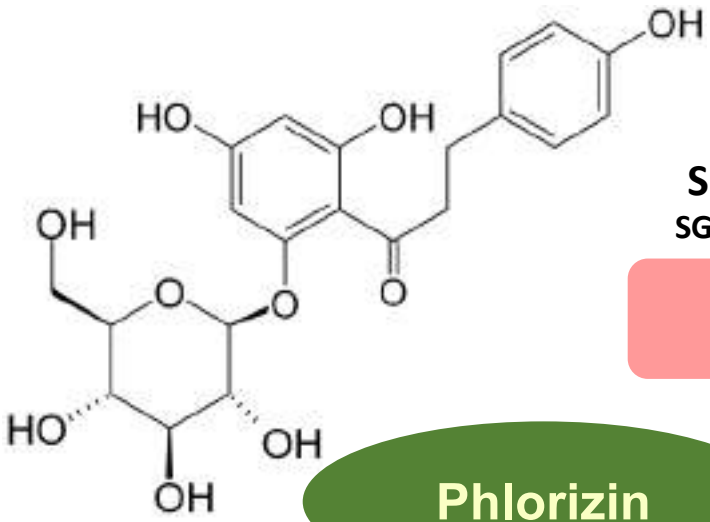
## Kidney SGLT2



- Almost completely expressed in the brush-border membrane of proximal renal tubular cells in the S1 + S2 segment
- Responsible for ~90% of the total renal glucose re-absorption
- Low-affinity ($K_m$ = ~2 mM), high-capacity transporter which transfers glucose and sodium with a $Na^+$:glucose coupling ratio of 1


1. Chao EC and Henry RR. *Nat Rev Drug Discov*. 2010;9:551–559;
2. Mather A and Pollock C. *Kidney Int Suppl.* 2011;(120):S1–6;
3. Wright EM, et al. *J Intern Med*. 2007;261:32–43.

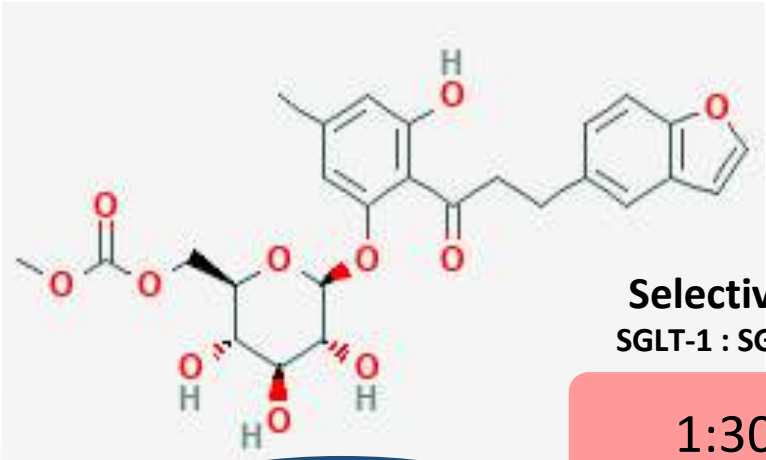
# Structure and selectivity profiles for SGLT2 over SGLT1




**Selectivity**
**SGLT-1 : SGLT-2**

1:11

**Phlorizin**



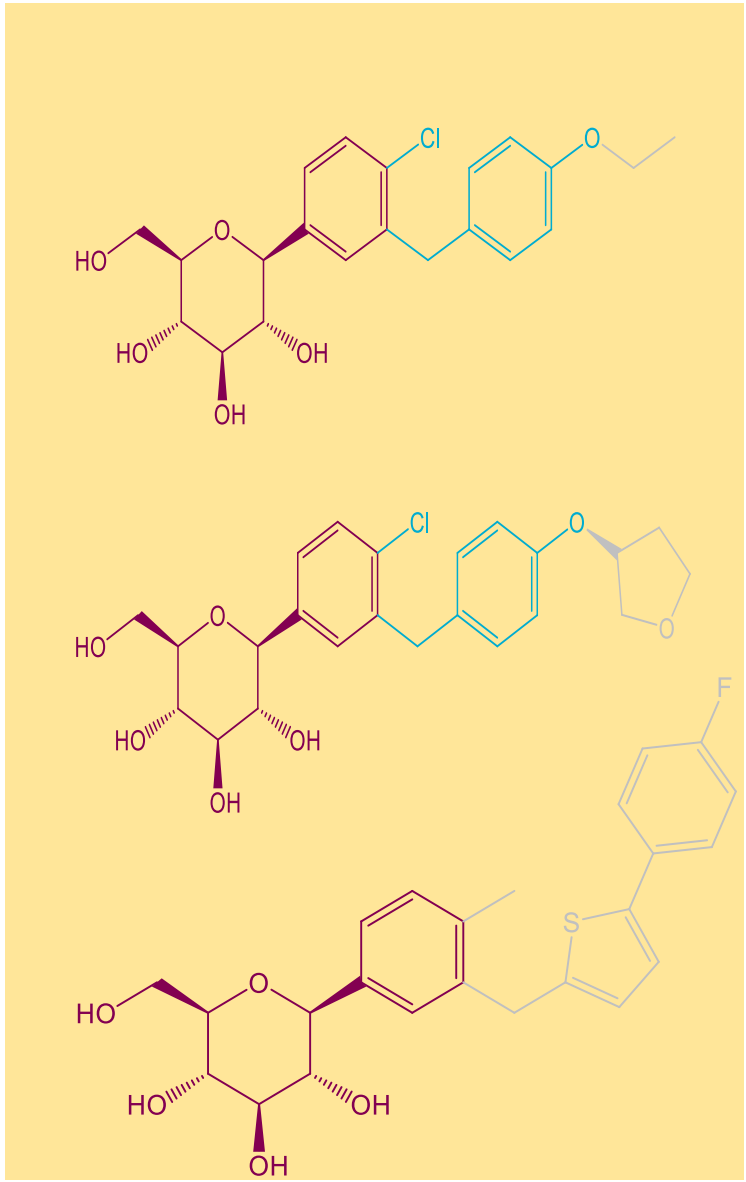

**Selectivity**
**SGLT-1 : SGLT-2**

1:30

**T-1095**

1) Ehrenkranz JR et al., Diabetes Metab Res Rev, 2005;21(1): 31-38
2) Oku A et al., Diabetes, 1999;48(9): 1794-1800

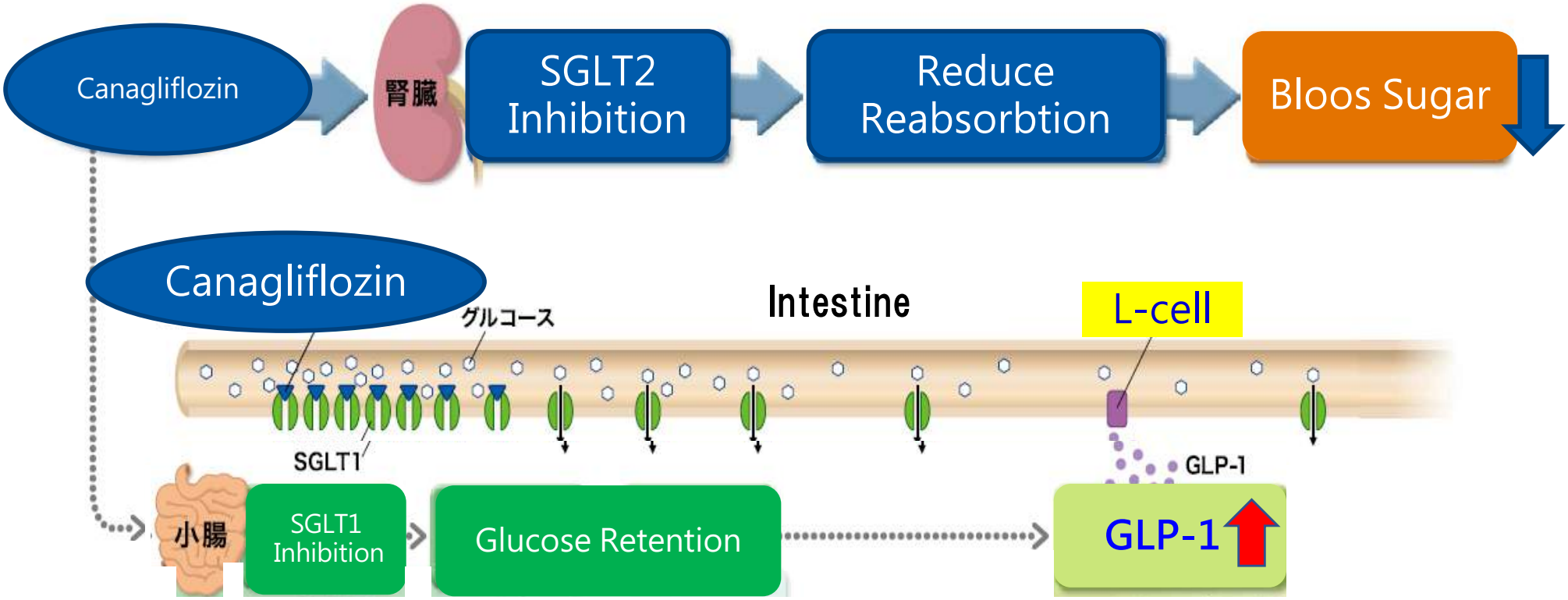
# Structure and selectivity profiles for SGLT2 over SGLT1




| | Selectivity SGLT-1 : SGLT-2 |
|---|---|
| Dapagliflozin | 1:1,400 |
| Empagliflozin | 1:5,000 |
| Canagliflozin | 1:160 |

*Diabetes, Obesity and Metabolism* 17: 188–197, 2015.

# Canagliflozin increase aGLP-1 through SGLT1 inhibition




J Clin Med Res. 2017;9(9):745-753

# Canagliflozin Lowers Postprandial Glucose and Insulin by Delaying Intestinal Glucose Absorption in Addition to Increasing Urinary Glucose Excretion

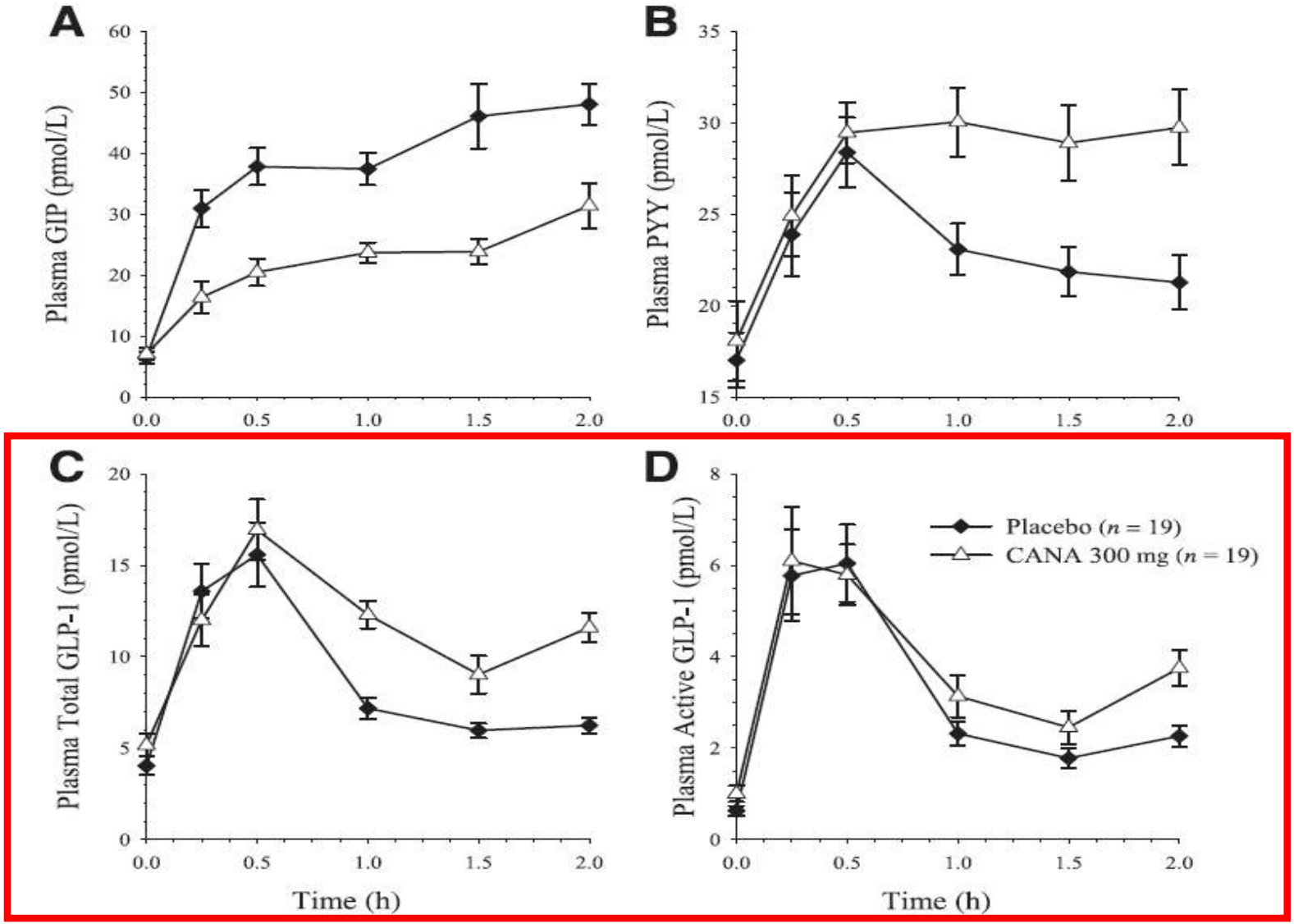
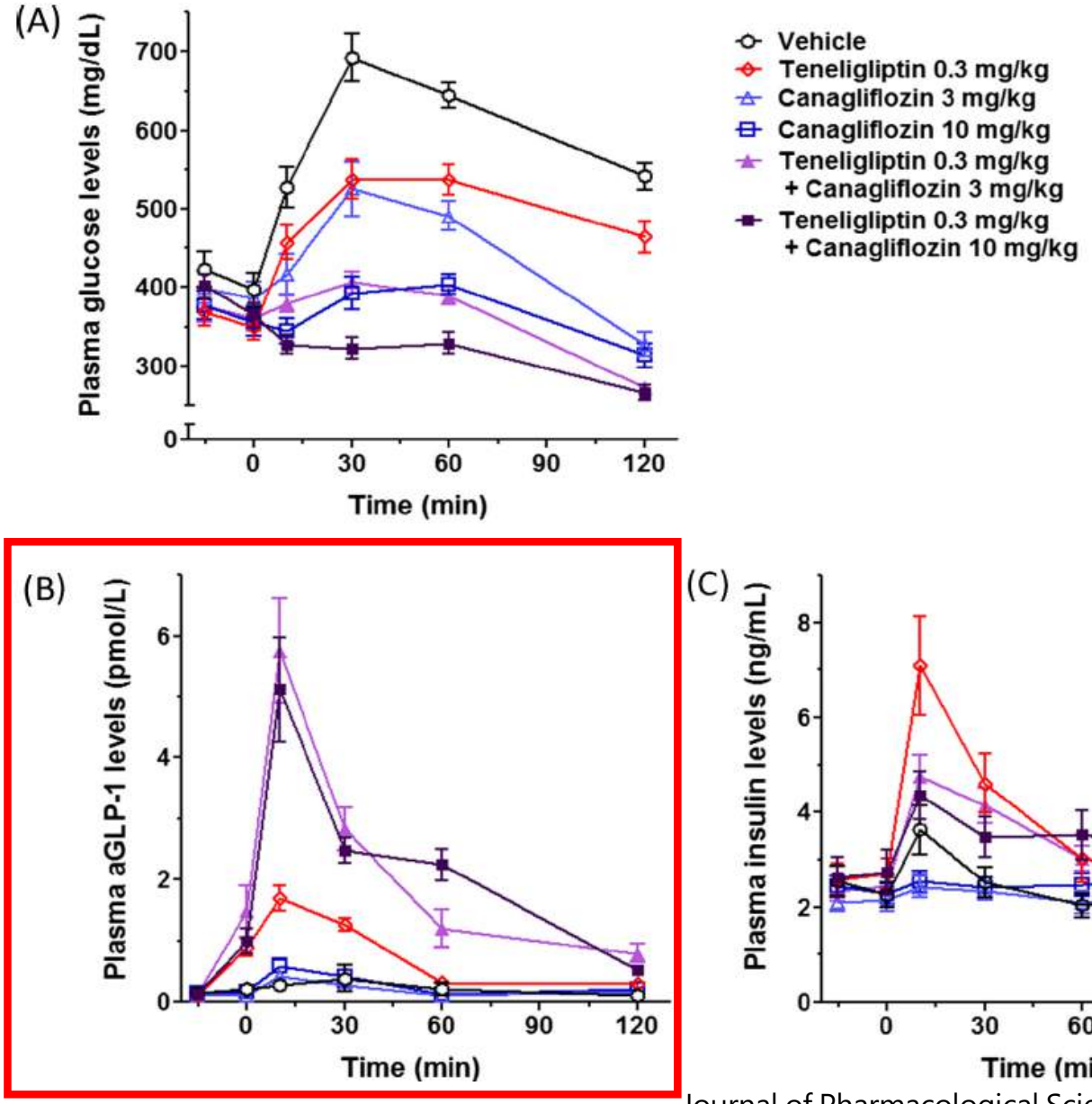



**Figure 3**—*Mean ± SEM plasma concentration-time profiles of GIP (A), PYY (B), total GLP-1 (C), and active GLP-1 (D). CANA, canagliflozin.* Diabetes Care 36:2154–2161, 2013 (Ref. 17)

# Effects of treatment with a combination of canagliflozin and teneligliptin during OGTT in ZDF rats




CAN-SLK-20181223

Journal of Pharmacological Sciences 127 (2015) 456-461 (Ref. 18)

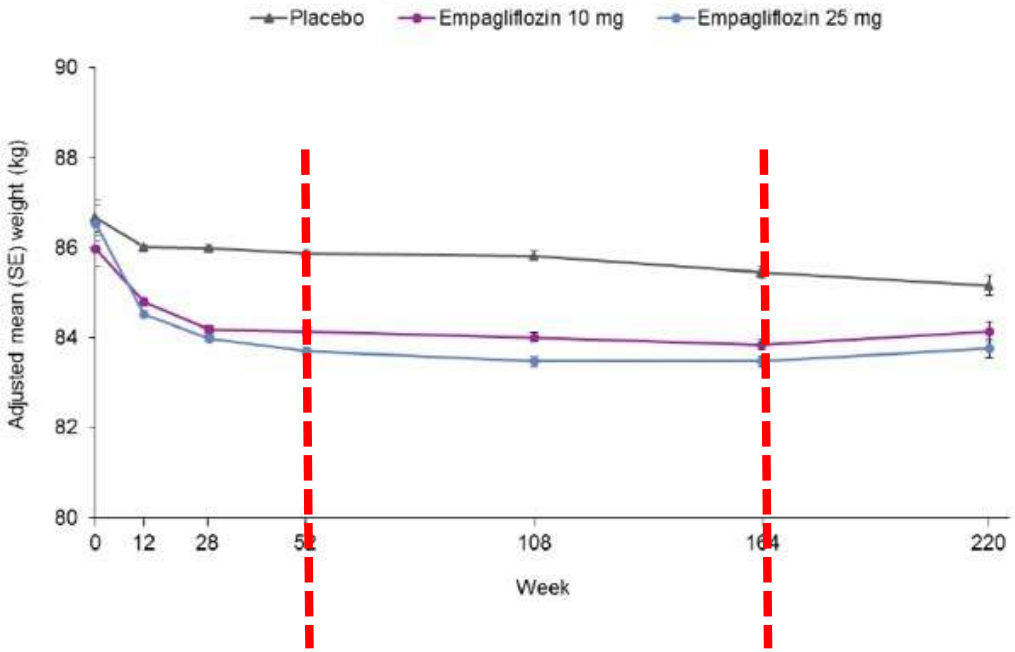
# Canagliflozin 的特色

- SGLT-2 i  with partial SGLT-1 i activity
- 下降 PC sugar 透過抑制 腸道 glucose 再吸收 (SGLT-1 i)
- 增加 GLP-1 activity
- Combined with DPP-4  更進一步增加GLP-1 濃度
- **→ SGLT-2 i with partial incretin effect**
- **→ Combined with DPP-4 is reasonable ！**

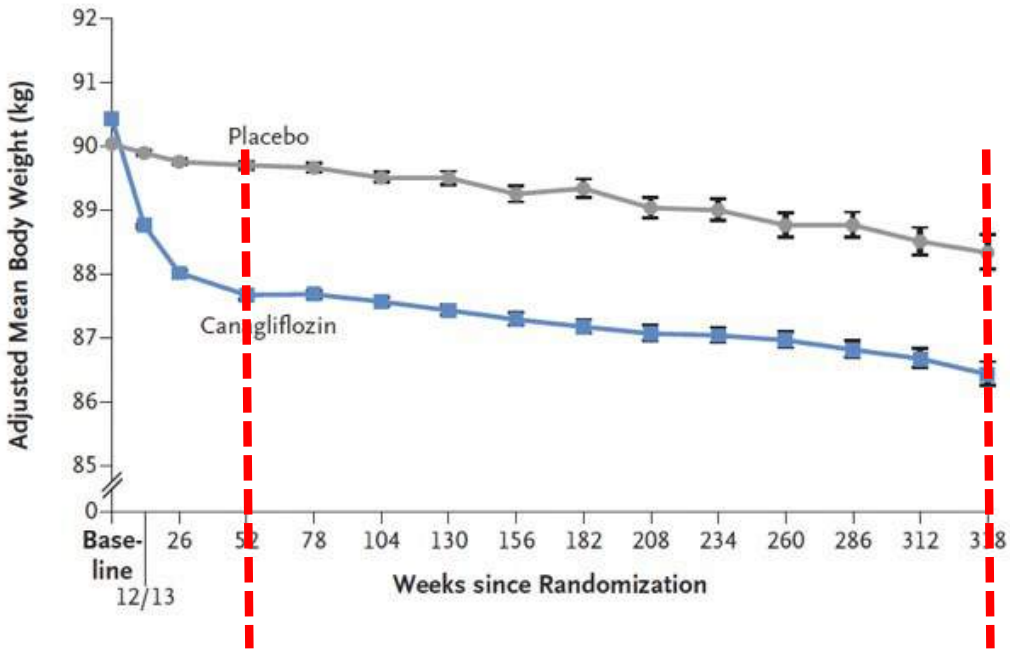
# EMPA-REG vs CANVAS : Body Weight

## Body weight

EMPA-REG

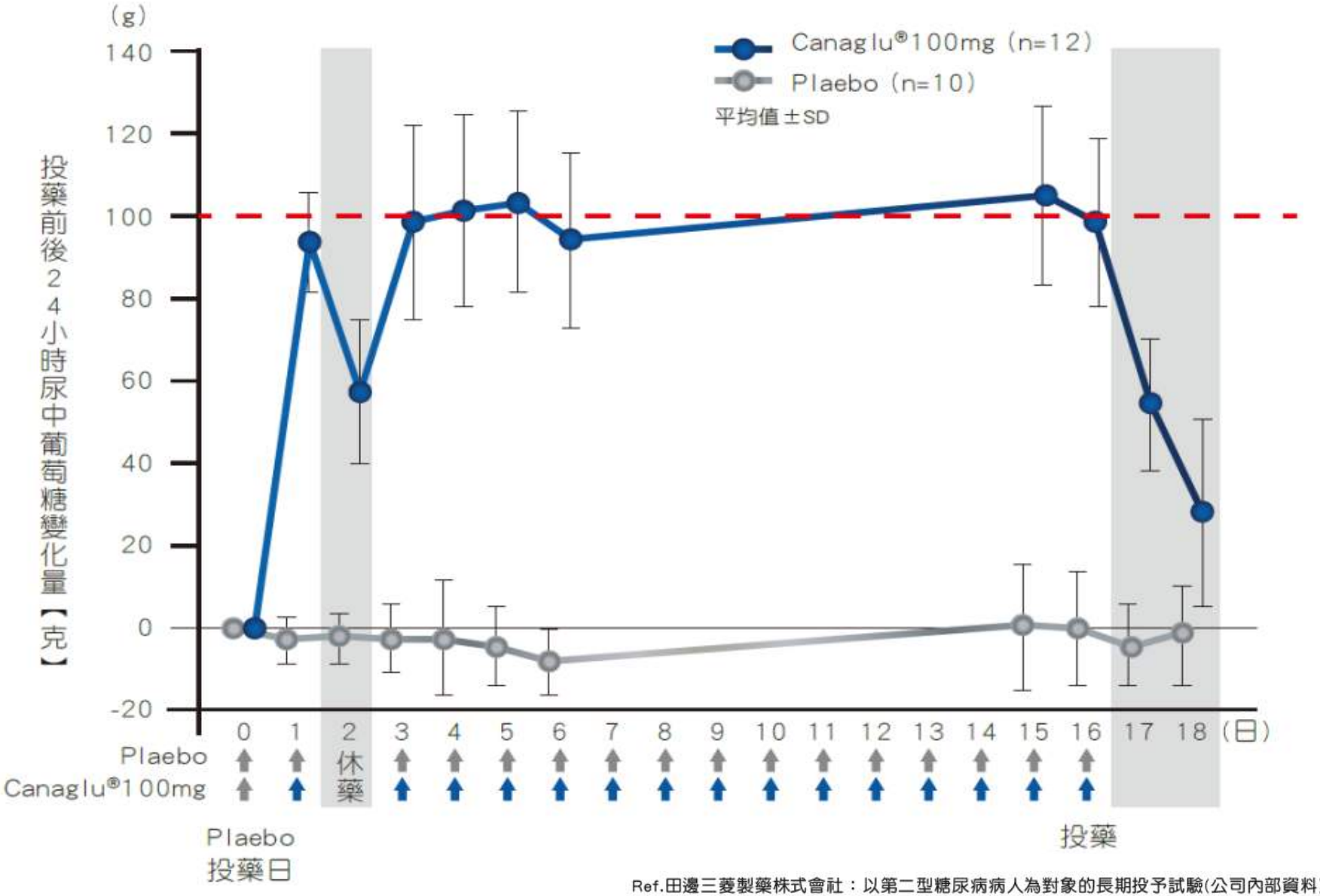



CANVAS




N Engl J Med 2017; 377:644-657 (Ref. 9)
N Engl J Med 2015; 373:2117-28 (Ref. 12)

# Glycosuria Effect of Canagliflozin

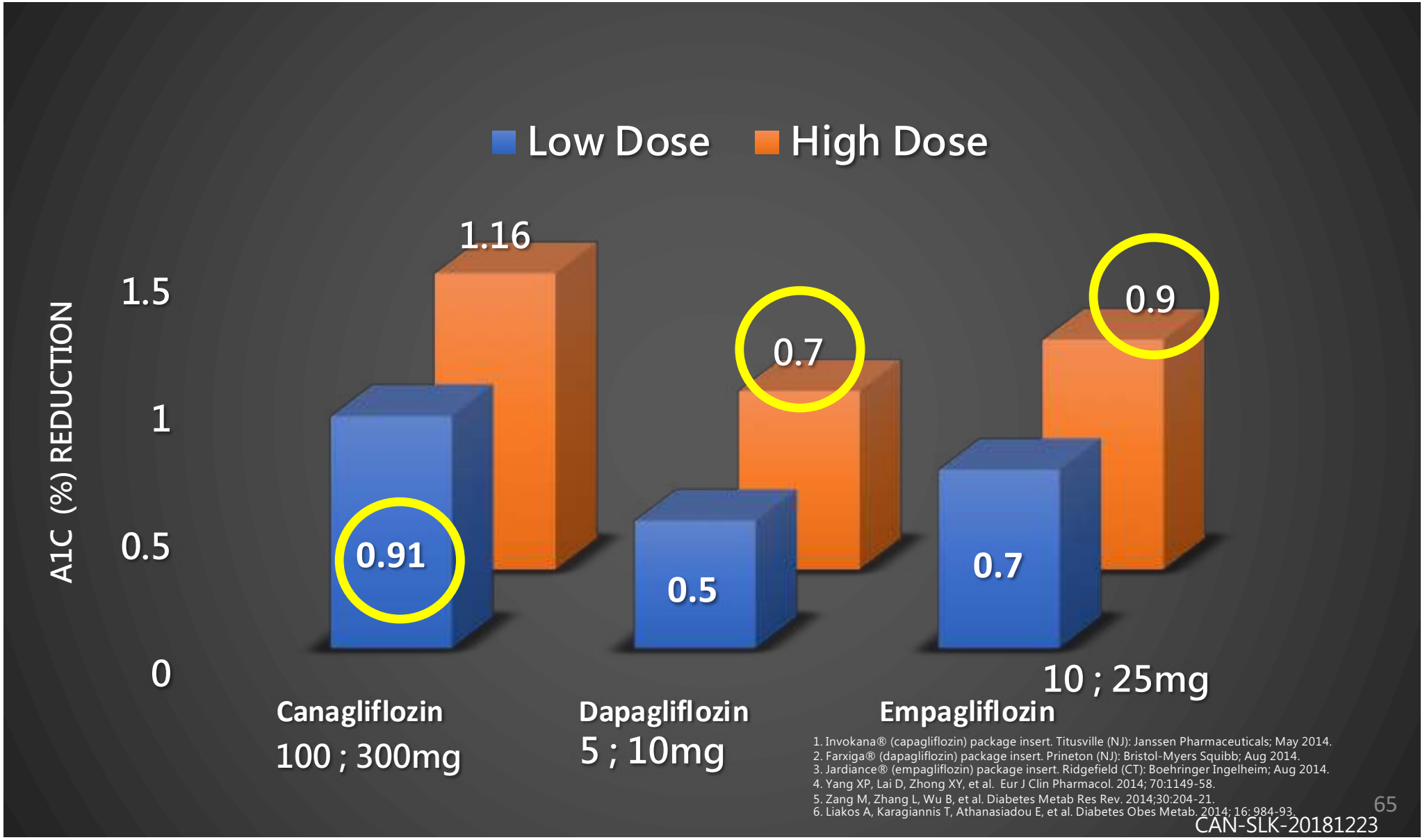



Ref.田邊三菱製藥株式會社：以第二型糖尿病病人為對象的長期投予試驗(公司內部資料)



CAN-SLK-20181223

# Monotherapy : A1c Reductions



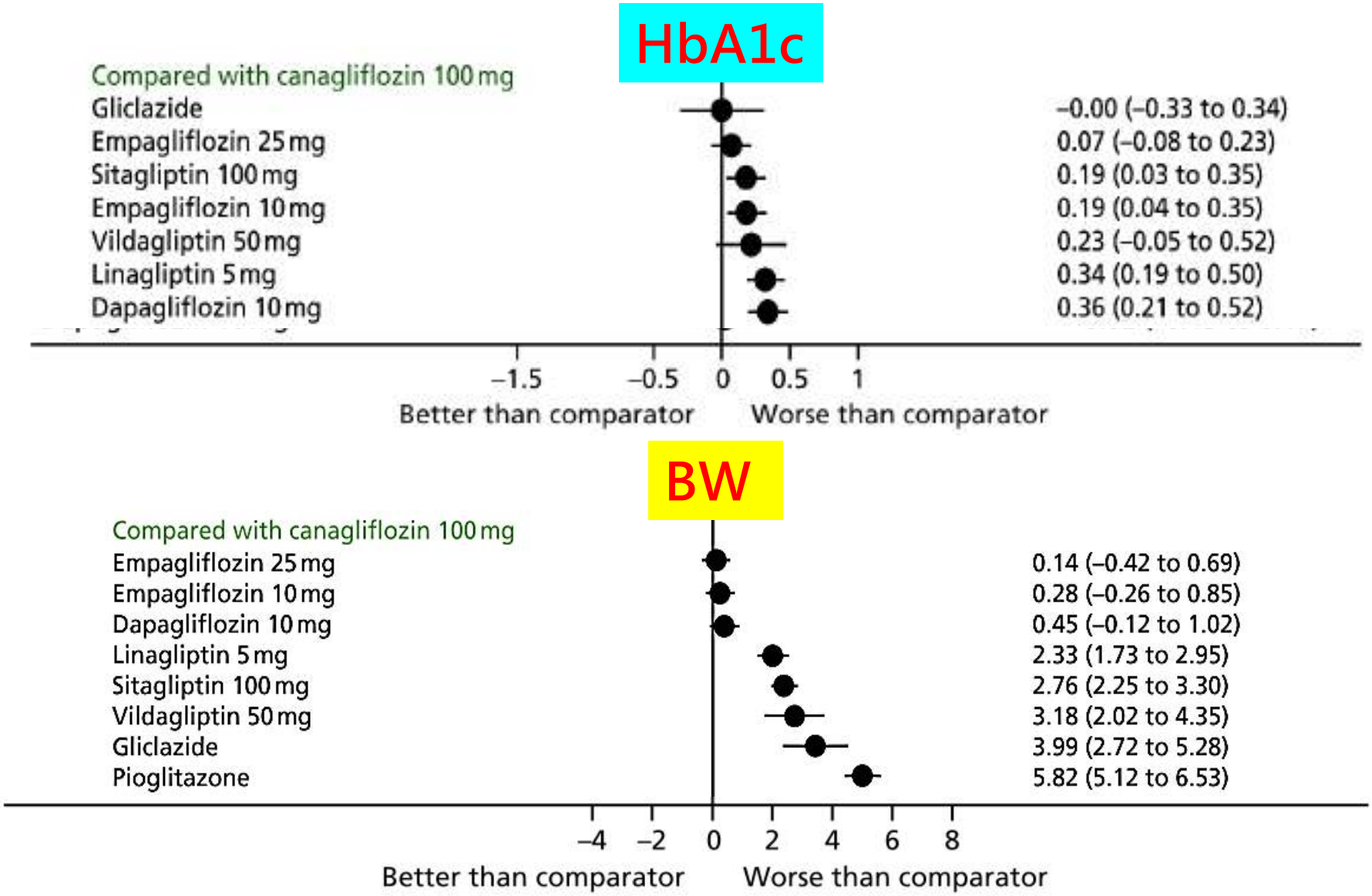


1. Invokana® (capagliflozin) package insert. Titusville (NJ): Janssen Pharmaceuticals; May 2014.
2. Farxiga® (dapagliflozin) package insert. Prineton (NJ): Bristol-Myers Squibb; Aug 2014.
3. Jardiance® (empagliflozin) package insert. Ridgefield (CT): Boehringer Ingelheim; Aug 2014.
4. Yang XP, Lai D, Zhong XY, et al. Eur J Clin Pharmacol. 2014; 70:1149-58.
5. Zang M, Zhang L, Wu B, et al. Diabetes Metab Res Rev. 2014;30:204-21.
6. Liakos A, Karagiannis T, Athanasiadou E, et al. Diabetes Obes Metab. 2014; 16: 984-93.




CAN-SLK-20181223

# Canagliflozin, dapagliflozin and empagliflozin for treating type 2 diabetes: Network Meta-analysis

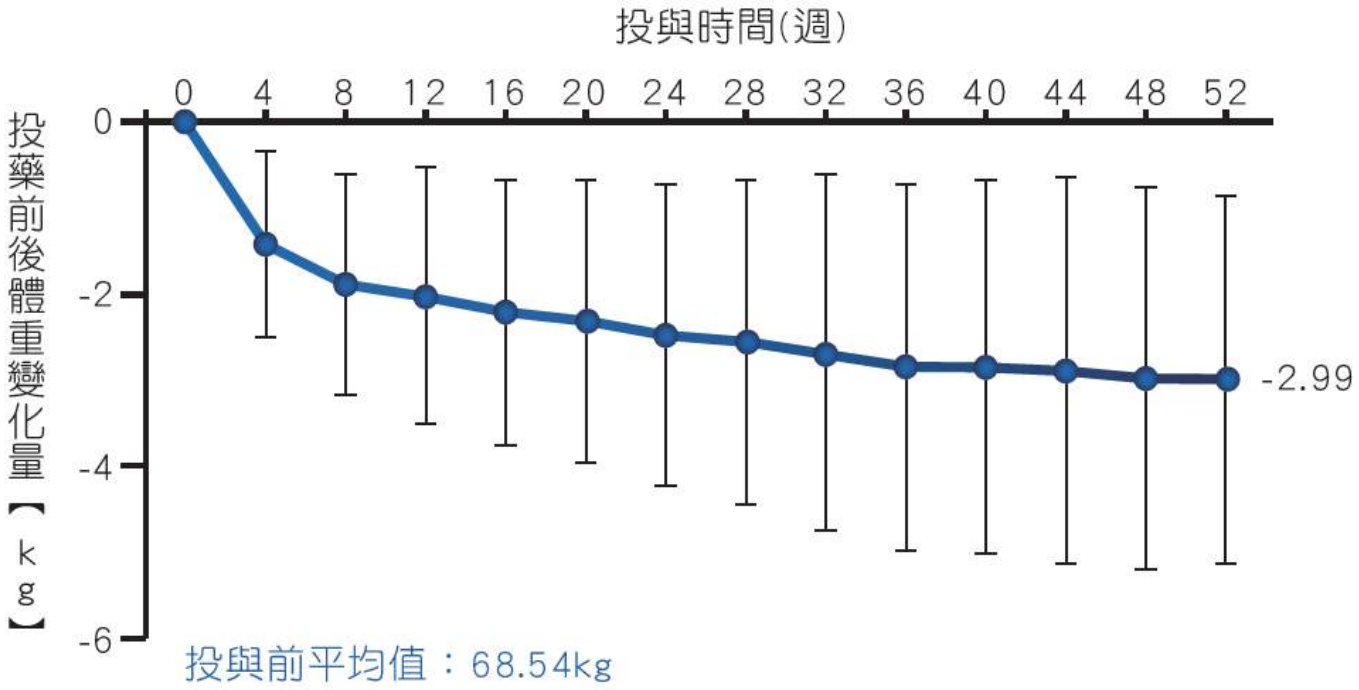



Health Technology Assessment, No. 21.2 (Ref. 6)

# Diabesity = Diabetes + Obesity

# Weight Loss Effect of Canagliflozin

單一投與Canaglu®100mg時病人體重變化情形(n=127)；52週LOCF

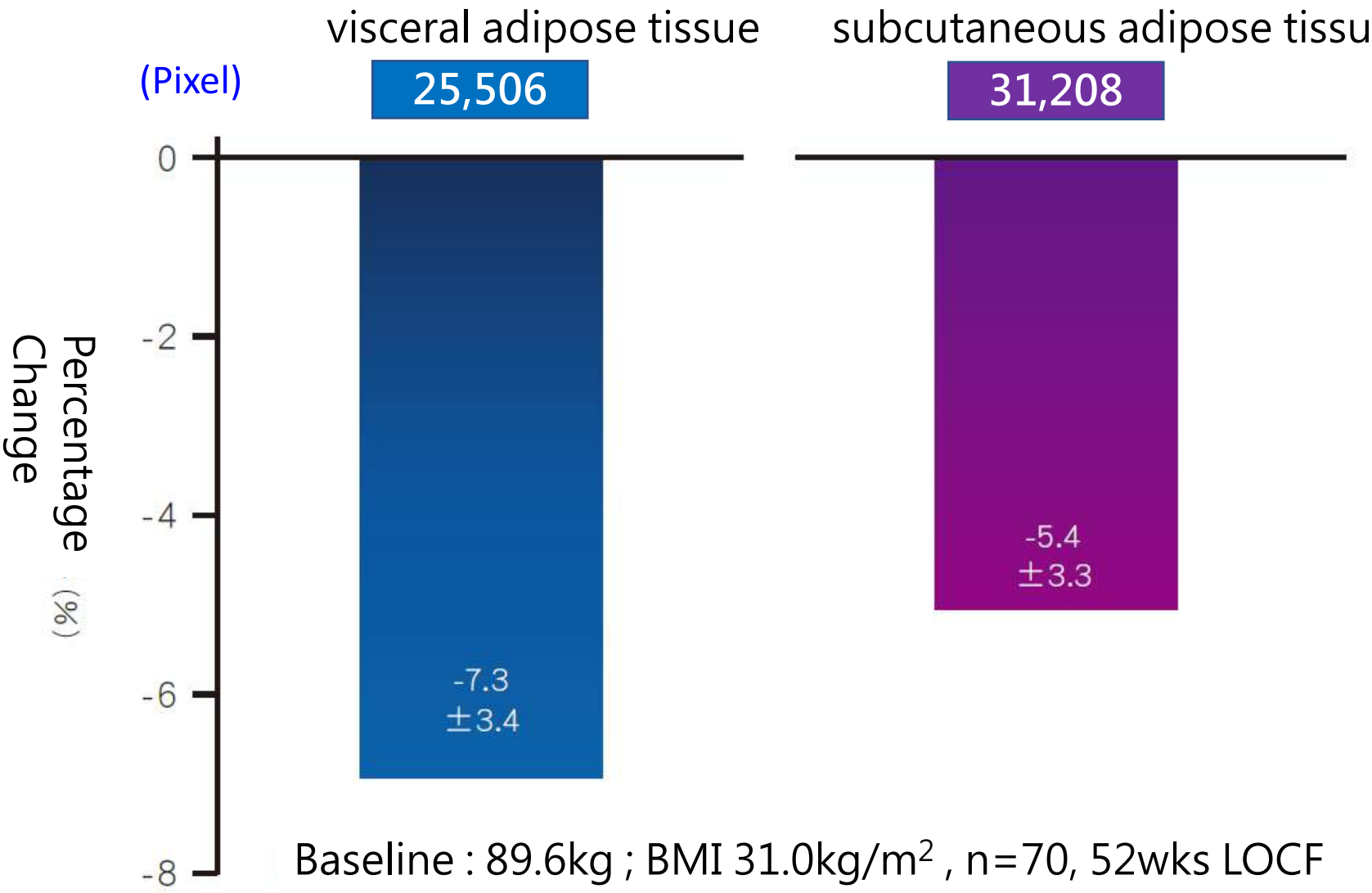



已經使用其他OAD治療再加上Canaglu®100mg之後的體重變化(52週LOCF)

| | DPP-4i (n=71) | SU (n=124) | BG (n=72) | α-GI (n=62) | TZD (n=63) | Glinide (n=65) |
|---|---|---|---|---|---|---|
| 投與前體重平均值(kg) | 69.23 | 70.30 | 74.45 | 69.27 | 73.81 | 69.19 |
| 變化量(kg) (平均值±SD) | -2.79 ±2.79 | -2.06 ±2.31 | -3.19 ±3.13 | -2.73 ±2.03 | -2.44 ±2.28 | -2.78 ±2.93 |

Ref.田邊三菱製藥株式會社：以第二型糖尿病病人為對象的長期投予試驗(公司內部資料)

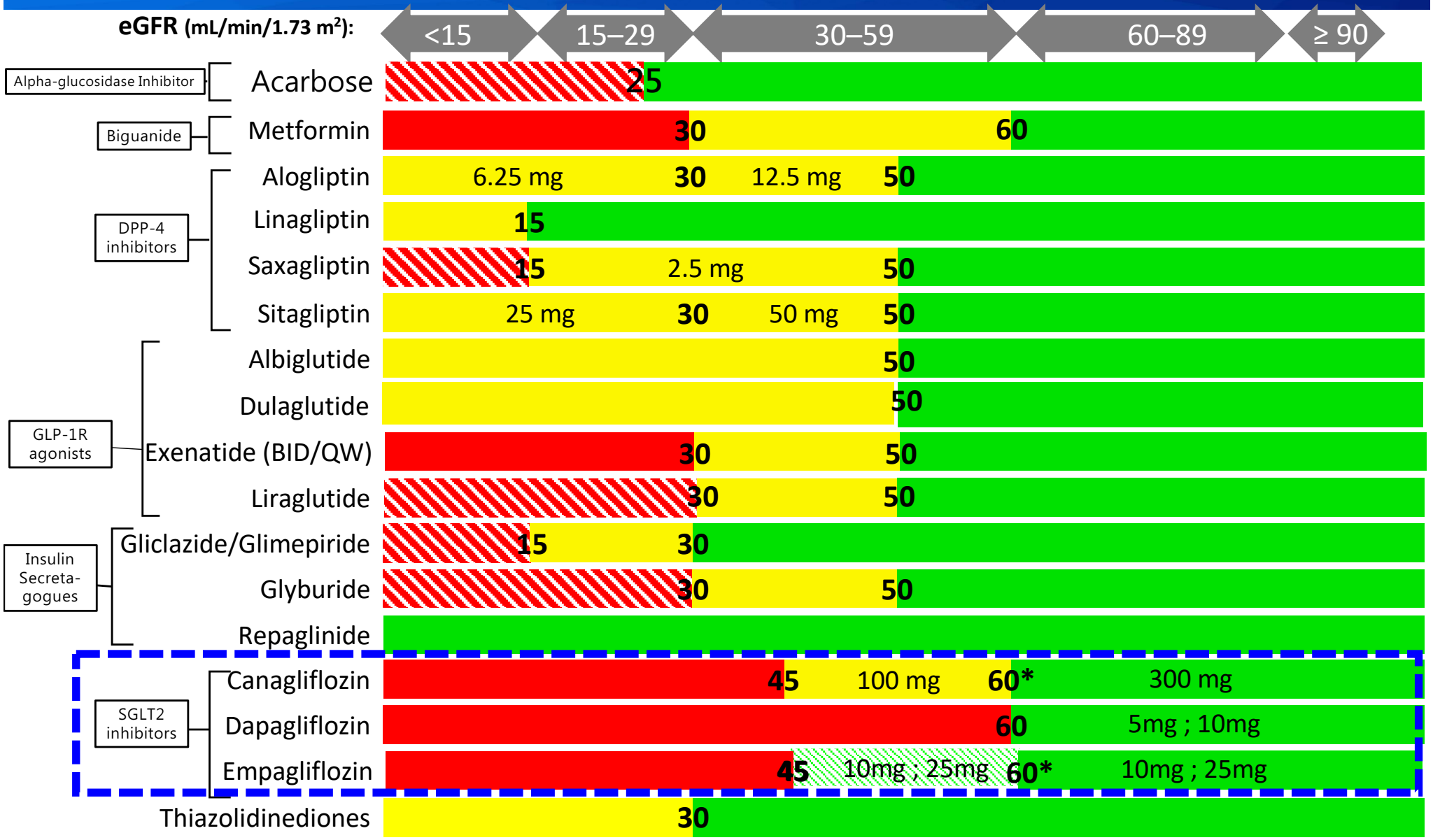
# Canagliflozin Reduce Adipose Tissue




Baseline : 89.6kg ; BMI 31.0kg/$m^2$ , n=70, 52wks LOCF

Lancet 2013; 382: 941–50 (Ref. 8)

# Antihyperglycemic agents and Renal Function

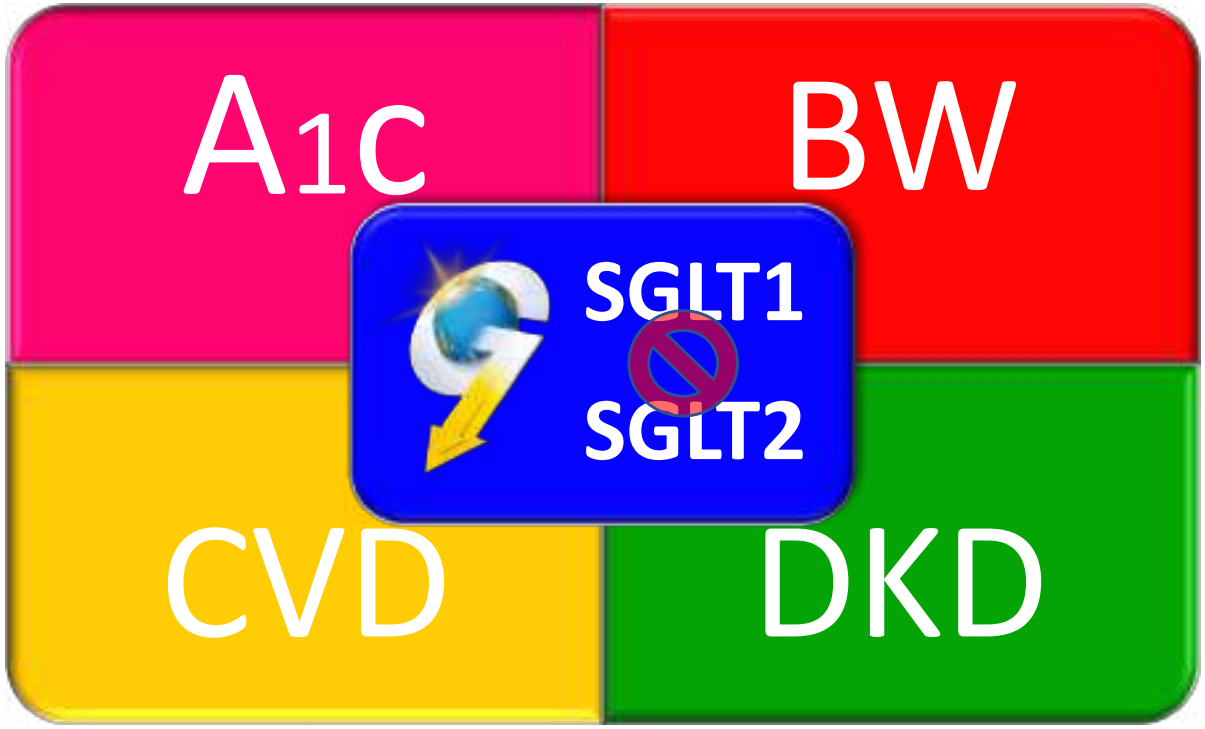



* = do not initiate if eGFR <60 ml/min

Contraindicated | Not recommended | Caution and/or reduce dose | Safe | No dose adjustment but close monitoring of renal function

Adapted from: Product Monographs as of March 2016 Harper W et al. Can J Diabetes 2015;39:440

# 抑制1+2、降低ABCD




| | |
|---|---|
| 1 | **SGLT1及SGLT2受體的雙重抑制效果**<br>Canaglu 100mg具有SGLT1抑制效果，可延遲小腸吸收葡萄糖，並刺激GLP-1分泌，提供持續有效的血糖和體重控制效果 |
| 2 | **排糖效果顯著 有效降低HbA1c**<br>Canaglu 100mg每日可排出87~100克葡萄糖，降低0.8%~1.27% HbA1c，並可減輕體重達3kg (約4%) |
| 3 | **可提供T2DM病人心血管與腎臟雙重治療效益**<br>ADA/AACE guideline建議優先處方SGLT2i包含Canagliflozin給合併ASCVD或是CHF/CKD的T2DM病人，臨床試驗證實Canagliflozin具有Primary / Secondary Prevention效果，能降低T2DM病人心血管風險並延緩腎臟惡化，且canagliflozin是唯一FDA核准降低MACE適應症的口服降血糖藥 |

# Canaglu 的 特色

- HbA1c 降幅最強, 性價比最高
- 體重下降最持久
- CVD 保護範圍最廣(3 個indications, pri+sec)
- DKD 試驗第一個發表
- GFR 適應範圍最廣