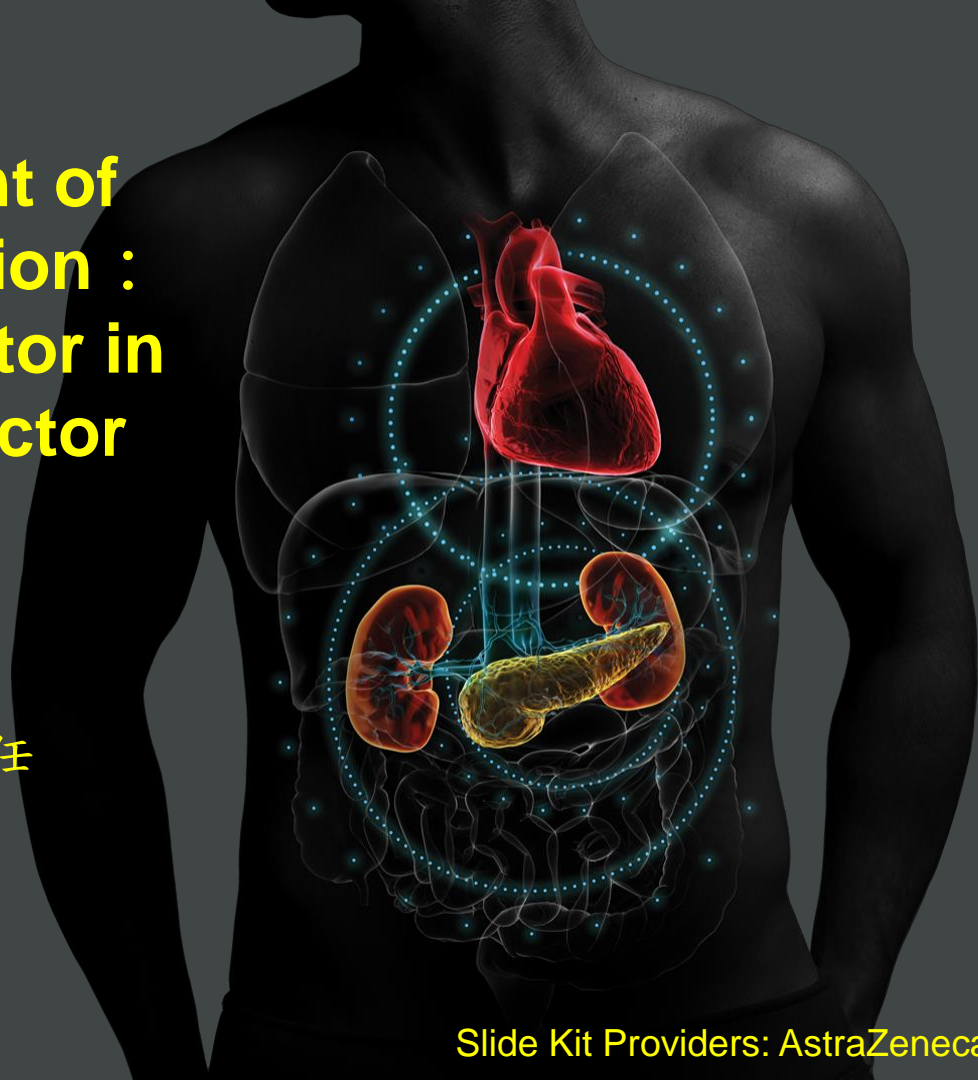
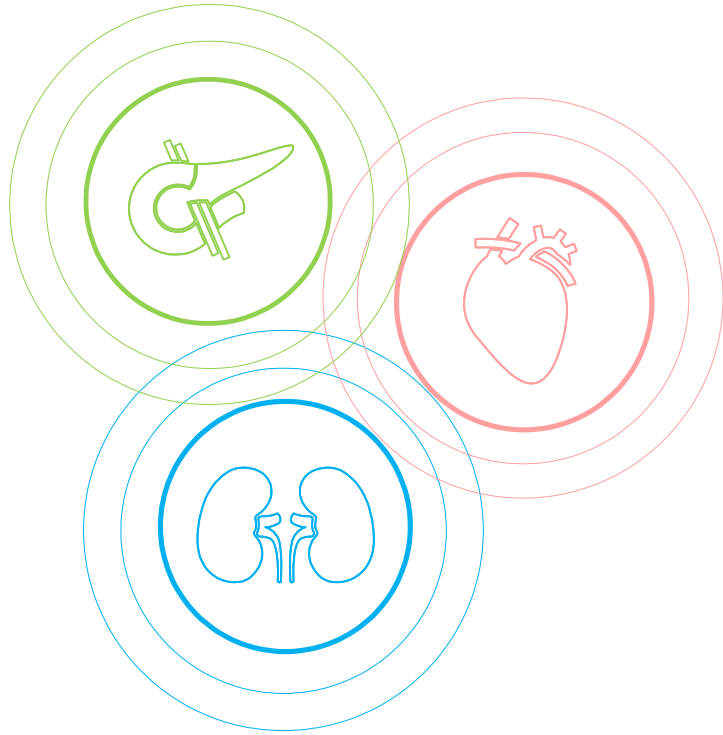


The 4th Advancement of Anti-diabetic Medication : Role of SGLT-2 Inhibitor in T2D with CV Risk Factor

王治元 醫師
臺大醫院代謝內分泌科
臺大醫學院內科教授
臺大醫院雲林分院內科部主任

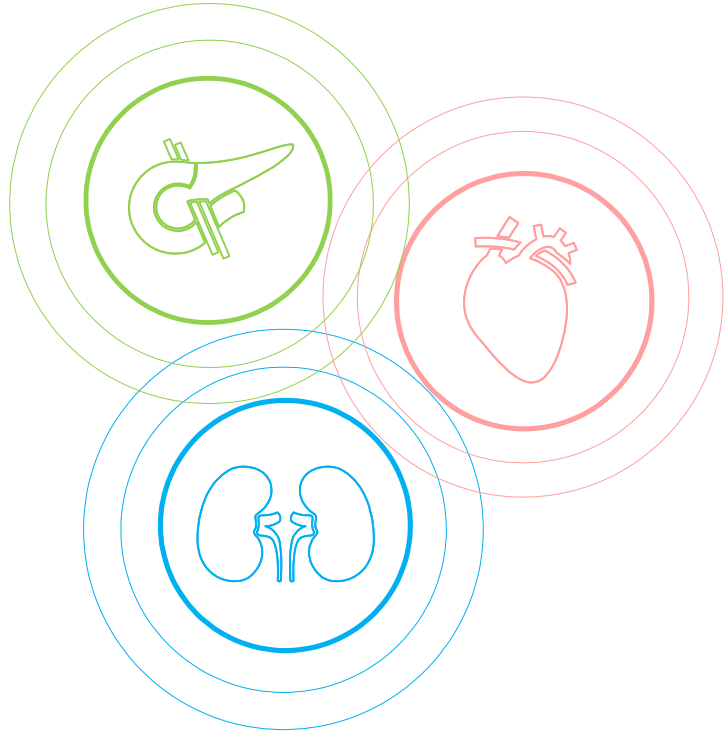


Outline



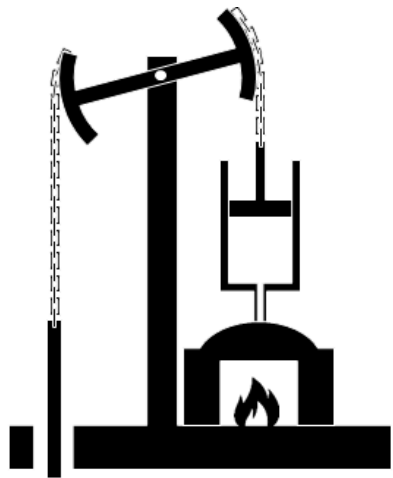
- **The four advancements of anti-diabetic medication**
- **What can SGLT-2 inhibitor help us as treating diabetic patients with CV risk factors?**
- **Conclusion**

Outline



- **The four advancements of anti-diabetic medication**
- What can SGLT-2 inhibitor help us as treating diabetic patients with CV risk factors?
- Conclusion

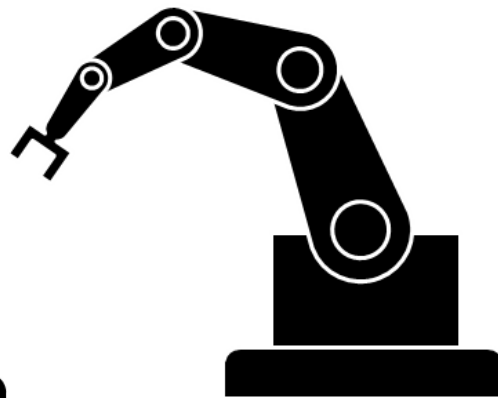
工業革命4.0



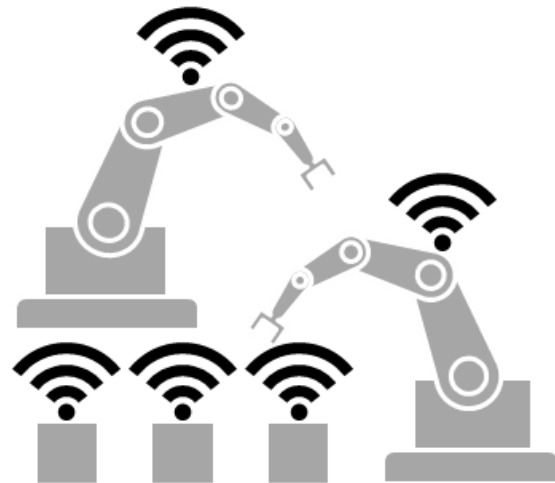
第一次工業革命：
機械化 1784年
(蒸氣·水力)



第二次工業革命：
生產線 1870年
(電力)



第三次工業革命：
電子自動化 1969年
(IT系統, 電腦)



第四次工業革命：
網絡實體化 現今
(CPS, 5G)



糖尿病藥物治療4.0

Preventing Complications





Comparison of the Effects of Glucagon-Like Peptide Receptor Agonists and Sodium-Glucose Cotransporter 2 Inhibitors for Prevention of Major Adverse Cardiovascular and Renal Outcomes in Type 2 Diabetes Mellitus

Systematic Review and Meta-Analysis of Cardiovascular Outcomes Trials

SGLT-2i, GLP-1 RA 突破成果

A total of **8 CV outcome trials**:

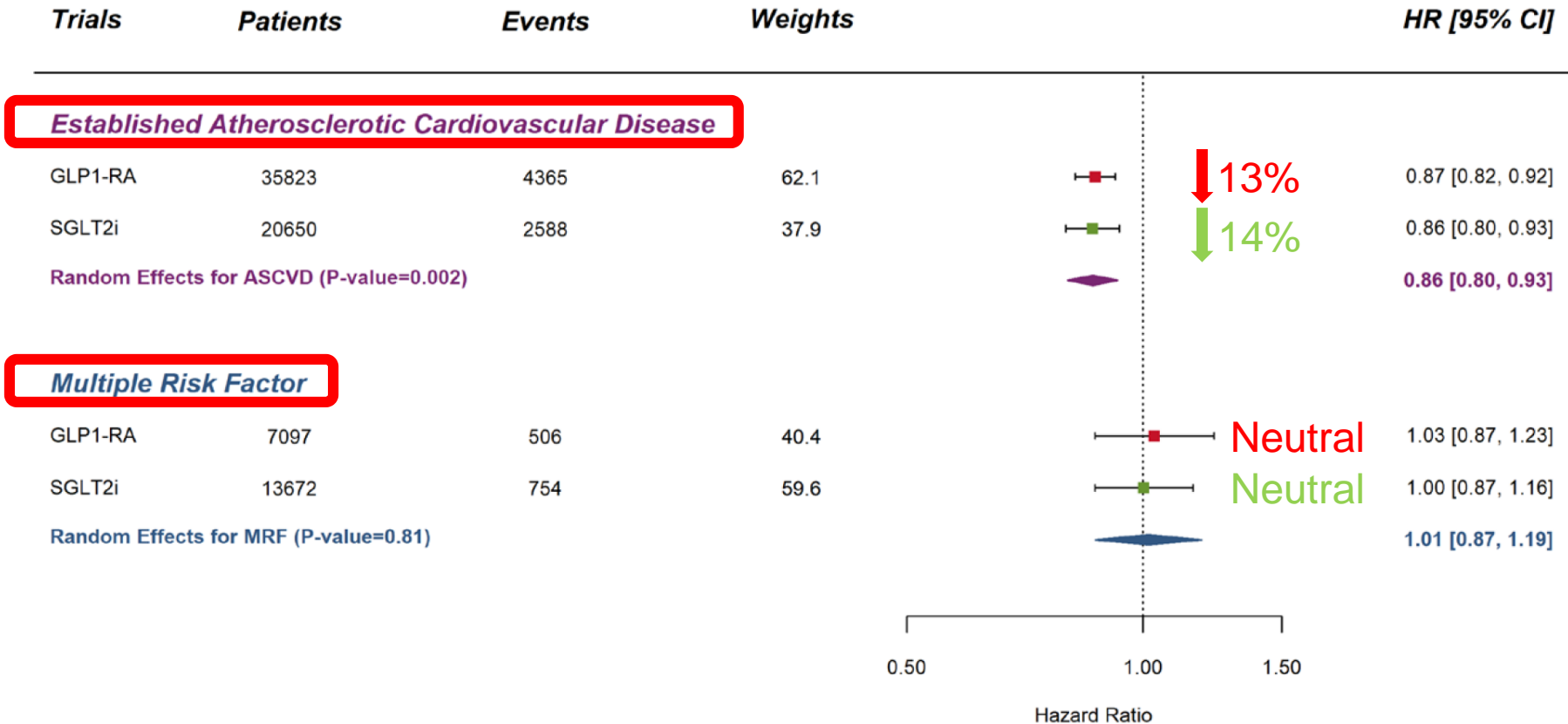
- 5 GLP1-RA trials (42,920 patients)
- 3 SGLT2i trials (34,322 patients)

Circulation. 2019 Apr 23;139(17):2022-2031.

Table 1. Summary of GLP1-RA and SGLT2i Cardiovascular Outcomes Trials

Trial	GLP1-RA					SGLT2i		
	ACS ELIXA	LEADER	SUSTAIN-6	EXSCEL	HARMONY	EMPA-REG OUTCOME	CANVAS Program	DECLARE-TIMI 58
Drug	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Albiglutide	Empagliflozin	Canagliflozin	Dapagliflozin
Median follow-up time, y	2.1	3.8	2.1	3.2	1.6	3.1	2.4	4.2
Trial participants, n	6068	9340	3297	14 752	9463	7020	10 142	17 160
Age, y, mean	60.3	64.3	64.6	62.0	64.1	63.1	63.3	63.9
Female sex, n (%)	2894 (30.7)	3337 (35.7)	1295 (39.3)	5603 (38.0)	2894 (30.6)	2004 (28.5)	3633 (35.8)	6422 (37.4)
Proportion of patients with established atherosclerotic cardiovascular disease, n (%)	6068 (100)	6775 (72.5)	2735 (83.0)	10 782 (73.1)	9463 (100)	7020 (100)	6656 (66)	6974 (41)
History of heart failure, n (%)	1922 (20.3)	1667 (17.8)	777 (23.6)	2389 (16.2)	1922 (20.3)	706 (10.1)	1461 (14.4)	1724 (10.0)
eGFR <60 ml/min per 1.73 m ² , n (%)	1407 (23.2)	2158 (23.1)	939 (28.5)	3191 (21.6)	NA	1819 (25.9)	2039 (20.1)	1265 (7.4)

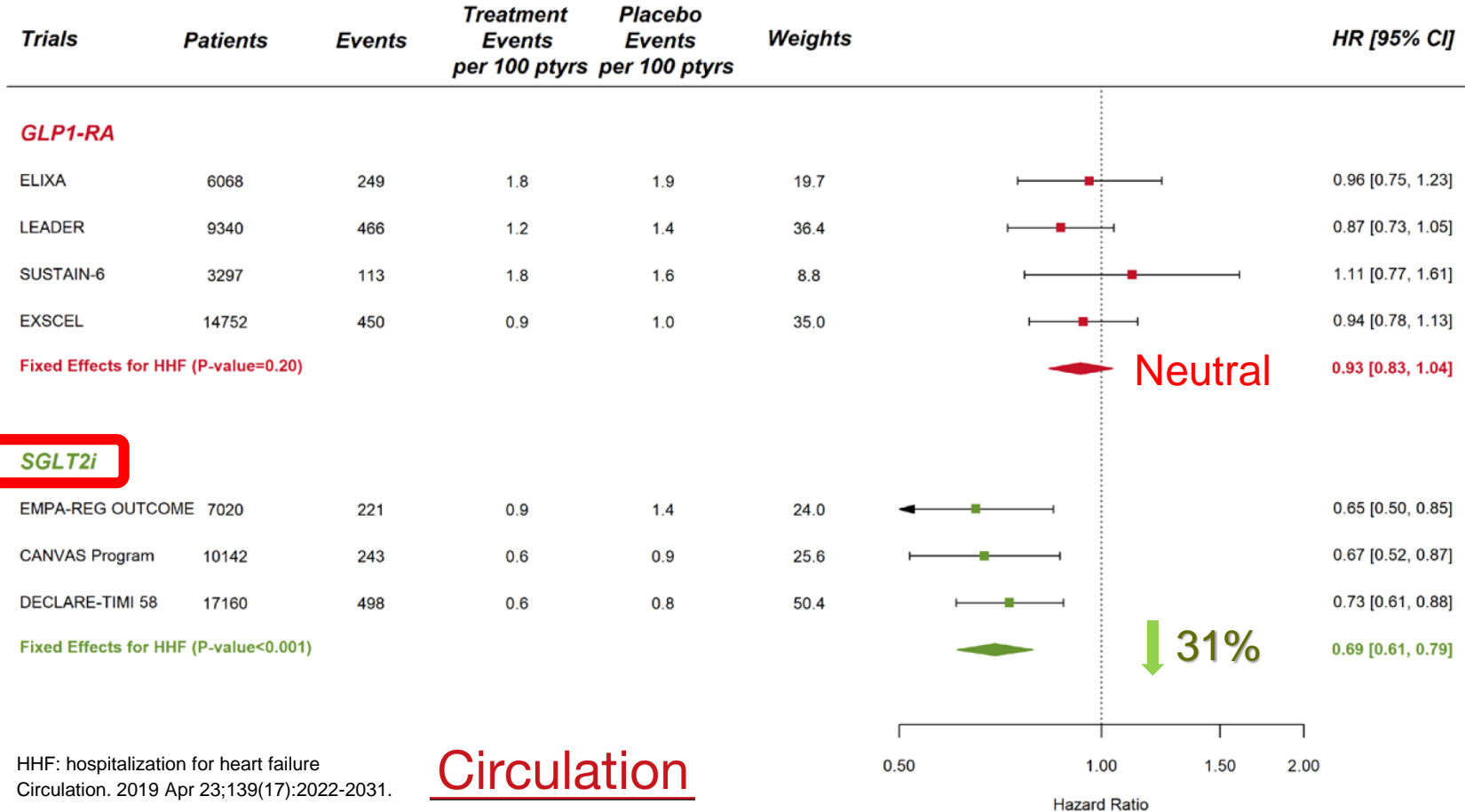
Meta-Analysis of GLP-1RA and SGLT-2i trials on MACE



MACE: myocardial infarction, stroke, and cardiovascular death
 Circulation. 2019 Apr 23;139(17):2022-2031.

Circulation

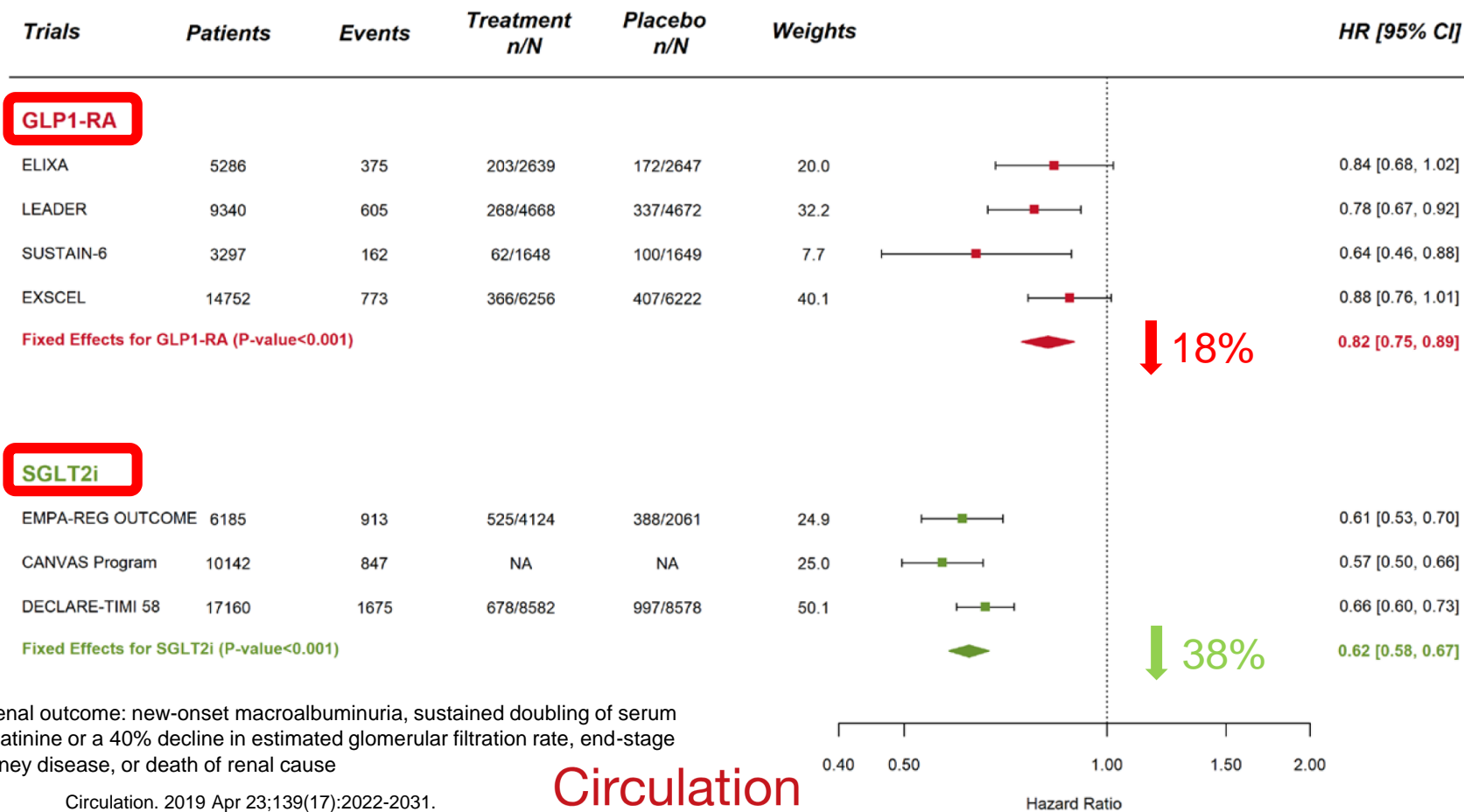
Meta-Analysis of GLP-1RA and SGLT-2i trials on HHF



HHF: hospitalization for heart failure
Circulation. 2019 Apr 23;139(17):2022-2031.

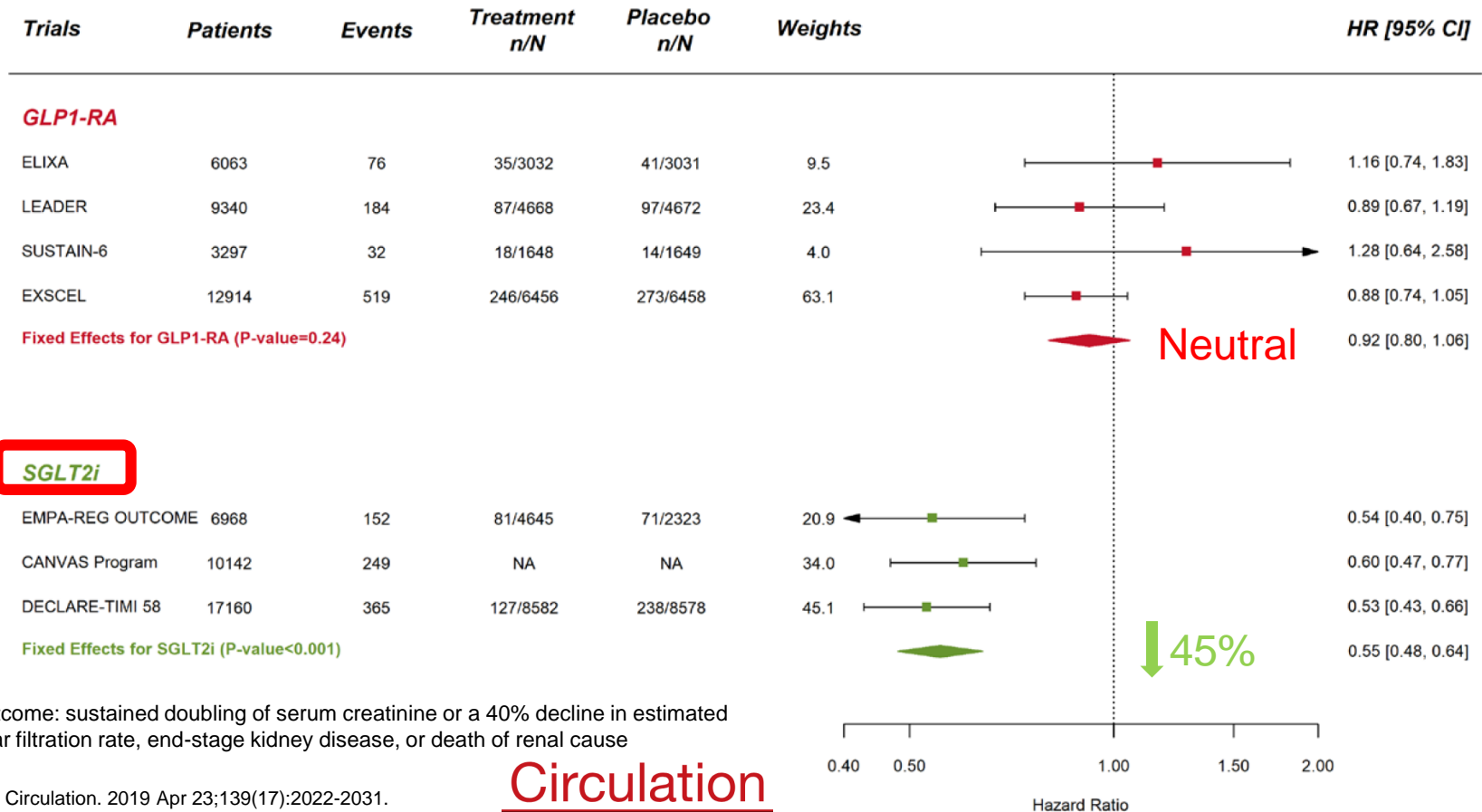
Circulation

Meta-Analysis of GLP-1RA and SGLT-2i trials on renal outcome*



*Renal outcome: new-onset macroalbuminuria, sustained doubling of serum creatinine or a 40% decline in estimated glomerular filtration rate, end-stage kidney disease, or death of renal cause

Meta-Analysis of GLP-1RA and SGLT-2i trials on renal outcome excluding Macroalbuminuria



Renal outcome: sustained doubling of serum creatinine or a 40% decline in estimated glomerular filtration rate, end-stage kidney disease, or death of renal cause

**FIRST-LINE therapy is metformin and comprehensive lifestyle (including weight management and physical activity)
if HbA_{1c} above target proceed as below**



ESTABLISHED ASCVD OR CKD

ASCVD PREDOMINATES

EITHER/OR

GLP-1 RA with proven CVD benefit¹

SGLT2i with proven CVD benefit¹, if eGFR adequate²

HF OR CKD PREDOMINATES

PREFERABLY

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate³

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate² add GLP-1 RA with proven CVD benefit¹

If HbA_{1c} above target

- If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:
- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
 - DPP-4i if not on GLP-1 RA
 - Basal insulin⁴
 - TZD⁵
 - SU⁶

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 benefit¹
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin⁴
- SU⁶

NO

WITHOUT ESTABLISHED ASCVD OR CKD

COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA

DPP-4i	GLP-1 RA	SGLT2i ²	TZD
If HbA_{1c} above target	If HbA_{1c} above target	If HbA_{1c} above target	If HbA_{1c} above target
SGLT2i ² OR TZD	SGLT2i ² OR TZD	GLP-1 RA OR DPP-4i OR TZD	SGLT2i ² OR DPP-4i OR GLP-1 RA
If HbA_{1c} above target			
Continue with addition of other agents as outlined above			
If HbA_{1c} above target			
Consider the addition of SU ⁶ OR basal insulin:			

COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

EITHER/OR

GLP-1 RA with good efficacy for weight loss⁸ SGLT2i²

If HbA_{1c} above target

SGLT2i² GLP-1 RA with good efficacy for weight loss⁸

If HbA_{1c} above target

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

PREFERABLY

COST IS A MAJOR ISSUE⁹⁻¹⁰

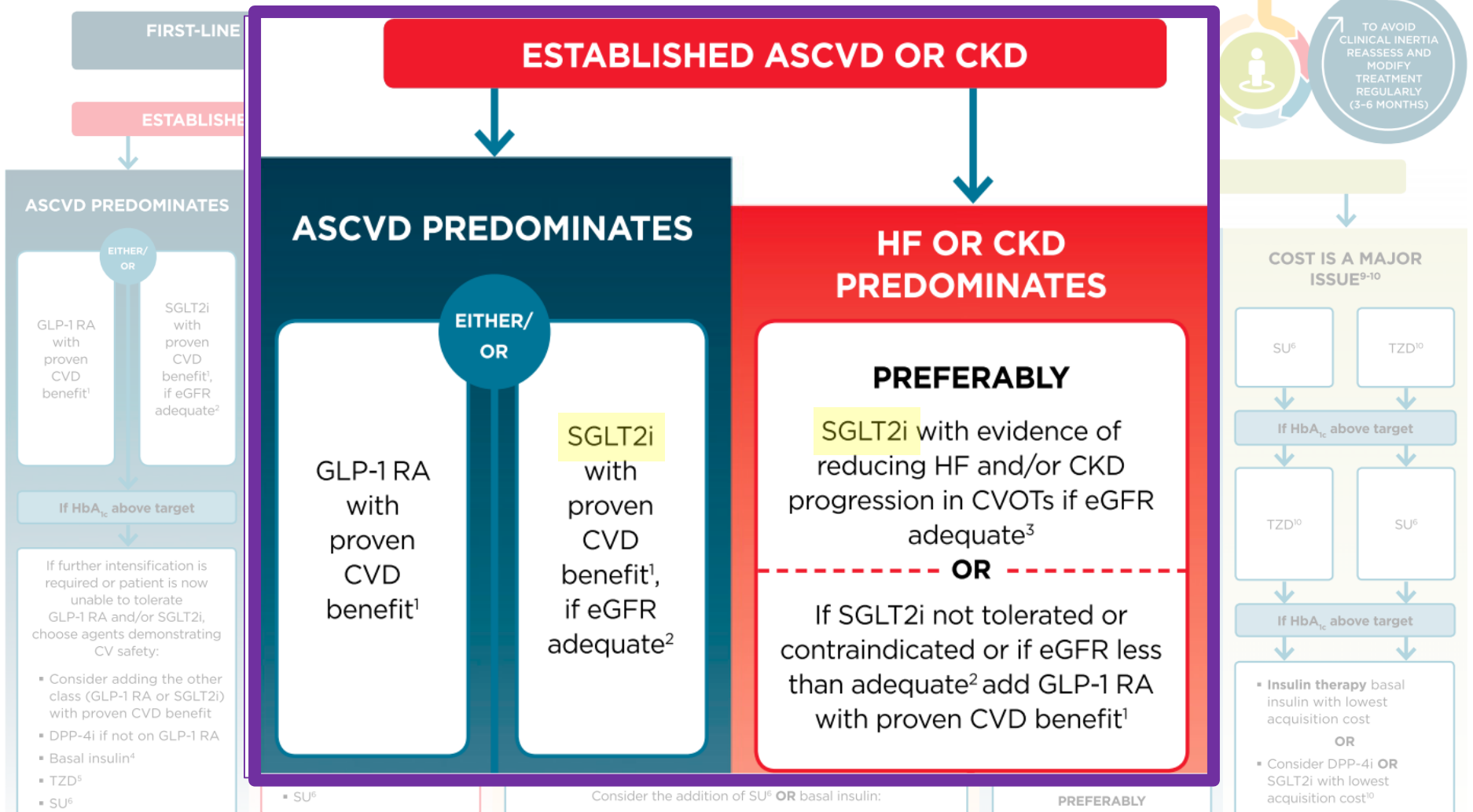
SU⁶ TZD¹⁰

If HbA_{1c} above target

TZD¹⁰ SU⁶

If HbA_{1c} above target

- Insulin therapy** basal insulin with lowest acquisition cost
- OR**
- Consider DPP-4i **OR** SGLT2i with lowest acquisition cost¹⁰



2018 ADA/EASD consensus: choosing glucose-lowering medication in those with established ASCVD or CKD



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 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 benefit¹ (see below)

如果血糖未達標, 建議增加SGLT-2i或GLP-1 RA

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 benefit¹ (see below)

如果血糖達標, 考慮替換為SGLT-2i或GLP-1 RA

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

2018 ACC針對T2D合併ASCVD病患治療共識： 考慮加上SGLT-2i or GLP-1 RA

EXPERT CONSENSUS DECISION PATHWAY

2018 ACC Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes and Atherosclerotic Cardiovascular Disease

A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways

Endorsed by the American Diabetes Association

Patient has T2DM and established clinical ASCVD

Address concurrently

Guideline-directed medical therapy (lifestyle, antiplatelet, blood pressure, lipids) and glucose-lowering therapy (metformin)

Consider addition of an SGLT2 inhibitor or GLP-1RA with demonstrated CV outcome benefit

Initiate clinician-patient discussion

No additional action taken at this time

SGLT2 inhibitor selected

GLP-1 RA selected



JACC

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

第 2 型糖尿病人高血糖的處理流程圖 (2018-2019年修訂版)



健康生活型態的飲食和運動及醫病共享決策



1. DAROC Clinical Practice Guidelines for Diabetes Care-2018, Taiwan, Diabetes Association of the R.O.C., 2018
2. <http://www.endo-dm.org.tw/dia/>

評估心腎共病

流程圖



2018糖尿病
臨床照護指引

DAROC Clinical Practice Guidelines
For Diabetes Care 2018

SGLT2i

心血管實證：有(建議使用)
心衰竭實證：有(建議使用)
腎病變實證：有
控制血糖效果：中等
體重：下降
低血糖：低
副作用：糖尿病酮酸中毒、
生殖泌尿道感染、骨折、
截肢、脫水

GLP1-RA

心血管實證：部分有(建議使用)
心衰竭實證：中立
腎病變實證：部分有
控制血糖效果：佳
體重：下降
低血糖：低
副作用：腸胃道

健康生活型態的飲食和運動及醫病共享決策

使用一種抗糖

初診斷建議首選

- 效果：佳
- 低血糖：低
- 體重：稍下降
- 副作用：腸胃道/乳酸

若單一治療未達標

SU/Glinide

- 心血管實證：缺
- 心衰竭實證：缺
- 腎病變實證：缺
- 控制血糖效果：佳
- 體重：增加
- 低血糖：中
- 副作用：低血糖

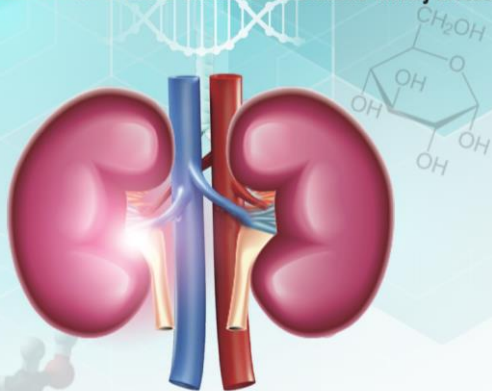


中華民國糖尿病學會
Diabetes Association of the Republic of China (Taiwan)

Guidelines for Diabetes Care-
Association of the R.O.C., 2018
tw/dia/

2019台灣糖尿病腎臟疾病 臨床照護指引

2019 Taiwan Clinical Practice Guideline for Diabetic Kidney Disease



社團法人中華民國糖尿病學會 編印

台灣腎臟醫學會

國家衛生研究院

社團法人中華民國內分泌學會

社團法人中華民國糖尿病衛教學會

共同推薦

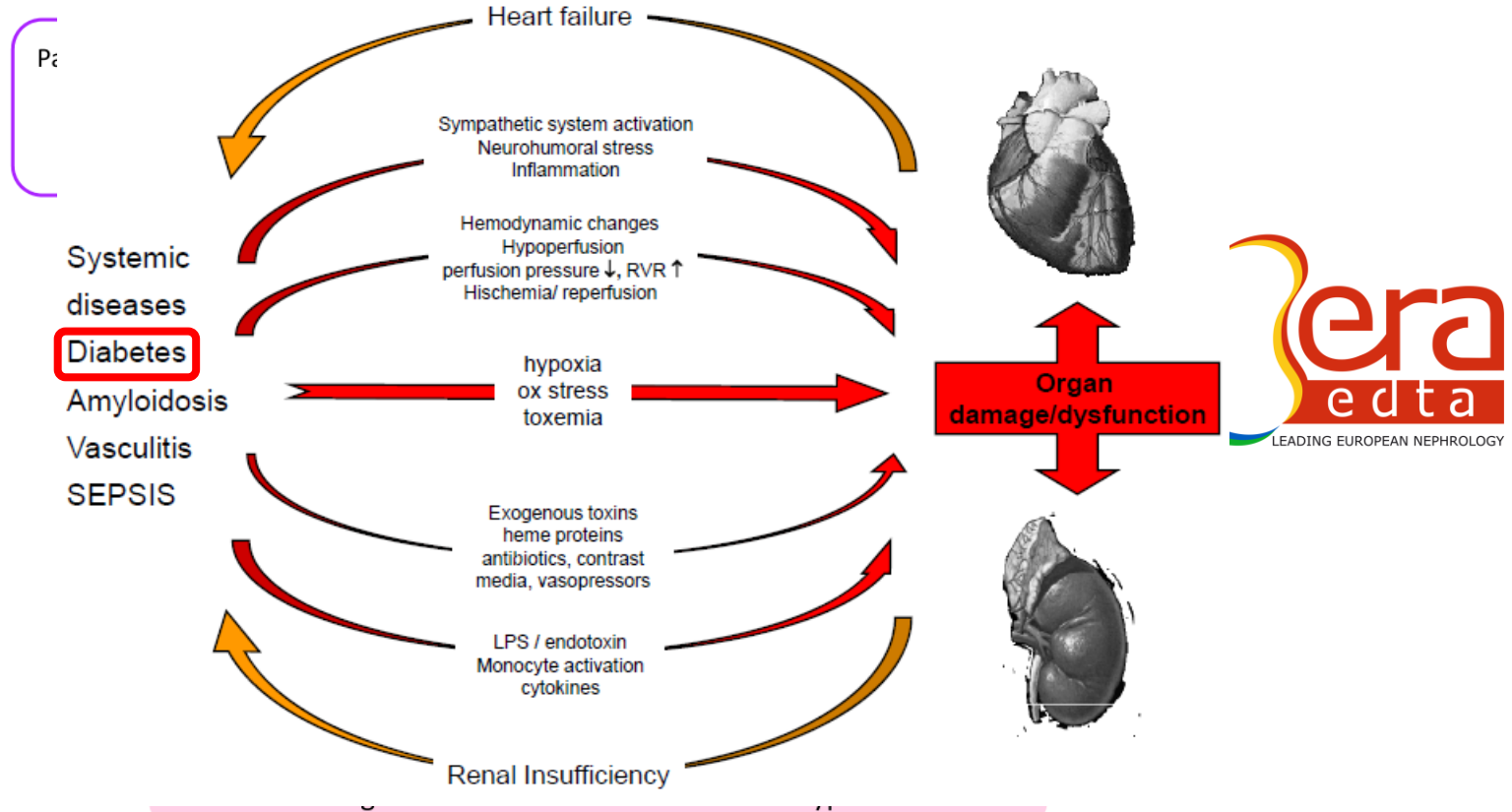


第五章 糖尿病腎臟疾病的預防與治療（藥物篇）

5.1 高血糖的控制及目標

臨床建議	證據等級	臨床建議強度	華人資料
理想的血糖控制可減少或延緩白蛋白尿的發生以及腎功能惡化。	高	強	有 ¹⁷⁵
有些鈉 - 葡萄糖共同輸送器 -2 抑制劑 (<u>SGLT2 inhibitors</u>)，與類升糖素胜肽 -1 受體促效劑 (GLP-1 receptor agonist) 呈現對降低 <u>糖尿病腎臟疾病惡化及心血管疾病風險</u> 有幫助。 SGLT2 inhibitors 對於腎功能不全患者使用的安全性與潛存的益處有待進一步研究。	中	中	

2019年歐洲腎臟學會(ERA-EDTA)對CKD合併Cardiovascular syndrome Type 1治療共識： A1c未達標，metformin後一線建議使用SGLT-2i



2019年歐洲腎臟學會(ERA-EDTA)對DM合併CKD治療共識： A1c已達標，建議考慮換藥成SGLT-2i

Patients with type 2 DM and CKD (eGFR <60 ml/min/1.73m² or eGFR >60 ml/min/1.73m² and macro- or microalbuminuria) on HbA1c target (HbA1c <7%) on therapy with metformin and additional recommended agents

If not on SGLT-2 inhibitor, consider switching one of additional agents to an SGLT-2 inhibitor with evidence for cardio- and nephroprotection¹

If HbA1c remains above target or SGLT-2 inhibitor is not tolerated or is contraindicated

If not on a GLP-1 receptor agonist, consider switching one of additional agents to a GLP-1 receptor agonist with evidence for cardio- and nephroprotection²

Reassess HbA1c in 3-months interval and adjust the treatment if above target³



Dapa-CKD將會是第一個針對CKD病患的renal outcome trial (2020年完成)

	Canagliflozin 100 mg	Dapagliflozin 5 or 10 mg	Empagliflozin 10 mg
Study	CREDESCENCE¹	DAPA-CKD²	EMPA-KIDNEY³
Estimated completion date	Jun. 28, 2019 → Oct. 30, 2018	Nov. 27, 2020	Jun. 30, 2022
Status	stopped early on demonstration of efficacy	ongoing	estimated to start Nov. 30, 2018
Study size (N)	4402	~4000	~5000
Planned study duration	~5.5 years (medium 2.6 years)	~4 years	~3.1 years
Patient population	T2D	with or without T2D	with or without diabetes (T2D or T1D)
Renal population inclusion criteria	eGFR ≥ 30 to < 90 mL/min/1.73 m ² UACR > 300 to ≤ 5000 mg/g	eGFR ≥ 25 to < 75 mL/min/1.73 m ² UACR ≥ 200 and ≤ 5000 mg/g	eGFR ≥ 20 to < 45 mL/min/1.73 m ² or eGFR ≥ 45 to < 90 mL/min/1.73 m ² with UACR ≥ 200 mg/g (or protein:creatinine ratio ≥ 300 mg/g)
Primary Endpoint	Doubling of serum creatinine, ESRD, renal or CV death	$\geq 50\%$ sustained decline in eGFR, ESRD, renal or CV death	1. $\geq 40\%$ sustained decline in eGFR, ESRD, sustained decline in eGFR to < 10 mL/min/1.73m ² , renal death 2. CV death

T1D, type 1 diabetes; T2D, type 2 diabetes; ESRD, end-stage renal disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; UACR, urinary albumin/creatinine ratio.

References: 1. ClinicalTrials.gov. CREDESCENCE. NCT02065791. <https://clinicaltrials.gov/ct2/show/NCT02065791> (Accessed on Dec. 12, 2018) 2. ClinicalTrials.gov. DAPA-CKD. NCT03036150.

<https://clinicaltrials.gov/ct2/show/NCT03036150> (Accessed on Dec. 12, 2018) 3. ClinicalTrials.gov. EMPA-KIDNEY. NCT03594110. <https://clinicaltrials.gov/ct2/show/NCT03594110> (Accessed on Dec. 12, 2018)

[Back to all news](#)

DAPA-HF Reveals Reduced Death, Hospitalizations from HF with Dapagliflozin

SEPTEMBER 01, 2019

Patrick Campbell

[@RealPatCampbell](#)



Hailed by AstraZeneca as the first trial examining use of an SGLT2 inhibitor for heart failure in patients with and without diabetes, the results of DAPA-HF, which were presented at ESC Congress 2019 in Paris, was one of the most anticipated presentations at this year's annual meeting.

Results of the study reveal that 10 mg dapagliflozin (Farxiga) reduced death and hospitalization by 26% in patients with heart failure and reduced ejection fraction with and without type 2 diabetes.

“The trial shows that dapagliflozin reduces death and hospitalization, and improves health-related quality of life, in patients with heart failure and reduced ejection fraction, with and without diabetes,” said lead investigator John McMurray, MD, professor at the University of Glasgow. “The clinical implications are potentially huge – few drugs achieve these results in heart failure and dapagliflozin does even when added to excellent standard therapy.”

The trial enrolled a cohort of 4744 patients from 20 countries and randomly assigned them to either dapagliflozin 10 mg once daily or a matching placebo. A total of 2373 patients received dapagliflozin while 2371 received placebo.



John McMurray, MD



Most Popular

[DocTalk Tweet Chat "Suicide Awareness" Scheduled for September 10](#)

[Esketamine Q&A with Carla Canuso and David Hough](#)

[Benjamin Click, MD: Treating the Gut and the Brain](#)

[DocTalk Podcast: TAVR with Dr. Kaneko and Dr. Hirji](#)

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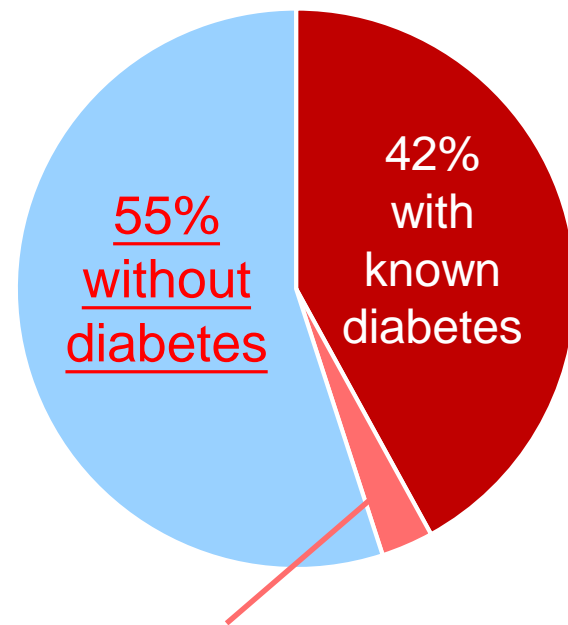
Dapa-HF baseline : 55%為非糖尿病患

The Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) trial: baseline characteristics

John J.V. McMurray^{1*}, David L. DeMets², Silvio E. Inzucchi³, Lars Køber⁴, Mikhail N. Kosiborod⁵, Anna Maria Langkilde⁶, Felipe A. Martinez⁷, Olof Bengtsson⁶, Piotr Ponikowski⁸, Marc S. Sabatine⁹, Mikaela Sjöstrand⁶, and Scott D. Solomon¹⁰, on behalf of the DAPA-HF Committees and Investigators

4774 patients high levels of background therapy:

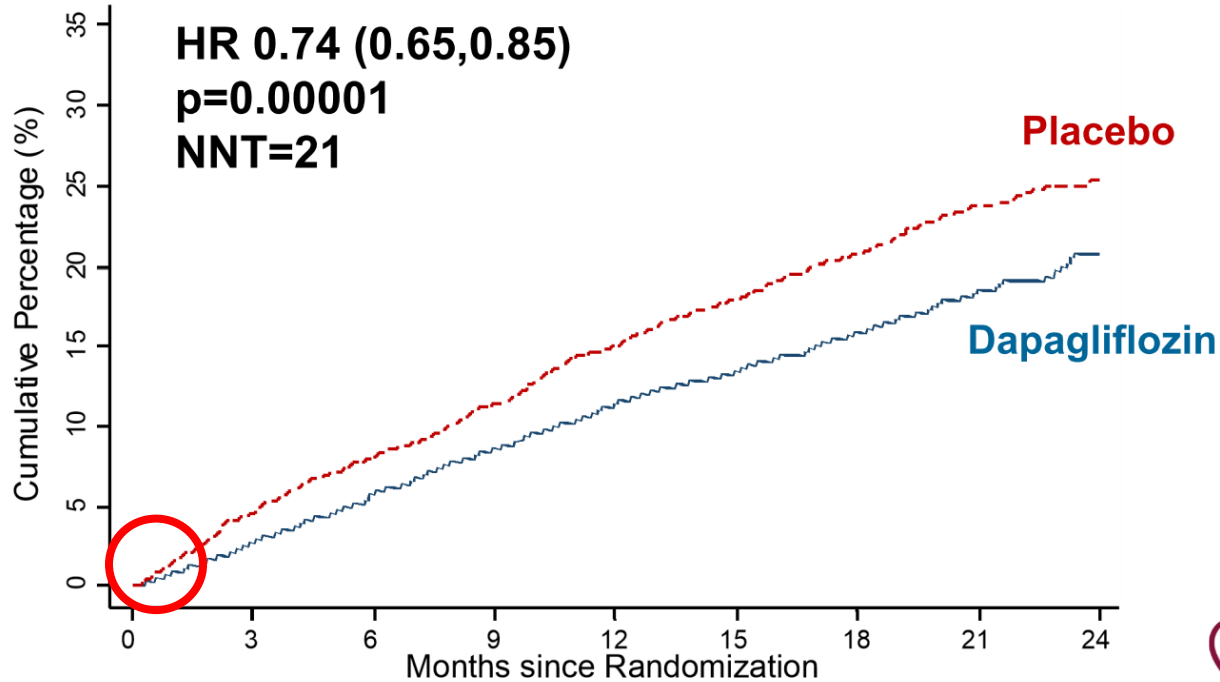
- 94% ACEI/ARB/ARNI
- 96% beta-blocker
- 71% mineralocorticoid receptor antagonist
- 26% had a defibrillator



3% with undiagnosed diabetes

Primary composite outcome

CV Death/HF hospitalization/Urgent HF visit

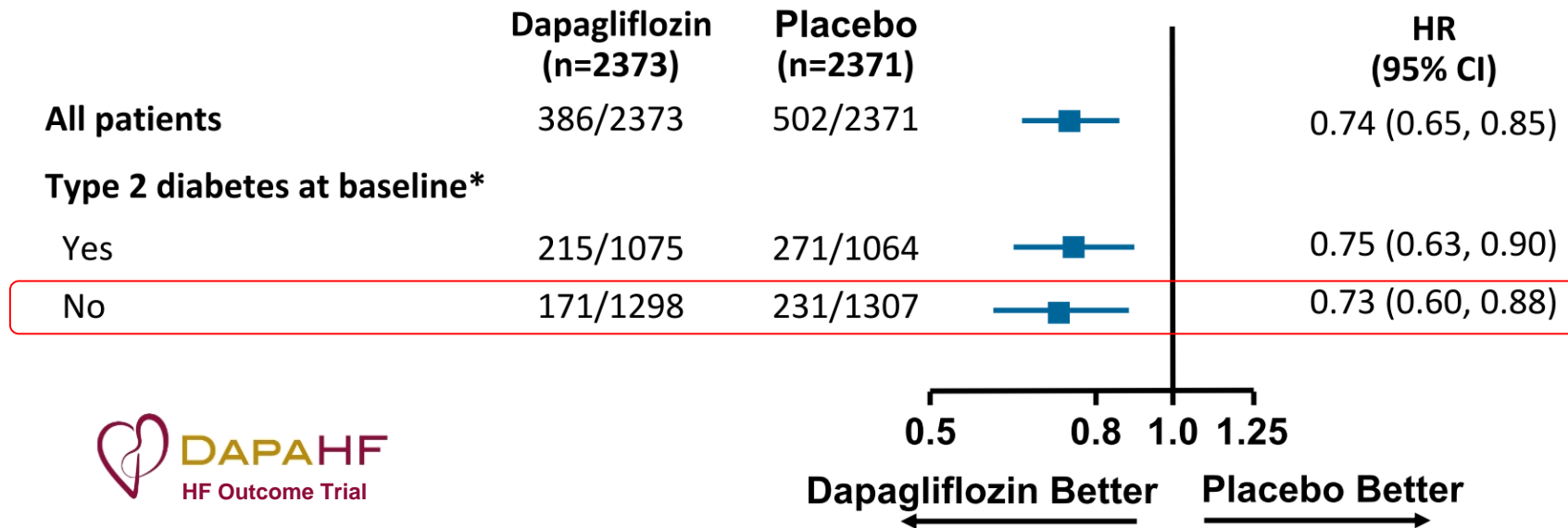


Number at Risk

Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

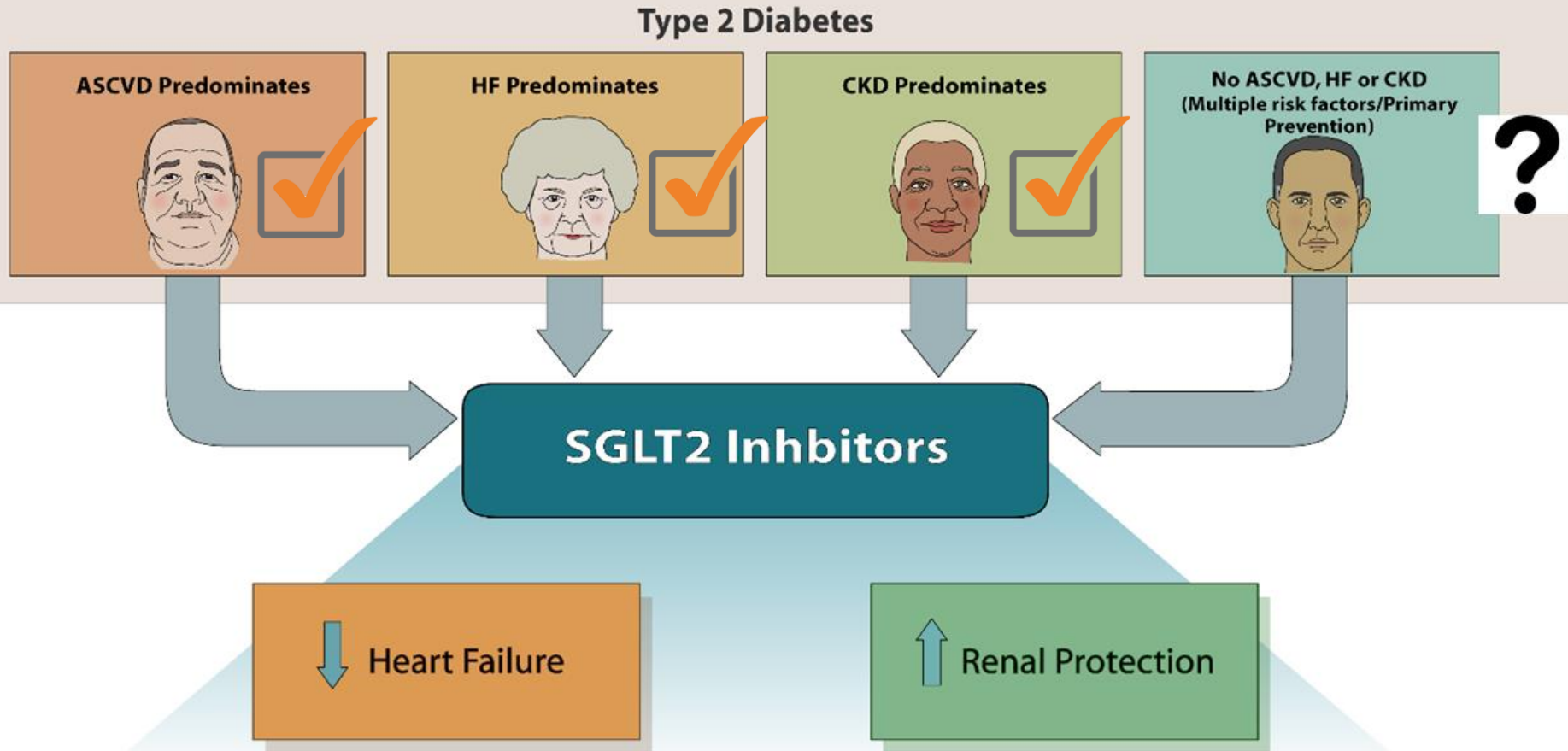


No diabetes/diabetes subgroup: Primary endpoint



*Defined as history of type 2 diabetes or HbA1c $\geq 6.5\%$ at both enrollment and randomization visits.

What do we know about SGLT-2i before 2019



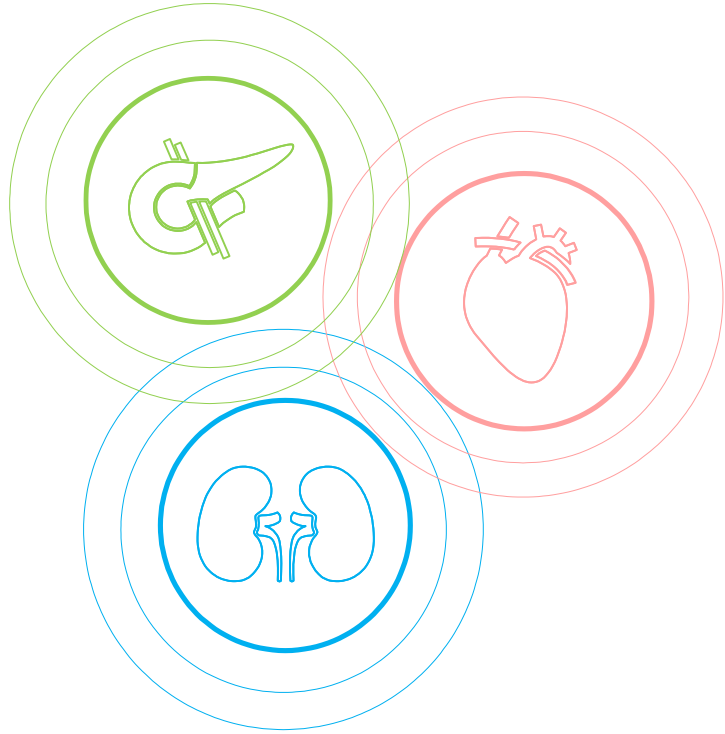
An iceberg floating in the ocean. The tip of the iceberg is visible above the water surface, while the much larger, submerged part is visible below. The water is a deep blue, and the sky is a lighter blue with some clouds. The text is overlaid on the image, with the top part above the water and the bottom part below the water.

79% T2D patients without CVD¹
72% T2D patients with eGFR \geq 60²
88% T2D patients without HF³

SGLT-2i的角色？

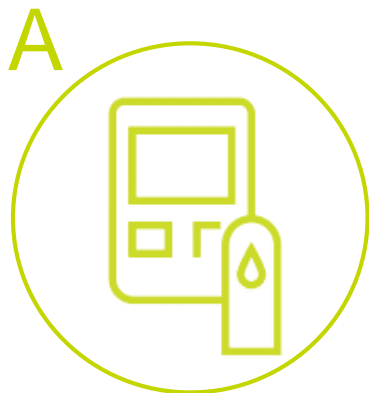
1. Curr Med Res Opin. 2016 Jul;32(7):1243-52.
2. Nephron. 2018;140(3):175-184.
3. Diabetes Care 2005 Mar; 28(3): 612-616.

Outline



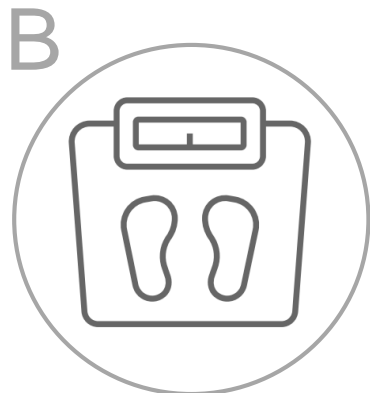
- The four advancements of anti-diabetic medication
- **What can SGLT-2 inhibitor help us as treating diabetic patients with CV risk factor?**
- Conclusion

SGLT-2i能帶給T2D病患的好處：ABCD



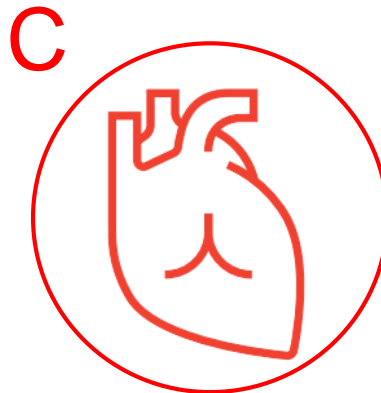
血糖控制

A1c



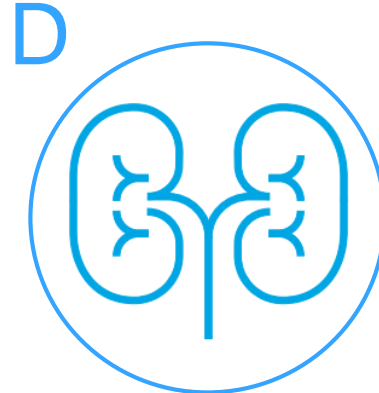
降低體重

Body weight



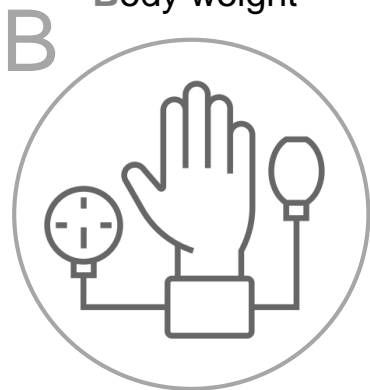
降低心血管風險

CV risk (HF)



降低腎臟惡化風險

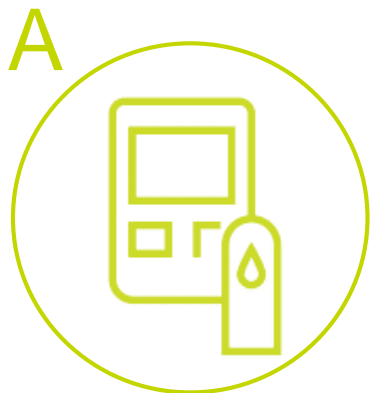
Diabetic kidney disease



降低血壓

Blood pressure

SGLT-2i能帶給T2D病患的好處：ABCD



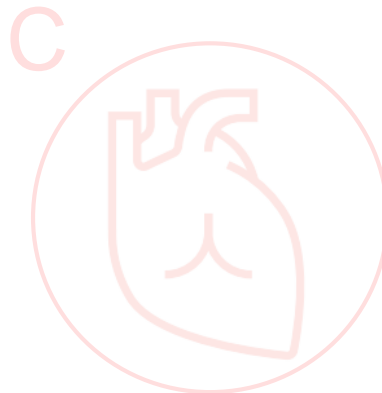
血糖控制

A1c



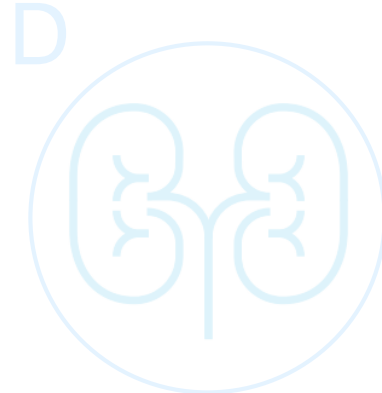
降低體重

Body weight



降低心血管風險

CV risk (HF)



降低腎臟惡化風險

Diabetic kidney disease



降低血壓

Blood pressure

TIR (Time in Range) recommendation at 2019 ADA Scientific Sessions

Medscape Diabetes & Endocrinology ▾

NEWS & PERSPECTIVE DRUGS & DISEASES CME & EDUCATION ACADEMY VIDEO

News > Medscape Medical News > Conference News > ADA 2019

New Statement on 'Time in Range' Targets for CGM Use in Diabetes

Miriam E. Tucker
June 18, 2019



American Diabetes Association. Diabetes Care

Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range

<https://doi.org/10.2337/dci19-0028>

Time in Range Recommendations for most people with type 1 or type 2 diabetes

70-180mg/dL	>70%
<70 mg/dL	<4%
<54 mg/dL (3 mmol/L)	<1%
>180 mg/dL	<25%
>250 mg/dL	<5%

以CGM (連續血糖監測) 評估 Dapagliflozin vs. Gliclazide的臨床試驗

- 發表於2019年ADA年會



97 uncontrolled T2DM individuals
drug naïve or on steady-dose
metformin monotherapy



Table 1. Baseline characteristics and patient disposition

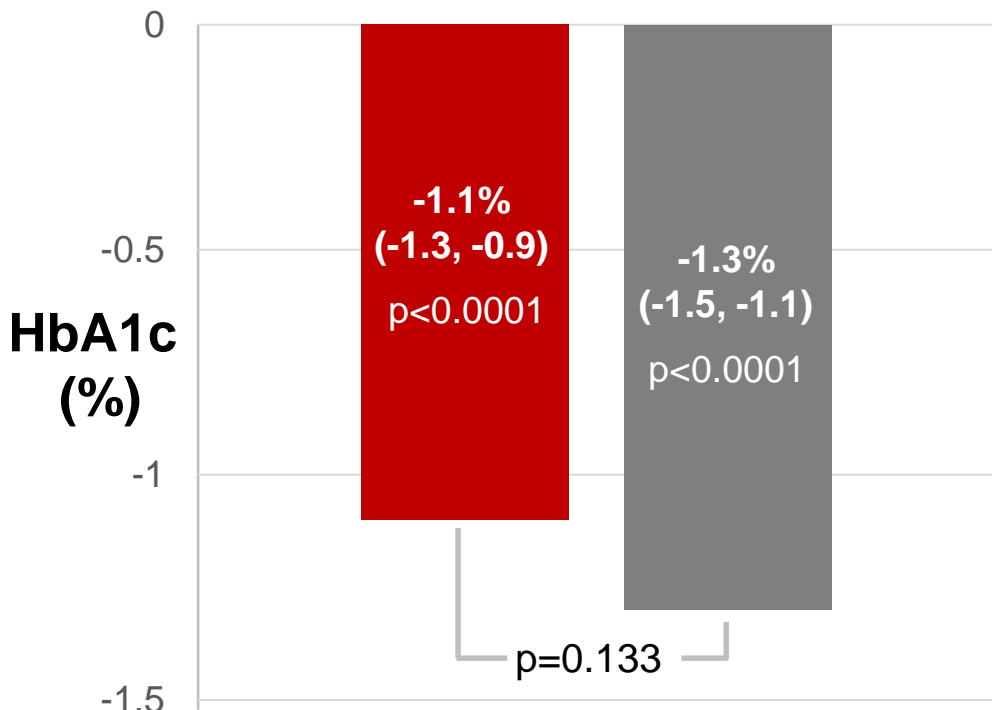
Variables	Dapagliflozin (n=42)	Gliclazide MR (n=52)	P-Value
Age (years)	57.0 ± 8.4	58.6 ± 8.9	0.39
Male sex, n (%)	21 (46.7)	28 (53.8)	0.54
Race, n (%)			0.71
White	33 (78.6)	44 (84.6)	
Black	4 (9.5)	3 (5.8)	
Hispanic/Latino	3 (7.1)	4 (7.7)	
Asian	2 (4.8)	1 (1.9)	
Diabetes duration (years)	4.0 (1.0-6.0)	4.0 (2.0-9.1)	0.30
Metformin daily dose (mg)	1412 ± 542	1581 ± 635	0.35
Drug naïve, n (%)	8 (19.0)	9 (17.3)	1.00
Body weight (kg)	83.9 ± 15.0	83.6 ± 17.3	0.93
BMI (kg/m ²)	31.2 ± 4.4	30.6 ± 5.0	0.49
eGFR (ml/min/1.73 m ²)	89 (77-105)	87 (77-99)	0.44

Dapagliflozin vs. Gliclazide

在A1c, FPG, PPG具一致的降糖表現

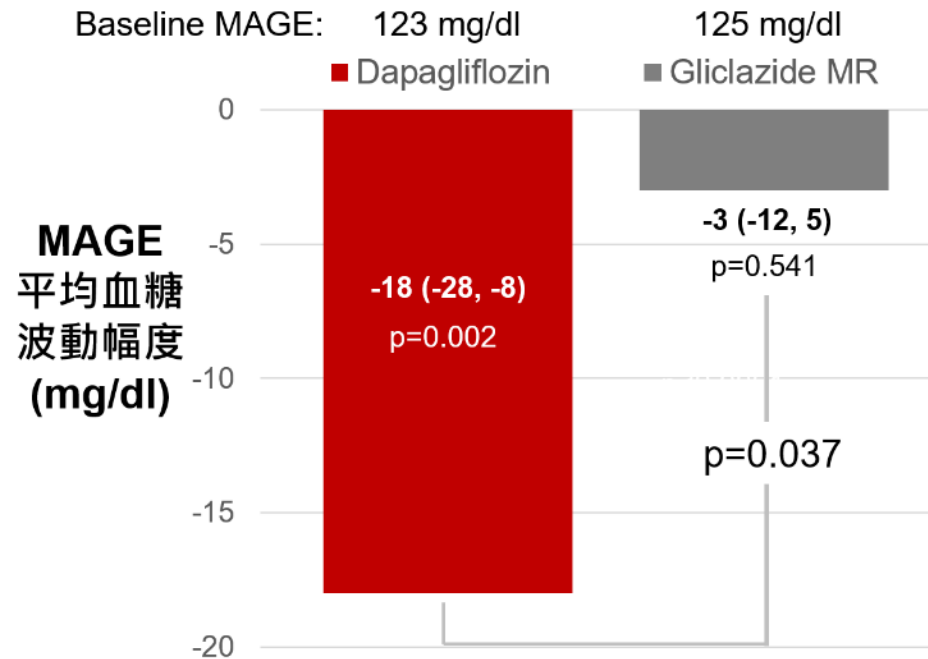
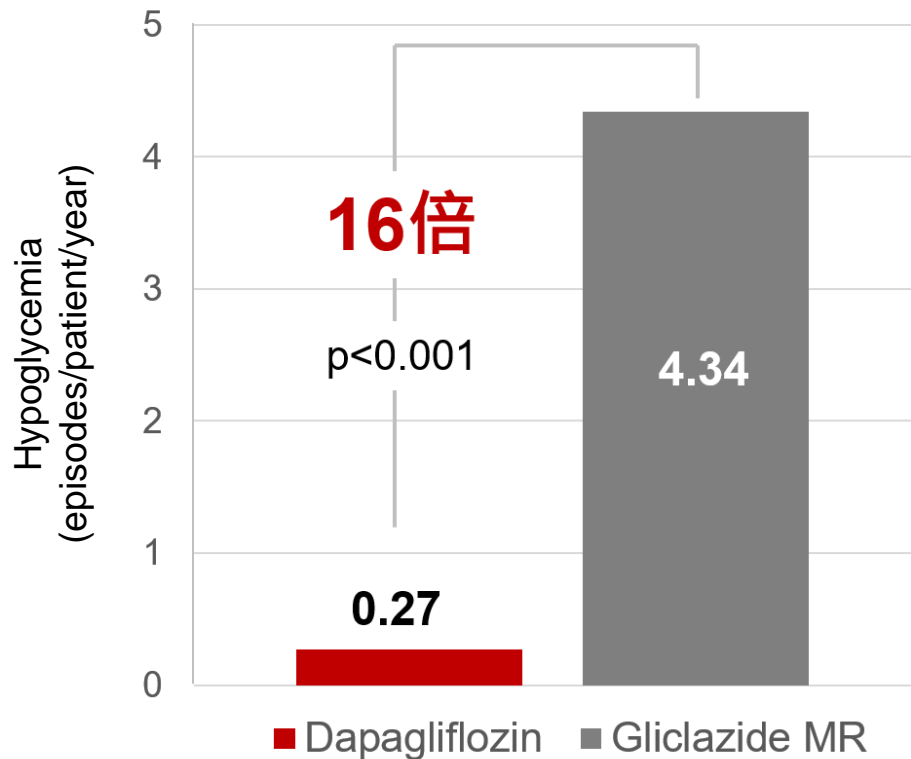
Baseline HbA1c: 8.1% 8.0%

■ Dapagliflozin ■ Gliclazide MR

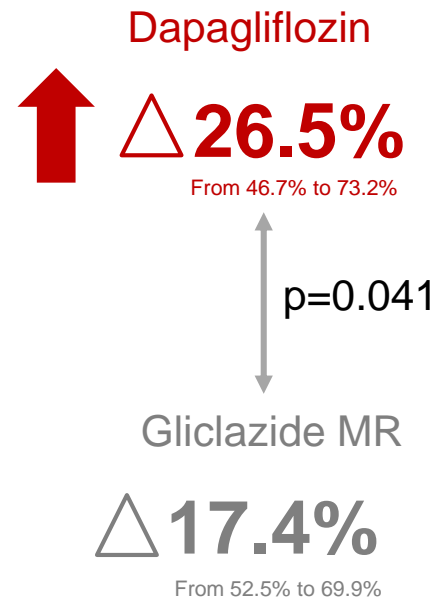
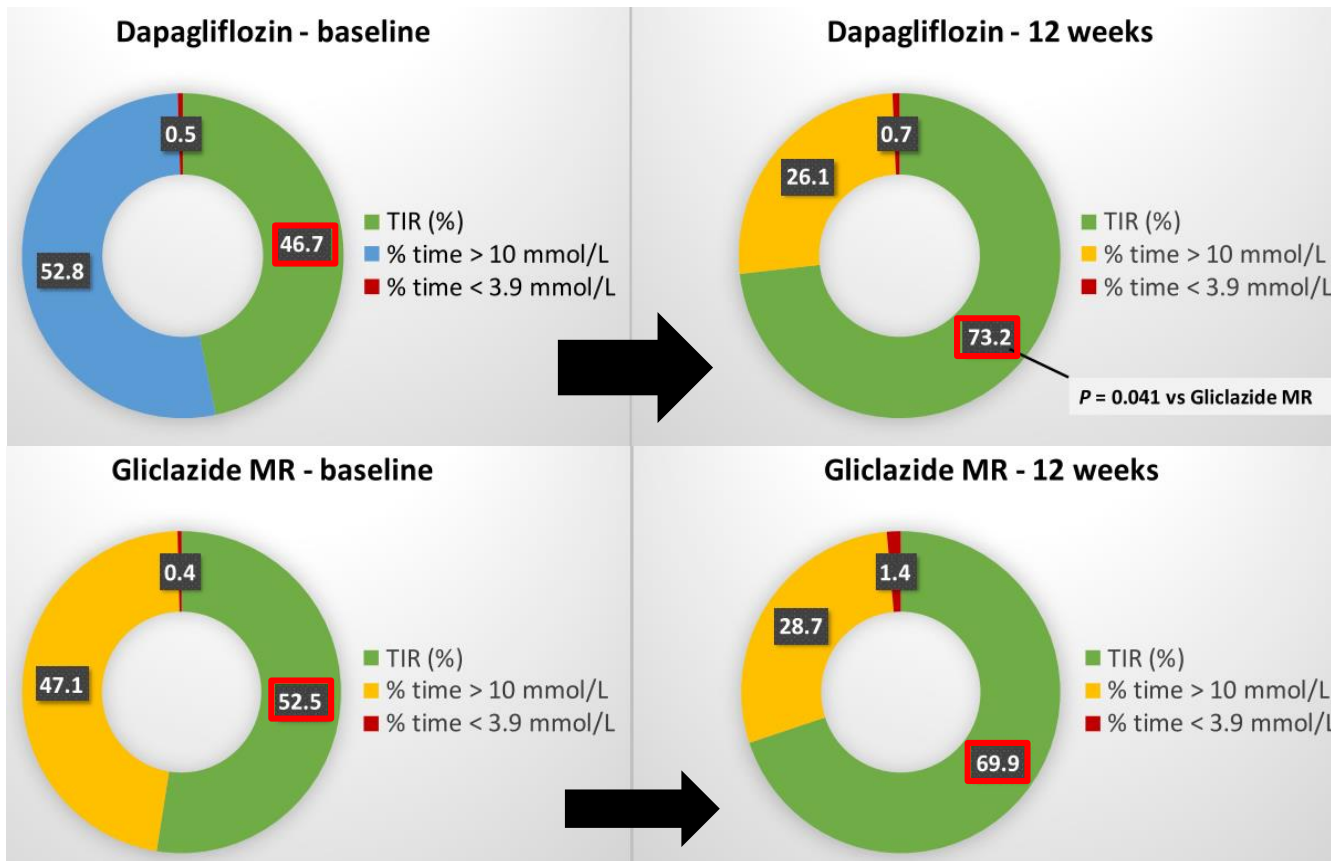


血糖	Dapagliflozin	Gliclazide MR
FPG (mg/dl)	Baseline: 161 Change: -31 p<0.0001	Baseline: 161 Change: -37 p<0.0001
	p=0.236	
PPG (mg/dl)	Baseline: 202 Change: -66 p<0.0001	Baseline: 199 Change: -56 p<0.0001
	p=0.312	

Dapagliflozin 低血糖風險低、更能降低 血糖波動



相較於 Gliclazide，Dapagliflozin 更能增加 TIR (Time in Range)



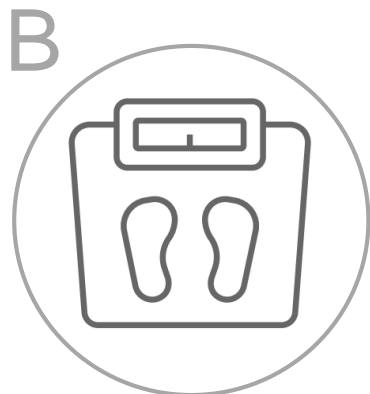
***TIR: 血糖維持目標範圍 (70-180 mg/dl) 內時間%**

SGLT-2i能帶給T2D病患的好處：ABCD



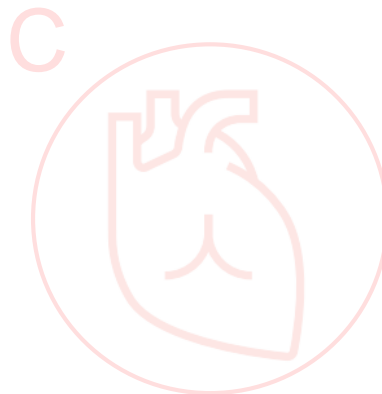
血糖控制

A1c



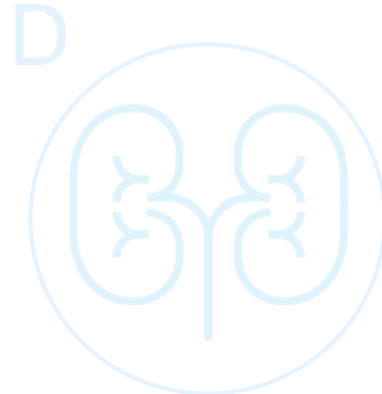
降低體重

Body weight



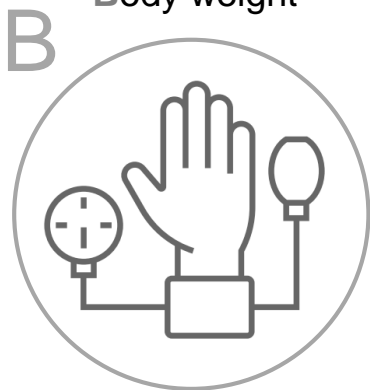
降低心血管風險

CV risk (HF)



降低腎臟惡化風險

Diabetic kidney disease



降低血壓

Blood pressure

DIVERSITYCVR Study:

比較T2D病患使用Dapagliflozin和Sitagliptin的療效

All SGLT-2i now could be prescribed in DM patients with eGFR >45 in Taiwan



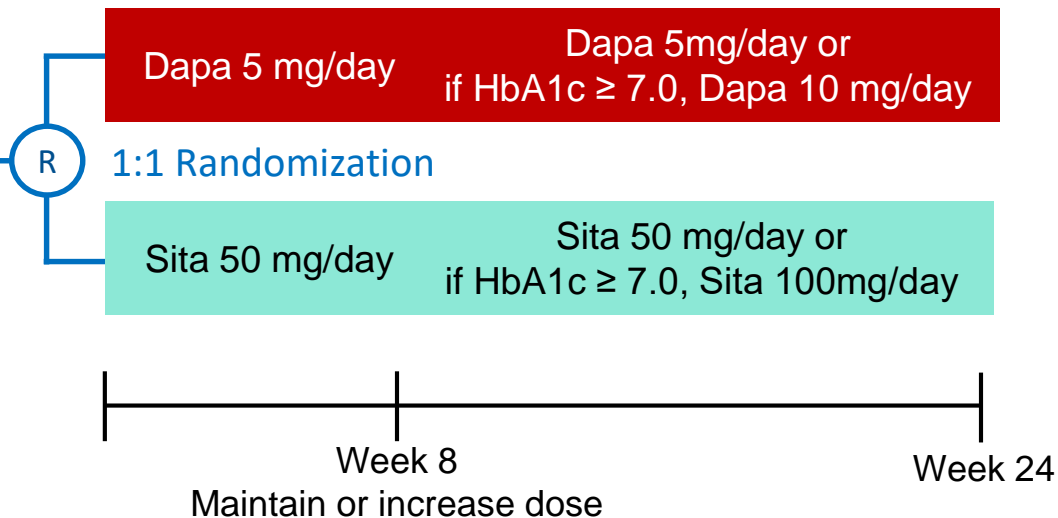
• 340 T2DM patients in Tokyo

• The inclusion criteria

- T2DM, age 20-80 years
- $7.1\% \leq \text{HbA1c} \leq 10.0\%$
- with metformin (250-2250mg) alone or with no glucose-lowering agents
- $\text{BMI} \geq 23 \text{ kg/m}^2$

• The exclusion criteria

- $\text{Cr} \geq 1.3 \text{ mg/dL}$ or
- $\text{eGFR} < 45 \text{ mL/min/1.73 m}^2$



The primary endpoints: Achievement ratio of all the following criteria

- (1) HbA1c below 7.0%
- (2) More than 3.0% body weight loss from baseline
- (3) Avoidance of hypoglycemia $\{< 3.0 \text{ mmol/L} (< 54 \text{ mg/dL})\}$



Dapa: dapagliflozin, Sita: sitagliptin, R: randomization

1. Cardiovasc Diabetol. 2018 Jun 12;17(1):86. 2. Fuchigami A, et al. Presented at: Scientific sessions of the 79th American Diabetes Association: June 7-11, 2019; San Francisco, CA, USA. 21-LB

病患平均A1c 7.8% 糖尿病年~6年



Table1. Baseline characteristics of patients in the two groups

Characteristics	Dapa group (n = 168)	Sita group (n = 163)	P value
Sex (male / female) n(%)	104(61.9)/64(38.1)	95(58.3)/68(41.7)	0.57
Age (years)	58.3 ± 12.4	57.9 ± 12.1	0.71
Body weight(kg)	74.5 ± 13.4	74.9 ± 15.0	0.84
BMI(kg/m ²)	27.8 ± 4.0	27.9 ± 4.2	0.76
Duration of diabetes (years)	6.0 ± 6.4	5.6 ± 5.8	0.47
HbA1c (NGSP%)	7.8 ± 0.8	7.8 ± 0.8	0.90
Fasting plasma glucose (mg/dL)	151.7 ± 33.4	152.1 ± 30.7	0.92
Current smoking	77(45.8)	83(50.9)	0.64
Macrovascular complications	14(8.3)	16(9.8)	0.70
Anti-diabetic drugs	100(59.5)	95(58.3)	0.82
Biguanides	100(59.5)	95(58.3)	0.82
Dose of Biguanides (mg)	561.9 ± 630.0	523.8 ± 577.3	0.57

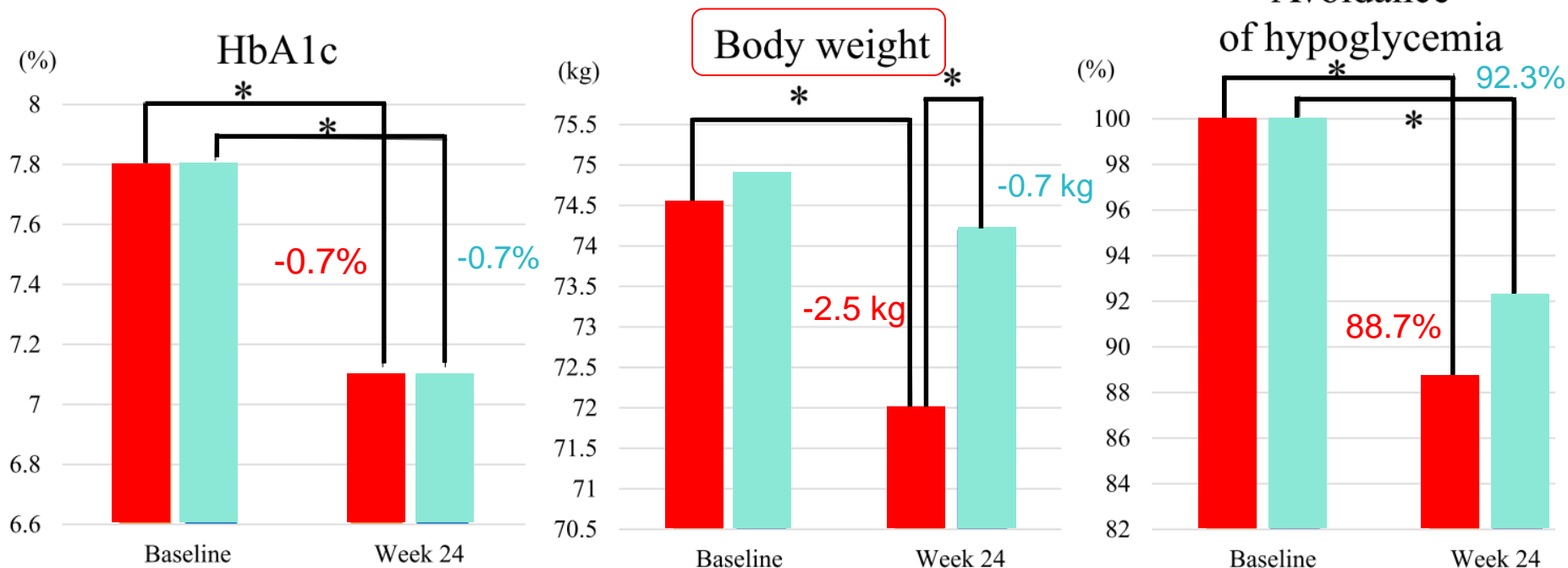
Dapa: dapagliflozin, Sita: sitagliptin, R: randomization

1. Cardiovasc Diabetol. 2018 Jun 12;17(1):86. 2. Fuchigami A, et al. Presented at: Scientific sessions of the 79th American Diabetes Association: June 7-11, 2019; San Francisco, CA, USA. 21-LB

Dapagliflozin和Sitagliptin具一致的降糖效果和低血糖風險，Dapagliflozin可額外降低體重



■ Dapa ■ Sita * P<0.05



Dapa: dapagliflozin, Sita: sitagliptin, R: randomization

1. Cardiovasc Diabetol. 2018 Jun 12;17(1):86. 2. Fuchigami A, et al. Presented at: Scientific sessions of the 79th American Diabetes Association: June 7-11, 2019; San Francisco, CA, USA. 21-LB

Dapagliflozin和Sitagliptin具一致的血糖達標率和低血糖風險，Dapagliflozin降低3%體重比率較高



Table2. Primary Outcomes

Data are expressed as number (%), mean \pm standard deviation (*n*), or median [first quartile, third quartile] (*n*). *P* values by the *t* test or Wilcoxon rank sum test for continuous data, and by Fisher exact test for categorical data.

	Dapa group n(%)	Sita group n(%)	P value
Achieving the composite endpoints	39(24.4)	22(13.8)	0.02
HbA1c < 7.0%	81 49.4%	80 50.0%	1.00
More than 3.0% body weight loss	87 54.4%	31(19.6%	<0.001
Avoidance of hypoglycemia	141 88.7%	144(92.3%	0.34

Dapa: dapagliflozin, Sita: sitagliptin, R: randomization

1. Cardiovasc Diabetol. 2018 Jun 12;17(1):86. 2. Fuchigami A, et al. Presented at: Scientific sessions of the 79th American Diabetes Association: June 7-11, 2019; San Francisco, CA, USA. 21-LB

Dapagliflozin可額外降低血壓和減少胰島素的分泌



Parameters	Dapa group	Sita group	P value
Systolic Blood Pressure(mmHg)			
Baseline	134.6 ± 15.9	132.8 ± 15.7	0.28
Week 24	130.4 ± 16.9	131.9 ± 16.3	0.42
Change	-4.1 ± 16.3	-1.4 ± 17.3	0.16
P value within group	0.002	0.31	
Diastolic Blood Pressure(mmHg)			
Baseline	80.5 ± 12.1	79.1 ± 11.0	0.25
Week 24	78.2 ± 12.2	78.7 ± 11.4	0.73
Change	-2.3 ± 11.5	-0.4 ± 12.1	0.15
P value within group	0.012	0.68	

Fasting plasma glucose(mg/dL)	Dapa group	Sita group	P value
Baseline	151.7 ± 33.4	152.1 ± 30.7	0.92
Week 24	130.8 ± 22.9	139.6 ± 31.5	0.005
Change	-19.1 ± 30.1	-12.9 ± 32.3	0.09
P value within group	<0.001	<0.001	
IRI(μU/mL) IRI: immunoreactive insulin			
Baseline	2.18 ± 0.67	2.25 ± 0.69	0.38
Week 24	1.95 ± 0.71	2.32 ± 0.61	<0.001
Change	-0.23 ± 0.55	0.09 ± 0.47	<0.001
P value within group	<0.001	0.046	



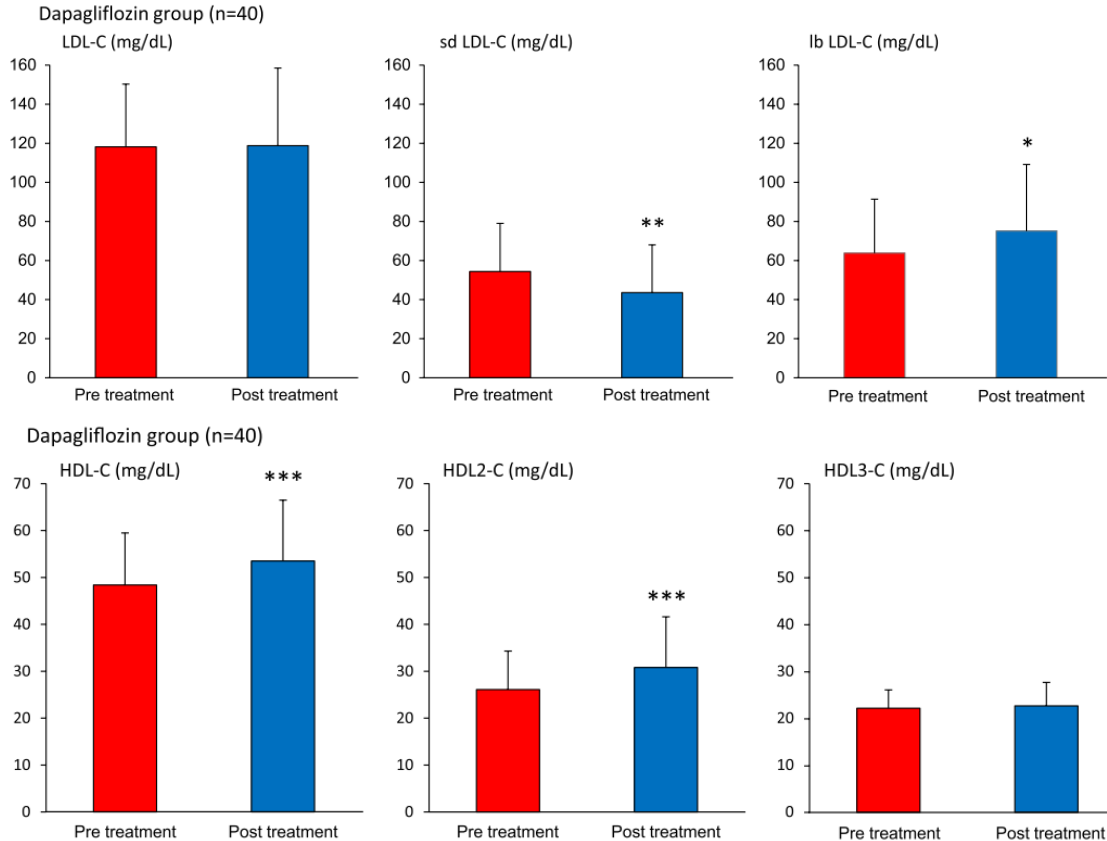
Dapagliflozin 比起 Sitagliptin 能降低 sd LDL-C 和增加 HDL2-C

	Dapagliflozin				Sitagliptin				p value ^b
	Pre treatment	Post treatment	% change	p value ^a	Pre treatment	Post treatment	% change	p value ^a	
Total-C (mg/dL)	193.5 ± 36.6	198.4 ± 45.9	2.5	0.863	192.5 ± 58.2	195.5 ± 38.9	1.6	0.720	0.102
TG (mg/dL)	152.6 ± 63.7	133.7 ± 75.8	-12.4	0.145	150.2 ± 85.2	144.6 ± 87.2	-3.7	0.245	0.928
HDL-C (mg/dL)	48.4 ± 11.1	53.5 ± 13.0	10.5	<0.001*	50.3 ± 9.25	50.3 ± 11.1	0	0.948	0.003*
LDL-C (mg/dL)	118.2 ± 32.1	118.8 ± 39.7	0.5	0.875	120.2 ± 35.1	114.7 ± 33.1	-4.6	0.257	0.323
Non HDL-C (mg/dL)	145.1 ± 36.0	144.9 ± 439	-0.1	0.947	142.2 ± 57.3	145.1 ± 38.4	2.9	0.717	0.328
Apo AI (mg/dL)	133.5 ± 21.6	143.5 ± 22.6	7.5	0.002*	134.9 ± 25.2	128.8 ± 30.7	-4.5	0.135	0.002*
Apo AII (mg/dL)	29.7 ± 4.5	30.9 ± 5.0	4.0	0.022*	30.5 ± 7.2	30.5 ± 7.2	0	0.945	0.148
Apo B (mg/dL)	100.1 ± 24.5	100.8 ± 28.1	0.7	0.777	102.3 ± 27.7	97.4 ± 26.5	-4.8	0.123	0.131
Apo CII (mg/dL)	4.8 ± 1.7	4.9 ± 2.2	2.1	0.362	5.4 ± 2.8	5.1 ± 2.6	-5.6	0.197	0.105
Apo CIII (mg/dL)	10.5 ± 3.2	11.4 ± 4.3	8.6	0.021*	10.1 ± 4.5	9.6 ± 4.0	-5.0	0.335	0.028*
Apo E (mg/dL)	4.4 ± 1.2	4.4 ± 1.5	0	0.530	4.3 ± 1.5	4.1 ± 1.0	-4.7	0.296	0.216
RLP-C (mg/dL)	6.8 ± 4.3	6.4 ± 5.1	-5.9	0.620	6.9 ± 8.0	6.1 ± 5.7	-11.6	0.303	0.750
HDL2-C (mg/dL)	26.1 ± 8.2	30.8 ± 10.8	18.0	<0.001*	26.6 ± 7.9	27.5 ± 8.4	3.4	0.334	0.013*
HDL3-C (mg/dL)	22.2 ± 3.9	22.7 ± 5.0	2.3	0.527	23.3 ± 5.2	22.2 ± 5.3	-4.7	0.132	0.130
sd LDL-C (mg/dL)	54.4 ± 24.6	43.6 ± 24.4	-19.9	0.005*	54.0 ± 22.5	50.4 ± 22.4	-6.7	0.368	0.003*
lb LDL-C (mg/dL)	63.8 ± 27.6	75.1 ± 34.1	17.7	0.026*	66.2 ± 26.3	64.3 ± 24.1	-2.9	0.671	0.029*

Patients were randomized to receive dapagliflozin (n=40) or sitagliptin (n=40) as add-on treatment for 12 weeks in Japan

Dapagliflozin suppresses potent atherogenic sd LDL-C and increased HDL2-C, a favorable cardiometabolic marker

Dapagliflozin能降低sd LDL-C和增加HDL2-C



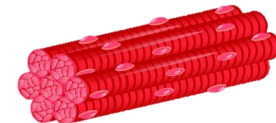
RCT, 80 patients with T2DM, 12 weeks
sd LDL: small dense LDL
lb LDL: large buoyant LDL

Dapagliflozin Reduces Fat Mass without Affecting Muscle Mass in Type 2 DiabetesSeigo Sugiyama^{1,2}, Hideaki Jinnouchi^{1,2,3}, Noboru Kurinami¹, Kunio Hieshima¹, Akira Yoshida¹, Katsunori Jinnouchi¹, Hiroyuki Nishimura¹, Tomoko Suzuki¹, Fumio Miyamoto¹, Keizo Kajiwara^{1,2} and Tomio Jinnouchi^{1,2}**Dapagliflozin Reduces Fat Mass without Affecting Muscle Mass in T2DM**

	Dapagliflozin (n = 28)		P value
	Baseline	6 months	
HbA1c (%)	7.9 (7.3–8.7)	6.8 (6.4–7.5)	p < 0.01
Absolute change (%)	-1.2 (-1.4– -0.5)		
Body weight (kg)	76.7 ± 7.4	73.3 ± 7.5	p < 0.01
Absolute change (kg)	-3.4 ± 2.6		†
Total Fat mass (kg)	24.9 ± 6.0 [‡]	21.8 ± 6.6	p < 0.01
Absolute change (kg)	-3.1 ± 2.6		†
Skeletal muscle mass (kg)	28.7 ± 4.0	28.5 ± 4.3	p = 0.34
Absolute change (kg)	-0.2 ± 1.2		
Skeletal muscle mass percentage (%)	37.5 ± 4.3	38.9 ± 5.0	p < 0.01
Absolute change (%)	↑ 1.5% 1.5 ± 1.7		‡



- 50 Japanese T2DM patients were treated with **dapagliflozin** (5 mg/day) or non-SGLT2i medicines for 6 months
- Fat/skeletal muscle mass was measured by direct segmental multi-frequency bioelectrical impedance analyzer (InBody770)
- Psoas muscle mass was measured by abdominal computed tomography (CT)



SGLT-2i能帶給T2D病患的好處：ABCD



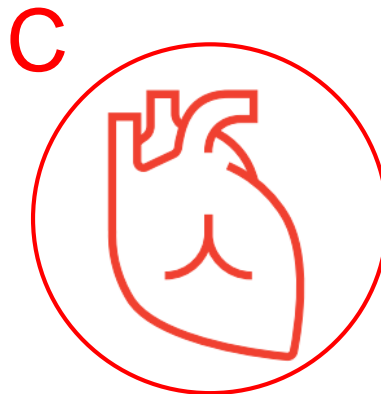
血糖控制

A1c



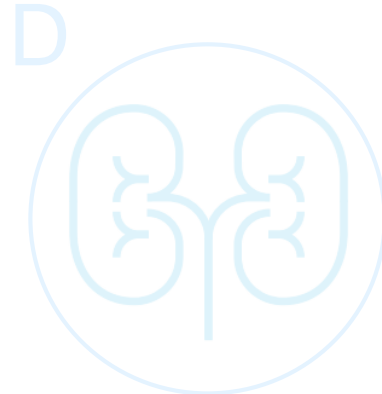
降低體重

Body weight



降低心血管風險

CV risk (HF)



降低腎臟惡化風險

Diabetic kidney disease

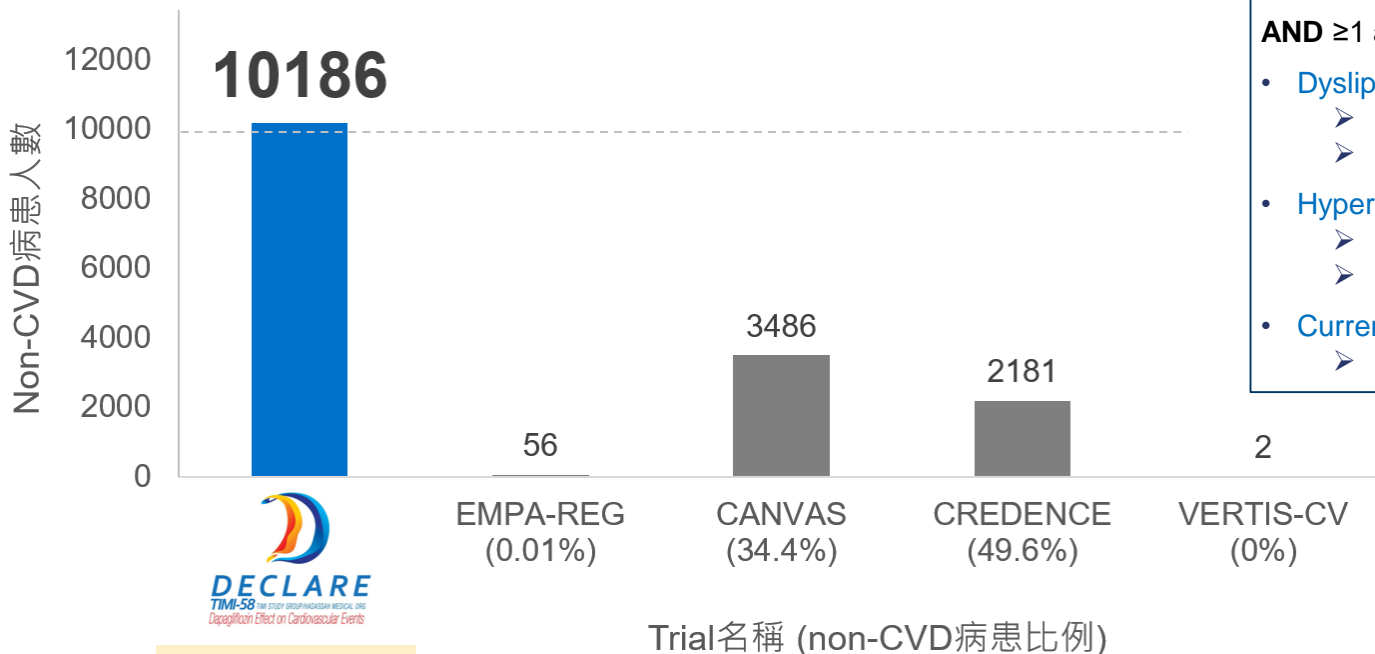


降低血壓

Blood pressure

DECLARE為唯一non-CVD病患超過萬人的T2DM CVOT

SGLT-2抑制劑心血管/腎臟試驗non-CVD人數



Multiple Risk Factors

Age ≥ 55 years (men), ≥ 60 years (women)

AND ≥ 1 additional risk factors:

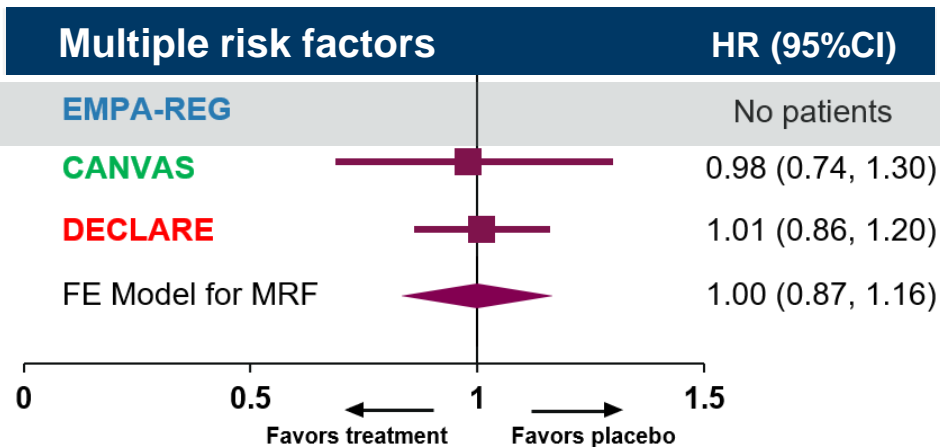
- **Dyslipidemia** (≥ 1 of following)
 - LDL-C > 130 mg/dL (> 3.36 mmol/L)
 - On lipid-lowering therapy
- **Hypertension** (≥ 1 of following)
 - BP $> 140/90$ mm Hg at enrolment
 - On antihypertensive therapy
- **Current smoking**
 - ≥ 5 cigarettes/day for ≥ 1 year



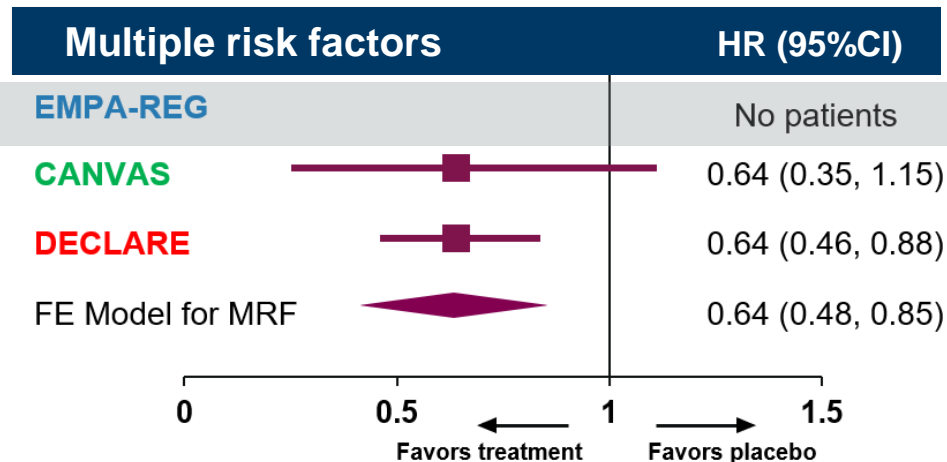
(59.3%)

DECLARE提供non-CVD病患心血管安全實證: MACE & hHF

MACE



Hospitalization for heart failure



↓ **36%**

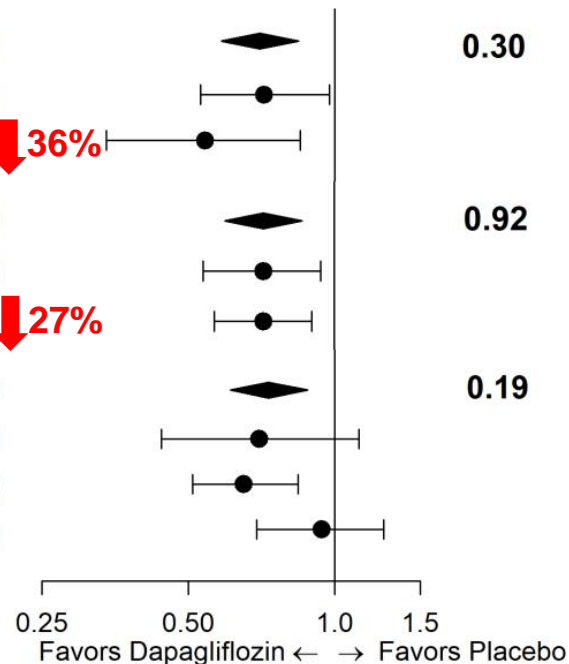
ASCVD = atherosclerotic CV disease; CV = cardiovascular; FE = fixed effects; hHF = hospitalized for heart failure; HR = hazard ratio; MACE = major cardiovascular adverse event; MRF = multiple risk factors; SGLT2 = sodium glucose co-transporter 2; T2D = type 2 diabetes.

1. Zelniker TA et al. Article and supplementary appendix. *Lancet*. 2019;393:31-39; 2. Einarson TR et al. *Cardiovasc Diabetol*. 2018;17:83.

DECLARE的心衰竭住院終點次分析



Outcomes	Dapagliflozin n/N	Placebo n/N	Hazard Ratio (95% CI)	P value for interaction
HHF	212/8582	286/8578	0.73 (0.61-0.88)	0.30
ASCVD	151/3474	192/3500	0.78 (0.63-0.97)	
MRF MRF: multiple risk factors 40.6% patients in DECLARE	61/5108	94/5078	0.64 (0.46-0.88) ↓ 36%	
HHF	212/8582	286/8578	0.73 (0.61-0.88)	0.92
Prior HF	87/852	115/872	0.73 (0.55-0.96)	
No HF 90% patients in DECLARE	125/7730	171/7706	0.73 (0.58-0.92) ↓ 27%	
HHF	212/8582	286/8578	0.73 (0.61-0.88)	0.19
<60 mL/min/1.73m ²	29/606	48/659	0.70 (0.44-1.12)	
60 to <90 mL/min/1.73m ²	99/3838	152/3894	0.65 (0.51-0.84)	
>=90 mL/min/1.73m ²	84/4137	86/4025	0.94 (0.69-1.26)	



The NEW ENGLAND
JOURNAL of MEDICINE

2019年ESC心衰竭臨床治療共識： Dapagliflozin應該要考慮用在T2D合併有CVD或high CV risk



European Journal of
Heart Failure

Research Article |  Token Access

Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of The Heart Failure Association of the European Society of Cardiology

First published: 26 May 2019 | <https://doi.org/10.1002/ejhf.1531>



Consensus recommendation.

- The 2019 expert consensus was that canagliflozin and **dapagliflozin** should also be **considered** for patients with T2DM and either established CV disease or at high CV risk in order to prevent or delay the onset of and hospitalisations for HF.

4.2. Adults With Type 2 Diabetes Mellitus

See Figure 2 for an algorithm for treatment of T2DM for primary prevention of cardiovascular disease.



Circulation

Recommendations for Adults With Type 2 Diabetes Mellitus		
Referenced studies that support recommendations are summarized in Online Data Supplement 10.		
COR	LOE	Recommendations
I	A	1. For all adults with T2DM, a tailored nutrition plan focusing on a heart-healthy dietary pattern is recommended to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors (S4.2-1, S4.2-2).
I	A	2. Adults with T2DM should perform at least 150 minutes per week of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors (S4.2-3, S4.2-4).
IIa	B-R	3. For adults with T2DM, it is reasonable to initiate metformin as first-line therapy along with lifestyle therapies at the time of diagnosis to improve glycemic control and reduce ASCVD risk (S4.2-5–S4.2-8).
IIb	B-R	4. For adults with T2DM and additional ASCVD risk factors who require glucose-lowering therapy despite initial lifestyle modifications and metformin, it may be reasonable to initiate a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide-1 receptor (GLP-1R) agonist to improve glycemic control and reduce CVD risk (S4.2-9–S4.2-14).



2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD)

Table 7 Cardiovascular risk categories in patients with diabetes^a

Very high risk	<p>Patients with DM and established CVD or other target organ damage^b or three or more major risk factors^c or early onset T1DM of long duration (>20 years)</p>
High risk	<p>Patients with DM duration ≥ 10 years without target organ damage plus any other additional risk factor</p>
Moderate risk	<p>Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years, without other risk factors</p>

CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

^aModified from the 2016 European Guidelines on cardiovascular disease prevention in clinical practice.²⁷

^bProteinuria, renal impairment defined as eGFR ≥ 30 mL/min/1.73 m², left ventricular hypertrophy, or retinopathy.

^cAge, hypertension, dyslipidemia, smoking, obesity.



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A Type 2 DM - Drug naïve patients

ASCVD, or high / very high CV risk (target organ damage or multiple risk factors)^a

+

?

-

We still need more solid evidence

SGLT2 inhibitor or
GLP-1 RA Monotherapy^b

If HbA_{1c} above target

Add Metformin

Metformin Monotherapy

If HbA_{1c} above target

DPP-4i

GLP-1 RA

SGLT2i
if eGFR
adequate

TZD

a. See Table 7; b. Use drugs with proven CVD benefit.

B Type 2 DM - On metformin

ASCVD, or high / very high CV risk (target organ damage or multiple risk factors)^a

+

-

Add SGLT2 inhibitor
or GLP-1 RA^b

If HbA_{1c} above target

- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
- DPP-4i if not on GLP-1 RA
- Basal insulin
- TZD (not in HF pat)
- SU

Continue Metformin
Monotherapy

If HbA_{1c} above target

DPP-4i

GLP-1 RA

SGLT2i
if eGFR
adequate

TZD

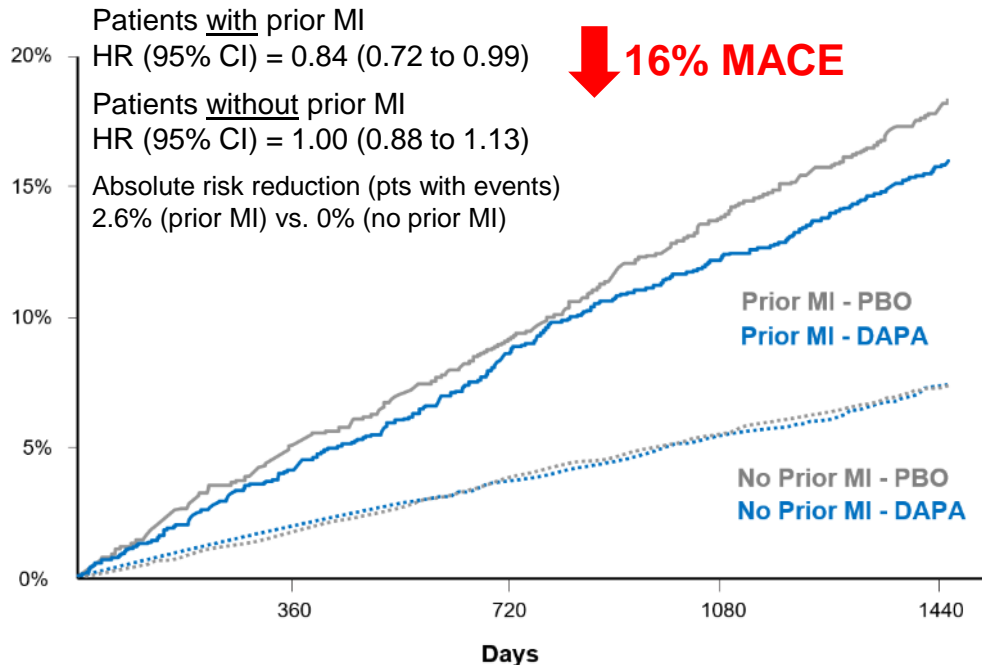
If HbA_{1c} above target

DECLARE次分析：T2D合并有心肌梗塞病患↓16%MACE

- 發表於2019年ACC年會



Patients with previous MI (n=3584); Primary Outcome – MACE



	HR (95 % CI)	P-interaction
MACE		
Prior MI	0.84 (0.72-0.99)	0.107
No Prior MI	1.00 (0.88-1.13)	
MI		
Prior MI	0.78 (0.63-0.95)	0.082
No Prior MI	0.99 (0.83-1.19)	
Ischemic stroke		
Prior MI	0.93 (0.66-1.30)	0.54
No Prior MI	1.05 (0.85-1.30)	
CV death		
Prior MI	0.92 (0.69-1.23)	0.56
No Prior MI	1.03 (0.82-1.28)	

0.25 0.50 1.00 2.00

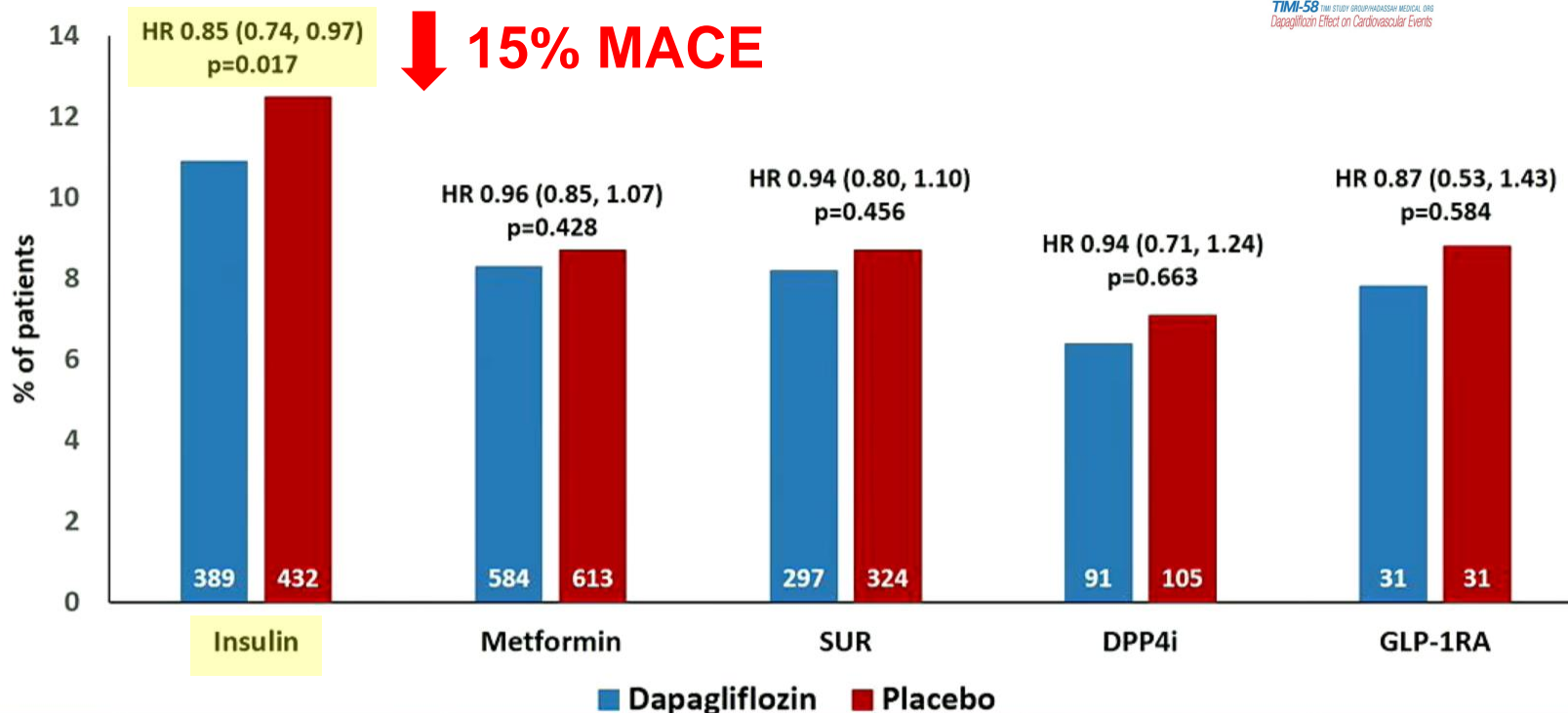
← DAPA better PBO better →

Prior MI ●
No Prior MI ▲

Prior MI was a prespecified subgroup of interest in DECLARE TIMI-58. CV = cardiovascular; DAPA = dapagliflozin; HR = hazard ratio; MACE = major adverse cardiovascular events; MI = myocardial infarction; PBO = placebo; T2D = type 2 diabetes. Circulation. 2019 May 28;139(22):2516-2527.



DECLARE次分析：合并insulin病患↓15%MACE



Dapagliflozin	3566	7020	3615	1418	397
Placebo	3445	7048	3707	1470	353

*Data on file, Astra Zeneca Clinical Study Report. Not verified by independent academic statistical analysis

SGLT-2i能帶給T2D病患的好處：ABCD



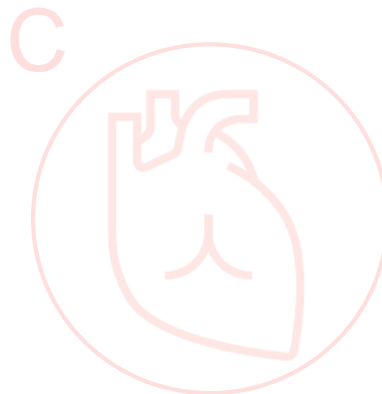
血糖控制

A1c



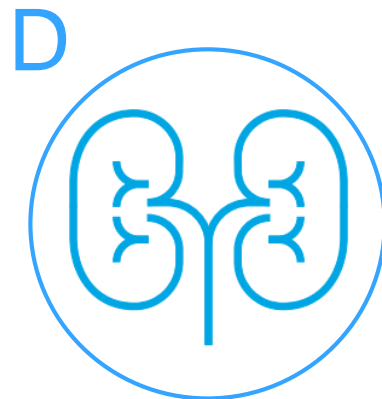
降低體重

Body weight



降低心血管風險

CV risk (HF)



降低腎臟惡化風險

Diabetic kidney disease



降低血壓

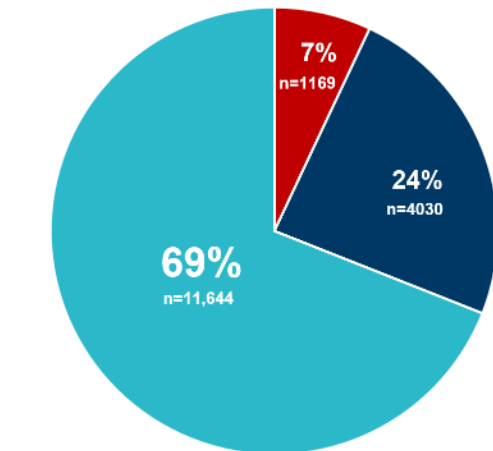
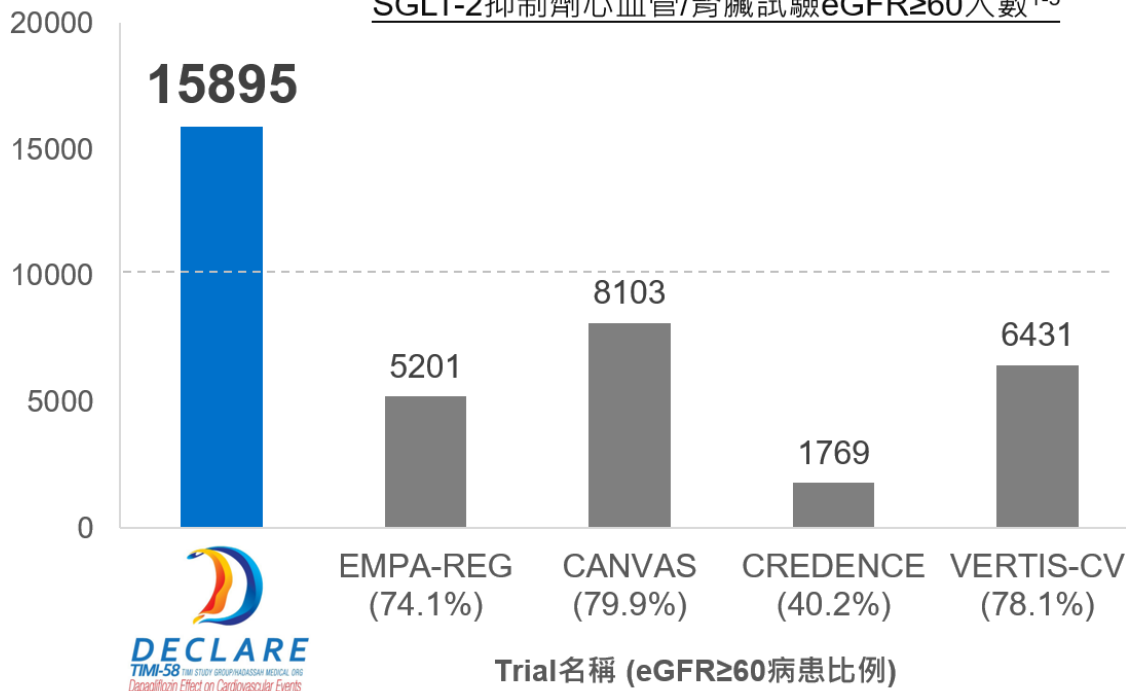
Blood pressure

DECLARE為唯一病患 eGFR≥60 超過萬人的心血管試驗

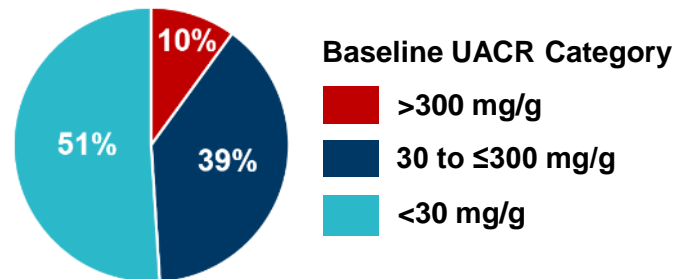
其收納病患的蛋白尿(UACR)分布接近真實世界

DECLARE收納病患蛋白尿(UACR)分布⁴

SGLT-2抑制劑心血管/腎臟試驗eGFR≥60人數¹⁻³



真實世界 T2D 病患蛋白尿(UACR)分布⁵



Trial名稱 (eGFR≥60病患比例)

(92.6%)

UACR = urine albumin-to-creatinine ratio

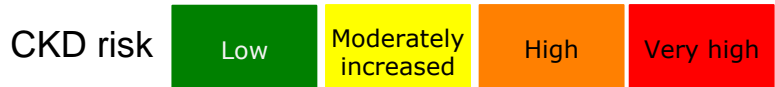
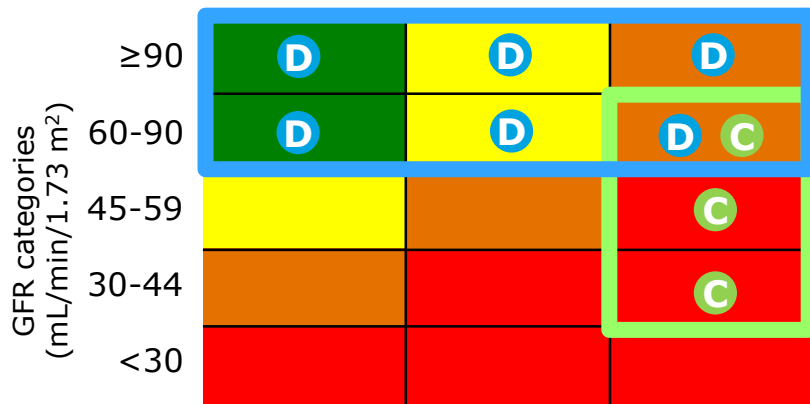
1. Lancet. 2019 Jan 5;393(10166):31-39. 2. N Engl J Med. 2019 Apr 14. doi: 10.1056/NEJMoa1811744. 3. Am Heart J. 2018 Dec;206:11-23.

4. Raz I et al. Presented at: ADA 79th Scientific Sessions; June 7-11, 2019; San Francisco, CA 244-OR. 5. Kidney Int. 2006 Jun;69(11):2057-63.

DECLARE、CREDESCENCE收納病患CKD stage分布及結果

Albuminuria categories (mg/g)

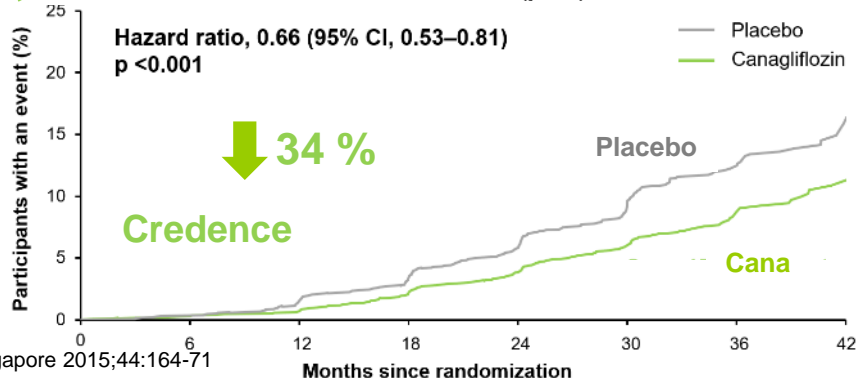
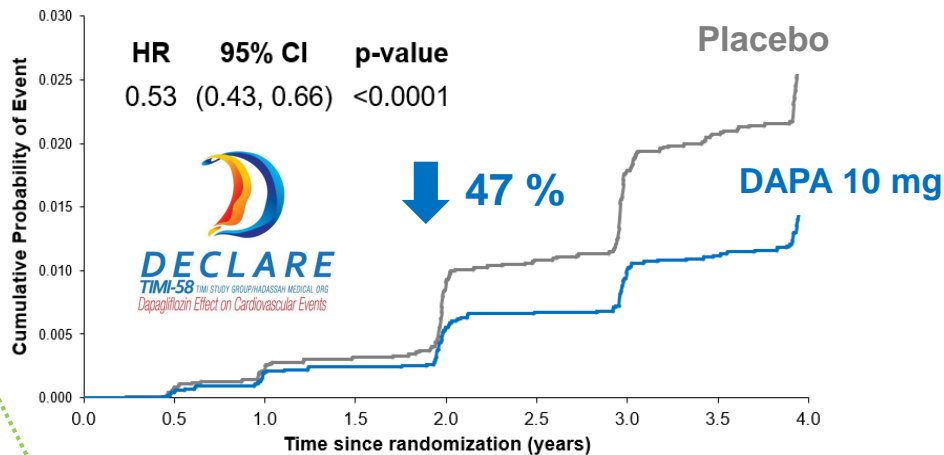
A1: <30 A2: 30-300 A3: >300



D : Declare **C** : Credence

 : 該腎功能區間佔真實T2D病患79%^{3*} : 10%^{3*}

Renal-specific composite outcome: decrease of 40% or more in eGFR to <60, ESRD, or renal death



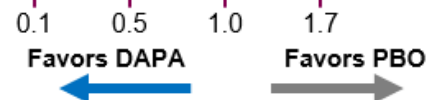
* The prevalence of CKD is based on Singapore in 2011-2013, N=1,861; T2D = Type 2 Diabetes ESRD = end-stage renal disease 1. N Engl J Med. 2019 Jan 24;380(4):347-357.

DECLARE的腎臟終點分析

- 發表於2019年ADA年會



	Dapagliflozin		Placebo		Hazard Ratio (95% CI)	P value
	n/N (%)	KM Event Rate (4 years)	n/N (%)	KM Event Rate (4 years)		
Renal-specific Outcome						
eGFR decrease $\geq 40\%$ to < 60 ; ESRD; or renal death	127/8582 (1.5)	1.5%	238/8578 (2.8)	2.6%	0.53 (0.43-0.66)	<0.0001
Individual Components						
eGFR decrease $\geq 40\%$ to < 60 ↓46%	120/8582 (1.4)	1.4%	221/8578 (2.6)	2.5%	0.54 (0.43-0.67)	<0.0001
End stage renal disease (ESRD) ↓69%	6/8582 (0.1)	0.1%	19/8578 (0.2)	0.2%	0.31 (0.13-0.79)	0.013
Renal death	6/8582 (0.1)	0.1%	10/8578 (0.1)	0.1%	0.60 (0.22-1.65)	0.32
ESRD or renal death	11/8582 (2.9)	0.1%	27/8578 (0.3)	0.3%	0.41 (0.20-0.82)	0.012

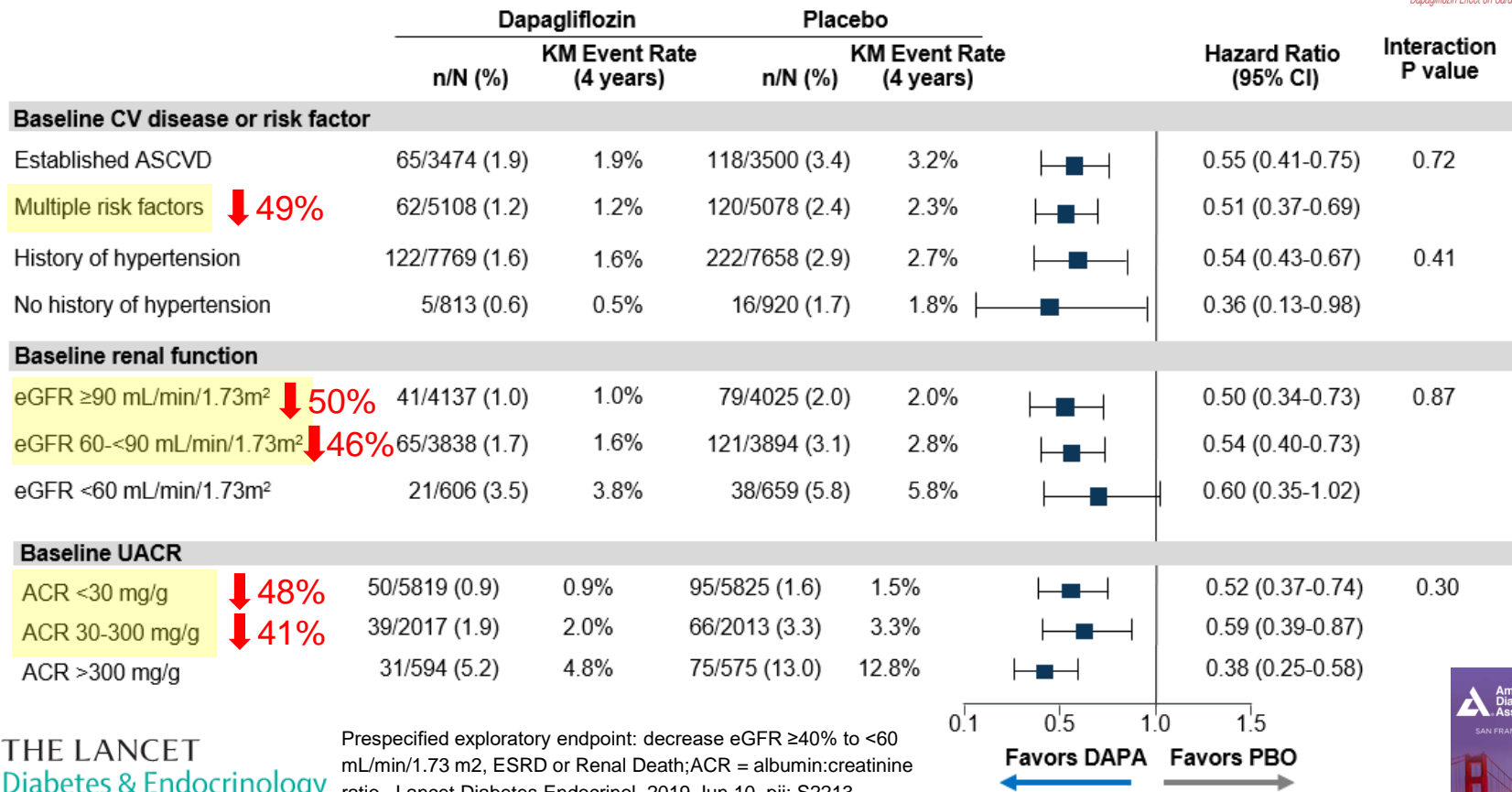


THE LANCET Diabetes & Endocrinology

Prespecified exploratory endpoint: decrease eGFR $\geq 40\%$ to < 60 mL/min/1.73 m², ESRD or Renal Death;
 DAPA = dapagliflozin; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease;
 PBO = placebo Lancet Diabetes Endocrinol. 2019 Jun 10. pii: S2213-8587(19)30180-9.

DECLARE的腎臟終點次分析：依據共病、腎功能

- 發表於2019年ADA年會



Prespecified exploratory endpoint: decrease eGFR ≥40% to <60 mL/min/1.73 m², ESRD or Renal Death; ACR = albumin:creatinine ratio. Lancet Diabetes Endocrinol. 2019 Jun 10. pii: S2213-8587(19)30180-9.



DECLARE : 蛋白尿的改變

- 發表於2019年ADA年會

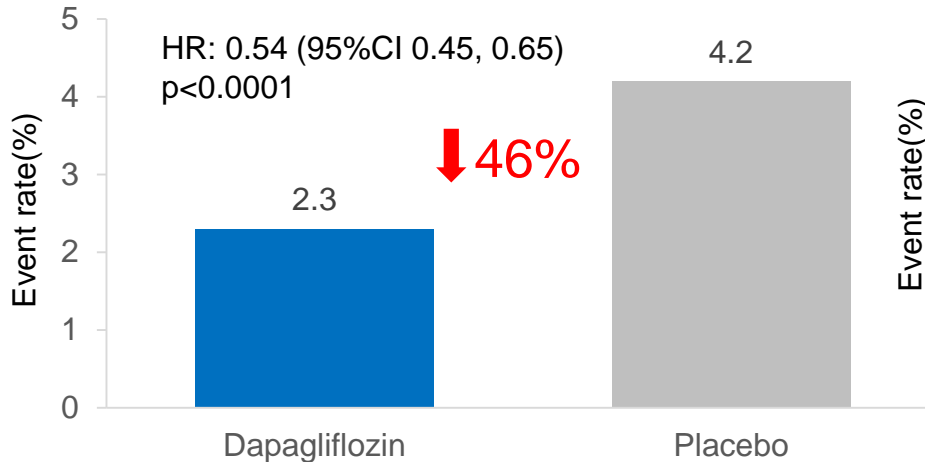
Dapagliflozin組

無/微量蛋白尿惡化成巨量蛋白尿風險下降46%

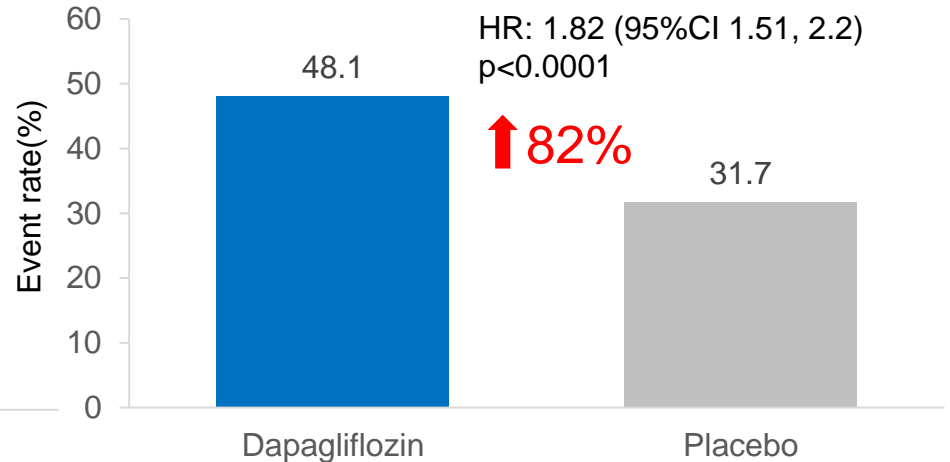
Dapagliflozin組

巨量蛋白尿改善成無/微量蛋白尿機會提升82%

Normo/Micro to Macro



Macro to Normo/Micro



Definitions of Albuminuria Categories

Macroalbuminuria	UACR ≥300 mg/g
Microalbuminuria	UACR ≥30 to <300 mg/g
Normoalbuminuria	UACR <30 mg/g

20190706 Taiwan Association Diabetes Educator Annual Meeting

Kidney outcomes associated with initiation of sodium–glucose cotransporter-2 inhibition versus other glucose lowering drugs – an analysis from the CVD-REAL study of five countries database



Chih-Yuan Wang;¹ Fang-Ju Lin;² Hiddo JL Heerspink;³ Avraham Karasik;⁴ Marcus Thuresson;⁵ Eric Wittbrodt;⁶ Peter Fenici;⁷ Mikhail Kosiborod⁸

,¹ National Taiwan University; ² Hospital National Taiwan University; ³University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; ⁴Tel Aviv University, Tel Aviv, Israel; ⁵Statisticon AB, Uppsala, Sweden; ⁶AstraZeneca, Gaithersburg, MD, USA; ⁷AstraZeneca, Cambridge, United Kingdom; ⁸Saint Luke's Mid America Heart Institute and University of Missouri-Kansas City, Kansas City, Missouri

XXXXX

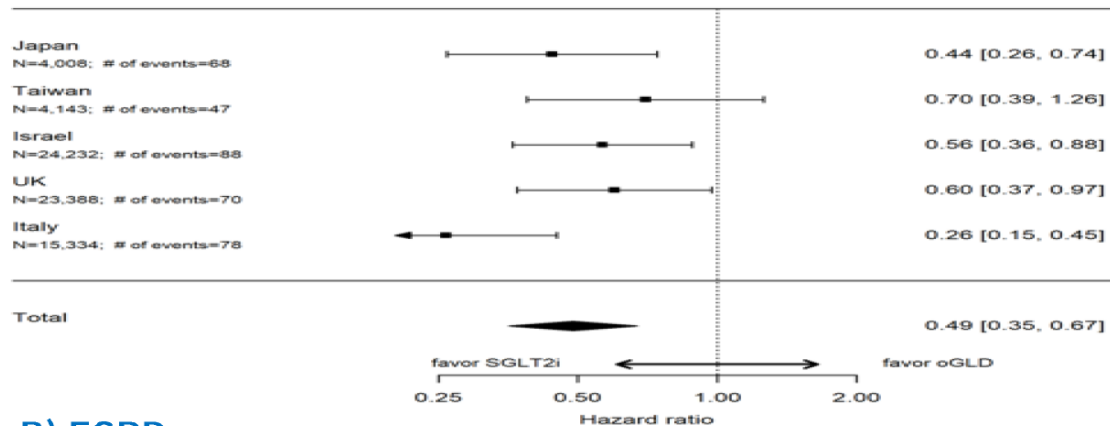
Table 1: Patient baseline characteristics

Mean (SD) Age, years
Women
CV-history
Myocardial infarction
Unstable angina
Heart failure
Metformin
Sulphonylurea
DPP4 inhibitor
Insulin
Anti hypertensive therapy
ACE Inhibitors
ARBs
Low ceiling diuretics
Statin therapy
LOOP diuretics
Mean (SD) eGFR, mL/min/1.73 m ²
eGFR <=60
eGFR 60-90
eGFR >90
Mean (SD) eGFR slope (estimated change per year)
Mean (SD) Hb1Ac, %

Figure 5: Hazard ratios for kidney outcomes

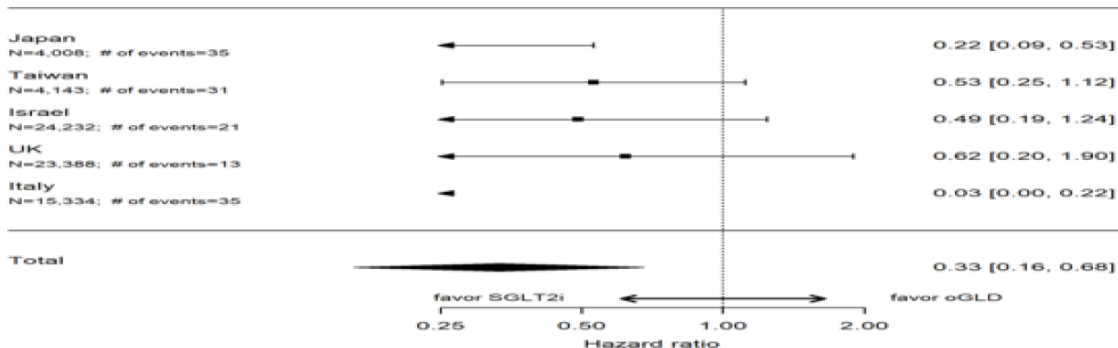
A) Composite of 50% eGFR decline or ESRD

SGLT2i vs oGLD comparison: $p < 0.001$; heterogeneity: $p = 0.101$



B) ESRD

SGLT2i vs oGLD comparison: $p < 0.001$; heterogeneity: $p = 0.048$



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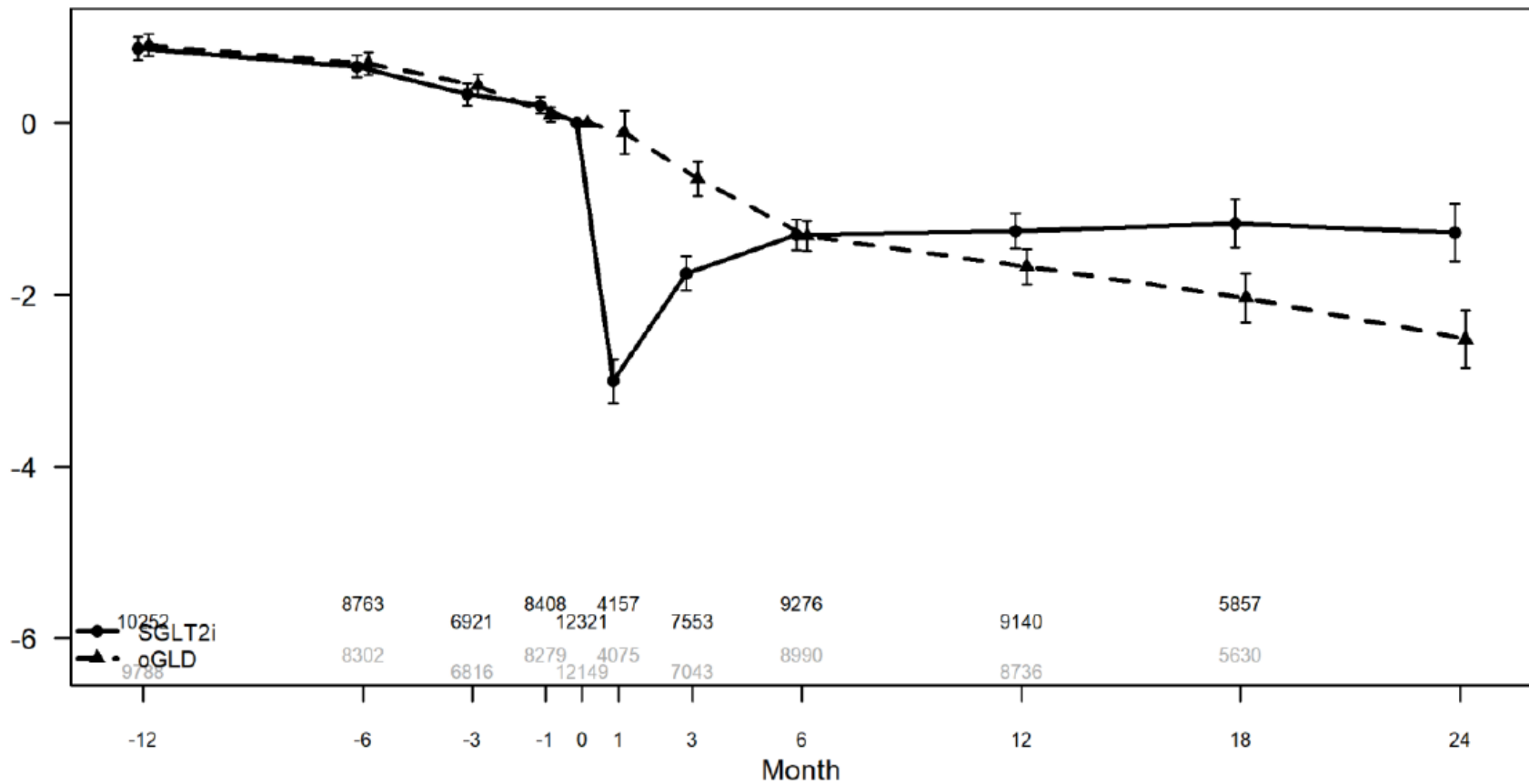
()

()

()

()

background (i.e. SGLT2=sodium -



SGLT-2i能帶給T2D病患的好處：ABCD



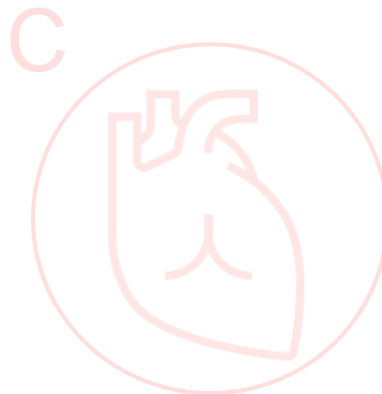
血糖控制

A1c



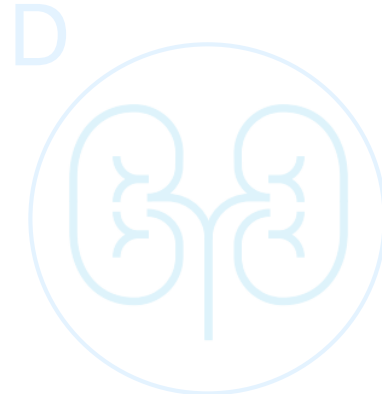
降低體重

Body weight



降低心血管風險

CV risk (HF)



降低腎臟惡化風險

Diabetic kidney disease



降低血壓

Blood pressure



安全性

Safety



SGLT-2 抑制劑 的眾多 安全性 議題



DECLARE
TIMI-58 TIMI STUDY GROUP/HADASSAH MEDICAL ORG
Dapagliflozin Effect on Cardiovascular Events

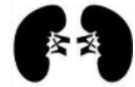
17,160 patients
median of 4.2 years



嚴重低血糖 ↓ 32%* (p=0.02)



AKI (急性腎損傷) ↓ 31%* (p=0.002)



膀胱癌 ↓ 43%* (p=0.02)



中風



截肢



骨折



會陰部壞死筋膜炎 (Fournier's gangrene)



UTI (泌尿道感染 ; 細菌)



容積不足症狀



0.9% vs 0.1%*



Genital infection (生殖器感染 ; 黴菌)

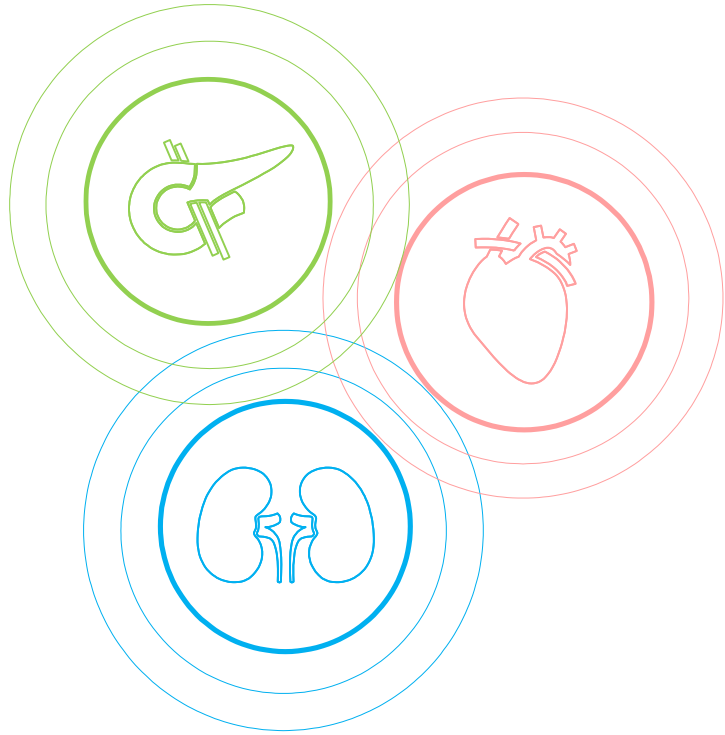


DKA (酮酸中毒) 0.3% vs 0.1%*



* Dapagliflozin vs placebo, SAE
AKI: acute kidney injury, UTI: urinary tract infection,
DKA: diabetic ketoacidosis
Wiviott SD, Raz I et al. N Engl J Med. 2018 Nov 10.
doi: 10.1056/NEJMoa1812389.

Outline



- The four advancements of anti-diabetic medication
- What can SGLT-2 inhibitor help us as treating diabetic patients with CV risk factors?
- **Conclusion**

Conclusion (1)



- **We are now at the moment of the 4th advancement of anti-diabetic medication: organ protection**
 - GLP-1 RA: MACE, renal outcome (mainly driven by macroalbuminuria)
 - SGLT-2i: MACE, HHF, renal outcome
- **New recommendation of GLP-1 RA or SGLT-2i in Taiwan, ADA/EASD, ACC, ERA-EDTA, AHA, ESC/EASD guidelines base on CVD, HF, DKD effects**
 - Add-on or switch therapy in patients with CVD, HF, CKD consideration
 - Early-use in patients with multiple CV risk factors
- **'Time in Range' statement published in 2019 ADA:**
 - >70% in blood sugar 70-180 mg/dl
- **Dapagliflozin vs. Gliclazide in 2019 ADA:**
 - A1c $\rightarrow\leftarrow$, FPG $\rightarrow\leftarrow$, PPG $\rightarrow\leftarrow$, hypo \downarrow 16 times
 - MAGE -18 vs -3 mg/dl (p=0.037), TIR \uparrow 26.5% vs 17.4% (p=0.041)



Conclusion (2)



- **Dapagliflozin vs. Sitagliptin in 2019 ADA**

- A1c < 7% → ←, hypo → ←, BW ↓ 2.5 kg, BP ↓ 4.1 mmHg
- Reduces fat mass without affecting muscle mass



- **DECLARE CV outcome in non-CVD patients** (↓36% hHF), **post-MI patients** (↓16% MACE, ↓ 22% MI risk), **Insulin user**(↓15% MACE)

- **DECLARE renal outcome in non-CKD patients** (eGFR ≥ 60: 93%; UACR < 30 mg/g: 69%)

- eGFR decline risk ↓ 46%, ESRD ↓ 69%
- UACR progression ↓ 46%, UACR Improvement ↑ 82%



- **DECLARE safety profile:**

- ↓ major hypo, AKI, bladder CA ; ↑ genital infection, DKA



Thanks very much for your listening!!

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