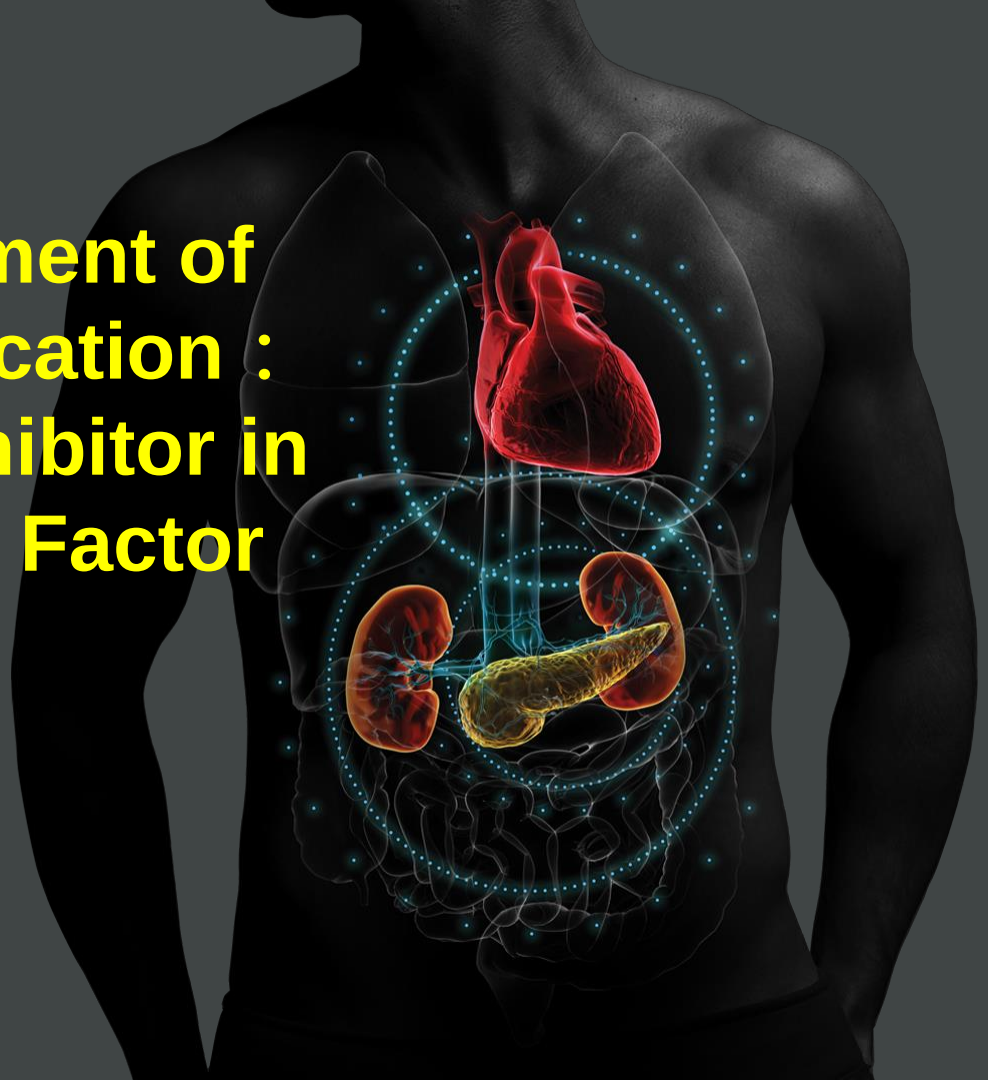
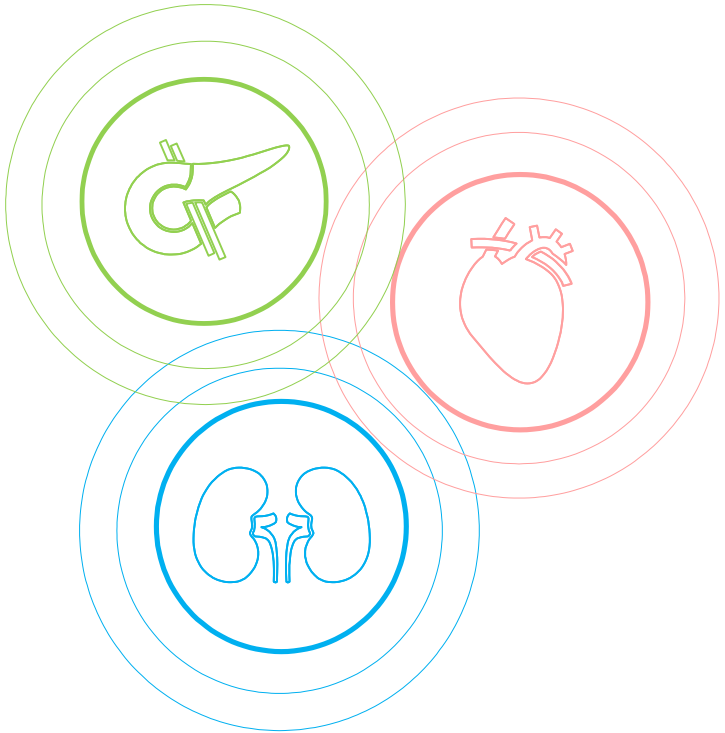
The 4th Advancement of Anti-diabetic Medication : Role of SGLT-2 Inhibitor in T2D with CV Risk Factor



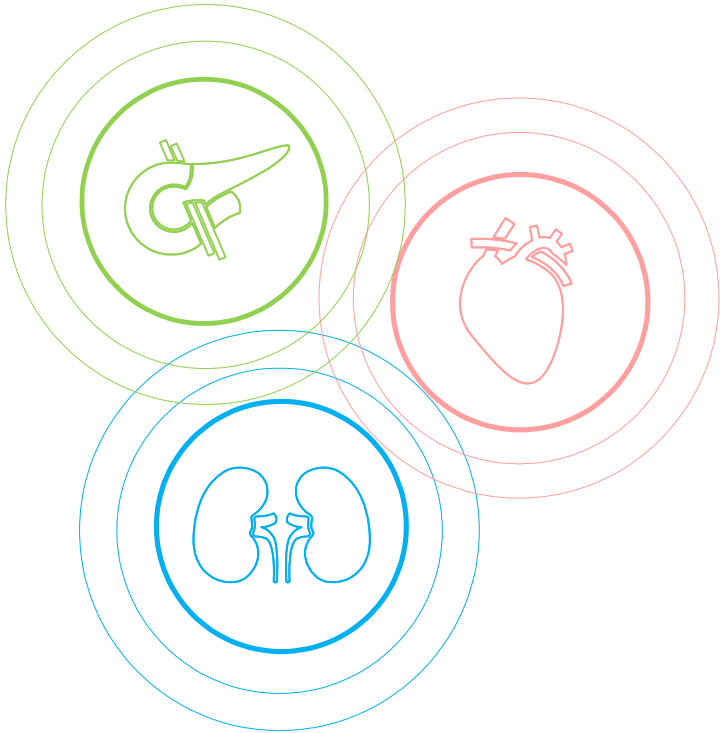
朱志勳 醫師
高雄榮民總醫院
內分泌新陳代謝科

Outline



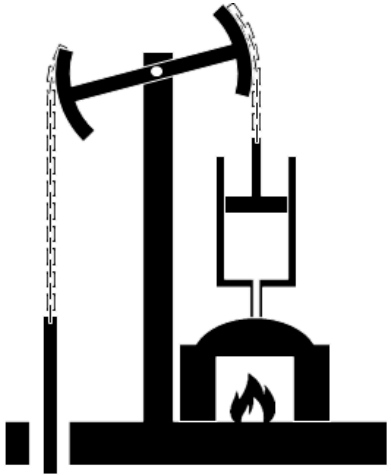
- **The four advancements of anti-diabetic medication**
- **What can SGLT-2 inhibitor help us as treating diabetic patients with CV risk factors?**
- **Conclusion**

Outline



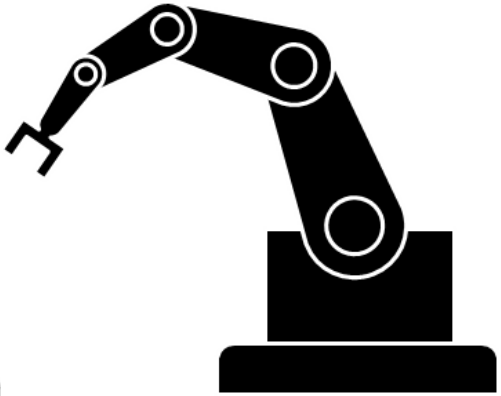
- **The four advancements of anti-diabetic medication**
- **What can SGLT-2 inhibitor help us as treating diabetic patients with CV risk factors?**
- **Conclusion**

工業革命4.0

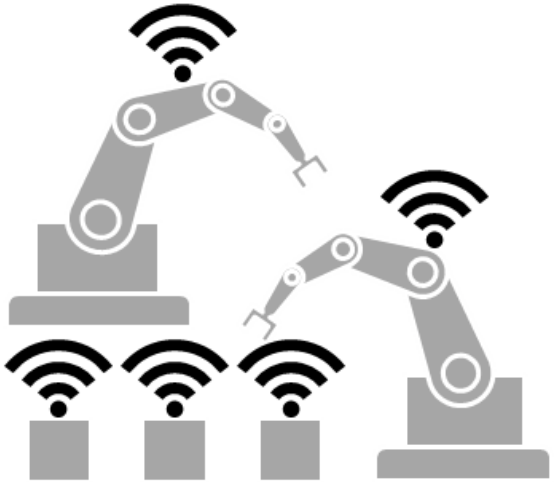


第一次工業革命：
機械化 1784年
(蒸氣，水力)

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)

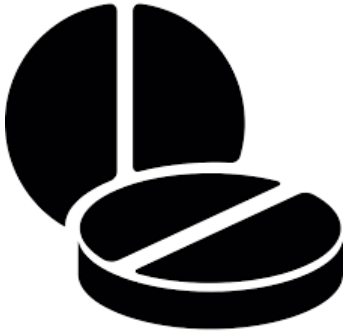


第四次工業革命：
網絡實體化 現今
(CPS, 5G)

IT: Information Technology, CPS: Cyber-Physical System

糖尿病藥物治療4.0

第一次治療突破：
胰島素 1922年



第二次治療突破：
口服藥 1956年
(SU: Sulfonylureas, Metformin 1957年)

第三次治療突破：
避免低血糖
(TZD 1997年,
DPP-4抑制劑 2006年)

第四次治療突破：
器官保護 現今
(GLP-1 RA 2007年,
SGLT-2抑制劑 2012年)
2008年 美國對新型糖尿病藥物上市需要做CVOT規定
2018年 ADA/EASD治療共識

RA: receptor agonist, CVOT: cardiovascular outcome trial

Circulation

ORIGINAL RESEARCH ARTICLE

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:

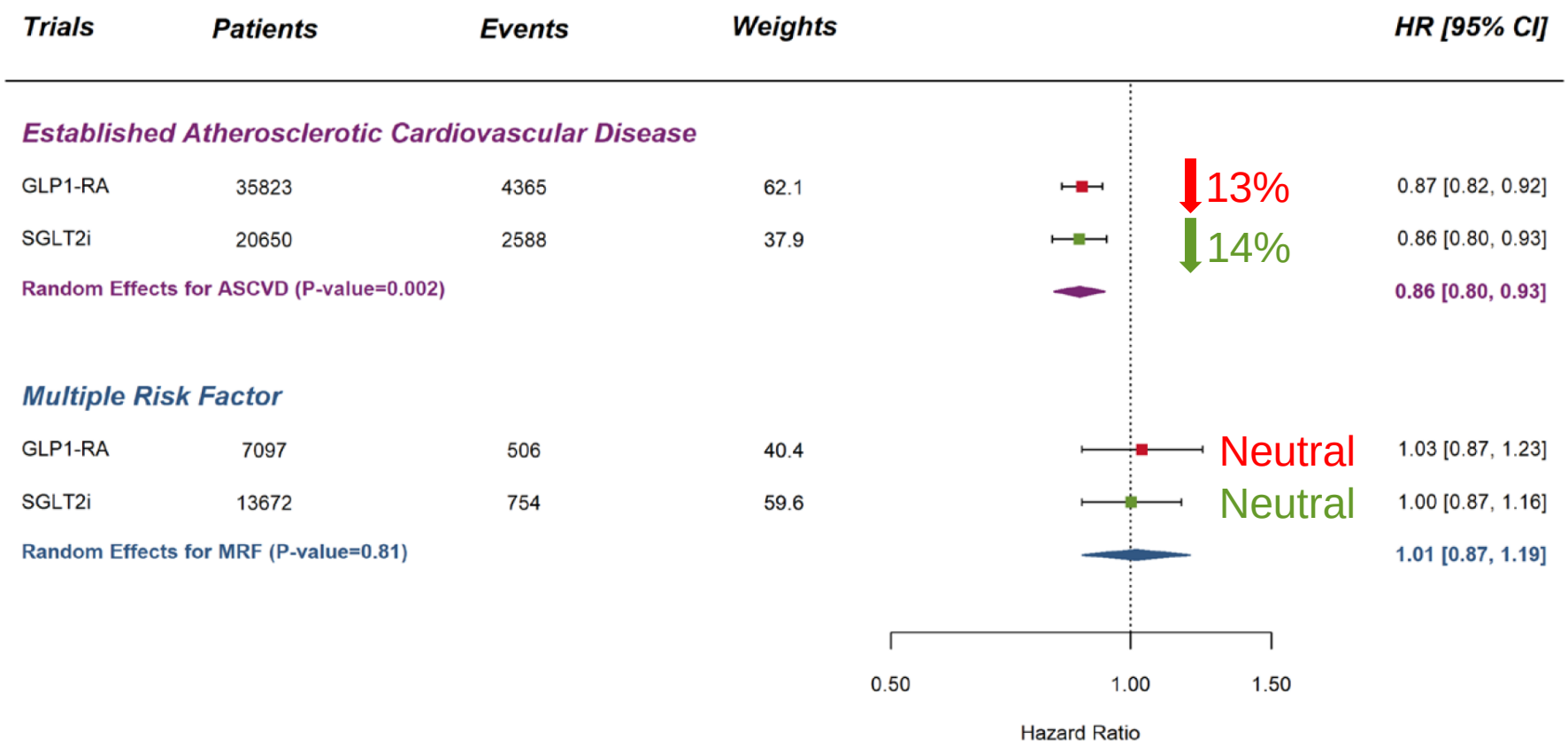
- 5 GLP1-RA trials (42,920 patients)
- 3 SGLT2i trials (34,322 patients)

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

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

	GLP1-RA					SGLT2i		
Trial	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



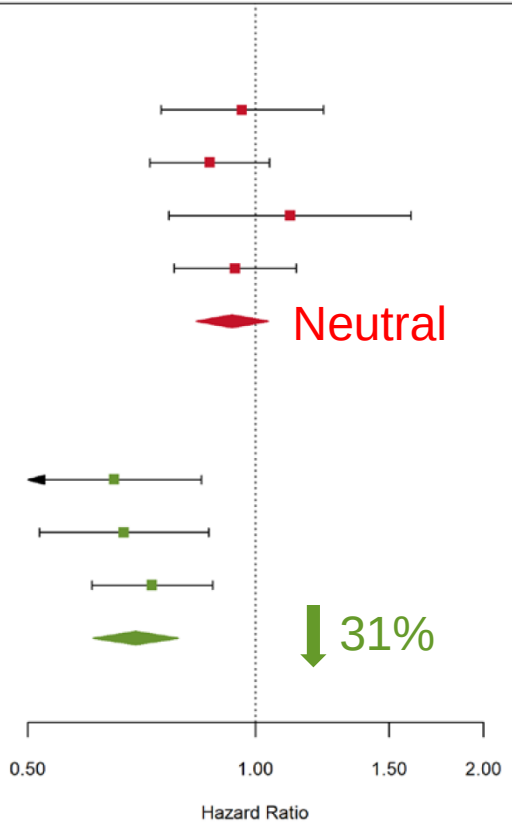
MACE: myocardial infarction, stroke, and cardiovascular death

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

Circulation

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

Trials	Patients	Events	Treatment Events per 100 ptyrs	Placebo Events per 100 ptyrs	Weights	HR [95% CI]
GLP1-RA						
ELIXA	6068	249	1.8	1.9	19.7	0.96 [0.75, 1.23]
LEADER	9340	466	1.2	1.4	36.4	0.87 [0.73, 1.05]
SUSTAIN-6	3297	113	1.8	1.6	8.8	1.11 [0.77, 1.61]
EXSCEL	14752	450	0.9	1.0	35.0	0.94 [0.78, 1.13]
Fixed Effects for HHF (P-value=0.20)						0.93 [0.83, 1.04]
SGLT2i						
EMPA-REG OUTCOME	7020	221	0.9	1.4	24.0	0.65 [0.50, 0.85]
CANVAS Program	10142	243	0.6	0.9	25.6	0.67 [0.52, 0.87]
DECLARE-TIMI 58	17160	498	0.6	0.8	50.4	0.73 [0.61, 0.88]
Fixed Effects for HHF (P-value<0.001)						0.69 [0.61, 0.79]



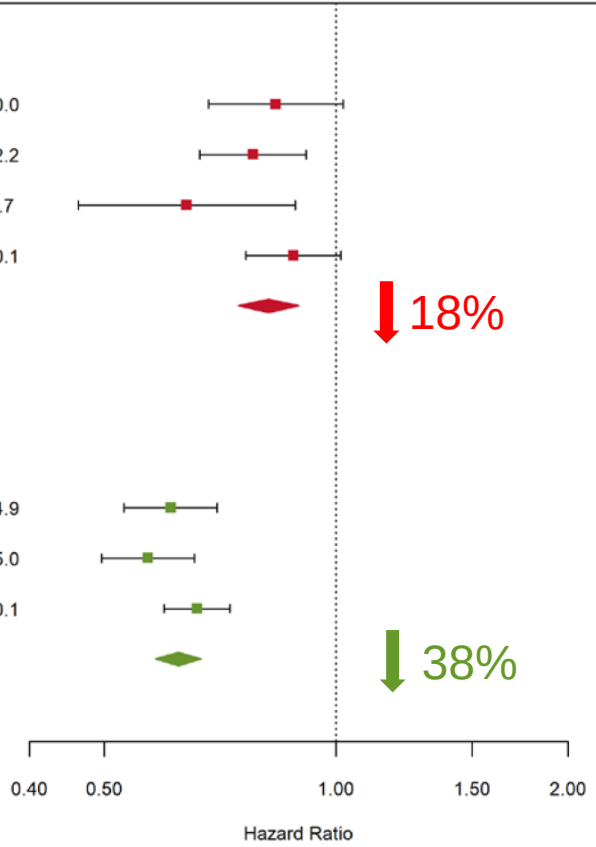
HHF: hospitalization for heart failure

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

Circulation

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

Trials	Patients	Events	Treatment n/N	Placebo n/N	Weights	HR [95% CI]
GLP1-RA						
ELIXA	5286	375	203/2639	172/2647	20.0	0.84 [0.68, 1.02]
LEADER	9340	605	268/4668	337/4672	32.2	0.78 [0.67, 0.92]
SUSTAIN-6	3297	162	62/1648	100/1649	7.7	0.64 [0.46, 0.88]
EXSCEL	14752	773	366/6256	407/6222	40.1	0.88 [0.76, 1.01]
Fixed Effects for GLP1-RA (P-value<0.001)						0.82 [0.75, 0.89]
SGLT2i						
EMPA-REG OUTCOME	6185	913	525/4124	388/2061	24.9	0.61 [0.53, 0.70]
CANVAS Program	10142	847	NA	NA	25.0	0.57 [0.50, 0.66]
DECLARE-TIMI 58	17160	1675	678/8582	997/8578	50.1	0.66 [0.60, 0.73]
Fixed Effects for SGLT2i (P-value<0.001)						0.62 [0.58, 0.67]

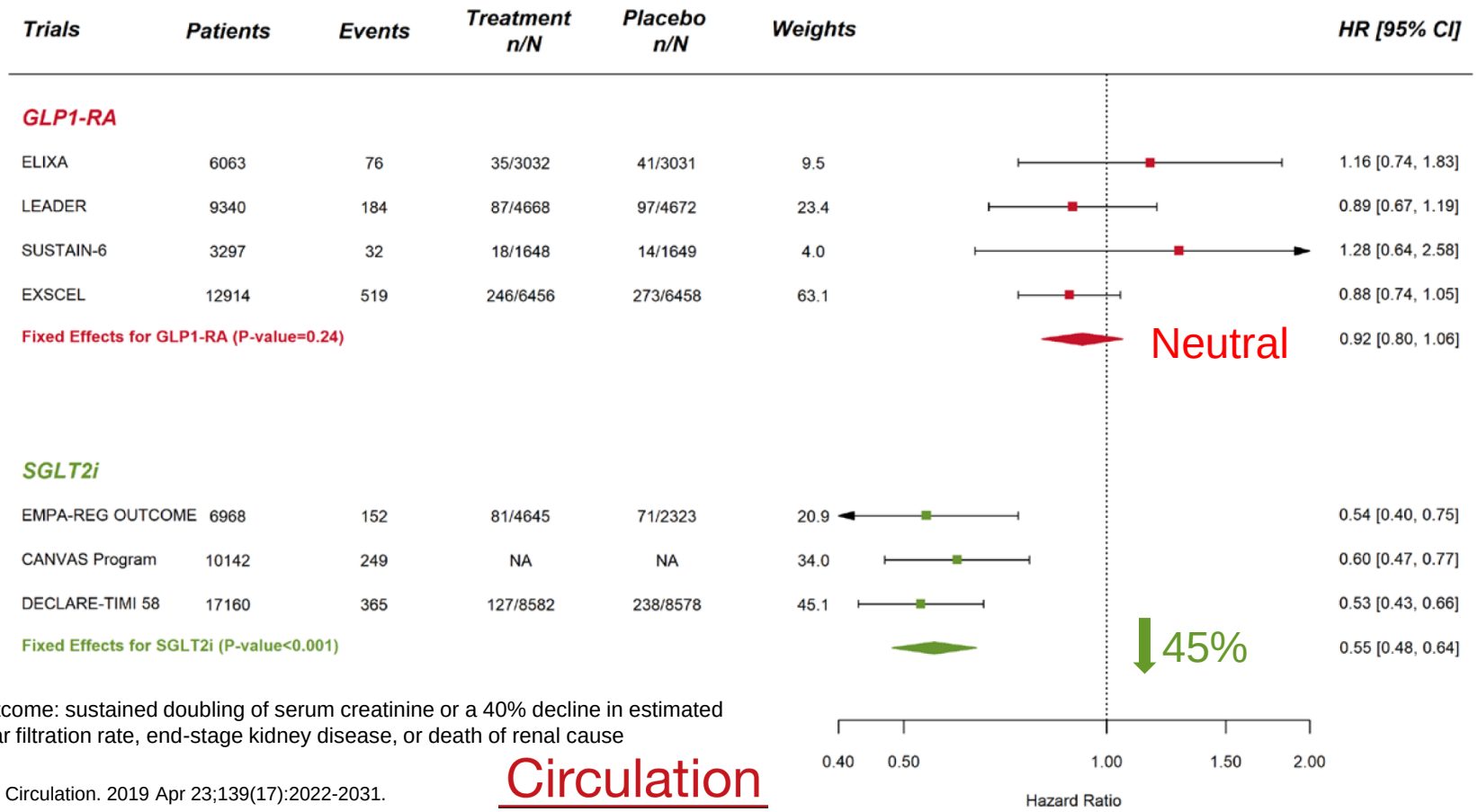


*Renal outcome: new-onset macroalbuminuria, sustained doubling of serum creatinine or a 40% decline in estimated glomerular filtration rate, end-stage kidney disease, or death of renal cause

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

Circulation

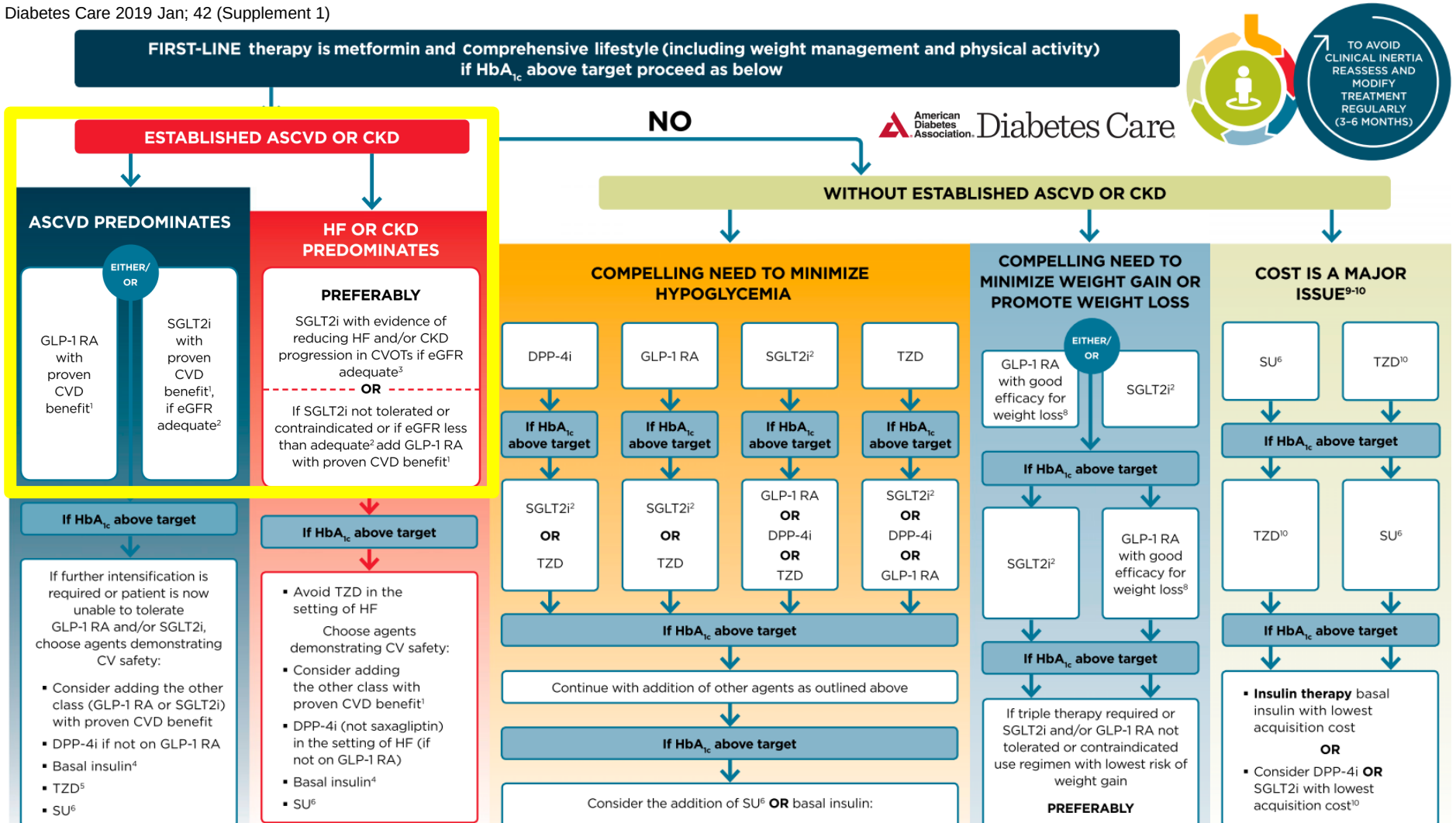
Meta-Analysis of GLP-1RA and SGLT-2i trials on renal outcome excluding macroalbuminuria

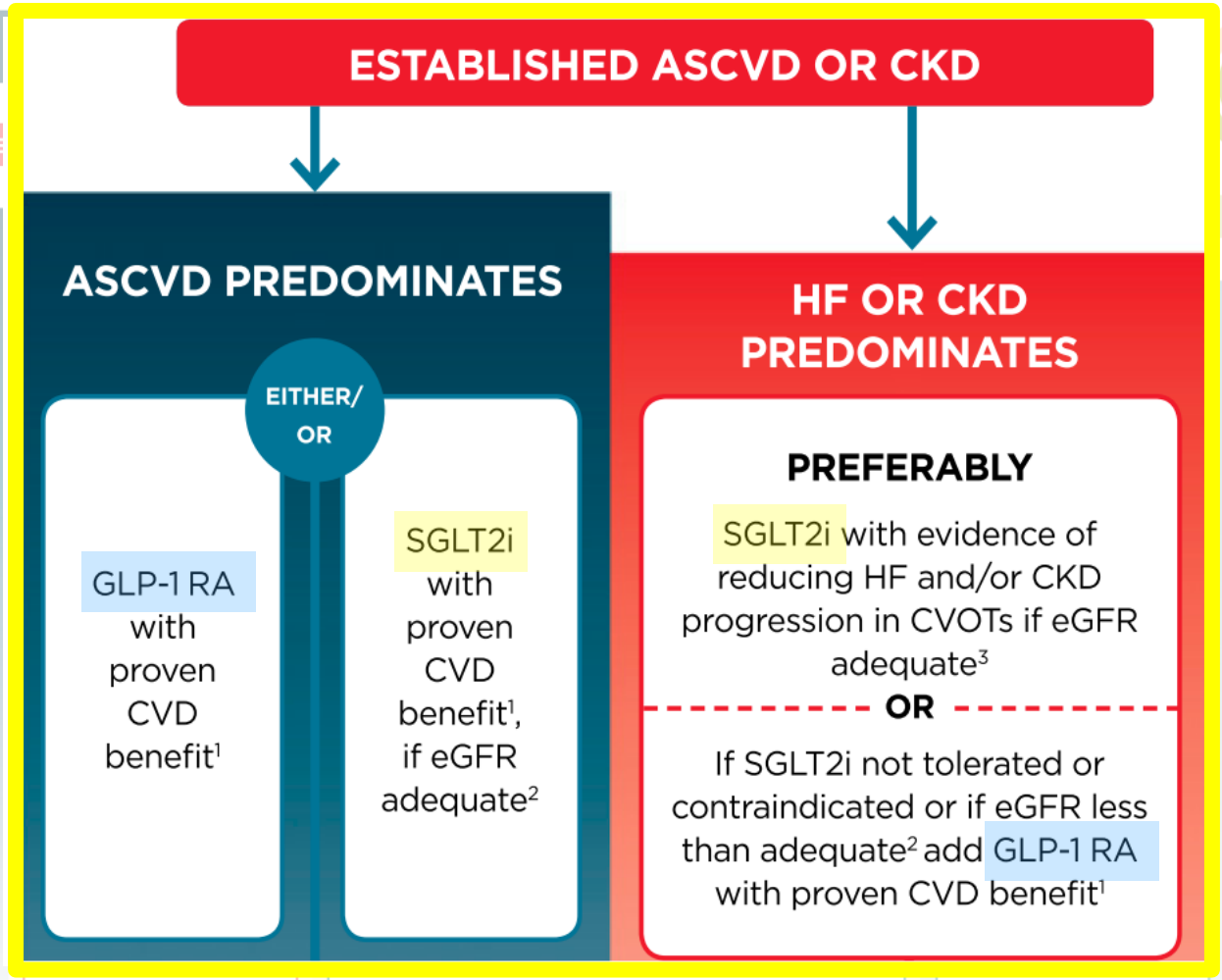


Renal outcome: sustained doubling of serum creatinine or a 40% decline in estimated glomerular filtration rate, end-stage kidney disease, or death of renal cause

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

Circulation


FIRST-LINE therapy is metformin and comprehensive lifestyle (including weight management and physical activity)
if HbA1c above target proceed as below
TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
American Diabetes Association. Diabetes Care
ESTABLISHED ASCVD OR CKD
NO
WITHOUT 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 HbA1c 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 HbA1c 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
COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA
DPP-4i
GLP-1 RA
SGLT2i2
TZD
If HbA1c above target
SGLT2i2 OR TZD
SGLT2i2 OR TZD
GLP-1 RA OR DPP-4i OR TZD
SGLT2i2 OR DPP-4i OR GLP-1 RA
If HbA1c above target
Continue with addition of other agents as outlined above
If HbA1c above target
Consider the addition of SU6 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 HbA1c above target
SGLT2i2
GLP-1 RA with good efficacy for weight loss8
If HbA1c 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 HbA1c above target
TZD10
SU6
If HbA1c above target
Insulin therapy basal insulin with lowest acquisition cost
OR
Consider DPP-4i OR SGLT2i with lowest acquisition cost10


ESTABLISHED ASCVD OR CKD
ASCVD PREDOMINATES
EITHER/ OR
GLP-1 RA with proven CVD benefit[1]
SGLT2i with proven CVD benefit[1], if eGFR adequate[2]
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]

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

Use principles in Figure 1

American Diabetes Association.

EASD
European Association for the Study of Diabetes

Use metformin unless contraindicated or not tolerated

If not at HbA_{1c} target:

如果血糖未達標, 建議增加SGLT-2i或GLP-1 RA

- 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:

如果血糖達標, 考慮替換為SGLT-2i或GLP-1 RA

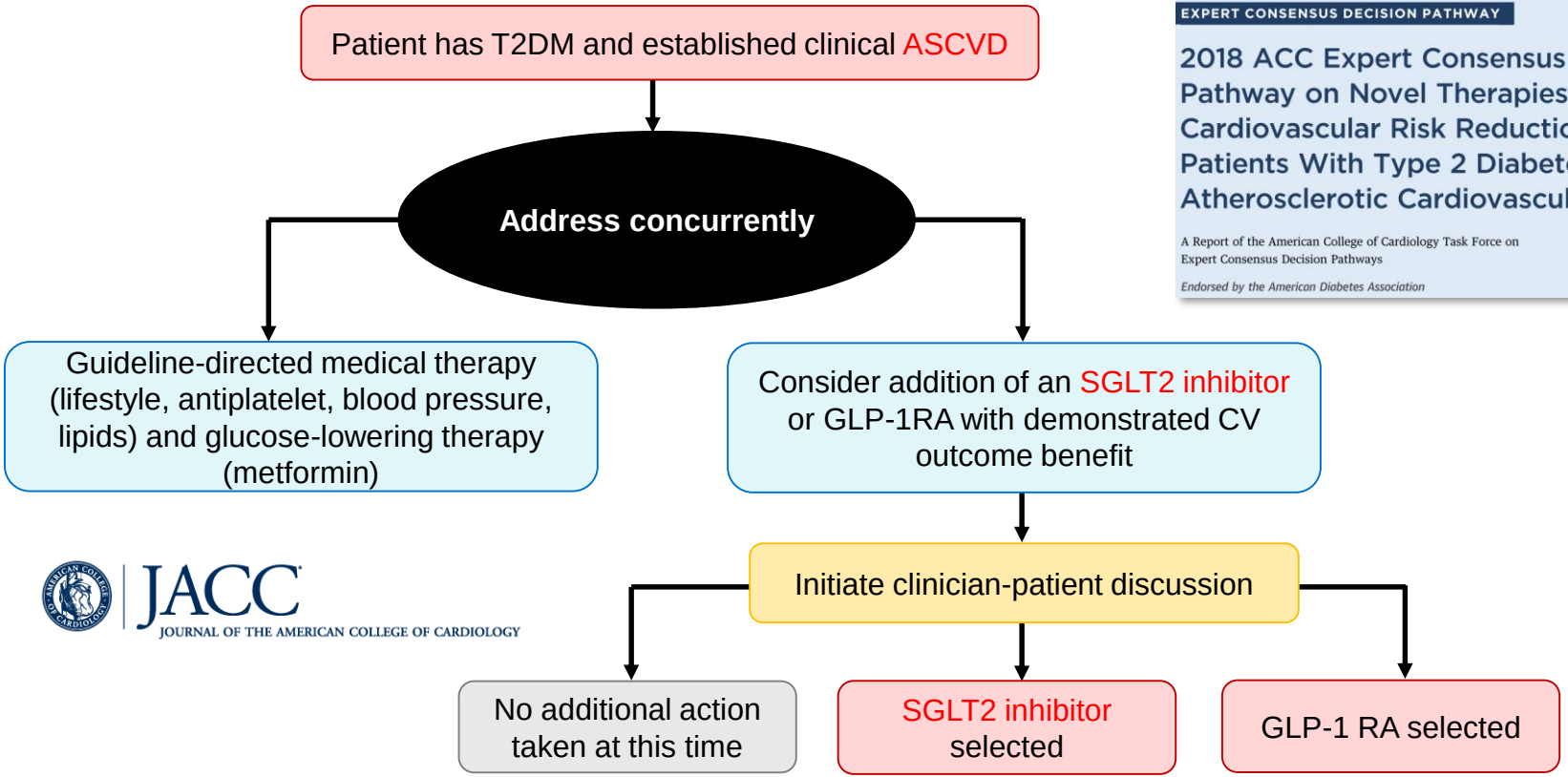
- If already on dual therapy, or multiple glucose-lowering therapies and not on an SGLT2i or GLP-1 RA, consider switching to one of these agents with proven cardiovascular benefit[1] (see below)

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: atherosclerotic cardiovascular disease, CKD: chronic kidney disease
Diabetes Care. 2018 Dec;41(12):2669-2701.

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



JACC
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

ACC: American College of Cardiology, CV: ardiovascular, J Am Coll Cardiol. 2018 Dec 18;72(24):3200-3223.

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

糖化血色素 < 8.5%

使用一種抗糖尿病藥

初診斷建議首選：Metformin

- 效果：佳
- 低血糖：低
- 體重：稍下降
- 副作用：腸胃道/乳酸血症

合併高血糖症狀

建議先以 Insulin 治療

糖化血色素 ≥ 8.5%

使用兩種抗糖尿病藥

建議 Metformin + 以下不同機轉的抗糖尿病

合併高血糖症狀

建議先以 Insulin 治療

若單一治療未達控制目標時，加上以下不同機轉的抗糖尿病藥，並評估心腎共病

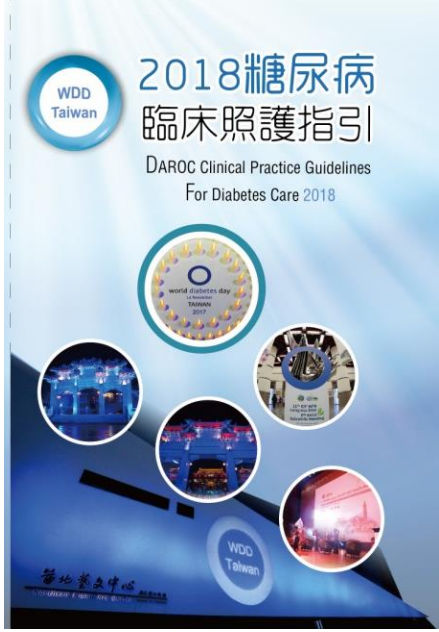
SU/Glinide	AGI	TZD	DPP4i	SGLT2i	GLP1-RA	Basal insulin
心血管實證：缺 心衰竭實證：缺 腎病變實證：缺 控制血糖效果：佳 體重：增加 低血糖：中 副作用：低血糖	心血管實證：中立 心衰竭實證：缺 腎病變實證：缺 控制血糖效果：中等 體重：稍下降 低血糖：低 副作用：腸胃道	心血管實證：有 心衰竭實證：不建議使用 腎病變實證：缺 控制血糖效果：佳 體重：增加 低血糖：低 副作用：水腫、心衰竭、骨折	心血管實證：中立 心衰竭實證：部分中立 腎病變實證：部分有 控制血糖效果：中等 體重：無影響 低血糖：低 副作用：少見	心血管實證：有(建議使用) 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	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	心血管實證：中立 心衰竭實證：中立 腎病變實證：中立 控制血糖效果：最佳 體重：增加 低血糖：高 副作用：低血糖

未達控制目標

再加上另一種不同機轉的抗糖尿病藥 (SU 和 Glinide 不建議合併，DPP4i 和 GLP1-RA 不建議合併)

未達控制目標

建議照會專科或強化注射型藥物治療

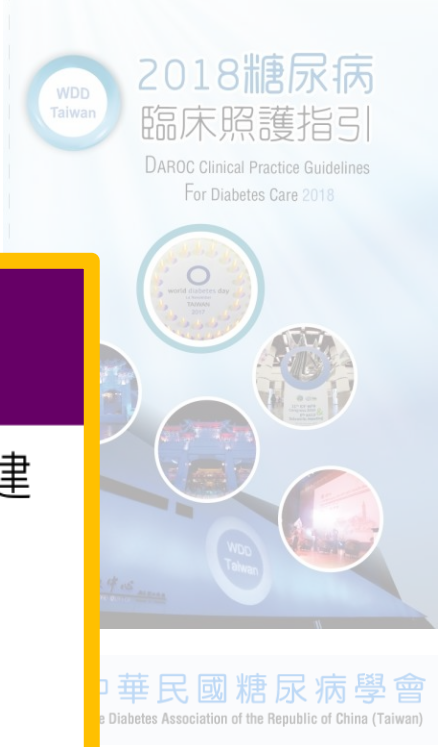


中華民國糖尿病學會
The Diabetes Association of the Republic of China (Taiwan)

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



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

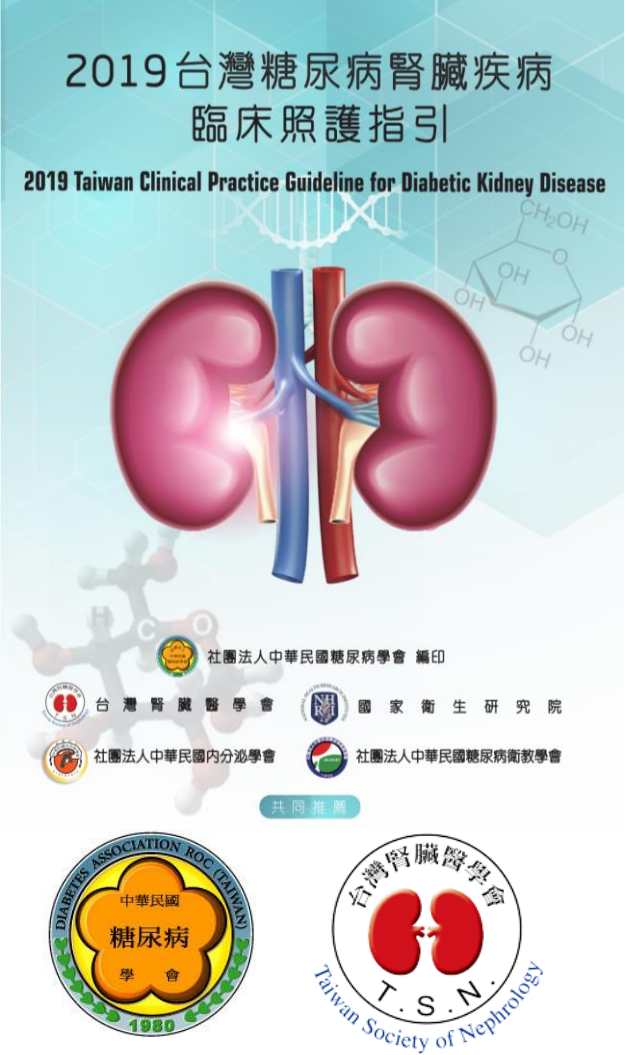
若單一治療未達

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

SGLT2i	GLP1-RA
心血管實證：有(建議使用)	心血管實證：部分有(建議使用)
心衰竭實證：有(建議使用)	心衰竭實證：中立
腎病變實證：有	腎病變實證：部分有
控制血糖效果：中等	控制血糖效果：佳
體重：下降	體重：下降
低血糖：低	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	副作用：腸胃道

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



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 (SGLT2 inhibitors)，與類升糖素胜肽 -1 受體促效劑 (GLP-1 receptor agonist) 呈現對降低糖尿病腎臟疾病惡化及心血管疾病風險有幫助。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 Taiwan Clinical Practice Guideline for Diabetic Kidney Disease. Diabetes Association of the R.O.C

2019年歐洲腎臟學會(ERA-EDTA)對DM合併CKD治療共識：A1c未達標，metformin後二線建議使用SGLT-2i

Patients with type 2 DM and CKD (eGFR <60 ml/min/1.73m^2 or eGFR >60 ml/min/1.73m^2 and macro- or microalbuminuria) not on HbA1c target (HbA1c >7%) on recommended metformin dose
or
not on HbA1c target (HbA1c >7%) and metformin is *not tolerated or is contraindicated*

⬇

Use SGLT-2 inhibitor with evidence for cardio- and nephroprotection[1]

⬇

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

⬇

Use GLP-1 receptor agonist with evidence for cardio- and nephroprotection[2]

⬇

If HbA1c remains above target or GLP-1 receptor agonist is not tolerated or is contraindicated

⬇

Use another antidiabetic agent (DDP-4 i, TZD, SU, or basal insulin) according to current recommendations for Type 2 DM[3]

era edta
LEADING EUROPEAN NEPHROLOGY

ERA-EDTA: European Renal Association-European Dialysis and Transplant Association
Nephrol Dial Transplant (2019) 34: 208–230

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/1.73m^2 or eGFR >60 ml/min/1.73m^2 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 nephroprotection[1]

↓

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 nephroprotection[2]

↓

Reassess HbA1c in 3-months interval and adjust the treatment if above target[3]

era edta
LEADING EUROPEAN NEPHROLOGY

ERA-EDTA: European Renal Association-European Dialysis and Transplant Association
Nephrol Dial Transplant (2019) 34: 208–230

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	CREDENCE[1]	DAPA-CKD[2]	EMPA-KIDNEY[3]
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	≥50% sustained decline in eGFR, ESRD, renal or CV death	1. ≥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. CREDENCE. 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)

Dapa-HF將會是第一個SGLT-2i的心衰竭試驗 (2019 AHA發表)

2014

Paradigm-HF[1]
Sacubitril/Valsartan

N= 8,442 pts with class II, III, or IV HF and an EF <= 40%

↓ 20% CV death or HHF
(September 11, 2014)

2018

DECLARE-TIMI 58[2]
Dapagliflozin

N=17,160 pts with T2DM + MRF or CVD

↓ 17% CV death or HHF
(November 10, 2018)

DECLARE TIMI-58

2019

PARAGON-HF[4]
Sacubitril/Valsartan

N= 8,442 pts with HFpEF (EF >= 45%), class II to IV HF

Neutral CV death or HHF
(May 31, 2019*)

Dapa-HF[3]
Dapagliflozin

N=4,744 pts with HFrEF ± T2DM

CV death or WHF
(July 17, 2019*, 5 month earlier)

DAPAHF
HF Outcome Trial

2020

EMPEROR-Reduced[5]
Empagliflozin

N=~2,850 pts with HFrEF ± T2DM

CV death or HHF
(June 1, 2020*)

EMPEROR-Preserved[6]
Empagliflozin

N=~6,000 pts with LVEF>40% ± T2DM

CV death or HHF
(October 23, 2020*)

2021

SOLOIST-WHF[7]
Sotagliflozin

N=~4,000 pts with WHF + T2DM

CV death or HHF
(January 2021*)

DELIVER[8]
Dapagliflozin

N=~4,700 pts with LVEF>40% ± T2DM

CV death or WHF
(June 22, 2021*)

DELIVER
HF Outcome Trial

*Estimated Study Completion Date, HF: heart failure, HHF: hospitalization for heart failure, MRF: multiple risk factors, CVD: cardiovascular disease, WHF: worsening heart failure event (hospitalization or equivalent event, i.e. an urgent heart failure visit), HFrEF: heart failure with reduced ejection fraction (LVEF≤40%), LVEF: left ventricular ejection fraction

1. N Engl J Med 2014; 371:993-1004. 2. N Engl J Med. 2019 Jan 24;380(4):347-357. 3. Eur J Heart Fail. 2019 May;21(5):665-675. 4. JACC Heart Fail. 2017 Jul;5(7):471-482. 5. https://clinicaltrials.gov/ct2/show/NCT03057977 6. https://clinicaltrials.gov/ct2/show/NCT03057951 7. https://clinicaltrials.gov/ct2/show/NCT03521934 (WHF-post worsening heart failure) 8. https://clinicaltrials.gov/ct2/show/NCT03619213

NOVARTIS

Novartis provides update on Phase III PARAGON-HF trial in heart failure patients with preserved ejection fraction (HFpEF)

Jul 29, 2019

ESC Congress
Paris 2019
Together with
World Congress
of Cardiology
31 August
- 4 September

The PARAGON-HF trial (sacubitril/valsartan versus the active comparator valsartan in 4,822 patients with HFpEF) narrowly misses statistical significance for its composite primary endpoint of reducing cardiovascular death and total heart failure hospitalizations; overall safety profile confirmed

Totality of evidence suggests potential clinically important benefit; results will be presented in September at the ESC Congress 2019, the annual meeting of the European Society of Cardiology (ESC)

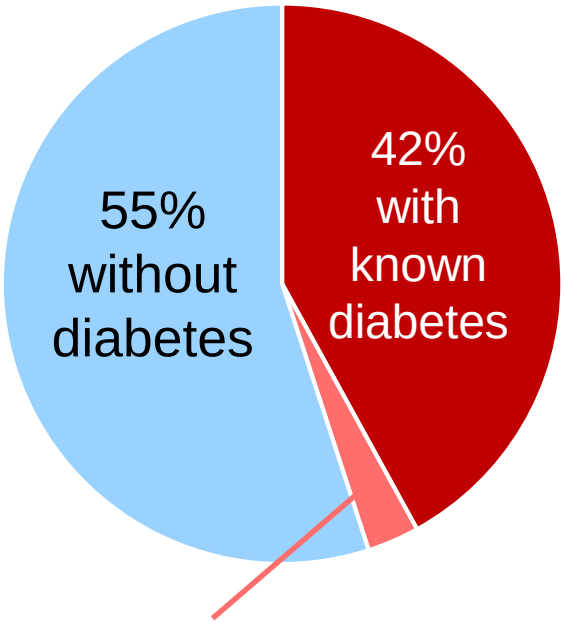
https://www.novartis.com/news/media-releases/novartis-provides-update-phase-iii-paragon-hf-trial-heart-failure-patients-preserved-ejection-fraction-hfpef

Dapa-HF baseline已發表：55%為非糖尿病患

ESC European Society of Cardiology
European Journal of Heart Failure (2019)
doi:10.1002/ejhf.1548
STUDY DESIGN
Received 19 March 2019; revised 23 May 2019; accepted 5 June 2019

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

John J.V. McMurray[1]*, David L. DeMets[2], Silvio E. Inzucchi[3], Lars Køber[4], Mikhail N. Kosiborod[5], Anna Maria Langkilde[6], Felipe A. Martinez[7], Olof Bengtsson[6], Piotr Ponikowski[8], Marc S. Sabatine[9], Mikaela Sjöstrand[6], and Scott D. Solomon[10], 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

ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, ARNI: angiotensin receptor–neprilysin inhibitor

Eur J Heart Fail. 2019 Jul 15. doi: 10.1002/ejhf.1548.

AstraZeneca

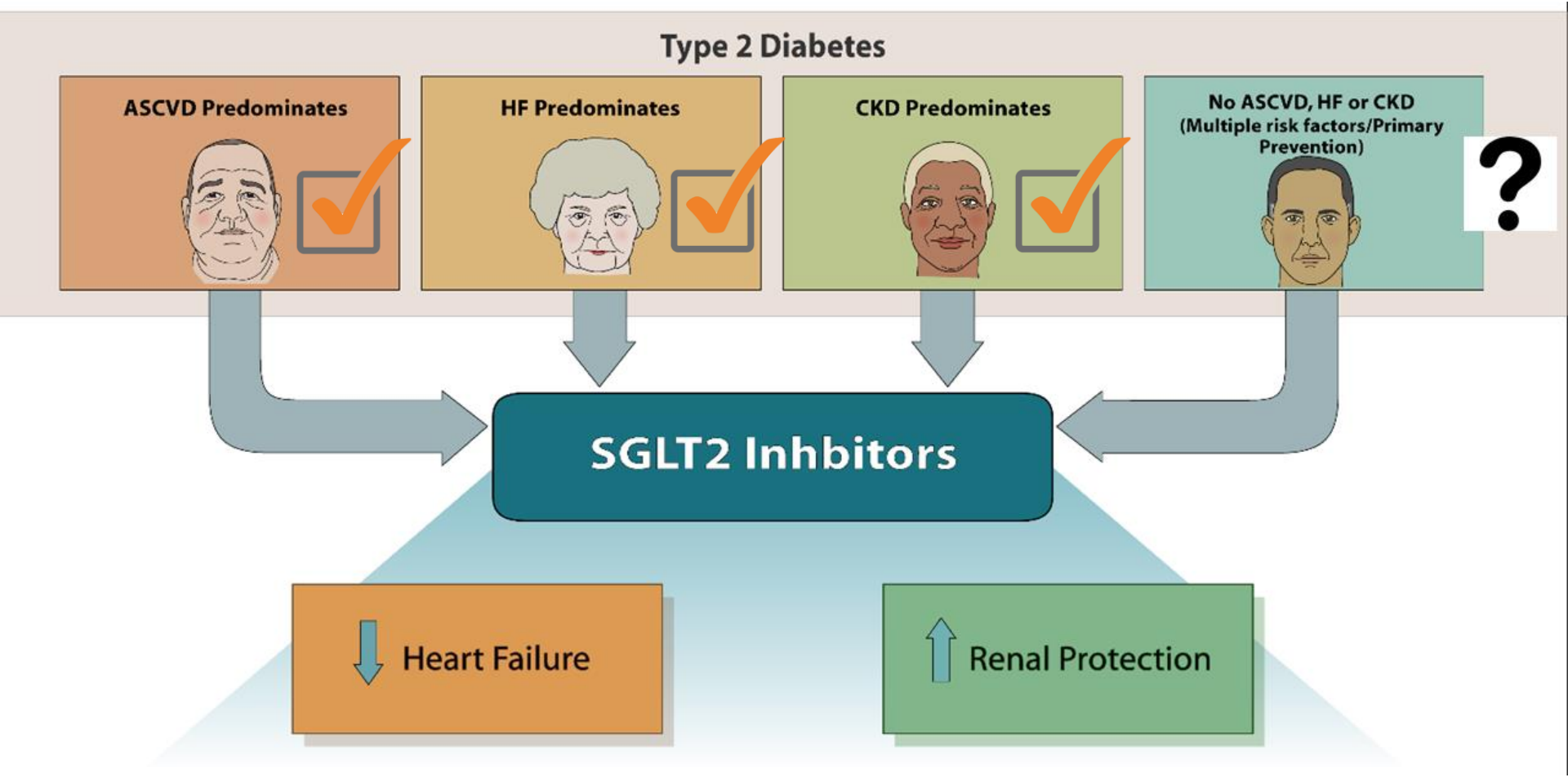
Farxiga met primary endpoint in landmark Phase III DAPA-HF trial for the treatment of patients with heart failure

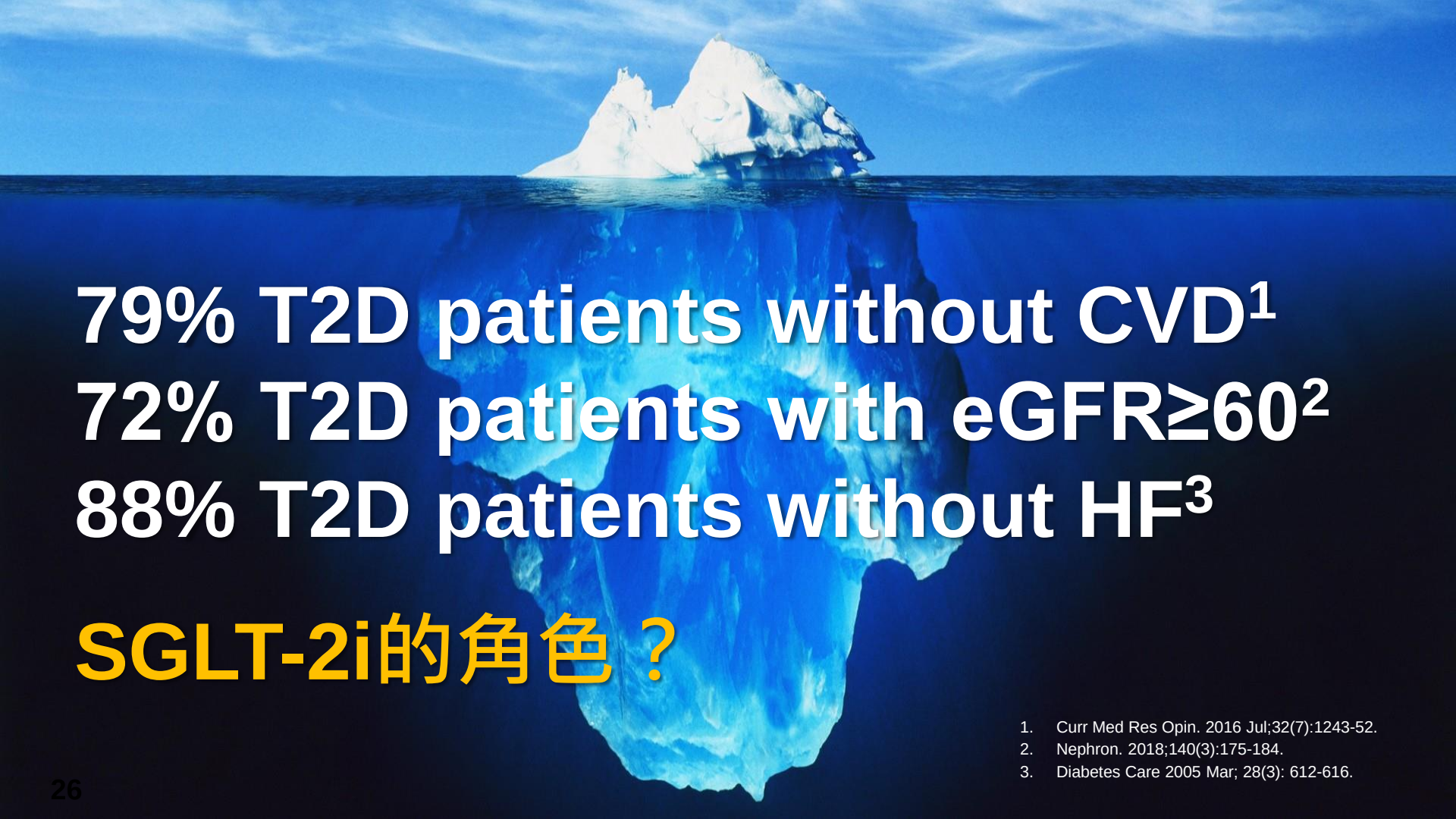
20 August 2019 07:00 BST

DAPA-HF is the first heart failure outcomes trial with an SGLT2 inhibitor in patients with and without type-2 diabetes

Farxiga significantly reduced the risk of cardiovascular death or worsening of heart failure when added to standard of care

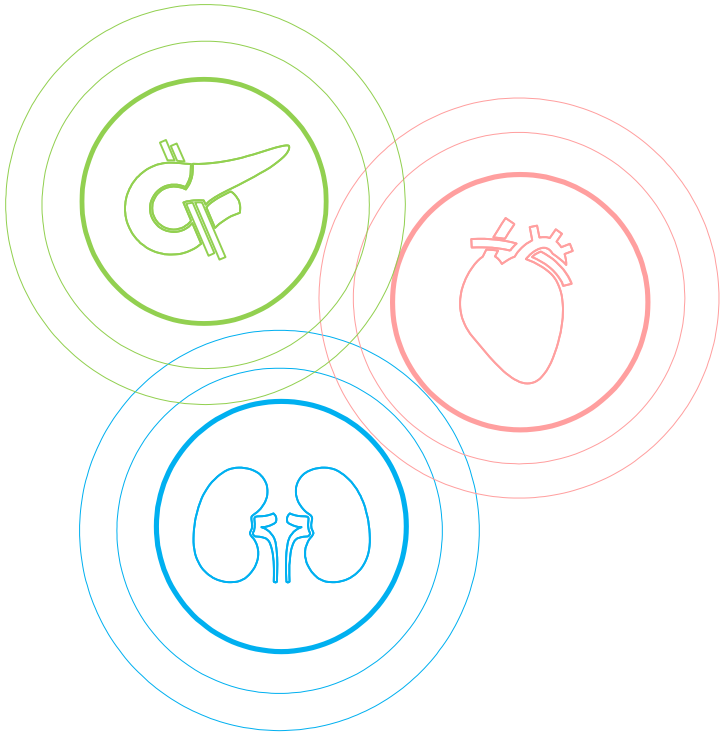
What do we know about SGLT-2i before DECLARE?





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

A

血糖控制

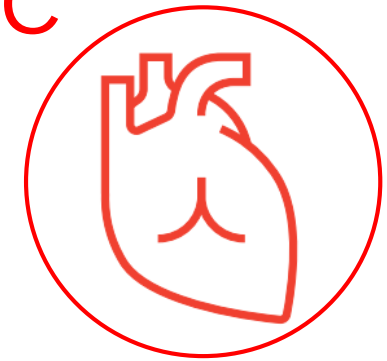
A1c

B

降低體重

Body weight

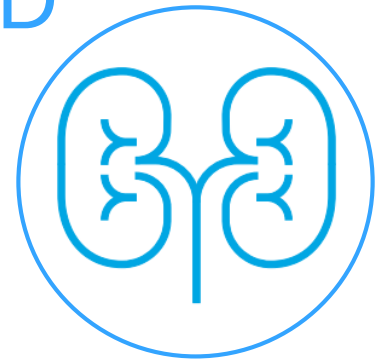
C



降低心血管風險

CV risk (HF)

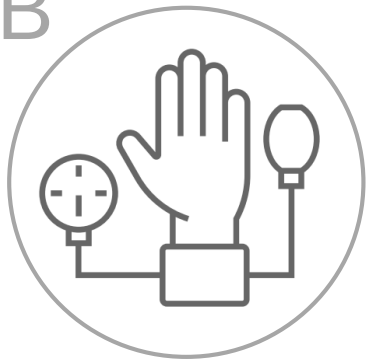
D



降低腎臟惡化風險

Diabetic kidney disease

B



降低血壓

Blood pressure

SGLT-2i能帶給T2D病患的好處：ABCD

A

血糖控制

A1c

B

降低體重

Body weight

C

降低心血管風險

CV risk (HF)

D

降低腎臟惡化風險

Diabetic kidney disease

B

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%

1. https://www.medscape.com/viewarticle/914551 2. Diabetes Care 2019 Jun; dci190028. https://doi.org/10.2337/dci19-0028

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

R

- 10 mg dapagliflozin once daily
- 60-120 mg of gliclazide MR once daily

12 weeks

Primary endpoint: **MAGE**

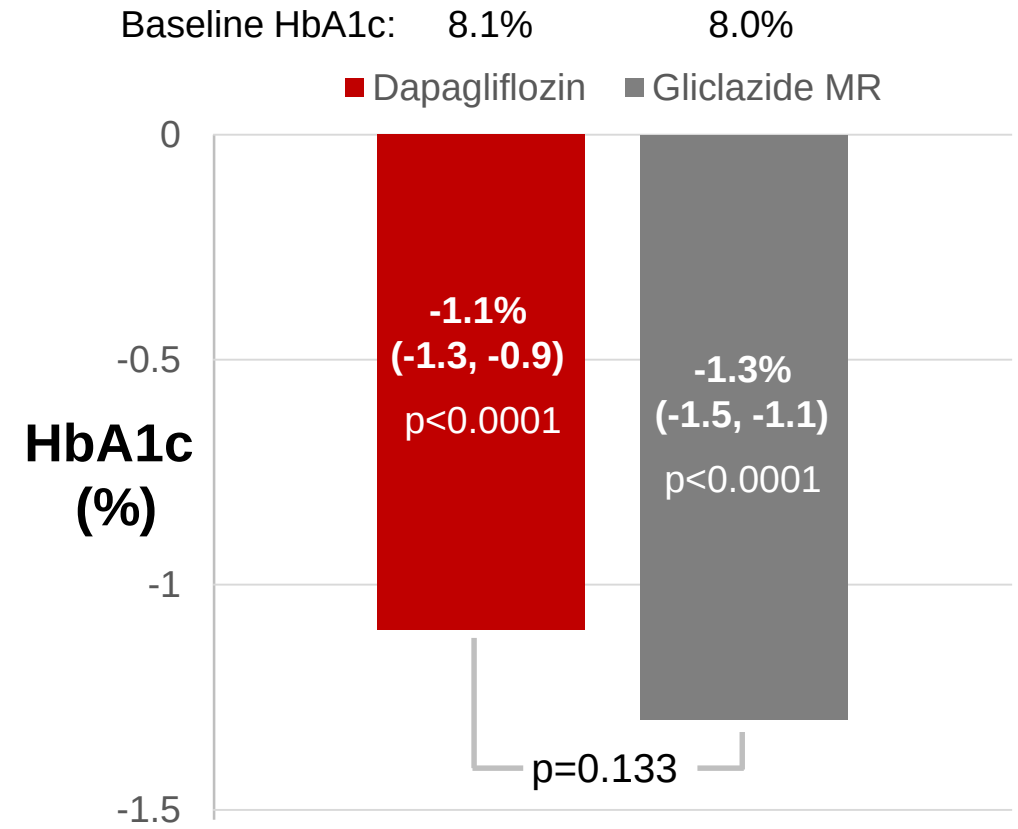
Table 1. Baseline characteristics and patient disposition

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/m²)	31.2 ± 4.4	30.6 ± 5.0	0.49
eGFR (ml/min/1.73 m²)	89 (77-105)	87 (77-99)	0.44

CGM: continuous glucose monitoring, MR: modified release, RCT: randomized controlled trial, R: randomization, MAGE: mean amplitude of glycemic excursions

ANDRE G.D. VIANNA, et al. Presented at: Scientific sessions of the 79th American Diabetes Association: June 7-11, 2019; San Francisco, CA, USA. 164-LB

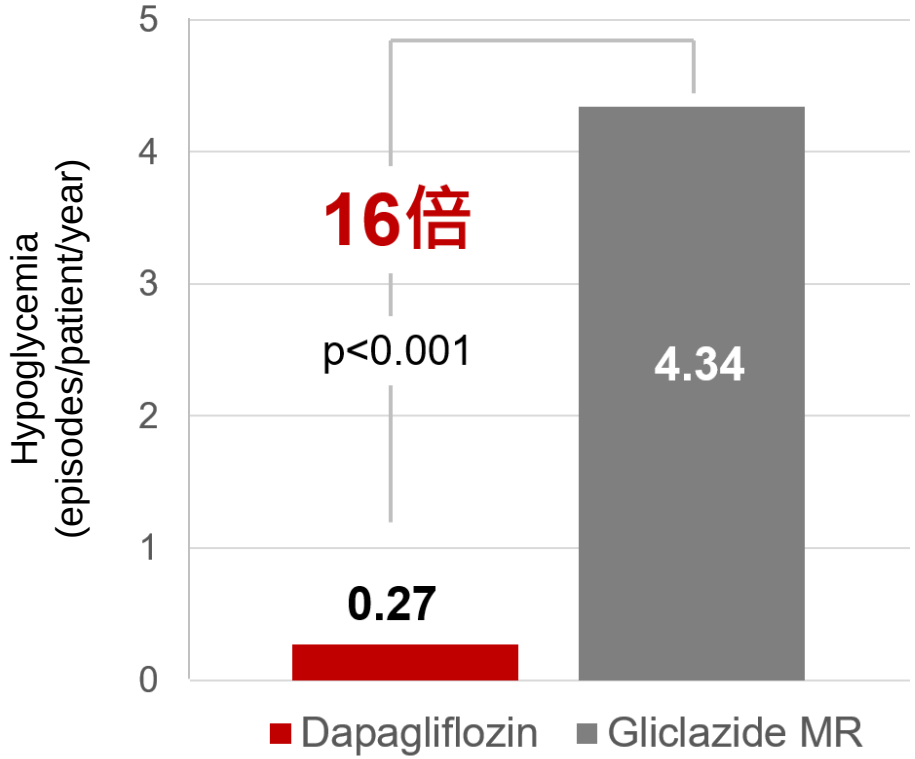
Dapagliflozin vs. Gliclazide
在A1c, FPG, PPG具一致的降糖表現

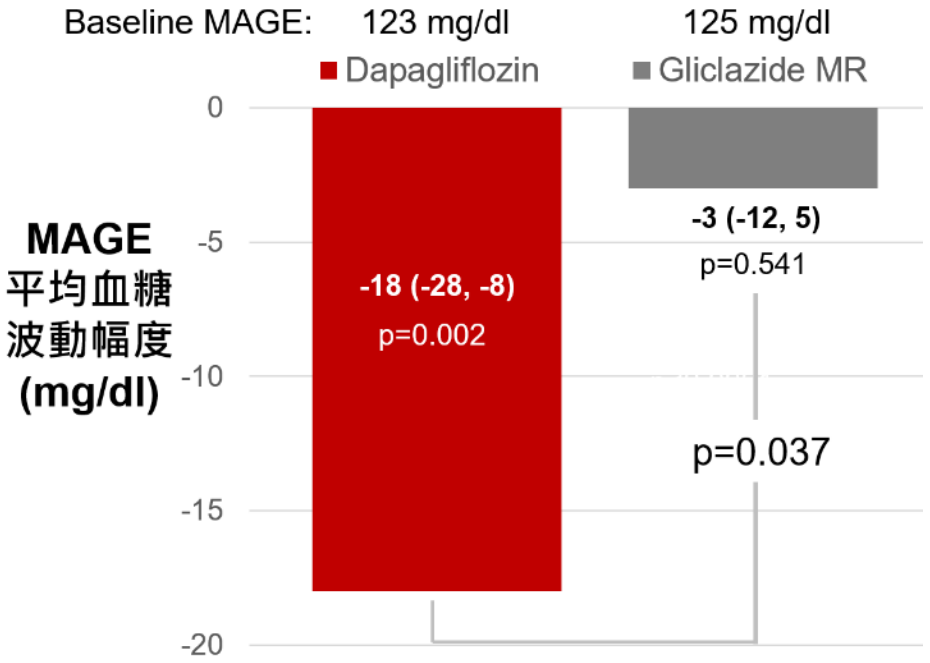


血糖	Dapagliflozin	Gliclazide MR
FPG (mg/dl)	Baseline: 161 Change: -31 p<0.0001	Baseline: 161 Change: -37 p<0.0001
	p=0.236	
PPG (mg/dl)	Baseline: 202 Change: -66 p<0.0001	Baseline: 199 Change: -56 p<0.0001
	p=0.312	

FPG: fasting plasma glucose, PPG: postprandial glucose ANDRE G.D. VIANNA, et al. Presented at: Scientific sessions of the 79th American Diabetes Association: June 7-11, 2019; San Francisco, CA, USA. 164-LB

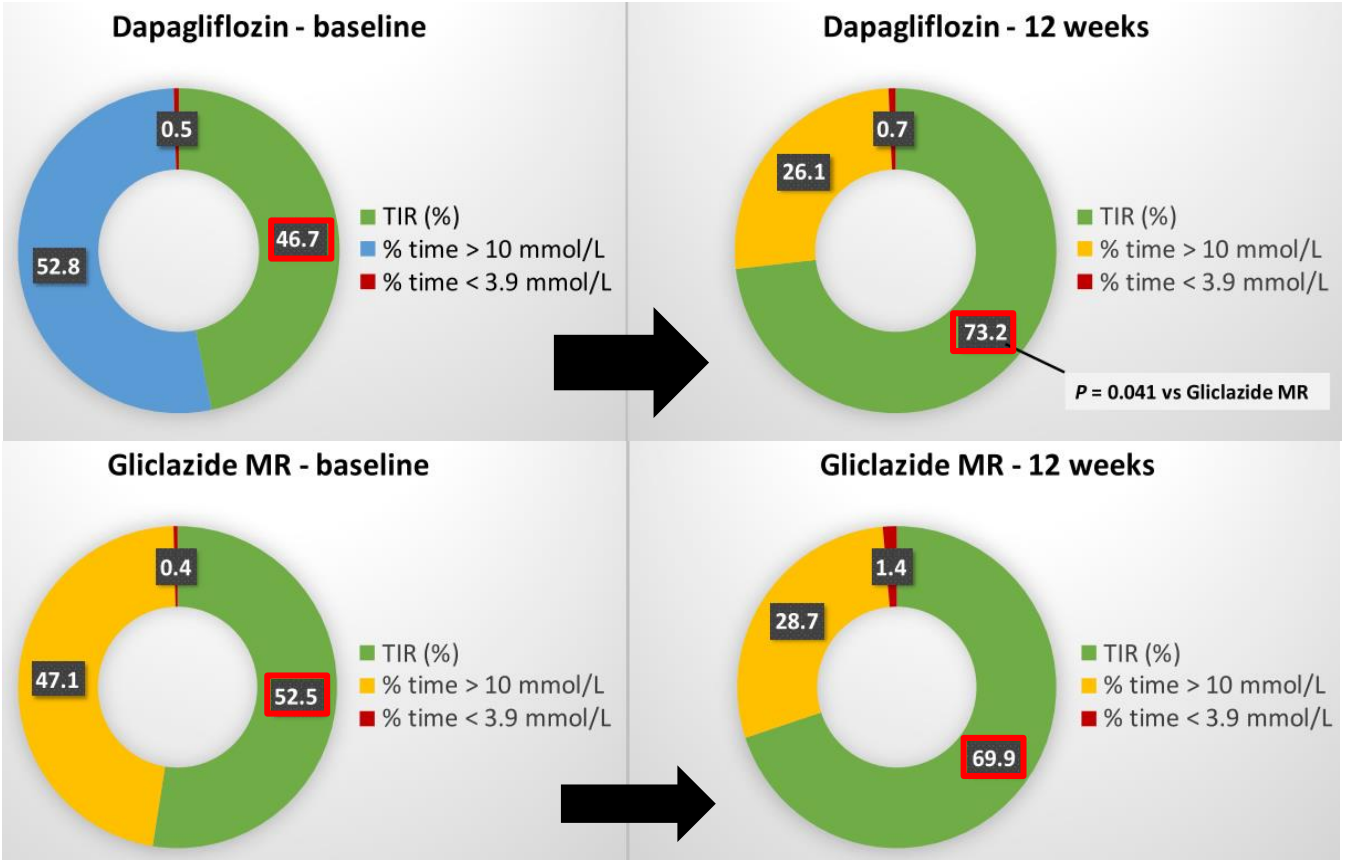
Dapagliflozin低血糖風險低、更能降低血糖波動





MAGE: Mean Amplitude of Glycemic Excursions ANDRE G.D. VIANNA, et al. Presented at: Scientific sessions of the 79th American Diabetes Association: June 7-11, 2019; San Francisco, CA, USA. 164-LB

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



Dapagliflozin

△26.5%

From 46.7% to 73.2%

p=0.041

Gliclazide MR

△17.4%

From 52.5% to 69.9%

***TIR: 血糖維持目標範圍 (70-180 mg/dl)內時間%**

TIR: time in range (70-180 mg/dL) ANDRE G.D. VIANNA, et al. Presented at: Scientific sessions of the 79th American Diabetes Association: June 7-11, 2019; San Francisco, CA, USA. 164-LB

SGLT-2i能帶給T2D病患的好處：ABCD

A

血糖控制

A1c

B

降低體重

Body weight

C

降低心血管風險

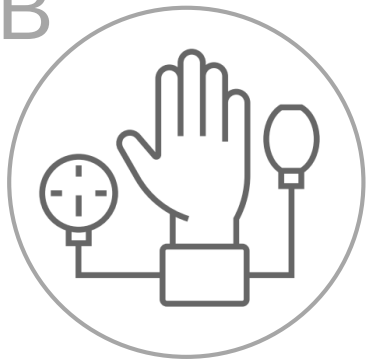
CV risk (HF)

D

降低腎臟惡化風險

Diabetic kidney disease

B



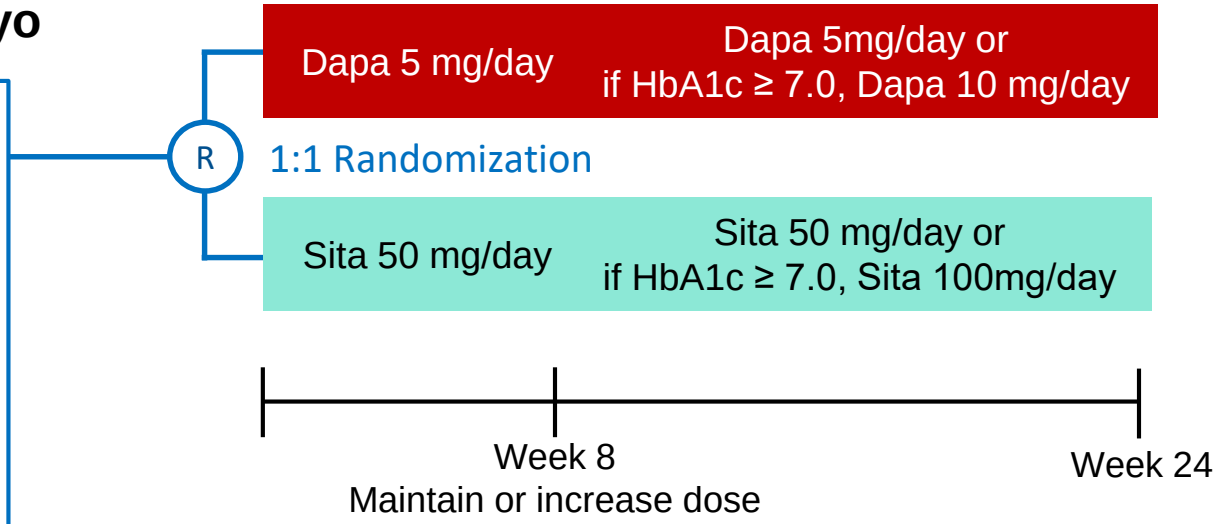
降低血壓

Blood pressure

DIVERSITYCVR Study:
比較T2D病患使用Dapagliflozin和Sitagliptin的療效

- **340 T2DM patients in Tokyo**

- **The inclusion criteria**
  - T2DM, age 20-80 years
  - 7.1% ≦ HbA1c ≦ 10.0%
  - with metformin (250-2250mg) alone or with no glucose-lowering agents
  - BMI ≧ 23 kg/m^2
- **The exclusion criteria**
  - Cr ≧ 1.3 mg/dL or
  - eGFR < 45 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 mmol/L (< 54 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

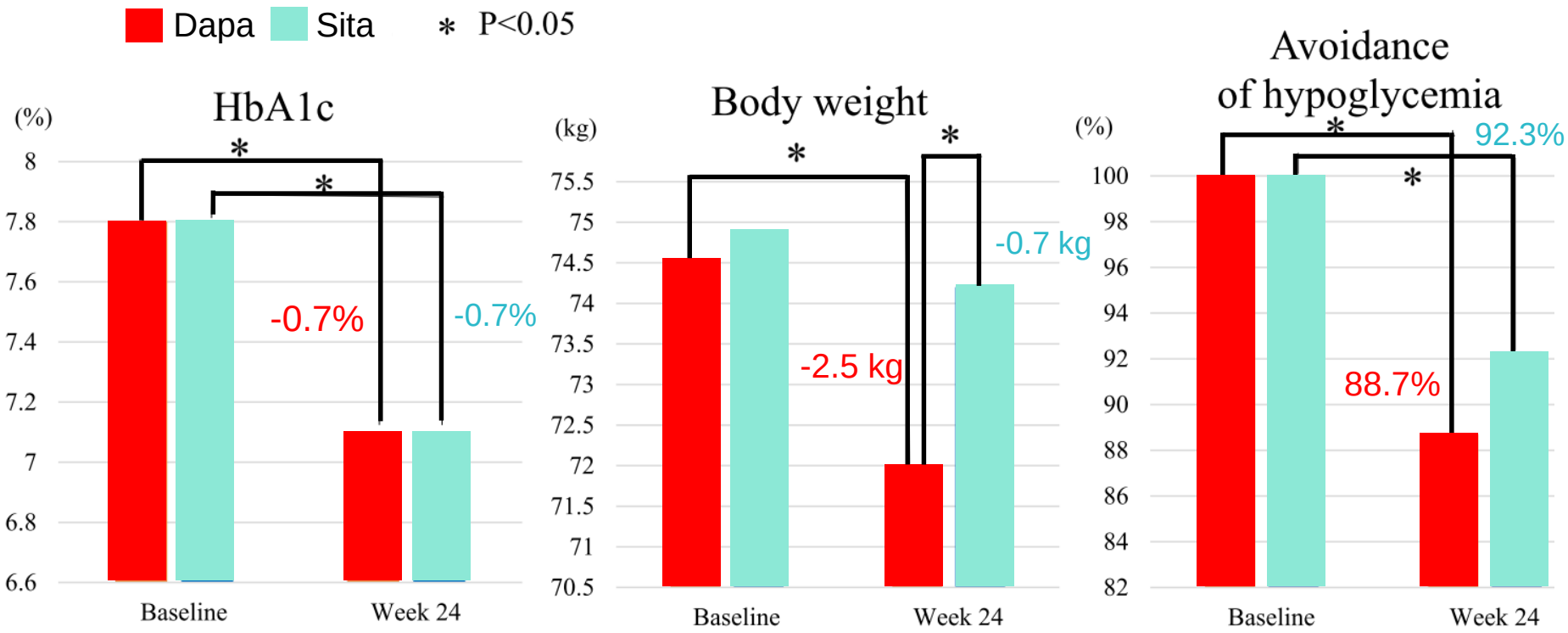
Table1. Baseline characteristics of patients in the two groups

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/m²)	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: 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 ± 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	

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

Original Article

J Atheroscler Thromb, 2018; 25: 000-000.
http://doi.org/10.5551/jat.40873

Dapagliflozin Reduces Fat Mass without Affecting Muscle Mass in Type 2 Diabetes

Seigo Sugiyama[1,2], Hideaki Jinnouchi[1,2,3], Noboru Kurinami[1], Kunio Hieshima[1], Akira Yoshida[1], Katsunori Jinnouchi[1], Hiroyuki Nishimura[1], Tomoko Suzuki[1], Fumio Miyamoto[1], 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 ± 1.7		‡

1.5%

- 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)

J Atheroscler Thromb. 2018 Jun 1;25(6):467-476.

SGLT-2i能帶給T2D病患的好處：ABCD

A

血糖控制

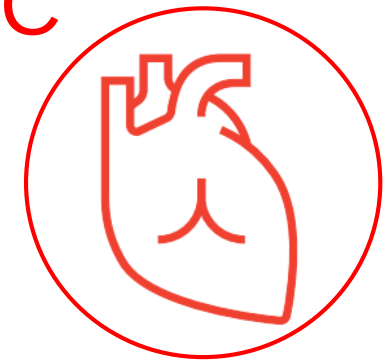
A1c

B

降低體重

Body weight

C



降低心血管風險

CV risk (HF)

D

降低腎臟惡化風險

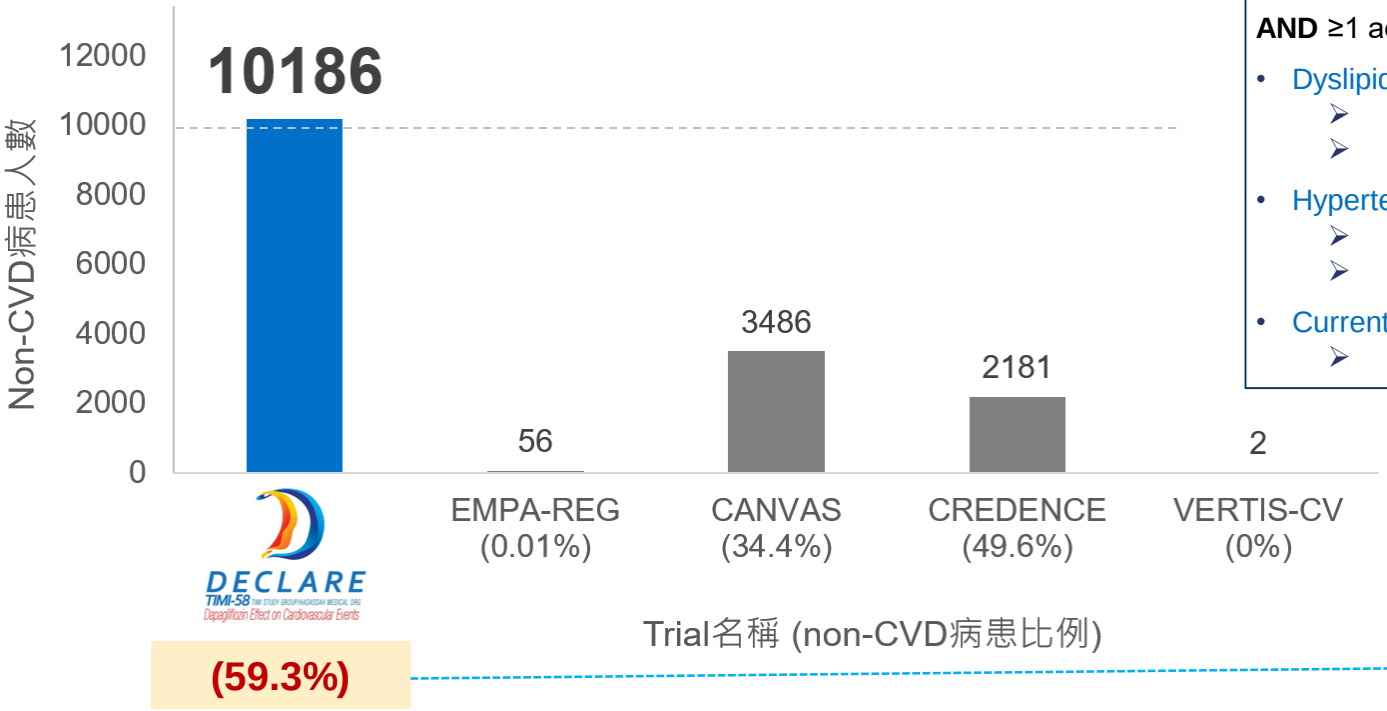
Diabetic kidney disease

B

降低血壓

Blood pressure

DECLARE為唯一non-CVD病患超過萬人的T2DM CVOT



Multiple Risk Factors

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

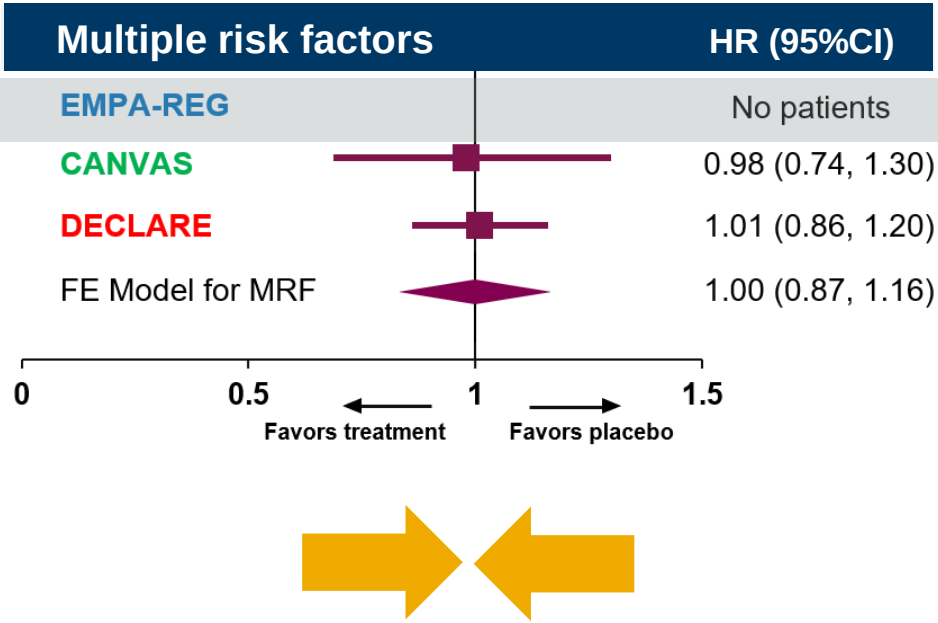
AND ≥1 additional risk factors:

- 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

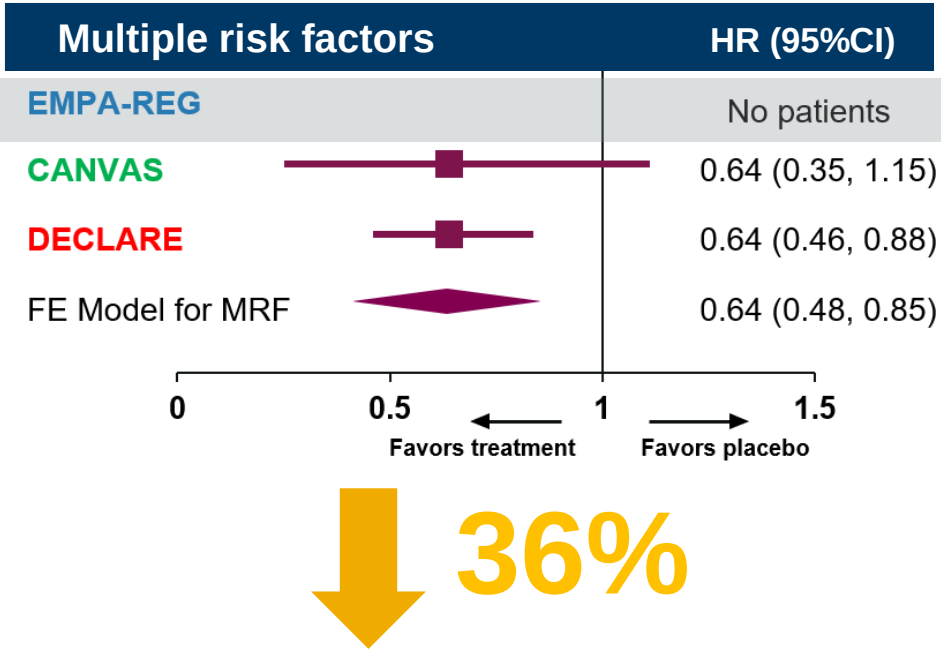
CVOT: Cardiovascular Outcome Trial 1. N Engl J Med. 2019 Jan 24;380(4):347-357. 2. N Engl J Med 2015;373:2117–2128. 3. N Engl J Med. 2017 Aug 17;377(7):644-657. 4. N Engl J Med. 2019 Apr 14. doi: 10.1056/NEJMoa1811744. 5. Am Heart J. 2018 Dec;206:11-23.

DECLARE提供non-CVD病患心血管安全實證: MACE & hHF

MACE



Hospitalization for heart failure



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

DECLARE
TIMI-58 Dapagliflozin Effect on Cardiovascular Events

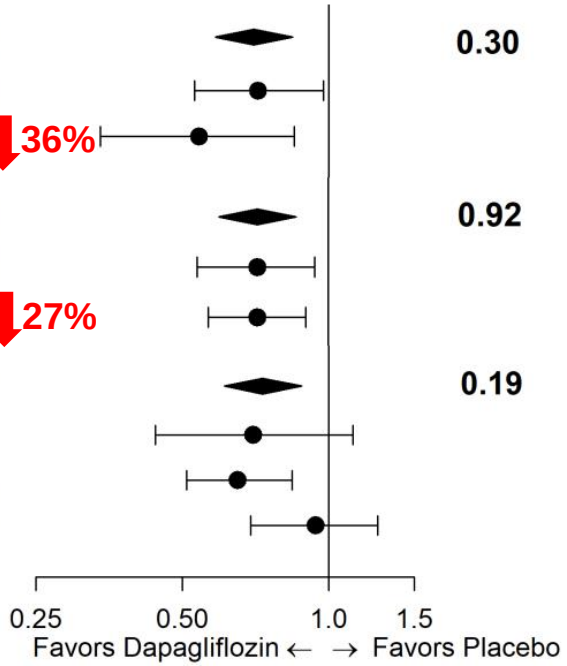
Outcomes	Dapagliflozin n/N	Placebo n/N	Hazard Ratio (95% CI)	P value for interaction
HHF	**212/8582**	**286/8578**	**0.73 (0.61-0.88)**	**0.30**
ASCVD	151/3474	192/3500	0.78 (0.63-0.97)	
MRF	61/5108	94/5078	0.64 (0.46-0.88)	
HHF	**212/8582**	**286/8578**	**0.73 (0.61-0.88)**	**0.92**
Prior HF	87/852	115/872	0.73 (0.55-0.96)	
No HF	125/7730	171/7706	0.73 (0.58-0.92)	
HHF	**212/8582**	**286/8578**	**0.73 (0.61-0.88)**	**0.19**
<60 mL/min/1.73m2	29/606	48/659	0.70 (0.44-1.12)	
60 to <90 mL/min/1.73m2	99/3838	152/3894	0.65 (0.51-0.84)	
>=90 mL/min/1.73m2	84/4137	86/4025	0.94 (0.69-1.26)	

MRF: multiple risk factors
40.6% patients in DECLARE

90% patients in DECLARE

36%

27%



The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med. 2019 Jan 24;380(4):347-357.

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

ESC
European Society of Cardiology

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.

Eur J Heart Fail. 2019 May 26. doi: 10.1002/ejhf.1531.

2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

AMERICAN COLLEGE of CARDIOLOGY

Circulation

4.2. Adults With Type 2 Diabetes Mellitus

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

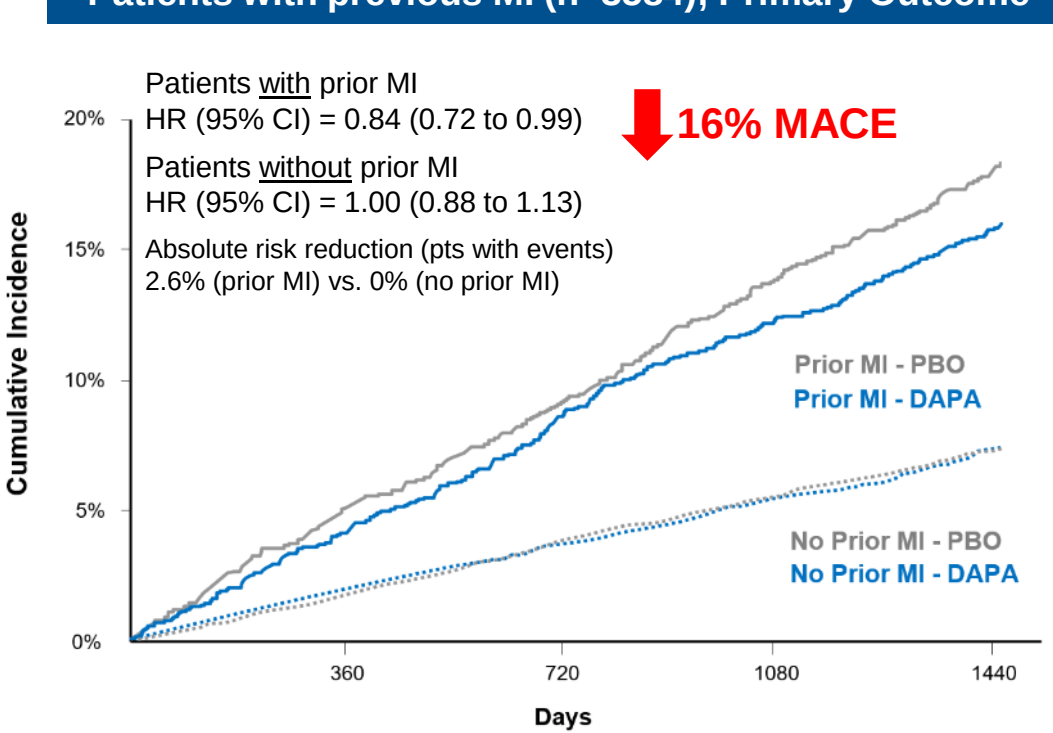
Recommendations for Adults With Type 2 Diabetes Mellitus Referenced studies that support recommendations are summarized in Online Data Supplement 10.		
COR	**LOE**	**Recommendations**
I	A	1. For all adults with T2DM, a tailored nutrition plan focusing on a heart-healthy dietary pattern is recommended 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).

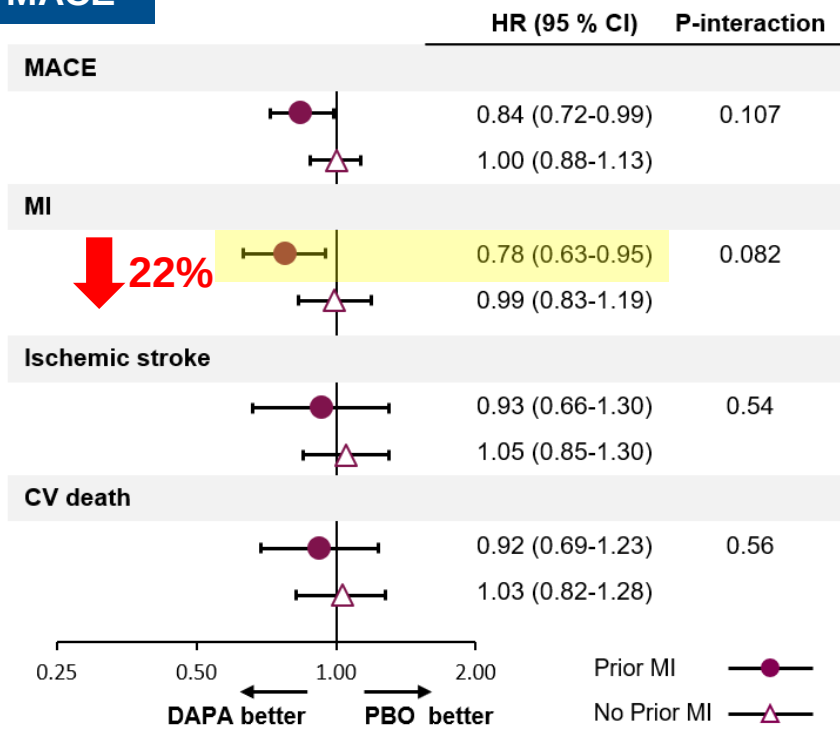
Circulation. 2019 Mar 17:CIR0000000000000678.

DECLARE次分析：T2D合併有心肌梗塞病患↓16%MACE

- 發表於2019年ACC年會

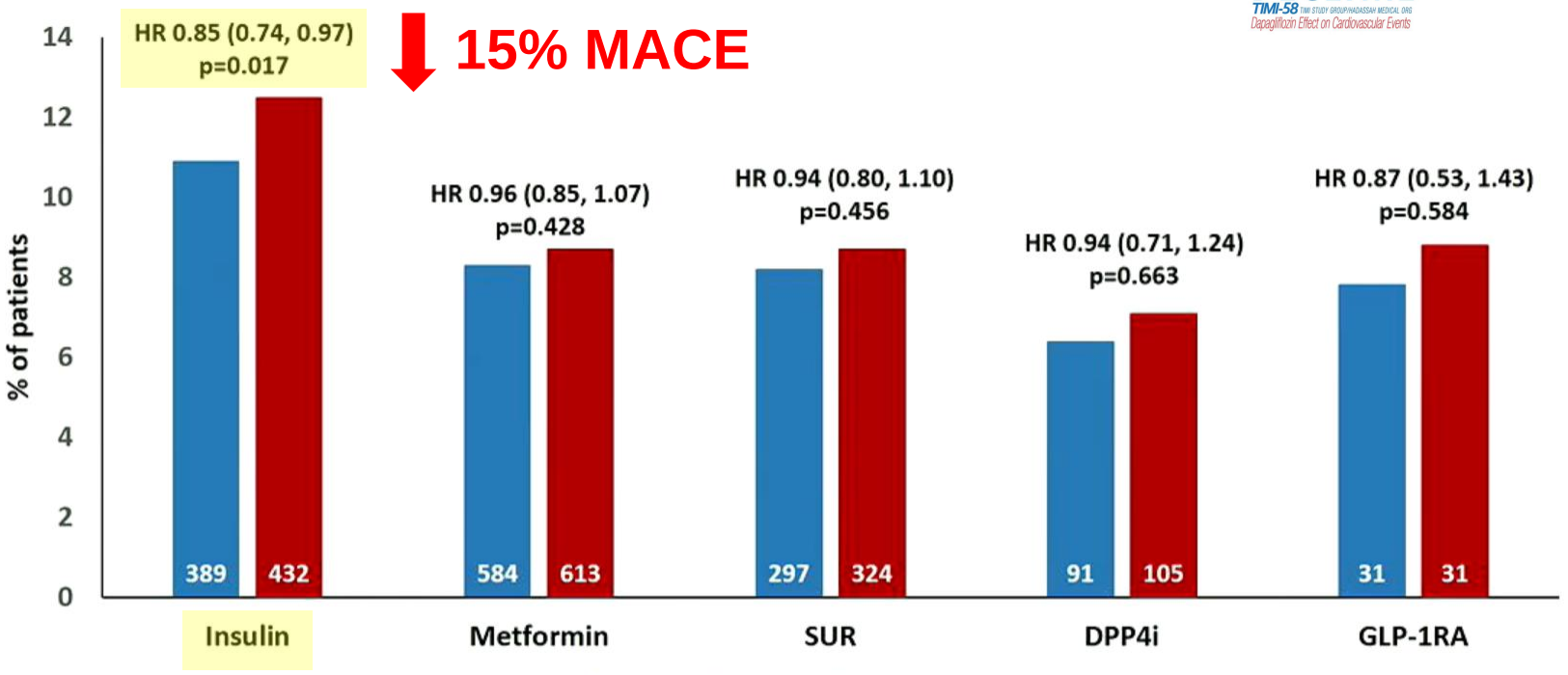
Patients with previous MI (n=3584); Primary Outcome – MACE





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：合併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

Itamar Raz et al. Presented at ADA 79th Scientific Sessions; June 7-11, 2019; San Francisco, CA; DECLARE-TIMI 58 Trial section

SGLT-2i能帶給T2D病患的好處：ABCD

A

血糖控制

A1c

B

降低體重

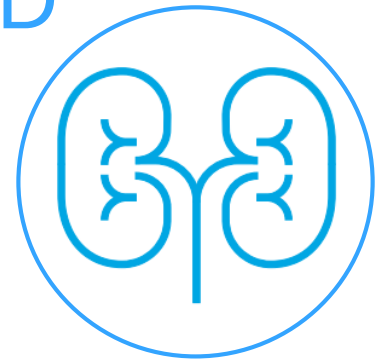
Body weight

C

降低心血管風險

CV risk (HF)

D



降低腎臟惡化風險

Diabetic kidney disease

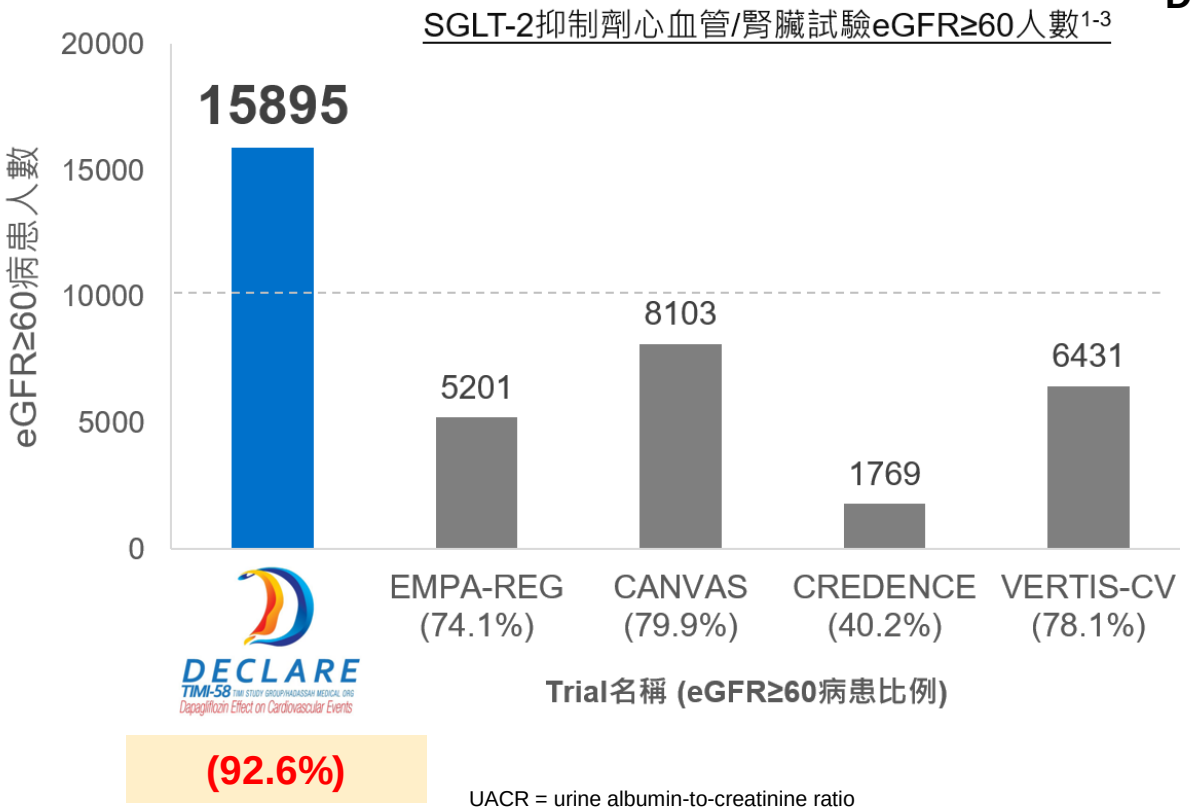
B

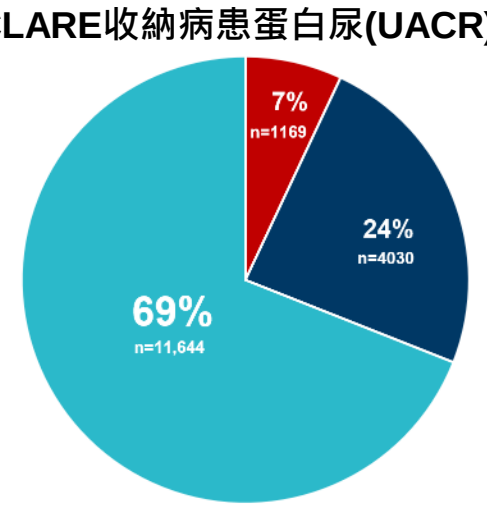
降低血壓

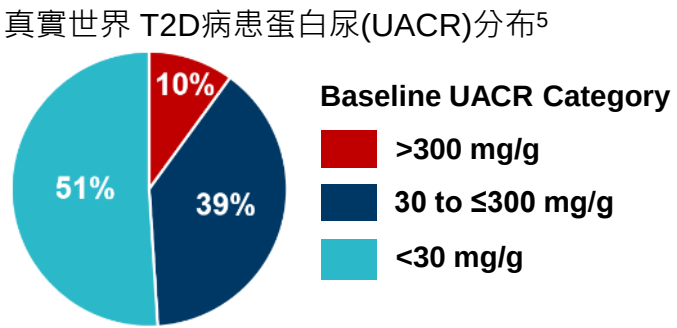
Blood pressure

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



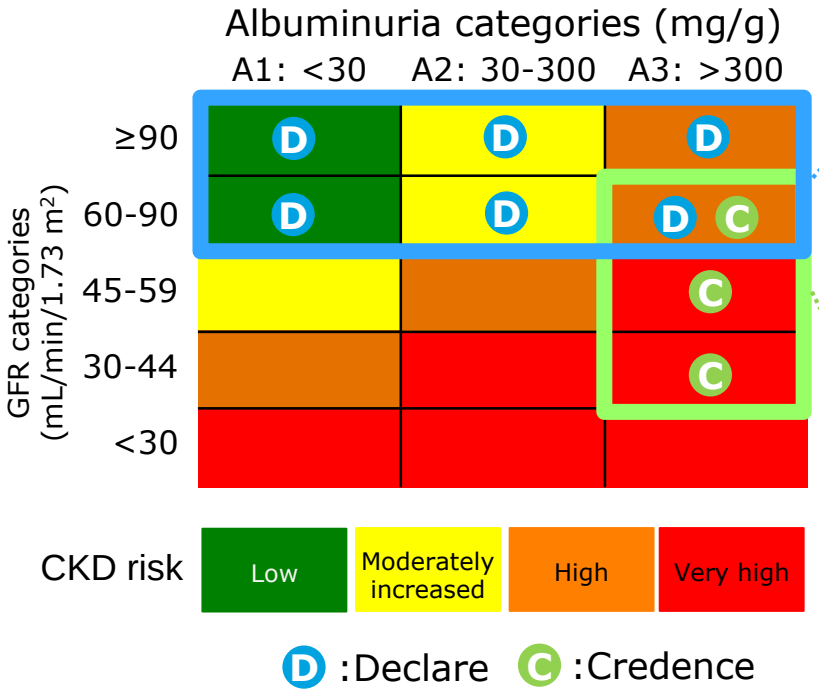




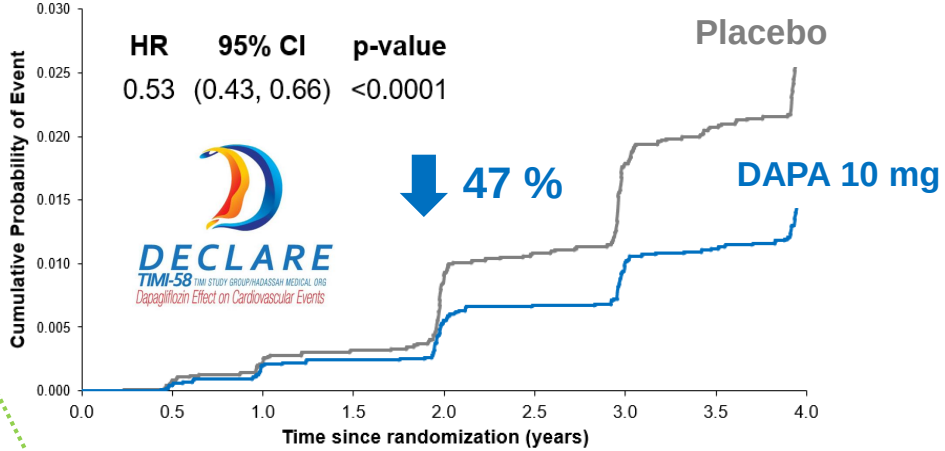
UACR = urine albumin-to-creatinine ratio

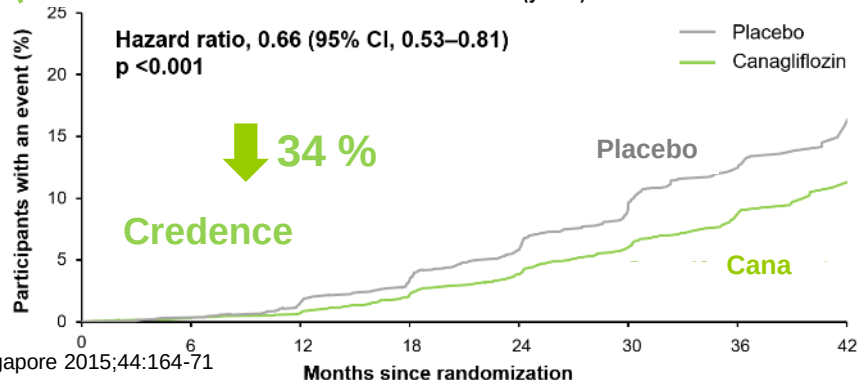
1. Lancet. 2019 Jan 5;393(10166):31-39. 2. N Engl J Med. 2019 Apr 14. doi: 10.1056/NEJMoa1811744. 3. Am Heart J. 2018 Dec;206:11-23.
4. Raz I et al. Presented at: ADA 79th Scientific Sessions; June 7-11, 2019; San Francisco, CA 244-OR. 5. Kidney Int. 2006 Jun;69(11):2057-63.

DECLARE、CREDENCE收納病患CKD stage分布及結果



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.

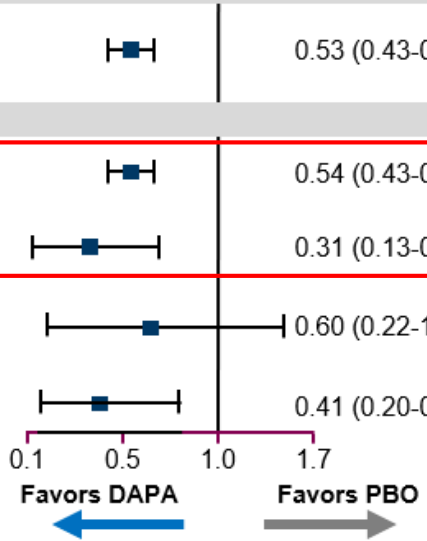
2.. N Engl J Med. 2019 Apr 14. doi: 10.1056/NEJMoa1811744. 3. Ann Acad Med Singapore 2015;44:164-71

DECLARE的腎臟終點分析

- 發表於2019年ADA年會

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

	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 ≥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 ≥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

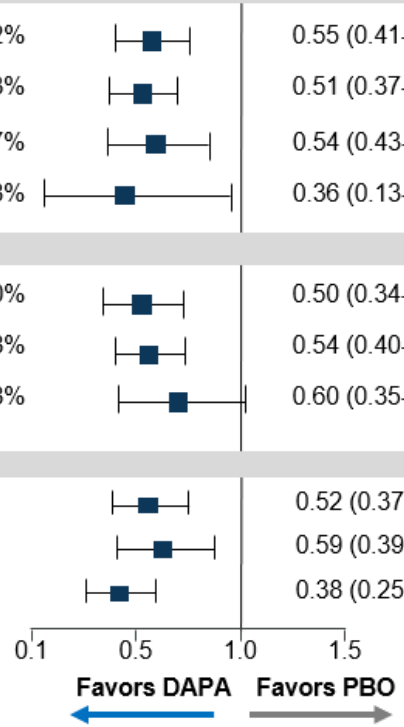
Prespecified exploratory endpoint: decrease eGFR ≥40% to <60 mL/min/1.73 m2, ESRD or Renal Death;
DAPA = dapagliflozin; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease;
PBO = placebo Lancet Diabetes Endocrinol. 2019 Jun 10. pii: S2213-8587(19)30180-9.

DECLARE的腎臟終點次分析：依據共病、腎功能

- 發表於2019年ADA年會

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

	Dapagliflozin n/N (%)	Dapagliflozin KM Event Rate (4 years)	Placebo n/N (%)	Placebo KM Event Rate (4 years)	Hazard Ratio (95% CI)	Interaction P value
Baseline CV disease or risk factor						
Established ASCVD	65/3474 (1.9)	1.9%	118/3500 (3.4)	3.2%	0.55 (0.41-0.75)	0.72
Multiple risk factors ↓49%	62/5108 (1.2)	1.2%	120/5078 (2.4)	2.3%	0.51 (0.37-0.69)	
History of hypertension	122/7769 (1.6)	1.6%	222/7658 (2.9)	2.7%	0.54 (0.43-0.67)	0.41
No history of hypertension	5/813 (0.6)	0.5%	16/920 (1.7)	1.8%	0.36 (0.13-0.98)	
Baseline renal function						
eGFR ≥90 mL/min/1.73m² ↓50%	41/4137 (1.0)	1.0%	79/4025 (2.0)	2.0%	0.50 (0.34-0.73)	0.87
eGFR 60-<90 mL/min/1.73m² ↓46%	65/3838 (1.7)	1.6%	121/3894 (3.1)	2.8%	0.54 (0.40-0.73)	
eGFR <60 mL/min/1.73m²	21/606 (3.5)	3.8%	38/659 (5.8)	5.8%	0.60 (0.35-1.02)	
Baseline UACR						
ACR <30 mg/g ↓48%	50/5819 (0.9)	0.9%	95/5825 (1.6)	1.5%	0.52 (0.37-0.74)	0.30
ACR 30-300 mg/g ↓41%	39/2017 (1.9)	2.0%	66/2013 (3.3)	3.3%	0.59 (0.39-0.87)	
ACR >300 mg/g	31/594 (5.2)	4.8%	75/575 (13.0)	12.8%	0.38 (0.25-0.58)	



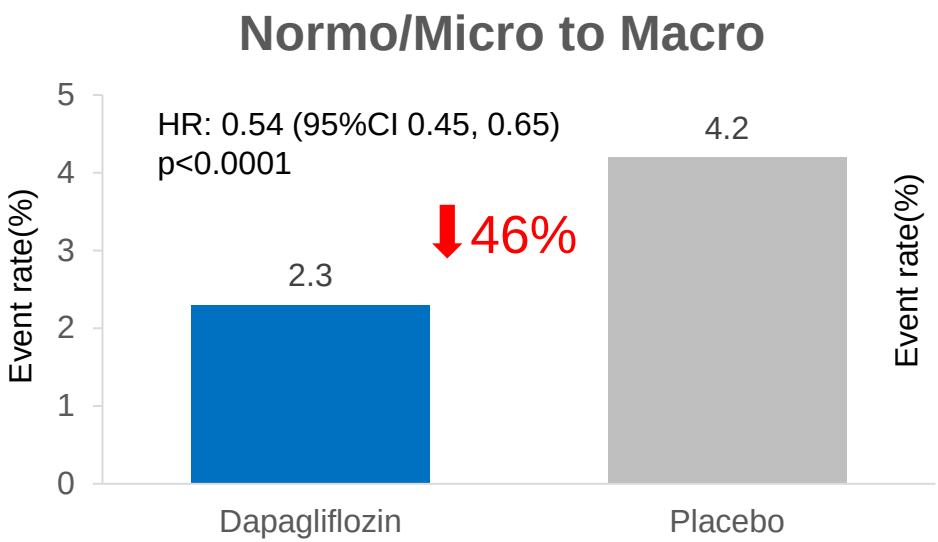
THE LANCET Diabetes & Endocrinology

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.

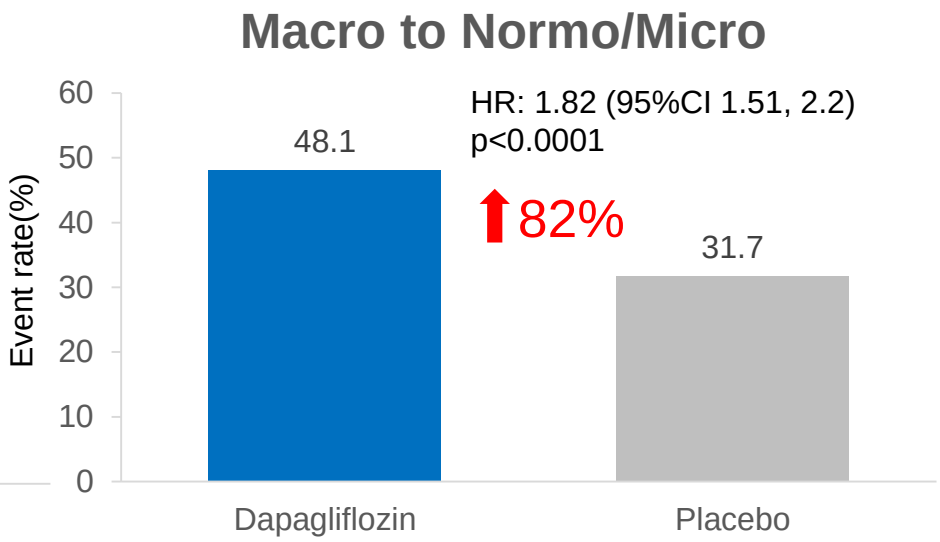
DECLARE：蛋白尿的改變

- 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%



Definitions of Albuminuria Categories	
Macroalbuminuria	UACR ≥300 mg/g
Microalbuminuria	UACR ≥30 to <300 mg/g
Normoalbuminuria	UACR <30 mg/g

DAPA = dapagliflozin; KM = Kaplan-Meier; Macro = macroalbuminuria; Micro = microalbuminuria; ; Normo = normoalbuminuria; UACR = urine albumin-to-creatinine ratio. Raz I et al. Presented at: ADA 79th Scientific Sessions; June 7-11, 2019; San Francisco, CA 244-OR.

SGLT-2i能帶給T2D病患的好處：ABCD

A

血糖控制

A1c

B

降低體重

Body weight

C

降低心血管風險

CV risk (HF)

D

降低腎臟惡化風險

Diabetic kidney disease

B

降低血壓

Blood pressure

安全性

Safety

The NEW ENGLAND JOURNAL of MEDICINE

SGLT-2 抑制劑的眾多安全性議題

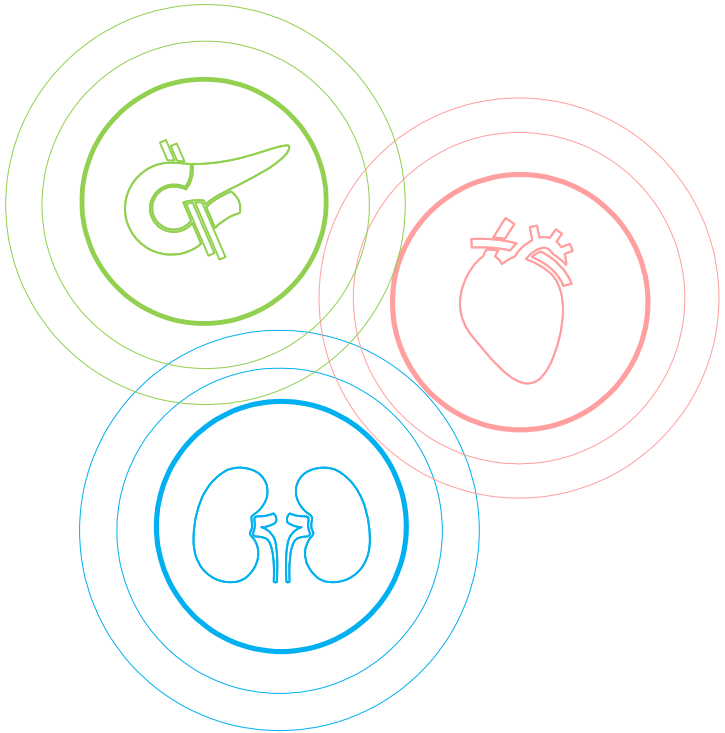
DECLARE
TIMI-58 TIMI STUDY GROUP/HADASSAH MEDICAL ORG
Dapagliflozin Effect on Cardiovascular Events

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
- ↑ **Genital infection** (生殖器感染；黴菌) 0.9% vs 0.1%*
- ↑ **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 and EASD, ACC, ERA-EDTA guidelines base on ASCVD, HF, DKD effects**
  - Add-on or switch therapy in patients with ASCVD, HF, CKD consideration

- **'Time in Range' statement published in 2019 ADA:**
  - >70% in blood sugar 70-180 mg/dl

- **Dapagliflozin vs. Gliclazide in 2019 ADA:**
  - A1c →←, FPG →←, PPG →←, hypo ↓ 16 times
  - MAGE -18 vs -3 mg/dl (p=0.037), TIR ↑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 <u>non-CVD</u> patients** (↓36% hHF), **post-MI patients** (↓16% MACE, ↓ 22% MI risk), **Insulin user**(↓15% MACE)

- **DECLARE renal outcome in <u>non-CKD</u> 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

SGLT-2i能帶給T2D病患的好處：ABCD

A

血糖控制

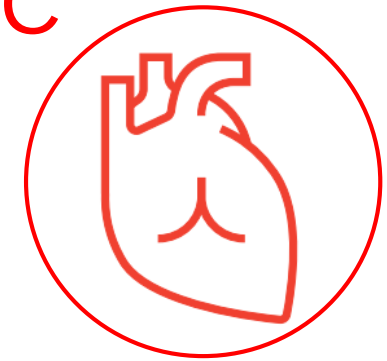
A1c

B

降低體重

Body weight

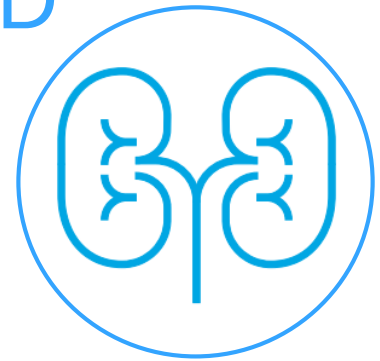
C



降低心血管風險

CV risk (HF)

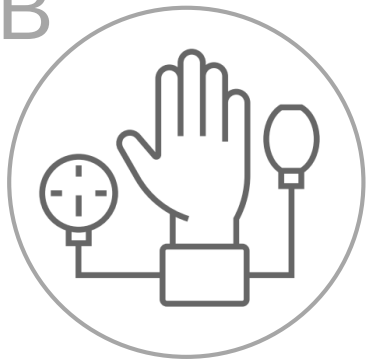
D



降低腎臟惡化風險

Diabetic kidney disease

B



降低血壓

Blood pressure

安全性

Safety